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(54) Title: ACSS2 INHIBITORS AND METHODS OF USE THEREOF

(57) Abstract: The present invention relates to novel ACSS2 inhibitors having activity as anti-cancer therapy, treatment of alcoholism, and viral infection (e.g., CMV), composition and methods of preparation thereof, and uses thereof for treating viral infection, alcoholism, alcoholic steatohepatitis (ASH), non-alcoholic steatohepatitis (NASH), obesity/weight gain, anxiety, depression, post-traumatic stress disorder, inflammatory/autoimmune conditions and cancer, including metastatic cancer, advanced cancer, and dmg resistant cancer of various types.

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 cnditions), 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 evidences from several studies suggest 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 inclouding 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 metabolismPNAS 115, (40), E9499-E9506, 2018).

[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 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 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 cells, Plos One,12 (12) 1-31, 2017).

SUMMARY OF THE INVENTION

[0014] This invention provides a compound or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula **I-III(a)**, 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, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula **I-III(a)**, 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-III(a)**, and by the structures listed in Table 1, as defined herein below, to a 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-III(a)**, 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 functionin a cell, comprising contacting a compound represented by the structure of formula **I-III(a)**, 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-III(a)**, 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-III(a)**, 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-III(a)**, 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-III(a)**, 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-III(a)**, 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-III(a)**, 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-III(a)**, 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-III(a)**, 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.

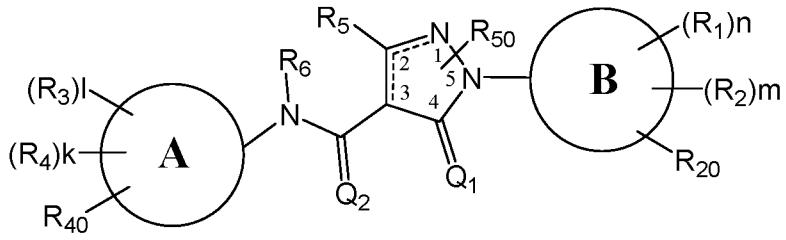
[0027] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a neuropsychiatric disease or disorder in a subject, comprising administering a compound represented by the structure of formula **I-III(a)**, and by the structures 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-III(a)**, 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 amethod of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject, comprising administering a compound represented by the structure of formula **I-III(a)**, 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**):



(**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 C_3-C_{10} cycloalkyl (e.g. cyclohexyl) or a single or fused C_3-C_{10} 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);

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring)

(e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, $NHC(O)$-R_{10} (e.g., $NHC(O)CH_3$), $NHCO$-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O$-R_{10} (e.g. $C(O)O$-CH_3, $C(O)O$-$CH(CH_3)_2$, $C(O)O$-CH_2CH_3), R_8-$C(O)$-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)$-R_{10} (e.g., $C(O)$-CH_3, $C(O)$-CH_2CH_3, $C(O)$-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)$-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH$-$R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ 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);

$\mathbf{R_3}$, $\mathbf{R_4}$ and $\mathbf{R_{40}}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), $NHCO$-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O$-R_{10} (e.g. $C(O)O$-CH_3, $C(O)O$-CH_2CH_3), R_8-$C(O)$-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)$-R_{10} (e.g., $C(O)$-CH_3, $C(O)$-CH_2CH_3, $C(O)$-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)$-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched

alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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., [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);

R_5 is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, iso-propyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), $C(=CH_2)$-R_{10} (e.g., $C(=CH_2)$-C(O)-OCH_3, $C(=CH_2)$-CN) substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

R_{50} is H, F, Cl, Br, I, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, propyl, iso-propyl, benzyl), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), substituted or unsubstituted benzyl, (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

wherein R_{50} is attached either to N_1 or to C_3 and if R_{50} is attached to N_1 than N_1-C_2 is a single bond and C_2-C_3 is a double bond, and if R_{50} is attached to C_3 than N_1-C_2 is a double bond and C_2-C_3 is a single bond;

R_6 is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

R_8 is $[CH_2]_p$

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

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

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

R_{10} and **R_{11}** are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., C(O)(OCH_3)), or $S(O)_2R$; or **R_{10}** and **R_{11}** are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

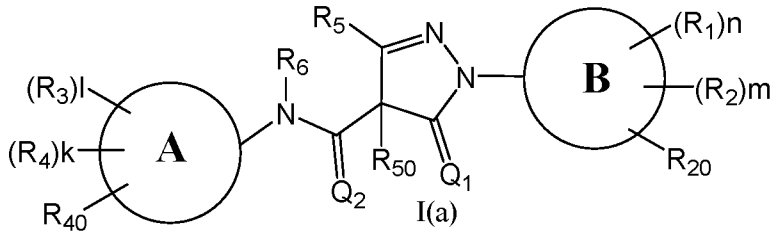
m, **n**, **l** and **k** are each independedntly an integer between 0 and 4 (e.g., 0, 1 or 2);

$\mathbf{Q_1}$ and $\mathbf{Q_2}$ are each independently S, O, N-OH, CH_2, $C(R)_2$ or N-OMe;

or its pharmaceutically acceptable salt, optical isomer, 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, if R_{50} is H then neither one of R_1, R_2 or R_{20} is H, and n and m are not 0.

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



I(a)

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 C_3-C_{10} cycloalkyl (e.g. cyclohexyl) or a single or fused C_3-C_{10} 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);

$\mathbf{R_1}$, $\mathbf{R_2}$ and $\mathbf{R_{20}}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, $C(O)O-CH(CH_3)_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-

butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ 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);

$\mathbf{R_3}$, $\mathbf{R_4}$ and $\mathbf{R_{40}}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), R_8-$C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH_3)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_5}$ is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, iso-propyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3,

CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), $C(=CH_2)$-R_{10} (e.g., $C(=CH_2)$-C(O)-OCH_3, $C(=CH_2)$-CN), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

R_{50} is H, F, Cl, Br, I, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, propyl, iso-propyl, benzyl), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), substituted or unsubstituted benzyl, (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

R_6 is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

R_8 is $[CH_2]_p$

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

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

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

R_{10} and **R_{11}** are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., C(O)(OCH_3)), or $S(O)_2R$; or **R_{10}** and **R_{11}** are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

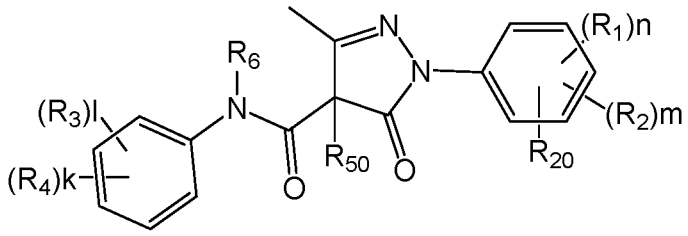
m, **n**, **l** and **k** are each independedntly an integer between 0 and 4 (e.g., 0, 1 or 2);

Q_1 and **Q_2** are each independently S, O, N-OH, CH_2, $C(R)_2$ or N-OMe;

or its pharmaceutically acceptable salt, optical isomer, 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, if R_{50} is H then neither one of R_1, R_2 or R_{20} is H, and n and m are not 0.

[0034] In various embodiments, this invention is directed to a compound represented by the structure of formula **I(b)**:



I(b)

wherein

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, $NHC(O)$-R_{10} (e.g., $NHC(O)CH_3$), $NHCO$-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O$-R_{10} (e.g. $C(O)O$-CH_3, $C(O)O$-$CH(CH_3)_2$, $C(O)O$-CH_2CH_3), R_8-$C(O)$-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)$-R_{10} (e.g., $C(O)$-CH_3, $C(O)$-CH_2CH_3, $C(O)$-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)$-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH$-$R_{10})$;

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, and **R_4** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-

R_{10} (e.g., $NHC(O)CH_3$), $NHCO\text{-}N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), $R_8\text{-}C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, $O\text{-}CH_2$-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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., [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);

R_{50} is H, F, Cl, Br, I, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, propyl, iso-propyl, benzyl), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), substituted or unsubstituted benzyl, (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

R_6 is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

R_8 is $[CH_2]_p$

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

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

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

R_{10} and **R_{11}** are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$; or **R_{10}** and **R_{11}** are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2\text{-}OH$, $CH_2CH_2\text{-}OH$), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

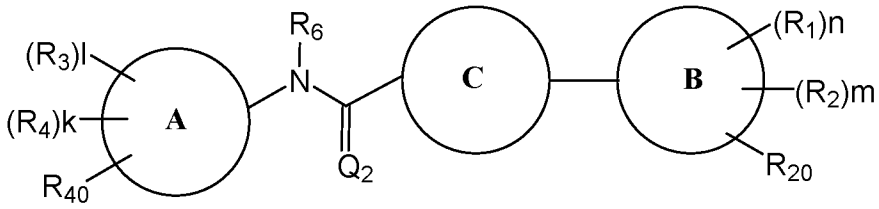
R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

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

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

[0035] In various embodiments, if R_{50} is H then neither one of R_1, R_2 or R_{20} is H, and n and m are not 0.

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

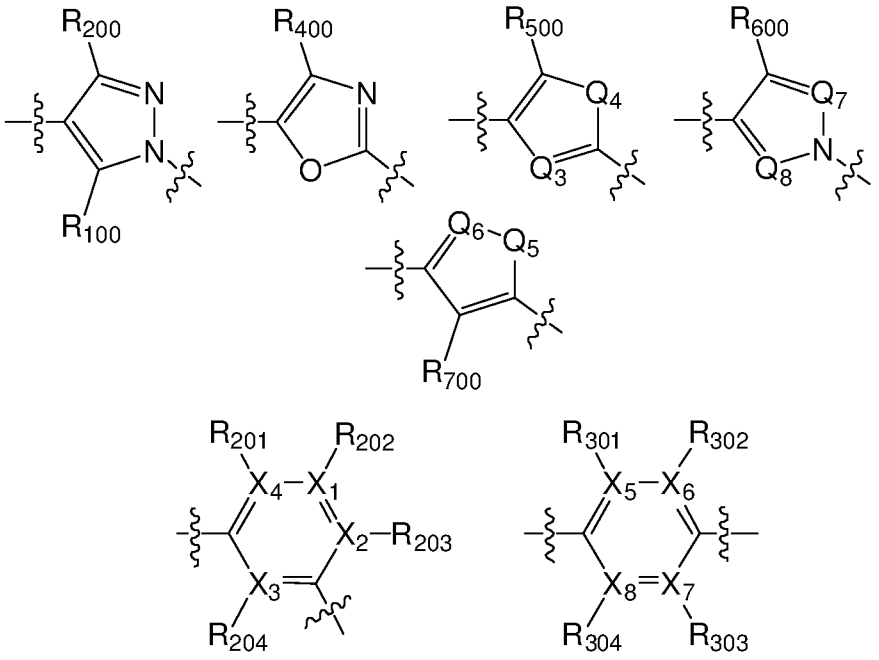


(**II**)

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 C_3-C_{10} cycloalkyl (e.g. cyclohexyl) or a single or fused C_3-C_{10} 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);

C ring is selected from the following (wavy line represents a connection point):



wherein

X_1, X_2, X_3, X_4, X_5, X_6, X_7 and X_8 are each independently N, N-O, or C,

wherein at least one of X_1, X_2, X_3, X_4, X_5, X_6, X_7 or X_8 is N, and

wherein if X_1, X_2, X_3, X_4, X_5, X_6, X_7 or X_8 is N than its respective substituent is nothing;

Q_3, Q_6, Q_7 and Q_8 are each independedntly N, N-O, CH or C(R);

Q_4 and Q_5 are each independedntly O, NH or N(R);

R_{200}, R_{400}, R_{500}, and R_{600} are each independently H or a C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl);

R_{201}, R_{202}, R_{203}, R_{204}, R_{301}, R_{302}, R_{303}, and R_{304} are each independently nothing, Hor a C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl);

R_{100} and R_{700} are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., $NHCH_3$), $N(R)_2$ (e.g., $N(CH_3)_2$), R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -OC(O)-$N(R_{10})(R_{11})$ (e.g. OC(O)-piperidine-$C(Me)_2CH_2OH$, OC(O)-piperazine-CH_2CH_2OH, OC(O)-piperidine-piperidine), -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. $C(O)O-CH_3$, $C(O)O-CH(CH_3)_2$, $C(O)O-CH_2CH_3$), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., $C(O)-CH_3$, $C(O)-CH_2CH_3$, $C(O)-CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)-CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl), (wherein

substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, $-R_8\text{-}O\text{-}R_{10}$, (e.g., $-CH_2\text{-}O\text{-}CH_3$), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, $-CH_2CN$, $-R_8CN$, NH_2, NHR, $N(R)_2$, $R_8\text{-}N(R_{10})(R_{11})$ (e.g., $CH_2\text{-}NH_2$, $CH_2\text{-}N(CH_3)_2$), $R_9\text{-}R_8\text{-}N(R_{10})(R_{11})$ (e.g., $C{\equiv}C\text{-}CH_2\text{-}NH_2$), $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)\text{-}R_{10}$ (e.g., $NHC(O)CH_3$), $NHCO\text{-}N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH(CH_3)_2$, $C(O)O\text{-}CH_2CH_3$), $R_8\text{-}C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), $-C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-$CH_2\text{-}C_6H_4$-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH{=}C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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, R_8-OH (e.g., CH_2-OH), R_8-SH, $-R_8\text{-}O\text{-}R_{10}$, (e.g., $CH_2\text{-}O\text{-}CH_3$) CF_3, CD_3, OCD_3, CN, NO_2, $-CH_2CN$, $-R_8CN$, NH_2, NHR, $N(R)_2$, $R_8\text{-}N(R_{10})(R_{11})$ (e.g., $CH_2\text{-}NH_2$, $CH_2\text{-}N(CH_3)_2$) $R_9\text{-}R_8\text{-}N(R_{10})(R_{11})$, $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $-NHCO\text{-}R_{10}$ (e.g., $NHC(O)CH_3$), $NHCO\text{-}N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), $R_8\text{-}C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), $-C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$),

C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_6}$ is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

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

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

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

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

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$; or $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

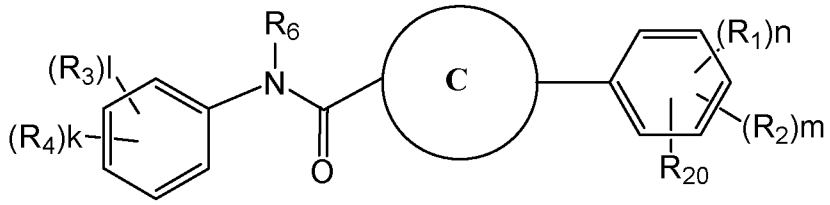
R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

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

$\mathbf{Q_2}$ is S, O, N-OH, CH_2, CH(R), $C(R)_2$ or N-OMe;

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

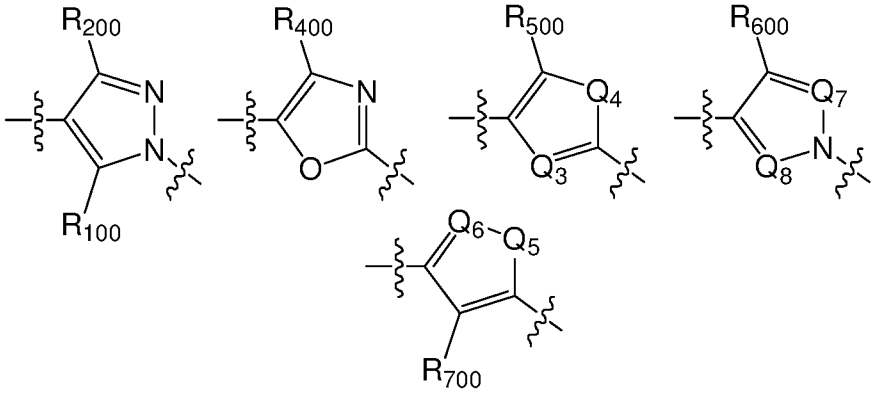
[0037] In various embodiments, this invention is directed to a compound represented by the structure of formula **II(a)**

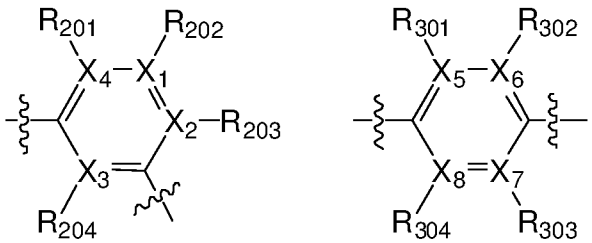


II(a)

wherein

C ring is selected from the following (wavy line represents a connection point):





wherein

X_1, X_2, X_3, X_4, X_5, X_6, X_7 and **X_8** are each independently N, N-O, or C,

wherein at least one of **X_1, X_2, X_3, X_4, X_5, X_6, X_7** or **X_8** is N, and

wherein if **X_1, X_2, X_3, X_4, X_5, X_6, X_7** or **X_8** is N than its respective substituent is nothing;

Q_3, Q_6, Q_7 and **Q_8** are each independedntly N, N-O, CH or C(R);

Q_4 and **Q_5** are each independedntly O, NH or N(R);

R_{200}, R_{400}, R_{500}, and **R_{600}** are each independently H or a C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl);

R_{201}, R_{202}, R_{203}, R_{204}, R_{301}, R_{302}, R_{303}, and **R_{304}** are each independently nothing, H or a C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl);

R_{100} and **R_{700}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., $NHCH_3$), $N(R)_2$ (e.g., $N(CH_3)_2$), R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -OC(O)-$N(R_{10})(R_{11})$ (e.g. OC(O)-piperidine-

$C(Me)_2CH_2OH$, OC(O)-piperazine-CH_2CH_2OH, OC(O)-piperidine-piperidine), $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$ (e.g., $NHC(O)CH_3$), $NHCO-N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O-R_{10}$ (e.g. $C(O)O-CH_3$, $C(O)O-CH(CH_3)_2$, $C(O)O-CH_2CH_3$), $R_8-C(O)-R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)-R_{10}$ (e.g., $C(O)-CH_3$, $C(O)-CH_2CH_3$, $C(O)-CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)-CF_3$), $-C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-$CH_2-C_6H_4-Cl$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)-CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH-R_{10})$;

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, $-R_8-O-R_{10}$, (e.g., $-CH_2-O-CH_3$), $R_8-(C_3-C_8$ cycloalkyl) (e.g., cyclohexyl), $R_8-(C_3-C_8$ heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, $-CH_2CN$, $-R_8CN$, NH_2, NHR, $N(R)_2$, $R_8-N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, $CH_2-N(CH_3)_2$), $R_9-R_8-N(R_{10})(R_{11})$ (e.g., $C\equiv C-CH_2-NH_2$), $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)-R_{10}$ (e.g., $NHC(O)CH_3$), $NHCO-N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O-R_{10}$ (e.g. $C(O)O-CH_3$, $C(O)O-CH(CH_3)_2$, $C(O)O-CH_2CH_3$), $R_8-C(O)-R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)-R_{10}$ (e.g., $C(O)-CH_3$, $C(O)-CH_2CH_3$, $C(O)-CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)-CF_3$), $-C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-$CH_2-C_6H_4-Cl$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$,$CF_2CH(CH_3)_2$,$CF(CH_3)-CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is

replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ 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);

$\mathbf{R_3}$ and $\mathbf{R_4}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), R_8-$C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_6}$ is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

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

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

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

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

R_{10} and **R_{11}** are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., C(O)(OCH_3)), or $S(O)_2R$; or **R_{10}** and **R_{11}** are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

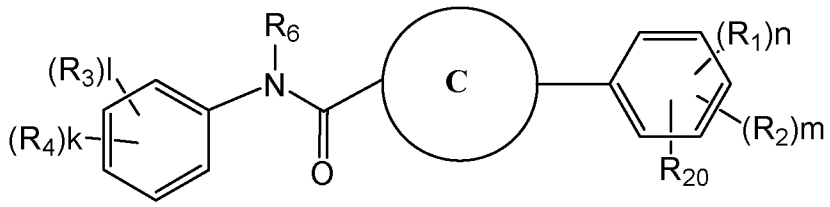
wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents 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);

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

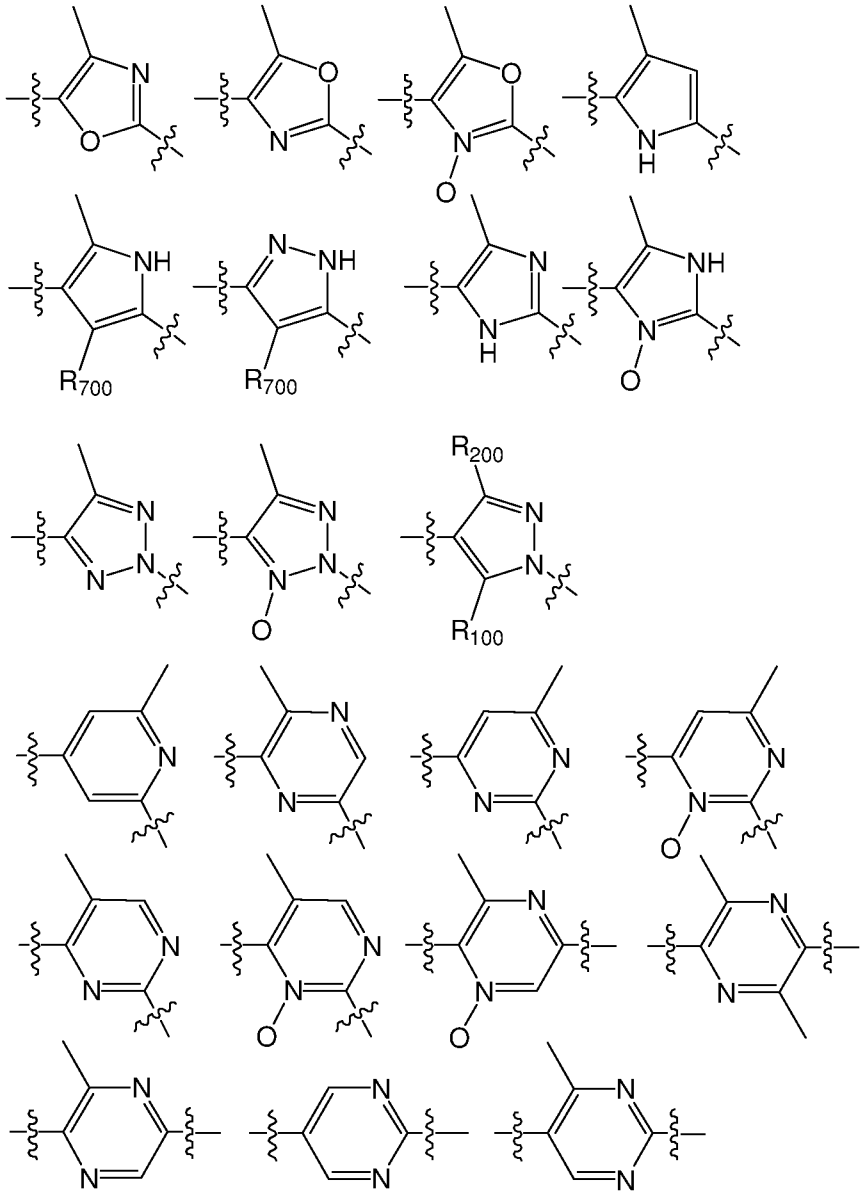
[0038] In various embodiments, this invention is directed to a compound represented by the structure of formula **II(b)**



II(b)

wherein

C ring is selected from the following (wavy line represents a connection point):



wherein

R_{200} is H or a C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl);

R_{100} and **R_{700}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., $NHCH_3$), $N(R)_2$ (e.g., $N(CH_3)_2$), R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -OC(O)-$N(R_{10})(R_{11})$ (e.g. OC(O)-piperidine-$C(Me)_2CH_2OH$, OC(O)-piperazine-CH_2CH_2OH, OC(O)-piperidine-piperidine), -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. $C(O)O-CH_3$, $C(O)O-CH(CH_3)_2$, $C(O)O-CH_2CH_3$), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., $C(O)-CH_3$, $C(O)-CH_2CH_3$, $C(O)-CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)-CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2,

3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)$_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, N(R)$_2$, CF_3, aryl, phenyl, C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), CH(CF_3)(NH-R_{10});

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, N(R)$_2$, R_8-N(R_{10})(R_{11}) (e.g., CH_2-NH_2, CH_2-N(CH_3)$_2$), R_9-R_8-N(R_{10})(R_{11}) (e.g., C≡C-CH_2-NH_2), B(OH)$_2$, -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3), NHCO-N(R_{10})(R_{11}) (e.g., NHC(O)N(CH_3)$_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-$CH(CH_3)_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -C(O)NH_2, C(O)NHR, C(O)N(R_{10})(R_{11}) (e.g., C(O)N(CH_3)$_2$), SO_2R, SO_2N(R_{10})(R_{11}) (e.g., SO_2N(CH_3)$_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)$_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or

unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ 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);

$\mathbf{R_3}$ and $\mathbf{R_4}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), R_8-$C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_6}$ is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

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

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

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

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

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$; or $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring

(e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

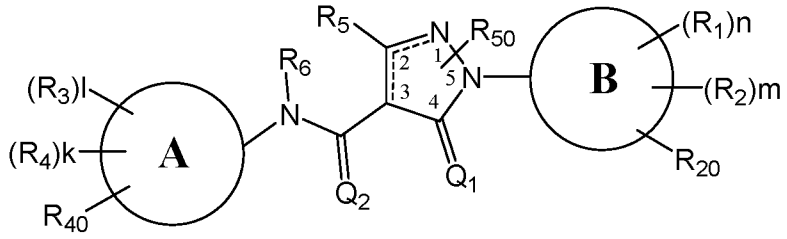
R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

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

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

[THREE SUBSITUENTS ON RING B]

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



III

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 C_3-C_{10} cycloalkyl (e.g. cyclohexyl) or a single or fused C_3-C_{10} 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);

R_1, R_2 and **R_{20}** are each independently F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3), NHCO-$N(R_{10})(R_{11})$ (e.g., NHC(O)$N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-$CH(CH_3)_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., CH_2C(O)CH_3), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -C(O)NH_2, C(O)NHR, C(O)$N(R_{10})(R_{11})$ (e.g., C(O)$N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., CH=$C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-

butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ 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);

$\mathbf{R_3}$, $\mathbf{R_4}$ and $\mathbf{R_{40}}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), R_8-$C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH_3)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_5}$ is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, iso-propyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3,

CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), $C(=CH_2)$-R_{10} (e.g., $C(=CH_2)$-C(O)-OCH_3, $C(=CH_2)$-CN) substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

R_{50} is H, F, Cl, Br, I, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, propyl, iso-propyl, benzyl), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), substituted or unsubstituted benzyl, (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

wherein R_{50} is attached either to N_1 or to C_3 and if R_{50} is attached to N_1 than N_1-C_2 is a single bond and C_2-C_3 is a double bond, and if R_{50} is attached to C_3 than N_1-C_2 is a double bond and C_2-C_3 is a single bond;

R_6 is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

R_8 is $[CH_2]_p$

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

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

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

R_{10} and **R_{11}** are each independently H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$; or **R_{10}** and **R_{11}** are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

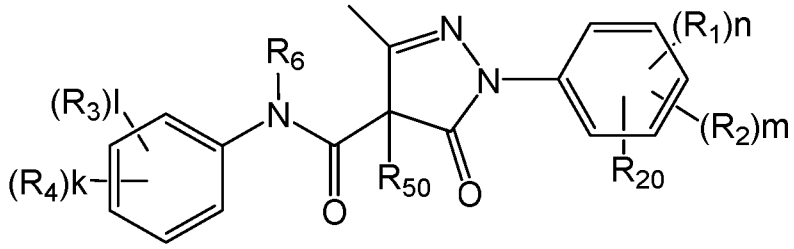
m and, **n,** are each independedntly an integer between 1 and 4 (e.g., 1 or 2);

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

Q_1 and **Q_2** are each independently S, O, N-OH, CH_2, $C(R)_2$ or N-OMe;

or its pharmaceutically acceptable salt, optical isomer, 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, this invention is directed to a compound represented by the structure of formula **III(a):**



III(a)

wherein

R_1, R_2 and **R_{20}** are each independently F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3), NHCO-$N(R_{10})(R_{11})$ (e.g., NHC(O)$N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-$CH(CH_3)_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., CH=$C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH$-$R_{10})$;

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, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-

$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O$-R_{10} (e.g. $C(O)O$-CH_3, $C(O)O$-CH_2CH_3), R_8-$C(O)$-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)$-R_{10} (e.g., $C(O)$-CH_3, $C(O)$-CH_2CH_3, $C(O)$-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)$-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH$-$R_{10})$;

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

$\mathbf{R_{50}}$ is H, F, Cl, Br, I, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, propyl, iso-propyl, benzyl), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), substituted or unsubstituted benzyl, (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

$\mathbf{R_6}$ is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

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

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

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

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

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$; or $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

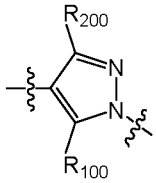
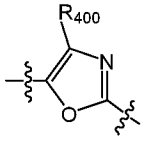
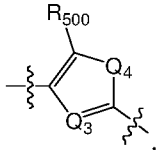
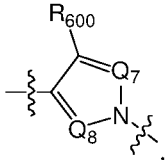
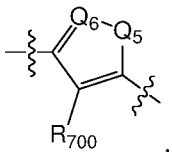
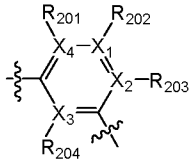
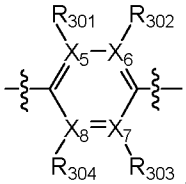
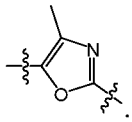
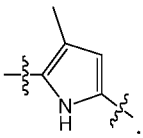
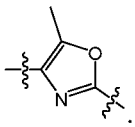
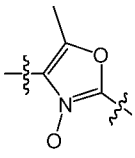
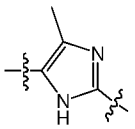
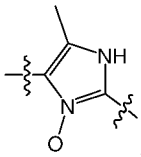
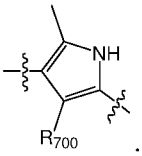
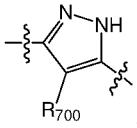
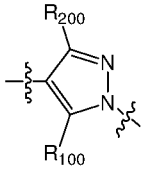
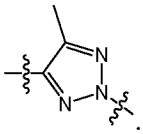
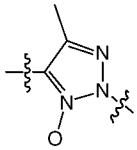
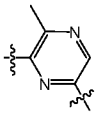
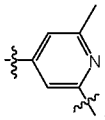
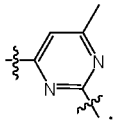
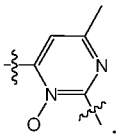
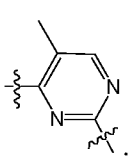
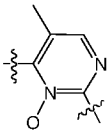
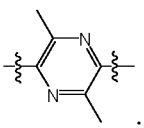
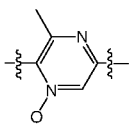
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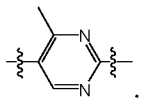
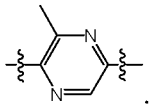
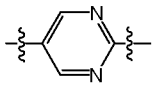
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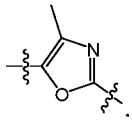
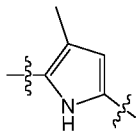
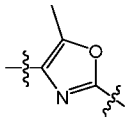
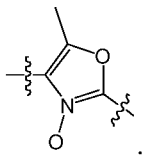
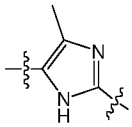
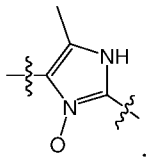
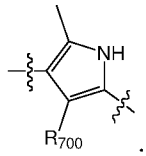
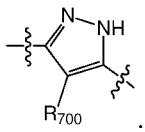
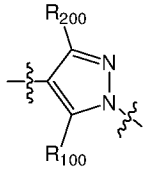
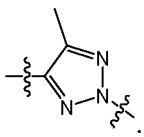
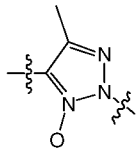
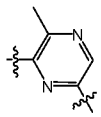
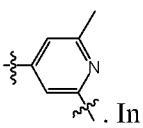
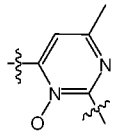
or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

[0041] In some embodiments, **A** of formula **I, I(a), II,** and/or **III** 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 C_3-C_{10} cycloalkyl ring. In other embodiments, A is cyclohexyl.

[0042] In some embodiments, **B** of formula **I, I(a), II,** and/or **III** 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 C_3-C_{10} cycloalkyl ring. In other embodiments, B is cyclohexyl.

[0043] In some embodiments, **C** of formula **II,** and/or **II(a)** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other

embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is .

[0044] In some embodiments, **C** of formula **II(b)** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is . In other embodiments, **C** is .

[0045] In some embodiments, $\mathbf{X_1}$ of compound of formula **II** and/or **II(a)** is C**.** In other embodiments, $\mathbf{X_1}$ is N**.** In other embodiments, $\mathbf{X_1}$ is N-O (i.e., *N*-oxide)**.**

[0046] In some embodiments, $\mathbf{X_2}$ of compound of formula **II** and/or **II(a)** is C. In other embodiments, $\mathbf{X_2}$ is N. In other embodiments, $\mathbf{X_2}$ is N-O (i.e., *N*-oxide).

[0047] In some embodiments, $\mathbf{X_3}$ of compound of formula **II** and/or **II(a)** is C. In other embodiments, $\mathbf{X_3}$ is N. In other embodiments, $\mathbf{X_3}$ is N-O (i.e., *N*-oxide).

[0048] In some embodiments, $\mathbf{X_4}$ of compound of formula **II** and/or **II(a)** is C. In other embodiments, $\mathbf{X_4}$ is N. In other embodiments, $\mathbf{X_4}$ is N-O (i.e., *N*-oxide).

[0049] In some embodiments, $\mathbf{X_5}$ of compound of formula **II** and/or **II(a)** is C. In other embodiments, $\mathbf{X_5}$ is N. In other embodiments, $\mathbf{X_5}$ is N-O (i.e., *N*-oxide).

[0050] In some embodiments, $\mathbf{X_6}$ of compound of formula **II** and/or **II(a)** is C. In other embodiments, $\mathbf{X_6}$ is N. In other embodiments, $\mathbf{X_6}$ is N-O (i.e., *N*-oxide).

[0051] In some embodiments, $\mathbf{X_7}$ of compound of formula **II** and/or **II(a)** is C. In other embodiments, $\mathbf{X_7}$ is N. In other embodiments, $\mathbf{X_7}$ is N-O (i.e., *N*-oxide).

[0052] In some embodiments, $\mathbf{X_8}$ of compound of formula **II** and/or **II(a)** is C. In other embodiments, $\mathbf{X_8}$ is N. In other embodiments, $\mathbf{X_8}$ is N-O (i.e., *N*-oxide).

[0053] In some embodiments, $\mathbf{R_{200}}$ of compound of formula **II, II(a)** and/or **II(b)** is H. In other embodiments, $\mathbf{R_{200}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{200}}$ is methyl. In other embodiments, $\mathbf{R_{200}}$ is ethyl. In other embodiments, $\mathbf{R_{200}}$ is propyl. In other embodiments, $\mathbf{R_{200}}$ is iso-propyl. In other embodiments, $\mathbf{R_{200}}$ is t-Bu. In other embodiments, $\mathbf{R_{200}}$ is iso-butyl. In other embodiments, $\mathbf{R_{200}}$ is pentyl. In other embodiments, $\mathbf{R_{200}}$ is benzyl.

[0054] In some embodiments, $\mathbf{R_{400}}$ of compound of formula **II** and/or **II(a)** is H. In other embodiments, $\mathbf{R_{400}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{400}}$ is methyl. In other embodiments, $\mathbf{R_{400}}$ is ethyl. In other embodiments, $\mathbf{R_{400}}$ is propyl. In other embodiments, $\mathbf{R_{400}}$ is iso-propyl. In other embodiments, $\mathbf{R_{400}}$ is t-Bu. In other embodiments, $\mathbf{R_{400}}$ is iso-butyl. In other embodiments, $\mathbf{R_{400}}$ is pentyl. In other embodiments, $\mathbf{R_{400}}$ is benzyl.

[0055] In some embodiments, $\mathbf{R_{500}}$ of compound of formula **II** and/or **II(a)** is H. In other embodiments, $\mathbf{R_{500}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{500}}$ is methyl. In other embodiments, $\mathbf{R_{500}}$ is ethyl. In other embodiments, $\mathbf{R_{500}}$ is propyl. In other embodiments, $\mathbf{R_{500}}$ is iso-propyl. In other embodiments, $\mathbf{R_{500}}$ is t-Bu. In other embodiments, $\mathbf{R_{500}}$ is iso-butyl. In other embodiments, $\mathbf{R_{500}}$ is pentyl. In other embodiments, $\mathbf{R_{500}}$ is benzyl.

[0056] In some embodiments, $\mathbf{R_{600}}$ of compound of formula **II** and/or **II(a)** is H. In other embodiments, $\mathbf{R_{600}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{600}}$ is methyl. In other embodiments, $\mathbf{R_{600}}$ is ethyl. In other embodiments, $\mathbf{R_{600}}$ is propyl. In other embodiments,

$\mathbf{R_{600}}$ is iso-propyl. In other embodiments, $\mathbf{R_{600}}$ is t-Bu. In other embodiments, $\mathbf{R_{600}}$ is iso-butyl. In other embodiments, $\mathbf{R_{600}}$ is pentyl. In other embodiments, $\mathbf{R_{600}}$ is benzyl.

[0057] In some embodiments, $\mathbf{R_{201}}$ of formula **II** and/or **II(a)** is nothing. In other embodiments, $\mathbf{R_{201}}$ is H. In other embodiments, $\mathbf{R_{201}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{201}}$ is methyl. In other embodiments, $\mathbf{R_{201}}$ is ethyl. In other embodiments, $\mathbf{R_{201}}$ is propyl. In other embodiments, $\mathbf{R_{201}}$ is iso-propyl. In other embodiments, $\mathbf{R_{201}}$ is t-Bu. In other embodiments, $\mathbf{R_{201}}$ is iso-butyl. In other embodiments, $\mathbf{R_{201}}$ is pentyl. In other embodiments, $\mathbf{R_{201}}$ is benzyl.

[0058] In some embodiments, $\mathbf{R_{202}}$ of formula **II** and/or **II(a)** is nothing. In other embodiments, $\mathbf{R_{202}}$ is H. In other embodiments, $\mathbf{R_{202}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{202}}$ is methyl. In other embodiments, $\mathbf{R_{202}}$ is ethyl. In other embodiments, $\mathbf{R_{202}}$ is propyl. In other embodiments, $\mathbf{R_{202}}$ is iso-propyl. In other embodiments, $\mathbf{R_{202}}$ is t-Bu. In other embodiments, $\mathbf{R_{201}}$ is iso-butyl. In other embodiments, $\mathbf{R_{202}}$ is pentyl. In other embodiments, $\mathbf{R_{202}}$ is benzyl.

[0059] In some embodiments, $\mathbf{R_{203}}$ of formula **II** and/or **II(a)** is nothing. In other embodiments, $\mathbf{R_{203}}$ is H. In other embodiments, $\mathbf{R_{203}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{203}}$ is methyl. In other embodiments, $\mathbf{R_{203}}$ is ethyl. In other embodiments, $\mathbf{R_{203}}$ is propyl. In other embodiments, $\mathbf{R_{203}}$ is iso-propyl. In other embodiments, $\mathbf{R_{203}}$ is t-Bu. In other embodiments, $\mathbf{R_{201}}$ is iso-butyl. In other embodiments, $\mathbf{R_{203}}$ is pentyl. In other embodiments, $\mathbf{R_{203}}$ is benzyl.

[0060] In some embodiments, $\mathbf{R_{204}}$ of formula **II** and/or **II(a)** is nothing. In other embodiments, $\mathbf{R_{204}}$ is H. In other embodiments, $\mathbf{R_{204}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{204}}$ is methyl. In other embodiments, $\mathbf{R_{204}}$ is ethyl. In other embodiments, $\mathbf{R_{204}}$ is propyl. In other embodiments, $\mathbf{R_{204}}$ is iso-propyl. In other embodiments, $\mathbf{R_{204}}$ is t-Bu. In other embodiments, $\mathbf{R_{204}}$ is iso-butyl. In other embodiments, $\mathbf{R_{204}}$ is pentyl. In other embodiments, $\mathbf{R_{204}}$ is benzyl.

[0061] In some embodiments, $\mathbf{R_{301}}$ of formula **II** and/or **II(a)** is nothing. In other embodiments, $\mathbf{R_{301}}$ is H. In other embodiments, $\mathbf{R_{301}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{301}}$ is methyl. In other embodiments, $\mathbf{R_{301}}$ is ethyl. In other embodiments, $\mathbf{R_{301}}$ is propyl. In other embodiments, $\mathbf{R_{301}}$ is iso-propyl. In other embodiments, $\mathbf{R_{301}}$ is t-Bu. In other embodiments, $\mathbf{R_{301}}$ is iso-butyl. In other embodiments, $\mathbf{R_{301}}$ is pentyl. In other embodiments, $\mathbf{R_{301}}$ is benzyl.

[0062] In some embodiments, $\mathbf{R_{302}}$ of formula **II** and/or **II(a)** is nothing. In other embodiments, $\mathbf{R_{302}}$ is H. In other embodiments, $\mathbf{R_{302}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{302}}$ is methyl. In other embodiments, $\mathbf{R_{302}}$ is ethyl. In other embodiments, $\mathbf{R_{302}}$ is propyl. In other embodiments, $\mathbf{R_{302}}$ is iso-propyl. In other embodiments, $\mathbf{R_{302}}$ is t-Bu. In other embodiments, $\mathbf{R_{302}}$ is iso-butyl. In other embodiments, $\mathbf{R_{302}}$ is pentyl. In other embodiments, $\mathbf{R_{302}}$ is benzyl.

[0063] In some embodiments, $\mathbf{R_{303}}$ of formula **II** and/or **II(a)** is nothing. In other embodiments, $\mathbf{R_{303}}$ is H. In other embodiments, $\mathbf{R_{303}}$ is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{303}}$ is methyl. In other embodiments, $\mathbf{R_{303}}$ is ethyl. In other embodiments, $\mathbf{R_{303}}$ is propyl. In other embodiments, $\mathbf{R_{303}}$ is iso-propyl. In other embodiments, $\mathbf{R_{303}}$ is t-Bu. In other embodiments, $\mathbf{R_{303}}$ is iso-butyl. In other embodiments, $\mathbf{R_{303}}$ is pentyl. In other embodiments, $\mathbf{R_{303}}$ is benzyl.

[0064] In some embodiments, R_{304} of formula **II** and/or **II(a)** is nothing. In other embodiments, R_{304} is H. In other embodiments, R_{304} is a C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_{304} is methyl. In other embodiments, R_{304} is ethyl. In other embodiments, R_{304} is propyl. In other embodiments, R_{304} is iso-propyl. In other embodiments, R_{304} is t-Bu. In other embodiments, R_{304} is iso-butyl. In other embodiments, R_{304} is pentyl. In other embodiments, R_{304} is benzyl.

[0065] In some embodiments, R_{100} of formula **II, II(a)** and/or **II(b)** is H. In other embodiments, R_{100} is F. In other embodiments, R_{100} is Cl. In other embodiments, R_{100} is Br. In other embodiments, R_{100} is I. In other embodiments, R_{100} is OH. In other embodiments, R_{100} is SH. In other embodiments, R_{100} is R_8-OH. In other embodiments, R_{100} is CH_2-OH. In other embodiments, R_{100} is R_8-SH. In other embodiments, R_{100} is -R_8-O-R_{10}. In other embodiments, R_{100} is -CH_2-O-CH_3. In other embodiments, R_{100} is R_8-(C_3-C_8 cycloalkyl). In other embodiments, R_{100} is R_8-(C_3-C_8 heterocyclic ring). In other embodiments, R_{100} is CH_2-imidazole. In other embodiments, R_{100} is indazole. In other embodiments, R_{100} is CF_3. In other embodiments, R_{100} is CD_3. In other embodiments, R_{100} is OCD_3. In other embodiments, R_{100} is CN. In other embodiments, R_{100} is NO_2. In other embodiments, R_{100} is -CH_2CN. In other embodiments, R_{100} is -R_8CN. In other embodiments, R_{100} is NH_2. In other embodiments, R_{100} is NHR. In other embodiments, R_{100} is $NHCH_3$. In other embodiments, R_{100} is $N(R)_2$. In other embodiments, R_{100} is $N(CH_3)_2$. In other embodiments, R_{100} is R_8-$N(R_{10})(R_{11})$. In other embodiments, R_{100} is CH_2-NH_2. In other embodiments, R_{100} is CH_2-$N(CH_3)_2$. In other embodiments, R_{100} is R_9-R_8-$N(R_{10})(R_{11})$. In other embodiments, R_{100} is C≡C-CH_2-NH_2. In other embodiments, R_{100} is $B(OH)_2$. In other embodiments, R_{100} is -OC(O)-$N(R_{10})(R_{11})$. In other embodiments, R_{100} is OC(O)-piperidine-$C(Me)_2CH_2OH$. In other embodiments, R_{100} is OC(O)-piperazine-CH_2CH_2OH. In other embodiments, R_{100} is OC(O)-piperidine-piperidine. In other embodiments, R_{100} is -$OC(O)CF_3$. In other embodiments, R_{100} is -OCH_2Ph. In other embodiments, R_{100} is NHC(O)-R_{10}. In other embodiments, R_{100} is $NHC(O)CH_3$). In other embodiments, R_{100} is NHCO-$N(R_{10})(R_{11})$. In other embodiments, R_{100} is $NHC(O)N(CH_3)_2$. In other embodiments, R_{100} is COOH. In other embodiments, R_{100} is -C(O)Ph. In other embodiments, R_{100} is C(O)O-R_{10}. In other embodiments, R_{100} is C(O)O-CH_3. In other embodiments, R_{100} is C(O)O-$CH(CH_3)_2$. In other embodiments, R_{100} is C(O)O-CH_2CH_3). In other embodiments, R_{100} is R_8-C(O)-R_{10}. In other embodiments, R_{100} is $CH_2C(O)CH_3$. In other embodiments, R_{100} is C(O)H. In other embodiments, R_{100} is C(O)-R_{10}. In other embodiments, R_{100} is C(O)-CH_3. In other embodiments, R_{100} is C(O)-CH_2CH_3. In other embodiments, R_{100} is C(O)-$CH_2CH_2CH_3$. In other embodiments, R_{100} is C_1-C_5 linear or branched C(O)-haloalkyl. In other embodiments, R_{100} is C(O)-CF_3. In other embodiments, R_{100} is -$C(O)NH_2$. In other embodiments, R_{100} is C(O)NHR. In other embodiments, R_{100} is $C(O)N(R_{10})(R_{11})$. In other embodiments, R_{100} is $C(O)N(CH_3)_2$. In other embodiments, R_{100} is SO_2R. In other embodiments, R_{100} is $SO_2N(R_{10})(R_{11})$. In other embodiments, R_{100} is $SO_2N(CH_3)_2$. In other embodiments, R_{100} is $SO_2NHC(O)CH_3$. In other embodiments, R_{100} is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_{100} is methyl. In other embodiments, R_{100} is 2, 3, or 4-CH_2-C_6H_4-Cl. In other embodiments, R_{100} is ethyl. In other embodiments, R_{100} is propyl. In other embodiments, R_{100} is iso-propyl. In other embodiments, R_{100} is t-Bu. In other embodiments, R_{100} is iso-butyl. In other embodiments, R_{100} is pentyl. In other embodiments, R_{100} is benzyl. In other embodiments, R_{100} is C_1-C_5 linear or branched, substituted or

unsubstituted alkenyl. In other embodiments, $\mathbf{R_{100}}$ is $CH=C(Ph)_2$. In other embodiments, $\mathbf{R_{100}}$ is C_1-C_5 linear, branched or cyclic haloalkyl. In other embodiments, $\mathbf{R_{100}}$ is CF_3. In other embodiments, $\mathbf{R_{100}}$ is CF_2CH_3. In other embodiments, $\mathbf{R_{100}}$ is CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, or $CF(CH_3)$-$CH(CH_3)_2$; each is a separate embodiment according to this invention. In other embodiments, $\mathbf{R_{100}}$ is C_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, $\mathbf{R_{100}}$ is methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, or O-tBu; each is a separate embodiment acoridng to this invention. In other embodiments, $\mathbf{R_{100}}$ is C_1-C_5 linear or branched thioalkoxy. In other embodiments, $\mathbf{R_{100}}$ is C_1-C_5 linear or branched haloalkoxy. In other embodiments, $\mathbf{R_{100}}$ is OCF_3. In other embodiments, $\mathbf{R_{100}}$ is $OCHF_2$. In other embodiments, $\mathbf{R_{100}}$ is C_1-C_5 linear or branched alkoxyalkyl. In other embodiments, $\mathbf{R_{100}}$ is substituted or unsubstituted C_3-C_8 cycloalkyl. In other embodiments, $\mathbf{R_{100}}$ is cyclopropyl. In other embodiments, $\mathbf{R_{100}}$ is cyclopentyl. In other embodiments, $\mathbf{R_{100}}$ is substituted or unsubstituted C_3-C_8 heterocyclic ring. In other embodiments, $\mathbf{R_{100}}$ is 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), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide; each is a separate embodiment according to this invention. In other embodiments, $\mathbf{R_{100}}$ is substituted or unsubstituted aryl. In other embodiments, $\mathbf{R_{100}}$ is phenyl. In other embodiments, $\mathbf{R_{100}}$ is substituted or unsubstituted benzyl. In other embodiments, $\mathbf{R_{100}}$ is. In other embodiments, substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof. In other embodiments, $\mathbf{R_{100}}$ is $CH(CF_3)(NH\text{-}R_{10})$.

[0066] In some embodiments, $\mathbf{R_{700}}$ of formula **II, II(a)** and/or **II(b)** is H. In other embodiments, $\mathbf{R_{700}}$ is F. In other embodiments, $\mathbf{R_{700}}$ is Cl. In other embodiments, $\mathbf{R_{700}}$ is Br. In other embodiments, $\mathbf{R_{700}}$ is I. In other embodiments, $\mathbf{R_{700}}$ is OH. In other embodiments, $\mathbf{R_{700}}$ is SH. In other embodiments, $\mathbf{R_{700}}$ is R_8-OH. In other embodiments, $\mathbf{R_{700}}$ is CH_2-OH. In other embodiments, $\mathbf{R_{700}}$ is R_8-SH. In other embodiments, $\mathbf{R_{700}}$ is $-R_8\text{-}O\text{-}R_{10}$. In other embodiments, $\mathbf{R_{700}}$ is $-CH_2\text{-}O\text{-}CH_3$. In other embodiments, $\mathbf{R_{700}}$ is R_8-(C_3-C_8 cycloalkyl). In other embodiments, $\mathbf{R_{700}}$ is R_8-(C_3-C_8 heterocyclic ring). In other embodiments, $\mathbf{R_{700}}$ is CH_2-imidazole. In other embodiments, $\mathbf{R_{700}}$ is indazole. In other embodiments, $\mathbf{R_{700}}$ is CF_3. In other embodiments, $\mathbf{R_{700}}$ is CD_3. In other embodiments, $\mathbf{R_{700}}$ is OCD_3. In other embodiments, $\mathbf{R_{700}}$ is CN. In other embodiments, $\mathbf{R_{700}}$ is NO_2. In other embodiments, $\mathbf{R_{700}}$ is $-CH_2CN$. In other embodiments, $\mathbf{R_{700}}$ is $-R_8CN$. In other embodiments, $\mathbf{R_{700}}$ is NH_2. In other embodiments, $\mathbf{R_{700}}$ is NHR. In other embodiments, $\mathbf{R_{700}}$ is $NHCH_3$. In other embodiments, $\mathbf{R_{700}}$ is $N(R)_2$. In other embodiments, $\mathbf{R_{700}}$ is $N(CH_3)_2$. In other embodiments, $\mathbf{R_{700}}$ is $R_8\text{-}N(R_{10})(R_{11})$. In other embodiments, $\mathbf{R_{700}}$ is $CH_2\text{-}NH_2$. In other embodiments, $\mathbf{R_{700}}$ is $CH_2\text{-}N(CH_3)_2$. In other embodiments, $\mathbf{R_{700}}$ is $R_9\text{-}R_8\text{-}N(R_{10})(R_{11})$. In other embodiments, $\mathbf{R_{700}}$ is $C{\equiv}C\text{-}CH_2\text{-}NH_2$. In other embodiments, $\mathbf{R_{700}}$ is $B(OH)_2$. In other embodiments, $\mathbf{R_{700}}$ is -OC(O)-$N(R_{10})(R_{11})$. In other embodiments, $\mathbf{R_{700}}$ is OC(O)-piperidine-$C(Me)_2CH_2OH$. In other embodiments, $\mathbf{R_{700}}$ is OC(O)-piperazine-CH_2CH_2OH. In other embodiments, $\mathbf{R_{700}}$ is OC(O)-piperidine-piperidine. In other embodiments, $\mathbf{R_{700}}$ is $-OC(O)CF_3$. In other embodiments, $\mathbf{R_{700}}$ is $-OCH_2Ph$. In other embodiments,

$\mathbf{R_{700}}$ is NHC(O)-R_{10}. In other embodiments, $\mathbf{R_{700}}$ is NHC(O)CH_3). In other embodiments, $\mathbf{R_{700}}$ is NHCO-$N(R_{10})(R_{11})$. In other embodiments, $\mathbf{R_{700}}$ is NHC(O)$N(CH_3)_2$. In other embodiments, $\mathbf{R_{700}}$ is COOH. In other embodiments, $\mathbf{R_{700}}$ is -C(O)Ph. In other embodiments, $\mathbf{R_{700}}$ is C(O)O-R_{10}. In other embodiments, $\mathbf{R_{700}}$ is C(O)O-CH_3. In other embodiments, $\mathbf{R_{700}}$ is C(O)O-$CH(CH_3)_2$. In other embodiments, $\mathbf{R_{700}}$ is C(O)O-CH_2CH_3). In other embodiments, $\mathbf{R_{700}}$ is R_8-C(O)-R_{10}. In other embodiments, $\mathbf{R_{700}}$ is $CH_2C(O)CH_3$. In other embodiments, $\mathbf{R_{700}}$ is C(O)H. In other embodiments, $\mathbf{R_{700}}$ is C(O)-R_{10}. In other embodiments, $\mathbf{R_{700}}$ is C(O)-CH_3. In other embodiments, $\mathbf{R_{700}}$ is C(O)-CH_2CH_3. In other embodiments, $\mathbf{R_{700}}$ is C(O)-$CH_2CH_2CH_3$. In other embodiments, $\mathbf{R_{700}}$ is C_1-C_5 linear or branched C(O)-haloalkyl. In other embodiments, $\mathbf{R_{700}}$ is C(O)-CF_3. In other embodiments, $\mathbf{R_{700}}$ is -C(O)NH_2. In other embodiments, $\mathbf{R_{700}}$ is C(O)NHR. In other embodiments, $\mathbf{R_{700}}$ is C(O)$N(R_{10})(R_{11})$. In other embodiments, $\mathbf{R_{700}}$ is C(O)$N(CH_3)_2$. In other embodiments, $\mathbf{R_{700}}$ is SO_2R. In other embodiments, $\mathbf{R_{700}}$ is $SO_2N(R_{10})(R_{11})$. In other embodiments, $\mathbf{R_{700}}$ is $SO_2N(CH_3)_2$. In other embodiments, $\mathbf{R_{100}}$ is $SO_2NHC(O)CH_3$. In other embodiments, $\mathbf{R_{700}}$ is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_{700}}$ is methyl. In other embodiments, $\mathbf{R_{700}}$ is 2, 3, or 4-CH_2-C_6H_4-Cl. In other embodiments, $\mathbf{R_{700}}$ is ethyl. In other embodiments, $\mathbf{R_{700}}$ is propyl. In other embodiments, $\mathbf{R_{700}}$ is iso-propyl. In other embodiments, $\mathbf{R_{700}}$ is t-Bu. In other embodiments, $\mathbf{R_{700}}$ is iso-butyl. In other embodiments, $\mathbf{R_{700}}$ is pentyl. In other embodiments, $\mathbf{R_{700}}$ is benzyl. In other embodiments, $\mathbf{R_{700}}$ is C_1-C_5 linear or branched, substituted or unsubstituted alkenyl. In other embodiments, $\mathbf{R_{700}}$ is CH=$C(Ph)_2$. In other embodiments, $\mathbf{R_{100}}$ is C_1-C_5 linear, branched or cyclic haloalkyl. In other embodiments, $\mathbf{R_{700}}$ is CF_3. In other embodiments, $\mathbf{R_{700}}$ is CF_2CH_3. In other embodiments, $\mathbf{R_{700}}$ is CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, or $CF(CH_3)$-$CH(CH_3)_2$; each is a separate embodiment according to this invention. In other embodiments, $\mathbf{R_{700}}$ is C_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, $\mathbf{R_{700}}$ is methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, or O-tBu; each is a separate embodiment acoridng to this invention. In other embodiments, $\mathbf{R_{700}}$ is C_1-C_5 linear or branched thioalkoxy. In other embodiments, $\mathbf{R_{700}}$ is C_1-C_5 linear or branched haloalkoxy. In other embodiments, $\mathbf{R_{700}}$ is OCF_3. In other embodiments, $\mathbf{R_{700}}$ is $OCHF_2$. In other embodiments, $\mathbf{R_{700}}$ is C_1-C_5 linear or branched alkoxyalkyl. In other embodiments, $\mathbf{R_{700}}$ is substituted or unsubstituted C_3-C_8 cycloalkyl. In other embodiments, $\mathbf{R_{700}}$ is cyclopropyl. In other embodiments, $\mathbf{R_{700}}$ is cyclopentyl. In other embodiments, $\mathbf{R_{700}}$ is substituted or unsubstituted C_3-C_8 heterocyclic ring. In other embodiments, $\mathbf{R_{700}}$ is 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), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide; each is a separate embodiment according to this invention. In other embodiments, $\mathbf{R_{700}}$ is substituted or unsubstituted aryl. In other embodiments, $\mathbf{R_{700}}$ is phenyl. In other embodiments, $\mathbf{R_{700}}$ is substituted or unsubstituted benzyl. In other embodiments, $\mathbf{R_{700}}$ is. In other embodiments, substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof. In other embodiments, $\mathbf{R_{700}}$ is $CH(CF_3)(NH$-$R_{10})$.

[0067] In some embodiments, $\mathbf{R_1}$ of formula **I, I(a), I(b), II, II(a)** and **II(b)** is H.

[0068] In other embodiments, **R_1** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is F. In other embodiments, R_1 is Cl. In other embodiments, R_1 is Br. In other embodiments, R_1 is I. In other embodiments, R_1 is R_8-(C_3-C_8 cycloalkyl). In other embodiments, R_1 is CH_2-cyclohexyl. In other embodiments, R_1 is R_8-(C_3-C_8 heterocyclic ring). In other embodiments, R_1 is CH_2-imidazole. In other embodiments, R_1 is CH_2-indazole. In other embodiments, R_1 is CF_3. In other embodiments, R_1 is $CF_2CH_2CH_3$. In other embodiments, R_1 is $CH_2CH_2CF_3$. In other embodiments, R_1 is $CF_2CH(CH_3)_2$. In other embodiments, R_1 is $CF(CH_3)$-$CH(CH_3)_2$. In other embodiments, R_1 is OCD_3. In other embodiments, R_1 is NO_2. In other embodiments, R_1 is NH_2. In other embodiments, R_1 is R_8-$N(R_{10})(R_{11})$. In other embodiments, R_1 is CH_2-NH_2. In other embodiments, R_1 is CH_2-$N(CH_3)_2$). In other embodiments, R_1 is R_9-R_8-$N(R_{10})(R_{11})$. In other embodiments, R_1 is C≡C-CH_2-NH_2. In other embodiments, R_1 is $B(OH)_2$. In other embodiments, R_1 is NHC(O)-R_{10}. In other embodiments, R_1 is $NHC(O)CH_3$. In other embodiments, R_1 is NHCO-$N(R_{10})(R_{11})$. In other embodiments, R_1 is $NHC(O)N(CH_3)_2$. In other embodiments, R_1 is COOH. In other embodiments, R_1 is C(O)O-R_{10}. In other embodiments, R_1 is C(O)O-$CH(CH_3)_2$. In other embodiments, R_1 is C(O)O-CH_3. In other embodiments, R_1 is $SO_2N(R_{10})(R_{11})$. In other embodiments, R_1 is $SO_2N(CH_3)_2$. In other embodiments, R_1 is $SO_2NHC(O)CH_3$. In other embodiments, R_1 is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_1 is methyl. In other embodiments, R_1 is ethyl. In other embodiments, R_1 is iso-propyl. In other embodiments, R_1 is t-Bu. In other embodiments, R_1 is iso-butyl. In other embodiments, R_1 is pentyl. In other embodiments, R_1 is propyl. In other embodiments, R_1 is benzyl. In other embodiments, R_1 is C_1-C_5 linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R_1 is $CH=C(Ph)_2$. In other embodiments, R_1 is 2-CH_2-C_6H_4-Cl. In other embodiments, R_1 is 3-CH_2-C_6H_4-Cl. In other embodiments, R_1 is 4-CH_2-C_6H_4-Cl. In other embodiments, R_1 is ethyl. In other embodiments, R_1 is iso-propyl. In other embodiments, R_1 is t-Bu. In other embodiments, R_1 is iso-butyl. In other embodiments, R_1 is pentyl. In other embodiments, R_1 is substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl). In other embodiments, R_1 is C_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, R_1 is methoxy. In other embodiments, R_1 is ethoxy. In other embodiments, R_1 is propoxy. In other embodiments, R_1 is isopropoxy. In other embodiments, R_1 is O-CH_2-cyclopropyl. In other embodiments, R_1 is O-cyclobutyl. In other embodiments, R_1 is O-cyclopentyl. In other embodiments, R_1 is O-cyclohexyl. In other embodiments, R_1 is O-1-oxacyclobutyl. In other embodiments, R_1 is O-2-oxacyclobutyl. In other embodiments, R_1 is 1-butoxy. In other embodiments, R_1 is 2-butoxy. In other embodiments, R_1 is O-tBu. In other embodiments, R_1 is C_1-C_5 linear, branched or cyclic alkoxy wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (O). In other embodiments, R_1 is O-1-oxacyclobutyl. In other embodiments, R_1 is O-2-oxacyclobutyl. In other embodiments, R_1 is C_1-C_5 linear or branched haloalkoxy. In other embodiments, R_1 is OCF_3. In other embodiments, R_1 is $OCHF_2$. In other embodiments, R_1 is substituted or unsubstituted C_3-C_8 heterocyclic ring. In other embodiments, R_1 is oxazole. In other embodiments, R_1 is methyl substituted oxazole. In other embodiments, R_1 is oxadiazole. In other embodiments, R_1 is methyl substituted oxadiazole. In other embodiments, R_1 is imidazole. In other embodiments, R_1 is

methyl substituted imidazole. In other embodiments, R_1 is pyridine. In other embodiments, R_1 is 2-pyridine. In other embodiments, R_1 is 3-pyridine. In other embodiments, R_1 is 3-methyl-2-pyridine. In other embodiments, R_1 is 4-pyridine. In other embodiments, R_1 is tetrazole. In other embodiments, R_1 is pyrimidine. In other embodiments, R_1 is pyrazine. In other embodiments, R_1 is oxacyclobutane. In other embodiments, R_1 is 1-oxacyclobutane. In other embodiments, R_1 is 2-oxacyclobutane. In other embodiments, R_1 is indole. In other embodiments, R_1 is pyridine oxide. In other embodiments, R_1 is protonated pyridine oxide. In other embodiments, R_1 is deprotonated pyridine oxide. In other embodiments, R_1 is 3-methyl-4H-1,2,4-triazole. In other embodiments, R_1 is 5-methyl-1,2,4-oxadiazole.In other embodiments, R_1 is substituted or unsubstituted aryl. In other embodiments, R_1 is phenyl. In other embodiments, R_1 is bromophenyl. In other embodiments, R_1 is 2-bromophenyl. In other embodiments, R_1 is 3-bromophenyl. In other embodiments, R_1 is 4-bromophenyl. In other embodiments, R_1 is substituted or unsubstituted benzyl. In other embodiments, R_1 is 4-Cl-benzyl. In other embodiments, R_1 is 4-OH-benzyl. In other embodiments, R_1 is benzyl. In other embodiments, R_1 is R_8-$N(R_{10})(R_{11})$. In other embodiments, R_1 is CH_2-NH_2. In other embodiments, substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, and/or NO_2, each is a separate embodiment according to this invention.

[0069] In some embodiments, **R_2** of formula **I, I(a), I(b), II, II(a)** and **II(b)** is H.

[0070] In some embodiments, **R_2** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is F. In other embodiments, R_2 is Cl. In other embodiments, R_2 is Br. In other embodiments, R_2 is I. In other embodiments, R_2 is R_8-(C_3-C_8 cycloalkyl). In other embodiments, R_2 is CH_2-cyclohexyl. In other embodiments, R_2 is R_8-(C_3-C_8 heterocyclic ring). In other embodiments, R_2 is CH_2-imidazole. In other embodiments, R_2 is CF_3. In other embodiments, R_2 is $CF_2CH_2CH_3$. In other embodiments, R_2 is $CH_2CH_2CF_3$. In other embodiments, R_2 is $CF_2CH(CH_3)_2$. In other embodiments, R_2 is $CF(CH_3)$-$CH(CH_3)_2$. In other embodiments, R_2 is OCD_3. In other embodiments, R_2 is NO_2. In other embodiments, R_2 is NH_2. In other embodiments, R_2 is R_8-$N(R_{10})(R_{11})$. In other embodiments, R_2 is CH_2-NH_2. In other embodiments, R_2 is CH_2-$N(CH_3)_2$). In other embodiments, R_2 is R_9-R_8-$N(R_{10})(R_{11})$. In other embodiments, R_2 is C≡C-CH_2-NH_2. In other embodiments, R_2 is $B(OH)_2$. In other embodiments, R_2 is NHC(O)-R_{10}. In other embodiments, R_2 is $NHC(O)CH_3$. In other embodiments, R_2 is NHCO-$N(R_{10})(R_{11})$. In other embodiments, R_2 is $NHC(O)N(CH_3)_2$. In other embodiments, R_2 is COOH. In other embodiments, R_2 is C(O)O-R_{10}. In other embodiments, R_2 is C(O)O-$CH(CH_3)_2$. In other embodiments, R_2 is C(O)O-CH_3. In other embodiments, R_2 is $SO_2N(R_{10})(R_{11})$. In other embodiments, R_2 is $SO_2N(CH_3)_2$. In other embodiments, R_2 is $SO_2NHC(O)CH_3$. In other embodiments, R_2 is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_2 is methyl. In other embodiments, R_2 is ethyl. In other embodiments, R_2 is iso-propyl. In other embodiments, R_2 is t-Bu. In other embodiments, R_2 is iso-butyl. In other embodiments, R_2 is pentyl. In other embodiments, R_2 is propyl. In other embodiments, R_2 is benzyl. In other embodiments, R_2 is C_1-C_5 linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R_2 is $CH=C(Ph)_2$. In other embodiments, R_2 is 2-CH_2-C_6H_4-Cl. In other embodiments, R_2 is 3-CH_2-C_6H_4-Cl. In other embodiments, R_2 is 4-CH_2-C_6H_4-Cl. In

other embodiments, R_2 is ethyl. In other embodiments, R_2 is iso-propyl. In other embodiments, R_2 is t-Bu. In other embodiments, R_2 is iso-butyl. In other embodiments, R_2 is pentyl. In other embodiments, R_2 is substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl). In other embodiments, R_2 is C_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, R_2 is methoxy. In other embodiments, R_2 is ethoxy. In other embodiments, R_2 is propoxy. In other embodiments, R_2 is isopropoxy. In other embodiments, R_2 is O-CH_2-cyclopropyl. In other embodiments, R_2 is O-cyclobutyl. In other embodiments, R_2 is O-cyclopentyl. In other embodiments, R_2 is O-cyclohexyl. In other embodiments, R_2 is O-1-oxacyclobutyl. In other embodiments, R_2 is O-2-oxacyclobutyl. In other embodiments, R_2 is 1-butoxy. In other embodiments, R_2 is 2-butoxy. In other embodiments, R_2 is O-tBu. In other embodiments, R_2 is C_1-C_5 linear or branched haloalkoxy. In other embodiments, R_2 is OCF_3. In other embodiments, R_2 is $OCHF_2$. In other embodiments, R_2 is substituted or unsubstituted C_3-C_8 heterocyclic ring. In other embodiments, R_2 is oxazole or methyl substituted oxazole. In other embodiments, R_2 is oxadiazole or methyl substituted oxadiazole. In other embodiments, R_2 is imidazole or methyl substituted imidazole. In other embodiments, R_2 is pyridine. In other embodiments, R_2 is 2-pyridine. In other embodiments, R_2 is 3-pyridine. In other embodiments, R_2 is 4-pyridine. In other embodiments, R_2 is 3-methyl-2-pyridine. In other embodiments, R_2 is tetrazole. In other embodiments, R_2 is pyrimidine. In other embodiments, R_2 is pyrazine. In other embodiments, R_2 is oxacyclobutane. In other embodiments, R_2 is 1-oxacyclobutane. In other embodiments, R_2 is 2-oxacyclobutane. In other embodiments, R_2 is indole. In other embodiments, R_2 is pyridine oxide. In other embodiments, R_2 is protonated pyridine oxide. In other embodiments, R_2 is deprotonated pyridine oxide. In other embodiments, R_2 is 3-methyl-4H-1,2,4-triazole. In other embodiments, R_2 is 5-methyl-1,2,4-oxadiazole.In other embodiments, R_2 is substituted or unsubstituted aryl. In other embodiments, R_2 is phenyl. In other embodiments, R_2 is bromophenyl. In other embodiments, R_2 is 2-bromophenyl. In other embodiments, R_2 is 3-bromophenyl. In other embodiments, R_2 is 4-bromophenyl. In other embodiments, R_2 is substituted or unsubstituted benzyl. In other embodiments, R_2 is benzyl. In other embodiments, R_1 is 4-Cl-benzyl. In other embodiments, R_1 is 4-OH-benzyl. In other embodiments, R_2 is R_8-$N(R_{10})(R_{11})$. In other embodiments, R_2 is CH_2-NH_2. In other embodiments, substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, and/or NO_2, each is a separate embodiment according to this invention.

[0071] In some embodiments, R_1 and R_2 of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** are joint together to form a pyrrol ring. In some embodiments, R_1 and R_2 are joint together to form a [1,3]dioxole 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 together to form a benzene ring. In some embodiments, R_1 and R_2 are joint together to form a pyridine ring.

[0072] In some embodiments, $\mathbf{R_{20}}$ of formula **I, I(a), I(b), II, II(a)** and **II(b)** is H.

[0073] In some embodiments, $\mathbf{R_{20}}$ of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** 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 R_8-(C_3-C_8 cycloalkyl). In other embodiments, R_{20} is CH_2-cyclohexyl. In other

embodiments, R_{20} is R_8-(C_3-C_8 heterocyclic ring). In other embodiments, R_{20} is CH_2-imidazole. In other embodiments, R_{20} is CF_3. In other embodiments, R_{20} is $CF_2CH_2CH_3$. In other embodiments, R_{20} is $CH_2CH_2CF_3$. In other embodiments, R_{20} is $CF_2CH(CH_3)_2$. In other embodiments, R_{20} is $CF(CH_3)$-$CH(CH_3)_2$. In other embodiments, R_{20} is OCD_3. In other embodiments, R_{20} is NO_2. In other embodiments, R_{20} is NH_2. In other embodiments, R_{20} is R_8-$N(R_{10})(R_{11})$. In other embodiments, R_{20} is CH_2-NH_2. In other embodiments, R_{20} is CH_2-$N(CH_3)_2$). In other embodiments, R_{20} is R_9-R_8-$N(R_{10})(R_{11})$. In other embodiments, R_{20} is $C\equiv C$-CH_2-NH_2. In other embodiments, R_{20} is $B(OH)_2$. 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 NHCO-$N(R_{10})(R_{11})$. In other embodiments, R_{20} is $NHC(O)N(CH_3)_2$. In other embodiments, R_{20} is COOH. In other embodiments, R_{20} is C(O)O-R_{10}. In other embodiments, R_{20} is C(O)O-$CH(CH_3)_2$. In other embodiments, R_{20} is C(O)O-CH_3. In other embodiments, R_{20} is $SO_2N(R_{10})(R_{11})$. In other embodiments, R_{20} is $SO_2N(CH_3)_2$. In other embodiments, R_{20} is $SO_2NHC(O)CH_3$. In other embodiments, R_{20} is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_{20} is methyl. In other embodiments, R_{20} is ethyl. In other embodiments, R_{20} is iso-propyl. In other embodiments, R_{20} is t-Bu. In other embodiments, R_{20} is iso-butyl. In other embodiments, R_{20} is pentyl. In other embodiments, R_{20} is propyl. In other embodiments, R_{20} is benzyl. In other embodiments, R_{20} is C_1-C_5 linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R_{20} is $CH=C(Ph)_2$. In other embodiments, R_{20} is 2-CH_2-C_6H_4-Cl. In other embodiments, R_{20} is 3-CH_2-C_6H_4-Cl. In other embodiments, R_{20} is 4-CH_2-C_6H_4-Cl. In other embodiments, R_{20} is ethyl. In other embodiments, R_{20} is iso-propyl. In other embodiments, R_{20} is t-Bu. In other embodiments, R_{20} is iso-butyl. In other embodiments, R_{20} is pentyl. In other embodiments, R_{20} is substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl). In other embodiments, R_{20} is C_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, R_{20} is methoxy. In other embodiments, R_{20} is ethoxy. In other embodiments, R_{20} is propoxy. In other embodiments, R_{20} is isopropoxy. In other embodiments, R_{20} is O-CH_2-cyclopropyl. In other embodiments, R_{20} is O-cyclobutyl. In other embodiments, R_{20} is O-cyclopentyl. In other embodiments, R_{20} is O-cyclohexyl. In other embodiments, R_{20} is O-1-oxacyclobutyl. In other embodiments, R_{20} is O-2-oxacyclobutyl. In other embodiments, R_{20} is 1-butoxy. In other embodiments, R_{20} is 2-butoxy. In other embodiments, R_{20} is O-tBu. In other embodiments, R_{20} is C_1-C_5 linear, branched or cyclic alkoxy wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (O). In other embodiments, R_{20} is O-1-oxacyclobutyl. In other embodiments, R_{20} is O-2-oxacyclobutyl. In other embodiments, R_{20} is C_1-C_5 linear or branched haloalkoxy. In other embodiments, R_{20} is OCF_3. In other embodiments, R_{20} is $OCHF_2$. In other embodiments, R_{20} is substituted or unsubstituted C_3-C_8 heterocyclic ring. In other embodiments, R_{20} is oxazole. In other embodiments, R_{20} is methyl substituted oxazole. In other embodiments, R_{20} is oxadiazole. In other embodiments, R_{20} is methyl substituted oxadiazole. In other embodiments, R_{20} is imidazole. In other embodiments, R_{20} is methyl substituted imidazole. In other embodiments, R_{20} is pyridine. In other embodiments, R_{20} is 2-pyridine. In other embodiments, R_{20} is 3-pyridine. In other embodiments, R_{20} is 4-pyridine. In other embodiments, R_{20} is 3-methyl-2-pyridine. In other embodiments, R_{20} is tetrazole. In other embodiments, R_{20} is pyrimidine. In other embodiments, R_{20} is pyrazine. In other embodiments, R_{20} is oxacyclobutane.

In other embodiments, R_{20} is 1-oxacyclobutane. In other embodiments, R_{20} is 2-oxacyclobutane. In other embodiments, R_{20} is indole. In other embodiments, R_{20} is pyridine oxide. In other embodiments, R_{20} is protonated pyridine oxide. In other embodiments, R_{20} is deprotonated pyridine oxide. In other embodiments, R_{20} is 3-methyl-4H-1,2,4-triazole. In other embodiments, R_{20} is 5-methyl-1,2,4-oxadiazole. In other embodiments, R_{20} is substituted or unsubstituted aryl. In other embodiments, R_{20} is phenyl. In other embodiments, R_{20} is bromophenyl. In other embodiments, R_{20} is 2-bromophenyl. In other embodiments, R_{20} is 3-bromophenyl. In other embodiments, R_{20} is 4-bromophenyl. In other embodiments, R_{20} is substituted or unsubstituted benzyl. In other embodiments, R_{20} is benzyl. In other embodiments, R_1 is 4-Cl-benzyl. In other embodiments, R_1 is 4-OH-benzyl. In other embodiments, R_{20} is R_8-N(R_{10})(R_{11}). In other embodiments, R_{20} is CH_2-NH_2. In other embodiments, substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, N(R)$_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, and/or NO_2, each is a separate embodiment according to this invention.

[0074] In some embodiments, **R_3** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is H. In other embodiments, R_3 is Cl. In other embodiments, R_3 is I. In other embodiments, R_3 is F. In other embodiments, R_3 is Br. In other embodiments, R_3 is OH. In other embodiments, R_3 is CD_3. In other embodiments, R_3 is OCD_3. In other embodiments, R_3 is R_8-OH. In other embodiments, R_3 is CH_2-OH. In other embodiments, R_3 is -R_8-O-R_{10}. In other embodiments, R_3 is CH_2-O-CH_3. In other embodiments, R_3 is R_8-N(R_{10})(R_{11}). In other embodiments, R_3 is CH_2-NH_2. In other embodiments, R_3 is CH_2-N(CH_3)$_2$. In other embodiments, R_3 is COOH. In other embodiments, R_3 is C(O)O-R_{10}. In other embodiments, R_3 is C(O)O-CH_2CH_3. In other embodiments, R_3 is R_8-C(O)-R_{10}. In other embodiments, R_3 is $CH_2C(O)CH_3$. In other embodiments, R_3 is C(O)-R_{10}. In other embodiments, R_3 is C(O)-CH_3. In other embodiments, R_3 is C(O)-CH_2CH_3. In other embodiments, R_3 is C(O)-$CH_2CH_2CH_3$. In other embodiments, R_3 is C_1-C_5 linear or branched C(O)-haloalkyl. In other embodiments, R_3 is C(O)-CF_3. 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 SO_2N(R_{10})(R_{11}). 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 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 C_1-C_5 linear, branched or cyclic haloalkyl. In other embodiments, R_3 is CF_2CH_3. In other embodiments, R_3 is CF_2-cyclobutyl. In other embodiments, R_3 is CH_2CF_3. In other embodiments, R_3 is $CF_2CH_2CH_3$. In other 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_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, R_3 is methoxy. In other 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 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 thiophene. In other 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 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 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 $CH(CF_3)(NH\text{-}R_{10})$.

[0075] In some embodiments, **R_4** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is H. In other embodiments, R_4 is Cl. In other embodiments, R_4 is I. In other embodiments, R_4 is F. In other embodiments, R_4 is Br. In other embodiments, R_4 is OH. In other embodiments, R_4 is CD_3. In other embodiments, R_4 is OCD_3. In other embodiments, R_4 is R_8-OH. In other embodiments, R_4 is CH_2-OH. In other embodiments, R_4 is $-R_8\text{-}O\text{-}R_{10}$. In other embodiments, R_4 is $CH_2\text{-}O\text{-}CH_3$. In other embodiments, R_4 is $R_8\text{-}N(R_{10})(R_{11})$. In other embodiments, R_4 is $CH_2\text{-}NH_2$. In other embodiments, R_4 is $CH_2\text{-}N(CH_3)_2$. In other embodiments, R_4 is COOH. In other embodiments, R_4 is $C(O)O\text{-}R_{10}$. In other embodiments, R_4 is $C(O)O\text{-}CH_2CH_3$. In other embodiments, R_4 is $R_8\text{-}C(O)\text{-}R_{10}$. In other embodiments, R_4 is $CH_2C(O)CH_3$. In other embodiments, R_4 is $C(O)\text{-}R_{10}$. In other embodiments, R_4 is $C(O)\text{-}CH_3$. In other embodiments, R_4 is $C(O)\text{-}CH_2CH_3$. In other embodiments, R_4 is $C(O)\text{-}CH_2CH_2CH_3$. In other embodiments, R_4 is C_1-C_5 linear or branched C(O)-haloalkyl. In other embodiments, R_4 is $C(O)\text{-}CF_3$. In other embodiments, R_4 is $C(O)N(R_{10})(R_{11})$. In other embodiments, R_4 is $C(O)N(CH_3)_2$). In other embodiments, R_4 is $SO_2N(R_{10})(R_{11})$. In other embodiments, R_4 is $SO_2N(CH_3)_2$. In other embodiments, R_4 is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_4 is methyl. In other embodiments, R_4 is $C(OH)(CH_3)(Ph)$. In other embodiments, R_4 is ethyl. In other embodiments, R_4 is propyl. In other embodiments, R_4 is iso-propyl. In other embodiments, R_4 is t-Bu. In other embodiments, R_4 is iso-butyl. In other embodiments, R_4 is pentyl. In other embodiments, R_4 is C_1-C_5 linear, branched or cyclic haloalkyl. In other embodiments, R_3 is CF_2CH_3. In other embodiments, R_3 is CF_2-cyclobutyl. In other embodiments, R_4 is CH_2CF_3. In other embodiments, R_4 is $CF_2CH_2CH_3$. In other embodiments, R_4 is CF_3. In other embodiments, R_4 is $CF_2CH_2CH_3$. In other embodiments, R_4 is $CH_2CH_2CF_3$. In other embodiments, R_4 is $CF_2CH(CH_3)_2$. In other embodiments, R_4 is $CF(CH_3)\text{-}CH(CH_3)_2$. In other embodiments, R_4 is C_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, R_4 is methoxy. In other embodiments, R_4 is isopropoxy. In other embodiments, R_4 is substituted or unsubstituted C_3-C_8 cycloalkyl. In other embodiments, R_4 is cyclopropyl. In other embodiments, R_4 is cyclopentyl. In other embodiments, R_4 is substituted or unsubstituted C_3-C_8 heterocyclic ring. In other embodiments, R_4 is thiophene. In other embodiments, R_4 is oxazole. In other embodiments, R_4 is isoxazole. In other embodiments, R_4 is imidazole. In other embodiments, R_4 is furane. In other embodiments, R_4 is triazole. In other embodiments, R_4 is pyridine. In other embodiments, R_4 is 2-pyridine. In other embodiments, R_4 is 3-pyridine. In other embodiments, R_4 is 4-pyridine. In other embodiments, R_4 is pyrimidine. In other embodiments, R_4 is pyrazine. In other embodiments, R_4 is oxacyclobutane. In other embodiments, R_4 is 1-oxacyclobutane. In other embodiments, R_4 is 2-oxacyclobutane. In other embodiments, R_4 is indole.

In other embodiments, R_4 is 3-methyl-4H-1,2,4-triazole. In other embodiments, R_4 is 5-methyl-1,2,4-oxadiazole. In other embodiments, R_4 is substituted or unsubstituted aryl. In other embodiments, R_4 is phenyl. In other embodiments, R_4 is $CH(CF_3)(NH\text{-}R_{10})$.

[0076] In some embodiments, R_3 and R_4 of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** are joint together to form a [1,3]dioxole ring. In some embodiments, R_3 and R_4 are joint together to form a furanone ring (e.g., furan-2(3H)-one). In some embodiments, R_3 and R_4 are joint together to form a benzene ring. In some embodiments, R_3 and R_4 are joint together to form a cyclopentene ring. In some embodiments, R_3 and R_4 are joint together to form an imidazole ring.

[0077] In some embodiments, $\mathbf{R_{40}}$ of formula **I, I(a), II** and **III** is H. In other embodiments, R_{40} is Cl. In other embodiments, R_{40} is I. In other embodiments, R_{40} is F. In other embodiments, R_{40} is Br. In other embodiments, R_{40} is OH. In other embodiments, R_{40} is CD_3. In other embodiments, R_{40} is OCD_3. In other embodiments, R_{40} is R_8-OH. In other embodiments, R_{40} is CH_2-OH. In other embodiments, R_{40} is $-R_8\text{-}O\text{-}R_{10}$. In other embodiments, R_{40} is $CH_2\text{-}O\text{-}CH_3$. In other embodiments, R_{40} is $R_8\text{-}N(R_{10})(R_{11})$. In other embodiments, R_{40} is $CH_2\text{-}NH_2$. In other embodiments, R_{40} is $CH_2\text{-}N(CH_3)_2$. In other embodiments, R_{40} is COOH. In other embodiments, R_{40} is $C(O)O\text{-}R_{10}$. In other embodiments, R_{40} is $C(O)O\text{-}CH_2CH_3$. In other embodiments, R_{40} is $R_8\text{-}C(O)\text{-}R_{10}$. In other embodiments, R_{40} is $CH_2C(O)CH_3$. In other embodiments, R_{40} is $C(O)\text{-}R_{10}$. In other embodiments, R_{40} is $C(O)\text{-}CH_3$. In other embodiments, R_{40} is $C(O)\text{-}CH_2CH_3$. In other embodiments, R_{40} is $C(O)\text{-}CH_2CH_2CH_3$. In other embodiments, R_{40} is C_1-C_5 linear or branched C(O)-haloalkyl. In other embodiments, R_{40} is $C(O)\text{-}CF_3$. In other embodiments, R_{40} is $C(O)N(R_{10})(R_{11})$. In other embodiments, R_{40} is $C(O)N(CH_3)_2$). In other embodiments, R_{40} is $SO_2N(R_{10})(R_{11})$. In other embodiments, R_{40} is $SO_2N(CH_3)_2$. In other embodiments, R_{40} is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_{40} is methyl. In other embodiments, R_{40} is $C(OH)(CH_3)(Ph)$. In other embodiments, R_{40} is ethyl. In other embodiments, R_{40} is propyl. In other embodiments, R_{40} is iso-propyl. In other embodiments, R_{40} is t-Bu. In other embodiments, R_{40} is iso-butyl. In other embodiments, R_{40} is pentyl. In other embodiments, R_{40} is C_1-C_5 linear, branched or cyclic haloalkyl. In other embodiments, R_{40} is CF_2CH_3. In other embodiments, R_{40} is CF_2-cyclobutyl. In other embodiments, R_{40} is CH_2CF_3. In other embodiments, R_{40} is $CF_2CH_2CH_3$. In other embodiments, R_{40} is CF_3. In other embodiments, R_{40} is $CF_2CH_2CH_3$. In other embodiments, R_{40} is $CH_2CH_2CF_3$. In other embodiments, R_{40} is $CF_2CH(CH_3)_2$. In other embodiments, R_{40} is $CF(CH_3)\text{-}CH(CH_3)_2$. In other embodiments, R_{40} is C_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, R_{40} is methoxy. In other embodiments, R_{40} is isopropoxy. In other embodiments, R_{40} is substituted or unsubstituted C_3-C_8 cycloalkyl. In other embodiments, R_{40} is cyclopropyl. In other embodiments, R_{40} is cyclopentyl. In other embodiments, R_{40} is substituted or unsubstituted C_3-C_8 heterocyclic ring. In other embodiments, R_{40} is thiophene. In other embodiments, R_{40} is oxazole. In other embodiments, R_{40} is isoxazole. In other embodiments, R_{40} is imidazole. In other embodiments, R_{40} is furane. In other embodiments, R_{40} is triazole. In other embodiments, R_{40} is pyridine. In other embodiments, R_{40} is 2-pyridine. In other embodiments, R_{40} is 3-pyridine. In other embodiments, R_{40} is 4-pyridine. In other embodiments, R_{40} is pyrimidine. In other embodiments, R_{40} is pyrazine. In other embodiments, R_{40} is oxacyclobutane. In other embodiments, R_{40} is 1-oxacyclobutane. In other embodiments, R_{40} is 2-

oxacyclobutane. In other embodiments, R_{40} is indole. In other embodiments, R_{40} is 3-methyl-4H-1,2,4-triazole. In other embodiments, R_{40} is 5-methyl-1,2,4-oxadiazole. In other embodiments, R_{40} is substituted or unsubstituted aryl. In other embodiments, R_{40} is phenyl. In other embodiments, R_{40} is $CH(CF_3)(NH\text{-}R_{10})$.

[0078] In some embodiments, **R_5** of formula **I, I(a)** and **III** is H. In other embodiments, R_5 is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_5 is methyl. In other embodiments, R_5 is CH_2SH. In other embodiments, R_5 is ethyl. In other embodiments, R_5 is iso-propyl. In other embodiments, R_5 is CH_2SH. In other embodiments, R_5 is C_2-C_5 linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R_5 is C_2-C_5 linear or branched, substituted or unsubstituted alkynyl. In other embodiments, R_5 is C(CH). In other embodiments, R_5 is C_1-C_5 linear or branched haloalkyl. In other embodiments, R_5 is CF_2CH_3. In other embodiments, R_5 is CH_2CF_3. In other embodiments, R_5 is $CF_2CH_2CH_3$. In other embodiments, R_5 is CF_3. In other embodiments, R_5 is $CF_2CH_2CH_3$. In other embodiments, R_5 is $CH_2CH_2CF_3$. In other embodiments, R_5 is $CF_2CH(CH_3)_2$. In other embodiments, R_5 is $CF(CH_3)\text{-}CH(CH_3)_2$. In other embodiments, R_5 is R_8-aryl. In other embodiments, R_5 is CH_2-Ph (i.e., benzyl). In other embodiments, R_5 is substituted or unsubstituted aryl. In other embodiments, R_5 is phenyl. In other embodiments, R_5 is substituted or unsubstituted heteroaryl. In other embodiments, R_5 is pyridine. In other embodiments, R_5 is 2-pyridine. In other embodiments, R_5 is 3-pyridine. In other embodiments, R_5 is 4-pyridine. In other embodiments, substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof; each represents a separate embodiment according to this invention.

[0079] In some embodiments, **R_{50}** of formula **I, I(a), I(b), III** and **III(a)** is H. In other embodiments, R_{50} is F. In other embodiments, R_{50} is Cl. In other embodiments, R_{50} is Br. In other embodiments, R_{50} is I. In other embodiments, R_{50} is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_{50} is C_1-C_5 linear or branched, alkyl, substituted with phenyl. In other embodiments, R_{50} is methyl. In other embodiments, R_{50} is CH_2SH. In other embodiments, R_{50} is ethyl. In other embodiments, R_{50} is propyl. In other embodiments, R_{50} is iso-propyl. In other embodiments, R_{50} is benzyl. In other embodiments, R_{50}'s substitutions include phenyl.

[0080] In some embodiments, **R_{50}** of formula **I** and **III** is connected to the N atom in position indicated as **1** in the structure (i.e., N_1). In other embodiments, **R_{50}** is connected to the C atom in position indicated as **3** in the structure (i.e., C_3).

[0081] In some embodiments, if R_{50} of formula **I, I(a), I(b)** is H then neither one of R_1, R_2 or R_{20} is H, and n and m are not 0.

[0082] In some embodiments, **R_6** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is H. In other embodiments, R_6 is C_1-C_5 linear or branched alkyl. In other embodiments, R_6 is methyl.

[0083] In some embodiments, **R_8** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is CH_2. In other embodiments, R_8 is CH_2CH_2. In other embodiments, R_8 is $CH_2CH_2CH_2$.

[0084] In some embodiments, **p** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is 1. In other embodiments, p is 2. In other embodiments, p is 3.

[0085] In some embodiments, **R_9** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is C≡C.

[0086] In some embodiments, **q** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is 2.

[0087] In some embodiments, **R_{10}** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is C_1-C_5 linear or branched alkyl. In other embodiments, R_{10} is H. In other embodiments, R_{10} is CH_3. In other embodiments, R_{10} is CH_2CH_3. In other embodiments, R_{10} is $CH_2CH_2CH_3$. In other embodiments, R_{10} is CN. In other embodiments, R_{10} is C(O)R. In other embodiments, R_{10} is $C(O)(OCH_3)$.

[0088] In some embodiments, **R_{11}** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is C_1-C_5 linear or branched alkyl. In other embodiments, R_{10} is H. In other embodiments, R_{11} is CH_3. In other embodiments, R_{11} is CN. In other embodiments, R_{11} is C(O)R. In other embodiments, R_{11} is $C(O)(OCH_3)$.

[0089] In some embodiments, **R_{10}** and **R_{11}** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** are joint to form a substituted or unsubstituted C_3-C_8 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 some embodiments, substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof; each represents a separate embodiment according to this invention.

[0090] In some embodiments, **R** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is H. In other embodiments, R is C_1-C_5 linear or branched alkyl. In other embodiments, R is methyl. In other embodiments, R is ethyl. In other embodiments, R is C_1-C_5 linear or branched alkoxy. In other embodiments, R is methoxy.

[0091] In some embodiments, **m** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is 1. In some embodiments, **m** of formula **I, I(a), I(b), II, II(a),** and **II(b),** is 0.

[0092] In some embodiments, **n** of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** is 1. In other embodiments, **n** is 0.

[0093] In some embodiments, **k** of formula **I, I(a), I(b), II, II(a)** and **II(b)** is 1. In other embodiments, **k** is 0.

[0094] In some embodiments, **l** of formula **I, I(a), I(b), II, II(a)** and **II(b)** is 1. In other embodiments, **l** is 0.

[0095] In some embodiments, **Q_1** of formula **I, I(a), II** and **III** is O.

[0096] In some embodiments, **Q_2** of formula **I, I(a), II** and **III** is O.

[0097] In some embodiments, **Q_3** of formula **II** and **II(a)** is N. In some embodiments, **Q_3** is CH. In some embodiments, **Q_3** is C(R). In some embodiments, **Q_3** is NO (*N*-oxide).

[0098] In some embodiments, **Q_6** of formula **II** and **II(a)** is N. In some embodiments, **Q_6** is CH. In some embodiments, **Q_6** is C(R) . In some embodiments, **Q_6** is NO (*N*-oxide).

[0099] In some embodiments, **Q_7** of formula **II** and **II(a)** is N. In some embodiments, **Q_7** is CH. In some embodiments, **Q_7** is C(R) . In some embodiments, **Q_7** is NO (*N*-oxide).

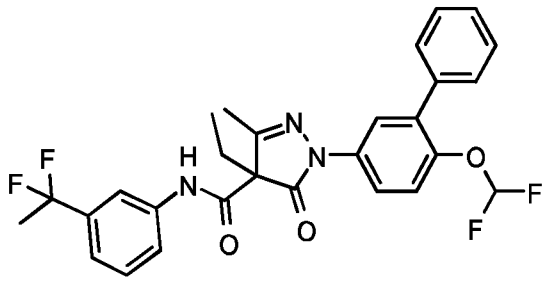
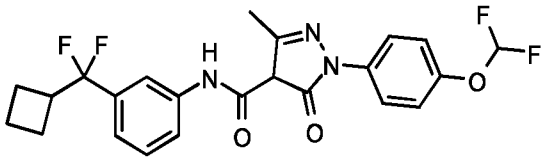
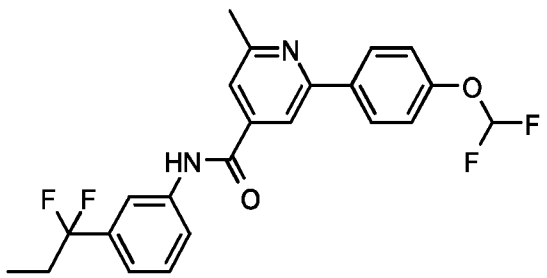
[00100] In some embodiments, **Q_8** of formula **II** and **II(a)** is N. In some embodiments, **Q_8** is CH. In some embodiments, **Q_8** is C(R) . In some embodiments, **Q_8** is NO (*N*-oxide).

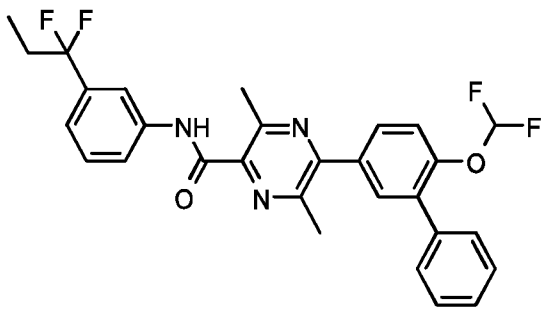
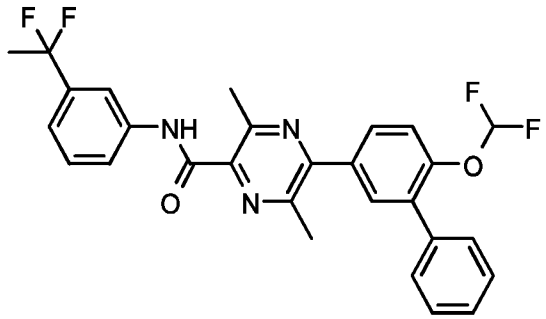
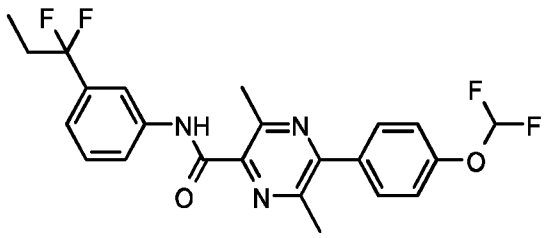
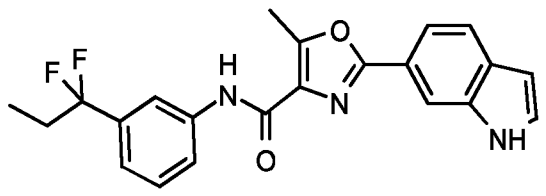
[00101] In some embodiments, Q_4 of formula **II** and **II(a)** is O. In some embodiments, Q_4 is NH. In some embodiments, Q_4 is N(R).

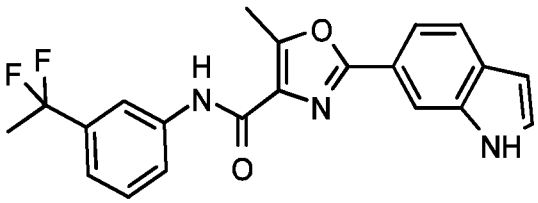
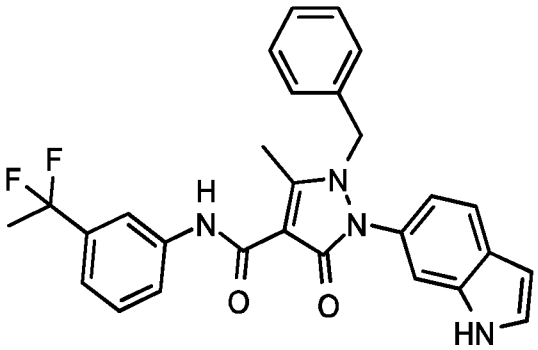
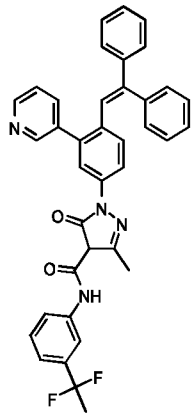
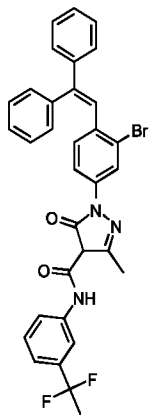
[00102] In some embodiments, Q_5 of formula **II** and **II(a)** is O. In some embodiments, Q_5 is NH. In some embodiments, Q_5 is N(R).

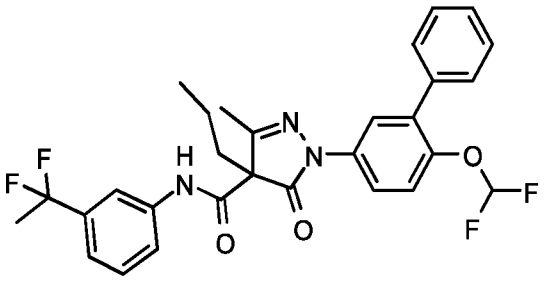
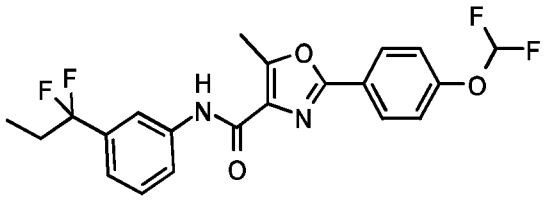
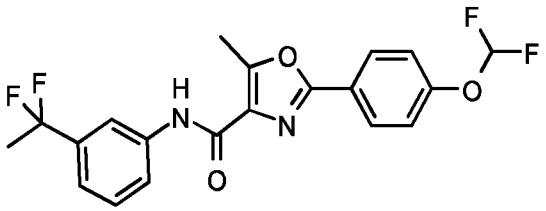
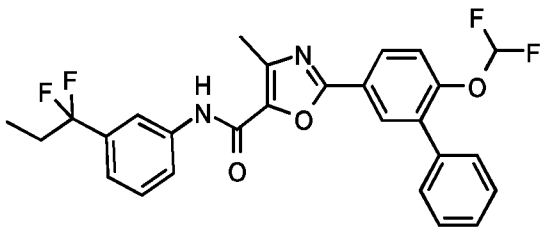
[00103] In various embodiments, this invention is directed to the compounds presented in Table 1, pharmaceutical compositions and/or method of use thereof:

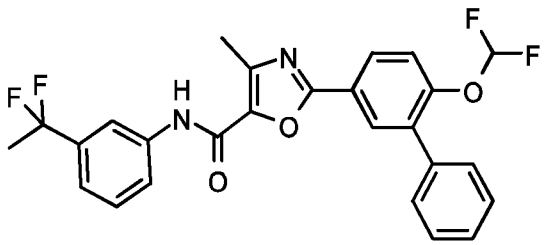
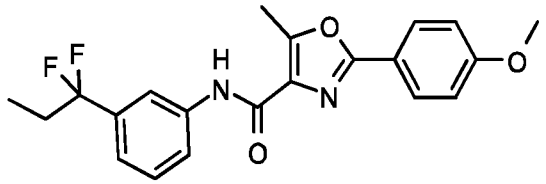
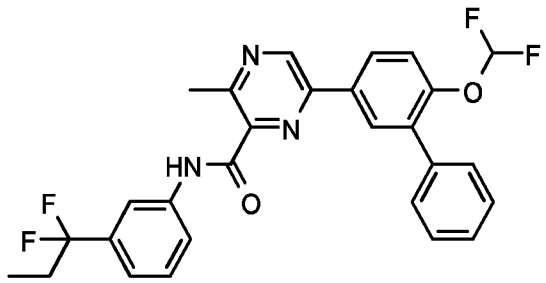
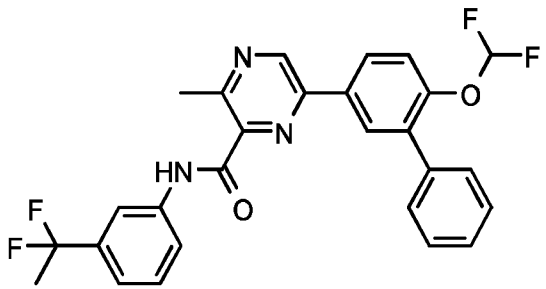
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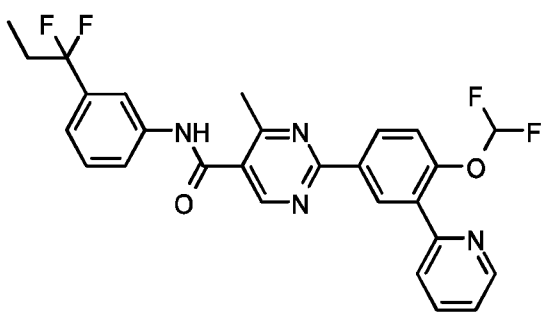
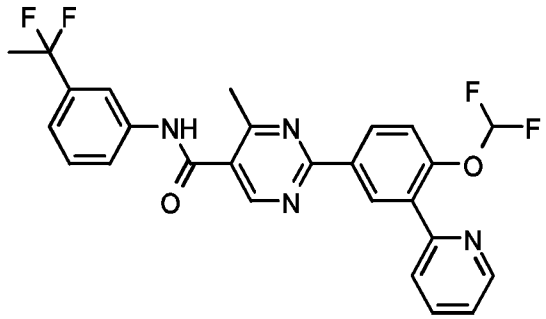
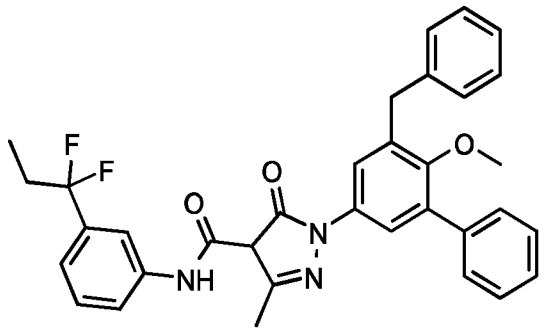
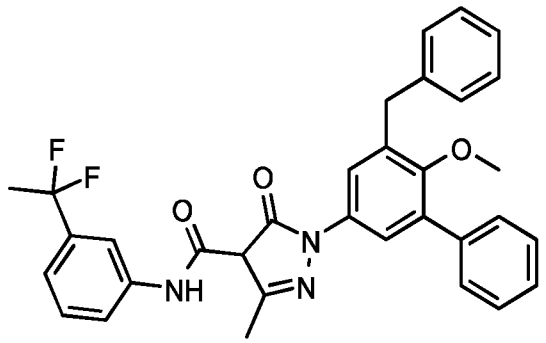
Compound Number	Compound Structure
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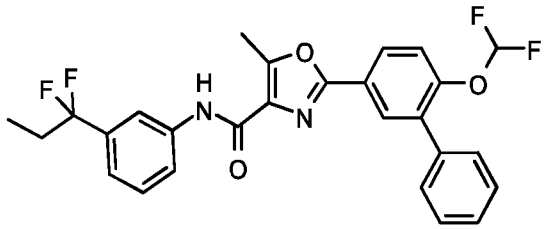
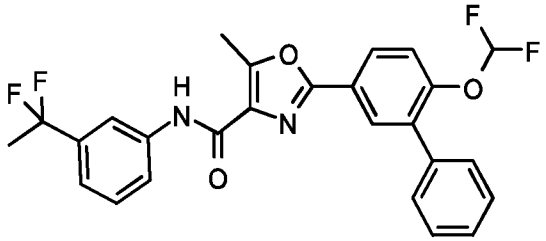
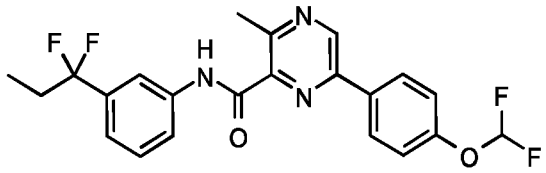
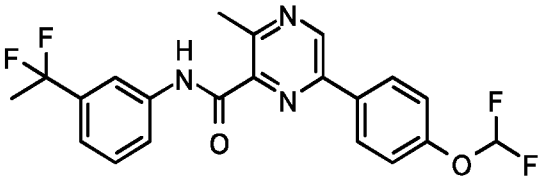
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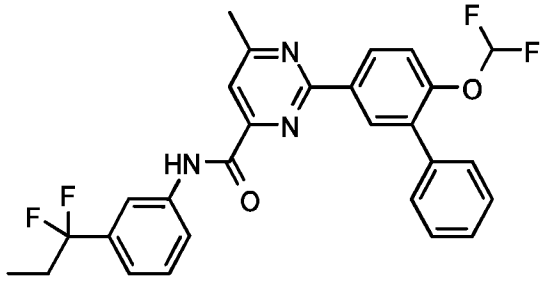
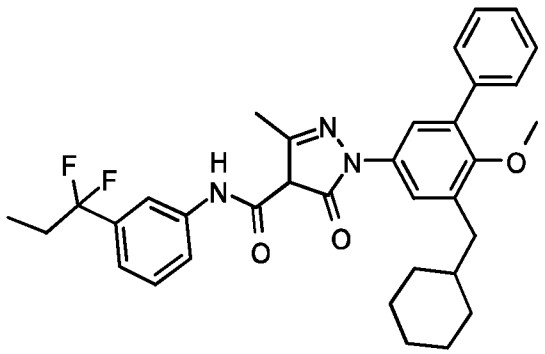
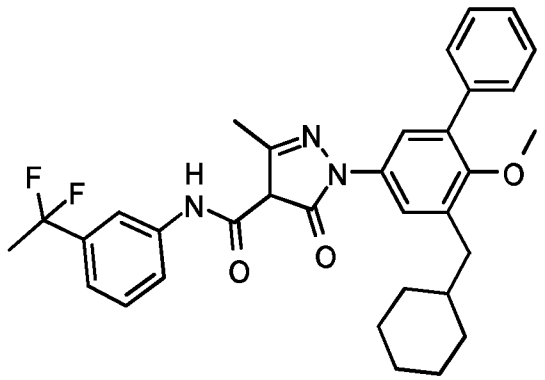
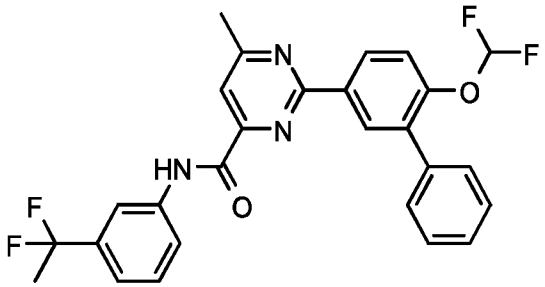
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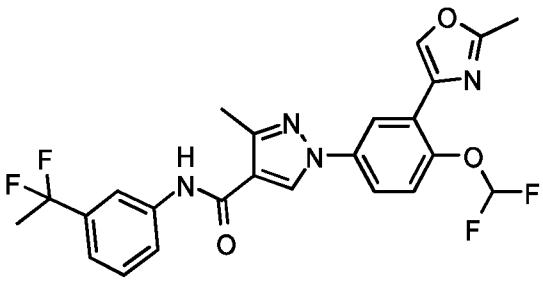
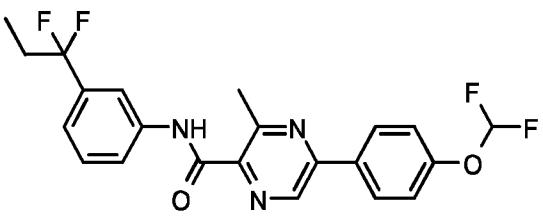
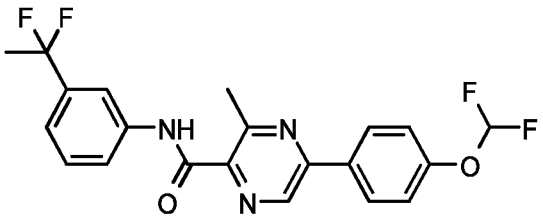
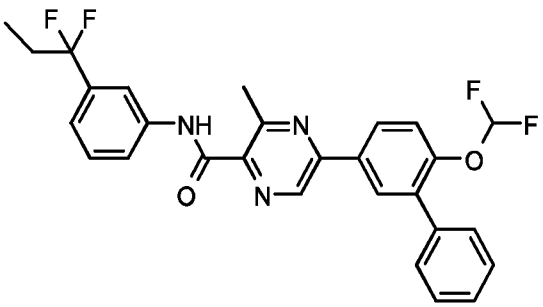
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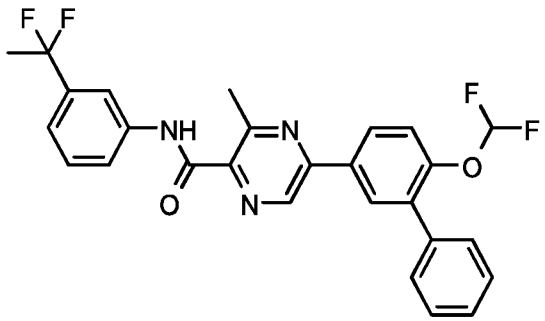
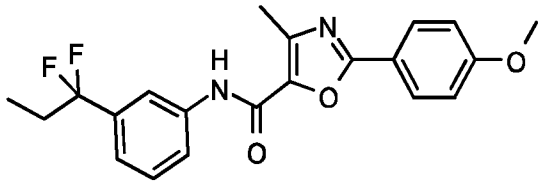
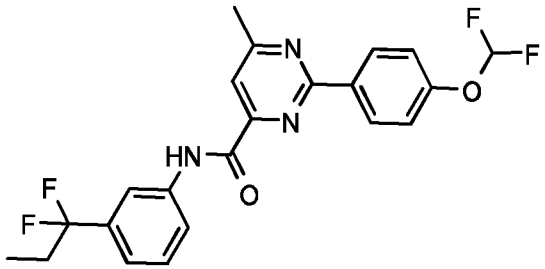
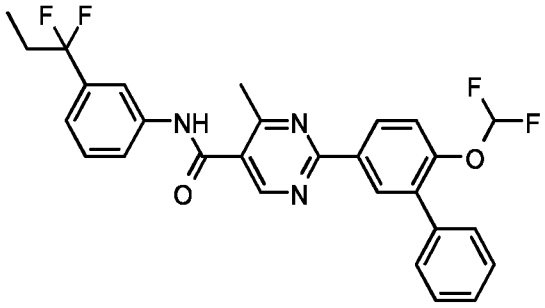
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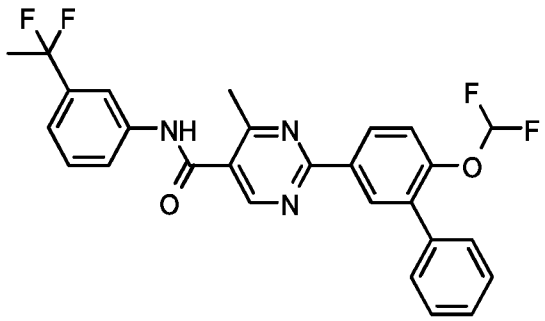
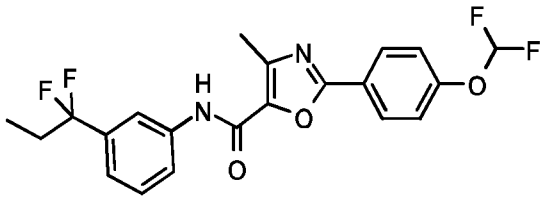
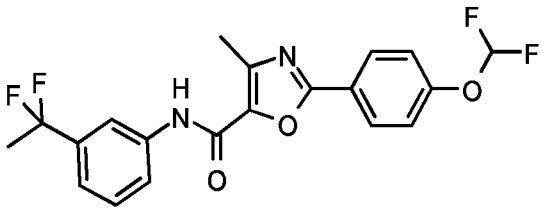
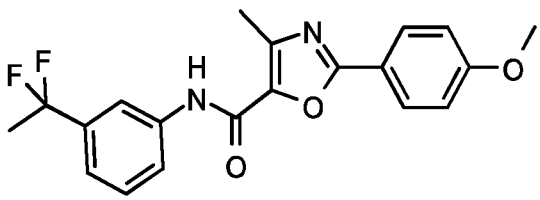
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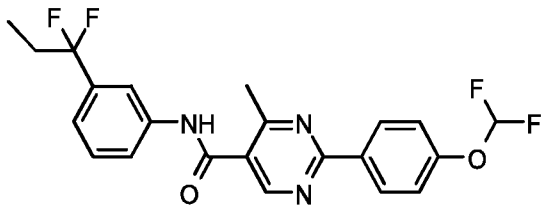
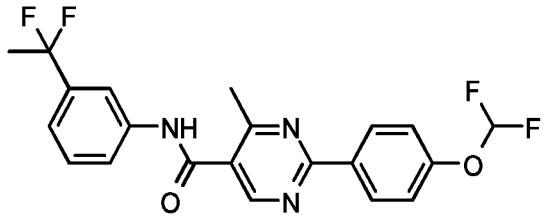
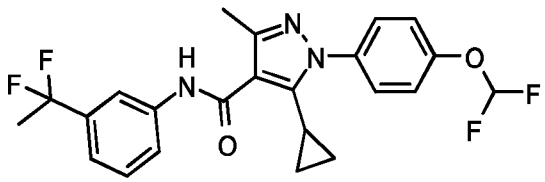
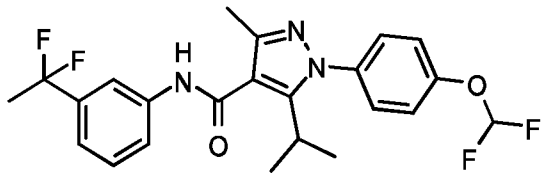
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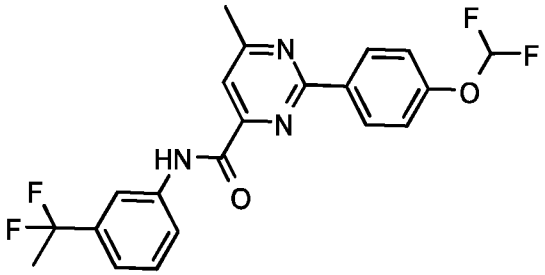
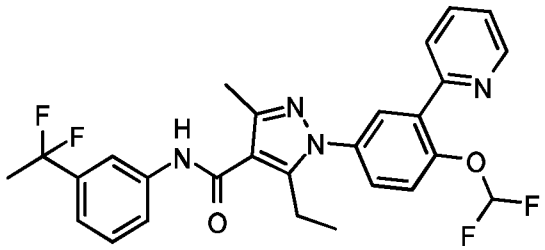
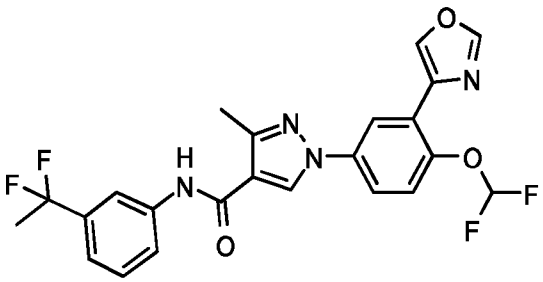
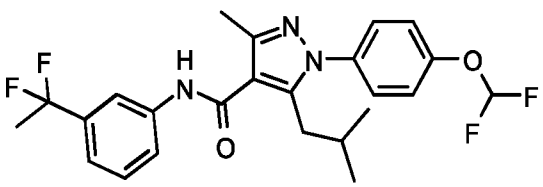
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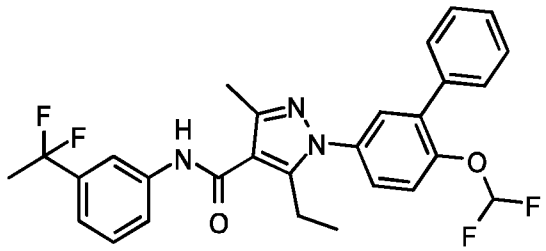
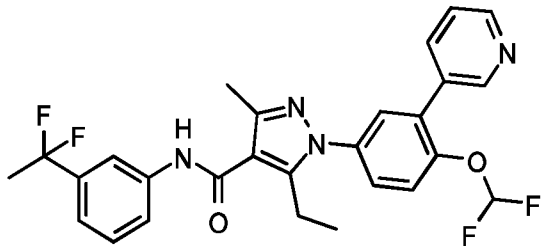
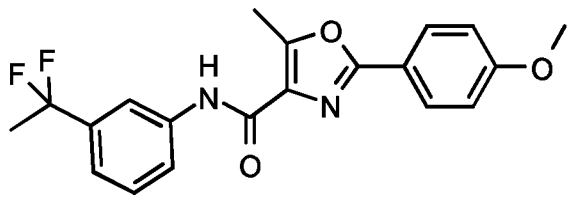
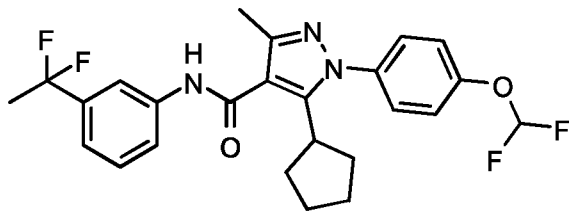
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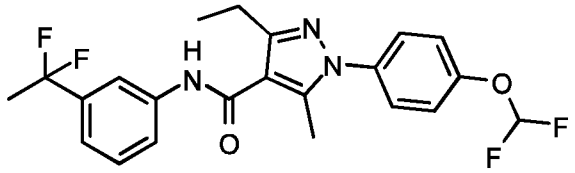
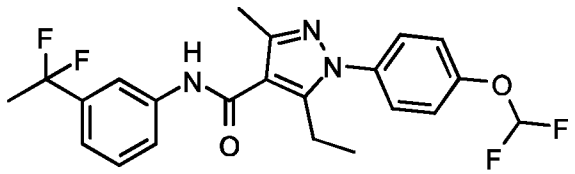
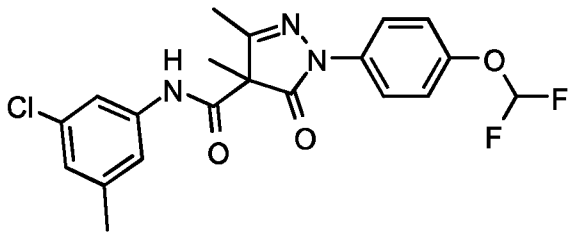
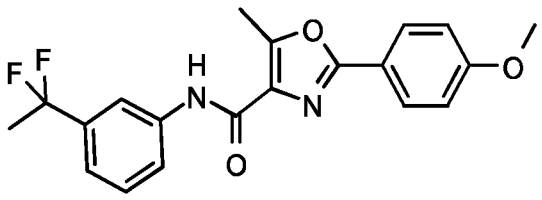
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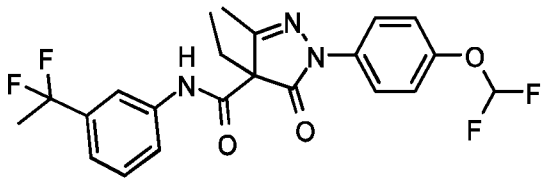
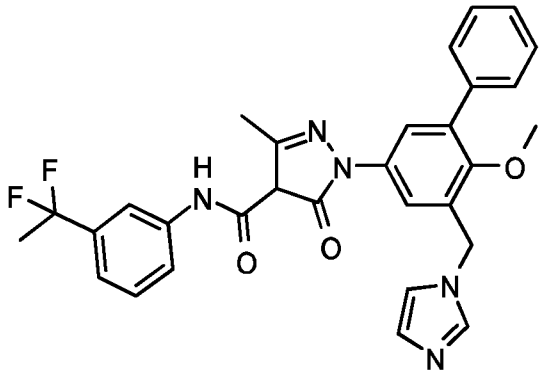
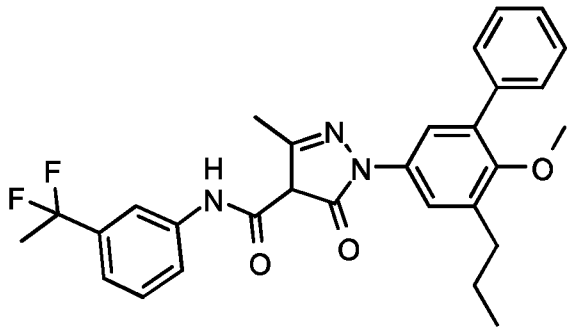
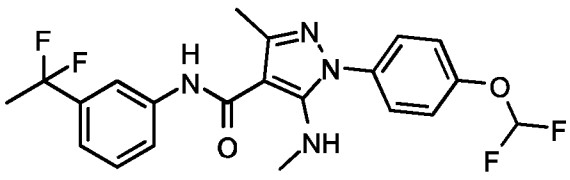
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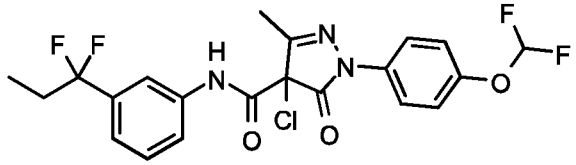
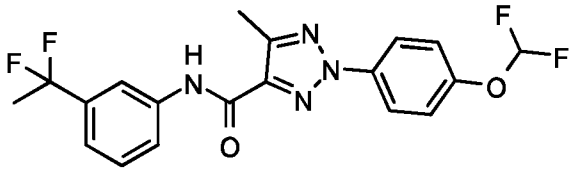
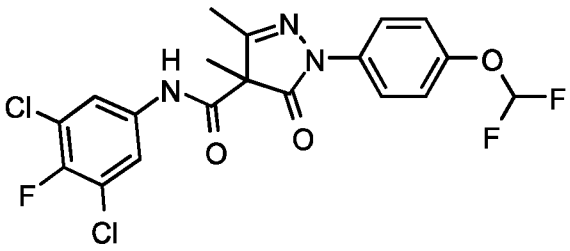
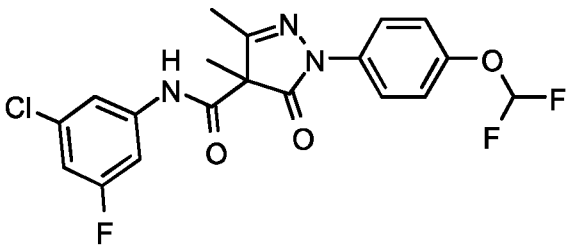
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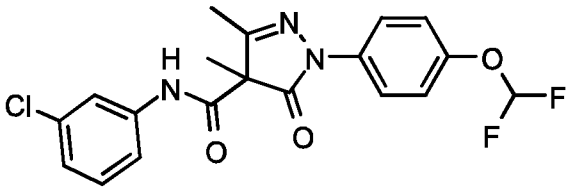
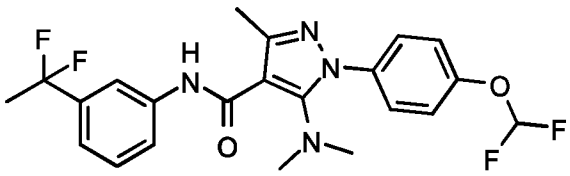
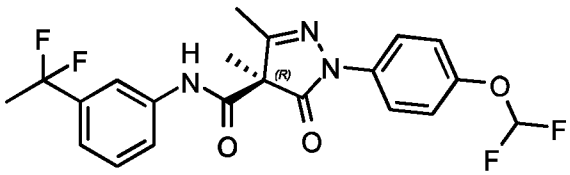
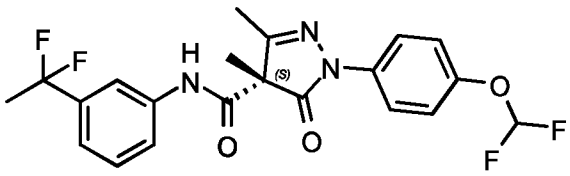
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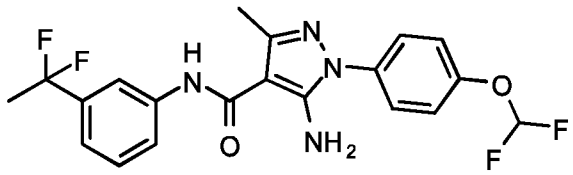
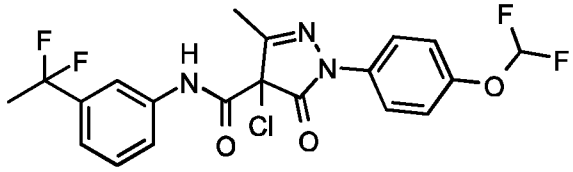
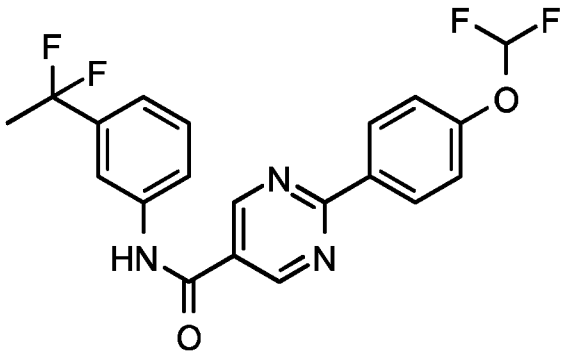
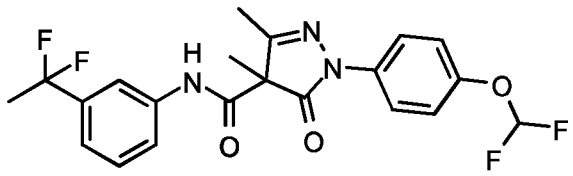
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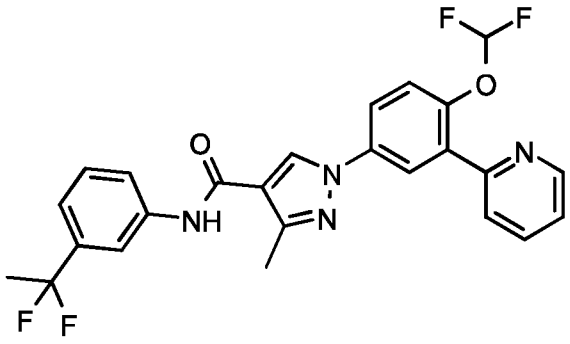
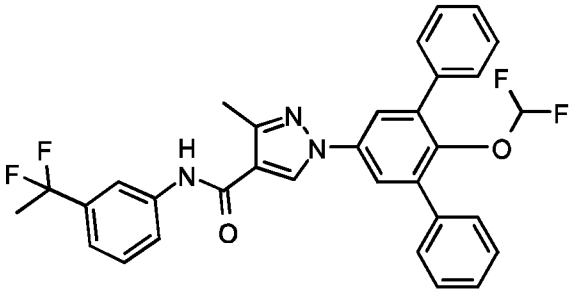
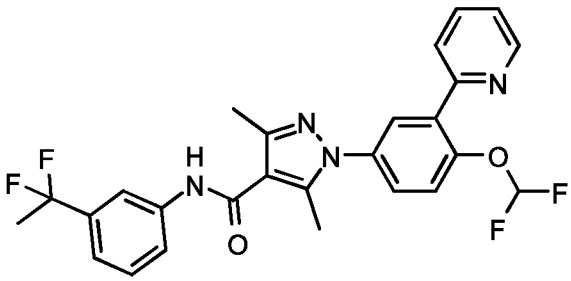
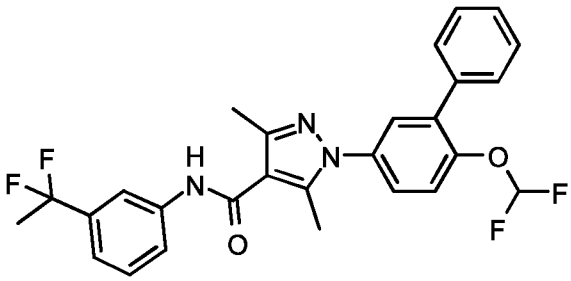
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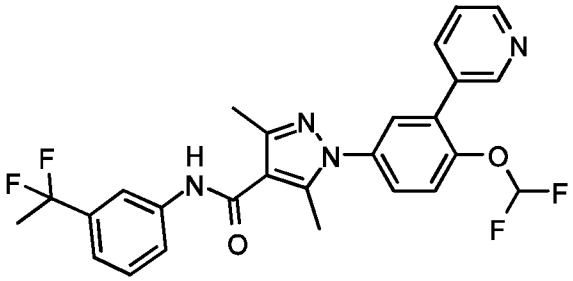
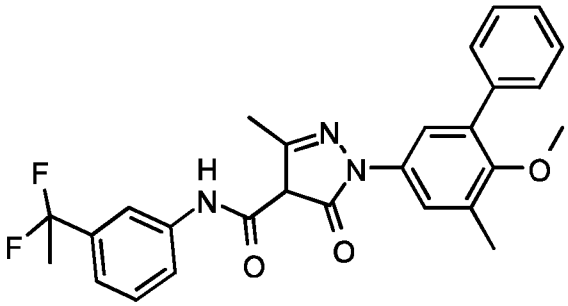
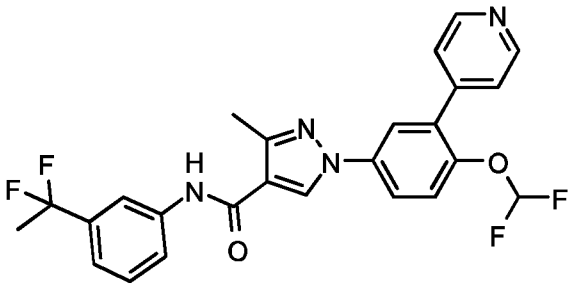
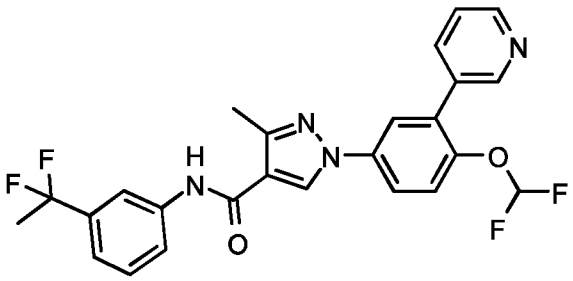
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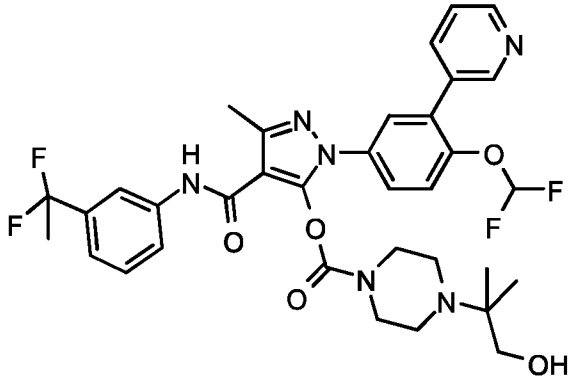
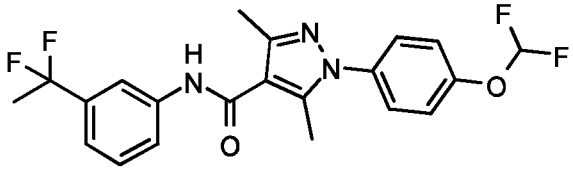
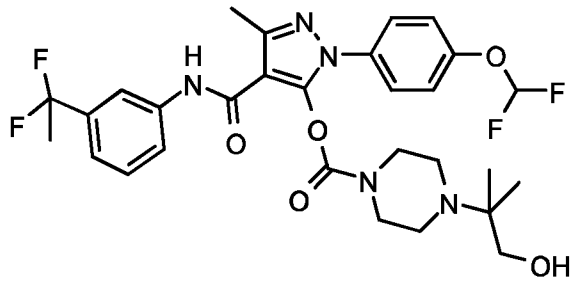
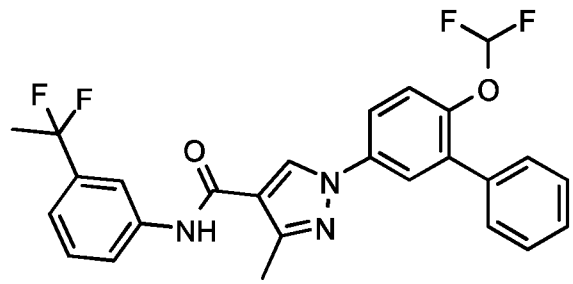
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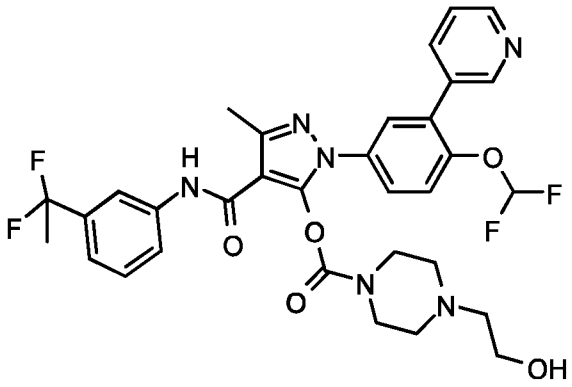
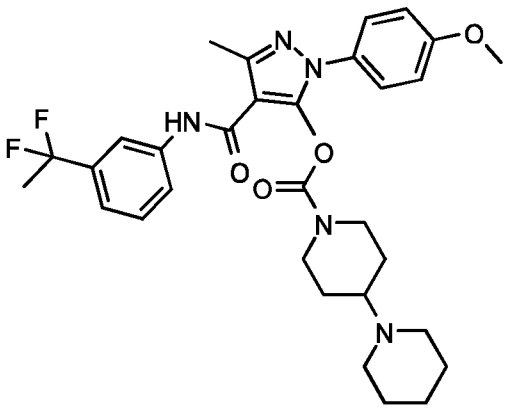
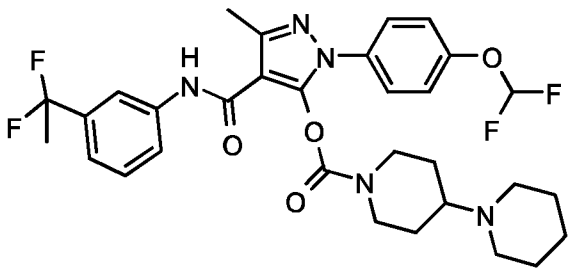
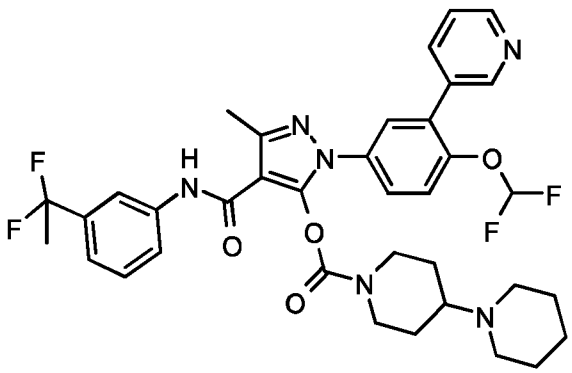
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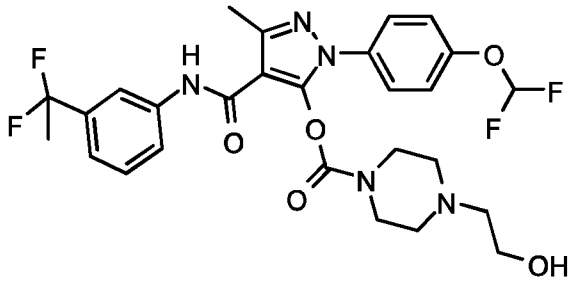
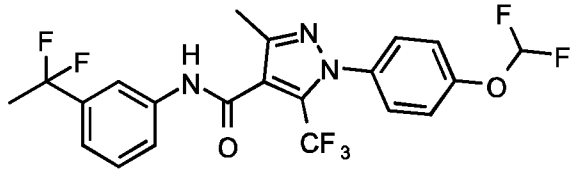
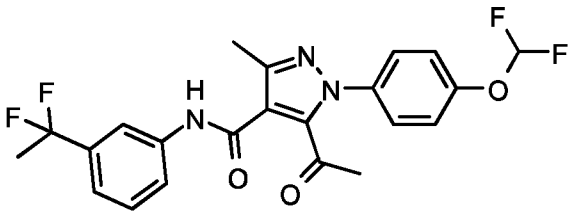
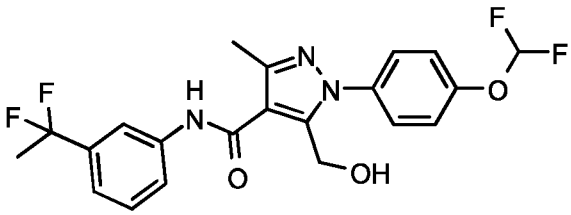
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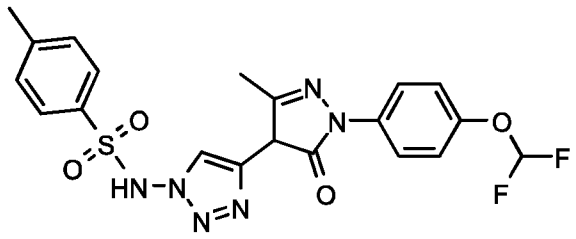
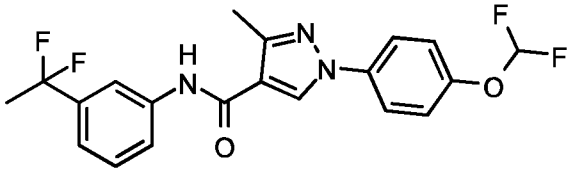
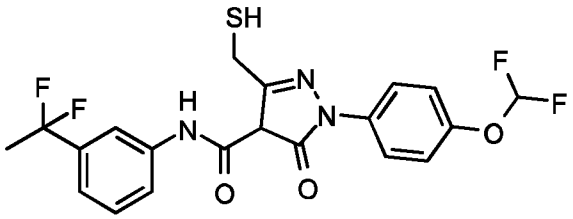
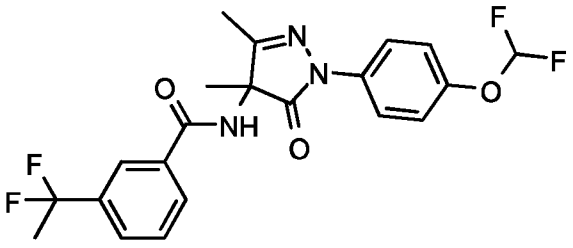
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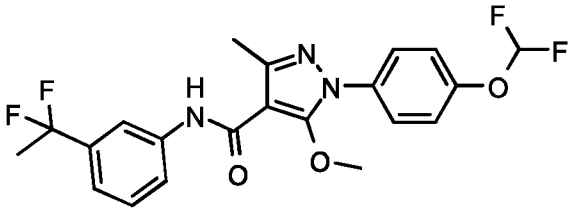
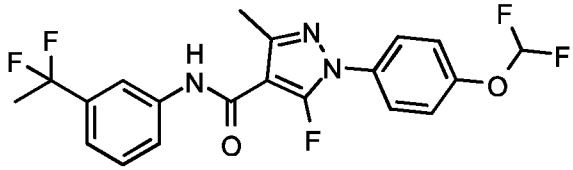
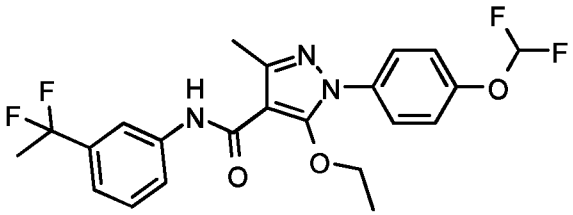
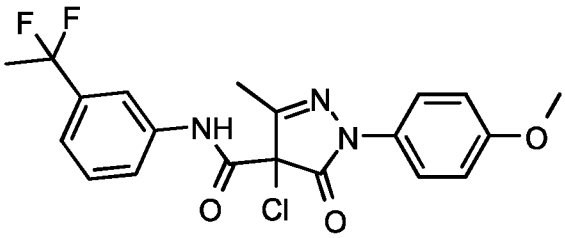
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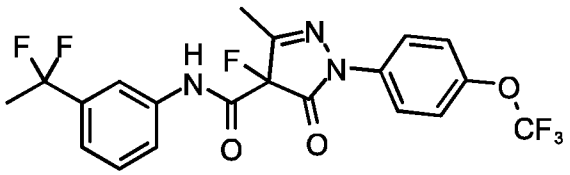
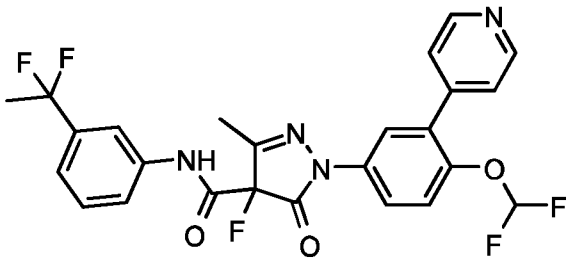
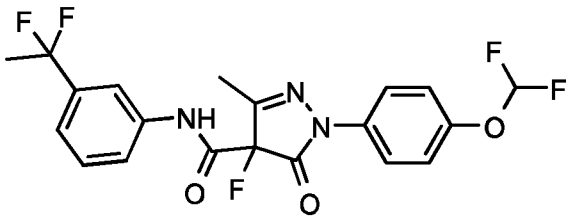
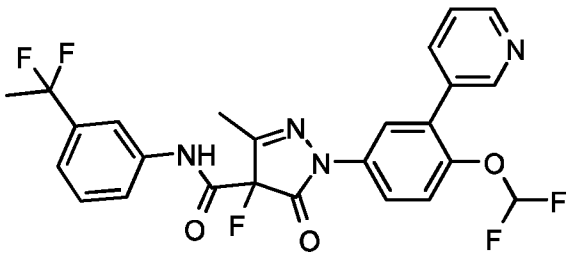
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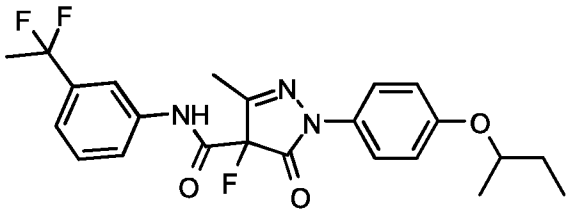
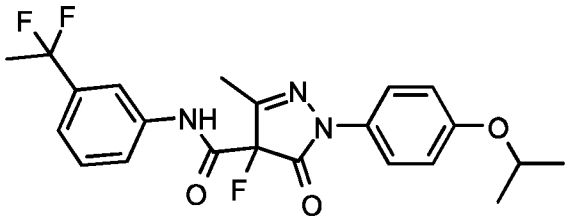
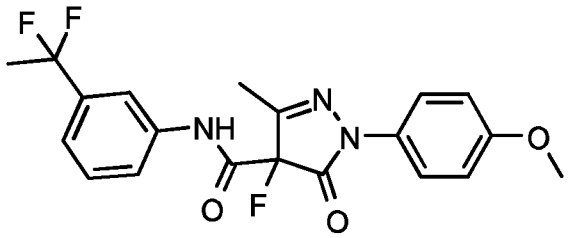
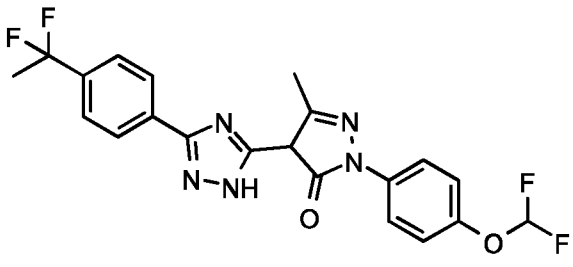
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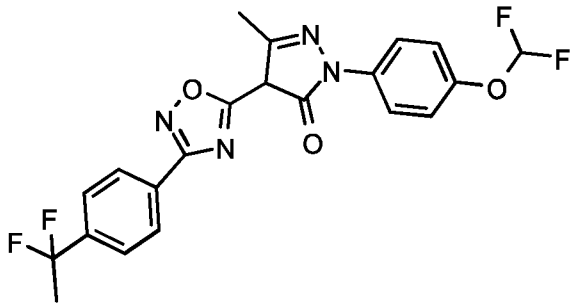
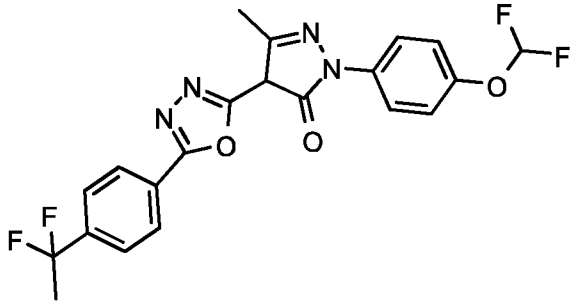
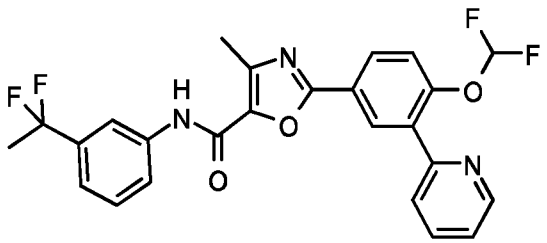
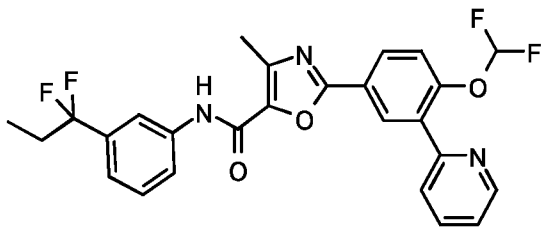
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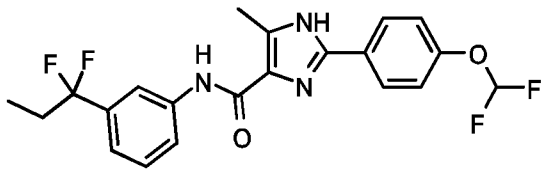
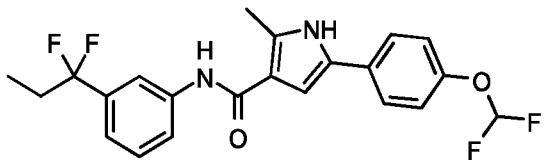
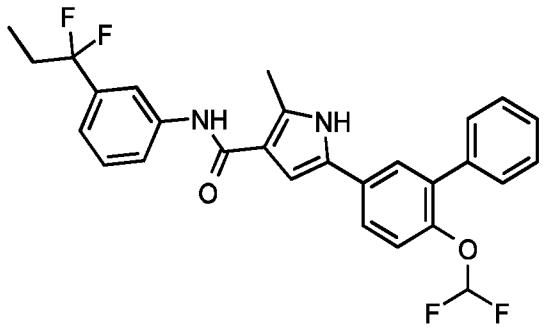
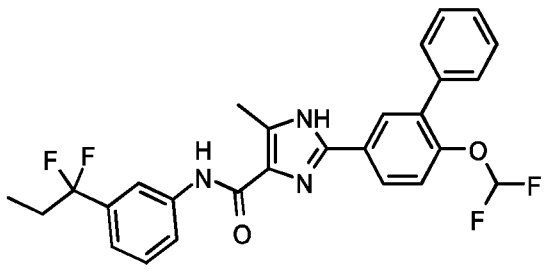
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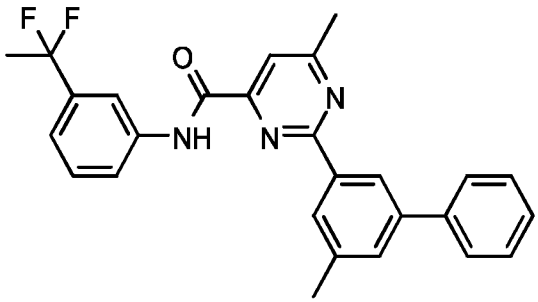
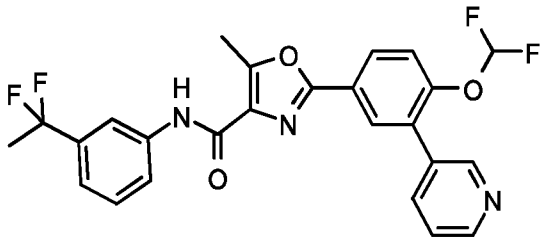
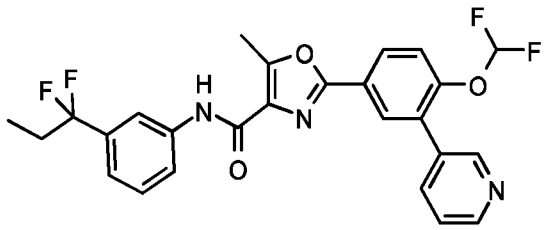
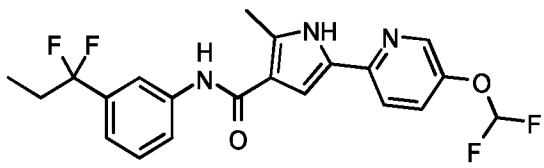
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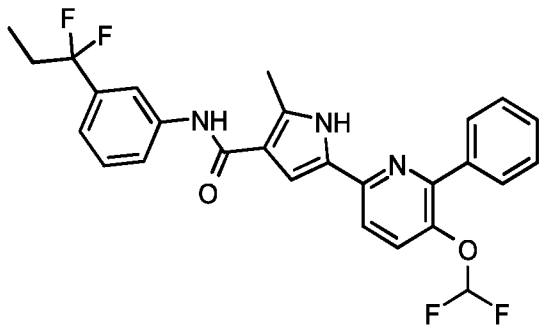
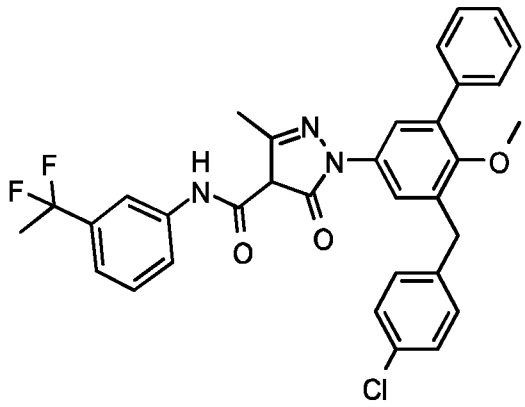
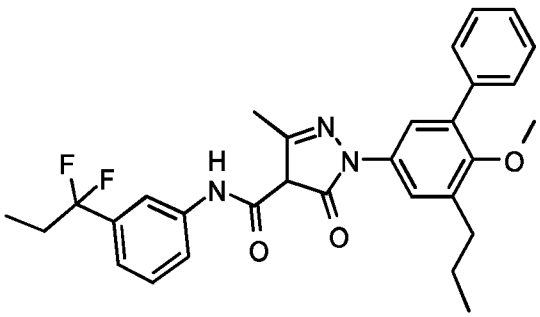
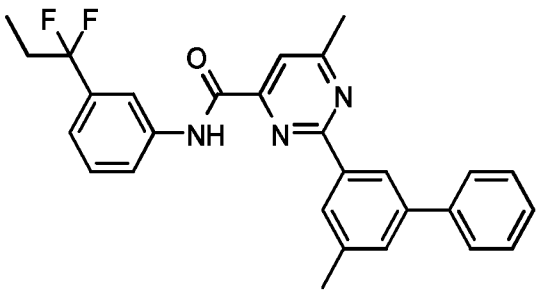
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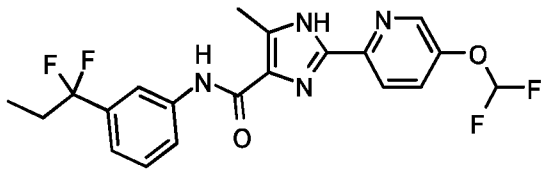
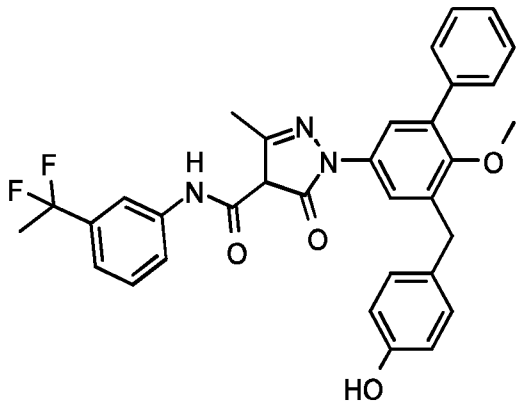
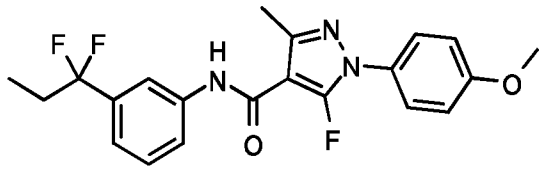
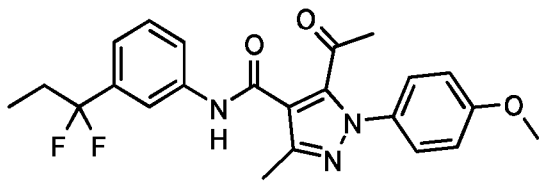
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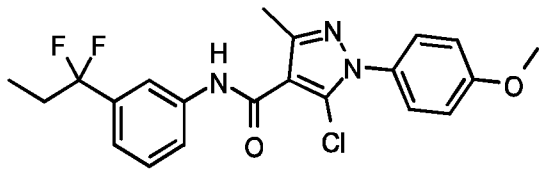
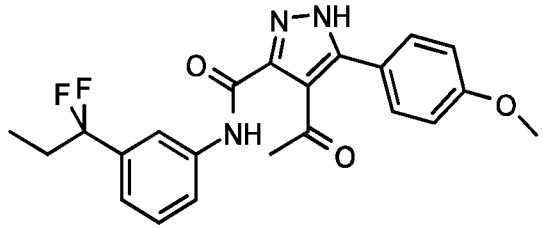
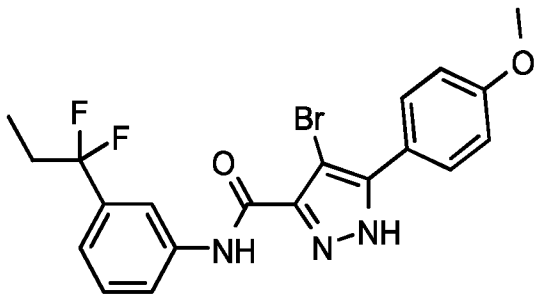
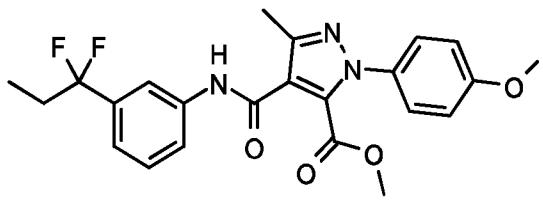
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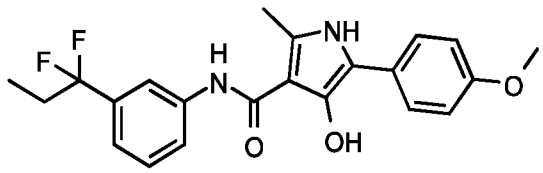
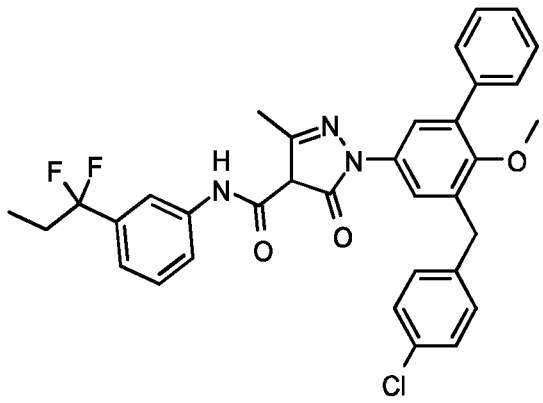
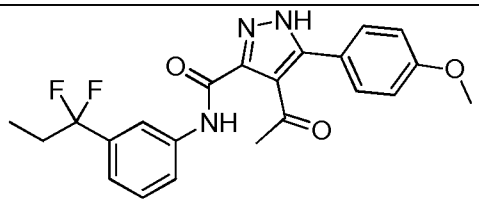
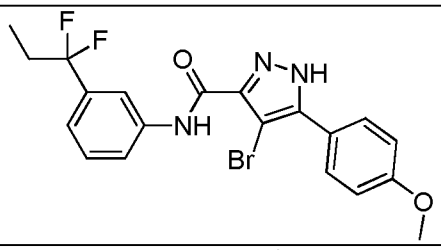
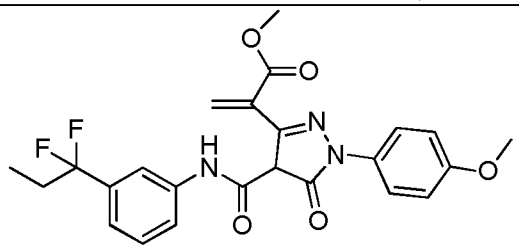
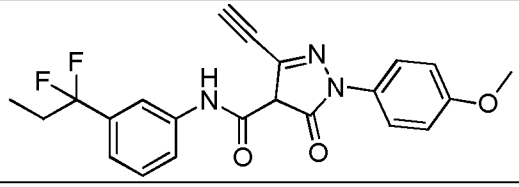
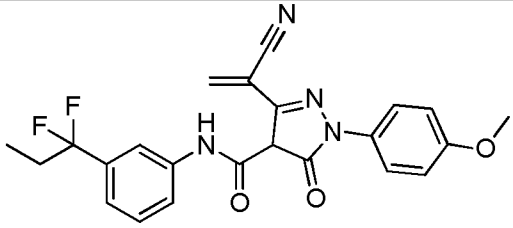
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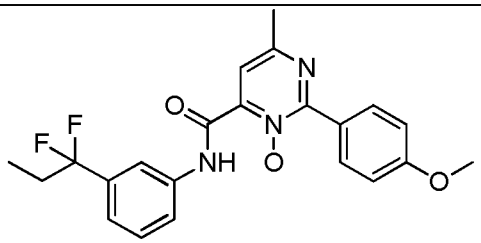
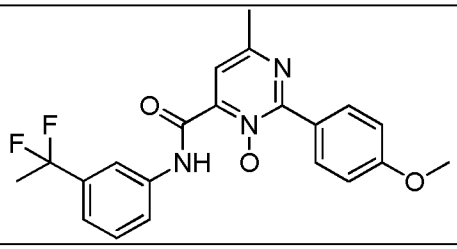
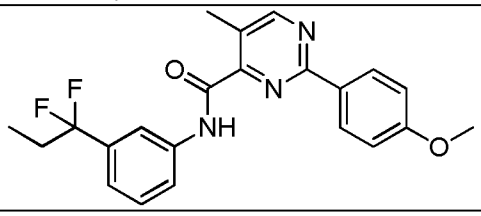
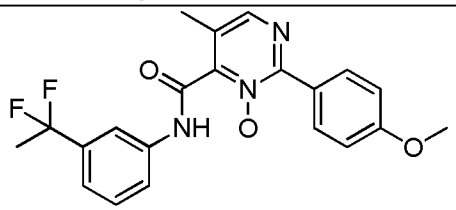
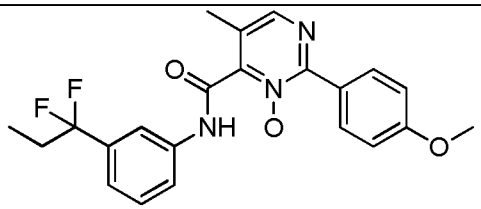
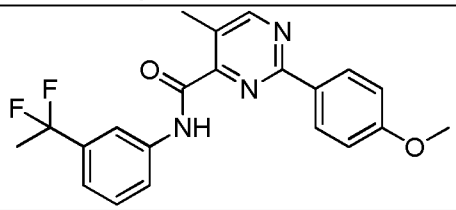
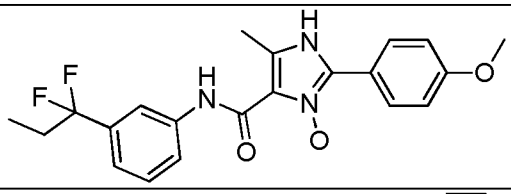
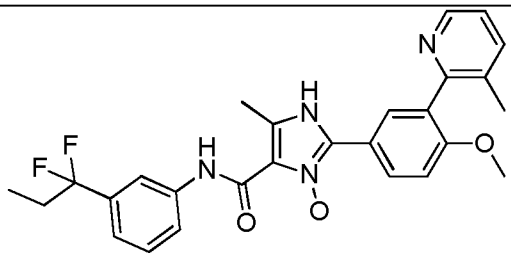
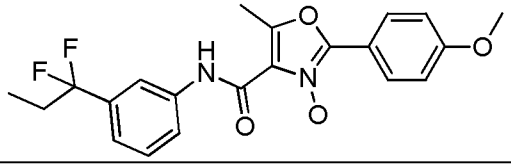
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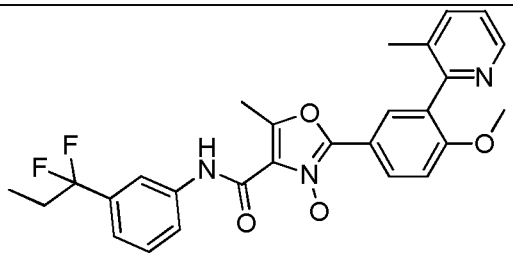
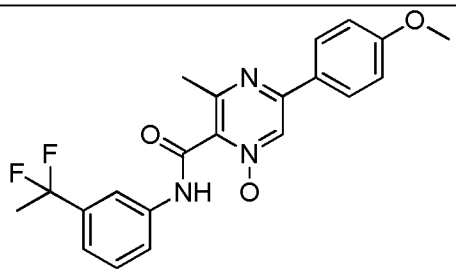
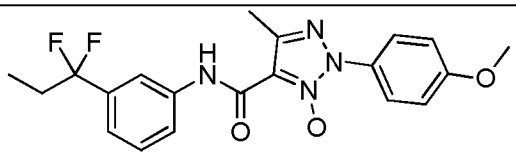
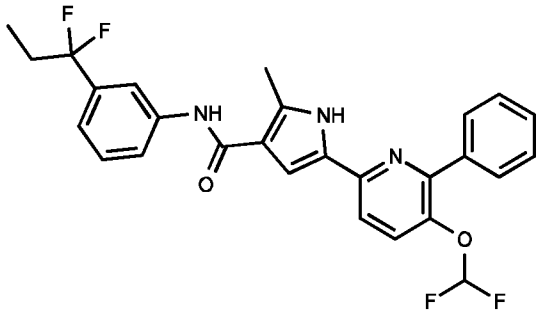
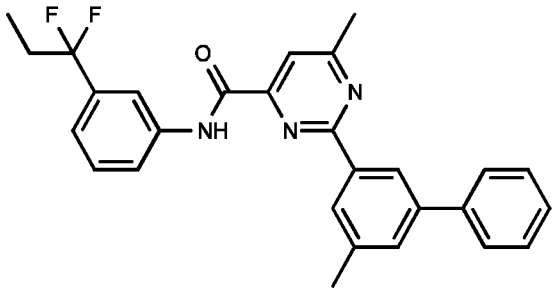
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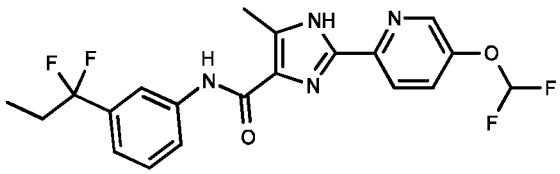
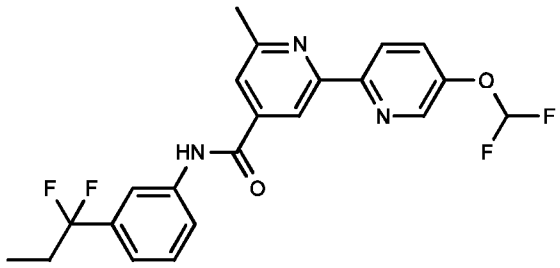
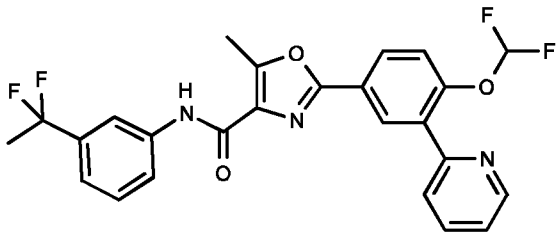
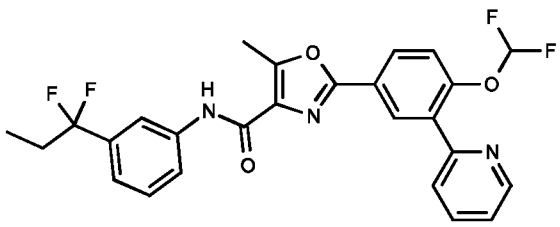
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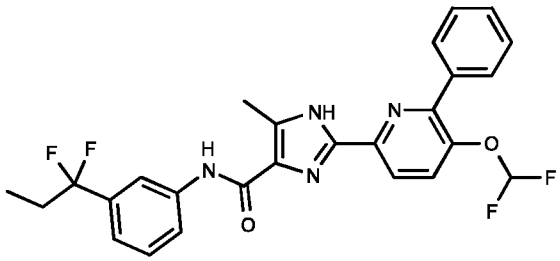
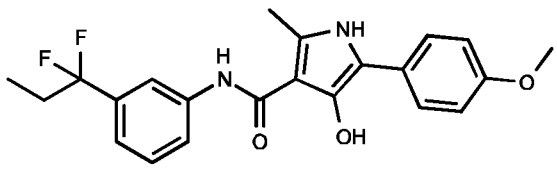
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[00104] It is well understood that in structures presented in this invention wherein the carbon atom has less than 4 bonds, H atoms are present to complete the valence of the carbon. It is well understood that in structures presented in this invention wherein the nitrogen atom has less than 3 bonds, H atoms are present to complete the valence of the nitrogen.

[00105] 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, optical isomer, 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.

[00106] In various embodiments, the **A** ring of formula **I, I(a), II** and **III** is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, 1-methylimidazole, isoquinoline, pyrazolyl, pyrrolyl, furanyl, thiophene-yl, isoquinolinyl, indolyl, 1H-indole, isoindolyl, naphthyl, anthracenyl, benzimidazolyl, indazolyl, 2H-indazole, triazolyl, 4,5,6,7-tetrahydro-2H-indazole, 3H-indol-3-one, purinyl, benzoxazolyl, 1,3-benzoxazolyl, benzisoxazolyl, benzothiazolyl, 1,3-benzothiazole, 4,5,6,7-tetrahydro-1,3-benzothiazole, quinazolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinolinyl, isoquinolinyl, 2,3-dihydroindenyl, indenyl, tetrahydronaphthyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepine , benzo[d][1,3]dioxole, acridinyl, benzofuranyl, 1-benzofuran, isobenzofuranyl, benzofuran-2(3H)-one, benzothiophenyl, benzoxadiazole, benzo[c][1,2,5]oxadiazolyl, benzo[*c*]thiophenyl, benzodioxolyl, benzo[d][1,3]dioxole, thiadiazolyl, [1,3]oxazolo[4,5-b]pyridine, oxadiaziolyl, imidazo[2,1-b][1,3]thiazole, 4H,5H,6H-cyclopenta[d][1,3]thiazole, 5H,6H,7H,8H-imidazo[1,2-a]pyridine, 7-oxo-6H,7H-[1,3]thiazolo[4,5-

d]pyrimidine, [1,3]thiazolo[5,4-b]pyridine, 2H,3H-imidazo[2,1-b][1,3]thiazole, thieno[3,2-d]pyrimidin-4(3H)-one, 4-oxo-4H-thieno[3,2-d][1,3]thiazin, 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, each definition is a separate embodiment according to this invention; or **A** is C_3-C_8 cycloalkyl (e.g. cyclohexyl) or C_3-C_8 heterocyclic ring including but not limited to: tetrahydropyran, piperidine, 1-methylpiperidine, tetrahydrothiophene 1,1-dioxide, 1-(piperidin-1-yl)ethanone or morpholine.

[00107] In various embodiments, the **B** ring of formula **I, I(a), II** and/or **III** is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, 1-methylimidazole, isoquinoline, pyrazolyl, pyrrolyl, furanyl, thiophene-yl, isoquinolinyl, indolyl, 1H-indole, isoindolyl, naphthyl, anthracenyl, benzimidazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, tetrahydronaphthyl 3,4-dihydro-2H-benzo[b][1,4]dioxepine, benzofuran-2(3H)-one, benzo[d][1,3]dioxole, indazolyl, 2H-indazole, triazolyl, 4,5,6,7-tetrahydro-2H-indazole, 3H-indol-3-one, purinyl, benzoxazolyl, 1,3-benzoxazolyl, benzisoxazolyl, benzothiazolyl, 1,3-benzothiazole, 4,5,6,7-tetrahydro-1,3-benzothiazole, quinazolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinolinyl, isoquinolinyl, acridinyl, benzofuranyl, 1-benzofuran, isobenzofuranyl, benzothiophenyl, benzoxadiazole, benzo[c][1,2,5]oxadiazolyl, benzo[*c*]thiophenyl, benzodioxolyl, thiadiazolyl, [1,3]oxazolo[4,5-b]pyridine, oxadiaziolyl, imidazo[2,1-b][1,3]thiazole, 4H,5H,6H-cyclopenta[d][1,3]thiazole, 5H,6H,7H,8H-imidazo[1,2-a]pyridine, 7-oxo-6H,7H-[1,3]thiazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-b]pyridine, 2H,3H-imidazo[2,1-b][1,3]thiazole, thieno[3,2-d]pyrimidin-4(3H)-one, 4-oxo-4H-thieno[3,2-d][1,3]thiazin, imidazo[1,2-a]pyridine, 1H-imidazo[4,5-b]pyridine, 3H-imidazo[4,5-b]pyridine, 3H-imidazo[4,5-c]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, pyrido[2,3-b]pyrazin or pyrido[2,3-b]pyrazin-3(4H)-one, 4H-thieno[3,2-b]pyrrole, quinoxalin-2(1H)-one, 1,2,3,4-tetrahydroquinoxaline, 1-(pyridin-1(2H)-yl)ethanone,1H-pyrrolo[2,3-b]pyridine, 1H-pyrrolo[3,2-b]pyridine, 7H-pyrrolo[2,3-d]pyrimidine, oxazolo[5,4-b]pyridine, thiazolo[5,4-b]pyridine, thieno[3,2-c]pyridine, C_3-C_8 cycloalkyl, or C_3-C_8 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.

[00108] In various embodiments, compound of formula **I, I(a), II** and/or **III** is substituted by R_1, R_2 and R_{20}. Single substituents can be present at the *ortho*, *meta*, or *para* positions.

[00109] In various embodiments, $\mathbf{R_1}$, $\mathbf{R_2}$ and $\mathbf{R_{20}}$ of formula **I-II(b)** are each independently H.

[00110] In various embodiments, $\mathbf{R_1}$, $\mathbf{R_2}$ and $\mathbf{R_{20}}$ of formula **I-III(a)** are each independently F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl), CH_2-cyclohexyl , R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3),

$NHCO\text{-}N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH(CH_3)_2$, $C(O)O\text{-}CH_2CH_3$), $R_8\text{-}C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-$CH_2\text{-}C_6H_4\text{-}Cl$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH{=}C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, $O\text{-}CH_2$-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), or $CH(CF_3)(NH\text{-}R_{10})$; each is a separate embodiment according to this invention. In other embodiments substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole), C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof; each is a separate embodiment according to this invention.

[00111] In some embodiments, $\mathbf{R_1}$ and $\mathbf{R_2}$ are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring. In some embodiments, R_1 and R_2 are joined together to form a 5 or 6 membered heterocyclic ring. In some embodiments, R_1 and R_2 are joined together to form a pyrrol ring. In some embodiments, R_1 and R_2 are joined together to form a [1,3]dioxole ring. In some embodiments, R_1 and R_2 are joined together to form a furan-2(3H)-one 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 joined together to form a pyridine ring. In some embodiments, R_1 and R_2 are joined together to form a morpholine ring. In some embodiments, R_1 and R_2 are joined together to form a piperazine ring. In some embodiments, R_1 and R_2 are joined together to form an imidazole ring. In some embodiments, R_1 and R_2 are joined together to form a pyrrole ring. In some embodiments, R_1 and R_2 are joined together to form a cyclohexene ring. In some embodiments, R_1 and R_2 are joined together to form a pyrazine ring.

[00112] In various embodiments, compound of formula I-III(a) is substituted by R_3 and R_4. Single substituents can be present at the *ortho*, *meta*, or *para* positions. In various embodiments, compound of formula I, I(a), II, and III is substituted by R_{40}. Single substituents can be present at the *ortho*, *meta*, or *para* positions.

[00113] In various embodiments, **R_3** and **R_4** of formula **I-III(a)** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH_3)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $CH(CF_3)(NH$-$R_{10})$; each represents a separate embodiment of this invention. In some embodiments, substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof; each represents a separate embodiment of this invention.

[00114] In some embodiments, **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. In some embodiments, **R_3** and **R_4** are joint together to form a 5 or 6 membered carbocyclic ring. In some embodiments, R_3 and R_4 are joined together to form a 5 or 6 membered heterocyclic ring. In some embodiments, R_3 and R_4 are joined together to form a dioxole ring. [1,3]dioxole ring. In some embodiments, R_3 and R_4 are joined together to form a dihydrofuran-2(3H)-one ring. In some embodiments, R_3 and R_4 are joined together to form a furan-2(3H)-one ring. In some embodiments, R_3 and R_4 are joined together to form a benzene ring. In some embodiments, R_3 and R_4 are joint together to form an imidazole ring. In some embodiments, R_3 and R_4 are joined together to form a pyridine ring. In some embodiments, R_3 and R_4 are joined together to form a pyrrole ring. In some embodiments, R_3 and R_4 are joined together to form a cyclohexene ring. In some embodiments, R_3 and R_4 are joined together to form a cyclopentene ring. In some embodiments, R_4 and R_3 are joint together to form a dioxepine ring.

[00115] In various embodiments, **R_{40}** of formula **I, I(a), II** and **III** is H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R,

$SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $CH(CF_3)(NH$-$R_{10})$; each represents a separate embodiment of this invention. In some embodiments, substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof; each represents a separate embodiment of this invention.

[00116] In various embodiments, $\mathbf{R_5}$ of compound of formula I, I(a) and III is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, iso-propyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., C(CH)), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine); each represents a separate embodiment of this invention. In other embodiments, substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof; each represents a separate embodiment of this invention.

[00117] In some embodiments, $\mathbf{R_{50}}$ of formula **I, I(a), I(b), III** and **III(a)** is H. In other embodiments, R_{50} is F. In other embodiments, R_{50} is Cl. In other embodiments, R_{50} is Br. In other embodiments, R_{50} is I. In other embodiments, R_{50} is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_{50} is C_1-C_5 linear or branched, alkyl, substituted with phenyl. In other embodiments, R_{50} is methyl. In other embodiments, R_{50} is CH_2SH. In other embodiments, R_{50} is ethyl. In other embodiments, R_{50} is propyl. In other embodiments, R_{50} is iso-propyl. In other embodiments, R_{50} is benzyl. In other embodiments, R_{50}'s substitutions include phenyl.

[00118] In some embodiments, $\mathbf{R_{50}}$ of formula **I** and **III** is connected to the N atom in position indicated as **1** in the structure (i.e., N_1). In other embodiments, $\mathbf{R_{50}}$ is connected to the C atom in position indicated as **3** in the structure (i.e., C_3).

[00119] In some embodiments, if R_{50} of formula **I, I(a), I(b)** is H then neither one of R_1, R_2 or R_{20} is H, and n and m are not 0.

[00120] In various embodiments, **n** of compound of formula **I-II(b)** is 0. In some embodiments, n is 0 or 1. In some embodiments, n of compound of formula **I-III(a)** is between 1 and 3. In some embodiments, n of compound of formula **I-III(a)** is between 1 and 4. In some embodiments, n of compound of formula **I-II(b)** is between 0 and 2. In some embodiments, n of compound of formula **I-II(b)** is between 0 and 3. In some embodiments, n of compound of formula **I-II(b)** is between 0 and 4.

In some embodiments, n of compound of formula **I-III(a)** is 1. In some embodiments, n of compound of formula **I-III(a)** is 2. In some embodiments, n of compound of formula **I-III(a)** is 3. In some embodiments, n of compound of formula **I-III(a)** is 4.

[00121] In various embodiments, **m** of compound of formula **I-II(b)** is 0. In some embodiments, m is 0 or 1. In some embodiments, m of compound of formula **I-III(a)** is between 1 and 3. In some embodiments, m of compound of formula **I-III(a)** is between 1 and 4. In some embodiments, m of compound of formula **I-II(b)** is between 0 and 2. In some embodiments, m of compound of formula **I-II(b)** is between 0 and 3. In some embodiments, m of compound of formula **I-II(b)** is between 0 and 4. In some embodiments, m of compound of formula **I-III(a)** is 1. In some embodiments, m of compound of formula **I-III(a)** is 2. In some embodiments, m of compound of formula **I-III(a)** is 3. In some embodiments, m of compound of formula **I-III(a)** is 4.

[00122] In various embodiments, **l** of compound of formula **I-III(a)** 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.

[00123] In various embodiments, **k** of compound of formula **I-III(a)** 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.

[00124] 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.

[00125] In various embodiments, $\mathbf{R_6}$ of compound of formula **I-III(a)** is H. In some embodiments, R_6 is C_1-C_5 linear or branched alkyl. In some embodiments, R_6 is methyl. In some embodiments, R_6 is ethyl. In some embodiments, R_6 is C(O)R wherein R is C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkoxy, phenyl, aryl or heteroaryl. In some embodiments, R_6 is $S(O)_2R$ wherein R is C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkoxy, phenyl, aryl or heteroaryl.

[00126] In various embodiments, $\mathbf{R_8}$ of compound of formula **I-III(a)** is CH_2. In some embodiments, R_8 is CH_2CH_2. In some embodiments, R_8 is $CH_2CH_2CH_2$. In some embodiments, R_8 is $CH_2CH_2CH_2CH_2$.

[00127] In various embodiments, **p** of compound of formula **I-III(a)** 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.

[00128] In some embodiments, $\mathbf{R_9}$ of compound of formula **I-III(a)** is C≡C. In some embodiments, R_9 is C≡C-C≡C. In some embodiments, R_9 is CH=CH. In some embodiments, R_9 is CH=CH-CH=CH.

[00129] In some embodiments, **q** of compound of formula **I-III(a)** 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.

[00130] In various embodiments, $\mathbf{R_{10}}$ of compound of formula **I-III(a)** is H. In some embodiments, R_{10} is C_1-C_5 linear or branched alkyl. In some embodiments, R_{10} is methyl. In some embodiments, R_{10} is ethyl. In some embodiments, R_{10} is propyl. In some embodiments, R_{10} is isopropyl. In some embodiments, R_{10} is butyl. In some embodiments, R_{10} is isobutyl. In some embodiments, R_{10} is t-butyl. In some embodiments, R_{10} is cyclopropyl. In some embodiments, R_{10} is pentyl. In some embodiments, R_{10} is isopentyl. In some embodiments, R_{10} is neopentyl. In some embodiments, R_{10} is benzyl. In some embodiments, R_{10} is C(O)R. In other embodiments, R_{10} is $C(O)(OCH_3)$. In other embodiments, R_{10} is CN. In some embodiments, R_{10} is $S(O)_2R$.

[00131] In various embodiments, $\mathbf{R_{11}}$ of compound of formula **I-III(a)** is H. In some embodiments, R_{11} is C_1-C_5 linear or branched alkyl. In some embodiments, R_{11} is methyl. In some embodiments, R_{11} is ethyl. In some embodiments, R_{11} is propyl. In some embodiments, R_{11} is isopropyl. In some embodiments, R_{11} is butyl. In some embodiments, R_{11} is isobutyl. In some embodiments, R_{11} is t-butyl. In some embodiments, R_{11} is cyclopropyl. In some embodiments, R_{11} is pentyl. In some embodiments, R_{11} is isopentyl. In some embodiments, R_{11} is neopentyl. In some embodiments, R_{11} is benzyl. In some embodiments, R_{11} is C(O)R. In other embodiments, R_{11} is $C(O)(OCH_3)$. In other embodiments, R_{11} is CN. In some embodiments, R_{11} is $S(O)_2R$.

[00132] In some embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ of formula **I, I(a), I(b), II, II(a), II(b), III** and **III(a)** are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joint to form a piperazine ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joint to form a piperidine ring. In some embodiments, substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof; each represents a separate embodiment according to this invention.

[00133] In various embodiments, **R** of compound of formula **I-III(a)** is H. In other embodiments, R is C_1-C_5 linear or branched alkyl. In other embodiments, R is methyl. In other embodiments, R is ethyl. In other embodiments, R is C_1-C_5 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 substiuents are joint together to form a 5 or 6 membered heterocyclic ring.

[00134] In various embodiments, $\mathbf{Q_1}$ of compound of formula **I, I(a), II** and/or **III** is O. In other embodiments, Q_1 is S. In other embodiments, Q_1 is N-OH. In other embodiments, Q_1 is CH_2. In other embodiments, Q_1 is $C(R)_2$. In other embodiments, Q_1 is N-OMe.

[00135] In various embodiments, $\mathbf{Q_2}$ of compound of formula **I, I(a), II** and/or **III** is O. In other embodiments, Q_2 is S. In other embodiments, Q_2 is N-OH. In other embodiments, Q_2 is CH_2. In other embodiments, Q_2 is $C(R)_2$. In other embodiments, Q_2 is N-OMe.

[00136] In some embodiments, Q_3 of formula **II** and **II(a)** is N. In some embodiments, Q_3 is CH. In some embodiments, Q_3 is C(R). In some embodiments, Q_3 is NO (*N*-oxide).

[00137] In some embodiments, Q_6 of formula **II** and **II(a)** is N. In some embodiments, Q_6 is CH. In some embodiments, Q_6 is C(R) . In some embodiments, Q_6 is NO (*N*-oxide).

[00138] In some embodiments, Q_7 of formula **II** and **II(a)** is N. In some embodiments, Q_7 is CH. In some embodiments, Q_7 is C(R) . In some embodiments, Q_7 is NO (*N*-oxide).

[00139] In some embodiments, Q_8 of formula **II** and **II(a)** is N. In some embodiments, Q_8 is CH. In some embodiments, Q_8 is C(R) . In some embodiments, Q_8 is NO (*N*-oxide).

[00140] In some embodiments, Q_4 of formula **II** and **II(a)** is O. In some embodiments, Q_4 is NH. In some embodiments, Q_4 is N(R).

[00141] In some embodiments, Q_5 of formula **II** and **II(a)** is O. In some embodiments, Q_5 is NH. In some embodiments, Q_5 is N(R).

[00142] As used herein, "single or fused aromatic or heteroaromatic ring systems" can be any such ring, including but not limited to phenyl, naphthyl, pyridinyl, (2-, 3-, and 4-pyridinyl), quinolinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, 1-methylimidazole, pyrazolyl, pyrrolyl, furanyl, thiophene-yl, quinolinyl, isoquinolinyl, 2,3-dihydroindenyl, indenyl, tetrahydronaphthyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepine , benzodioxolyl, benzo[d][1,3]dioxole, tetrahydronaphthyl, indolyl, 1H-indole, isoindolyl, anthracenyl, benzimidazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, indazolyl, 2H-indazole, triazolyl, 4,5,6,7-tetrahydro-2H-indazole, 3H-indol-3-one, purinyl, benzoxazolyl, 1,3-benzoxazolyl, benzisoxazolyl, benzothiazolyl, 1,3-benzothiazole, 4,5,6,7-tetrahydro-1,3-benzothiazole, quinazolinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinoxaline, 1-(pyridin-1(2H)-yl)ethanone, cinnolinyl, phthalazinyl, quinolinyl, isoquinolinyl, acridinyl, benzofuranyl, 1-benzofuran, isobenzofuranyl, benzofuran-2(3H)-one, benzothiophenyl, benzoxadiazole, benzo[c][1,2,5]oxadiazolyl, benzo[*c*]thiophenyl, benzodioxolyl, thiadiazolyl, [1,3]oxazolo[4,5-b]pyridine, oxadiaziolyl, imidazo[2,1-b][1,3]thiazole, 4H,5H,6H-cyclopenta[d][1,3]thiazole, 5H,6H,7H,8H-imidazo[1,2-a]pyridine, 7-oxo-6H,7H-[1,3]thiazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-b]pyridine, 2H,3H-imidazo[2,1-b][1,3]thiazole, thieno[3,2-d]pyrimidin-4(3H)-one, 4-oxo-4H-thieno[3,2-d][1,3]thiazin, imidazo[1,2-a]pyridine, 1H-imidazo[4,5-b]pyridine, 1H-imidazo[4,5-c]pyridine, 3H-imidazo[4,5-c]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, 1H-pyrrolo[2,3-b]pyridine, pyrido[2,3-b]pyrazine, pyrido[2,3-b]pyrazin-3(4H)-one, 4H-thieno[3,2-b]pyrrole, quinoxalin-2(1H)-one, 1H-pyrrolo[3,2-b]pyridine, 7H-pyrrolo[2,3-d]pyrimidine, oxazolo[5,4-b]pyridine, thiazolo[5,4-b]pyridine, thieno[3,2-c]pyridine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, etc.

[00143] As used herein, the term "alkyl" can be any straight- or branched-chain alkyl group containing up to about 30 carbons unless otherwise specified. In various embodiments, an alkyl includes C_1-C_5 carbons. In some embodiments, an alkyl includes C_1-C_6 carbons. In some embodiments, an alkyl includes C_1-C_8 carbons. In some embodiments, an alkyl includes C_1-C_{10} carbons. In some embodiments, an alkyl is a C_1-C_{12} carbons. In some embodiments, an alkyl is a C_1-C_{20} carbons. In some embodiments,

branched alkyl is an alkyl substituted by alkyl side chains of 1 to 5 carbons. In various embodiments, the alkyl group may be unsubstituted. In some embodiments, the alkyl group may be substituted by a halogen, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO_2H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C_1-C_5 linear or branched haloalkoxy, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, -CH_2CN, NH_2, NH-alkyl, N(alkyl)$_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -$C(O)NH_2$ or any combination thereof.

[00144] The alkyl group can be a sole substituent, or it can be a component of a larger substituent, such as in an alkoxy, alkoxyalkyl, haloalkyl, arylalkyl, alkylamino, dialkylamino, alkylamido, alkylurea, etc. Preferred alkyl groups are methyl, ethyl, and propyl, and thus halomethyl, dihalomethyl, trihalomethyl, haloethyl, dihaloethyl, trihaloethyl, halopropyl, dihalopropyl, trihalopropyl, methoxy, ethoxy, propoxy, arylmethyl, arylethyl, arylpropyl, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, methylamido, acetamido, propylamido, halomethylamido, haloethylamido, halopropylamido, methyl-urea, ethyl-urea, propyl-urea, 2, 3, or 4-CH_2-C_6H_4-Cl, C(OH)(CH_3)(Ph), etc.

[00145] 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-Butenyl, *cis*-2-Butenyl, and Isobutylenyl), 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".

[00146] 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 Isobutylynyl), Pentyne (i.e., 1-Pentynyl, 2-Pentenyl), Hexyne (e.g., 1-Hexynyl, 2-Hexeynyl, 3-Hexynyl, etc.), which may all be substituted as defined herein above for the term "alkyl".

[00147] As used herein, the term "aryl" refers to any aromatic ring that is directly bonded to another group and can be either substituted or unsubstituted. The aryl group can be a sole substituent, or the aryl group can be a component of a larger substituent, such as in an arylalkyl, arylamino, arylamido, etc. Exemplary aryl groups include, without limitation, phenyl, tolyl, xylyl, furanyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, thiazolyl, oxazolyl, isooxazolyl, pyrazolyl, imidazolyl, thiophene-yl, pyrrolyl, indolyl, phenylmethyl, phenylethyl, phenylamino, phenylamido, 3-methyl-4H-

1,2,4-triazolyl, 5-methyl-1,2,4-oxadiazolyl, etc. Substitutions include but are not limited to: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 linear or branched alkoxy, C_1-C_5 linear or branched haloalkoxy, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2, $-CH_2CN$, NH_2, NH-alkyl, $N(alkyl)_2$, hydroxyl, $-OC(O)CF_3$, $-OCH_2Ph$, -NHCO-alkyl, COOH, -C(O)Ph, C(O)O-alkyl, C(O)H, $-C(O)NH_2$ or any combination thereof.

[00148] 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.

[00149] As used herein, the term "aminoalkyl" refers to an amine group substituted by an alkyl group as defined above. Aminoalkyl refers to monoalkylamine, dialkylamine or trialkylamine. Nonlimiting examples of aminoalkyl groups are $-N(Me)_2$, -NHMe, $-NH_3$.

[00150] A "haloalkyl" group refers, in some embodiments, to an alkyl group as defined above, which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I. The term "haloalkyl" include but is not limited to fluoroalkyl, i.e., to an alkyl group bearing at least one fluorine atom. Nonlimiting examples of haloalkyl groups are CF_3, CF_2CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$ and $CF(CH_3)$-$CH(CH_3)_2$.

[00151] 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 $CFCF_2$, CF=CH-CH_3, $CFCH_2$, $CHCF_2$, $CFCHCH_3$, $CHCHCF_3$, and CF=C-$(CH_3)_2$ (both *E* and *Z* isomers where applicable).

[00152] A "halophenyl" group refers, in some embodiments, to a phenyl substitutent which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I. In one embodiment, the halophenyl is 4-chlorophenyl.

[00153] An "alkoxyalkyl" group refers, in some embodiments, to an alkyl group as defined above, which is substituted by alkoxy group as defined above, e.g. by methoxy, ethoxy, propoxy, i-propoxy, t-butoxy etc. Nonlimiting examples of alkoxyalkyl groups are $-CH_2$-O-CH_3, $-CH_2$-O-$CH(CH_3)_2$, $-CH_2$-O-$C(CH_3)_3$, $-CH_2$-CH_2-O-CH_3, $-CH_2$-CH_2-O-$CH(CH_3)_2$, $-CH_2$-CH_2-O-$C(CH_3)_3$.

[00154] A "cycloalkyl" or "carbocyclic" group refers, in various embodiments, to a ring structure comprising carbon atoms as ring atoms, which may be either saturated or unsaturated, substituted or unsubstituted, single or fused. In some embodiments the cycloalkyl is a 3-10 membered ring. In some embodiments the cycloalkyl is a 3-12 membered ring. In some embodiments the cycloalkyl is a 6 membered ring. In some embodiments the cycloalkyl is a 5-7 membered ring. In some embodiments the cycloalkyl is a 3-8 membered ring. In some embodiments, the cycloalkyl group may be unsubstituted or substituted by a halogen, alkyl, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO_2H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C_1-C_5 linear or branched haloalkoxy, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, $-CH_2CN$, NH_2, NH-alkyl, $N(alkyl)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, $-C(O)NH_2$ or any combination thereof. In some

embodiments, the cycloalkyl ring may be fused to another saturated or unsaturated cycloalkyl or heterocyclic 3-8 membered ring. In some embodiments, the cycloalkyl ring is a saturated ring. In some embodiments, the cycloalkyl ring is an unsaturated ring. Non limiteing examples of a cycloalkyl group comprise cyclohexyl, cyclohexenyl, cyclopropyl, cyclopropenyl, cyclopentyl, cyclopentenyl, cyclobutyl, cyclobutenyl, cycloctyl, cycloctadienyl (COD), cycloctaene (COE) etc.

[00155] A "heterocycle" or "heterocyclic" group refers, in various embodiments, to a ring structure comprising in addition to carbon atoms, sulfur, oxygen, nitrogen or any combination thereof, as part of the ring. A "heteroaromatic ring" refers in various embodiments, to an aromatic ring structure comprising in addition to carbon atoms, sulfur, oxygen, nitrogen or any combination thereof, as part of the ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-10 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-12 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 6 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 5-7 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-8 membered ring. In some embodiments, the heterocycle group or heteroaromatic ring may be unsubstituted or substituted by a halogen, alkyl, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO_2H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C_1-C_5 linear or branched haloalkoxy, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, -CH_2CN, NH_2, NH-alkyl, N(alkyl)$_2$, -OC(O)CF_3, -OCH_2Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH_2 or any combination thereof. In some embodiments, the heterocycle ring or heteroaromatic ring may be fused to another saturated or unsaturated cycloalkyl or heterocyclic 3-8 membered ring. In some embodiments, the heterocyclic ring is a saturated ring. In some embodiments, the heterocyclic ring is an unsaturated ring. Non limiting examples of a heterocyclic ring or heteroaromatic ring systems comprise pyridine, piperidine, morpholine, piperazine, thiophene, pyrrole, benzodioxole, benzofuran-2(3H)-one, benzo[d][1,3]dioxole, indole, oxazole, isoxazole, imidazole and 1-methylimidazole, furane, triazole, pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), naphthalene, tetrahydrothiophene 1,1-dioxide, thiazole, benzimidazole, piperidine, 1-methylpiperidine, isoquinoline, 1,3-dihydroisobenzofuran, benzofuran, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, or indole.

[00156] In various embodiments, this invention provides a compound of this invention or its isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, 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, prodrug, isotopic variant (deuterated analog), PROTAC, polymorph, or crystal of the compound of this invention.

[00157] In various embodiments, the term "isomer" includes, but is not limited to, optical isomers and analogs, structural isomers and analogs, conformational isomers and analogs, and the like. In some embodiments, the isomer is an optical isomer.

[00158] In various embodiments, this invention encompasses the use of various optical isomers of the compounds of the invention. It will be appreciated by those skilled in the art that the compounds of the present invention may contain at least one chiral center. Accordingly, the compounds used in the methods of the present invention may exist in, and be isolated in, optically-active or racemic forms. Accordingly, the compounds according to this invention may exist as optically-active isomers (enantiomers or diastereomers, including but not limited to: the *(R)*, *(S)*, *(R)(R)*, *(R)(S)*, *(S)(S)*, *(S)(R)*, *(R)(R)(R)*, *(R)(R)(S)*, *(R)(S)(R)*, *(S)(R)(R)*, *(R)(S)(S)*, *(S)(R)(S)*, *(S)(S)(R)* or *(S)(S)(S)* isomers); as racemic mixtures, or as enantiomerically enriched mixtures. Some compounds may also exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereroisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of the various conditions described herein.

[00159] 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).

[00160] 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.

[00161] 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.

[00162] 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.

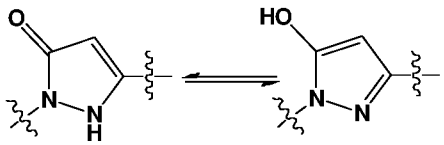
[00163] Compounds of the present invention may exist in the form of one or more of the possible tautomers and depending on the conditions it may be possible to separate some or all of the tautomers

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:



[00164] The invention includes "pharmaceutically acceptable salts" of the compounds of this invention, which may be produced, by reaction of a compound of this invention with an acid or base. Certain compounds, particularly those possessing acid or basic groups, can also be in the form of a salt, preferably a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to those salts that retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxylic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, *N*-acetylcysteine and the like. Other salts are known to those of skill in the art and can readily be adapted for use in accordance with the present invention.

[00165] 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.

[00166] In various embodiments, examples of organic salts of amines may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are acetates, arginines, aspartates, ascorbates, adipates, anthranilates, algenates, alkane carboxylates, substituted alkane carboxylates, alginates, benzenesulfonates, benzoates, bisulfates, butyrates, bicarbonates, bitartrates, citrates, camphorates, camphorsulfonates, cyclohexylsulfamates, cyclopentanepropionates, calcium edetates, camsylates, carbonates, clavulanates, cinnamates, dicarboxylates, digluconates, dodecylsulfonates, dihydrochlorides, decanoates, enanthuates, ethanesulfonates, edetates, edisylates, estolates, esylates, fumarates, formates, fluorides, galacturonates gluconates, glutamates, glycolates, glucorate, glucoheptanoates, glycerophosphates,

gluceptates, glycollylarsanilates, glutarates, glutamate, heptanoates, hexanoates, hydroxymaleates, hydroxycarboxlic acids, hexylresorcinates, hydroxybenzoates, hydroxynaphthoates, hydrofluorates, lactates, lactobionates, laurates, malates, maleates, methylenebis(beta-oxynaphthoate), malonates, mandelates, mesylates, methane sulfonates, methylbromides, methylnitrates, methylsulfonates, monopotassium maleates, mucates, monocarboxylates, naphthalenesulfonates, 2-naphthalenesulfonates, nicotinates, nitrates, napsylates, *N*-methylglucamines, oxalates, octanoates, oleates, pamoates, phenylacetates, picrates, phenylbenzoates, pivalates, propionates, phthalates, phenylacetate, pectinates, phenylpropionates, palmitates, pantothenates, polygalacturates, pyruvates, quinates, salicylates, succinates, stearates, sulfanilate, subacetates, tartrates, theophyllineacetates, *p*-toluenesulfonates (tosylates), trifluoroacetates, terephthalates, tannates, teoclates, trihaloacetates, triethiodide, tricarboxylates, undecanoates and valerates.

[00167] 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.

[00168] In some embodiments, examples of organic salts of carboxylic acids or hydroxyl may be selected from arginine, organic amines to include aliphatic organic amines, alicyclic organic amines, aromatic organic amines, benzathines, *t*-butylamines, benethamines (*N*-benzylphenethylamine), dicyclohexylamines, dimethylamines, diethanolamines, ethanolamines, ethylenediamines, hydrabamines, imidazoles, lysines, methylamines, meglamines, *N*-methyl-*D*-glucamines, *N,N'*-dibenzylethylenediamines, nicotinamides, organic amines, ornithines, pyridines, picolies, piperazines, procain, tris(hydroxymethyl)methylamines, triethylamines, triethanolamines, trimethylamines, tromethamines and ureas.

[00169] In various embodiments, the salts may be formed by conventional means, such as by reacting the free base or free acid form of the product with one or more equivalents of the appropriate acid or base in a solvent or medium in which the salt is insoluble or in a solvent such as water, which is removed in vacuo or by freeze drying or by exchanging the ions of a existing salt for another ion or suitable ion-exchange resin.

Pharmaceutical composition

[00170] 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.

[00171] 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.

[00172] 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.

[00173] 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.

[00174] 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.

[00175] For oral therapeutic administration, these active compounds can be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compound in these compositions can, of course, be varied and can conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions according to the present invention are prepared so that an oral dosage unit contains between about 1 mg and 800 mg of active compound.

[00176] 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.

[00177] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[00178] The compounds or pharmaceutical compositions of the present invention may also be administered in injectable dosages by solution or suspension of these materials in a physiologically acceptable diluent with a pharmaceutical adjuvant, carrier or excipient. Such adjuvants, carriers and/or excipients include, but are not limited to, sterile liquids, such as water and oils, with or without the addition of a surfactant and other pharmaceutically and physiologically acceptable components. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions.

[00179] These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols such as, propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00180] 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.

[00181] 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 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 embodiments, anti-cancer monoclonal antibodies are conjugated or linked to a compound of this invention as described hereinabove.

[00182] In various embodiments, the compounds of this invention are administered in combination with an agent treating Alzheimer's disease.

[00183] In various embodiments, the compounds of this invention are administered in combination with an anti-viral agent.

[00184] In various embodiments, the compounds of this invention are administered in combination with 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.

[00185] 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.

[00186] 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 compositions orally, topically, transdermally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes, such as, that of the nose, throat, and bronchial tubes.

Biological Activity

[00187] In various embodiments, the invention provides compounds and compositions, including any embodiment described herein, for use in any of the methods of this invention. In various embodiments, use of a compound of this invention or a composition comprising the same, will have utility in inhibiting, suppressing, enhancing or stimulating a desired response in a subject, as will be understood by one skilled in the art. In some embodiments, the compositions may further comprise additional active ingredients, whose activity is useful for the particular application for which the compound of this invention is being administered.

[00188] 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. 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.

[00189] 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

[00190] 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.

[00191] 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.

[00192] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00193] 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.

[00194] 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.

[00195] 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 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 some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00196] ACSS2-mediated acetate metabolism contributes to lipid synthesis and aggressive growth in glioblastoma and breast cancer.

[00197] 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 cells, Plos One,12 (12) 1-31, 2017).

[00198] 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 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00199] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00200] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00201] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00202] 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 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00203] 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**).

[00204] 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, 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 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 pancreatic cancer comprising administering a compound of this invention to a subject suffering from pancreatic cancer under conditions effective to treat, 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 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 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00207] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00208] 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.

[00209] 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 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.

[00210] 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 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 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 accomulation 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00212] 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 antoher 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.

[00213] 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 antoher 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 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.

[00214] 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 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.

[00215] 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, 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 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.

[00216] 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, 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 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.

[00217] 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, 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 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.

[00218] 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, 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 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.

[00219] 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 cance, Lewis lung carcinoma (LLC), colon carcinoma, renal cell carcinoma, and/or mammary carcinoma; each represents a separate embodiment accordin g 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.

[00220] 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 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, 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, metasatic squamous carcinoma, multiple myeloma, plasma cell neoplasms, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, osteosarcoma, ovarian cancer, ovarian 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 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.

[00221] 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 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).

[00222] In various embodiments "drug-resistant cancer" refers to cancer cells that acquire resistance to 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.

[00223] 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.

[00224] 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.

[00225] 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.

[00226] 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.

[00227] 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.

[00228] 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.

[00229] 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.

[00230] 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.

[00231] 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.

[00232] 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.

[00233] 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).

[00234] 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.

[00235] 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.

[00236] 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.

[00237] 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.

[00238] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00239] 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 $\leqslant$ 20-30 g/day. On the contrary, AFLD is defined as the presence of steatosis and alcohol consumption >20-30 g/day.

[00240] 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.

[00241] 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.

[00242] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00243] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00244] 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.

[00245] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00246] 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**).

[00247] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00248] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00249] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00250] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00251] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00252] 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 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.

[00253] Accordingly, in various embodiments, this invention is directed to a method of treating, 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, 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00254] 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, 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00255] 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00256] In various embodiments, this invention is directed to a method of treating, suppressing, reducing 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00257] In some embodiments, this invention is directed to a method of treating, suppressing, reducing 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 any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00258] In some embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject, comprising administering a compound of this invention, to a subject suffering from an autoimmune disease or disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the autoimmune disease or disorder in said subject. In some embodiments, the compound is 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.

[00259] 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.

[00260] 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 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.

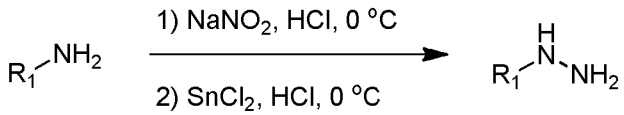
[00261] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention.

EXAMPLES

EXAMPLE 1

Synthetic Details for Compounds of the Invention

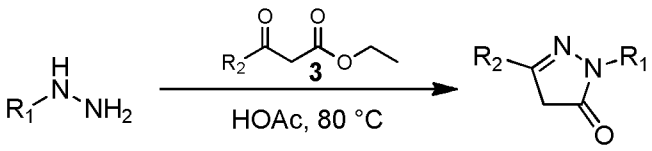
General Procedure I: Synthesis of hydrazine 2



1 **2**

[00262] To a round-bottom flask equipped with a magnetic stir bar were added amine **1** (1.0 *eq*), water and hydrochloride acid (12 M, 10 *eq*). Then a saturated solution of sodium nitrite (1.2 *eq*) in water was added into the previous solution at 0°C. The mixture was stirred at 0 ~ 5 °C for 0.5 h. Then a solution of tin(II) chloride dihydrate (2.2 *eq*) in hydrochloride acid (12 M, 15.0 *eq*) was added at 0~5 °C dropwise. The mixture was stirred at 5°C for 0.5 h. The resulting precipitate was collected by filtration to afford **2** as hydrochloride. Sometimes, the hydrazine was dissolved in water and needed to be extracted from the aqueous layer after neutralized the reaction solution.

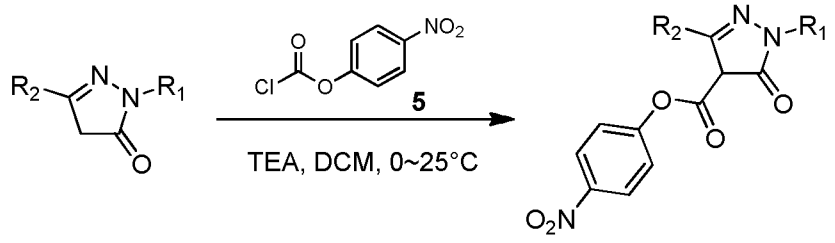
General Procedure II: The general synthesis of pyrazol 4



2 **4**

[00263] To a round-bottom flask equipped with a magnetic stir bar was added compound **3** (1.0 *eq*) followed by the addition of acetic acid. Then compound **2** (1.0 *eq*) was added into the mixture. The mixture was stirred at 80 °C under an atmosphere of nitrogen for **3~10** h. The solution was concentrated and the residue was triturated with ethyl acetate or ethanol to give compound **4**.

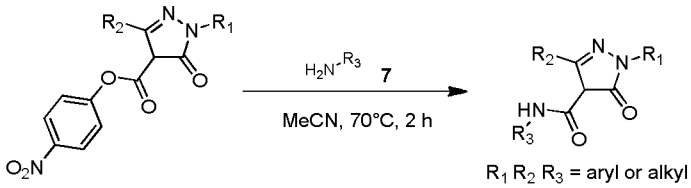
General Procedure III: The general synthesis of active ester 6



4 6

[00264] To a round-bottom flask equipped with a magnetic stir bar were added compound **4** (1.0 *eq*) and dichloromethane. Then triethylamine (2.0 *eq*) was added to the solution and the reaction mixture was stirred at 25°C for 0.5 h. Compound **5** (1.0 *eq*) was added and the solution was stirred at 25°C for 2.5 h under an atmosphere of nitrogen. The reaction solution was concentrated in vacuum to give compound **6** which was used directly for next step.

General Procedure IV: The general synthesis of target



6

[00265] To a round-bottom flask equipped with a magnetic stir bar was added compound **6** (1.80 *eq*) in acetonitrile. Then benzotriazol-1-ol (2.0 *eq*), amine **7** (1.0 *eq*) and diisopropylethylamine (3.0 *eq*) were added. The mixture was stirred at 70 °C for 2 h before concentrated. The residue was purified by prep-HPLC to afford target compounds.

General Procedure V: The general synthesis of target



4

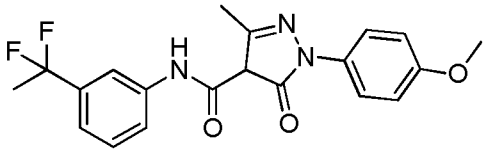
[00266] To a solution of compound **4** (1.0 *eq*) in dichloromethane (1 ~ 10 mL) was added triethylamine (2.0 *eq*) with stirring. Compound **8** (1.00 *eq*) was added and the mixture was stirred at 20 °C for 10 h. The reaction mixture was concentrated under vacuum, and the residue was purified by prep-HPLC to give compounds.

[00267] Compounds were synthesized according to the general schemes outlined above unless disclosed otherwise.

Synthetic details and analytical data for compound of the invention

[00268] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-methoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

Compound ID: 265i

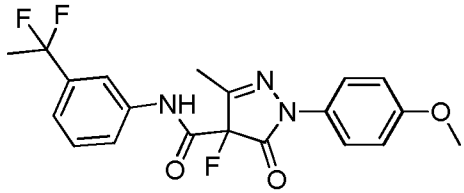


[00269] **Compound 265i** was obtained via general procedure IV from 1-(4-methoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-(1,1-difluoroethyl)aniline.

LCMS: (ESI) *m/z* 388.2 $[M+H]^+$.

^{1}H NMR: (400 MHz, MeOD-d_4) δ: 7.90 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.52 - 7.48 (m, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.10 - 7.06 (m, 2H), 3.85 (s, 3H), 2.60 (s, 3H), 1.92 (t, J = 18.4 Hz, 3H).

[00270] ***N*-(3-(1,1-difluoroethyl)phenyl)-4-fluoro-1-(4-methoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (Compound 209)**



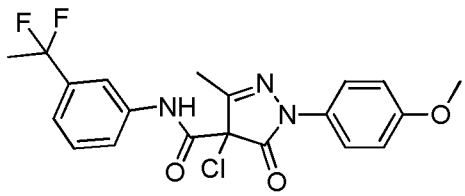
[00271] To a solution of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-methoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (**Compound 265i**) (200 mg, 508 umol, 1.0 *eq*) in toluene (4 mL) was added 1,4-diazabicyclo[2,2,2,]octane (86.9 mg, 774 umol, 1.5 *eq*) followed by *N*-fluorobenzenesulfonimide (244 mg, 774 umol, 1.5 *eq*). The solution was stirred at 25 °C for 12 hours. The solution was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225%FA)-ACN]; B%: 48%-78%, 10min) to give 90.0 mg (44% yield) of **Compound 209** as a yellow solid.

[00272] **LCMS**: (ESI) *m/z*: 406.0 $[M+H]^+$.

[00273] **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.03 (s, 1H), 7.98 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.66 - 7.64 (m, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.07 - 7.04 (m, 2H), 3.79 (s, 3H), 2.23 (d, J = 1.6 Hz, 3H), 1.95 (t, J = 18.8 Hz, 3H).

[00274] **Synthesis of 4-chloro-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-methoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

[00275] **Compound ID: 202**



[00276] A mixture of **265i** (100 mg, 254 umol, 1.0 *eq*), 1-chloropyrrolidine-2,5-dione (50.0 mg, 381 umol, 1.5 *eq*) and 1,4-diazabicyclo[2.2.2]octane (42.0 mg, 381 umol, 1.5 *eq*) in toluene (2 mL) was stirred at 25 °C for 12 h. The mixture was concentrated in vacuum to give a brown solid. The solid was purified

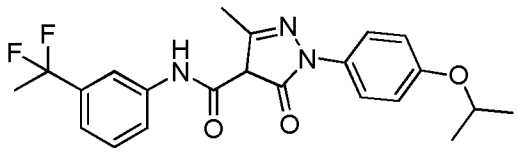
by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [0.225% formic acid];B%: 70%-88%, 6min) to give 20.0 mg (18% yield) of **Compound 202** as a yellow gum.

[00277] **LCMS**: (ESI) *m/z* 444.0 $[M+Na]^+$.

[00278] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.56 (s, 1H), 7.86 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.50 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 9.2 Hz, 2H), 3.79 (s, 3H), 2.26 (s, 3H), 1.96 (t, J = 18.8 Hz, 3H).

[00279] ***N*-[3-(1,1-difluoroethyl)phenyl]-1-(4-isopropoxyphenyl)-3-methyl-5-oxo-4*H*-pyrazole-4-carboxamide**

Compound ID: 447i



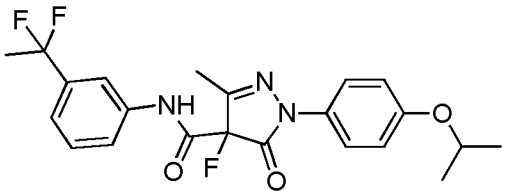
[00280] **Compound 447i** was obtained via general procedure IV from (4-nitrophenyl) 1-(4-isopropoxyphenyl)-3-methyl-5-oxo-4*H*-pyrazole-4-carboxylate and 3-(1,1-difluoroethyl)aniline.

[00281] **LCMS**: (ESI) *m/z* 416.0 $[M+H]^+$.

[00282] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 11.32 (s, 1H), 8.66 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.20 (s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.71 (s, 2H), 7.58 (t, J = 8.0 Hz, 1H), 7.54 - 7.45 (m, 2H), 7.34 (d, J = 7.6 Hz, 1H), 2.63 (s, 6H), 2.30 (s, 3H).

[00283] **Synthesis of N-(3-(1,1-difluoroethyl)phenyl)-4-fluoro-1-(4-isoprop oxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide**

[00284] **Compound ID: 208**



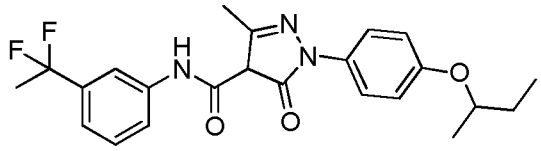
[00285] To a solution of *N*-[3-(1,1-difluoroethyl)phenyl]-1-(4-isopropoxyphenyl)-3-methyl-5-oxo-4*H*-pyrazole-4-carboxamide **(447i)** (50.0 mg, 120 umol, 1.0 *eq*) in toluene (3 mL) was added 1,4-diazabicyclo[2,2,2,]octane (27.0 mg, 241 umol, 2.0 *eq*), followed by *N*-fluorobenzenesulfonimide (56.9 mg, 181 umol, 1.5 *eq*). The solution was stirred at 25 °C for 12 h. The solution was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um;mobile phase: [water(0.225%FA)-ACN];B%: 70%-100%,9min) to give 25 mg (48% yield) of **Compound 208** as a yellow gum..

[00286] **LCMS**: (ESI) *m/z*: 434.0 $[M+H]^+$;

[00287] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 7.88 (s, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.67 (d, J = 2.0 Hz, 2H), 7.46 - 7.43 (m, 1H), 7.39 - 7.37 (m, 1H), 6.97 - 6.94 (m, 2H), 4.64 - 4.54 (m, 1H), 2.23 (s, 3H), 1.94 (t, J = 18.0 Hz, 3H), 1.35 (d, J = 6.0 Hz, 6H).

[00288] ***N*-[3-(1,1-difluoroethyl)phenyl]-3-methyl-5-oxo-1-(4-sec-butoxyphenyl)-4*H*-pyrazole-4-carboxamide**

Compound ID: 444i



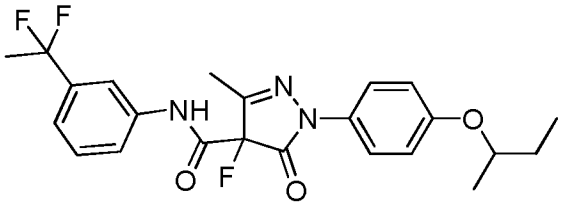
[00289] **Compound 444i** was obtained via general procedure IV from (4-nitrophenyl) 3-methyl-5-oxo-1-(4-sec-butoxyphenyl)-4*H*-pyrazole-4-carboxylate and 3-(1,1-difluoroethyl)aniline.

[00290] **LCMS**: (ESI) *m/z* 430.2 $[M+H]^+$.

[00291] **^{1}H NMR**: (400MHz, DMSO-d_6) δ: 7.90 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 73.6 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 4.45 - 4.34 (m, 1H), 2.55 (s, 3H), 1.92 (t, J = 18.4 Hz, 3H), 1.75 - 1.64 (m, 2H), 1.29 (d, J = 6.4 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H).

[00292] **Synthesis of N-[3-(1,1-difluoroethyl)phenyl]-4-fluoro-3-methyl-5- oxo-1-(4-sec-butoxyphenyl)pyrazole-4-carboxamide**

Compound ID: 207



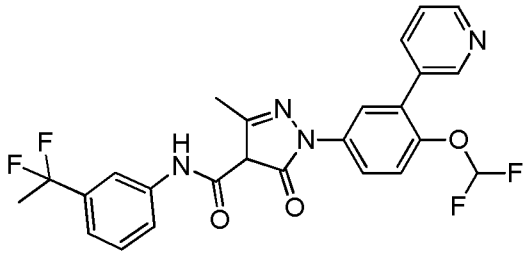
[00293] To a solution of *N*-[3-(1,1-difluoroethyl)phenyl]-3-methyl-5-oxo-1-(4-sec-butoxyphenyl)-4*H*-pyrazole-4-carboxamide **(444i)** (35.0 mg, 80.3 umol, 1.0 *eq*) in toluene (2 mL) was added 1,4-diazabicyclo[2,2,2,]octane (18.0 mg, 161 umol, 2.0 eq), followed by *N*-fluorobenzenesulfonimide (38.0 mg, 120 umol, 1.5 eq). The solution was stirred at 25 °C for 12 h. The solution was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um;mobile phase: [water(0.225%FA)-ACN];B%: 70%-100%,9min) to give 28 mg (78% yield) of **Compound 207** as a yellow gum.

[00294] **LCMS**: (ESI) *m/z*: 448.1 $[M+H]^+$;

[00295] **^{1}H NMR**: (400MHz, MeOD-d_4) δ: 7.88 (s, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.67 (d, J = 2.4 Hz, 2H), 7.47 - 7.44 (m, 1H), 7.39 - 7.37 (m, 1H), 6.98 - 6.95 (m, 2H), 4.41 - 4.32 (m, 1H), 2.23 (s, 3H), 1.91 (t, J = 18.0 Hz, 3H), 1.73 - 1.62 (m, 2H), 1.27 (d, J = 6.0 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H).

[00296] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

Compound ID: 455i



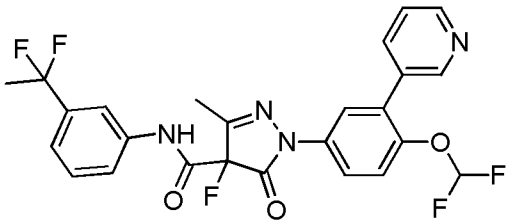
[00297] **Compound 455i** was obtained via general procedure IV from 4-nitrophenyl 1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-(1, 1-difluoroethyl)aniline.

[00298] **LCMS**: (ESI) *m/z* 501.1 $[M+H]^+$.

[00299] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.80 (s, 1H), 8.63 - 8.61 (m, 1H), 8.19 - 8.15 (m, 1H), 7.90 (d, J = 2.4 Hz, 2H), 7.82 (d, J = 2.4 Hz, 1H), 7.65 - 7.62 (m, 2H), 7.49 (d, J = 8.8 Hz, 1H), 7.41 - 7.35 (m, 1H), 7.25 - 7.20 (m, 1H), 6.87 (t, J = 73.2 Hz, 1H), 2.60 (s, 3H), 1.92 (t, J = 13.2 Hz, 3H).

[00300] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-4-fluoro-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

Compound ID: 206



[00301] To a solution of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide **(455i)** (30.0 mg, 58.5 umol, 1.0 *eq*) in toluene (2.0 mL) was added 1,4-diazabicyclo[2.2.2]octane (13.1 mg, 117 umol, 2.0 *eq*) followed by *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (27.7 mg, 87.7 umol, 1.5 *eq*). The solution was stirred at 25 °C for 12 h. The solution was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18150*25* 10um;mobile phase: [water(0.225%FA)-ACN];B%: 55%-85%,9min) to give 9.50 mg (31% yield) of **Compound 206** as a white solid.

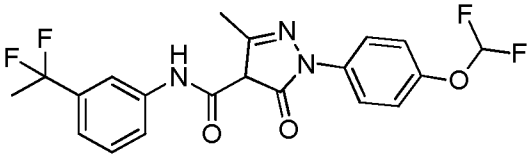
[00302] **LCMS**: (ESI) *m/z* 519.0 $[M+H]^+$.

[00303] **^{1}H NMR**: (400MHz, MeOD-d_4) δ: 8.85 (s, 1 H), 8.69 (s, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 8.06 - 8.01 (m, 2 H), 7.90 (s, 1 H), 7.80 -7.76 (m, 2 H), 7.49 - 7.40 (m, 3 H), 6.87 (t, J = 73.2 Hz, 1 H), 2.30 (s, 3 H), 1.93 (t, 18.4 Hz, 3 H).

[00304] **^{19}F NMR**: (400MHz, MeOD) δ: - 83.405, -88.945 , -173.954.

[00305] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

Compound ID: 298i



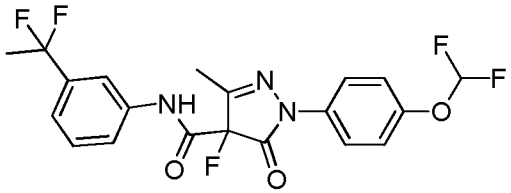
[00306] **Compound 298i** was obtained via general procedure IV from 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-(1,1-difluoroethyl)aniline.

[00307] **LCMS**: (ESI) *m/z*: 424.2 $[M+H]^+$.

[00308] **^{1}H NMR**: (400MHz, MeOD-d_4) δ: 7.90 (s, 1H), 7.69 - 7.66 (m, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.32 - 7.30 (m, 2H), 7.24 (d, J = 7.6 Hz, 1H), 6.89 (t, J = 72.0 Hz, 1H), 2.61 (d, J = 3.6 Hz, 3H), 1.92 (t, J = 18.0 Hz, 3H).

[00309] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-4-fluoro-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

Compound ID: 205



[00310] **Compound 205** was obtained via similar procedure of **Compound 209** from *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide **(298i)**.

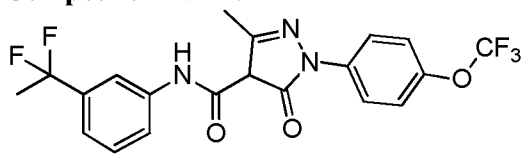
[00311] **LCMS**: (ESI) *m/z*: 464.1 $[M+Na]^+$.

[00312] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.86-7.89 (m, 3H), 7.76 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.25 - 7.23 (m, 2H), 6.84 (t, J = 74.0 Hz, 1H), 2.26 (d, J = 2.0 Hz, 3H), 1.92 (t, J = 18.4 Hz, 3H).

^{19}F NMR (400 MHz, MeOD-d_4) δ: -83.49, -88.98, -173.95.

[00313] ***N*-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-1-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

Compound ID: 226i



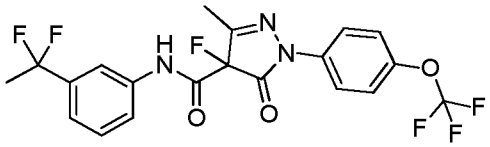
[00314] **Compound 226i** was obtained via general procedure IV from 3-methyl-5-oxo-1-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-(1,1-difluoroethyl)aniline.

LCMS: (ESI) *m/z* 442.1 $[M+H]^+$.

^{1}H NMR: (400MHz, DMSO-d_6) δ: 10.77 (s, 1H), 7.94 (s, 1H), 7.91 - 7.84 (m, 2H), 7.65 - 7.58 (m, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.24 - 7.18 (m, 1H), 2.54 (s, 3H), 1.96 (t, J = 18.8 Hz, 3H).

[00315] **N-(3-(1,1-difluoroethyl)phenyl)-4-fluoro-3-methyl-5-oxo-1-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-1H-pyrazole-4-carboxamide**

Compound ID: 203



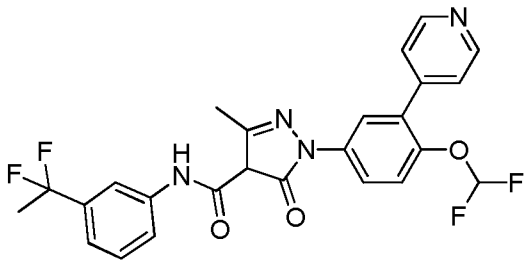
[00316] To a solution of *N*-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-1-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-1*H*-pyrazole-4-carboxamide (**226i**) (20.0 mg, 45.3 umol, 1.0 *eq*) in toluene (1 mL) was added *N*-fluorobis(benzenesulfon)imide (21.4 mg, 67.9 umol, 1.5 *eq*) and 1,4-diaza-bicyclo[2.2.2]octane (7.6 mg, 67.9 umol, 1.5 *eq*). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC(column: Phenomenex Synergi C18 150*25*10um;mobile phase: [water(0.225%FA)-ACN];B%: 55% - 85%,10min) to give 10 mg (48% yield) of **Compound 203** as a white solid.

[00317] **LCMS: (ESI)** *m/z*: 459.9 $[M+H]^+$.

[00318] **^{1}H NMR:** (400MHz, MeOD-*d4*) δ: 8.00 - 7.93 (m, 2H), 7.87 (s, 1H), 7.77 (br d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.38 (br d, J = 9.2 Hz, 3H), 2.27 (d, J = 1.6 Hz, 3H), 1.92 (t, J = 18.4 Hz, 3H).

[00319] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-4-yl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

Compound ID: 315i



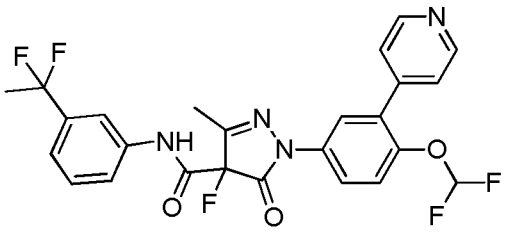
[00320] **Compoun 315i** was obtained via general procedure IV from 4-nitrophenyl 1-(4-(difluoromethoxy)-3-(pyridin-4-yl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-(1,1-difluoroethyl)aniline.

[00321] **LCMS**: (ESI) *m/z*: 501.1 $[M+H]^+$.

[00322] **^{1}H NMR**: (400MHz, MeOD-d_4) δ: 8.67 (d, J = 5.6 Hz, 2H), 8.01 (d, J = 2.4 Hz, 1H), 7.93 - 7.90(m, 2H), 7.78 (d, J = 5.6 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.85 (t, J = 73.2 Hz, 1H), 2.53 (s, 3H), 1.92 (t, J = 18.0 Hz, 3H).

[00323] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-4-yl)phenyl)-4-fluoro-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide**

Compound ID: 204



[00324] **Compound 204** was obtained via similar procedure of **Compoun 209** from *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-4-yl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (**315i**).

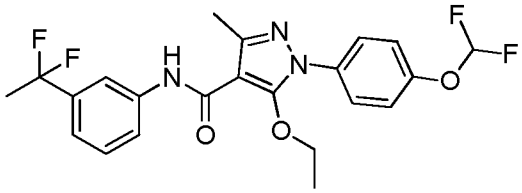
[00325] **LCMS**: (ESI) *m/z*: 519.1 $[M+H]^+$.

[00326] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.63 (s, 2H), 8.01 - 7.98 (m, 2H), 7.88 (s, 1H), 7.76 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 5.6 Hz, 2H), 7.49 - 7.43 (m, 2H), 7.39 - 7.37 (m, 1H), 6.82 (t, J = 73.2 Hz, 1H), 2.28 (d, J = 1.2 Hz, 3H), 1.92 (t, J = 18.4 Hz, 3H).

[00327] **^{19}F NMR** (400 MHz, MeOD-d_4) δ: -83.37, -88.99, -173.93.

[00328] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-ethoxy-3-methyl-1*H*-pyrazole-4-carboxamide**

[00329] **Compound ID: 201**



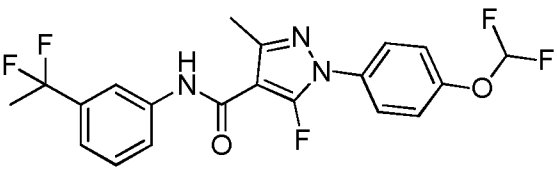
[00330] A mixture of 1-(4-(difluoromethoxy)phenyl)-5-ethoxy-3-methyl-1*H*-pyrazole-4-carboxylic acid (50.0 mg, 142 umol, 1.0 *eq*), triethylamine (43.1 mg, 425 umol, 3.0 *eq*), [dimethylamino(triazolo[4,5-b]pyridin-3-yloxy)methylidene]-dimethylazanium; hexafluorophosphate (108 mg, 284 umol, 2.0 *eq*) in dichloromethane (5 mL) was stirred at 25 °C for 30 min. To the mixture was added 3-(1,1-difluoroethyl)aniline (33.4 mg, 213 umol, 1.5 *eq*). The mixture was stirred at 50°C for 11.5 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenexluna C18 150*25 10 u; mobile phase: [water (0.225%FA)-ACN]; B%: 54%-84%, 10 min) to give 24.0 mg (37% yield) of **Compound 201** as a brown solid.

[00331] **LCMS**: (ESI) *m/z*: 452.1 $[M+H]^+$.

[00332] **^{1}H NMR**(400 MHz, MeOD-d_4) δ: 7.91 (s, 1H), 7.71 - 7.69 (m, 3H), 7.44 (t, J = 8.0 Hz, 1H), 7.32 - 7.28 (m, 3H), 6.91 (t, J = 74.0 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.43 (s, 3H), 1.92 (t, J = 18.0 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H).

[00333] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-fluoro-3-methyl-1*H*-pyrazole-4-carboxamide**

[00334] **Compound ID: 200**



[00335] To a solution of N-(3-(1,1-difluoroethyl)phenyl)-3-oxo-2-(trifluoromethyl)butanamide (300 mg, 970 umol, 1.0 *eq*) and [4-(difluoromethoxy)phenyl]hydrazine (163 mg, 776 umol, 0.8 *eq*, HCl) in ethyl alcohol (5 mL) was added triethylamine (294 mg, 2.91 mmol, 3.0 *eq*). The mixture was stirred at 80 °C for

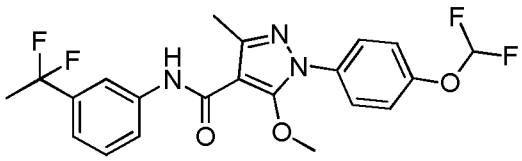
1 h. The mixture was concentrated under reduced pressure to give a brown oil. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25 10u; mobile phase: [water(0.225% aqueous formic acid solution)-acetonitrile];B%:52%-82%,10min) to give 25 mg (6% yield) of **Compound 200** as a yellow solid.

[00336] **LCMS:** (ESI) m/z 426.1[M+H]$^+$.

[00337] **^{1}H NMR:** (400MHz, MeOD-d_4) δ: 7.87 (s, 1H), 7.71 (br d, J = 7.6 Hz, 3H), 7.44 (t, J = 8.0 Hz, 1H), 7.37 - 7.28 (m, 3H), 6.92 (t, J = 65.6 Hz, 1H), 2.47 (s, 3H), 1.93 (t, J = 18.0 Hz, 3H).

[00338] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-methoxy-3-methyl-1*H*-pyrazole-4-carboxamide**

[00339] **Compound ID: 199**



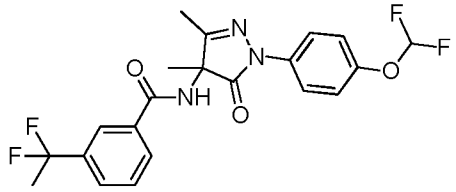
[00340] **Compound 199** was obtained via similar procedure of **Compound 201** from 1-(4-(difluoromethoxy)phenyl)-5-methoxy-3-methyl-1*H*-pyrazole-4-carboxylic acid and 3-(1,1-difluoroethyl)aniline.

[00341] **LCMS**: (ESI) *m/z*: 438.1 [M+H]$^+$.

[00342] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.91 (s, 1H), 7.72 - 7.67 (m, 3H), 7.45 (t, J = 8.0 Hz, 1H), 7.32 - 7.30 (m, 3H), 6.91 (t, J = 72.4 Hz, 1H), 3.95 (s, 3H), 2.43 (s, 3H), 1.93 (t, J = 18.4 Hz, 3H).

[00343] **Synthesis of 3-(1,1-difluoroethyl)-*N*-(1-(4-(difluoromethoxy)phenyl)-3,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)benzamide**

Compound ID: 198



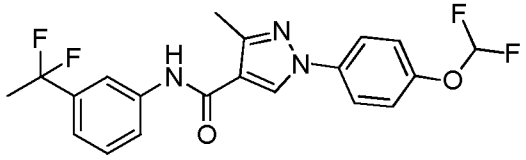
[00344] To a solution of 3-(1,1-difluoroethyl)benzoic acid (98.2 mg, 484 umol, 1.0 *eq*) in pyridine (4 mL) was added 1-ethyl-(3-(3-dimethylamino)propyl)-carbodiimide hydrochloride (102 mg, 531 umol, 1.1 *eq*). The mixture was stirred at 25 °C for 10 min. Then 4-amino-1-(4-(difluoromethoxy)phenyl)-3,4-dimethyl-1*H*-pyrazol-5(4*H*)-one (130 mg, 483 umol, 1 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 2 hr. The mixture was concentrated under reduced pressure to give a yellow oil. The yellow oil was purified by prep-HPLC (column: Shim-pack C18 150*25*10um;mobile phase: [water(0.225%FA)-ACN];B%: 46%-76%,10min) to give 54.7 mg (26% yield) of **Compound 198** as a white solid.

[00345] **LCMS:** (ESI) *m/z*: 437.9[M+H]$^+$.

[00346] **^{1}H NMR:** (400MHz, DMSO-d_6) δ: = 9.42 (s, 1H), 8.10 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.91 - 7.84 (m, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.67 - 7.60 (m, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.22 (t, J = 74.4 Hz, 1H), 2.07 - 1.95 (m, 6H), 1.53 (s, 3H).

[00347] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazole-4-carboxamide**

Compound ID: 196



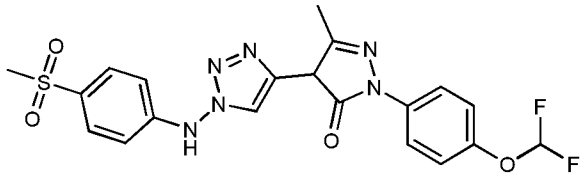
[00348] **Compound 196** was obtained via similar procedure of **Compound 201** and 3-(1,1-difluoroethyl)aniline.

[00349] **LCMS**: (ESI) *m/z*: 408.0 $[M+H]^+$.

[00350] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.78 (s, 1H), 7.90 (s, 1H), 7.82 - 7.78 (m, 2H), 7.77 - 7.72 (m, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.33 - 7.26 (m, 3H), 6.88 (t, J = 73.6 Hz, 1H), 2.55 (s, 3 H), 1.93 (t, J = 18.0 Hz, 3 H).

[00351] **Synthesis of 1-(4-(difluoromethoxy)phenyl)-3-methyl-4-(1-((4-(methylsulfonyl)phenyl)amino)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrazol-5(4*H*)-one (195)**

Compound ID : 195



[00352] To a 50 mL round-bottom flask equipped with a magnetic stir bar was added 4-(2,2-dichloroacetyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (100 mg, 285 umol, 1.0 *eq*) followed by the addition of methanol (3 mL). Then reagent tosylhydrazine (106 mg, 570 umol, 2.0 *eq*) and acetic acid (1.71 mg, 28.5 umol, 0.10 *eq*) was added into the mixture at 25 °C. The mixture was stirred at 25 °C for 21 h to afford solution A.

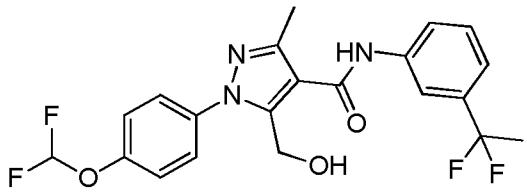
[00353] To another 50 mL round-bottom flask equipped with a magnetic stir bar was added 4-(1,1-difluoroethyl)aniline (66.2 mg, 342 umol, 1.2 *eq*, hydrochloride) followed by the addition of methanol (3 mL). Then diisopropylethylamine (221mg, 1.71 mmol, 6.0 *eq*) was added into the mixture at 25 °C before the addition of the previous solution A. The reaction was stirred at 25 °C for 2 h. The solution was concentrated and the residue was purified by prep-HPLC (Waters Xbridge: flow rate: 25 mL/min; gradient: 1% – 24% B over 10 min; mobile phase A: 0.05% aqueous ammonia hydroxide (v/v)) to afford 24.6 mg (18% yield) of **195** as a white solid.

[00354] **LCMS**: (ESI) *m/z*: 477.3 $[M+H]^+$.

[00355] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.77 (d, J=8.8 Hz, 2H), 7.52 (s, 1H), 7.40 - 7.24 (m, 4H), 7.08 (d, J=8.0 Hz, 1H), 7.11 - 6.67 (t, J=74.0 Hz, 1H), 2.35 (s, 3H), 2.00 (s, 3H).

[00356] **Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy) phenyl]-5-(hydroxymethyl)-3-methyl-pyrazole-4-carboxamide (194)**

Compound ID: 194



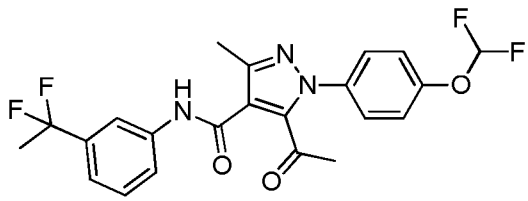
[00357] To a solution of 1-[4-(difluoromethoxy)phenyl]-5-(hydroxymethyl)-3-methyl -pyrazole-4-carboxylic acid (150 mg, 501 umol, 1.0 *eq*) and 3-(1,1-difluoroethyl) aniline (119 mg, 754 umol, 1.5 *eq*) in dichloromethane (5 mL) was added 1*H*-benzo[*d*][1,2,3]triazol-1-ol (102 mg, 754 umol, 1.5 *eq*) and *N*1-((ethylimino) methylene)-*N*3,*N*3-dimethylpropane-1,3-diamine hydrochloride (145 mg, 754 umol, 1.5 *eq*) , the mixture was stirred at 25 °C for 2 hr. The mixture was concentrated under reduced pressure affording the crude product as light yellow oil. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 10/1 to 0/1) to give a crude product. The crude product was purified by preparative HPLC: (Phenomenex Gemini C18 column: Waters Xbridge 150*25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-acetonitrile]; B%: 42%-72%, 10min) to give 100 mg (46% yield) of **194** as a white solid.

[00358] **LCMS**: (ESI) *m/z*: 438.1 $[M+H]^+$.

[00359] **^{1}H NMR:** (400 MHz, $CDCl_3$-*d*) δ: 8.23 (br s, 1H), 7.73 - 7.63 (m, 2H), 7.49 - 7.34 (m, 3H), 7.27 (s, 3H), 6.75 - 6.30 (m, 1H), 4.66 (br d, *J* = 4.4 Hz, 2H), 4.31 (br s, 1H), 2.58 (s, 3H), 2.00 - 1.83 (m, 4H).

[00360] **Synthesis of 5-acetyl-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazole-4-carboxamide (193)**

Compound ID: 193



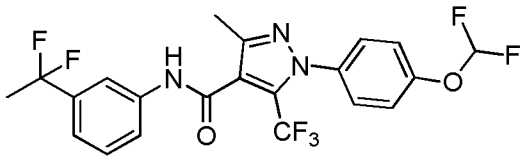
[00361] To a solution of 5-acetyl-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*- pyrazole-4-carboxylic acid (298 mg, 869 umol, 1.0 *eq*) in *N*, *N*-dimethyl-formamide (15 mL) was added triethylamine (194 mg, 1.92 mmol, 2.2 *eq*) and 2-(3*H*-[1,2,3] triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium (438 mg, 1.15 mmol, 1.3 *eq*) , the reaction mixture was stirred at 25 °C for 15 min. Then 3-(1,1-difluoroethyl) aniline (226 mg, 1.44 mmol, 1.7 *eq*) was added to the mixture and the solution was stirred at 25 °C for 20 min. The mixture was concentrated under reduced pressure affording a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 10/1 to 1/1) to give a crude product. The crude product was purified by preparative HPLC: (Phenomenex Gemini C18 column: Waters Xbridge 150*25 5u; mobile phase: [water (0.05% ammonia hydroxide v/v)-acetonitrile]; B%: 42%-72%, 10min) to give 150 mg (38% yield) of **193** was obtained as a white solid.

[00362] **LCMS**: (ESI) *m/z*: 450.3 $[M+H]^+$.

[00363] **^{1}H NMR:** (400 MHz, $CDCl_3$-*d*) *δ*: 9.66 (br s, 1H), 7.83 (s, 1H), 7.72 (br d, *J* =8.2 Hz, 1H), 7.48 - 7.33 (m, 3H), 7.27 (s, 3H), 6.79 - 6.31 (m, 1H), 2.59 (s, 3H), 2.16 (s, 3H), 1.91 (t, *J* = 18.2 Hz, 3H).

[00364] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide (192)**

Compound ID : 192



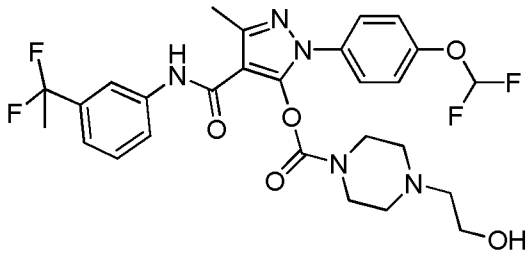
[00365] **192** was obtained via similar procedure of 186 from 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid and 3-(1,1-difluoroethyl)aniline

[00366] **LCMS**: (ESI) *m/z*: 476.0 $[M+H]^+$.

[00367] **^{1}H NMR** (400 MHz, MeOD-d_4) *δ*: 7.90 (s, 1H)), 7.75 - 7.73 (d, *J* = 8 Hz, 1H), 7.57-7.55 (d, *J* = 8.8 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.37 -7.35 (d, *J* = 8.8 Hz, 3H), 6.991 (t, *J* = 73.2, 1H), 2.428 (s, 3H), 1.953 (t, *J* = 18.4 Hz, 3H).

[00368] **Synthesis of 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazol-5-yl 4-(2-hydroxyethyl)piperazine-1-carboxylate (191)**

Compound ID : 191



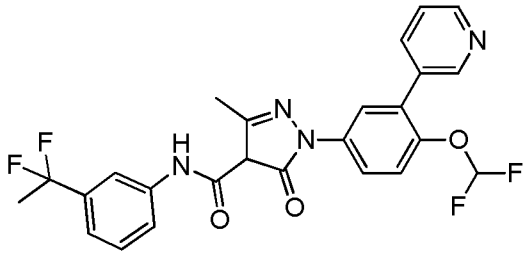
[00369] **191** was obtained via similar procedure of **189** from 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazol-5-yl (2,2,2-trichloroethyl) carbonate and 2-(piperazin-1-yl)ethanol.

[00370] **LCMS**: (ESI) *m/z*: 580.5 $[M+H]^+$.

[00371] **^{1}H NMR** (400MHz, MeOD-d_4) *δ* : 7.74 (d, *J* = 8.8 Hz, 2H), 7.52 - 7.46 (m, 1H), 7.45 - 7.40 (m, 1H), 7.32 (s, 1H), 7.26 (br d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.97 (s, 1H), 6.79 (s, 1H), 6.60 (s, 1H), 3.83 - 3.75 (m, 2H), 3.75 - 3.45 (m, 4H), 3.18 - 2.87 (m, 6H), 2.32 (s, 3H), 1.98 - 1.87 (m, 3H).

[00372] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (310i)**

Compound ID: 310i



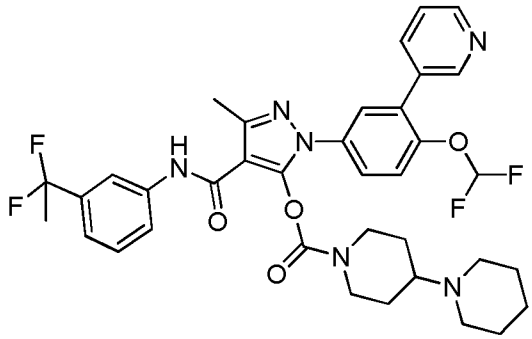
[00373] **Compound 310i** was obtained via general procedure IV from 4-nitrophenyl 1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-(1, 1-difluoroethyl)aniline.

[00374] **LCMS**: (ESI) *m/z* 501.1 $[M+H]^+$.

[00375] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.80 (s, 1H), 8.63 - 8.61 (m, 1H), 8.19 - 8.15 (m, 1H), 7.90 (d, J = 2.4 Hz, 2H), 7.82 (d, J = 2.4 Hz, 1H), 7.65 - 7.62 (m, 2H), 7.49 (d, J = 8.8 Hz, 1H), 7.41 - 7.35 (m, 1H), 7.25 - 7.20 (m, 1H), 6.87 (t, J = 73.2 Hz, 1H), 2.60 (s, 3H), 1.92 (t, J = 13.2 Hz, 3H).

[00376] **Synthesis of 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-1*H*-pyrazol-5-yl [1,4'-bipiperidine]-1'-carboxylate (190)**

Compound ID: 190



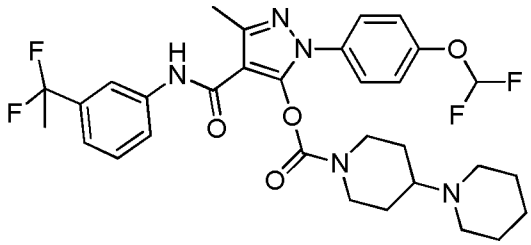
[00377] To a 50 mL round-bottom flask equipped with a magnetic stir bar was added **310i** (50.0 mg, 97.9 umol, 1.0 *eq*) followed by the addition of dichloromethane (5 mL). The solution was cooled to 0 °C. Next, triethylamine (39.6 mg, 391 umol, 4.0 *eq*) followed by 2,2,2-trichloroethyl carbonochloridate (35.3 mg, 166 umol, 1.7 *eq*) was added dropwise. The mixture was allowed to warm to 25 °C and stir for 2 h. Then 1-(4-piperidyl)piperidine (41.2 mg, 245 umol, 2.5 *eq*) was added. The solution was stirred at 25 °C for 12 h. The mixture was concentrated under reduced pressure affording the crude product as black oil. The crude product was purified by prep-HPLC (column: Xtimate C18 150*25mm*5um; mobile phase: [water (0.05% ammonia hydroxide v/v)-acetonitrile]; B%: 20%-50%, 10min) to give a white solid. The white solid was triturated with acetonitrile (0.5 mL) to give 4.00 mg (6% yield) of **190** as a white solid.

[00378] **LCMS**: (ESI) *m/z*: 695.4 $[M+H]^+$.

[00379] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.74 (d, J = 1.6 Hz, 1H), 8.54 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.95 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.42 - 7.40 (m, 1H), 7.33 - 7.32 (m, 2H), 7.31 (d, J = 3.6 Hz, 1H), 6.74 (t, J = 74.0 Hz, 1H), 4.20 (d, J = 13.2 Hz, 2H), 2.87 - 2.80 (m, 4H), 2.33 (s, 3H), 1.91 (t, J = 18.4 Hz, 3H), 1.81 - 1.80 (m, 2H), 1.80 - 1.78 (m, 4H), 1.70 - 1.69 (m, 2H), 1.69 - 1.29 (m, 5H).

[00380] **Synthesis of 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazol-5-yl [1,4'-bipiperidine]-1'-carboxylate (189)**

Compound ID : 189



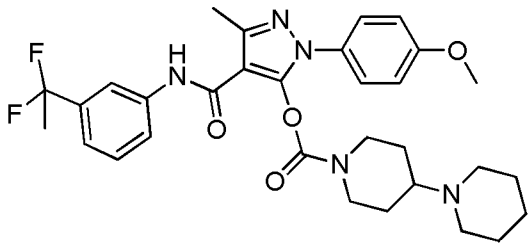
[00381] To a 10 mL round-bottom flask equipped with a magnetic stir bar was added 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazol-5-yl (2,2,2-trichloroethyl) carbonate (220 mg, 367 umol, 1.0 *eq*), triethylamine (112 mg, 1.10 mmol, 3.0 *eq*) followed by the addition of dichloromethane (2 mL). Then reagent 1-(4-piperidyl)piperidine (74.2 mg, 441 umol, 1.2 *eq*) was added into the mixture at 25 °C. The mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to give a crude product as a brown oil. The crude product was purified by preparative HPLC: (column: Shim-pack C18 150*25*10um; mobile phase: [Water-acetonitrile]; B%: 22%-52%, 10min) to give 79.0 mg (33% yield) of **189** as an off-white solid.

[00382] **LCMS**: (ESI) *m/z*: 618.5 $[M+H]^+$.

[00383] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.77-7.80 (m, 2H), 7.49 (t, *J*=7.6 Hz, 1H), 7.41-7.423(m, 1H), 7.33 (s, 1H), 7.27 (d, *J*=8.0 Hz, 1H), 7.15 (d, *J*=9.2 Hz , 2H), 6.79 (t, *J*=74.0 Hz, 1H), 4.20 (d, *J*=14.4 Hz, 2H), 3.04-3.20 (m, 5H), 3.14 (t, *J*=12.8 Hz, 2H), 2.33 (s, 3H), 1.93 (t, *J*=18.4 Hz, 3H), 1.78-1.89(m, 6H), 1.63 (s, 2H), 1.48 (d, *J*=9.2 Hz, 2H).

[00384] **Synthesis of 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazol-5-yl [1,4'-bipiperidine]-1'-carboxylate (188)**

Compound ID : 188



[00385] **188** was obtained via similar procedure of **189** from 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazol-5-yl (2,2,2-trichloroethyl) carbonate and 1-(4-piperidyl)piperidine

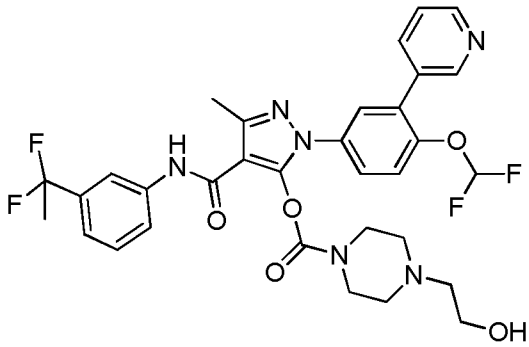
[00386] **LCMS**: (ESI) *m/z*: 582.4 $[M+H]^+$.

[00387] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.54-7.58 (m, 2H), 7.43 (t, *J*=7.6 Hz, 1H), 7.39-7.41 (m, 1H), 7.31 (s, 1H), 7.26 (d, *J*=8.0 Hz, 1H), 6.92-6.95 (m, 2H), 4.20 (d, *J*=12.4 Hz, 2H), 3.80 (s, 3H), 3.02-3.14 (m, 5H), 2.81 (t, *J*=12.0 Hz, 2H), 2.30 (s, 3H), 1.93 (t, *J*=11.2 Hz, 3H) 1.76-1.83 (m, 6H), 1.60 (s, 2H), 1.43 (d, *J*=8.8 Hz, 2H).

[00388] **Synthesis of 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)-3-**

(pyridin-3-yl)phenyl)-3-methyl-1*H*-pyrazol-5-yl 4-(2-hydroxyethyl)piperazine-1-carboxylate (187)

Compound ID: 187



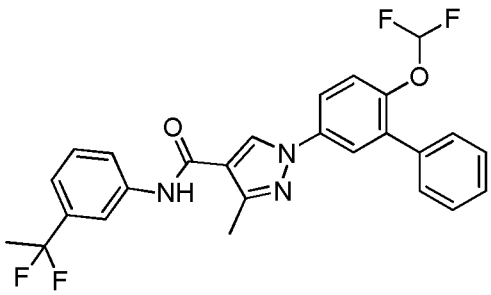
[00389] **187** was obtained via the similar synthetic method of **190** from **310i** and 2-(piperazin-1-yl)ethanol.

[00390] **LCMS**: (ESI) *m/z*: 657.6 $[M+H]^+$.

[00391] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.74 (d, J = 1.6 Hz, 1H), 8.53 (d, J = 1.6 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.60 - 7.55 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.40 - 7.30 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 6.74 (t, J = 73.6 Hz, 1H), 3.72 - 3.59 (m, 6H), 3.30 - 2.40 (m, 6H), 2.82 (s, 3H), 1.91 (t, J = 18.4 Hz, 3H).

[00392] **Synthesis of ethyl 1-(3-bromo-4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylate (186)**

Compound ID : 186



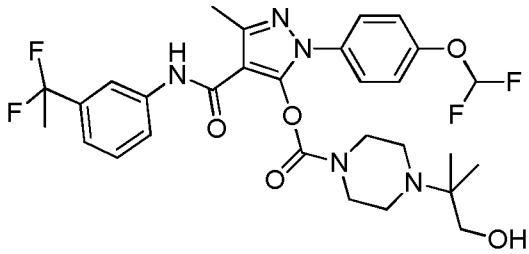
[00393] To a 8 mL round-bottom flask equipped with a magnetic stir bar was added 1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3-methyl-1*H*-pyrazole-4-carboxylic acid (30.0 mg, 74.9 umol, 1.0 *eq*) and *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (16.6 mg, 87.0 umol, 1.1 *eq*) followed by the addition of pyridine (2 mL). Then reagent 3-(1,1-difluoroethyl)aniline (16.3 mg, 104 umol, 1.4 *eq*) was added into the mixture at 25 °C. The mixture was stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure affording the crude product as yellow oil. The crude product was purified by preparative HPLC: (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225%formic acid)-acetonitrile]; B%: 60%-90%, 10min) to give 16.0 mg (43% yield) of **186** as a yellow solid.

[00394] **LCMS**: (ESI) *m/z*: 484.1 $[M+H]^+$.

[00395] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.87 (s, 1H)), 7.94 (s, 1H), 7.87 (d, J = 2.8 Hz, 1H), 7.83 (dd, J = 2.8, 8.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.64 - 7.58 (m, 2H), 7.54 - 7.43 (m, 5H), 7.32 (d, J = 7.8 Hz, 1H), 6.973 (t, J = 68.0, 1H), 2.60 (s, 3H), 1.97 (t, J = 18.4 Hz, 3H)

[00396] **Synthesis of 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazol-5-yl 4-(1-hydroxy-2-methylpropan-2-yl)piperazine-1-carboxylate (185)**

Compound ID : 185



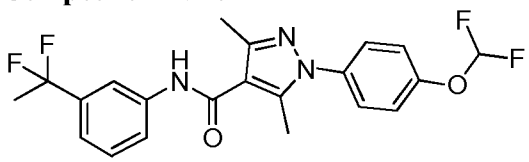
[00397] **185** was obtained via similar procedure of **189**

[00398] **LCMS**: (ESI) *m/z*: 608.4 $[M+H]^+$.

[00399] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.78 (d, *J*=8.8 Hz, 2H), 7.42~7.52 (m, 2H), 7.32 (s, 1H), 7.26 (d, *J*=8.0 Hz, 1H), 7.14 (d, *J*= 8.8 Hz, 2H), 6.78 (t, *J*= 74.4, 1H), 4.13 (s, 2H), 3.58 (s, 2H), 3.20 (s, 6H), 2.33 (s, 3H), 1.93 (t, *J*=18.4 Hz, 3H) ,1.29 (s, 6H).

[00400] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxamide (184)**

Compound ID: 184



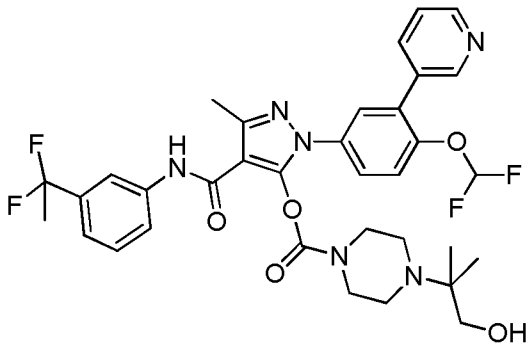
[00401] To a solution of 1-(4-(difluoromethoxy)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxylic acid (150 mg, 531 umol, 1.0 *eq*) in pyridine (5 mL) was added *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (132 mg, 691 umol, 1.3 *eq*). The solution was stirred at 25 °C for 5 min and then 3-(1,1-difluoroethyl)aniline (108 mg, 691 umol, 1.3 *eq*) was added. The solution was stirred at 25 °C for 30 min and then stirred at 60 °C for 2 h. The solution was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi Max-RP 150*50mm*10 um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 55%-85%, 11min) to give 84.9 mg (38% yield) of **184** as a yellow solid.

[00402] **LCMS:** (ESI) *m/z*: 422.0 $[M+H]^+$.

[00403] **^{1}H NMR:** (400 MHz, MeOD-d_4) δ: 7.91 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.40 - 7.30 (m, 3H), 6.96 (t, *J* = 74.0 Hz, 1H), 2.46 (s, 3H), 2.45 (s, 3H), 1.95 (t, *J* = 18.0 Hz, 3H)

[00404] **Synthesis of 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-1*H*-pyrazol-5-yl 4-(1-hydroxy-2-methylpropan-2-yl)piperazine-1-carboxylate (183)**

Compound ID: 183



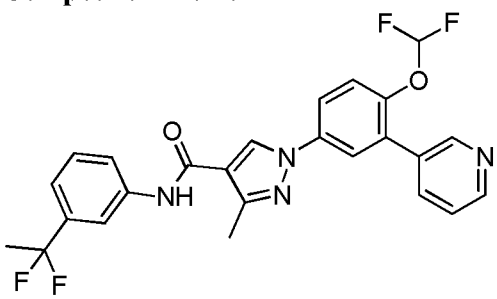
[00405] **183** was obtained via the similar synthetic method of **190** from **310i** and 2-methyl-2-(piperazin-1-yl)propan-1-ol.

[00406] **LCMS**: (ESI) *m/z*: 685.6 $[M+H]^+$.

[00407] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.73 (s, 1H), 8.53 (dd, J = 1.2 Hz, 4.8 Hz, 1H), 8.05 - 8.02 (m, 2H), 7.99 (d, J = 2.4 Hz, 1H), 7.56 - 7.45 (m, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.44 - 7.38 (m, 2H), 7.34 - 7.28 (m, 1H), 6.73 (t, J = 74.0 Hz, 1H), 3.74 (br s, 2H), 3.58 - 3.42 (m, 4H), 3.21 - 2.83 (m, 4H), 2.33 (s, 3H), 1.91 (t, J = 18.0 Hz, 3H), 1.13 (s, 6H).Synthesis of 182

[00408] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxamide (182)**

Compound ID : 182



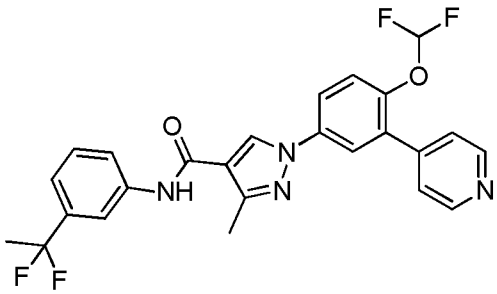
[00409] **182** was obtained via similar procedure of 186 from 1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid and 3-(1,1-difluoroethyl)aniline

[00410] **LCMS**: (ESI) *m/z*: 485.2 $[M+H]^+$.

[00411] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.89 (s, 1H), 8.76 (d, J = 1.6 Hz, 1H), 8.63 - 8.56 (m, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.95 - 7.86 (m, 3H), 7.75 (d, J = 7.6 Hz, 1H), 7.58 - 7.50 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.29 (d, J =8.4 Hz, 1H), 6.86 (t, J = 73.6 Hz, 1H), 2.57 (s, 3H), 1.93 (t, J = 18.0 Hz, 3H).

[00412] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-4-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxamide (181)**

Compound ID : 181



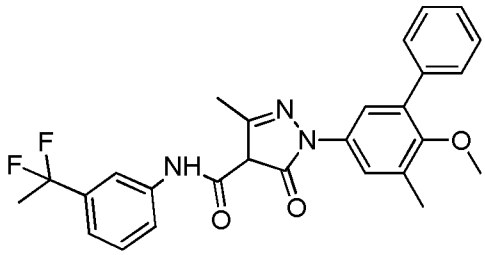
[00413] **181** was obtained via similar procedure of **186** from 1-(4-(difloromethoxy)-3-(pyridin-4-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid and 3-(1,1-difluoroethyl)aniline

[00414] **LCMS**: (ESI) *m/z*: 485.2[M+H]$^+$.

[00415] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.89 (s, 1H), 8.66 (d, J = 5.6 Hz, 2H), 7.95 - 7.90 (m, 3H), 7.75 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 6.0 Hz, 2H), 7.51 (d, J = 8.8 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 73.2 Hz, 1H), 2.56 (s, 3H), 1.93 (t, J = 18.0 Hz, 3H).

[00416] **Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-1-(4-methoxy-3-methyl-5-phenyl-phenyl)-3-methyl-5-oxo-4*H*-pyrazole-4-carboxamide (180)**

Compound ID: 180



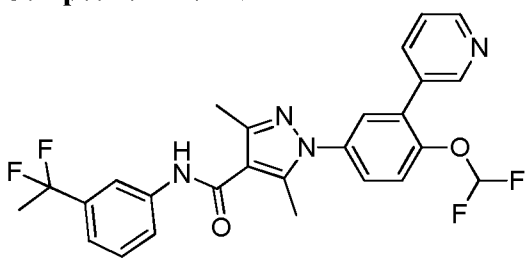
[00417] **180** was obtained via general procedure IV from (4-nitrophenyl) 1-(4-methoxy-3-methyl-5-phenyl-phenyl)-3-methyl-5-oxo-4*H*-pyrazole-4-carboxylate

[00418] **LCMS**: (ESI) *m/z*: 478.3 [M+H]$^+$.

[00419] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 7.77(s, 1H), 7.58(d, J = 8.0 Hz, 1 H), 7.47(d, J = 7.2 Hz, 7.36 - 7.30(m , 5 H), 7.23-7.21(m, 2 H), 3.32(s, 3 H), 2.49(s ,3 H), 2.27(s , 3 H), 1.90(t, J = 18.0 Hz, 3 H).

[00420] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxamide (179)**

Compound ID : 179



[00421] To a 10 mL round-bottom flask equipped with a magnetic stir bar was added 1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxylic acid (105 mg, 271 umol, 1.0 *eq*), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (78.0 mg, 406 umol, 1.5 *eq*) followed by the addition of pyridine (5 mL). Then 3-(1,1-difluoroethyl)aniline (85.2 mg, 542 umol,

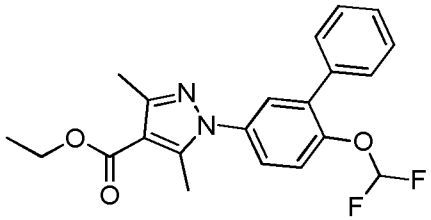
2.0 *eq*) was added into the mixture at 25 °C. The mixture was stirred at 25°C for 12 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 35%-65%, min) to give 14.6 mg (11% yield) of **179** as a yellow solid.

[00422] **LCMS**: (ESI) *m/z*: 499.1 $[M+H]^+$.

[00423] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.74 (s, 1H), 8.58 (d, *J*=4.4 Hz, 1H), 7.96 (d, *J*=8.0 Hz, 1H), 7.71 (s, 1H), 7.64 (d, *J*=8.4 Hz, 1H), 7.63-7.59 (m, 4H), 7.54 (t, *J*=8.8 Hz, 1H), 7.44-7.31 (m, 1H), 6.92 (t, *J*=73.2 Hz, 1H), 1.93 (d, *J*=16.4 Hz, 6H), 1.93 (t, *J*=18.4 Hz, 3H).

Synthesis of 178

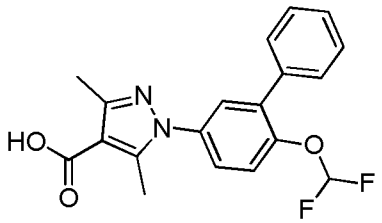
[00424] **Step 1: Synthesis of ethyl 1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3,5-dimethyl-1*H*-pyrazole-4-carboxylate (178-A)**



[00425] **178-A** was obtained via similar procedure of 2-(difluoromethoxy)-5-nitro-1,1'-biphenyl from **179-C** and phenylboronic acid.

[00426] **LCMS**: (ESI) *m/z*: 387.1 [M+H

[00427] **Step 2: Synthesis of 1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3,5-dimethyl-1*H*-pyrazole-4-carboxylic acid (178-B)**

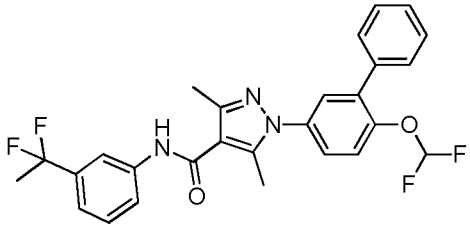


[00428] **178-B** was obtained via similar procedure of **179-E** from **178-A**

[00429] **LCMS**: (ESI) *m/z*: 359.1 $[M+H]^+$.

[00430] **Step 3: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxamide (178)**

Compound ID : 178



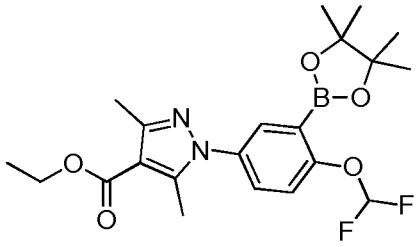
[00431] **178** was obtained via similar procedure of **179** from **178-B** and 3-(1,1-difluoroethyl)aniline

[00432] **LCMS**: (ESI) *m/z*: 498.2 $[M+H]^+$.

[00433] **^{1}H NMR** (400 MHz, MeOD-d_4) δ :7.89 (s, 1H), 7.72 (d, *J*=7.6 Hz, 1H), 7.38-7.58 (m, 9H), 7.30 (d, *J*=8.0 Hz, 1H), 6.80 (t, *J*=73.6 Hz, 1H), 2.47 (d, *J*=13.6 Hz, 6H), 1.93 (t, *J*=18.4 Hz, 3H).

Synthesis of 177

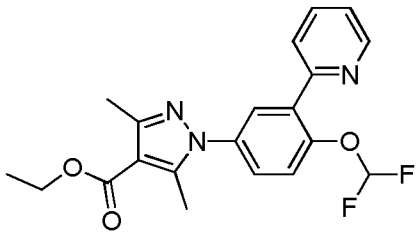
[00434] **Step 1: ethyl ethyl 1-(4-(difluoromethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxylate (177-A)**



[00435] To a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **179-C** (200 mg, 497 umol, 1.0 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (252 mg, 993 umol, 2.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (36.3 mg, 49.6 umol, 0.10 *eq*) followed by the addition of dioxane (15 mL). Then potassium acetate (97.5 mg, 994 umol, 2.0 *eq*) was added into the mixture at 25 °C. The mixture was heated to 85 °C and stirred for 12 h under nitrogen protection. The mixture was filtered, 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 100/1 to 60/1) to give 210 mg (crude) of **177-A** as a brown oil.

[00436] **LCMS**: (ESI) *m/z*: 355.1 $[M+H]^+$.

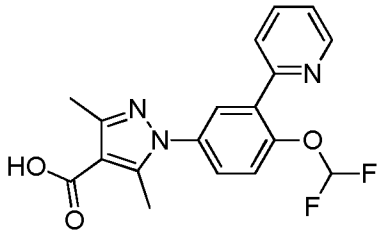
[00437] **Step 2: ethyl 1-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxylate (177-B)**



[00438] To a 50 mL round-bottom flask equipped with a magnetic stir bar was added **177-A** (210 mg, 593 umol, 1.0 *eq*), 2-bromopyridine (114. mg, 722umol, 1.2 *eq*), sodium bicarbonate (121 mg, 1.40 mmol, 2.4 *eq*) followed by the addition of dioxane (12 mL) and water (4 mL). Then 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (70.4 mg, 96.2 umol, 1.62e-1 *eq*) was added into the mixture at 25 °C. The flask was then evacuated and backfilled with nitrogen for three times. The mixture was stirred at 85 °C under an atmosphere of nitrogen for 12 h. The mixture was filtered, 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 20/1 to 5/1) to give 160 mg (60% yield) of **177-B** as a light yellow oil.

[00439] **LCMS**: (ESI) *m/z*: 388.0 $[M+H]^+$.

[00440] **Step 3: ethyl 1-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxylic acid (177-C)**

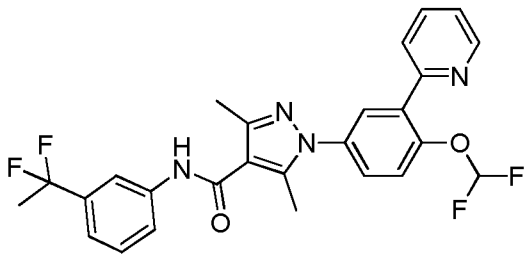


[00441] To a 10 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **177-B** (160 mg, 353 umol, 1.0 *eq*) followed by the addition of solvent ethanol (5 mL) and water (1 mL). Then sodium hydroxide (42.4 mg, 1.06 mmol, 3.0 *eq*) was added into the mixture at 25 °C. The mixture was heated to 50 °C and stirred for 4 h. To the mixture was added sodium hydroxide (141 mg, 3.53 mmol, 10 *eq*) again, and the mixture was stirred at 80°C for 4 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in water (10 mL). The pH of the mixture was adjusted to 6. The mixture was extracted with ethyl acetate (10mL x 3).The combined organic layer was washed with brine (15 mL), dried over sodium sulfate, filtered and concentrated to give 140mg (89% yield) of **177-C** as a yellow solid.

[00442] **LCMS**: (ESI) *m/z*: 360.1 $[M+H]^+$.

[00443] **Step 4: *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxamide (177)**

Compound ID : 177



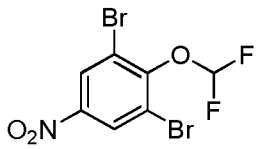
[00444] **177** was obtained via similar procedure of **186** from **177-C** and 3-(1,1-difluoroethyl)aniline

[00445] **LCMS**: (ESI) *m/z*: 499.3 $[M+H]^+$.

[00446] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.67 (d, *J*=4.4 Hz, 1H), 7.82-7.96 (m, 4H), 7.72 (d, *J*=8.4 Hz, 1H), 7.62 (dd, *J*=2.4, 8.8 Hz, 1H), 7.43-7.52 (m, 3H), 7.30 (d, *J*=7.6 Hz, 1H), 6.94 (t, *J*=73.2 Hz 1H), 2.48 (d, *J*=19.8 Hz, 6H), 1.93 (t, *J*=18.0 Hz, 3H).

Synthesis of 176

[00447] **Step 1: 2,6-dibromo-4-nitrophenol (176-A)**

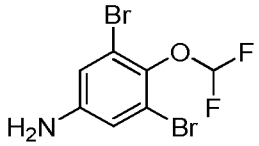


[00448] To a 250 mL round-bottom flask equipped with a magnetic stir bar was added 2,6-dibromo-4-nitro-phenol (8.00 g, 27.0 mmol, 1.0 *eq*) followed by the addition of acetonitrile (100 mL), potassium carbonate (7.45 g, 53.9 mmol, 2.0 *eq*) was added. The solution was cooled to 0 °C. Next, ethyl 2-bromo-2,2-difluoro-acetate (8.20 g, 40.4 mmol, 1.5 *eq*) was added dropwise. The mixture was heated to 80 °C and stirred for 12 h. The mixture was filtered. The filtrate was concentrated. The residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous layer was extracted with ethyl acetate

(100 mL x 2). The combined organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue as a brown oil. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 20/1) to give 15.0 g (80% yield) of **176-A** as a brown oil.

[00449] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.40 (s, 2H), 6.64 (t, J = 73.2 Hz, 1H).

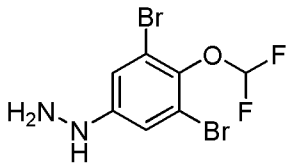
[00450] **Step2 : 1,3-dibromo-2-(difluoromethoxy)-5-nitrobenzene (176-B)**



[00451] To a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **176-A** (500 mg, 1.44 mmol, 1.0 *eq*) followed by the addition of water (1 mL) and methanol (5 mL). Then ammonium chloride (771 mg, 14.4 mmol, 10 *eq*) and iron powder (804 mg, 14.4 mmol, 10 *eq*) were added into the mixture at 25 °C. The mixture was heated to 80 °C and stirred for 2 h. The mixture was diluted by slow addition of water (30 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer 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 affording the residue to give 400 mg (64% yield) of **176-B** as a yellow solid.

[00452] **LCMS**: (ESI) *m/z*: 317.8[M+H]$^+$.

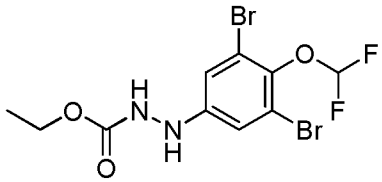
[00453] **Step 3: 3,5-dibromo-4-(difluoromethoxy)aniline (176-C)**



[00454] **176-C** was obtained via general procedure I from **176-B**

[00455] **LCMS**: (ESI) *m/z*: 296.1 [M+H]$^+$.

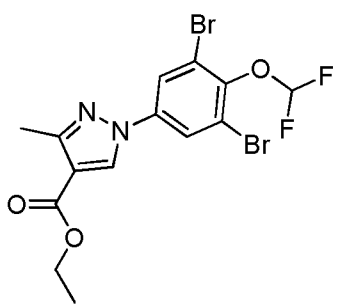
[00456] **Step 4: (3,5-dibromo-4-(difluoromethoxy)phenyl)hydrazine (176-D)**



[00457] **176-D** was obtained via similar procedure of **186-A** from **176-C** and ethyl carbonochloridate

[00458] **LCMS**: (ESI) *m/z*: 404.9[M+H]$^+$.

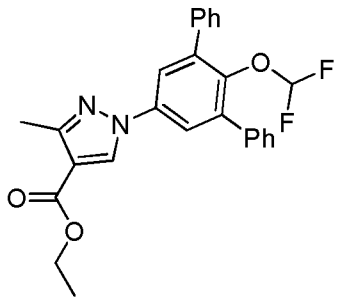
[00459] **Step 5: ethyl 2-(3,5-dibromo-4-(difluoromethoxy)phenyl)hydrazinecarboxylate (176-E)**



[00460] **176-E** was obtained via similar procedure of **186-B** from **176-D** and ethyl (2E)-2-(methoxymethylene)-3-oxo-butanoate

[00461] **LCMS**: (ESI) *m/z*: 454.9 $[M+H]^+$.

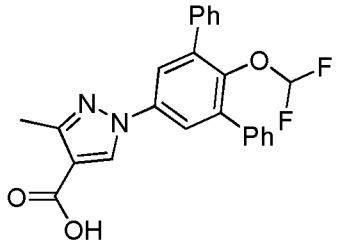
[00462] **Step 6: ethyl 1-(3,5-dibromo-4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylate (176-F)**



[00463] **176-F** was obtained via similar procedure of **186-C** from **176-E** and phenylboronic acid

[00464] **LCMS**: (ESI) *m/z*: 449.0$[M+H]^+$.

[00465] **Step 7: 1-(2'-(difluoromethoxy)-[1,1':3',1''-terphenyl]-5'-yl)-3-methyl-1*H*-pyrazole-4-carboxylic acid (176-G)**



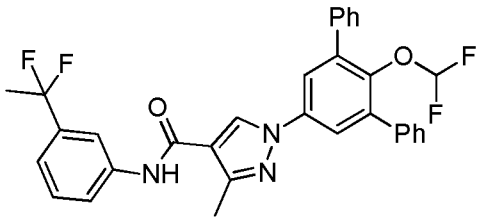
[00466] **176-G** was obtained via similar procedure of **186-D** from **176-F** and sodium hydroxide

[00467] **LCMS**: (ESI) *m/z*: 421.1 $[M+H]^+$.

[00468] **Spectra:**

[00469] **Step 8: *N*-(3-(1,1-difluoroethyl)phenyl)-1-(2'-(difluoromethoxy)-[1,1':3',1''-terphenyl]-5'-yl)-3-methyl-1*H*-pyrazole-4-carboxamide (176)**

[00470] **Compound ID : 176**



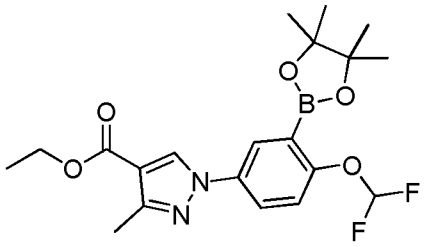
[00471] **176** was obtained via similar procedure of **186** from **176-G** and 3-(1,1-difluoroethyl)aniline

[00472] **LCMS**: (ESI) *m/z*: 559.19$[M+H]^+$.

[00473] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.95 (s, 1H), 7.90 (s, 1H), 7.83 (s, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.68 - 7.61 (m, 4H), 7.55 - 7.47 (m, 4H), 7.47 - 7.38 (m, 3H), 7.28 (d, J = 7.6 Hz, 1H),5.90 (t, J = 73.2 Hz, 1H), 2.57 (s, 3H), 1.93 (t, J = 18.0 Hz, 3H).

Synthesis of 175

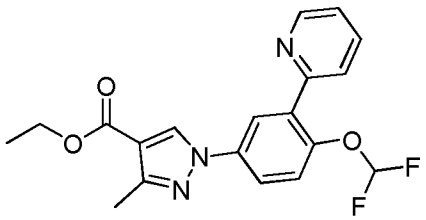
[00474] **Step 1: Synthesis of ethyl 1-[4-(difluoromethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-methyl-pyrazole-4-carboxylate (175-A)**



[00475] To a 100 mL round-bottom flask equipped with a magnetic stir bar was added **186-B** (0.400 g, 1.02 mmol, 1.0 *eq*) followed by the addition of dioxane (15 mL). Then potassium acetate (200 mg, 2.04 mmol, 2.0 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (517 mg, 2.04 mmol, 2.0 *eq*) and 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (74.5 mg, 102 umol, 0.10 *eq*) were added into the mixture at 20 °C. The flask was then evacuated and backfilled with nitrogen for three times. The mixture was stirred at 90 °C under an atmosphere of nitrogen for 12 h. The mixture was diluted with water (20 mL), and then 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, from 30/1 to 5/1) to give 410 mg (78% yield) of **175-A** as a white solid.

[00476] **LCMS**: (ESI) *m/z*: 423.1 $[M+H]^+$.

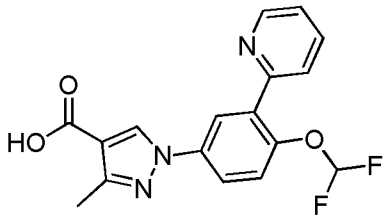
[00477] **Step 2: Synthesis of ethyl 1-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-3-methyl-pyrazole-4-carboxylate (175-B)**



[00478] A mixture of **175-A** (410 mg, 796 umol, 1.0 *eq*), 2-bromopyridine (230 mg, 1.46 mmol, 1.8 *eq*), sodium bicarbonate (163 mg, 1.94 mmol, 2.4 *eq*) and 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (71.0 mg, 97.0 umol, 1.2e-1.0 *eq*) in dioxane (8 mL) and water (2 mL) was degassed and purged with nitrogen for 3 times. And then the mixture was stirred at 90 °C for 4 hr under nitrogen atmosphere. The mixture was diluted with water (40 mL), and extracted with ethyl acetate (30 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 silica gel column chromatography (petroleum ether/ethyl acetate, from 30/1 to 3/1) to give 300 mg (75% yield) of **175-B** as a white solid.

[00479] **LCMS**: (ESI) *m/z*: 374.1 $[M+H]^+$.

[00480] **Step 3: Synthesis of 1-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-3-methyl-pyrazole-4-carboxylic acid (175-C)**

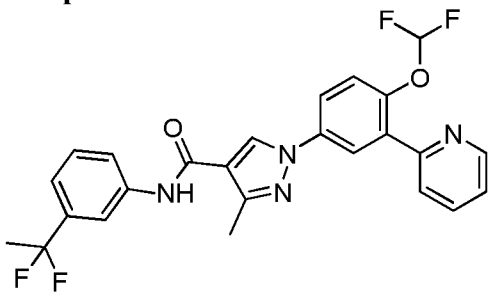


[00481] To a solution of **175-B** (270 mg, 615 umol, 1.0 *eq*) in ethyl alcohol (5 mL) and water(1 mL) was added sodium hydroxide (73.8 mg, 1.84 mmol, 3.0 *eq*). The mixture was heated to 50 °C and stirred for 2 hr. The mixture was concentrated in vacuum. The residue was diluted with water (20 mL), and washed with methyl tertiary butyl ether (10 mL). The pH of aqueous phase was adjusted to 5~6, then extracted with ethyl acetate (15 mL x 2). The combined organic layer was washed with brine (20 mL), dried over anhydrous, filtered and concentrated under reduced pressure to give 140 mg (54% yield) of **175-C** as a white solid.

[00482] **LCMS**: (ESI) *m/z*: 344.2 $[M+H]^+$.

[00483] **Step 4: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-3-methyl-pyrazole-4-carboxamide (175)**

Compound ID: 175



[00484] To a solution of **175-C** and 3-(1,1-difluoroethyl)aniline (41.4 mg, 263 umol, 1.0 *eq*) in pyridine (10 mL) was added *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (75.8 mg, 395 umol, 1.5 *eq*). The mixture was stirred at 25 °C for 2 hr. The mixture was concentrated in vacuum. The residue was diluted with water (20 mL), and 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 prep-HPLC (column: Waters Xbridge 150*25 5u; mobile phase: [water (10 mM ammonium hydrogen carbonate)-acetonitrile]; B%: 48%-78%, 10min), then freeze-dried to give 53.9 mg (35% yield) of **175** as a white solid

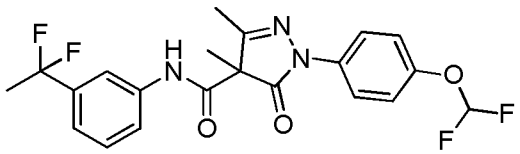
[00485] **LCMS**: (ESI) *m/z*: 485.2$[M+H]^+$.

[00486] **^{1}H NMR**: (400MHz, MeOD-d_4) δ: 8.87 (s, 1H), 8.71-8.69 (m, 1H), 8.13 (d, J = 3.2 Hz, 1H), 7.97 - 7.89 (m, 3H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.50 - 7.41 (m, 3H), 7.29 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 73.6 Hz, 1H), 2.56 (s, 3H), 1.93 (t, J = 18.4 Hz, 3H).

Synthesis of 174

[00487] **Step 1: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (174)**

Compound ID: 174



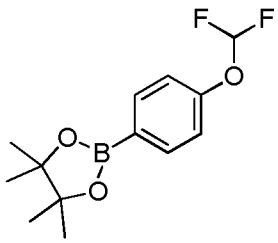
[00488] To a solution of **298i** (100 mg, 236 umol, 1.0 *eq*) in tetrahydrofuran (2 mL) was added tetrabutyl ammonium fluoride (1 M in tetrahydrofuran, 283 uL, 1.2 *eq*) and iodomethane (50.0 mg, 354 umol, 1.5 *eq*). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 3/1) to give 6.70 mg (6% yield) of **174** as yellow gum.

[00489] **LCMS**: (ESI) *m/z*: 438.2 $[M+H]^+$.

[00490] **^{1}H NMR**: (400MHz, MeOD-d_4) δ: 7.97 (d, J = 9.2 Hz, 2H), 7.78 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.82 (t, J = 74.4 Hz, 1H), 2.30 (s, 3H), 1.90 (t, J = 18.4 Hz, 3H), 1.76 (s, 3H).

Synthesis of 173

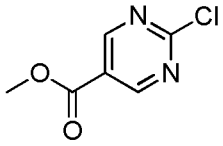
[00491] **Step 1: Synthesis of 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (173-A)**



[00492] To a 50 mL round-bottom flask equipped with a magnetic stir bar was added 1-bromo-4-(difluoromethoxy)benzene (500 mg, 2.24 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 (1.14 g, 4.48 mmol, 2.0 *eq*), potassium acetate (440 mg, 4.48 mmol, 2.0 *eq*) followed by the addition of dioxane (20 mL). Then 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (164 mg, 224 umol, 0.10 *eq*) was added into the mixture at 25 °C. The flask was then evacuated and backfilled with nitrogen for three times. The mixture was stirred at 85 °C under an atmosphere of nitrogen for 12 hr. The mixture was filtered, 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 50/1 to 25/1) to give 500 mg (71% yield) of **173-A** as a colorless oil.

[00493] **LCMS**: (ESI) *m/z*: 271.1 $[M+H]^+$.

[00494] **Step 2: Synthesis of methyl 2-chloropyrimidine-5-carboxylate (173-B)**

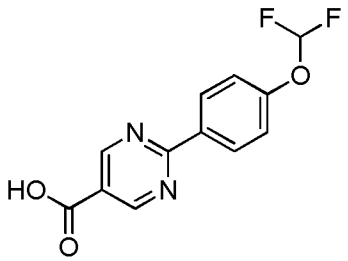


[00495] To a 100 mL round-bottom flask equipped with a magnetic stir bar was added 2-

chloropyrimidine-5-carboxylic acid (1.00 g, 6.31 mmol, 1.0 *eq*) followed by the addition of toluene (30 mL) and methanol (12 mL). Then diazomethyl(trimethyl)silane (2 M, 6.31 mL, 2.0 *eq*) was added into the mixture at 25 °C. The mixture was stirred at 25 °C for 0.5 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 30/1 to 25/1) to give 0.700 g (61% yield) of **173-B** as a white solid.

[00496] **LCMS**: (ESI) *m/z*: 173.0 $[M+H]^+$.

[00497] **Step 3: Synthesis of 2-(4-(difluoromethoxy)phenyl)pyrimidine-5-carboxylic acid (173-C)**

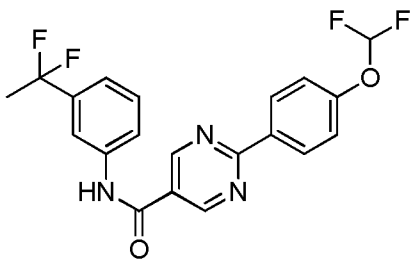


[00498] To a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **173-B** (224 mg, 1.24 mmol, 1.3 *eq*), **173-A** (250 mg, 792 umol, 8.3e-1 *eq*), sodium bicarbonate (240 mg, 2.86 mmol, 3.0 *eq*) followed by the addition of dioxane (12 mL) and water (4 mL). Then1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (69.8 mg, 95.4 umol, 0.10 *eq*) was added into the mixture at 25 °C. The mixture was heated to 85 °C and stirred for 12 hr. The mixture was filtered, the filtrate was diluted with water (10 ml). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with ethyl acetate (20 mL). The pH of the aqueous phase was adjusted to 4. The mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 250 mg (88% yield) of **173-C** as a yellow solid.

[00499] **LCMS**: (ESI) *m/z*: 267.1 $[M+H]^+$.

[00500] **Step 4: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)pyrimidine-5-carboxamide (173)**

Compound ID : 173



[00501] **173** was obtained via similar procedure of **179** from **173-C** and 3-(1,1-difluoroethyl)aniline

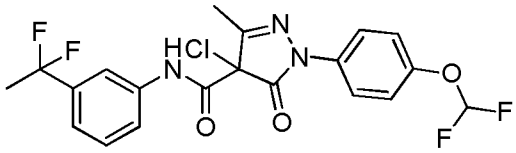
[00502] **LCMS**: (ESI) *m/z* 406.1 $[M+H]^{+\cdot}$

[00503] **1H NMR** (400 MHz, MeOD-d_4) δ: 9.32 (s, 2H), 8.56-8.58 (m, 2H), 7.97 (s, 1H), 7.83 (d, *J*=8.00 Hz, 1H), 7.48 (t, *J*=7.6 Hz, 1H), 7.35 (d, *J*=7.2 Hz, 1H), 7.29 (d, *J*=8.8 Hz, 2H), 6.97 (t, *J*=73.6 Hz, 1H), 1.94 (t, *J*=18.4 Hz, 3H).

Synthesis of 172

[00504] **Step 1: Synthesis of 4-chloro-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (172)**

Compound ID: 172



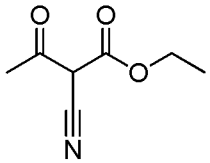
[00505] To a solution of **298i** (0.100 g, 236 umol, 1.0 *eq*) in tetrahydrofuran (2 mL) was added dropwise a solution of 1-chloropyrrolidine-2,5-dione (47.3 mg, 354 umol, 1.5 *eq*) in tetrahydrofuran (2 mL) at 0 °C. The mixture was stirred at 0 °C for 5 min. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225%formic acid)-acetonitrile]; B%: 68%-98%, 9min) to give 39.7 mg (34% yield) of **172** as a yellow oil.

[00506] **LCMS**: (ESI) *m/z*: 480.0 $[M+Na]^+$.

[00507] **^{1}H NMR** (400MHz, $CDCl_3$-*d*) δ: 8.82 (br s, 1H), 7.91 (d, *J*=9.2 Hz, 2H), 7.73 (s, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.44 (t, *J*=8.0 Hz, 1H), 7.36 (d, *J*=8.0 Hz, 1H), 7.21 (d, *J*=9.2 Hz, 2H), 6.52 (t, *J*=73.6 Hz, 1H), 2.47 (s, 3H), 1.93 (t, *J*=18.4 Hz, 3H).

Synthesis of 171

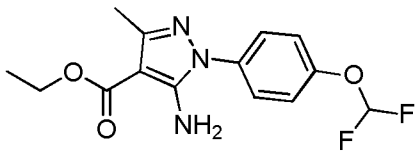
[00508] **Step 1: Synthesis of ethyl 2-cyano-3-oxobutanoate (171-A)**



[00509] To a solution of ethyl 5-methylisoxazole-4-carboxylate (9.00 g, 58.0 mmol, 1.0 *eq*) in ethanol (100 mL) was added sodium ethoxide (7.89 g, 116 mmol, 2.0 *eq*) slowly at 0 °C, then the solution was stirred at 20 °C for 12 h. The solution was diluted with water (50 mL), adjusted to pH=1 with hydrochloric acid (1 M), extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and concentrated to give 8.50 g (94% yield) of **171-A** as a yellow oil.

[00510] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 13.62(s, 1H), 4.33(dd, *J*= 14.4 Hz, 7.2 Hz, 2H), 2.34(s, 3H), 1.36(t, *J*= 7.2 Hz, 3H).

[00511] **Step2: Synthesis of ethyl 5-amino-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylate (171-B)**



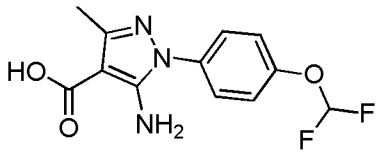
[00512] To a mixture of **171-A** (2.00 g, 12.9 mmol, 1.0 *eq*) and (4-(difluoromethoxy)phenyl)hydrazine.

[00513] (2.24 g, 12.9 mmol, 1.0 *eq*) in ethyl acetate (20 mL) was added propylphosphonic anhydride (16.4 g, 25.8 mmol, 50% purity, 2.0 *eq*), the suspension was stirred at 50 °C for 12 h. The solution was

poured into water (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with saturated sodium bicarbonate solution (20 mL) and then brine (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 10/1 to 5/1) to give 600 mg (15% yield) of **171-B** as a red solid.

[00514] **LCMS**:(ESI) *m/z*: 311.9 $[M+H]^+$.

[00515] **Step3: Synthesis of 5-amino-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid (171-C)**

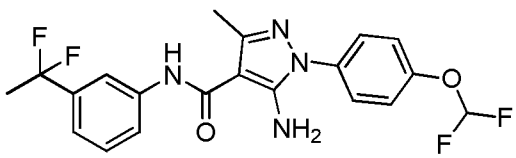


[00516] To a solution of **171-B** (200 mg, 643 umol, 1.0 *eq*) in methanol (3 mL) /water (1 mL) was added lithium hydroxide hydrate (135 mg, 3.21 mmol, 5.0 *eq*), the solution was stirred at 50 °C for 30 mins. The solution was concentrated. The residue was diluted with water (3 mL). The filtrated was adjusted to pH=3 with hydrochloric acid (1 M). The suspension was filtered and washed with water (5 mL x 3). The filter cake was dried under vacuum to give 100 mg (53% yield) of **171-C** as a white solid.

[00517] **LCMS**: (ESI) *m/z*: 284.0 $[M+H]^+$.

[00518] **Step4: Synthesis of 5-amino-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1*H*-pyrazole-4-carboxamide (171)**

Compound ID: **171**



[00519] To a solution of **171-C** (100 mg, 337 umol, 1.0 *eq*) and 3-(1,1-difluoroethyl)aniline (79.55 mg, 506.14 umol, 1.5 *eq*) in pyridine (5 mL) was added *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (97.0 mg, 506 umol, 1.5 *eq*), the solution was stirred at 50 °C for 12 h. The solution was concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 5/1 to 1/1) to afford a gray solid. The solid was purified by preparative HPLC (column: Waters Xbridge 150*25 5u; mobile phase: [water (10mM ammonium bicarbonate)-acetonitrile]; B%: 42%-72%, 10min) to give 11.2 mg (8% yield) of **171** as a white solid.

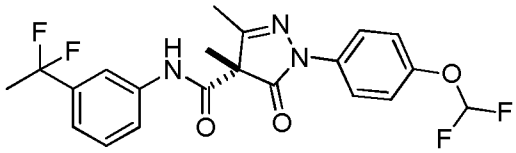
[00520] **LCMS**: (ESI) *m/z*: 423.2 $[M+H]^+$.

[00521] **^{1}H NMR**(400MHz, DMSO-d_6) δ: 8.92(s, 1H), 7.91(s, 1H), 7.73(d, *J*= 8.4Hz, 1H), 7.62-7.59(m, 2H), 7.44(t, *J*= 7.6Hz, 1H), 7.31(d, *J*= 4.4Hz, 2H), 7.23(d, *J*= 7.6Hz, 1H), 7.34(t, *J*= 60.4Hz, 1H), 6.29 (s, 2H), 2.44(s, 3H), 1.97(t, *J*= 18.8Hz, 3H).

Synthesis of 170

[00522] **Step 1: Synthesis of (4S)-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (170)**

Compound ID: 170



[00523] 15.0 mg of **174** was purified by SFC (column: DAICEL CHIRALCEL OJ-H(250mm*30mm,5um);mobile phase: [Neu-methanol];B%: 20%-20%,3.7 min ; 50 min) to give 3.90 mg (27% yield) of **170** as yellow oil.

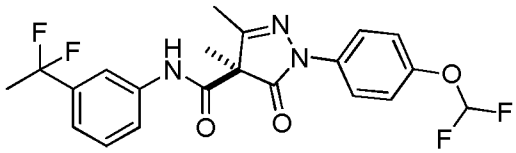
[00524] **LCMS**: (ESI) *m/z*: 438.3 $[M+H]^+$.

[00525] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 7.97 (d, J = 9.2 Hz, 2H), 7.78 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.82 (t, J = 74.4 Hz, 1H), 2.30 (s, 3H), 1.90 (t, J = 18.4 Hz, 3H), 1.76 (s, 3H).

Synthesis of 169

[00526] **Step 1: Synthesis of (4R)-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3,4-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (169)**

Compound ID: 169



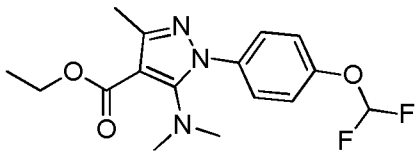
[00527] 15.0 mg of **174** was purified by SFC (column: DAICEL CHIRALCEL OJ-H(250mm*30mm,5um);mobile phase: [Neu-methanol];B%: 20%-20%,3.7 min ; 50 minmin) to give 5.50 mg (38% yield) of **169** as yellow oil.

[00528] **LCMS**: (ESI) *m/z*: 438.3 $[M+H]^+$.

[00529] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 7.97 (d, J = 9.2 Hz, 2H), 7.78 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.82 (t, J = 74.4 Hz, 1H), 2.30 (s, 3H), 1.90 (t, J = 18.4 Hz, 3H), 1.76 (s, 3H).

Synthesis of 168

[00530] **Step1: Synthesis of ethyl 1-(4-(difluoromethoxy)phenyl)-5-(dimethylamino)-3-methyl-1*H*-pyrazole-4-carboxylate (168-A)**

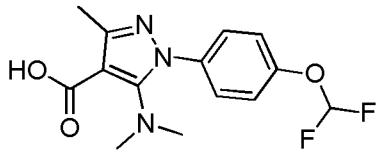


[00531] To a solution of **171-B** (160 mg, 514 umol, 1.0 *eq*) in *N*,*N*-dimethylformamide (5 mL) was added sodium hydride (41.1 mg, 1.03 mmol, 60% purity, 2.0 *eq*) at 0 °C. The solution was stirred at 0 °C for 30 mins. Then iodomethane (80.2 mg, 565 umol, 1.1 *eq*) was added into the solution and the reaction mixture was stirred at 25°C for stirred for 2 h. The solution was poured into water (10 mL), extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (20 mL),

dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 10/1 to 2/1) to afford 60.0 mg (30% yield) of **168-A** as a white solid.

[00532] **LCMS**: (ESI) *m/z*: 340.1 $[M+H]^+$.

[00533] **Step 2: Synthesis of 1-(4-(difluoromethoxy)phenyl)-5-(dimethylamino)-3-methyl-1*H*-pyrazole-4-carboxylic acid (168-B)**

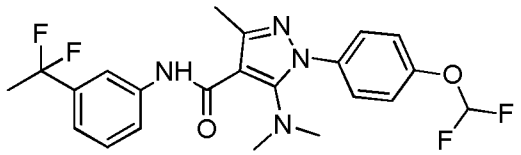


[00534] **168-B** was obtained via similar procedure of **171-C** from **168-A** and sodium hydroxide.

[00535] **LCMS**: (ESI) *m/z*: 312.2 $[M+H]^+$.

[00536] **Step 3: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-(dimethylamino)-3-methyl-1*H*-pyrazole-4-carboxamide (168)**

Compound ID: 168



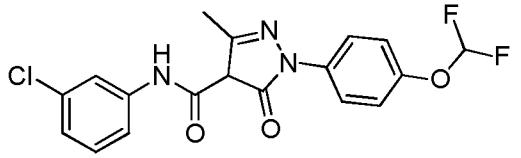
[00537] **168** was obtained via similar procedure of **171** from **168-B**.

[00538] **LCMS**: (ESI) *m/z*: 451.2 $[M+H]^+$.

[00539] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.22(s, 1H), 7.99(s, 1H), 7.73(d, *J*= 7.2 Hz, 1H), 7.65-7.63(m, 2H), 7.44(t, *J*= 8.0 Hz, 1H), 7.33- 7.30(m, 2H), 7.31(t, *J* = 74.0 Hz, 1H), 7.26(d, *J*= 7.6 Hz ,1H), 2.70-2.65(m, 6H), 2.28(s, 3H), 1.96(t, *J*= 18.8 Hz, 3H).

Synthesis of 167

[00540] **Step 1: Synthesis of *N*-(3-chlorophenyl)-1-[4-(difluoromethoxy)phenyl]-3-methyl-5-oxo-4*H*-pyrazole-4-carboxamide (167-A)**



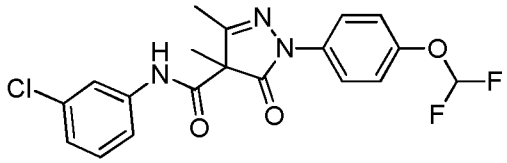
[00541] **167-A** was obtained via general procedure IV from 4-nitrophenyl 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate

[00542] and 3-chloroaniline.

[00543] **LCMS**: (ESI) *m/z*: 394.1 $[M+H]^+$.

[00544] **Step 2: Synthesis of *N*-(3-chlorophenyl)-1-[4-(difluoromethoxy)phenyl]-3,4-dimethyl-5-oxo-pyrazole-4-carboxamide (167)**

Compound ID: 167



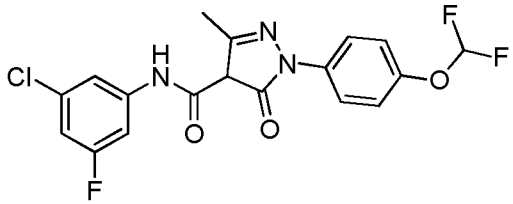
[00545] To a solution of **167-A** (55.0 mg, 135 umol, 1.0 *eq*) in tetrahydrofuran (5 mL) was added iodomethane (28.8 mg, 203 umol, 1.5 *eq*) and tetrabutylammonium fluoride (1 M, 203 uL, 1.5 *eq*). It was stirred at 25 °C for 12 h. The mixture was concentrated under reduced pressure to give a residue. It was purified by Prep-TLC (**petroleum ether/ethyl acetate** =5/1) to afford a crude product. The crude product was further purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 50%-80%, 10min) to give 1.10 mg (2% yield) of **167** as a white solid.

[00546] **LCMS**: (ESI) *m/z*: 408.2 $[M+H]^+$.

[00547] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.96 (d, J = 9.2 Hz, 2H), 7.72 (t, J = 2.0 Hz, 1H), 7.46~7.44 (m, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 7.16~7.14 (m, 1H), 6.82 (t, J = 74.0 Hz, 1H), 2.29 (s, 3H), 1.75 (s, 3H).

Synthesis of 166

[00548] **Step 1: Synthesis of *N*-(3-chloro-5-fluoro-phenyl)-1-[4-(difluoromethoxy)phenyl]-3-methyl-5-oxo-4*H*-pyrazole-4-carboxamide (166-A)**

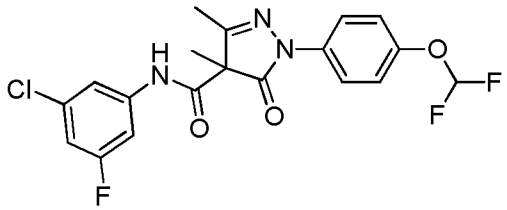


[00549] **166-A** was obtained via general procedure IV from 4-nitrophenyl 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-chloro-5-fluoro-aniline.

[00550] **LCMS**: (ESI) *m/z*: 434.1 $[M+H]^+$.

[00551] **Step 2: Synthesis of *N*-(3-chloro-5-fluoro-phenyl)-1-[4-(difluoromethoxy)phenyl]-3,4-dimethyl-5-oxo-pyrazole-4-carboxamide (166)**

Compound ID: 166



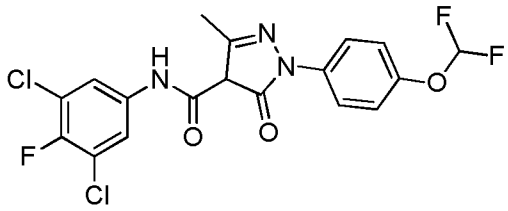
[00552] **166** was obtained via similar procedure of **167** from **166-A** and iodomethane

[00553] **LCMS**: (ESI) *m/z*: 425.9 $[M+H]^+$.

[00554] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.95 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 7.46~7.43 (m, 1H), 7.21 (d, J = 8.8 Hz, 2H), 6.98~6.96 (m, 1H), 6.82 (t, J = 74.0 Hz, 1H), 2.28 (s, 3H), 1.75 (s, 3H)

Synthesis of 165

[00555] **Step 1: Synthesis of *N*-(3,5-dichloro-4-fluoro-phenyl)-1-[4-(difluoromethoxy)phenyl]-3-methyl-5-oxo-4*H*-pyrazole-4-carboxamide (165-A)**

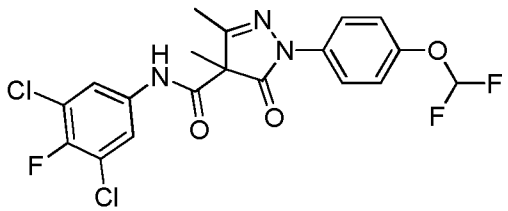


[00556] **165-A** was obtained via general procedure IV from 4-nitrophenyl 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3,5-dichloro-4-fluoro-aniline.

[00557] **LCMS**: (ESI) *m/z*: 446.1 $[M+H]^+$.

[00558] **Step 2: Synthesis of *N*-(3,5-dichloro-4-fluoro-phenyl)-1-[4-(difluoromethoxy)phenyl]-3,4-dimethyl-5-oxo-pyrazole-4-carboxamide (165)**

Compound ID: 165



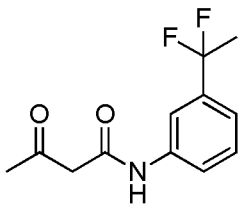
[00559] **165** was obtained via similar procedure of **167** from **165-A** and iodomethane

[00560] **LCMS**: (ESI) *m/z*: 460.1 $[M+H]^+$.

[00561] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.95 (d, J = 9.2 Hz, 2H), 7.75 (s, 1H), 7.73 (s, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.82 (t, J = 74.0 Hz, 1H), 2.28 (s, 3H), 1.74 (s, 3H).

Synthesis of 164

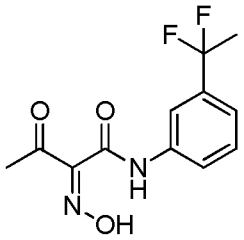
[00562] **Step 1: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-3-oxobutanamide (164-A)**



[00563] 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 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 **164-A** as a brown solid.

[00564] **LCMS**: (ESI) *m/z*: 242.5 $[M+H]^+$.

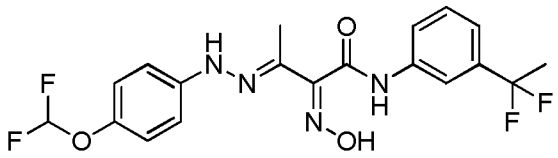
[00565] **Step 2: Synthesis of (Z)-*N*-(3-(1,1-difluoroethyl)phenyl)-2-(hydroxyimino)-3-oxobutanamide (164-B)**



[00566] To a 50 mL round-bottom flask equipped with a magnetic stir bar was added **164-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. Next, 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), the resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was 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 **164-B** as a yellow oil.

[00567] **LCMS**: (ESI) *m/z*: 271.1 $[M+H]^+$.

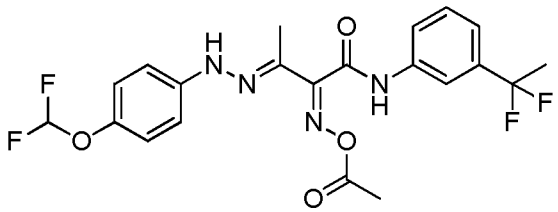
[00568] **Step 3: Synthesis of (2Z,3E)-*N*-(3-(1,1-difluoroethyl)phenyl)-3-(2-(4-(difluoromethoxy)phenyl)hydrazono)-2-(hydroxyimino)butanamide (164-C)**



[00569] To a 10 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **164-B** (130 mg, 405 umol, 1.0 *eq*) and (4-(difluoromethoxy)phenyl)hydrazine (106 mg, 562 umol, 1.4 *eq*) followed by the addition of ethanol (4 mL). The mixture was heated to 80 °C and stirred for 0.5 hr. The mixture was concentrated under reduced pressure to give 180 mg (crude) of **164-C** as a brown oil.

[00570] **LCMS**: (ESI) *m/z*: 427.1 $[M+H]^+$.

[00571] **Step 4: Synthesis of (2Z,3E)-2-(acetoxyimino)-N-(3-(1,1-difluoroethyl)phenyl)-3-(2-(4-(difluoromethoxy)phenyl)hydrazono)butanamide (164-D)**

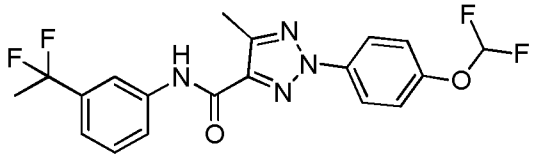


[00572] A mixture of **164-C** (180 mg, 422 umol, 1.0 *eq*) in acetic anhydride (3 mL) was stirred at 50 °C for 2 hr. The mixture was quenched by slow addition of methanol (10 mL). The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 44%-74%, 10min) to give 40.0 mg (20% yield) of **164-D** as a yellow solid.

[00573] **LCMS**: (ESI) *m/z*: 469.3 $[M+H]^+$.

[00574] **Step 4: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)-5-methyl-2H-1,2,3-triazole-4-carboxamide (164)**

Compound ID : 164



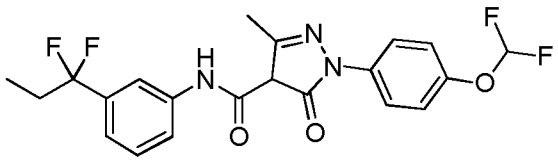
[00575] To a 10 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **164-D** (35.0 mg, 73.8 umol, 1.0 *eq*) followed by the addition of *N*, *N*-dimethylformamide (2 mL). Then potassium carbonate (102 mg, 738 umol, 10 *eq*) was added into the mixture. The mixture was heated to 50 °C and stirred for 1 hr. The mixture was filtered to give a filtrate. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225%formic acid)-acetonitrile]; B%: 65%-95%, 9min) to give 20.0 mg (67% yield) of **164** as a white solid.

[00576] **LCMS**: (ESI) *m/z*: 409.0 $[M+H]^+$.

[00577] **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.54 (s, 1H), 8.15-8.19 (m, 2H), 8.08 (s, 1H), 7.95 (d, *J*=8.0 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.44 (d, *J*=9.2 Hz, 2H), 7.35 (t, *J*=73.6 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 2.59 (s, 3H), 1.98 (t, *J*=18.8 Hz, 3H).

Synthesis of 163

[00578] **Step 1: 1-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (163-A)**



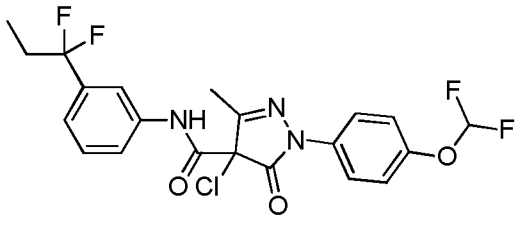
[00579] **163-A** was obtained via general procedure IV from 4-nitrophenyl 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-(1,1-difluoropropyl)aniline

[00580] **LCMS**: (ESI) *m/z*: 438.1 $[M+H]^+$.

[00581] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.88 (s, 1H), 7.68-7.73 (m, 2H), 7.66 (br d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.71-7.13 (m, 1H), 2.65 (s, 3H), 2.10-2.31 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H).

[00582] **Step 2: 4-chloro-1-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (163)**

Compound ID : 163



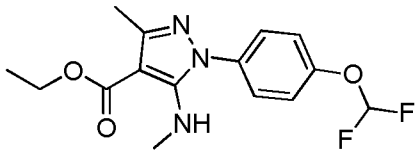
[00583] To a 10mL round-bottom flask equipped with a magnetic stir bar was added **163-A** (30.0 mg, 60.9 umol, 1.0 *eq*) followed by the addition of tetrahydrofuran (1 mL). Then reagent 1-chloropyrrolidine-2,5-dione (9.16 mg, 68.6 umol, 1.1 *eq*) was added into the mixture at 25 °C. The mixture was stirred at 25 °C for 10 min. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi Max-RP 150*50mm*10 um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 50%-80%, 10min) to give 20.0 mg (66% yield) of **163** as a yellow oil.

[00584] **LCMS**: (ESI) *m/z*: 438.2 $[M+H]^+$.

[00585] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.82 (br s, 1H), 7.86-7.98 (m, 2H), 7.62-7.70 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.31 (br d, J = 7.2 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.29-6.77 (m, 1H), 2.47 (s, 3H), 2.08-2.23 (m, 2H), 1.00 (t, J = 7.6Hz, 3H).

Synthesis of 162

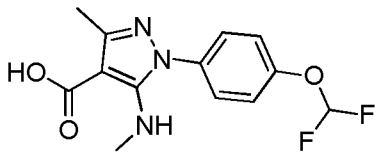
[00586] **Step 1: Synthesis of ethyl 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-(methylamino)-1*H*-pyrazole-4-carboxylate (162-A)**



[00587] **162-A** was obtained via similar procedure of **168-A** from **171-B** and iodomethane.

[00588] **LCMS**: (ESI) *m/z*: 326.1 $[M+H]^+$.

[00589] **Step 2: Synthesis of 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-(methylamino)-1*H*-pyrazole-4-carboxylic acid (162-B)**

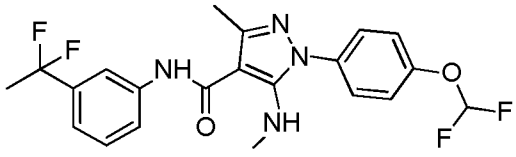


[00590] **162-B** was obtained via similar procedure of **168-B** from **162-A** and sodium hydroxide.

[00591] **LCMS**: (ESI) *m/z*: 298.0 $[M+H]^+$.

[00592] **Step 3: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-(methylamino)-1*H*-pyrazole-4-carboxamide (162)**

Compound ID: 162



[00593] To a solution of **162-B** (300 mg, 970 umol, 1.0 *eq*) and 1*H*-benzo[*d*][1,2,3]triazol-1-ol (576 mg, 1.51 mmol, 1.6 *eq*) in *N*,*N*-dimethylformamide (10 mL) was *N*,*N*-diisopropylethylamine (261 mg, 2.02 mmol, 2.1 *eq*), the solution was stirred at 30 °C for 15 mins. Then 3-(1,1-difluoroethyl)aniline (159 mg, 1.01 mmol, 1.0 *eq*) was added into the solution and the mixture was stirred at 80 °C for 12 h. The solution was concentrated. The residue was purified by prep-HPLC (column: Waters Xbridge 150*25 5u; mobile phase: [water (10mM ammonium bicarbonate)-acetonitrile]; B%: 42%-72%, 10min) to give 129 mg

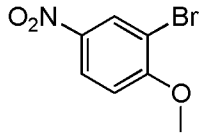
(31% yield) of **162** as a gray solid.

[00594] **LCMS**: (ESI) *m/z*: 437.2 $[M+H]^+$.

[00595] **^{1}H NMR**(400Hz, DMSO-d_6) δ: 9.46(s, 1H), 7.96(s, 1H), 7.72(d, *J*= 8.4Hz, 1H), 7.58-7.55(m, 2H), 7.43(t, *J*= 8.0Hz, 1H), 7.32(d, *J*= 8.8Hz, 2H), 7.31(t, *J*= 74.0Hz, 1H), 7.23(d, *J*= 7.6Hz, 1H), 6.19(dd, *J*= 10.8Hz, 5.6Hz, 1H), 2.55(s, 3H), 2.35(s, 3H), 1.96(t, *J*= 18.8Hz, 3H).

Synthesis of 161

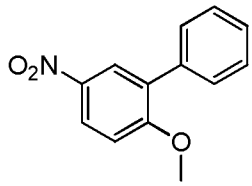
[00596] **Step 1: Synthesis of 2-bromo-1-methoxy-4-nitrobenzene (161-A)**



[00597] To a solution of 2-bromo-4-nitro-phenol (50.0 g, 229 mmol, 1.0 *eq*) and potassium carbonate (63.4 g, 459 mmol, 2.0 *eq*) in *N*,*N*-dimethylformamide (300 mL) was added iodomethane (130 g, 917 mmol, 4 .0 *eq*) dropwise at 25 °C, and the reaction mixture was stirred at 50 °C for 12 hr. To the reaction mixture was added water (500 mL). The suspension was filtrated and the filter cake was washed with water (300 mL). The solid was concentrated under reduced pressure to give 80.0 g (crude) of **161-A** as a white solid.

[00598] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 8.48 (d, *J* = 2.8 Hz, 1H), 8.21 - 8.24 (m, 1H), 6.97 (d, *J* = 9.2 Hz, 1H), 4.02 (s, 3H).

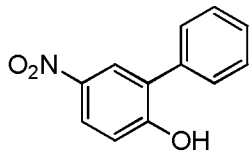
[00599] **Step 2: Synthesis of 2-methoxy-5-nitro-1,1'-biphenyl (161-B)**



[00600] To a solution of **161-A** (10.0 g, 43.1 mmol, 1.0 *eq*) and phenylboronic acid (21.0 g, 172 mmol, 4.0 *eq*) in dioxane (150 mL)was added a solution of potassium carbonate (11.9 g, 86.2 mmol, 2.0 *eq*) in water (15 mL) and 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.58 g, 2.15 mmol, 0.050 *eq*). The suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under nitrogen at 80 °C for 16 hr. To the reaction mixture was added water (200 mL), and the reaction mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layer was dried over with sodium sulfate, filtered, concentrated under reduced pressure to give a residue. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 1/0 to 10/1*)* to give 6.28 g (63% yield) of **161-B** as a light brown solid.

[00601] **LCMS**: (ESI) *m/z*: 230.2 $[M+H]^+$.

[00602] **Step 3: Synthesis of 5-nitro-[1,1'-biphenyl]-2-ol (161-C)**

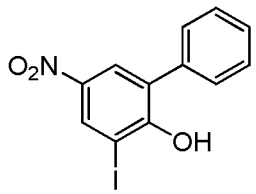


[00603] To a solution of **161-B** (6.28 g, 27.1 mmol, 1.0 *eq*) in *N*,*N*-dimethylacetamide (60 mL) was

added lithium chloride (9.17 g, 216 mmol, 8.0 *eq*) at 25 °C, the reaction mixture was stirred at 145 °C for 48 hr. To the reaction mixture was added water (300 mL), the mixture was extracted with ethyl acetate (300 mL x 3), the combined organic layer was washed with brine (200 mL x 3), dried over with sodium sulfate, filtered, concentrated under reduced pressure to give a residue. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 10/1 to 5/1) to give 5.50 g (69% yield) of **161-C** as a yellow solid.

[00604] **LCMS**: (ESI) *m/z*: 216.1 $[M+H]^+$.

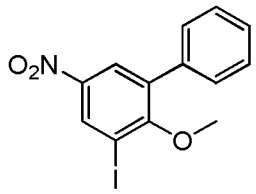
[00605] **Step 4: Synthesis of 3-iodo-5-nitro-[1,1'-biphenyl]-2-ol (161-D)**



[00606] To a solution of **161-C** (5.50 g, 18.7 mmol, 1.0 *eq*) in dimethyl sulfoxide (50 mL) was added iodine (13.0 g, 51.1 mmol, 2.7 *eq*), then the reaction mixture was stirred at 110 °C for 4 hr. To the reaction mixture was added saturated sodium thiosulfate (50 mL), and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (50 mL x 3), dried over with sodium sulfate, filtered, concentrated under reduced pressure to give a residue. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 1/0 to 10/1) to give 6.50 g (crude) of **161-D** as yellow oil.

[00607] **LCMS**: (ESI) *m/z*: 342.0 $[M+H]^+$.

[00608] **Step 5: Synthesis of 3-iodo-2-methoxy-5-nitro-1,1'-biphenyl (161-E)**

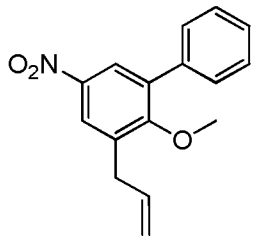


[00609] To a solution of **161-D** (5.00 g, 14.7 mmol, 1.0 *eq*) in *N*,*N*-dimethylformamide (50 mL) was added iodomethane (6.24 g, 44.0 mmol, 3.0 *eq*) and potassium carbonate (6.08 g, 44.0 mmol, 3 .0 *eq*), the solution was stirred at 50 °C for 12 h. The solution was poured into water (100 mL), extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 1/0 to 10/1) to give 5.00 g (95% yield) of **161-E** as a white solid.

[00610] **LCMS**: (ESI) *m/z*: 356.0 $[M+H]^+$.

[00611] **^{1}H NMR** (400Hz, $CDCl_3$-*d*) δ: 8.63(d, *J* = 2.4 Hz, 1H), 8.23(d, *J*= 2.8 Hz, 1H), 7.59-7.56(m, 2H), 7.51-7.46(m, 3H), 3.47(s, 3H).

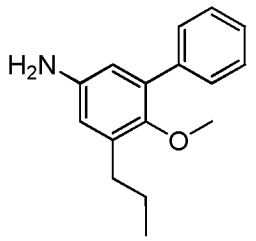
[00612] **Step 6: Synthesis of 3-allyl-2-methoxy-5-nitro-1,1'-biphenyl (161-F)**



[00613] A solution of **161-E** (2.00 g, 5.57 mmol, 1.0 *eq*), cesium fluoride (3.39 g, 22.3 mmol, 4.0 *eq*) and tetrakis(triphenylphosphine)platinum (644 mg, 557 umol, 0.10 *eq*) in tetrahydrofuran (20 mL) was stirred at 20 °C under nitrogen for 30 mins. Then 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.34 g, 13.9 mmol, 2.5 *eq*) in tetrahydrofuran (3 mL) was added. The suspension was stirred at 75 °C for 10 h. The reaction was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether, from 0/1 to 1/2) to afford 1.05 g (70% yield) of **161-F** as off-white solid.

[00614] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 8.13 (d, *J*=2.8, 1H), 8.08 (d, *J*=2.8, 1H), 7.59 - 7.57 (m, 2H), 7.50 - 7.46 (m, 2H), 7.44 - 7.41 (m, 1H), 6.05-5.99 (m, 1H), 5.22 - 5.15 (m, 2H), 3.54 (d, *J*=6.4 Hz, 2H), 3.42 (s, 3H).

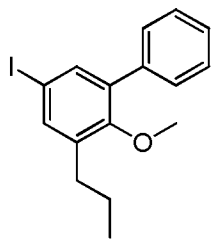
[00615] **Step 7: Synthesis of 6-methoxy-5-propyl-[1,1'-biphenyl]-3-amine (161-G)**



[00616] To a solution of **161-F** (1.00 g, 3.71 mmol, 1.0 *eq*) in methanol (20 mL) was added Pd/C (0.100 g, 371 umol, 10% purity, 0.10 *eq*). The suspension was degassed and purged with hydrogen for three times. The reaction was stirred at 20 °C under hydrogen (15 psi) for 1 h. The suspension was filtered and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether=1/5) to give 0.750 g (75% yield) of **161-G** as a yellow oil.

[00617] **LCMS**: (ESI) *m/z*: 242.1 $[M+H]^+$.

[00618] **Step 8: Synthesis of 5-iodo-2-methoxy-3-propyl-1,1'-biphenyl (161-H)**

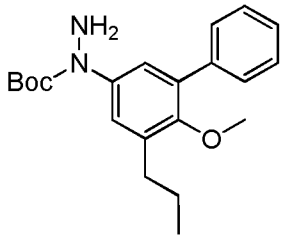


[00619] To a suspension of **161-G** (0.750 g, 2.80 mmol, 1.0 *eq*) in hydrochloric acid (3 M, 2.93 mL, 3.14 *eq*) and acetonitrile (5 mL) was added sodium nitrite (289 mg, 4.20 mmol, 1.5 *eq*) in water (10 mL) at 0 °C. The mixture was stirred at 0 °C for 10 mins. Then potassium iodide (2.32 g, 14.0 mmol, 5.0 *eq*) in water (5 mL) was added. The suspension was stirred at 0 °C for 20 min and at 60 °C for 1 h. The reaction was extracted with ethyl acetate (15 mL x 3), the combined organic layer was washed with

saturated aqueous sodium bisulfite solution (20 mL) and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ ethyl acetate, 1/10) to afford 0.850 g (86% yield) of **161-H** as yellow oil.

[00620] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 7.56 - 7.51 (m, 2H), 7.50 (q, *J*=2.4 Hz, 2H), 7.44 - 7.39 (m, 2H), 7.38 - 7.33 (m, 1H), 3.32 (s, 3H), 2.65 - 2.57 (t, *J*=7.6 Hz, 2H), 1.67 (m, 2H), 1.01 (t, *J*=7.2 Hz, 3H)

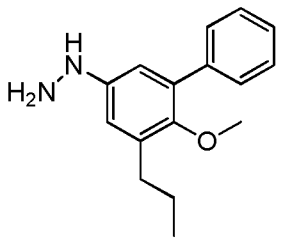
[00621] **Step 9: Synthesis of *tert*-butyl 1-(6-methoxy-5-propyl-[1,1'-biphenyl]-3-yl)hydrazinecarboxylate (161-I)**



[00622] To a solution of **161-H** (0.500 g, 1.42 mmol, 1.0 *eq*), *tert*-butyl *N*-aminocarbamate (225 mg, 1.70 mmol, 1.2 *eq*) and cesium carbonate (694 mg, 2.13 mmol, 1.5 *eq*) in *N*,*N*-dimethylformamide (5 mL) was added cuprous iodide (27.0 mg, 142 umol, 0.10 *eq*) and 1,10-phenanthroline (51.2 mg, 284 umol, 0.20 *eq*). The reaction was stirred at 80 °C for 10 h. The reaction was diluted with ethyl acetate (10 mL) and filtered, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/5) to afford 0.210 g (42% yield) of **161-I** as yellow oil.

[00623] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.56 (d, *J*=7.2 Hz, 2H), 7.42 (t, *J*=7.2 Hz, 2H), 7.38 - 7.31 (m, 1H), 7.22 (d, *J*=6.0 Hz, 2H), 3.31 (br s, 3H), 2.73 - 2.62 (m, 2H), 1.70 (qd, *J*=7.2, 15.2 Hz, 2H), 1.50 (s, 9H), 1.02 (t, *J*=7.2 Hz, 3H).

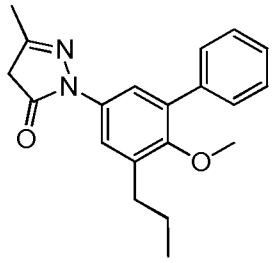
[00624] **Step 10: Synthesis of (6-methoxy-5-propyl-[1,1'-biphenyl]-3-yl)hydrazine (161-J)**



[00625] A solution of **161-I** (0.200 g, 561 umol, 1.0 *eq*) in hydrogen chloride/ethyl acetate (4 M, 1 mL, 7.1 *eq*) and ethyl acetate (4 mL) was stirred at 30 °C for 0.5 h. The mixture was stirred at 30 °C for another 2 h. The reaction mixture was concentrated in vacuo to give 0.180 g (crude, hydrochloride) of **161-J** as light-yellow oil.

[00626] **LCMS**: (ESI) *m/z*: 257.1 $[M+H]^+$.

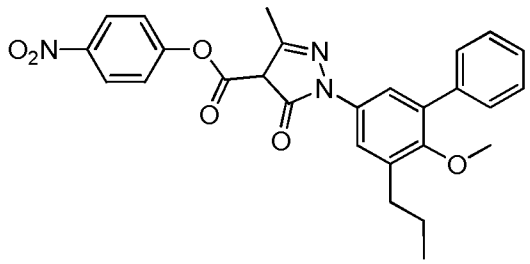
[00627] **Step 11: Synthesis of 1-(6-methoxy-5-propyl-[1,1'-biphenyl]-3-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (161-K)**



[00628] **161-K** was obtained via general procedure II from **161-J**

[00629] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 7.68 - 7.55 (m, 2H), 7.45 - 7.27 (m, 5H), 3.43 - 3.27 (m, 3H), 2.74 - 2.54 (m, 2H), 2.33 - 2.08 (m, 3H), 1.73 - 1.64 (m, 2H), 1.05 - 0.91 (m, 3H).

[00630] **Step 12: Synthesis of 4-nitrophenyl 1-(6-methoxy-5-propyl-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate (161-L)**

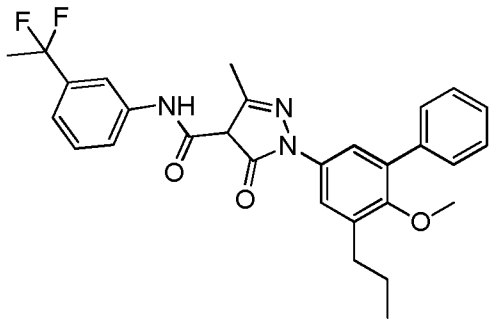


[00631] **161-L** was obtained via general procedure III from **161-K**

[00632] **LCMS**: (ESI) *m/z*: 488.0 $[M+H]^+$.

[00633] **Step 13: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(6-methoxy-5-propyl-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (161)**

Compound ID: 161



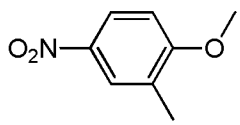
[00634] **161** was obtained via general procedure from **161-L** and 3-(1,1-difluoroethyl)aniline

[00635] **LCMS**: (ESI) *m/z*: 506.5 $[M+H]^+$.

[00636] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.92 (s, 1H), 7.66-7.62 (m, 3H), 7.58 (br s, 2H), 7.46 - 7.41 (m, 2H), 7.40 - 7.33 (m, 2H), 7.18 (br d, *J*=7.6 Hz, 1H), 3.34 (s, 3H), 2.77 (t, *J*=7.6 Hz,, 2H), 2.48 (s, 3H), 1.92 (t, *J*=18.4 Hz, 3H), 1.79 - 1.69 (m, 2H), 1.04 (t, *J*=7.2 Hz, 3H).

Synthesis of 160

[00637] **Step 1: Synthesis of 1-methoxy-2-methyl-4-nitrobenzene (160-A)**

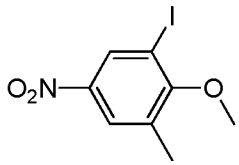


[00638] To a solution of 2-methyl-4-nitro-phenol (4.00 g, 26.1 mmol, 1.0 *eq*) and potassium carbonate

(7.22 g, 52.2 mmol, 2.0 *eq*) in *N*,*N*-dimethylformamide (200 mL) was added iodomethane (14.8 g, 104 mmol, 4.0 *eq*) dropwise at 25 °C, and the reaction mixture was stirred at 50 °C for 12 hr. To the reaction mixture was added water (500 mL). The suspension was filtrated and the filter cake was washed with water (300 mL). The solid was concentrated under reduced pressure to give 3.20 g (crude) of **160-A** as an off-white solid.

[00639] **LCMS**: (ESI) *m/z*: 168.1 $[M+H]^+$.

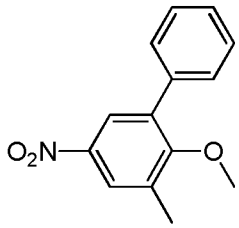
[00640] **Step 2: Synthesis of 1-iodo-2-methoxy-3-methyl-5-nitrobenzene (160-B)**



[00641] To a solution of **160-A** (3.20 g, 19.1 mmol, 1.0 *eq*) and iodine (7.29 g, 28.7 mmol, 1.5 *eq*) in dichloromethane (30 mL) was added oxo((trifluoromethyl)sulfonyl)silver (7.38 g, 28.7 mmol, 1.5 *eq*) at 25 °C, then the reaction was stirred at 30 °C for 12 hr. The reaction mixture was filtered, the filtrate was washed with saturated sodium thiosulfate (100 mL x 2), and the water phase was extracted with dichloromethane (80 mL x 3). The combined organic layer was washed with brine (100 mL x 2), dried over with anhydrous sodium sulfate, filtered, concentrated under reduced pressure to give a residue. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 10/1 to 5/1) to give 5.60 g (97% yield) of **160-B** as a light brown solid.

[00642] **LCMS**: (ESI) *m/z*: 294.0 $[M+H]^+$.

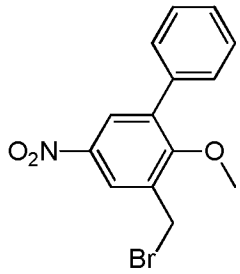
[00643] **Step 3: Synthesis of 2-methoxy-3-methyl-5-nitro-1,1'-biphenyl (160-C)**



[00644] To a solution of **160-B** (5.60 g, 18.7 mmol, 1.0 *eq*) and phenylboronic acid (4.55 g, 37.3 mmol, 2.0 *eq*) in dioxane (50 mL)was added a solution of sodium bicarbonate (3.13 g, 37.3 mmol, 2.0 *eq*) in water (5 mL) and 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.37 g, 1.87 mmol, 0.10 *eq*). The suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under nitrogen at 80 °C for 12 hr. To the reaction mixture was added water (100 mL), and the reaction mixture was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine, dried over with anhydrous sodium sulfate, filtered, concentrated under reduced pressure to give a residue. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 1/0 to 10/1) to give 3.20 g (67% yield) of **160-C** as a light yellow oil.

[00645] **LCMS**: (ESI) *m/z*: 244.1 $[M+H]^+$.

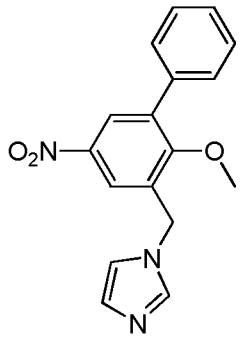
[00646] **Step 4: Synthesis of 3-(bromomethyl)-2-methoxy-5-nitro-1,1'-biphenyl (160-D)**



[00647] To a solution of **160-C** (3.20 g, 12.5 mmol, 1.0 *eq*) in carbon tetrachloride (30 mL) was added dropwise a solution of benzoyl peroxide (605 mg, 2.50 mmol, 0.2 0*eq*) and 1-bromopyrrolidine-2,5-dione (3.34 g, 18.7 mmol, 1.5 *eq*) in carbon tetrachloride (30 mL) at 0 °C, the reaction mixture was stirred at 80 °C for 12 hr. The reaction was washed with water (25 mL x 2), the combined aqueous layer was extracted with dichloromethane (25 mL x 3). The combined organic layer was washed with brine (100 mL), dried over with anhydrous sodium sulfate, filtered, concentrated under reduced pressure to give a residue. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 1/0 to 10/1) to give 3.50 g (87% yield) of **160-D** as a light yellow oil.

[00648] **LCMS**: (ESI) *m/z*: 324.1 $[M+H]^+$.

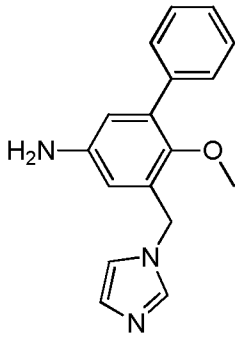
[00649] **Step 5: Synthesis of 1-((2-methoxy-5-nitro-[1,1'-biphenyl]-3-yl)methyl)-1*H*-imidazole (160-E)**



[00650] To a solution of **160-D** (3.50 g, 10.9 mmol, 1.0 *eq*) in dichloromethane (10 mL) was added imidzole (7.40 g, 109 mmol, 10 *eq*) at 25 °C, then the reaction mixture was stirred at 25 °C for 12 hr. To the reaction mixture was added water (10 mL), then the mixture was extracted with dichloromethane (20 mL x 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure to give a residue. The crude product was purified by silica gel column chromatography (ethyl acetate/methanol, from 1/0 to 3/1) to give 1.50 g (45% yield) of **160-E** as a light yellow oil.

[00651] **LCMS**: (ESI) *m/z*: 310.0 $[M+H]^+$.

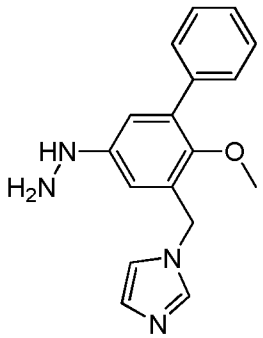
[00652] **Step 6: Synthesis of 5-((1*H*-imidazol-1-yl)methyl)-6-methoxy-[1,1'-biphenyl]-3-amine (160-F)**



[00653] To a solution of **160-E** (1.50 g, 4.85 mmol, 1.0 *eq*) in ethanol (20 mL) / water (5 mL) was added iron powder (1.35 g, 24.3 mmol, 5.0 *eq*) and ammonium chloride (1.30 g, 24.3 mmol, 5.0 *eq*). The suspension was stirred at 50 °C for 2 hours. The suspension was filtered and the filtrate was concentrated to give a residue. The residue was partitioned between ethyl acetate (40 mL) and water (40 mL). The aqueous layer 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 to give 900 mg (64% yield) of **160-F** as a yellow oil.

[00654] **LCMS**: (ESI) *m/z*: 280.1 $[M+H]^+$.

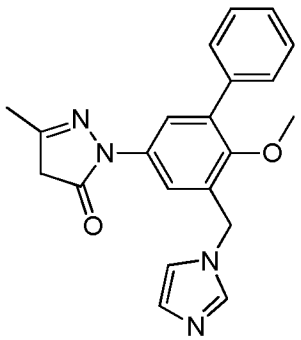
[00655] **Step 7: Synthesis of 1-((5-hydrazinyl-2-methoxy-[1,1'-biphenyl]-3-yl)methyl)-1*H*-imidazole (160-G)**



[00656] **160-G** was obtained via general procedure I from **160-F**.

[00657] **LCMS**: (ESI) *m/z*: 295.1 $[M+H]^+$.

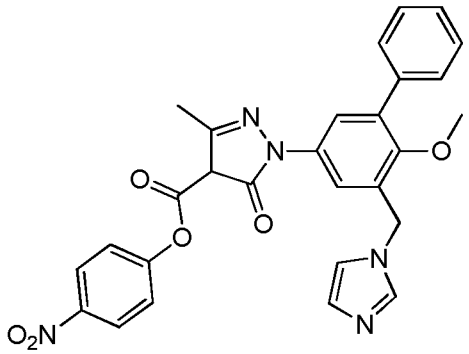
[00658] **Step 8: Synthesis of 1-(5-((1*H*-imidazol-1-yl)methyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (160-H)**



[00659] **160-H** was obtained via general procedure II from **160-G**.

[00660] **LCMS**: (ESI) *m/z*: 361.4 $[M+H]^+$.

[00661] **Step 9: Synthesis of 4-nitrophenyl 1-(5-((1*H*-imidazol-1-yl)methyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate (160-I)**

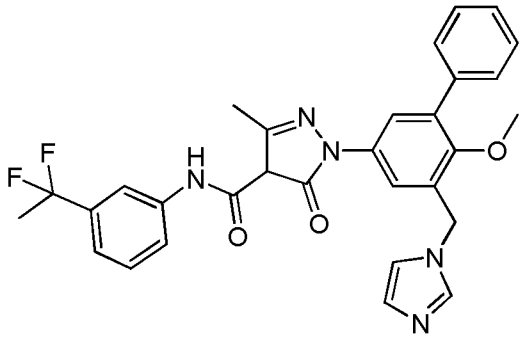


[00662] **160-I** was obtained via general procedure III from **160-H**.

[00663] **LCMS**: (ESI) *m/z*: 526.1 $[M+H]^+$.

[00664] **Step 10: Synthesis of 1-(5-((1*H*-imidazol-1-yl)methyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (160)**

Compound ID: 160



[00665] **160** was obtained via general procedure IV from **160-I**.

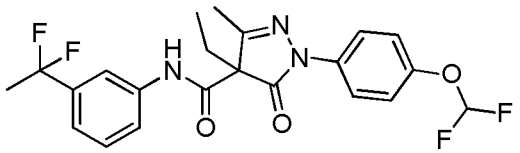
[00666] **LCMS**: (ESI) *m/z*: 544.4 $[M+H]^+$.

[00667] **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.26(s, 1H), 8.21(s, 3H), 7.90-7.87(m, 2H), 7.77(s, 1H), 7.57-7.55(m, 2H), 7.48(t, *J*= 7.6 Hz, 2H), 7.39(t, *J*= 3.2 Hz, 1H), 7.34-7.26(m, 2H), 7.19(s, 1H), 7.04(d, *J*= 7.6 Hz, 1H), 6.91(s, 1H), 5.24(s, 2H), 3.19(s, 3H), 2.24(s, 3H), 1.94(t, *J*= 21.6 Hz, 3H).

Synthesis of 159

[00668] **Step 1: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-4-ethyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (159)**

Compound ID: 159



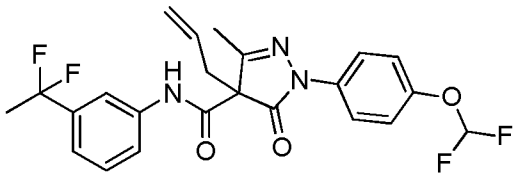
[00669] To a solution of **172** (0.100 g, 183 umol, 1.0 *eq*) in tetrahydrofuran (2 mL) was ethylmagnesium bromide (1 M, 275 uL, 1.5 *eq*) at -78 °C. The mixture was stirred at -78 °C for 0.5 hr. The mixture was quenched with saturated ammonium chloride aqueous (10 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (petroleum ether/ ethyl acetate, 5/1) to give 3.00 mg (4% yield) of **159** as a yellow oil.

[00670] **LCMS**: (ESI) *m/z*: 452.2 $[M+H]^+$.

[00671] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 7.97 (d, J=8.0 Hz, 2H), 7.78 (s, 1H), 7.62 (d, J=8.4 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.22 (d, J=9.2 Hz, 2H), 6.82 (t, J=74.0 Hz, 1H), 2.43 - 2.36 (m, 1H), 2.33 (s, 3H), 2.32 - 2.22 (m, 1H), 1.90 (t, J=18.4 Hz, 3H), 0.86 (t, J=7.2 Hz, 3H).

Synthesis of 158

[00672] **Step 1: Synthesis of 4-allyl-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (158-A)**

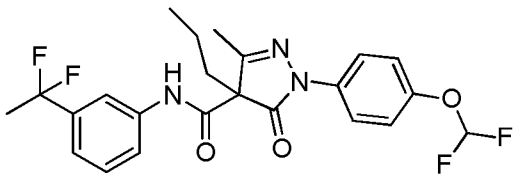


[00673] A mixture of **298i** (100 mg, 236 umol, 1.0 *eq*), 3-iodoprop-1-ene (59.5 mg, 354 umol, 1.5 *eq*) and tetrabutylammonium fluoride (1 M, 354 uL, 1.5 *eq*) in tetrahydrofuran (5 mL) was stirred at 10 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 20/1) to afford 60.0 mg impure product. The impure product was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 55%-85%, 10min) to give 10.0 mg (9% yield) of **158-A** as a white solid.

[00674] **LCMS**: (ESI) *m/z*: 464.2 $[M+H]^+$.

[00675] **Step 2: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4-propyl-4,5-dihydro-1*H*-pyrazole-4-carboxamide (158)**

Compound ID: 158



[00676] To a solution of **158-A** (20.0 mg, 43.2 umol, 1.0 *eq*) in methanol (3 mL) was added Pd/C (10.0 mg, 10% purity) under nitrogen atmosphere. The suspension was degassed and purged with hydrogen for 3 times. The mixture was stirred under hydrogen (15 psi) at 20 °C for 1 hr. The mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225%formic acid)-acetonitrile]; B%: 68%-98%, 9min) to give 2.00 mg (10% yield) of **158** as a yellow oil.

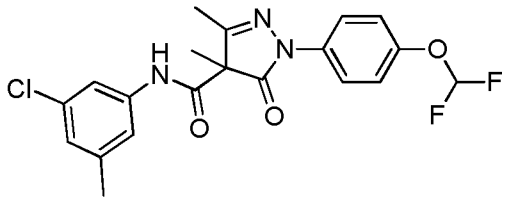
[00677] **LCMS**: (ESI) *m/z*: 466.2 $[M+H]^+$.

[00678] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 7.96 (d, J=9.2 Hz, 2H), 7.78 (s, 1H), 7.63 (d, J=8.4 Hz, 1H), 7.42 (t, J=8.0 Hz, 1H), 7.31 (d, J=7.2 Hz, 1H), 7.22 (d, J=9.2 Hz, 2H), 6.82 (t, J=74.0 Hz, 1H), 2.35 - 2.19 (m, 5H), 1.90 (t, J=18.4 Hz, 3H), 1.28 - 1.13 (m, 2H), 0.97 (t, J=7.2 Hz, 3H).

Synthesis of 157

[00679] **Step 1: Synthesis of *N*-(3-chloro-5-methyl-phenyl)-1-[4-(difluoromethoxy)phenyl]-3,4-dimethyl-5-oxo-pyrazole-4-carboxamide (157)**

Compound ID: 157



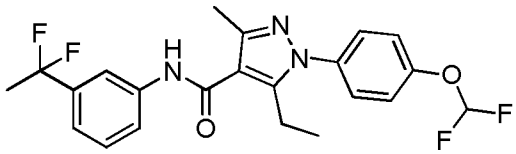
[00680] **157** was obtained via similar procedure of **167** from **393-A** and iodomethane

[00681] **LCMS**: (ESI) *m/z*: 422.0 $[M+H]^+$.

[00682] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.96 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 7.27 (s, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.99 (s, 1H), 6.82 (t, J = 74 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 1.75 (s, 3H)

[00683] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-ethyl-3-methyl-1*H*-pyrazole-4-carboxamide (156)**

Compound ID : 156



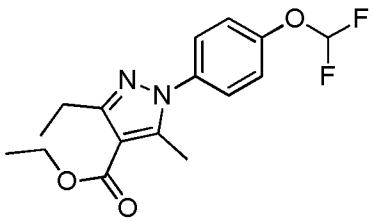
[00684] **156** was obtained via similar procedure of **179** from **156-C** and 3-(1,1-difluoroethyl)aniline

[00685] **LCMS**: (ESI) *m/z*: 436.0 $[M+H]^{+.}$

[00686] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.88 (s, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.51-7.53 (m, 2H), 7.45 (t, J=8.0 Hz, 1H), 7.29-7.35 (m, 3H), 6.94 (t, J=73.6 Hz, 1H), 2.87 (q, J=7.6 Hz, 2H), 2.42 (s, 3H), 1.93 (t, J=18.22 Hz, 3H), 1.27 (t, J=7.6 Hz, 3H).

Synthesis of 155

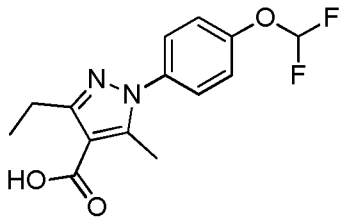
[00687] **Step 1: Synthesis of ethyl 1-(4-(difluoromethoxy)phenyl)-3-ethyl-5-methyl-1*H*-pyrazole-4-carboxylate (155-A)**



[00688] **155-A** was obtained via similar procedure of **156-B** from **156-A** and (4-(difluoromethoxy)phenyl)hydrazine

[00689] **LCMS**: (ESI) *m/z*: 325.1 $[M+H]^+$.

[00690] **Step 2: Synthesis of 1-(4-(difluoromethoxy)phenyl)-3-ethyl-5-methyl-1*H*-pyrazole-4-carboxylic acid (155-B)**

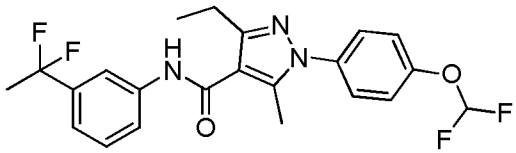


[00691] **155-B** was obtained via similar procedure of **156-C** from **156-B** and sodium hydroxide.

[00692] **LCMS**: (ESI) *m/z*: 297.5 $[M+H]^+$.

[00693] **Step 3: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-ethyl-5-methyl-1*H*-pyrazole-4-carboxamide (155)**

Compound ID : 155



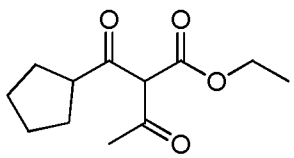
[00694] **155** was obtained via similar procedure of **179** from **155-B** and 3-(1,1-difluoroethyl)aniline

[00695] **LCMS**: (ESI) *m/z*: 436.2 $[M+H]^+$.

[00696] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.89 (s, 1H), 7.71 (d, *J*=8.0 Hz, 1H), 7.49-7.52 (m, 2H), 7.45 (t, *J*=8.0 Hz, 1H), 7.29-7.36 (m, 3H), 6.96 (t, *J*=73.6 Hz, 1H), 2.87 (q, *J*=7.6 Hz, 2H), 2.44 (s, 3H), 1.94 (t, *J*=18.0 Hz, 3H), 1.08 (t, *J*=7.6 Hz, 3H).

Synthesis of 154

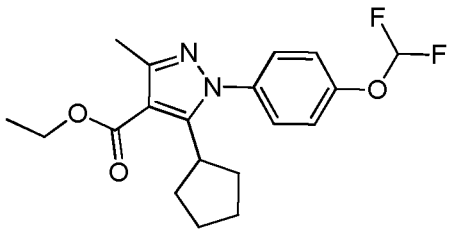
[00697] **Step 1: Synthesis of ethyl 2-(cyclopentanecarbonyl)-3-oxo-butanoate (154-A)**



[00698] To a solution of ethyl 3-oxobutanoate (5.00 g, 38.4 mmol, 1.0 *eq*) in dichloromethane (50 mL) was added magnesium chloride (7.32 g, 76.8 mmol, 2.0 *eq*) and pyridine (6.08 g, 76.8 mmol, 2.0 *eq*). The suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under nitrogen at 0 °C for 1 hr. Then to the reaction mixture was added a solution of cyclopentanecarbonyl chloride (5.09 g, 38.4 mmol, 1.0 *eq*) in dichloromethane (25 mL) dropwise at 0 °C, the mixture was stirred at 20 °C under nitrogen for 1 hr. The solution was poured into water (100 mL), extracted with dichloromethane (100 mL x 3). The combined organic phase was washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica column (petroleum ether/ethyl acetate, from 1/0 to 10/1) to give 3.00 g (34% yield) of **154-A** as a yellow oil.

[00699] **LCMS**: (ESI) *m/z*: 272.2 $[M+H]^+$.

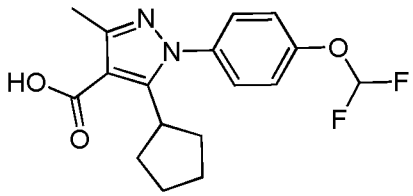
[00700] **Step 2: Synthesis of ethyl 2-(cyclopentanecarbonyl)-3-oxo-butanoate (154-B)**



[00701] **154-B** was obtained via general procedure II from **154-A LCMS**: (ESI) *m/z*: 365.2 $[M+H]^+$.

[00702] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ:7.39-7.35(m, 2H), 7.26-7.23(m, 2H), 6.57(t, *J*= 73.2 Hz, 1H), 4.33(dd, *J*= 14.4 Hz, 6.8 Hz, 2H), 3.15-3.05(m, 1H), 2.47(s, 3H), 2.27-2.08(m, 2H), 1.90-1.79(m, 4H), 1.60-1.54(m, 2H), 1.39(t, *J*= 6.8 Hz, 3H).

[00703] **Step 3: Synthesis of 5-cyclopentyl-1-[4-(difluoromethoxy)phenyl]-3-methyl-pyrazole-4-carboxylic acid (154-C)**

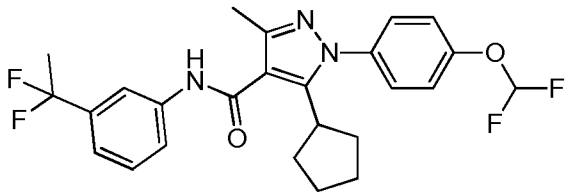


[00704] To a solution of **154-B** (250 mg, 663 umol, 1.0 *eq*) in methanol (4 mL) and water (4 mL) was added sodium hydroxide (265 mg, 6.63 mmol, 10 *eq*), the solution was stirred at 50 °C for 12 h. The solution was concentrated. The residue was diluted with water (10 mL), the pH of the mixture was adjusted to 2 with hydrochloric acid (1 M). The suspension was filtered and washed with water (10 mL x 3). The filter cake was dried in vacuum.The residue was purified by silica column (petroleum ether/ ethyl acetate, from 3/1 to 1/1) to give160 mg (71% yield) of **154-C** as a white solid.

[00705] **LCMS**: (ESI) *m/z*: 337.1 $[M+H]^+$.

[00706] **Step 4: Synthesis of 5-cyclopentyl-*N*-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)phenyl]-3-methyl-pyrazole-4-carboxamide (154)**

Compound ID: 154



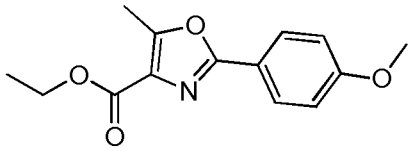
[00707] To a solution of **154-C** (160 mg, 476 umol, 1.0 *eq*) in pyridine (5 mL) was added 3-(1,1-difluoroethyl)aniline (150 mg, 951 umol, 2.0 *eq*) and *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (182 mg, 951 umol, 2.0 *eq*), the solution was stirred at 70 °C for 5 h. The solution was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 54%-84%, 10min) to give 25.6 mg (11% yield) of **154** as a white solid.

[00708] **LCMS**: (ESI) *m/z*: 476.1 $[M+H]^+$.

[00709] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 7.87(s, 1H), 7.71(d, *J*= 8.4 Hz, 1H), 7.47-7.42(m, 3H), 7.35-7.30(m, 3H), 6.95(t, *J*= 73.2 Hz, 1H), 3.06-2.97(m, 1H), 2.36(s, 3H), 1.98-1.89(m, 7H), 1.79-1.69(m, 2H), 1.56-1.48(m, 2H).

Synthesis of 153

[00710] **Step 1: Synthesis of ethyl 2-(4-methoxyphenyl)-5-methyloxazole-4-carboxylate (153-A)**

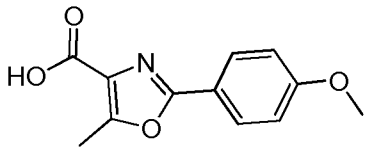


[00711] To a solution of (4-methoxyphenyl)methanamine (2.00 g, 14.6 mmol, 1.5 *eq*) in *N*, *N*-dimethyl-formamide (20 mL) was added ethyl 3-oxobutanoate (1.26 g, 9.72 mmol, 1.0 *eq*), copper acetate monohydrate (194 mg, 972 umol, 0.10 *eq*), *tert*-butyl hydroperoxid (1.75 g, 19.4 mmol, 2.0 *eq*) and iodine (2.96 g, 11.7 mmol, 1.2 *eq*), the suspension was stirred at 25 °C for 4 h. The solution was poured into water (20 mL), extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica column (petroleum ether/ ethyl acetate, from 10/1 to 5/1) to give 600 mg (19% yield) of **153-A** as a white solid.

[00712] **LCMS**: (ESI) *m/z*: 262.2 $[M+H]^+$.

[00713] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 8.01-7.99(m, 2H), 6.96-6.94(m, 2H), 4.41(dd, *J*= 14.4 Hz, 7.2 Hz, 2 H), 3.86(s, 3H), 2.68(s, 3H), 1.41(t, *J*= 7.2 Hz, 3H).

[00714] **Step 2: Synthesis of 2-(4-methoxyphenyl)-5-methyl-oxazole-4-carboxylic acid (153-B)**

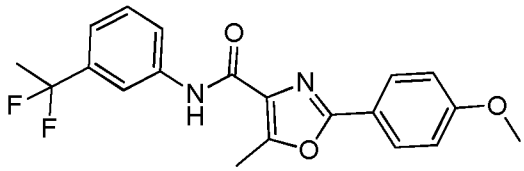


[00715] **153-B** was obtained via similar procedure of **154-C** from **153-A** and sodium hydroxide.

[00716] **LCMS**: (ESI) *m/z*: 234.2 $[M+H]^+$.

[00717] **Step 3: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-2-(4-methoxyphenyl)-5-methyl-oxazole-4-carboxamide (153)**

Compound ID: 153



[00718] **153** was obtained via similar procedure of **154** from **153-B**.

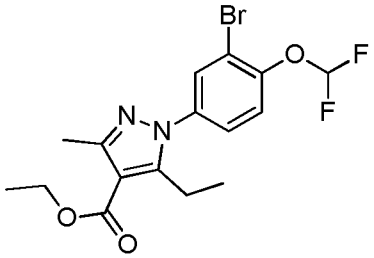
[00719] **LCMS**: (ESI) *m/z*: 373.1 $[M+H]^+$.

[00720] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.11(s, 1H), 8.13(s, 1H), 8.01(d, *J*= 8.8 Hz, 2H), 7.96(d, *J*= 8.0 Hz, 1H), 7.47(t, *J*=12.0 Hz, 1H), 7.29(d, *J*= 7.6 Hz, 1H), 7.13(d, *J*= 8.8 Hz, 2H), 3.85(s, *J*= 3H), 2.70(s, 3H), 1.98(t, *J*= 18.8 Hz, 3H).

Synthesis of 152

[00721] **Step 1: Synthesis of ethyl 1-[3-bromo-4-(difluoromethoxy)phenyl]-5-ethyl-3-methyl-**

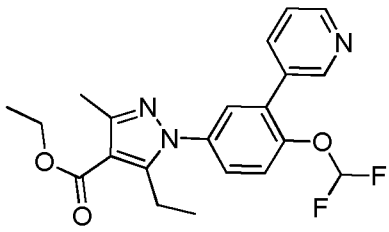
pyrazole-4-carboxylate (152-A)



[00722] A mixture of **156-A** (2.00 g, 10.7 mmol, 1.0 *eq*) and **179-B** (3.73 g, 12.9 mmol, 1.2 *eq*, hydrochloride) was dissolved in acetic acid (20 mL). It was stirred at 50 °C for 30 min. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (**petroleum ether/ethyl acetate=1/0** to **10/1**) to obtain 3.00 g (61% yield) of **152-A** as a red solid.

[00723] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.82 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.47 (s, 1H), 7.00 (t, J = 72.8 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 2.90 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.6 Hz, 3H)

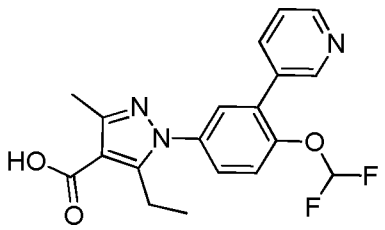
[00724] **Step 2: Synthesis of ethyl 1-[4-(difluoromethoxy)-3-(3-pyridyl)phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxylate (152-B)**



[00725] A mixture of **152-A** (400 mg, 878 umol, 1.0 *eq*), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (269 mg, 1.31 mmol, 1.5 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (32.0 mg, 43.8 umol, 0.050 *eq*), sodium hydrogen carbonate (147 mg, 1.75 mmol, 2.0 *eq*) in water (2 mL) and dioxane (10 mL) was stirred at 90 °C for 12 h under nitrogen. The reaction was diluted with water (40 mL). Then it was extracted with ethyl acetic (50 mL x 2) and the organic layer was washed with water (100 mL x 3) and brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to obtain the crude product. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, from 1/0 to 10/1). The residue was further purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5um; mobile phase: [water (0.05% ammonia hydroxide v/v)-acetonitrile]; B%: 53%-55%, 10min). Then it was extracted with dichloromethane (20 mL x 2) and dried over sodium sulfate, filtered and concentrated to obtain 190 mg (54% yield) of **152-B** as a yellow solid.

[00726] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.73 (d, J = 1.6 Hz, 1H), 8.58 (dd, J = 1.6, 3.6 Hz, 1H), 8.05 ~8.03 (m, 1H), 7.61~7.53 (m, 4H), 6.94 (t, J = 73.2 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 2.95 (q, J = 7.2 Hz, 2H), 2.46 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.6 Hz, 3H).

[00727] **Step 3: Synthesis of 1-[4-(difluoromethoxy)-3-(3-pyridyl)phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxylic acid (152-C)**

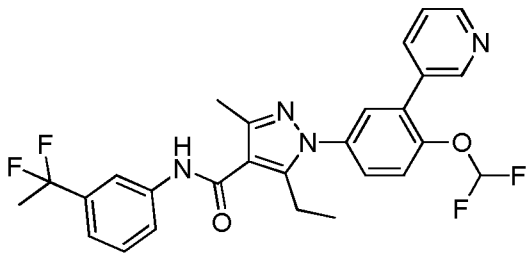


[00728] A mixture of **152-B** (190 mg, 473 umol, 1.0 *eq*) and sodium hydroxide (94.7 mg, 2.37 mmol, 5.0 *eq*) in ethanol (3 mL) and water (1 mL) was stirred at 50 °C for 12 h. The reaction mixture was diluted with water (40 mL) and adjusted pH to 7 with hydrochloric acid (1 M). Then it was extracted with ethyl acetic (30 mL x 2) and the organic layer was washed with brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to obtain 140 mg (crude) of **152-C** as a yellow solid.

[00729] **LCMS:** (ESI) *m/z*: 374.1 $[M+H]^+$.

[00730] **Step 4: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)-3-(3-pyridyl)phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxamide (152)**

Compound ID: 152



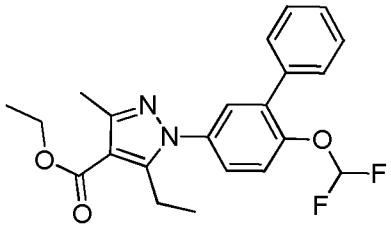
[00731] To a solution of **152-C** (140 mg, 375 umol, 1.0 *eq*) and 3-(1,1-difluoroethyl)aniline (58.93 mg, 375 umol, 1.0 *eq*) in pyridine (3 mL) was added *N*-[3-(Dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (108 mg, 562 umol, 1.5 *eq*). It was stirred at 70 °C for 12 h. The mixture was concentrated under reduced pressure to remove pyridine. Then it was diluted with water (30 mL) and extracted with ethyl acetic (30 mL x 2). The organic layer was washed with water (50 mL x 3) and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to obtain the crude product. The residue was purified by prep-HPLC (column: Waters Xbridge 150*25 5um; mobile phase: [water (10mM ammonium bicarbonate)-acetonitrile]; B%: 36%-66%, 10min). Then it was freeze-dried to obtain 42.5 mg (22% yield) of **152** as a white solid.

[00732] **LCMS:** (ESI) *m/z*: 513.2 $[M+H]^+$.

[00733] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.74 (d, J = 1.6 Hz, 1H), 8.59 (dd, J = 4.8, 1.2 Hz, 1H), 8.05 (dt, J = 8.4, 2.0 Hz, 1H), 7.89 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.62~7.52 (m, 4H), 7.45 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 6.94 (t, J = 72.8 Hz, 1H), 2.94 (q, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H), 1.13 (t, J = 7.6 Hz, 3H).

Synthesis of 151

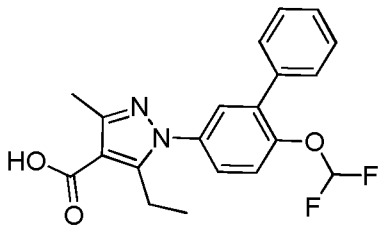
[00734] **Step 1: Synthesis of ethyl 1-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxylate (151-A)**



[00735] **151-A** was obtained via similar procedure of **152-B** from **152-A** and phenylboronic acid.

[00736] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.55 ~7.39 (m, 8H), 6.82 (t, J = 73.2 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 2.94 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H).

[00737] **Step 2: Synthesis of 1-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxylic acid (151-B)**

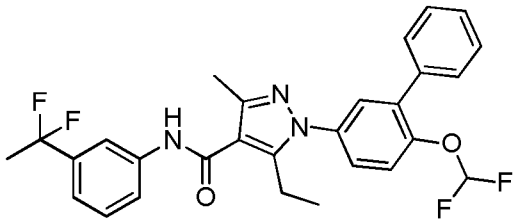


[00738] **151-B** was obtained via similar procedure of **152-C** from **151-A** and sodium hydroxide.

[00739] **LCMS:** (ESI) m/z: 373.1 $[M+H]^+$.

[00740] **Step 3: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxamide (151)**

Compound ID: 151



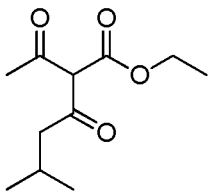
[00741] **151** was obtained via similar procedure of **152** from **151-C** and 3-(1,1-difluoroethyl)aniline.

[00742] **LCMS:** (ESI) m/z: 512.2 $[M+H]^+$.

[00743] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.89 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.56 ~7.41 (m, 9H), 7.31 (d, J = 7.2 Hz, 1H), 6.82 (t, J = 73.6 Hz, 1H), 2.93 (q, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.94 (t, J = 18.0 Hz, 3H), 1.13 (t, J = 7.6 Hz, 3H).

Synthesis of 150

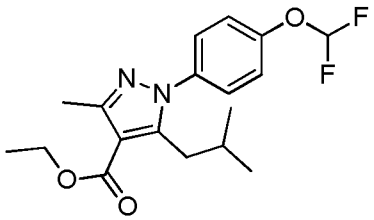
[00744] **Step 1: Synthesis of ethyl 2-acetyl-5-methyl-3-oxohexanoate (150-A)**



[00745] **150-A** was obtained via similar procedure of **156-A** from ethyl 3-oxobutanoate and 3-methylbutanoyl chloride

[00746] **^{1}H NMR** (400 MHz, DMSO-d_4) δ: 4.18-4.25 (m, 1H), 2.23-2.50 (m, 3H), 1.93-2.07 (m, 4H), 1.19-1.28 (m, 2H), 0.75-0.91 (m, 6H).

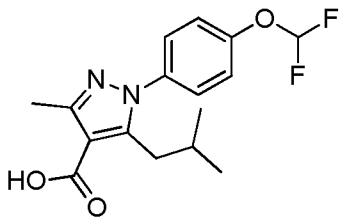
[00747] **Step 2: Synthesis of ethyl 1-(4-(difluoromethoxy)phenyl)-5-isobutyl-3-methyl-1*H*-pyrazole-4-carboxylate (150-B)**



[00748] **150-B** was obtained via similar procedure of **156-B** from 150-A and (4-(difluoromethoxy)phenyl)hydrazine

[00749] **LCMS**: (ESI) *m/z*: 353.1 $[M+H]^{+.}$

[00750] **Step 3: Synthesis of 1-(4-(difluoromethoxy)phenyl)-5-isobutyl-3-methyl-1*H*-pyrazole-4-carboxylic acid (150-C)**

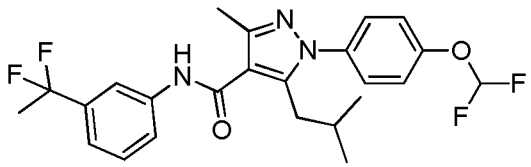


[00751] **150-C** was obtained via similar procedure of **156-C** from **150-B** and sodium hydroxide.

[00752] **LCMS**: (ESI) *m/z*: 325.1 $[M+H]^+$.

[00753] **Step 4: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-isobutyl-3-methyl-1*H*-pyrazole-4-carboxamide (150)**

Compound ID : 150



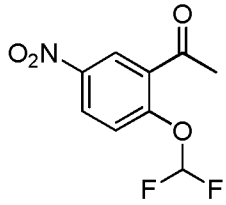
[00754] **150** was obtained via similar procedure of **179** from **150-C** and 3-(1,1-difluoroethyl)aniline

[00755] **LCMS:** (ESI) *m/z*: 464.3 $[M+H]^+$.

[00756] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.87 (s, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.43-7.50 (m, 3H), 7.30-7.36 (m, 3H), 6.96 (t, J=73.2 Hz, 1H), 2.78 (d, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.94 (t, J=18.4 Hz, 3H), 1.67-1.73 (m, 1H), 0.76 (d, J=6.8 Hz, 6H).

Synthesis of 149

[00757] **Step 1: 1-(2-(difluoromethoxy)-5-nitrophenyl)ethanone (149-A)**

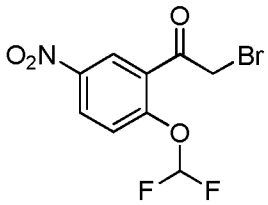


[00758] To a mixture of 2-bromo-1-(difluoromethoxy)-4-nitrobenzene (16.0 g, 48.4 mmol, 1.0 *eq*), tributyl(1-ethoxyvinyl)stannane (22.6 g, 67.7 mmol, 1.4 *eq*), lithium chloride (4.10 g, 96.7 mmol, 2.0 *eq*) in dioxane (150 mL) was added tetrakis(triphenylphosphine)platinum (5.59 g, 4.84 mmol, 0.10 *eq*). The flask was then evacuated and backfilled with nitrogen for three times. The mixture was stirred at 100 °C under an atmosphere of nitrogen for 12 hr. To the mixture was added hydrochloric acid (6M, 100 mL), the result mixture was stirred at 25 °C for 15 min. The mixture was quenched by slow addition of saturated aqueous potassium fluoride (50 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture 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 affording the residue as a yellow oil. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give 11.0 g (98% yield) of **149-A** as a yellow oil.

[00759] **LCMS**: (ESI) *m/z*: 291.1 $[M+H]^+$.

[00760] **^{1}H NMR** (400 MHz, $CDCl_3$-d_4) δ: 8.57 (d, *J*=2.8 Hz, 1H), 8.31 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.29 (d, *J* = 9.2 Hz, 1H), 6.41-6.93 (m, 1H), 2.52-2.67 (m, 1H), 2.52-2.72 (m, 3H)

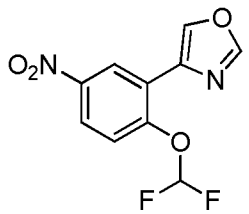
[00761] **Step 2: 2-bromo-1-(2-(difluoromethoxy)-5-nitrophenyl)ethanone (149-B)**



[00762] To a 250 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **149-A** (11.0 g, 47.6 mmol, 1.0 *eq*) followed by the addition of acetonitrile (100 mL). Then 1-bromopyrrolidine-2,5-dione (10.2 g, 57.1 mmol, 1.2 *eq*) and 4-methylbenzenesulfonic acid (1.64 g, 9.52 mmol, 0.20 *eq*) were added into the mixture at 25 °C. The mixture was heated to 70 °C and stirred for 12 h. The mixture was diluted by slow addition of water (20 mL). The mixture was quenched by slow addition of saturated aqueous ammonium chloride (200 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with ethyl acetate (80 mL x 3). The combined organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue as a yellow oil. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give 14.0 g (95% yield) of **149-B** as a yellow oil.

[00763] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 8.67-8.77 (m, 1H), 8.41-8.51 (m, 1H), 7.34-7.48 (m, 1H), 6.58-6.99 (m, 2H), 4.26-4.77 (m, 2H).

[00764] **Step 3: 4-(2-(difluoromethoxy)-5-nitrophenyl)oxazole (149-C)**

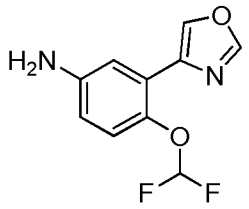


[00765] To a 10 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **149-B** (4.00 g, 12.9 mmol, 1.0 *eq*) followed by the addition of formamide (5.65 g, 125 mmol, 9.7 *eq*) at 25 °C. The mixture was heated to 100 °C and stirred for 2 h. The mixture was concentrated under reduced pressure affording the crude product as yellow solid. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give 1.90g (46% yield) of **149-C**as a yellow solid.

[00766] **LCMS**: (ESI) *m/z*: 257.0 $[M+H]^+$.

[00767] **^{1}H NMR** (400 MHz, $CDCl_3$-d_4) δ: 9.01 (d, J = 2.8 Hz, 1H), 8.18 (d, J = 1.2 Hz, 1H), 8.13 (dd, J = 9.0, 2.8 Hz, 1H), 7.93 (d, J = 0.8 Hz, 1H), 7.21 (d, J = 9.2 Hz, 1H), 6.46-6.89 (m, 2H).

[00768] **Step4: 4-(difluoromethoxy)-3-(oxazol-4-yl)aniline (149-D)**

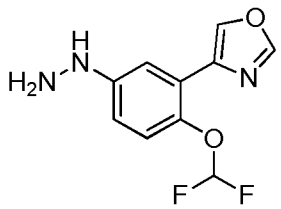


[00769] To a solution of **149-C**(1.90 g, 7.42 mmol, 1.0 *eq*) in methanol (10 mL) was added Pd/C (1.00 g, 10% purity) under hydrogen atmosphere. The suspension was degassed and purged with hydrogen for 3 times. The mixture was stirred under hydrogen (15 psi) at 25 °C for 2 hr. The mixture was filtered, the filtrate was concentrated under reduced pressure to give a yellow oil. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give 1.40 g (46% yield) of **149-D** as a yellow solid.

[00770] **LCMS**: (ESI) *m/z*: 227.1$[M+H]^+$

[00771] **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 8.59 (s, 2H), 8.44 (s, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.12-7.63 (m, 3H).

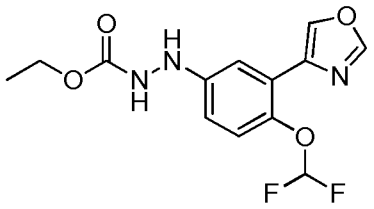
[00772] **Step5: 4-(2-(difluoromethoxy)-5-hydrazinylphenyl)oxazole (149-E)**



[00773] **149-E** was obtained via general procedure I from **149-D**

[00774] **LCMS**: (ESI) *m/z*: 242.3 $[M+H]^+$.

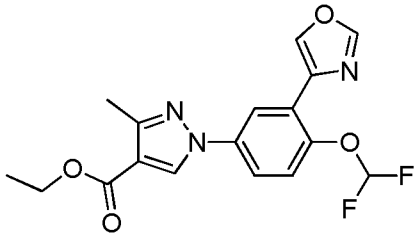
[00775] **Step6: ethyl 2-(4-(difluoromethoxy)-3-(oxazol-4-yl)phenyl)hydrazinecarboxylate (149-F)**



[00776] **149-F** was obtained via similar procedure of **186-A** from **149-E** and ethyl carbonochloridate

[00777] **LCMS**: (ESI) *m/z*: 314.0 $[M+H]^+$.

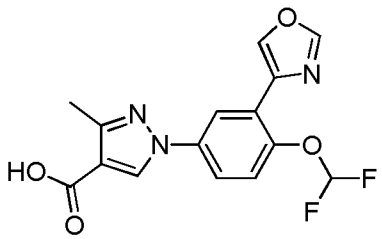
[00778] **Step7: ethyl 1-(4-(difluoromethoxy)-3-(oxazol-4-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylate (149-G)**



[00779] **149-G** was obtained via similar procedure of **186-B** from **149-F** and ethyl (2E)-2-(methoxymethylene)-3-oxo-butanoate

[00780] **LCMS**: (ESI) *m/z*: 364.1$[M+H]^+$.

[00781] **Step 8: 1-(4-(difluoromethoxy)-3-(oxazol-4-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid (149-H)**

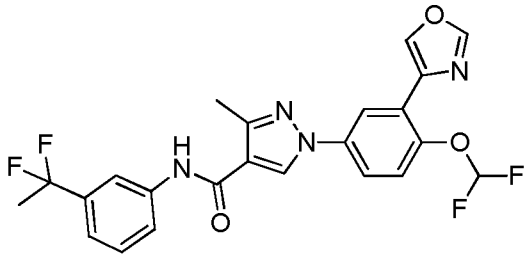


[00782] **149-H** was obtained via similar procedure of **186-D** from **176-G** and sodium hydroxide

[00783] **LCMS**: (ESI) *m/z*: 336.0$[M+H]^+$.

[00784] **Step9: *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(oxazol-4-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxamide (149)**

Compound ID : 149



[00785] **149** was obtained via similar procedure of **186** from **149-H** and 3-(1,1-difluoroethyl)aniline

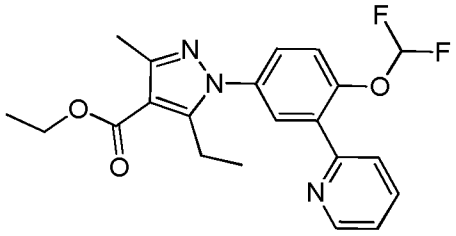
[00786] **LCMS**: (ESI) *m/z*: 475.1$[M+H]^+$.

[00787] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.89 (s, 1H), 8.56 (d, *J*=2.76 Hz, 1H), 8.39 (s, 1H), 8.32 (d, *J*=0.64 Hz, 1H), 7.94 (s, 1H), 7.74-7.85 (m, 2H), 7.40-7.50 (m, 2H), 7.30 (d, *J*=7.64 Hz, 1H), 6.89-7.28

(m, 1H), 2.59 (s, 3H), 1.96 (t, *J*=18.24 Hz, 3H).

Synthesis of 148

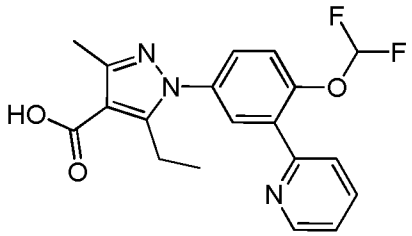
[00788] **Step 1: Synthesis of ethyl 1-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxylate (148-A)**



[00789] **148-A** was obtained via similar procedure of 2-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-5-methyl-4*H*-pyrazol-3-one from [4-(difluoromethoxy)-3-(2-pyridyl)phenyl]hydrazine and **156-A**.

[00790] **LCMS**: (ESI) *m/z*: 402.2 $[M+H]^+$.

[00791] **Step 2: Synthesis of 1-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxylic acid (148-B)**

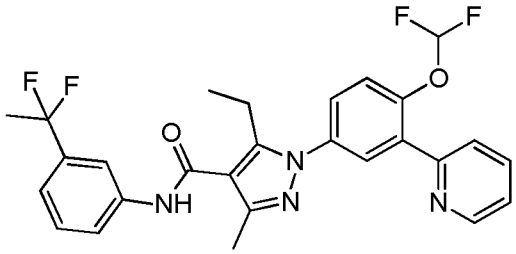


[00792] **148-B** was obtained via similar procedure of **154-C** from **148-A** and sodium hydroxide.

[00793] **LCMS**: (ESI) *m/z*: 374.1 $[M+H]^+$.

[00794] **Step 3: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxamide (148)**

Compound ID: 148



[00795] **148** was obtained via similar procedure of **154** from **148-B** and 3-(1,1-difluoroethyl)aniline.

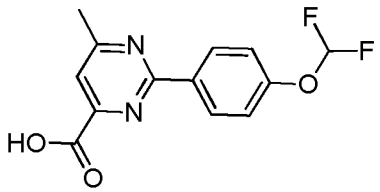
[00796] **LCMS**: (ESI) *m/z*: 513.2 $[M+H]^+$.

[00797] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H), 8.80 - 8.63 (m, 1H), 8.00 (s, 1H), 7.97 - 7.92 (m, 1H), 7.89 (d, *J* = 2.8 Hz, 1H), 7.88 - 7.84 (m, 1H), 7.79 - 7.73 (m, 1H), 7.65 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.55 (s, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.48 - 7.45 (m, 1H), 7.44 (td, *J* = 1.2, 3.0, 4.4 Hz, 1H), 7.37 (s, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.19 (s, 1H), 2.88 (q, *J* = 7.4 Hz, 2H), 2.37 (s, 3H), 1.96 (t, *J* = 18.8 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H).

Synthesis of 147

[00798] **Step 1: Synthesis of 2-(4-(difluoromethoxy)phenyl)-6-methylpyrimidine-4-carboxylic acid**

(147-A)

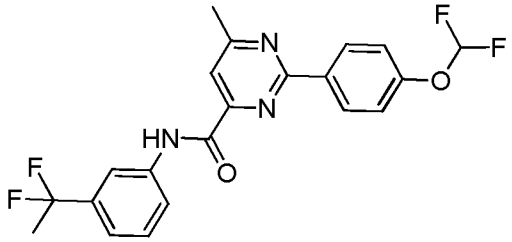


[00799] **147-A** was obtained via similar procedure of **173-C** from **173-A** and methyl 2-chloro-6-methyl-pyrimidine-4-carboxylate

[00800] **LCMS**: (ESI) *m/z*: 281.1 $[M+H]^+$.

[00801] **Step 2: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)-6-methylpyrimidine-4-carboxamide (147)**

Compound ID : 147



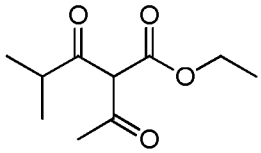
[00802] **147** was obtained via similar procedure of **173** from **147-A** and 3-(1,1-difluoroethyl)aniline

[00803] **LCMS**: (ESI) *m/z*: 420.0 $[M+H]^+$.

[00804] **^{1}H NMR** (400 MHz, MeOD-d_4) δ : 8.66-8.71 (m, 2H), 8.09 (s, 1H), 7.91-7.97 (m, 2H), 7.50 (t, *J*=8.0 Hz, 1H), 7.37 (d, *J*=7.6 Hz, 1H), 7.29 (d, *J*=8.8 Hz, 2H), 6.96 (t, *J*=74.0Hz, 1H), 2.70 (s, 3H), 1.96 (t, *J*=18.4 Hz, 3H).

Synthesis of 146

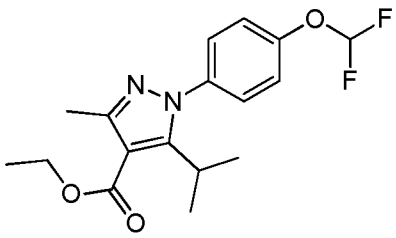
[00805] **Step 1: Synthesis of ethyl 2-acetyl-4-methyl-3-oxo-pentanoate (146-A)**



[00806] **146-A** was obtained via similar procedure of **154-A**.

[00807] **LCMS**: (ESI) *m/z*: 201.2 $[M+H]^+$.

[00808] **Step 2: Synthesis of ethyl 1-(4-(difluoromethoxy)phenyl)-5-isopropyl-3-methyl-1*H*-pyrazole-4-carboxylate (146-B)**

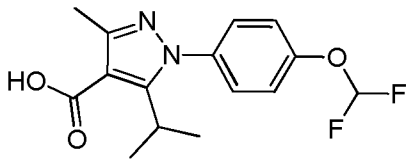


[00809] **146-B** was obtained via similar procedure of **154-B** from **146-A** and (4-(difluoromethoxy)phenyl)hydrazine

[00810] **LCMS**: (ESI) *m/z*: 339.1 $[M+H]^+$.

[00811] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 7.41 - 7.31 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.77 - 6.36 (m, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.28 (td, *J* = 7.2, 14.2 Hz, 1H), 2.47 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.32 (d, *J* = 7.2 Hz, 6H).

[00812] **Step 3: Synthesis of 1-[4-(difluoromethoxy)phenyl]-5-isopropyl-3-methyl-pyrazole-4-carboxylic acid (146-C)**

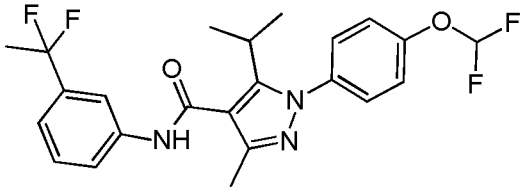


[00813] **146-C** was obtained via similar procedure of **154-C** from **146-B** and sodium hydroxide.

[00814] **LCMS**: (ESI) *m/z*: 311.1 $[M+H]^+$.

[00815] **Step 4: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)phenyl]-5-isopropyl-3-methyl-pyrazole-4-carboxamide (146)**

Compound ID: 146



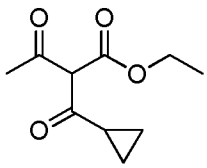
[00816] **146** was obtained via similar procedure of **154** from **146-C** and 3-(1,1-difluoroethyl)aniline.

[00817] **LCMS**: (ESI) *m/z*: 450.2 $[M+H]^+$.

[00818] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.35 (s, 1H), 8.02 (s, 1H), 7.77 (br d, *J* = 8.2 Hz, 1H), 7.57 - 7.53 (m, 1H), 7.51 - 7.41 (m, 3H), 7.36 (s, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.22 - 7.16 (m, 1H), 2.97 (q, *J* = 7.0 Hz, 1H), 2.29 (s, 3H), 1.96 (t, *J* = 18.8 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 6H).

Synthesis of 145

[00819] **Step 1: Synthesis of ethyl 2-(cyclopropanecarbonyl)-3-oxo-butanoate (145-A)**



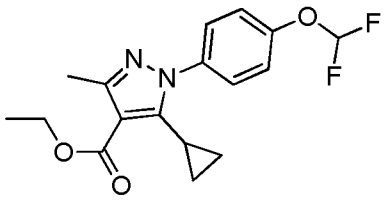
[00820] A mixture of ethyl 3-oxobutanoate (5.0 g, 38.4 mmol, 1.0 *eq*), magnesium chloride (7.32 g, 76.8 mmol, 2.0 *eq*) and pyridine (6.08 g, 76.8 mmol, 2.0 *eq*) in dichloromethane (30 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 0 °C for 1 h under nitrogen atmosphere, then the mixture was added cyclopropanecarbonyl chloride (4.00 g, 38.4 mmol, 1.0 *eq*) in dichloromethane (10 mL) dropwise at 0 °C. The mixture was stirred at 20 °C for 1 h under an atmosphere of nitrogen. The mixture was cooled to 0 °C. To the mixture was added 6 M hydrochloric acid (40 mL), the resulting mixture was stirred at 0 °C for 10 min and then transferred to a separatory funnel, and the aqueous layer mixture was extracted with dichloromethane (40 mL x 2), the combined organic layer was washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure affording the residue. The residue was purified by silica gel column chromatography

(petroleum ether/ethyl acetate, from 100/1 to 20/1) to give 6.50 g (58% yield) of **145-A** as a light yellow liquid.

[00821] **LCMS**: (ESI) *m/z*: 199.09 $[M+H]^+$.

[00822] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) *δ*: 4.32 -4.28 (m, 2H), 2.49 -2.40 (m, 1H), 2.31 (s, 3H), 1.35 - 1.32 (m, 3H), 1.23-1.20 (m, 2H), 1.01 -0.97 (m, 2H).

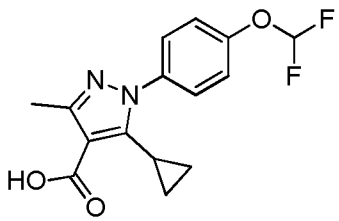
[00823] **Step 2: Synthesis of ethyl 5-cyclopropyl-1-[4-(difluoromethoxy)phenyl]-3-methyl-pyrazole-4-carboxylate (145-B)**



[00824] To a solution of (4-(difluoromethoxy)phenyl)hydrazine (2.70 g, 12.5 mmol, 1.2 *eq*, hydrochloride) in acetic acid (30 mL) was added **145-A** (3.00 g, 10.3 mmol, 1.0 *eq*). The mixture was stirred at 50 °C for 1 h. The mixture was concentrated in vacuum directly to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 50/1 to 5/1) to give the crude product, then the crude product was purified by prep-HPLC, column(Phenomenex Synergi C18 150*25*10um; mobile phase:[water (0.2%formic acid)-acetonitrile];B%: 50%-80%,11min) to give 0.100 g (3% yield) of **145-B** as a light yellow oil.

[00825] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) *δ* : 7.53 -7.50 (m, 2H), 7.22 (d, *J*=8.8 Hz, 2H), 6.57 (s, 1H), 4.35 (q, *J*=7.2 Hz, 2H), 2.48 (s, 3H), 2.00-1.97 (m, 1H), 1.40 (t, *J*=7.2 Hz, 3H), 0.92 (dd, *J*=6.8 Hz, 2H), 0.50 -0.44 (m, 2H).

[00826] **Step 3: Synthesis of 5-cyclopropyl-1-[4-(difluoromethoxy)phenyl]-3-methyl-pyrazole-4-carboxylic acid (145-C)**

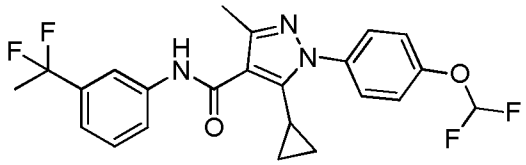


[00827] To a solution of **145-B** (0.100 g, 297 umol, 1.0 *eq*) in ethanol (1 mL) was added sodium hydroxide (0.120 g, 2.97 mmol, 10 *eq*) and water (1 mL). The mixture was stirred at 80 °C for 2 h. The mixture was diluted with water (30 mL), and extracted with ethyl acetate (10 mL x 3), then the pH of aqueous phase was adjusted to 2 by hydrochloric acid (1 M). Next extracted with ethyl acetate (10 mL x 3), the combined organic layer was washed with brine (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 1.60 g (crude) of **145-C** as a light yellow solid.

[00828] **LCMS**: (ESI) *m/z*: 309.10 $[M+H]^+$.

[00829] **Step 4: Synthesis of 5-cyclopropyl-*N*-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)phenyl]-3-methyl-pyrazole-4-carboxamide (145)**

Compound ID: 145



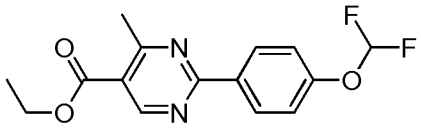
[00830] To a solution of **145-C** (65.0 mg, 211 umol, 1.0 *eq*) in pyridine (1 mL) was added *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (61.0 mg, 316 umol, 1.5 *eq*) and 3-(1,1-difluoroethyl)aniline (40.0 mg, 253 umol, 1.2 *eq*). The mixture was stirred at 50 °C for 1 h. The mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um;mobile phase: [water (0.225%formic acid)- acetonitrile]; B%: 50%-80%,10 min) to give 16.6 mg (17% yield) of **145** as a yellow solid.

[00831] **LCMS**: (ESI) *m/z*: 447.9 $[M+H]^+$

[00832] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 7.92 (s, 1H), 7.73 (d, *J*=8.4 Hz, 1H), 7.62 (d, *J*=9.2 Hz, 2H), 7.46 (t, *J*=8.0 Hz 1H), 7.35 -7.29 (m, 3H), 6.94 (t, *J*=74.0 Hz, 1H), 2.40 (s, 3H), 2.14 -2.05 (m, 1H), 1.94 (t, *J*=18.4 Hz, 3H), 0.89 (dd, *J*=8.4, 1.6 Hz, 2H), 0.51 (dd, *J*=5.6, 1.6 Hz, 2H).

Synthesis of 144

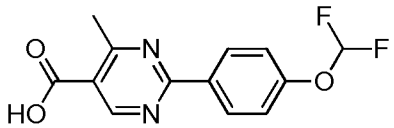
[00833] **Step 1: Synthesis of ethyl 2-[4-(difluoromethoxy)phenyl]-4-methyl-pyrimidine-5-carboxylate (144-A)**



[00834] **144-A** was obtained via similar procedure of **152-B** from **173-A** and ethyl 2-chloro-4-methylpyrimidine-5-carboxylate.

[00835] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 9.18 (s, 1H), 8.55 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.97 (t, *J* = 73.6 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.87 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H).

[00836] **Step 2: Synthesis of 2-[4-(difluoromethoxy)phenyl]-4-methyl-pyrimidine-5-carboxylic acid (144-B)**

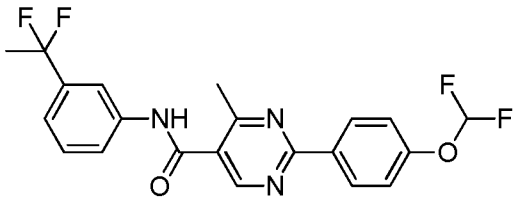


[00837] **144-B** was obtained via similar procedure of **152-C** from **144-A** and lithium hydroxide hydrate.

[00838] **LCMS:** (ESI) *m/z*: 281.1 $[M+H]^+$.

[00839] **Step 3: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-2-[4-(difluoromethoxy)phenyl]-4-methyl-pyrimidine-5-carboxamide (144)**

Compound ID: 144



[00840] To a solution of **144-B** (75.0 mg, 268 umol, 1.0 *eq*) in *N*,*N*-dimethylformamide (5 mL) was added 1*H*-benzo[*d*][1,2,3]triazol-1-ol (102 mg, 268 umol, 1.0 *eq*) and *N*,*N*-diisopropylethylamine (69.2 mg, 535 umol, 2.0 *eq*). It was stirred at 10 °C for 30 min. Then 3-(1,1-difluoroethyl)aniline (42.1 mg, 268 umol, 1.0 *eq*) was added into the mixture. It was stirred at 10 °C for 12 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 50%-80%, 10 min). Then it was freeze-dried to obtain 25.6 mg (23% yield) of **144** as a yellow solid.

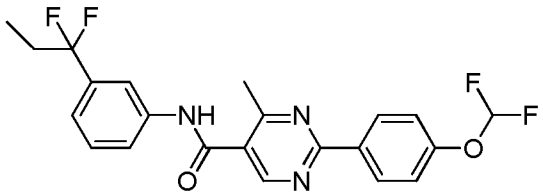
[00841] **LCMS:** (ESI) *m/z*: 420.1 $[M+H]^+$.

[00842] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.90 (s, 1H), 8.54 (d, J = 8.8 Hz, 2H), 7.95 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.34 (dd, J = 8.0, 0.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 6.96 (t, J = 74.0 Hz, 1H), 2.74 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H).

Synthesis of 143

[00843] **Step 1: Synthesis of 2-[4-(difluoromethoxy)phenyl]-*N*-[3-(1,1-difluoropropyl)phenyl]-4-methyl-pyrimidine-5-carboxamide (143)**

Compound ID: 143



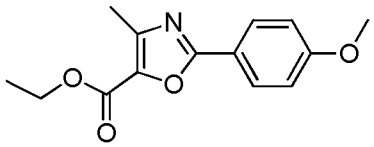
[00844] **143** was obtained via similar procedure of **144** from **144-B** and 3-(1,1-difluoropropyl)aniline.

[00845] **LCMS:** (ESI) *m/z*: 433.9 $[M+H]^+$.

[00846] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.90 (s, 1H), 8.54 (d, J = 8.8 Hz, 2H), 7.90 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.32 ~7.25 (m, 3H), 6.96 (t, J = 74.0 Hz, 1H), 2.74 (s, 3H), 2.20 (td, J = 16.0, 7.6 Hz, 2H), 0.99 (t, J = 7.6 Hz, 3H).

Synthesis of 142

[00847] **Step 1: Synthesis of ethyl 2-(4-methoxyphenyl)-4-methyloxazole-5-carboxylate (142-A)**

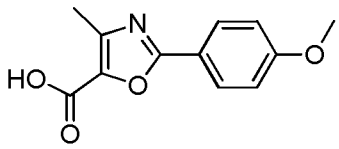


[00848] To a 10 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added 4-methoxybenzamide (500 mg, 3.31 mmol, 1.0 *eq*) followed by the addition of ethyl 2-chloro-3-oxo-butanoate (1.63 g, 9.92 mmol, 3.0 *eq*). The mixture was heated to 130 °C and stirred for 12 hr. The mixture was quenched by slow addition of brine (5 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with ethyl acetate (3 mL x 3). The combined organic layer was washed with brine (4 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 10/1) to give 460 mg (49% yield)

of **142-A** as a yellow solid.

[00849] **LCMS**: (ESI) *m/z*: 262.2 $[M+H]^+$.

[00850] **Step 2: Synthesis of 2-(4-methoxyphenyl)-4-methyloxazole-5-carboxylic acid (142-B)**

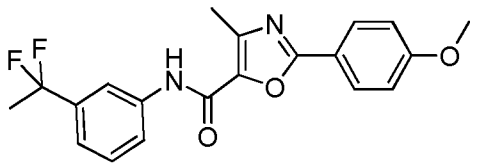


[00851] To a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **142-A** (200 mg, 707 umol, 1.0 *eq*) followed by the addition of ethanol (5 mL) and water (5 mL). Then sodium hydroxide (283 mg, 7.07 mmol, 10 *eq*) was added into the mixture. The mixture was heated to 80 °C and stirred for 2 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in water (5 mL). The pH of the mixture was adjusted to 3 by hydrogen chloride solution (6M). The mixture was extracted with ethyl acetate (5 mL x 2). The combined organic layer was washed with brine (4 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 170 mg (95% yield) of **142-B** as a light yellow solid.

[00852] LCMS: (ESI) *m/z*: 233.8 [M+H]+.

[00853] **Step 3: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-methoxyphenyl)-4-methyloxazole-5-carboxamide (142)**

Compound ID : 142



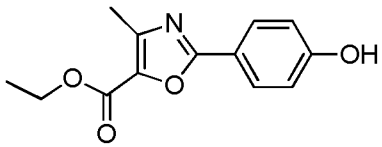
[00854] **142** was obtained via similar procedure of **173** from **142-B** and 3-(1,1-difluoroethyl)aniline.

[00855] **LCMS**: (ESI) *m/z*: 373.1 $[M+H]^+$.

[00856] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.16-8.18 (m, 2H), 7.96 (s, 1H), 7.82-7.84 (m, 1H), 7.46 (t, *J*=8.0 Hz, 1H), 7.33 (dd, *J*=0.8, 7.6 Hz, 1H), 7.08-7.11 (m, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 1.94 (t, *J*=18.4 Hz, 3H).

Synthesis of 141

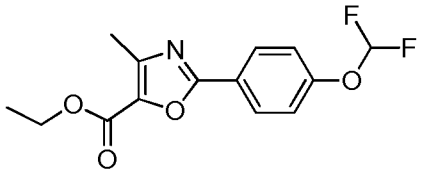
[00857] **Step 1: Synthesis of ethyl 2-(4-hydroxyphenyl)-4-methyloxazole-5-carboxylate (141-A)**



[00858] **141-A** was obtained via similar procedure of **142-A** from 4-hydroxybenzamide and ethyl 2-chloro-3-oxo-butanoate.

[00859] **LCMS**: (ESI) *m/z*: 248.2 $[M+H]^+$.

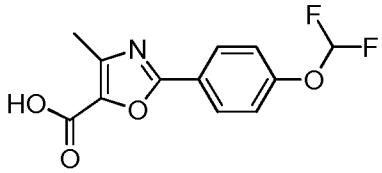
[00860] **Step 2: Synthesis of ethyl 2-(4-(difluoromethoxy)phenyl)-4-methyloxazole-5-carboxylate (141-B)**



[00861] To a 100 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **141-A** (2.00 g, 7.02 mmol, 1.0 *eq*), sodium;2-chloro-2,2-difluoro-acetate (1.60 g, 10.5 mmol, 1.5 *eq*) followed by the addition of *N*,*N*-dimethylformamide (20 mL). Then sodium carbonate (1.49 g, 14.0 mmol, 2.0 *eq*) was added into the mixture. The mixture was heated to 100 °C and stirred for 2 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (30 mL) and water (50 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 15/1 to 10/1) to give 1.09 g (50% yield) of **141-B** as a white solid.

[00862] **LCMS**: (ESI) *m/z*: 298.1 $[M+H]^+$.

[00863] **Step 3: Synthesis of 2-(4-(difluoromethoxy)phenyl)-4-methyloxazole-5-carboxylic acid (141-C)**

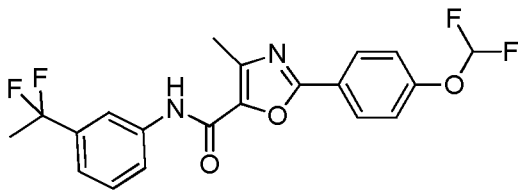


[00864] **141-C** was obtained via similar procedure of **142-B** from **141-B** and sodium hydroxide.

[00865] **LCMS**: (ESI) *m/z*: 270.0 $[M+H]^+$.

[00866] **Step 4: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)-4-methyloxazole-5-carboxamide (141)**

Compound ID : 141



[00867] **141** was obtained via similar procedure of **142** from **141-C** and 3-(1,1-difluoroethyl)aniline.

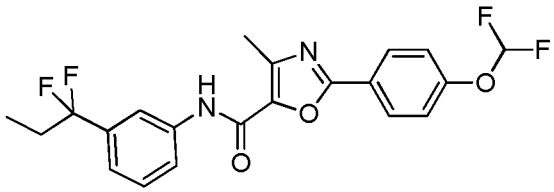
[00868] **LCMS**: (ESI) *m/z*: 409.1 $[M+H]^+$.

[00869] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.25-8.28 (m, 2H),7.95 (s, 1H), 7.83 (d, *J*=8.4 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.30-7.34 (m, 3H), 6.98 (t, *J*=73.2 Hz, 1H), 2.56 (s, 3H), 1.94 (t, *J*=18.4 Hz, 3H).

Synthesis of 140

[00870] **Step 1: Synthesis of 2-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-4-methyloxazole-5-carboxamide (140)**

Compound ID : 140



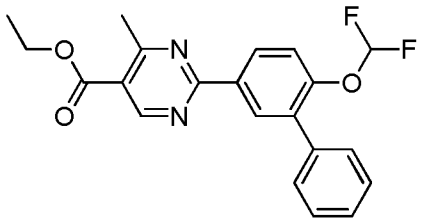
[00871] **140** was obtained via similar procedure of **142** from **141-C** and 3-(1,1-difluoropropyl)aniline.

[00872] **LCMS**: (ESI) *m/z*: 423.1 $[M+H]^{+.}$

[00873] **1H NMR** (400 MHz, MeOD-d_4) δ: 8.25-8.29 (m, 2H), 7.91 (s, 1H), 7.84 (d, *J*=8.4 Hz, 1H), 7.46 (t, *J*=8.0 Hz, 1H), 7.27-7.32 (m, 3H), 6.98 (t, *J*=73.6 Hz, 1H), 2.56 (s, 3H), 2.15-2.25 (m, 2H), 1.00 (t, *J*=7.2 Hz, 3H).

Synthesis of 139

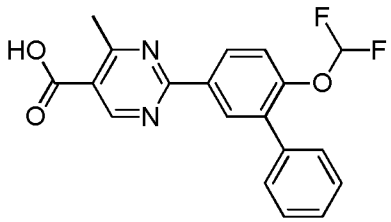
[00874] **Step 1: Synthesis of ethyl 2-[4-(difluoromethoxy)-3-phenyl-phenyl]-4-methyl-pyrimidine-5-carboxylate (139-A)**



[00875] **139-A** was obtained via similar procedure of **152-B** from **127-C** and ethyl 2-chloro-4-methylpyrimidine-5-carboxylate.

[00876] **LCMS:** (ESI) *m/z*: 385.0 $[M+H]^{+}$.

[00877] **Step 2: Synthesis of 2-[4-(difluoromethoxy)-3-phenyl-phenyl]-4-methyl-pyrimidine-5-carboxylic acid (139-B)**

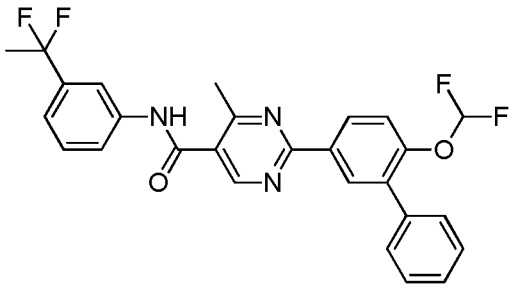


[00878] **139-B** was obtained via similar procedure of **144-B** from **139-A** and lithium hydroxide hydrate.

[00879] **LCMS:** (ESI) *m/z*: 357.0 $[M+H]^{+}$.

[00880] **Step 3: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-2-[4-(difluoromethoxy)-3-phenyl-phenyl]-4-methyl-pyrimidine-5-carboxamide (139)**

Compound ID: 139



[00881] **139** was obtained via similar procedure of **144** from **139-B** and 3-(1,1-difluoroethyl)aniline.

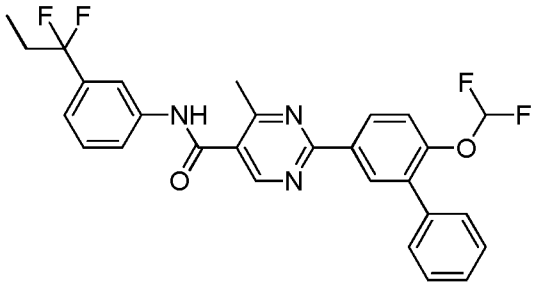
[00882] **LCMS:** (ESI) *m/z*: 496.1 $[M+H]^+$.

[00883] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.91 (s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.54 ~8.51 (m, 1H), 7.95 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.57 ~7.54 (m, 2H), 7.50 ~7.45 (m, 3H), 7.43 ~7.38 (m, 2H), 7.34 (d, J = 8.4 Hz, 1H), 6.84 (t, J = 74.0 Hz, 1H), 2.75 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H)

Synthesis of 138

[00884] **Step 1: Synthesis of 2-[4-(difluoromethoxy)-3-phenyl-phenyl]-*N*-[3-(1,1-difluoropropyl)phenyl]-4-methyl-pyrimidine-5-carboxamide (138)**

Compound ID: 138



[00885] **138** was obtained via similar procedure of **139** from **139-B** and 3-(1,1-difluoropropyl)aniline.

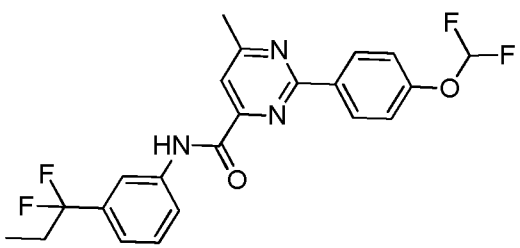
[00886] **LCMS:** (ESI) *m/z*: 509.9 $[M+H]^+$.

[00887] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.91 (s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.54 ~8.51 (m, 1H), 7.90 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.57 ~7.54 (m, 2H), 7.50 ~7.45 (m, 3H), 7.43 ~7.39 (m, 2H), 7.30 (d, J = 8.0 Hz, 1H), 6.84 (t, J = 73.6 Hz, 1H), 2.75 (s, 3H), 2.27 ~2.12 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H).

Synthesis of 137

[00888] **Step 1: Synthesis of 2-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-6-methylpyrimidine-4-carboxamide (137)**

Compound ID : 137



[00889] **137** was obtained via similar procedure of **147** from **147-A** and 3-(1,1-difluoropropyl)aniline

[00890] **LCMS**: (ESI) *m/z*: 434.0 $[M+H]^+$.

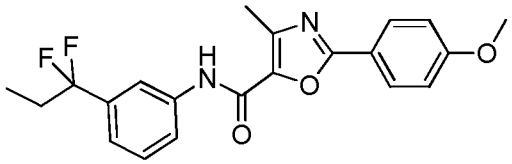
[00891] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.68-8.72 (m, 2H), 8.06 (s, 1H), 7.93-7.95 (m, 2H), 7.50 (t,

J=8.0 Hz, 1H), 7.29-7.34 (m, 3H), 6.96 (t, *J*= 73.6 Hz, 1H), 2.71 (s, 3H), 2.17-2.27 (m, 2H), 1.01 (t, *J*=7.6 Hz, 3H).

Synthesis of 136

[00892] **Step 1: Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-2-(4-methoxyphenyl)-4-methyloxazole-5-carboxamide (136)**

Compound ID : 136



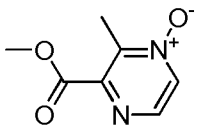
[00893] **136** was obtained via similar procedure of **142** from **142-C** and 3-(1,1-difluoropropyl)aniline

[00894] **LCMS**: (ESI) *m/z*: 387.1 $[M+H]^{+.}$

[00895] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.16 (d, *J*=8.8 Hz, 2H), 7.91 (s, 1H), 7.83 (d, *J*=8.0 Hz, 1H), 7.46 (t, *J*=8.0 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 1H), 7.08 (d, *J*=9.2 Hz, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 2.15-2.25 (m, 2H), 1.00 (t, *J*=7.2 Hz, 3H).

Synthesis of 135

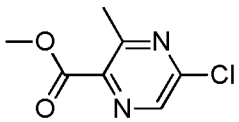
[00896] **Step 1: Synthesis of methyl 3-methyl-4-oxido-pyrazin-4-ium-2-carboxylate (135-A)**



[00897] To a solution of methyl 3-methylpyrazine-2-carboxylate (4.00 g, 26.3 mmol, 1.0 *eq*) in dichloromethane (100 mL) was added hydrogen peroxide (4.17 g, 36.8 mmol, 1.4 *eq*) (30% aqueous) at 0 °C, following added trifluoroacetic anhydride (7.18 g, 34.2 mmol, 1.3 *eq*). The mixture was stirred at 0 °C for 1 h, then it was stirred at 25 °C for 16 h. The mixture was quenched with saturated sodium sulfite aqueous (100 mL) and extracted with dichloromethane (100 mL x 2). The combined organic extracts were dried over sodium sulfate, filtered and concentrated in vacuum to give 5.50 g (crude, mixture) of **135-A** as a yellow solid.

[00898] **LCMS:** (ESI) *m/z*: 169.0 $[M+H]^+$.

[00899] **Step 2: Synthesis of methyl 5-chloro-3-methyl-pyrazine-2-carboxylate (135-B)**

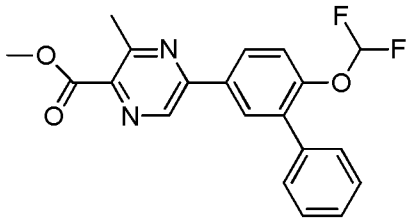


[00900] To a solution of **135-A** (5.50 g, 32.7 mmol, 1.0 *eq*) in toluene (50 mL) was added phosphorous oxychloride (10.0 g, 65.4 mmol, 2.0 *eq*), following added dimethyl formamide (239 mg, 3.27 mmol, 0.10 *eq*). The mixture was stirred at 65 °C for 12 h. The mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and washed with saturated sodium hydrogen carbonate solution (100 mL). The aqueous layer was back-extracted with ethyl acetate (100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column

chromatography on silica gel (petroleum ether/ethyl acetate, from 20/1 to 10/1) to give 400 mg (7% yield) of **135-B1** as a white solid.

[00901] **^{1}H NMR:** (400 MHz, $CDCl_3$-*d*) δ: 8.52 (s, 1H), 4.02 (s, 3H), 2.86 (s, 3H).

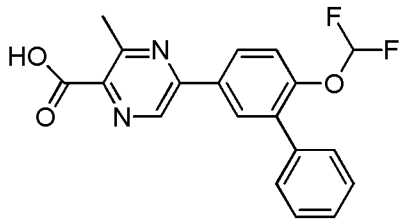
[00902] **Step 3: Synthesis of methyl 5-[4-(difluoromethoxy)-3-phenyl-phenyl]-3-methyl-pyrazine-2-carboxylate (135-C)**



[00903] **135-C** was obtained via similar procedure of **152-B** from **135-B** and **127-C**.

[00904] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 8.95 (s, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.58 ~7.54 (m, 2H), 7.52 ~7.47 (m, 2H), 7.45 ~7.39 (m, 2H), 6.43 (t, *J* = 73.6 Hz, 1H), 4.04 (s, 3H), 2.94 (s, 3H)

[00905] **Step 4: Synthesis of 5-[4-(difluoromethoxy)-3-phenyl-phenyl]-3-methyl-pyrazine-2-carboxylic acid (135-D)**

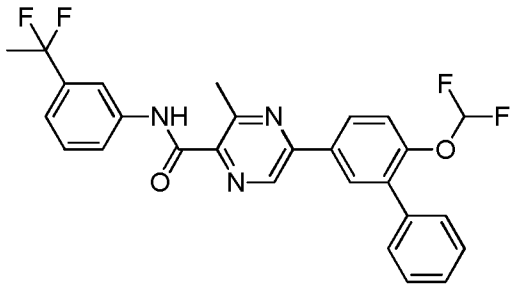


[00906] **135-D** was obtained via similar procedure of **144-B** from **135-C** and lithium hydroxide hydrate.

[00907] **LCMS:** (ESI) *m/z*: 357.1 $[M+H]^+$.

[00908] **Step 5: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-5-[4-(difluoromethoxy)-3-phenyl-phenyl]-3-methyl-pyrazine-2-carboxamide (135)**

Compound ID: 135



[00909] **135** was obtained via similar procedure of **144** from **135-D** and 3-(1,1-difluoroethyl)aniline.

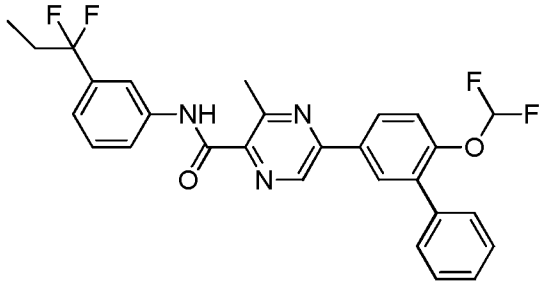
[00910] **LCMS:** (ESI) *m/z*: 496.2 $[M+H]^+$.

[00911] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 9.10 (s, 1H), 8.27 ~8.22 (m, 2H), 8.04 (s, 1H), 7.85 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.58 ~7.55 (m, 2H), 7.51 ~7.41 (m, 5H), 7.32 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.84 (t, *J* = 73.6, 1H), 2.99 (s, 3H), 1.95 (t, *J* = 18.3 Hz, 3H).

Synthesis of 134

[00912] **Step 1: Synthesis of 5-[4-(difluoromethoxy)-3-phenyl-phenyl]-*N*-[3-(1,1-difluoropropyl)phenyl]-3-methyl-pyrazine-2-carboxamide (134)**

Compound ID: 134



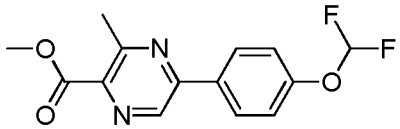
[00913] **134** was obtained via similar procedure of **135** from **135-D** and 3-(1,1-difluoropropyl)aniline

[00914] **LCMS:** (ESI) *m/z*: 510.2 $[M+H]^+$.

[00915] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 9.08 (s, 1H), 8.26 ~8.21 (m, 2H), 7.99 (s, 1H), 7.84 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.58 ~7.55 (m, 2H), 7.50 ~7.41 (m, 5H), 7.27 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.84 (t, J = 73.6 Hz, 1H), 2.98 (s, 3H), 2.28 ~2.13 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).

Synthesis of 133

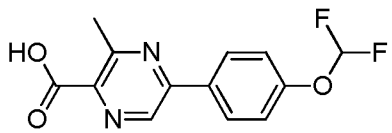
[00916] **Step 1: Synthesis of methyl 5-(4-(difluoromethoxy)phenyl)-3-methylpyrazine-2-carboxylate (133-A)**



[00917] A mixture of **135-B** (150 mg, 803 umol, 1.0 *eq*) , **173-A** (327 mg, 965 umol, 1.2 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (29.4 mg, 40.2 umol, 0.05 *eq*), sodium bicarbonate (135 mg, 1.6 mmol, 2.0 *eq*) in dioxane (4 mL) and water (1 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 90 °C for 2 h under nitrogen atmosphere. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (30 mL x 1), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give 0.160 g (66% yield) of **133-A** as a white solid.

[00918] **LCMS**: (ESI) *m/z*: 295.0 $[M+H]^+$.

[00919] **Step 2: Synthesis of 5-(4-(difluoromethoxy)phenyl)-3-methylpyrazine-2-carboxylic acid (133-B)**



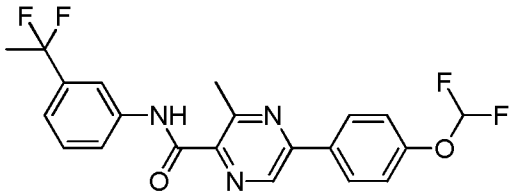
[00920] To a solution of **133-A** (0.240 g, 816 umol, 1.0 *eq*) in tetrahydrofuran (3 mL), methanol (3 mL) and water (3 mL) was added lithium hydroxide hydrate (103 mg, 2.45 mmol, 3.0 *eq*). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated in vacuum. The residue was diluted with water (30 mL), and adjusted with hydrochloric acid aqueous (1 M) to pH=5, then extracted with ethyl acetate

(30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated to give 0.210 g (crude) of **133-B** as a white solid.

[00921] **LCMS**: (ESI) *m/z*: 281.1 $[M+H]^+$.

[00922] **Step 3: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-5-(4-(difluoromethoxy)phenyl)-3-methylpyrazine-2-carboxamide (133)**

Compound ID: 133



[00923] To a solution of **133-B** (70.0 mg, 249.8 umol, 1.0 *eq*) in *N*,*N*-dimethylformamide (3 mL) was added 1*H*-benzo[d][1,2,3]triazol-1-ol (104 mg, 274 umol, 1.1 *eq*) and *N*,*N*-diisopropylethylamine (64.6 mg, 500 umol, 2.0 *eq*). The mixture was stirred at 20 °C for 0.5 h. Then 3-(1,1-difluoroethyl)aniline (39.3 mg, 250 umol, 1.0 *eq*) was added. The mixture was stirred at 20 °C for another 1 h. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (0.225%formic acid)-acetonitrile]; B%: 62%-92%, 10min) to give 41.8 mg (40% yield) of **133** as a white solid.

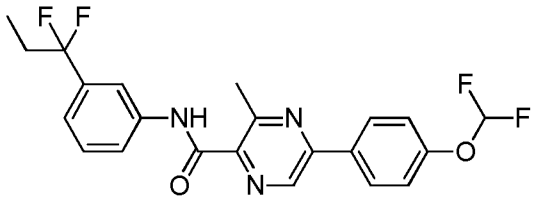
[00924] **LCMS**: (ESI) *m/z*: 420.1 $[M+H]^+$.

[00925] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 9.05 (s, 1H), 8.26 (d, *J*=8.8 Hz, 2H), 8.04 (s, 1H), 7.85 (d, *J*=8.0 Hz, 1H), 7.47 (t, *J*=8.0 Hz, 1H), 7.32 (d, *J*=8.8 Hz, 3H), 6.96 (t, *J*=74.0 Hz, 1H), 2.99 (s, 3H), 1.95 (t, *J*=18.4 Hz, 3H).

Synthesis of 132

[00926] **Step 1: Synthesis of 5-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3-methylpyrazine-2-carboxamide (132)**

Compound ID: 132



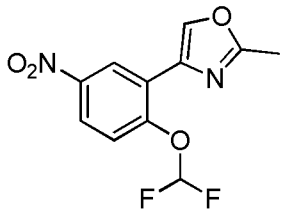
[00927] **132** was obtained via similar procedure of **133** from **133-B** and 3-(1,1-difluoropropyl)aniline.

[00928] **LCMS**: (ESI) *m/z*: 434.1 $[M+H]^+$.

[00929] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 9.04 (s, 1H), 8.26 (d, *J*=8.8 Hz, 2H), 7.99 (s, 1H), 7.85 (d, *J*=8.0 Hz, 1H), 7.47 (t, *J*=8.0 Hz, 1H), 7.32 (d, *J*=8.8 Hz, 2H), 7.28 (d, *J*=8.0 Hz, 1H), 6.96 (t, *J*=74.0 Hz, 1H), 2.98 (s, 3H), 2.21 (dt, *J*=7.6, 16.0 Hz, 2H), 1.00 (t, *J*=7.6 Hz, 3H).

Synthesis of 131

[00930] **Step1: 4-(2-(difluoromethoxy)-5-nitrophenyl)-2-methyloxazole (131-A)**

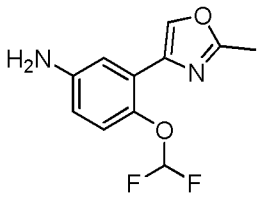


[00931] **131-A** was obtained via similar procedure of **149-C** from **149-B** and acetamide.

[00932] **LCMS**: (ESI) *m/z*: 271.0 $[M+H]^+$.

[00933] **^{1}H NMR** (400 MHz, CDCl-*d*) δ: 9.04 (d, *J*=2.8 Hz, 1H), 8.18 (dd, *J*=9.2, 2.9 Hz, 1H), 8.10 (s, 1H), 7.24-7.27 (m, 1H), 6.52-6.93 (m, 1H), 2.55 (s, 3H).

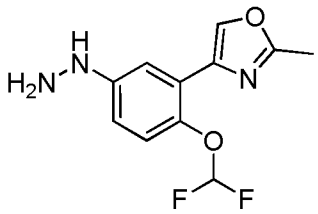
[00934] **Step2: 4-(difluoromethoxy)-3-(2-methyloxazol-4-yl)aniline (131-B)**



[00935] **131-B** was obtained via similar procedure of **149-D** from **149-A** and hydrogen

[00936] **LCMS**: (ESI) *m/z*: 241.1$[M+H]^+$.

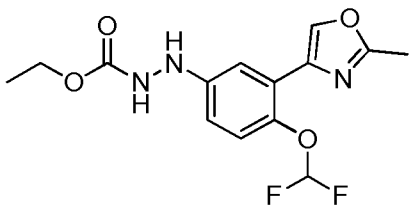
[00937] **Step 3: 4-(2-(difluoromethoxy)-5-hydrazinylphenyl)-2-methyloxazole (131-C)**



[00938] **131-C** was obtained via general procedure I from **131-B**

[00939] **LCMS**: (ESI) *m/z*: 256.1$[M+H]^+$.

[00940] **Step 4: ethyl 2-(4-(difluoromethoxy)-3-(2-methyloxazol-4-yl)phenyl)hydrazinecarboxylate (131-D)**

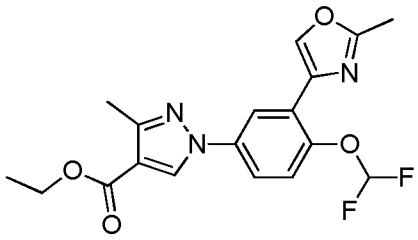


[00941] **131-D** was obtained via similar procedure of **186-A** from **131-C** and ethyl carbonochloridate

[00942] **LCMS**: (ESI) *m/z*: 328.1$[M+H]^+$.

[00943] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 7.95 (s, 1H), 7.50 (br d, *J*=2.6 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.68 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.09-6.55 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.39-2.47 (m, 3H), 1.15-1.21 (m, 3H).

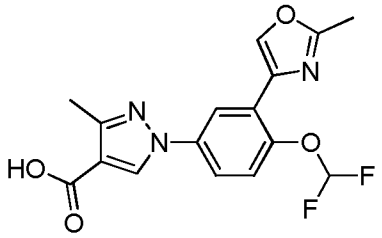
[00944] **Step 5: ethyl 1-(4-(difluoromethoxy)-3-(2-methyloxazol-4-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylate (131-E)**



[00945] **131-E** was obtained via similar procedure of **186-B** from **131-D** and (2E)-2-(ethoxymethylene)-3-oxo-butanoate.

[00946] **LCMS**: (ESI) *m/z*: 378.1[M+H]$^+$.

[00947] **Step6: 1-(4-(difluoromethoxy)-3-(2-methyloxazol-4-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid (131-F)**

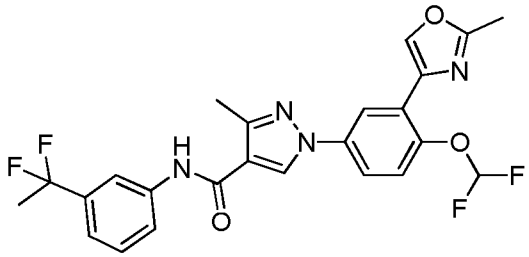


[00948] **131-F** was obtained via similar procedure of **186-D** from **131-E** and sodium hydroxide

[00949] **LCMS**: (ESI) *m/z*: 350.1[M+H]$^+$.

[00950] **Step7: *N*-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(2-methyloxazol-4-yl)phenyl)-3-methyl-1*H*-pyrazole-4-carboxamide (131)**

Compound ID : 131



[00951] **131** was obtained via similar procedure of **186** from **131-F** and 3-(1,1-difluoroethyl)aniline

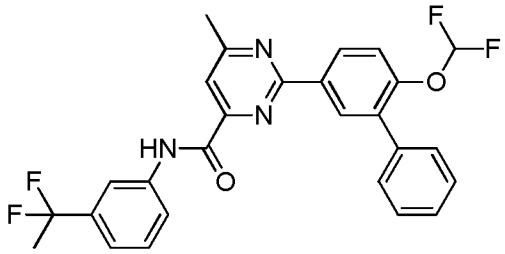
[00952] **LCMS**: (ESI) *m/z*: 489.1[M+H]$^+$.

[00953] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.88 (s, 1H), 8.50 (d, *J*=2.8 Hz, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.75-7.82 (m, 2H), 7.40-7.49 (m, 2H), 7.28-7.33 (m, 1H), 6.85-7.27 (m, 1H), 2.59 (s, 3H), 2.56 (s, 3H), 1.96 (t, *J*=18.4 Hz, 3H).

Synthesis of 130

[00954] **Step 1: *N*-(3-(1,1-difluoroethyl)phenyl)-2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-6-methylpyrimidine-4-carboxamide (130)**

Compound ID : 130



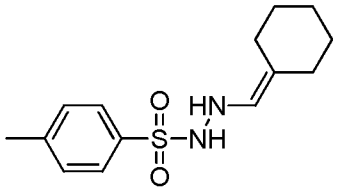
[00955] **130** was obtained via similar procedure of **173** from **127-D** and 3-(1,1-difluoroethyl)aniline

[00956] **LCMS**: (ESI) *m/z*: 496.1[M+H]$^+$.

[00957] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.72 (dd, J = 2.0, 8.4 Hz, 1 H), 8.69 (d, J = 2.0 Hz, 1H), 8.07 (s, 1H), 7.96 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.63 - 7.58 (m, 2H), 7.52 - 7.35 (m, 6H), 6.85 (t, J = 73.6 Hz, 1H), 2.72 (s, 3H), 1.96 (t, J = 18.0 Hz, 3H).

Synthesis of 129

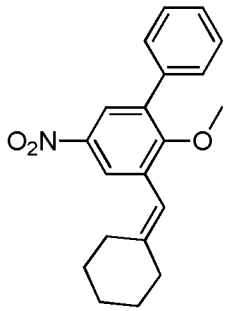
[00958] **Step 1: Synthesis of *N*'-(cyclohexylidenemethyl)-4-methylbenzenesulfonohydrazide (129-A)**



[00959] To a solution of 4-methylbenzenesulfonohydrazide (8.30 g, 44.6 mmol, 1.0 *eq*) in methanol (50 mL) was added cyclohexanecarbaldehyde (5.00 g, 44.6 mmol, 1.0 *eq*). The solution was stirred at 20 °C for 3 h. The reaction was cooled down to 0 °C and the resulting precipitate was filtered and the filter cake was dried in vacuo to afford 5.10 g (41% yield) of **129-A** as an off-white solid.

[00960] **^{1}H NMR** (400 MHz, $CDCl_3$-d) δ: 7.7.82(d, J = 8.4 Hz,2H), 7.60 (br s, 1H), 7.33 (d, J=8.0 Hz, 2H), 7.08 (d, J=5.2 Hz, 1H), 2.45 (s, 3H), 2.28 - 2.15 (m, 1H), 1.80 - 1.65 (m, 5H), 1.29 - 1.07 (m, 5H).

[00961] **Step 2: Synthesis of 3-(cyclohexylidenemethyl)-2-methoxy-5-nitro-1,1'-biphenyl (129-B)**

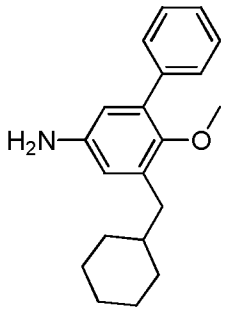


[00962] To a suspension of **161-E** (1.00 g, 2.82 mmol, 1.0 *eq*), **129-A** (1.18 g, 4.22 mmol, 1.5 *eq*) in dioxane (15 mL), which was purgassed with nitrogen for three times, was added tri(dibenzylideneaceton)dipalladium(0) (258 mg, 282 umol, 0.10 *eq*), dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphane (268 mg, 563 umol, 0.20 *eq*) and lithium;2-methylpropan-2-olate (789 mg, 9.86 mmol, 3.5 *eq*). The reaction mixture was stirred at 85 °C under an atmosphere of nitrogen for 10 h. The reaction was diluted with ethyl acetate (50 mL). The suspension was filtered and washed with

ethyl acetate (30 mL x 3). The combined filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/ petroleum ether, 1/60) to afford 2.50 g (79% yield) of **129-B** was obtained as a yellow oil.

[00963] **LCMS**: (ESI) *m/z*: 324.2 $[M+H]^+$.

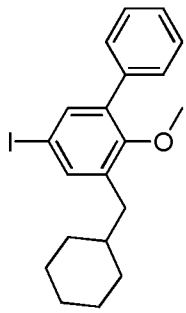
[00964] **Step 3: Synthesis of 5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-amine (129-C)**



[00965] **129-C** was obtained via similar procedure of **161-G** from **129-B** and hydrogen.

[00966] **LCMS**: (ESI) *m/z*: 296.2 $[M+H]^+$.

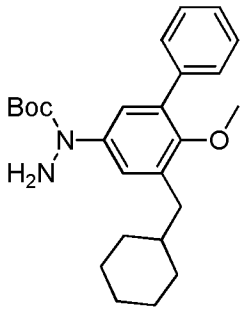
[00967] **Step 4: Synthesis of 3-(cyclohexylmethyl)-5-iodo-2-methoxy-1,1'-biphenyl (129-D)**



[00968] **129-D** was obtained via similar procedure of **161-H** from **129-C** and sodium nitrite, potassium iodide

[00969] **^{1}H NMR** (400MHz, $CDCl_3$-*d*) δ: 7.56 - 7.49 (m, 3H), 7.46 - 7.40 (m, 3H), 7.38 - 7.33 (m, 1H), 3.30 (s, 3H), 2.50 (d, *J*=7.2 Hz, 2H), 1.80 - 1.52 (m, 7H), 1.24 - 1.20 (m, 2H), 1.09 - 0.96 (m, 2H).

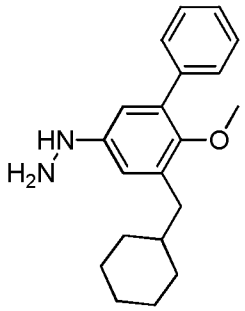
[00970] **Step 5: Synthesis of *tert*-butyl 1-(5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-yl)hydrazinecarboxylate (129-E)**



[00971] **129-E** was obtained via similar procedure of **161-I** from **129-D** and *ter*t-butyl hydrazinecarboxylate

[00972] **LCMS**: (ESI) *m/z*: 338.2 $[M-t\text{BuO}]^+$.

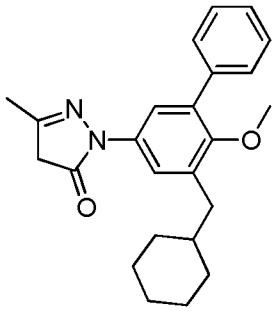
[00973] **Step 6: Synthesis of (5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-yl)hydrazine (129-F)**



[00974] **129-F** was obtained via similar procedure of **161-J** from **129-E** and hydrogen chloride/ethyl acetate

[00975] **LCMS**: (ESI) *m/z*: 311.2 $[M+H]^+$.

[00976] **Step 7: Synthesis of 1-(5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (129-G)**

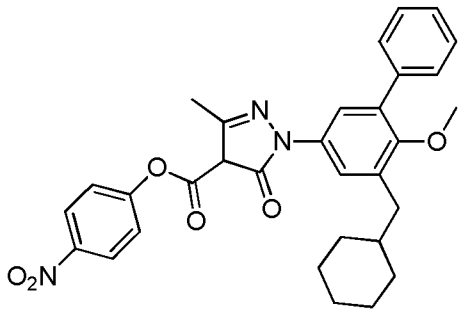


[00977] **129-G** was obtained via general procedure II from **129-F**

[00978] **LCMS**: (ESI) *m/z*: 377.2 $[M+H]^+$.

[00979] **^{1}H NMR** (400MHz, MeOD-d_4) δ: 7.66 - 7.59 (m, 2H), 7.56 - 7.32 (m, 5H), 3.34 (s, 3H), 2.64 (d, J = 7.6 Hz, 2H), 2.30 (s, 3H), 1.81 - 1.68 (m, 5H), 1.36 - 1.26 (m, 4H), 1.14 - 1.02 (m, 2H).

[00980] **Step 8: Synthesis of 4-nitrophenyl 1-(5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate (129-H)**

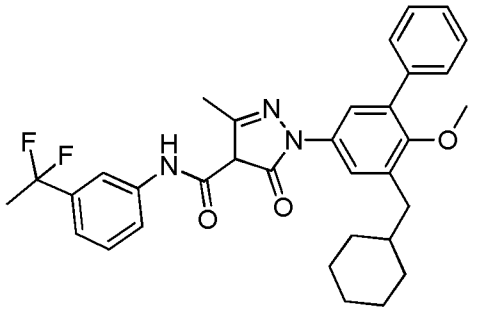


[00981] **129-H** was obtained via general procedure III from **129-G**

[00982] **LCMS**: (ESI) *m/z*: 542.2 $[M+H]^+$.

[00983] **Step 9: Synthesis of 1-(5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (129)**

Compound ID: 129



[00984] **129** was obtained via general procedure IV from **129-H** and 3-(1,1-difluoroethyl)aniline

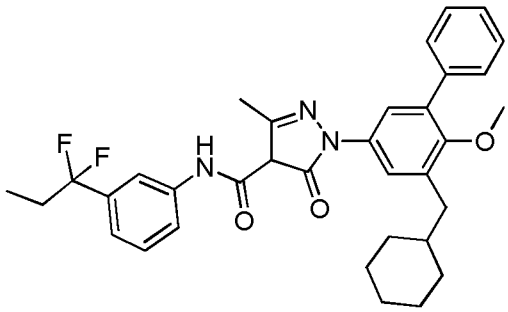
[00985] **LCMS**: (ESI) *m/z*: 560.3 $[M+H]^+$.

[00986] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.81 (br s, 1H), 7.56 - 7.48 (m, 3H), 7.42 - 7.23 (m, 6H), 7.12 (d, *J*=7.6 Hz, 1H), 3.22 (s, 3H), 2.51 (d, *J*=7.2 Hz, 2H), 2.46 (s, 3H), 1.88 - 1.77 (d, *J*=28.0 Hz, 3H), 1.67 - 1.58 (m, 6H), 1.20 - 1.11 (m, 3H), 1.01 - 0.90 (m, 2H).

Synthesis of 128

[00987] **Step 1: Synthesis of 1-(5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (128)**

Compound ID: 128



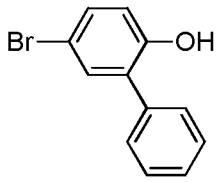
[00988] **128** was obtained via general procedure IV from **129-H** and 3-(1,1-difluoropropyl)aniline

[00989] **LCMS**: (ESI) *m/z*: 574.3 $[M+H]^+$.

[00990] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.77 (br s, 1H), 7.54 - 7.51 (bm, 3H), 7.39 - 7.23 (m, 6H), 7.10 (d, *J*=7.6 Hz, 1H), 3.24 (s, 3H), 2.59 - 2.42 (m, 5H), 2.08 (qt, *J*=7.8, 15.6 Hz, 2H), 1.71 - 1.54 (m, 6H), 1.26 - 1.09 (m, 3H), 1.03 - 0.91 (m, 2H), 0.88 (t, *J*=7.6 Hz, 3H).

Synthesis of 127

[00991] **Step 1: Synthesis of 5-bromo-[1,1'-biphenyl]-2-ol (127-A)**

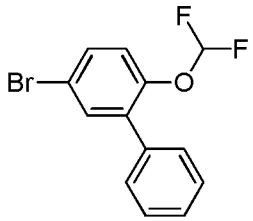


[00992] To a 50 mL round-bottom flask equipped with a magnetic stir bar was added 2-phenylphenol (4.00 g, 23.5 mmol, 1.0 *eq*) followed by the addition of dichloromethane (10 mL). The solution was cooled to -20 °C. Next, bromine (3.76 g, 23.5 mmol, 1.0 *eq*) in dichloromethane (5 mL) was added dropwise. The mixture was allowed to warm to 25°C and stir for 12 hr. The mixture was diluted by dichloromethane to 80 mL. The mixture was quenched by slow addition of saturated aqueous

ammonium sodium sulfite (50 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with saturated aqueous dichloromethane (80 mL x 3). The combined organic layer was washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue as a yellow oil. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 10/1) to give 5.50 g (86% yield) of **127-A** as a colorless oil.

[00993] **LCMS**: (ESI) *m/z*: 249.0 $[M+H]^+$.

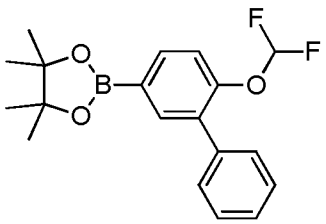
[00994] **Step 2: Synthesis of 5-bromo-2-(difluoromethoxy)-1,1'-biphenyl (127-B)**



[00995] To a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **127-A** (3.30 g, 12.2 mmol, 1.0 *eq*) followed by the addition of acetonitrile (15 mL) and water (6 mL) .Then reagent potassium hydroxide (6.84 g, 122 mmol, 10 *eq*) and 1-[[bromo(difluoro)methyl]-ethoxy-phosphoryl]oxyethane (3.25 g, 12.2 mmol, 1.0 *eq*) was added into the mixture at 0 °C. The mixture was heated to 25 °C and stirred for 2 hr. The mixture was quenched by slow addition of water (100 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture 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 affording the residue as a colorless oil. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 1/0 to 1/0) to give 2.00 g (55% yield) of **127-B** as a colorless oil.

[00996] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 7.57 (d, *J*=2.4 Hz, 1H), 7.36-7.51 (m, 6H), 7.15 (d, *J*=8.8 Hz, 1H), 6.04-6.53 (m, 1H).

[00997] **Step 3: Synthesis of 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (127-C)**

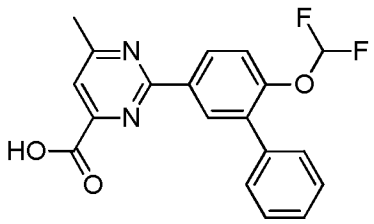


[00998] To a 100 mL round-bottom flask equipped with a magnetic stir bar was added **127-B** (2.00 g, 6.69 mmol, 1.0 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.40 g, 13.4 mmol, 2.0 *eq*), potassium acetate (1.31 g, 13.4 mmol, 2.0 *eq*) followed by the addition of dioxane (20 mL). Then 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (489 mg, 668 umol, 0.10 *eq*) was added into the mixture at 25 °C. The flask was then evacuated and backfilled with nitrogen for three times. The mixture was stirred at 85 °C under an atmosphere of nitrogen for 12 hr. The mixture was filtered, 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 50/1 to

25/1) to give 3.00 g (98% yield) of **127-C** as a yellow oil.

[00999] **LCMS**: (ESI) *m/z*: 347.2 $[M+H]^+$.

[001000] **Step 4: Synthesis of 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-6-methylpyrimidine-4-carboxylic acid (127-D)**

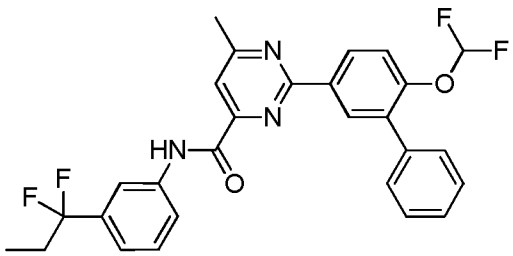


[001001] To a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **127-C** (244 mg, 536 umol, 1.0 *eq*), methyl 2-chloro-6-methyl-pyrimidine-4-carboxylate (100 mg, 536 umol, 1.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (39.2 mg, 53.6 umol, 0.10 *eq*) followed by the addition of dioxane (10 mL) and water (3 mL). Then reagent sodium bicarbonate (90.0 mg, 1.07 mmol, 2.0 *eq*) was added into the mixture. The mixture was heated to 90 °C and stirred for 12 hr. The mixture was filtered, the filtrate was diluted with water (50 ml), the pH of the mixture was adjusted to 10 by sodium hydroxide solution (1 M). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with ethyl acetate (50 mL x 2). The pH of the aqueous phase was adjusted to 4 by hydrogen chloride solution (6 M). The mixture was extracted with ethyl acetate (40 mL x 3).The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 150 mg (71% yield) of **127-D** as a yellow oil.

[001002] **LCMS**: (ESI) *m/z*: 357.0 $[M+H]^+$.

[001003] **Step 4: Synthesis of 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-6-methylpyrimidine-4-carboxamide (127)**

Compound ID : 127



[001004] **127** was obtained via similar procedure of **173** from **127-D** and 3-(1,1-difluoropropyl)aniline

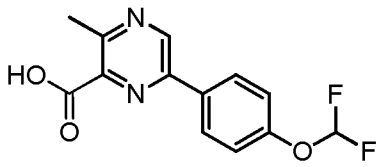
[001005] **LCMS**: (ESI) *m/z*: 510.2 $[M+H]^+$.

[001006] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.66-8.69 (m, 2H), 8.02 (s, 1H), 7.88-7.92 (m, 2H), 7.57-7.59 (m, 2H), 7.46-7.51 (m, 3H), 7.39-7.43 (m, 2H), 7.32 (d, *J*=7.6 Hz, 1H), 6.82 (t, *J*=74.0 Hz, 1H), 2.70 (s, 3H), 2.13-2.28 (m, 2H), 1.00 (t, *J*=7.6 Hz, 3H).

Synthesis of 126

[001007] **Step 1: Synthesis of 6-(4-(difluoromethoxy)phenyl)-3-methylpyrazine-2-**

carboxylic acid (126-A)

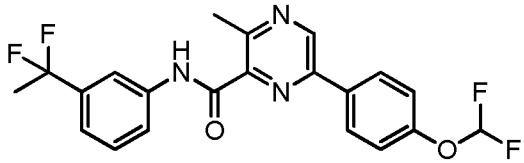


[001008] **126-A** was obtained via similar procedure of **173-C** from **173-A** and **118-B**.

[001009] **LCMS**: (ESI) *m/z*: 280.8 $[M+H]^+$.

[001010] **Step 2: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-6-(4-(difluoromethoxy)phenyl)-3-methylpyrazine-2-carboxamide (126)**

Compound ID : 126



[001011] **126** was obtained via similar procedure of **173** from **126-A** and 3-(1,1-difluoroethyl)aniline

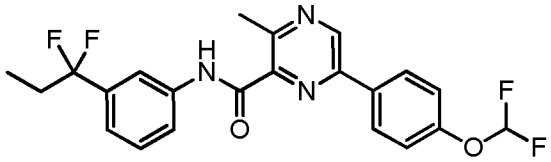
[001012] **LCMS**: (ESI) *m/z*: 420.1 $[M+H]^+$.

[001013] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 9.18 (s, 1H), 8.26-8.34 (m, 2H), 8.06 (s, 1H), 7.88 (br d, *J*=8.4 Hz, 1H), 7.50 (t, *J*=8.0 Hz, 1H), 7.31-7.39 (m, 3H), 6.76-7.18 (m, 1H), 2.93 (s, 3H), 1.97 ppm (t, *J*=18.4 Hz, 3H).

Synthesis of 125

[001014] **Step 1: Synthesis of 6-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3-methylpyrazine-2-carboxamide (125)**

Compound ID : 125



[001015] **125** was obtained via similar procedure of **173** from **126-A** and 3-(1,1-difluoropropyl)aniline

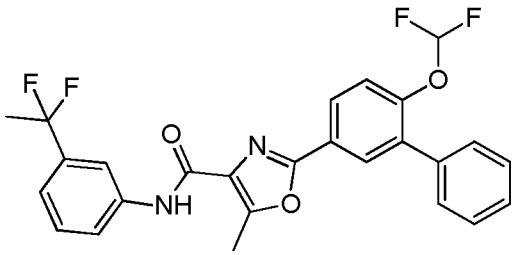
[001016] **LCMS**: (ESI) *m/z*: 434.1 $[M+H]^+$.

[001017] **^{1}H NMR** (400 MHz, MeOD-d_4) δ : 9.18 (s, 1H), 8.23-8.37 (m, 2H), 8.02 (s, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 7.45-7.56 (m, 1H), 7.27-7.38 (m, 3H), 6.71-7.22 (m, 1H), 2.93 (s, 3H), 2.14-2.31 (m, 2H), 1.02 (t, *J*=7.6 Hz, 3H).

Synthesis of 124

[001018] **Step 1: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-2-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-methyl-oxazole-4-carboxamide (124)**

Compound ID: 124



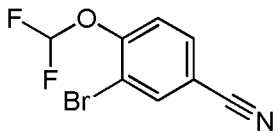
[001019] **124** was obtained via similar procedure of **154** from **123-E** and 3-(1,1-difluoroethyl)aniline.

[001020] **LCMS**: (ESI) *m/z*: 485.3 $[M+H]^+$.

[001021] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.17 (d, J = 2.4 Hz, 1H), 8.12 (dd, J = 2.4, 8.5 Hz, 1H), 7.99 (s, 1H), 7.80 (dd, J = 1.0, 8.2 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.52 - 7.40 (m, 5H), 7.31 (dd, J = 0.8, 7.7 Hz, 1H), 7.03 - 6.63 (m, 1H), 2.76 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H).

Synthesis of 123

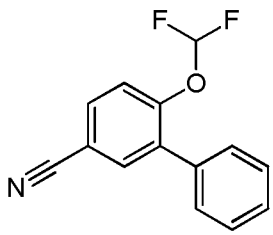
[001022] **Step 1: Synthesis of 3-bromo-4-(difluoromethoxy)benzonitrile (123-A)**



[001023] To a solution of 3-bromo-4-hydroxy-benzonitrile (10.0 g, 50.5 mmol, 1.0 *eq*) and (2-chloro-2,2-difluoro-acetyl)oxysodium (11.6 g, 75.8 mmol, 1.5 *eq*) in *N*,*N*-dimethyl-formamide (100 mL) was added sodium carbonate (8.03 g, 75.8 mmol, 1.5 *eq*), the solution was stirred at 100 °C for 12 h. The mixture was quenched by slow addition of saturated aqueous water (200 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 10/1) to give 6.00 g (48% yield) of **123-A** as a white solid.

[001024] **LCMS**: (ESI) *m/z*: 247.9, 249.9 $[M+H]^+$.

[001025] **Step 2: Synthesis of 4-(difluoromethoxy)-3-phenyl-benzonitrile (123-B)**

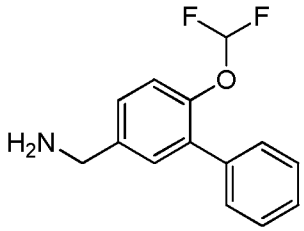


[001026] To a solution of **123-A** (1.50 g, 6.05 mmol, 1.0 *eq*) and phenylboronic acid (1.47 g, 12.1 mmol, 2.0 *eq*) in dioxane (20 mL) was added a solution of potassium carbonate (1.67 g, 12.1 mmol, 2.0 *eq*) in water (4 mL) and 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (443 mg, 605 umol, 0.10 *eq*). The suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under nitrogen at 80 °C for 12 hr. To the reaction mixture was added

water (20 mL), the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (50 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, from 1/0 to 10/1) to give 1.50 g (99% yield) of **123-B** as a light yellow solid.

[001027] **LCMS**: (ESI) *m/z*: 246.1 $[M+H]^+$.

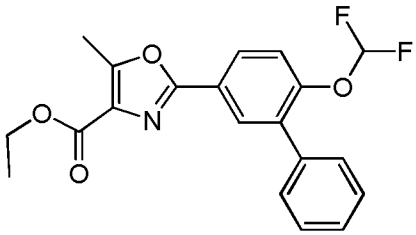
[001028] **Step 3: Synthesis of [4-(difluoromethoxy)-3-phenyl-phenyl]methanamine (123-C)**



[001029] To a solution of **123-B** (1.50 g, 5.99 mmol, 1.0 *eq*) in saturated ammonia/methanol (10 mL) was added raney nickel (524 mg, 6.12 mmol, 1.0 *eq*). The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 25 °C for 1 hr. The mixture was filtered, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 10/1 to 5/1) to give 1.40 g (78% yield) of **123-C** as a light green oil.

[001030] **LCMS**: (ESI) *m/z*: 250.1 $[M+H]^+$.

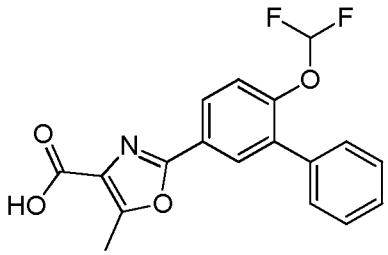
[001031] **Step 4: Synthesis of ethyl 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-5-methyloxazole-4-carboxylate (123-D)**



[001032] **123-D** was obtained via similar procedure of **153-A** from **123-C**.

[001033] **LCMS**: (ESI) *m/z*: 374.1 $[M+H]^+$.

[001034] **Step 5: Synthesis of 2-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-methyl-oxazole-4-carboxylic acid (123-E)**

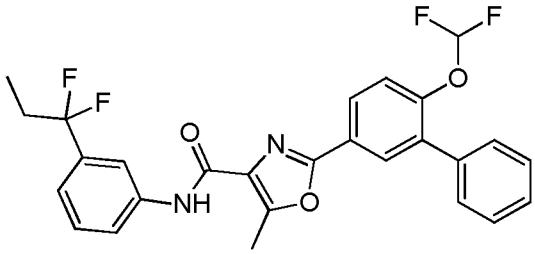


[001035] **123-E** was obtained via similar procedure of **154-C** from **123-D** and sodium hydroxide.

[001036] **LCMS**: (ESI) *m/z*: 346.0 $[M+H]^+$.

[001037] **Step 6: Synthesis of 2-[4-(difluoromethoxy)-3-phenyl-phenyl]-*N*-[3-(1,1-difluoropropyl)phenyl]-5-methyl-oxazole-4-carboxamide (123)**

Compound ID: 123



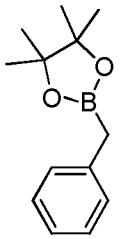
[001038] **123** was obtained via similar procedure of **154** from **123-E** and 3-(1,1-difluoropropyl)aniline.

[001039] **LCMS**: (ESI) *m/z*: 499.3 $[M+H]^+$.

[001040] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.17 (d, J = 2.4 Hz, 1H), 8.11 (dd, J = 2.4, 8.5 Hz, 1H), 7.95 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.51 - 7.39 (m, 5H), 7.26 (d, J = 7.8 Hz, 1H), 7.03 - 6.63 (m, 1H), 2.76 (s, 3H), 2.29 - 2.10 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).

Synthesis of 122

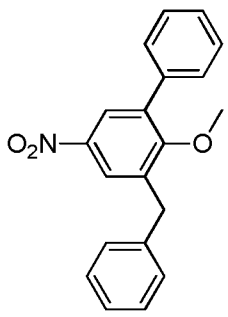
[001041] **Step 1: Synthesis of 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (122-A)**



[001042] To a solution of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (44.5 g, 175 mmol, 1.5 *eq*) , triphenylphosphine (3.99 g, 15.2 mmol, 0.13 *eq*), lithium methanolate (4 M, 58.5 mL, 2.0 *eq*) and copper iodide (2.23 g, 11.7 mmol, 0.10 *eq*) in *N*,*N*-dimethylformamide (100 mL) was added a solution of bromomethylbenzene (20.0 g, 117 mmol, 1.0 *eq*) in *N*,*N*-dimethylformamide (200 mL). The suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under nitrogen at 20 °C for 12 hours. The suspension was filtered and the filtrate was concentrated. The residue was purified by silica column (petroleum ether/ethyl acetate, from 1/ 0 to 10/ 1) to give 5.00 g (20% yield) of **122-A** as a white solid.

[001043] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 7.17-7.04(m, 5 H), 2.22(s, 2H), 1.15(s, 12 H).

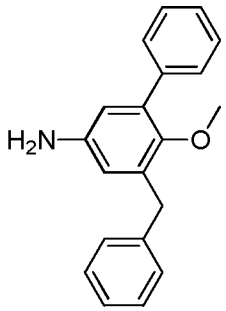
[001044] **Step 2: Synthesis of 3-benzyl-2-methoxy-5-nitro-1,1'-biphenyl (122-B)**



[001045] To a solution of **161-E** (3.00 g, 8.45 mmol, 1.0 *eq*) and sodium carbonate (1.79 g, 16.9 mmol, 2.0 *eq*) in dioxane (30 mL) /water (6 mL) was added **122-A** (4.85 g, 22.2 mmol, 2.6 *eq*) and 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (618 mg, 845 umol, 0.10 *eq*) . The suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under

nitrogen at 90 °C for 12 hours. 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. The residue was purified by silica column (petroleum ether/ ethyl acetate, from 1/0 to 10/1) to give 5.00 g (62% yield) of **122-B** as a white solid.

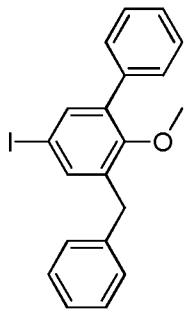
[001046] **Step 3: Synthesis of 5-benzyl-6-methoxy-[1,1'-biphenyl]-3-amine (122-C)**



[001047] To a solution of **122-B** (5.00 g, 15.7 mmol, 1.0 *eq*) in methanol (50 mL) was added Pd/C (500 mg, 10% purity). The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 20 °C for 12 hours. The suspension was filtered and the filtrate was concentrated to give 4.00 g (76% yield) of **122-C** as a colorless oil.

[001048] **LCMS**: (ESI) *m/z*: 290.1 $[M+H]^+$.

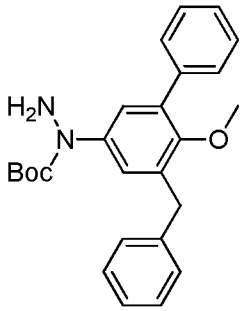
[001049] **Step 4: Synthesis of 3-benzyl-5-iodo-2-methoxy-1,1'-biphenyl (122-D)**



[001050] To a solution of **122-C** (3.00 g, 8.98 mmol, 1.0 *eq*) in hydrochloric acid (3 M, 40 mL, 13 *eq*) was added dropwise a solution of sodium nitrite (858 mg, 12.4 mmol, 1.4 *eq*) in water (10 mL) at 0 °C, the solution was stirred at 0 °C for 30 min. Then potassium iodide (8.61 g, 51.9 mmol, 5.8 *eq*) was added into the solution and the mixture was stirred at 20 °C for 2 h. The solution was poured into water (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica column (petroleum ether) to give 1.70 g (47% yield) of **122-D** as a brown oil.

[001051] **LCMS**: (ESI) *m/z*: 273.1 $[M-I]^+$.

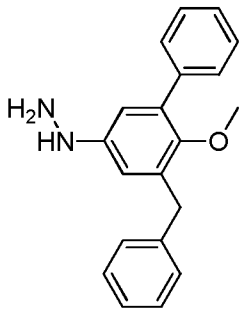
[001052] **Step 5: Synthesis of *tert*-butyl 1-(5-benzyl-6-methoxy-[1,1'-biphenyl]-3-yl)hydrazinecarboxylate (122-E)**



[001053] A mixture of **122-D** (850 mg, 2.12 mmol, 1.0 *eq*), *tert*-butyl *N*-aminocarbamate (337 mg, 2.55 mmol, 1.2 *eq*), 1,10-phenanthroline (38.3 mg, 212 umol, 0.10 *eq*), copper iodide (40.5 mg, 212 umol, 0.10 *eq*) and cesium carbonate (1.38 g, 4.25 mmol, 2.0 *eq*) in *N*,*N*-dimethylformamide (20 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 80 °C for 12 hr under nitrogen atmosphere. The solution was poured into water (30 mL), extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica column (petroleum ether/ethyl acetate, from 10/1 to 5/1 to give 1.30 g (72% yield) of **122-E** as a light yellow oil.

[001054] **LCMS**: (ESI) *m/z*: 427.3 $[M+Na]^+$.

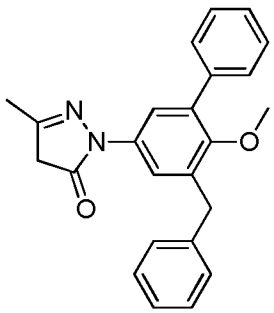
[001055] **Step 6: Synthesis of (5-benzyl-6-methoxy-[1,1'-biphenyl]-3-yl)hydrazine (122-F)**



[001056] To a solution of **122-E** (1.25 g, 2.96 mmol, 1.0 *eq*) in ethyl acetate (10 mL) was added hydrogen chloride/ethyl acetate (4 M, 10 mL, 14 *eq*). The solution was stirred at 25 °C for 1 h. The solution was concentrated to give 1.00 g (90% yield, hydrochloride) of **122-F** as a white solid.

[001057] **LCMS**: (ESI) *m/z*: 305.2 $[M+H]^+$.

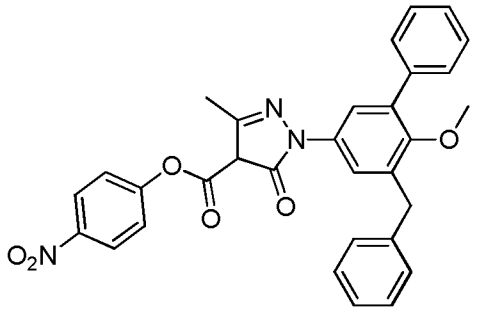
[001058] **Step 7: Synthesis of 1-(5-benzyl-6-methoxy-[1,1'-biphenyl]-3-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (122-G)**



[001059] **122-G** was obtained via general procedure II from **122-F**

[001060] **LCMS**: (ESI) *m/z*: 371.2 $[M+H]^+$.

[001061] **Step 8: Synthesis of 4-nitrophenyl 1-(5-benzyl-6-methoxy-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate (122-H)**

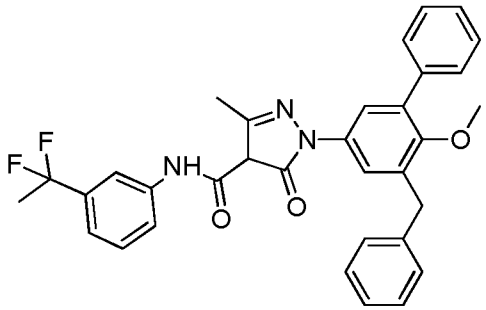


[001062] **122-H** was obtained via general procedure III from **122-G**

[001063] **LCMS**: (ESI) *m/z*: 536.2 $[M+H]^+$.

[001064] **Step 9: Synthesis of 1-(5-benzyl-6-methoxy-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (122)**

Compound ID: 122



[001065] **122** was obtained via general procedure IV from **122-H** and 3-(1,1-difluoroethyl)aniline

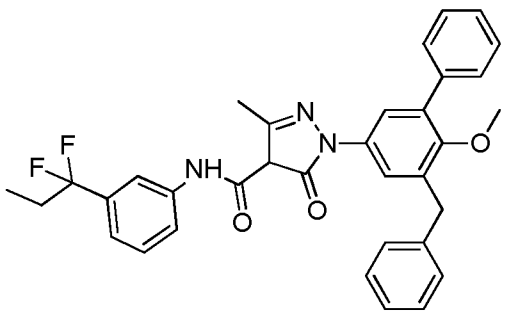
[001066] **LCMS**: (ESI) *m/z*: 554.3 $[M+H]^+$.

[001067] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.91(s, 1H), 7.93(s, 1H), 7.70-7.58(m, 5H), 7.49(t, *J*= 7.2 Hz, 2H), 7.42-7.37(m, 2H), 7.34-7.28(m,4H), 7.22-7.16(m, 2H), 4.06(s, 2H), 3.18(s, 3H), 2.48(s, 3H), 1.95(t, *J*= 18.8 Hz, 3H).

Synthesis of 121

[001068] **Step 1: Synthesis of 1-(5-benzyl-6-methoxy-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (121)**

Compound ID: 121



[001069] **121** was obtained via general procedure IV from **122-H** and 3-(1,1-difluoropropyl)aniline

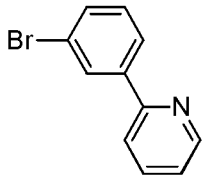
[001070] **LCMS**: (ESI) *m/z*: 568.3 $[M+H]^+$.

[001071] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.88(s, 1H), 7.89(s, 1H), 7.69-7.59(m, 5H), 7.49(t, *J*= 7.6 Hz, 2H), 7.43-7.38(m, 2H), 7.34-7.28(m, 4H), 7.22-7.12(m, 2H), 4.06(s, 2H), 3.18(s, 3H), 2.51(s,

3H), 2.24-2.14(m, 2H), 0.91(t, *J*= 7.6 Hz, 3H).

Synthesis of 120

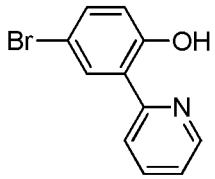
[001072] **Step 1: Synthesis of 2-(3-bromophenyl)pyridine (120-A)**



[001073] A mixture of (3-bromophenyl)boronic acid (5.00 g, 24.9 mmol, 1.0 *eq*), 2-bromopyridine (3.93 g, 24.9 mmol, 1.0 *eq*), tetrakis(triphenylphosphine)platinum (288 mg, 249 umol, 0.010 *eq*), sodium carbonate (5.81 g, 54.8 mmol, 2.2 *eq*) in 1,2-dimethoxyethane (63 mL), ethanol (20 mL) and water (28 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 90 °C for 18 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 (100 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 10/1 to 5/1) to give 5.60 g (83% yield) of **120-A** as a yellow oil.

[001074] **LCMS**: (ESI) *m/z*: 234.0, 236.0 $[M+H]^+$.

[001075] **Step 2: Synthesis of 4-bromo-2-(pyridin-2-yl)phenol (120-B)**

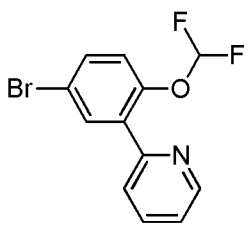


[001076] A mixture of **120-A** (2.30 g, 8.45 mmol, 1.0 *eq*), *tert*-butyl hydroperoxide (6.53 g, 50.70mmol, 6.0 *eq*) and palladium acetate (94.9 mg, 422 umol, 0.050 *eq*) in dichloroethane (30 mL) was stirred at 115 °C for 36 h in a 100 mL of sealed tube. The mixture was quenched with saturated sodium sulfite aqueous (50 mL) and extracted with dichloromethane (50 mL x 2). The combined organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give 0.530 g (25% yield) of **120-B** as a yellow solid.

[001077] **LCMS**: (ESI) *m/z*: 250.0 $[M+H]^+$.

[001078] **^{1}H NMR**: (400MHz, $CDCl_3$-*d*) δ: 14.40 (br s, 1H), 8.54 (dt, *J*=5.2, 1.2 Hz, 1H), 7.92 - 7.87 (m, 3H), 7.39 (dd, *J*=2.4, 8.8 Hz, 1H), 7.34 - 7.28 (m, 1H), 6.93 (d, *J*=8.8 Hz, 1H).

[001079] **Step 3: Synthesis of 2-(5-bromo-2-(difluoromethoxy)phenyl)pyridine (120-C)**

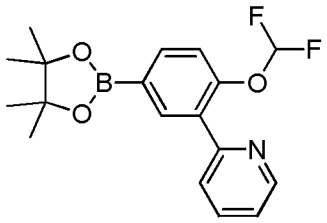


[001080] To a solution of **120-B** (1.05 g, 4.18 mmol, 1.0 *eq*) in acetonitrile (15 mL) and water

(5 mL) was added potassium hydroxide (2.35 g, 41.8 mmol, 10 *eq*) and 1-[[bromo(difluoro)methyl]-ethoxy-phosphoryl]oxyethane (2.23 g, 8.36 mmol, 2.0 *eq*). The mixture was stirred at 20 °C for 12 h. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic phase was separated, washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give 0.890 g (57% yield) of **120-C** as a yellow oil.

[001081] **LCMS**: (ESI) *m/z*: 301.7 $[M+H]^+$.

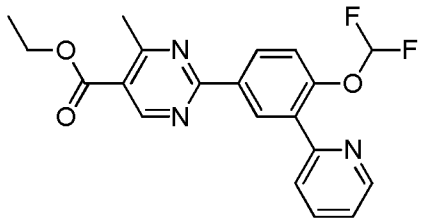
[001082] **Step 4: Synthesis of 2-(2-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine (120-D)**



[001083] A mixture of **120-C** (0.790 g, 2.13 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 (1.08 g, 4.26 mmol, 2.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (78.0 mg, 107 umol, 0.050 *eq*), potassium acetate (419 mg, 4.26 mmol, 2.0 *eq*) in dioxane (15 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 90 °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 (50 mL x 2), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give 0.760 g (75% yield) of **120-D** as a colorless oil.

[001084] **LCMS**: (ESI) *m/z*: 348.1 $[M+H]^+$.

[001085] **Step 5: Synthesis of ethyl 2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-4-methylpyrimidine-5-carboxylate (120-E)**

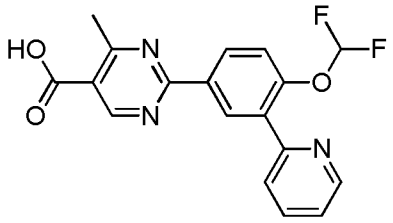


[001086] **120-E** was obtained via similar procedure of **133-A** from **120-D** and ethyl 2-chloro-4-methylpyrimidine-5-carboxylate.

[001087] **LCMS**: (ESI) *m/z*: 386.1 $[M+H]^+$.

[001088] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 9.21 (s, 1H), 8.96 (d, *J*=2.0 Hz, 1H), 8.78 (d, *J*=4.8Hz, 1H), 8.60 (d, *J*=8.4 Hz, 1H), 7.82 - 7.74 (m, 2H), 7.36 (d, *J*=8.8 Hz, 1H), 7.32 (d, *J*=2.0 Hz, 1H), 6.61 (t, *J*=74.4 Hz, 1H), 4.44 (q, *J*=7.2 Hz, 2H), 2.90 (s, 3H), 1.44 (t, *J*=7.2 Hz, 3H).

[001089] **Step 6: Synthesis of 2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-4-methylpyrimidine-5-carboxylic acid (120-F)**

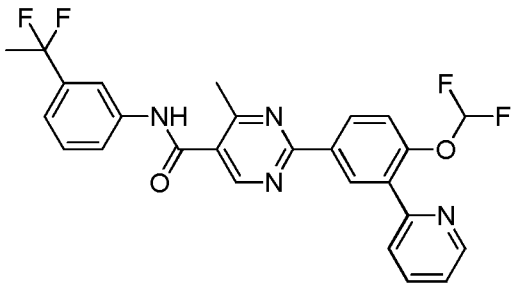


[001090] **120-F** was obtained via similar procedure of **133-B** from **120-E**.

[001091] **LCMS**: (ESI) *m/z*: 358.0 $[M+H]^+$.

[001092] **Step 7: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-4-methylpyrimidine-5-carboxamide (120)**

Compound ID: 120



[001093] **120** was obtained via similar procedure of **133** from **120-F** and 3-(1,1-difluoroethyl)aniline.

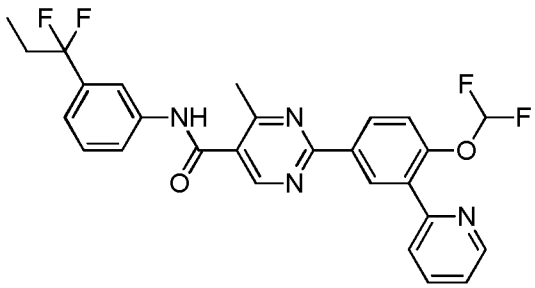
[001094] **LCMS**: (ESI) *m/z*: 497.2 $[M+H]^+$.

[001095] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.92 (s, 1H), 8.83 (d, *J*=2.0 Hz, 1H), 8.69 (d, *J*=4.8 Hz, 1H), 8.64 (dd, *J*=2.4, 8.8 Hz, 1H), 7.98 - 7.93 (m, 2H), 7.82 - 7.77 (m, 2H), 7.50 - 7.44 (m, 3H), 7.35 (d, *J*=7.6 Hz, 1H), 6.97 (t, *J*=73.6 Hz, 1H), 2.75 (s, 3H), 1.94 (t, *J*=18.4 Hz, 3H).

Synthesis of 119

[001096] **Step 1: Synthesis of 2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-4-methylpyrimidine-5-carboxamide (119)**

Compound ID: 119



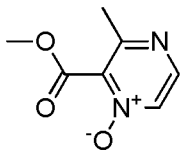
[001097] **119** was obtained via similar procedure of **133** from **120-F** and 3-(1,1-difluoropropyl)aniline.

[001098] **LCMS**: (ESI) *m/z*: 511.3 $[M+H]^+$.

[001099] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.91 (s, 1H), 8.83 (d, *J*=2.4 Hz, 1H), 8.69 (d, *J*=4.4 Hz, 1H), 8.62 (dd, *J*=2.4, 8.8 Hz, 1H), 7.97 - 7.93 (m, 1H), 7.90 (s, 1H), 7.82 - 7.77 (m, 2H), 7.50 - 7.44 (m, 3H), 7.30 (d, *J*=7.6 Hz, 1H), 6.96 (t, *J*=73.6 Hz, 1H), 2.75 (s, 3H), 2.23 - 2.13 (m, 2H), 1.94 (t, *J*=7.6 Hz, 3H).

Synthesis of 118

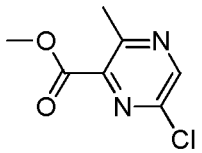
[001100] **Step 1: Synthesis of 2-(methoxycarbonyl)-3-methylpyrazine 1-oxide (118-A)**



[001101] **118-A** was obtained via similar procedure of **135-A** from methyl 3-methylpyrazine-2-carboxylate and hydrogen peroxide

[001102] **LCMS:** (ESI) *m/z*: 169.0 $[M+H]^+$.

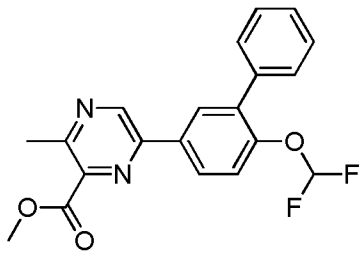
[001103] **Step 2: Synthesis of methyl 6-chloro-3-methylpyrazine-2-carboxylate (118-B)**



[001104] **118-B** was obtained via similar procedure of **135-B** from **118-A** and phosphoryl trichloride

[001105] **^{1}H NMR:** (400 MHz, $CDCl_3$-*d*) δ: 8.64 (s, 1H), 4.01 (s, 3H), 2.84 (s, 3H).

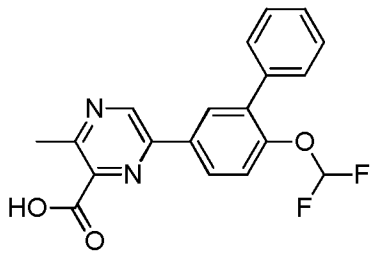
[001106] **Step 3: Synthesis of methyl 6-[4-(difluoromethoxy)-3-phenyl-phenyl]-3-methyl-pyrazine-2-carboxylate (118-C)**



[001107] **118-C** was obtained via similar procedure of **135-C** from **118-B** and **127-C**.

[001108] **^{1}H NMR:** (400 MHz, $CDCl_3$-*d*) δ: 9.03 (s, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 8.02 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.57 ~7.53 (m, 2H), 7.51 ~7.37 (m, 4H), 6.41 (t, *J* = 73.6 Hz, 1H), 4.03 (s, 3H), 2.86 (s, 3H).

[001109] **Step 4: Synthesis of 6-[4-(difluoromethoxy)-3-phenyl-phenyl]-3-methyl-pyrazine-2-carboxylic acid (118-D)**



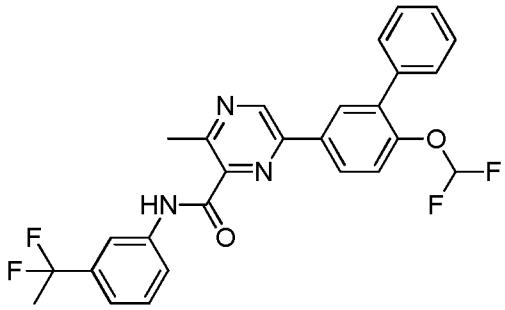
[001110] **118-D** was obtained via similar procedure of **135-D** from **118-C** and lithium hydroxide hydrate.

[001111] **LCMS:** (ESI) *m/z*: 357.2 $[M+H]^+$.

[001112] **Step 5: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-6-[4-(difluoromethoxy)-3-**

phenyl-phenyl]-3-methyl-pyrazine-2-carboxamide (118)

Compound ID: 118



[001113] **118** was obtained via similar procedure of **135** from **118-D** and 3-(1,1-difluoroethyl)aniline.

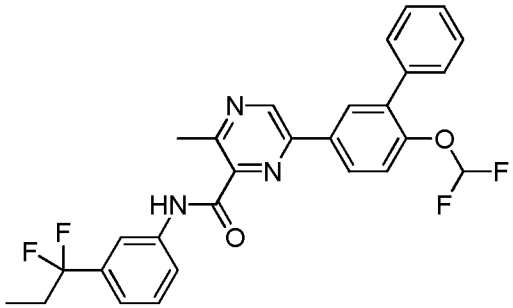
[001114] **LCMS:** (ESI) *m/z*: 496.3 $[M+H]^+$.

[001115] **^{1}H NMR:** (400 MHz, MeOD-d_4) δ: 9.22 (s, 1H), 8.31 -8.27 (m, 2H), 8.01 (s, 1H), 7.86 -7.83 (m, 1H), 7.61 -7.58 (m, 2H), 7.50 -7.45 (m, 4H), 7.43 -7.38 (m, 1H), 7.34 (dd, J = 7.6, 0.8 Hz, 1H), 6.82 (t, J= 73.6 Hz, 1H), 2.91 (s, 3H), 1.95 (t, J = 18.4 Hz, 3H).

Synthesis of 117

[001116] **Step 1: Synthesis of 6-[4-(difluoromethoxy)-3-phenyl-phenyl]-*N*-[3-(1,1-difluoropropyl)phenyl]-3-methyl-pyrazine-2-carboxamide (117)**

Compound ID: 117



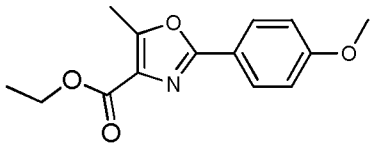
[001117] **117** was obtained via similar procedure of **118** from **118-D** and 3-(1,1-difluoropropyl)aniline.

[001118] **LCMS:** (ESI) *m/z*: 510.3 $[M+H]^+$.

[001119] **^{1}H NMR:** (400 MHz, MeOD-d_4) δ: 9.23 (s, 1H), 8.30 ~8.27 (m, 2H), 7.97 (s, 1H), 7.87 ~7.83 (m, 1H), 7.61 ~7.58 (m, 2H), 7.50 ~7.45 (m, 4H), 7.43 ~7.38 (m, 1H), 7.30 (d, J = 7.2 Hz, 1H), 6.82 (t, J = 74 Hz, 1H), 2.92 (s, 3H), 2.28 ~2.13 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H).

Synthesis of 116

[001120] **Step 1: Synthesis of ethyl 2-(4-methoxyphenyl)-5-methyloxazole-4-carboxylate (116-A)**

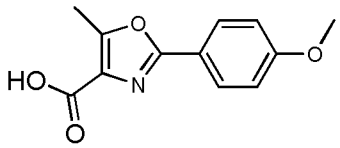


[001121] To a solution of (4-methoxyphenyl)methanamine (1.50 g, 10.9 mmol, 1.0 *eq*) and ethyl

3-oxobutanoate (1.42 g, 10.9 mmol, 1.0 *eq*) in *N*,*N*-dimethylformamide (10 mL) was added iodine (3.33 g, 13.12 mmol, 1.2 *eq*), copper acetate (199 mg, 1.09 mmol, 0.10 *eq*) and *tert*-butyl hydroperoxide (1.97 g, 21.8 mmol, 2.0 *eq*). The mixture was stirred at 50 °C for 12 hr. The mixture was quenched by slow addition of saturated sodium bisulfite solution. The resulting mixture was transferred to a separatory funnel, and aqueous layer mixture was extracted with ethyl acetate (5mL x 3). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording a light yellow oil. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 30/1 to 20/1) to give 107 mg (1% yield) of **116-A** as a light yellow oil.

[001122] **LCMS**: (ESI) *m/z*: 262.1 $[M+H]^+$.

[001123] **Step 2: Synthesis of 2-(4-methoxyphenyl)-5-methyloxazole-4-carboxylic acid (116-B)**

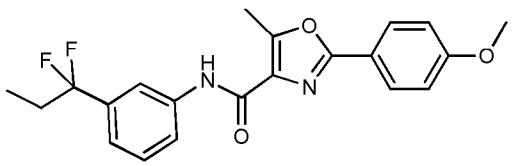


[001124] To a solution of **116-A** (107 mg, 207 umol, 1.0 *eq*) in ethanol (1 mL) and water (0.2 mL) was added sodium hydroxide (41.5 mg, 1.04 mmol, 5.0 *eq*). Then the mixture was stirred at 50 °C for 4 hr. The reaction mixture was concentrated under reduced pressure to remove ethanol. The pH of mixture was adjusted to 2 by using hydrochloric acid (1 M), the crude product was separate out to give 50.0 mg (50% yield) of **116-B** as a light yellow solid.

[001125] **LCMS**: (ESI) *m/z*: 234.0 $[M+H]^+$.

[001126] **Step 3: Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-2-(4-methoxyphenyl)-5-methyloxazole-4-carboxamide (116)**

Compound ID : 116



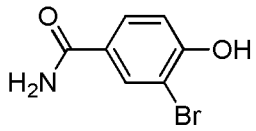
[001127] To a solution of **116-B** (50.0 mg, 103 umol, 1.0 *eq*) and 3-(1,1-difluoropropyl)aniline (17.7 mg, 103 umol, 1.0 *eq*) in pyridine (0.5 mL) was added *N*-[3-(Dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (39.6 mg, 207 umol, 2.0 *eq*). Then the mixture was stirred at 25 °C for 12 hr. The mixture was concentrated under reduced pressure to remove pyridine. The crude product was purified by preparative TLC (petroleum ether/ethyl acetate= 3/1) to give a crude product. The crude product was purified by preparative HPLC (Phenomenex luna C18 column (250 x 50 mm, 10 um); flow rate: 25 mL/min; gradient: 68% - 98% B over 9 min; mobile phase A: 0.075% aqueous trifluoroacetic acid, mobile phase B: acetonitrile) to give 3.90 mg (10% yield) of **116** as a yellow solid

[001128] **LCMS**: (ESI) *m/z*: 387.4 $[M+H]^+$.

[001129] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.07 - 7.99 (dt, 2H), 7.96 - 7.93 (s, 1H), 7.85 - 7.75 (dd, 1H), 7.49 - 7.41 (t, 1H), 7.30 - 7.23 (d, 1H), 7.12 - 7.03 (dt, 2H), 3.92 - 3.83 (s, 3H), 2.78 - 2.68 (s, 3H), 2.27 - 2.12 (td, 2H), 1.05 - 0.94 (t, 3H).

Synthesis of 115

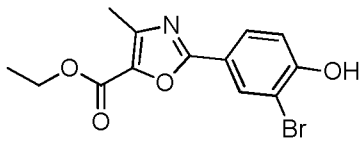
[001130] **Step 1: Synthesis of 3-bromo-4-hydroxybenzamide (115-A)**



[001131] To a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added 3-bromo-4-hydroxy-benzonitrile (2.00 g, 10.1 mmol, 1.0 *eq*) followed by the addition of sulfuric acid (98%, 20 mL). Then the mixture was heated to 80 °C and stirred for 2 h. The solution was poured into water (100 mL), the mixture was extracted with ethyl acetate (40 mL x 3). The combined organic layer was washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1.40 g (55% yield) of **115-A** as a yellow solid.

[001132] **LCMS**: (ESI) *m/z*: 216.0 $[M+H]^+$.

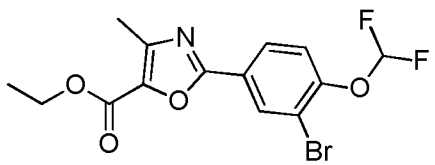
[001133] **Step 2: Synthesis of ethyl 2-(3-bromo-4-hydroxyphenyl)-4-methyloxazole-5-carboxylate (115-B)**



[001134] To a 10 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **115-A** (1.20 g, 5.01 mmol, 1.0 *eq*) followed by the addition of ethyl 2-chloro-3-oxo-butanoate (1.24 g, 7.51 mmol, 1.5 *eq*). The mixture was heated to 130 °C and stirred for 12 h. The mixture was quenched by slow addition of saturated sodium chloride solution (50 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 10/1) to give 1.50 g (75% yield) of **115-B** as a yellow solid.

[001135] **LCMS**: (ESI) *m/z*: 326.0 $[M+H]^+$.

[001136] **Step 3: Synthesis of ethyl 2-(3-bromo-4-(difluoromethoxy)phenyl)-4-methyloxazole-5-carboxylate (115-C)**

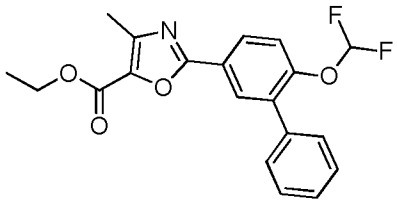


[001137] To a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser was added **115-B** (1.30 g, 3.27 mmol, 1.0 *eq*), sodium;2-chloro-2,2-difluoro-acetate (747 mg, 4.90 mmol, 1.5 *eq*) followed by the addition of *N*,*N*-dimethylformamide (8 mL). Then sodium carbonate

(693 mg, 6.54 mmol, 2.0 *eq*) was added into the mixture. The mixture was heated to 100 °C and stirred for 2 h. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (80 mL) and water (80 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 15/1 to 10/1) to give 600 mg (44% yield) of **115-C** as a white solid.

[001138] **LCMS**: (ESI) *m/z*: 376.0 $[M+H]^+$.

[001139] **Step 4: Synthesis of ethyl 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-4-methyloxazole-5-carboxylate (115-D)**

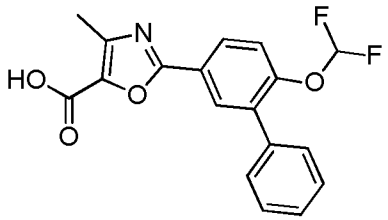


[001140] To a solution of **115-C** (300 mg, 726 umol, 1.0 *eq*) and phenylboronic acid (124 mg, 1.02 mmol, 1.4 *eq*) in dioxane (15 mL) and water (3 mL) was added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (53.1 mg, 72.6 umol, 0.10 *eq*) and sodium bicarbonate (152 mg, 1.81 mmol, 2.5 *eq*). The solution was stirred at 90 °C for 12 h. The solution was filtered through a celite pad and the filtrate was diluted with ethyl acetate (100 mL). The mixture was washed with brine (100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=10/1) to give 280 mg (99% yield) of **115-D** as a yellow solid.

[001141] **LCMS**: (ESI) *m/z*: 374.0 $[M+H]^+$.

[001142] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 8.19 (d, *J* = 2.8 Hz, 1H), 8.12 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.57 - 7.50 (m, 2H), 7.50 - 7.38 (m, 3H), 7.35 (d, *J* = 8.8 Hz, 1H), 6.44 (t, *J* = 73.6 H, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.55 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H).

[001143] **Step 5: Synthesis of 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-4-methyloxazole-5-carboxylic acid (115-E)**



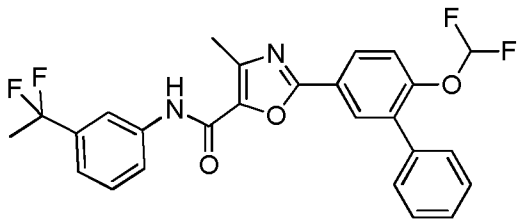
[001144] To a solution of **115-D** (280 mg, 724 umol, 1 *eq*) in ethanol (10 mL) and water (2 mL) was added sodium hydroxide (72.4 mg, 1.81 mmol, 2.5 *eq*). The solution was stirred at 15 °C for 12 h. The organic solvent was removed under reduced pressure. The residue was diluted with water (50 mL) and acidified by aqueous hydrochloric acid (6 M) to pH = 2. The mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous

sodium sulfate, filtered and concentrated to give 240 mg (96% yield) of **115-E** as a white solid.

[001145] **LCMS**: (ESI) *m/z*: 346.0 $[M+H]^+$.

[001146] **Step 6: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-4-methyloxazole-5-carboxamide (115)**

Compound ID: 115



[001147] To a solution of **115-E** (50.0 mg, 144.8 umol, 1.0 *eq*) in *N*,*N*-dimethylformamide (1 mL) was added [dimethylamino(triazol[4,5-b]pyridin-3-yloxy)methylidene]-dimethylazanium;hexafluorophosphate (60.6 mg, 159 umol, 1.1 *eq*) and *N*-ethyl-*N*-isopropylpropan-2-amine (74.9 mg, 579 umol, 4.0 *eq*). The solution was stirred at 15 °C for 10 min and then 3-(1,1-difluoroethyl)aniline (29.6 mg, 188 umol, 1.3 *eq*) was added. The solution was sitrred at 15 °C for 2 h. The solution was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 61%-91%, 10min) to give 43.9 mg (39% yield) of **115** as a yellow solid.

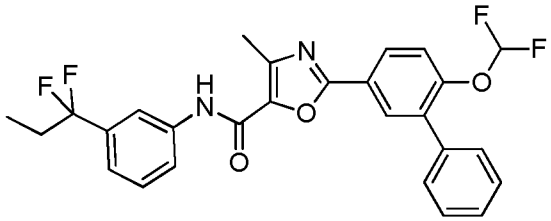
[001148] **LCMS**: (ESI) *m/z*: 485.2 $[M+H]^+$.

[001149] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.35 (d, J = 2.0 Hz, 1H), 8.25 (dd, J = 2.0, 8.4 Hz, 1H), 7.93 (s, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.59 - 7.53 (m, 2H), 7.51 - 7.38 (m, 5H), 7.33 (dd, J = 0.8, 8.0 Hz, 1H), 6.87 (t, J = 73.6 Hz, 1H), 2.58 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H)

Synthesis of 114

[001150] **Step 1: Synthesis of 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-4-methyloxazole-5-carboxamide (114)**

Compound ID: 114



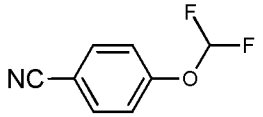
[001151] **114** was obtained via the similar synthetic method of **115** from **115-E** and 3-(1,1-difluoropropyl)aniline.

[001152] **LCMS**: (ESI) *m/z*: 499.2 $[M+H]^+$.

[001153] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.35 (d, J = 2.0 Hz, 1H), 8.26 (dd, J = 2.0, 8.8 Hz, 1H), 7.88 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.60 - 7.53 (m, 2H), 7.52 - 7.37 (m, 5H), 7.28 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 73.2 Hz, 1H), 2.58 (s, 3H), 2.32 - 2.08 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H).

Synthesis of 113

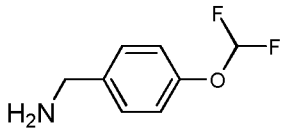
[001154] **Step 1: Synthesis of 4-(difluoromethoxy)benzonitrile (113-A)**



[001155] **113-A** was obtained via similar procedure of **123-A** from 4-hydroxybenzonitrile and (2-chloro-2,2-difluoro-acetyl)oxysodium

[001156] **LCMS**: (ESI) *m/z*: 170.1 $[M+H]^+$.

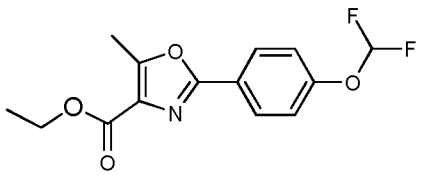
[001157] **Step 2: Synthesis of (4-(difluoromethoxy)phenyl)methanamine (113-B)**



[001158] **113-B** was obtained via similar procedure of **123-C** from **113-A** and hydrogen

[001159] **LCMS**: (ESI) *m/z*: 174.1 $[M+H]^+$.

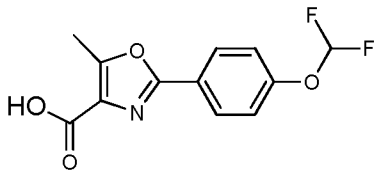
[001160] **Step 3: Synthesis of ethyl 2-(4-(difluoromethoxy)phenyl)-5-methyloxazole-4-carboxylate (113-C)**



[001161] To a solution of **113-B** (1.23 g, 7.11 mmol, 1.9 *eq*) in ethyl acetate (15 mL) was added ethyl 3-oxobutanoate (500 mg, 3.84 mmol, 1.0 *eq*), tertbutylammoniumiodide (284 mg, 768 umol, 0.20 *eq*) and *tert*-butyl hydroperoxide (1.38 g, 15.4 mmol, 4.0 *eq*), the solution was stirred at 40 °C for 10 h. The reaction was poured into water (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica column (petroleum ether/ethyl acetate, from 5/ 1 to 1/1) to give 220 mg (16% yield) of **113-C** as a gray solid

[001162] **LCMS**: (ESI) *m/z*: 297.8 $[M+H]^+$.

[001163] **Step 4: Synthesis of ethyl 2-(4-(difluoromethoxy)phenyl)-5-methyloxazole-4-carboxylic acid (113-D)**

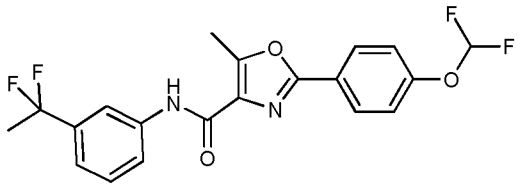


[001164] **113-D** was obtained via similar procedure of **116-B** from **113-C** and sodium hydroxide

[001165] **LCMS**: (ESI) *m/z*: 270.0 $[M+H]^+$.

[001166] **Step 5: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)-5-methyloxazole-4-carboxamide (113)**

Compound ID : 113



[001167] **113** was obtained via similar procedure of **116** from **113-D** and 3-(1,1-difluoroethyl)aniline

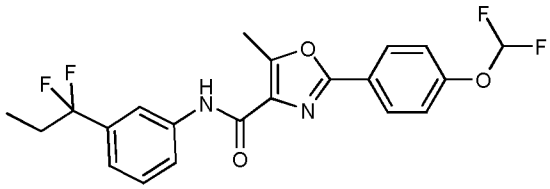
[001168] **LCMS**: (ESI) *m/z*: 409.0 $[M+H]^+$.

[001169] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.17 - 8.12 (m, 2H), 8.02 - 7.98 (s, 1H), 7.83 - 7.79 (d, J = 8.4 Hz, 1H), 7.49 - 7.43 (t, J = 8.0 Hz, 1H), 7.34 - 7.28 (m, 3H), 7.16 - 6.77 (t, J = 73.4 Hz 1H), 2.76 (s, 3H), 1.95 (t, J = 18.2 Hz, 3H).

Synthesis of 112

[001170] **Step 1: Synthesis of 2-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-5-methyloxazole-4-carboxamide (112)**

Compound ID : 112



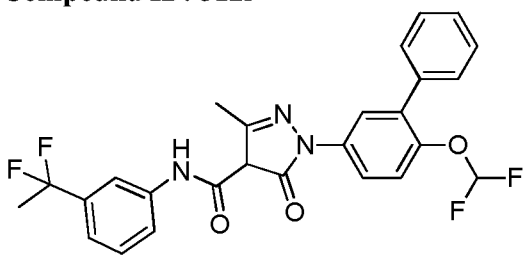
[001171] **112** was obtained via similar procedure of **116** from **113-D** and 3-(1,1-difluoropropyl)aniline

[001172] **LCMS**: (ESI) *m/z*: 423.1 $[M+H]^+$.

[001173] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.08 - 8.17 (td, 2 H) 7.95 (s, 1 H) 7.80 (dd, J=8.12, 1.16 Hz, 1 H) 7.45 (t, J=7.96 Hz, 1 H) 7.24 - 7.33 (td, 3 H) 6.75 - 7.15 (t, 1 H) 2.74 (s, 3 H) 2.12 - 2.27 (td, 2 H) 1.00 (t, J=7.52 Hz, 3 H).

[001174] ***N*-(3-(1,1-difluoroethyl)phenyl)-1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (312i)**

Compound ID: 312i



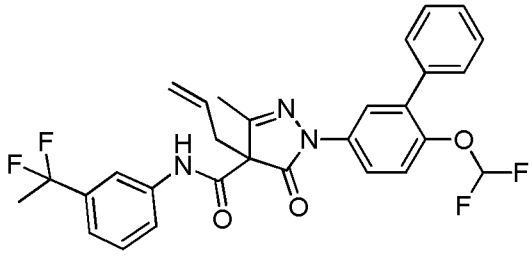
[001175] **Compound 312i** was obtained via general procedure IVfrom 4-nitrophenyl 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and 3-(1,1-difluoroethyl)aniline.

[001176] **LCMS**: (ESI) *m/z*: 500.1 $[M+H]^+$.

[001177] **^{1}H NMR**: (400MHz, MeOD-d_4) δ: 7.92 (s , 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.72 (dd, J = 2.8, 8.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.46 (t, J = 7.2 Hz, 2H), 7.42 - 7.38 (m, 3H), 7.22 (d, J = 8.0 Hz, 1H), 6.71 (t, J = 74.0 Hz, 1H), 2.59 (s, 3H), 1.92 (t, J = 18.4 Hz, 3H).

Synthesis of 111

[001178] **Step 1: Synthesis of 4-allyl-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (111-A)**

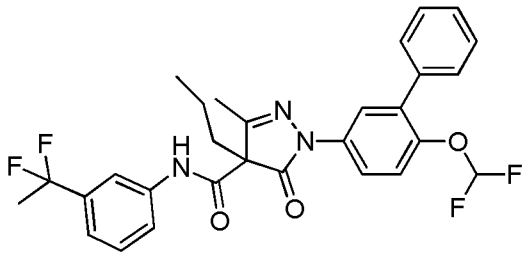


[001179] **111-A** was obtained via similar procedure of **158-A** from **312i** and 3-iodoprop-1-ene.

[001180] **LCMS**: (ESI) m/z: 540.2 $[M+H]^+$.

[001181] **Step 2: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4-propyl-4,5-dihydro-1*H*-pyrazole-4-carboxamide (111)**

Compound ID: 111



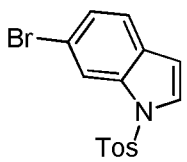
[001182] **111** was obtained via similar procedure of **158** from **111-A**.

[001183] **LCMS**: (ESI) m/z: 542.3 $[M+H]^+$.

[001184] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.01 (s, 1H), 7.96 (d, J=9.2 Hz, 1H), 7.79 (s, 1H), 7.62 (d, J=7.6 Hz, 1H), 7.53 - 7.49 (m, 2H), 7.47 - 7.38 (m, 4H), 7.35 - 7.29 (m, 2H), 6.66 (t, J= 74.0 Hz, 1H), 2.35 - 2.20 (m, 5H), 1.90 (t, J=18.4 Hz, 3H), 1.27 - 1.14 (m, 2H), 0.97 (t, J=7.2 Hz, 3H).

Synthesis of 410

[001185] **Step 1: Synthesis of** 6-bromo-1-(p-tolylsulfonyl)indole **(410i-A)**

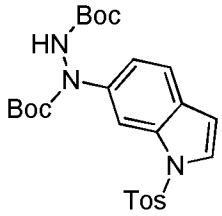


[001186] To a suspension of sodium hydride (4.10 g, 102 mmol, 60% purity, 2.0 *eq*) in *N*,*N*-dimethyl formamide (50 mL) was added dropwise a solution of 6-bromo-1*H*-indole (10.0 g, 51.0 mmol, 1.0 *eq*) in *N*,*N*-dimethyl formamide (50 mL) at 0 °C. The mixture was warmed to 20 °C and stirred for 1 h. Then the mixture was re-cooled to 0 °C, and a solution of 4-methylbenzene-1-sulfonyl chloride

(15.0 g, 76.5 mmol, 1.5 *eq*) in *N*,*N*-dimethyl formamide (50 mL) was added dropwise. After the addition, the mixture was warmed to 20 °C and stirred for another 12 h. The two batches were combined, then poured into cool saturated ammonium chloride (1.5 L), then filtered. The filter cake was collected and dried in vacuo to give 35.0 g (crude) of **410i-A** as brown solid.

[001187] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 8.05 (s, 1H), 7.88 (d, *J*=8.0 Hz, 2H), 7.84 (d, *J*=3.6 Hz, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.45 - 7.37 (m, 3H), 6.86 (d, *J*=3.6 Hz, 1H), 2.32 (s, 3H).

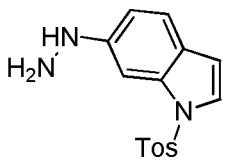
[001188] **Step 2: Synthesis of *tert*-butyl *N*-(tert-butoxycarbonylamino)-*N*-[1-(p-tolylsulfonyl)indol-6-yl]carbamate (410i-B)**



[001189] A mixture of **410i-A** (8.00 g, 22.8 mmol, 1.0 *eq*), *tert*-butyl *N*-(*tert*-butoxycarbonylamino)carbamate (7.40 g, 32.0 mmol, 1.4 *eq*), cesium carbonate (15.0 g, 45.7 mmol, 2.0 *eq*) and1,10-phenanthroline (1.20 g, 6.85 mmol, 0.30 *eq*) and copper iodide (4.40 g, 22.9 mmol, 1.0 eq) in *N*,*N*-dimethyl formamide (30 mL) was degassed and purged with nitrigen for 3 times, and then the mixture was stirred at 80 °C for 12 hr under nitrigen atmosphere. The mixture was concentrated in vacuum directly to give a residue, then the residue was diluted with ethyl acetate (100 mL) and filtered, the filtrate was concentrated under reduced pressure to give the crude. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 30/1 to 5/1) to give 29.0 g (79% yield) of **410i-B** as a yellow oil.

[001190] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 8.08 (s, 1H), 7.77 (d, *J*=7.6 Hz, 2H), 7.53 (d, *J*=3.2 Hz, 1H), 7.43 (d, *J*=8.4 Hz, 1H), 7.22 (d, *J*=8.0 Hz, 2H), 6.86 (br s, 1H), 6.60 (d, *J*=3.6 Hz, 1H), 2.34 (s, 3H), 1.55 -1.51 (m, 18H).

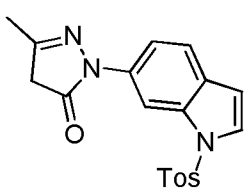
[001191] **Step 3: Synthesis of [1-(p-tolylsulfonyl)indol-6-yl]hydrazine (410i-C)**



[001192] To a solution of **410i-B** (29.0 g, 57.8 mmol, 1.0 *eq*) in ethyl acetate (100 mL) was added ethyl acetate/ hydrochloride (4 M, 100 mL, 6.9 *eq*). The mxiture was stirred at 30 °C for 1 h. The mixture was concentrated in vacuum directly to give 16.0 g (crude,hydrochloride) **410i-C** as a brown solid.

[001193] **LCMS**: (ESI) *m/z*: 302.09 $[M+H]^+$.

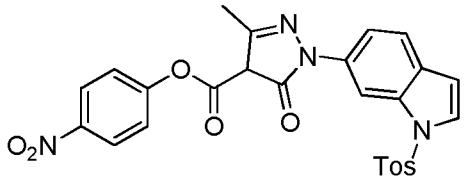
[001194] **Step 4: Synthesis of 5-methyl-2-[1-(p-tolylsulfonyl)indol-6-yl]-4*H*-pyrazol-3-one (410i-D)**



[001195] **410i-D** was obtained via general procedure II from **410i-C**

[001196] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.30 (d, J=1.6 Hz, 1H), 7.86 (d, J=8.4 Hz, 2H), 7.77 (d, J=3.6 Hz, 1H), 7.70 (d, J=8.4 Hz, 1H), 7.45 (dd, J=8.4, 2.0 Hz, 1H), 7.33 (d, J=8.4 Hz, 2H), 6.80 (d, J=3.6 Hz, 1H), 2.37 (s, 3H), 2.35 (s, 3H).

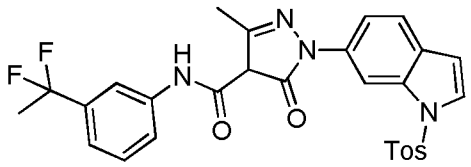
[001197] **Step 5: Synthesis of (4-nitrophenyl) 3-methyl-5-oxo-1-[1-(p-tolylsulfonyl)indol-6-yl]-4*H*-pyrazole-4-carboxylate (410i-E)**



[001198] **410i-E** was obtained via general procedure III from **410i-D**

[001199] **LCMS**: (ESI) m/z: 533.1 $[M+H]^+$.

[001200] **Step 6: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-3-methyl-5-oxo-1-[1-(p-tolylsulfonyl)indol-6-yl]-4*H*-pyrazole-4-carboxamide (410i-F)**

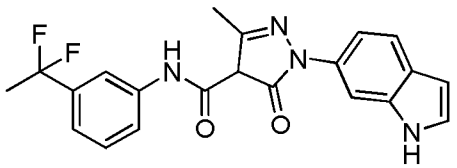


[001201] **410i-F** was obtained via general procedure IV from **410i-E**

[001202] **LCMS**: (ESI) m/z: 550.9 $[M+H]^+$.

[001203] **Step 7: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-1-(1*H*-indol-6-yl)-3-methyl-5-oxo-4*H*-pyrazole-4-carboxamide (410i)**

Compound ID: 410i



[001204] To a solution of **410i-F** (4.40 g, 6.23 mmol, 1.0 *eq*) in ethanol (30 mL) was added potassium hydroxide (1.40 g, 24.0 mmol, 3.9 *eq*) and water (3 mL). The mixture was stirred at 70 °C for 4 hr. The mixture was concentrated in vacuum to give a residue, the residue diluted with ethyl acetate (300 mL), then washed with hydrochloride (200 mL x 1, 1 M), the organic layer was washed was brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by reversed-phase HPLC [water(0.1%formic acid)-acetonitrile];B%: 10%-60%,60 min), then the cutter stock was concentrated under reduced pressure to give the impure product. The impure product was triturated with methyl tertiary butyl ether (30 mL) at 20 °C for 15 min, filtered and the filter cake was concentrated under reduced pressure to give 3.20 g (63% yield) of **410i** as a yellow solid.

[001205] **LCMS**: (ESI) m/z: 397.4 $[M+H]^+$.

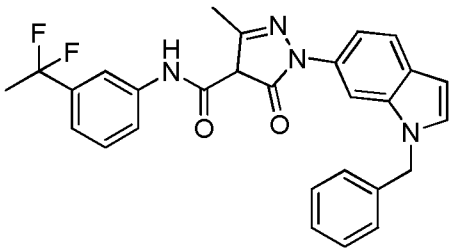
[001206] **^{1}H NMR**: (400MHz, MeOD-d_4) δ: 7.92 (s, 1H), 7.71 (d, J=8.4 Hz, 1H), 7.65 (s, 2H),

7.44 -7.36 (m, 2H), 7.25 (d, *J*=0.4 Hz, 1H), 7.18 (dd, *J*=8.4, 2.0 Hz, 1H), 6.54 (dd, *J*=3.2, 0.8 Hz, 1H), 2.63 (s, 3H), 1.92 (t, *J*=18.0 Hz, 3H).

Synthesis of 367i

[001207] **Step 1: Synthesis of 1-(1-benzylindol-6-yl)-*N*-[3-(1,1-difluoroethyl)phenyl]-3-methyl-5-oxo-4*H*-pyrazole-4-carboxamide (367i)**

[001208] **Compound ID: 367i**



[001209] To a solution of **410i** (100 mg, 227 umol, 1.0 *eq*) in *N*,*N*-dimethyl formadide (5 mL) was added sodium hydride (12.9 mg, 322 umol, 60% purity, 1.4 *eq*) at 0 °C slowly under nitrogen, the mixture was stirred 0.5 h, then the (bromomethyl)benzene (36.7 mg, 214 umol, 9.5*e*-1.0 *eq*) was injected and the mixture was stirred at 20 °C for 0.5 h. The mixture was quenched with water (30 mL), then extracted with ethyl acetate (20 mL x 3), the combined organic layer was washed with brine (30 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (dichloromethane/methanol=10/1) to give a crude product, then the crude product was purified by column:(Boston Green ODS 150*30mm*5um;mobile phase: [water (0.225% formic acid)-acetonitrile];B%: 55%-85%, 10min) to give 23.1 mg (21% yield) of **367i** as a white solid.

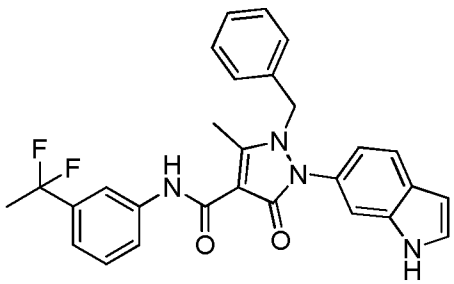
[001210] **LCMS**: (ESI) *m/z*: 487.2[M+H]$^+$.

[001211] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.95 (s, 1H), 7.95 (s, 1H), 7.81 (s, 1H), 7.69 (d, *J*=8.4 Hz, 1H), 7.60 (s, 1H), 7.58 (d, *J*=3.2 Hz, 1H), 7.42 (s, 1H), 7.36 -7.29 (m, 3H), 7.28 -7.23 (m, 1H), 7.22 -7.16 (m, 3H), 6.58 (d, *J*=3.2 Hz, 1H), 5.46 (s, 2H), 2.53 (s, 3H), 1.96 (t, *J*=18.8 Hz, 3H).

Synthesis of 108

[001212] **Step 1: Synthesis of 1-benzyl-*N*-[3-(1,1-difluoroethyl)phenyl]-2-(1*H*-indol-6-yl)-5-methyl-3-oxo-pyrazole-4-carboxamide (108)**

Compound ID: 108



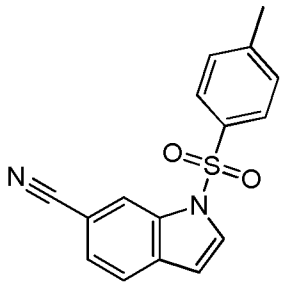
[001213] **108** was obtained via similar procedure of **367i** from **410i** and (bromomethyl)benzene.

[001214] **LCMS**: (ESI) *m/z*: 487.3[M+H]$^+$.

[001215] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 11.37 (br s, 1H), 11.00 (s, 1H), 7.92 (s, 1H), 7.64 (d, *J*=8.4 Hz, 1H), 7.58 (d, *J*=6.8 Hz, 1H), 7.50 (t, *J*=2.8 Hz, 1H), 7.43 (t, *J*=8.0 Hz, 1H), 7.33 -7.26 (m, 4H), 7.22 (d, *J*=7.6 Hz, 1H), 6.91 (d, *J*=6.4 Hz, 2H), 6.84 (dd, *J*=8.4, 1.6 Hz, 1H), 6.53 (br s, 1H), 5.10 (s, 2H), 2.74 (s, 3H), 1.95 (t, *J*=18.8 Hz, 3H).

Synthesis of 107

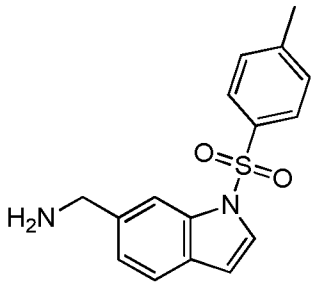
[001216] **Step 1: Synthesis of 1-(p-tolylsulfonyl)indole-6-carbonitrile (107-A)**



[001217] To a solution of 6-bromo-1-(p-tolylsulfonyl)indole (4.50 g, 12.9 mmol, 1.0 *eq*) in dry *N*,*N*-dimethyl-formamide (80 mL) was added dicyanozinc (1.13 g, 9.64 mmol, 0.75 *eq*), the reaction was stirred at 25 °C for 20 min under nitrogen. Then to the reaction mixture was added tetrakis(triphenylphosphine)platinum (1.48 g, 1.28 mmol, 0.10 *eq*), the suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under nitrogen at 95 °C for 16 hr. After cooling to room temperature, the mixture was poured into aqueous saturated sodium carbonate solution (50 mL) and extracted with ethyl acetate (20 mL x 4). Combined organic extracts were washed with brine and dried over sodium sulfate, filtered, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 1*/0 to 9/1*) to give 3.50 g (83% yield) of **107-A** as a light yellow solid.

[001218] **LCMS**: (ESI) *m/z*: 297.1 [M+H]$^+$.

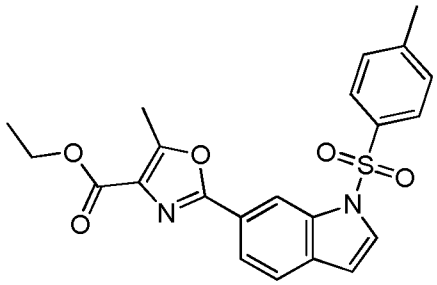
[001219] **Step 2: Synthesis of [1-(p-tolylsulfonyl)indol-6-yl]methanamine (107-B)**



[001220] **107** was obtained via similar procedure of **123-C** from **107-A** and hydrogen.

[001221] **LCMS**: (ESI) *m/z*: 284.2 [M+H]$^+$.

[001222] **Step 3: Synthesis of ethyl 5-methyl-2-[1-(*p*-tolylsulfonyl)indol-6-yl]oxazole-4-carboxylate (107-C)**

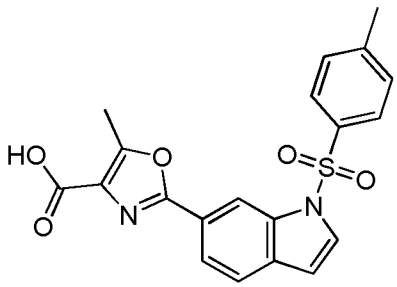


[001223] To a solution of **107-B** (2.20 g, 7.32 mmol, 1.0 *eq*) in ethyl acetate (30 mL) was added ethyl 3-oxobutanoate (477 mg, 3.66 mmol, 0.50 *eq*), *tert*-butyl hydroperoxid (2.64 g, 29.3 mmol, 4.0 *eq*), tetrabutylammonium;iodide (541 mg, 1.46 mmol, 0.20 *eq*), the suspension was stirred at 40 °C for 12 h. The reaction was washed with water (50 mL), the aqueous layer mixture was extracted with ethyl acetate (50 mL x 2). The combined organic layers were 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, from *10/1 to 3/1)* to give 600 mg (17% yield) of **107-C** as a light yellow solid.

[001224] **LCMS**: (ESI) *m/z*: 425.0 $[M+H]^+$.

[001225] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 8.56 - 8.48 (m, 1H), 7.97 (d, J = 3.8 Hz, 1H), 7.90 - 7.83 (m, 3H), 7.76 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 6.94 (dd, J = 0.8, 3.7 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 2.71 (s, 3H), 2.31 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H).

[001226] **Step 4: Synthesis of 5-methyl-2-[1-(p-tolylsulfonyl)indol-6-yl]oxazole-4-carboxylic acid (107-D)**

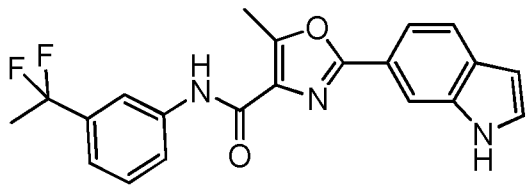


[001227] **107-D** was obtained via similar procedure of **154-C** from **107-C** and sodium hydroxide.

[001228] **LCMS**: (ESI) *m/z*: 397.1 $[M+H]^+$.

[001229] **Step 5: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-2-(1*H*-indol-6-yl)-5-methyl-oxazole-4-carboxamide (107)**

Compound ID: 107



[001230] **107** was obtained via similar procedure of **154** from **107-D** and 3-(1,1-difluoroethyl)aniline.

[001231] **LCMS**: (ESI) *m/z*: 382.2 $[M+H]^+$.

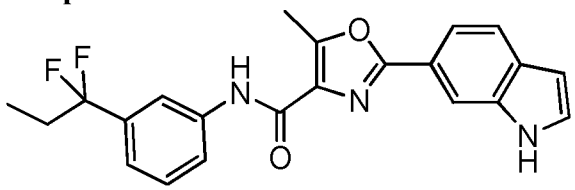
[001232] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 11.48 (br s, 1H), 10.14 (s, 1H), 8.14 (d, J = 13.2

Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.78 - 7.74 (m, 1H), 7.73 - 7.69 (m, 1H), 7.56 (t, *J* = 2.8 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 6.54 (t, *J* = 2.0 Hz, 1H), 2.73 (s, 3H), 1.98 (t, *J* = 18.8 Hz, 3H).

Synthesis of 106

[001233] **Step 1: Synthesis of *N*-[3-(1,1-difluoroethyl)phenyl]-2-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-methyl-oxazole-4-carboxamide (106)**

Compound ID: 106



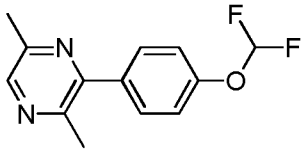
[001234] **106** was obtained via similar procedure of **154** from **107-D** and 3-(1,1-difluoropropyl)aniline.

[001235] **LCMS**: (ESI) *m/z*: 396.2 $[M+H]^+$.

[001236] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 8.11 (d, *J* = 5.8 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.78 - 7.74 (m, 1H), 7.73 - 7.69 (m, 1H), 7.56 (t, *J* = 2.8 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.54 (t, *J* = 1.8 Hz, 1H), 2.73 (s, 3H), 2.29 - 2.15 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

Synthesis of 105

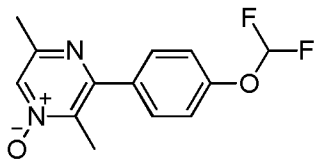
[001237] **Step 1: Synthesis of 3-(4-(difluoromethoxy)phenyl)-2,5-dimethylpyrazine (105-A)**



[001238] To a solution of 3-chloro-2,5-dimethyl-pyrazine (1.00 g, 7.01 mmol, 1.0 *eq*) in dioxane (10 mL) /water (2 mL) was added **173-A** (2.84 g, 10.5 mmol, 1.5 *eq*) , 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (513 mg, 701 umol, 0.10 *eq*) and sodium bicarbonate (1.18 g, 14.0 mmol, 2.0 *eq*). The suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under nitrogen at 80 °C for 2 hours. The solution was poured into water (10 mL), extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica column (petroleum ether/ethyl acetate, from 20/1 to 10/1) to give 1.00 g (55% yield) of **105-A** as a white solid.

[001239] **LCMS**: (ESI) *m/z*: 251.1 $[M+H]^+$.

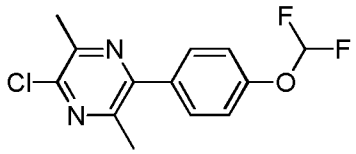
[001240] **Step 2: Synthesis of 3-(4-(difluoromethoxy)phenyl)-2,5-dimethylpyrazine 1-oxide (105-B)**



[001241] To a solution of **105-B** (1.00 g, 3.82 mmol, 1.0 *eq*) in dichloromethane (15 mL) was added a solution of hydrogen peroxide (883 mg, 7.79 mmol, 30% purity, 2.0 *eq*) and trifluoroaceticanhydride (1.23 g, 5.86 mmol, 1.5 *eq*) at 0 °C. The solution was stirred at 40 °C for 12 hours. The solution was poured into saturated sodium sulfite solution (15 mL), extracted with ethyl acetate (15 mL x 3). The combined organic phase was washed with brine (15 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica column (petroleum ether/ethyl acetate, from 10/1 to 5/1) to give **105-B** as a white solid.

[001242] **LCMS**: (ESI) *m/z*: 267.1 $[M+H]^+$.

[001243] **Step 3: Synthesis of 2-chloro-5-(4-(difluoromethoxy)phenyl)-3,6-dimethylpyrazine (105-C)**

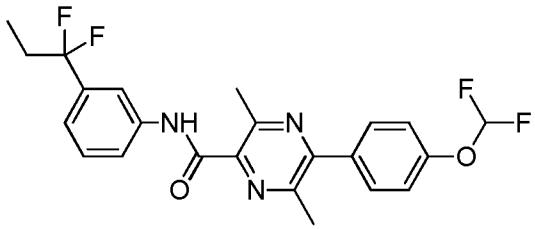


[001244] To a solution of **105-B** (800 mg, 2.90 mmol, 1.0 *eq*) in toluene (10 mL) was added phosphoryl trichloride (1.33 g, 8.69 mmol, 3.0 *eq*) and *N*,*N*-dimethylformamide (21.2 mg, 290 umol, 0.10 *eq*), the solution was stirred at 60 °C for 12 h. The solution was poured into ice-water (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with saturated sodium bicarbonate solution (20 mL) and brine (20 mL). The organic phase was dried with anhydrous sodium sulfate, filtered and concentrated to give 300 mg (36% yield) of **105-C** as a white solid.

[001245] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 7.60-7.57(m, 2H), 7.24(d, *J*= 8.8 Hz, 2H), 6.58(t, *J*=73.6 Hz, 1H), 2.67(s, 3H), 2.58(s, 3H).

[001246] **Step 4: Synthesis of 5-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3,6-dimethylpyrazine-2-carboxamide (105)**

Compound ID: 105



[001247] To a solution of **105-C** (100 mg, 351 umol, 1.0 *eq*) and 3-(1,1-difluoropropyl)aniline (60.1 mg, 351 umol, 1.0 *eq*) in *N*,*N*-dimethylformamide (1 mL) was added molybdenumhexacarbonyl (46.4 mg, 176 umol, 0.50 *eq*), palladium acetate (2.37 mg, 10.5 umol, 0.030 *eq*) , bis(1-adamantyl)-butyl-phosphane (7.56 mg, 21.1 umol, 0.060 *eq*) and 1,8-diazabicyclo[5.4.0]undec-7-ene (80.2 mg, 527 umol, 1.5 *eq*) under nitrogen. The suspension was degassed under vacuum and purged with nitrogen several times. The mixture was stirred under nitrogen at 130 °C for 2 hours under microwave (2 bar). The solution was poured into water (5 mL), extracted with ethyl acetate (5 mL x 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (0.225%formic acid)-acetonitrile]; B%: 65%-95%, 10min) to

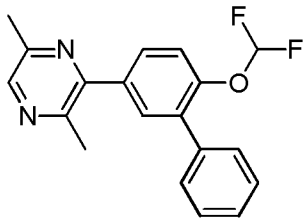
give 11.0 mg (7% yield) of **105** as a white solid.

[001248] **LCMS**: (ESI) *m/z*: 448.1 $[M+H]^+$.

[001249] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.78(s, 1H), 8.06(s, 1H), 7.96(d, *J*= 8.4 Hz, 1H), 7.80(d, *J*= 8.4 Hz, 1H), 7.51(t, *J*= 8.0 Hz, 1H), 7.38(t, *J*= 74.0 Hz, 1H), 7.34(d, *J*= 8.8 Hz, 2H), 7.27(d, *J*= 8.0 Hz, 1H), 2.78(s, 3H), 2.67(s, 3H), 2.29-2.15(m, 2H), 0.94(t, *J*= 7.2 Hz, 3H).

Synthesis of 104

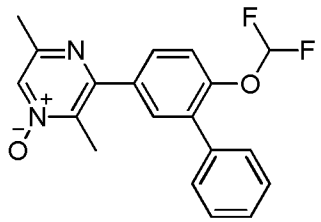
[001250] **Step 1: Synthesis of 3-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-2,5-dimethylpyrazine (104-A)**



[001251] **104-A** was obtained via similar procedure of **105-A** from **127-C** and 3-chloro-2,5-dimethyl-pyrazine.

[001252] **LCMS**: (ESI) *m/z*: 327.1 $[M+H]^+$.

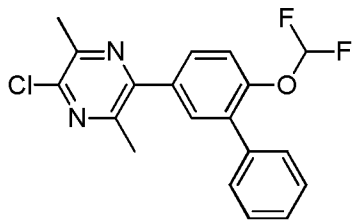
[001253] **Step 2: Synthesis of 3-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-2,5-dimethylpyrazine 1-oxide (104-B)**



[001254] **104-B** was obtained via similar procedure of **105-B** from **104-A** and hydrogen peroxide.

[001255] **LCMS**: (ESI) *m/z*: 343.1 $[M+H]^+$.

[001256] **Step 3: Synthesis of 2-chloro-5-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3,6-dimethylpyrazine (104-C)**



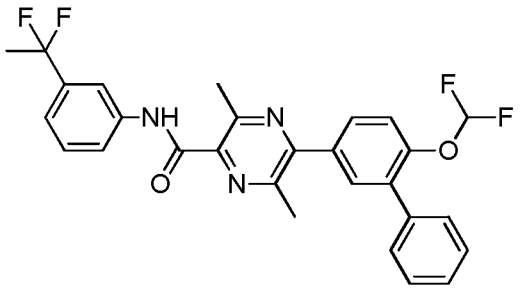
[001257] **104-C** was obtained via similar procedure of **105-C** from **104-B** and phosphoryl trichloride.

[001258] **LCMS**: (ESI) *m/z*: 361.0 $[M+H]^+$.

[001259] **^{1}HNMR** (400 MHz, $CDCl_3$-*d*) δ: 7.63(d, *J*= 2.4 Hz, 1H), 7.58-7.52(m, 3H), 7.48-7.44(m, 2H), 7.42-7.36(m, 2H), 6.40(t, *J*= 74.0 Hz, 1H), 2.68(s, 3H), 2.63(s, 3H).

[001260] **Step 4: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-5-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3,6-dimethylpyrazine-2-carboxamide (104)**

Compound ID: 104



[001261] **104** was obtained via similar procedure of **105** from **104-C** and 3-(1,1-difluoroethyl)aniline

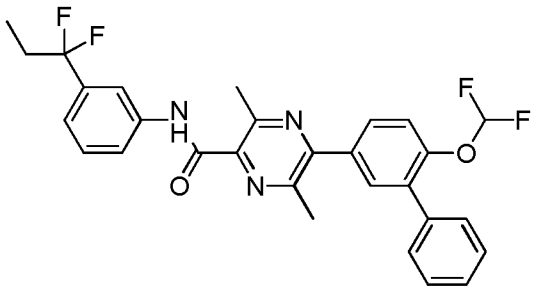
[001262] **LCMS**: (ESI) *m/z*: 510.2 $[M+H]^+$.

[001263] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.79(s, 1H), 8.11(s ,1H), 7.96(d, *J*= 8.0 Hz, 1H), 7.82(dd, *J*= 8.4 Hz, *J*= 2.4 Hz, 1H), 7.78(d, *J*= 2.0 Hz, 1H), 7.56-7.48(m, 6H), 7.45-7.41(m, 1H), 7.32(d, *J*= 8.0 Hz, 1H), 7.31(t, *J*= 73.6 Hz, 1H), 2.79(s, 3H), 2.73(s, 3H), 1.99(t, *J*= 18.8 Hz, 3H).

Synthesis of 103

[001264] **Step 1: Synthesis of 5-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3,6-dimethylpyrazine-2-carboxamide (103)**

Compound ID: 103



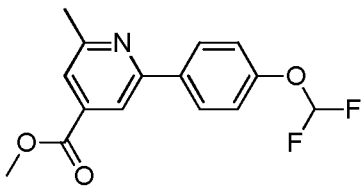
[001265] **103** was obtained via similar procedure of **105** from **104-C** and 3-(1,1-difluoropropyl)aniline

[001266] **LCMS**: (ESI) *m/z*: 524.2 $[M+H]^+$.

[001267] **^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 10.78(s, 1H), 8.06(s, 1H), 7.96(d, *J*= 8.4 Hz, 1H), 7.82(dd, *J*= 8.4 Hz, *J*= 2.4 Hz, 1H), 7.78(d, *J*= 2.0 Hz, 1H), 7.56-7.48(m, 6H), 7.46-7.41(m, 1H), 7.31(t, *J*= 38.0 Hz, 1H), 2.79(s, 3H), 2.73(s, 3H), 2.27-2.15(m, 2H), 0.94(t, *J*= 7.2 Hz, 3H).

Synthesis of 102

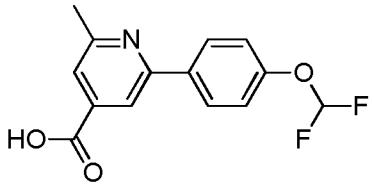
[001268] **Step 1: Synthesis of methyl 2-[4-(difluoromethoxy)phenyl]-6-methyl-pyridine-4-carboxylate (102-A)**



[001269] **102-A** was obtained via similar procedure of **144-A** from **173-A** and methyl 2-chloro-6-methylisonicotinate.

[001270] **^{1}H NMR:** (400 MHz, $CDCl_3$-*d*) δ: 8.10 ~8.05 (m, 3H), 7.66 (d, *J* = 0.8 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.58 (t, *J* = 73.6 Hz, 1H), 3.99 (s, 3H), 2.70 (s, 3H)

[001271] **Step 2: Synthesis of 2-[4-(difluoromethoxy)phenyl]-6-methyl-pyridine-4-carboxylic acid (102-B)**

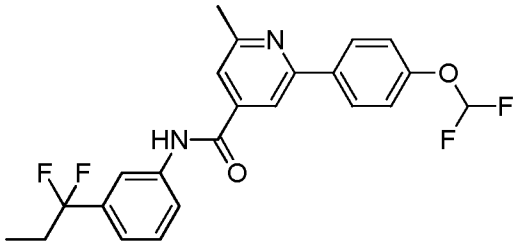


[001272] **102-B** was obtained via similar procedure of **144-B** from **152-B** and lithium hydroxide hydrate.

[001273] **LCMS:** (ESI) *m/z*: 280.1 $[M+H]^+$.

[001274] **Step 3: Synthesis of 2-[4-(difluoromethoxy)phenyl]-*N*-[3-(1,1-difluoropropyl)phenyl]-6-methyl-pyridine-4-carboxamide (102)**

Compound ID: 102



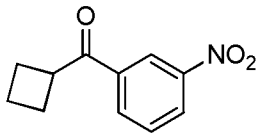
[001275] **102** was obtained via similar procedure of **144** from **102-B** and 3-(1,1-difluoropropyl)aniline

[001276] **LCMS:** (ESI) *m/z*: 433.3 $[M+H]^+$.

[001277] **^{1}H NMR** (400 MHz, MeOD) δ: 8.14 - 8.11 (m, 2H), 8.10 - 8.09 (m, 1H), 7.95 - 7.91 (m, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 0.8 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.30 (s, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 2.69 (s, 3H), 2.27 - 2.12 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H).

Synthesis of 101

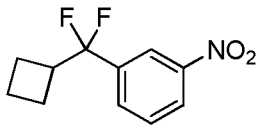
[001278] **Step 1: Synthesis of cyclobutyl(3-nitrophenyl)methanone (101-A)**



[001279] **101-A** was obtained via similar procedure of 2-methyl-1-(3-nitrophenyl)propan-1-one from cyclobutyl(phenyl)methanone and nitric acid.

[001280] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 8.70 (t, *J* = 2.0 Hz, 1H), 8.41 (ddd, *J* = 1.2, 2.4, 8.2 Hz, 1H), 8.24 (td, *J* = 1.2, 8.0 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 4.08 - 4.00 (m, 1H), 2.49 - 2.35 (m, 4H), 2.21 - 2.10 (m, 1H), 2.02 - 1.92 (m, 1H)

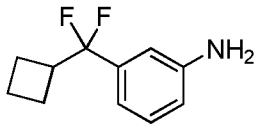
[001281] **Step 2: Synthesis of 1-(cyclobutyldifluoromethyl)-3-nitrobenzene (101-B)**



[001282] **101-B** was obtained via similar procedure of 1-(1,1-difluoro-2-methylpropyl)-3-nitrobenzene from **101-A** and diethylaminosulfur trifluoride.

[001283] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 8.34 - 8.28 (m, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 3.07 - 2.91 (m, 1H), 2.29 - 2.17 (m, 2H), 2.06 - 1.83 (m, 4H).

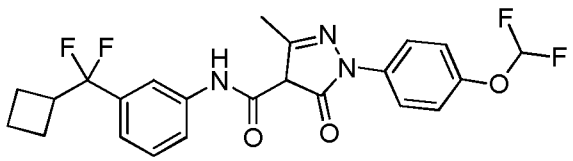
[001284] **Step 3: Synthesis of 3-(cyclobutyldifluoromethyl)aniline (101-C)**



[001285] **101-C** was obtained via similar procedure of 3-(1,1-difluoro-2-methylpropyl)aniline from **101-B** and iron powder.

[001286] **LCMS**: (ESI) *m/z*: 198.1 $[M+H]^+$.

[001287] **Step 4: Synthesis of *N*-(3-(cyclobutyldifluoromethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (101) Compound ID: 101**



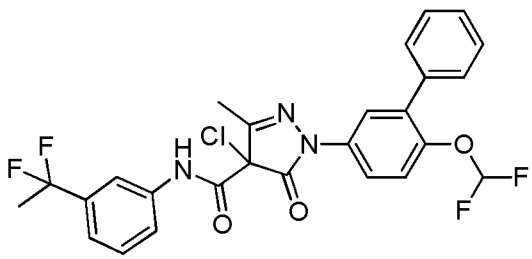
[001288] **101** was obtained via general procedure Ⅳ from 4-nitrophenyl 1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxylate and **101-C**

[001289] **LCMS**: (ESI) *m/z*: 464.2 $[M+H]^+$.

[001290] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.82 (br s, 3H), 7.63 (br d, *J* = 8.0 Hz, 1H), 7.35 (br s, 1H), 7.26 - 7.07 (m, 3H), 6.80 (t, *J* = 74.4 Hz, 1H), 3.28 - 2.99 (m, 1H), 2.45 (br s, 3H), 2.31 - 2.10 (m, 2H), 2.05 - 1.88 (m, 3H), 1.88 - 1.78 (m, 1H).

Synthesis of 100

[001291] **Step 1: Synthesis of 4-chloro-*N*-(3-(1,1-difluoroethyl)phenyl)-1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (100-A)**



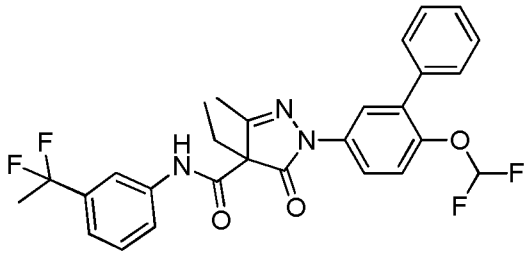
[001292] **100-A** was obtained via similar procedure of **172** from **312i**.

[001293] **LCMS**: (ESI) *m/z*: 551.1 $[M+NH_4]^+$.

[001294] **Step 2: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(6-(difluoromethoxy)-[1,1'-**

biphenyl]-3-yl)-4-ethyl-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (100)

Compound ID: 100



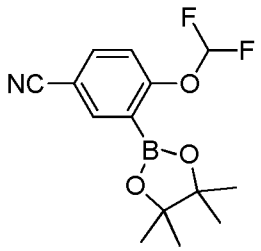
[001295] **100** was obtained via similar procedure of **158** from **100-A**.

[001296] **LCMS**: (ESI) *m/z*: 528.3 $[M+H]^+$.

[001297] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.02 (d, *J*=2.8 Hz, 1H), 7.96 (dd, *J*=2.8, 8.8 Hz, 1H), 7.78 (s, 1H), 7.62 (d, *J*=7.6 Hz, 1H), 7.53 - 7.48 (m, 2H), 7.46 - 7.37 (m, 4H), 7.35 - 7.29 (m, 2H), 6.65 (t, *J*=74.0 Hz, 1H), 2.41 - 2.35 (m, 1H), 2.33 (s, 3H), 2.32 - 2.28 (m, 1H), 1.89 (t, *J*=18.4 Hz, 3H), 0.87 (t, *J*=7.6 Hz, 3H).

Synthesis of 213

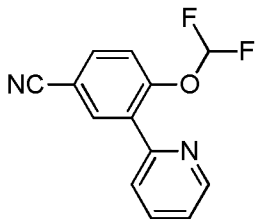
[001298] **Step 1: Synthesis of 4-(difluoromethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (213-A)**



[001299] To a solution of **123-A** (1.5 g, 6.05 mmol, 1.0 *eq*) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.00 g, 7.86 mmol, 1.3 *eq*) in dioxane (25 mL) was added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (443 mg, 605 umol, 0.10 *eq*) followed by potassium acetate (1.48 g, 15.1 mmol, 2.5 *eq*). The solution was stirred at 90 °C for 12 h under nitrogen atomosphere. The solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=50/1 to 20/1) to give 2.25 g (crude) of **213-B** as a yellow oil.

[001300] **LCMS**: (ESI) *m/z*: 214.1 $[M-82]^+$.

[001301] **Step 2: Synthesis of 4-(difluoromethoxy)-3-(pyridin-2-yl)benzonitrile (213-B)**

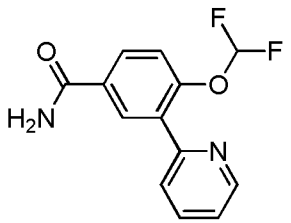


[001302] To a solution of **213-A** (2.24 g, 7.60 mmol, 1.5 *eq*) and 2-bromopyridine (800 mg, 5.06 mmol, 1.0 *eq*) in dioxane (30 mL) and water (6 mL) was added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (371 mg, 506 umol, 0.10 *eq*) and potassium

carbonate (2.10 g, 15.2 mmol, 3.0 *eq*). The solution was stirred at 90 °C for 12 h. The solution was partitioned between ethyl acetate (150 mL) and water (150 mL). The aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (petroleum ether/ethyl acetate=3/1) to give 1.33 g (83% yield) of **213-B** as a white solid.

[001303] **LCMS**: (ESI) *m/z*: 247.0 $[M+H]^+$.

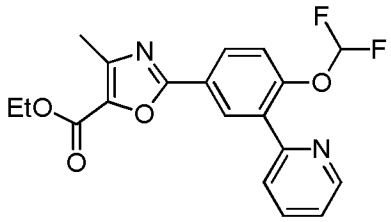
[001304] **Step 3: Synthesis of 4-(difluoromethoxy)-3-(pyridin-2-yl)benzamide (213-C)**



[001305] To a solution of **213-B** (1.33 g, 4.20 mmol, 1.0 *eq*) in dimethylsulfoxide (15 mL) was added potassium carbonate (1.12 g, 8.10 mmol, 1.9 *eq*) followed by hydrogen peroxide (919 mg, 8.10 mmol, 30% purity, 1.9 *eq*). The solution was stirred at 20 °C for 15 min. To the solution was added saturated sodium sulfite (20 mL) and the mixture was stirred at 20 °C for 30 min. The solution was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1.10 g (97% yield) of **213-C** as a white solid.

[001306] **LCMS**: (ESI) *m/z*: 265.0 $[M+H]^+$.

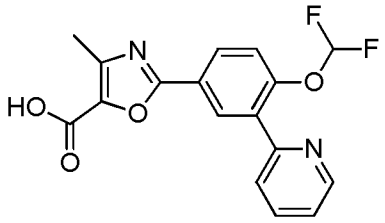
[001307] **Step 4: Synthesis of ethyl 2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-4-methyloxazole-5-carboxylate (213-D)**



[001308] To a solution of **213-C** (370 mg, 1.38 mmol, 1.0 *eq*) in *N*,*N*-dimethylformamide (1 mL) was added ethyl 2-chloro-3-oxo-butanoate (691 mg, 4.20 mmol, 3.1 *eq*). The solution was stirred at 130 °C for 20 h. The solution was partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1) to give 190 mg (30% yield) of **213-D** as a brown oil.

[001309] **LCMS**: (ESI) *m/z*: 375.0 $[M+H]^+$.

[001310] **Step 5: Synthesis of 2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-4-methyloxazole-5-carboxylic acid (213-E)**

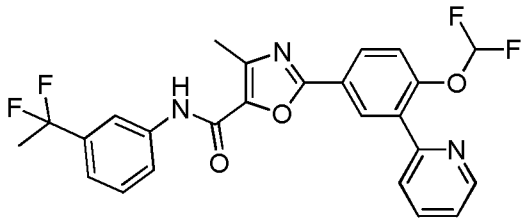


[001311] To a solution of **213-D** (180 mg, 391 umol, 1.0 *eq*) in ethanol (3 mL) and water (1 mL) was added sodium hydroxide (47.0 mg, 1.17 mmol, 3.0 *eq*). The solution was stirred at 20 °C for 12 h. The solution was partitioned between ethyl acetate (50 mL) and aqueous sodium hydroxide (1 M, 50 mL). The organiclayer was separated and the aqueous layer was acidified to pH = 3 by addition of aqueous hydrochloric acid (6 M). The mixture was extracted with ethyl acetate (40 mL x 3), washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 140 mg (90% yield) of **213-E** as a yellow solid.

[001312] **LCMS**: (ESI) *m/z*: 347.0 $[M+H]^+$.

[001313] **Step 6: Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-4-methyloxazole-5-carboxamide (213)**

Compound ID: 213



[001314] To a solution of **213-E** (30.0 mg, 75.9 umol, 1.0 *eq*) in *N*,*N*-dimethylformamide (0.5 mL) was added [dimethylamino(triazol[4,5-b]pyridin-3-yloxy)methylidene]-dimethylazanium;hexafluorophosphate (40.4 mg, 106 umol, 1.4 *eq*) and *N*-ethyl-*N*-isopropylpropan-2-amine (29.4 mg, 228 umol, 3.0 *eq*). The solution was stirred at 20 °C for 10 min and then 3-(1,1-difluoroethyl)aniline (16.7 mg, 106 umol, 1.4 *eq*) was added. The solution was stirred at 20 °C for 5 h. The solution was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 60%-90%, 9min) to give 41.7 mg (67% yield) of **213** as a yellow solid.

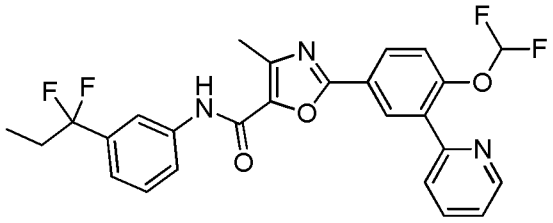
[001315] **LCMS**: (ESI) *m/z*: 486.3 $[M+H]^+$.

[001316] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.72 (d, J = 4.8 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.34 (dd, J = 2.0, 8.4 Hz, 1H), 8.00 (dt, J = 2.0, 7.6 Hz, 1H), 7.93 (s, 1H), 7.86 - 7.78 (m, 2H), 7.54 - 7.48 (m, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 78.0 Hz, 1H), 6.99 (t, J = 73.2 Hz, 1H), 2.57 (s, 3H), 1.93 (t, J = 18.4 Hz, 3H)

Synthesis of 214

[001317] **Step 1: Synthesis of 2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-4-methyloxazole-5-carboxamide (214)**

Compound ID: 214



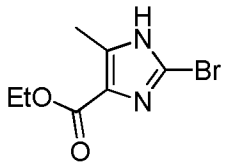
[001318] **214** was obtained via the similar synthetic method for **213**.

[001319] **LCMS**: (ESI) *m/z*: 500.4 $[M+H]^+$.

[001320] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.73 (d, J = 4.8 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.35 (dd, J = 2.0, 8.4 Hz, 1H), 8.03 (dt, J = 1.6, 7.6 Hz, 1H), 7.91 - 7.80 (m, 3H), 7.56 - 7.49 (m, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 73.2, 1H), 2.57 (s, 3H), 2.15 - 2.11 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H)

Synthesis of 215

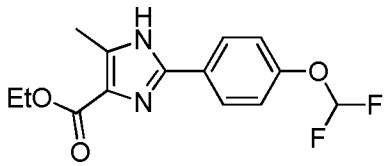
[001321] **Step 1: Synthesis of ethyl 2-bromo-5-methyl-1*H*-imidazole-4-carboxylate (215-A)**



[001322] To a solution of ethyl 5-methyl-1*H*-imidazole-4-carboxylate (3.00 g, 19.5 mmol, 1.0 *eq*) in acetonitrile (40 mL) was added 1-bromopyrrolidine-2,5-dione (3.64 g, 20.4 mmol, 1.1 *eq*) portion wises. The mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1) to give 1.90 g (41% yield) of **215-A** as a yellow solid.

[001323] **^{1}H NMR**: (400 MHz, $CDCl_3$-*d*) δ: 10.78 (br s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 2.55 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H).

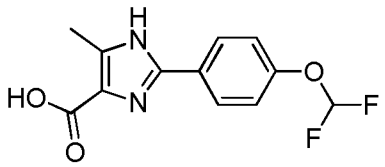
[001324] **Step 2: Synthesis of ethyl 2-(4-(difluoromethoxy)phenyl)-5-methyl-1*H*-imidazole-4-carboxylate (215-B)**



[001325] To a solution of **215-A** (300 mg, 1.29 mmol, 1.0 *eq*) and **173-A** (487 mg, 1.80 mmol, 1.4 *eq*) in dioxane (15 mL) and water (4 mL) was added cesium carbonate (1.05 g, 3.22 mmol, 2.5 *eq*) and 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (94.2 mg, 129 umol, 0.10 *eq*). The solution was stirred at 80 °C for 12 h. The solution was filtered through a celite pad and the filtrate was partitioned between ethyl acetate (80 mL) and water (80 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1) to give 300 mg (78% yield) of **215-B** as a white solid.

[001326] **LCMS**: (ESI) *m/z*: 297.1 $[M+H]^+$.

[001327] **Step 3: Synthesis of 2-(4-(difluoromethoxy)phenyl)-5-methyl-1*H*-imidazole-4-carboxylic acid (215-C)**

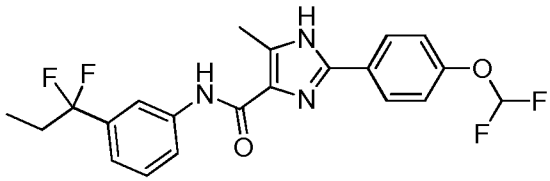


[001328] To a mixture of **215-B** (300 mg, 1.01 mmol, 1.0 *eq*) in ethanol (10 mL) and water (3 mL) was added sodium hydroxide (203 mg, 5.06 mmol, 5.0 *eq*). The mixture was heated to 90 °C and stirred for 12 hours. The organic solvent was removed by reduced pressure and water (2 mL) was added. Then the mixture was adjusted to pH = 5 by addition of aqueous hydrochloric acid (1 M) along with precipitate was formed. Filtration and concentration give 250 mg (77% yield) of **215-C** as an off-white solid.

[001329] **LCMS**: (ESI) *m/z*: 269.0 $[M+H]^+$.

[001330] **Step 4: Synthesis of 2-(4-(difluoromethoxy)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-5-methyl-1*H*-imidazole-4-carboxamide (215)**

Compound ID: 215



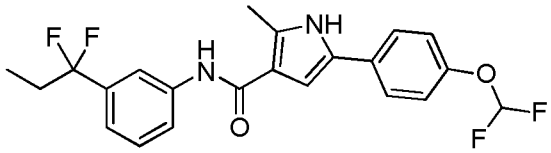
[001331] To a solution of **215-C** (100 mg, 312 umol, 1.0 *eq*) in *N*,*N*-dimethylformamide (5 mL) was added *N*-ethyl-*N*-isopropylpropan-2-amine (202 mg, 1.56 mmol, 5.0 *eq*), [dimethylamino(triazol[4,5-b]pyridin-3-yloxy)methylidene]-dimethylazanium;hexafluorophosphate (142 mg, 374 umol, 1.2 *eq*) and *N*-ethyl-*N*-isopropylpropan-2-amine (38.1 mg, 312 umol, 1.0 *eq*). Then the mixture was stirred for 20 minutes, after that it was added 3-(1,1-difluoropropyl)aniline (80.1 mg, 468 umol, 1.5 *eq*) and stirred at 20 °C for 2 hours. The solution was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225%formic acid)-acetonitrile]; B%: 50%-80%, 10min) to give 26.9 mg (20% yield) of **215** as a white solid.

[001332] **LCMS**: (ESI) *m/z*: 422.0 $[M+H]^+$.

[001333] **^{1}H NMR**: (400 MHz, MeOD-d_4) δ: 8.01 - 7.90 (m, 3H), 7.75 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.29 - 7.16 (m, 3H), 6.89 (t, J = 73.6 Hz, 1H), 2.61 (s, 3H), 2.25 - 2.10 (m, 2H), 0.99 (t, J = 7.6 Hz, 1H)

[001334] **Synthesis of 5-[4-(difluoromethoxy)phenyl]-*N*-[3-(1,1-difluoropropyl)phenyl]-2-methyl-1*H*-pyrrole-3-carboxamide (216)**

Compound ID: 216



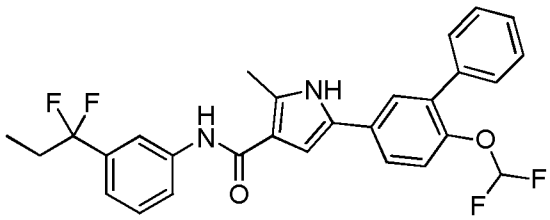
[001335] **216** was obtained via similar procedure of **152** from 5-[4-(difluoromethoxy)phenyl]-2-methyl-1*H*-pyrrole-3-carboxylic acid and 3-(1,1-difluoropropyl)aniline

[001336] **LCMS:** (ESI) *m/z*: 421.0 $[M+H]^+$.

[001337] **^{1}H NMR:** (400 MHz, MeOD-d_4) δ: 7.88 (s, 1H), 7.74 (dd, J = 8.0, 1.2 Hz, 1H), 7.65 ~7.61 (m, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.98 (s, 1H), 6.81 (t, J = 74.4 Hz, 1H), 2.58 (s, 3H), 2.19 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).

[001338] **Synthesis of 5-[4-(difluoromethoxy)-3-phenyl-phenyl]-*N*-[3-(1,1-difluoropropyl)phenyl]-2-methyl-1*H*-pyrrole-3-carboxamide (217)**

Compound ID: 217



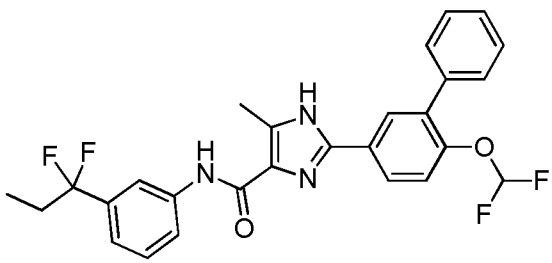
[001339] **217** was obtained via similar procedure of **216** from 5-[4-(difluoromethoxy)-3-phenyl-phenyl]-2-methyl-1*H*-pyrrole-3-carboxylic acid and 3-(1,1-difluoropropyl)aniline

[001340] **LCMS:** (ESI) *m/z*: 497.2 $[M+H]^+$.

[001341] **^{1}H NMR:** (400 MHz, MeOD-d_4) δ: 7.88 (s, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.63 (dd, J = 8.4, 2.4 Hz, 1H), 7.56 ~7.53 (m, 2H), 7.47 ~7.42 (m, 2H), 7.41 ~7.36 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 7.6, 0.8 Hz, 1H), 7.05 (s, 1H), 6.64 (t, J = 74.4 Hz, 1H), 2.58 (s, 3H), 2.19 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).

[001342] **Synthesis of 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-5-methyl-1*H*-imidazole-4-carboxamide (218)**

Compound ID : 218



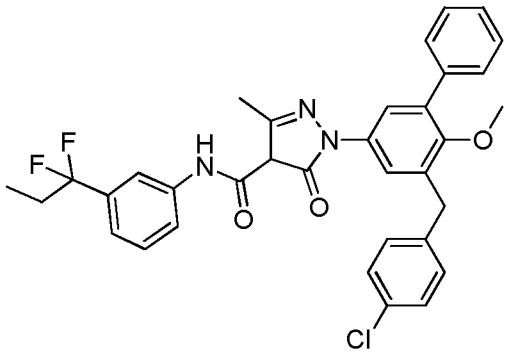
[001343] **218** was obtained via similar procedure of **173** from 2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole-4-carboxylic acid and 3-(1,1-difluoropropyl)aniline

[001344] **LCMS**: (ESI) *m/z*: 498.2 $[M+H]^+$.

[001345] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.06 (d, J=2.4 Hz, 1H), 7.96 (dd, J=2.4, 8.4 Hz, 1H), 7.92 (s, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.55-7.57 (m, 2H), 7.37-7.48 (m, 5H), 7.22 (d, J=8.0 Hz, 1H), 6.76 (t, J=74.0 Hz,1H), 2.63 (s, 3H), 2.11-2.25 (m, 2H), 0.98 (t, J=7.6 Hz, 3H).

[001346] **Synthesis of 1-(5-(4-chlorobenzyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (236)**

Compound ID : 236



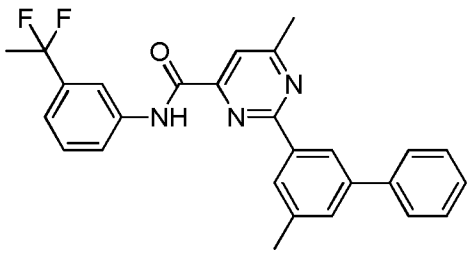
[001347] **236** was obtained via general procedure IV

[001348] **LCMS**: (ESI) m/z: 602.3 $[M+H]^+$.

[001349] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.87 (s, 1H), 7.63 (d, J=7.2 Hz, 3H), 7.39-7.48 (m, 6H), 7.30 (s, 4H), 7.20 (d, J=7.6 Hz, 1H), 4.10 (s, 2H), 3.22 (s, 3H), 2.60 (s, 3H), 2.11-2.23 (m, 2H), 0.98 (t, J=7.2 Hz, 3H).

[001350] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-6-methyl-2-(5-methyl-[1,1'-biphenyl]-3-yl)pyrimidine-4-carboxamide (219)**

Compound ID: 219



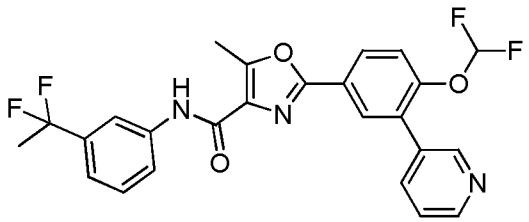
[001351] **219** was obtained via similar procedure of **133** from 6-methyl-2-(5-methyl-[1,1'-biphenyl]-3-yl)pyrimidine-4-carboxylic acid and 3-(1,1-difluoroethyl)aniline.

[001352] **LCMS**: (ESI) m/z: 444.2 $[M+H]^+$.

[001353] **^{1}H NMR** (400 MHz, $CDCl_3$-d) δ: 10.09 (br s, 1H), 8.53 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 7.96 (s, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.73 (d, J=7.6 Hz, 2H), 7.61 (s, 1H), 7.53 - 7.47 (m, 3H), 7.42 (d, J=7.6 Hz, 1H), 7.36 (d, J=8.4 Hz, 1H), 2.76 (s, 3H), 2.58 (s, 3H), 1.98 (t, J=18.4 Hz, 3H).

[001354] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-5-methyloxazole-4-carboxamide (220)**

Compound ID: 220



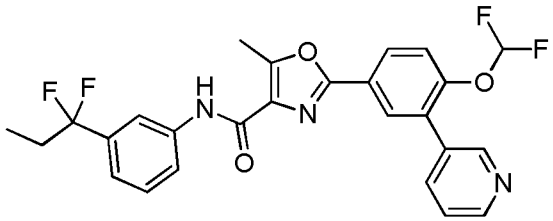
[001355] **220** was obtained via similar procedure of **123** from 2-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-5-methyloxazole-4-carboxylic acid and 3-(1,1-difluoroethyl)aniline.

[001356] **LCMS**: (ESI) *m/z*: 486.3 $[M+H]^+$.

[001357] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 8.92 (s, 1H), 8.84 - 8.79 (m, 1H), 8.71 - 8.66 (m, 1H), 8.14 (d, J = 2.2 Hz, 1H), 8.10 (dd, J = 2.2, 8.6 Hz, 1H), 7.92 (td, J = 2.0, 7.8 Hz, 1H), 7.87 (s, 1H), 7.82 (br d, J = 8.0 Hz, 1H), 7.46 - 7.40 (m, 3H), 7.29 (d, J = 7.8 Hz, 1H), 6.71 - 6.33 (m, 1H), 2.81 (s, 3H), 1.96 (t, J = 18.2 Hz, 3H).

[001358] **Synthesis of 2-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-5-methyloxazole-4-carboxamide (221)**

Compound ID: 221



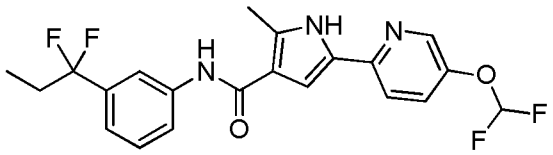
[001359] **221** was obtained via similar procedure of **123** from 2-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-5-methyloxazole-4-carboxylic acid and 3-(1,1-difluoropropyl)aniline.

[001360] **LCMS**: (ESI) *m/z*: 500.3 $[M+H]^+$.

[001361] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 8.91 (s, 1H), 8.87 - 8.77 (m, 1H), 8.74 - 8.64 (m, 1H), 8.15 (d, J = 2.2 Hz, 1H), 8.10 (dd, J = 2.2, 8.6 Hz, 1H), 7.92 (br d, J = 8.0 Hz, 1H), 7.83 (br d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.46 - 7.40 (m, 3H), 7.24 (s, 1H), 6.71 - 6.34 (m, 1H), 2.81 (s, 3H), 2.19 (dt, J = 7.6, 16.1 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).

[001362] **Synthesis of 5-(5-(difluoromethoxy)pyridin-2-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (222)**

Compound ID: 222



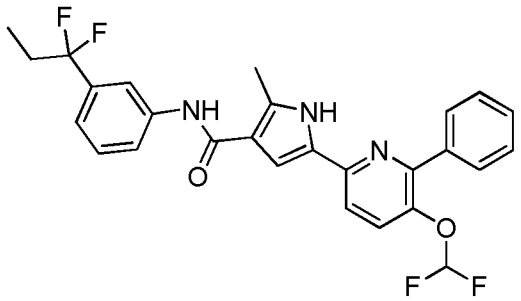
[001363] **222** was obtained via similar procedure of **216** from 5-(5-(difluoromethoxy)pyridin-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylic acid and 3-(1,1-difluoropropyl)aniline.

[001364] **LCMS:** (ESI) *m/z*: 421.9 $[M+H]^+$.

[001365] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 9.50 (br s, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.57 ~7.53 (m, 2H), 7.51 ~7.47 (m, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 2.8 Hz, 1H), 6.56 (t, *J* = 72.8 Hz, 1H), 2.68 (s, 3H), 2.25~2.10 (m, 2H), 1.01 (t, *J* = 7.6 Hz, 3H).

[001366] **Synthesis of 5-(5-(difluoromethoxy)-6-phenylpyridin-2-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (223)**

Compound ID: 223



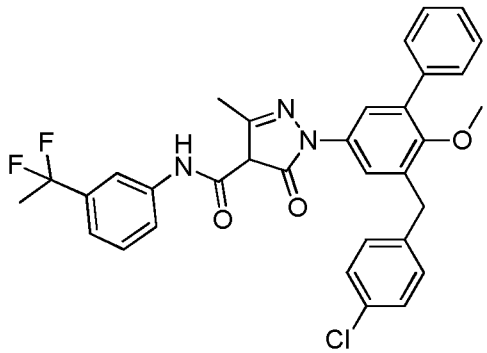
[001367] **223** was obtained via similar procedure of **222** from 5-(5-(difluoromethoxy)-6-phenylpyridin-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylic acid and 3-(1,1-difluoropropyl)aniline.

[001368] **LCMS:** (ESI) *m/z*: 498.1 $[M+H]^+$.

[001369] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.96 ~7.92 (m, 2H), 7.89 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 0.8 Hz, 2H), 7.51 ~7.40 (m, 4H), 7.30 (s, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 73.6 Hz, 1H), 2.60 (s, 3H), 2.27~ 2.12 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).

[001370] **Synthesis of 1-(5-(4-chlorobenzyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (224)**

Compound ID : 224



[001371] **224** was obtained via general procedure IV

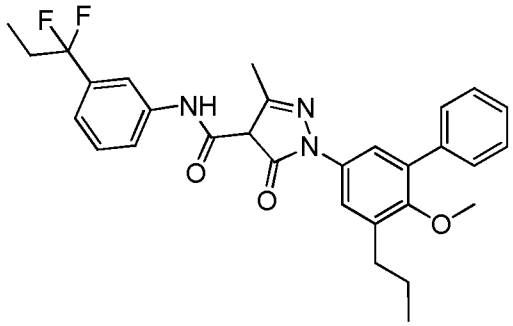
[001372] **LCMS**: (ESI) *m/z*: 588.2 $[M+H]^+$.

[001373] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.91 (s, 1H), 7.63 (d, *J*=7.2 Hz, 3H), 7.54 (d, *J*=16.4 Hz, 2H), 7.34-7.48 (m, 4H), 7.29 (s, 4H), 7.22 (d, *J*=8.0 Hz, 1H), 4.09 (s, 2H), 3.21 (s, 3H), 2.56 (s, 3H), 1.92 (t, *J*=18.4 Hz, 3H).

[001374] **Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-1-(6-methoxy-5-propyl-[1,1'-**

biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (225)

Compound ID: 225



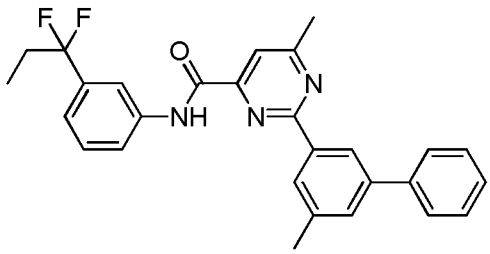
[001375] **225** was obtained via general procedure IV

[001376] **LCMS**: (ESI) *m/z*: 520.3 $[M+H]^+$.

[001377] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.87 (s, 1H), 7.66 - 7.61 (m, 3H), 7.48 - 7.44 (m, 4H), 7.43 - 7.37 (m, 2H), 7.20 (d, *J*=8.0 Hz, 1H), 3.36 (s, 3H), 2.75 (t, *J*=8.0 Hz, 2H), 2.62 (s, 3H), 2.24 - 2.11 (m, 2H), 1.79 - 1.70 (m, 2H), 1.05 (t, *J*=7.6 Hz, 3H), 0.98 (t, *J*=7.6 Hz, 3H).

[001378] **Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-6-methyl-2-(5-methyl-[1,1'-biphenyl]-3-yl)pyrimidine-4-carboxamide (226)**

Compound ID: 226



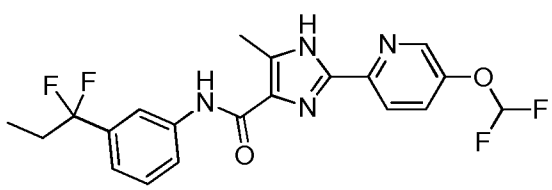
[001379] **226** was obtained via similar procedure of **133** from 6-methyl-2-(5-methyl-[1,1'-biphenyl]-3-yl)pyrimidine-4-carboxylic acid and 3-(1,1-difluoropropyl)aniline.

[001380] **LCMS**: (ESI) *m/z*: 458.2 $[M+H]^+$.

[001381] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 10.08 (s, 1H), 8.53 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 7.89 (d, *J*=10.0 Hz, 2H), 7.73 (d, *J*=7.6 Hz, 2H), 7.61 (s, 1H), 7.53 - 7.47 (m, 3H), 7.42 (d, *J*=7.6 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 2.76 (s, 3H), 2.58 (s, 3H), 2.27 - 2.14 (m, 2H), 1.04 (t, *J*=7.6 Hz, 3H).

[001382] **Synthesis of 2-(5-(difluoromethoxy)pyridin-2-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-5-methyl-1*H*-imidazole-4-carboxamide (227)**

Compound ID : 227



[001383] To a 10 mL round-bottom flask equipped with a magnetic stir bar was added 2-(5-(difluoromethoxy)pyridin-2-yl)-5-methyl-1*H*-imidazole-4-carboxylic acid (50.0 mg, 158 umol, 1.0 *eq*),

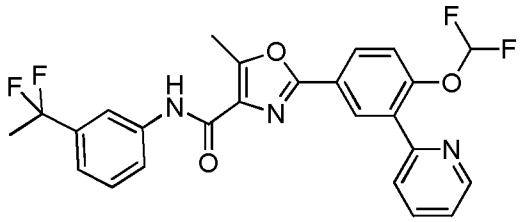
3-(1,1-difluoropropyl)aniline (53.9 mg, 315 umol, 2.0 *eq*) followed by the addition of *N*,*N*-dimethylformamide (4 mL). Then 1*H*-benzo[d][1,2,3]triazol-1-ol (180 mg, 473 umol, 3.0 *eq*), *N*,*N*-diisopropylethylamine (102 mg, 788 umol, 5.0 *eq*), *N*,*N*-dimethylpyridin-4-amine (38.5 mg, 315 umol, 2.0 *eq*) was added into the mixture. The mixture was stirred at 25 °C for 12 hr. The mixture was filtered, the filtrate was used for purification directly. The solution was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 48%-78%, min) to give 29.8 mg (45% yield) of **227** as a yellow solid.

[001384] **LCMS**: (ESI) *m/z*: 423.1 $[M+H]^+$.

[001385] **^{1}H NMR** (MeOD-d_4, 400 MHz) δ: 8.49 (s, 1H), 8.18 (dd, *J*=8.4, 1.2 Hz, 1H), 7.95 (s, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 7.71 (d, *J*=8.8 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 1H), 7.23 (d, *J*=7.6 Hz, 1H), 6.98 (t, *J*=72.8 Hz, 1H), 2.64 (s, 3H), 2.12-2.30 (m, 2H), 0.99 (t, *J*=7.2 Hz, 3H).

[001386] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-5-methyloxazole-4-carboxamide (258)**

Compound ID: 258



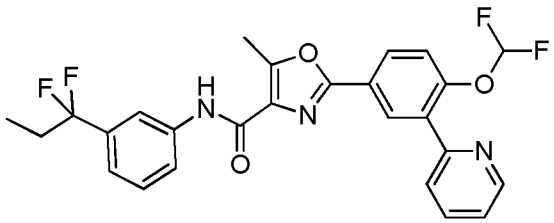
[001387] **258** was obtained via similar procedure of **220**

[001388] **LCMS**: (ESI) *m/z*: 486.0 $[M+H]^+$.

[001389] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.71 - 8.70 (m, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.20 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.99 (s, 1H), 7.96 (td, *J* = 1.6, 7.6 Hz, 1H), 7.83 - 7.80 (m, 2H), 7.49 - 7.43 (m, 3H), 7.31 (dd, *J* = 0.8, 7.6 Hz 1H), 6.97 (t, *J* = 73.2 Hz, 3H), 2.76 (s, 3H), 1.94 (t, *J* = 18.0 Hz, 3H).

[001390] **Synthesis of 2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-*N*-(3-(1,1-difluoropropyl)phenyl)-5-methyloxazole-4-carboxamide (259)**

Compound ID: 259



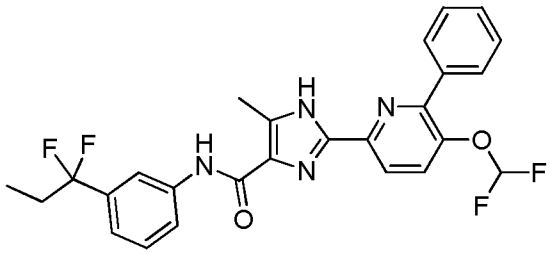
[001391] **259** was obtained via similar procedure of **258**

[001392] **LCMS**: (ESI) *m/z*: 500.2 $[M+H]^+$.

[001393] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.71 - 8.70 (m, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 2.4, 8.8 Hz, 1H), 7.96 - 7.95 (m, 2H), 7.83 - 7.81 (m, 2H), 7.50 - 7.45 (m, 3H), 7.27 (d, J = 6.8 Hz, 1H), 6.97 (t, J = 73.2 Hz, 1H), 2.79 (s, 3H), 2.27 - 2.13 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).

[001394] **Synthesis of 2-(5-(difluoromethoxy)-6-phenylpyridin-2-yl)-*N*-(3-(1,1-difluoropropyl)phenyl)-5-methyl-1*H*-imidazole-4-carboxamide (260)**

Compound ID: 260



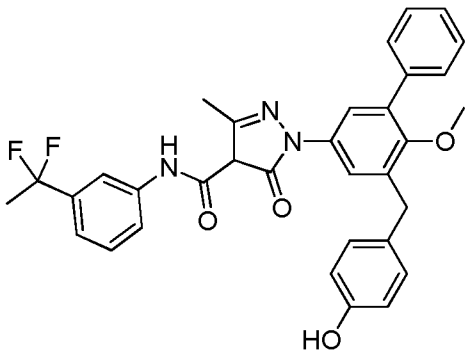
[001395] **260** was obtained via similar procedure of **227**.

[001396] **LCMS**: (ESI) m/z: 499.1 $[M+H]^+$.

[001397] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 8.18 (d, J = 8.8 Hz, 1H), 7.99 ~7.95 (m, 3H), 7.85 ~7.78 (m, 2H), 7.52 ~7.42 (m, 4H), 7.24 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 72.8 Hz, 1H), 2.65 (s, 3H), 2.28 ~2.14 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H).

[001398] **Synthesis of *N*-(3-(1,1-difluoroethyl)phenyl)-1-(5-(4-hydroxybenzyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (228)**

Compound ID: 228



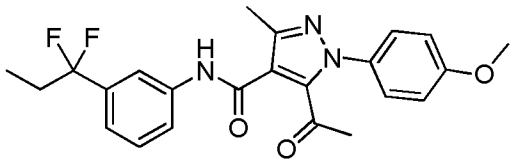
[001399] To a solution of 1-(5-(4-(benzyloxy)benzyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-*N*-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-4-carboxamide (30.0 mg, 43.7 umol, 1.0 *eq*) in methanol (2 mL) was added Pd/C (10.0 mg, 10% purity). The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15psi) at 25 °C for 0.5 h. The suspension was filtered and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.1% trifluoroacetic acid)-acetonitrile]; B%: 54%-84%, 10min) to give 12.9 mg (51% yield) of **228** as a yellow solid.

[001400] **LCMS**: (ESI) m/z: 570.3 $[M+H]^+$.

[001401] **^{1}H NMR** (400Hz, MeOD-d_4) δ: 7.90(s ,1H), 7.61(d, J= 6.8 Hz, 3H), 7.46-7.36(m, 6H), 7.36-7.10 (m, 1H), 7.09(d, J= 8.4 Hz, 2H), 6.71(d, J=8.4 Hz, 2H), 3.99(s, 2H), 3.20(s, 3H), 2.57(s, 3H), 1.91(t, J= 16.4 Hz, 3H).

[001402] **Synthesis of 5-acetyl-*N*-(3-(1,1-difluoropropyl)phenyl)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxamide**

Compound ID: 230



[001403] **230** was obtained via similar procedure of **193** from 5-acetyl-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid and 3-(1,1-difluoropropyl)aniline.

[001404] **LCMS**: (ESI) *m/z*: 428.1 $[M+H]^+$.

[001405] **^{1}H NMR** (400 MHz, $CDCl_3$-*d*) δ: 9.94 (s, 1H), 7.83 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.64 (s, 3H), 2.26 -2.16 (m, 2H), 2.15 (s, 3H), 1.02 (t, J = 7.6 Hz, 3H).

[001406] **Synthesis of 5-chloro-*N*-(3-(1,1-difluoropropyl)phenyl)-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole-4-carboxamide (231)**

Compound ID: 231



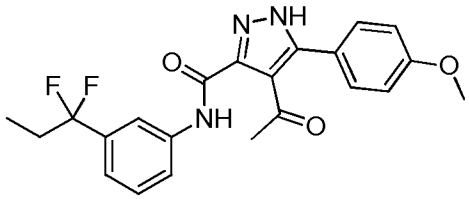
[001407] **231** was obtained via similar procedure of **222** from 5-chloro-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid and 3-(1,1-difluoropropyl)aniline.

[001408] **LCMS:** (ESI) *m/z*: 419.9 $[M+H]^+$.

[001409] **^{1}H NMR** (MeOD-d_4, 400 MHz) δ: 7.85 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.43-7.45 (m, 3H), 7.27 (d, J = 8.0 Hz, 1H), 7.08-7.09 (m, 2H), 3.88 (s, 3H), 2.45 (s, 3H), 2.19 (m, 2H), 0.99 (t, J=7.6 Hz, 3H).

[001410] **Synthesis of 4-acetyl-*N*-(3-(1,1-difluoropropyl)phenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxamide (232)**

Compound ID: 232



[001411] To a solution of 4-acetyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid (45.0

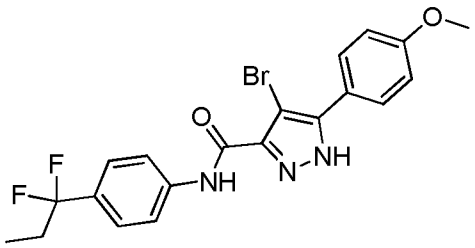
mg, 173 umol, 1.0 *eq*), 3-(1,1-difluoropropyl)aniline (59.2 mg, 346 umol, 2.0 *eq*) in pyridine (3 mL) was added *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (99.4 mg, 519 umol, 3.0 *eq*), the mixture was stirred at 25 °C for 12 hr. The reaction was concentrated to give a residue. The residue was purified by preparative HPLC column: Shim-pack C18 150*25*10 um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 50%-80%,10 min to give 41.0 mg (41% yield) of **232** as a yellow solid.

[001412] **LCMS**: (ESI) *m/z*: 414.2 $[M+H]^+$.

[001413] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.95(s, 1H), 7.79 - 7.81 (d, *J*= 8.0 Hz, 1H), 7.44 - 7.49 (m, 3H), 7.26 - 7.28 (d, *J*= 8.0 Hz, 1H), 7.06 - 7.08 (d, *J*= 8.0 Hz, 2H), 3.86(s, 3H), 2.31(s, 3H), 2.09 - 2.22 (m, 2H), 0.97 - 1.00 (t, *J*= 7.6 Hz, 3H).

[001414] **Synthesis of 4-bromo-*N*-(4-(1,1-difluoropropyl)phenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxamide (233)**

Compound ID: 233



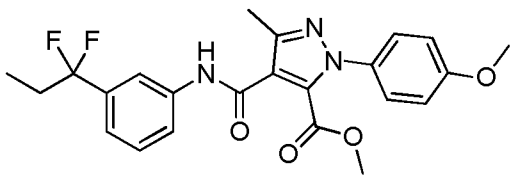
[001415] **233** was obtained via similar procedure of **258** from 4-bromo-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid and 3-(1,1-difluoropropyl)aniline.

[001416] **LCMS**: (ESI) *m/z*: 450.1$[M+H]^+$.

[001417] **^{1}H NMR** (400 MHz, MeOD-d_4) δ: 7.95 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 2.15-2.25 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H).

[001418] **Synthesis of methyl 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (234)**

Compound ID: 234



[001419] To a solution of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid (65.0 mg, 151 umol, 1.0 *eq*) and potassium carbonate (41.8 mg, 303 umol, 2.0 *eq*) in *N*,*N*-dimethylformamide (4 mL) was added iodomethane (215 mg, 1.51 mmol, 10 *eq*), the reaction mixture was stirred at 25 °C for 30 min. The reaction mixture was washed with saturated sodium bicarbonate (20 mL), the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC:

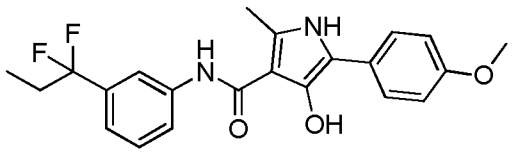
(Phenomenex Gemini C18 column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 45%-75%, 7min) to give 38.1 mg (57% yield) of **234** as a white solid.

[001420] **LCMS**: (ESI) *m/z*: 444.2 $[M+H]^+$.

[001421] **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.48 (s, 1H), 7.91 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 9.2 Hz, 2H), 3.83 (s, 3H), 3.64 (s, 3H), 2.33 (s, 3H), 2.14-2.25 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H).

[001422] **Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-4-hydroxy-5-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (235)**

Compound ID: 235

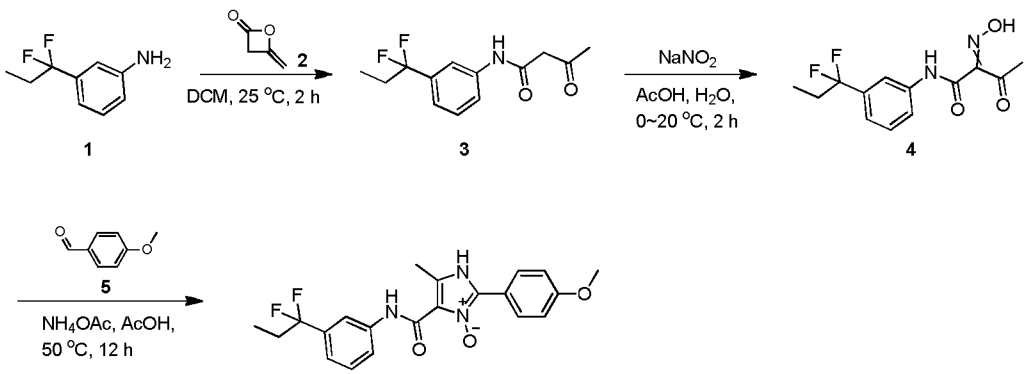


[001423] To a solution of 4-hydroxy-5-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid (70.0 mg, 283 umol, 1.0 *eq*) in *N*,*N*-dimethylformamide (1 mL) was added 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (161 mg, 425 umol, 1.5 *eq*), *N*,*N*-diisopropylethylamine (110 mg, 849 umol, 3.0 *eq*), 3-(1,1-difluoropropyl)aniline (58.2 mg, 340 umol, 1.2 *eq*) at 25 °C, and stirred for 12 h. The reaction mixture was quenched with water (10 mL), extracted with ethyl acetate (30 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate =1/1) to give a crude product. The crude product was triturated with methanol (1 mL), filtered and dried over under reduced pressure to give 2.00 mg (2% yield) of **235** as white solid.

[001424] **LCMS**: (ESI) *m/z*: 401.1 $[M+H]^+$.

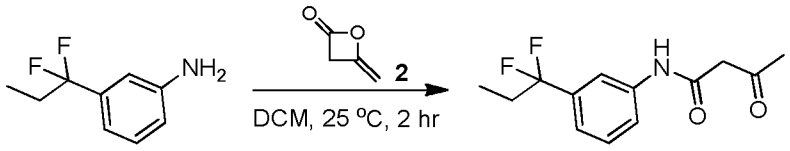
[001425] **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.96 - 10.82 (br s, 1H), 10.19 (s, 1H), 7.78(s, 1H), 7.73 - 7.71 (m, 2H), 7.58 - 7.43 (m, 1H), 7.43 - 7.35 (m, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 3.70 (s, 3H), 2.52(s, 3H), 2.22 - 2.13 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H).

Synthesis of 248



Scheme 1

[001426] **Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-3-oxobutanamide (248-A)**



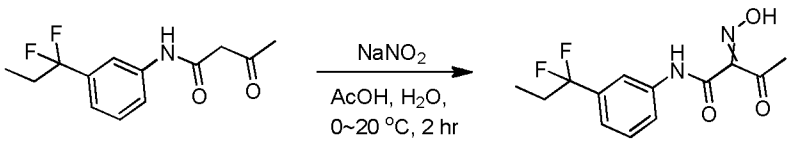
1 3

[001427] To a solution of 3-(1,1-difluoropropyl)aniline (1.00 g, 5.84 mmol, 1.0 *eq*) in dichloromethane (10 mL) was added 4-methyleneoxetan-2-one (589 mg, 7.01 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 2 h. The reaction mixture was 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 350 mg, (22% yield) of **248-A** as a yellow gum.

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

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ: 9.30 (s, 1H), 7.71 - 7.54 (m, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 3.59 (s, 2H), 2.31 (s, 3H), 2.19 - 2.07 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H).

[001428] **Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-2-(hydroxyimino)-3-oxobutanamide (248-B)**



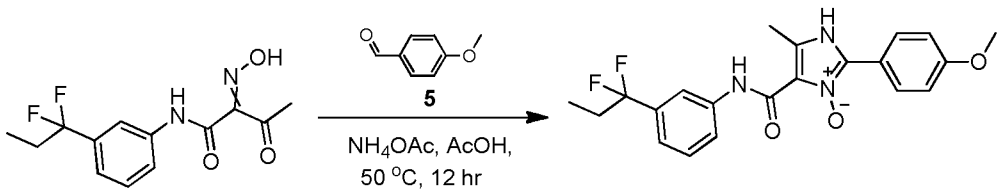
3 4

[001429] To a solution of **248-A** (100 mg, 392 umol, 1.0 *eq*) in acetic acid (3 mL) was added a solution of sodium nitrite (54.1 mg, 784 umol, 2.0 *eq*) in water (2 mL) at 0 °C. It was stirred at 20 °C for 2 hr. The reaction was diluted with water (30 mL) and then extracted with ethyl acetate (30 mL). The organic layer was washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 110 mg (crude) of **248-B** as yellow oil.

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

[001430] **Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxyphenyl)-5-methyl-1*H*-imidazole 3-oxide (248)**

Compound ID: 248



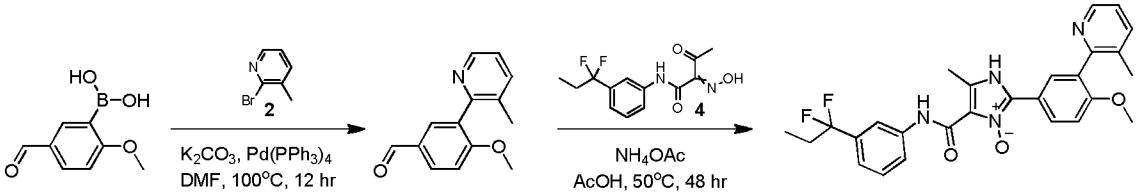
[001431] To a solution of **248-B** (60.0 mg, 211 umol, 1.0 *eq*) in acetic acid (2 mL) was added 4-methoxybenzaldehyde (28.7 mg, 211 umol, 1.0 *eq*) and ammonium acetate (65.1 mg, 844 umol, 4.0 *eq*). It was stirred at 50 °C for 12 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 42%-72%, 10 min) to give 106 mg (82%

yield) of **248** as a yellow solid.

LCMS: (ESI) *m/z*: 402.1 $[M+H]^+$.

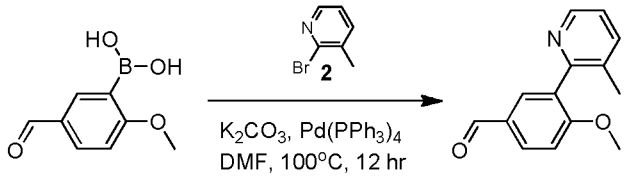
^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.77 (s, 1H), 13.21 (s, 1H), 8.39 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 2.60 (s, 3H), 2.27 - 2.17 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H).

Synthesis of 249



Scheme 2

[001432] **Synthesis of 4-methoxy-3-(3-methylpyridin-2-yl)benzaldehyde (249-A)**

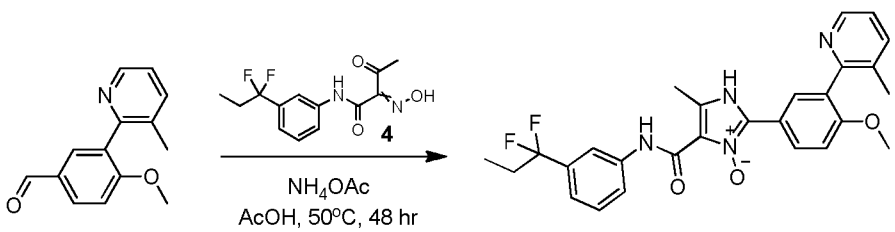


[001433] To a mixture of 2-bromo-3-methyl-pyridine (500 mg, 2.91 mmol, 1.0 *eq*) and (5-formyl-2-methoxy-phenyl)boronic acid (628 mg, 3.49 mmol, 1.2 *eq*) in *N*,*N*-dimethylformamide (20 mL) degassed and purged with nitrogen for 3 times, then added potassium carbonate (803 mg, 5.81 mmol, 2.0 *eq*) and tetrakis(triphenylphosphine)platinum (168 mg, 145 umol, 0.050 *eq*) , the mixture was stirred at 100 °C for 12 hr under nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether / ethyl acetate, from 1/0 to 2/3) to give 560 mg (85 % yield) of **249-A** as a colorless oil.

^{1}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).

[001434] **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 (249)**

Compound ID: 249



[001435] To a mixture of **249-A** (40.0 mg, 176 umol, 1.0 *eq*) and **248-B** (50.0 mg, 176 umol, 1.0 *eq*) in acetic acid (5 mL) was added ammonium acetate (54.2 mg, 704 umol, 4.0 *eq*), then the mixture was stirred at 50 °C for 48 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (0.225%formic acid)-acetonitrile]; B%: 30%-60%, 7min) to give 19.8 mg (23% yield) of **249** as a white solid.

LCMS: (ESI) *m/z*: 493.0 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.88 (s, 1H), 12.45(s, 1H),7.74 (d, J = 7.2 Hz, 1H), 7.65 (dd, J = 0.08, 4.8 Hz, 1H), 7.50 (s, 1H), 7.10 (s, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.63 (t, J = 8.0 Hz, 1H), 6.57 - 6.49 (m, 2H), 6.39 (d, J = 7.8 Hz, 1H), 3.01 (s, 3H), 1.76 (s, 3H), 1.45 - 1.34 (m, 2H), 1.29 (s, 3H), 0.10 (t, J = 7.2 Hz, 3H).

Analytical data summary for compounds of the invention

Compound Number	IUPAC Compound name, Mass Spectra and H-NMR data
100	N-(3-(1,1-difluoroethyl)phenyl)-1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-4-ethyl-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 528.3 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.02 (d, J=2.8 Hz, 1H), 7.96 (dd, J=2.8, 8.8 Hz, 1H), 7.78 (s, 1H), 7.62 (d, J=7.6 Hz, 1H), 7.53 - 7.48 (m, 2H), 7.46 - 7.37 (m, 4H), 7.35 - 7.29 (m, 2H), 6.65 (t, J=74.0 Hz, 1H), 2.41 - 2.35 (m, 1H), 2.33 (s, 3H), 2.32 - 2.28 (m, 1H), 1.89 (t, J=18.4 Hz, 3H), 0.87 (t, J=7.6 Hz, 3H).
101	N-(3-(cyclobutyldifluoromethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 464.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.82 (br s, 3H), 7.63 (br d, J = 8.0 Hz, 1H), 7.35 (br s, 1H), 7.26 - 7.07 (m, 3H), 6.80 (t, J = 74.4 Hz, 1H), 3.28 - 2.99 (m, 1H), 2.45 (br s, 3H), 2.31 - 2.10 (m, 2H), 2.05 - 1.88 (m, 3H), 1.88 - 1.78 (m, 1H).
102	2-[4-(difluoromethoxy)phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-6-methyl-pyridine-4-carboxamide LCMS: (ESI) m/z: 433.3 [M+H]+; 1H NMR (400 MHz, MeOD) δ: 8.14 - 8.11 (m, 2H), 8.10 - 8.09 (m, 1H), 7.95 - 7.91 (m, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.28 (d, J = 8.8 Hz, 2H), 2.69 (s, 3H), 2.27 - 2.12 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).
103	5-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoropropyl)phenyl)-3,6-dimethylpyrazine-2-carboxamide LCMS: (ESI) m/z: 524.2 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 10.78(s, 1H), 8.06(s, 1H), 7.96(d, J= 8.4 Hz, 1H), 7.82(dd, J= 8.4 Hz, J= 2.4 Hz, 1H), 7.78(d, J= 2.0 Hz, 1H), 7.56-7.48(m, 6H), 7.46-7.41(m, 1H), 7.31(t, J= 38.0 Hz, 1H), 2.79(s, 3H), 2.73(s, 3H), 2.27-2.15(m, 2H), 0.94(t, J= 7.2 Hz, 3H).
104	N-(3-(1,1-difluoroethyl)phenyl)-5-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3,6-dimethylpyrazine-2-carboxamide LCMS: (ESI) m/z: 510.2 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 10.79(s, 1H), 8.11(s ,1H), 7.96(d, J= 8.0 Hz, 1H), 7.82(dd, J= 8.4 Hz, J= 2.4 Hz, 1H), 7.78(d, J= 2.0 Hz, 1H), 7.56-7.48(m, 6H), 7.45-7.41(m, 1H), 7.32(d, J= 8.0 Hz, 1H), 7.31(t, J= 73.6 Hz, 1H), 2.79(s, 3H), 2.73(s, 3H), 1.99(t, J= 18.8 Hz, 3H).
105	5-(4-(difluoromethoxy)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-3,6-dimethylpyrazine-2-carboxamide

	LCMS: (ESI) m/z: 448.1 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 10.78(s, 1H), 8.06(s, 1H), 7.96(d, J= 8.4 Hz, 1H), 7.80(d, J= 8.4 Hz, 1H), 7.51(t, J= 8.0 Hz, 1H), 7.38(t, J= 74.0 Hz, 1H), 7.34(d, J= 8.8 Hz, 2H), 7.27(d, J= 8.0 Hz, 1H), 2.78(s, 3H), 2.67(s, 3H), 2.29-2.15(m, 2H), 0.94(t, J= 7.2 Hz, 3H).
106	N-[3-(1,1-difluoroethyl)phenyl]-2-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-methyl-oxazole-4-carboxamide LCMS: (ESI) m/z: 396.2 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ: 8.11 (d, J = 5.8 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.78 - 7.74 (m, 1H), 7.73 - 7.69 (m, 1H), 7.56 (t, J = 2.8 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.54 (t, J = 1.8 Hz, 1H), 2.73 (s, 3H), 2.29 - 2.15 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).
107	N-(3-(1,1-difluoroethyl)phenyl)-2-(1H-indol-6-yl)-5-methyloxazole-4-carboxamide LCMS: (ESI) m/z: 382.2 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 11.48 (br s, 1H), 10.14 (s, 1H), 8.14 (d, J = 13.2 Hz, 2H), 7.98 (d, J = 8.0 Hz, 1H), 7.78 - 7.74 (m, 1H), 7.73 - 7.69 (m, 1H), 7.56 (t, J = 2.8 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 6.54 (t, J = 2.0 Hz, 1H), 2.73 (s, 3H), 1.98 (t, J = 18.8 Hz, 3H).
108	1-benzyl-N-[3-(1,1-difluoroethyl)phenyl]-2-(1H-indol-6-yl)-5-methyl-3-oxo-pyrazole-4-carboxamide LCMS: (ESI) m/z: 487.3[M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 11.37 (br s, 1H), 11.00 (s, 1H), 7.92 (s, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.58 (d, J=6.8 Hz, 1H), 7.50 (t, J=2.8 Hz, 1H), 7.43 (t, J=8.0 Hz, 1H), 7.33 -7.26 (m, 4H), 7.22 (d, J=7.6 Hz, 1H), 6.91 (d, J=6.4 Hz, 2H), 6.84 (dd, J=8.4, 1.6 Hz, 1H), 6.53 (br s, 1H), 5.10 (s, 2H), 2.74 (s, 3H), 1.95 (t, J=18.8 Hz, 3H).
111	N-(3-(1,1-difluoroethyl)phenyl)-1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4-propyl-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 542.3 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.01 (s, 1H), 7.96 (d, J=9.2 Hz, 1H), 7.79 (s, 1H), 7.62 (d, J=7.6 Hz, 1H), 7.53 - 7.49 (m, 2H), 7.47 - 7.38 (m, 4H), 7.35 - 7.29 (m, 2H), 6.66 (t, J= 74.0 Hz, 1H), 2.35 - 2.20 (m, 5H), 1.90 (t, J=18.4 Hz, 3H), 1.27 - 1.14 (m, 2H), 0.97 (t, J=7.2 Hz, 3H).
112	2-(4-(difluoromethoxy)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-5-methyloxazole-4-carboxamide LCMS: (ESI) m/z: 423.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.08 - 8.17 (td, 2 H) 7.95 (s, 1 H) 7.80 (dd, J=8.12, 1.16 Hz, 1 H) 7.45 (t, J=7.96 Hz, 1 H) 7.24 - 7.33 (td, 3 H) 6.75 - 7.15 (t, 1 H) 2.74 (s, 3 H) 2.12 - 2.27 (td, 2 H) 1.00 (t, J=7.52 Hz, 3 H).
113	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)-5-methyloxazole-4-carboxamide LCMS: (ESI) m/z: 409.0 [M+H]+. 1H NMR (400 MHz, MeOD-d4) δ: 8.17 - 8.12 (m, 2H), 8.02 - 7.98 (s, 1H), 7.83 - 7.79 (d, J = 8.4 Hz, 1H), 7.49 - 7.43 (t, J = 8.0 Hz, 1H), 7.34 - 7.28 (m, 3H), 7.16 - 6.77 (t, J = 73.4 Hz 1H), 2.76 (s, 3H), 1.95 (t, J = 18.2 Hz, 3H).
114	2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoropropyl)phenyl)-4-methyloxazole-5-carboxamide LCMS: (ESI) m/z: 499.2 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.35 (d, J = 2.0 Hz, 1H), 8.26 (dd, J = 2.0, 8.8 Hz, 1H), 7.88 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.60 - 7.53 (m, 2H), 7.52 - 7.37 (m, 5H), 7.28 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 73.2 Hz, 1H), 2.58 (s, 3H), 2.32 - 2.08 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H).
115	N-(3-(1,1-difluoroethyl)phenyl)-2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-4-methyloxazole-5-carboxamide LCMS: (ESI) m/z: 485.2 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.35 (d, J = 2.0 Hz, 1H), 8.25 (dd, J = 2.0, 8.4 Hz, 1H), 7.93 (s, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.59 - 7.53 (m, 2H), 7.51 - 7.38 (m, 5H),

	7.33 (dd, J = 0.8, 8.0 Hz, 1H), 6.87 (t, J = 73.6 Hz, 1H), 2.58 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H).
116	N-(3-(1,1-difluoropropyl)phenyl)-2-(4-methoxyphenyl)-5-methyloxazole-4-carboxamide LCMS: (ESI) m/z: 387.4 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.07 - 7.99 (dt, 2H), 7.96 - 7.93 (s, 1H), 7.85 - 7.75 (dd, 1H), 7.49 - 7.41 (t, 1H), 7.30 - 7.23 (d, 1H), 7.12 - 7.03 (dt, 2H), 3.92 - 3.83 (s, 3H), 2.78 - 2.68 (s, 3H), 2.27 - 2.12 (td, 2H), 1.05 - 0.94 (t, 3H).
117	6-[4-(difluoromethoxy)-3-phenyl-phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-3-methyl-pyrazine-2-carboxamide LCMS: (ESI) m/z: 510.3 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 9.23 (s, 1H), 8.30 -8.27 (m, 2H), 7.97 (s, 1H), 7.87 -7.83 (m, 1H), 7.61 -7.58 (m, 2H), 7.50 -7.45 (m, 4H), 7.43 -7.38 (m, 1H), 7.30 (d, J = 7.2 Hz, 1H), 6.82 (t, J = 74 Hz, 1H), 2.92 (s, 3H), 2.28 -2.13 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H).
118	N-[3-(1,1-difluoroethyl)phenyl]-6-[4-(difluoromethoxy)-3-phenyl-phenyl]-3-methyl-pyrazine-2-carboxamide LCMS: (ESI) m/z: 496.3 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 9.22 (s, 1H), 8.31 -8.27 (m, 2H), 8.01 (s, 1H), 7.86 -7.83 (m, 1H), 7.61 -7.58 (m, 2H), 7.50 -7.45 (m, 4H), 7.43 -7.38 (m, 1H), 7.34 (dd, J = 7.6, 0.8 Hz, 1H),6.82 (t, J= 73.6 Hz, 1H), 2.91 (s, 3H), 1.95 (t, J = 18.4 Hz, 3H).
119	2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-4-methylpyrimidine-5-carboxamide LCMS: (ESI) m/z: 511.3 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.91 (s, 1H), 8.83 (d, J=2.4 Hz, 1H), 8.69 (d, J=4.4 Hz, 1H), 8.62 (dd, J=2.4, 8.8 Hz, 1H), 7.97 - 7.93 (m, 1H), 7.90 (s, 1H), 7.82 - 7.77 (m, 2H), 7.50 - 7.44 (m, 3H), 7.30 (d, J=7.6 Hz, 1H), 6.96 (t, J=73.6 Hz, 1H), 2.75 (s, 3H), 2.23 - 2.13 (m, 2H), 1.94 (t, J=7.6 Hz, 3H).
120	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-4-methylpyrimidine-5-carboxamide LCMS: (ESI) m/z: 497.2 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.92 (s, 1H), 8.83 (d, J=2.0 Hz, 1H), 8.69 (d, J=4.8 Hz, 1H), 8.64 (dd, J=2.4, 8.8 Hz, 1H), 7.98 - 7.93 (m, 2H), 7.82 - 7.77 (m, 2H), 7.50 - 7.44 (m, 3H), 7.35 (d, J=7.6 Hz, 1H), 6.97 (t, J=73.6 Hz, 1H), 2.75 (s, 3H), 1.94 (t, J=18.4 Hz, 3H).
121	1-(5-benzyl-6-methoxy-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 568.3 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 10.88(s, 1H), 7.89(s, 1H), 7.69-7.59(m, 5H), 7.49(t, J= 7.6 Hz, 2H), 7.43-7.38(m, 2H), 7.34-7.28(m, 4H), 7.22-7.12(m, 2H), 4.06(s, 2H), 3.18(s, 3H), 2.51(s, 3H),2.24-2.14(m, 2H), 0.91(t, J= 7.6 Hz, 3H).
122	1-(5-benzyl-6-methoxy-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 554.3 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 10.91(s, 1H), 7.93(s, 1H), 7.70-7.58(m, 5H), 7.49(t, J= 7.2 Hz, 2H), 7.42-7.37(m, 2H), 7.34-7.28(m,4H), 7.22-7.16(m, 2H), 4.06(s, 2H), 3.18(s, 3H), 2.48(s, 3H), 1.95(t, J= 18.8 Hz, 3H).
123	2-[4-(difluoromethoxy)-3-phenyl-phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-5-methyl-oxazole-4-carboxamide LCMS: (ESI) m/z: 499.3 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.17 (d, J = 2.4 Hz, 1H), 8.11 (dd, J = 2.4, 8.5 Hz, 1H), 7.95 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.51 - 7.39 (m, 5H), 7.26 (d, J = 7.8 Hz, 1H), 7.03 - 6.63 (m, 1H), 2.76 (s, 3H), 2.29 - 2.10 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).
124	N-[3-(1,1-difluoroethyl)phenyl]-2-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-methyl-oxazole-4-carboxamide LCMS: (ESI) m/z: 485.3 [M+H]+;

	1H NMR: (400 MHz, MeOD-d4) δ: 8.17 (d, J = 2.4 Hz, 1H), 8.12 (dd, J = 2.4, 8.5 Hz, 1H), 7.99 (s, 1H), 7.80 (dd, J = 1.0, 8.2 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.52 - 7.40 (m, 5H), 7.31 (dd, J = 0.8, 7.7 Hz, 1H), 7.03 - 6.63 (m, 1H), 2.76 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H).
125	6-(4-(difluoromethoxy)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-3-methylpyrazine-2-carboxamide LCMS: (ESI) m/z: 434.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ : 9.18 (s, 1H), 8.23-8.37 (m, 2H), 8.02 (s, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.45-7.56 (m, 1H), 7.27-7.38 (m, 3H), 6.71-7.22 (m, 1H), 2.93 (s, 3H), 2.14-2.31 (m, 2H), 1.02 (t, J=7.6 Hz, 3H).
126	N-(3-(1,1-difluoroethyl)phenyl)-6-(4-(difluoromethoxy)phenyl)-3-methylpyrazine-2-carboxamide LCMS: (ESI) m/z: 420.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 9.18 (s, 1H), 8.26-8.34 (m, 2H), 8.06 (s, 1H), 7.88 (br d, J=8.4 Hz, 1H), 7.50 (t, J=8.0 Hz, 1H), 7.31-7.39 (m, 3H), 6.76-7.18 (m, 1H), 2.93 (s, 3H), 1.97(t, J=18.4 Hz, 3H).
127	2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoropropyl)phenyl)-6-methylpyrimidine-4-carboxamide LCMS: (ESI) m/z: 510.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.66-8.69 (m, 2H), 8.02 (s, 1H), 7.88-7.92 (m, 2H), 7.57-7.59 (m, 2H), 7.46-7.51 (m, 3H), 7.39-7.43 (m, 2H), 7.32 (d, J=7.6 Hz, 1H), 6.82 (t, J=74.0 Hz, 1H), 2.70 (s, 3H), 2.13-2.28 (m, 2H), 1.00 (t, J=7.6 Hz, 3H).
128	1-(5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 574.3 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.77 (br s, 1H), 7.54 - 7.51 (bm, 3H), 7.39 - 7.23 (m, 6H), 7.10 (d, J=7.6 Hz, 1H), 3.24 (s, 3H), 2.59 - 2.42 (m, 5H), 2.08 (qt, J=7.8, 15.6 Hz, 2H), 1.71 - 1.54 (m, 6H), 1.26 - 1.09 (m, 3H), 1.03 - 0.91 (m, 2H), 0.88 (t, J=7.6 Hz, 3H).
129	1-(5-(cyclohexylmethyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 560.3 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.81 (br s, 1H), 7.56 - 7.48 (m, 3H), 7.42 - 7.23 (m, 6H), 7.12 (d, J=7.6 Hz, 1H), 3.22 (s, 3H), 2.51 (d, J=7.2 Hz, 2H), 2.46 (s, 3H), 1.88 - 1.77 (d, J=28.0 Hz, 3H), 1.67 - 1.58 (m, 6H), 1.20 - 1.11 (m, 3H), 1.01 - 0.90 (m, 2H).
130	N-(3-(1,1-difluoroethyl)phenyl)-2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-6-methylpyrimidine-4-carboxamide LCMS: (ESI) m/z: 496.1[M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.72 (dd, J = 2.0, 8.4 Hz, 1 H), 8.69 (d, J = 2.0 Hz, 1H), 8.07 (s, 1H), 7.96 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.63 - 7.58 (m, 2H), 7.52 - 7.35 (m, 6H), 6.85 (t, J = 73.6 Hz, 1H), 2.72 (s, 3H), 1.96 (t, J = 18.0 Hz, 3H).
131	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(2-methyloxazol-4-yl)phenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 489.1[M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.88 (s, 1H), 8.50 (d, J=2.8 Hz, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.75-7.82 (m, 2H), 7.40-7.49 (m, 2H), 7.28-7.33 (m, 1H), 6.85-7.27 (m, 1H), 2.59 (s, 3H), 2.56 (s, 3H), 1.96 (t, J=18.4 Hz, 3H).
132	5-(4-(difluoromethoxy)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-3-methylpyrazine-2-carboxamide LCMS: (ESI) m/z: 434.1 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 9.04 (s, 1H), 8.26 (d, J=8.8 Hz, 2H), 7.99 (s, 1H), 7.85 (d, J=8.0 Hz, 1H), 7.47 (t, J=8.0 Hz, 1H), 7.32 (d, J=8.8 Hz, 2H), 7.28 (d, J=8.0 Hz, 1H), 6.96 (t, J=74.0 Hz, 1H), 2.98 (s, 3H), 2.21 (dt, J=7.6, 16.0 Hz, 2H), 1.00 (t, J=7.6 Hz, 3H).
133	N-(3-(1,1-difluoroethyl)phenyl)-5-(4-(difluoromethoxy)phenyl)-3-methylpyrazine-2-carboxamide LCMS: (ESI) m/z: 420.1 [M+H]+;

	1H NMR: (400 MHz, MeOD-d4) δ: 9.05 (s, 1H), 8.26 (d, J=8.8 Hz, 2H), 8.04 (s, 1H), 7.85 (d, J=8.0 Hz, 1H), 7.47 (t, J=8.0 Hz, 1H), 7.32 (d, J=8.8 Hz, 3H), 6.96 (t, J=74.0 Hz, 1H), 2.99 (s, 3H), 1.95 (t, J=18.4 Hz, 3H).
134	5-[4-(difluoromethoxy)-3-phenyl-phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-3-methyl-pyrazine-2-carboxamide LCMS: (ESI) m/z: 510.2 [M+H]+. 1H NMR (400 MHz, MeOD-d4) δ: 9.08 (s, 1H), 8.26 -8.21 (m, 2H), 7.99 (s, 1H), 7.84 (dd, J = 8.0, 0.8 Hz, 1H), 7.58 -7.55 (m, 2H), 7.50 -7.41 (m, 5H), 7.27 (dd, J = 7.6, 0.8 Hz, 1H), 6.84 (t, J = 73.6 Hz, 1H), 2.98 (s, 3H), 2.28 -2.13 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H).
135	N-[3-(1,1-difluoroethyl)phenyl]-5-[4-(difluoromethoxy)-3-phenyl-phenyl]-3-methyl-pyrazine-2-carboxamide LCMS: (ESI) m/z: 496.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 9.10 (s, 1H), 8.27 -8.22 (m, 2H), 8.04 (s, 1H), 7.85 (dd, J = 8.0, 1.2 Hz, 1H), 7.58 -7.55 (m, 2H), 7.51 -7.41 (m, 5H), 7.32 (dd, J = 7.6, 0.8 Hz, 1H), 6.84 (t, J = 73.6, 1H), 2.99 (s, 3H), 1.95 (t, J = 18.4 Hz, 3H).
136	N-(3-(1,1-difluoropropyl)phenyl)-2-(4-methoxyphenyl)-4-methyloxazole-5-carboxamide LCMS: (ESI) m/z: 387.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.16 (d, J=8.8 Hz, 2H), 7.91 (s, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.08 (d, J=9.2 Hz, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 2.15-2.25 (m, 2H), 1.00 (t, J=7.2 Hz, 3H).
137	2-(4-(difluoromethoxy)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-6-methylpyrimidine-4-carboxamide LCMS: (ESI) m/z: 434.0 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.68-8.72 (m, 2H), 8.06 (s, 1H), 7.93-7.95 (m, 2H), 7.50 (t, J=8.0 Hz, 1H), 7.29-7.34 (m, 3H), 6.96 (t, J= 73.6 Hz, 1H), 2.71 (s, 3H), 2.17-2.27 (m, 2H), 1.01 (t, J=7.6 Hz, 3H).
138	2-[4-(difluoromethoxy)-3-phenyl-phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-4-methyl-pyrimidine-5-carboxamide LCMS: (ESI) m/z: 509.9 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.91 (s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.54 -8.51 (m, 1H), 7.90 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.57 -7.54 (m, 2H), 7.50 -7.45 (m, 3H), 7.43 -7.39 (m, 2H), 7.30 (d, J = 8.0 Hz, 1H), 6.84 (t, J = 73.6 Hz, 1H), 2.75 (s, 3H), 2.27 -2.12 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H).
139	N-[3-(1,1-difluoroethyl)phenyl]-2-[4-(difluoromethoxy)-3-phenyl-phenyl]-4-methyl-pyrimidine-5-carboxamide LCMS: (ESI) m/z: 496.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.91 (s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.54 -8.51 (m, 1H), 7.95 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.57 -7.54 (m, 2H), 7.50 -7.45 (m, 3H), 7.43 -7.38 (m, 2H), 7.34 (d, J = 8.4 Hz, 1H), 6.84 (t, J = 74.0 Hz, 1H), 2.75 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H).
140	2-(4-(difluoromethoxy)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-4-methyloxazole-5-carboxamide LCMS: (ESI) m/z: 423.1 [M+H]+. 1H NMR (400 MHz, MeOD-d4) δ: 8.25-8.29 (m, 2H), 7.91 (s, 1H), 7.84 (d, J=8.4 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 7.27-7.32 (m, 3H), 6.98 (t, J=73.6 Hz, 1H), 2.56 (s, 3H), 2.15-2.25 (m, 2H), 1.00 (t, J=7.2 Hz, 3H).
141	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)-4-methyloxazole-5-carboxamide LCMS: (ESI) m/z: 409.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.25-8.28 (m, 2H),7.95 (s, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.46 (t, J=7.6 Hz, 1H), 7.30-7.34 (m, 3H), 6.98 (t, J=73.2 Hz, 1H), 2.56 (s, 3H), 1.94 (t, J=18.4 Hz, 3H).
142	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-methoxyphenyl)-4-methyloxazole-5-carboxamide LCMS: (ESI) m/z: 373.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.16-8.18 (m, 2H), 7.96 (s, 1H), 7.82-7.84 (m, 1H),

	7.46 (t, J=8.0 Hz, 1H), 7.33 (dd, J=0.8, 7.6 Hz, 1H), 7.08-7.11 (m, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 1.94 (t, J=18.4 Hz, 3H).
143	2-[4-(difluoromethoxy)phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-4-methyl-pyrimidine-5-carboxamide LCMS: (ESI) m/z: 433.9 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.90 (s, 1H), 8.54 (d, J = 8.8 Hz, 2H), 7.90 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.32 -7.25 (m, 3H), 6.96 (t, J = 74.0 Hz, 1H), 2.74 (s, 3H), 2.20 (td, J = 16.0, 7.6 Hz, 2H), 0.99 (t, J = 7.6 Hz, 3H).
144	N-[3-(1,1-difluoroethyl)phenyl]-2-[4-(difluoromethoxy)phenyl]-4-methyl-pyrimidine-5-carboxamide LCMS: (ESI) m/z: 420.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.90 (s, 1H), 8.54 (d, J = 8.8 Hz, 2H), 7.95 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.34 (dd, J = 8.0, 0.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 6.96 (t, J = 74.0 Hz, 1H), 2.74 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H).
145	5-cyclopropyl-N-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)phenyl]-3-methyl-pyrazole-4-carboxamide LCMS: (ESI) m/z: 447.9 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 7.92 (s, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.62 (d, J=9.2 Hz, 2H), 7.46 (t, J=8.0 Hz 1H), 7.35 -7.29 (m, 3H), 6.94 (t, J=74.0 Hz, 1H), 2.40 (s, 3H), 2.14 -2.05 (m, 1H), 1.94 (t, J=18.4 Hz, 3H), 0.89 (dd, J=8.4, 1.6 Hz, 2H), 0.51 (dd, J=5.6, 1.6 Hz, 2H).
146	N-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)phenyl]-5-isopropyl-3-methyl-pyrazole-4-carboxamide LCMS: (ESI) m/z: 450.2 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 10.35 (s, 1H), 8.02 (s, 1H), 7.77 (br d, J = 8.2 Hz, 1H), 7.57 - 7.53 (m, 1H), 7.51 - 7.41 (m, 3H), 7.36 (s, 2H), 7.27 (d, J = 7.6 Hz, 1H), 7.22 - 7.16 (m, 1H), 2.97 (q, J = 7.0 Hz, 1H), 2.29 (s, 3H), 1.96 (t, J = 18.8 Hz, 3H), 1.25 (d, J = 7.0 Hz, 6H).
147	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)-6-methylpyrimidine-4-carboxamide LCMS: (ESI) m/z: 420.0 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ : 8.66-8.71 (m, 2H), 8.09 (s, 1H), 7.91-7.97 (m, 2H), 7.50 (t, J=8.0 Hz, 1H), 7.37 (d, J=7.6 Hz, 1H), 7.29 (d, J=8.8 Hz, 2H), 6.96 (t, J=74.0Hz, 1H), 2.70 (s, 3H), 1.96 (t, J=18.4 Hz, 3H).
148	N-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxamide LCMS: (ESI) m/z: 513.2 [M+H]+. 1H NMR: (400 MHz, DMSO-d6) δ: 10.09 (s, 1H), 8.80 - 8.63 (m, 1H), 8.00 (s, 1H), 7.97 - 7.92 (m, 1H), 7.89 (d, J = 2.8 Hz, 1H), 7.88 - 7.84 (m, 1H), 7.79 - 7.73 (m, 1H), 7.65 (dd, J = 2.8, 8.8 Hz, 1H), 7.55 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.48 - 7.45 (m, 1H), 7.44 (td, J = 1.2, 3.0, 4.4 Hz, 1H), 7.37 (s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.19 (s, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.96 (t, J = 18.8 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H).
149	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(oxazol-4-yl)phenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 475.1[M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.89 (s, 1H), 8.56 (d, J=2.76 Hz, 1H), 8.39 (s, 1H), 8.32 (d, J=0.64 Hz, 1H), 7.94 (s, 1H), 7.74-7.85 (m, 2H), 7.40-7.50 (m, 2H), 7.30 (d, J=7.64 Hz, 1H), 6.89-7.28 (m, 1H), 2.59 (s, 3H), 1.96 (t, J=18.24 Hz, 3H).
150	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-isobutyl-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 464.3 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.87 (s, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.43-7.50 (m, 3H), 7.30-7.36 (m, 3H), 6.96 (t, J=73.2 Hz, 1H), 2.78 (d, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.94 (t, J=18.4 Hz, 3H), 1.67-1.73 (m, 1H), 0.76 (d, J=6.8 Hz, 6H).
151	N-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)-3-phenyl-phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxamide

	LCMS: (ESI) m/z: 512.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.89 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.56 -7.41 (m, 9H), 7.31 (d, J = 7.2 Hz, 1H), 6.82 (t, J = 73.6 Hz, 1H), 2.93 (q, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.94 (t, J = 18.0 Hz, 3H), 1.13 (t, J = 7.6 Hz, 3H).
152	N-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)-3-(3-pyridyl)phenyl]-5-ethyl-3-methyl-pyrazole-4-carboxamide LCMS: (ESI) m/z: 513.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.74 (d, J = 1.6 Hz, 1H), 8.59 (dd, J = 4.8, 1.2 Hz, 1H), 8.05 (dt, J = 8.4, 2.0 Hz, 1H), 7.89 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.62-7.52 (m, 4H), 7.45 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 6.94 (t, J = 72.8 Hz, 1H), 2.94 (q, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.94 (t, J = 18.4 Hz, 3H), 1.13 (t, J = 7.6 Hz, 3H).
153	N-[3-(1,1-difluoroethyl)phenyl]-2-(4-methoxyphenyl)-5-methyl-oxazole-4-carboxamide LCMS: (ESI) m/z: 373.1 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 10.11(s, 1H), 8.13(s, 1H), 8.01(d, J= 8.8 Hz, 2H), 7.96(d, J= 8.0 Hz, 1H), 7.47(t, J=12.0 Hz, 1H), 7.29(d, J= 7.6 Hz, 1H), 7.13(d, J= 8.8 Hz, 2H), 3.85(s, J= 3H), 2.70(s, 3H), 1.98(t, J= 18.8 Hz, 3H).
154	5-cyclopentyl-N-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)phenyl]-3-methyl-pyrazole-4-carboxamide LCMS: (ESI) m/z: 476.1 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 7.87(s, 1H), 7.71(d, J= 8.4 Hz, 1H), 7.47-7.42(m, 3H), 7.35-7.30(m, 3H), 6.95(t, J= 73.2 Hz, 1H), 3.06-2.97(m, 1H), 2.36(s, 3H), 1.98-1.89(m, 7H), 1.79-1.69(m, 2H), 1.56-1.48(m, 2H).
155	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-ethyl-5-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 436.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.89 (s, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.49-7.52 (m, 2H), 7.45 (t, J=8.0 Hz, 1H), 7.29-7.36 (m, 3H), 6.96 (t, J=73.6 Hz, 1H), 2.87 (q, J=7.6 Hz, 2H), 2.44 (s, 3H), 1.94 (t, J=18.0 Hz, 3H), 1.08 (t, J=7.6 Hz, 3H).
156	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-ethyl-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 436.0 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.88 (s, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.51-7.53 (m, 2H), 7.45 (t, J=8.0 Hz, 1H), 7.29-7.35 (m, 3H), 6.94 (t, J=73.6 Hz, 1H), 2.87 (q, J=7.6 Hz, 2H), 2.42 (s, 3H), 1.93 (t, J=18.22 Hz, 3H), 1.27 (t, J=7.6 Hz, 3H).
157	N-(3-chloro-5-methyl-phenyl)-1-[4-(difluoromethoxy)phenyl]-3,4-dimethyl-5-oxo-pyrazole-4-carboxamide LCMS: (ESI) m/z: 422.0 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.96 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 7.27 (s, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.99 (s, 1H), 6.82 (t, J = 74 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 1.75 (s, 3H).
158	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4-propyl-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 466.2 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 7.96 (d, J=9.2 Hz, 2H), 7.78 (s, 1H), 7.63 (d, J=8.4 Hz, 1H), 7.42 (t, J=8.0 Hz, 1H), 7.31 (d, J=7.2 Hz, 1H), 7.22 (d, J=9.2 Hz, 2H), 6.82 (t, J=74.0 Hz, 1H), 2.35 - 2.19 (m, 5H), 1.90 (t, J=18.4 Hz, 3H), 1.28 - 1.13 (m, 2H), 0.97 (t, J=7.2 Hz, 3H).
159	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-4-ethyl-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 452.2 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 7.97 (d, J=8.0 Hz, 2H), 7.78 (s, 1H), 7.62 (d, J=8.4 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.22 (d, J=9.2 Hz, 2H), 6.82 (t, J=74.0 Hz, 1H), 2.43 - 2.36 (m, 1H), 2.33 (s, 3H), 2.32 - 2.22 (m, 1H), 1.90 (t, J=18.4 Hz, 3H), 0.86 (t, J=7.2 Hz, 3H).
160	1-(5-((1H-imidazol-1-yl)methyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide

	LCMS: (ESI) m/z: 544.4 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ: 11.26(s, 1H), 8.21(s, 3H), 7.90-7.87(m, 2H), 7.77(s, 1H), 7.57-7.55(m, 2H), 7.48(t, J= 7.6 Hz, 2H), 7.39(t, J= 3.2 Hz, 1H), 7.34-7.26(m, 2H), 7.19(s, 1H), 7.04(d, J= 7.6 Hz, 1H), 6.91(s, 1H), 5.24(s, 2H), 3.19(s, 3H), 2.24(s, 3H), 1.94(t, J= 21.6 Hz, 3H).
161	N-(3-(1,1-difluoroethyl)phenyl)-1-(6-methoxy-5-propyl-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 506.5 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.92 (s, 1H), 7.66-7.62 (m, 3H), 7.58 (br s, 2H), 7.46 - 7.41 (m, 2H), 7.40 - 7.33 (m, 2H), 7.18 (br d, J=7.6 Hz, 1H), 3.34 (s, 3H), 2.77 (t, J=7.6 Hz,, 2H), 2.48 (s, 3H), 1.92 (t, J=18.4 Hz, 3H), 1.79 - 1.69 (m, 2H), 1.04 (t, J=7.2 Hz, 3H).
162	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-(methylamino)-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 437.2 [M+H]+; 1H NMR(400Hz, DMSO-d6) δ: 9.46(s, 1H), 7.96(s, 1H), 7.72(d, J= 8.4Hz, 1H), 7.58-7.55(m, 2H), 7.43(t, J= 8.0Hz, 1H), 7.32(d, J= 8.8Hz, 2H), 7.31(t, J= 74.0Hz, 1H), 7.23(d, J= 7.6Hz, 1H), 6.19(dd, J= 10.8Hz, 5.6Hz, 1H), 2.55(s, 3H), 2.35(s, 3H), 1.96(t, J= 18.8Hz, 3H).
163	4-chloro-1-(4-(difluoromethoxy)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 438.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.82 (br s, 1H), 7.86-7.98 (m, 2H), 7.62-7.70 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.31 (br d, J = 7.2 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.29-6.77 (m, 1H), 2.47 (s, 3H), 2.08-2.23 (m, 2H), 1.00 (t, J = 7.6Hz, 3H).
164	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)-5-methyl-2H-1,2,3-triazole-4-carboxamide LCMS: (ESI) m/z: 409.0 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ: 10.54 (s, 1H), 8.15-8.19 (m, 2H), 8.08 (s, 1H), 7.95 (d, J=8.0 Hz, 1H), 7.49 (t, J=7.6 Hz, 1H), 7.44 (d, J=9.2 Hz, 2H), 7.35 (t, J=73.6 Hz, 1H), 7.32 (d, J=8.0 Hz, 1H), 2.59 (s, 3H), 1.98 (t, J=18.8 Hz, 3H).
165	N-(3,5-dichloro-4-fluoro-phenyl)-1-[4-(difluoromethoxy)phenyl]-3,4-dimethyl-5-oxo-pyrazole-4-carboxamide LCMS: (ESI) m/z: 460.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.95 (d, J = 9.2 Hz, 2H), 7.75 (s, 1H), 7.73 (s, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.82 (t, J = 74.0 Hz, 1H), 2.28 (s, 3H), 1.74 (s, 3H).
166	N-(3-chloro-5-fluoro-phenyl)-1-[4-(difluoromethoxy)phenyl]-3,4-dimethyl-5-oxo-pyrazole-4-carboxamide LCMS: (ESI) m/z: 425.9 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.95 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 7.46-7.43 (m, 1H), 7.21 (d, J = 8.8 Hz, 2H), 6.98-6.96 (m, 1H), 6.82 (t, J = 74.0 Hz, 1H), 2.28 (s, 3H), 1.75 (s, 3H).
167	N-(3-chlorophenyl)-1-[4-(difluoromethoxy)phenyl]-3,4-dimethyl-5-oxo-pyrazole-4-carboxamide LCMS: (ESI) m/z: 408.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.96 (d, J = 9.2 Hz, 2H), 7.72 (t, J = 2.0 Hz, 1H), 7.46-7.44 (m, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 7.16-7.14 (m, 1H), 6.82 (t, J = 74.0 Hz, 1H), 2.29 (s, 3H), 1.75 (s, 3H).
168	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-5-(dimethylamino)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 451.2 [M+H]+; 1H NMR: (400 MHz, DMSO-d6) δ: 10.22(s, 1H), 7.99(s, 1H), 7.73(d, J= 7.2 Hz, 1H), 7.65-7.63(m, 2H), 7.44(t, J= 8.0 Hz, 1H), 7.33- 7.30(m, 2H), 7.31(t, J = 74.0 Hz, 1H), 7.26(d, J= 7.6 Hz ,1H), 2.70-2.65(m, 6H), 2.28(s, 3H), 1.96(t, J= 18.8 Hz, 3H).
169	(4R)-N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 438.3 [M+H]+;

	1H NMR: (400 MHz, MeOD-d4) δ: 7.97 (d, J = 9.2 Hz, 2H), 7.78 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.82 (t, J = 74.4 Hz, 1H), 2.30 (s, 3H), 1.90 (t, J = 18.4 Hz, 3H), 1.76 (s, 3H).
170	(4S)-N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 438.3 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 7.97 (d, J = 9.2 Hz, 2H), 7.78 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.82 (t, J = 74.4 Hz, 1H), 2.30 (s, 3H), 1.90 (t, J = 18.4 Hz, 3H), 1.76 (s, 3H).
171	5-amino-N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 423.2 [M+H]+; 1H NMR(400MHz, DMSO-d6) δ: 8.92(s, 1H), 7.91(s, 1H), 7.73(d, J= 8.4Hz, 1H), 7.62-7.59(m, 2H), 7.44(t, J= 7.6Hz, 1H), 7.31(d, J= 4.4Hz, 2H), 7.23(d, J= 7.6Hz, 1H), 7.34(t, J= 60.4Hz, 1H), 2.44(s, 3H), 1.97(t, J= 18.8Hz, 3H).
172	4-chloro-N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 480.0 [M+Na]+; 1H NMR (400MHz, CDCl3-d) δ: 8.82 (br s, 1H), 7.91 (d, J=9.2 Hz, 2H), 7.73 (s, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.21 (d, J=9.2 Hz, 2H), 6.52 (t, J=73.6 Hz, 1H), 2.47 (s, 3H), 1.93 (t, J=18.4 Hz, 3H).
173	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)phenyl)pyrimidine-5-carboxamide LCMS: (ESI) m/z 406.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 9.32 (s, 2H), 8.56-8.58 (m, 2H), 7.97 (s, 1H), 7.83 (d, J=8.00 Hz, 1H), 7.48 (t, J=7.6 Hz, 1H), 7.35 (d, J=7.2 Hz, 1H), 7.29 (d, J=8.8 Hz, 2H), 6.97 (t, J=73.6 Hz, 1H), 1.94 (t, J=18.4 Hz, 3H).
174	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 438.2 [M+H]+; 1H NMR: (400MHz, MeOD-d4) δ: 7.97 (d, J = 9.2 Hz, 2H), 7.78 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.82 (t, J = 74.4 Hz, 1H), 2.30 (s, 3H), 1.90 (t, J = 18.4 Hz, 3H), 1.76 (s, 3H).
175	N-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy)-3-(2-pyridyl)phenyl]-3-methyl-pyrazole-4-carboxamide LCMS: (ESI) m/z: 485.2[M+H]+; 1H NMR: (400MHz, MeOD-d4) δ: 8.87 (s, 1H), 8.71-8.69 (m, 1H), 8.13 (d, J = 3.2 Hz, 1H), 7.97 - 7.89 (m, 3H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.50 - 7.41 (m, 3H), 7.29 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 73.6 Hz, 1H), 2.56 (s, 3H), 1.93 (t, J = 18.4 Hz, 3H).
176	N-(3-(1,1-difluoroethyl)phenyl)-1-(2'-(difluoromethoxy)-[1,1':3',1''-terphenyl]-5'-yl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 560.3[M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.95 (s, 1H), 7.90 (s, 1H), 7.83 (s, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.68 - 7.61 (m, 4H), 7.55 - 7.47 (m, 4H), 7.47 - 7.38 (m, 3H), 7.28 (d, J = 7.6 Hz, 1H),5.90 (t, J = 73.2 Hz, 1H), 2.57 (s, 3H), 1.93 (t, J = 18.0 Hz, 3H).
177	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 499.3 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.67 (d, J=4.4 Hz, 1H), 7.82-7.96 (m, 4H), 7.72 (d, J=8.4 Hz, 1H), 7.62 (dd, J=2.4, 8.8 Hz, 1H), 7.43-7.52 (m, 3H), 7.30 (d, J=7.6 Hz, 1H), 6.94 (t, J=73.2 Hz 1H), 2.48 (d, J=19.8 Hz, 6H), 1.93 (t, J=18.0 Hz, 3H).
178	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide

	LCMS: (ESI) m/z: 498.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ :7.89 (s, 1H), 7.72 (d, J=7.6 Hz, 1H), 7.38-7.58 (m, 9H), 7.30 (d, J=8.0 Hz, 1H), 6.80 (t, J=73.6 Hz, 1H), 2.47 (d, J=13.6 Hz, 6H), 1.93 (t, J=18.4 Hz, 3H).
179	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 499.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.74 (s, 1H), 8.58 (d, J=4.4 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 7.71 (s, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.63-7.59 (m, 4H), 7.54 (t, J=8.8 Hz, 1H), 7.44-7.31 (m, 1H), 6.92 (t, J=73.2 Hz, 1H), 1.93 (d, J=16.4 Hz, 6H), 1.93 (t, J=18.4 Hz, 3H).
180	N-[3-(1,1-difluoroethyl)phenyl]-1-(4-methoxy-3-methyl-5-phenyl-phenyl)-3-methyl-5-oxo-4H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 478.3 [M+H]+; 1H NMR: (400 MHz, CDCl3-d) δ: 7.77(s, 1H), 7.58(d, J = 8.0 Hz, 1 H), 7.47(d, J = 7.2 Hz,2H), 7.36 - 7.30(m , 5 H), 7.23-7.21(m, 2 H), 3.32(s, 3 H), 2.49(s ,3 H), 2.27(s , 3 H), 1.90(t, J = 18.0 Hz, 3 H).
181	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-4-yl)phenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 485.2[M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.89 (s, 1H), 8.66 (d, J = 5.6 Hz, 2H), 7.95 - 7.90 (m, 3H), 7.75 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 6.0 Hz, 2H), 7.51 (d, J = 8.8 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 73.2 Hz, 1H), 2.56 (s, 3H), 1.93 (t, J = 18.0 Hz, 3H).
182	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 485.2 [M+H]+. 1H NMR (400 MHz, MeOD-d4) δ: 8.89 (s, 1H), 8.76 (d, J = 1.6 Hz, 1H), 8.63 - 8.56 (m, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.95 - 7.86 (m, 3H), 7.75 (d, J = 7.6 Hz, 1H), 7.58 - 7.50 (m, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.29 (d, J =8.4 Hz, 1H), 6.86 (t, J = 73.6 Hz, 1H), 2.57 (s, 3H), 1.93 (t, J = 18.0 Hz, 3H).
183	4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-1H-pyrazol-5-yl 4-(1-hydroxy-2-methylpropan-2-yl)piperazine-1-carboxylate LCMS: (ESI) m/z: 685.6 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.73 (s, 1H), 8.53 (dd, J = 1.2 Hz, 4.8 Hz, 1H), 8.05 - 8.02 (m, 2H), 7.99 (d, J = 2.4 Hz, 1H), 7.56 - 7.45 (m, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.44 - 7.38 (m, 2H), 7.34 - 7.28 (m, 1H), 6.73 (t, J = 74.0 Hz, 1H), 3.74 (br s, 2H), 3.58 - 3.42 (m, 4H), 3.21 - 2.83 (m, 4H), 2.33 (s, 3H), 1.91 (t, J = 18.0 Hz, 3H), 1.13 (s, 6H).
184	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3,5-dimethyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 422.0 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 7.91 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.40 - 7.30 (m, 3H), 6.96 (t, J = 74.0 Hz, 1H), 2.46 (s, 3H), 2.45 (s, 3H), 1.95 (t, J = 18.0 Hz, 3H).
185	4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1H-pyrazol-5-yl 4-(1-hydroxy-2-methylpropan-2-yl)piperazine-1-carboxylate LCMS: (ESI) m/z: 608.4 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.78 (d, J=8.8 Hz, 2H), 7.42~7.52 (m, 2H), 7.32 (s, 1H), 7.26 (d, J=8.0 Hz, 1H), 7.14 (d, J= 8.8 Hz, 2H), 6.78 (t, J= 74.4, 1H), 4.13 (s, 2H), 3.58 (s, 2H), 3.20 (s, 6H), 2.33 (s, 3H), 1.93 (t, J=18.4 Hz, 3H) ,1.29 (s, 6H).
186	N-(3-(1,1-difluoroethyl)phenyl)-1-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 484.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.87 (s, 1H)), 7.94 (s, 1H), 7.87 (d, J = 2.8 Hz, 1H),

	7.83 (dd, J = 2.8, 8.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.64 - 7.58 (m, 2H), 7.54 - 7.43 (m, 5H), 7.32 (d, J = 7.8 Hz, 1H), 6.973 (t, J = 68.0, 1H), 2.60 (s, 3H), 1.97 (t, J = 18.4 Hz, 3H).
187	4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-1H-pyrazol-5-yl 4-(2-hydroxyethyl)piperazine-1-carboxylate LCMS: (ESI) m/z: 657.6 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.74 (d, J = 1.6 Hz, 1H), 8.53 (d, J = 1.6 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.60 - 7.55 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.40 - 7.30 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 6.74 (t, J = 73.6 Hz, 1H), 3.72 - 3.59 (m, 6H), 3.30 - 2.40 (m, 6H), 2.82 (s, 3H), 1.91 (t, J = 18.4 Hz, 3H).
188	4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5-yl [1,4'-bipiperidine]-1'-carboxylate LCMS: (ESI) m/z: 582.4 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.54-7.58 (m, 2H), 7.43 (t, J=7.6 Hz, 1H), 7.39-7.41 (m, 1H), 7.31 (s, 1H), 7.26 (d, J=8.0 Hz, 1H), 6.92-6.95 (m, 2H), 4.20 (d, J=12.4 Hz, 2H), 3.80 (s, 3H), 3.02-3.14 (m, 5H), 2.81 (t, J=12.0 Hz, 2H), 2.30 (s, 3H), 1.93 (t, J=11.2 Hz, 3H) 1.76-1.83 (m, 6H), 1.60 (s, 2H), 1.43 (d, J=8.8 Hz, 2H).
189	4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1H-pyrazol-5-yl [1,4'-bipiperidine]-1'-carboxylate LCMS: (ESI) m/z: 618.5 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.77-7.80 (m, 2H), 7.49 (t, J=7.6 Hz, 1H), 7.41-7.423(m, 1H), 7.33 (s, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.15 (d, J=9.2 Hz , 2H), 6.79 (t, J=74.0 Hz, 1H), 4.20 (d, J=14.4 Hz, 2H), 3.04-3.20 (m, 5H), 3.14 (t, J=12.8 Hz, 2H), 2.33 (s, 3H), 1.93 (t, J=18.4 Hz, 3H), 1.78-1.89(m, 6H), 1.63 (s, 2H), 1.48 (d, J=9.2 Hz, 2H).
190	4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-3-methyl-1H-pyrazol-5-yl [1,4'-bipiperidine]-1'-carboxylate LCMS: (ESI) m/z: 695.4 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.74 (d, J = 1.6 Hz, 1H), 8.54 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.95 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.42 - 7.40 (m, 1H), 7.33 - 7.32 (m, 2H), 7.31 (d, J = 3.6 Hz, 1H), 6.74 (t, J = 74.0 Hz, 1H), 4.20 (d, J = 13.2 Hz, 2H), 2.87 - 2.80 (m, 4H), 2.33 (s, 3H), 1.91 (t, J = 18.4 Hz, 3H), 1.81 - 1.80 (m, 2H), 1.80 - 1.78 (m, 4H), 1.70 - 1.69 (m, 2H), 1.69 - 1.29 (m, 5H).
191	4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1H-pyrazol-5-yl 4-(2-hydroxyethyl)piperazine-1-carboxylate LCMS: (ESI) m/z: 580.5 [M+H]+; 1H NMR (400MHz, MeOD-d4) δ : 7.74 (d, J = 8.8 Hz, 2H), 7.52 - 7.46 (m, 1H), 7.45 - 7.40 (m, 1H), 7.32 (s, 1H), 7.26 (br d, J = 8.4 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 6.97 (s, 1H), 6.79 (s, 1H), 6.60 (s, 1H), 3.83 - 3.75 (m, 2H), 3.75 - 3.45 (m, 4H), 3.18 - 2.87 (m, 6H), 2.32 (s, 3H), 1.98 - 1.87 (m, 3H).
192	N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 476.0 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.90 (s, 1H)), 7.75 - 7.73 (d, J = 8 Hz, 1H), 7.57-7.55 (d, J = 8.8 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.37 -7.35 (d, J = 8.8 Hz, 3H), 6.991 (t, J = 73.2, 1H), 2.428 (s, 3H), 1.953 (t, J = 18.4 Hz, 3H).
193	5-acetyl-N-(3-(1,1-difluoroethyl)phenyl)-1-(4-(difluoromethoxy)phenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 450.3 [M+H]+; 1H NMR: (400 MHz, CDCl3-d) δ: 9.66 (br s, 1H), 7.83 (s, 1H), 7.72 (br d, J =8.2 Hz, 1H), 7.48 - 7.33 (m, 3H), 7.27 (s, 3H), 6.79 - 6.31 (m, 1H), 2.59 (s, 3H), 2.16 (s, 3H), 1.91 (t, J = 18.2 Hz, 3H).
194	N-[3-(1,1-difluoroethyl)phenyl]-1-[4-(difluoromethoxy) phenyl]-5-(hydroxymethyl)-3-methyl-pyrazole-4-carboxamide LCMS: (ESI) m/z: 438.1 [M+H]+;

	1H NMR: (400 MHz, CDCl3-d) δ: 8.23 (br s, 1H), 7.73 - 7.63 (m, 2H), 7.49 - 7.34 (m, 3H), 7.27 (s, 3H), 6.75 - 6.30 (m, 1H), 4.66 (br d, J = 4.4 Hz, 2H), 4.31 (br s, 1H), 2.58 (s, 3H), 2.00 - 1.83 (m, 4H).
195	1-(4-(difluoromethoxy)phenyl)-3-methyl-4-(1-((4-(methylsulfonyl)phenyl)amino)-1H-1,2,3-triazol-4-yl)-1H-pyrazol-5(4H)-one LCMS: (ESI) m/z: 477.3 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.77 (d, J=8.8 Hz, 2H), 7.52 (s, 1H), 7.40 - 7.24 (m, 4H), 7.08 (d, J=8.0 Hz, 1H), 7.11 - 6.67 (t, J=74.0 Hz, 1H), 2.35 (s, 3H), 2.00 (s, 3H).
213	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-4-methyloxazole-5-carboxamide LCMS: (ESI) m/z: 486.3 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.72 (d, J = 4.8 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.34 (dd, J = 2.0, 8.4 Hz, 1H), 8.00 (dt, J = 2.0, 7.6 Hz, 1H), 7.93 (s, 1H), 7.86 - 7.78 (m, 2H), 7.54 - 7.48 (m, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 78.0 Hz, 1H), 6.99 (t, J = 73.2 Hz, 1H), 2.57 (s, 3H), 1.93 (t, J = 18.4 Hz, 3H)
214	2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-4-methyloxazole-5-carboxamide LCMS: (ESI) m/z: 500.4 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.73 (d, J = 4.8 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.35 (dd, J = 2.0, 8.4 Hz, 1H), 8.03 (dt, J = 1.6, 7.6 Hz, 1H), 7.91 - 7.80 (m, 3H), 7.56 - 7.49 (m, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.00 (t, J = 73.2, 1H), 2.57 (s, 3H), 2.15 - 2.11 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H)
215	2-(4-(difluoromethoxy)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-5-methyl-1H-imidazole-4-carboxamide LCMS: (ESI) m/z: 422.0 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 8.01 - 7.90 (m, 3H), 7.75 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.29 - 7.16 (m, 3H), 6.89 (t, J = 73.6 Hz, 1H), 2.61 (s, 3H), 2.25 - 2.10 (m, 2H), 0.99 (t, J = 7.6 Hz, 1H).
216	5-[4-(difluoromethoxy)phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-2-methyl-1H-pyrrole-3-carboxamide LCMS: (ESI) m/z: 421.0 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 7.88 (s, 1H), 7.74 (dd, J = 8.0, 1.2 Hz, 1H), 7.65 - 7.61 (m, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.98 (s, 1H), 6.81 (t, J = 74.4 Hz, 1H), 2.58 (s, 3H), 2.19 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).
217	5-[4-(difluoromethoxy)-3-phenyl-phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-2-methyl-1H-pyrrole-3-carboxamide LCMS: (ESI) m/z: 497.2 [M+H]+; 1H NMR: (400 MHz, MeOD-d4) δ: 7.88 (s, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.63 (dd, J = 8.4, 2.4 Hz, 1H), 7.56 -7.53 (m, 2H), 7.47 -7.42 (m, 2H), 7.41 -7.36 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 7.6, 0.8 Hz, 1H), 7.05 (s, 1H), 6.64 (t, J = 74.4 Hz, 1H), 2.58 (s, 3H), 2.19 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).
218	2-(6-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoropropyl)phenyl)-5-methyl-1H-imidazole-4-carboxamide LCMS: (ESI) m/z: 498.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.06 (d, J=2.4 Hz, 1H), 7.96 (dd, J=2.4, 8.4 Hz, 1H), 7.92 (s, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.55-7.57 (m, 2H), 7.37-7.48 (m, 5H), 7.22 (d, J=8.0 Hz, 1H), 6.76 (t, J=74.0 Hz,1H), 2.63 (s, 3H), 2.11-2.25 (m, 2H), 0.98 (t, J=7.6 Hz, 3H).
219	N-(3-(1,1-difluoroethyl)phenyl)-6-methyl-2-(5-methyl-[1,1'-biphenyl]-3-yl)pyrimidine-4-carboxamide LCMS: (ESI) m/z: 444.2 [M+H]+; 1H NMR (400 MHz, CDCl3-d) δ: 10.09 (br s, 1H), 8.53 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 7.96 (s, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.73 (d, J=7.6 Hz, 2H), 7.61 (s, 1H), 7.53 - 7.47 (m, 3H), 7.42 (d, J=7.6 Hz, 1H), 7.36 (d, J=8.4 Hz, 1H), 2.76 (s, 3H), 2.58 (s, 3H), 1.98 (t, J=18.4 Hz, 3H).

220	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-5-methyloxazole-4-carboxamide LCMS: (ESI) m/z: 486.3 [M+H]+; 1H NMR (400 MHz, CDCl3-d) δ: 8.92 (s, 1H), 8.84 - 8.79 (m, 1H), 8.71 - 8.66 (m, 1H), 8.14 (d, J = 2.2 Hz, 1H), 8.10 (dd, J = 2.2, 8.6 Hz, 1H), 7.92 (td, J = 2.0, 7.8 Hz, 1H), 7.87 (s, 1H), 7.82 (br d, J = 8.0 Hz, 1H), 7.46 - 7.40 (m, 3H), 7.29 (d, J = 7.8 Hz, 1H), 6.71 - 6.33 (m, 1H), 2.81 (s, 3H), 1.96 (t, J = 18.2 Hz, 3H).
221	2-(4-(difluoromethoxy)-3-(pyridin-3-yl)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-5-methyloxazole-4-carboxamide LCMS: (ESI) m/z: 500.3 [M+H]+; 1H NMR (400 MHz, CDCl3-d) δ: 8.91 (s, 1H), 8.87 - 8.77 (m, 1H), 8.74 - 8.64 (m, 1H), 8.15 (d, J = 2.2 Hz, 1H), 8.10 (dd, J = 2.2, 8.6 Hz, 1H), 7.92 (br d, J = 8.0 Hz, 1H), 7.83 (br d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.46 - 7.40 (m, 3H), 7.24 (s, 1H), 6.71 - 6.34 (m, 1H), 2.81 (s, 3H), 2.19 (dt, J = 7.6, 16.1 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).
222	5-(5-(difluoromethoxy)pyridin-2-yl)-N-(3-(1,1-difluoropropyl)phenyl)-2-methyl-1H-pyrrole-3-carboxamide LCMS: (ESI) m/z: 421.9 [M+H]+; 1H NMR (400 MHz, CDCl3-d) δ: 9.50 (br s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.57 -7.53 (m, 2H), 7.51 -7.47 (m, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.56 (t, J = 72.8 Hz, 1H), 2.68 (s, 3H), 2.25-2.10 (m, 2H), 1.01 (t, J = 7.6 Hz, 3H).
223	5-(5-(difluoromethoxy)-6-phenylpyridin-2-yl)-N-(3-(1,1-difluoropropyl)phenyl)-2-methyl-1H-pyrrole-3-carboxamide LCMS: (ESI) m/z: 498.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.96 -7.92 (m, 2H), 7.89 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 0.8 Hz, 2H), 7.51 -7.40 (m, 4H), 7.30 (s, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.76 (t, J = 73.6 Hz, 1H), 2.60 (s, 3H), 2.27-2.12 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H).
224	1-(5-(4-chlorobenzyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoroethyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 588.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.91 (s, 1H), 7.63 (d, J=7.2 Hz, 3H), 7.54 (d, J=16.4 Hz, 2H), 7.34-7.48 (m, 4H), 7.29 (s, 4H), 7.22 (d, J=8.0 Hz, 1H), 4.09 (s, 2H), 3.21 (s, 3H), 2.56 (s, 3H), 1.92 (t, J=18.4 Hz, 3H).
225	N-(3-(1,1-difluoropropyl)phenyl)-1-(6-methoxy-5-propyl-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 520.3 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.87 (s, 1H), 7.66 - 7.61 (m, 3H), 7.48 - 7.44 (m, 4H), 7.43 - 7.37 (m, 2H), 7.20 (d, J=8.0 Hz, 1H), 3.36 (s, 3H), 2.75 (t, J=8.0 Hz, 2H), 2.62 (s, 3H), 2.24 - 2.11 (m, 2H), 1.79 - 1.70 (m, 2H), 1.05 (t, J=7.6 Hz, 3H), 0.98 (t, J=7.6 Hz, 3H).
226	N-(3-(1,1-difluoropropyl)phenyl)-6-methyl-2-(5-methyl-[1,1'-biphenyl]-3-yl)pyrimidine-4-carboxamide LCMS: (ESI) m/z: 458.2 [M+H]+; 1H NMR (400 MHz, CDCl3-d) δ: 10.08 (s, 1H), 8.53 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 7.89 (d, J=10.0 Hz, 2H), 7.73 (d, J=7.6 Hz, 2H), 7.61 (s, 1H), 7.53 - 7.47 (m, 3H), 7.42 (d, J=7.6 Hz, 1H), 7.32 (d, J=8.0 Hz, 1H), 2.76 (s, 3H), 2.58 (s, 3H), 2.27 - 2.14 (m, 2H), 1.04 (t, J=7.6 Hz, 3H).
227	2-(5-(difluoromethoxy)pyridin-2-yl)-N-(3-(1,1-difluoropropyl)phenyl)-5-methyl-1H-imidazole-4-carboxamide LCMS: (ESI) m/z: 423.1 [M+H]+; 1H NMR (MeOD-d4, 400 MHz) δ: 8.49 (s, 1H), 8.18 (dd, J=8.4, 1.2 Hz, 1H), 7.95 (s, 1H), 7.79 (d, J=8.0 Hz, 1H), 7.71 (d, J=8.8 Hz, 1H), 7.44 (t, J=7.6 Hz, 1H), 7.23 (d, J=7.6 Hz, 1H), 6.98 (t, J=72.8 Hz, 1H), 2.64 (s, 3H), 2.12-2.30 (m, 2H), 0.99 (t, J=7.2 Hz, 3H).
228	N-(3-(1,1-difluoroethyl)phenyl)-1-(5-(4-hydroxybenzyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 570.3 [M+H]+;

	1H NMR (400Hz, MeOD-d4) δ: 7.90(s ,1H), 7.61(d, J= 6.8 Hz, 3H), 7.46-7.38(m, 6H),7.36-7.10 (m, 1H), 7.09(d, J= 8.4 Hz, 2H), 6.71(d, J=8.4 Hz, 2H), 3.99(s, 2H), 3.20(s, 3H), 2.57(s, 3H), 1.91(t, J= 16.4 Hz, 3H).
229	N-(3-(1,1-difluoropropyl)phenyl)-5-fluoro-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 404.2 [M+H]+; 1H NMR (400 MHz, CDCl3-d) δ: 7.74 - 7.65 (m, 2H), 7.53 (br d, J = 8.4 Hz, 3H), 7.42 (br t, J = 7.6 Hz, 1H), 7.26 - 7.22 (m, 1H), 7.06 - 6.98 (m, 2H), 3.92 - 3.81 (m, 3H), 2.58 (s, 3H), 2.17 (dt, J = 8.0, 16.0 Hz, 2H), 1.01 (br t, J = 7.6 Hz, 3H).
230	5-acetyl-N-(3-(1,1-difluoropropyl)phenyl)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 428.1 [M+H]+; 1H NMR (400 MHz, CDCl3-d) δ: 9.94 (s, 1H), 7.83 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.64 (s, 3H), 2.26 -2.16 (m, 2H), 2.15 (s, 3H), 1.02 (t, J = 7.6 Hz, 3H).
231	5-chloro-N-(3-(1,1-difluoropropyl)phenyl)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 419.9 [M+H]+; 1H NMR (MeOD-d4, 400 MHz) δ: 7.85 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.43-7.45 (m, 3H), 7.27 (d, J = 8.0 Hz, 1H), 7.08-7.09 (m, 2H), 3.88 (s, 3H), 2.45 (s, 3H), 2.19 (m, 2H), 0.99 (t, J=7.6 Hz, 3H).
232	4-acetyl-N-(3-(1,1-difluoropropyl)phenyl)-5-(4-methoxyphenyl)-1H-pyrazole-3-carboxamide LCMS: (ESI) m/z: 414.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.95(s, 1H), 7.79 - 7.81 (d, J= 8.0 Hz, 1H), 7.44 - 7.49 (m, 3H), 7.26 - 7.28 (d, J= 8.0 Hz, 1H), 7.06 - 7.08 (d, J= 8.0 Hz, 2H), 3.86(s, 3H), 2.31(s, 3H), 2.09 - 2.22 (m, 2H), 0.97 - 1.00 (t, J= 7.6 Hz, 3H).
233	4-bromo-N-(4-(1,1-difluoropropyl)phenyl)-5-(4-methoxyphenyl)-1H-pyrazole-3-carboxamide LCMS: (ESI) m/z: 450.1[M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.95 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 2.15-2.25 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H).
234	methyl 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate LCMS: (ESI) m/z: 444.2 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ: 10.48 (s, 1H), 7.91 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 9.2 Hz, 2H), 3.83 (s, 3H), 3.64 (s, 3H), 2.33 (s, 3H), 2.14-2.25 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H).
235	N-(3-(1,1-difluoropropyl)phenyl)-4-hydroxy-5-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxamide LCMS: (ESI) m/z: 401.1 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ: 10.96 - 10.82 (bs, 1H), 10.19 (s, 1H), 7.78(s, 1H), 7.73 - 7.71 (m, 2H), 7.58 - 7.43 (m, 1H), 7.43 - 7.35 (m, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 3.70 (s, 3H), 2.52(s, 3H), 2.22 - 2.13 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H).
236	1-(5-(4-chlorobenzyl)-6-methoxy-[1,1'-biphenyl]-3-yl)-N-(3-(1,1-difluoropropyl)phenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-4-carboxamide LCMS: (ESI) m/z: 602.3 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 7.87 (s, 1H), 7.63 (d, J=7.2 Hz, 3H), 7.39-7.48 (m, 6H), 7.30 (s, 4H), 7.20 (d, J=7.6 Hz, 1H), 4.10 (s, 2H), 3.22 (s, 3H), 2.60 (s, 3H), 2.11-2.23 (m, 2H), 0.98 (t, J=7.2 Hz, 3H).
247	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-methoxyphenyl)-5-methylpyrimidine-4-carboxamide LCMS: (ESI) m/z: 384.2 [M+H]+;

	1H NMR (400 MHz, CDCl3-d) δ: 10.27 (br s, 1H), 8.79 (s, 1H), 8.41 (dd, J=7.2 , 2.0 Hz, 2H), 7.93 (s, 1H), 7.86(s, 1 H), 7.49 (d, J=8.0 Hz, 1H), 7.33 (d, J=7.6 Hz, 1H), 7.07 (dd, J=7.2 , 2.4 Hz, 2H), 3.92 (s, 3 H), 2.78 (s, 3H), 1.99(t, J=18.4 Hz, 3H).
248	4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxyphenyl)-5-methyl-1H-imidazole 3-oxide LCMS: (ESI) m/z: 402.1 [M+H]+; 1H NMR (400 MHz, DMSO-d6) 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).
249	4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-3-(3-methylpyridin-2-yl)phenyl)-5-methyl-1H-imidazole 3-oxide LCMS: (ESI) m/z: 493.0 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ: 12.88 (s, 1H), 12.45(s, 1H),7.74 (d, J = 7.2 Hz, 1H), 7.65 (dd, J = 0.08, 4.8 Hz, 1H), 7.50 (s, 1H), 7.10 (s, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.63 (t, J = 8.0 Hz, 1H), 6.57 - 6.49 (m, 2H), 6.39 (d, J = 7.8 Hz, 1H), 3.01 (s, 3H), 1.76 (s, 3H), 1.45 - 1.34 (m, 2H), 1.29 (s, 3H), 0.10 (t, J = 7.2 Hz, 3H).
250	4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxyphenyl)-5-methyloxazole 3-oxide LCMS: (ESI) m/z: 403.0 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ: 12.81 (s, 1H), 8.42 - 8.39 (m, 2H), 7.94 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 9.2 Hz, 2H), 3.87 (s, 3H), 2.74 (s, 3H), 2.28 - 2.18 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).
251	4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-3-(3-methylpyridin-2-yl)phenyl)-5-methyloxazole 3-oxide LCMS: (ESI) m/z: 494.2 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ: 12.75 (s, 1H), 8.49 - 8.44 (m, 2H), 8.35 (d, J = 2.4 Hz, 1H), 7.92 (s, 1H), 7.75 - 7.70 (m, 2H), 7.50 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 4.8, 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 2.74 (s, 3H), 2.27 - 2.17 (m, 2H), 2.10 (s, 3H), 0.92 (t, J = 7.2 Hz, 3H).
253	5-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxyphenyl)-4-methyl-2H-1,2,3-triazole 1-oxide LCMS: (ESI) m/z: 403.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.21 - 8.15 (m, 1H), 8.10 - 8.03 (m, 2H), 8.00 - 7.93 (m, 1H), 7.75 - 7.68 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.43 - 7.35 (m, 2H), 4.5(s, 3H), 2.89 (s, 3H), 2.51 - 2.38 (m, 2H), 1.26 - 1.21 (m, 3H).
257	5'-(difluoromethoxy)-N-(3-(1,1-difluoropropyl)phenyl)-6-methyl-[2,2'-bipyridine]-4-carboxamide LCMS: (ESI) m/z: 434.0 [M+H]+; 1H NMR (MeOD-d4, 400 MHz) δ: 8.58 (s, 1H), 8.54 (d, J=2.8 Hz, 1H), 8.47 (d, J=8.8 Hz, 1H), 7.91-7.97 (m, 1H), 7.84 (d, J=8.0 Hz, 1H), 7.68-7.77 (m, 2H), 7.47 (t, J=8.0 Hz, 1H), 7.29 (d, J=7.6 Hz, 1H), 7.01 (t, J=73.2 Hz, 1H), 2.69 (s, 3H), 2.11-2.28 (m, 2H), 0.99 (t, J=7.2 Hz, 3H).
258	N-(3-(1,1-difluoroethyl)phenyl)-2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-5-methyloxazole-4-carboxamide LCMS: (ESI) m/z: 486.0 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.71 - 8.70 (m, 1H), 8.44 (d, J = 2.0 Hz, 1H), 8.20 (dd, J = 2.4, 8.8 Hz, 1H), 7.99 (s, 1H), 7.96 (td, J = 1.6, 7.6 Hz, 1H), 7.83 - 7.80 (m, 2H), 7.49 - 7.43 (m, 3H), 7.31 (dd, J = 0.8, 7.6 Hz 1H), 6.97 (t, J = 73.2 Hz, 3H), 2.76 (s, 3H), 1.94 (t, J = 18.0 Hz, 3H).
259	2-(4-(difluoromethoxy)-3-(pyridin-2-yl)phenyl)-N-(3-(1,1-difluoropropyl)phenyl)-5-methyloxazole-4-carboxamide LCMS: (ESI) m/z: 500.2 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.71 - 8.70 (m, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 2.4, 8.8 Hz, 1H), 7.96 - 7.95 (m, 2H), 7.83 - 7.81 (m, 2H), 7.50 - 7.45 (m, 3H),

	7.27 (d, J = 6.8 Hz, 1H), 6.97 (t, J = 73.2 Hz, 1H), 2.79 (s, 3H), 2.27 - 2.13 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).
260	2-(5-(difluoromethoxy)-6-phenylpyridin-2-yl)-N-(3-(1,1-difluoropropyl)phenyl)-5-methyl-1H-imidazole-4-carboxamide LCMS: (ESI) m/z: 499.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.18 (d, J = 8.8 Hz, 1H), 7.99 -7.95 (m, 3H), 7.85 - 7.78 (m, 2H), 7.52 -7.42 (m, 4H), 7.24 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 72.8 Hz, 1H),2.65 (s, 3H), 2.28 -2.14 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H).
272	N-(3-(1,1-difluoropropyl)phenyl)-6-methoxy-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide LCMS: (ESI) m/z: 387.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ:7.92 (s, 1H), 7.72 (d, J = 2.8 Hz, 2H), 7.55 (d, J = 9.0 Hz, 1H), 7.43 (s, 1H), 7.37 (dd, J = 2.8, 9.0 Hz, 1H), 7.27 - 7.18 (m, 1H), 3.92 (s, 3H), 2.88 (s, 3H), 2.13-2.27 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H).
273	N-(3-(1,1-difluoropropyl)phenyl)-7-methoxy-2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxamide LCMS: (ESI) m/z: 387.1 [M+H]+; 1H NMR (400 MHz, MeOD-d4) δ: 8.20 (d, J = 9.0 Hz, 1H), 7.90 (s, 1H), 7.70 (br d, J = 8.3 Hz, 1H), 7.46 - 7.39 (m, 1H), 7.21 (br d, J = 7.8 Hz, 1H), 7.12 - 7.01 (m, 1H), 7.00 - 6.90 (m, 1H), 3.92 (s, 3H), 2.87 (s, 3H), 2.26 - 2.14 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).
275	N-(3-(1,1-difluoropropyl)phenyl)-3-hydroxy-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)piperidine-4-carboxamide LCMS: (ESI) m/z: 525.4 [M+H]+; 1H NMR (400 MHz, CDCl3-d) δ: 9.22 (s, 0.6H), 8.56 (s, 0.4H), 7.69 - 7.50 (m, 2H), 7.44 - 7.30 (m, 3H), 7.17 - 7.11 (m, 3H), 6.97 - 6.95 (m, 2H), 6.86 - 6.80 (m, 2H), 4.04 (s, 0.6H), 3.88 - 3.78 (m, 7H), 3.64-3.60 (m, 0.4H), 3.34 (s, 0.6H), 3.13 - 3.09 (m, 0.6H), 3.03-3.01(m, 0.4), 3.00 - 2.90 (m, 1H), 2.83 - 2.80 (m, 0.4H), 2.62 - 2.58 (m, 0.6H), 2.46 - 2.39 (m, 0.4H), 2.19 - 2.01 (m, 5.4H), 1.93 - 1.86 (m, 0.6H), 0.98 - 0.93 (m, 3H).

EXAMPLE 2

Biological activity of compounds of the invention

ACSS2 cell-free activity assay (Cell-free IC_{50})

[001436] The assay is based on a coupling reaction with Pyrophosphatase**:** ACSS2 is converting ATP+CoA+Acetate => 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).

Cell-free IC_{50} determination:

[001437] 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 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. IC_{50} values were calculated using non-linear regression curve fit with 0% and 100% constrains (CDD Vault, Collaborative Drug Discovery, Inc.).

Results:

[001438] The results are presented in Table 2 below:

Compound No.	ACSS2 Biochemical IC50
100	+
101	++
102	+
103	+
104	+
105	+
106	+
107	+
108	+
109	++
110	++
111	+
112	++
113	+
114	+
115	+
116	+
117	+
118	+
119	+
120	+
121	++
122	+++
123	+
124	+
125	+
126	+
127	+
128	++
129	++
130	++
131	+
132	+
133	+
134	+
135	++
136	++
137	++
138	+
139	+
140	+

141	+
142	+
143	+
144	+
145	++
146	+
147	++
148	+
149	+
150	+
151	+
152	+
153	+
154	+
155	+
156	+
157	+
158	+
159	++
160	+++
161	+++
162	++
163	+++
164	+
165	+
166	+
167	+
168	++
169	+
170	+
171	+
172	++
173	+
174	+
175	++
176	++
177	++
178	++
179	++
180	++
181	++
182	++
183	+
184	+
185	+
186	++
187	+

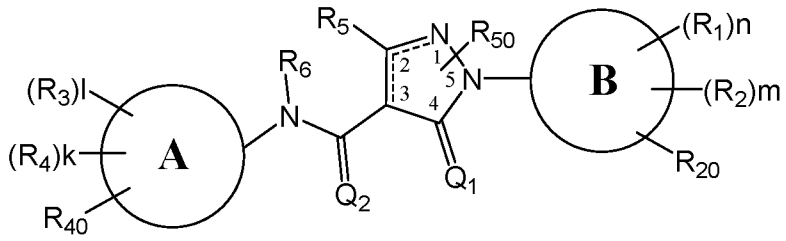
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190	++
191	++
192	++
193	+
194	++
195	+
196	++
197	+
198	+
199	++
200	+
201	+
202	++
203	+
204	+++
205	+++
206	+++
207	+++
208	+++
209	+++
213	+
214	+
215	+
216	+
217	+
218	+
219	+
220	+
221	+
222	+
223	+
224	++
225	++
226	+
227	+
228	++
229	++
230	+
231	+
232	+
233	+
234	+
235	+
236	++
237	+

247	++
248	+++
249	+++
250	+
251	+
253	+
254	+
255	+
256	+
257	+
258	+
259	+
260	+
261	+
262	+
263	+
264	+
265	+
266	+
267	+
268	+
269	+
270	+
271	++
272	++
273	++
274	+++
275	+
276	+
277	+++
278	+
279	+

(+) IC_{50} >100nM
(++) IC_{50} 1-100nM
(+++) IC_{50} <1nM

WHAT IS CLAIMED:

1. A compound represented by the structure of formula (I):



(I)

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 C_3-C_{10} cycloalkyl (e.g. cyclohexyl) or a single or fused C_3-C_{10} 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);

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. $C(O)O-CH_3$, $C(O)O-CH(CH_3)_2$, $C(O)O-CH_2CH_3$), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., $C(O)-CH_3$, $C(O)-CH_2CH_3$, $C(O)-CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)-CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl

(e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ 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);

$\mathbf{R_3}$, $\mathbf{R_4}$ and $\mathbf{R_{40}}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), R_8-$C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_5}$ is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, iso-propyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), $C(=CH_2)\text{-}R_{10}$ (e.g., $C(=CH_2)$-C(O)-OCH_3, $C(=CH_2)$-CN) substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

$\mathbf{R_{50}}$ is H, F, Cl, Br, I, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, propyl, iso-propyl, benzyl), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)\text{-}CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), substituted or unsubstituted benzyl, (wherein substitutions include: F, Cl, Br, I, C_1-

C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

wherein R_{50} is attached either to N_1 or to C_3 and if R_{50} is attached to N_1 than N_1-C_2 is a single bond and C_2-C_3 is a double bond, and if R_{50} is attached to C_3 than N_1-C_2 is a double bond and C_2-C_3 is a single bond; and wherein if R_{50} is H then neither one of R_1, R_2 or R_{20} is H, and n and m are not 0;

R_6 is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

R_8 is $[CH_2]_p$

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

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

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

R_{10} and **R_{11}** are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$; or **R_{10}** and **R_{11}** are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

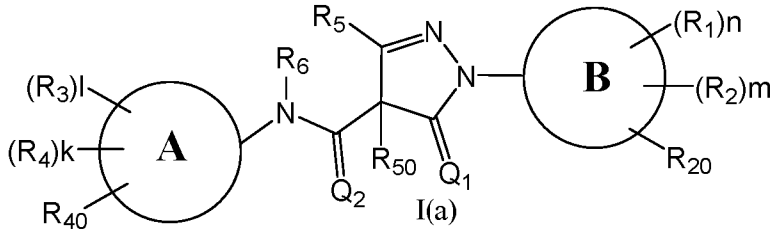
R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

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

Q_1 and **Q_2** are each independently S, O, N-OH, CH_2, $C(R)_2$ or N-OMe;

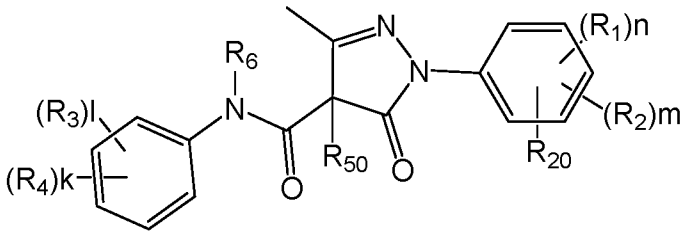
or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

2. The compound of claim 1, represented by the structure of formula **I(a)**:



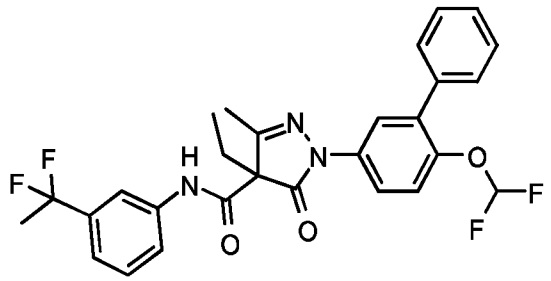
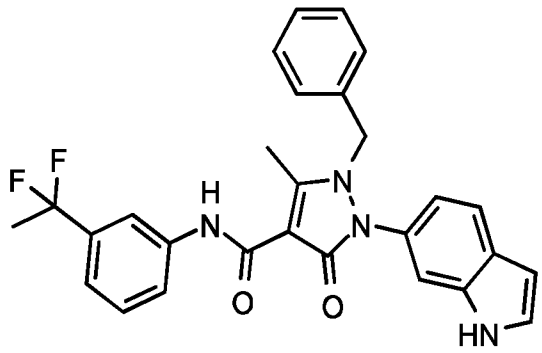
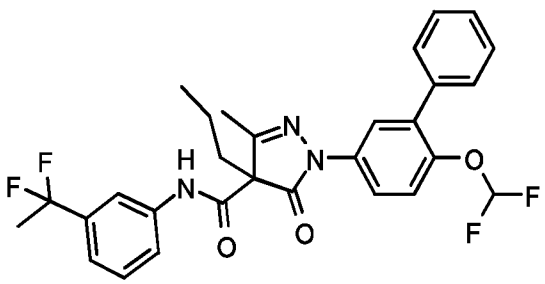
I(a)

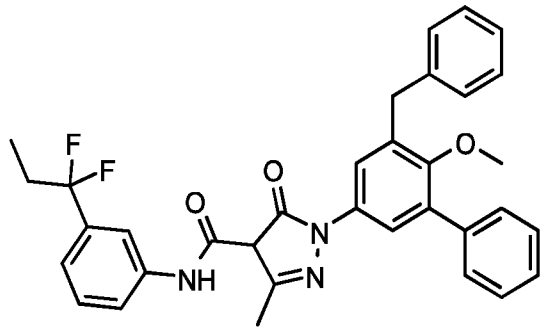
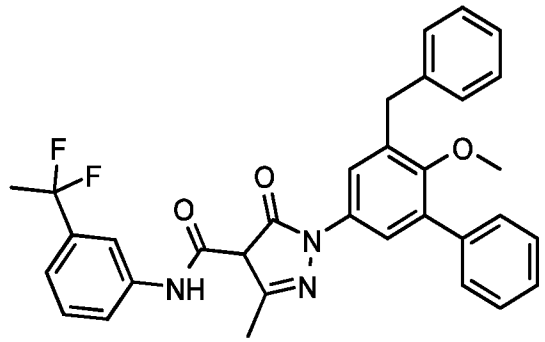
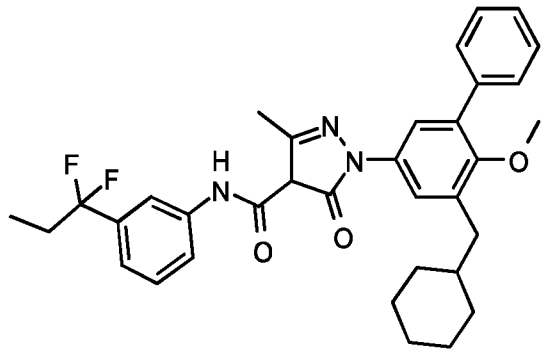
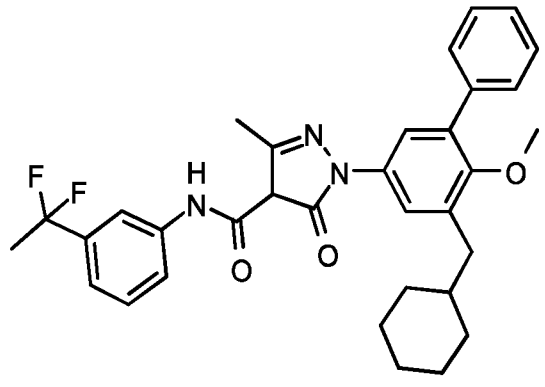
3. The compound of claim 1 or 2, represented by the structure of formula **I(b)**:

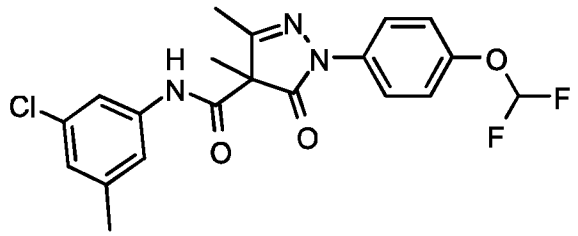
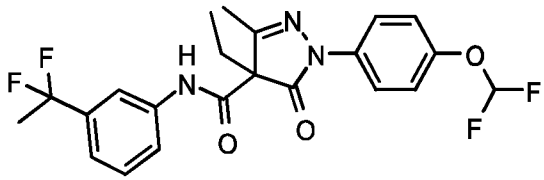
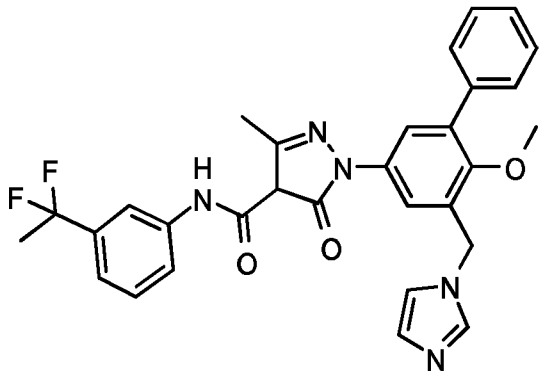
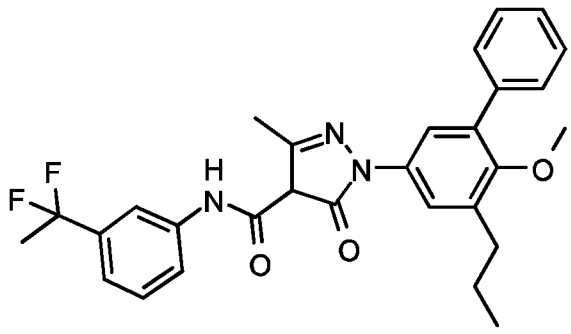


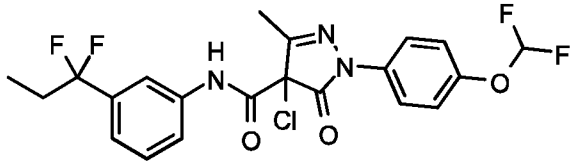
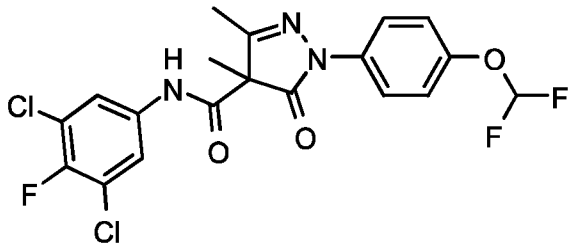
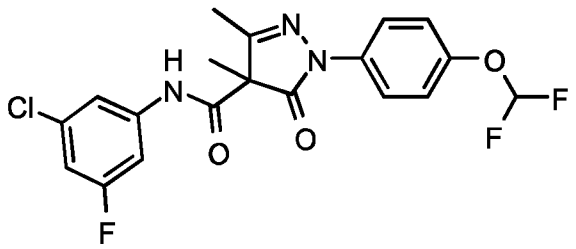
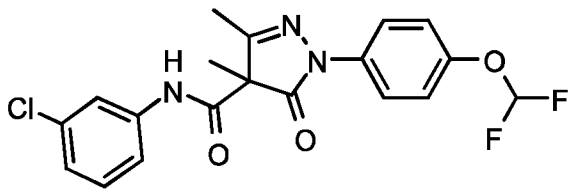
I(b).

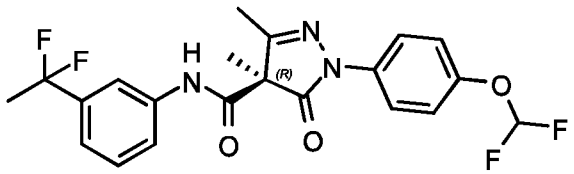
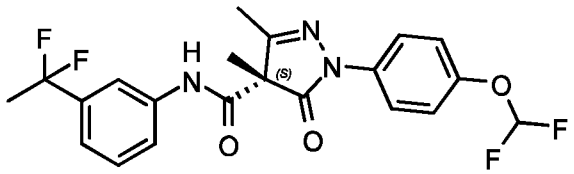
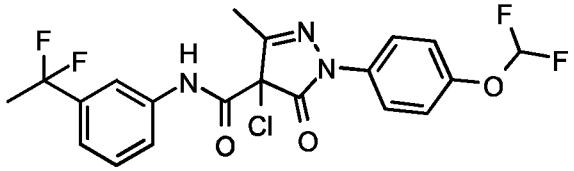
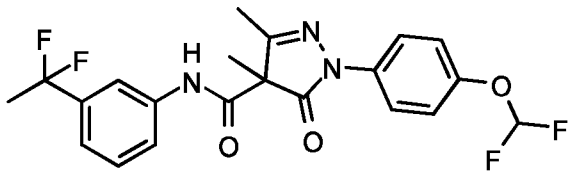
4. The compound of claim 1, selected from the following:

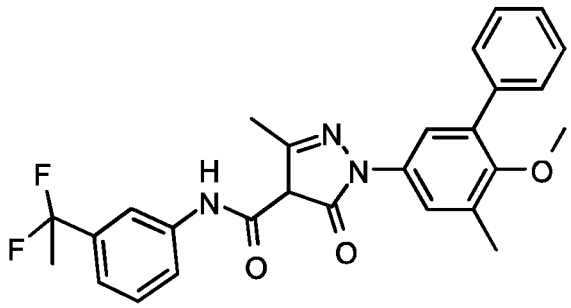
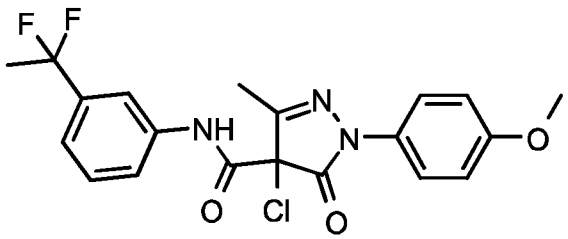
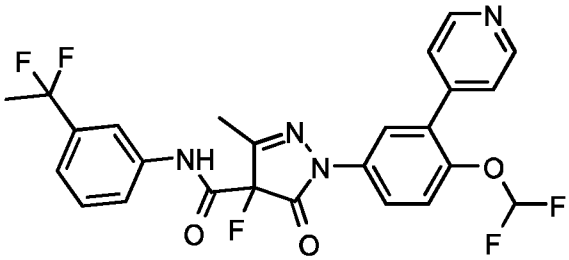
Compound Number	Compound Structure
100	
108	
111	

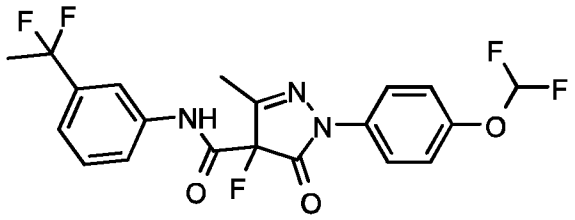
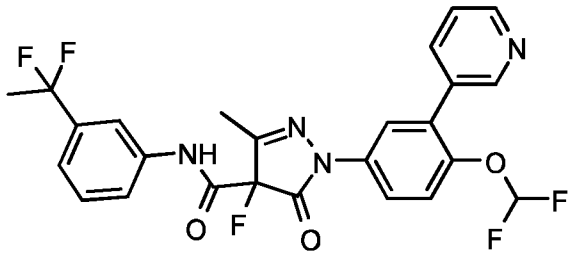
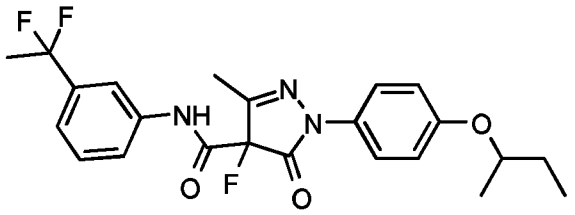
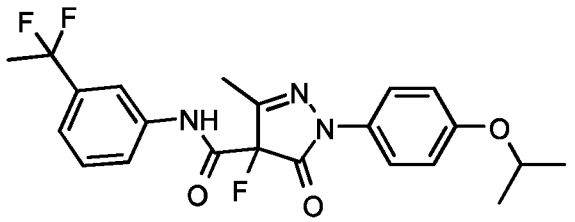
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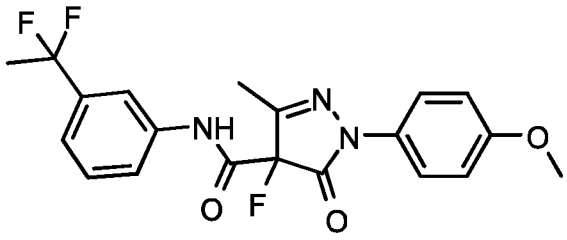
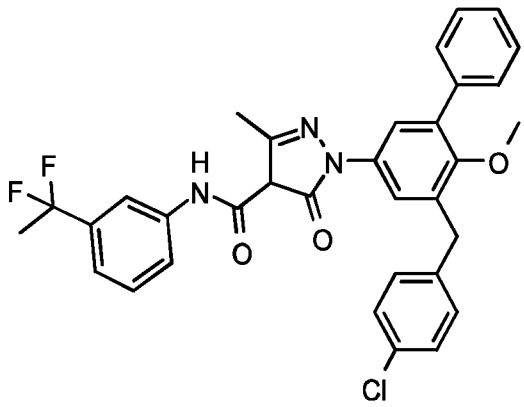
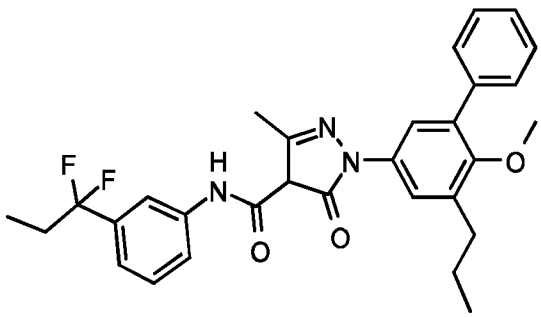
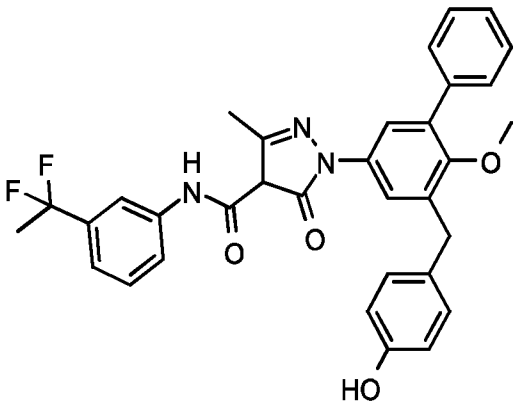
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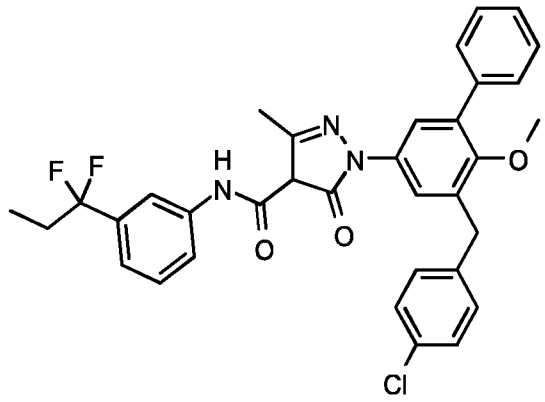
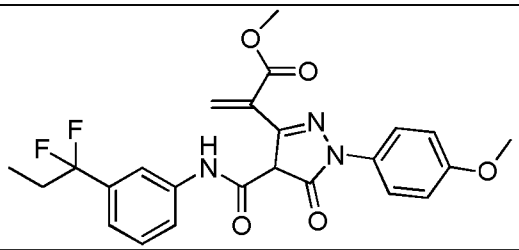
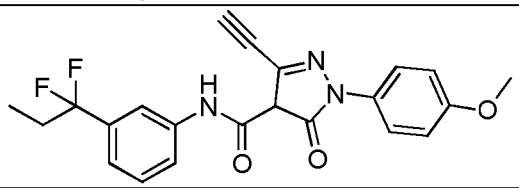
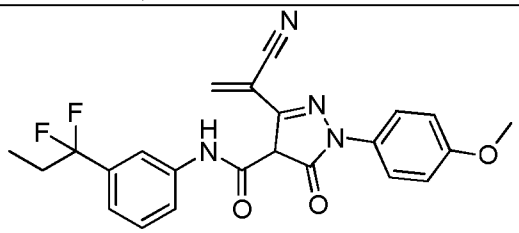
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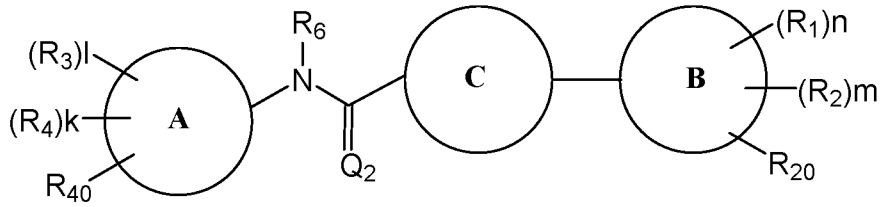
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or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

5. A compound represented by the structure of formula (II):

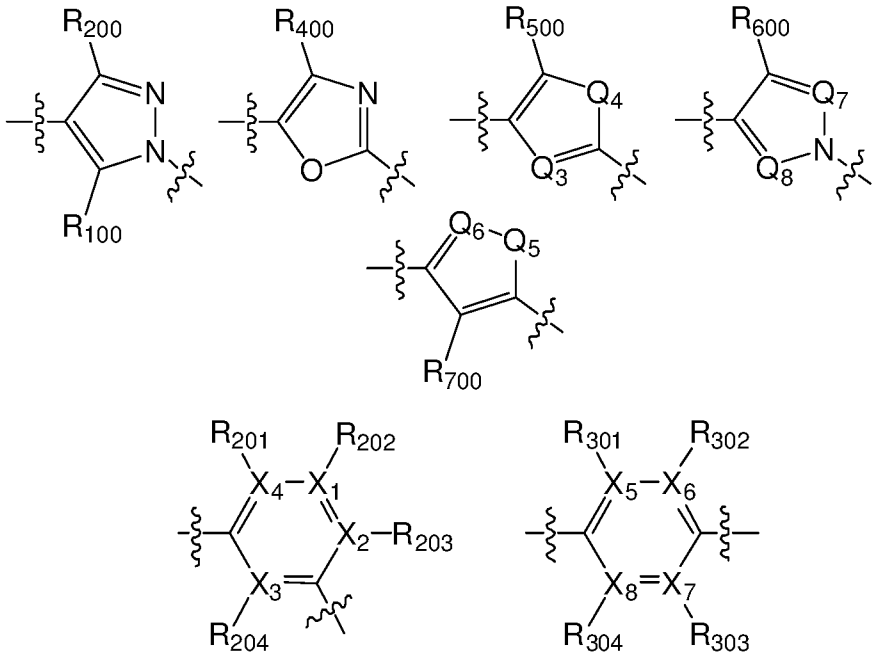


(**II**)

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 C_3-C_{10} cycloalkyl (e.g. cyclohexyl) or a single or fused C_3-C_{10} 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);

C ring is selected from the following (wavy line represents a connection point):



wherein

X_1, X_2, X_3, X_4, X_5, X_6, X_7 and **X_8** are each independently N, N-O, or C,

wherein at least one of **X_1, X_2, X_3, X_4, X_5, X_6, X_7** or **X_8** is N, and

wherein if **X_1, X_2, X_3, X_4, X_5, X_6, X_7** or **X_8** is N than its respective substituent is nothing;

Q_3, **Q_6**, **Q_7** and **Q_8** are each independedntly N, N-O, CH or C(R);

Q_4 and **Q_5** are each independedntly O, NH or N(R);

R_{200}, **R_{400}**, **R_{500}**, and **R_{600}** are each independently H or a C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl);

R_{201}, **R_{202}**, **R_{203}**, **R_{204}**, **R_{301}**, **R_{302}**, **R_{303}**, and **R_{304}** are each independently nothing, H or a C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl);

R_{100} and **R_{700}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR (e.g., $NHCH_3$), $N(R)_2$ (e.g., $N(CH_3)_2$), R_8-N(R_{10})(R_{11}) (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-N(R_{10})(R_{11}) (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -OC(O)-N(R_{10})(R_{11}) (e.g. OC(O)-piperidine-$C(Me)_2CH_2OH$, OC(O)-piperazine-CH_2CH_2OH, OC(O)-piperidine-piperidine), -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., $NHC(O)CH_3$), NHCO-N(R_{10})(R_{11}) (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, $C(O)O-CH(CH_3)_2$, $C(O)O-CH_2CH_3$), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, $C(O)-CH_2CH_3$, $C(O)-CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)-CF_3$), -$C(O)NH_2$, C(O)NHR, C(O)N(R_{10})(R_{11}) (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$,

$SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)$_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, N(R)$_2$, CF_3, aryl, phenyl, C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH$-$R_{10})$;

R_1, R_2 and **R_{20}** are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., CH_2-cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, N(R)$_2$, R_8-N(R_{10})(R_{11}) (e.g., CH_2-NH_2, CH_2-N(CH_3)$_2$), R_9-R_8-N(R_{10})(R_{11}) (e.g., C≡C-CH_2-NH_2), B(OH)$_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R_{10} (e.g., NHC(O)CH_3), NHCO-N(R_{10})(R_{11}) (e.g., NHC(O)N(CH_3)$_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-CH(CH_3)$_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., CH_2C(O)CH_3), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -C(O)NH_2, C(O)NHR, C(O)N(R_{10})(R_{11}) (e.g., C(O)N(CH_3)$_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)$_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole,

protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole), C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ 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);

$\mathbf{R_3}$, $\mathbf{R_4}$ and $\mathbf{R_{40}}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), R_8-$C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $C(OH)(CH_3)(Ph)$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alksoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_6}$ is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

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

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

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

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

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., $C(O)(OCH_3)$), or $S(O)_2R$; or $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring

(e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

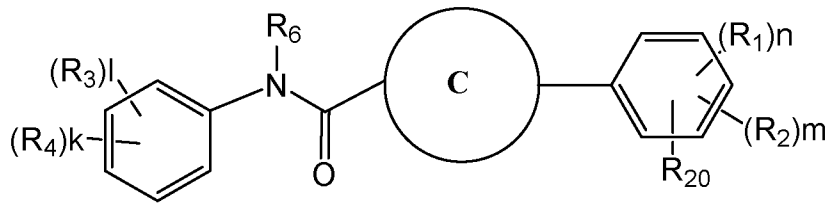
R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

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

$\mathbf{Q_2}$ is S, O, N-OH, CH_2, CH(R), $C(R)_2$ or N-OMe;

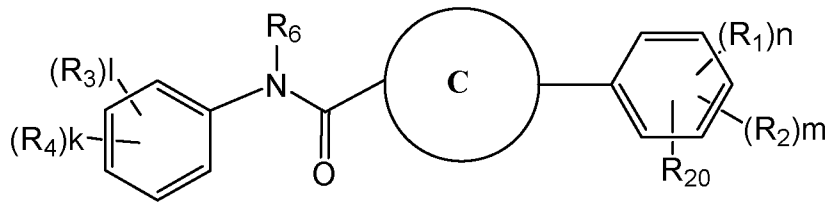
or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

6. The compound of claim 5, represented by the structure of formula **II(a):**



II(a)

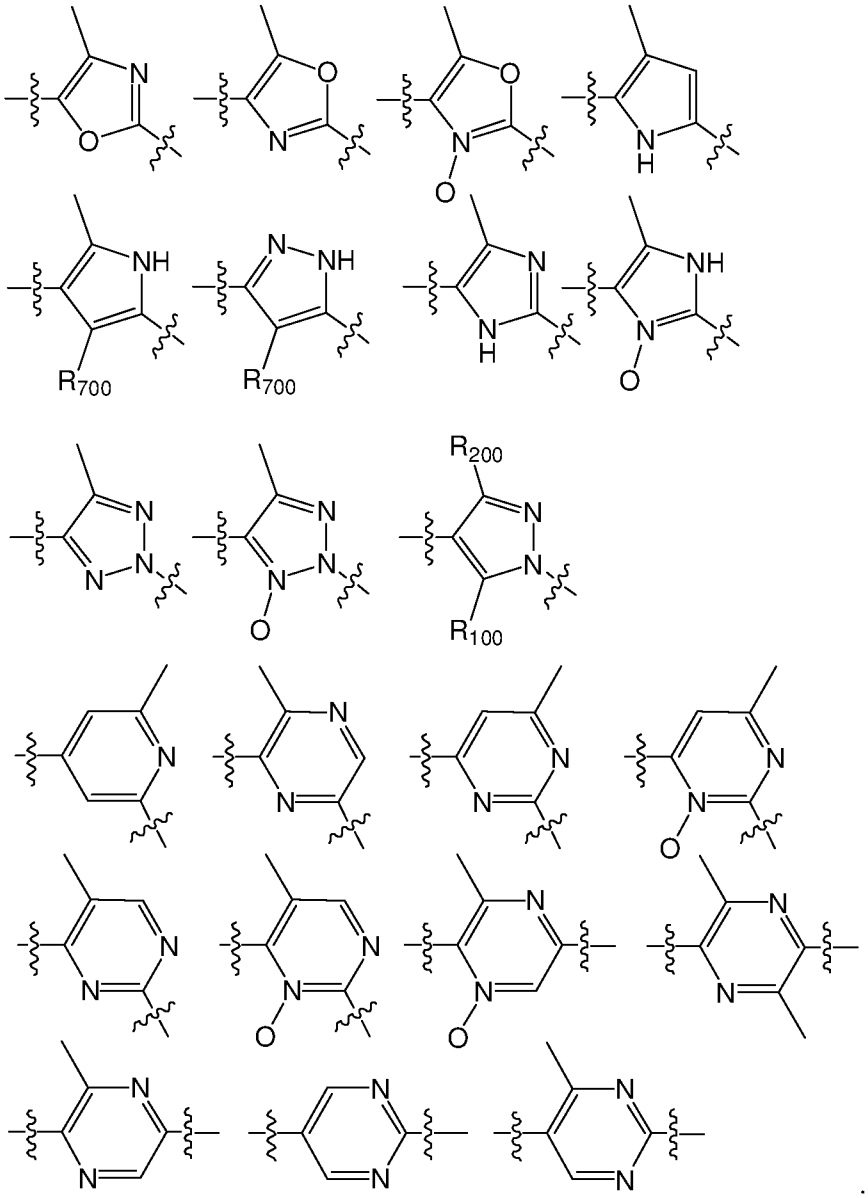
7. The compound of claim 5 or 6, represented by the structure of formula **II(b)**:



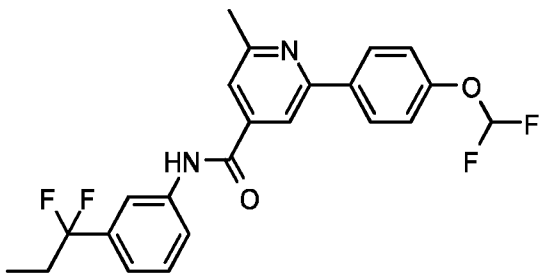
II(b)

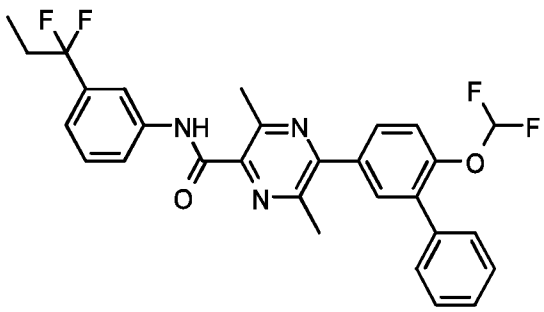
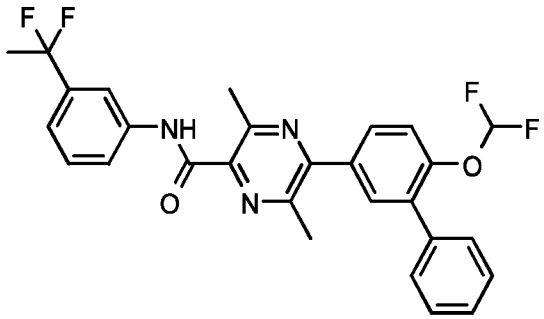
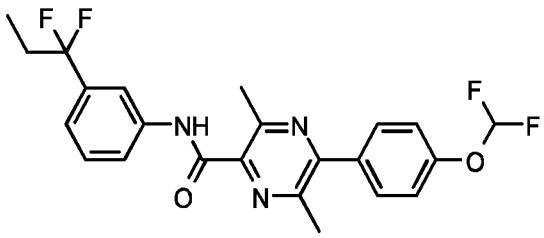
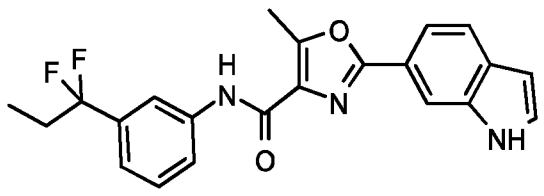
wherein

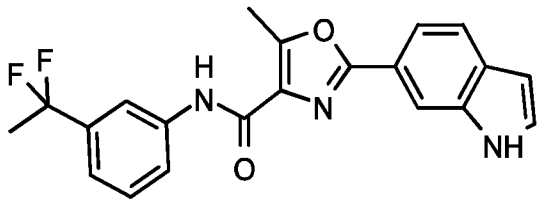
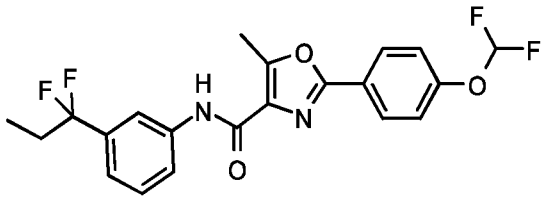
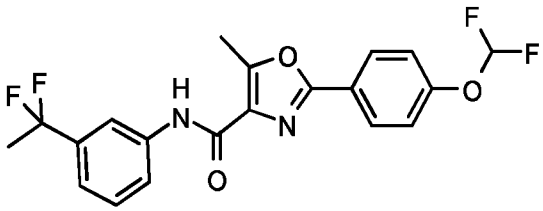
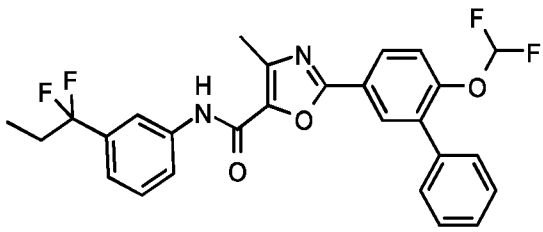
C ring is selected from the following (wavy line represents a connection point):

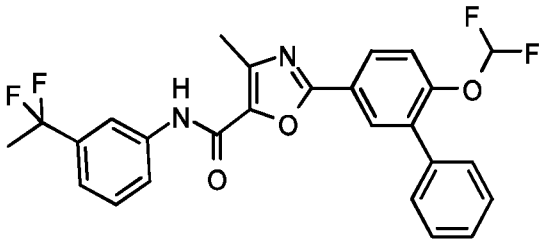
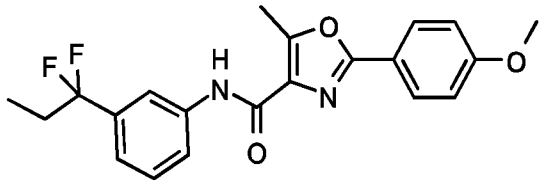
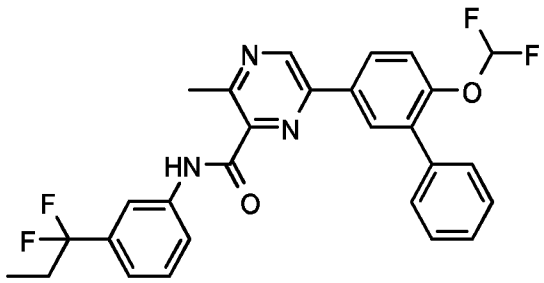
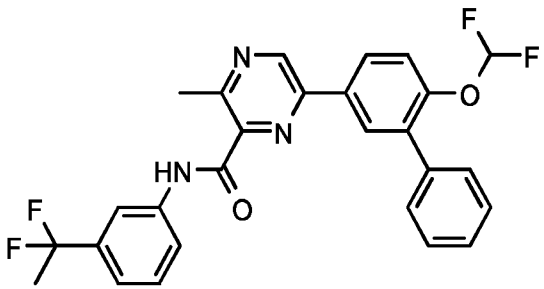


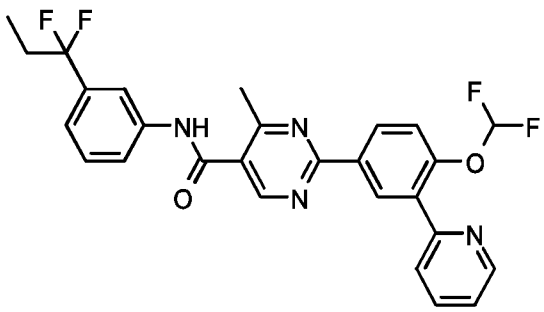
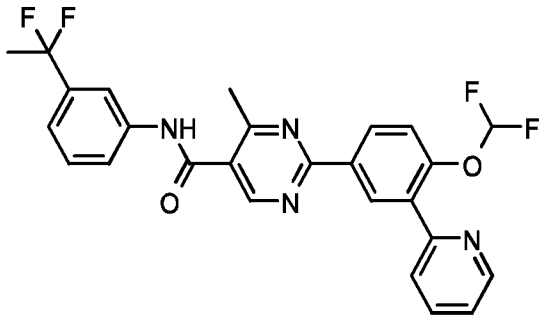
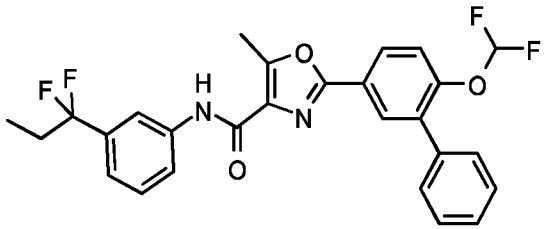
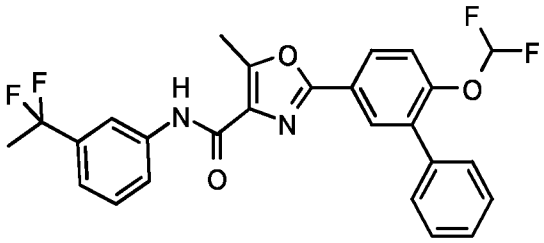
8. The compound of claim 5, selected from the following:

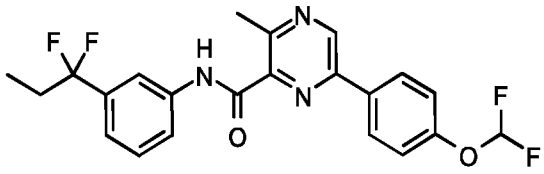
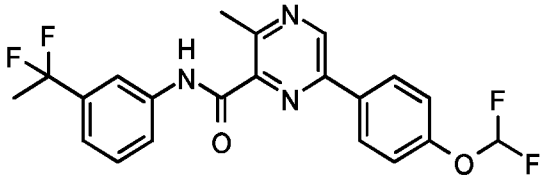
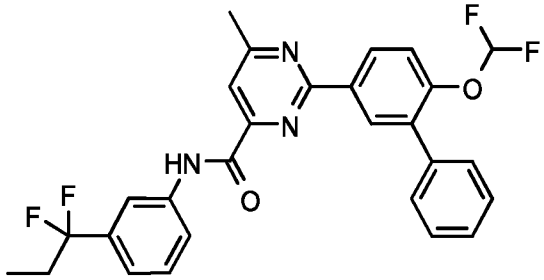
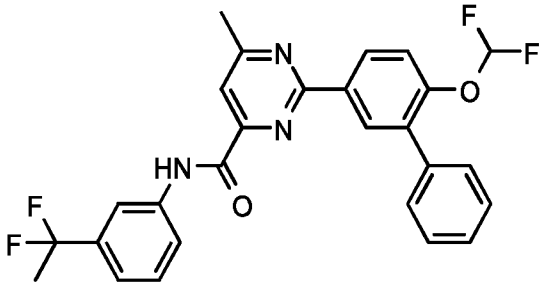
Compound Number	Compound Structure
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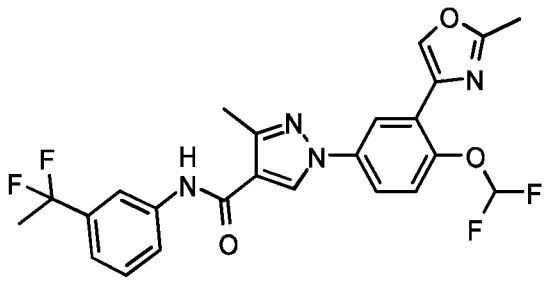
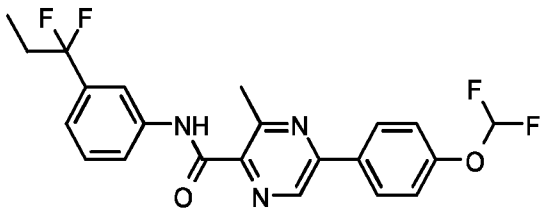
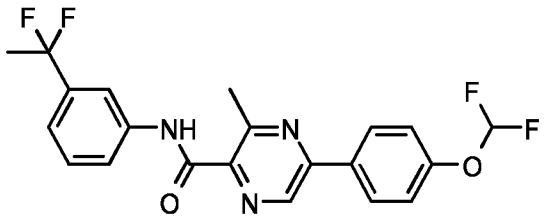
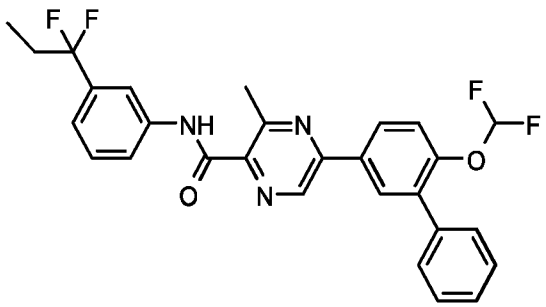
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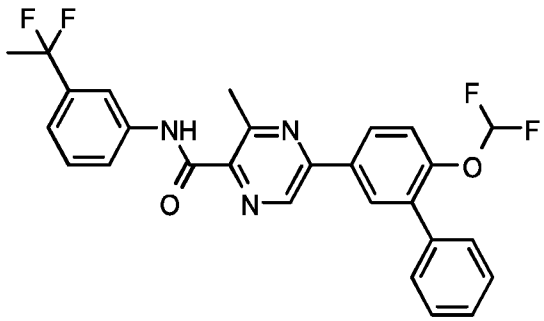
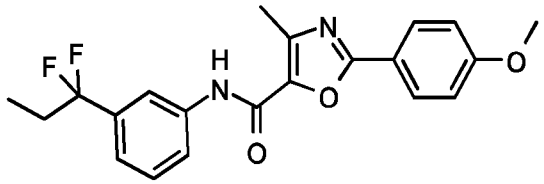
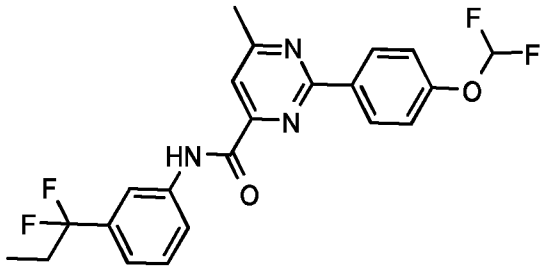
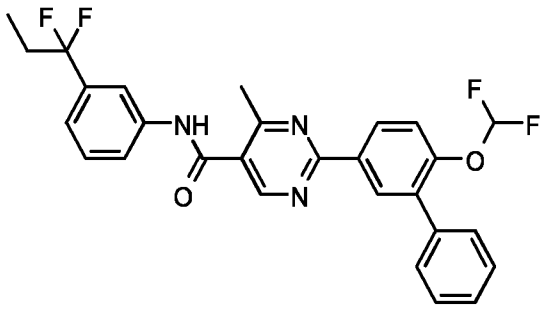
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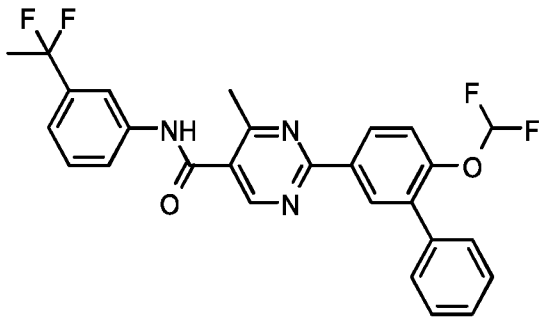
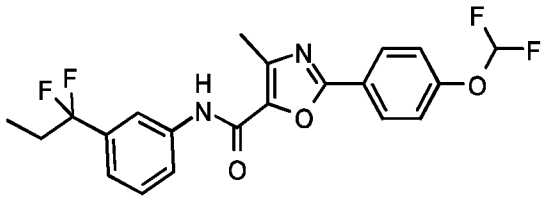
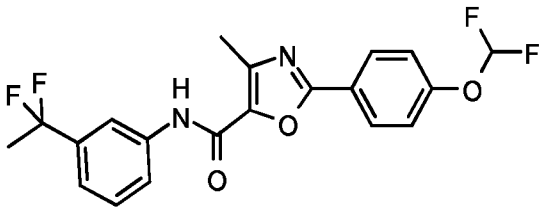
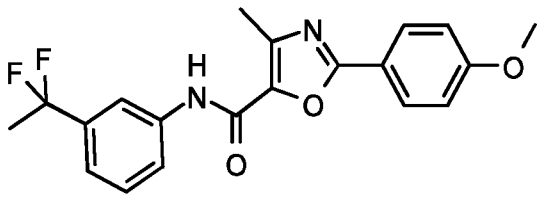
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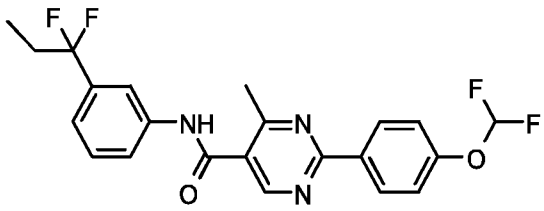
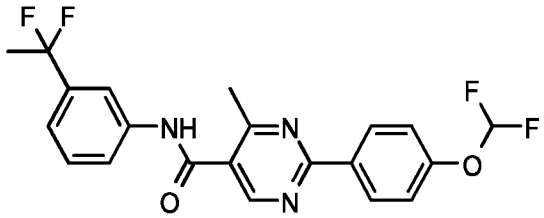
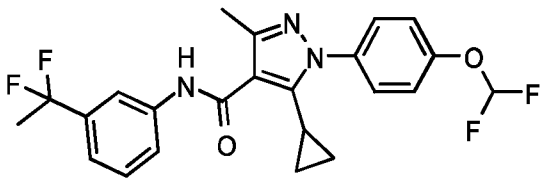
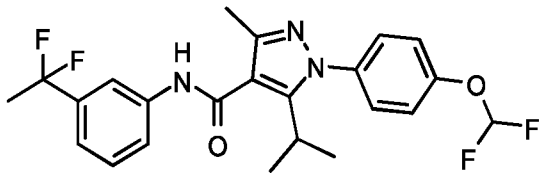
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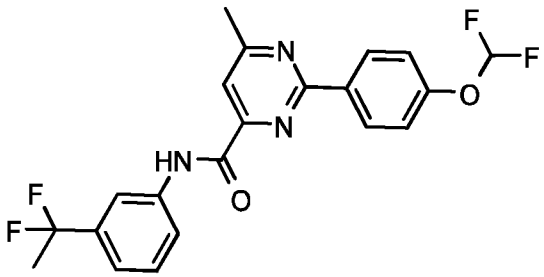
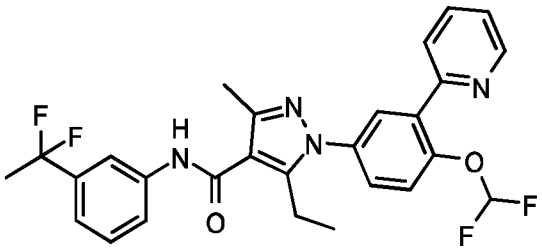
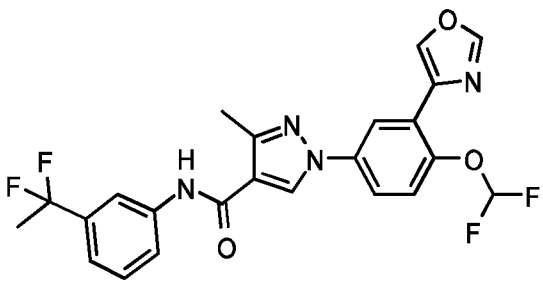
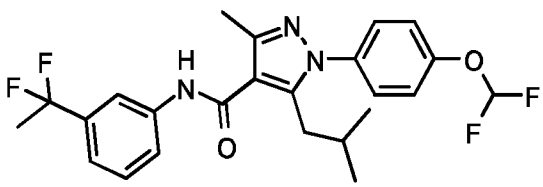
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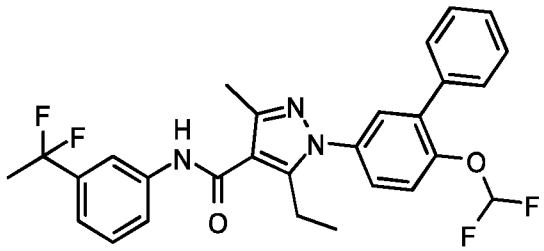
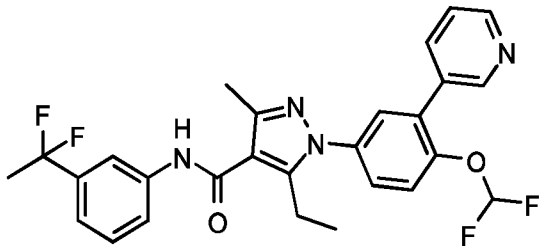
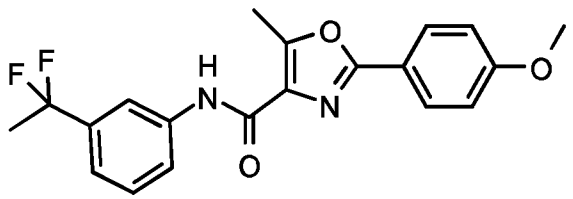
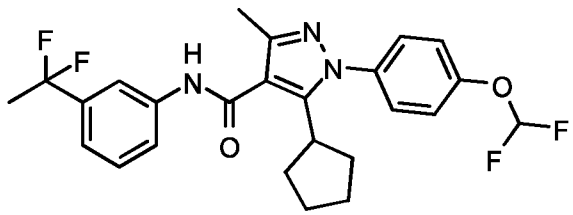
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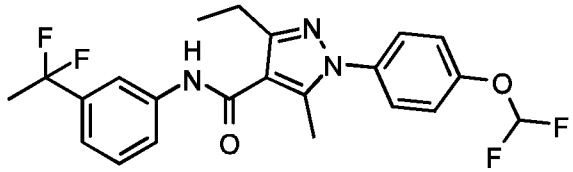
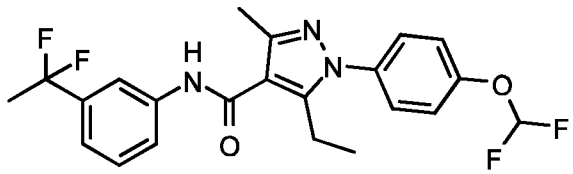
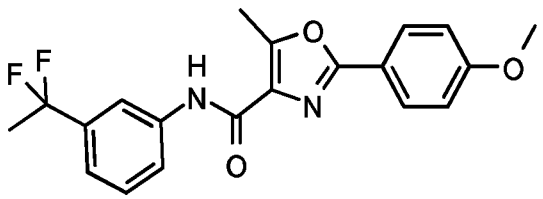
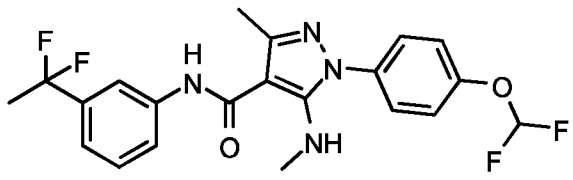
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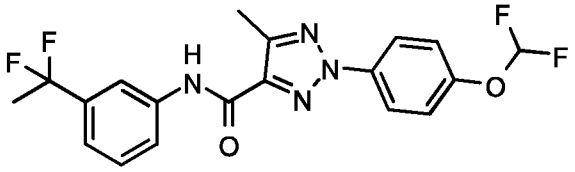
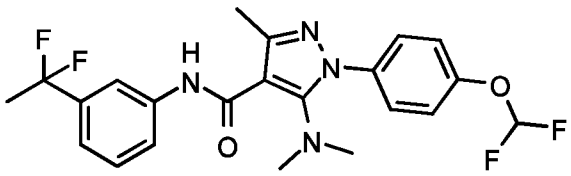
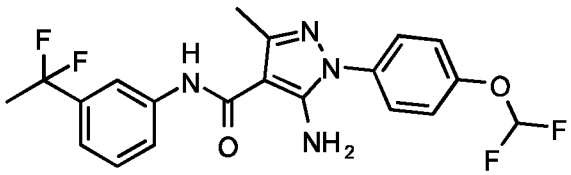
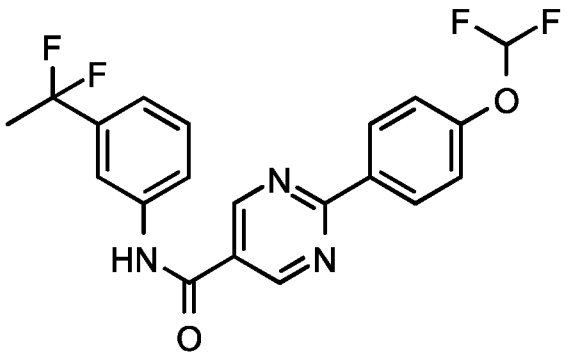
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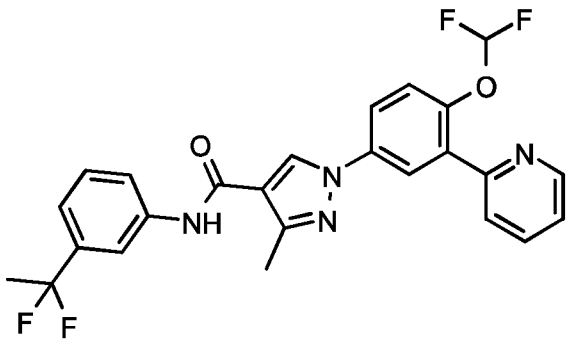
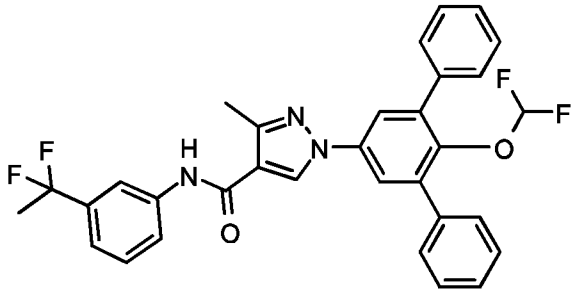
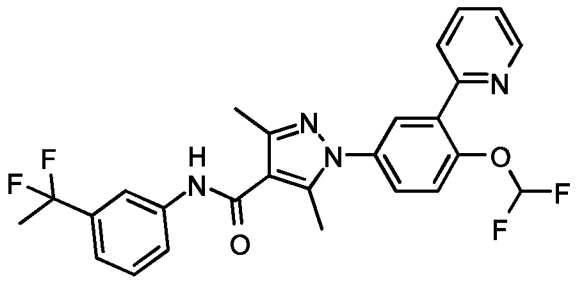
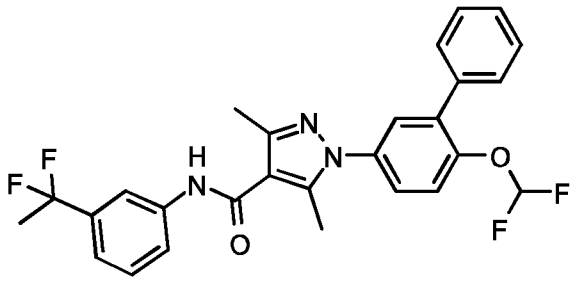
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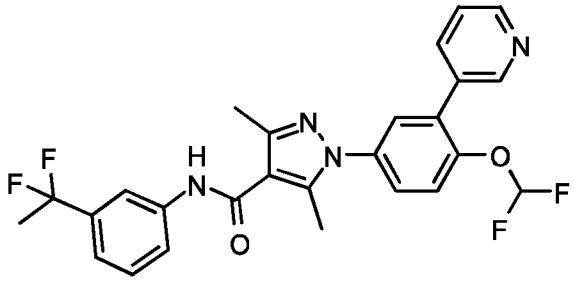
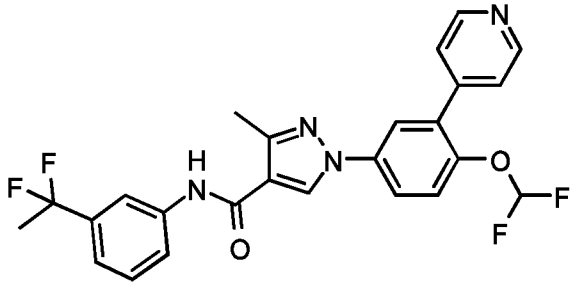
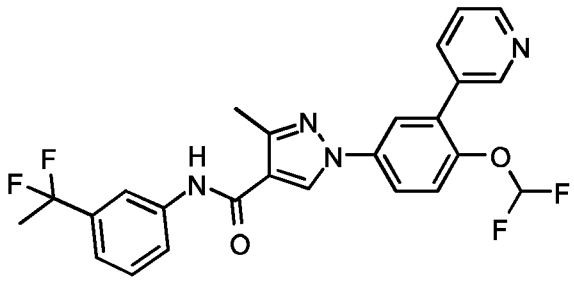
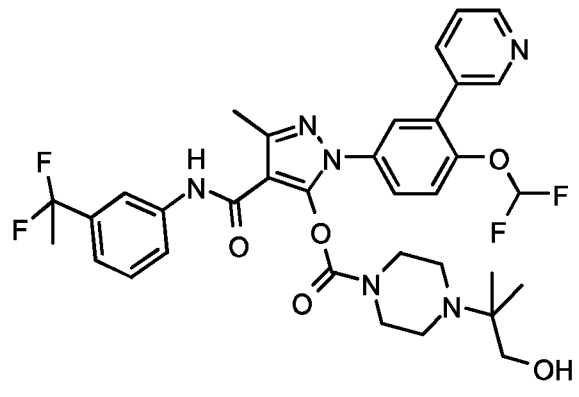
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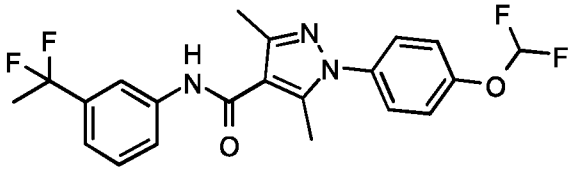
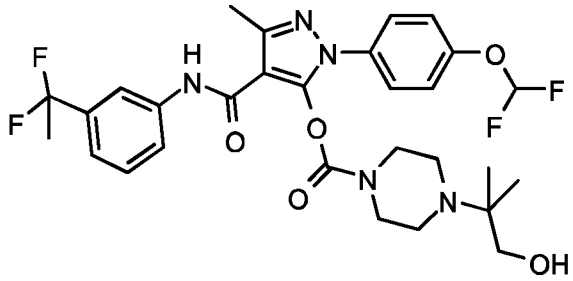
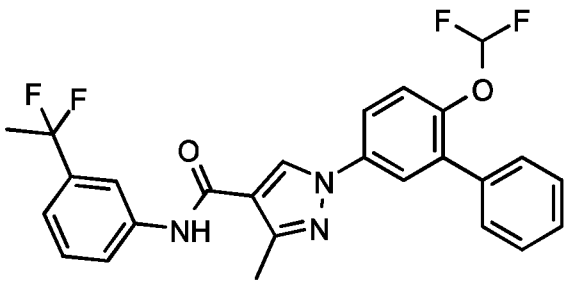
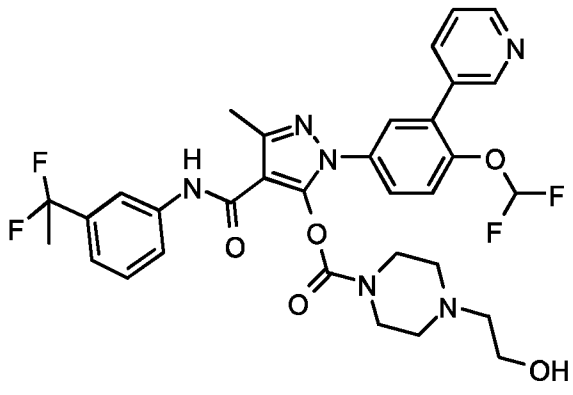
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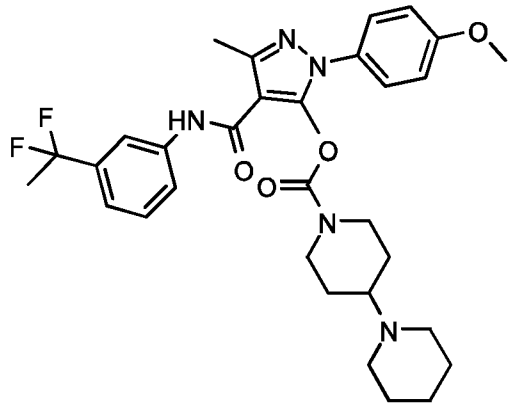
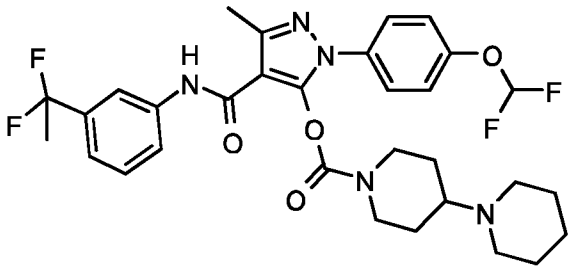
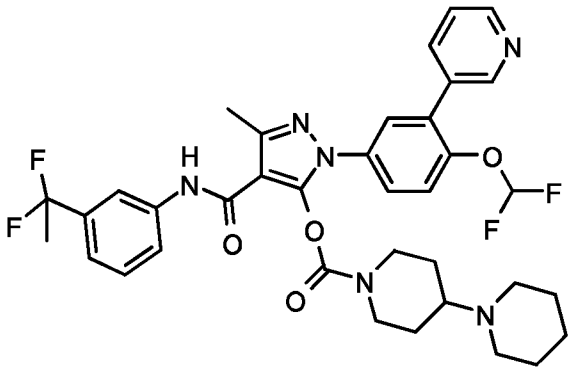
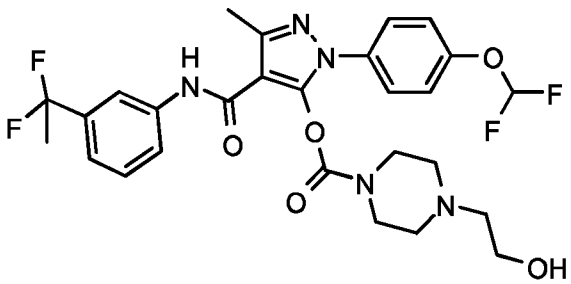
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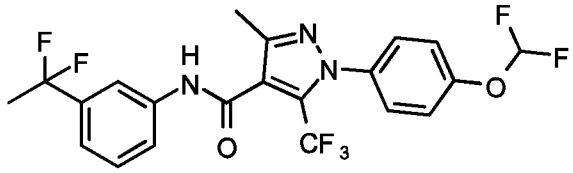
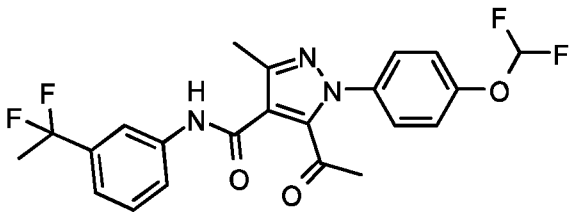
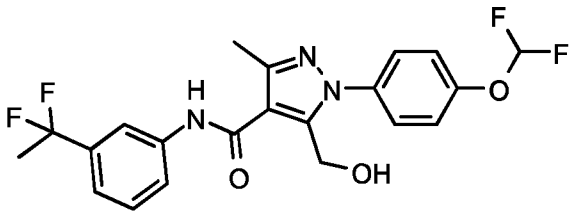
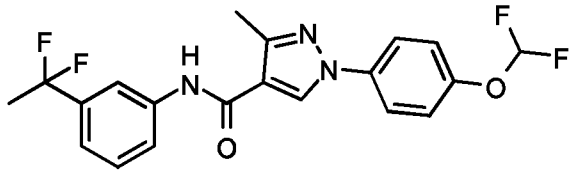
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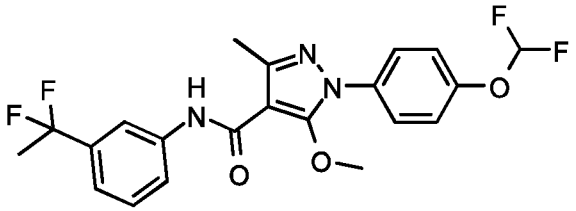
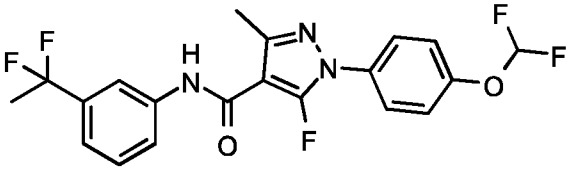
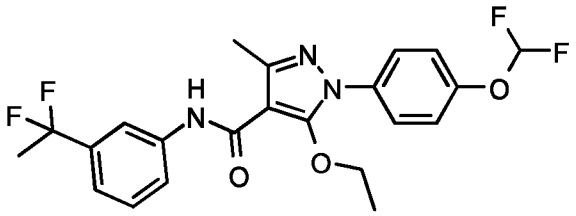
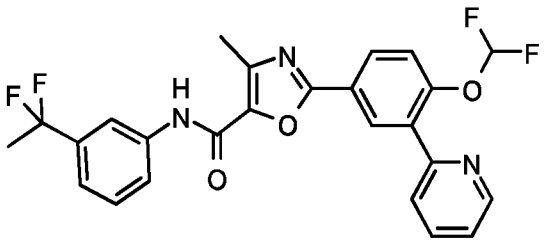
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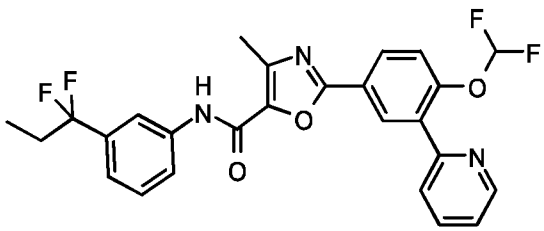
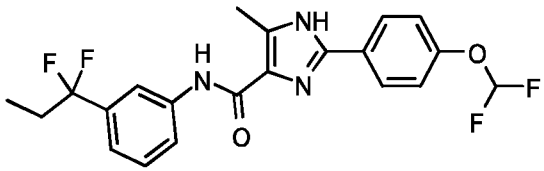
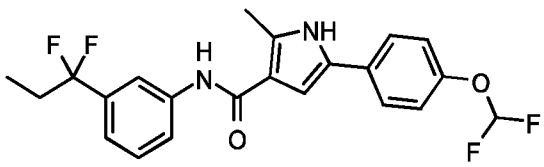
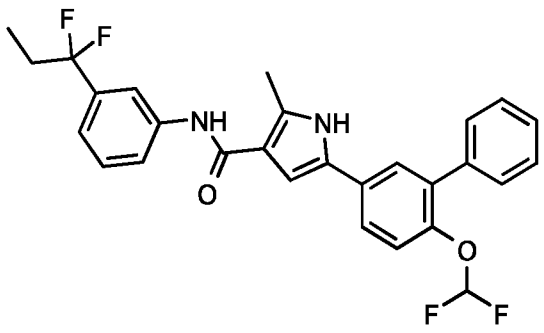
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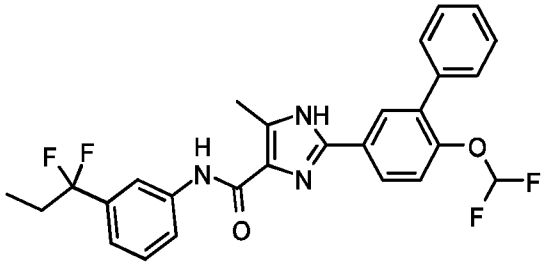
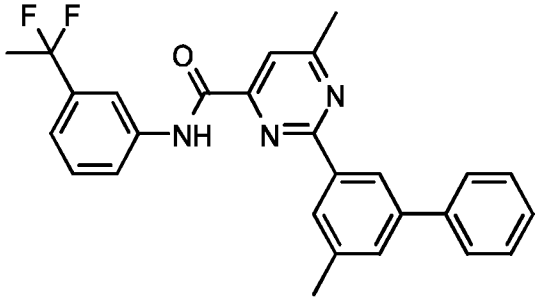
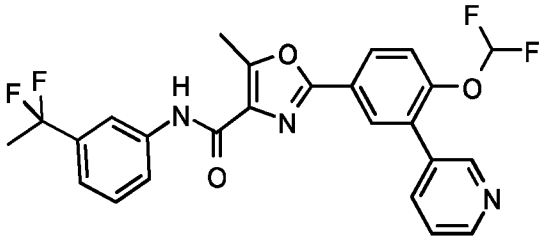
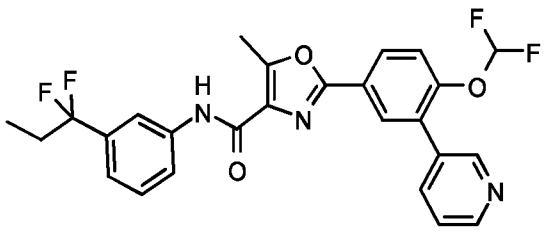
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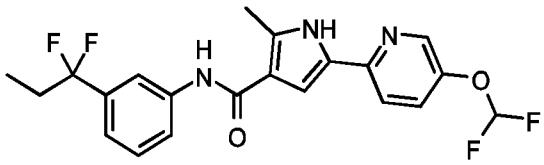
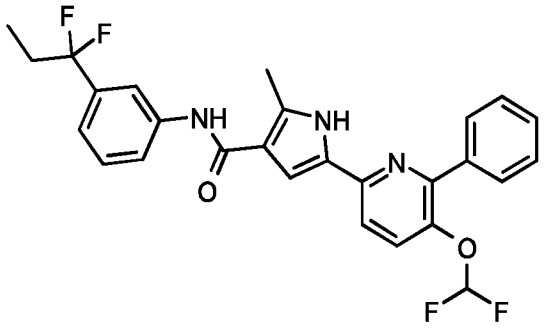
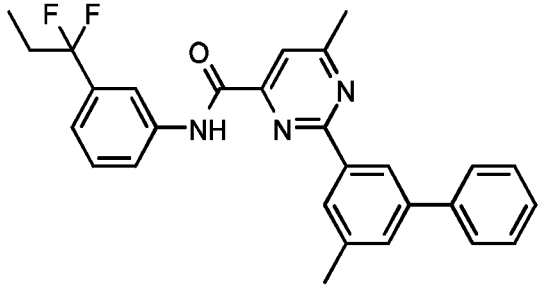
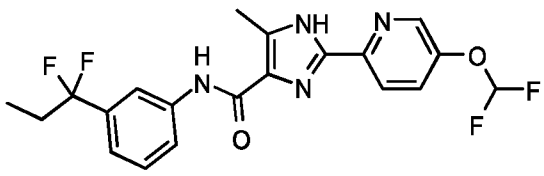
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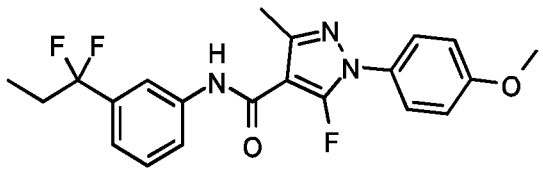
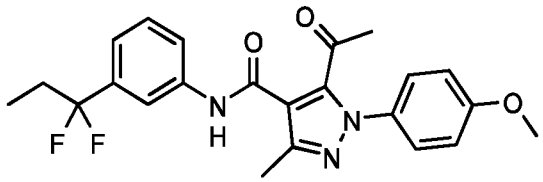
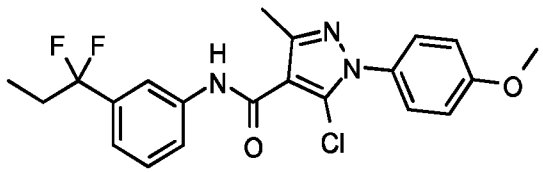
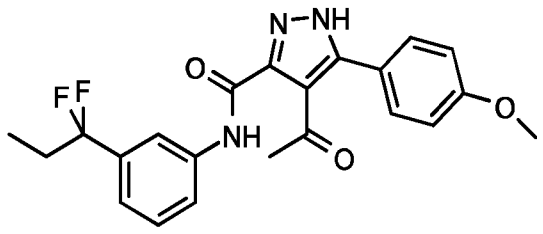
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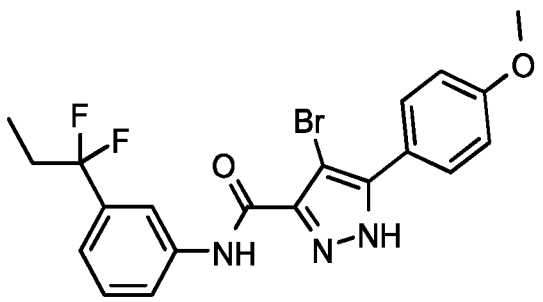
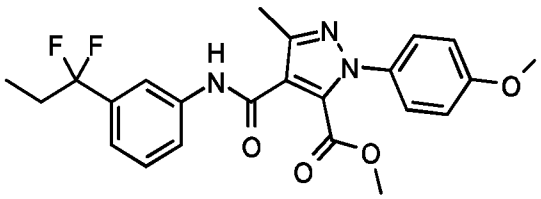
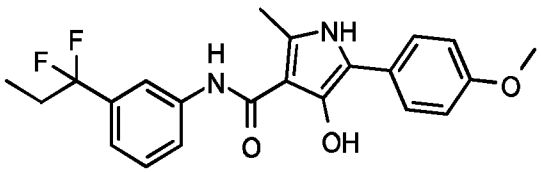
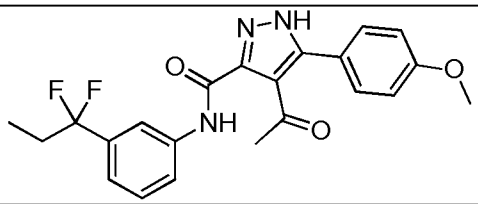
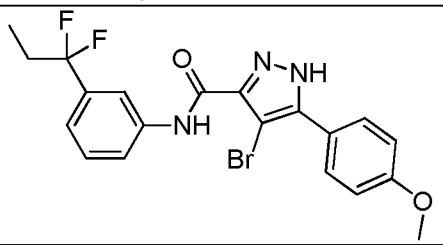
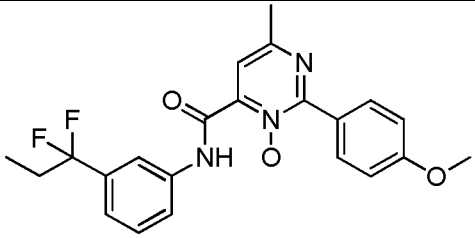
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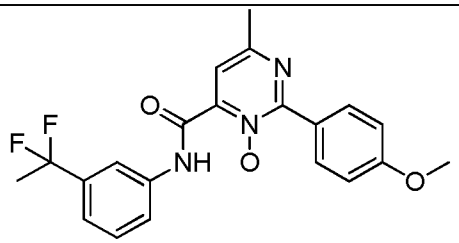
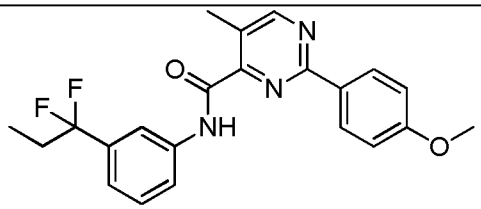
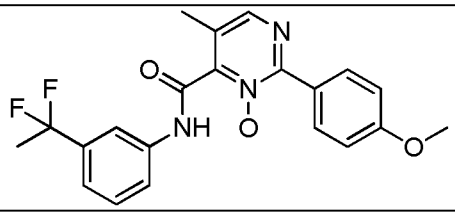
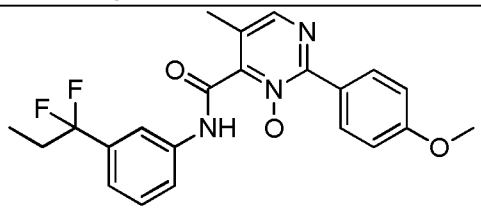
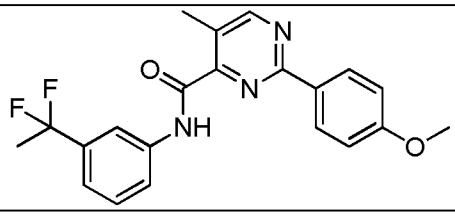
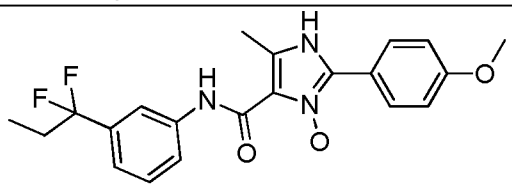
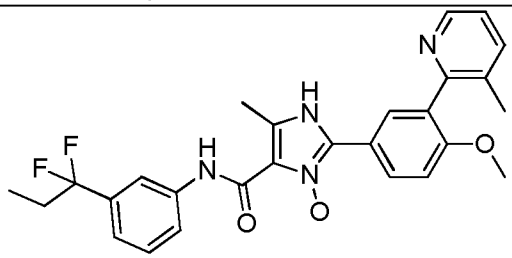
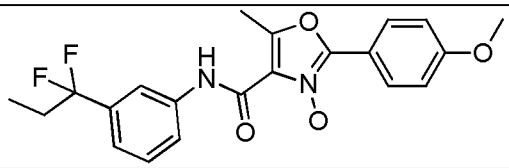
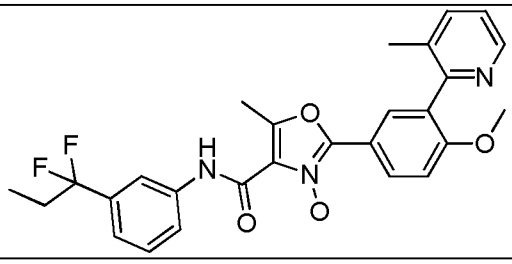
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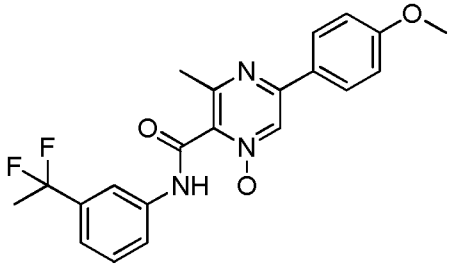
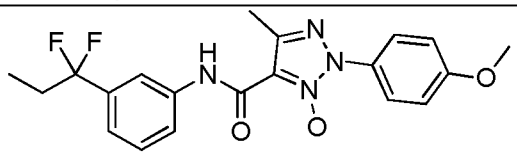
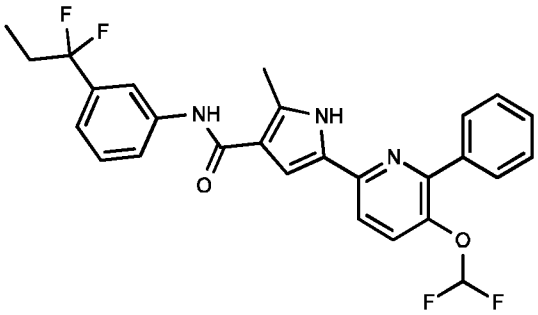
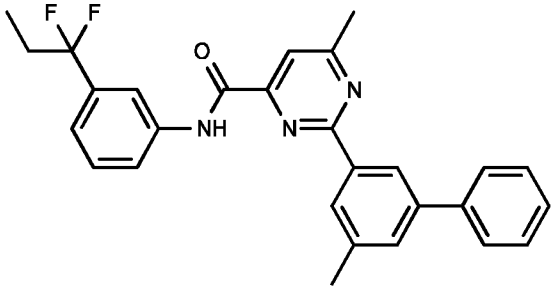
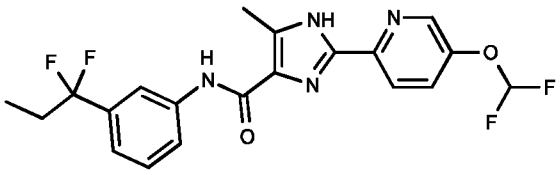
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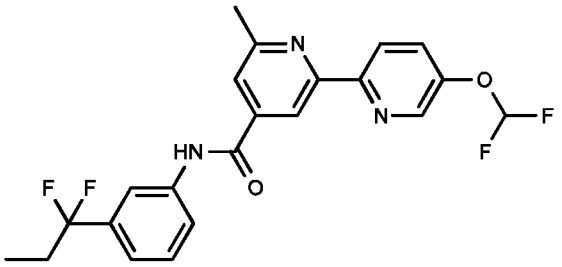
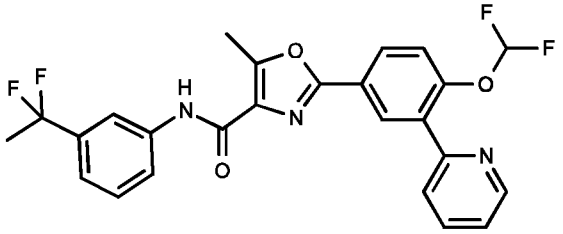
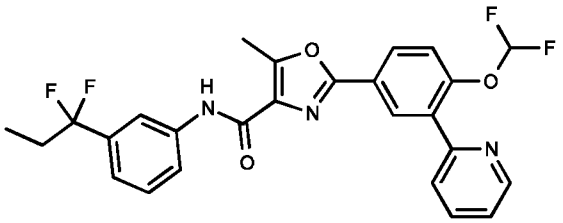
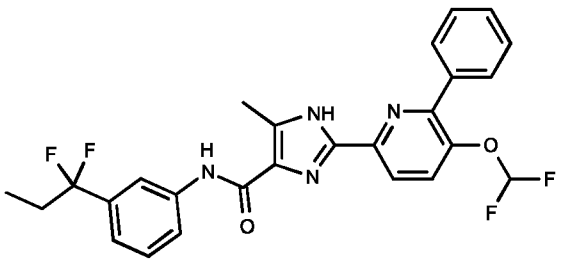
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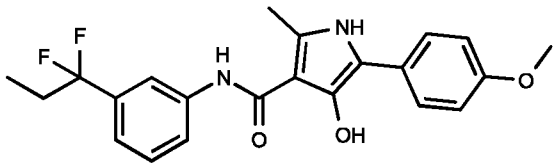
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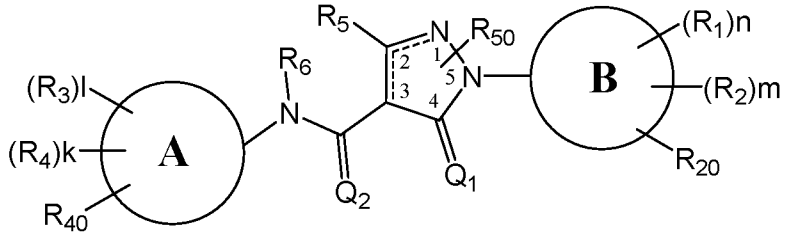
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or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

9. A compound represented by the structure of formula (III):



(III)

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 C_3-C_{10} cycloalkyl (e.g. cyclohexyl) or a single or fused C_3-C_{10} 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);

R_1, R_2 and **R_{20}** are each independently F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., -CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl) (e.g., cyclohexyl), R_8-(C_3-C_8 heterocyclic ring) (e.g., CH_2-imidazole, CH_2-indazole), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$ (e.g., C≡C-CH_2-NH_2), $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, NHC(O)-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, C(O)O-R_{10} (e.g. C(O)O-CH_3, C(O)O-$CH(CH_3)_2$, C(O)O-CH_2CH_3), R_8-C(O)-R_{10} (e.g., $CH_2C(O)CH_3$), C(O)H, C(O)-R_{10} (e.g., C(O)-CH_3, C(O)-CH_2CH_3, C(O)-$CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$, $SO_2NHC(O)CH_3$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, 2, 3, or 4-CH_2-C_6H_4-Cl, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl, benzyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl (e.g., $CH=C(Ph)_2$)), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)$-$CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-

butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy (e.g., OCF_3, $OCHF_2$), C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 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, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), (wherein substitutions include: F, Cl, Br, I, C_1-C_5 linear or branched alkyl (e.g. methyl, ethyl), OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, heteroaryl (e.g., imidazole) C_3-C_8 cycloalkyl (e.g., cyclohexyl), halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ 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);

$\mathbf{R_3}$, $\mathbf{R_4}$ and $\mathbf{R_{40}}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g., CH_2-OH), R_8-SH, -R_8-O-R_{10}, (e.g., CH_2-O-CH_3) CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH_2, CH_2-$N(CH_3)_2$) R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, -NHCO-R_{10} (e.g., $NHC(O)CH_3$), NHCO-$N(R_{10})(R_{11})$ (e.g., $NHC(O)N(CH_3)_2$), COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$ (e.g. $C(O)O\text{-}CH_3$, $C(O)O\text{-}CH_2CH_3$), R_8-$C(O)\text{-}R_{10}$ (e.g., $CH_2C(O)CH_3$), C(O)H, $C(O)\text{-}R_{10}$ (e.g., $C(O)\text{-}CH_3$, $C(O)\text{-}CH_2CH_3$, $C(O)\text{-}CH_2CH_2CH_3$), C_1-C_5 linear or branched C(O)-haloalkyl (e.g., $C(O)\text{-}CF_3$), -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$ (e.g., $C(O)N(CH_3)_2$), SO_2R, $SO_2N(R_{10})(R_{11})$ (e.g., $SO_2N(CH_3)_2$), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH_3)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CF_3, CF_2CH_3, CF_2-cyclobutyl, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$, $CF(CH_3)\text{-}CH(CH_3)_2$), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH_2-cyclopropyl), C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl, cyclopentyl), substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, 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, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof), $CH(CF_3)(NH\text{-}R_{10})$;

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

$\mathbf{R_5}$ is H, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, iso-propyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3,

CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), $C(=CH_2)$-R_{10} (e.g., $C(=CH_2)$-C(O)-OCH_3, $C(=CH_2)$-CN) substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

R_{50} is H, F, Cl, Br, I, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH, ethyl, propyl, iso-propyl, benzyl), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine), substituted or unsubstituted benzyl, (wherein substitutions include: F, Cl, Br, I, OH, SH, C_1-C_5 linear or branched alkyl, OH, alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof);

wherein R_{50} is attached either to N_1 or to C_3 and if R_{50} is attached to N_1 than N_1-C_2 is a single bond and C_2-C_3 is a double bond, and if R_{50} is attached to C_3 than N_1-C_2 is a double bond and C_2-C_3 is a single bond;

R_6 is H, C_1-C_5 linear or branched alkyl (e.g., methyl), C(O)R, or $S(O)_2R$;

R_8 is $[CH_2]_p$

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

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

R_{10} and **R_{11}** are each independedntly H, CN, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C(O)R (e.g., C(O)(OCH_3)), or $S(O)_2R$; or **R_{10}** and **R_{11}** are joint to form a substituted or unsubstituted C_3-C_8 heterocyclic ring (e.g., piperazine, piperidine),

wherein substitutions include: F, Cl, Br, I, OH, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), C_3-C_8 heterocyclic ring (e.g., piperidine), alkoxy, $N(R)_2$, CF_3, aryl, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2 or any combination thereof)

R is H, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substiuents are joint together to form a 5 or 6 membered heterocyclic ring;

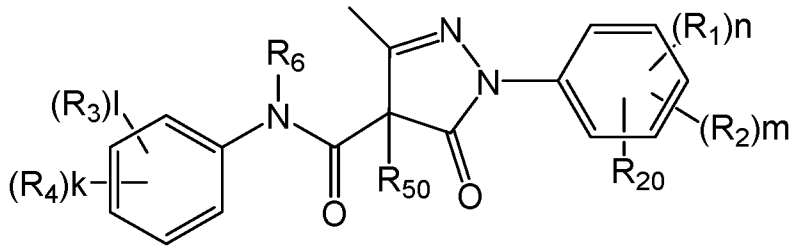
m and, **n,** are each independedntly an integer between 1 and 4 (e.g., 1 or 2);

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

Q_1 and **Q_2** are each independently S, O, N-OH, CH_2, $C(R)_2$ or N-OMe;

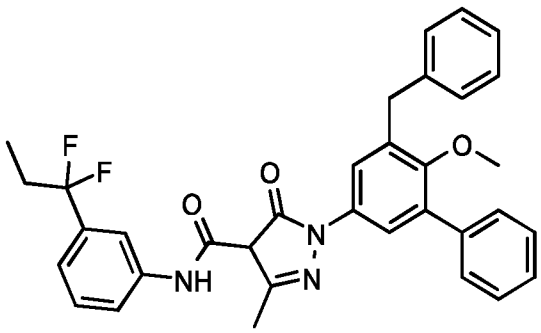
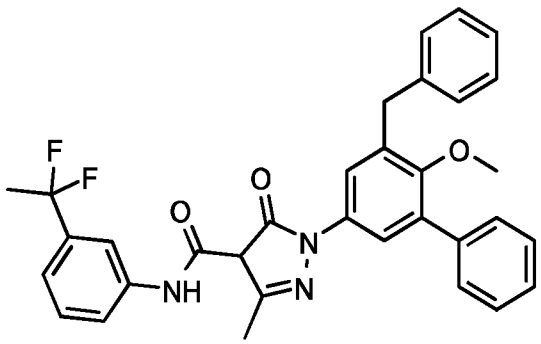
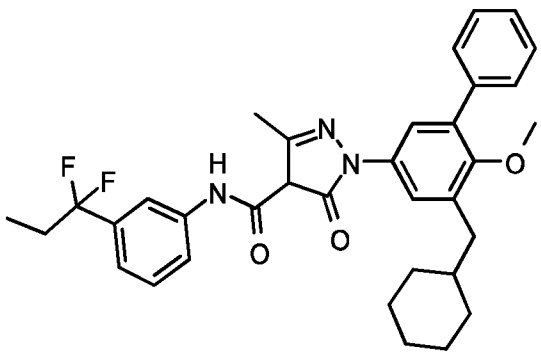
or its pharmaceutically acceptable salt, optical isomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof.

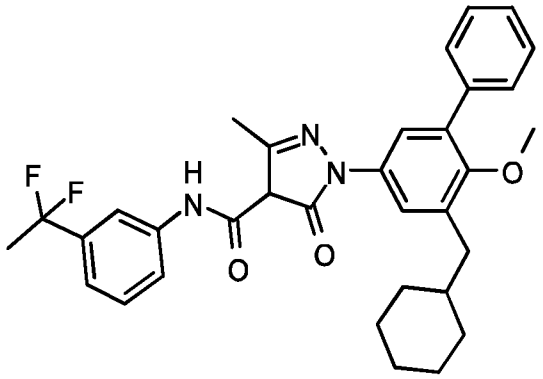
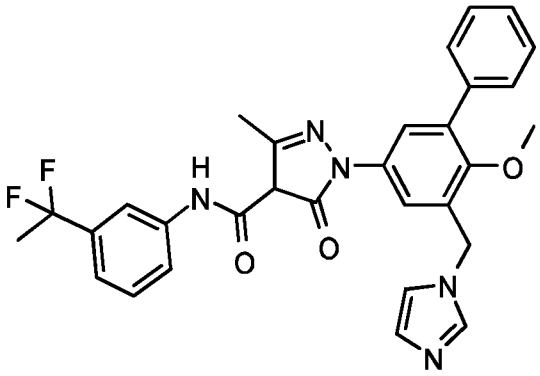
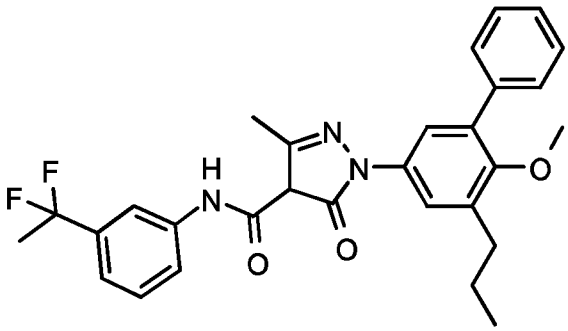
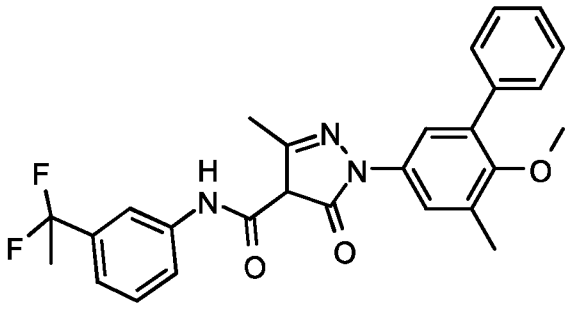
10. The compound of claim 9, represented by the structure of formula III(a):

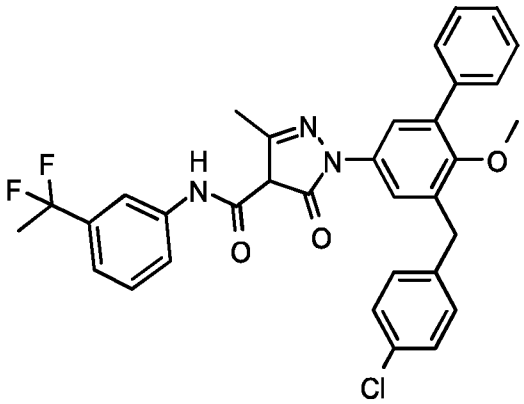
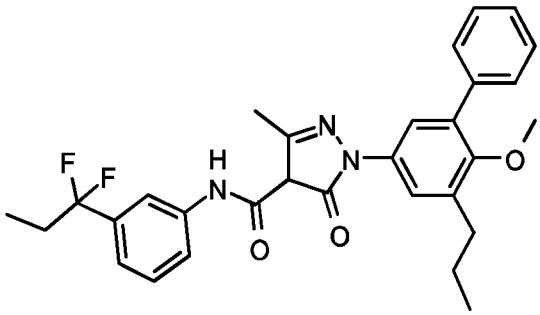
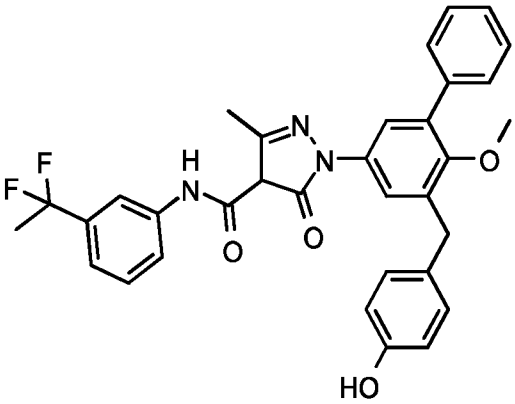
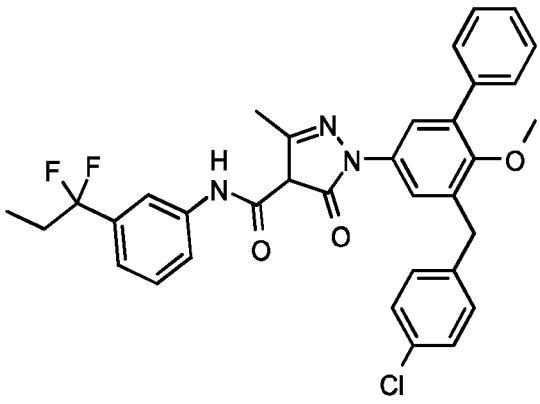


III(a).

11. The compound of claim 9 or 10, selected from the following:

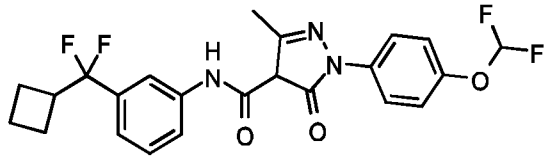
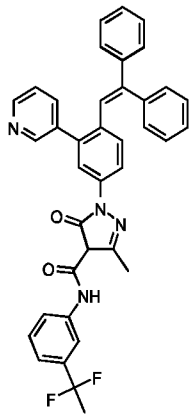
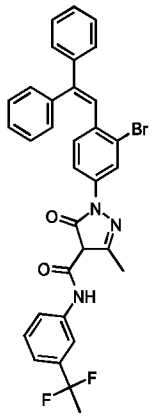
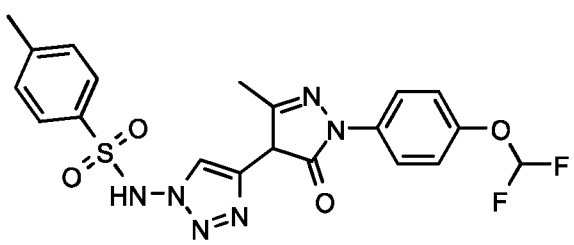
Compound Number	Compound Structure
121	
122	
128	

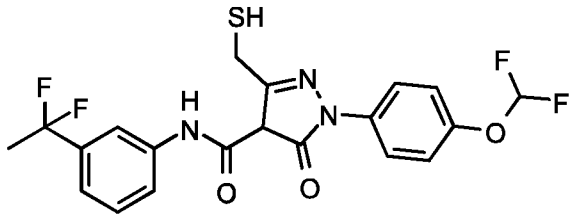
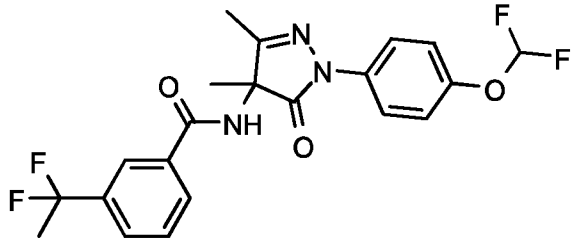
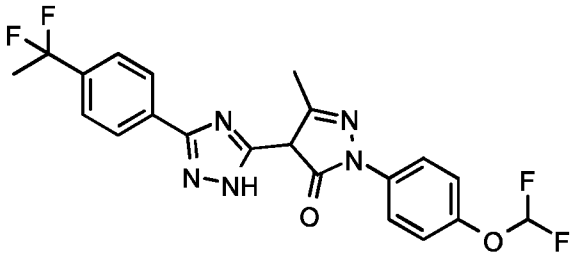
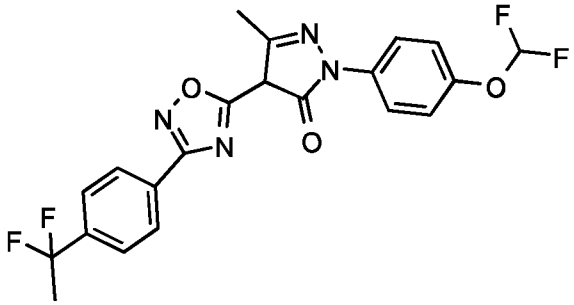
129	
160	
161	
180	

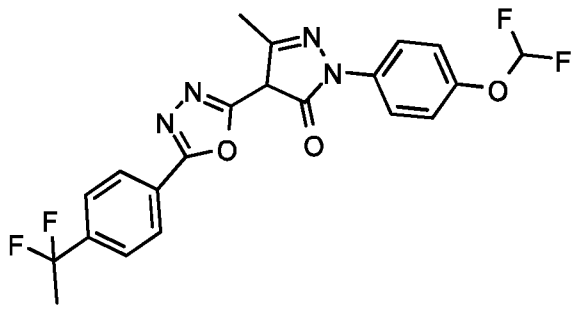
224	
225	
228	
236	

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

12. A compound represented by any one of the following:

Compound Number	Compound Structure
101	
109	
110	
195	

197	
198	
210	
211	

212	

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

13. A method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer comprising administering a compound according to any one of the preceding claims to a subject suffering from cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit said cancer.

14. The method of claim 13, wherein 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.

15. The method of claim 13 or 14, wherein the cancer is early cancer, advanced cancer, invasive cancer, metastatic cancer, drug resistant cancer or any combination thereof.

16. The method of any one of claims 13 to 15, wherein the subject has been previously treated with chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof.
17. The method of any one of claims 13 to 16, wherein the compound is administered in combination with an anti-cancer therapy.
18. The method of claim 17, wherein the anti-cancer therapy is chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof.
19. A method of suppressing, reducing or inhibiting tumour growth in a subject, comprising administering a compound according to any one of claims 1 to 12, to a subject suffering from cancer under conditions effective to suppress, reduce or inhibit said tumour growth in said subject.
20. The method of claim 19, wherein the tumor growth is enhanced by increased acetate uptake by cancer cells of said cancer.
21. The method of claim 20, wherein the increased acetate uptake is mediated by ACSS2.
22. The method of claim 20 or 21, wherein the cancer cells are under hypoxic stress.
23. The method of claim 19, wherein the tumor growth is suppressed due to suppression of lipid (e.g., fatty acid) synthesis and/or regulating histones acetylation and function induced by ACSS2 mediated acetate metabolism to acetyl-CoA.
24. A method of suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function in a cell, comprising contacting a compound according to any one of claims 1 to 12, with a cell under conditions effective to suppress, reduce or inhibit lipid synthesis and/or regulating histones acetylation and function in said cell.
25. The method of claim 24, wherein the cell is a cancer cell.
26. 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 according to any one of claims 1 to 12, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.
27. A method of suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell, comprising contacting a compound according to any one of claims 1 to 12 with a cell, under conditions effective to suppress, reduce or inhibit acetyl-CoA synthesis from acetate in said cell.
28. The method of claim 27, wherein the cell is a cancer cell.
29. The method of claim 27 or 28, wherein the synthesis is mediated by ACSS2.
30. A method of suppressing, reducing or inhibiting acetate metabolism in a cancer cell, comprising contacting a compound according to any one of claims 1 to 12 with a cancer cell, under conditions effective to suppress, reduce or inhibit acetate metabolism in said cells.
31. The method of claim 30, wherein the acetate metabolism is mediated by ACSS2.
32. The method of claim 30 or 31, wherein the cancer cell is under hypoxic stress.
33. A method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject, comprising administering a compound according to any one of claims 1 to 12, 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.

34. 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 according to any one of claims 1 to 12, 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.

35. The method of claim 34, wherein the viral infection is human cytomegalovirus (HCMV) infection.

36. 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 according to any one of claims 1 to 12, 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.

37. 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 according to any one of claims 1 to 12, 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.

38. 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 according to any one of claims 1 to 12, 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.

39. 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 according to any one of claims 1 to 12, 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.

40. The method of claim 39, wherein the metabolic disorder is selected from: obesity, weight gain, hepatic steatosis and fatty liver disease.

41. 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 according to any one of claims 1 to 12, 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.

42. The method of claim 41, wherein the neuropsychiatric disease or disorder is selected from: anxiety, depression, schizophrenia, autism and post-traumatic stress disorder.

43. A method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting inflammatory condition in a subject, comprising administering a compound according to any one of claims 1 to 12, 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.

44. 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 according to any one of claims 1 to 12, 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.

45. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2020/050524

A. CLASSIFICATION OF SUBJECT MATTER
See extra sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See extra sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See extra sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAS Registry Number: 373639-90-8; CA Index Name: Benzamide, N-[4,5-dihydro-5-oxo-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-yl]-3-nitro-; Entered STN: 05 Dec 2001. Also published in URL: <http://www.chemspider.com/Chemical-Structure.514218.html>, and as PubChem CID: 591511 ("3-Nitro-N-[5-oxo-1-(2,4,6-trichlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl] benzamide"; Create date: 27 March 2005. URL: <https://pubchem.ncbi.nlm.nih.gov/compound/591511>). 05 Dec 2001 (2001/12/05)	1,2,9
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 Sep 2020	07 Sep 2020

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Telephone No. 972-73-3927252

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International application No.
PCT/IL2020/050524

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X	WO 2011/143425 A2 (VERTEX PHARMACEUTICALS INCORPORATED [US]) 17 Nov 2011 (2011/11/17) Claims and compound IV-1.	5-7,13-19,45
X	Kort, M. E. et al. Subtype-selective Nav1.8 sodium channel blockers: Identification of potent, orally active nicotinamide derivatives. Bioorganic & medicinal chemistry letters (15 November 2010), Volume 20, Issue 22, pages: 6812-6815. DOI: <10.1016/j.bmcl.2010.08.121>. Retrieved from URL: <https://booksc.org/book/3440001/08cc58> 15 Nov 2010 (2010/11/15) Table 1, compounds 7, 8 and 12-18.	5-7,45
X	CA 2984073 A1 (Nuchem Therapeutics Inc. [CA]) 27 Apr 2019 (2019/04/27) Claims and specific compounds (such as N-1402, N-0701, N-0879, N-0969, N-0981, N-0988, N-1435, N-1436 and many more).	5-7,45
A	WO 2019/067528 A1 (THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA [US]) 04 Apr 2019 (2019/04/04) For example, see compounds ADG-204, ADG-205, ADG-206 and ADG-207, and claims 21-24.	1-45
A	WO 2015/175845 A1 (PELOTON THERAPEUTICS, INC. [US]) 19 Nov 2015 (2015/11/19) Claims 1, 8 and table 1.	1-45

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PCT/IL2020/050524

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Banerjee, M. et al. Small molecule ACSS2 inhibitors target acetate metabolizing tumor cells in hypoxic conditions [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2018; 2018 Apr 14-18; Chicago, IL. Philadelphia (PA): AACR. Cancer Research (July 2018), Volume 78, Issue: 13-Suppl. Abstract No. 3510. DOI: <10.1158/1538-7445.AM2018-3510>. Retrieved from URL: <https://cancerres.aacrjournals.org/content/78/13_Supplement/3510>. Also see: < https://www.curadev.in/images/AACR_2018_Annual_Meeting.jpg>. 31 Jul 2018 (2018/07/31)	1-45
A	Wen, H. et al. Glucose-derived acetate and ACSS2 as key players in cisplatin resistance in bladder cancer. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids (March 2019), Volume 1864, Issue 3, pages: 413-421. Available online 5 June 2018. DOI: <10.1016/j.bbalip.2018.06.005>. Retrieved from URL: <https://booksc.org/book/70595821/f8db2c>. 05 Jun 2018 (2018/06/05)	1-45
P,X	WO 2019/097515 A1 (METABOMED LTD [IL]) 23 May 2019 (2019/05/23) The whole document. Especially Table 1 (such as compound 190, 224, 338 and 339).	1-45
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2020/050524

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (20200101) C07D 231/26, C07D 231/22, C07D 231/14, C07D 231/38, C07D 213/56, C07D 233/66, C07D 207/36, C07D 239/28, C07D 241/24, C07D 241/26, C07D 249/04, C07D 263/34, C07D 401/04, C07D 401/10, C07D 401/14, C07D 403/04, C07D 403/10, C07D 403/12, C07D 403/14, C07D 413/04, C07D 413/10, A61K 31/4152, A61K 31/415, A61K 31/4155, A61K 31/4192, A61K 31/421, A61K 31/404, A61K 31/4164, A61K 31/4178, A61K 31/4439, A61K 31/444, A61K 31/4196, A61K 31/4245, A61K 31/4418, A61K 31/496, A61K 31/4965, A61K 31/505, A61K 31/506, A61K 31/454, A61K 31/4545, A61K 31/40, A61P 35/00, A61P 25/32, A61P 31/12, A61P 1/16, A61P 3/00, A61P 25/00, A61P 25/18, A61P 25/24, A61P 29/00, A61P 37/00
CPC (20130101) C07D 231/26, C07D 231/22, C07D 231/14, C07D 231/38, C07D 213/56, C07D 233/66, C07D 207/36, C07D 239/28, C07D 241/24, C07D 241/26, C07D 249/04, C07D 263/34, C07D 401/04, C07D 401/10, C07D 401/14, C07D 403/04, C07D 403/10, C07D 403/12, C07D 403/14, C07D 413/04, C07D 413/10, A61K 31/4152, A61K 31/415, A61K 31/4155, A61K 31/4192, A61K 31/421, A61K 31/404, A61K 31/4164, A61K 31/4178, A61K 31/4439, A61K 31/444, A61K 31/4196, A61K 31/4245, A61K 31/4418, A61K 31/496, A61K 31/4965, A61K 31/505, A61K 31/506, A61K 31/454, A61K 31/4545, A61K 31/40, A61P 35/00, A61P 25/32, A61P 31/12, A61P 1/16, A61P 3/00, A61P 25/00, A61P 25/18, A61P 25/24, A61P 29/00, A61P 37/00

B. FIELDS SEARCHED:

* Minimum documentation searched (classification system followed by classification symbols)

IPC (20200101) C07D 231/26, C07D 231/22, C07D 231/14, C07D 231/38, C07D 213/56, C07D 233/66, C07D 207/36, C07D 239/28, C07D 241/24, C07D 241/26, C07D 249/04, C07D 263/34, C07D 401/04, C07D 401/10, C07D 401/14, C07D 403/04, C07D 403/10, C07D 403/12, C07D 403/14, C07D 413/04, C07D 413/10, A61K 31/4152, A61K 31/415, A61K 31/4155, A61K 31/4192, A61K 31/421, A61K 31/404, A61K 31/4164, A61K 31/4178, A61K 31/4439, A61K 31/444, A61K 31/4196, A61K 31/4245, A61K 31/4418, A61K 31/496, A61K 31/4965, A61K 31/505, A61K 31/506, A61K 31/454, A61K 31/4545, A61K 31/40, A61P 35/00, A61P 25/32, A61P 31/12, A61P 1/16, A61P 3/00, A61P 25/00, A61P 25/18, A61P 25/24, A61P 29/00, A61P 37/00
CPC (20130101) C07D 231/26, C07D 231/22, C07D 231/14, C07D 231/38, C07D 213/56, C07D 233/66, C07D 207/36, C07D 239/28, C07D 241/24, C07D 241/26, C07D 249/04, C07D 263/34, C07D 401/04, C07D 401/10, C07D 401/14, C07D 403/04, C07D 403/10, C07D 403/12, C07D 403/14, C07D 413/04, C07D 413/10, A61K 31/4152, A61K 31/415, A61K 31/4155, A61K 31/4192, A61K 31/421, A61K 31/404, A61K 31/4164, A61K 31/4178, A61K 31/4439, A61K 31/444, A61K 31/4196, A61K 31/4245, A61K 31/4418, A61K 31/496, A61K 31/4965, A61K 31/505, A61K 31/506, A61K 31/454, A61K 31/4545, A61K 31/40, A61P 35/00, A61P 25/32, A61P 31/12, A61P 1/16, A61P 3/00, A61P 25/00, A61P 25/18, A61P 25/24, A61P 29/00, A61P 37/00

* Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: CAPLUS, BIOSIS, EMBASE, MEDLINE, MARPAT, REGISTRY, Google Scholar, DWPI
Search terms used: ACSS2, acyl-coenzyme A synthetase short-chain family member 2, acyl-coenzyme A synthetase short-chain, ACAS2, ACSA, dJ1161H23.1, acyl-CoA synthetase short chain family member 2, acetyl-coenzyme A Synthetase 2, acetyl-coenzyme A synthetase, ACECS1, ACECS, histone, acetyl*, acetate, alcoholism, alcohol abuse, acetyl-CoA, *cancer*, *carcinoma*, *melanoma*, *tumor*, *tumour*, *prolifer*, *neoplas*, apoptosis, cell death, arrest, hypoxic stress, lipid synthesis, fatty acid synthesis, *viral, *virus, steatohepatitis, NASH, alcoholic steatohepatitis, metabolic disorder, obesity, weight gain, hepatic steatosis, fatty liver, NAFLD, *psychiatr*, *anxiety, *depression, *schizophrenia, autism, post-traumatic stress disorder, PTSD, *inflamma*, autoimmun*, *immun*.