

COMPOSITIONS AND INHIBITORS OF POLRMT

CROSS-REFERENCE TO APPLICATIONS

[0001] The present application claims priority to US provisional application number 63/546,388 filed on October 30, 2023, the entirety of which is incorporated herein.

FIELD OF THE INVENTION

[0002] The present disclosure relates to POLRMT modulators, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof. The present disclosure also relates to novel oxadiazole compositions, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof. The present disclosure also relates to methods of making the modulator compounds and/or oxadiazole compositions. The present disclosure further relates to methods of using such compounds and compositions, including to inhibit or promote POLRMT.

BACKGROUND OF THE INVENTION

[0003] Human mitochondrial RNA polymerase, POLRMT (also referred to as h- mtRNAP), is a nuclear-encoded single-subunit DNA-dependent RNA polymerase. POLRMT is 1230 amino acids in length and consists of three distinct regions: (1) a C- terminal polymerase domain (CTD) (residues 648–1230); (2) an N-terminal domain (NTD) (residues 369–647); and (3) an N-terminal extension (NTE) (residues 1–368). See, e.g., Arnold, J.J., et al., "Human mitochondrial RNA polymerase: Structure-function, mechanism and inhibition," *Biochim. Biophys. Acta*, 1819, 948-960 (2012). It is structurally related to the single-subunit RNA polymerase encoded by bacteriophage T7. The CTD is also known as the catalytic domain due to its function of catalyzing nucleotide incorporation into a growing RNA molecule during transcription. This domain is highly conserved across species, whereas by contrast the NTE demonstrates significant sequence variability, suggesting organism-specific roles for this domain of POLRMT.

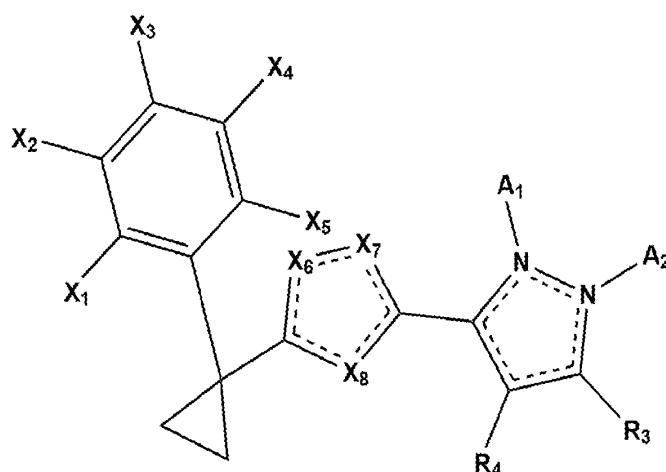
[0004] POLRMT is of fundamental importance for both expression and replication of the human mitochondrial genome. While aspects of POLRMT biochemistry are known, its full physiological role in mitochondrial gene expression and homeostasis, as well as its underlying impact in the etiology of various disease states, remains unclear. Its dysfunction and/or deregulation impacts mitochondrial metabolism, sometimes through the OXPHOS system, which ultimately contributes to many metabolic, degenerative and age-related diseases such as cancer, diabetes, obesity, and Alzheimer's disease. Pharmacological inhibition of POLRMT is one means by which to gain a further understanding of the role of this polymerase in cell physiology

and the development of disease. Regulation of metabolic mechanisms, including oxidative phosphorylation, with POLRMT modulators affords an opportunity for intervention in complex disorders. In view of the numerous and varied roles of POLRMT, the need exists for potent and specific modulators of POLRMT.

SUMMARY OF THE INVENTION

[0005] Briefly, therefore, the present disclosure is directed to compounds, pharmaceutically acceptable salts of the compounds, and methods of using the compounds, salts of the compounds to treat various neurodegenerative and metabolic disorders, cancer, and also disorders related to aging and mitochondrial diseases.

[0006] In a first aspect of the present disclosure, the present disclosure provides a compound, which, according to an embodiment of the present disclosure is a compound represented by Formula (I),



Formula (I).

[0007] In some embodiments, X_1 - X_5 are each independently a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6 alkoxy, optionally substituted with an aryl, a C_3 - C_{10} cycloalkyl, $-C(O)NH_2$, $-C(O)NHY^1$, $-C(O)NY^1Y^2$, $-COOH$, $-C(O)OY^1$, $-Y^1COOH$, or $-Y^1OY^2$.

[0008] In some embodiments, Y^1 and Y^2 are each independently a C_1 - C_6 alkyl optionally substituted with one or more halogen or hydroxy.

[0009] In some embodiments, X_6 - X_8 are each independently a C, N, S, or O.

[0010] In some embodiments, R_3 is a halogen, a hydrogen, a C_1 - C_6 alkyl, a C_1 - C_6 alkyl substituted with one or more halogen, or a C_3 - C_6 cycloalkyl.

[0011] In some embodiments, R_4 is a hydrogen, a C_1 - C_6 alkyl, or a C_1 - C_6 alkyl substituted with one or more halogen.

[0012] In some embodiments, if R_3 and R_4 are optionally interconnected they form a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

[0013] In some embodiments, A_1 and A_2 are each independently a hydrogen, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, an aryl, substituted aryl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_3 - C_6 heterocyclyl, substituted C_3 - C_6 heterocyclyl, or absent.

[0014] In some embodiments, A_1 and A_2 may optionally be substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, $-C(O)NH_2$, $-CS(O)_2Y^3$, a $-CY^1S(O)_2Y^3$.

[0015] In some embodiments, Y^3 is independently hydrogen or C_1 - C_4 alkyl optionally substituted with one or more groups selected from the group consisting of halogen, hydroxyl, C_1 - C_4 haloalkoxyl, and C_1 - C_4 alkoxyl.

[0016] Some aspects of the present disclosure include compounds described above, wherein the compound has a POLRMT IC_{50} of 200 nM or less.

[0017] Some aspects of the present disclosure include a pharmaceutical composition comprising a compound according to any of the previous claims.

[0018] Some aspects of the present disclosure are directed towards a method of inhibiting the activity of POLRMT comprising administering a compound of any of the previous claims to a subject in need thereof.

[0019] Other aspects and iterations of the present disclosure are detailed below.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Modulators of POLRMT are useful in compositions and methods suitable for treating many disorders, such as cancer, neurodegenerative disorders, metabolic disorders, as well as diseases related to aging and mitochondrial diseases. Provided herein are novel compositions, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof. Provided herein are compounds of Formulae (I), (IIa), (IIa-2), (IIb-1), (IIb-2)a, (IIc), (IIc-1), (IIc-2a), (IIc-2b), (IId), (IIe), (IIe), (IIe), (III), (IIIa), (IIIb), (IV), (IVa), (IVb), (Va), (Va-1), (Vb), and (Vb-1) pharmaceutically acceptable salts thereof, prodrugs thereof, and pharmaceutical compositions comprising such compounds, their salts, or their prodrugs that are useful as inhibitors of POLRMT.

(I) Definitions

[0021] The term “alkyl” as used herein refers to both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms in a specified range. For example, the term “C₁-C₆ alkyl” means linear or branched chain alkyl groups, including all possible isomers, having 1, 2, 3, 4, 5, or 6 carbon atoms. Furthermore, alkyl groups allow for substituents to be located on any of the carbon atoms. For example, a substituted C₃ alkyl group allows for the substituent to be located on any of the three carbon atoms.

[0022] The term “alkoxy” or “alkoxyl” as used herein refers to an -O-alkyl group. For example, the term “C₁-C₄ alkoxy” means -O-C₁-C₄ alkyl. Examples of alkoxy include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), and the like.

[0023] The term “haloalkoxy” or “haloalkoxyl” as used herein refers to an -O-alkyl group in which at least one of the hydrogen atoms of the alkyl group is replaced with a halogen atom. Examples of haloalkoxy include trifluoromethoxy, 2,2,2-trifluoroethoxy, and the like. **[0027]** The term “alkanoyl” or “acyl” as used herein refers to an -C(O)-alkyl group. For example, the term “C₁-C₆ alkanoyl” means -C(O)-C₁-C₆ alkyl. Examples of alkanoyl include acetyl, propionyl, butyryl, and the like.

[0024] The term “bicyclic” as used herein refers to a saturated or unsaturated 6- to 12-membered ring consisting of two joined cyclic substructures, and includes fused, bridged, and spiro bicyclic rings.

[0025] The term “heterobicyclic” as used herein refers to a bicyclic ring that contains 1 or more heteroatom(s) in one or more rings that are optionally substituted or oxidized, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. Examples of heterobicyclic rings include, but are not limited to, 8-azabicyclo[3.2.1]octan-8-yl, 3-oxa-8-azabicyclo[3.2.1]octan-8-yl, 8-oxa-3-azabicyclo[3.2.1]octan-3-yl, and 5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl.

[0026] The term “cycloalkyl” as used herein refers to a cyclized alkyl ring having the indicated number of carbon atoms in a specified range. Thus, for example, “C₃-C₆ cycloalkyl” encompasses each of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0027] The term “aryl” as used herein refers to a monocyclic or fused bicyclic ring system having the characteristics of aromaticity, wherein at least one ring contains a completely conjugated pi-electron system. Typically, aryl groups contain 6 to 14 carbon atoms (“C₆-C₁₄ aryl”) or preferably, 6 to 12 carbon atoms (“C₆-C₁₂ aryl”). Fused aryl groups may include an

aryl ring (e.g., a phenyl ring) fused to another aryl ring, or fused to a saturated or partially unsaturated carbocyclic or heterocyclic ring. The point of attachment to the base molecule on such fused aryl ring systems may be a C atom of the aromatic portion or a C or N atom of the non-aromatic portion of the ring system. Examples, without limitation, of aryl groups include phenyl, biphenyl, naphthyl, anthracenyl, indanyl, indenyl, and tetrahydronaphthyl.

[0028] The term “cycloaryl” herein refers to a polycyclic group wherein an aryl group is fused to a 5- or 6-membered aliphatic or heterocyclic ring. For example, “C₆-C₁₂ cycloaryl” means a C₆-C₁₂ aryl fused to a 5- or 6-membered aliphatic or heterocyclic ring. One example of C₆ cycloaryl is 2,3-dihydrobenzo[b][1,4]dioxine.

[0029] The term “heteroaryl” as used herein refers to (i) a 5- or 6-membered ring having the characteristics of aromaticity containing at least one heteroatom selected from N, O and S, wherein each N is optionally in the form of an oxide, and (ii) a 9- or 10- membered bicyclic fused ring system, wherein the fused ring system of (ii) contains at least one heteroatom independently selected from N, O and S, wherein each ring in the fused ring system contains zero, one or more than one heteroatoms, at least one ring is aromatic, each N is optionally in the form of an oxide, and each S in a ring which is not aromatic is optionally S(O) or S(O)₂. Typically, heteroaryl groups contain 5 to 14 ring atoms (“5-14 membered heteroaryl”), and preferably 5 to 12 ring atoms (“5-12 membered heteroaryl”). Heteroaryl rings are attached to the base molecule via a ring atom of the heteroaromatic ring, such that aromaticity is maintained. Suitable 5- and 6-membered heteroaromatic rings include, for example, pyridyl, 3-fluoropyridyl, 4-fluoropyridyl, 3- methoxypyridyl, 4-methoxypyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl (i.e., 1,2,3-triazolyl or 1,2,4- triazolyl), tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl (i.e., the 1,2,3-, 1,2,4-, 1,2,5- (furazanyl), or 1,3,4- isomer), oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Suitable 9- and 10-membered heterobicyclic, fused ring systems include, for example, benzofuranyl, indolyl, indazolyl, naphthyridinyl, isobenzofuranyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, chromenyl, quinolinyl, isoquinolinyl, benzopiperidinyl, benzofuranyl, imidazo[1,2-a]pyridinyl, benzotriazolyl, indazolyl, indolinyl, and isoindolinyl.

[0030] The term “heteroaryloxy” or “heteroaryloxy” as used herein refers to an -O- heteroaryl group. **[0035]** The term “heterocycle”, “heterocyclyl”, or “heterocyclic” as used herein represents a stable 3- to 10-membered monocyclic, non-aromatic ring that is either saturated or unsaturated, and that consists of carbon atoms and from one to two heteroatoms selected from the group consisting of N, O, and S. Examples include oxiranyl, aziridinyl, oxetanyl, azetidiny,

tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, piperazinyl, azepanyl, oxepanyl, and oxazepanyl.

[0031] The term “oxo” as used herein refers to a group which consists of oxygen which is double bonded to carbon or any other element.

[0032] The term “imine” as used herein refers to a group containing a carbon-nitrogen double bond.

[0033] The term “carboxyl” as used herein refers to a combination of two functional groups attached to a single carbon atom, namely, hydroxyl (OH) and carbonyl (O).

[0034] The term “optionally substituted” or “optional substituents” as used herein means that the groups are either unsubstituted or substituted with one or more of the substituents specified. When the groups are substituted with more than one substituent, the substituents may be the same or different. Furthermore, when using the terms “independently,” “independently are,” and “independently selected from” mean that the groups may be the same or different.

[0035] The term “deuterium” as used herein refers to an isotope of hydrogen that has one proton and one neutron in its nucleus and that has twice the mass of ordinary hydrogen. Deuterium herein is represented by the symbol “D”.

[0036] The term “deuterated” by itself or used to modify a compound or group as used herein refers to the presence of at least one deuterium atom attached to carbon. For example, the term “deuterated compound” refers to a compound which contains one or more carbon-bound deuterium(s). In a deuterated compound of the present invention, when a particular position is designated as having deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015 %.

[0037] The term “undeuterated” or “non-deuterated” as used herein refers to the ratio of deuterium atoms of which is not more than the natural isotopic deuterium content, which is about 0.015 %; in other words, all hydrogen are present at their natural isotopic percentages. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition.

[0038] The term “isotopic enrichment factor” as used herein refers to the ratio between the isotope abundance and the natural abundance of a specified isotope.

[0039] The term “isotopologue” as used herein refers to a species in which the chemical structure differs from a specific compound of the invention only in the isotopic composition thereof.

[0040] The term “substantially free of other stereoisomers” as used herein means less than 10 % of other stereoisomers, preferably less than 5 % of other stereoisomers, more preferably less than 2 % of other stereoisomers and most preferably less than 1 % of other stereoisomers are present.

[0041] The term “pharmaceutically acceptable salt” as used herein refers to a salt that is not biologically or otherwise undesirable (e.g., not toxic or otherwise harmful). A salt of a compound of the invention is formed between an acid and a basic group of the compound, or a base and an acidic group of the compound. For example, when the compounds of the invention contain at least one basic group (i.e., groups that may be protonated), the invention includes the compounds in the form of their acid addition salts with organic or inorganic acids such as, for example, but not limited to salts with hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, benzenesulfonic acid, acetic acid, citric acid, glutamic acid, lactic acid, and methanesulfonic acid. When compounds of the invention contain one or more acidic groups (e.g., a carboxylic acid), the invention includes the pharmaceutically acceptable salts of the compounds formed with but not limited to alkali metal salts, alkaline earth metal salts or ammonium salts. Examples of such salts include, but are not limited to, sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Additional examples of such salts may be found in Stahl, P. H. et al. *Pharmaceutical Salts: Properties, Selection, and Use*, 2nd Revised Edition, Wiley, 2011.

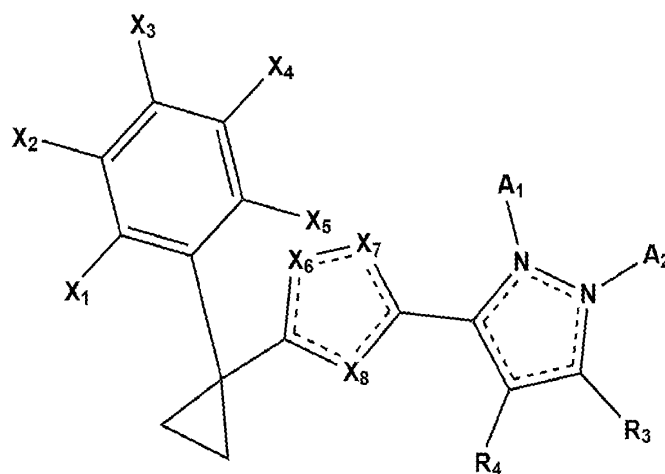
[0042] The term “prodrug” as used herein refers to derivatives of compounds of the invention which may have reduced pharmacological activity, but can, when administered to a patient, be converted into the inventive compounds. Design and use of prodrugs may be found in “Pro-drugs as Novel Delivery Systems,” Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and “Bioreversible Carriers in Drug Design,” Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association), the disclosures of which are incorporated herein by reference in their entireties. The terms “treatment”, “treating” and “treat” as used herein, include their generally accepted meanings, i.e., the management and care of a patient for the purpose of preventing, reducing the risk in incurring or developing a given condition or disease, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, delaying, or reversing the progression or severity, and holding in check existing characteristics of a disease, disorder, or pathological condition, including the alleviation or relief of symptoms or complications, or the cure or elimination of the disease, disorder, or condition.

[0043] The term “therapeutically effective amount” as used herein refers to that amount of compound of the invention that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other. As will be recognized by a person of ordinary skill in the art, a therapeutically effective amount of the compounds of the invention will vary and will depend on the diseases treated, the severity of the disease, the route of administration, and the gender, age, and general health condition of the subject to whom the compound is being administered. The therapeutically effective amount may be administered as a single dose once a day, or as split doses administered multiple (e.g., two, three or four) times a day. The therapeutically effective amount may also be administered through continuous dosing, such as through infusion or with an implant.

(II) Compounds

A. General Structures

[0044] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (I):



Formula (I);

wherein

X₁-X₅ are each independently a hydrogen, a halogen, a hydroxy, a cyano, a C₁-C₆ alkyl, a substituted C₁-C₆ alkyl, a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, a C₁-C₆ alkoxy, optionally substituted with an aryl, a C₃-C₁₀ cycloalkyl, -C(O)NH₂, -C(O)NHY¹, -C(O)NY¹Y², -COOH, -C(O)OY¹, -Y¹COOH, or -Y¹OY²;

Y¹ and Y² are each independently a C₁-C₆ alkyl optionally substituted with one or more halogen or hydroxy;

X₆-X₈ are each independently a C, N, S, or O;

R₃ is a halogen, a hydrogen, a C₁-C₆ alkyl, a C₁-C₆ alkyl substituted with one or more halogen, or a C₃-C₆ cycloalkyl;

R₄ is a hydrogen, a C₁-C₆ alkyl, or a C₁-C₆ alkyl substituted with one or more halogen;

if R₃ and R₄ are optionally interconnected they form a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring;

A₁ and A₂ are each independently a hydrogen, a C₁-C₆ alkyl, a substituted C₁-C₆ alkyl, an aryl, substituted aryl, a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, a C₃-C₆ heterocyclyl, substituted C₃-C₆ heterocyclyl, or absent;

wherein A₁ and A₂ may optionally be substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, -C(O)NH₂, -CS(O)₂Y³, a -CY¹S(O)₂Y³;

Y³ is independently a hydrogen or a C₁-C₄ alkyl optionally substituted with one or more groups selected from the group consisting of a halogen, a hydroxyl, a C₁-C₄ haloalkoxyl, and a C₁-C₄ alkoxyl;

with the proviso that formula (I) excludes the following compounds:

5-[5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl]-3-[1-(5-fluoro-2-methylphenyl)cyclopropyl]-1,2,4-oxadiazole;

3-[1-(3-methylphenyl)cyclopropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-1,2,4-oxadiazole;

3-[1-(3-Methoxyphenyl)cyclopropyl]-5-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]-1,2,4-oxadiazole;

3-[1-(5-fluoro-2-methylphenyl)cyclopropyl]-5-(5-methoxy-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole;

5-(1-methyl-1*H*-pyrazol-3-yl)-3-(1-phenylcyclopropyl)-1,2,4-oxadiazole;

3-[1-(3,5-Dimethylphenyl)cyclopropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-1,2,4-oxadiazole;
1-methyl-5-(3-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-2,3-dihydro-1*H*-pyrazol-3-ol, 1,2-Dihydro-1-methyl-5-[3-[1-[3-(trifluoromethyl)phenyl]cyclopropyl]-1,2,4-oxadiazol-5-yl]-3*H*-pyrazol-3-one;

5-(1-Methyl-1*H*-pyrazol-5-yl)-3-[1-[3-(trifluoromethyl)phenyl]cyclopropyl]-1,2,4-oxadiazole;

3-[1-(3-Methoxyphenyl)cyclopropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-1,2,4-oxadiazole;

3-[1-(3-Bromophenyl)cyclopropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-1,2,4-oxadiazole;

and

5-(3-Ethyl-1-methyl-1*H*-pyrazol-5-yl)-3-[1-(3-methylphenyl)cyclopropyl]-1,2,4-oxadiazole.

[0045] In some aspects, X_1 - X_5 may each independently be a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6 alkoxy, optionally substituted with an aryl, a C_3 - C_{10} cycloalkyl, $-C(O)NH_2$, $-C(O)NHY^1$, $-C(O)NY^1Y^2$, $-COOH$, $-C(O)OY^1$, $-Y^1COOH$, or $-Y^1OY^2$, wherein Y^1 and Y^2 are each independently a C_1 - C_6 alkyl optionally substituted with one or more halogen or hydroxy.

[0046] In some aspects, X_6 - X_8 may each independently be a C, N, S, or O.

[0047] In some aspects, R_3 may be a halogen, a hydrogen, a C_1 - C_6 alkyl, a C_1 - C_6 alkyl substituted with one or more halogen, or a C_3 - C_6 cycloalkyl.

[0048] In some aspects, R_4 may be a hydrogen, a C_1 - C_6 alkyl, or a C_1 - C_6 alkyl substituted with one or more halogen.

[0049] In other aspects, R_3 and R_4 may optionally be interconnected to form a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

[0050] In some aspects, A_1 and A_2 may each independently be a hydrogen, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, an aryl, substituted aryl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_3 - C_6 heterocyclyl, substituted C_3 - C_6 heterocyclyl, or absent.

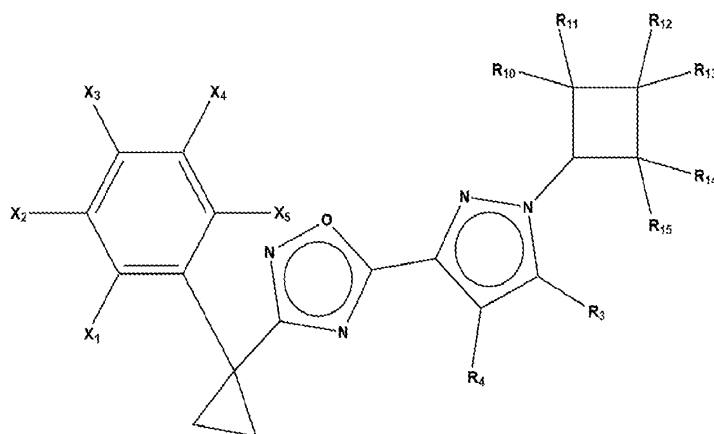
[0051] In some aspects, A_1 and A_2 are each independently be one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, $-C(O)NH_2$, $-CS(O)_2Y^3$, a $-CY^1S(O)_2Y^3$, wherein Y^3 may be independently a hydrogen or a C_1 - C_4 alkyl optionally substituted with one or more groups selected from the group consisting of a halogen, a hydroxyl, a C_1 - C_4 haloalkoxyl, and a C_1 - C_4 alkoxy.

[0052] In some aspects, A_1 and A_2 may each independently be $-C(O)NY^3Y^4$, $-CY^1(O)NY^3Y^4$, or $-NY^3Y^4$. In some aspects, Y^3 is independently a hydrogen or a C_1 - C_4 alkyl optionally substituted with one or more groups selected from the group consisting of a halogen, a hydroxyl, a C_1 - C_4 haloalkoxyl, and a C_1 - C_4 alkoxy. In some aspects, Y^4 is independently Y^3 , cyano, C_3 - C_6 cycloheteroalkyl, C_1 - C_6 amide, C_1 - C_6 amine, C_1 - C_6 carboxyl, aryl, C_1 - C_6 alkyl optionally

substituted with one or more halogen groups, 5- or 6-membered heterocyclyl, or C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ hydroxy, or -C(O)C₁-C₄ alkyl optionally substituted with one or more halogen groups. In yet other aspects, Y³ and Y⁴ are attached to the same nitrogen atom, Y³ and Y⁴ together with their connecting nitrogen form a 4- to 6-membered heterocyclic ring optionally containing one or more heteroatoms that is N, O, S, S(O), SO₂, or S(O)NY³, and such heterocyclic ring is optionally substituted with one or more groups, each group independently selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxyl, carboxyl, oxo, and C₁-C₄ alkylcarboxylate.

B. Compounds with Formulae (IIa-1) and (IIa-2)

[0053] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (IIa-1):



Formula (IIa-1).

[0054] In some aspects, X₁-X₅ may each independently be a hydrogen, a halogen, a hydroxy, a cyano, a C₁-C₆ alkyl, a substituted C₁-C₆ alkyl, a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, a C₁-C₆ alkoxy, optionally substituted with an aryl, a C₃-C₁₀ cycloalkyl, -C(O)NH₂, -C(O)NHY¹, -C(O)NY¹Y², -COOH, -C(O)OY¹, -Y¹COOH, or -Y¹OY², wherein Y¹ and Y² are each independently a C₁-C₆ alkyl optionally substituted with one or more halogen or hydroxy.

[0055] In some aspects, R₃ may be a halogen, a hydrogen, a C₁-C₆ alkyl, a C₁-C₆ alkyl substituted with one or more halogen, or a C₃-C₆ cycloalkyl.

[0056] In some aspects, R₄ may be a hydrogen, a C₁-C₆ alkyl, or a C₁-C₆ alkyl substituted with one or more halogen.

[0057] In other aspects, R₃ and R₄ may optionally be interconnected to form a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered

heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

[0058] In some aspects, R_{10} - R_{15} may each independently be a hydrogen, an alkoxy, a halogen, a C_1 - C_6 alkyl, or a carboxylic acid.

[0059] In some examples, X_1 may be a C_1 - C_6 alkyl or a halogen.

[0060] In some examples, X_2 may be a hydrogen or a halogen.

[0061] In some examples, X_3 may be a hydrogen, a halogen, or a C_1 - C_6 alkyl.

[0062] In some examples, X_4 may be hydrogen.

[0063] In some examples, X_5 may be a hydrogen or a C_1 - C_6 alkyl.

[0064] In some examples, at least two of X_2 - X_5 are hydrogen.

[0065] In some examples, at least three of X_2 - X_5 are hydrogen.

[0066] In some examples, X_2 - X_5 may be hydrogen.

[0067] In some examples, X_1 may be methyl or Cl.

[0068] In some examples, X_2 may be Cl or hydrogen and X_3 may be methyl, F, Cl, or hydrogen.

[0069] In some examples, R_3 may be a hydrogen, a methyl or $-\text{CHF}_2$.

[0070] In some examples, R_4 may be hydrogen.

[0071] In some examples, R_{10} - R_{15} may each independently be a hydrogen, a methyl, a methoxy, a halogen, a carboxylic acid, or an amide.

[0072] In some examples, R_3 may be $-\text{CHF}_2$, methyl, or hydrogen, and R_4 is hydrogen.

[0073] In some examples, the X_1 may be halogen or methyl and R_3 may be methyl, $-\text{CHF}_2$, or $-\text{CF}_3$.

[0074] In some examples, the X_2 may be hydrogen or halogen and R_3 may be methyl, $-\text{CHF}_2$, or $-\text{CF}_3$.

[0075] In some examples, the X_3 may be hydrogen or halogen and R_3 may be methyl, $-\text{CHF}_2$, or $-\text{CF}_3$.

[0076] In some examples, X_1 - X_3 may each be independently hydrogen, halogen, or methyl, and R_3 may be methyl, $-\text{CHF}_2$, or $-\text{CF}_3$.

[0077] In some examples, X_1 - X_3 may each be independently hydrogen, halogen, or methyl, and R_3 - R_4 are independently hydrogen, methyl, $-\text{CHF}_2$, or $-\text{CF}_3$.

[0078] In some examples, at least one of R_{10} - R_{15} is carboxylic acid.

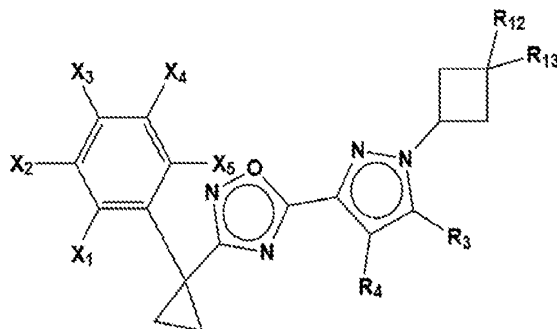
[0079] In some examples, at least one of R_{10} - R_{11} is carboxylic acid

[0080] In some examples, at least one of R_{12} - R_{13} is carboxylic acid

[0081] In some examples, at least one of R_{14} - R_{15} is carboxylic acid.

[0082] In some examples, R₁₂-R₁₃ may each independently be hydrogen, fluorine, methyl, methoxy, or carboxylic acid.

[0083] In some examples, R₁₀-R₁₁ and R₁₄-R₁₅ may be hydrogen and the compound may be represented by Formula (IIa-2):



Formula (IIa-2).

[0084] In some embodiments of Formula (IIa-2), X₁-X₅ may each independently be hydrogen, halogen, or C₁-C₆ alkyl.

[0085] In some embodiments of Formula (IIa-2), R₃ may be halogen, hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, or C₃-C₆ cycloalkyl.

[0086] In some embodiments of Formula (IIa-2), R₄ may be hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl.

[0087] In some embodiments of Formula (IIa-2), R₁₂ and R₁₃ are each independently a C₁-C₆ alkyl, a hydrogen, a halogen, a carboxylic acid, an alkoxy, or an amide.

[0088] In some embodiments of Formula (IIa-2), X₁ may be methyl.

[0089] In some embodiments of Formula (IIa-2), X₃ may be a halogen or a hydrogen.

[0090] In some embodiments of Formula (IIa-2), X₂, X₄, and X₅ may be hydrogen.

[0091] In some embodiments of Formula (IIa-2), R₃ may be hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl.

[0092] In some embodiments of Formula (IIa-2), R₄ may be hydrogen.

[0093] In some embodiments of Formula (IIa-2), R₁₂ and R₁₃ may each independently be hydrogen, carboxylic acid, alkoxy, or amide.

[0094] In some embodiments of Formula (IIa-2), X₁ may be methyl, X₂, X₄, and X₅ are hydrogen, X₃ may be a halogen or a hydrogen, R₃ may be hydrogen, C₁-C₆ alkyl, or substituted C₁-C₆ alkyl, R₄ may be hydrogen, and R₁₂ and R₁₃ may each independently be hydrogen, carboxylic acid, alkoxy, or amide.

[0095] In some embodiments of Formula (IIa-2), R₃ may be difluoromethyl.

[0096] In some embodiments of Formula (IIa-2), R₁₀ may be carboxylic acid and R₁₁ may be hydrogen.

[0097] In some embodiments of Formula (IIa-2), R₁₀ may be amide and R₁₁ may be hydrogen.

[0098] In some embodiments of Formula (IIa-2), X₁ may be a halogen.

[0099] In some embodiments of Formula (IIa-2), X₂ may be hydrogen or halogen.

[0100] In some embodiments of Formula (IIa-2), X₃ may be methyl, halogen, or hydrogen.

[0101] In some embodiments of Formula (IIa-2), X₄ and X₅ may be hydrogen

[0102] In some embodiments of Formula (IIa-2), X₁ may be a halogen, X₂ is hydrogen or halogen, X₃ is methyl, halogen, or hydrogen, and X₄ and X₅ are hydrogen.

[0103] In some embodiments of Formula (IIa-2), R₃ may be difluoromethyl and R₄ may be hydrogen

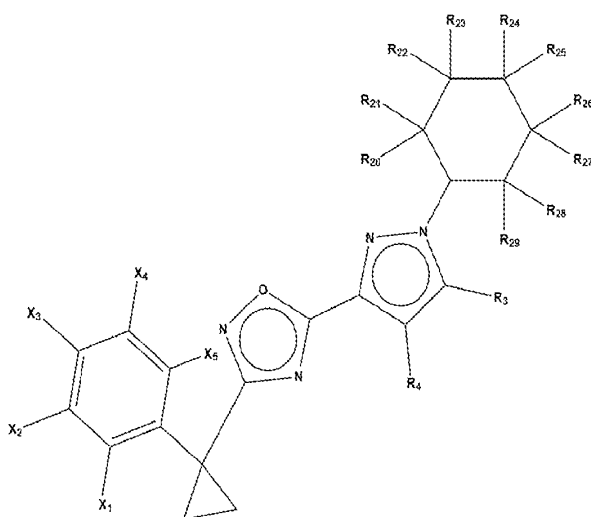
[0104] In some embodiments of Formula (IIa-2), R₁₂ and R₁₃ are each independently hydrogen or carboxylic acid.

[0105] In some embodiments of Formula (IIa-2), R₁₀ may be carboxylic acid and R₁₁ may be methoxy.

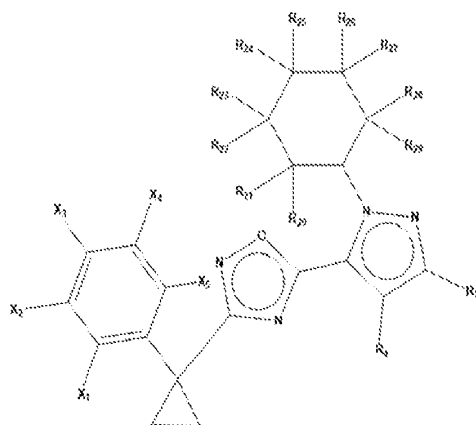
[0106] In some embodiments of Formula (IIa-2), R₁₀ may be carboxylic acid and R₁₁ may be methyl.

C. Compounds with Formulae (IIb-1) & (IIb-2)

[0107] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formulae (IIb-1) & (IIb-2):



Formula (IIb-1); or



Formula (IIb-2).

[0108] In some aspects, X_1 - X_5 may each independently be a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6 alkoxy, optionally substituted with an aryl, a C_3 - C_{10} cycloalkyl, $-C(O)NH_2$, $-C(O)NHY^1$, $-C(O)NY^1Y^2$, $-COOH$, $-C(O)OY^1$, $-Y^1COOH$, or $-Y^1OY^2$, wherein Y^1 and Y^2 are each independently a C_1 - C_6 alkyl optionally substituted with one or more halogen or hydroxy.

[0109] In some aspects, R_3 may be a halogen, a hydrogen, a C_1 - C_6 alkyl, a C_1 - C_6 alkyl substituted with one or more halogen, or a C_3 - C_6 cycloalkyl.

[0110] In some aspects, R_4 may be a hydrogen, a C_1 - C_6 alkyl, or a C_1 - C_6 alkyl substituted with one or more halogen.

[0111] In other aspects, R_3 and R_4 may optionally be interconnected to form a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

[0112] In some aspects, R_{20} - R_{29} may each independently be a hydrogen, a C_1 - C_6 alkyl, a carboxylic acid, an amide, a substituted amide, an alkoxy, or a halogen.

[0113] In some examples, X_1 may be a C_1 - C_6 alkyl.

[0114] In some examples, X_1 may be a methyl.

[0115] In some examples, X_2 and X_4 may be hydrogen.

[0116] In some examples, X_3 may be a hydrogen or halogen.

[0117] In some examples, X_5 may be a hydrogen or a C_1 - C_6 alkyl.

[0118] In some examples, at least two of X_2 - X_5 may be hydrogen.

[0119] In some examples, at least three of X_2 - X_5 may be hydrogen.

[0120] In some examples, X_2 - X_5 may be hydrogen.

- [0121] In some examples, R_3 may be a hydrogen, a methyl, or $-\text{CHF}_2$.
- [0122] In some examples, R_4 may be hydrogen.
- [0123] In some examples, R_{20} - R_{29} are each independently a hydrogen, a C_1 - C_6 alkyl, an alkoxy, a halogen, a carboxylic acid, amide, or a substituted amide.
- [0124] In some examples, the substituted amide may be substituted with one or more C_1 - C_6 alkyl.
- [0125] In some examples, at least one of R_{20} - R_{29} may be carboxylic acid, amide, or substituted amide.
- [0126] In some examples, at least one of R_{20} - R_{21} may be carboxylic acid, amide, or substituted amide.
- [0127] In some examples, at least one of R_{22} - R_{23} may be carboxylic acid, amide, or substituted amide.
- [0128] In some examples, at least one of R_{24} - R_{25} may be carboxylic acid, amide, or substituted amide.
- [0129] In some examples, at least one of R_{26} - R_{27} may be carboxylic acid, amide, or substituted amide.
- [0130] In some examples, at least one of R_{28} - R_{29} may be carboxylic acid, amide, or substituted amide.
- [0131] In some examples, X_1 may be halogen or methyl and R_3 may be hydrogen, methyl, CHF_2 , or CF_3 .
- [0132] In some examples, X_2 may be hydrogen or halogen and R_3 may be hydrogen, methyl, CHF_2 , or CF_3 .
- [0133] In some examples, X_3 may be hydrogen or halogen and R_3 may be hydrogen, methyl, CHF_2 , or CF_3 .
- [0134] In some examples, X_1 - X_3 may each independently be hydrogen, halogen, or methyl, and R_3 is H, methyl, CHF_2 , or CF_3 .
- [0135] In some examples, X_1 - X_3 may each independently be hydrogen, halogen, or methyl, X_4 - X_5 may each independently be hydrogen or halogen, and R_3 - R_4 may independently be hydrogen, methyl, CHF_2 , or CF_3 .
- [0136] In some examples, X_1 - X_3 may each independently be hydrogen, fluorine, chlorine, bromine, or methyl, X_4 - X_5 are each independently hydrogen or halogen, and R_3 - R_4 are independently hydrogen, methyl, CHF_2 , or CF_3 .
- [0137] In some examples, at least one of R_{20} - R_{29} may be carboxylic acid.

[0138] In some examples, at least one of R_{20} - R_{23} may be carboxylic acid.

[0139] In some examples, at least one of R_{24} - R_{25} may be carboxylic acid.

[0140] In some examples, at least one of R_{26} - R_{29} may be carboxylic acid.

[0141] In some examples, R_{24} - R_{25} may each independently be hydrogen, fluorine, methyl, methoxy, or carboxylic acid.

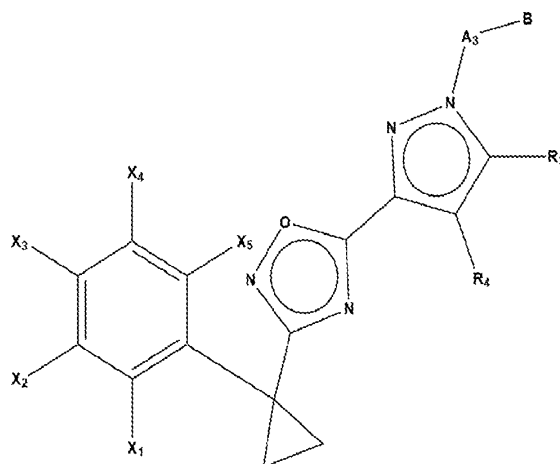
[0142] In some examples, R_{24} - R_{25} may each independently be hydrogen or carboxylic acid.

[0143] In some examples, wherein R_3 and R_4 may be interconnected to form a 5-membered cyclic ring.

[0144] In some examples, R_3 and R_4 may be interconnected to form a phenyl ring.

D. Compounds with Formulas (IIc), (IIc-1), (IIc-2a), and (IIc-2b)

[0145] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (IIc):



Formula (IIc).

[0146] In some aspects, X_1 - X_5 may each independently be a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6 alkoxy, optionally substituted with an aryl, a C_3 - C_{10} cycloalkyl, $-C(O)NH_2$, $-C(O)NHY^1$, $-C(O)NY^1Y^2$, $-COOH$, $-C(O)OY^1$, $-Y^1COOH$, or $-Y^1OY^2$. Y^1 and Y^2 may each be independently a C_1 - C_6 alkyl optionally substituted with one or more halogen or hydroxy.

[0147] In some aspects, R_3 may be a halogen, a hydrogen, a C_1 - C_6 alkyl, a C_1 - C_6 alkyl substituted with one or more halogen, or a C_3 - C_6 cycloalkyl.

[0148] In some aspects, R_4 may be a hydrogen, a C_1 - C_6 alkyl, or a C_1 - C_6 alkyl substituted with one or more halogen.

[0149] In other aspects, R₃ and R₄ may optionally be interconnected to form a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

[0150] In other aspects, A₃ is a hydrogen, a C₁-C₆ alkyl, a C₂-C₆ branched alkyl, a C₁-C₆ alkyl substituted with heterocyclyl, a C₁-C₆ alkyl substituted with a substituted heterocyclyl, or a C₁-C₆ alkyl substituted C₁-C₆ alkoxy.

[0151] In other aspects, B is -C(O)OH, -C(O)NH₂, C(O)NHY³, C(O)NY³Y⁴, -CS(O)₂Y³, -Y³CS(O)₂Y³, or absent. Y³ and Y⁴ may each independently be a C₁-C₄ alkyl optionally substituted with one or more groups selected from the group consisting of a halogen, a hydroxyl, a C₁-C₄ haloalkoxyl, and a C₁-C₄ alkoxy.

[0152] In some examples, X₁ is a hydrogen, a halogen, a cyano, a C₁-C₆ alkyl, a substituted C₁-C₆ alkyl, a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, a C₁-C₆ alkoxy, a C₁-C₆ cycloalkoxy, -COOH, -C(O)NH₂, -C(O)NHY¹, or -C(O)NY¹Y² and Y¹ and Y² are methyl.

[0153] In some examples, X₁ is a C₁-C₆ alkyl. For examples, the C₁-C₆ alkyl may be methyl or ethyl.

[0154] In some examples, X₁ is halogen. For example, the halogen may be fluorine, chlorine, or bromine.

[0155] In some examples, the C₃-C₆ cycloalkyl may be cyclopropyl

[0156] In some examples, X₁ may be -CH₂OCH₃, -CH₂OH, or -CF₃.

[0157] In some examples, X₁ may be -C(O)NH₂, -C(O)NHCH₃, or -C(O)NCH₃CH₃.

[0158] In some examples, X₂ and X₃ may be a hydrogen, a halogen, or a C₁-C₆ alkyl.

[0159] In some examples, X₄ may be a hydrogen, a halogen, a hydroxy, a methoxy, a C₁-C₆ alkyl, or a substituted C₁-C₆ alkyl. For example, the substituted C₁-C₆ alkyl may be -CH₂OH.

[0160] In some examples, X₅ may be a hydrogen, halogen, hydroxy, methoxy, a C₁-C₆ alkyl, or a substituted C₁-C₆ alkyl.

[0161] In some examples, A₃ may be a C₁-C₆ alkyl or substituted C₁-C₆ alkyl and B is carboxylic acid. For example, A₃ may be methyl, ethyl, 1-methyl-methyl, dimethyl-methyl, methyl ethyl, dimethyl ethyl, or methyl-cyclopropyl. Furthermore, the methyl may be connected to a thiazole via a carbon-carbon bond. The methyl may also be connected to a phenyl or a cyclopropyl.

[0162] In some aspects, the substituted C₁-C₆ alkyl may be substituted methyl, substituted ethyl, or substituted propyl. For example, the substituted methyl may be -C(H)(CH₃).

Alternatively, the substituted ethyl may be $-\text{CH}_2\text{CH}(\text{OCH}_3)$, $-\text{CH}_2\text{CH}(\text{OH})$, $-\text{CH}_2\text{C}(\text{CH}_3)\text{H}$, or $\text{CH}_2\text{C}(\text{CH}_3)_2$.

[0163] In some examples, X_1 may be C_1 - C_6 alkyl or halogen.

[0164] In some examples, X_2 may be hydrogen or halogen.

[0165] In some examples, X_3 may be hydrogen, C_1 - C_6 alkyl, or halogen.

[0166] In some examples, X_4 may be hydrogen.

[0167] In some examples, X_1 may be C_1 - C_6 alkyl or hydrogen.

[0168] In some examples, R_3 may be C_1 - C_6 alkyl substituted with one or more halogen. For example, R_3 may be $-\text{CHF}_2$ or $-\text{CF}_3$.

[0169] In some examples, R_4 may be hydrogen.

[0170] In some examples, X_1 - X_5 may each independently be hydrogen, a halogen, or a C_1 - C_6 alkyl.

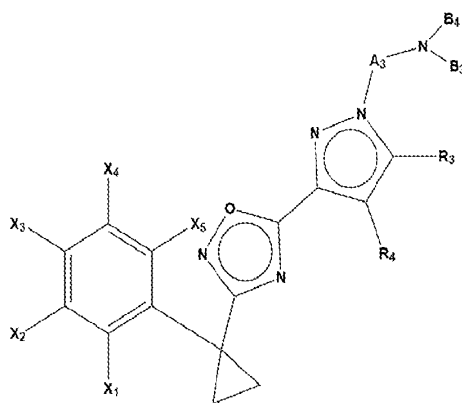
[0171] In some examples, X_3 - X_4 may each independently be hydrogen, methyl, cyclopropyl, $-\text{CHF}_2$, or $-\text{CF}_3$.

[0172] In some examples, A_3 may be substituted with at least one halogen, ester, ether, or carboxylic acid.

[0173] In some examples, A_3 may be substituted with at least one $-\text{C}(\text{O})\text{NH}_2$, $-\text{CS}(\text{O})_2\text{Y}^3$, or $-\text{CY}^1\text{S}(\text{O})_2\text{Y}^3$.

[0174] In some examples, B may be carboxylic acid, amide, methanesulfonamide, methoxy, substituted amide, amine, substituted amine, or substituted sulfoxide.

[0175] In some examples, B may be amine or substituted amine with Formula (IIc-1):



Formula (IIc-1).

[0176] In some embodiments of Formula (IIc-1), X_1 may be a C_1 - C_6 alkyl.

[0177] In some embodiments of Formula (IIc-1), X_2 - X_5 may be hydrogen.

[0178] In some embodiments of Formula (IIc-1), R₃ may be -CHF₂.

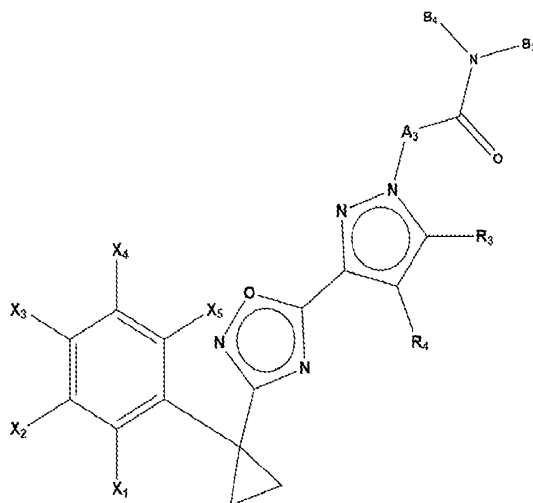
[0179] In some embodiments of Formula (IIc-1), R₄ may be hydrogen.

[0180] In some embodiments of Formula (IIc-1), A₃ may be a C₁-C₆ alkyl.

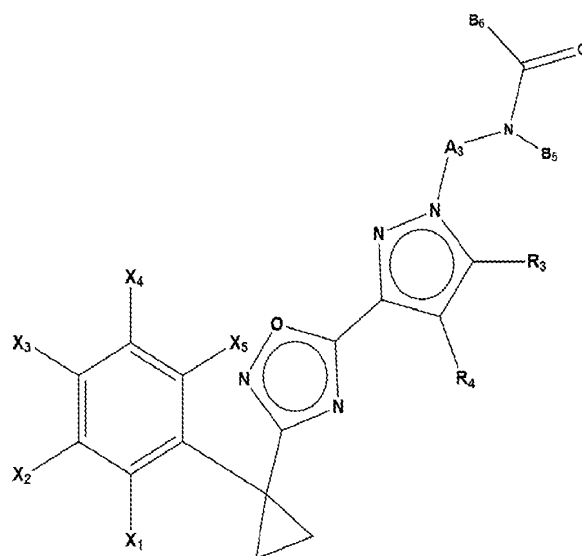
[0181] In some embodiments of Formula (IIc-1), B₃ and B₄ may each independently be hydrogen or a C₁-C₆ alkyl.

[0182] In some embodiments of Formula (IIc-1), X₁ is a C₁-C₆ alkyl, X₂-X₅ are hydrogen, R₃ is -CHF₂, R₄ is hydrogen, A₃ is a C₁-C₆ alkyl; and B₃ and B₄ are each independently hydrogen or a C₁-C₆ alkyl.

[0183] In some examples, B may be amide or substituted amide with Formula (IIc-2a) or Formula (IIc-2b):



Formula (IIc-2a); or



Formula (IIc-2b).

[0184] In some embodiments of Formulae (IIc-2a) and (IIc-2b), X_1 may be C_1 - C_6 alkyl or halogen.

[0185] In some embodiments of Formulae (IIc-2a) and (IIc-2b), X_2 - X_4 may be hydrogen or halogen.

[0186] In some embodiments of Formulae (IIc-2a) and (IIc-2b), X_5 may be hydrogen, halogen, or C_1 - C_6 alkyl.

[0187] In some embodiments of Formulae (IIc-2a) and (IIc-2b), R_3 may be $-CHF_2$, $-CF_3$ or a C_3 - C_6 cycloalkyl.

[0188] In some embodiments of Formulae (IIc-2a) and (IIc-2b), R_4 may be hydrogen.

[0189] In some embodiments of Formulae (IIc-2a) and (IIc-2b), A_3 may be a C_1 - C_6 alkyl or branched C_1 - C_6 alkyl.

[0190] In some embodiments of Formulae (IIc-2a) and (IIc-2b), B_3 and B_4 may be each independently hydrogen, a C_1 - C_6 alkyl, a substituted a C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted a C_3 - C_6 cycloalkyl, a C_3 - C_6 heterocyclyl, a substituted a C_3 - C_6 heterocyclyl, phenyl, substituted phenyl.

[0191] In some embodiments of Formulae (IIc-2a) and (IIc-2b), if B_3 and B_4 are optionally interconnected they form a 4-membered, 5- membered, 6- membered cycloalkyl ring, substituted cycloalkyl ring, heterocyclyl ring, or substituted heterocyclyl ring.

[0192] In some embodiments of Formulae (IIc-2a) and (IIc-2b), B_5 and B_6 may each independently be hydrogen or C_1 - C_6 alkyl.

[0193] In some embodiments of Formulae (IIC-2a) and (IIC-2b), the C₁-C₆ alkyl may be methyl or ethyl.

[0194] In some embodiments of Formulae (IIC-2a) and (IIC-2b), the branched C₁-C₆ alkyl may be -CH₂(CH₃)-.

[0195] In some embodiments of Formulae (IIC-2a) and (IIC-2b), the substituted C₁-C₆ alkyl may be -CH₂CH₂OCH₃, -CH₂C(CH₃)₂OH, -CH₂CH₂OH, -CH₂COOH, -CH(CH₃)COOH, -C(CH₃)₂COOH, methyl-pyridyl, methyl-methyl substituted-pyridyl, methyl cyclopropyl, methyl cyclobutyl, -CH₂CONH₂, CH₂CONHCH₃, -CH₂CH₂N(CH₃)₂, -CH(CH₃)CONH₂, or -CH₂CF₃.

[0196] In some embodiments of Formulae (IIC-2a) and (IIC-2b), A₃ may be ethyl and B may be methanesulfonamide

[0197] In some embodiments of Formulae (IIC-2a) and (IIC-2b), A₃ may be ethyl and B may be methoxy.

[0198] In some embodiments of Formulae (IIC-2a) and (IIC-2b), A₃ may be ethyl and B may be substituted sulfoxide.

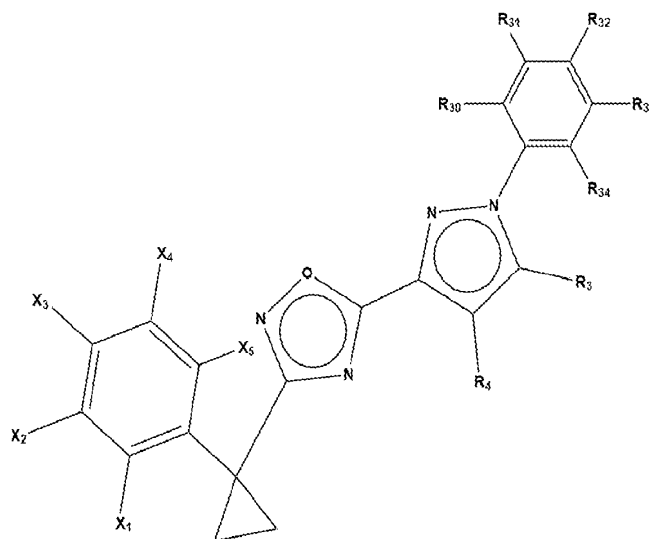
[0199] In some embodiments of Formulae (IIC-2a) and (IIC-2b), R₃ may be -CHF₂, halogen, cyclopropyl, or methyl.

[0200] In some embodiments of Formulae (IIC-2a) and (IIC-2b), R₄ may be hydrogen or methyl.

[0201] In some embodiments of Formulae (IIC-2a) and (IIC-2b), R₃ and R₄ may be connected to form a 5-membered cycloalkyl ring.

E. Compounds with Formula (IId)

[0202] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (IId):



Formula (IId).

[0203] In some aspects, X_1 - X_5 may each independently be a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6 alkoxy, optionally substituted with an aryl, a C_3 - C_{10} cycloalkyl, $-C(O)NH_2$, $-C(O)NHY^1$, $-C(O)NY^1Y^2$, $-COOH$, $-C(O)OY^1$, $-Y^1COOH$, or $-Y^1OY^2$. Y^1 and Y^2 may each be independently a C_1 - C_6 alkyl optionally substituted with one or more halogen or hydroxy.

[0204] In some aspects, R_3 may be a halogen, a hydrogen, a C_1 - C_6 alkyl, a C_1 - C_6 alkyl substituted with one or more halogen, or a C_3 - C_6 cycloalkyl.

[0205] In some aspects, R_4 may be a hydrogen, a C_1 - C_6 alkyl, or a C_1 - C_6 alkyl substituted with one or more halogen.

[0206] In other aspects, R_3 and R_4 may optionally be interconnected to form a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

[0207] In some aspects, R_{30} - R_{34} may each independently be a hydrogen, a carboxylic acid, an ester, a halogen, an amide, a substituted amide, a cyano, an ether, or a C_1 - C_6 alkyl.

[0208] In some examples, X_1 may be a C_1 - C_6 alkyl or a halogen. The C_1 - C_6 alkyl may be methyl. The halogen may be chlorine.

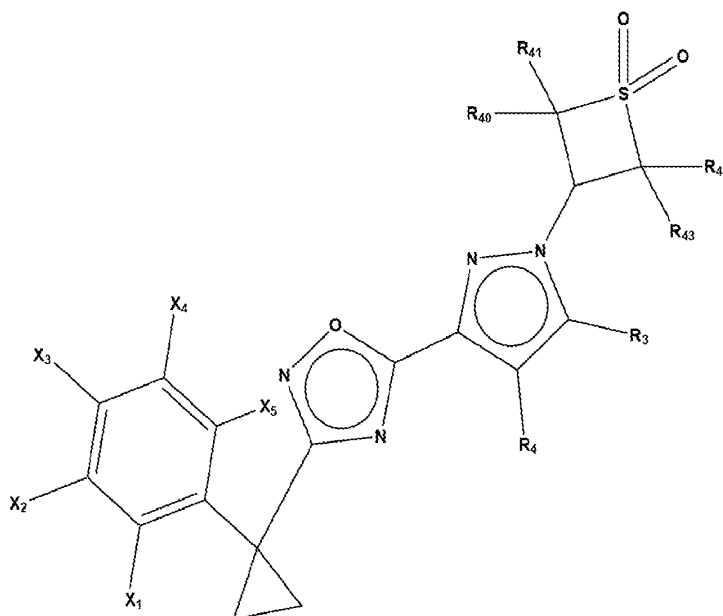
[0209] In some examples, X_2 and X_4 may each independently be a hydrogen or a halogen.

[0210] In some examples, X_3 may be a hydrogen, a C_1 - C_6 alkyl or a halogen. The C_1 - C_6 alkyl may be methyl. The halogen may be chlorine or fluorine.

- [0211] In some examples, X_5 may be a C_1 - C_6 alkyl or a hydrogen.
- [0212] In some examples, at least two of X_2 - X_5 may be hydrogen.
- [0213] In some examples, at least three of X_2 - X_5 may be hydrogen.
- [0214] In some examples, X_2 - X_5 may be hydrogen.
- [0215] In some examples, R_3 may be C_1 - C_6 alkyl or C_1 - C_6 alkyl substituted with one or more halogen. The C_1 - C_6 alkyl substituted with one or more halogen may be $-CHF_2$. The C_1 - C_6 alkyl may be methyl.
- [0216] In some examples, R_4 may be hydrogen.
- [0217] In some examples, R_{30} - R_{34} may be hydrogen.
- [0218] In some examples, R_{30} may be methyl, methoxy, carboxylic acid, $-C(O)OCH_3$, cyano, amide, or substituted amide.
- [0219] In some examples, R_{31} may be methyl, methoxy, carboxylic acid, $-C(O)OCH_3$, cyano, amide, or substituted amide.
- [0220] In some examples, R_{32} may be methyl, methoxy, carboxylic acid, $-C(O)OCH_3$, cyano, amide, or substituted amide.
- [0221] In some examples, R_{33} may be methyl, methoxy, carboxylic acid, $-C(O)OCH_3$, cyano, amide, or substituted amide.
- [0222] In some examples, R_{34} may be methyl, methoxy, carboxylic acid, $-C(O)OCH_3$, cyano, amide, or substituted amide.
- [0223] In some examples, at least two of R_{30} - R_{34} may be hydrogen, $-OCH_3$, $-COOH$, $-C(O)NH_2$, $-C(O)NHCH_3$, cyano, methyl, $-C(O)OCH_3$, or fluorine.
- [0224] In some examples, X_1 - X_5 may each independently be hydrogen, halogen, Cl, F, or methyl, and R_3 - R_4 are independently H, methyl, CHF_2 , or CF_3 .
- [0225] In some examples, at least one of R_{30} - R_{34} may be carboxylic acid.
- [0226] In some examples, at least one of R_{30} - R_{34} may be amide.
- [0227] In some examples, at least one of R_{30} - R_{34} may be ester.
- [0228] In some examples, at least one of R_{30} - R_{34} may be ether.
- [0229] In some examples, at least one of R_{30} - R_{34} may be cyano.
- [0230] In some examples, at least one of R_{30} - R_{34} may be methyl.
- [0231] In some examples, at least two of R_{30} - R_{34} may be carboxylic acid, amide, ester, ether, cyano, or methyl.

F. Compounds with Formula (Ile)

[0232] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (Ile):



Formula (Ile);

wherein

X_1 - X_5 are each independently a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6 alkoxy, optionally substituted with an aryl, a C_3 - C_{10} cycloalkyl, $-C(O)NH_2$, $-C(O)NHY^1$, $-C(O)NY^1Y^2$, $-COOH$, $-C(O)OY^1$, $-Y^1COOH$, or $-Y^1OY^2$;

Y^1 and Y^2 are each independently a C_1 - C_6 alkyl optionally substituted with one or more halogen or hydroxy;

R_3 is a halogen, a hydrogen, a C_1 - C_6 alkyl, a C_1 - C_6 alkyl substituted with one or more halogen, or a C_3 - C_6 cycloalkyl;

R_4 is a hydrogen, a C_1 - C_6 alkyl, or a C_1 - C_6 alkyl substituted with one or more halogen;

if R_3 and R_4 are optionally interconnected they form a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring; and

R_{40} - R_{43} are independently hydrogen, a C_1 - C_6 alkyl, or a substituted C_1 - C_6 alkyl.

[0233] In some embodiments, X_1 may be a C_1 - C_6 alkyl or a halogen. In some examples, X_1 may be methyl. In some examples, X_1 may be chlorine.

[0234] In some embodiments, X_2 , X_4 , and X_5 may be hydrogen.

[0235] In some embodiments, X_3 may be a hydrogen or halogen.

[0236] In some embodiments, at least two of X_2 - X_5 may be hydrogen.

[0237] In some embodiments, at least three of X_2 - X_5 may be hydrogen.

[0238] In some embodiments, X_2 - X_5 may be hydrogen.

[0239] In some embodiments, R_3 may be straight or branched C_1 - C_6 alkyl optionally substituted with one or more halogen. For example, the straight or branched C_1 - C_6 alkyl may be substituted with one or more fluorine.

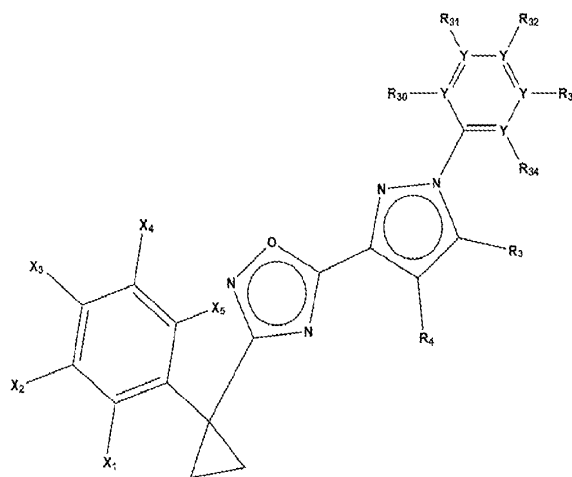
[0240] In some embodiments, R_3 may be $-CHF_2$ or $-CF_3$.

[0241] In some embodiments, R_4 may be hydrogen.

[0242] In some embodiments, X_1 - X_3 may each independently be hydrogen, fluorine, chlorine, bromine, or methyl, X_4 - X_5 may each independently be hydrogen or halogen, and R_3 - R_4 may each independently be hydrogen, methyl, $-CHF_2$, or $-CF_3$.

G. Compounds with Formula (IIf)

[0243] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (IIf):



Formula (IIf);

wherein

X_1 - X_5 are each independently a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6

alkoxy, optionally substituted with an aryl, a C₃-C₁₀ cycloalkyl, -C(O)NH₂, -C(O)NHY¹, -C(O)NY¹Y², -COOH, -C(O)OY¹, -Y¹COOH, or -Y¹OY²;

Y¹ and Y² are each independently a C₁-C₆ alkyl optionally substituted with one or more halogen or hydroxy;

Y is carbon or nitrogen;

R₃₀-R₃₄ are each independently a hydrogen, a carboxylic acid, a halogen, an amide, a substituted amide, a cyano, a C₁-C₆ alkyl, or absent;

R₃ is a halogen, a hydrogen, a C₁-C₆ alkyl, a C₁-C₆ alkyl substituted with one or more halogen, or a C₃-C₆ cycloalkyl;

R₄ is a hydrogen, a C₁-C₆ alkyl, or a C₁-C₆ alkyl substituted with one or more halogen;

if R₃ and R₄ are optionally interconnected they form a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring; and

R₃₀-R₃₄ are each independently be a hydrogen, a carboxylic acid, an ester, a halogen, an amide, a substituted amide, a cyano, an ether, a C₁-C₆ alkyl, or absent.

[0244] In some embodiments, X₁ and X₂ may be halogen. The halogen may be fluorine or chlorine.

[0245] In some embodiments, X₂, X₃, and X₅ may be hydrogen.

[0246] In some embodiments, at least two of X₂-X₅ may be hydrogen.

[0247] In some embodiments, at least three of X₂-X₅ may be hydrogen.

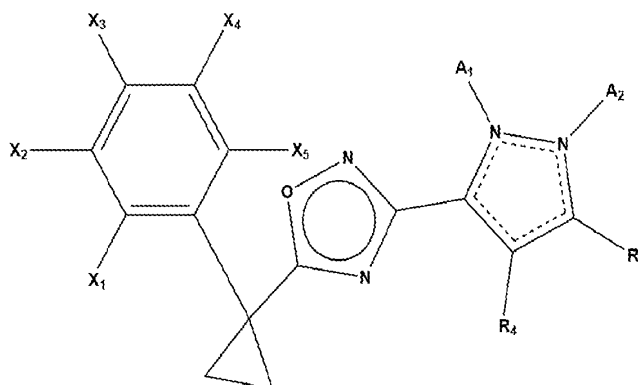
[0248] In some embodiments, at least one Y may be nitrogen.

[0249] In some embodiments, R₃₀-R₃₄ may each independently be a hydrogen or absent.

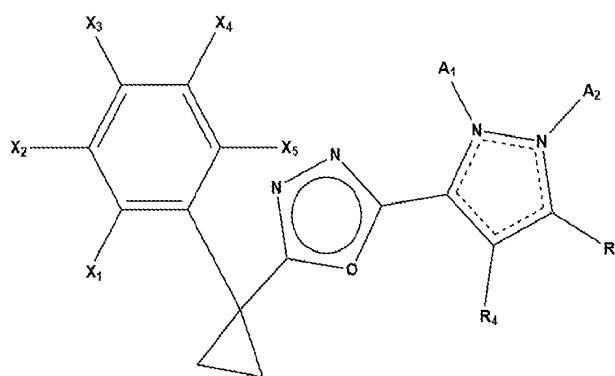
[0250] In some embodiments, R₃ may be -CH(CH₃)₂.

H. Compounds with Formulae (III), (IIIa), (IIIb), (IV), (IVa), and (IVb)

[0251] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (III) or Formula (IV):



Formula (III); or



Formula (IV).

[0252] In some aspects, X_1 - X_5 may each independently be a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6 alkoxy, optionally substituted with an aryl, a C_3 - C_{10} cycloalkyl, $-C(O)NH_2$, $-C(O)NHY^1$, $-C(O)NY^1Y^2$, $-COOH$, $-C(O)OY^1$, $-Y^1COOH$, or $-Y^1OY^2$. Y^1 and Y^2 may each be independently a C_1 - C_6 alkyl optionally substituted with one or more halogen or hydroxy.

[0253] In some aspects, R_3 may be a halogen, a hydrogen, a C_1 - C_6 alkyl, a C_1 - C_6 alkyl substituted with one or more halogen, or a C_3 - C_6 cycloalkyl.

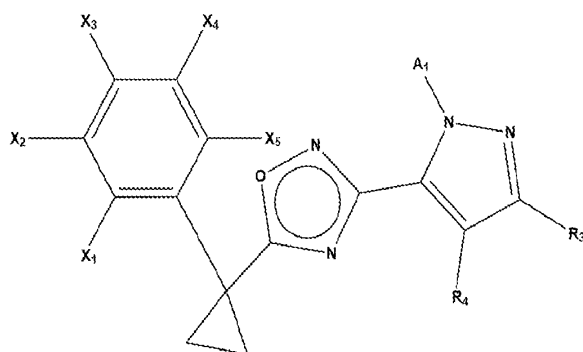
[0254] In some aspects, R_4 may be a hydrogen, a C_1 - C_6 alkyl, or a C_1 - C_6 alkyl substituted with one or more halogen.

[0255] In other aspects, R_3 and R_4 may optionally be interconnected to form a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

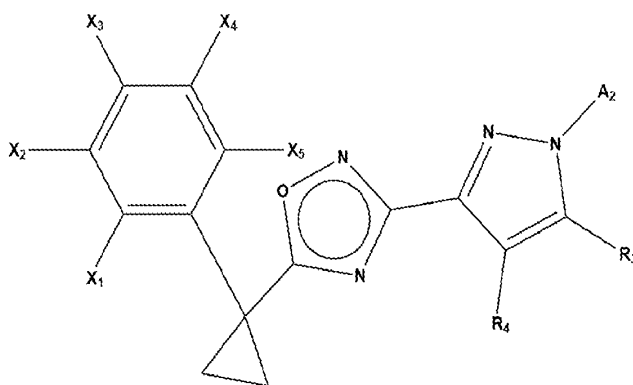
[0256] In some aspects, A_1 and A_2 may each independently be a hydrogen, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, an aryl, substituted aryl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6

cycloalkyl, a C₃-C₆ heterocyclyl, substituted C₃-C₆ heterocyclyl, or absent. A₁ and A₂ may optionally be substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, -C(O)NH₂, -CS(O)₂Y³, a -CY¹S(O)₂Y³. Y³ may independently be a hydrogen or a C₁-C₄ alkyl optionally substituted with one or more groups selected from the group consisting of a halogen, a hydroxyl, a C₁-C₄ haloalkoxyl, and a C₁-C₄ alkoxy.

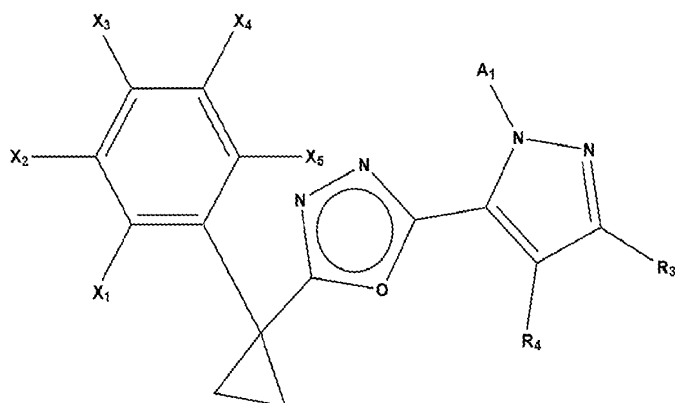
[0257] In some aspects, the present disclosure is directed to a compound with any one or Formulae (IIIa), (IIIb), (IVa), and (IVb):



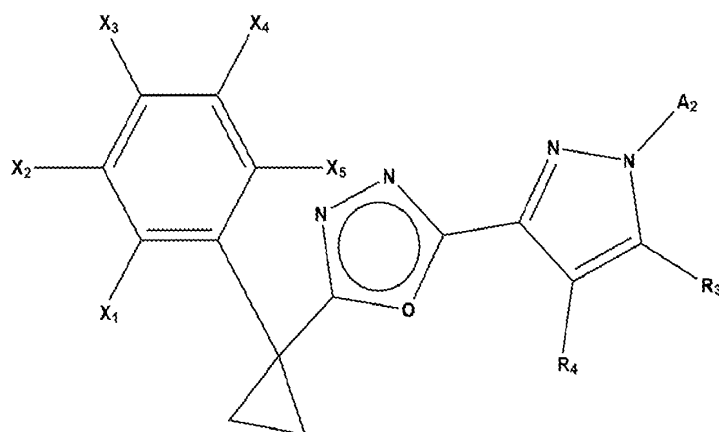
Formula (IIIa);



Formula (IIIb);



Formula (IVa); or



Formula (IVb).

[0258] In some embodiments, X_1 may be C_1 - C_6 alkyl.

[0259] In some embodiments, X_2 , X_3 , and X_5 may be hydrogen.

[0260] In some embodiments, X_4 may be hydrogen or fluorine.

[0261] In some embodiments, A_1 and A_2 may each be independently a hydrogen, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, an aryl, substituted aryl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_3 - C_6 heterocyclyl, or substituted C_3 - C_6 heterocyclyl. A_1 and A_2 may optionally be substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, $-C(O)NH_2$, $-CS(O)_2Y^3$, a $-CY^1S(O)_2Y^3$.

[0262] In some embodiments, R_3 may be C_1 - C_6 alkyl substituted with one or more halogen.

[0263] In some embodiments, R_4 may be a hydrogen.

[0264] In some embodiments, X_1 may be methyl.

[0265] In some embodiments, X_4 may be hydrogen or fluorine.

[0266] In some embodiments, at least two of X_2 - X_5 may be hydrogen.

[0267] In some embodiments, at least three of X_2 - X_5 are hydrogen.

[0268] In some embodiments, A_1 and A_2 may be substituted C_1 - C_6 alkyl. A_1 and A_2 may be substituted ethyl. The ethyl may be substituted with carboxylic acid or amide.

[0269] In some embodiments, A_1 and A_2 may be $-\text{CH}(\text{CH}_3)\text{COOH}$.

[0270] In some embodiments, A_1 and A_2 may be $-\text{CH}_2\text{CH}_3\text{COOH}$.

[0271] In some embodiments, A_1 and A_2 may be $-\text{CH}_2\text{CH}_3\text{CONH}_2$.

[0272] In some embodiments, A_1 and A_2 may be substituted C_3 - C_6 cycloalkyl.

[0273] In some embodiments, the substituted C_3 - C_6 cycloalkyl may be a cyclobutyl or cyclohexyl substituted with one or more carboxylic acid.

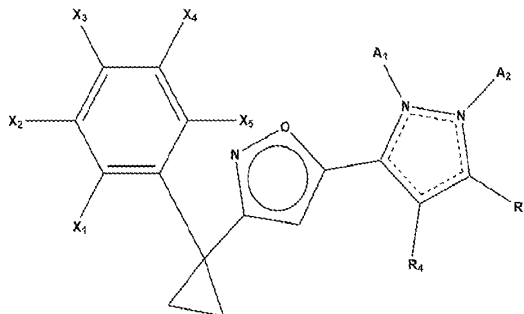
[0274] In some embodiments, A_1 and A_2 may be substituted phenyl. The phenyl may be substituted with one or more carboxylic acid.

[0275] In some embodiments, R_3 may be $-\text{CHF}_2$ or $-\text{CF}_3$.

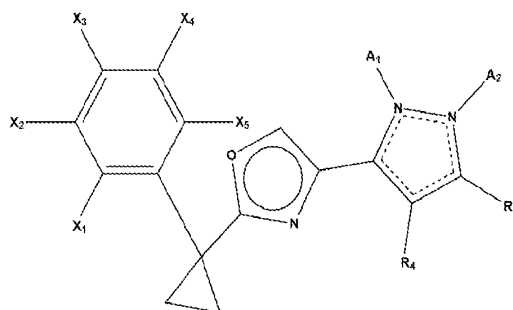
[0276] In some embodiments, X_1 - X_5 may each independently be hydrogen, halogen, or methyl.

I. Compounds with Formulae (Va), (Va-1), (Vb), or (Vb-1)

[0277] The present disclosure is directed to a compound, or a pharmaceutically acceptable salt thereof, according to Formula (III) or Formula (IV):



Formula (Va); or



Formula (Vb);

wherein

X₁-X₅ are each independently a hydrogen, a halogen, a hydroxy, a cyano, a C₁-C₆ alkyl, a substituted C₁-C₆ alkyl, a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, a C₁-C₆ alkoxy, optionally substituted with an aryl, a C₃-C₁₀ cycloalkyl, -C(O)NH₂, -C(O)NHY¹, -C(O)NY¹Y², -COOH, -C(O)OY¹, -Y¹COOH, or -Y¹OY²;

Y¹ and Y² are each independently a C₁-C₆ alkyl optionally substituted with one or more halogen or hydroxy;

A₁ and A₂ are each independently a hydrogen, a C₁-C₆ alkyl, a substituted C₁-C₆ alkyl, an aryl, substituted aryl, a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, a C₃-C₆ heterocyclyl, substituted C₃-C₆ heterocyclyl, or absent;

wherein A₁ and A₂ may optionally be substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, -C(O)NH₂, -CS(O)₂Y³, a -CY¹S(O)₂Y³;

Y³ is independently a hydrogen or a C₁-C₄ alkyl optionally substituted with one or more groups selected from the group consisting of a halogen, a hydroxyl, a C₁-C₄ haloalkoxyl, and a C₁-C₄ alkoxy;

R₃ is a halogen, a hydrogen, a C₁-C₆ alkyl, a C₁-C₆ alkyl substituted with one or more halogen, or a C₃-C₆ cycloalkyl; and

R₄ is a hydrogen, a C₁-C₆ alkyl, or a C₁-C₆ alkyl substituted with one or more halogen;

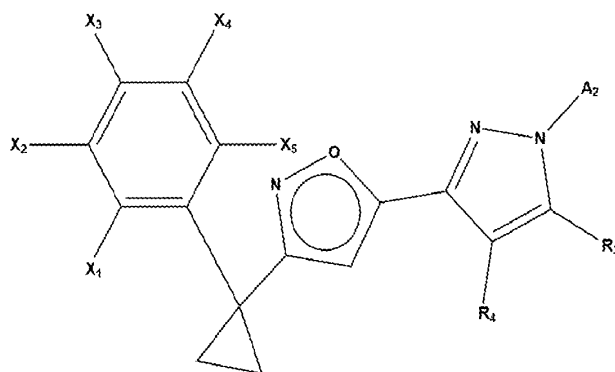
if R₃ and R₄ are optionally interconnected they form a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

[0278] In some embodiments, A₁-A₂ are independently hydrogen or methyl.

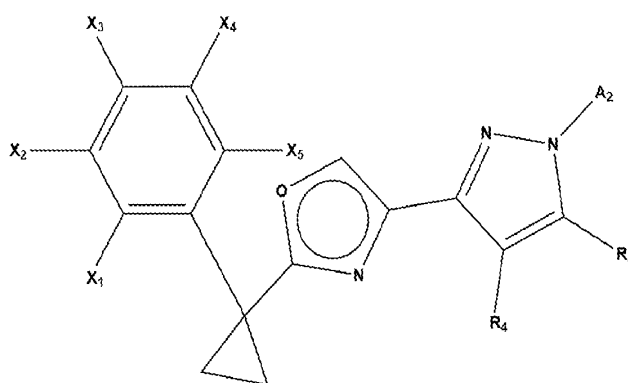
[0279] In some embodiments, X₁-X₅ may be independently hydrogen, halogen, or methyl.

[0280] In some embodiments, R₃-R₄ may be independently hydrogen, -CHF₂ or -CF₃.

[0281] In some aspects, A₁ may be absent and the compound is with Formula (Va-1) or Formula (Vb-1):



Formula (Va-1); or



Formula (Va-2);

wherein:

X₁ is C₁-C₆ alkyl;

X₂, X₃, and X₅ are hydrogen;

X₄ is hydrogen or halogen;

A₂ is C₁-C₆ alkyl;

R₃ is hydrogen or C₁-C₆ alkyl substituted with one or more halogen; and

R₄ is hydrogen.

[0282] In some embodiments, at least two of X₂-X₅ may be hydrogen.

[0283] In some embodiments, at least three of X₂-X₅ may be hydrogen.

[0284] In some embodiments, X₂-X₅ may be hydrogen.

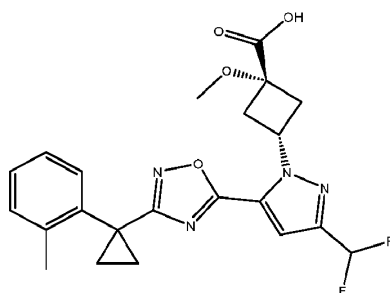
[0285] In some embodiments, the C₁-C₆ alkyl may be methyl.

[0286] In some embodiments, the C₁-C₆ alkyl substituted with one or more halogen may be -CHF₂ or -CF₃.

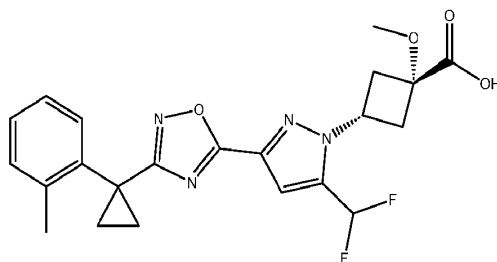
J. Compounds

[0287] The disclosure is intended to encompass the compounds listed below and the non-stereochemistry and the alternative stereochemistry of the compounds listed below.

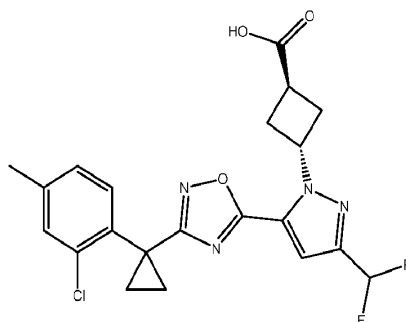
[0288] In certain embodiments, the compound is **Compound 1**, or a pharmaceutically acceptable salt thereof:



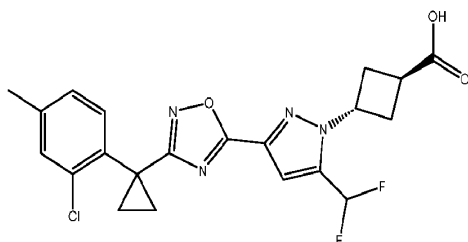
[0289] In certain embodiments, the compound is **Compound 2**, or a pharmaceutically acceptable salt thereof:



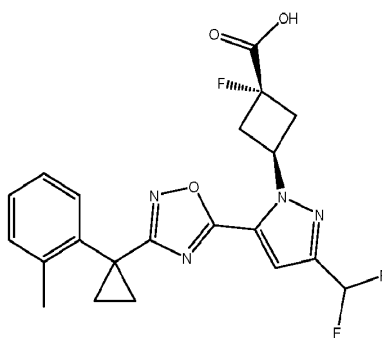
[0290] In certain embodiments, the compound is **Compound 3**, or a pharmaceutically acceptable salt thereof:



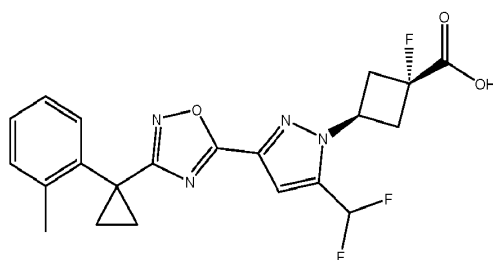
[0291] In certain embodiments, the compound is **Compound 4**, or a pharmaceutically acceptable salt thereof:



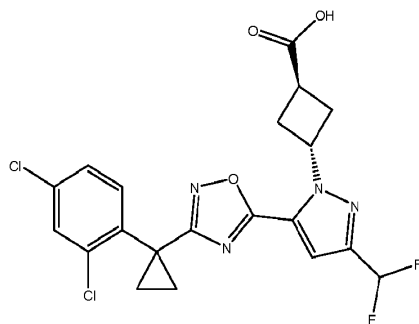
[0292] In certain embodiments, the compound is **Compound 5**, or a pharmaceutically acceptable salt thereof:



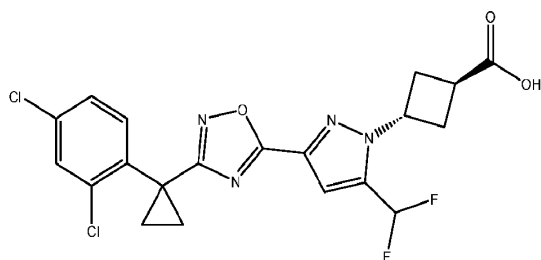
[0293] In certain embodiments, the compound is **Compound 6**, or a pharmaceutically acceptable salt thereof:



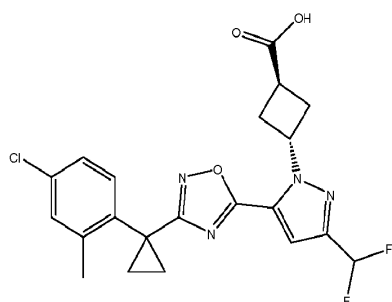
[0294] In certain embodiments, the compound is **Compound 7**, or a pharmaceutically acceptable salt thereof:



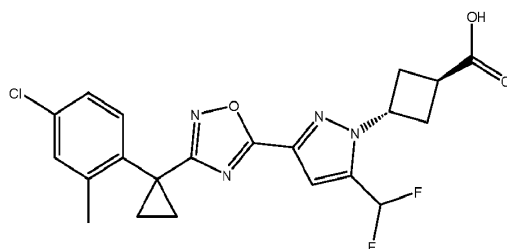
[0295] In certain embodiments, the compound is **Compound 8**, or a pharmaceutically acceptable salt thereof:



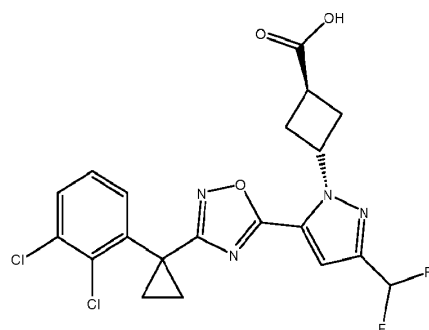
[0296] In certain embodiments, the compound is **Compound 9**, or a pharmaceutically acceptable salt thereof:



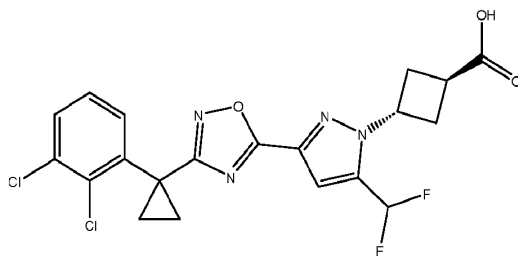
[0297] In certain embodiments, the compound is **Compound 10**, or a pharmaceutically acceptable salt thereof:



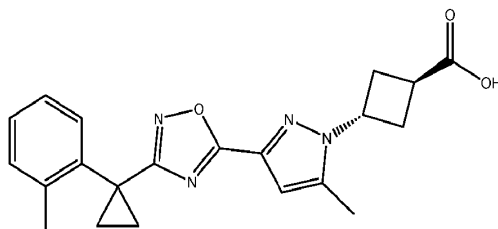
[0298] In certain embodiments, the compound is **Compound 11**, or a pharmaceutically acceptable salt thereof:



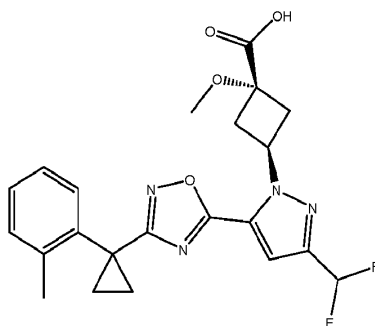
[0299] In certain embodiments, the compound is **Compound 12**, or a pharmaceutically acceptable salt thereof:



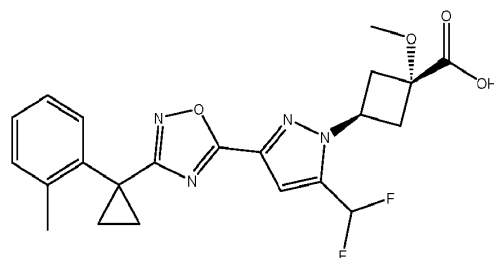
[0300] In certain embodiments, the compound is **Compound 13**, or a pharmaceutically acceptable salt thereof:



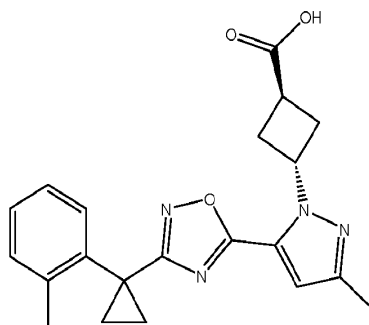
[0301] In certain embodiments, the compound is **Compound 14**, or a pharmaceutically acceptable salt thereof:



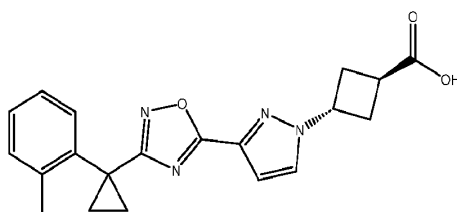
[0302] In certain embodiments, the compound is **Compound 15**, or a pharmaceutically acceptable salt thereof:



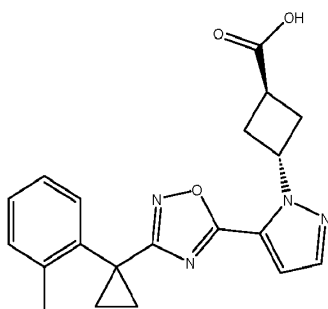
[0303] In certain embodiments, the compound is **Compound 16**, or a pharmaceutically acceptable salt thereof:



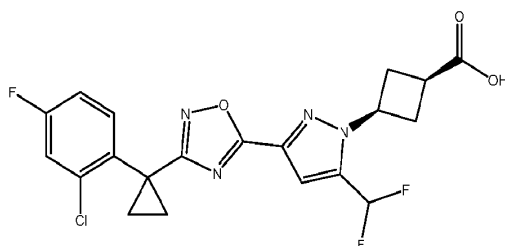
[0304] In certain embodiments, the compound is **Compound 17**, or a pharmaceutically acceptable salt thereof:



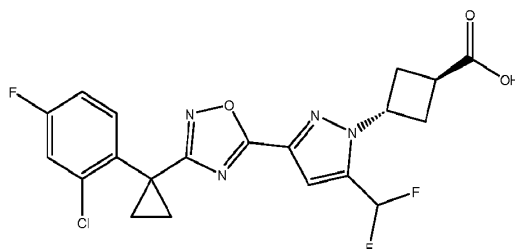
[0305] In certain embodiments, the compound is **Compound 18**, or a pharmaceutically acceptable salt thereof:



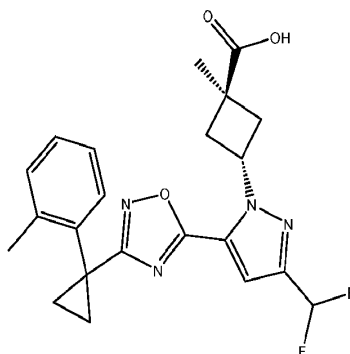
[0306] In certain embodiments, the compound is **Compound 19**, or a pharmaceutically acceptable salt thereof:



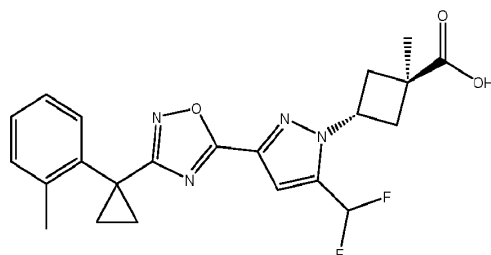
[0307] In certain embodiments, the compound is **Compound 20**, or a pharmaceutically acceptable salt thereof:



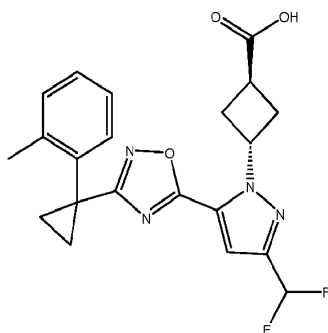
[0308] In certain embodiments, the compound is **Compound 21**, or a pharmaceutically acceptable salt thereof:



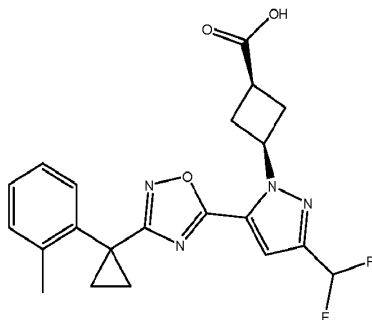
[0309] In certain embodiments, the compound is **Compound 22**, or a pharmaceutically acceptable salt thereof:



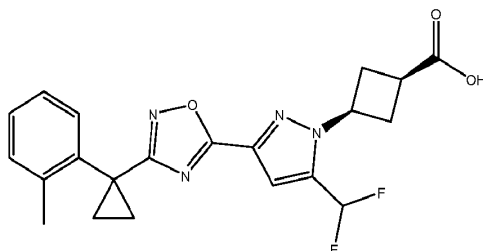
[0310] In certain embodiments, the compound is **Compound 23** or a pharmaceutically acceptable salt thereof:



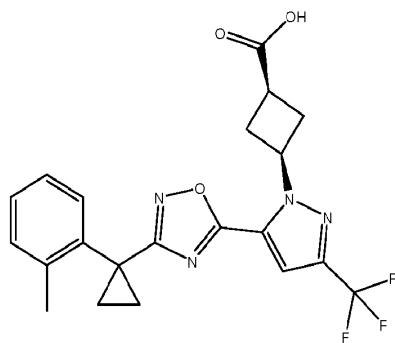
[0311] In certain embodiments, the compound is **Compound 24**, or a pharmaceutically acceptable salt thereof:



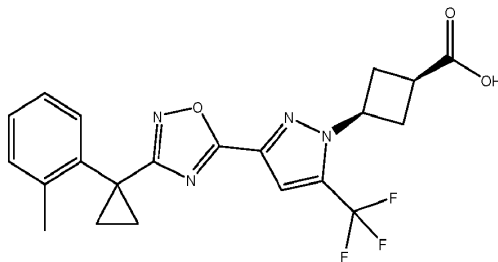
[0312] In certain embodiments, the compound is **Compound 25**, or a pharmaceutically acceptable salt thereof:



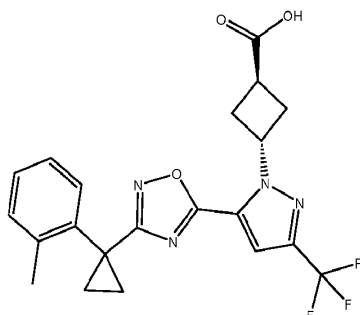
[0313] In certain embodiments, the compound is **Compound 26**, or a pharmaceutically acceptable salt thereof:



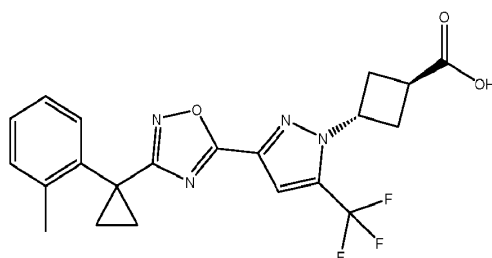
[0314] In certain embodiments, the compound is **Compound 27**, or a pharmaceutically acceptable salt thereof:



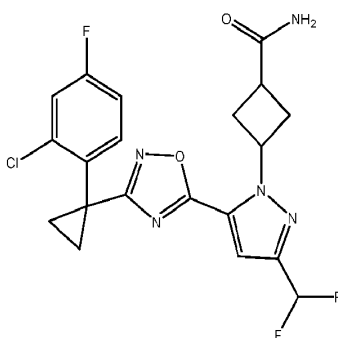
[0315] In certain embodiments, the compound is **Compound 28**, or a pharmaceutically acceptable salt thereof:



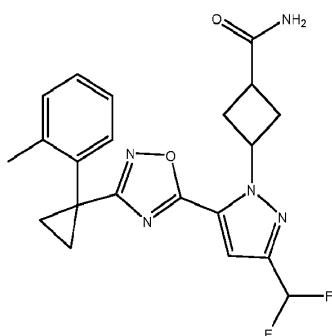
[0316] In certain embodiments, the compound is **Compound 29**, or a pharmaceutically acceptable salt thereof:



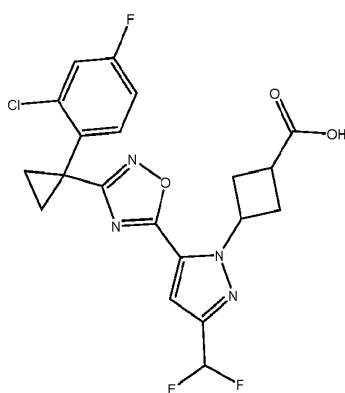
[0317] In certain embodiments, the compound is **Compound 30**, or a pharmaceutically acceptable salt thereof:



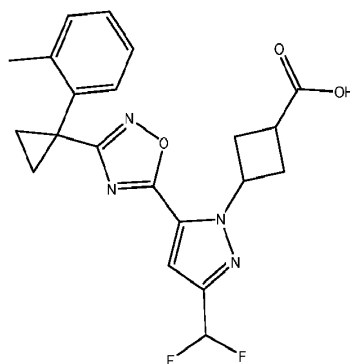
[0318] In certain embodiments, the compound is **Compound 31**, or a pharmaceutically acceptable salt thereof:



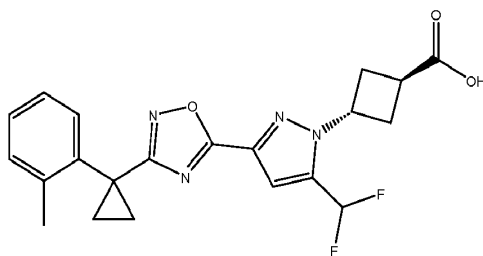
[0319] In certain embodiments, the compound is **Compound 32**, or a pharmaceutically acceptable salt thereof.



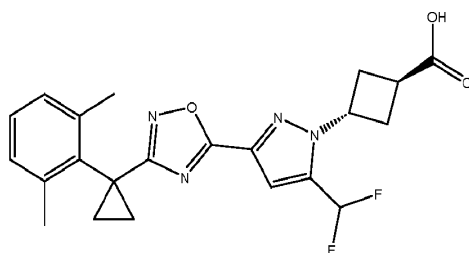
[0320] In certain embodiments, the compound is **Compound 33**, or a pharmaceutically acceptable salt thereof.



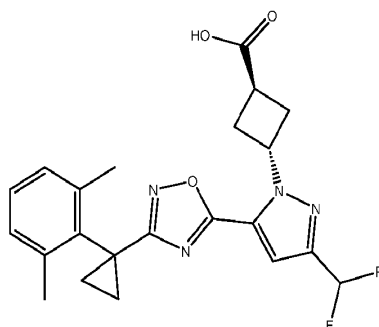
[0321] In certain embodiments, the compound is **Compound 34**, or a pharmaceutically acceptable salt thereof.



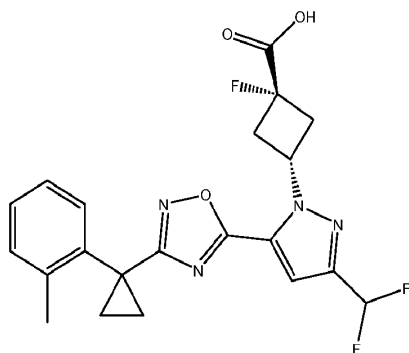
[0322] In one embodiment, the compound is **Compound 332**, or a pharmaceutically acceptable salt thereof:



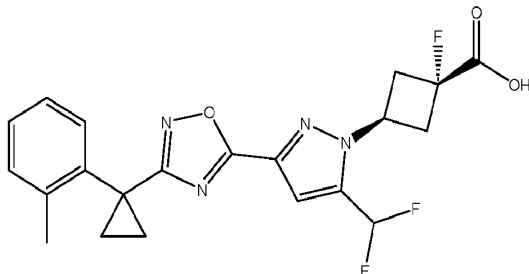
[0323] In one embodiment, the compound is **Compound 333**, or a pharmaceutically acceptable salt thereof:



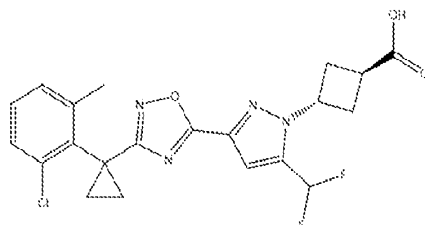
[0324] In one embodiment, the compound is **Compound 348**, or a pharmaceutically acceptable salt thereof:



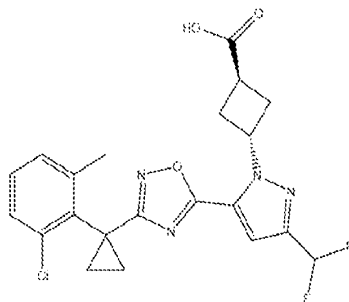
[0325] In one embodiment, the compound is **Compound 349**, or a pharmaceutically acceptable salt thereof:



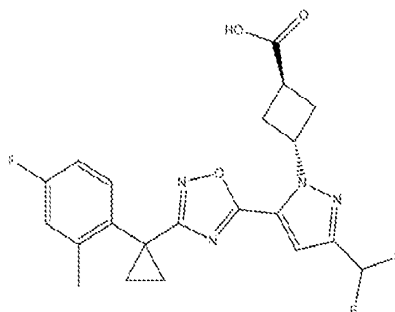
[0326] In one embodiment, the compound is **Compound 358**, or a pharmaceutically acceptable salt thereof:



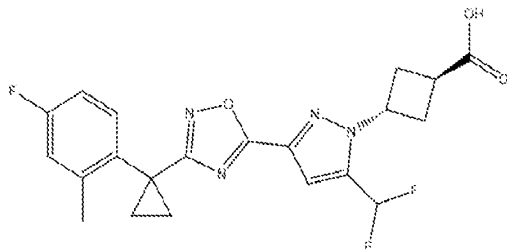
[0327] In one embodiment, the compound is **Compound 359**, or a pharmaceutically acceptable salt thereof:



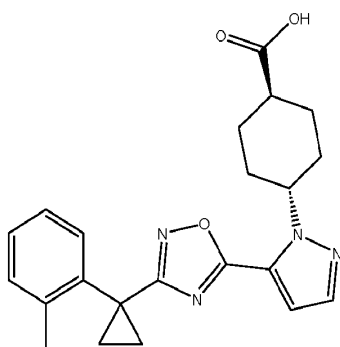
[0328] In one embodiment, the compound is **Compound 368**, or a pharmaceutically acceptable salt thereof:



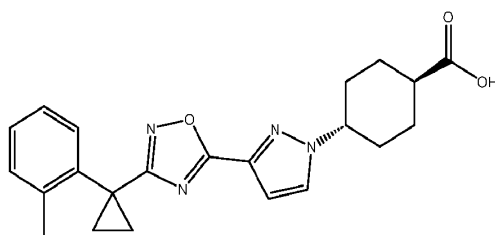
[0329] In one embodiment, the compound is **Compound 369**, or a pharmaceutically acceptable salt thereof:



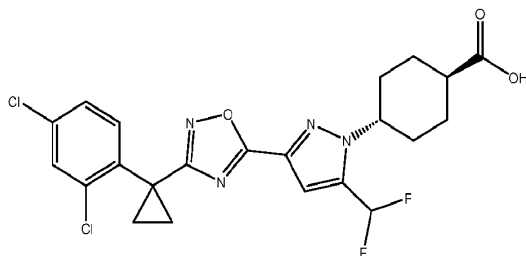
[0330] In certain embodiments, the compound is **Compound 35**, or a pharmaceutically acceptable salt thereof:



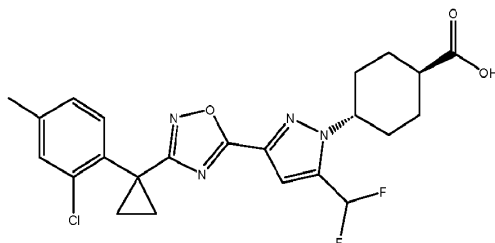
[0331] In certain embodiments, the compound is **Compound 36**, or a pharmaceutically acceptable salt thereof:



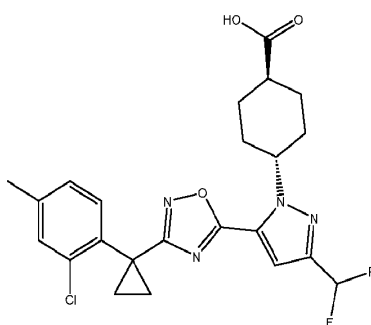
[0332] In certain embodiments, the compound is **Compound 37**, or a pharmaceutically acceptable salt thereof:



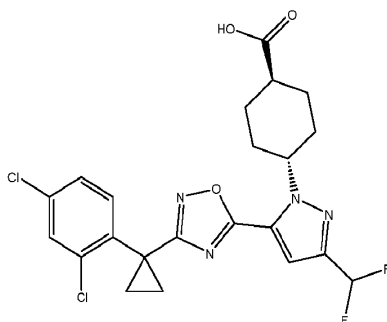
[0333] In certain embodiments, the compound is **Compound 38**, or a pharmaceutically acceptable salt thereof:



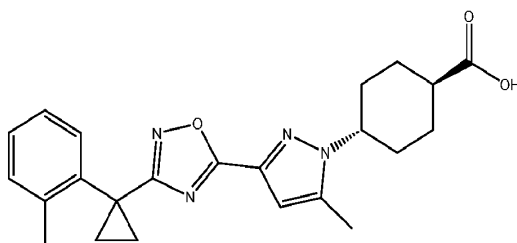
[0334] In certain embodiments, the compound is **Compound 39**, or a pharmaceutically acceptable salt thereof:



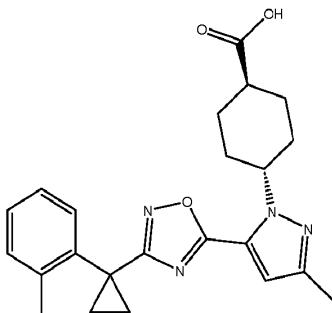
[0335] In certain embodiments, the compound is **Compound 40**, or a pharmaceutically acceptable salt thereof:



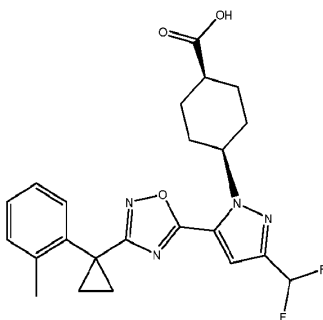
[0336] In certain embodiments, the compound is **Compound 41**, or a pharmaceutically acceptable salt thereof:



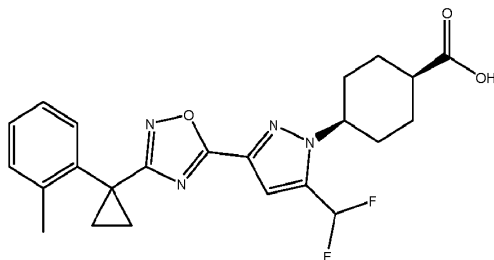
[0337] In certain embodiments, the compound is **Compound 42**, or a pharmaceutically acceptable salt thereof:



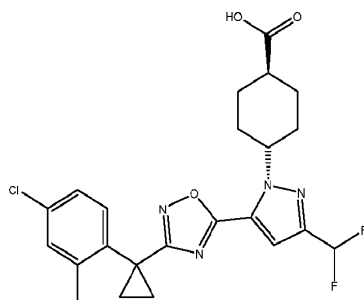
[0338] In certain embodiments, the compound is **Compound 43**, or a pharmaceutically acceptable salt thereof:



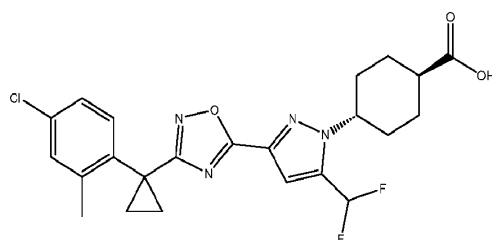
[0339] In certain embodiments, the compound is **Compound 44**, or a pharmaceutically acceptable salt thereof:



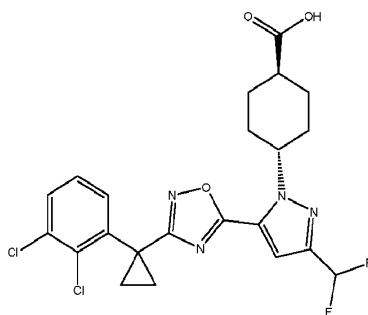
[0340] In certain embodiments, the compound is **Compound 45**, or a pharmaceutically acceptable salt thereof:



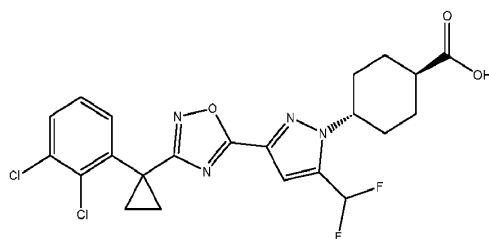
[0341] In certain embodiments, the compound is **Compound 46**, or a pharmaceutically acceptable salt thereof:



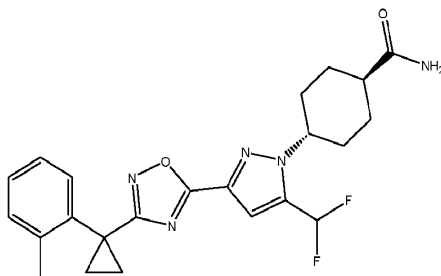
[0342] In certain embodiments, the compound is **Compound 47**, or a pharmaceutically acceptable salt thereof:



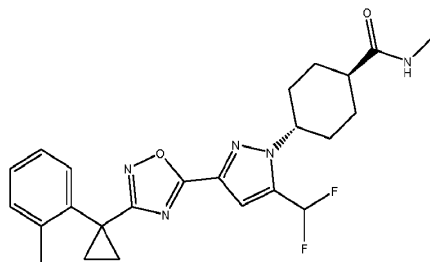
[0343] In certain embodiments, the compound is **Compound 48**, or a pharmaceutically acceptable salt thereof:



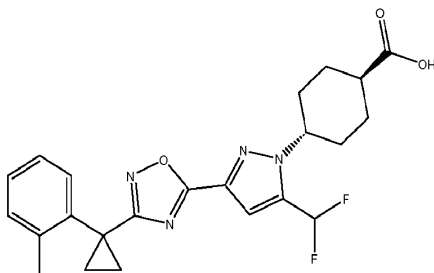
[0344] In certain embodiments, the compound is **Compound 49**, or a pharmaceutically acceptable salt thereof:



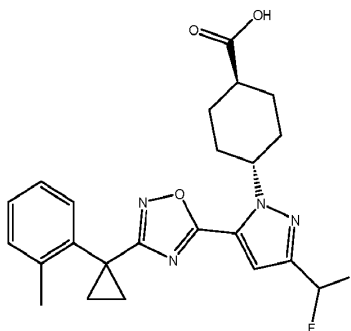
[0345] In certain embodiments, the compound is **Compound 50**, or a pharmaceutically acceptable salt thereof:



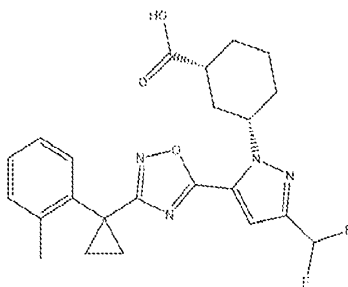
[0346] In certain embodiments, the compound is **Compound 51**, or a pharmaceutically acceptable salt thereof:



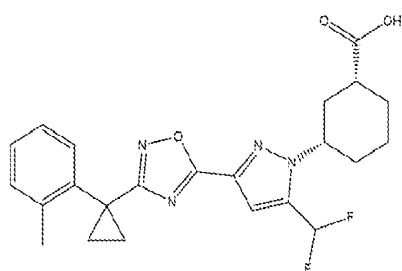
[0347] In certain embodiments, the compound is **Compound 52**, or a pharmaceutically acceptable salt thereof:



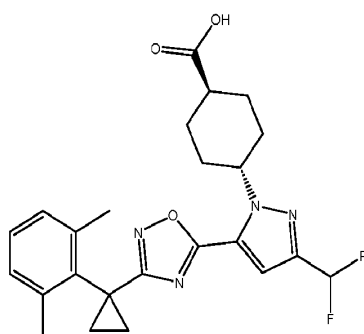
[0348] In one embodiment, the compound is **Compound 316**, or a pharmaceutically acceptable salt thereof:



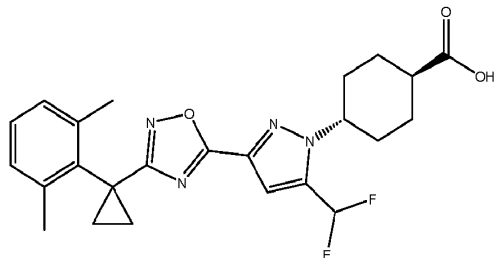
[0349] In one embodiment, the compound is **Compound 317**, or a pharmaceutically acceptable salt thereof:



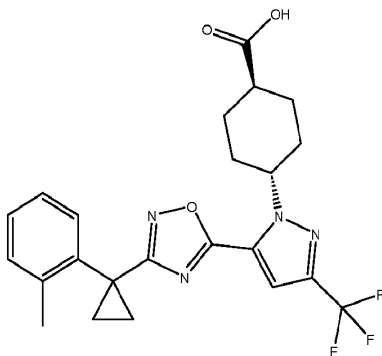
[0350] In one embodiment, the compound is **Compound 335**, or a pharmaceutically acceptable salt thereof:



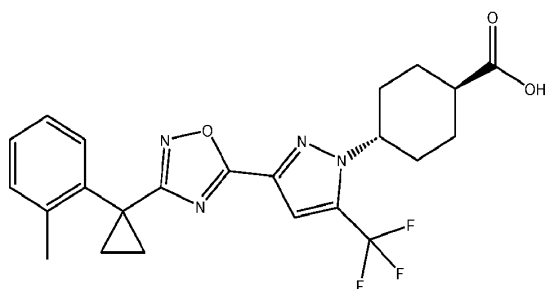
[0351] In one embodiment, the compound is **Compound 336**, or a pharmaceutically acceptable salt thereof:



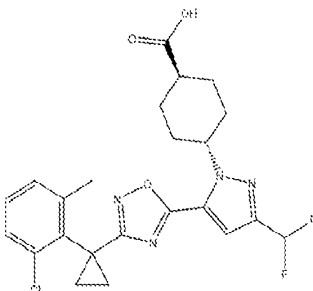
[0352] In one embodiment, the compound is **Compound 346**, or a pharmaceutically acceptable salt thereof:



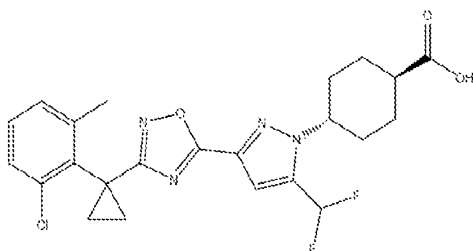
[0353] In one embodiment, the compound is **Compound 347**, or a pharmaceutically acceptable salt thereof:



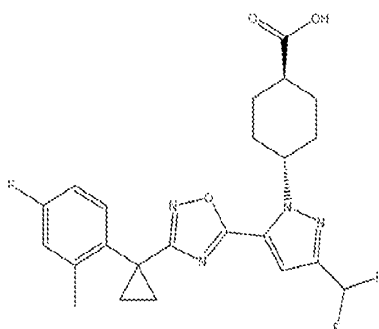
[0354] In one embodiment, the compound is **Compound 355**, or a pharmaceutically acceptable salt thereof:



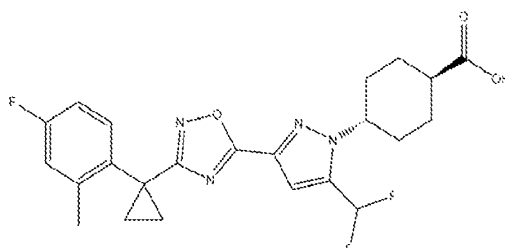
[0355] In one embodiment, the compound is **Compound 356**, or a pharmaceutically acceptable salt thereof:



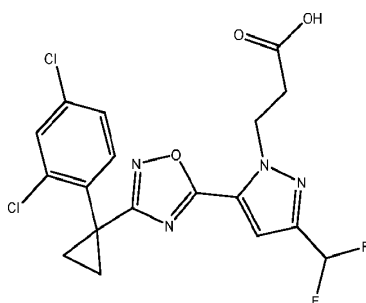
[0356] In one embodiment, the compound is **Compound 366**, or a pharmaceutically acceptable salt thereof:



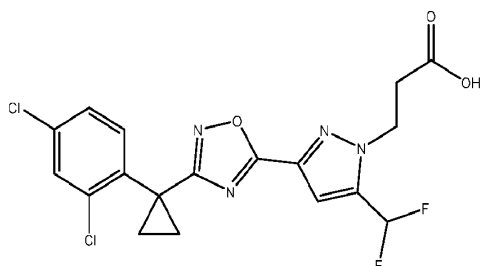
[0357] In one embodiment, the compound is **Compound 367**, or a pharmaceutically acceptable salt thereof:



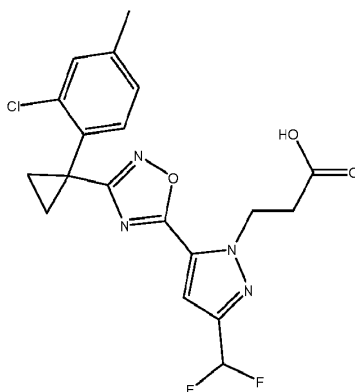
[0358] In certain embodiments, the compound is **Compound 53**, or a pharmaceutically acceptable salt thereof:



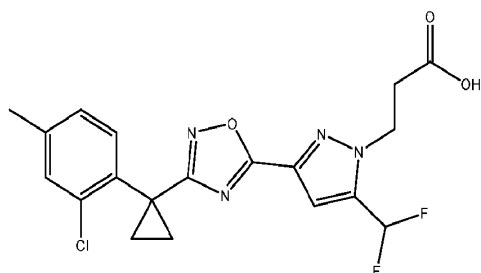
[0359] In certain embodiments, the compound is **Compound 54**, or a pharmaceutically acceptable salt thereof:



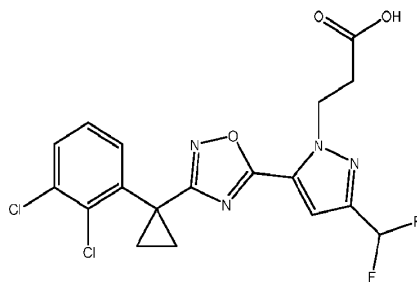
[0360] In certain embodiments, the compound is **Compound 55**, or a pharmaceutically acceptable salt thereof:



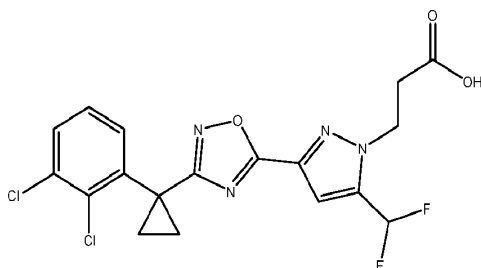
[0361] In certain embodiments, the compound is **Compound 56**, or a pharmaceutically acceptable salt thereof:



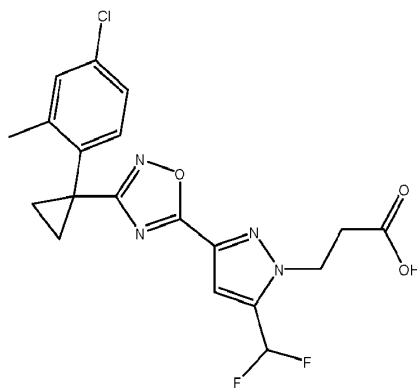
[0362] In certain embodiments, the compound is **Compound 57**, or a pharmaceutically acceptable salt thereof:



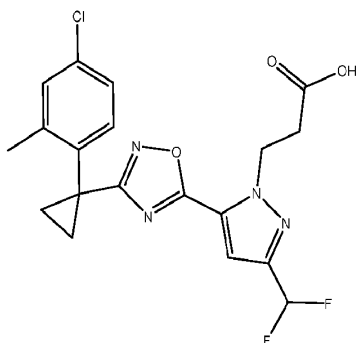
[0363] In certain embodiments, the compound is **Compound 58**, or a pharmaceutically acceptable salt thereof:



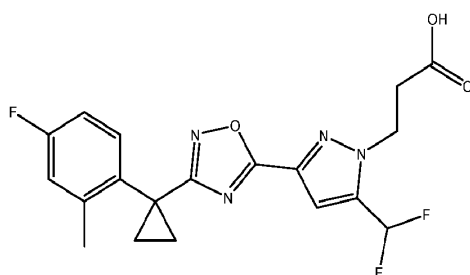
[0364] In certain embodiments, the compound is **Compound 59**, or a pharmaceutically acceptable salt thereof:



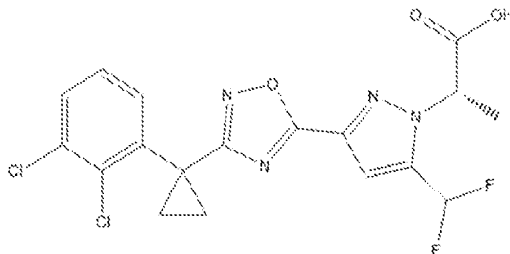
[0365] In certain embodiments, the compound is **Compound 60**, or a pharmaceutically acceptable salt thereof:



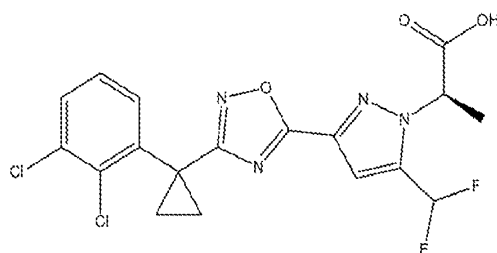
[0366] In certain embodiments, the compound is **Compound 61**, or a pharmaceutically acceptable salt thereof:



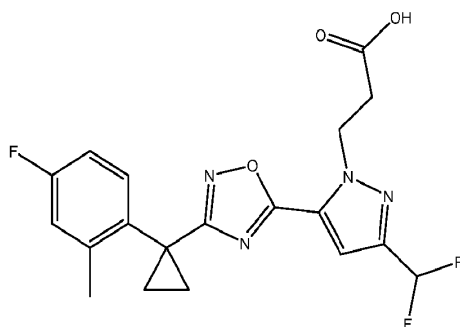
[0367] In certain embodiments, the compound is **Compound 62**, or a pharmaceutically acceptable salt thereof:



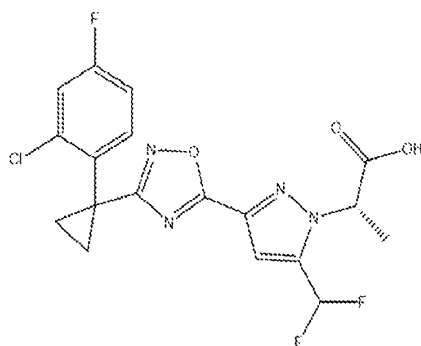
[0368] In certain embodiments, the compound is **Compound 63**, or a pharmaceutically acceptable salt thereof:



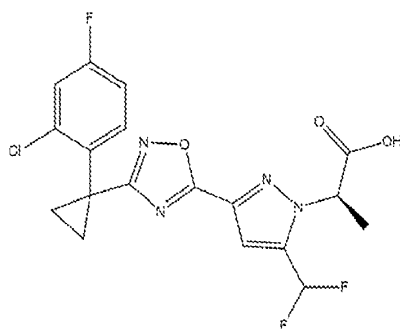
[0369] In certain embodiments, the compound is **Compound 64**, or a pharmaceutically acceptable salt thereof:



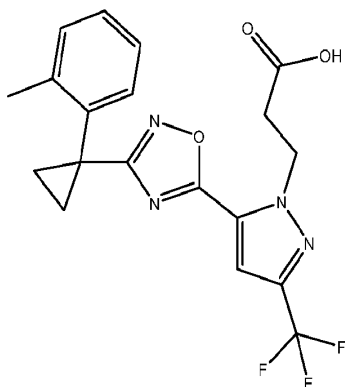
[0370] In certain embodiments, the compound is **Compound 65**, or a pharmaceutically acceptable salt thereof:



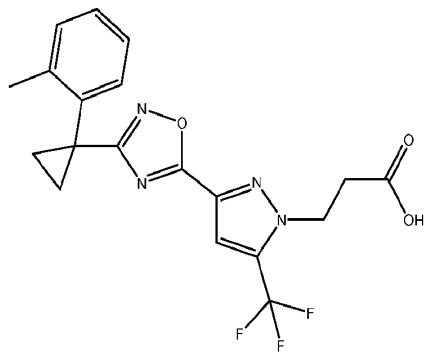
[0371] In certain embodiments, the compound is **Compound 66**, or a pharmaceutically acceptable salt thereof:



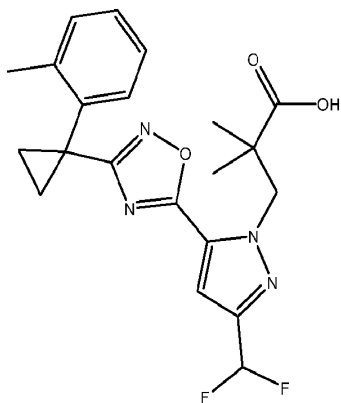
[0372] In certain embodiments, the compound is **Compound 67**, or a pharmaceutically acceptable salt thereof:



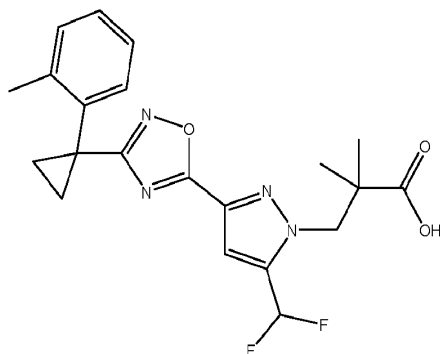
[0373] In certain embodiments, the compound is **Compound 68**, or a pharmaceutically acceptable salt thereof:



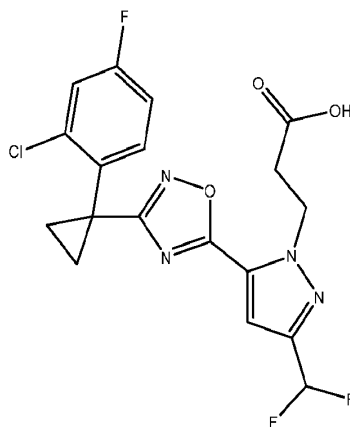
[0374] In certain embodiments, the compound is **Compound 69**, or a pharmaceutically acceptable salt thereof:



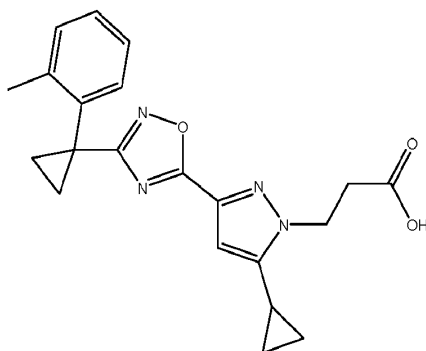
[0375] In certain embodiments, the compound is **Compound 70**, or a pharmaceutically acceptable salt thereof:



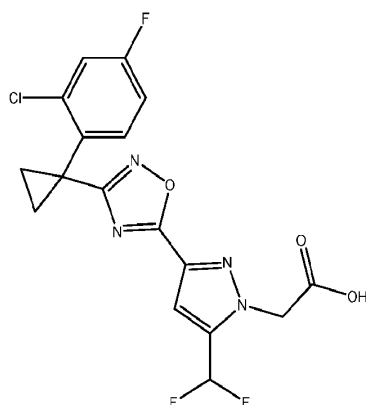
[0376] In certain embodiments, the compound is **Compound 71**, or a pharmaceutically acceptable salt thereof.



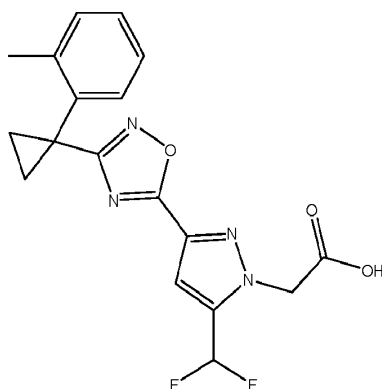
[0377] In certain embodiments, the compound is **Compound 72**, or a pharmaceutically acceptable salt thereof.



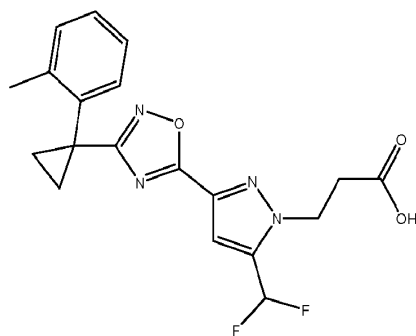
[0378] In certain embodiments, the compound is **Compound 73**, or a pharmaceutically acceptable salt thereof.



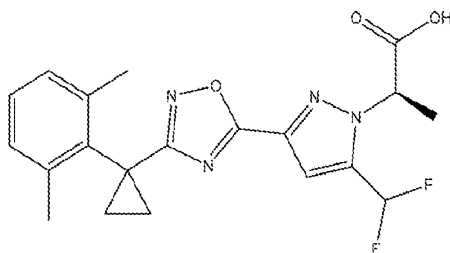
[0379] In certain embodiments, the compound is **Compound 74**, or a pharmaceutically acceptable salt thereof:



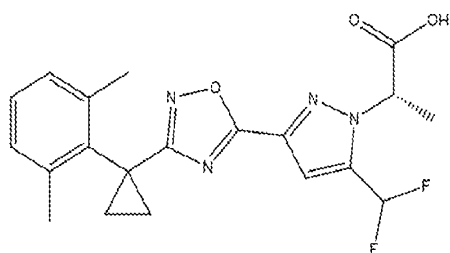
[0380] In certain embodiments, the compound is **Compound 75**, or a pharmaceutically acceptable salt thereof:



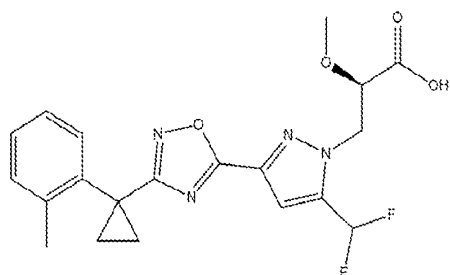
[0381] In one embodiment, the compound is **Compound 319**, or a pharmaceutically acceptable salt thereof:



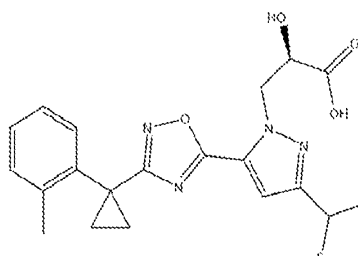
[0382] In one embodiment, the compound is **Compound 320**, or a pharmaceutically acceptable salt thereof:



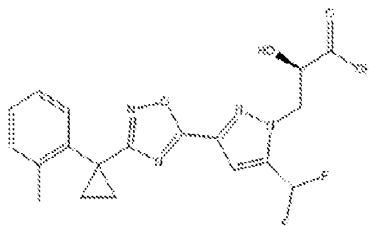
[0383] In one embodiment, the compound is **Compound 324**, or a pharmaceutically acceptable salt thereof:



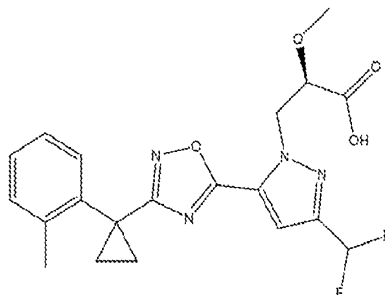
[0384] In one embodiment, the compound is **Compound 325**, or a pharmaceutically acceptable salt thereof:



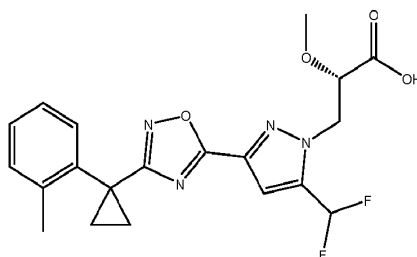
[0385] In one embodiment, the compound is **Compound 326**, or a pharmaceutically acceptable salt thereof:



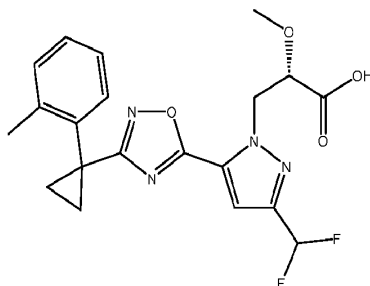
[0386] In one embodiment, the compound is **Compound 327**, or a pharmaceutically acceptable salt thereof:



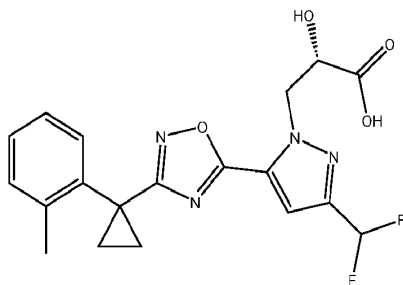
[0387] In one embodiment, the compound is **Compound 328**, or a pharmaceutically acceptable salt thereof:



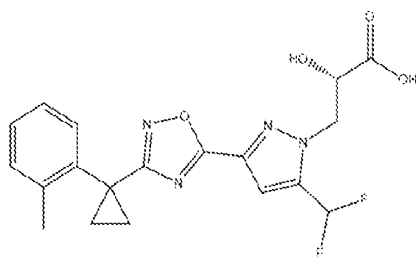
[0388] In one embodiment, the compound is **Compound 329**, or a pharmaceutically acceptable salt thereof:



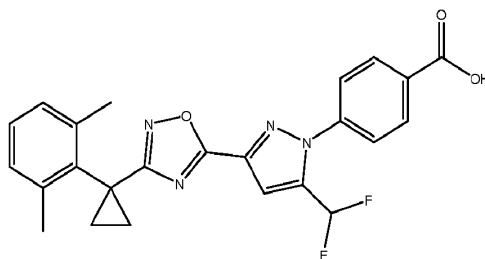
[0389] In one embodiment, the compound is **Compound 330**, or a pharmaceutically acceptable salt thereof:



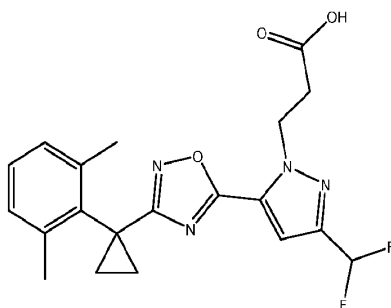
[0390] In one embodiment, the compound is **Compound 331**, or a pharmaceutically acceptable salt thereof:



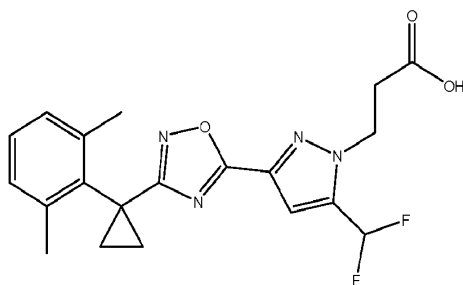
[0391] In one embodiment, the compound is **Compound 334**, or a pharmaceutically acceptable salt thereof:



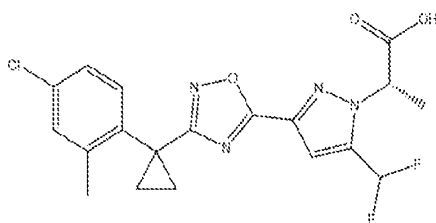
[0392] In one embodiment, the compound is **Compound 337**, or a pharmaceutically acceptable salt thereof:



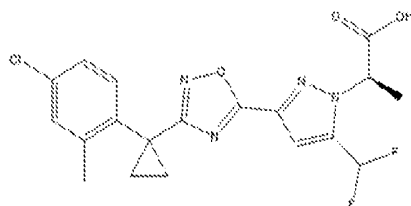
[0393] In one embodiment, the compound is **Compound 338**, or a pharmaceutically acceptable salt thereof:



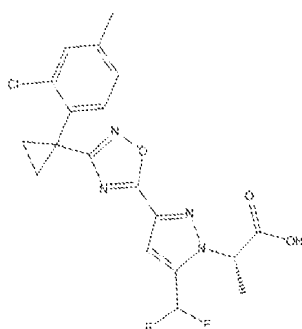
[0394] In one embodiment, the compound is **Compound 350**, or a pharmaceutically acceptable salt thereof:



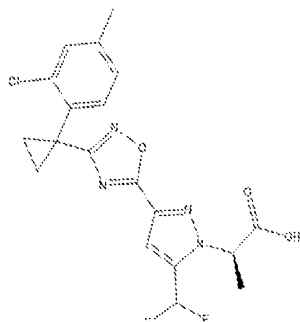
[0395] In one embodiment, the compound is **Compound 351**, or a pharmaceutically acceptable salt thereof:



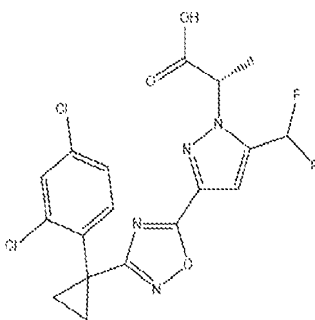
[0396] In one embodiment, the compound is **Compound 352**, or a pharmaceutically acceptable salt thereof:



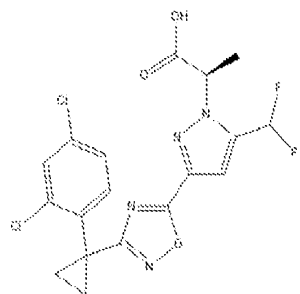
[0397] In one embodiment, the compound is **Compound 353**, or a pharmaceutically acceptable salt thereof:



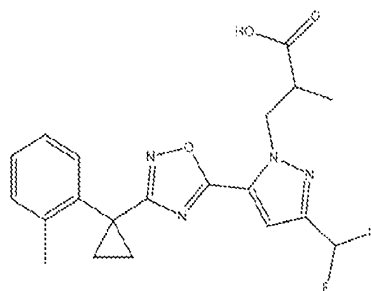
[0398] In one embodiment, the compound is **Compound 354**, or a pharmaceutically acceptable salt thereof:



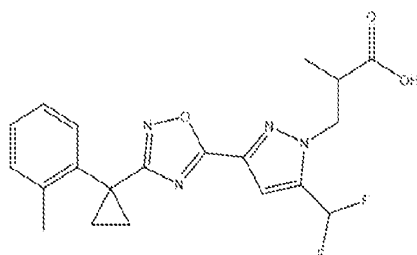
[0399] In one embodiment, the compound is **Compound 357**, or a pharmaceutically acceptable salt thereof:



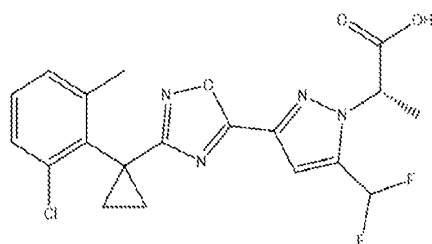
[0400] In one embodiment, the compound is **Compound 360**, or a pharmaceutically acceptable salt thereof:



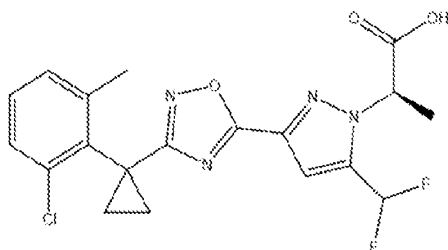
[0401] In one embodiment, the compound is **Compound 361**, or a pharmaceutically acceptable salt thereof:



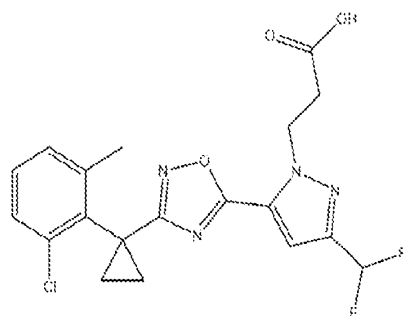
[0402] In one embodiment, the compound is **Compound 362**, or a pharmaceutically acceptable salt thereof:



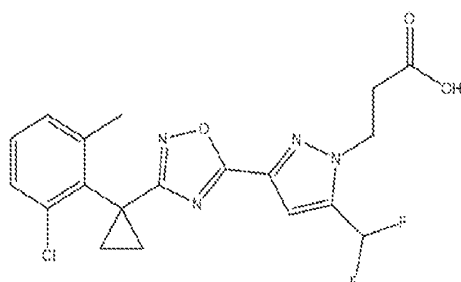
[0403] In one embodiment, the compound is **Compound 363**, or a pharmaceutically acceptable salt thereof:



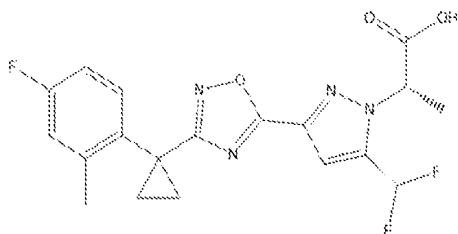
[0404] In one embodiment, the compound is **Compound 364**, or a pharmaceutically acceptable salt thereof:



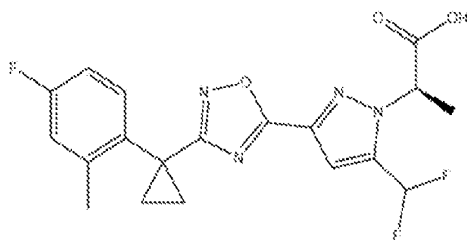
[0405] In one embodiment, the compound is **Compound 365**, or a pharmaceutically acceptable salt thereof:



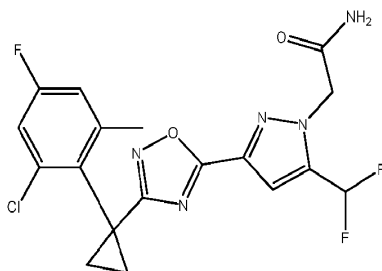
[0406] In one embodiment, the compound is **Compound 370**, or a pharmaceutically acceptable salt thereof:



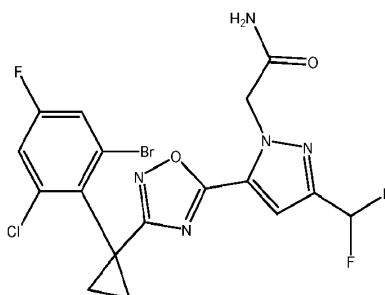
[0407] In one embodiment, the compound is **Compound 371**, or a pharmaceutically acceptable salt thereof:



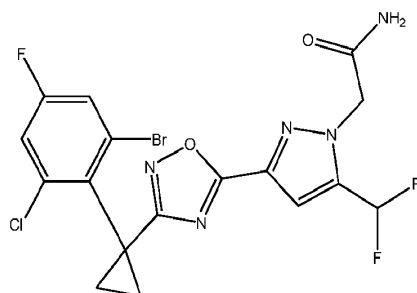
[0408] In certain embodiments, the compound is **Compound 76**, or a pharmaceutically acceptable salt thereof:



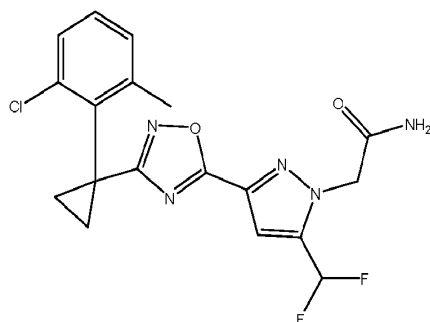
[0409] In certain embodiments, the compound is **Compound 77**, or a pharmaceutically acceptable salt thereof.



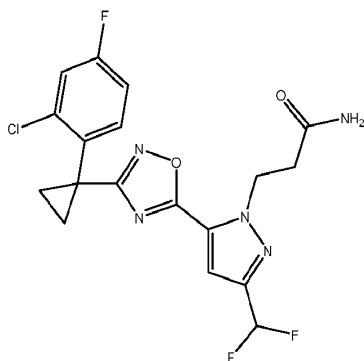
[0410] In certain embodiments, the compound is **Compound 78**, or a pharmaceutically acceptable salt thereof.



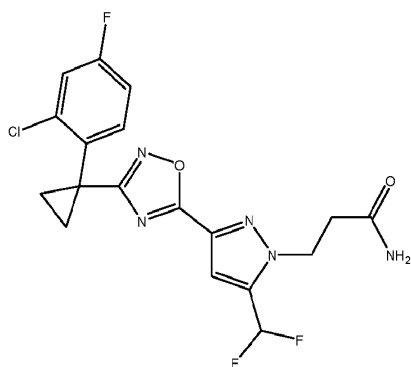
[0411] In certain embodiments, the compound is **Compound 79**, or a pharmaceutically acceptable salt thereof.



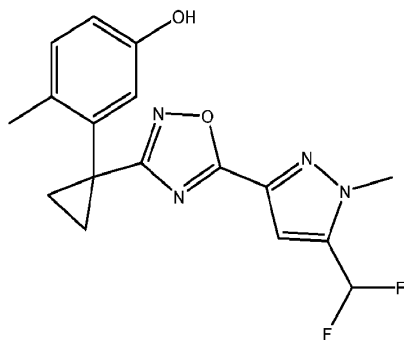
[0412] In certain embodiments, the compound is **Compound 80**, or a pharmaceutically acceptable salt thereof.



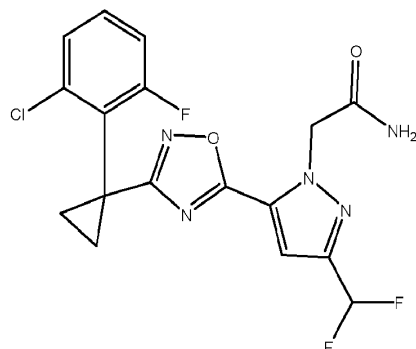
[0413] In certain embodiments, the compound is **Compound 81**, or a pharmaceutically acceptable salt thereof:



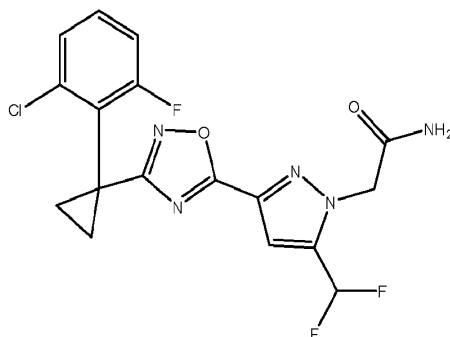
[0414] In certain embodiments, the compound is **Compound 82**, or a pharmaceutically acceptable salt thereof:



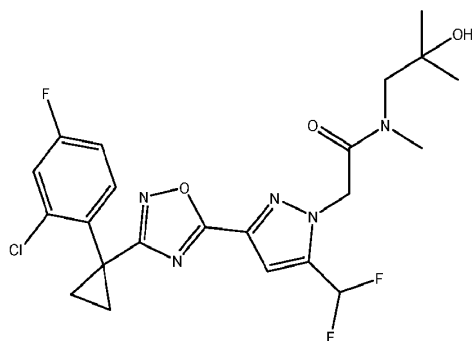
[0415] In certain embodiments, the compound is **Compound 83**, or a pharmaceutically acceptable salt thereof:



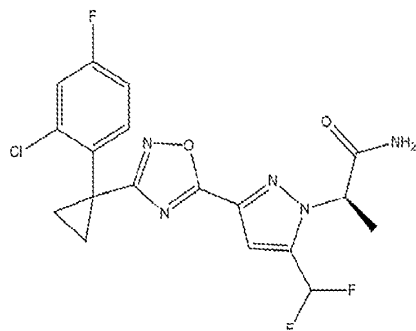
[0416] In certain embodiments, the compound is **Compound 84**, or a pharmaceutically acceptable salt thereof.



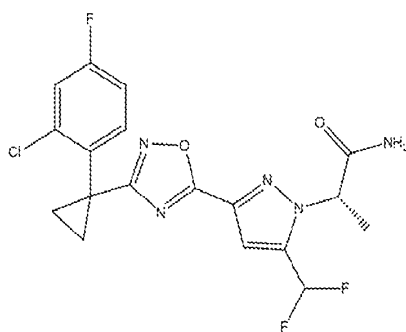
[0417] In certain embodiments, the compound is **Compound 85**, or a pharmaceutically acceptable salt thereof.



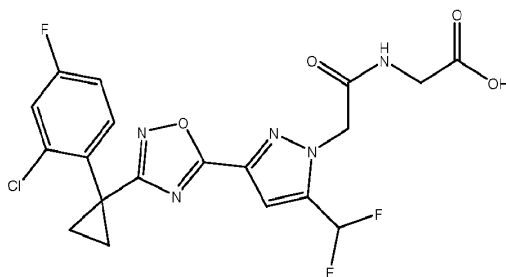
[0418] In certain embodiments, the compound is **Compound 86**, or a pharmaceutically acceptable salt thereof.



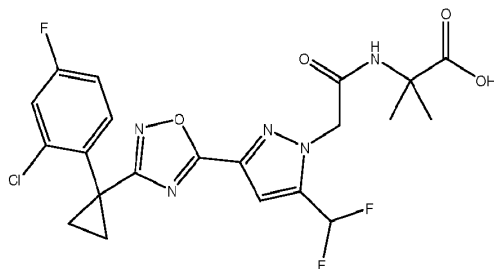
[0419] In certain embodiments, the compound is **Compound 87**, or a pharmaceutically acceptable salt thereof.



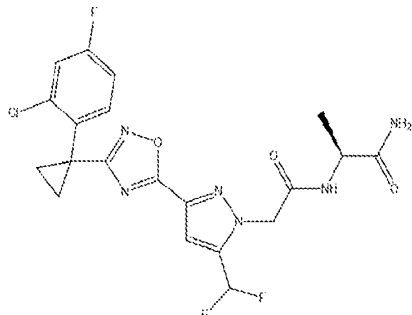
[0420] In certain embodiments, the compound is **Compound 88**, or a pharmaceutically acceptable salt thereof.



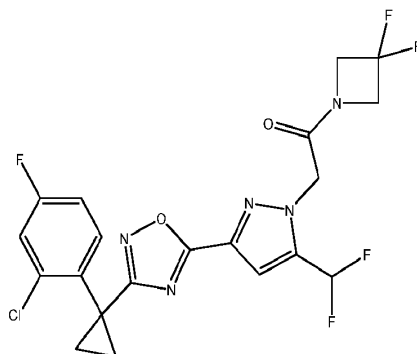
[0421] In certain embodiments, the compound is **Compound 89**, or a pharmaceutically acceptable salt thereof.



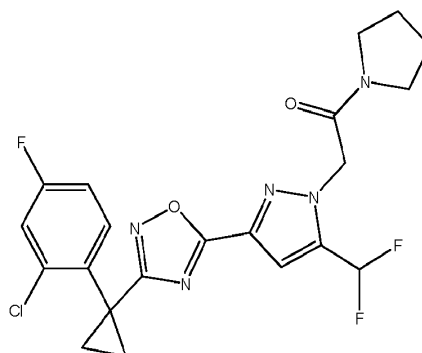
[0422] In certain embodiments, the compound is **Compound 90**, or a pharmaceutically acceptable salt thereof:



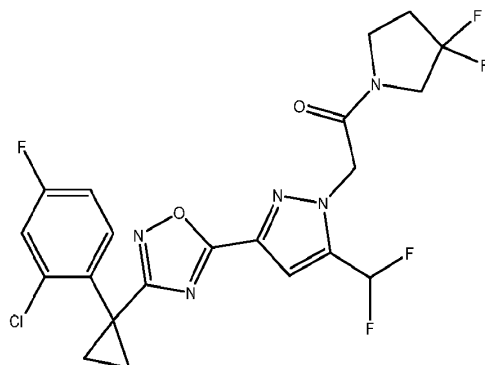
[0423] In certain embodiments, the compound is **Compound 91**, or a pharmaceutically acceptable salt thereof:



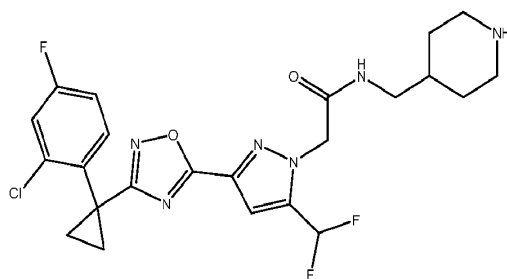
[0424] In certain embodiments, the compound is **Compound 92**, or a pharmaceutically acceptable salt thereof:



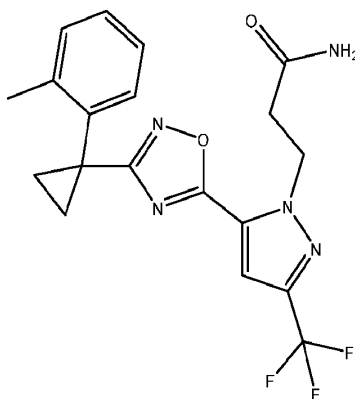
[0425] In certain embodiments, the compound is **Compound 93**, or a pharmaceutically acceptable salt thereof:



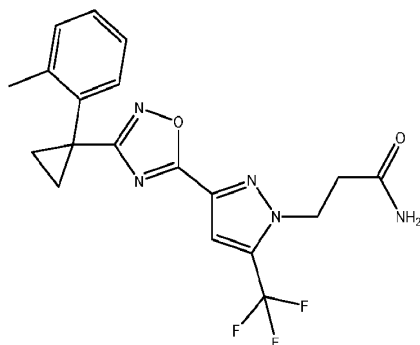
[0426] In certain embodiments, the compound is **Compound 94**, or a pharmaceutically acceptable salt thereof:



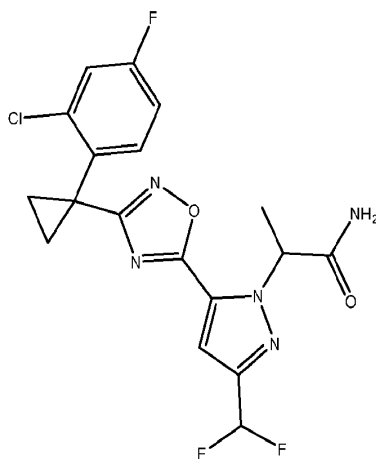
[0427] In certain embodiments, the compound is **Compound 95**, or a pharmaceutically acceptable salt thereof:



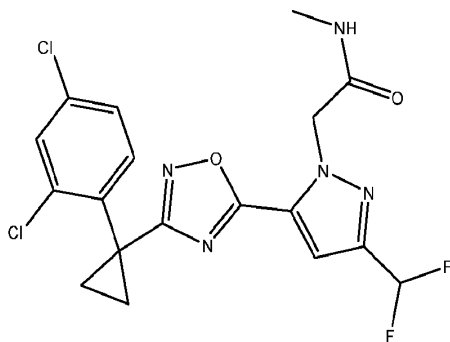
[0428] In certain embodiments, the compound is **Compound 96**, or a pharmaceutically acceptable salt thereof:



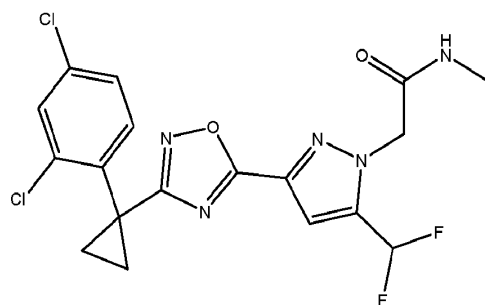
[0429] In certain embodiments, the compound is **Compound 97**, or a pharmaceutically acceptable salt thereof:



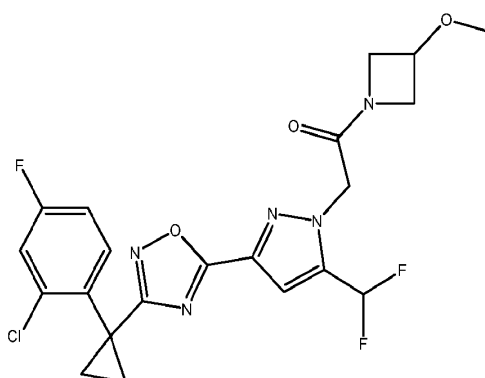
[0430] In certain embodiments, the compound is **Compound 98**, or a pharmaceutically acceptable salt thereof:



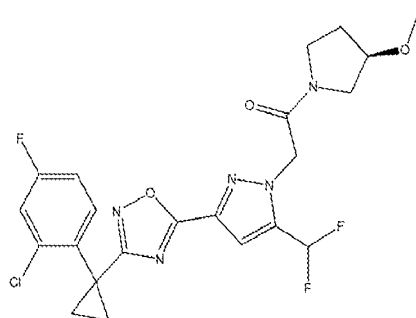
[0431] In certain embodiments, the compound is **Compound 99**, or a pharmaceutically acceptable salt thereof:



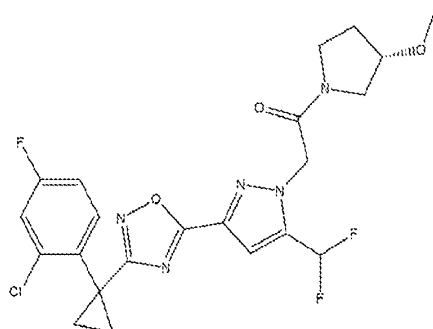
[0432] In certain embodiments, the compound is **Compound 100**, or a pharmaceutically acceptable salt thereof.



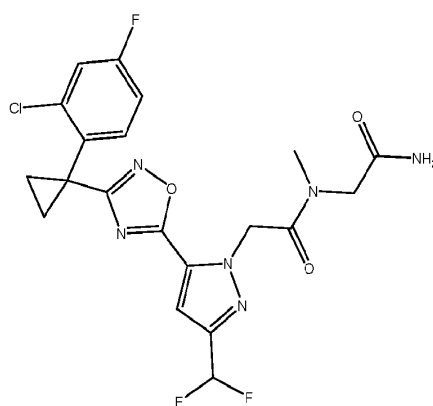
[0433] In certain embodiments, the compound is **Compound 101**, or a pharmaceutically acceptable salt thereof.



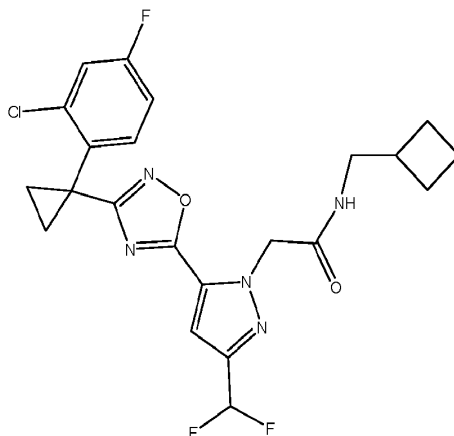
[0434] In certain embodiments, the compound is **Compound 102**, or a pharmaceutically acceptable salt thereof.



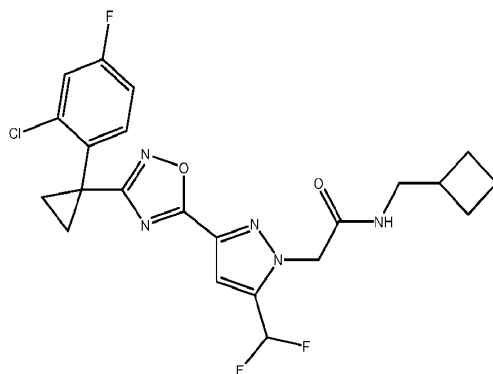
[0435] In certain embodiments, the compound is **Compound 103**, or a pharmaceutically acceptable salt thereof:



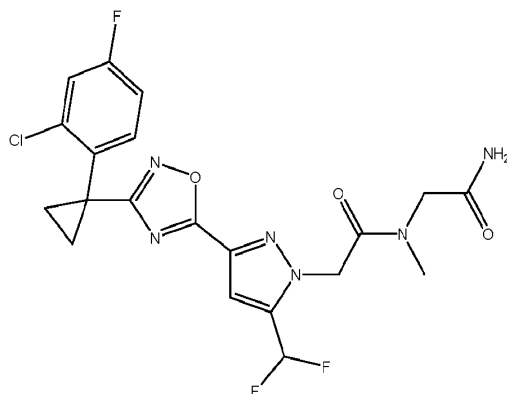
[0436] In certain embodiments, the compound is **Compound 104**, or a pharmaceutically acceptable salt thereof:



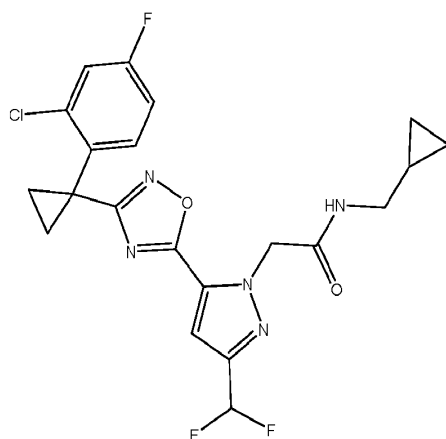
[0437] In certain embodiments, the compound is **Compound 105**, or a pharmaceutically acceptable salt thereof:



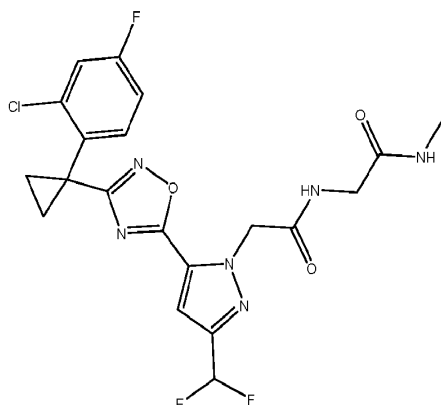
[0438] In certain embodiments, the compound is **Compound 106**, or a pharmaceutically acceptable salt thereof:



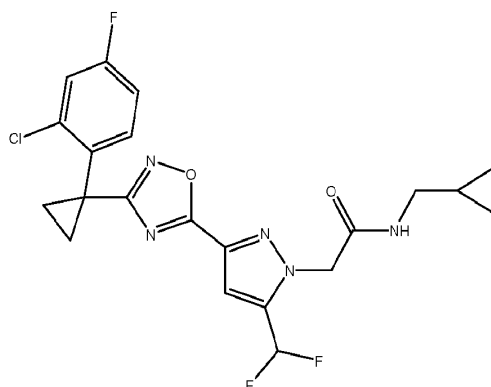
[0439] In certain embodiments, the compound is **Compound 107**, or a pharmaceutically acceptable salt thereof:



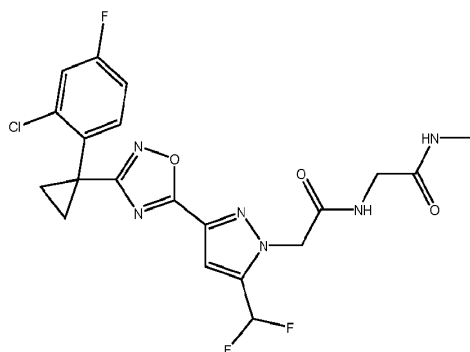
[0440] In certain embodiments, the compound is **Compound 108**, or a pharmaceutically acceptable salt thereof:



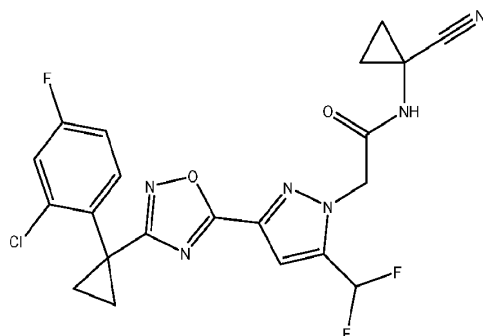
[0441] In certain embodiments, the compound is **Compound 109**, or a pharmaceutically acceptable salt thereof:



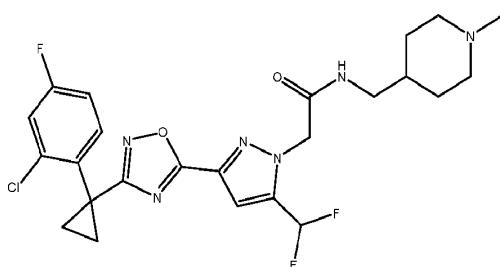
[0442] In certain embodiments, the compound is **Compound 110**, or a pharmaceutically acceptable salt thereof:



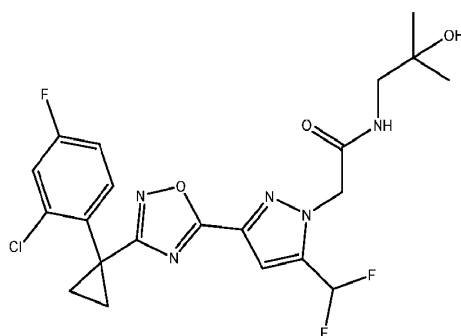
[0443] In certain embodiments, the compound is **Compound 111**, or a pharmaceutically acceptable salt thereof:



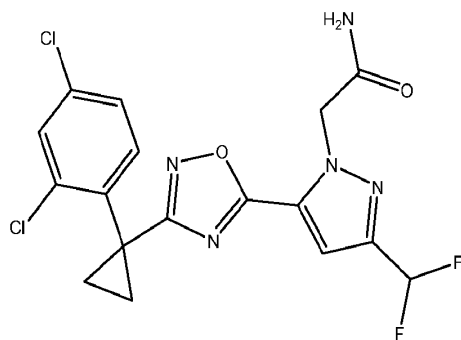
[0444] In certain embodiments, the compound is **Compound 112**, or a pharmaceutically acceptable salt thereof:



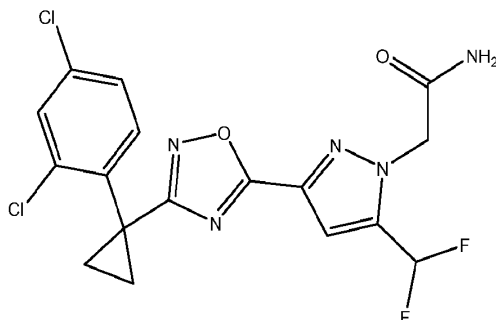
[0445] In certain embodiments, the compound is **Compound 113**, or a pharmaceutically acceptable salt thereof:



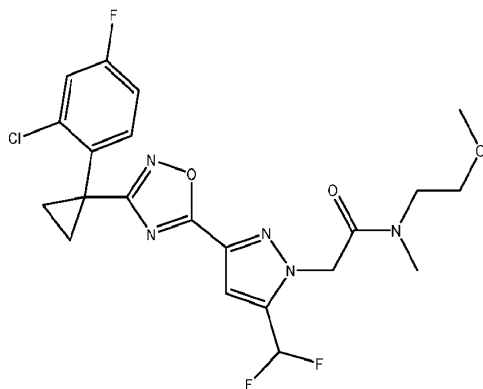
[0446] In certain embodiments, the compound is **Compound 114**, or a pharmaceutically acceptable salt thereof:



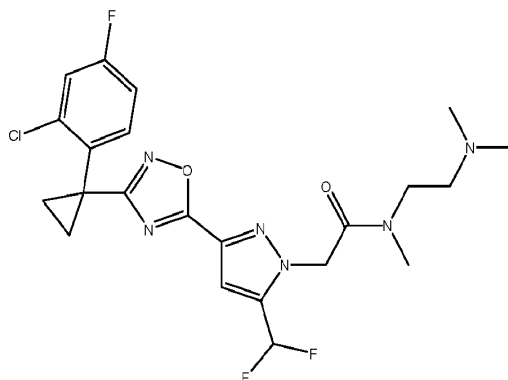
[0447] In certain embodiments, the compound is **Compound 115**, or a pharmaceutically acceptable salt thereof:



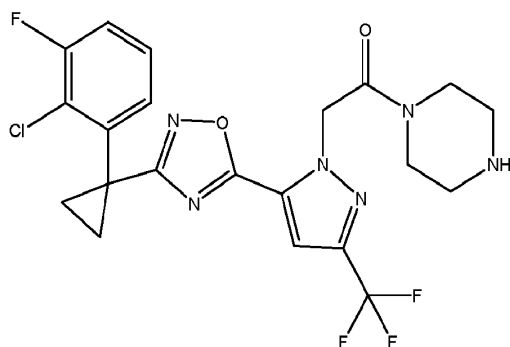
[0448] In certain embodiments, the compound is **Compound 116**, or a pharmaceutically acceptable salt thereof:



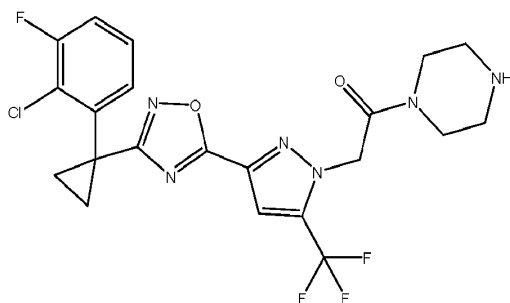
[0449] In certain embodiments, the compound is **Compound 117**, or a pharmaceutically acceptable salt thereof:



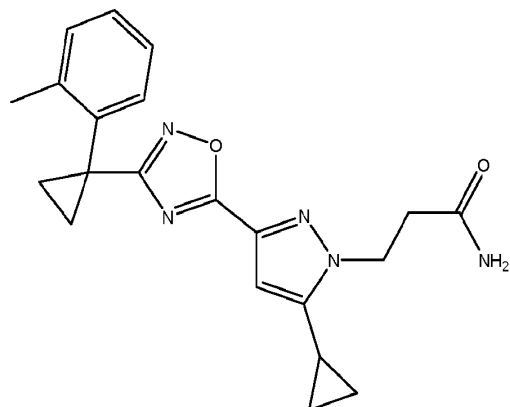
[0450] In certain embodiments, the compound is **Compound 118**, or a pharmaceutically acceptable salt thereof:



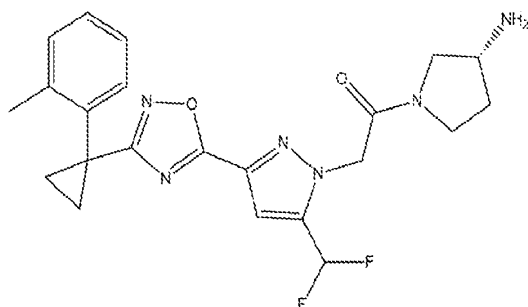
[0451] In certain embodiments, the compound is **Compound 119**, or a pharmaceutically acceptable salt thereof:



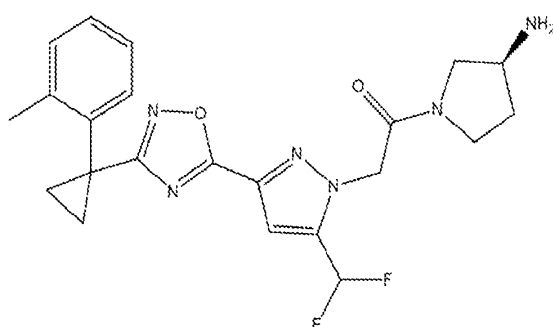
[0452] In certain embodiments, the compound is **Compound 120**, or a pharmaceutically acceptable salt thereof:



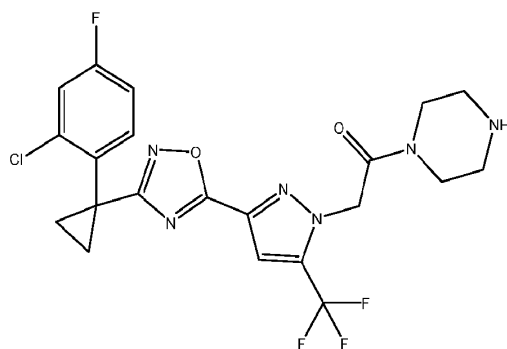
[0453] In certain embodiments, the compound is **Compound 121**, or a pharmaceutically acceptable salt thereof:



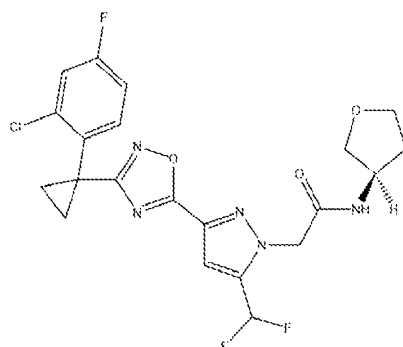
[0454] In certain embodiments, the compound is **Compound 122**, or a pharmaceutically acceptable salt thereof.



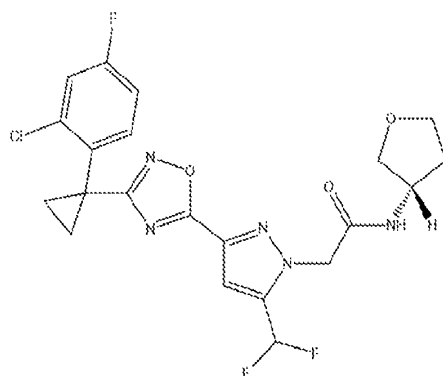
[0455] In certain embodiments, the compound is **Compound 123**, or a pharmaceutically acceptable salt thereof.



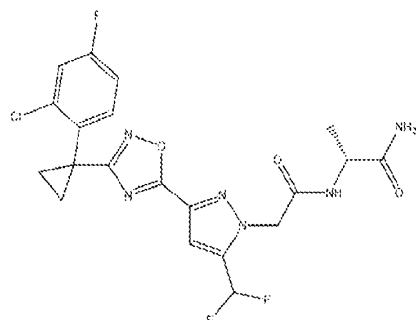
[0456] In certain embodiments, the compound is **Compound 124**, or a pharmaceutically acceptable salt thereof.



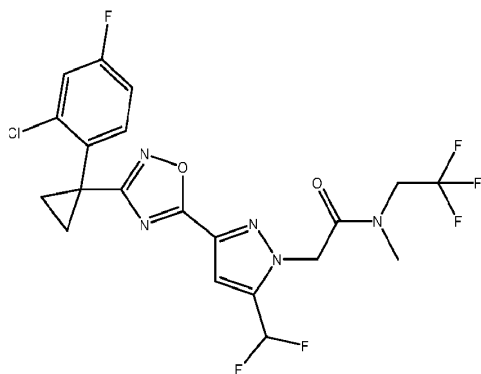
[0457] In certain embodiments, the compound is **Compound 125**, or a pharmaceutically acceptable salt thereof.



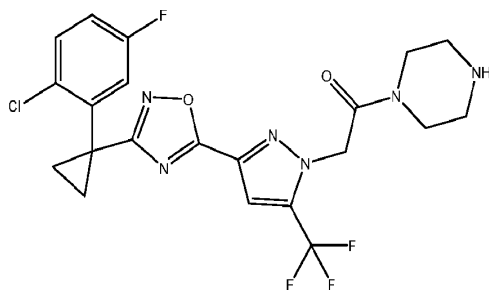
[0458] In certain embodiments, the compound is **Compound 126**, or a pharmaceutically acceptable salt thereof.



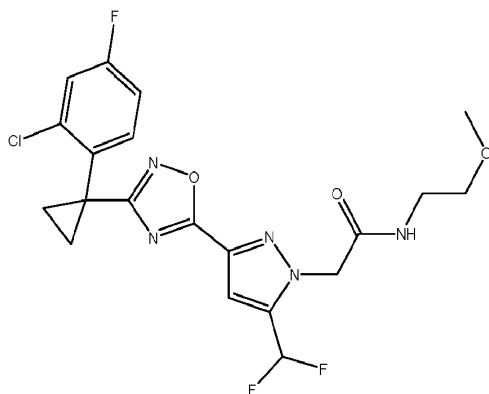
[0459] In certain embodiments, the compound is **Compound 127**, or a pharmaceutically acceptable salt thereof.



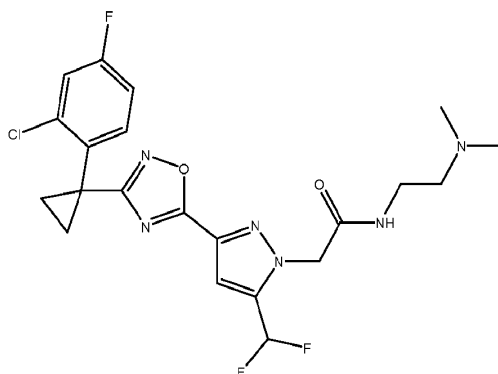
[0460] In certain embodiments, the compound is **Compound 128**, or a pharmaceutically acceptable salt thereof:



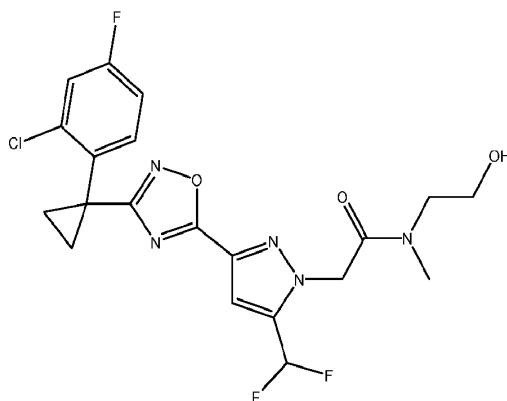
[0461] In certain embodiments, the compound is **Compound 129**, or a pharmaceutically acceptable salt thereof:



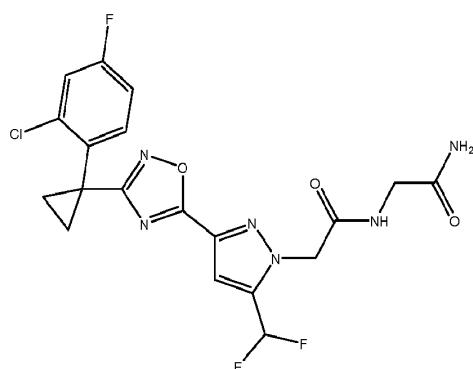
[0462] In certain embodiments, the compound is **Compound 130**, or a pharmaceutically acceptable salt thereof:



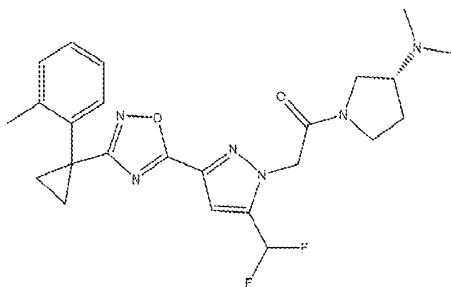
[0463] In certain embodiments, the compound is **Compound 131**, or a pharmaceutically acceptable salt thereof:



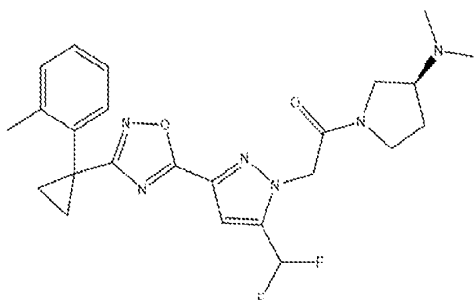
[0464] In certain embodiments, the compound is **Compound 132**, or a pharmaceutically acceptable salt thereof:



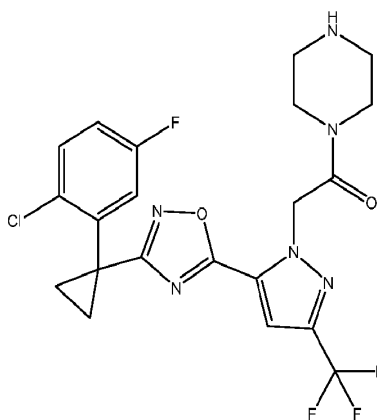
[0465] In certain embodiments, the compound is **Compound 133**, or a pharmaceutically acceptable salt thereof:



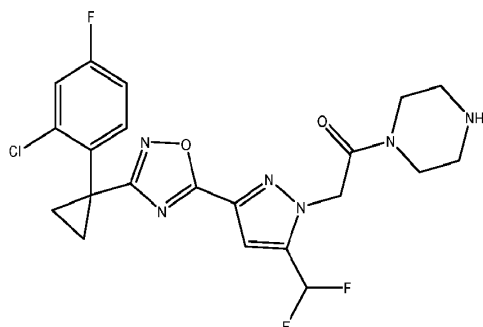
[0466] In certain embodiments, the compound is **Compound 134**, or a pharmaceutically acceptable salt thereof.



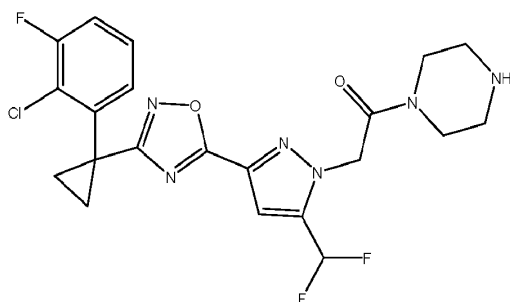
[0467] In certain embodiments, the compound is **Compound 135**, or a pharmaceutically acceptable salt thereof.



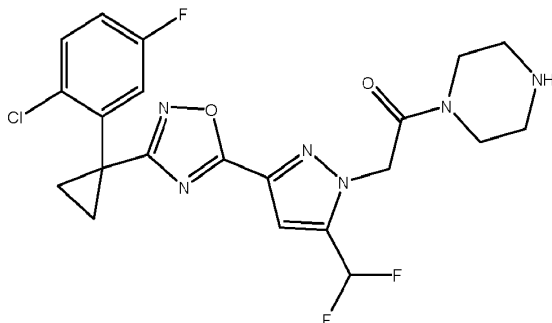
[0468] In certain embodiments, the compound is **Compound 136**, or a pharmaceutically acceptable salt thereof.



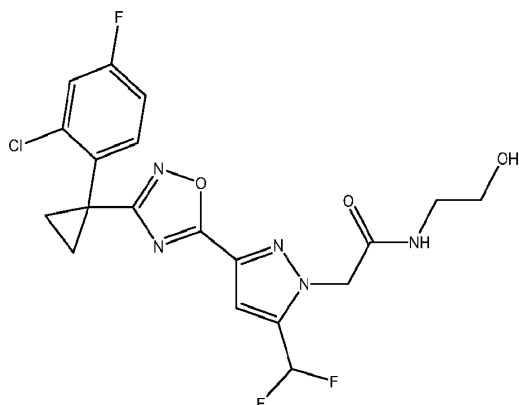
[0469] In certain embodiments, the compound is **Compound 137**, or a pharmaceutically acceptable salt thereof:



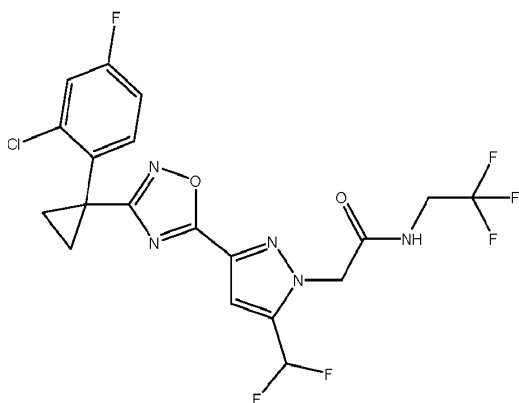
[0470] In certain embodiments, the compound is **Compound 138**, or a pharmaceutically acceptable salt thereof:



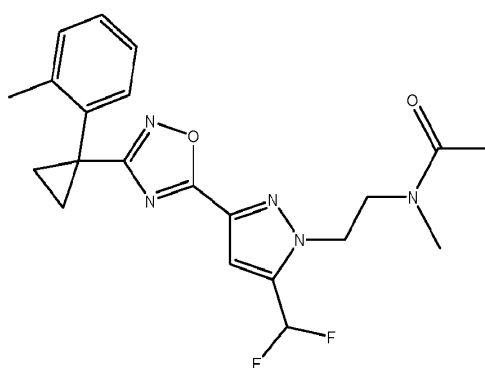
[0471] In certain embodiments, the compound is **Compound 139**, or a pharmaceutically acceptable salt thereof:



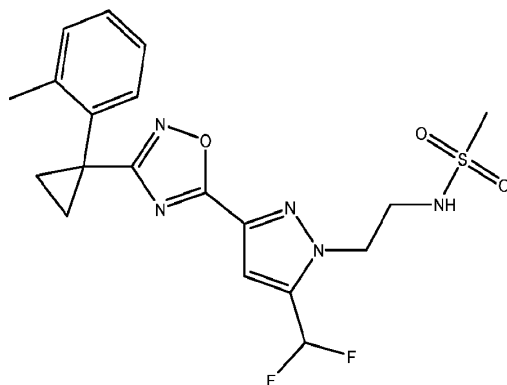
[0472] In certain embodiments, the compound is **Compound 140**, or a pharmaceutically acceptable salt thereof:



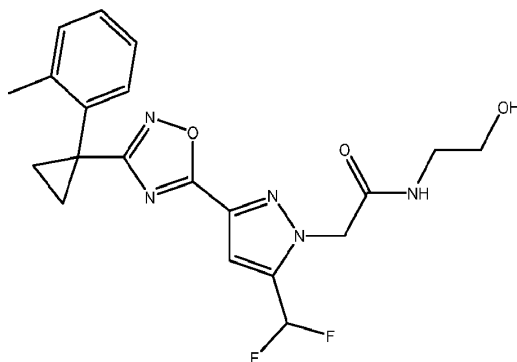
[0473] In certain embodiments, the compound is **Compound 141**, or a pharmaceutically acceptable salt thereof:



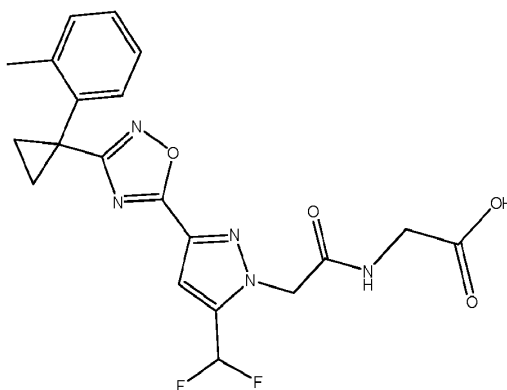
[0474] In certain embodiments, the compound is **Compound 142**, or a pharmaceutically acceptable salt thereof:



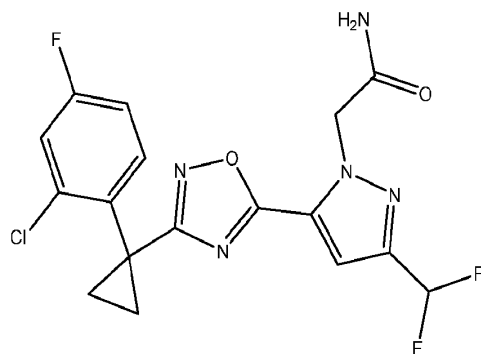
[0475] In certain embodiments, the compound is **Compound 143**, or a pharmaceutically acceptable salt thereof.



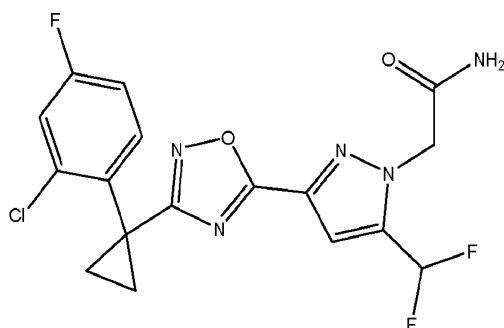
[0476] In certain embodiments, the compound is **Compound 144**, or a pharmaceutically acceptable salt thereof.



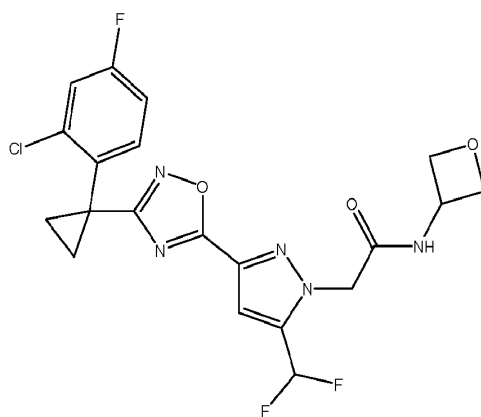
[0477] In certain embodiments, the compound is **Compound 145**, or a pharmaceutically acceptable salt thereof.



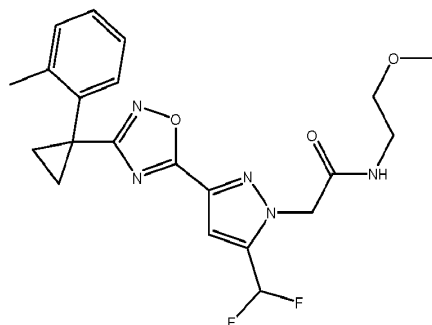
[0478] In certain embodiments, the compound is **Compound 146**, or a pharmaceutically acceptable salt thereof:



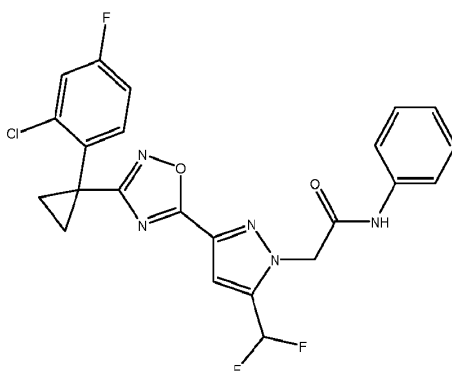
[0479] In certain embodiments, the compound is **Compound 147**, or a pharmaceutically acceptable salt thereof:



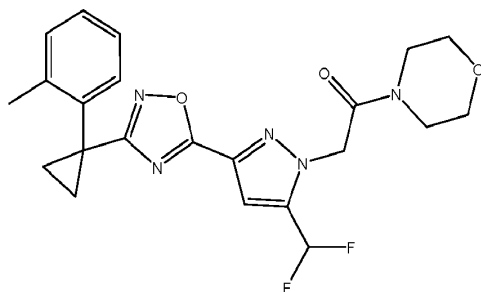
[0480] In certain embodiments, the compound is **Compound 148**, or a pharmaceutically acceptable salt thereof:



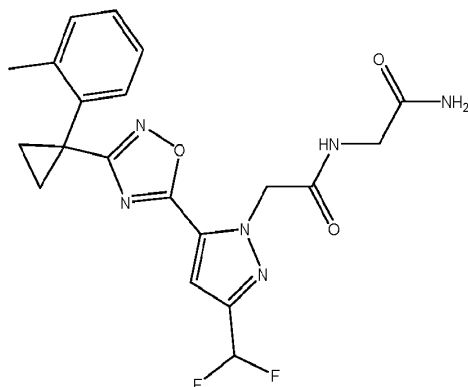
[0481] In certain embodiments, the compound is **Compound 149**, or a pharmaceutically acceptable salt thereof:



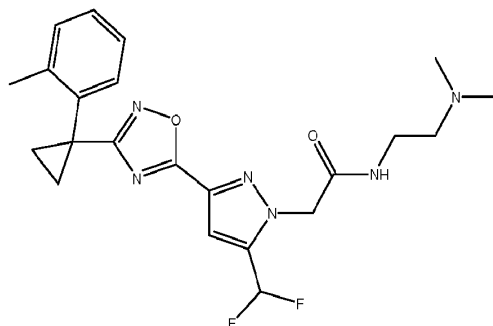
[0482] In certain embodiments, the compound is **Compound 150**, or a pharmaceutically acceptable salt thereof:



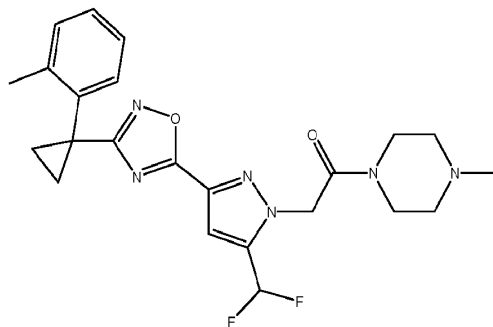
[0483] In certain embodiments, the compound is **Compound 151**, or a pharmaceutically acceptable salt thereof:



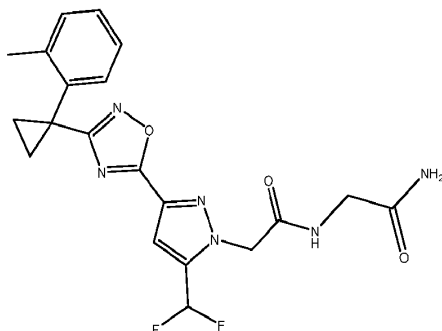
[0484] In certain embodiments, the compound is **Compound 152**, or a pharmaceutically acceptable salt thereof:



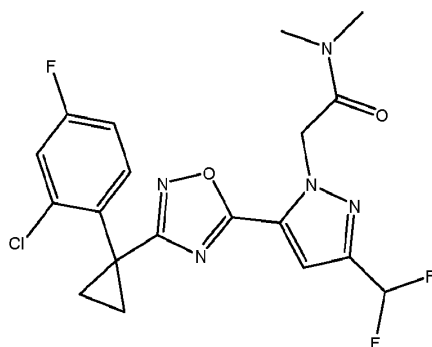
[0485] In certain embodiments, the compound is **Compound 153**, or a pharmaceutically acceptable salt thereof:



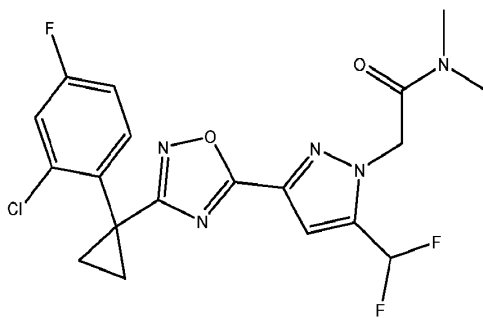
[0486] In certain embodiments, the compound is **Compound 154**, or a pharmaceutically acceptable salt thereof:



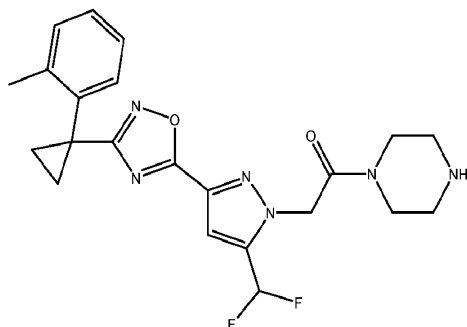
[0487] In certain embodiments, the compound is **Compound 155**, or a pharmaceutically acceptable salt thereof:



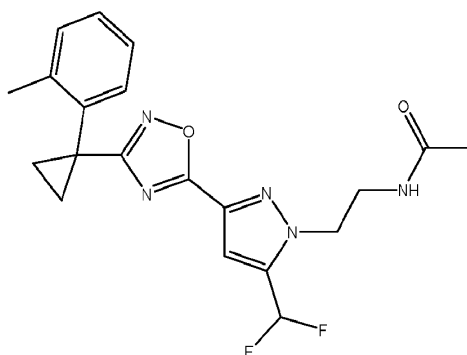
[0488] In certain embodiments, the compound is **Compound 156**, or a pharmaceutically acceptable salt thereof:



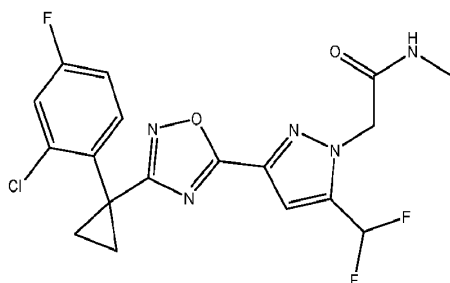
[0489] In certain embodiments, the compound is **Compound 157**, or a pharmaceutically acceptable salt thereof:



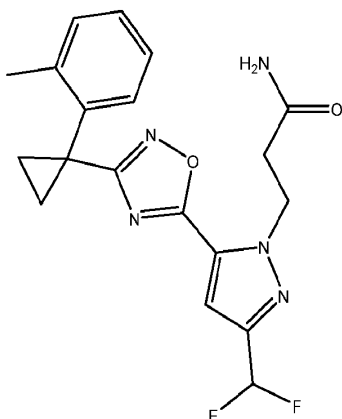
[0490] In certain embodiments, the compound is **Compound 158**, or a pharmaceutically acceptable salt thereof:



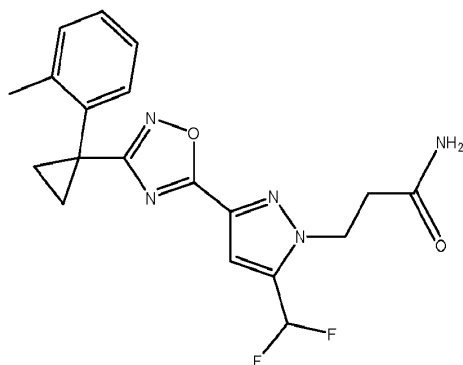
[0491] In certain embodiments, the compound is **Compound 159**, or a pharmaceutically acceptable salt thereof:



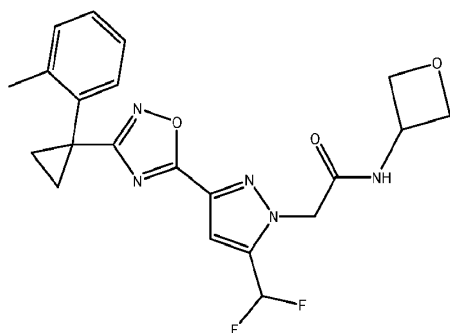
[0492] In certain embodiments, the compound is **Compound 160**, or a pharmaceutically acceptable salt thereof:



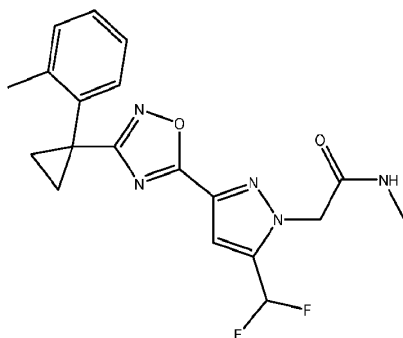
[0493] In certain embodiments, the compound is **Compound 161**, or a pharmaceutically acceptable salt thereof.



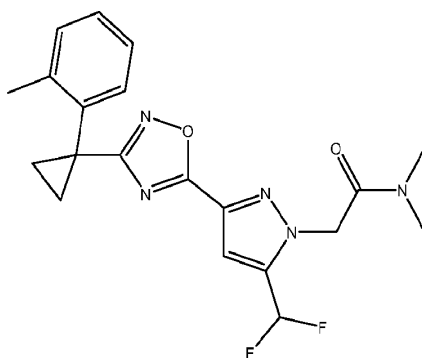
[0494] In one embodiment, the compound is **Compound 162**, or a pharmaceutically acceptable salt thereof.



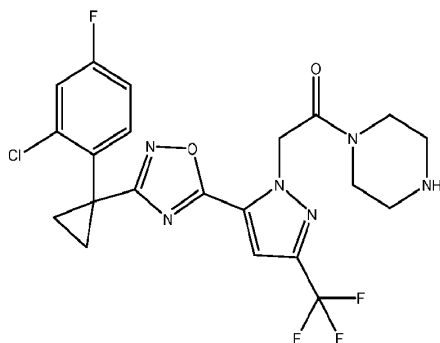
[0495] In one embodiment, the compound is **Compound 163**, or a pharmaceutically acceptable salt thereof.



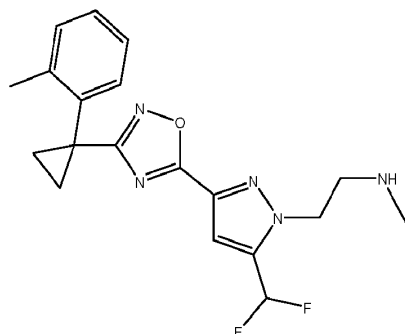
[0496] In one embodiment, the compound is **Compound 164**, or a pharmaceutically acceptable salt thereof:



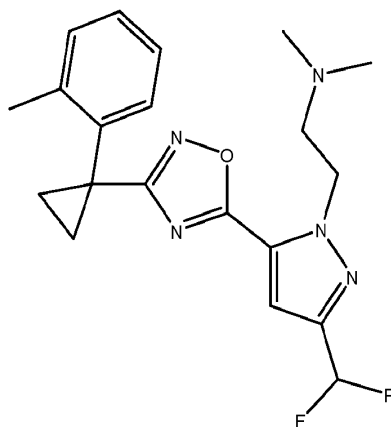
[0497] In one embodiment, the compound is **Compound 165**, or a pharmaceutically acceptable salt thereof:



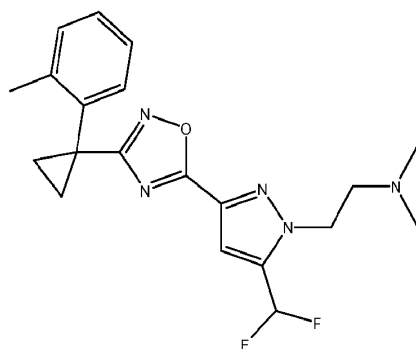
[0498] In one embodiment, the compound is **Compound 166**, or a pharmaceutically acceptable salt thereof:



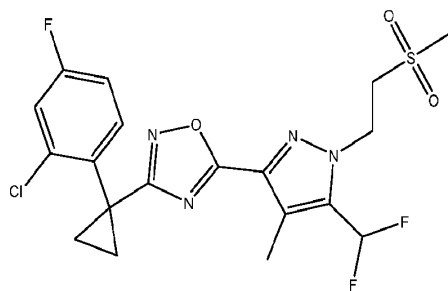
[0499] In one embodiment, the compound is **Compound 167**, or a pharmaceutically acceptable salt thereof:



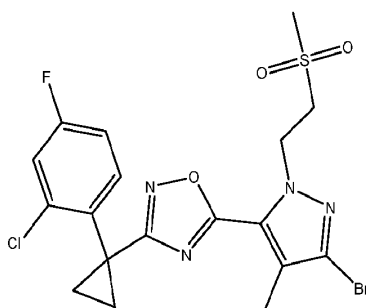
[0500] In one embodiment, the compound is **Compound 168**, or a pharmaceutically acceptable salt thereof:



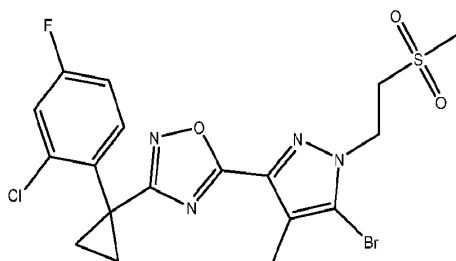
[0501] In one embodiment, the compound is **Compound 169**, or a pharmaceutically acceptable salt thereof:



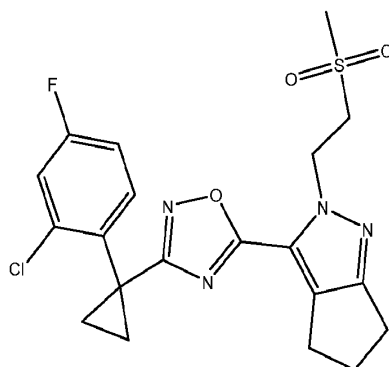
[0502] In one embodiment, the compound is **Compound 170**, or a pharmaceutically acceptable salt thereof.



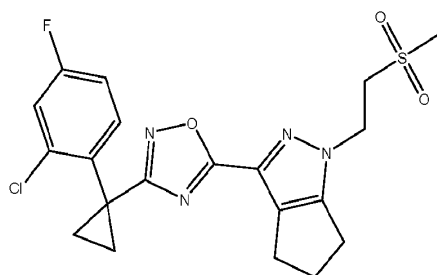
[0503] In one embodiment, the compound is **Compound 171**, or a pharmaceutically acceptable salt thereof.



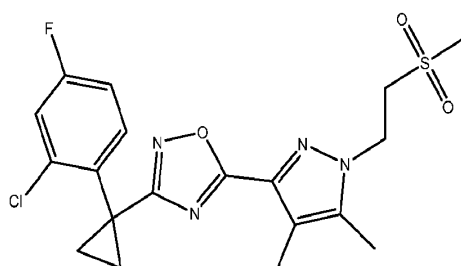
[0504] In one embodiment, the compound is **Compound 172**, or a pharmaceutically acceptable salt thereof.



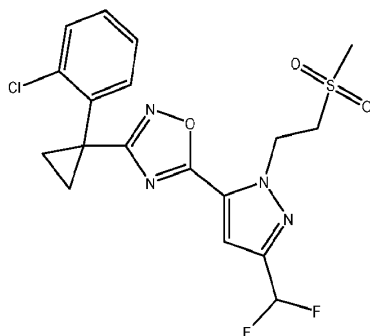
[0505] In one embodiment, the compound is **Compound 173**, or a pharmaceutically acceptable salt thereof:



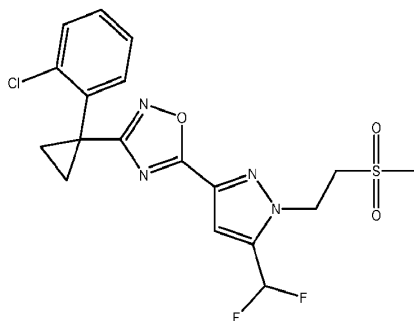
[0506] In one embodiment, the compound is **Compound 174**, or a pharmaceutically acceptable salt thereof:



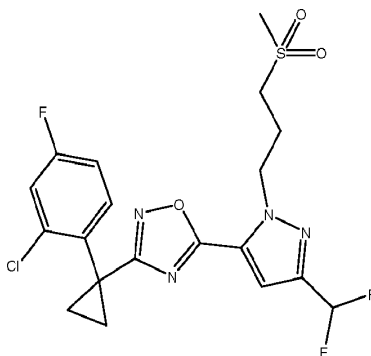
[0507] In one embodiment, the compound is **Compound 175**, or a pharmaceutically acceptable salt thereof:



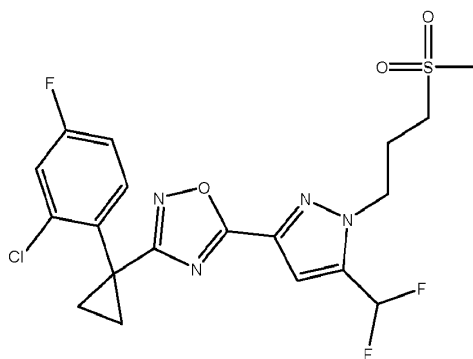
[0508] In one embodiment, the compound is **Compound 176**, or a pharmaceutically acceptable salt thereof:



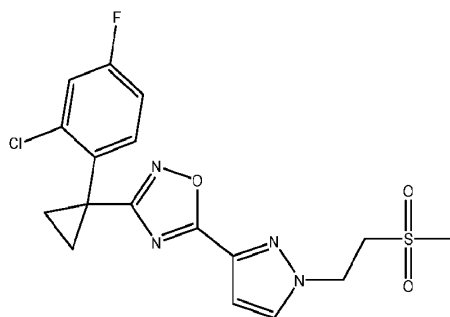
[0509] In one embodiment, the compound is **Compound 177**, or a pharmaceutically acceptable salt thereof:



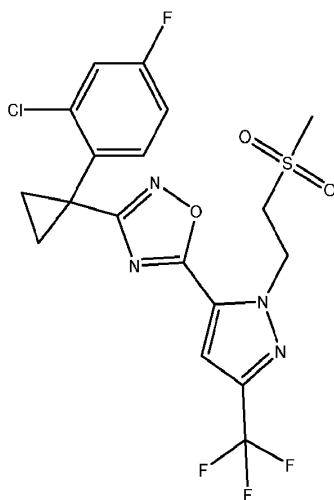
[0510] In one embodiment, the compound is **Compound 178**, or a pharmaceutically acceptable salt thereof:



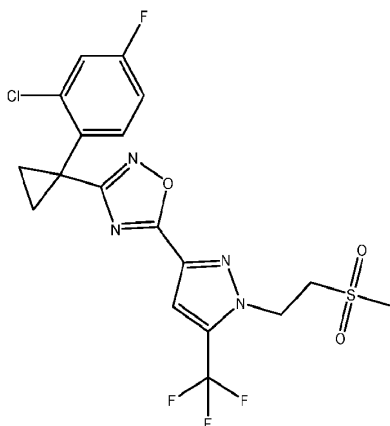
[0511] In one embodiment, the compound is **Compound 179**, or a pharmaceutically acceptable salt thereof:



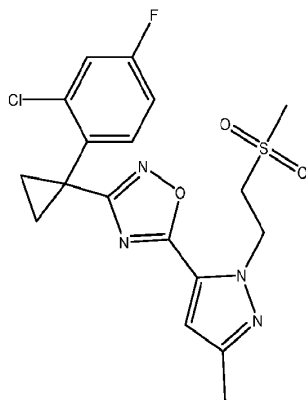
[0512] In one embodiment, the compound is **Compound 180**, or a pharmaceutically acceptable salt thereof:



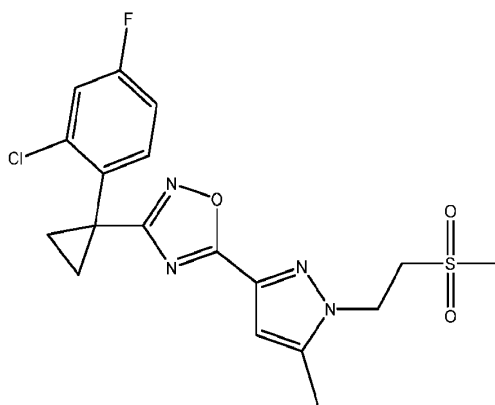
[0513] In one embodiment, the compound is **Compound 181**, or a pharmaceutically acceptable salt thereof:



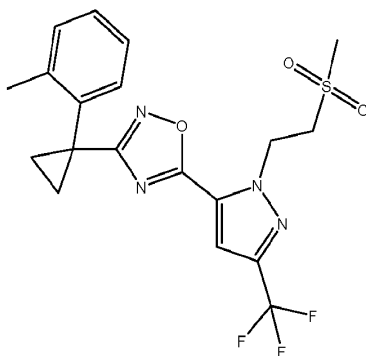
[0514] In one embodiment, the compound is **Compound 182**, or a pharmaceutically acceptable salt thereof:



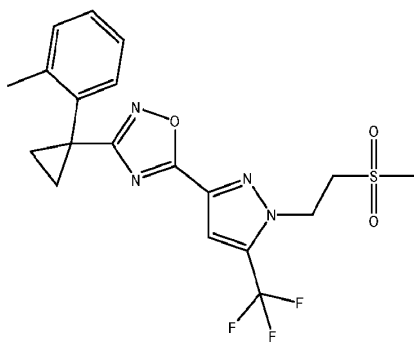
[0515] In one embodiment, the compound is **Compound 183**, or a pharmaceutically acceptable salt thereof:



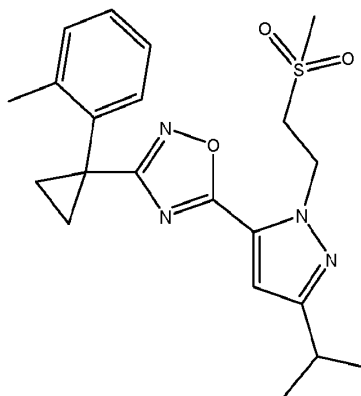
[0516] In one embodiment, the compound is **Compound 184**, or a pharmaceutically acceptable salt thereof:



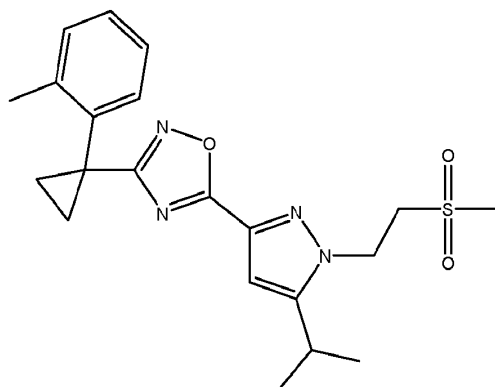
[0517] In one embodiment, the compound is **Compound 185**, or a pharmaceutically acceptable salt thereof:



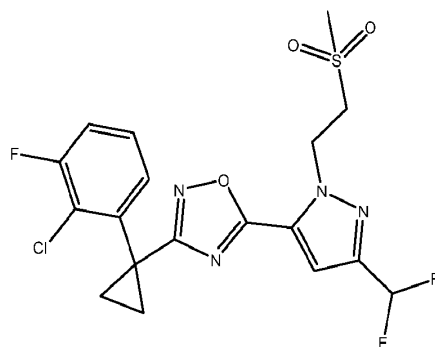
[0518] In one embodiment, the compound is **Compound 186**, or a pharmaceutically acceptable salt thereof:



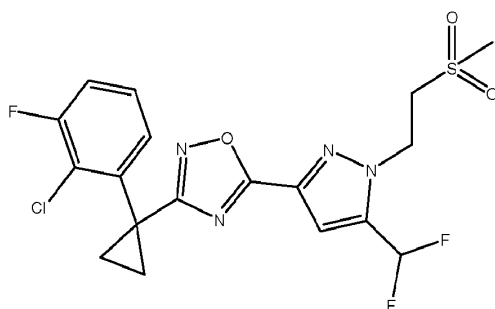
[0519] In one embodiment, the compound is **Compound 187**, or a pharmaceutically acceptable salt thereof:



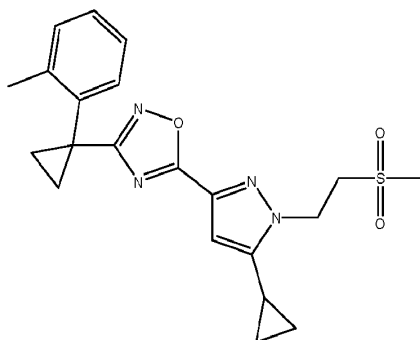
[0520] In one embodiment, the compound is **Compound 188**, or a pharmaceutically acceptable salt thereof:



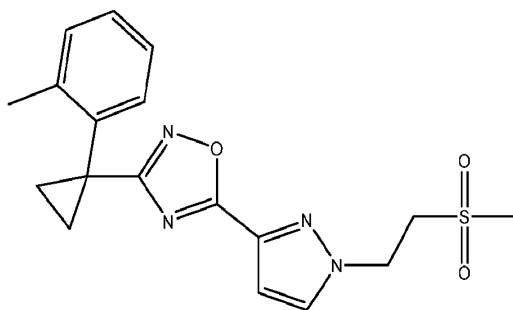
[0521] In one embodiment, the compound is **Compound 189**, or a pharmaceutically acceptable salt thereof:



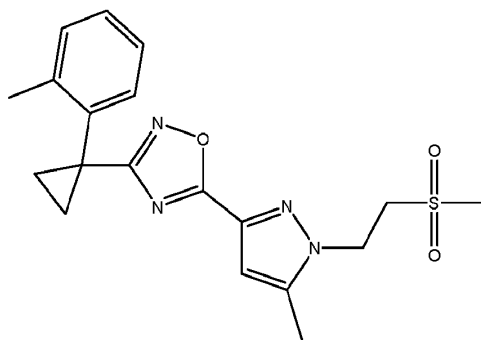
[0522] In one embodiment, the compound is **Compound 190**, or a pharmaceutically acceptable salt thereof:



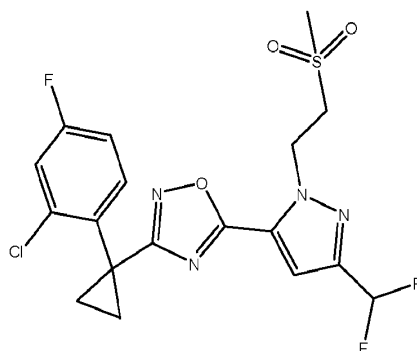
[0523] In one embodiment, the compound is **Compound 191**, or a pharmaceutically acceptable salt thereof:



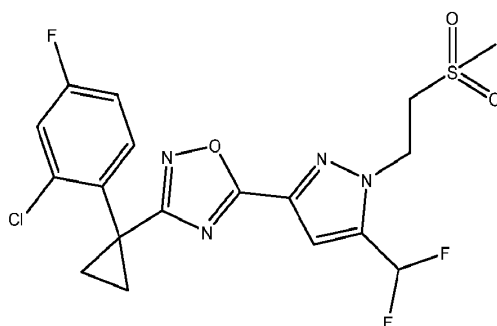
[0524] In one embodiment, the compound is **Compound 192**, or a pharmaceutically acceptable salt thereof:



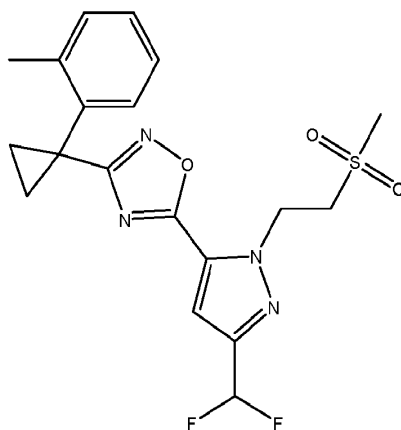
[0525] In one embodiment, the compound is **Compound 193**, or a pharmaceutically acceptable salt thereof:



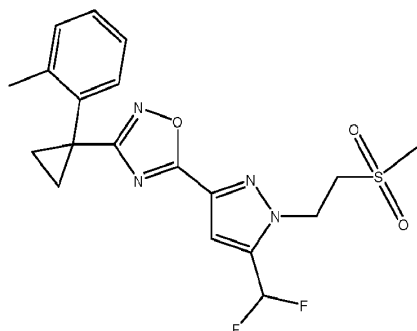
[0526] In one embodiment, the compound is **Compound 194**, or a pharmaceutically acceptable salt thereof:



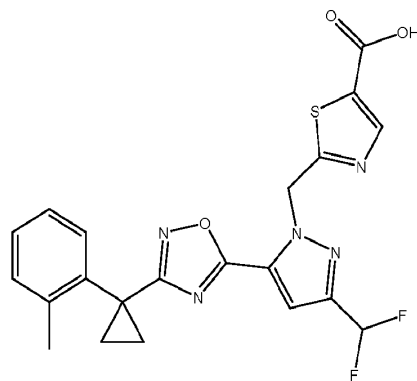
[0527] In one embodiment, the compound is **Compound 195**, or a pharmaceutically acceptable salt thereof:



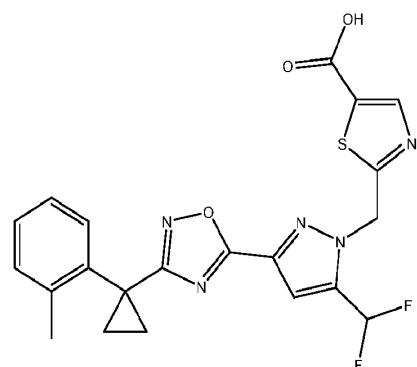
[0528] In one embodiment, the compound is **Compound 196**, or a pharmaceutically acceptable salt thereof:



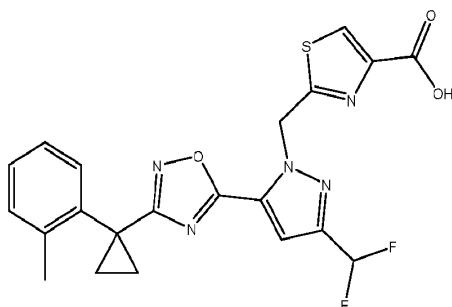
[0529] In one embodiment, the compound is **Compound 197**, or a pharmaceutically acceptable salt thereof:



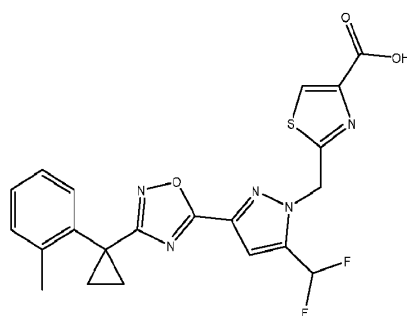
[0530] In one embodiment, the compound is **Compound 198**, or a pharmaceutically acceptable salt thereof:



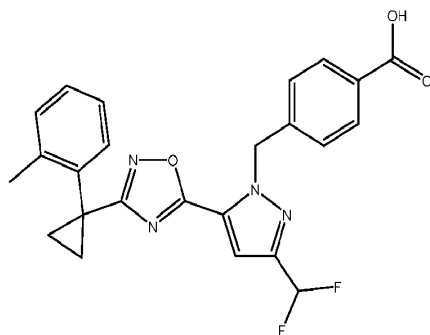
[0531] In one embodiment, the compound is **Compound 199**, or a pharmaceutically acceptable salt thereof:



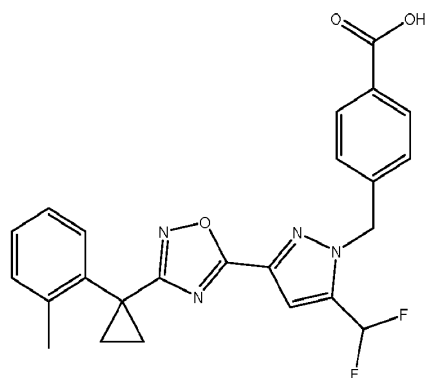
[0532] In one embodiment, the compound is **Compound 200**, or a pharmaceutically acceptable salt thereof:



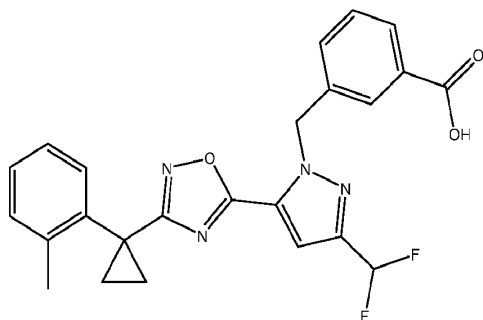
[0533] In one embodiment, the compound is **Compound 201**, or a pharmaceutically acceptable salt thereof:



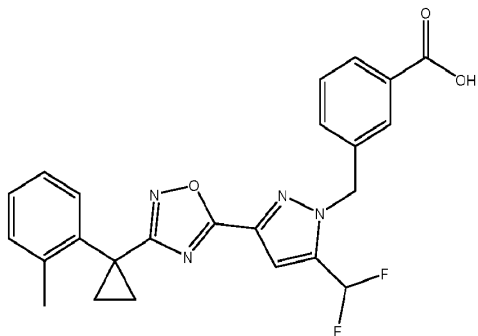
[0534] In one embodiment, the compound is **Compound 202**, or a pharmaceutically acceptable salt thereof:



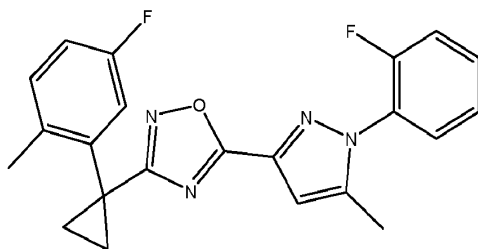
[0535] In one embodiment, the compound is **Compound 203**, or a pharmaceutically acceptable salt thereof:



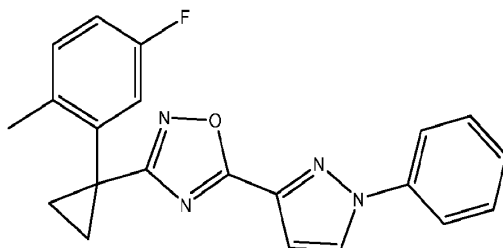
[0536] In one embodiment, the compound is **Compound 204**, or a pharmaceutically acceptable salt thereof:



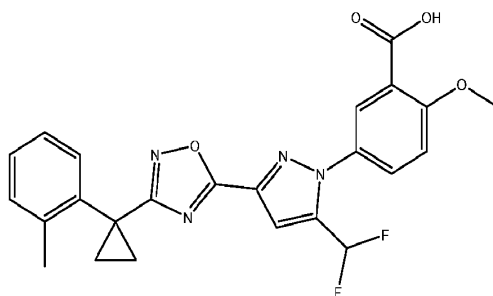
[0537] In one embodiment, the compound is **Compound 205**, or a pharmaceutically acceptable salt thereof:



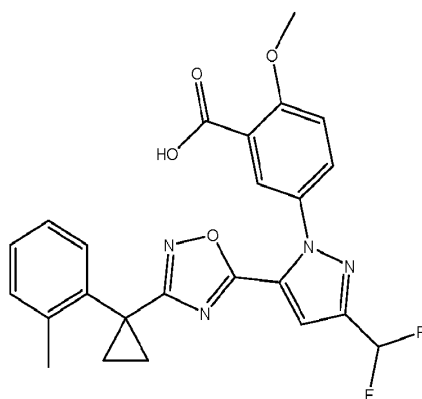
[0538] In one embodiment, the compound is **Compound 206**, or a pharmaceutically acceptable salt thereof:



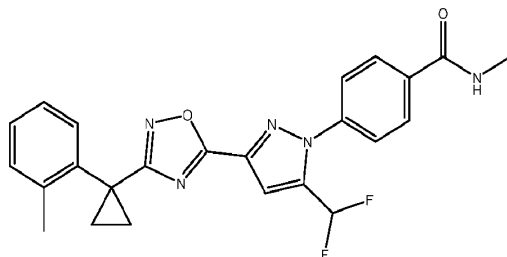
[0539] In one embodiment, the compound is **Compound 207**, or a pharmaceutically acceptable salt thereof:



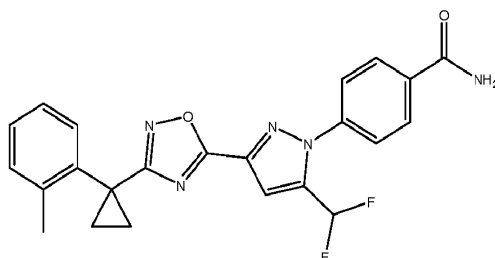
[0540] In one embodiment, the compound is **Compound 208**, or a pharmaceutically acceptable salt thereof:



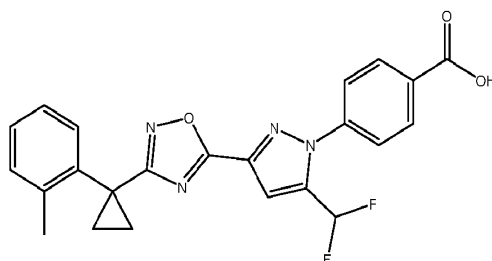
[0541] In one embodiment, the compound is **Compound 209**, or a pharmaceutically acceptable salt thereof:



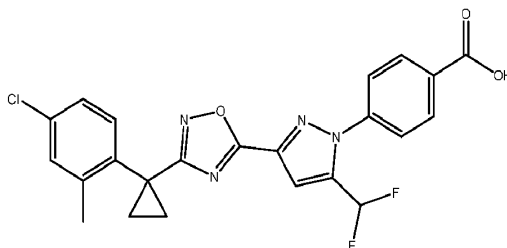
[0542] In one embodiment, the compound is **Compound 210**, or a pharmaceutically acceptable salt thereof:



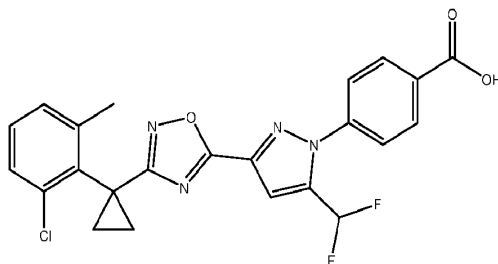
[0543] In one embodiment, the compound is **Compound 211**, or a pharmaceutically acceptable salt thereof:



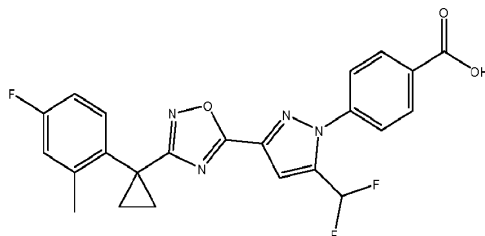
[0544] In one embodiment, the compound is **Compound 212**, or a pharmaceutically acceptable salt thereof:



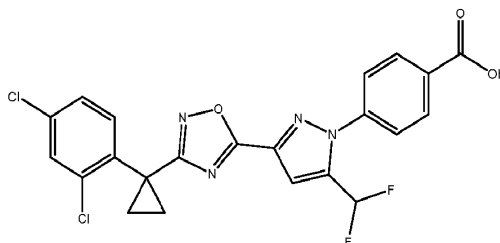
[0545] In one embodiment, the compound is **Compound 213**, or a pharmaceutically acceptable salt thereof:



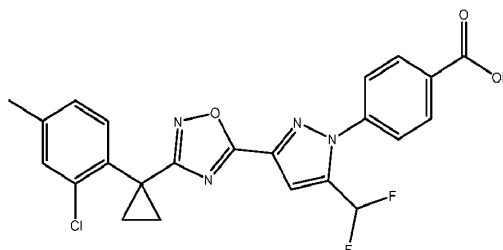
[0546] In one embodiment, the compound is **Compound 214**, or a pharmaceutically acceptable salt thereof:



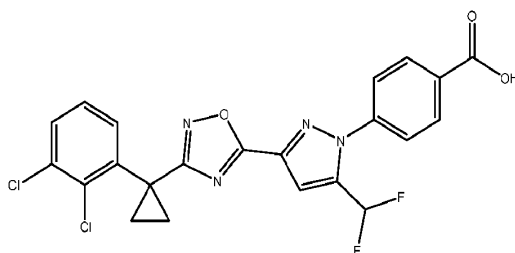
[0547] In one embodiment, the compound is **Compound 215**, or a pharmaceutically acceptable salt thereof:



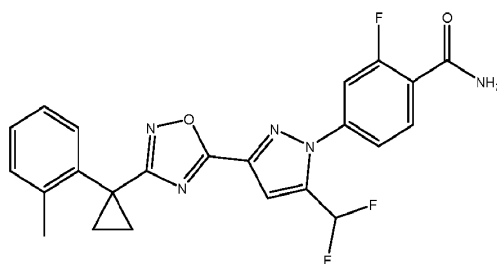
[0548] In one embodiment, the compound is **Compound 216**, or a pharmaceutically acceptable salt thereof:



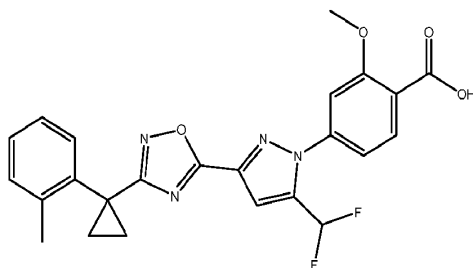
[0549] In one embodiment, the compound is **Compound 217**, or a pharmaceutically acceptable salt thereof:



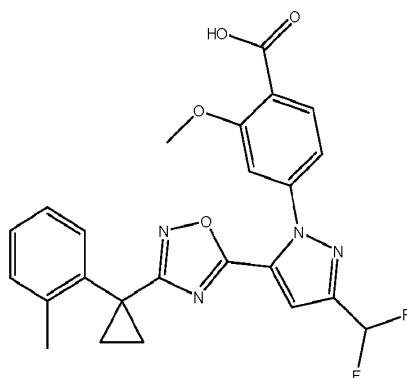
[0550] In one embodiment, the compound is **Compound 218**, or a pharmaceutically acceptable salt thereof:



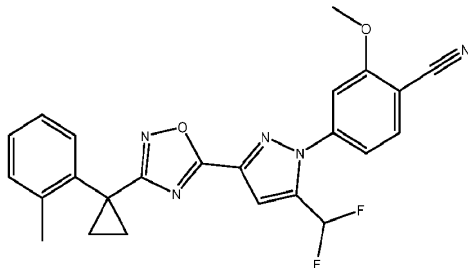
[0551] In one embodiment, the compound is **Compound 219**, or a pharmaceutically acceptable salt thereof:



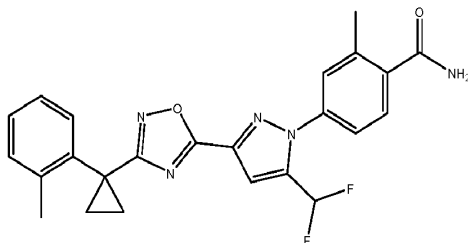
[0552] In one embodiment, the compound is **Compound 220**, or a pharmaceutically acceptable salt thereof:



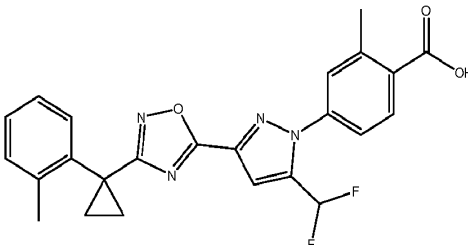
[0553] In one embodiment, the compound is **Compound 221**, or a pharmaceutically acceptable salt thereof:



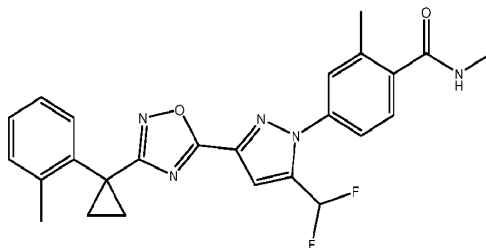
[0554] In one embodiment, the compound is **Compound 222**, or a pharmaceutically acceptable salt thereof:



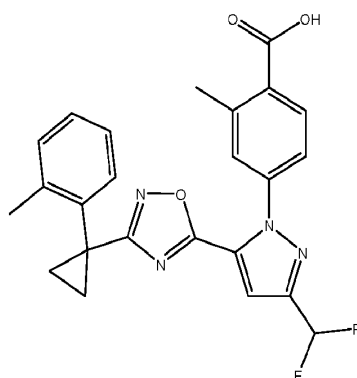
[0555] In one embodiment, the compound is **Compound 223**, or a pharmaceutically acceptable salt thereof:



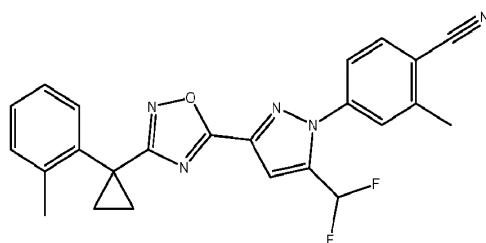
[0556] In one embodiment, the compound is **Compound 224**, or a pharmaceutically acceptable salt thereof:



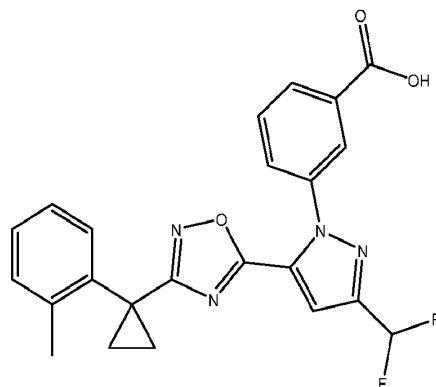
[0557] In one embodiment, the compound is **Compound 225**, or a pharmaceutically acceptable salt thereof:



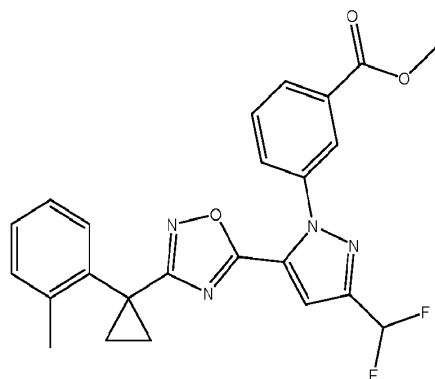
[0558] In one embodiment, the compound is **Compound 226**, or a pharmaceutically acceptable salt thereof:



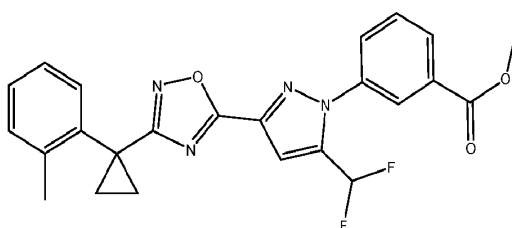
[0559] In one embodiment, the compound is **Compound 227**, or a pharmaceutically acceptable salt thereof:



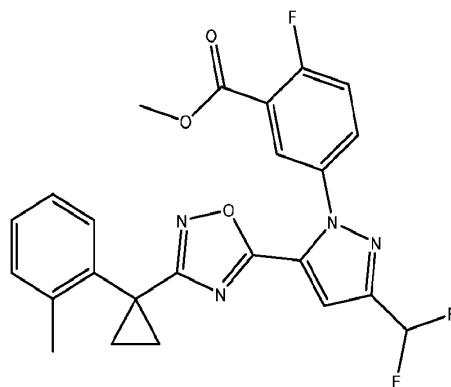
[0560] In one embodiment, the compound is **Compound 228**, or a pharmaceutically acceptable salt thereof:



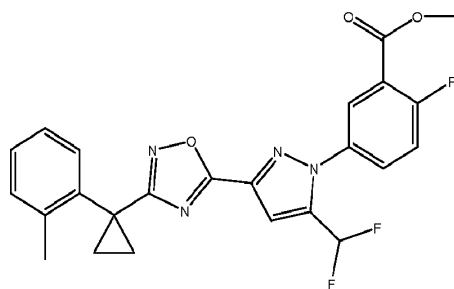
[0561] In one embodiment, the compound is **Compound 229**, or a pharmaceutically acceptable salt thereof:



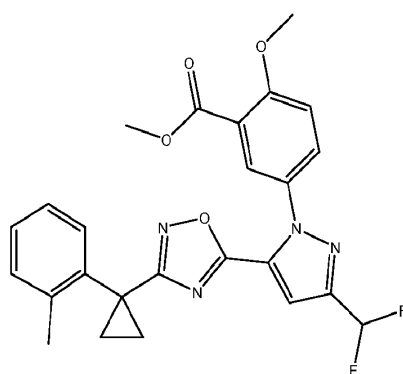
[0562] In one embodiment, the compound is **Compound 230**, or a pharmaceutically acceptable salt thereof:



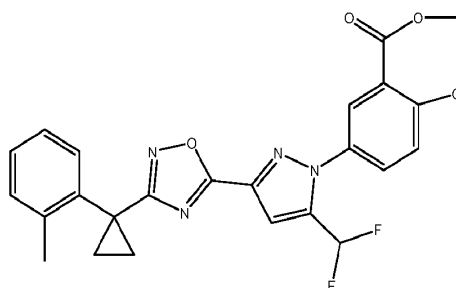
[0563] In one embodiment, the compound is **Compound 231**, or a pharmaceutically acceptable salt thereof:



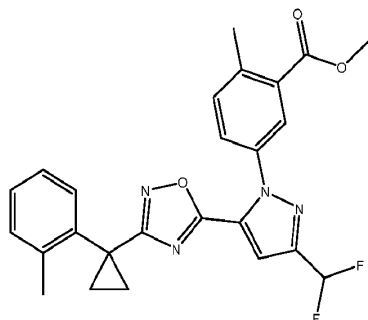
[0564] In one embodiment, the compound is **Compound 232**, or a pharmaceutically acceptable salt thereof:



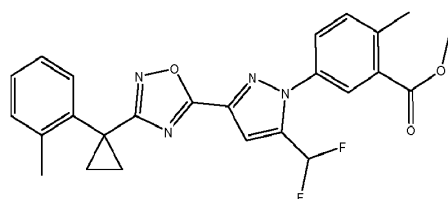
[0565] In one embodiment, the compound is **Compound 233**, or a pharmaceutically acceptable salt thereof:



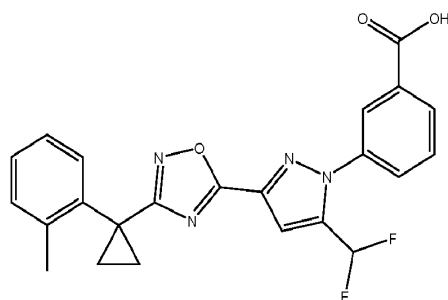
[0566] In one embodiment, the compound is **Compound 234**, or a pharmaceutically acceptable salt thereof:



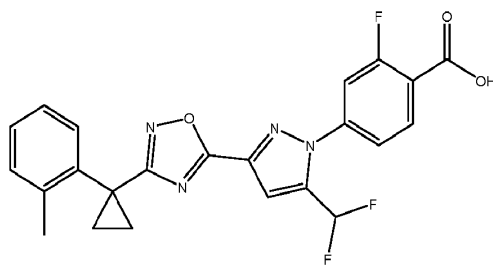
[0567] In one embodiment, the compound is **Compound 235**, or a pharmaceutically acceptable salt thereof:



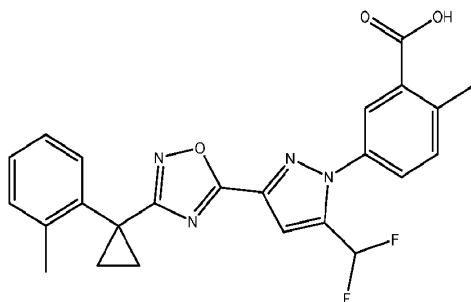
[0568] In one embodiment, the compound is **Compound 236**, or a pharmaceutically acceptable salt thereof:



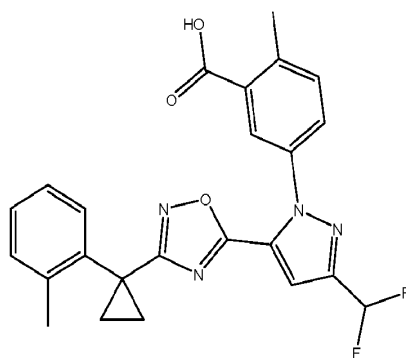
[0569] In one embodiment, the compound is **Compound 237**, or a pharmaceutically acceptable salt thereof:



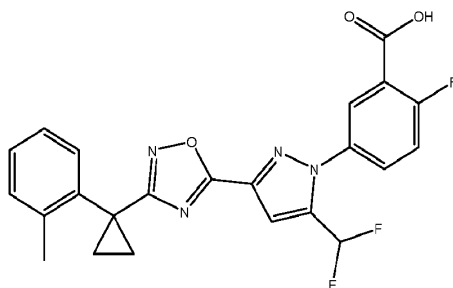
[0570] In one embodiment, the compound is **Compound 238**, or a pharmaceutically acceptable salt thereof:



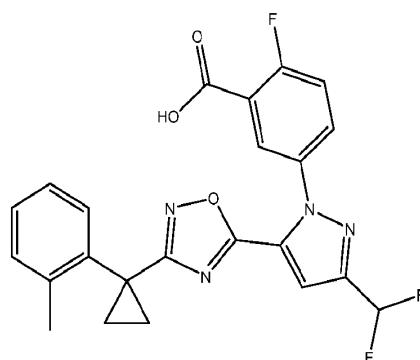
[0571] In one embodiment, the compound is **Compound 239**, or a pharmaceutically acceptable salt thereof:



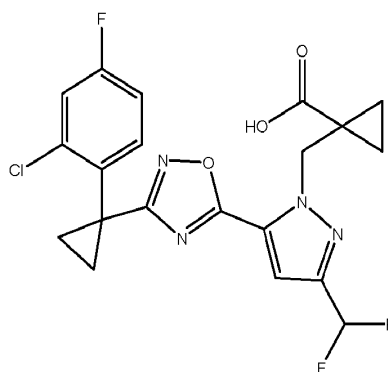
[0572] In one embodiment, the compound is **Compound 240**, or a pharmaceutically acceptable salt thereof:



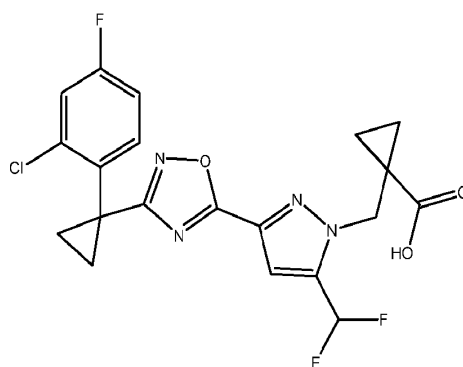
[0573] In one embodiment, the compound is **Compound 241**, or a pharmaceutically acceptable salt thereof:



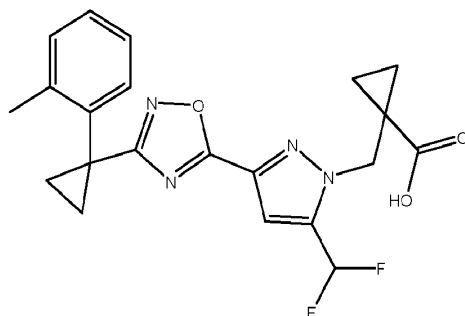
[0574] In one embodiment, the compound is **Compound 242**, or a pharmaceutically acceptable salt thereof:



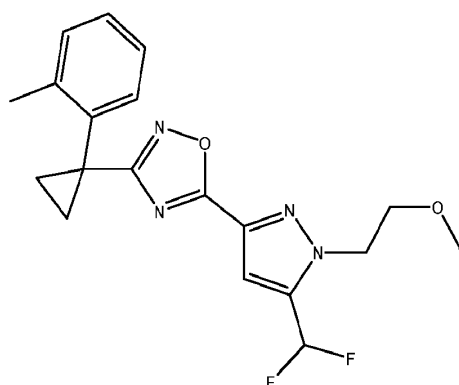
[0575] In one embodiment, the compound is **Compound 243**, or a pharmaceutically acceptable salt thereof:



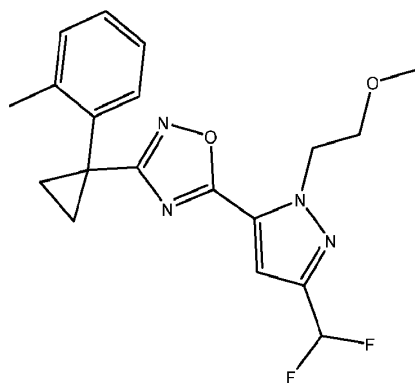
[0576] In one embodiment, the compound is **Compound 244**, or a pharmaceutically acceptable salt thereof:



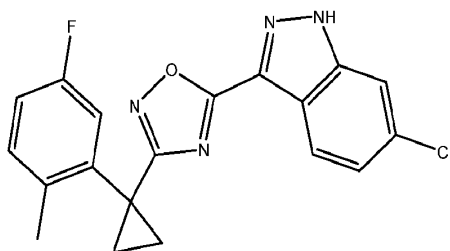
[0577] In one embodiment, the compound is **Compound 245**, or a pharmaceutically acceptable salt thereof:



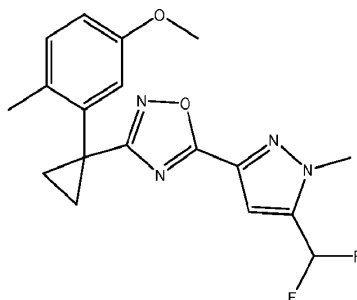
[0578] In one embodiment, the compound is **Compound 246**, or a pharmaceutically acceptable salt thereof:



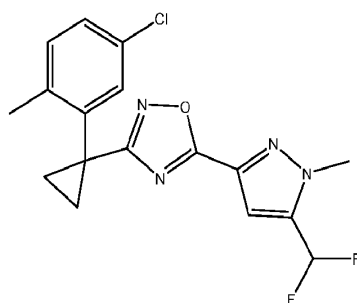
[0579] In one embodiment, the compound is **Compound 247**, or a pharmaceutically acceptable salt thereof:



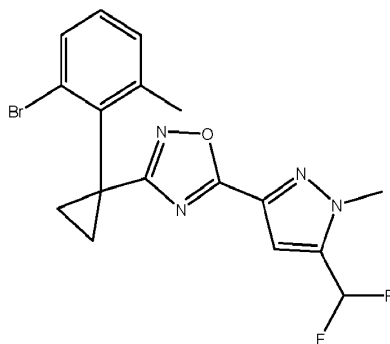
[0580] In one embodiment, the compound is **Compound 248**, or a pharmaceutically acceptable salt thereof:



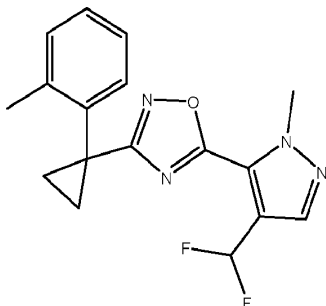
[0581] In one embodiment, the compound is **Compound 249**, or a pharmaceutically acceptable salt thereof:



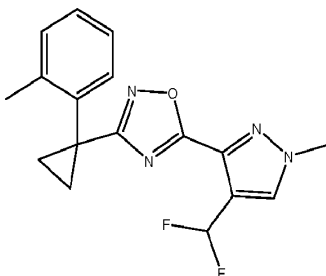
[0582] In one embodiment, the compound is **Compound 250**, or a pharmaceutically acceptable salt thereof:



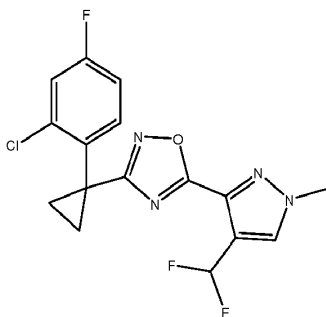
[0583] In one embodiment, the compound is **Compound 251**, or a pharmaceutically acceptable salt thereof:



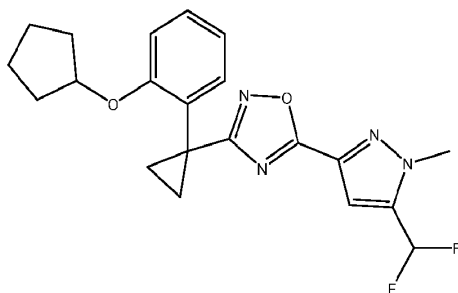
[0584] In one embodiment, the compound is **Compound 252**, or a pharmaceutically acceptable salt thereof:



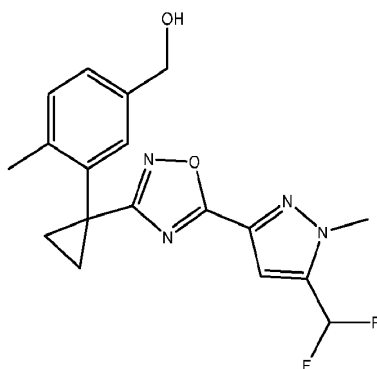
[0585] In one embodiment, the compound is **Compound 253**, or a pharmaceutically acceptable salt thereof:



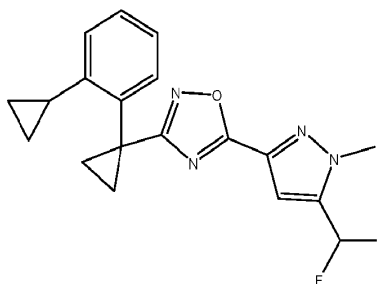
[0586] In one embodiment, the compound is **Compound 254**, or a pharmaceutically acceptable salt thereof:



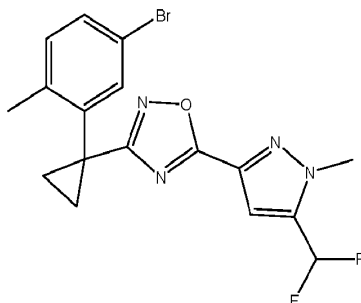
[0587] In one embodiment, the compound is **Compound 255**, or a pharmaceutically acceptable salt thereof:



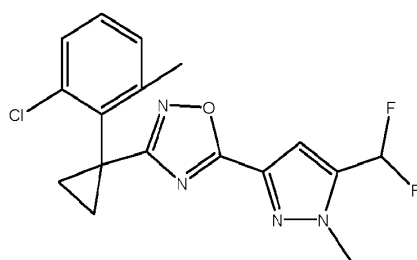
[0588] In one embodiment, the compound is **Compound 256**, or a pharmaceutically acceptable salt thereof:



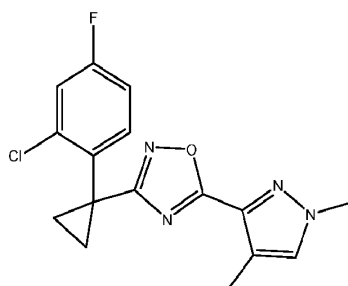
[0589] In one embodiment, the compound is **Compound 257**, or a pharmaceutically acceptable salt thereof:



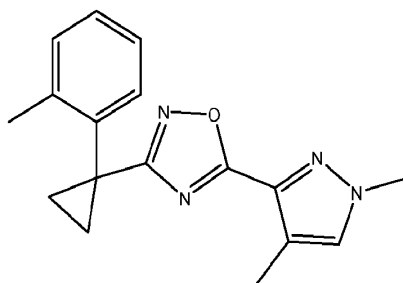
[0590] In one embodiment, the compound is **Compound 258**, or a pharmaceutically acceptable salt thereof:



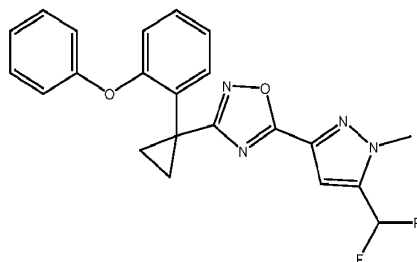
[0591] In one embodiment, the compound is **Compound 259**, or a pharmaceutically acceptable salt thereof:



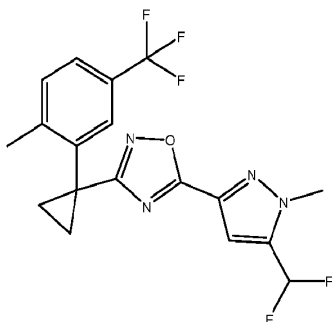
[0592] In one embodiment, the compound is **Compound 260**, or a pharmaceutically acceptable salt thereof:



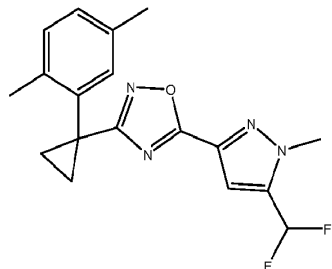
[0593] In one embodiment, the compound is **Compound 261**, or a pharmaceutically acceptable salt thereof:



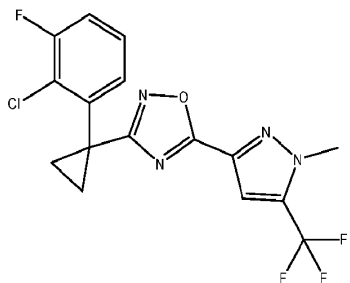
[0594] In one embodiment, the compound is **Compound 262**, or a pharmaceutically acceptable salt thereof:



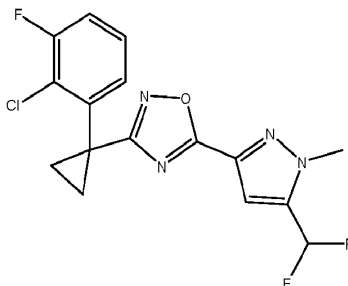
[0595] In one embodiment, the compound is **Compound 263**, or a pharmaceutically acceptable salt thereof:



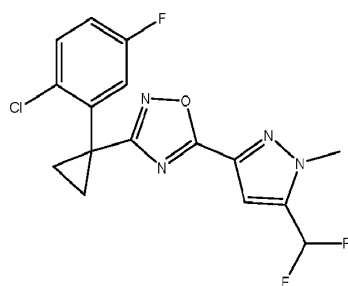
[0596] In one embodiment, the compound is **Compound 264**, or a pharmaceutically acceptable salt thereof:



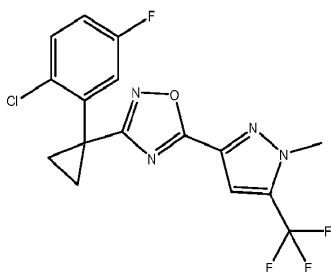
[0597] In one embodiment, the compound is **Compound 265**, or a pharmaceutically acceptable salt thereof:



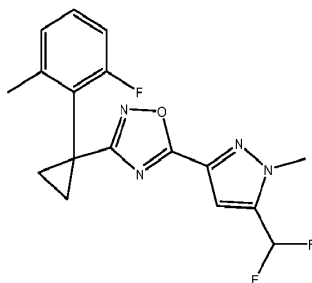
[0598] In one embodiment, the compound is **Compound 266**, or a pharmaceutically acceptable salt thereof:



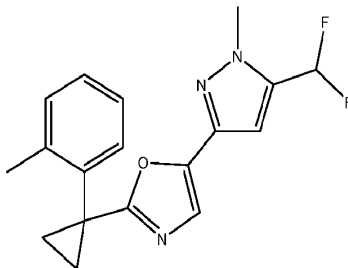
[0599] In one embodiment, the compound is **Compound 267**, or a pharmaceutically acceptable salt thereof:



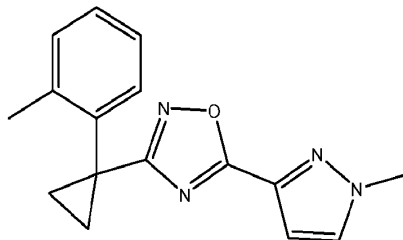
[0600] In one embodiment, the compound is **Compound 268**, or a pharmaceutically acceptable salt thereof:



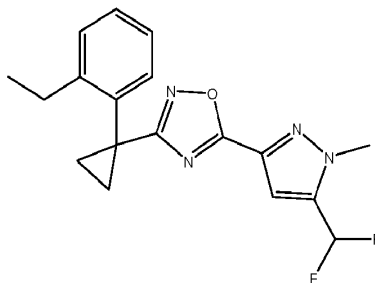
[0601] In one embodiment, the compound is **Compound 269**, or a pharmaceutically acceptable salt thereof:



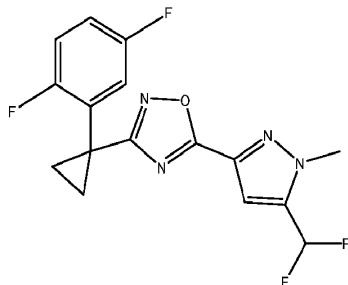
[0602] In one embodiment, the compound is **Compound 270**, or a pharmaceutically acceptable salt thereof:



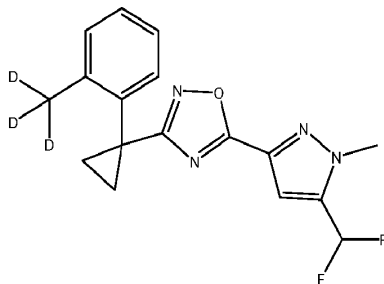
[0603] In one embodiment, the compound is **Compound 271**, or a pharmaceutically acceptable salt thereof:



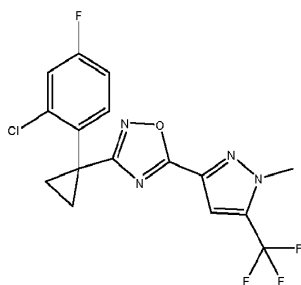
[0604] In one embodiment, the compound is **Compound 272**, or a pharmaceutically acceptable salt thereof:



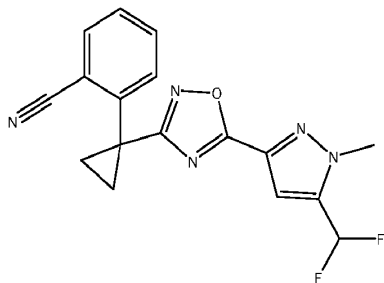
[0605] In one embodiment, the compound is **Compound 273**, or a pharmaceutically acceptable salt thereof:



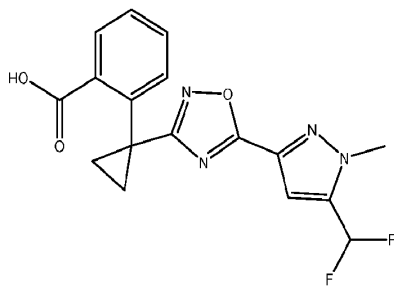
[0606] In one embodiment, the compound is **Compound 274**, or a pharmaceutically acceptable salt thereof:



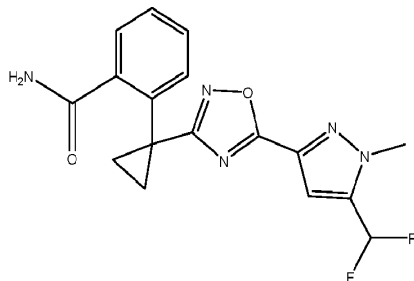
[0607] In one embodiment, the compound is **Compound 275**, or a pharmaceutically acceptable salt thereof:



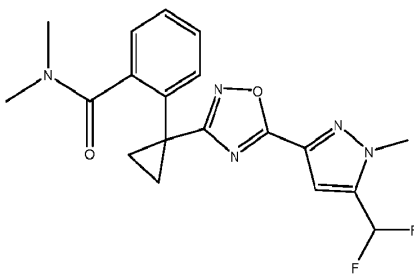
[0608] In one embodiment, the compound is **Compound 276**, or a pharmaceutically acceptable salt thereof:



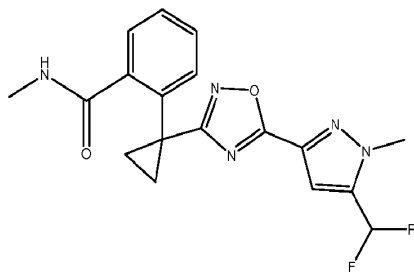
[0609] In one embodiment, the compound is **Compound 277**, or a pharmaceutically acceptable salt thereof:



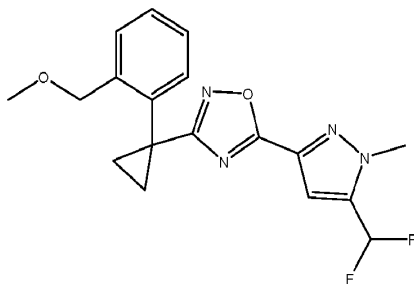
[0610] In one embodiment, the compound is **Compound 278**, or a pharmaceutically acceptable salt thereof:



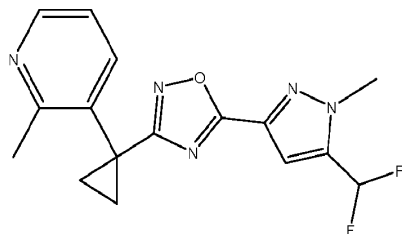
[0611] In one embodiment, the compound is **Compound 279**, or a pharmaceutically acceptable salt thereof:



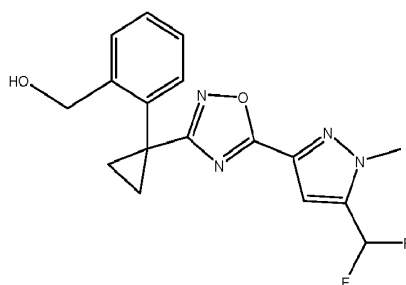
[0612] In one embodiment, the compound is **Compound 280**, or a pharmaceutically acceptable salt thereof:



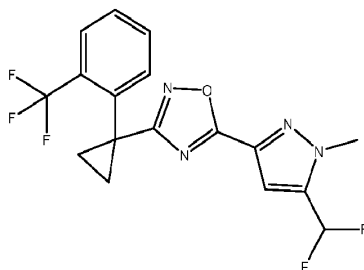
[0613] In one embodiment, the compound is **Compound 281**, or a pharmaceutically acceptable salt thereof:



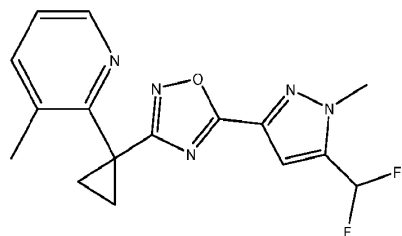
[0614] In one embodiment, the compound is **Compound 282**, or a pharmaceutically acceptable salt thereof:



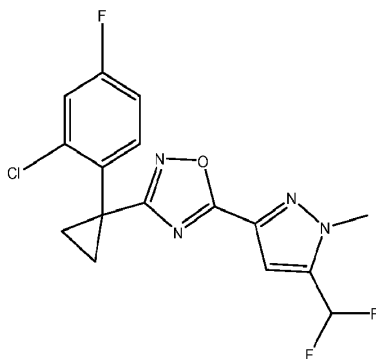
[0615] In one embodiment, the compound is **Compound 283**, or a pharmaceutically acceptable salt thereof:



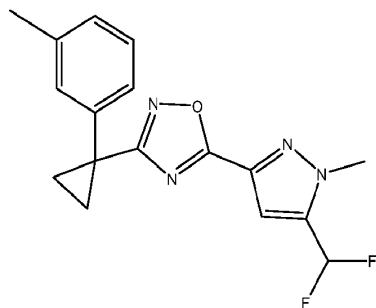
[0616] In one embodiment, the compound is **Compound 284**, or a pharmaceutically acceptable salt thereof:



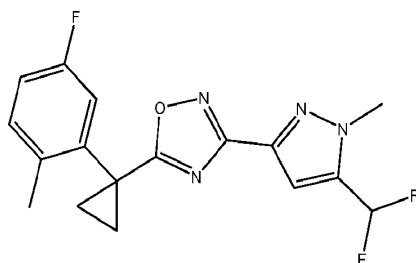
[0617] In one embodiment, the compound is **Compound 285**, or a pharmaceutically acceptable salt thereof:



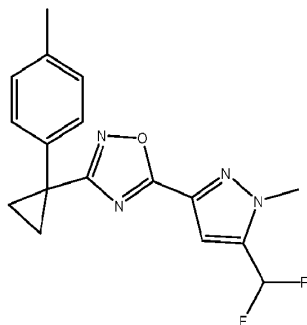
[0618] In one embodiment, the compound is **Compound 286**, or a pharmaceutically acceptable salt thereof:



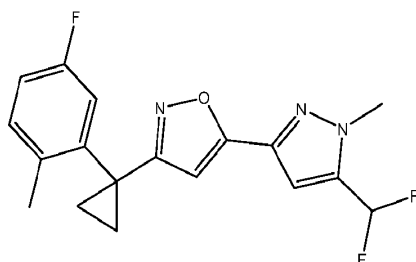
[0619] In one embodiment, the compound is **Compound 287**, or a pharmaceutically acceptable salt thereof:



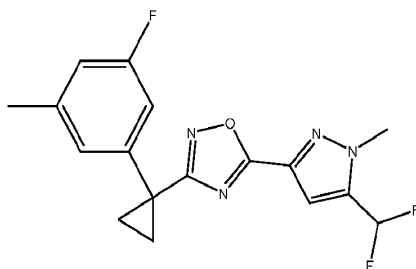
[0620] In one embodiment, the compound is **Compound 288**, or a pharmaceutically acceptable salt thereof:



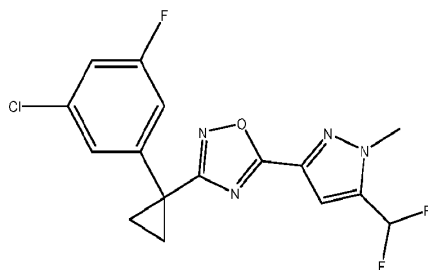
[0621] In one embodiment, the compound is **Compound 289**, or a pharmaceutically acceptable salt thereof:



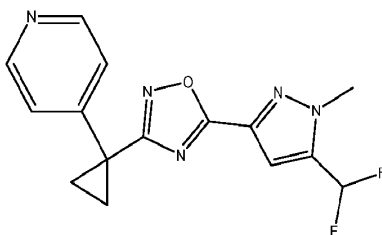
[0622] In one embodiment, the compound is **Compound 290**, or a pharmaceutically acceptable salt thereof:



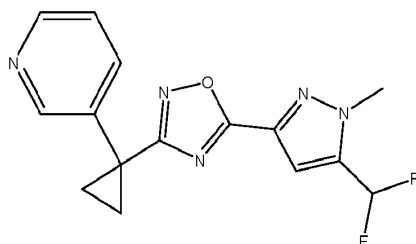
[0623] In one embodiment, the compound is **Compound 291**, or a pharmaceutically acceptable salt thereof:



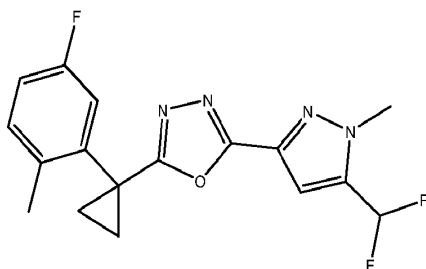
[0624] In one embodiment, the compound is **Compound 292**, or a pharmaceutically acceptable salt thereof:



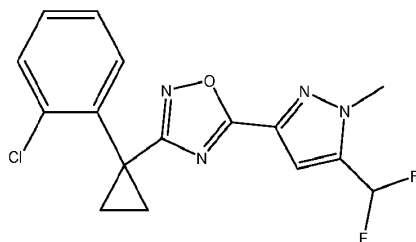
[0625] In one embodiment, the compound is **Compound 293**, or a pharmaceutically acceptable salt thereof:



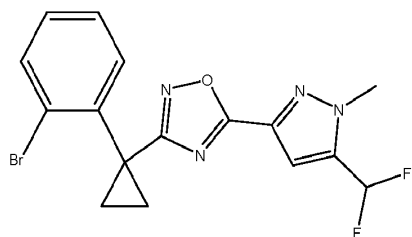
[0626] In one embodiment, the compound is **Compound 294**, or a pharmaceutically acceptable salt thereof:



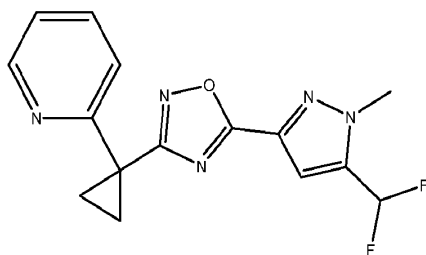
[0627] In one embodiment, the compound is **Compound 295**, or a pharmaceutically acceptable salt thereof:



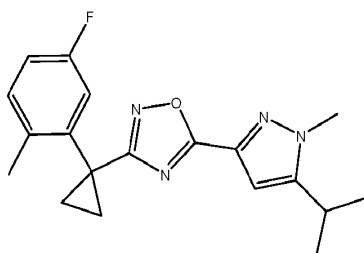
[0628] In one embodiment, the compound is **Compound 296**, or a pharmaceutically acceptable salt thereof:



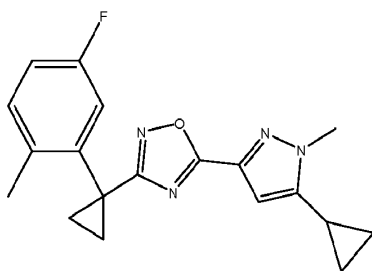
[0629] In one embodiment, the compound is **Compound 297**, or a pharmaceutically acceptable salt thereof:



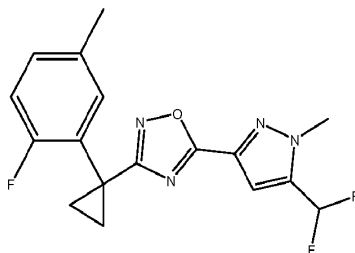
[0630] In one embodiment, the compound is **Compound 298**, or a pharmaceutically acceptable salt thereof:



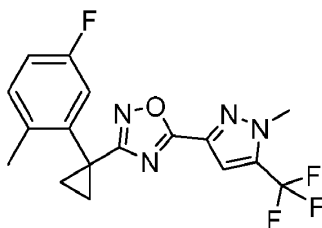
[0631] In one embodiment, the compound is **Compound 299**, or a pharmaceutically acceptable salt thereof:



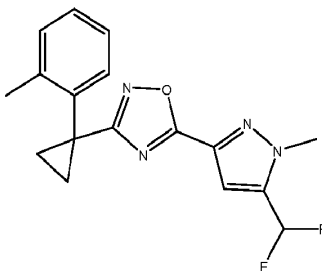
[0632] In one embodiment, the compound is **Compound 300**, or a pharmaceutically acceptable salt thereof:



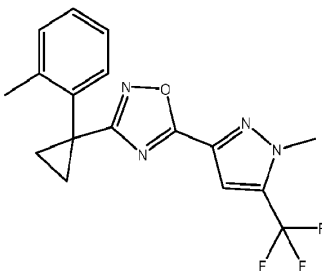
[0633] In one embodiment, the compound is **Compound 301**, or a pharmaceutically acceptable salt thereof:



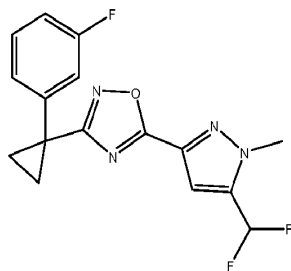
[0634] In one embodiment, the compound is **Compound 302**, or a pharmaceutically acceptable salt thereof:



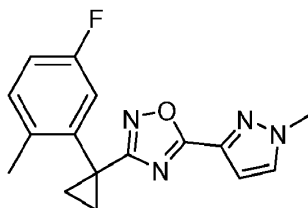
[0635] In one embodiment, the compound is **Compound 303**, or a pharmaceutically acceptable salt thereof:



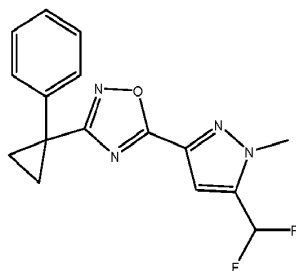
[0636] In one embodiment, the compound is **Compound 304**, or a pharmaceutically acceptable salt thereof:



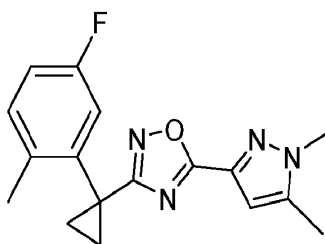
[0637] In one embodiment, the compound is **Compound 305**, or a pharmaceutically acceptable salt thereof:



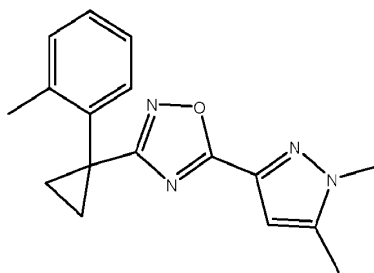
[0638] In one embodiment, the compound is **Compound 306**, or a pharmaceutically acceptable salt thereof:



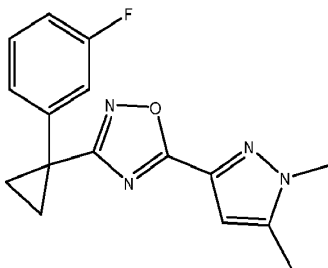
[0639] In one embodiment, the compound is **Compound 307**, or a pharmaceutically acceptable salt thereof:



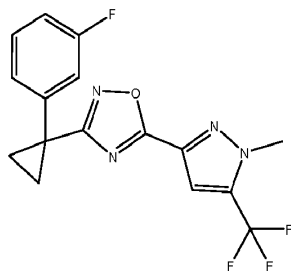
[0640] In one embodiment, the compound is **Compound 308**, or a pharmaceutically acceptable salt thereof:



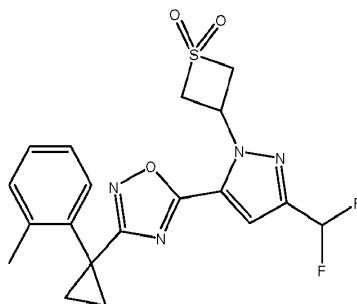
[0641] In one embodiment, the compound is **Compound 309**, or a pharmaceutically acceptable salt thereof:



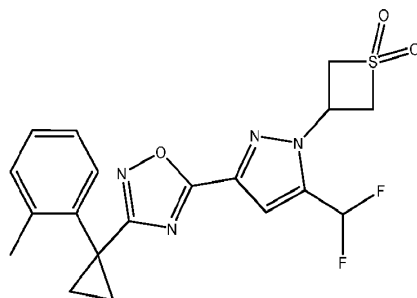
[0642] In one embodiment, the compound is **Compound 310**, or a pharmaceutically acceptable salt thereof:



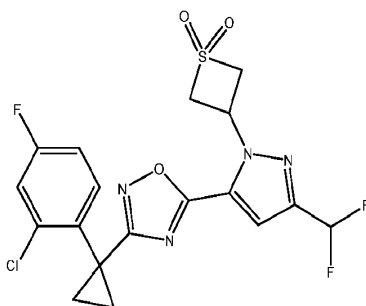
[0643] In one embodiment, the compound is **Compound 311**, or a pharmaceutically acceptable salt thereof:



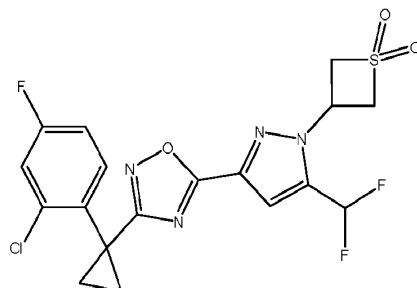
[0644] In one embodiment, the compound is **Compound 312**, or a pharmaceutically acceptable salt thereof:



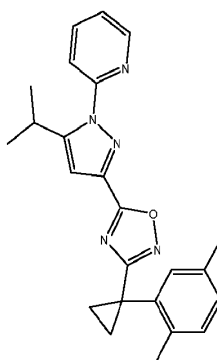
[0645] In one embodiment, the compound is **Compound 313**, or a pharmaceutically acceptable salt thereof:



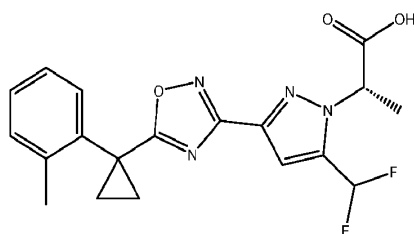
[0646] In one embodiment, the compound is **Compound 314**, or a pharmaceutically acceptable salt thereof:



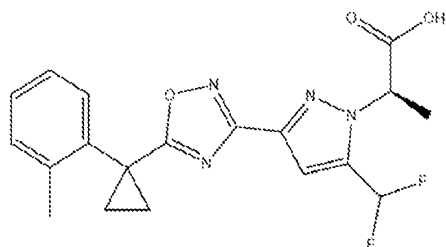
[0647] In one embodiment, the compound is **Compound 315**, or a pharmaceutically acceptable salt thereof:



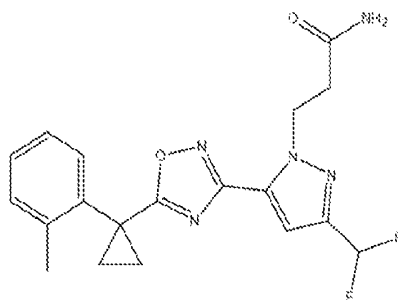
[0648] In one embodiment, the compound is **Compound 318**, or a pharmaceutically acceptable salt thereof:



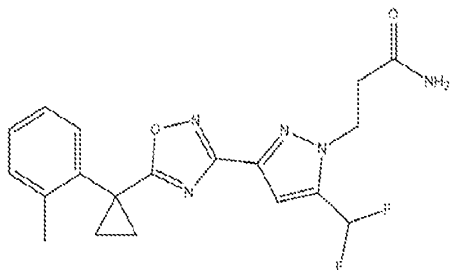
[0649] In one embodiment, the compound is **Compound 321**, or a pharmaceutically acceptable salt thereof:



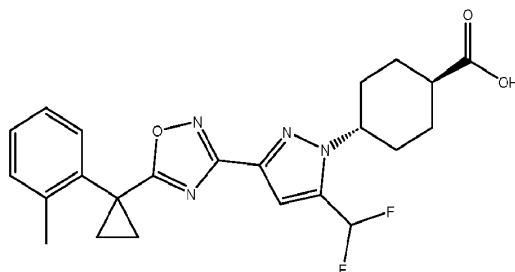
[0650] In one embodiment, the compound is **Compound 322**, or a pharmaceutically acceptable salt thereof:



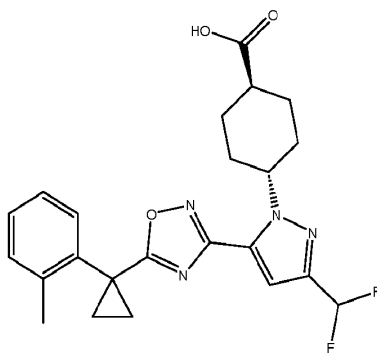
[0651] In one embodiment, the compound is **Compound 323**, or a pharmaceutically acceptable salt thereof:



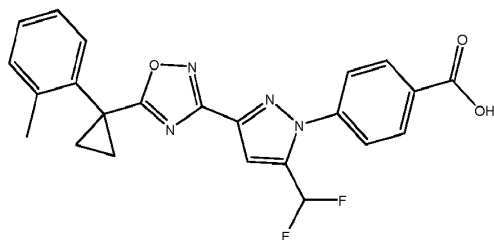
[0652] In one embodiment, the compound is **Compound 339**, or a pharmaceutically acceptable salt thereof:



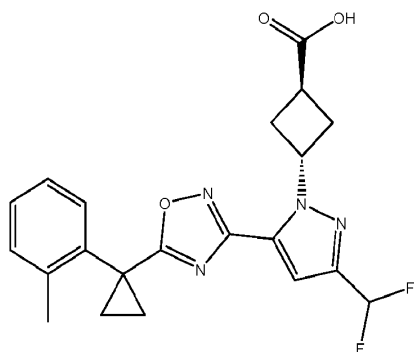
[0653] In one embodiment, the compound is **Compound 340**, or a pharmaceutically acceptable salt thereof:



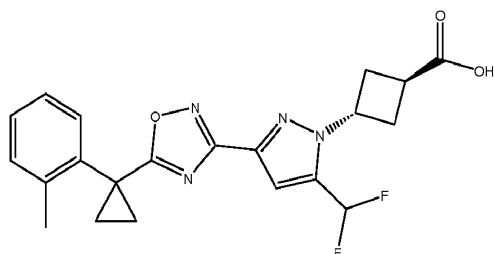
[0654] In one embodiment, the compound is **Compound 341**, or a pharmaceutically acceptable salt thereof:



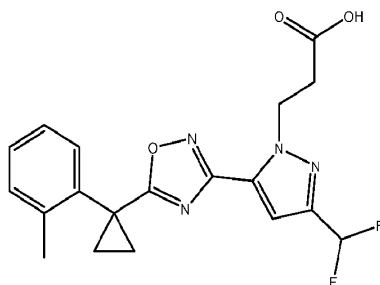
[0655] In one embodiment, the compound is **Compound 342**, or a pharmaceutically acceptable salt thereof:



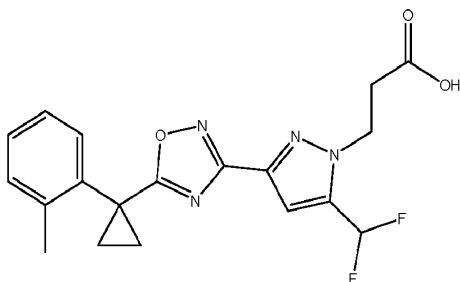
[0656] In one embodiment, the compound is **Compound 343**, or a pharmaceutically acceptable salt thereof:



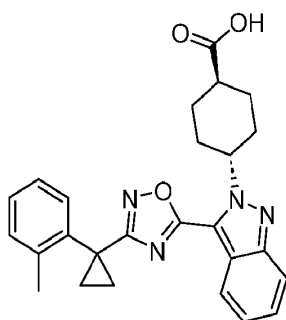
[0657] In one embodiment, the compound is **Compound 344**, or a pharmaceutically acceptable salt thereof:



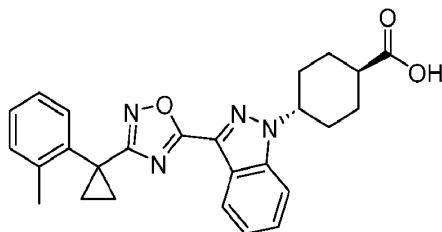
[0658] In one embodiment, the compound is **Compound 345**, or a pharmaceutically acceptable salt thereof:



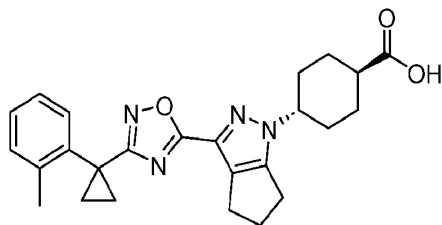
[0659] In one embodiment, the compound is **Compound 372**, or a pharmaceutically acceptable salt thereof:



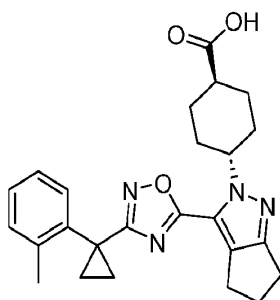
[0660] In one embodiment, the compound is **Compound 373**, or a pharmaceutically acceptable salt thereof:



[0661] In one embodiment, the compound is **Compound 374**, or a pharmaceutically acceptable salt thereof:



[0662] In one embodiment, the compound is **Compound 375**, or a pharmaceutically acceptable salt thereof:



[0663] In certain embodiments, the compound inhibits POLRMT.

[0664] In certain embodiments, the compound promotes POLRMT.

[0665] The compounds of the present invention may contain asymmetric carbon atoms (sometimes as the result of a deuterium atom) and thereby may exist as either individual stereoisomers or mixtures of the enantiomers or mixtures of diastereomers. Accordingly, a compound of the present invention may exist as either a racemic mixture, a mixture of diastereomers, or as individual stereoisomers that are substantially free of other stereoisomers. Synthetic, separation, or purification methods to be used to obtain an enantiomer of a given compound are known in the art and are applicable for obtaining the compounds identified herein.

[0666] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound. Carbon atoms labelled with * or ** refer to a compound that is chiral but the absolute stereochemistry has not been determined.

[0667] The compounds of the present invention may contain double bonds that may exist in more than one geometric isomer. Examples of such double bonds are carbon-carbon double bonds which form alkenes. In the case of carbon-carbon double bonds, the geometric isomers may be E or Z isomers.

[0668] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the geometric isomerism and has one or more possible geometric isomers, it is understood to represent all possible geometric isomers of the compound.

[0669] Certain compounds of the present invention may be able to exist as tautomers. All tautomeric forms of these compounds, whether isolated individually or in mixtures, are within the scope of the present invention. For example, in instances where an —OH substituent is

permitted on a heteroaromatic ring and ketoenol tautomerism is possible, it is understood that the substituent might in fact be present, in whole or in part, in the oxo (=O) form.

[0670] Compounds of the present invention may exist in amorphous form and/or one or more crystalline forms. As such all amorphous and crystalline forms and mixtures thereof of the compounds of the invention are intended to be included within the scope of the present invention. In addition, some of the compounds of the present invention may form solvates with water (i.e., a hydrate) or common organic solvents. Such solvates and hydrates, particularly the pharmaceutically acceptable solvates and hydrates, of the compounds of this invention are likewise encompassed within the scope of the compounds of the invention and the pharmaceutically acceptable salts thereof, along with un-solvated and anhydrous forms of such compounds.

[0671] In one embodiment, deuterium isotope content at the deuterium substituted position is greater than the natural isotopic deuterium content (0.015%), more preferably greater than 50%, more preferably greater than 60%, more preferably greater than 75%, more preferably greater than 90%, more preferably greater than 95%, more preferably greater than 97%, more preferably greater than 99%. It will be understood that some variation of natural isotopic abundance may occur in any compound depending upon the source of the reagents used in the synthesis. Thus, a preparation of undeuterated compounds may inherently contain small amounts of deuterated isotopologues, such amounts being insignificant as compared to the degree of stable isotopic substitution of the deuterated compounds of the invention. See, e.g., Gannes, L Z et al., *Comp Biochem Physiol Mol Integr Physiol*, 119, 725 (1998). Replacement of hydrogen with deuterium may affect the activity, toxicity, and pharmacokinetics (e.g., absorption, distribution, metabolism, and excretion ("ADME")) of some drugs. For instance, such replacement may alter the chemical stability and biochemical reactivity of a compound through kinetic isotope effects. Because of the increased mass of deuterium relative to hydrogen, epimerization at stereogenic carbons may be slowed down when hydrogen is replaced with deuterium. See Pirali et al, *J. Med. Chem.* 62, 5276-97 (2019). Additionally, the presence of deuterium may affect how a molecule interacts with enzymes, thereby impacting enzyme kinetics. While in certain cases the increased mass of deuterium as compared to hydrogen may stabilize a compound and thereby improve activity, toxicity, or half-life, such impact is not predictable. In other instances deuteration may have little to no impact on these properties, or may affect them in an undesirable manner. Whether and/or how such replacement will impact drug properties may only be determined if the drug is synthesized, evaluated, and compared to

its non-deuterated counterpart. Because some drugs have multiple sites of metabolism or more than one active sites for binding to a target, it is unpredictable as to which sites may benefit by deuterium replacement or to what extent isotope enrichment is necessary to produce a beneficial effect.

(III) Methods of making of compounds

[0672] The starting materials and reagents used in each step in the preparation are known and may be readily prepared or purchased from commercial sources.

[0673] The compound obtained in each step may also be used for the next reaction as a reaction mixture thereof or after obtaining a crude product thereof. Alternatively, the compound obtained in each step may be isolated and/or purified from the reaction mixture by a separation means such as concentration, crystallization, recrystallization, distillation, solvent extraction, fractionation, chromatography and the like according to a conventional method.

[0674] In each reaction step, while the reaction time varies depending on the reagents and solvents to be used, unless otherwise specified, it is generally 1 min. to 48 h., preferably 10 min. to 8 h. In the reaction of each step, while the reaction temperature varies depending on the reagents and solvents to be used, unless otherwise specified, it is generally -78 °C to 300 °C, preferably -78 °C to 150 °C. In the reaction of each step, unless otherwise specified, a reagent is used in 0.5 equivalent to 20 equivalents, preferably 0.8 equivalent to 5 equivalents, relative to the substrate. When a reagent is used as a catalyst, the reagent is used in 0.001 equivalent to 1 equivalent, preferably 0.01 equivalent to 0.2 equivalent, relative to the substrate. When the reagent is also a reaction solvent, the reagent is used in a solvent amount.

[0675] In the reaction of each step, unless otherwise specified, it is performed without solvent or by dissolving or suspending in a suitable solvent. Specific examples of the solvent include the following. Alcohols: methanol, ethanol, tert-butyl alcohol, 2- methoxyethanol and the like; ethers: diethyl ether, diphenyl ether, tetrahydrofuran, 1,2- dimethoxyethane and the like; aromatic hydrocarbons: chlorobenzene, toluene, xylene and the like; saturated hydrocarbons: cyclohexane, hexane and the like; amides: N,N- dimethylformamide, N-methylpyrrolidone and the like; halogenated hydrocarbons: dichloromethane, carbon tetrachloride and the like; nitriles: acetonitrile and the like; sulfoxides: dimethyl sulfoxide and the like; aromatic organic bases: pyridine and the like; acid anhydrides: acetic anhydride and the like; organic acids: formic acid, acetic acid, trifluoroacetic acid and the like; inorganic acids: hydrochloric acid, sulfuric acid and the like; esters: ethyl acetate and the like; ketones: acetone, methyl ethyl ketone and the like; and water.

[0676] Two or more kinds of the above-mentioned solvents may be used by mixing at an appropriate ratio.

[0677] Unless otherwise specified, the reaction of each step is performed according to a known method, for example, the methods described in "Reactions and Syntheses: In the Organic Chemistry Laboratory 2nd Edition" (Lutz F. Tietze, Theophil Eicher, Ulf Diederichsen, Andreas Speicher, Nina Schützenmeister) Wiley, 2015; "Organic Syntheses Collective Volumes 1 – 12" (John Wiley & Sons Inc); "Comprehensive Organic Transformations, Third Edition" (Richard C. Larock) Wiley, 2018 and the like.

[0678] In each step, protection or deprotection of a functional group is performed by a known method, for example, the methods described in "Protective Groups in Organic Synthesis, 4th Ed." (Theodora W. Greene, Peter G. M. Wuts) Wiley-Interscience, 2007; "Protecting Groups 3rd Ed." (P. J. Kocienski) Thieme, 2004 and the like.

[0679] Deuterated POLRMT modulators of the present invention may be prepared using chemical reactions known to a person of ordinary skill in the art using deuterated starting materials or reagents. Deuterium-containing reagents are well known in the art and may be prepared using known procedures or purchased from commercial sources. The deuterated compounds obtained may be characterized by analytical techniques known to persons of ordinary skill in the art. For example, nuclear magnetic resonance ("NMR") may be used to determine a compound's structure while mass spectroscopy ("MS") may be used to determine the amount of deuterium atom in the compound by comparison to its non-deuterated form.

(IV) Compositions

[0680] The present invention further includes pharmaceutical compositions of the compounds or a pharmaceutically acceptable salt of said compounds. In addition to the compound of the invention or a salt thereof, the pharmaceutical compositions comprise one or more pharmaceutically acceptable excipients, such excipients being compatible with other ingredients in the composition and also being not toxic or otherwise harmful. Examples of excipients include carriers, lubricants, binders, disintegrants, solvents, solubilizing agents, suspending agents, isotonic agents, buffers, soothing agents, preservatives, antioxidants, colorants, taste-modifying agents, absorbents, and/or wetting agents.

[0681] The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical, buccal, sublingual, vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. Such compositions may be prepared by any

methods well known in the art of pharmaceutical formulations and pharmacy. See, e.g., Remington: The Science and Practice of Pharmacy, Elsevier Science, 23rd ed. (2020).

[0682] Formulations for parenteral administration include sterile aqueous or non- aqueous solutions, suspensions, or emulsions. A variety of aqueous carriers may be used, e.g., water, buffered water, saline, and the like. Examples of other suitable vehicles include polypropylene glycol, polyethylene glycol, vegetable oils, hydrogels, gelatin, hydrogenated naphthalenes, and injectable organic esters, such as ethyl oleate. Such formulations may also contain auxiliary substances, such as preserving, wetting, buffering, emulsifying, and/or dispersing agents. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the active ingredients. Alternatively, the compositions may be administered by oral ingestion. Compositions intended for oral use may be prepared in solid or liquid forms, according to any method known to a person of ordinary skill in the art for the manufacture of pharmaceutical compositions. Solid dosage forms for oral administration include capsules (both soft and hard gelatin capsules), tablets, powders, and granules. Generally, these pharmaceutical preparations contain active ingredients admixed with pharmaceutically acceptable excipients. These excipients include, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, sucrose, glucose, mannitol, cellulose, starch, calcium phosphate, sodium phosphate, kaolin and the like; binding agents, buffering agents, and/or lubricating agents (e.g., magnesium stearate) may also be used. Tablets and capsules may additionally be prepared with release-controlling coatings such as enteric coatings. The compositions may optionally contain sweetening, flavoring, coloring, perfuming, and preserving agents in order to provide a more palatable preparation.

[0683] In another embodiment, a pharmaceutical composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any pharmaceutically active compound; preferably the second therapeutic agent is known to correct mitochondrial dysfunction. Alternatively, the compounds of the invention and second therapeutic agent may be administered together (within less than 24 hours of one another, consecutively or simultaneously) but in separate pharmaceutical compositions. In certain embodiments, the compounds of the invention and second therapeutic agent may be administered separately (e.g., more than 24 hours of one another.) If the second therapeutic agent acts synergistically with the compounds of this invention, the therapeutically effective amount of such compounds and/or the second therapeutic agent may be less than such amount required when either is administered alone.

[0684] For the treatment of cancer, the compounds described herein may be administered in combination with a chemotherapeutic agent. Therapeutically effective amounts of the additional chemotherapeutic agent(s) are well known to those skilled in the art. However, it is well within the attending physician to determine the amount of other chemotherapeutic agent(s) to be delivered. Examples of these chemotherapeutic agents include, but are not limited to, Abitrexate (Methotrexate Injection), Abraxane (Paclitaxel Injection), Actemra (Tocilizumab), Adcetris (Brentuximab Vedotin Injection), Adriamycin (Doxorubicin), Aducril Injection (5-FU (fluorouracil)), Afinitor (Everolimus), Afinitor Disperz (Everolimus), Aldara (Imiquimod), Alimta (PEMET EXED), Alkeran Injection (Melphalan Injection), Alkeran Tablets (Melphalan), Aredia (Pamidronate), Arimidex (Anastrozole), Aromasin (Exemestane), Arranon (Nelarabine), Arzerra (Ofatumumab Injection), Avastin (Bevacizumab), Avelumab, Bexxar (Tositumomab), BiCNU (Carmustine), Blenoxane (Bleomycin), Blincyto (Blinatumomab), Bosulif (Bosutinib), Busulfex Injection (Busulfan Injection), Campath (Alemtuzumab), Camptosar (Irinotecan), Caprelsa (Vandetanib), Casodex (Bicalutamide), CeeNU (Lomustine), CeeNU Dose Pack (Lomustine), Cerubidine (Daunorubicin), Clolar (Clofarabine Injection), Cometriq (Cabozantinib), Cosmegen (Dactinomycin), CytosarU (Cytarabine), Cytoxan (Cytoxan), Cytoxan Injection (Cyclophosphamide Injection), Cyramza (Ramucirumab), Dacogen (Decitabine), Darzalex (Daratumumab), DaunoXome (Daunorubicin Lipid Complex Injection), Decadron (Dexamethasone), DepoCyt (Cytarabine Lipid Complex Injection), Dexamethasone Intensol (Dexamethasone), Dexpak Taperpak (Dexamethasone), Docefrez (Docetaxel), Doxil (Doxorubicin Lipid Complex Injection), Droxia (Hydroxyurea), DTIC (Decarbazine), Durvalumab, Eligard (Leuprolide), Ellence (Ellence (epirubicin)), Eloxatin (Eloxatin (oxaliplatin)), Elspar (Asparaginase), Emcynt (Estramustine), Empliciti (Elotuzumab), Enhertu (fam- trastuzumab deruxtecan-nxki), Erbitux (Cetuximab), Erivedge (Vismodegib), Erwinaze (Asparaginase Erwinia chrysanthemi), Ethyol (Amifostine), Etopophos (Etoposide Injection), Eulexin (Flutamide), Fareston (Toremifene), Faslodex (Fulvestrant), Femara (Letrozole), Firmagon (Degarelix Injection), Fludara (Fludarabine), Folex (Methotrexate Injection), Folutyn (Pralatrexate Injection), FUDR (FUDR (floxuridine)), Gazyva (Obinutuzumab), Gemzar (Gemcitabine), Gilotrif (Afatinib), Gleevec (Imatinib Mesylate), Gliadel Wafer (Carmustine wafer), Halaven (Eribulin Injection), Herceptin (Trastuzumab), Hexalen (Altretamine), Hycamtin (Topotecan), Hycamtin (Topotecan), Hydrea (Hydroxyurea), Iclusig (Ponatinib), Idamycin PFS (Idarubicin), Ifex (Ifosfamide), Inlyta (Axitinib), Intron A alfab (Interferon alfa-2a), Iressa (Gefitinib), Istodax (Romidepsin Injection), Ixempra (Ixabepilone Injection), Jakafi (Ruxolitinib), Jevtana (Cabazitaxel Injection), Kadcyla

(Ado-trastuzumab Emtansine), Kyprolis (Carfilzomib), Leflunomide (SU101), Lartruvo (Olaratumab), Leukeran (Chlorambucil), Leukine (Sargramostim), Leustatin (Cladribine), Libtayo (Cemiplimab), Lupron (Leuprolide), Lupron Depot (Leuprolide), Lupron DepotPED (Leuprolide), Lysodren (Mitotane), Marqibo Kit (Vincristine Lipid Complex Injection), Matulane (Procarbazine), Megace (Megestrol), Mekinist (Trametinib), Mesnex (Mesna), Mesnex (Mesna Injection), Metastron (Strontium-89 Chloride), Mexate (Methotrexate Injection), Mustargen (Methotrexate Injection), Mutamycin (Mitomycin), Myleran (Busulfan), Mylotarg (Gemtuzumab Ozogamicin), Navelbine (Vinorelbine), Neosar Injection (Cyclophosphamide Injection), Neulasta (filgrastim), Neulasta (pegfilgrastim), Neupogen (filgrastim), Nexavar (Sorafenib), Nilandron (Nilandron (nilutamide)), Nipent (Pentostatin), Nolvadex (Tamoxifen), Novantrone (Mitoxantrone), Oncaspar (Pegaspargase), Oncovin (Vincristine), Ontak (Denileukin Diffitox), Onxol (Paclitaxel Injection), Panretin (Alitretinoin), Paraplatin (Carboplatin), Perjeta (Pertuzumab Injection), Platinol (Cisplatin), Platinol (Cisplatin Injection), PlatinolAQ (Cisplatin), PlatinolAQ (Cisplatin Injection), Pomalyst (Pomalidomide), Portrazza (Necitumumab), Prednisone Intensol (Prednisone), Proleukin (Aldesleukin), Purinethol (Mercaptopurine), Reclast (Zoledronic acid), Revlimid (Lenalidomide), Removab (Catumaxomab), Rheumatrex (Methotrexate), Rituxan (Rituximab), RoferonA alfaa (Interferon alfa-2a), Rubex (Doxorubicin), Sandostatin (Octreotide), Sandostatin LAR Depot (Octreotide), Sarclisa (Isatuximab-irfc), Soltamox (Tamoxifen), Sprycel (Dasatinib), Sterapred (Prednisone), Sterapred DS (Prednisone), Stivarga (Regorafenib), Supprelin LA (Histrelin Implant), Sutent (Sunitinib), Sylatron (Peginterferon Alfa-2b Injection (Sylatron)), Synribo (Omacetaxine Injection), Tabloid (Thioguanine), Taflinar (Dabrafenib), Tarceva (Erlotinib), Targretin Capsules (Bexarotene), Tasigna (Decarbazine), Taxol (Paclitaxel Injection), Taxotere (Docetaxel), Tecentriq (Atezolizumab), Temodar (Temozolomide), Temodar (Temozolomide Injection), Tepadina (Thiotepa), Thalomid (Thalidomide), TheraCys BCG (BCG), Thioplex (Thiotepa), TICE BCG (BCG), Toposar (Etoposide Injection), Torisel (Temozolomide), Treanda (Bendamustine hydrochloride), Tremelimumab, Trelstar (Triptorelin Injection), Trexall (Methotrexate), Trisenox (Arsenic trioxide), Tykerb (lapatinib), Unituxin (Dinutuximab), Valstar (Valrubicin Intravesical), Vantas (Histrelin Implant), Vectibix (Panitumumab), Velban (Vinblastine), Velcade (Bortezomib), Vepesid (Etoposide), Vepesid (Etoposide Injection), Vesanoide (Tretinoin), Vidaza (Azacitidine), Vincasar PFS (Vincristine), Vincex (Vincristine), Votrient (Pazopanib), Vumon (Teniposide), Wellcovorin IV (Leucovorin Injection), Xalkori (Crizotinib), Xeloda (Capecitabine), Xtandi (Enzalutamide), Yervoy (Ipilimumab Injection), Zaltrap (Ziv-aflibercept Injection), Zanosar

(Streptozocin), Zelboraf (Vemurafenib), Zevalin (Ibritumomab Tiuxetan), Zoladex (Goserelin), Zolanza (Vorinostat), Zometa (Zoledronic acid), Zortress (Everolimus), Zytiga (Abiraterone), Nimotuzumab and immune checkpoint inhibitors such as nivolumab, pembrolizumab/MK-3475, pidilizumab and AMP-224 targeting PD-1; and BMS-935559, MEDI4736, MPDL3280A and MSB0010718C targeting.

EXAMPLES

[0685] The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

[0686] The structures of the compounds are confirmed by either mass spectrometry or nuclear magnetic resonance spectroscopy (NMR), where peaks assigned to the characteristic protons in the title compound are presented where appropriate. ¹H NMR shift (δ H) are given in parts per million (ppm) down field from an internal reference standard. Acceptable ¹H NMR shifts and masses are within 5% of the reported values (i.e., all reported measurement values herein also include $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$, and/or $\pm 1\%$). All reported LCMS values herein also include $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$, and/or $\pm 1\%$.

[0687] The abbreviations used herein are known to a person of ordinary skill in the art. A partial list of abbreviations that may be used herein include: acetonitrile (MeCN), ammonium carbonate (NH₄)₂CO₃, ammonium chloride (NH₄Cl), aqueous (aq.), 1,1'-bis(diphenylphosphino)ferrocene (dppf), 1,3-bis(diphenylphosphino)propane (dppp), bis(pinacolato)diboron (B₂pin₂), N-bromosuccinimide (NBS), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP), boron tribromide (BBr₃), butyl lithium (BuLi), calculated (Calcd.), cesium carbonate (Cs₂CO₃), dichloromethane (DCM, CH₂Cl₂), N,N-dicyclohexylcarbodiimide (DCC), dichloroethane (DCE), diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), N,N-diisopropylethylamine (DIPEA), 4-dimethylaminopyridine (DMAP), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), di-tert-butyl decarbonate (Boc₂O), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), electrospray ionization (ESI), enantiomeric excess (ee), ethyl acetate (EtOAc), hour (h.), N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU), high performance liquid chromatography (HPLC), hydroxybenzotriazole (HOBt), isopropyl alcohol (IPA), lithium hydroxide monohydrate (LiOH H₂O), methanol (MeOH), methyl iodide (MeI), minutes (min.), potassium carbonate (K₂CO₃), liquid chromatography-mass spectrometry (LCMS),

phenyliodide(III) diacetate (PIDA), propylphosphonic anhydride (T3P), reverse phase (RP), room/ambient temperature (rt, RT), silver oxide (Ag₂O), sodium hydride (NaH), sodium sulfate (Na₂SO₃), supercritical fluid chromatography (SFC), tetrahydrofuran (THF), triethylamine (Et₃N), thionyl chloride (SOCl₂), triphenylphosphine (PPh₃), dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane (XPhos). Table 1 provides a listing of example compounds of the present invention and IC₅₀ values for inhibition of POLRMT.

[0688] The following examples illustrate various non-limiting embodiments of the present disclosure.

[0689] Table 1 correlates Example number with Compound number.

Compound	Example
Compound 301	1
Compound 307	2
Compound 305	3
Compound 299	4
Compound 298	5
Compound 315	7
Compound 205	8
Compound 304	9
Compound 310	10
Compound 309	11
Compound 308	12
Compound 303	13
Compound 302	14
Compound 270	15
Compound 260	16
Compound 245	17
Compound 161	18
Compound 191	19
Compound 190	20
Compound 192	21
Compound 187	22
Compound 68	23
Compound 96	24
Compound 72	25
Compound 185	26
Compound 163	27
Compound 164	28

Compound 162	29
Compound 157	30
Compound 152	31
Compound 158	32
Compound 153	33
Compound 196	34
Compound 75	35
Compound 168	36a
Compound 167	36b
Compound 154	37
Compound 244	38
Compound 70	39
Compound 312	40a
Compound 311	40b
Compound 166	41
Compound 34	42
Compound 142	43
Compound 74	44
Compound 141	45
Compound 150	46
Compound 144	47
Compound 148	48
Compound 143	49
Compound 134	50
Compound 133	51
Compound 122	52
Compound 121	53
Compound 120	54
Compound 252	55a
Compound 251	55b
Compound 269	56
Compound 156	57a
Compound 155	57b
Compound 194	58
Compound 87	59
Compound 86	60
Compound 178	61
Compound 314	62
Compound 81	63

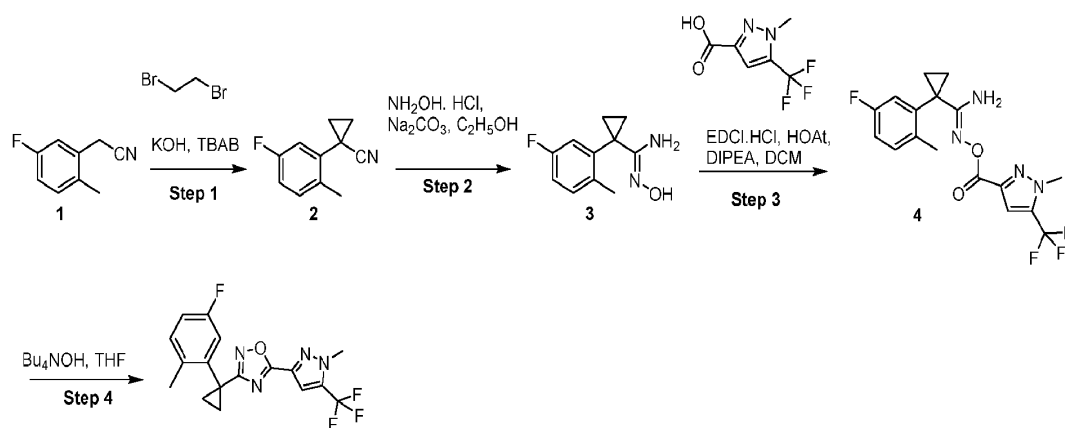
Compound 146	64
Compound 149	65
Compound 140	66
Compound 139	67
Compound 132	68
Compound 131	69
Compound 130	70
Compound 129	71
Compound 127	72
Compound 126	73
Compound 117	74
Compound 116	75
Compound 113	76
Compound 112	77
Compound 111	78
Compound 110	79
Compound 109	80
Compound 106	81
Compound 105	82
Compound 102	83
Compound 101	84
Compound 100	85
Compound 93	86
Compound 92	87
Compound 91	88
Compound 85	89
Compound 125	90
Compound 124	91
Compound 165	92
Compound 94	93
Compound 88	94
Compound 136	95
Compound 123	96
Compound 66	97
Compound 65	98
Compound 183	99
Compound 181	100
Compound 147	101
Compound 179	102

Compound 253	103
Compound 174	104
Compound 173	105
Compound 171	106a
Compound 170	106b
Compound 259	107
Compound 169	108
Compound 73	109
Compound 89	110
Compound 243	111a
Compound 242	111b
Compound 306	112
Compound 300	113
Compound 297	114
Compound 296	115
Compound 295	116
Compound 293	117
Compound 292	118
Compound 291	119
Compound 290	120
Compound 288	121
Compound 286	122
Compound 284	123
Compound 283	124
Compound 281	125
Compound 272	126
Compound 266	127
Compound 265	128
Compound 263	129
Compound 262	130
Compound 261	131
Compound 276	132
Compound 277	133
Compound 279	134
Compound 278	135
Compound 275	136
Compound 280	137
Compound 282	138
Compound 271	139

Compound 273	140
Compound 256	141
Compound 268	142
Compound 258	143
Compound 257	144
Compound 255	145
Compound 254	146
Compound 249	147
Compound 248	148
Compound 82	149
Compound 289	150
Compound 287	151
Compound 294	152
Compound 264	153
Compound 267	154
Compound 246	155
Compound 138	156
Compound 137	157
Compound 189	158a
Compound 189	158b
Compound 128	159
Compound 119	160
Compound 115	161a
Compound 114	161b
Compound 99	162
Compound 250	163
Compound 176	164a
Compound 175	164b
Compound 84	165a
Compound 83	165b
Compound 79	166
Compound 78	167a
Compound 77	167b
Compound 76	168
Compound 285	169
Compound 274	170
Compound 159	183
Compound 206	184
Compound 90	185a

Compound 202	200a
Compound 201	200b
Compound 198	201a
Compound 197	201b
Compound 54	202a
Compound 53	202b
Compound 2	203a
Compound 1	203b
Compound 372	204a
Compound 373	204b
Compound 375	205a
Compound 374	205b

Example 1: Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Compound 301)



Example 1

Scheme 1

[0690] Synthesis of 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonitrile, 2 [Step 1]: To a stirred solution of KOH (2.3 g, 40.2 mmol) in water (10 mL), 2-(5-fluoro-2-methylphenyl)acetonitrile (1, 500 mg, 3.4 mmol) and TBAB (216 mg, 0.67 mmol) were added at 0 °C. After 5 min, 1,2-dibromoethane (1.5 mL, 16.8 mmol) was added dropwise and the resulting reaction mixture was heated at 60 °C for 12 h. After completion, the reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonitrile (2, 450 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ

7.33-7.29 (m, 1H), 7.22-7.11 (m, 1H), 7.06-7.02(m, 1H), 2.44 (s, 3H), 2.29 (s, 3H), 1.69 (s, 2H), 1.41 (s, 2H) [Note: HNMR showed extra peaks.]

[0691] Synthesis of (Z)-1-(5-fluoro-2-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide, 3 [Step 2]: To a stirred solution of 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonitrile (2, 450 mg, 2.6 mmol) in ethanol (2 mL), Na₂CO₃ (545 mg, 5.1 mmol) was added followed by NH₂OH.HCl (355 g, 5.1 mmol) and the reaction mixture was heated to reflux at 70 °C for 12h. After completion, the volatiles were evaporated under reduced pressure. The reduced mass was diluted with water and extracted with ethyl acetate (thrice). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-1-(5-fluoro-2-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (3, 450 mg). LCMS (ESI) Calcd for C₁₁H₁₃FN₂O: 208.1, found [M+H]⁺ = 209.1.

[0692] Synthesis of (Z)-1-(5-fluoro-2-methylphenyl)-*N'*-((1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 4, [Step 3]: To a stirred solution of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid (100 mg, 0.5 mmol) and (Z)-1-(5-fluoro-2-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (3, 160 mg, 0.8 mmol) in dichloromethane (3 mL), *N,N*-Diisopropylethylamine (0.2 mL, 1.03 mmol), EDCI.HCl (128 mg, 0.7 mmol) and HOAt (15 mg, 0.1 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was concentrated under reduced pressure, dissolved with ethyl acetate, washed with water (twice) and brine. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-1-(5-fluoro-2-methylphenyl)-*N'*-((1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (4, 150 mg). LCMS (ESI) Calcd for C₁₇H₁₆F₄N₄O₂: 384.1, found [M+H]⁺ = 385.1.

[0693] Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 1 [Step 4]: To a stirred solution of (Z)-1-(5-fluoro-2-methylphenyl)-*N'*-((1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (4, 150 mg, 0.4 mmol) in THF (2 mL), tetrabutylammonium hydroxide (25 mg, 0.04 mmol, 1M in methanol) was added and the resulting reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water (twice), dried over anhydrous Na₂SO₄, filtered and concentrated again under reduced pressure. The product was purified

through reverse phase prep-HPLC and lyophilized to afford 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 1, 25 mg). LCMS (ESI) Calcd for $C_{17}H_{14}F_4N_4O$: 366.1, found $[M+H]^+ = 367.1$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.65 (s, 1H), 7.27-7.20 (m, 2H), 7.10-7.06 (m, 1H), 4.10 (s, 3H), 2.22 (s, 3H), 1.67-1.65 (m, 2H), 1.46-1.44 (m, 2H).

Example 2: Synthesis of 5-(1,5-dimethyl-1H-pyrazol-3-yl)-3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 2):

[0694] 5-(1,5-dimethyl-1H-pyrazol-3-yl)-3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole was synthesized Scheme 1 using 1,5-dimethyl-1H-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for $C_{17}H_{17}FN_4O$: 312.1, found $[M+H]^+ = 313.2$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.26-7.19 (m, 2H), 7.09-7.04 (m, 1H), 6.71 (s, 1H), 3.84 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H), 1.65-1.63 (m, 2H), 1.42-1.39 (m, 2H).

Example 3: Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 3):

[0695] 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 1 using 1-methyl-1H-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for $C_{16}H_{15}FN_4O$: 298.1, found $[M+H]^+ = 299.2$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.96 (s, 1H), 7.27-7.20 (m, 2H), 7.09-7.06 (m, 1H), 6.91 (s, 1H), 3.97 (s, 3H), 2.22 (s, 3H), 1.65 (m, 2H), 1.42 (m, 2H).

Example 4: Synthesis of 5-(5-cyclopropyl-1-methyl-1H-pyrazol-3-yl)-3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 4):

[0696] 5-(5-cyclopropyl-1-methyl-1H-pyrazol-3-yl)-3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 1 using 5-cyclopropyl-1-methyl-1H-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for $C_{19}H_{19}FN_4O$: 338.2, found $[M+H]^+ = 339.2$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.26-7.19 (m, 2H), 7.09-7.05 (m, 1H), 6.58 (s, 1H), 3.95 (s, 3H), 2.20 (s, 3H), 1.99-1.92 (m, 1H), 1.64-1.61 (m, 2H), 1.42-1.39 (m, 2H), 1.00-0.93 (m, 2H), 0.75-0.72 (m, 2H).

Example 5: Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(5-isopropyl-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 5)

[0697] 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(5-isopropyl-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 1 using 5-isopropyl-1-methyl-1H-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for $C_{19}H_{21}FN_4O$: 340.2, found $[M+H]^+ = 341.2$. 1H NMR

(400 MHz, DMSO- d_6 , at 100 °C) δ_H 7.24-7.17 (m, 2H), 7.05-7.01 (m, 1H), 6.67 (s, 1H), 3.89 (s, 3H), 3.11-3.08 (m, 1H), 2.25 (s, 3H), 1.67 (brs, 2H), 1.40 (brs, 2H), 1.26-1.25 (d, 6H).

Example 6: Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-phenyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 6)

[0698] 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-phenyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 1 using 1-phenyl-1H-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for $C_{21}H_{17}FN_4O$: 360.3, found $[M+H]^+ = 361.2$. 1H NMR (400MHz, DMSO- d_6): δ 8.78 (d, 1H), 7.39 (d, 2H), 7.56 (t, 2H), 7.42 (t, 1H), 7.27-7.22 (m, 3H), 7.11-7.06 (m, 1H), 2.24 (s, 3H), 1.68 (s, 2H), 1.46-1.43 (m, 2H).

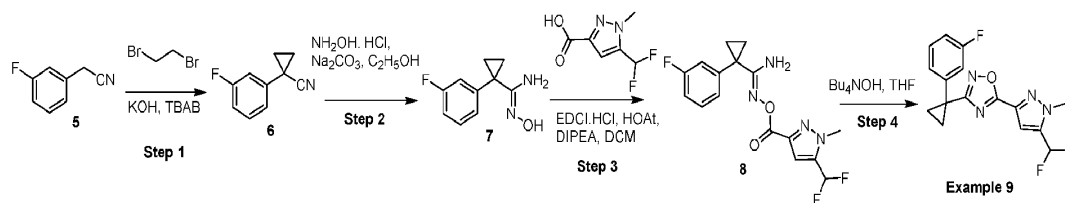
Example 7: Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(5-isopropyl-1-(pyridin-2-yl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 7)

[0699] 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(5-isopropyl-1-(pyridin-2-yl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 1 using 5-isopropyl-1-(pyridin-2-yl)-1H-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for $C_{23}H_{22}FN_5O$: 403.2, found $[M+H]^+ = 404.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 8.59-8.58 (m, 1H), 8.10-8.07 (m, 1H), 7.86-7.84 (m, 1H), 7.55-7.52 (m, 1H), 7.27-7.21 (m, 2H), 7.10-7.04 (m, 2H), 3.82-3.75 (m, 1H), 2.23 (s, 3H), 1.68 (m, 2H), 1.45 (m, 2H), 1.24-1.22 (m, 6H).

Example 8: Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-(2-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 8)

[0700] 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-(2-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 1 using 1-(2-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for $C_{22}H_{18}F_2N_4O$: 392.4, found $[M+H]^+ = 393.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.67-7.63 (m, 2H), 7.57 (t, 1H), 7.45 (t, 1H), 7.27-7.20 (m, 2H), 7.10-7.05 (m, 1H), 7.00 (s, 1H), 2.23 (s, 6H), 1.67 (t, 2H), 1.45 (t, 2H).

Example 9: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (Example 9)



Scheme 2

[0701] Synthesis of 1-(3-fluorophenyl)cyclopropane-1-carbonitrile, 6 [Step 1]: To a stirred solution of KOH (3.7 g, 66.6 mmol) in water (10 mL), 2-(3-fluorophenyl)acetonitrile (5, 750 mg, 5.6 mmol) and TBAB (360 mg, 1.1 mmol) were added at 0 °C. After 5 min, 1,2-dibromoethane (2.4 mL, 27.7 mmol) was added dropwise and the resulting reaction mixture was heated at 60 °C for 12 h. After completion, the reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(3-fluorophenyl)cyclopropane-1-carbonitrile (6, 710 mg). ¹H NMR (400 MHz, CDCl₃) δ_H 7.35-7.25 (m, 1H), 7.08 (d, 1H), 6.99-6.95 (m, 2H), 1.59-1.24 (m, 4H). [Note: ¹H NMR contain extra peak.]

[0702] Synthesis of (Z)-1-(3-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide, 7 [Step 2]: To a stirred solution of 1-(3-fluorophenyl)cyclopropane-1-carbonitrile (6, 700 mg, 4.3 mmol) in ethanol (10 mL), Na₂CO₃ (920 mg, 8.7 mmol) was added followed by NH₂OH.HCl (605 g, 8.7 mmol) and the reaction mixture was heated to reflux at 70 °C for 12 h. After completion, the volatiles were evaporated under reduced pressure, diluted with water and extracted with ethyl acetate (thrice). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-1-(3-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (7, 450 mg). LCMS (ESI) Calcd for C₁₀H₁₁FN₂O: 194.1, found [M+H]⁺ = 195.0.

[0703] Synthesis of (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(3-fluorophenyl)cyclopropane-1-carboximidamide, 8 [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (120 mg, 0.7 mmol) and (Z)-1-(3-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (7, 200 mg, 1.0 mmol) in dichloromethane (3 mL), *N,N*-Diisopropylethylamine (0.2 mL, 1.4 mmol), EDCI.HCl (170 mg, 0.9 mmol) and HOAt (20 mg, 0.1 mmol) were added at 0 °C and reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was concentrated under reduced pressure, dissolved with ethyl acetate, washed with water (twice) and brine. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(3-fluorophenyl)cyclopropane-1-carboximidamide (8, 180 mg). LCMS (ESI) calculated for C₁₆H₁₅F₃N₄O₂: 352.1, found [M+H]⁺ = 353.3.

[0704] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole, Example 9 [Step 4]: To a stirred solution of (Z)-*N'*-

((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(3-fluorophenyl)cyclopropane-1-carboximidamide (8, 180 mg, 0.5 mmol) in THF (2 mL), tetrabutylammonium hydroxide (33 mg, 0.05 mmol, 1M in methanol) was added and resulting reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water (twice), dried over anhydrous Na₂SO₄, filtered and concentrated again under reduced pressure. The product was purified through reverse phase prep-HPLC and lyophilized to afford 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (Example 9, 80 mg). LCMS (ESI) Calcd for C₁₆H₁₃F₃N₄O: 334.1, found [M+H]⁺ = 335.1. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.5-7.24 (t, 1H), 7.43-7.39 (m, 1H), 7.29-7.27 (m, 3H), 7.17-7.11 (m, 1H), 4.05 (s, 3H), 1.60-1.57 (m, 2H), 1.49-1.46 (m, 2H).

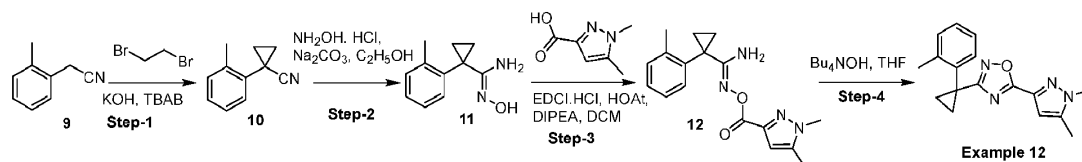
Example 10: Synthesis of 3-(1-(3-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 10)

[0705] 3-(1-(3-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 2 using 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for C₁₆H₁₂F₄N₄O: 352.1, found [M+H]⁺ = 353.2. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.66 (s, 1H), 7.44-7.38 (m, 1H), 7.29 (d, 2H), 7.17-7.12 (m, 1H), 4.11 (s, 3H), 1.61-1.59 (m, 2H), 1.50-1.48 (m, 2H).

Example 11: Synthesis of 5-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-(1-(3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole

[0706] 5-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-(1-(3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 2 using 1,5-dimethyl-1*H*-pyrazole-3-carboxylic acid. LCMS (ESI) Calcd for C₁₆H₁₅FN₄O: 298.1, found [M+H]⁺ = 299.2. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.42-7.37 (m, 1H), 7.28 (d, 2H), 7.15-7.11 (t, 1H), 6.72 (s, 1H), 3.84 (s, 3H), 2.31 (s, 3H), 1.58-1.55 (m, 2H), 1.46-1.43 (m, 2H).

Example 12: Synthesis of 5-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole



Scheme 3

[0707] Synthesis of 1-(*o*-tolyl)cyclopropane-1-carbonitrile, 10 [Step 1]: To a stirred solution of NaOH (31.79 g, 457 mmol) in water (50 mL), 2-(*o*-tolyl)acetonitrile (9, 5 g, 38.1 mmol) and TBAB (2.46 g, 7.62 mmol) were added at 0°C. After 5 min 1,2-dibromoethane (29 mL, 191 mmol) was added dropwise and the resulting reaction mixture was heated at 60°C for 12 hr. After completion, reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(*o*-tolyl)cyclopropane-1-carbonitrile (10, 5 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.35-7.20 (m, 6H), 2.47 (s, 3H), 2.29 (s, 3H), 1.70-1.67 (m, 2H), 1.36-1.33 (m, 2H) [Note: HNMR contain extra peak.]

[0708] Synthesis of (Z)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide, 11 [Step 2]: To a stirred solution of 1-(*o*-tolyl)cyclopropane-1-carbonitrile (10, 2.00 g, 12.7 mmol) in ethanol (10mL), Na₂CO₃ (2.7 g, 25.4 mmol) was added followed by NH₂OH.HCl (177 g, 25.4 mmol) and the reaction mixture was refluxed at 70°C for 12h. After completion, volatiles are evaporated under reduced pressure, diluted with water and extracted with ethyl acetate (thrice). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 900 mg). LCMS (ESI) calculated for C₁₁H₁₄N₂O [M]: 190.1, found [M+H]⁺: 190.7.

[0709] Synthesis of (Z)-*N'*-((1,5-dimethyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide, 12, [Step 3]: To a stirred solution of 1,5-dimethyl-1*H*-pyrazole-3-carboxylic acid (50 mg, 0.4 mmol) and (Z)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 100 mg, 0.5 mmol) in dichloromethane (2 mL), *N,N*-Diisopropylethylamine (0.1 mL, 0.7 mmol), EDCI.HCl (90 mg, 0.5 mmol) and HOAt (9.7 mg, 0.1 mmol) were added at 0 °C and reaction mixture was stirred at ambient temperature for 16h. After completion the reaction mixture was concentrated under reduced pressure, dissolved with ethyl acetate, washed with water (twice) and brine. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-*N'*-((1,5-dimethyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (12, 100 mg). LCMS (ESI) Calcd for C₁₇H₂₀N₄O₂: 312.2, found [M+H]⁺ = 313.2.

[0710] Synthesis of 5-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 12 [Step 4]: To a stirred solution of (Z)-*N'*-((1,5-dimethyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (12, 100 mg, 0.3 mmol) in THF (2 mL), tetrabutylammonium hydroxide(105 mg, 0.2 mmol, 1M in methanol) was added and resulting

reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water (twice), dried over anhydrous Na₂SO₄, filtered and concentrated again under reduced pressure. The product was purified through reverse phase prep-HPLC and lyophilized to afford 5-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 12, 50 mg). LCMS (ESI) Calcd for C₁₇H₁₈N₄O: 294.1, found [M+H]⁺ = 295.2. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.37 (d, 1H), 7.23-7.18 (m, 3H), 6.70 (s, 1H), 3.84 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 1.63 (m, 2H), 1.36 (m, 2H).

Example 13: Synthesis of 5-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 13)

[0711] 5-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 3 using 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid.

[0712] LCMS (ESI) Calcd for C₁₇H₁₅F₃N₄O: 348.1, found [M+H]⁺ = 349.2. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 1H NMR (400 MHz, DMSO-*d*₆) δ_H 7.63 (s, 1H), 7.38 (d, 1H), 7.24-7.19 (m, 3H), 4.10 (s, 3H), 2.32 (d, 3H), 1.66 (brs, 2H), 1.40 (brs, 2H).

Example 14: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 14)

[0713] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 3 using 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid.

[0714] LCMS (ESI) Calcd for C₁₇H₁₆F₂N₄O: 330.1, found [M+H]⁺ = 331.2. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.50-7.19 (m, 6H), 4.04 (s, 3H), 2.26 (s, 3H), 1.66 (brs, 2H), 1.39 (brs, 2H).

Example 15: Synthesis of 5-(1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 15)

[0715] 5-(1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 3 using 1-methyl-1*H*-pyrazole-3-carboxylic acid.

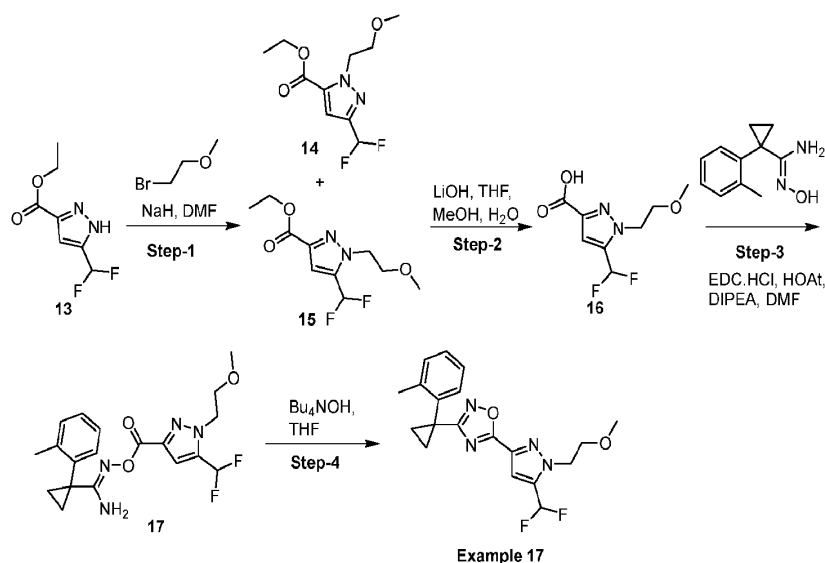
[0716] LCMS (ESI) Calcd for C₁₆H₁₆N₄O: 280.1, found [M+H]⁺ = 281.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.95 (s, 1H), 7.37 (d, 1H), 7.26-7.18 (m, 3H), 6.91 (brs, 1H), 3.97 (s, 3H), 2.26 (s, 3H), 1.65 (brs, 2H), 1.37 (brs, 2H).

Example 16: Synthesis of 5-(1,4-dimethyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 16)

[0717] 5-(1,4-dimethyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 3 using 1,4-dimethyl-1*H*-pyrazole-3-carboxylic acid.

[0718] LCMS (ESI) Calcd. for $C_{17}H_{18}N_4O$: 294.2, found $[M+H]^+ = 295.1$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.75 (s, 1H), 7.37 (d, 1H), 7.25-7.19 (m, 3H), 3.89 (s, 3H), 2.26 (d, 6H), 1.65 (s, 2H), 1.37 (s, 2H).

Example 17: Synthesis of 5-(5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 17)



Scheme 4

[0719] Synthesis of ethyl 5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylate, 15 [Step 1]: To a stirred solution of ethyl 5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate (13, 2.0 g, 10.5 mmol) in DMF (50 mL) at 0°C, sodium hydride (505 mg, 12.6 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 1 h and 1-bromo-2-methoxy-ethane (1.5 g, 10.5 mmol) was added. The reaction mixture was stirred at ambient temperature for 16 h and quenched with crushed ice. The resulting mixture was extracted with ethyl acetate and washed with ice cold water and brine. The combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford ethyl 5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylate (15, 400 mg). LCMS (ESI) Calcd. $C_{10}H_{14}F_2N_2O_3$: 248.1, found $[M+H]^+ = 249.2$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.43-7.05 (m, 2H), 4.46 (t, 2H), 4.31-4.26 (m, 2H), 3.70 (t, 2H), 3.21 (s, 3H), 1.29 (t, 3H). Note: Isolated 900 mg other isomer 14 and the structure was confirmed by NOE experiment.

[0720] Ethyl 3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-5-carboxylate, 14: LCMS (ESI) Calcd. $C_{10}H_{14}F_2N_2O_3$: 248.1, found $[M+H]^+ = 249.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.19-6.92 (m, 2H), 4.70 (t, 2H), 4.34-4.29 (m, 2H), 3.69 (t, 2H), 3.19 (s, 3H), 1.31 (t, 3H).

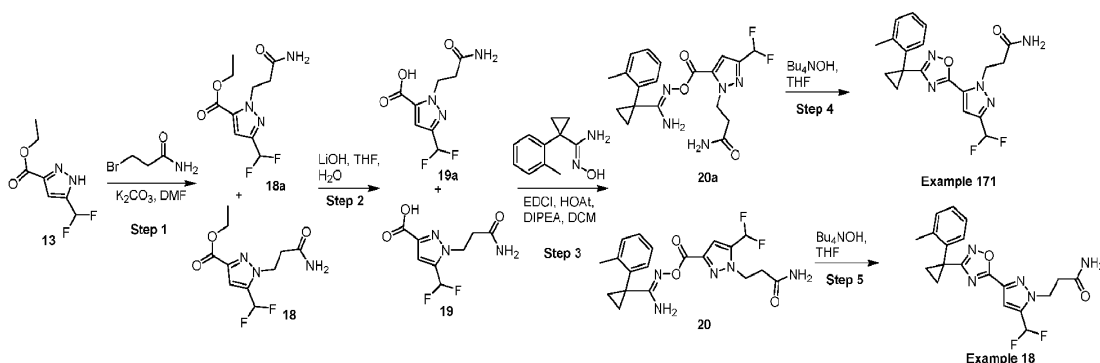
[0721] Synthesis of 5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylic acid, 16 [Step 2]: To an ice cold solution of ethyl 5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylate (15, 420 mg, 1.4 mmol) in THF (4 mL) and methanol (1 mL), an aqueous solution of lithium hydroxide (135 mg, 3.2 mmol) in water (2 mL) was added dropwise. The reaction mixture was stirred at ambient temperature for 2 h and volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with a mixture of dichloromethane and isopropyl alcohol (9:1). Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylic acid (16, 320 mg). LCMS (ESI) Calcd. for $C_{18}H_{10}F_2N_2O_2$: 220.1, found $[M+H]^+ = 221.2$.

[0722] Synthesis of (Z)-*N'*-((5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide, 17 [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylic acid (16, 320 mg, 1.5 mmol), and (Z)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 275 mg, 1.5 mmol) in dichloromethane (15 mL), *N,N*-diisopropylethylamine (0.6 mL, 4.4 mmol), 1-hydroxy-7-azabenzotriazole (40 mg, 0.3 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (360 mg, 1.9 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-*N'*-((5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (17, 540 mg). LCMS (ESI) Calcd. for $C_{19}H_{22}F_2N_4O_3$: 392.2, found $[M+H]^+ = 393.2$.

[0723] Synthesis of 5-(5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 17 [Step 4]: To a stirred solution of (Z)-*N'*-((5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (17, 540 mg, 1.4 mmol) in tetrahydrofuran (10 mL), tetra butyl ammonium hydroxide (39.6 mg, 0.2 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 12 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product

was purified by reverse phase prep HPLC to afford 5-(5-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 17, 287 mg). LCMS (ESI) Calcd. for $C_{19}H_{20}F_2N_4O_2$: 374.2, found $[M+H]^+ = 375.3$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.47-7.24 (m, 3H), 7.23-7.20 (m, 3H), 4.52 (t, 2H), 3.72 (t, 2H), 3.22 (s, 3H), 2.27 (s, 3H), 1.68-1.65 (m, 2H), 1.41-1.38 (m, 2H). Note: Another isomer was formed during alkylation.

Example 18: Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propenamide (Example 18)



Scheme 5

[0724] Synthesis of ethyl 1-(3-amino-3-oxo-propyl)-5-(difluoromethyl)pyrazole-3-carboxylate, 18 and ethyl 2-(3-amino-3-oxo-propyl)-5-(difluoromethyl)pyrazole-3-carboxylate, 18a [Step 1]: To a stirred solution of ethyl 5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate (13, 500 mg, 2.6 mmol) in dimethylformamide (25 mL), potassium carbonate (1.8 g, 13.1 mmol) was added. After 1 h, 3-bromopropanamide (600 mg, 3.9 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was diluted with ethyl acetate and washed with ice-cold water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford a mixture of ethyl 1-(3-amino-3-oxo-propyl)-5-(difluoromethyl)pyrazole-3-carboxylate and ethyl 2-(3-amino-3-oxo-propyl)-5-(difluoromethyl)pyrazole-3-carboxylate (18 and 18a, 470 mg). LCMS (ESI) Calcd. for $C_{10}H_{13}F_2N_3O_3$: 261.1, found $[M+H]^+ = 262.2$.

[0725] Synthesis of 1-(3-amino-3-oxo-propyl)-5-(difluoromethyl)pyrazole-3-carboxylic acid, 19 and 1-(3-amino-3-oxopropyl)-3-(difluoromethyl)-1*H*-pyrazole-5-carboxylic acid, 19a [Step 2]: To a cold solution mixture of ethyl 1-(3-amino-3-oxopropyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate and ethyl 1-(3-amino-3-oxopropyl)-3-(difluoromethyl)-1*H*-pyrazole-5-carboxylate (18 and 18a, 300 mg, 1.2 mmol) in tetrahydrofuran (4 mL) and methanol (1 mL), a solution of lithium hydroxide (95 mg, 2.3 mmol) in water (2 mL) was added drop-wise. The reaction mixture was

stirred at ambient temperature for 3 h. After completion, the volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with a mixture of ethyl acetate and isopropyl alcohol (1:9).

Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The products were purified by column chromatography to afford a mixture of 1-(3-amino-3-oxo-propyl)-5-(difluoromethyl)pyrazole-3-carboxylic acid and 1-(3-amino-3-oxopropyl)-3-(difluoromethyl)-1*H*-pyrazole-5-carboxylic acid (19 and 19a, 240 mg).

LCMS (ESI) Calcd. for $C_8H_9F_2N_3O_3$: 405.2, found $[M+H]^+ = 406.4$.

[0726] Synthesis of (Z)-3-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide, 20 and (Z)-3-(5-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide, 20a [Step 3]: To a stirred solution mixture of 1-(3-amino-3-oxo-propyl)-5-(difluoromethyl)pyrazole-3-carboxylic acid and 1-(3-amino-3-oxopropyl)-3-(difluoromethyl)-1*H*-pyrazole-5-carboxylic acid (19 and 19a, 240 mg, 1.0 mmol) in dichloromethane (10 mL), *N,N*-Diisopropylethylamine (330 mg, 2.6 mmol), 1-hydroxy-7-azabenzotriazole (30 mg, 0.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (255 mg, 1.3 mmol) and (Z)-*N*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 235 mg, 1.2 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The products were purified by combi-flash chromatography to afford the first product as (Z)-3-(5-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide (20a, 120 mg) and the second product as (Z)-3-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide (20, 90 mg). LCMS (ESI) Calcd. for $C_{19}H_{21}F_2N_5O_3$: 405.2, found $[M+H]^+ = 406.4$.

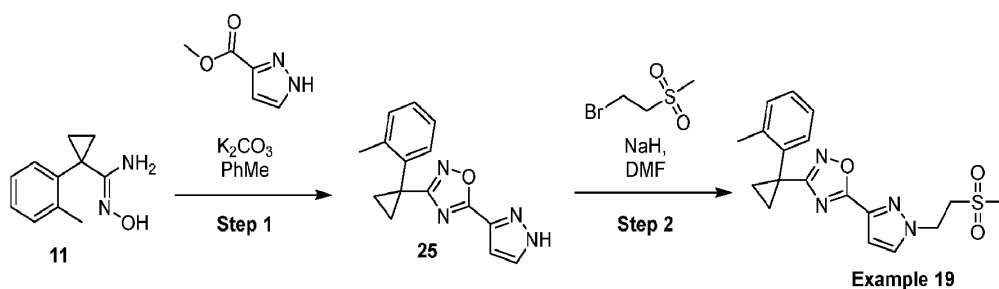
Note: Structure of both the isomers were confirmed based on NOE experiments of the final products.

[0727] Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanamide, Example 171 [Step 4]: To a stirred solution of (Z)-3-(5-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide (20a, 60 mg, 0.2 mmol) in tetrahydrofuran (5 mL), tetra butyl ammonium hydroxide (0.03 mL, 0.03 mmol, 1M in methanol) was added. The resulting reaction mixture was stirred at ambient temperature for 2 h and concentrated under reduced pressure. The residue

was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanamide (Example 171, 9 mg). LCMS (ESI) Calcd. for $C_{19}H_{19}F_2N_5O_2$: 387.2, found $[M+H]^+ = 388.3$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.56-7.18 (m, 7H), 6.98 (brs, 1H), 4.48 (t, 2H), 2.74 (t, 2H), 2.26 (s, 3H), 1.65 (brs, 2H), 1.39 (brs, 2H).

[0728] Synthesis of 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanamide, Example 18 [Step 5]: To a stirred solution of (Z)-3-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide (20, 80 mg, 0.2 mmol) in tetrahydrofuran (2 mL), tetra butyl ammonium hydroxide (10 mg, 0.04 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 2 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water followed by brine wash. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanamide (Example 18, 22 mg). LCMS (ESI) Calcd. for $C_{19}H_{19}F_2N_5O_2$: 387.2, found $[M+H]^+ = 388.3$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.39-6.90 (m, 8H), 4.79 (t, 2H), 2.68 (t, 2H), 2.29 (s, 3H), 1.71 (brs, 2H), 1.42 (brs, 2H). Note: Structure was confirmed based on NOE experiment.

Example 19: Synthesis of 5-(1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 19)



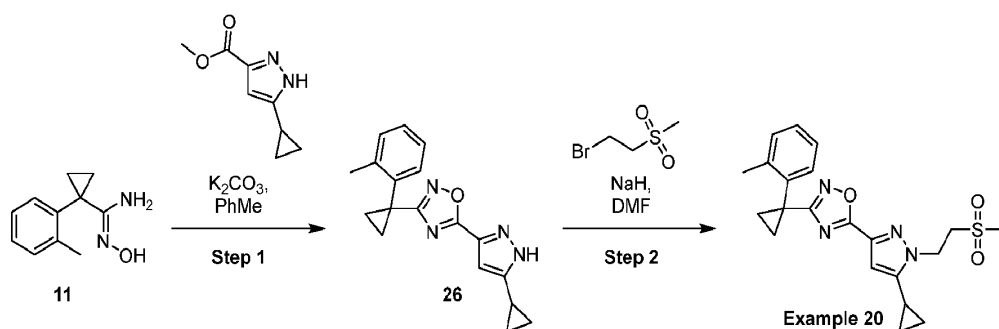
Scheme 6

[0729] Synthesis of 5-(1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, 25 [Step 1]: To a suspension of methyl 1*H*-pyrazole-3-carboxylate (265 mg, 2.1 mmol) and (Z)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 400 mg, 2.1 mmol) in toluene (4 mL) was added potassium carbonate (581 mg, 4.2 mmol), and the reaction mixture was heated to reflux. After

16 h, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The compound was purified by column chromatography to afford 5-(1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (25, 360 mg). LCMS calcd. for $C_{15}H_{14}N_4O$: 266.12, found $[M+H]^+ = 267.3$. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 13.75 (brs, 1H), 8.00 (d, 1H), 7.39-7.37 (m, 1H), 7.24-7.20 (m, 3H), 6.92 (d, 1H), 2.27 (s, 3H), 1.66-1.65 (m, 2H), 1.38-1.37 (m, 2H).

[0730] Synthesis of 5-(1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 19 [Step 2]: To an ice-cold solution of 5-(1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (25, 150 mg, 0.6 mmol) in THF (6 mL) was added NaH (27 mg, 60% in mineral oil, 0.7 mmol). After 15 min, 1-bromo-2-(methylsulfonyl)ethane (126 mg, 0.7 mmol) was added, and the reaction mixture was allowed to warm to ambient temperature. After 16 h, the reaction mixture was quenched with cold water, and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The compound was purified by column chromatography using 0-50% ethyl acetate in hexanes to afford 5-(1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 19, 125 mg). LCMS calcd. for $C_{18}H_{20}N_4O_3S$: 372.13, found $[M+H]^+ = 373.1$. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 8.09 (d, 1H), 7.38-7.36 (m, 1H), 7.26-7.17 (m, 3H), 6.95 (d, 1H), 4.70 (t, 2H), 3.77 (t, 2H), 2.96 (s, 3H), 2.26 (s, 3H), 1.67-1.64 (m, 2H), 1.39-1.36 (m, 2H). Structure of the compound was supported by NOE data.

Example 20: Synthesis of 5-(5-cyclopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 20)



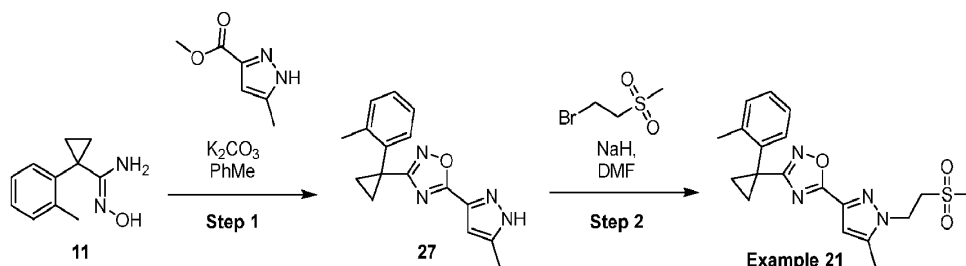
Scheme 7

[0731] Synthesis of 5-(5-cyclopropyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, 26 [Step 1]: To a suspension of methyl 5-cyclopropyl-1*H*-pyrazole-3-carboxylate (349 mg, 2.1 mmol) and (*Z*)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 400 mg,

2.1 mmol) in toluene (4 mL) was added potassium carbonate (581 mg, 4.2 mmol), and the reaction mixture was heated to reflux. After 16 h, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. Purification on a silica gel column afforded 5-(5-cyclopropyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (26, 350 mg). LCMS calcd. for C₁₈H₁₈N₄O: 306.15, found [M+H]⁺ = 307.3. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 13.49 (brs, 1H), 7.38-7.36 (m, 1H), 7.25-7.18 (m, 3H), 6.57-6.56 (m, 1H), 2.26 (s, 3H), 1.99-1.93 (m, 1H), 1.63 (brs, 2H), 1.37-1.36 (m, 2H), 1.00-0.96 (m, 2H), 0.80-0.77 (m, 2H).

[0732] Synthesis of 5-(5-cyclopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 20 [Step 2]: To an ice-cold solution of 5-(5-cyclopropyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (26, 150 mg, 0.5 mmol) in THF (5 mL) was added NaH (24 mg, 60% in mineral oil, 0.6 mmol). After 15 min, 1-bromo-2-(methylsulfonyl)ethane (110 mg, 0.6 mmol) was added, and the reaction mixture was allowed to warm to ambient temperature. After 16 h, the reaction mixture was quenched with cold water, and extracted with ethyl acetate. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The compound was purified by column chromatography using 0-50% ethyl acetate in hexanes to afford 5-(5-cyclopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 20, 110 mg). LCMS calcd. for C₂₁H₂₄N₄O₃S: 412.16, found [M+H]⁺ = 413.2. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.37-7.36 (m, 1H), 7.25-7.17 (m, 3H), 6.63 (s, 1H), 4.70 (t, 2H), 3.77 (t, 2H), 3.00 (s, 3H), 2.25 (s, 3H), 2.07-2.00 (m, 1H), 1.63 (brs, 2H), 1.37 (brs, 2H), 1.03-0.99 (m, 2H), 0.79-0.78 (m, 2H). Protons of one cyclopropyl ring appeared as two broad singlets. Structure of the compound was supported by NOE data.

Example 21: Synthesis of 5-(5-methyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 21)



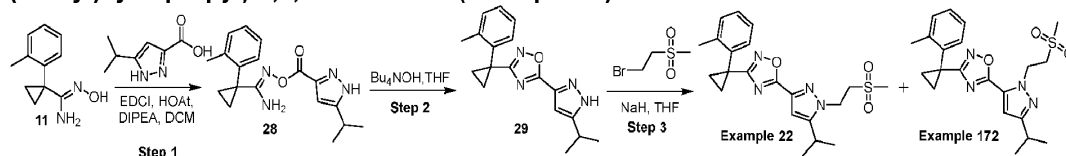
Scheme 8

[0733] Synthesis of 5-(5-methyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, 27 [Step 1]: To a suspension of methyl 5-methyl-1*H*-pyrazole-3-carboxylate (295 mg, 2.1 mmol)

and (Z)-N'-hydroxy-1-(o-tolyl)cyclopropane-1-carboximidamide (11, 400 mg, 2.1 mmol) in toluene (4 mL) was added potassium carbonate (581 mg, 4.2 mmol), and the reaction mixture was heated to reflux. After 16 h, the reaction mixture was filtered through a celite pad, and the filtrate concentrated under reduced pressure. The compound was purified by column chromatography to afford 5-(5-methyl-1*H*-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (27, 450 mg). LCMS calcd. for C₁₆H₁₆N₄O: 280.13, found [M+H]⁺ = 281.3. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 13.43 (brs, 1H), 7.38-7.36 (m, 1H), 7.26-7.17 (m, 3H), 6.65 (s, 1H), 2.30 (s, 3H), 2.26 (s, 3H), 1.65-1.63 (m, 2H), 1.38-1.35 (m, 2H).

[0734] Synthesis of 5-(5-methyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 21 [Step 2]: To an ice-cold solution of 5-(5-methyl-1*H*-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (27, 100 mg, 0.4 mmol) in THF (4 mL) was added NaH (17 mg, 60% in mineral oil, 0.4 mmol). After 15 min, 1-bromo-2-(methylsulfonyl)ethane (80 mg, 0.4 mmol) was added, and the reaction mixture was allowed to warm to ambient temperature. After 16 h, the reaction mixture was quenched with cold water, and extracted with ethyl acetate. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The compound was purified by column chromatography using 0-50% ethyl acetate in hexanes to afford 5-(5-methyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 21, 68 mg). LCMS calcd. for C₁₉H₂₂N₄O₃S: 386.14, found [M+H]⁺ = 387.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.38-7.36 (m, 1H), 7.22-7.19 (m, 3H), 6.74 (s, 1H), 4.56 (t, 2H), 3.74 (t, 2H), 2.96 (s, 3H), 2.38 (s, 3H), 2.26 (s, 3H), 1.64 (brs, 2H), 1.37 (brs, 2H). Protons of the cyclopropyl ring appeared as two broad singlets. Structure of the compound was supported by NOE experiment.

Example 22: Synthesis of 5-(5-isopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 22)



Scheme 9

[0735] Synthesis of (Z)-N'-((5-isopropyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(o-tolyl)cyclopropane-1-carboximidamide, 28 [Step 1]: To a stirred solution of 5-isopropyl-1*H*-pyrazole-3-carboxylic acid (220 mg, 1.4 mmol) and (Z)-N'-hydroxy-1-(o-tolyl)cyclopropane-1-carboximidamide (11, 407 mg, 2.1 mmol) in dichloromethane (5 mL), *N,N*-diisopropylethylamine (1.2 mL, 7.1 mmol), EDCI.HCl (545 mg, 2.8 mmol) and HOAt (40 mg, 0.3 mmol) were added at 0 °C. The reaction mixture was

stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with water and extracted with dichloromethane. The organic extract was washed with brine and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (Z)-N'-((5-isopropyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (28, 500 mg). LCMS (ESI) calcd. for C₁₈H₂₂N₄O₂: 326.1, [M+H]⁺ = 327.4.

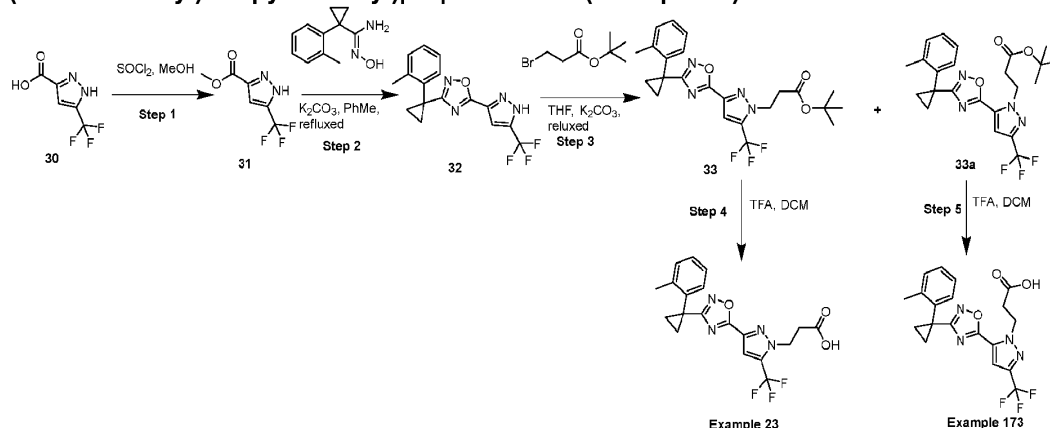
[0736] Synthesis of 5-(5-isopropyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, 29 [Step 2]: To a stirred solution of (Z)-N'-((5-isopropyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (28, 465 mg, 1.4 mmol) in THF (5 mL), tetrabutylammonium hydroxide (0.1 mL, 0.1 mmol, 1M in methanol) was added at ambient temperature. The reaction was stirred at ambient temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate and washed with water. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by combiflash chromatography to afford 5-(5-isopropyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (29, 156 mg). LCMS (ESI) calcd. for C₁₈H₂₀N₄O: 308.1, [M+H]⁺ = 309.4.

[0737] Synthesis of 5-(5-isopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole and 5-(3-isopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 22 & Example 172 [Step 3]: To a stirred solution of 5-(5-isopropyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (29, 155 mg, 0.5 mmol) in THF (5 mL), NaH (25 mg, 0.6 mmol, 60% in oil) was added at 0 °C under nitrogen atmosphere and the reaction mixture was stirred for 10 min. Into the reaction mixture, 1-bromo-2-(methylsulfonyl)ethane (114 mg, 0.6 mmol) was added and stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by combiflash chromatography to afford 5-(5-isopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 22, 100 mg) as Peak-1 and 5-(3-isopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 172, 20 mg) as peak-2. NOTE: The exact structure was confirmed by NOE of peak 1 and Peak-2.

[0738] Analytical data of 5-(5-isopropyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 22 (Peak-1): LCMS (ESI) calcd. for C₂₁H₂₆N₄O₃S: 414.1, [M+H]⁺ = 415.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.38-7.36 (m, 1H), 7.21-7.13 (m, 3H),

6.78 (s, 1H), 4.57 (t, 2H), 3.76 (t, 2H), 3.18-3.15 (m, 1H), 2.98 (s, 3H), 2.25 (s, 3H), 1.70-1.64 (m, 2H), 1.45-1.37 (m, 2H), 1.25-1.23 (m, 6H).

Example 23: Synthesis of 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)propanoic acid (Example 23)



Scheme 10

[0739] Synthesis of methyl 5-(trifluoromethyl)-1H-pyrazole-3-carboxylate, 31 [Step 1]: To a stirred solution of 5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (30, 900 mg, 5.0 mmol) in methanol (20 mL) at 0 °C was added thionyl chloride (0.73 mL, 10.0 mmol) dropwise. The reaction mixture was allowed to stir at ambient temperature for 14 h and volatiles were evaporated. The residue was diluted with ethyl acetate and washed with saturated solution of sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford methyl 5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (31, 550 mg). LCMS (ESI) Calcd. for $C_6H_5F_3N_2O_2$: 194.0, found $[M-H]^- = 193.1$.

[0740] Synthesis of 3-(1-(*o*-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 32 [Step 2]: To a stirred solution of (*Z*)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 600 mg, 3.2 mmol) in toluene (15 mL) was added potassium carbonate (872 mg, 6.3 mmol) and methyl 5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (31, 612 mg, 3.2 mmol). Resulting reaction mixture was refluxed for 16 h and filtered through a celite bed. Combined filtrate was concentrated and the product was purified by column chromatography to afford 3-(1-(*o*-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (32, 400 mg). LCMS (ESI) Calcd. for $C_{16}H_{13}F_3N_4O$: 334.1, found $[M+H]^+ = 335.0$.

[0741] Synthesis of *tert*-butyl 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoate, 33 and *tert*-butyl 3-(5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoate, 33a [Step 3]: To a stirred solution of 3-(1-(*o*-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (32, 300 mg, 1.0 mmol) in THF (10 mL) was added potassium carbonate (186 mg, 1.4 mmol). After 10 min., *tert*-butyl 3-bromopropanoate (281 mg, 1.4 mmol) was added. The reaction mixture was refluxed for 14 h, filtered and combined filtrate was concentrated under reduced pressure. The products were purified by reverse phase preparative HPLC to afford the first product as *tert*-butyl 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoate, Peak 1 (33, 50 mg) and the second product as *tert*-butyl 3-(5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoate, Peak-2 (33a, 75 mg). The structure of the regiomers were confirmed by 2D NMR analyses.

[0742] *tert*-butyl 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoate, Peak 1 (33): LCMS (ESI) Calcd. for C₂₃H₂₅F₃N₄O₃: 462.19, found [M+H]⁺ = 463.10.

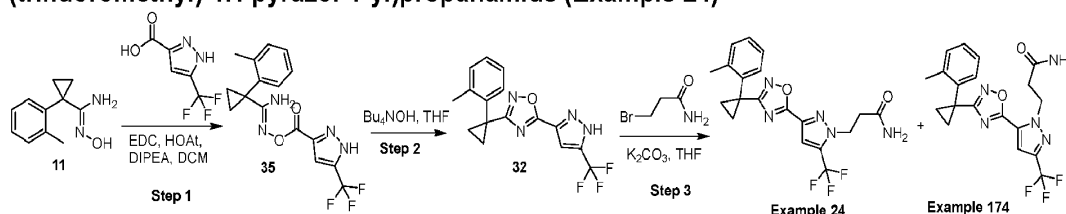
[0743] *tert*-butyl 3-(5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoate, Peak-2 (33a): LCMS (ESI) Calcd. for C₂₃H₂₅F₃N₄O₃: 462.19, found [M+H]⁺ = 463.10.

[0744] Synthesis of 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid, Example 23 [Step 4]: To a stirred solution of *tert*-butyl 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoate (33, 50 mg, 0.1 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (0.08 mL, 1.1 mmol). The reaction mixture was allowed to stir at ambient temperature for 16 h and volatiles were evaporated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid (Example 23, 15 mg). LCMS (ESI) Calcd. for C₁₉H₁₇F₃N₄O₃: 406.13, found [M+H]⁺ = 407.10. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.63 (s, 1H), 7.38 (d, 1H), 7.24-7.19 (m, 3H), 4.53 (t, 2H), 2.92 (t, 2H), 2.26 (s, 3H), 1.68-1.65 (m, 2H), 1.41-1.39 (m, 2H). One acid proton was exchangeable.

[0745] Synthesis of 3-(5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid, Example 173 [Step 5]: To a stirred solution of *tert*-butyl 3-(5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoate (33a, 75 mg, 0.2 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (0.12 mL, 1.6

mmol). The reaction mixture was allowed to stir at ambient temperature for 16 h and volatiles were evaporated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford 3-(5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid (Example 173, 30 mg). LCMS (ESI) Calcd. for $C_{19}H_{17}F_3N_4O_3$: 406.13, found $[M+H]^+ = 407.10$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.64 (s, 1H), 7.38 (d, 1H), 7.25-7.18 (m, 3H), 4.84 (t, 2H), 2.85 (t, 2H), 2.29 (s, 3H), 1.71-1.68 (m, 2H), 1.45-1.42 (m, 2H). One acid proton was exchangeable.

Example 24: Synthesis of 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanamide (Example 24)



Scheme 11

[0746] Synthesis of 1-(*o*-tolyl)-*N'*-((5-(trifluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 35 [Step 1]: To a stirred solution of *N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 500 mg, 2.6 mmol) and 5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid (520 mg, 2.9 mmol) in dichloromethane (8 mL) were added DIPEA (1.4 mL, 7.9 mmol), EDC.HCl (1.0 g, 5.3 mmol) and HOAt (55 mg, 0.5 mmol) at 0 °C and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was diluted with dichloromethane and washed with water. Organic extract was collected, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduce pressure to afford 1-(*o*-tolyl)-*N'*-((5-(trifluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (35, 500 mg). LCMS (ESI) Calcd for $C_{16}H_{15}F_3N_4O_2$: 352.3, found $[M+H]^+ = 353.1$.

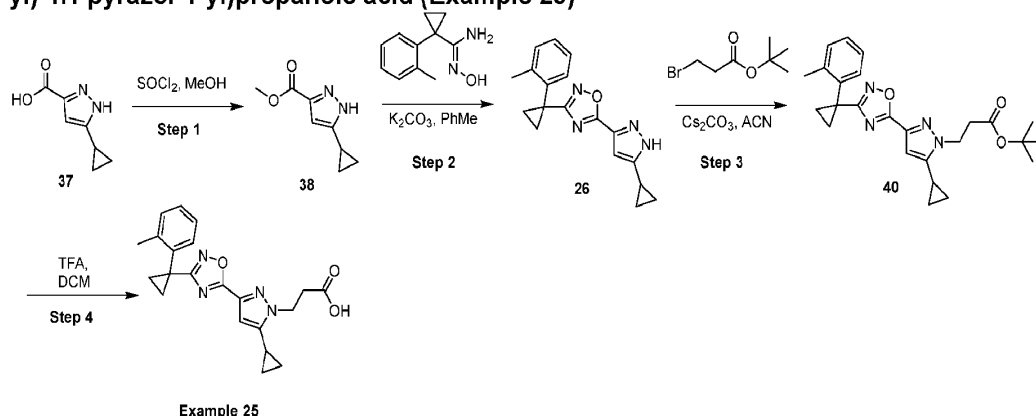
[0747] Synthesis of 3-(1-(*o*-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, 32 [Step 2]: To a stirred solution of 1-(*o*-tolyl)-*N'*-((5-(trifluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (35, 500 mg, 1.4 mmol) in THF (4 mL) was added tetrabutylammonium hydroxide (185 mg, 0.3 mmol) and the reaction mixture was stirred at ambient temperature for 2 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water. The combined organic extract was collected, washed with brine, dried over anhydrous Na_2SO_4 and, concentrated under reduced pressure. The product was purified by column chromatography to afford 3-(1-(*o*-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-

1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (32, 300 mg). LCMS (ESI) Calcd for C₁₆H₁₃F₃N₄O: 334.3, found [M+H]⁺ = 335.3.

[0748] Synthesis of 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanamide & 3-(5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanamide, Example 24 & Example 174 [Step 3]: To a stirred solution of 3-(1-(*o*-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (32, 280 mg, 0.8 mmol) in THF (5mL) was added K₂CO₃ (462 mg, 3.4 mmol) at 0 °C. After 15 min 3-bromopropanamide (255 mg, 1.7 mmol) was added to the reaction mixture and stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water. The combined organic extract was collected, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by column chromatography and isolated compound was lyophilized to afford 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanamide (Example 24, 62 mg) and 3-(5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanamide (Example 174, 62 mg). Note: Structure was confirmed by HMBC & HSQC.

[0749] Analytical data of 3-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)propanamide, Example 24: LCMS (ESI) Calcd for C₁₉H₁₈F₃N₅O₂: 405.3, found [M+H]⁺ = 406.3. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.62 (s, 1H), 7.49 (brs, 1H), 7.38 (d, 1H), 7.24-7.20 (m, 3H), 6.90 (brs, 1H), 4.52 (t, 2H), 2.78 (t, 2H), 2.26 (s, 3H), 1.66 (s, 2H), 1.40 (s, 2H).

Example 25: Synthesis of 3-(5-cyclopropyl-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanoic acid (Example 25)



Scheme 12

[0750] Synthesis of methyl 5-cyclopropyl-1H-pyrazole-3-carboxylate, 38 [Step 1]: To a stirred solution of 5-cyclopropyl-1H-pyrazole-3-carboxylic acid (37, 1.5 g, 9.8 mmol) in methanol (30 mL) at 0 °C was added thionyl chloride (1.4 mL, 19.7 mmol) dropwise. The reaction mixture was allowed to stir at ambient temperature for 14 h, quenched with saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated to afford methyl 5-cyclopropyl-1H-pyrazole-3-carboxylate (38, 720 mg). LCMS (ESI) Calcd. for $C_8H_{10}N_2O_2$: 166.0, found $[M+H]^+$ = 167.2.

[0751] Synthesis of 5-(5-cyclopropyl-1H-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole, 26 [Step 2]: To a stirred solution of (Z)-N'-hydroxy-1-(o-tolyl)cyclopropane-1-carboximidamide (11, 700 mg, 3.7 mmol) in toluene (15 mL) were added potassium carbonate (1.0 g, 7.4 mmol) and methyl 5-cyclopropyl-1H-pyrazole-3-carboxylate (38, 611 mg, 3.7 mmol). Resulting reaction mixture was heated at 110 °C for 16 h, filtered through a celite bed and concentrated under reduced pressure. The product was purified by column chromatography to afford 5-(5-cyclopropyl-1H-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (26, 500 mg). LCMS (ESI) Calcd. for $C_{18}H_{18}N_4O$: 306.1, found $[M+H]^+$ = 360.8.

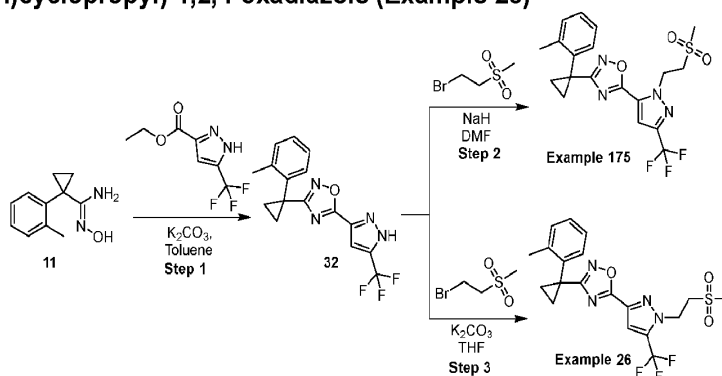
[0752] Synthesis of *tert*-butyl 3-(5-cyclopropyl-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propanoate, 40 [Step 3]: To a stirred solution of 5-(5-cyclopropyl-1H-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (26, 250 mg, 0.8 mmol) in acetonitrile (10 mL) was added Cs_2CO_3 (399 mg, 1.2 mmol) and *tert*-butyl 3-bromopropanoate (205 mg, 0.9 mmol). The reaction mixture was stirred at 70 °C for 14 h, filtered, the filtrate was concentrated under reduced pressure. The product was purified by column chromatography to afford *tert*-butyl 3-(5-cyclopropyl-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propanoate (40, 175 mg). LCMS (ESI) Calcd. for $C_{25}H_{30}N_4O_3$: 434.2, found $[M+H]^+$ = 435.4.

[0753] Synthesis of 3-(5-cyclopropyl-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propanoic acid, Example 25 [Step 4]: To a stirred solution of *tert*-butyl 3-(5-cyclopropyl-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propanoate (40, 175 mg, 0.4 mmol) in dichloromethane (8 mL) at 0 °C was added trifluoroacetic acid (0.31 mL, 4.0 mmol). The reaction mixture was allowed to stir at ambient temperature for 16 h and volatiles were evaporated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford

[0754] 3-(5-cyclopropyl-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propanoic acid (Example 25, 95 mg). LCMS (ESI) Calcd. for $C_{21}H_{22}N_4O_3$: 378.1, found $[M+H]^+$

= 379.2. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 7.36 (d, 1H), 7.21-7.19 (m, 3H), 6.55 (s, 1H), 4.43 (t, 2H), 2.77 (t, 2H), 2.24 (s, 3H), 2.07-2.03 (m, 1H), 1.62 (brs, 2H), 1.35 (brs, 2H), 0.98-0.96 (m, 2H), 0.74-0.73 (m, 2H). Structure was confirmed by 2D NMR analysis.

Example 26: Synthesis of 5-(1-(2-(methylsulfonyl)ethyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 26)



Scheme 13

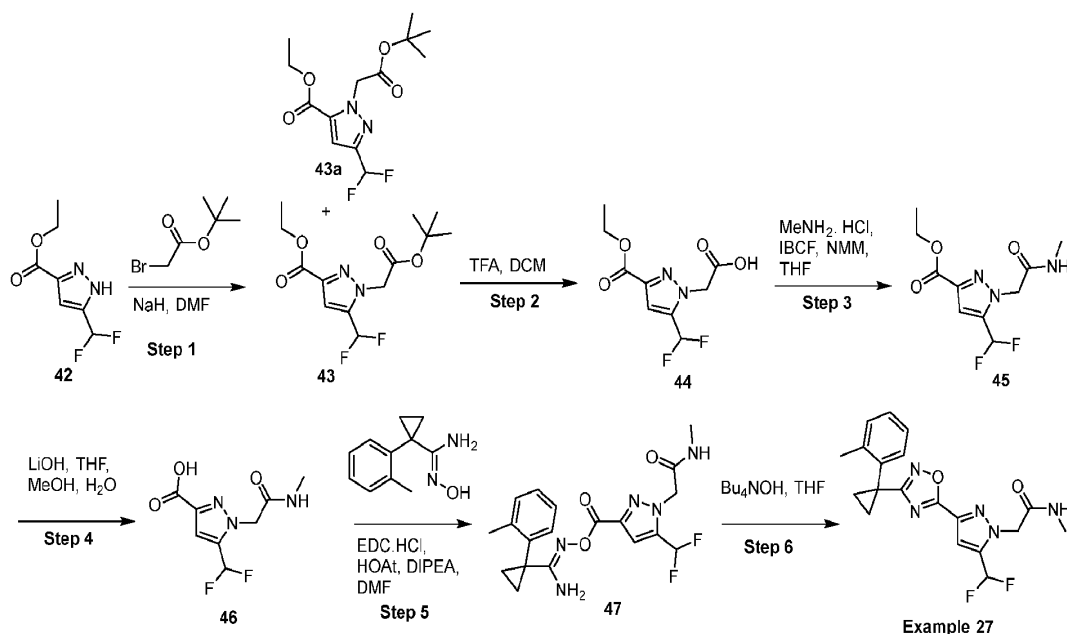
[0755] Synthesis of 3-(1-(o-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 32 [Step 1]: To a stirred solution of (Z)-N'-hydroxy-1-(o-tolyl)cyclopropane-1-carboximidamide (11, 410 mg, 2.2 mmol) and ethyl 5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (450 mg, 2.2 mmol) in toluene (6 mL) was added potassium carbonate (600 mg, 4.3 mmol) at ambient temperature and reaction mixture was allowed to stir at 110 °C for 16 h. After completion, the reaction mixture was cooled to ambient temperature and diluted with water and extracted with dichloromethane. The organic extract was washed with brine and dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by combiflash chromatography to afford 3-(1-(o-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (32, 450 mg). LCMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_4\text{O}$: 334.1, $[\text{M}+\text{H}]^+ = 335.3$.

[0756] Synthesis of 5-(1-(2-(methylsulfonyl)ethyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 175 [Step 2]: To a stirred solution of 3-(1-(o-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (32, 250 mg, 0.7 mmol) in THF (5 mL) was added NaH (60% in oil suspension) (35 mg, 0.9 mmol) at 0 °C under nitrogen atmosphere and the reaction mixture was stirred for 10 min at same condition. To this reaction mixture was added 1-bromo-2-(methylsulfonyl)ethane (170 mg, 0.9 mmol) and the reaction mixture was stirred for 16 h at ambient temperature. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic extract was

dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by combiflash chromatography to afford 5-(1-(2-(methylsulfonyl)ethyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 175, 80 mg). LCMS (ESI) calcd. for $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_3\text{S}$: 440.1, $[\text{M}+\text{H}]^+ = 441.0$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 7.72 (s, 1H), 7.38-7.37 (m, 1H), 7.23-7.20 (m, 3H), 5.12 (t, 2H), 3.78 (t, 2H), 3.00 (s, 3H), 2.29 (s, 3H), 1.75 (s, 2H), 1.43 (s, 2H). NOTE: The exact structure was confirmed by HMBC.

[0757] Synthesis of 5-(1-(2-(methylsulfonyl)ethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 26 [Step 3]: To a stirred solution of 3-(1-(*o*-tolyl)cyclopropyl)-5-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (32, 220 mg, 0.7 mmol) in THF (5 mL) was added K_2CO_3 (182 mg, 1.3 mmol) at 0 °C under nitrogen atmosphere and the reaction mixture was stirred for 10 min at same condition. To this reaction mixture was added 1-bromo-2-(methylsulfonyl)ethane (185 mg, 1 mmol) and the reaction mixture was stirred for 16 h at ambient temperature. After completion, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by combiflash chromatography to afford 5-(1-(2-(methylsulfonyl)ethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 26, 25 mg). LCMS (ESI) calcd. for $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_3\text{S}$: 440.11, $[\text{M}+\text{H}]^+ = 441.0$, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 7.69 (s, 1H), 7.39-7.37 (m, 1H), 7.26-7.18 (m, 3H), 4.77 (t, 2H), 3.85 (t, 2H), 3.08 (s, 3H), 2.26 (s, 3H), 1.66 (s, 2H), 1.41 (s, 2H). NOTE: The exact structure was confirmed by HMBC.

Example 27: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylacetamide (Example 27)



Scheme 14

[0758] Synthesis of ethyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-(difluoromethyl)-1H-pyrazole-3-carboxylate, 43 [Step 1]: To a stirred solution of ethyl 5-(difluoromethyl)-1H-pyrazole-3-carboxylate (42, 800 mg, 4.2 mmol) in dimethylformamide (5 mL) at 0 °C, sodium hydride (200 mg, 5.1 mmol, 60% dispersion in mineral oil) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 1 h and *tert*-butyl 2-bromoacetate (985 mg, 5.1 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was quenched with crushed ice, extracted with ethyl acetate. The organic extract was washed with ice cold water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford ethyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-(difluoromethyl)-1H-pyrazole-3-carboxylate (43, 500 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.41-7.11 (m, 2H), 5.19 (s, 2H), 4.32-4.27 (m, 2H), 1.41 (s, 9H), 1.30 (t, 3H). Note: Isolated 300 mg of ethyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-3-(difluoromethyl)-1H-pyrazole-5-carboxylate (43a) and the structure of desired isomer was confirmed by NOE experiment. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.20-6.93 (m, 2H), 5.25 (s, 2H), 4.32-4.27 (m, 2H), 1.41 (s, 9H), 1.29 (t, 3H).

[0759] Synthesis of 2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetic acid, 44 [Step 2]: To a stirred solution of ethyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-(difluoromethyl)-1H-pyrazole-3-carboxylate (43, 200 mg, 0.7 mmol) in dichloromethane (1 mL), trifluoroacetic acid (1.0 mL, 13.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at ambient

temperature for 3 h. After completion the volatiles were evaporated under reduced pressure to afford 2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetic acid (44, 120 mg). LCMS (ESI) Calcd. for C₉H₁₀F₂N₂O₄: 248.0, found [M+H]⁺ = 249.2.

[0760] Synthesis of ethyl 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate, 45 [Step 3]: To a stirred solution of 2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetic acid (44, 400 mg, 1.6 mmol) in dry tetrahydrofuran (3 mL), 4-methylmorpholine (0.6 mL, 5.6 mmol) and isobutyl chloroformate (0.3 mL, 2.4 mmol) were added. The reaction mixture was stirred at -15 °C for 15 min and methanamine hydrochloride (545 mg, 8.1 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for additional 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford ethyl 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (45, 110 mg). LCMS (ESI) Calcd. C₁₀H₁₃F₂N₃O₃: 261.1, found [M+H]⁺ = 262.2.

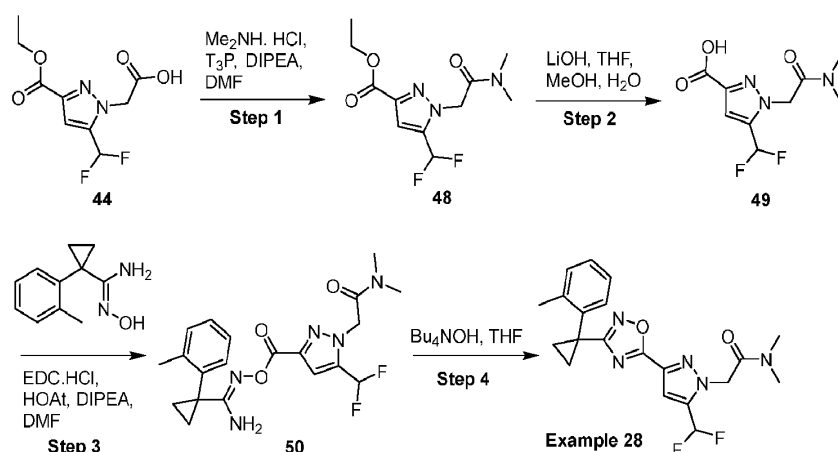
[0761] Synthesis of 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid, 46 [Step 4]: To a cold solution of ethyl 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (45, 110 mg, 0.4 mmol) in tetrahydrofuran (4 mL) and methanol (1 mL), a solution of lithium hydroxide (26.5 mg, 0.6 mmol) in water (2 mL) was added drop-wise. The reaction mixture was stirred at ambient temperature for 16 h and volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with a mixture of ethyl acetate and isopropyl alcohol (9:1). Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid (46, 80 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 13.03 (brs, 1H), 8.19 (d, 1H), 7.23 (t, 1H), 7.01 (s, 1H), 4.97 (s, 2H), 2.62 (d, 3H).

[0762] Synthesis of (Z)-2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-methylacetamide, 47 [Step 5]: To a stirred solution of 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid (46, 80 mg, 0.3 mmol) and (Z)-*N*'-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 105 mg, 0.6 mmol) in dichloromethane (5 mL), *N,N*-diisopropylethylamine (0.3 mL, 1.7 mmol), 1-Hydroxy-7-azabenzotriazole (9.3 mg, 0.1 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (98.7 mg, 0.5 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and

washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-methylacetamide (47, 130 mg). LCMS (ESI) Calcd. for $C_{19}H_{21}F_2N_5O_3$: 405.2, found $[M+H]^+ = 406.4$.

[0763] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylacetamide, Example 27 [Step 6]: To a stirred solution of (Z)-2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-methylacetamide (47, 130 mg, 0.3 mmol) in tetrahydrofuran (2 mL), tetra butyl ammonium hydroxide (41.6 mg, 0.1 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC purification to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylacetamide (Example 27, 15 mg). LCMS Calcd. for $C_{19}H_{19}F_2N_5O_2$: 387.2, found $[M+H]^+ = 388.3$. 1H NMR (400 MHz, DMSO- d_6) δ_H 8.22-8.21 (m, 1H), 7.42-7.15 (m, 6H), 5.06 (s, 2H), 2.62 (d, 3H), 2.26 (s, 3H), 1.67-1.65 (m, 2H), 1.41-1.38 (m, 2H).

Example 28: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide (Example 28)



Scheme 15

[0764] Synthesis of ethyl 5-(difluoromethyl)-1-(2-(dimethylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate, 48 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetic acid (44, 350 mg, 1.4 mmol) in dry dimethylformamide (5 mL), *N,N*-diisopropylethylamine (0.9 mL, 4.9 mmol) and *N*-methylmethanamine hydrochloride (1.2 g, 14.1 mmol) were added. After 10 min, T₃P (1.3 mL, 4.2 mmol, 50 % in ethyl acetate) was added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was quenched with ice-cold water and extracted with ethyl acetate. Combined organic extract was washed with ice-cold water, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford ethyl 5-(difluoromethyl)-1-(2-(dimethylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (48, 180 mg). LCMS (ESI) Calcd. C₁₁H₁₅F₂N₃O₃: 275.1, found [M+H]⁺ = 276.2.

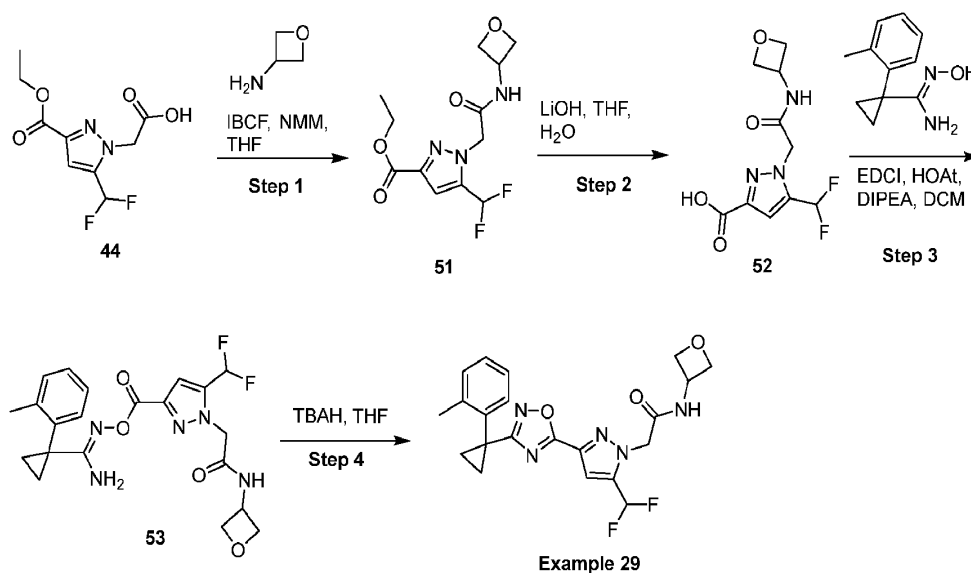
[0765] Synthesis of 5-(difluoromethyl)-1-(2-(dimethylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid, 49 [Step 2]: To a cold solution of ethyl 5-(difluoromethyl)-1-(2-(dimethylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (48, 180 mg, 0.7 mmol) in tetrahydrofuran (4 mL) and methanol (1 mL) mixture, a solution of lithium hydroxide monohydrate (40 mg, 1.0 mmol) in water (1 mL) was added dropwise. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with a mixture of ethyl acetate and isopropyl alcohol (9:1). Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 5-(difluoromethyl)-1-(2-(dimethylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid (49, 110 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 13.05 (brs, 1H), 7.41-7.00 (m, 2H), 5.34-5.16 (s, 1H), 3.04-2.89 (m, 3H), 2.85-2.73 (s, 3H). ¹H NMR indicated the product as mixture of rotamers.

[0766] Synthesis of (Z)-2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide, 50 [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-(2-(dimethylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid (49, 110 mg, 0.5 mmol) and (Z)-*N*'-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 85.5 mg, 0.5 mmol) in dichloromethane (2 mL), *N,N*-diisopropylethylamine (0.3 mL, 1.6 mmol), 1-Hydroxy-7-azabenzotriazole (12.3 mg, 0.1 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112.1 mg, 0.6 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-2-(3-(((amino(1-(*o*-

tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide (50, 160 mg). LCMS (ESI) Calcd. for $C_{20}H_{23}F_2N_5O_3$: 419.2 found $[M+H]^+ = 420.4$.

[0767] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide, Example 28 [Step 4]: To a stirred solution of (*Z*)-2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide (50, 130 mg, 0.3 mmol) in tetrahydrofuran (2 mL), tetra butyl ammonium hydroxide (41.6 mg, 0.1 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC purification to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylacetamide (Example 28, 25 mg). LCMS (ESI) Calcd. for $C_{20}H_{21}F_2N_5O_2$: 401.1, found $[M+H]^+ = 402.3$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.38 (d, 1H), 7.34-7.08 (m, 5H), 5.44 (s, 2H), 3.05 (s, 3H), 2.85 (s, 3H), 2.26 (s, 3H), 1.67-1.66 (m, 2H), 1.41-1.38 (m, 2H).

Example 29: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide (Example 29)



Scheme 16

[0768] Synthesis of ethyl 5-(difluoromethyl)-1-(2-(oxetan-3-ylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate, 3 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetic acid (44, 300 mg, 1.2 mmol) in dry tetrahydrofuran (10 mL), *n*-methyl morpholine (245 mg, 2.4 mmol) and isobutyl chloroformate (165 mg, 1.2 mmol) were added at -15 °C. After 15 min, oxetan-3-amine (105 mg, 1.5 mmol) was added at -15 °C and the reaction mixture was stirred at same temperature for additional 2 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by combi flash chromatography to afford ethyl 5-(difluoromethyl)-1-(2-(oxetan-3-ylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (51, 340 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 9.11 (d, 1H), 7.36-7.07 (m, 2H), 5.06 (s, 2H), 4.82-4.77 (m, 1H), 4.75-4.70 (m, 2H), 4.43 (t, 2H), 4.31-4.26 (m, 2H), 1.29 (t, 3H).

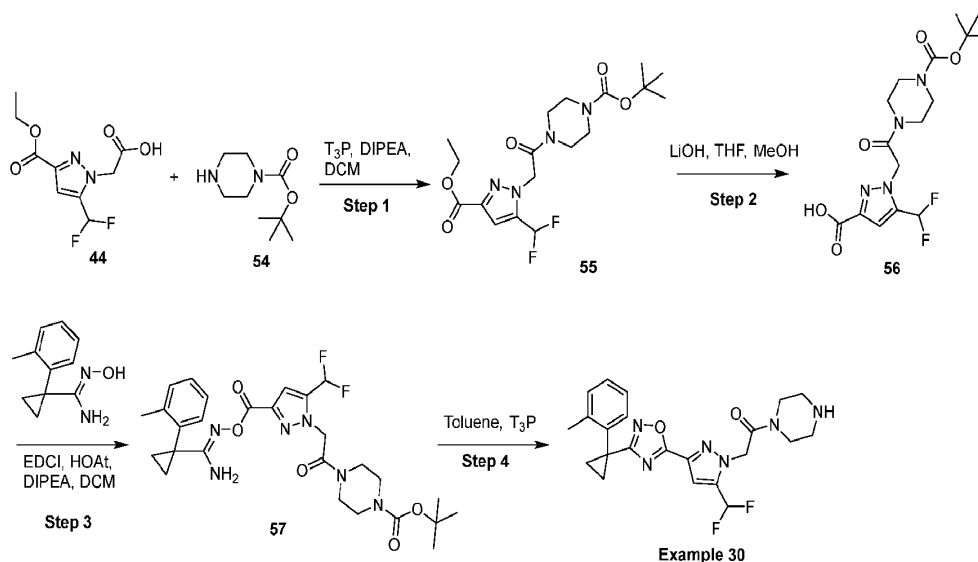
[0769] Synthesis of 5-(difluoromethyl)-1-(2-(oxetan-3-ylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid, 52 [Step 2]: To a cold solution of ethyl 5-(difluoromethyl)-1-(2-(oxetan-3-ylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (51, 170 mg, 0.6 mmol) in tetrahydrofuran (3 mL), a solution of lithium hydroxide (45 mg, 1.1 mmol) in water (1 mL) was added drop-wise. The reaction mixture was stirred at ambient temperature for 3 h. After completion, the volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with ethyl acetate (twice). Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 5-(difluoromethyl)-1-(2-(oxetan-3-ylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid (52, 140 mg). LCMS (ESI) Calcd. for C₁₀H₁₁F₂N₃O₄: 275.1 found [M+H]⁺ = 276.2.

[0770] Synthesis of (Z)-2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(oxetan-3-yl)acetamide, 53 [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-(2-(oxetan-3-ylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid (52, 160 mg, 0.6 mmol) in dichloromethane (10 mL), *N,N*-diisopropylethylamine (185 mg, 1.5 mmol), 1-hydroxy-7-azabenzotriazole (15.8 mg, 0.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (145 mg, 0.8 mmol) and (Z)-*N*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 135 mg, 0.7 mmol) were added at 30 °C. The reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-2-(3-(((amino(1-(*o*-

tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-*N*-(oxetan-3-yl)acetamide (53, 260 mg). LCMS (ESI) Calcd. for $C_{21}H_{23}F_2N_5O_4$: 447.2, found $[M+H]^+ = 448.4$.

[0771] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-(oxetan-3-yl)acetamide, Example 29 [Step 4]: To a stirred solution of (Z)-2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(oxetan-3-yl)acetamide (53, 260 mg, 0.6 mmol) in tetrahydrofuran (5 mL), tetra butyl ammonium hydroxide (30 mg, 0.1 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 2 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-(oxetan-3-yl)acetamide (Example 29, 75 mg). LCMS (ESI) Calcd. for $C_{21}H_{21}F_2N_5O_3$: 429.1, found $[M+H]^+ = 430.35$. 1H NMR (400 MHz, DMSO- d_6) δ_H 9.15 (d, 1H), 7.41-7.38 (m, 1H), 7.31-7.14 (m, 5H), 5.29 (s, 2H), 4.82-4.77 (m, 1H), 4.74-4.70 (m, 2H), 4.45-4.42 (m, 2H), 2.26 (s, 3H), 1.60 (brs, 2H), 1.31 (brs, 2H).

Example 30: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 30)



Scheme 17

[0772] Synthesis of *tert*-butyl 4-(2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate, 55 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetic acid (44, 300 mg, 1.2 mmol) in dichloromethane (5 mL), *N,N*-diisopropylethylamine (0.04 mL, 0.2 mmol) and propane phosphonic acid anhydride (0.06 mL, 0.20 mmol, 50% in ethyl acetate) were added. After 15 min, *tert*-butyl piperazine-1-carboxylate (54, 225 mg, 1.2 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with dichloromethane, washed with saturated solution of aqueous sodium bicarbonate followed by brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford *tert*-butyl 4-(2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (55, 450 mg). LCMS (ESI) Calcd. for C₁₈H₂₆F₂N₄O₅: 416.2, found [M+H]⁺ = 417.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.30-7.03 (m, 2H), 5.43 (s, 2H), 4.31-4.26 (m, 2H), 3.49-3.47 (m, 2H), 3.43-3.42 (m, 4H), 3.32-3.30 (m, 2H), 1.42 (s, 9H), 1.29 (t, 3H).

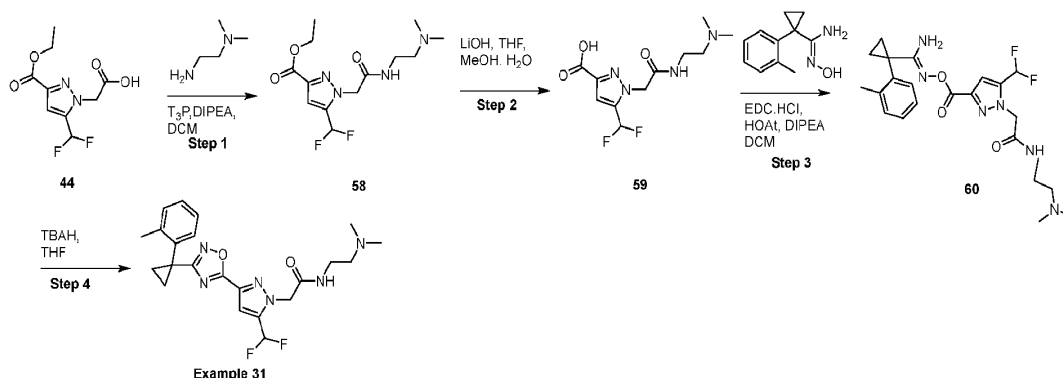
[0773] Synthesis of 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-2-oxoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylic acid, 56 [Step 2]: To an ice cold solution of *tert*-butyl 4-(2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (55, 100 mg, 0.2 mmol) in tetrahydrofuran (1 mL) and methanol (1 mL), a solution of lithium hydroxide (10 mg, 0.2 mmol) in water (1 mL) was added drop-wise. The reaction mixture was stirred at ambient temperature for 3 h. After completion, the volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with a mixture of ethyl acetate and isopropyl alcohol (9:1). Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-2-oxoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylic acid (56, 90 mg). LCMS (ESI) Calcd. for C₁₆H₂₂F₂N₄O₅: 388.2, found [M-H]⁻ = 387.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.16-7.01 (m, 2H), 5.40 (s, 2H), 3.49-3.42 (m, 8H), 1.42 (s, 9H).

[0774] Synthesis of *tert*-butyl (Z)-4-(2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate, 57 [Step 3]: To a stirred solution of 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-2-oxoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylic acid (56, 40 mg, 0.10 mmol), and (Z)-*N*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 20 mg, 0.1 mmol) in dichloromethane (2 mL), *N,N*-diisopropylethylamine (0.05 mL, 0.3 mmol), 1-

Hydroxy-7-azabenzotriazole (2.8 mg, 0.02 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (23.7 mg, 0.1 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford *tert*-butyl (Z)-4-(2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (57, 80 mg). LCMS (ESI) Calcd. for C₂₇H₃₄F₂N₆O₅: 560.3, found [M+H]⁺ = 561.5.

[0775] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one, Example 30 [Step 4]: To a stirred solution of *tert*-butyl (Z)-4-(2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (57, 80 mg, 0.1 mmol) in toluene (2 mL), propane phosphonic acid anhydride (0.05 mL, 0.2 mmol, 50% in ethyl acetate) was added. The resulting reaction mixture was heated at 90 °C for 12 h and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC purification to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 30, 12 mg). LCMS (ESI) Calcd. for C₂₂H₂₄F₂N₆O₂: 442.1, found [M+H]⁺ = 443.2. ¹H NMR (400 MHz, DMSO-*d*₆ and two drops of D₂O) δ_H 7.37-7.05 (m, 6H), 5.41 (s, 2H), 3.41-3.35 (m, 4H), 2.74-2.72 (m, 2H), 2.65-2.63 (m, 2H), 2.24 (s, 3H), 1.66-1.63 (m, 2H), 1.39-1.36 (m, 2H).

Example 31: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-N-(2-(dimethylamino)ethyl)acetamide (Example 31)



Scheme 18

[0776] Synthesis of ethyl 5-(difluoromethyl)-1-(2-((2-(dimethylamino)ethyl)amino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate, 58 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-

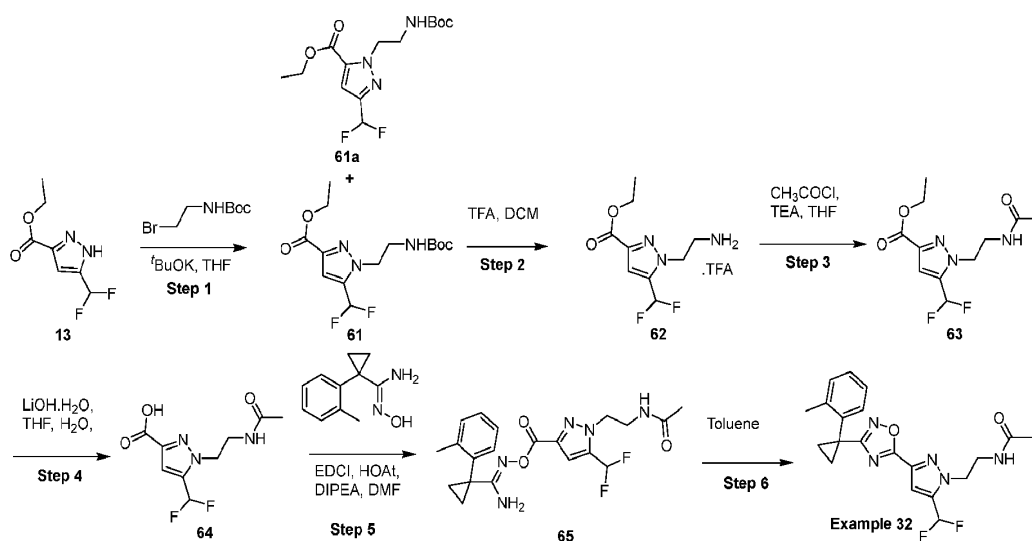
(ethoxycarbonyl)-1*H*-pyrazol-1-yl)acetic acid (44, 300 mg, 1.2 mmol) in dichloromethane (5 mL) were added DIPEA (0.6 mL, 3.6 mmol) and propyl phosphonic anhydride (50% in ethyl acetate) (0.9 mL, 3.02 mmol). After 15 min, *N,N*-dimethylethane-1,2-diamine (106 mg, 1.2 mmol) was added and the resulting reaction mixture was allowed to stir at ambient temperature for 16 h. The reaction mixture was diluted with dichloromethane, washed with saturated solution of sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by combiflash chromatography to afford ethyl 5-(difluoromethyl)-1-(2-((2-(dimethylamino)ethyl)amino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (58, 200 mg). LCMS (ESI) Calcd. for $C_{13}H_{20}F_2N_4O_3$: 318.1, found $[M+H]^+ = 319.1$

[0777] Synthesis of 5-(difluoromethyl)-1-(2-((2-(dimethylamino)ethyl)amino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid, 59 [Step 2]: To a stirred solution of ethyl 5-(difluoromethyl)-1-(2-((2-(dimethylamino)ethyl)amino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (58, 200 mg, 1.5 mmol) in a mixture of THF (3 mL) and methanol (1 mL), was added a solution of lithium hydroxide monohydrate (52 mg, 1.2 mmol) in water (2 mL). The reaction mixture was stirred at ambient temperature for 2 h and volatiles were evaporated under reduced pressure. The residue was acidified with 1 (N) HCl and white precipitate was filtered and dried under reduced pressure to afford 5-(difluoromethyl)-1-(2-((2-(dimethylamino)ethyl)amino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid (59, 160 mg). The product was carried to next step without further purification.

[0778] Synthesis of (Z)-2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-(dimethylamino)ethyl)acetamide, 60 [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-(2-((2-(dimethylamino)ethyl)amino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylic acid (59, 160 mg, 0.5 mmol) in DMF (3 mL), DIPEA (0.3 mL, 1.65 mmol), EDC.HCl (158 mg, 0.8 mmol) and HOAt (15 mg, 0.1 mmol) were added at ambient temperature. After 15 min, (Z)-*N*'-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 105 mg, 0.5 mmol) was added. Resulting reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-*N*'-(((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(5-methoxy-2-methylphenyl)cyclopropane-1-carboximidamide (60, 220 mg). LCMS (ESI) Calcd. for $C_{22}H_{28}F_2N_6O_3$: 462.2, found $[M+H]^+ = 462.8$. The product was carried to next step without further purification.

[0779] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-(2-(dimethylamino)ethyl)acetamide, Example 31 [Step 4]: A solution of (*Z*)-*N*'-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(5-methoxy-2-methylphenyl)cyclopropane-1-carboximidamide (60, 100 mg, 0.2 mmol) in toluene (2 mL), was added propyl phosphonic anhydride (50% in ethyl acetate) (0.1 mL, 0.3 mmol). Resulting reaction mixture was stirred at 90 °C for 16 h, diluted with ethyl acetate and washed with saturated solution of sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to give 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-(2-(dimethylamino)ethyl)acetamide (Example 31, 16 mg). LCMS (ESI) Calcd. for C₂₂H₂₆F₂N₆O₂: 444.2, found [M+H]⁺ = 445.2. ¹H NMR (400 MHz, DMSO-*d*₆ at HT): δ_H 8.17 (brs, 1H), 7.39-7.12 (m, 6H), 5.10 (s, 2H), 3.31 (t, 2H), 2.67 (brs, 2H), 2.43 (s, 6H), 2.30 (s, 3H), 1.70-1.67 (m, 2H), 1.41-1.38 (m, 2H).

Example 32: Synthesis of *N*-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)acetamide (Example 32)



Scheme 19

[0780] Synthesis of ethyl 1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate, 61 [Step 1]: To a stirred solution of ethyl 5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate (13, 200 mg, 1.0 mmol) in tetrahydrofuran (5 mL), potassium *tert*-butoxide (355 mg, 3.1 mmol) was added. The reaction mixture was heated at 80 °C for 30 min and *tert*-butyl

N-(2-bromoethyl)carbamate (235 mg, 1.0 mmol) was added. The resulting reaction mixture was heated at 80 °C for 6 h. After completion, the reaction mixture was quenched with crushed ice, extracted with ethyl acetate and washed with ice cold water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford ethyl 1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate (61, 50 mg). LCMS (ESI) Calcd. for C₁₄H₂₁F₂N₃O₄: 333.1, found [M+H]⁺ = 334.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.27 (t, 1H), 7.03 (s, 1H), 6.97-6.94 (m, 1H), 4.30-4.25 (m, 4H), 3.36-3.34 (m, 2H), 1.32 (s, 9H), 1.30 (t, 3H). Note: Structure of desired regio-isomer was confirmed by NOE experiment.

[0781] Synthesis of ethyl 1-(2-aminoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate 2,2,2-trifluoroacetate, 62 [Step 2]: To a stirred solution of ethyl 1-(2-((*tert*-butoxycarbonyl)amino)ethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate (61, 200 mg, 0.6 mmol) in dichloromethane (2 mL), trifluoroacetic acid (0.1 mL, 1.2 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at ambient temperature for 2 h. After completion, the volatiles were evaporated under reduced pressure to afford ethyl 1-(2-aminoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate 2,2,2-trifluoroacetate (62, 150 mg). LCMS (ESI) Calcd. for C₁₄H₂₁F₂N₃O₄: 233.1 found [M+H]⁺ = 234.1.

[0782] Synthesis of ethyl 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate, 63 [Step 3]: To a stirred solution of ethyl 1-(2-aminoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylate 2,2,2-trifluoroacetate (62, 250 mg, 0.8 mmol) in tetrahydrofuran at 0 °C, triethyl amine (0.3 mL, 2.3 mmol) and acetyl chloride (0.1 mL, 2.3 mmol) were added. The reaction mixture was stirred at ambient temperature for 2 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford ethyl 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (63, 150 mg). LCMS (ESI) Calcd. for C₁₁H₁₅F₂N₃O₃: 275.1, found [M+H]⁺ = 276.3.

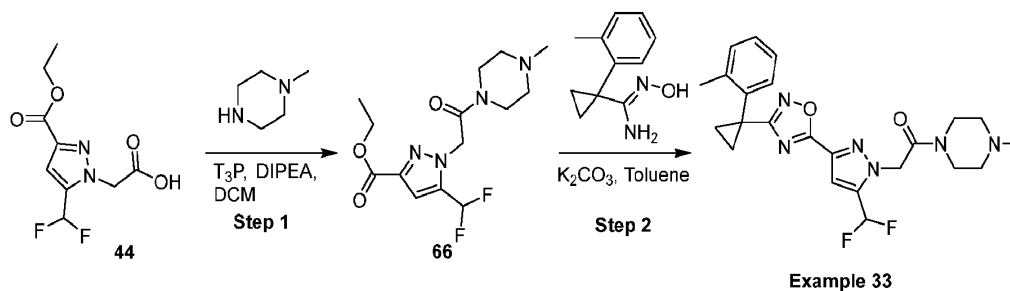
[0783] Synthesis of 1-(2-acetamidoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylic acid, 64 [Step 4]: To a cold solution of ethyl 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (63, 250 mg, 0.9 mmol) in tetrahydrofuran (4 mL), a solution of lithium hydroxide monohydrate (76.3 mg, 1.8 mmol) in water (2 mL) was added drop-wise. The reaction mixture was stirred at ambient temperature for 3 h. After completion, the volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with a mixture of dichloromethane and

isopropyl alcohol (9:1). Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 1-(2-acetamidoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylic acid (64, 140 mg). LCMS (ESI) Calcd. for $C_9H_{11}F_2N_3O_3$: 247.1, found $[M+H]^+ = 248.0$.

[0784] Synthesis of (Z)-*N*-(2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)ethyl)acetamide, 65 [Step 5]: To a stirred solution of 1-(2-acetamidoethyl)-5-(difluoromethyl)-1*H*-pyrazole-3-carboxylic acid (64, 130 mg, 0.5 mmol), and (Z)-*N*'-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (120 mg, 0.6 mmol) in dichloromethane (15 mL), *N,N*-diisopropylethylamine (0.3 mL, 1.6 mmol), 1-Hydroxy-7-azabenzotriazole (15 mg, 0.1 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (130 mg, 0.7 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-*N*-(2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)ethyl)acetamide (65, 120 mg). LCMS (ESI) Calcd. for $C_{20}H_{23}F_2N_5O_3$: 419.2, found $[M+H]^+ = 420.2$.

[0785] Synthesis of *N*-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)acetamide, Example 32 [Step 6]: A solution of (Z)-*N*-(2-(3-(((amino(1-(*o*-tolyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)ethyl)acetamide (65, 100 mg, 0.2 mmol) in toluene (3 mL) was heated at 80 °C for 16 h. After completion, the reaction mixture was concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford *N*-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)acetamide (Example 32, 71 mg). LCMS (ESI) Calcd. for $C_{20}H_{21}F_2N_5O_2$: 401.1, found $[M+H]^+ = 402.3$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.97-7.96 (m, 1H), 7.45-7.19 (m, 6H), 4.36 (t, 2H), 3.49 (t, 2H), 2.27 (s, 3H), 1.74 (s, 3H), 1.66-1.65 (m, 2H), 1.40-1.39 (m, 2H).

Example 33: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one (Example 33)



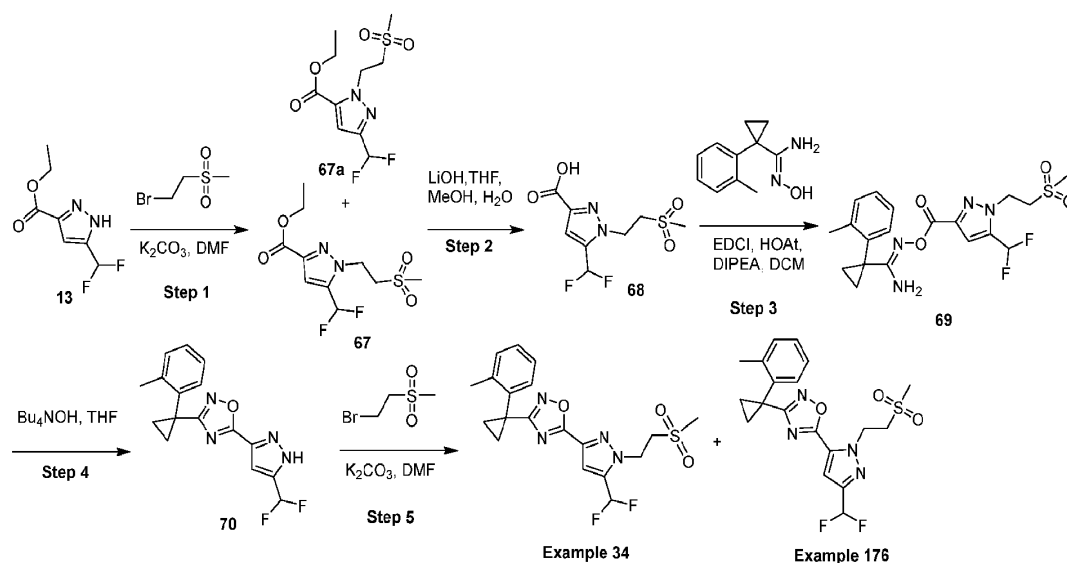
Scheme 20

[0786] Synthesis of ethyl 5-(difluoromethyl)-1-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1H-pyrazole-3-carboxylate, 66 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetic acid (44, 200 mg, 0.8 mmol) in dichloromethane (5 mL), *N,N*-Diisopropylethylamine (0.4 mL, 2.4 mmol) and propane phosphonic acid anhydride (0.4 mL, 1.2 mmol, 50% in ethyl acetate) were added. After 15 min, 1-methylpiperazine (95 mg, 1.0 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with dichloromethane, washed with saturated solution of aqueous sodium bicarbonate followed by brine wash. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford 5-(difluoromethyl)-1-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1H-pyrazole-3-carboxylate (66, 280 mg). LCMS (ESI) Calcd. for $C_{14}H_{20}F_2N_4O_3$: 330.2, found $[M+H]^+$ = 331.2. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.30-7.03 (m, 2H), 5.40 (s, 2H), 4.33-4.26 (m, 2H), 3.48-3.34 (m, 4H), 2.37 (brs, 2H), 2.27 (brs, 2H), 2.20 (s, 3H), 1.29 (t, 3H).

[0787] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one, Example 33 [Step 2]: To a stirred solution of ethyl 5-(difluoromethyl)-1-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1H-pyrazole-3-carboxylate (66, 280 mg, 0.9 mmol) in toluene (8 mL), potassium carbonate (140 mg, 1.0 mmol) and (*Z*)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (160 mg, 0.8 mmol) were added. The reaction mixture was stirred at 90 °C for 16 h and concentrated under reduced pressure. The resultant residue was diluted with ethyl acetate and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC purification to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one (Example 33, 51 mg). LCMS (ESI) Calcd. for $C_{23}H_{26}F_2N_6O_2$:

456.2, found $[M+H]^+ = 457.3$. 1H NMR (400 MHz, methanol- d_4) δ_H 7.38 (d, 1H), 7.23-6.90 (m, 5H), 5.42 (s, 2H), 3.68 (brs, 4H), 2.75-2.67 (m, 4H), 2.49 (s, 3H), 2.31 (s, 3H), 1.75-1.74 (m, 2H), 1.40-1.38 (m, 2H).

Example 34: Synthesis of 5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 34)



Scheme 21

[0788] Synthesis of ethyl 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylate, 67 [Step 1]: To a stirred suspension of ethyl 5-(difluoromethyl)-1H-pyrazole-3-carboxylate (13, 1.0 g, 5.3 mmol) and potassium carbonate (2.9 g, 21.0 mmol) in DMF (60 mL) at 0 °C, 1-bromo-2-(methylsulfonyl)ethane (1.5 g, 7.9 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with ice cold water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford ethyl 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylate (67, 420 mg). LCMS (ESI) calcd. for $C_{10}H_{14}F_2N_2O_4S$: 296.0, found $[M+H]^+ = 297.0$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.38 (t, 1H), 7.09 (s, 1H), 4.70 (t, 2H), 4.32-4.27 (m, 2H), 3.78-3.74 (m, 2H), 3.07 (s, 3H), 1.29 (t, 3H). Note: Structure was confirmed based on NOE experiment of compounds 67 and 67a.

[0789] Synthesis of 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylic acid, 68 [Step 2]: To an ice cold solution of ethyl 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-

pyrazole-3-carboxylate (67, 420 mg, 1.4 mmol) in tetrahydrofuran (6 mL) and methanol (1 mL), an aqueous solution (2 mL) of lithium hydroxide (120 mg, 2.8 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with a mixture of dichloromethane and isopropyl alcohol (9:1). Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazole-3-carboxylic acid (68, 350 mg). LCMS (ESI) Calcd. for $C_8H_{10}F_2N_2O_4S$: 268.0, found $[M+H]^+ = 269.0$.

[0790] Synthesis of (Z)-*N'*-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide, 69 [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazole-3-carboxylic acid (68, 350 mg, 1.3 mmol), and (Z)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 248.2 mg, 1.3 mmol) in dichloromethane (10 mL), *N,N*-diisopropylethylamine (335 mg, 2.6 mmol), 1-hydroxy-7-azabenzotriazole (36 mg, 0.3 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (325 mg, 1.7 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-*N'*-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (69, 300 mg). LCMS (ESI) Calcd. for $C_{19}H_{22}F_2N_4O_4S$: 440.1, found $[M+H]^+ = 441.4$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.51-7.24 (m, 4H), 7.17-7.16 (m, 2H), 6.12 (brs, 2H), 4.68 (t, 2H), 3.76 (t, 2H), 3.04 (s, 3H), 2.40 (s, 3H), 1.43 (brs, 2H), 1.00 (brs, 2H).

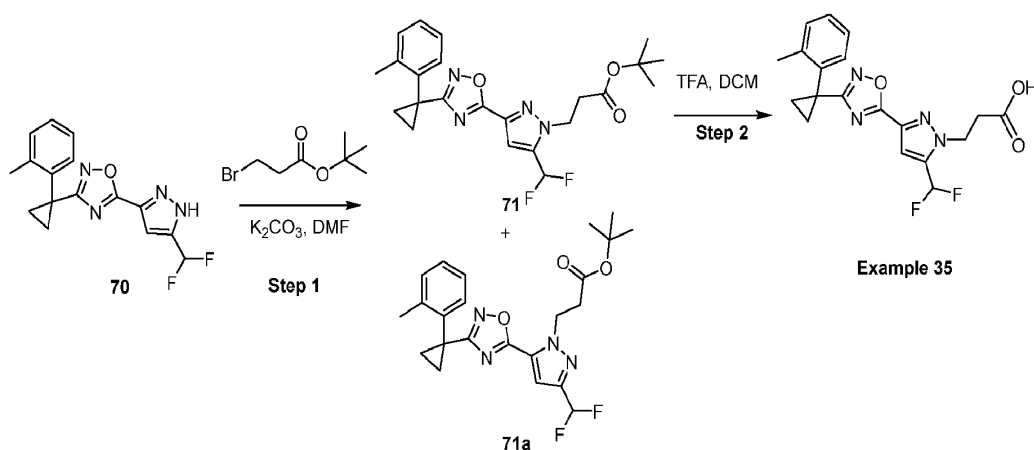
[0791] Synthesis of 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, 70 [Step 4]: To a stirred solution of (Z)-*N'*-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (69, 300 mg, 0.7 mmol) in tetrahydrofuran (10 mL), tetra butyl ammonium hydroxide (35 mg, 0.1 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 12 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 200 mg). LCMS (ESI) Calcd. for $C_{16}H_{14}F_2N_4O$: 316.1, found $[M+H]^+ = 317.2$.

[0792] Synthesis 5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 34 and 5-(3-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 176

[Step 5]: To a stirred suspension of 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 200 mg, 0.6 mmol) and potassium carbonate (350 mg, 2.5 mmol) in DMF (10 mL) at 0 °C, 1-bromo-2-(methylsulfonyl)ethane (175 mg, 1.0 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with ice-cold water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product were purified by reverse phase preparative HPLC to afford the first product as 5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 34, 46 mg) as Peak-1 and the second product as 5-(3-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 176, 30 mg) as Peak-2.

[0793] 5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 34 (Peak-1): LCMS (ESI) Calcd. for $C_{19}H_{20}F_2N_4O_3S$: 422.1, found $[M+H]^+ = 423.3$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.55-7.29 (m, 3H), 7.24-7.20 (m, 3H), 4.76 (t, 2H), 3.80 (t, 2H), 3.07 (s, 3H), 2.26 (s, 3H), 1.66-1.65 (m, 2H), 1.41-1.39 (m, 2H). Note: The structure of the final oxadiazoles was confirmed by NOE experiments and another isomer was formed during alkylation.

Example 35: Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanoic acid (Example 35)

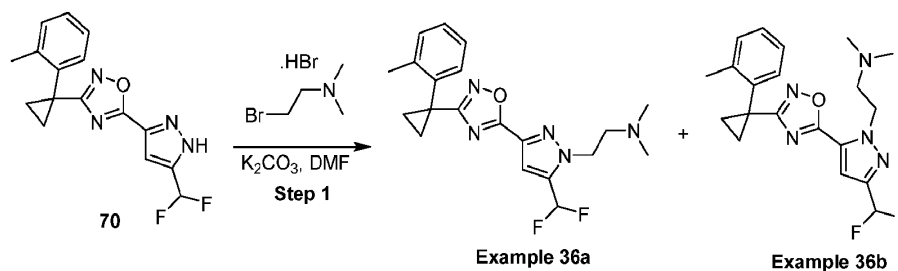


Scheme 22

[0794] Synthesis of *tert*-butyl 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanoate, 71 [Step 1]: To a stirred suspension of 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 400 mg, 1.3 mmol) and potassium carbonate (1.2 g, 8.9 mmol) in dimethylformamide (10 mL) at 0 °C, *tert*-butyl 3-bromopropanoate (395 mg, 1.9 mmol) was added. The resulting reaction mixture was allowed to stir at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with ice-cold water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford *tert*-butyl 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanoate (71, 130 mg). LCMS (ESI) Calcd. for C₂₃H₂₆F₂N₄O₃: 444.2, found [M+H]⁺ = 445.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.37-7.22 (m, 5H), 4.51 (t, 2H), 2.86 (t, 2H), 2.26 (s, 3H), 1.65 (brs, 2H), 1.39 (brs, 3H), 1.35 (s, 9H). Note: Structure was confirmed based on NOE experiment.

[0795] Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanoic acid, Example 35 [Step 2]: To a stirred solution of *tert*-butyl 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanoate (71, 120 mg, 0.3 mmol) in dichloromethane (15 mL), trifluoroacetic acid (0.4 mL, 5.4 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 6 h. After completion, the volatiles were removed under reduced pressure. The product was purified by reverse phase prep HPLC to afford 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)propanoic acid (Example 35, 35 mg). LCMS (ESI) Calcd. for C₁₉H₁₈F₂N₄O₃: 388.1, found [M+H]⁺ = 389.3. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 12.54 (brs, 1H), 7.56-7.29 (m, 2H), 7.26-7.18 (m, 4H), 4.52 (t, 2H), 2.90 (t, 2H), 2.26 (s, 3H), 1.66 (brs, 2H), 1.39 (brs, 2H). Note: Another isomer was formed during alkylation.

Examples 36a & 36b: 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylethan-1-amine (Example 36a) & 2-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylethan-1-amine (Example 36b)



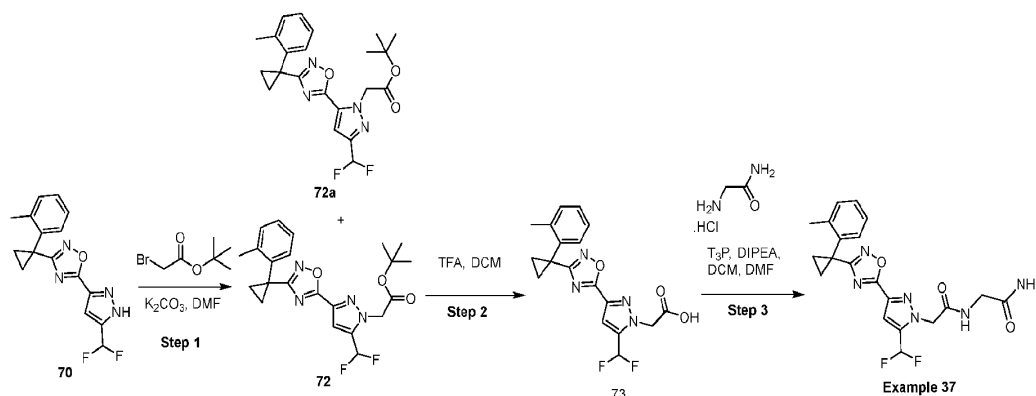
Scheme 23

[0796] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-N,N-dimethylethan-1-amine, 36a & 2-(3-(difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-N,N-dimethylethan-1-amine, 36b [Step 1]: To a stirred solution of 5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 120 mg, 0.38 mmol) in dimethylformamide (3 mL), potassium carbonate (105 mg, 0.76 mmol) and 2-bromo-N,N-dimethyl-ethanamine hydrobromide (106 mg, 0.46 mmol) were added. The resulting reaction mixture was allowed to stir at ambient temperature for 16 h, diluted with ethyl acetate, washed with ice-cold water and brine. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The products were purified by reverse phase preparative HPLC to afford peak-1 as 2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-N,N-dimethylethan-1-amine (36a, 14 mg) and peak-2 as 2-(3-(difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-N,N-dimethylethan-1-amine (36b, 25 mg).

[0797] 2-(5-(Difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-N,N-dimethylethan-1-amine, Example 36a: LCMS (ESI) Calcd. for $C_{20}H_{23}F_2N_5O$: 387.1, found $[M + H]^+ = 388.2$, 1H NMR (400 MHz, DMSO- d_6): δ_H 7.51-7.20 (m, 6H), 4.42 (t, 2H), 2.70-2.68 (m, 2H), 2.27 (s, 3H), 2.18 (s, 6H), 1.66 (brs, 2H), 1.39 (brs, 2H).

[0798] 2-(3-(Difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-N,N-dimethylethan-1-amine, 36b: LCMS (ESI) Calcd. for $C_{20}H_{23}F_2N_5O$: 387.1, found $[M + H]^+ = 388.2$, 1H NMR (400 MHz, DMSO- d_6): δ_H 7.39-7.36 (m, 2H), 7.25-6.97 (m, 4H), 4.68 (t, 2H), 2.65 (t, 2H), 2.28 (s, 3H), 2.11 (s, 6H), 1.70-1.67 (m, 2H), 1.45-1.43 (m, 2H).

Example 37: Synthesis of N-(2-amino-2-oxoethyl)-2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetamide (Example 37)



Scheme 24

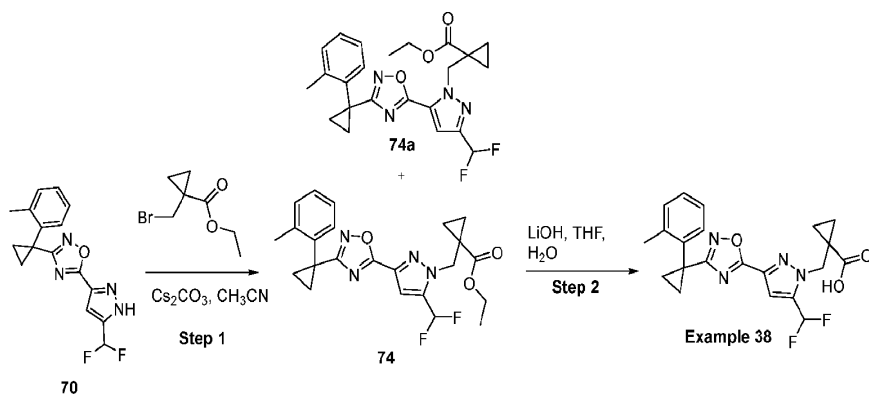
[0799] Synthesis of *tert*-butyl-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetate, 72 [Step 1]: To a stirred suspension of 5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 600 mg, 1.9 mmol) and potassium carbonate (265 mg, 1.9 mmol) in dimethylformamide (20 mL) at 0 °C, *tert*-butyl 2-bromoacetate (72, 555 mg, 2.9 mmol) was added. The resulting reaction mixture was allowed to stir at ambient temperature for 16 h, diluted with ethyl acetate and washed with ice-cold water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford *tert*-butyl 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetate (70, 120 mg) and *tert*-butyl 2-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetate (72a, 200 mg).

[0800] Analytical data of *tert*-butyl-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetate, 72: LCMS (ESI) Calcd. for $C_{22}H_{24}F_2N_4O_3$: 430.2, found $[M+H]^+ = 431.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.46-7.19 (m, 6H), 5.26 (s, 2H), 2.27 (s, 3H), 1.67 (brs, 2H), 1.41 (s, 9H), 1.25 (brs, 2H). Note: Structure was confirmed based NOE experiment.

[0801] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetic acid, 73 [Step 2]: To a stirred solution of *tert*-butyl 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetate (72, 120 mg, 0.3 mmol) in dichloromethane (15 mL), trifluoroacetic acid (317.9 mg, 2.8 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 6 h and the volatiles were reduced under reduced pressure to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetic acid (73, 100 mg). LCMS (ESI) Calcd. for $C_{18}H_{16}F_2N_4O_3$: 374.1, found $[M+H]^+ = 375.2$.

[0802] Synthesis of *N*-(2-amino-2-oxoethyl)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetamide, Example 37 [Step 3]: To a stirred solution of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetic acid (73, 90 mg, 0.2 mmol) and 2-aminoacetamide hydrochloride (35 mg, 0.3 mmol) in dichloromethane (10 mL) and dimethylformamide (0.5 mL), *N,N*-Diisopropylethylamine (155 mg, 1.2 mmol) and propane phosphonic acid anhydride (0.1 mL, 0.4 mmol, 50% in ethyl acetate) were added. The resulting reaction mixture was allowed to stir at ambient temperature for 16 h, diluted with dichloromethane and washed with water and brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford *N*-(2-amino-2-oxoethyl)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetamide (Example 37, 26 mg). LCMS (ESI) Calcd. for C₂₀H₂₀F₂N₆O₃: 430.2, found [M+H]⁺ = 431.3. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 8.55 (t, 1H), 7.41-7.37 (m, 2H), 7.30-7.28 (m, 2H), 7.24-7.20 (m, 3H), 7.14-7.12 (m, 1H), 5.18 (s, 2H), 3.70 (d, 2H), 2.26 (s, 3H), 1.66 (brs, 2H), 1.39 (brs, 2H). Note: Another isomer was formed during alkylation.

Example 38: Synthesis of 1-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid (Example 38)



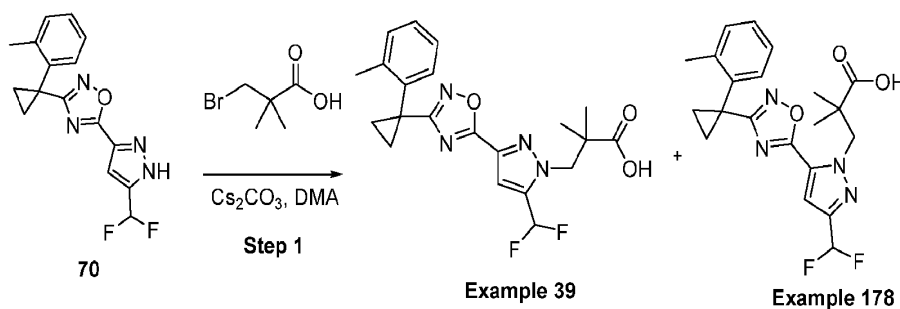
Scheme 25

[0803] Synthesis of ethyl 1-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)cyclopropane-1-carboxylate, 74 [Step 1]: To a stirred solution of 5-[5-(difluoromethyl)-1*H*-pyrazol-3-yl]-3-[1-(*o*-tolyl)cyclopropyl]-1,2,4-oxadiazole (70, 200 mg, 0.632 mmol) in acetonitrile (6 mL) was added Cs₂CO₃ (515 mg, 1.6 mmol). After 5 min, ethyl 1-(bromomethyl)cyclopropanecarboxylate (262 mg, 1.3 mmol) was added and the reaction mixture was stirred at 90 °C for 16 h. The reaction mixture was diluted ethyl acetate and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous

sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography to give ethyl 1-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)cyclopropane-1-carboxylate (74, 130 mg). Structure of regiomers were confirmed by NOE experiment. LCMS (ESI) Calcd. for $C_{23}H_{24}F_2N_4O_3$: 422.18, found $[M+H]^+ = 443.4$. Note: Other regio-isomer was also formed.

[0804] Synthesis of 1-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid, Example 38 [Step 2]: To a solution of ethyl 1-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)cyclopropane-1-carboxylate (74, 110 mg, 0.3 mmol) in THF (2 mL) and water (2 mL), lithium hydroxide monohydrate (32 mg, 0.770 mmol) was added. The reaction mixture was stirred at 70 °C for 4 h and volatiles were evaporated under reduced pressure. The residual aqueous phase was acidified with 1(N) HCl and extracted with ethyl acetate (thrice). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to give 1-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid (Example 38, 37 mg). LCMS (ESI) Calcd. for $C_{21}H_{20}F_2N_4O_2$: 414.2, found $[M+H]^+ = 415.3$. 1H NMR (400 MHz, DMSO- d_6): δ_H 12.62 (brs, 1H), 7.64-7.20 (m, 6H), 4.52 (s, 2H), 2.27 (s, 3H), 1.66 (brs, 2H), 1.39 (brs, 2H), 1.23 (brs, 2H), 1.14 (brs, 2H).

Example 39: Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid (Example 39)



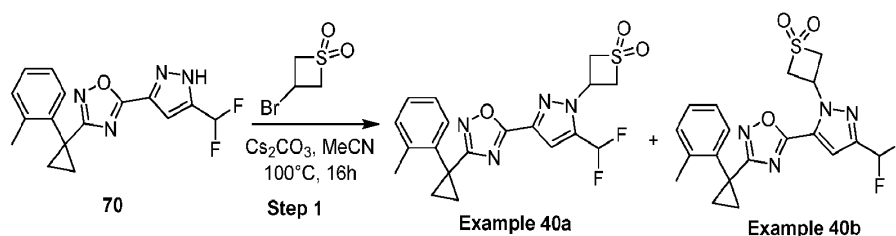
Scheme 26

[0805] Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid, Example 39 and 3-(3-(difluoromethyl)-5-(3-(1-(*o*-

tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid, Example 178 [Step 1]: To a stirred solution of 5-[5-(difluoromethyl)-1*H*-pyrazol-3-yl]-3-[1-(*o*-tolyl)cyclopropyl]-1,2,4-oxadiazole (220 mg, 0.7 mmol) in DMA (2 mL), Cs₂CO₃ (680 mg, 2.09 mmol) and 3-bromo-2,2-dimethylpropanoic acid (227 mg, 1.25 mmol) were added. Resulting reaction mixture was stirred at 90 °C for 16 h, diluted with ethyl acetate and washed with water followed by brine. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to give the first product as 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid, Peak 1 (Example 39, 29 mg) and the second product as 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid, Peak 2 (Example 178, 38 mg).

[0806] 3-(5-(Difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid (Example 39): LCMS (ESI) Calcd. for C₂₁H₂₂F₂N₄O₃: 416.2, found [M+H]⁺ = 417.3. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 12.67 (brs, 1H), 7.54-7.19 (m, 6H), 4.46 (s, 2H), 2.27 (s, 3H), 1.67- 1.65 (m, 2H), 1.40-1.37 (m, 2H), 1.13 (s, 6H).

Examples 40a & 40b: Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide (Example 40a) and 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide (Example 40b)



Scheme 27

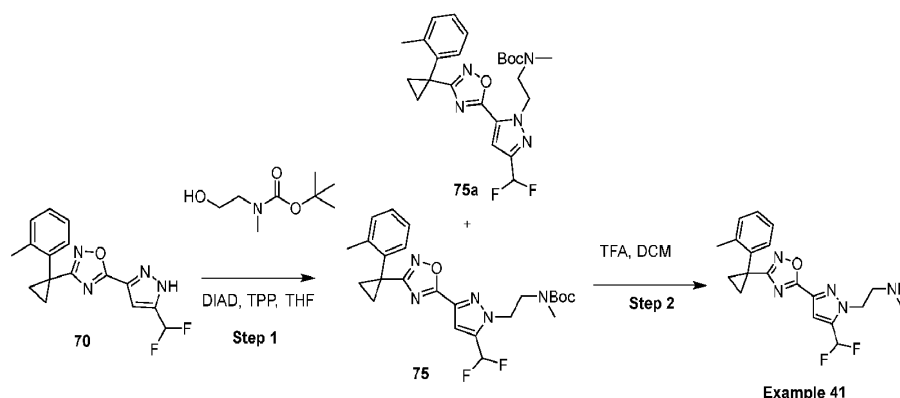
[0807] Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide, Example 40a & 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide, Example 40b [Step 1]: 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 200 mg, 0.6 mmol) in acetonitrile (2 mL), cesium carbonate (410 mg, 1.3 mmol) was added at 0 °C. After 15 min, 3-bromothietane 1,1-dioxide (290 mg, 1.6 mmol) was added to the reaction mixture and the reaction mixture was heated at 100 °C for 16 h. After completion, the mixture was diluted with water and partitioned with ethyl acetate. The combined organic layer was collected,

washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC to afford 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide (Example 40a, 25 mg) as peak 1 and 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide (Example 40b, 20 mg) as peak 2.

[0808] 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide, Example 40a [Peak-1]: LCMS (ESI) Calcd for $\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_4\text{O}_3\text{S}$: 420.1, found $[\text{M}+\text{H}]^+ = 421.1$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 7.53-7.20 (m, 6H), 5.65-5.61 (m, 1H), 4.84-4.82 (m, 4H), 2.27 (s, 3H), 1.68-1.67 (brs, 2H), 1.42-1.39 (brs, 2H).

[0809] 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide, Example 40b [Peak-2]: LCMS (ESI) Calcd for $\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_4\text{O}_3\text{S}$: 420.1, found $[\text{M}+\text{H}]^+ = 421.3$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$ at 100 $^\circ\text{C}$): δ_{H} 7.43-7.10 (m, 6H), 5.97 (brs, 1H), 4.85-4.74 (m, 4H), 2.33 (s, 3H), 1.77 (s, 2H), 1.45 (s, 2H).

Example 41: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylethan-1-amine (Example 41)



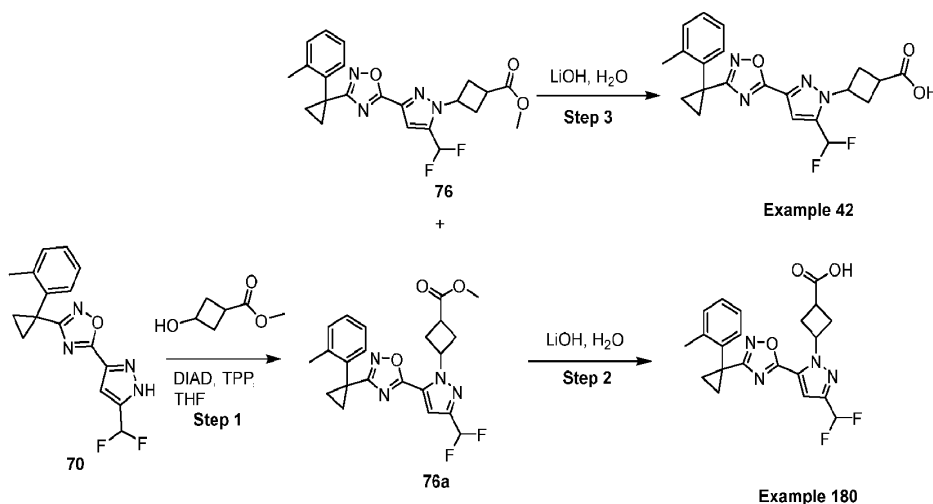
Scheme 28

[0810] Synthesis of *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate, 75 [Step 1]: To a stirred solution of triphenylphosphine (1.2g, 1.9 mmol) in THF (15 mL) and DIAD (383.6 mg, 1.9 mmol) at 0 $^\circ\text{C}$, 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 400 mg, 1.3 mmol) and *tert*-butyl (2-hydroxyethyl)(methyl)carbamate (332 mg, 1.9 mmol) were added. Resulting reaction mixture was allowed to stir at ambient temperature for 16 h and filtered through a celite pad. Combined filtrate was evaporated under reduced pressure. The product was purified by flash column chromatography to afford first product as *tert*-butyl (2-(3-

(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate (75a, 230 mg) and second product was *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate (75, 230 mg). LCMS (ESI) Calcd. for $C_{24}H_{29}F_2N_5O_3$: 473.2 found $[M+H]^+ = 474.2$. The structure of these regio-isomer was determined in the next step.

[0811] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylethan-1-amine, Example 41 [Step 2]: To a stirred solution of *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate (75, 230 mg, 0.5 mmol) in dichloromethane (10 mL), trifluoroacetic acid (114.0 mg, 2.4 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h and volatiles were reduced under reduced pressure. The product was purified by reverse phase preparative HPLC to give 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylethan-1-amine, (Example 41, 15 mg). LCMS (ESI) Calcd. for $C_{19}H_{21}F_2N_5O$: 373.17, found $[M+H]^+ = 374.2$, 1H NMR (400 MHz, DMSO- d_6) δ_H 7.52-7.720 (m, 6H), 4.37 (t, 2H), 2.91 (t, 2H), 2.26 (s, 6H), 1.66 (brs, 2H), 1. (brs, 2H). The structure was confirmed based on NOE experiment.

Example 42: Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylic acid (Example 42)



Scheme 29

[0812] Synthesis of methyl 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylate, 76a and methyl 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylate, 76 [Step 1]:

To a stirred solution of DIAD (330 mg, 1.9 mmol) in THF (15 mL) at 0 °C, triphenylphosphine (1.1 g, 1.9 mmol) was added. After 5 min., methyl 3-hydroxycyclobutanecarboxylate (247 mg, 1.9 mmol) and 5-[5-(difluoromethyl)-1*H*-pyrazol-3-yl]-3-[1-(*o*-tolyl)cyclopropyl]-1,2,4-oxadiazole (70, 400 mg, 1.3 mmol) was added and the resulting reaction mixture was stirred at ambient temperature for 12 h, filtered through a celite bed and combined filtrate was concentrated under reduced pressure. The products were purified by column chromatography to give the first product as methyl 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylate, Peak 1 (76a, 220 mg) and the second product as methyl 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylate, Peak 2 (76, 110 mg). The structure of regiomers were confirmed by NOE experiment.

[0813] Methyl 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylate, Peak 1 (**76a**): LCMS (ESI) Calcd. for C₂₂H₂₂F₂N₄O₃: 428.2, found [M+H]⁺ = 429.4.

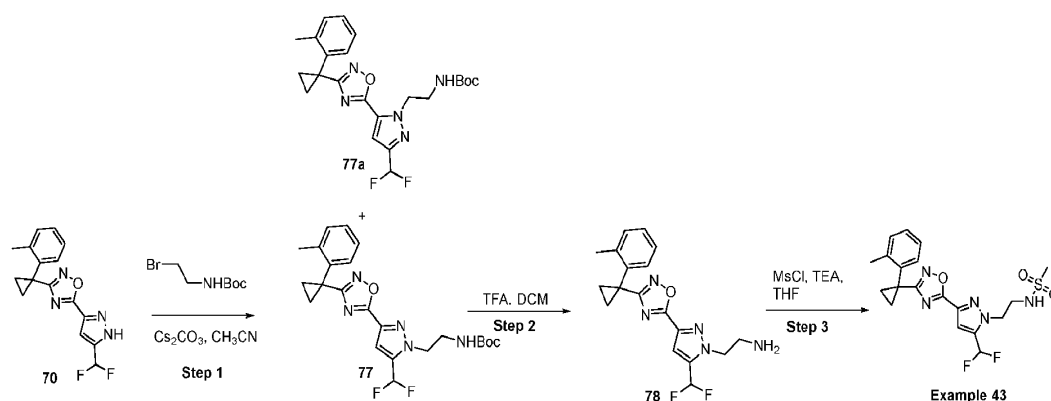
[0814] Methyl 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylate, Peak 2 (**76**): LCMS (ESI) Calcd. for C₂₂H₂₂F₂N₄O₃: 428.2, found [M+H]⁺ = 429.4.

[0815] Synthesis of 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylic acid, Example 180 [Step 2]: To a solution of methyl 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylate (76a, 220 mg, 0.5 mmol) in THF (2 mL), a solution of lithium hydroxide monohydrate (65 mg, 1.5 mmol) in water (2 mL) was added. The reaction mixture was stirred at 70 °C for 4 h and volatiles were evaporated under reduced pressure, acidified with 1(N) HCl, and extracted with ethyl acetate. Combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to give 3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylic acid (Example 180, 45 mg). LCMS (ESI) Calcd. for C₂₁H₂₀F₂N₄O₃: 414.1, found [M+H]⁺ = 415.2. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.39-7.00 (m, 6H), 5.79 (t, 1H), 3.11-3.07 (d, 1H), 2.85-2.78 (m, 2H), 2.67-2.63 (m, 2H), 2.30 (s, 3H), 1.71 (brs, 2H), 1.44 (brs, 2H). One acid proton is exchangeable.

[0816] Synthesis of 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylic acid, Example 42 [Step 3]: To a solution of methyl 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-

1-carboxylate (76, 100 mg, 0.2 mmol) in THF (2 mL), a solution of lithium hydroxide monohydrate (29 mg, 0.7 mmol) in water (2 mL) was added. The reaction mixture was stirred at 70 °C for 4 h and volatiles were evaporated under reduced pressure, acidified with 1(N) HCl, and extracted with ethyl acetate. Combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to give 3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)cyclobutane-1-carboxylic acid (Example 42, 25 mg). LCMS (ESI) Calcd. for C₂₁H₂₀F₂N₄O₃: 414.15, found [M+H]⁺ = 415.25. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.53-7.20 (m, 6H), 5.24-5.20 (m, 1H), 3.13-3.10 (m, 1H), 2.89-2.81 (m, 2H), 2.67-2.62 (m, 2H), 2.27 (s, 3H), 1.67 (brs, 2H), 1.40 (brs, 2H). One acid proton is exchangeable.

Example 43: Synthesis of N-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)methanesulfonamide (Example 43)



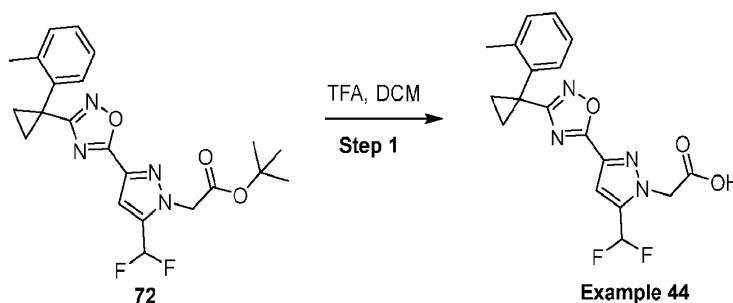
Scheme 30

[0817] Synthesis of ethyl *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)carbamate, 77 [Step 1]: To a stirred solution of 5-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1,2,4-oxadiazole (70, 340 mg, 1.0 mmol) in acetonitrile (15 mL) was added Cs₂CO₃ (1.0 g, 3.2 mmol) and *tert*-butyl (2-bromoethyl)carbamate (482 mg, 2.1 mmol). Resulting reaction mixture was allowed to stir at 80 °C for 16 h. The reaction mixture was diluted with ethyl acetate and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography to afford ethyl *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)carbamate (77, 170 mg). LCMS (ESI) Calcd. for C₂₃H₂₇F₂N₅O₃: 459.2, found [M+H]⁺ = 460.4. Note: Other regio-isomer (77a) was also formed.

[0818] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethan-1-amine, 78 [Step 2]: To a stirred solution of ethyl *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)carbamate (77, 170 mg, 0.37 mmol) in dichloromethane (5 mL), was added TFA (0.2 mL, 2.6 mmol). Resulting reaction mixture was stirred at ambient temperature for 16 h and volatiles were evaporated under reduced pressure to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethan-1-amine (78, 120 mg). The product was carried to next step without further purification. LCMS (ESI) Calcd. for $C_{18}H_{19}F_2N_5O$: 359.1, found $[M+H]^+ = 360.1$

[0819] Synthesis of *N*-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)methanesulfonamide, Example 43 [Step 3]: To a stirred solution of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethan-1-amine (78, 120 mg, 0.3 mmol) in THF (5 mL), triethylamine (0.13 mL, 19.7 mmol) and methanesulfonyl chloride (0.04 mL, 0.5 mmol) were added at 0 °C. Resulting reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate and washed with saturated solution of sodium bicarbonate followed by brine. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford *N*-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)methanesulfonamide (Example 43, 50 mg). LCMS (ESI) Calcd. for $C_{19}H_{21}F_2N_5O_3S$: 437.1, found $[M+H]^+ = 438.1$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.49-7.20 (m, 7H), 4.21(t, 2H), 3.44-3.42 (m, 2H), 2.87 (s, 3H), 2.32 (s, 3H), 1.67 (brs, 2H), 1.40 (brs, 2H).

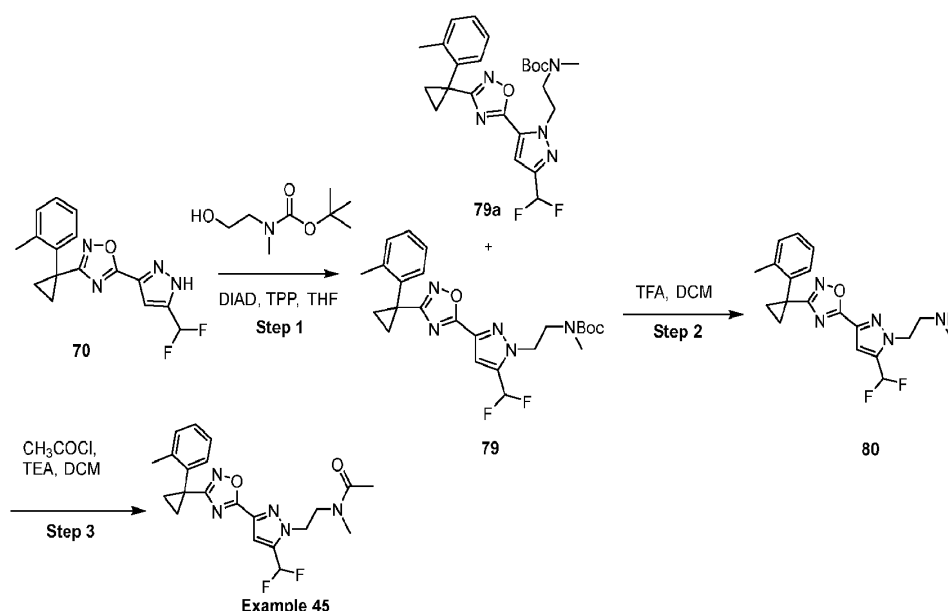
Example 44: Synthesis of 2-[5-(difluoromethyl)-3-[3-[1-(*o*-tolyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-1*H*-pyrazol-1-yl]acetic acid (Example 44)



Scheme 31

Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetic acid, Example 44 [Step 1]: To a stirred solution of *tert*-butyl 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetate (72, 200 mg, 0.5 mmol) in dichloromethane (10 mL), trifluoroacetic acid (0.36 mL, 4.7 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h and volatiles were reduced under reduced pressure. The product was purified by reverse phase preparative HPLC to give 2-[5-(difluoromethyl)-3-[3-(1-(*o*-tolyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-1*H*-pyrazol-1-yl]acetic acid (Example 44, 176 mg). LCMS (ESI) Calcd. For C₁₈H₁₆F₂N₄O₃: 374.1, found [M+H]⁺ = 375.2, ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.39-7.12 (m, 6H), 4.83 (brs, 2H), 2.27 (s, 3H), 1.67-1.65 (m, 2H), 1.39 (brs, 2H). One acid proton is exchangeable.

Example 45: Synthesis of N-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)-N-methylacetamide (Example 45)



Scheme 32

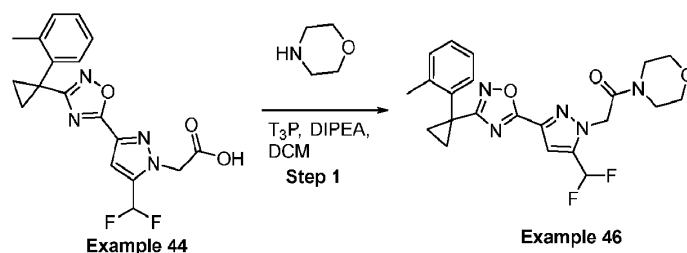
[0820] Synthesis of *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate, 79 [Step 1]: To a stirred solution of triphenylphosphine (1.2g, 1.9 mmol) in THF (15 mL) and DIAD (383.6 mg, 1.9 mmol) at 0 °C, 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 400 mg, 1.3 mmol) and *tert*-butyl (2-hydroxyethyl)(methyl)carbamate (332 mg, 1.9 mmol) were added. Resulting reaction mixture was allowed to stir at ambient temperature for 16 h and filtered through a celite pad. Combined filtrate was evaporated under reduced pressure. The product was purified by flash column chromatography to afford first product as *tert*-butyl (2-(3-

(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate (79a, 230 mg) and second product was *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate (79, 230 mg). LCMS (ESI) Calcd. for $C_{24}H_{29}F_2N_5O_3$: 473.2 found $[M+H]^+ = 474.2$. The structure of these regio-isomer was determined in the next step.

[0821] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylethan-1-amine, 80 [Step 2]: To a stirred solution of *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate (79, 230 mg, 0.5 mmol) in dichloromethane (10 mL), trifluoroacetic acid (114.0 mg, 2.4 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h and volatiles were reduced under reduced pressure. The product was purified by reverse phase preparative HPLC to give 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylethan-1-amine, (80, 15 mg). LCMS (ESI) Calcd. for $C_{19}H_{21}F_2N_5O$: 373.17, found $[M+H]^+ = 374.2$, 1H NMR (400 MHz, DMSO- d_6) δ_H 7.52-7.720 (m, 6H), 4.37 (t, 2H), 2.91 (t, 2H), 2.26 (s, 6H), 1.66 (brs, 2H), 1. (brs, 2H). The structure was confirmed based on NOE experiment.

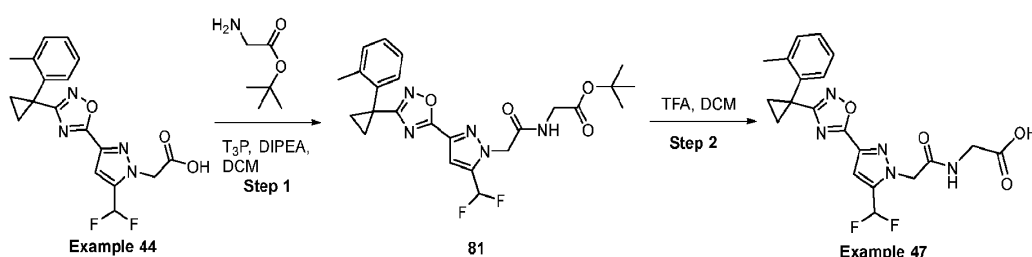
[0822] Synthesis of *N*-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)-*N*-methylacetamide, Example 45 [Step 3]: To a stirred solution of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-methylethan-1-amine (80, 250 mg, 0.7 mmol) in dichloromethane (10 mL) were added triethylamine (0.5 mL, 3.4 mmol) and acetyl chloride (0.14 mL, 2.0 mmol) was added at 0 °C. The reaction mixture was stirred at 25 °C for 6 h and volatiles were evaporated under reduced pressure. The product was purified by reverse phase preparative HPLC to give *N*-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethyl)-*N*-methylacetamide (Example 45, 24 mg). LCMS (ESI) Calcd. for $C_{21}H_{23}F_2N_5O_2$: 415.18, found $[M+H]^+ = 416.29$. 1H NMR (400 MHz, DMSO- d_6 at 100 °C) δ_H 7.44-7.17 (m, 6H), 4.48 (brs, 2H), 3.75 (brs, 2H), 2.82 (brs, 3H), 2.31 (s, 3H), 1.90 (s, 3H), 1.71-1.68 (m, 2H), 1.40-1.37 (m, 2H).

Example 46: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-morpholinoethan-1-one (Example 46)



[0823] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-1-morpholinoethan-1-one, Example 46 [Step 1]: To a stirred solution of 2-[5-(difluoromethyl)-3-[3-[1-(o-tolyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-1H-pyrazol-1-yl]acetic acid (Example 44, 120 mg, 0.321 mmol) in dichloromethane (10 mL) were added DIPEA (0.6 mL, 3.6 mmol) and propyl phosphonic anhydride (50% in ethyl acetate) (0.16 mL, 0.962 mmol). After 15 min, morpholine (2, 34.4 mg, 0.4 mmol) was added and the resulting reaction mixture was allowed to stir at ambient temperature for 16 h, diluted with dichloromethane and washed with saturated solution of sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by prep HPLC to give 2-[5-(difluoromethyl)-3-[3-[1-(o-tolyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]pyrazol-1-yl]-1-morpholinoethanone (Example 46, 42 mg). LCMS (ESI) Calcd. for $C_{22}H_{23}F_2N_5O_3$: 443.2 found $[M+H]^+ = 444.3$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.39-7.06 (m, 6H), 5.49 (s, 2H), 3.66 (t, 2H), 3.58 (t, 2H), 3.51 (t, 2H), 3.44 (t, 2H), 2.27 (s, 3H), 1.67-1.66 (m, 2H), 1.41-1.38 (brs, 2H).

Example 47: Synthesis of (2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetyl)glycine (Example 47)

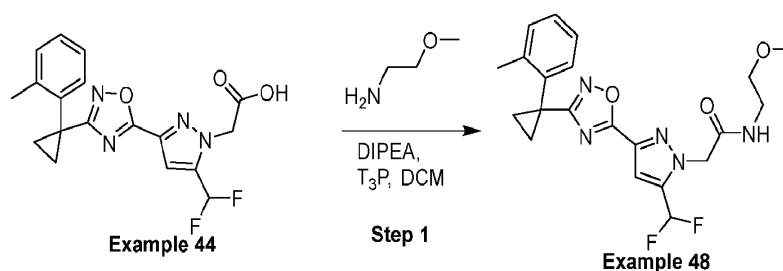


[0824] Synthesis of *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetyl)glycinate, 81 [Step 1]: To a stirred solution of 2-[5-(difluoromethyl)-3-[3-[1-(o-tolyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-1H-pyrazol-1-yl]acetic acid (Example 44, 220 mg, 0.6 mmol) in dichloromethane (15 mL) were added DIPEA (227 mg, 1.8 mmol) and propyl

phosphonic anhydride (50% in ethyl acetate) (0.45 mL, 1.5 mmol). After 15 min, *tert*-butyl glycinate (157 mg, 1.2 mmol) was added and the resulting reaction mixture was allowed to stir at ambient temperature for 16 h. The reaction mixture was diluted with dichloromethane, washed with saturated solution of sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to give *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)glycinate (81, 76 mg). LCMS (ESI) Calcd. for $C_{24}H_{27}F_2N_5O_4$: 487.2, found $[M+H]^+ = 488.4$.

[0825] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)glycine, Example 47 [Step 2]: To a stirred solution of *tert*-butyl (2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)glycinate (81, 60 mg, 0.1 mmol) in dichloromethane (5 mL), trifluoroacetic acid (1 mL, 13.0 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h and volatiles were reduced under reduced pressure. The product was purified by reverse phase preparative HPLC to give 2-[[2-[5-(difluoromethyl)-3-[3-[1-(*o*-tolyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]pyrazol-1-yl]acetyl]amino]acetic acid (Example 47, 37 mg.). LCMS (ESI) Calcd. for $C_{20}H_{19}F_2N_5O_4$: 431.1, found $[M+H]^+ = 432.2$. 1H NMR (400 MHz, DMSO- d_6): δ_H 12.80 (brs, 1H), 8.64 (brs, 1H) 7.41-7.14 (m, 6H), 5.17 (s, 2H), 3.81 (s, 2H), 2.26 (s, 3H), 1.66 (brs, 2H), 1.39 (brs, 2H).

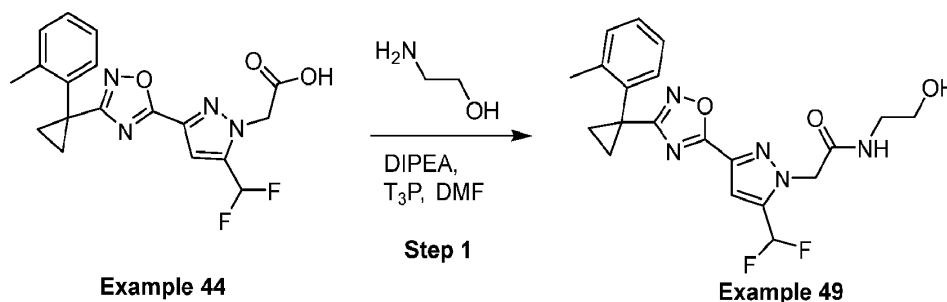
Example 48: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-N-(2-methoxyethyl)acetamide (Example 48)



[0826] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-N-(2-methoxyethyl)acetamide, Example 48 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetic acid (Example 44, 70 mg, 0.18 mmol) in dichloromethane (3 mL), *N,N*-diisopropylethylamine (0.10

mL, 0.56 mmol) and propane phosphonic acid anhydride (50% in ethyl acetate) (0.08 mL, 0.28 mmol) were added. After 15 min, 2-methoxyethan-1-amine (17 mg, 0.22 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h, diluted with dichloromethane, washed with saturated solution of aqueous sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-(2-methoxyethyl)acetamide (Example 48, 20 mg). LCMS (ESI) Calcd. for $C_{21}H_{23}F_2N_5O_3$: 431.2, found $[M + H]^+ = 432.3$, 1H NMR (400 MHz, $DMSO-d_6$): δ_H 8.44 (t, 1H), 7.41-7.14 (m, 6H), 5.09 (s, 2H), 3.38-3.35 (m, 2H), 3.32-3.26 (m, 5H), 2.26 (s, 3H), 1.66 (brs, 2H), 1.39 (brs, 2H).

Example 49: Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-(2-hydroxyethyl)acetamide (Example 49)

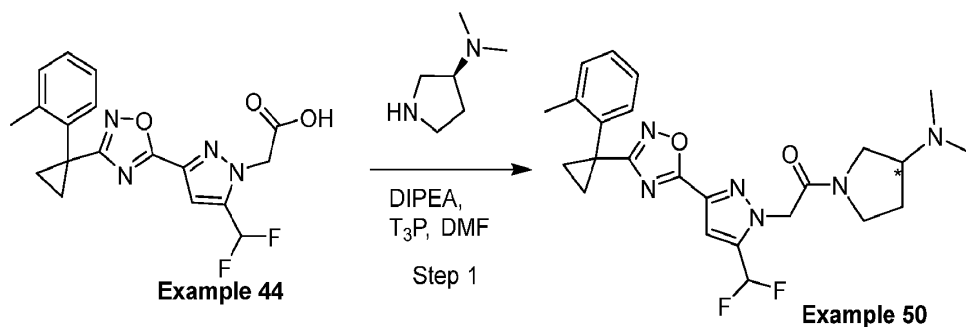


Scheme 36

[0827] Synthesis of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-(2-hydroxyethyl)acetamide, Example 49 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetic acid (Example 44, 120 mg, 0.3 mmol) in *N,N*-dimethylformamide (2 mL), *N,N*-diisopropylethylamine (0.2 mL, 1.0 mmol) and T_3P (0.1 mL, 0.5 mmol, 50% in ethyl acetate) were added. After 15 min, 2-aminoethan-1-ol (0.04 mL, 0.6 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate, washed with ice cold water followed by brine. Combined organic extracts was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-*N*-(2-hydroxyethyl)acetamide (Example 49, 20 mg). LCMS (ESI) Calcd. for $C_{20}H_{21}F_2N_5O_3$: 417.2, found $[M+H]^+ = 418.3$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 8.36 (t, 1H), 7.41-7.14 (m, 6H), 5.09 (s,

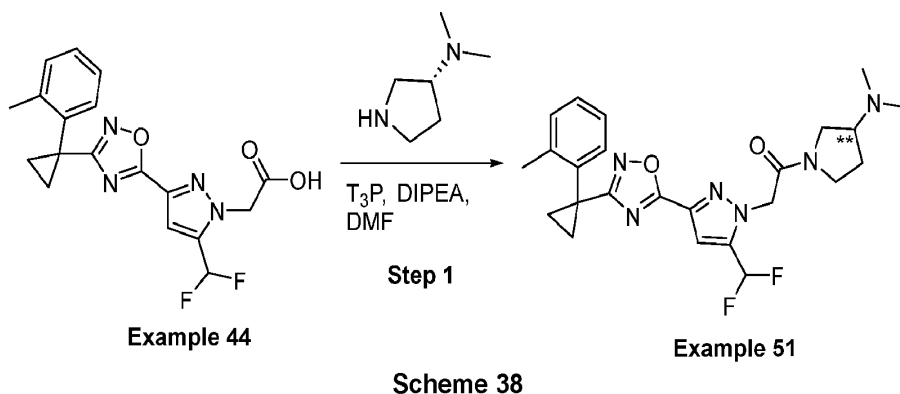
2H), 4.75 (t, 1H), 3.45-3.40 (m, 2H), 3.18-3.14 (m, 2H), 2.26 (s, 3H) 1.68-1.65 (m, 2H), 1.41-1.38 (m, 2H).

Example 50: Synthesis of (S)-2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-1-(3-(dimethylamino)pyrrolidin-1-yl)ethan-1-one (Example 50)



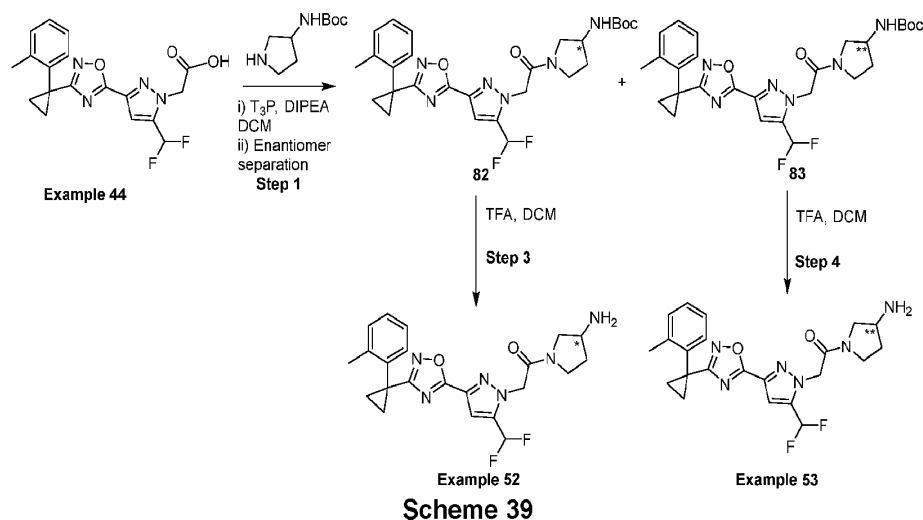
[0828] Synthesis of (S)-2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-N-(2-hydroxyethyl)acetamide, Example 50 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)acetic acid (Example 44, 100 mg, 0.3 mmol) in *N,N*-dimethylformamide (2 mL), *N,N*-diisopropylethylamine (0.1 mL, 0.8 mmol) and T₃P (0.1 mL, 0.4 mmol, 50% in ethyl acetate) were added. After 15 min, (S)-*N,N*-dimethylpyrrolidin-3-amine (60 mg, 0.5 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h, diluted with ethylacetate, washed with ice cold water followed by brine. Combined organic extract were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford (S)-2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-1-(3-(dimethylamino)pyrrolidin-1-yl)ethan-1-one (Example 50, 36 mg). LCMS (ESI) Calcd. for C₂₄H₂₈F₂N₆O₂: 470.2, found [M+H]⁺ = 471.2. ¹H NMR (400 MHz, DMSO-*d*₆, 100 °C) δ_H 7.40-7.38 (m, 1H), 7.32-7.06 (m, 5H), 5.31 (brs, 2H), 3.78-3.71 (m, 1H), 3.56-3.52 (m, 1H), 3.32 (m, 1H), 2.88-2.86 (m, 1H), 2.76 (m, 1H), 2.30 (m, 3H), 2.22-2.13 (m, 6H), 2.03-2.00 (m, 1H), 1.87 (m, 1H), 1.69 (m, 2H), 1.39 (m, 2H).

Example 51: Synthesis of (R)-2-(5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-1-(3-(dimethylamino)pyrrolidin-1-yl)ethan-1-one (Example 51)



[0829] Synthesis of (*R*)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-(3-(dimethylamino)pyrrolidin-1-yl)ethan-1-one, Example 51 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetic acid (Example 44, 100 mg, 0.3 mmol) in DMF (2 mL), DIPEA (0.13 mL, 0.8 mmol) and propane phosphonic acid anhydride (50% in ethyl acetate) (0.12 mL, 0.40 mmol) were added. After 15 mins, (*R*)-*N,N*-dimethylpyrrolidin-3-amine (30 mg, 0.3 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h, diluted with dichloromethane, washed with saturated solution of sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC method to afford (*R*)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-(3-(dimethylamino)pyrrolidin-1-yl)ethan-1-one (Example 51, 38 mg). LCMS (ESI) Calcd. for C₂₄H₂₈F₂N₆O₂: 470.2, found [M+H]⁺ = 471.2. ¹H NMR (400 MHz, DMSO-*d*₆ at 100 °C): 7.40-7.05 (m, 6H), 5.34-5.31 (m, 2H), 3.78-3.72 (m, 1H), 3.55-3.50 (m, 1H), 3.36-3.31 (m, 1H), 2.91-2.87 (m, 1H), 2.76-2.72 (m, 1H), 2.30 (m, 3H), 2.22-2.12 (m, 6H), 2.02 (m, 1H), 1.89-1.86 (m, 1H), 1.69 (m, 2H), 1.39 (m, 2H).

Example 52 & Example 53: Synthesis of (*S*)-1-(3-(aminopyrrolidin-1-yl)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethan-1-one (Example 52 & Example 53)



[0830] Synthesis of *tert*-butyl (S)-(1-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate, 83 and *tert*-butyl (S)-(1-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate, 83 [Step 1]: To a stirred solution of 2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetic acid (Example 44, 300 mg, 0.8 mmol) in DMF (5 mL), DIPEA (0.42 mL, 2.4 mmol) and propane phosphonic acid anhydride (50% in ethyl acetate) (0.48 mL, 1.6 mmol) were added. After 15 min, *tert*-butyl pyrrolidin-3-ylcarbamate (299 mg, 1.6 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate, washed with ice cold water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford *tert*-butyl (1-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate (380 mg). The enantiomers were separated by normal phase chiral HPLC to afford the first product as *tert*-butyl (S)-(1-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate, Peak 1 (82, 150 mg) and the second product as *tert*-butyl (*R*)-(1-(2-(5-(difluoromethyl)-3-(3-(1-phenylcyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate, Peak 2 (83, 150 mg). The absolute stereochemistries of these compounds were not determined.

[0831] *tert*-butyl (S)-(1-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate, Peak 1 (82): LCMS (ESI) Calcd. for $C_{27}H_{32}F_2N_6O_4$: 542.2, found $[M+H]^+ = 543.3$,

[0832] *tert*-butyl (R)-(1-(2-(5-(difluoromethyl)-3-(3-(1-phenylcyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate, Peak 2 (83): LCMS (ESI) Calcd. for $C_{27}H_{32}F_2N_6O_4$: 542.2, found $[M+H]^+ = 543.4$.

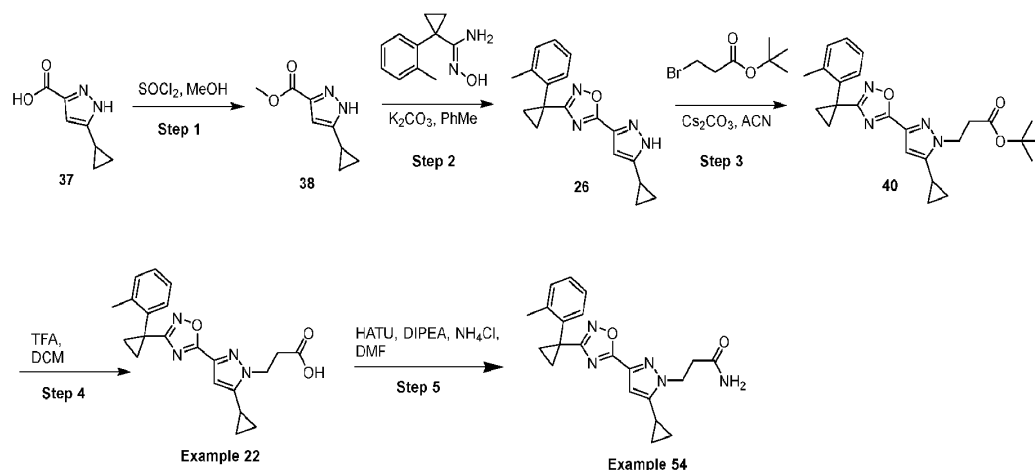
[0833] Chiral HPLC method: Chiral separation was performed on an Agilent 1200 series instrument. Column: CHIRALPAK IC (250 X 20 mm) 5 μ , operating at ambient temperature with a flow rate of 18.0 mL/min. Mobile phase: 70% Hexane, 15% EtOH and 15% dichloromethane, held isocratic mixture up to 16 min at a wavelength of 250 nm.

[0834] Synthesis of (S)-1-(3-aminopyrrolidin-1-yl)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethan-1-one, Example 52, [Step 3]: To a stirred solution of *tert*-butyl (S)-(1-(2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate (82, 150 mg, 0.3 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1.0 mL, 13.1 mmol) at 0 °C. The resulting reaction mixture was allowed to stir at ambient temperature for 2 h and volatiles were evaporated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford (S)-1-(3-aminopyrrolidin-1-yl)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethan-1-one (Example 52, 47 mg). LCMS (ESI) Calcd. for $C_{22}H_{24}F_2N_6O_2$: 442.19, found $[M+H]^+ = 443.20$. 1H NMR (400 MHz, DMSO- d_6 and 2 drops of D_2O): δ_H 7.37-7.35 (m, 1H), 7.32-7.05 (m, 5H), 5.30-5.27 (m, 2H), 3.62-3.31 (m, 4H), 3.15-3.06 (m, 1H), 2.24 (s, 3H), 2.08-1.97 (m, 1H), 1.72-1.60 (m, 3H), 1.39-1.36 (m, 2H). Two amine protons are exchangeable.

[0835] Synthesis of (R)-1-(3-aminopyrrolidin-1-yl)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethan-1-one, Example 53 [Step 4]: To a stirred solution of *tert*-butyl (R)-(1-(2-(5-(difluoromethyl)-3-(3-(1-phenylcyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)acetyl)pyrrolidin-3-yl)carbamate (83, 150 mg, 0.3 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1.0 mL, 13.1 mmol) at 0 °C. The resulting reaction mixture was allowed to stir at ambient temperature for 2 h and volatiles were evaporated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford (R)-1-(3-aminopyrrolidin-1-yl)-2-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)ethan-1-one (Example 53, 48 mg). LCMS (ESI) Calcd. for $C_{22}H_{24}F_2N_6O_2$: 442.19, found $[M+H]^+ = 443.20$. 7.37-7.35 (m, 1H), 7.32-7.05 (m, 5H), 5.30-5.27

(m, 2H), 3.62-3.31 (m, 4H), 3.15-3.06 (m, 1H), 2.24 (s, 3H), 2.08-1.97 (m, 1H), 1.72-1.60 (m, 3H), 1.39-1.36 (m, 2H). Two amine protons are exchangeable.

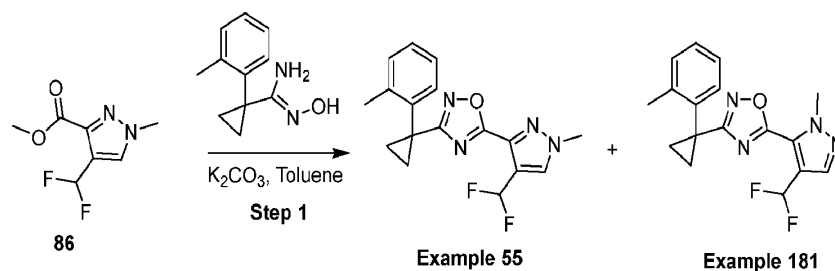
Example 54: Synthesis of 3-(5-cyclopropyl-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propenamide (Example 54)



Scheme 40

[0836] Synthesis of 3-(5-cyclopropyl-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propenamide, Example 54 [Step 5]: To a stirred solution of 3-(5-cyclopropyl-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propanoic acid (Example 22, 60 mg, 0.16 mmol) in DMF (3 mL), were added HATU (90 mg, 0.24 mmol), DIPEA (0.14 mL, 0.8 mmol) and ammonium chloride (25 mg, 0.5 mmol). The reaction mixture was stirred at ambient temperature for 14 h, diluted ethyl acetate and washed with water followed by brine. Combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford 3-(5-cyclopropyl-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)propenamide (Example 54, 47 mg). LCMS (ESI) Calcd. for $C_{21}H_{23}N_5O_2$: 377.19, found $[M+H]^+ = 378.10$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.44 (brs, 1H), 7.37 (d, 1H), 7.23-7.19 (m, 3H), 6.92 (brs, 1H), 6.55 (s, 1H), 4.44 (t, 2H), 2.70 (t, 2H), 2.25 (s, 3H), 2.04 (brs, 1H), 1.64-1.61 (m, 2H), 1.37-1.35 (m, 2H), 0.99-0.96 (m, 2H), 0.76-0.73 (m, 2H).

Examples 55a & 55b: Synthesis of 5-(4-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 55a) and 5-(4-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 55b)



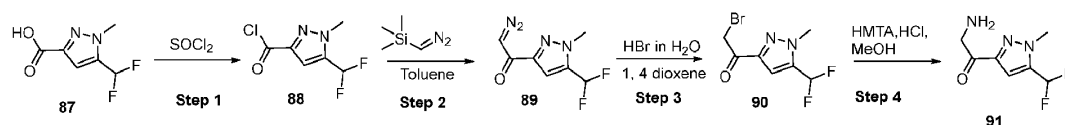
Scheme 41

[0837] Synthesis of 5-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole & 5-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 55a and Example 55b [Step 1]: To a stirred solution of methyl 4-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylate (86, 200 mg, 1 mmol) (along with other regioisomer) in toluene (2 mL), K_2CO_3 (270 mg, 2.0 mmol) and *N*-hydroxy-1-(*o*-tolyl)cyclopropanecarboxamidine (180 mg, 1.0 mmol) were added and reaction mixture was allowed to stir at 90 °C for 16 h. After completion the reaction mixture was diluted with ethyl acetate and partitioned with water. Combined organic layer was dried over anhydrous Na_2SO_4 , filtered, concentrated under reduced pressure. The product was purified and separated by reverse phase prep-HPLC to afford 5-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 55a, 65 mg) as peak 1 and 5-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 55b, 90 mg) as peak 2.

[0838] Analytical data of 5-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 55a: LCMS (ESI) Calcd for $C_{17}H_{16}F_2N_4O$: 330.3, found $[M+H]^+ = 331.0$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 8.39 (s, 1H), 7.41-7.13 (m, 5H), 4.00 (s, 3H), 2.27 (s, 3H), 1.69-1.66 (m, 2H), 1.41-1.38 (m, 2H).

[0839] Analytical data of 5-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 55b: LCMS (ESI) Calcd for $C_{17}H_{16}F_2N_4O$: 330.3, found $[M+H]^+ = 331.0$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.97 (s, 1H), 7.38 (d, 1H), 7.27-7.11 (m, 4H), 4.18 (s, 3H), 2.30 (s, 3H), 1.73-1.70 (m, 2H), 1.45-1.42 (s, 2H). Note: The exact structure of peak 1 & peak 2 was confirmed by NOE experiments.

Example 56: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-2-(1-(*o*-tolyl)cyclopropyl)oxazole (Example 56)



Scheme 42

[0840] Synthesis of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl chloride, 88 [Step 1]:

To a stirred solution of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxylic acid (87, 140 mg, 0.8 mmol) in SOCl_2 (5.0 mL, 70 mmol) was heated at 60 °C added and stirred for 2 h. After completion volatiles was evaporated under reduced pressure to afford 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl chloride (88, 150 mg) which was confirmed in next step.

[0841] Synthesis of 2-diazo-1-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)ethan-1-one, 89

[Step 2]: To a solution of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl chloride (88, 150 mg, 0.8 mmol) in Toluene (2 mL), (Trimethylsilyl)diazomethane (2M in hexane) (2.0 mL, 4 mmol) was added dropwise at 0 °C. The reaction was stirred at ambient temperature for 16 h. Reaction mixture was directly forwarded to next step. LCMS Calcd. for $\text{C}_7\text{H}_6\text{F}_2\text{N}_4\text{O}$: [M] = 200.15, found $[\text{M}+\text{H}]^+ = 201.2$.

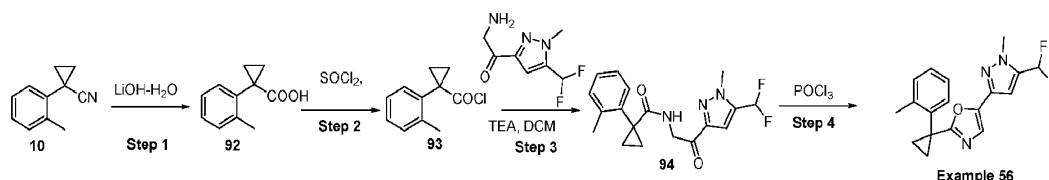
[0842] Synthesis of 2-bromo-1-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)ethan-1-one, 90

[Step 3]: To a stirred solution of 2-diazo-1-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)ethan-1-one (150 mg, 0.8 mmol) in 1,4-Dioxane (2mL), HBr in H_2O (48%) (1.0 mL, 20 mmol) was added slowly at 0 °C and stirred for 1 h at ambient temperature. The reaction was concentrated to dryness and the residue was taken up in EtOAc and the organic extracts were washed with water then saturated brine solution. The organic extracts were then separated and dried (MgSO_4) under reduced pressure which was purified by flash column chromatography to afford 2-bromo-1-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)ethan-1-one (90, 190 mg). LCMS Calcd. for $\text{C}_7\text{H}_7\text{BrF}_2\text{N}_2\text{O}$: [M] = 253, found $[\text{M}+\text{H}]^+ = 255$.

Synthesis of 2-amino-1-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)ethan-1-one, 91 [Step 4]:

To a solution of 2-bromo-1-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)ethan-1-one (150 mg, 0.6 mmol) in Chloroform (2 mL), Hexamethylenetetramine (0.06 mL, 1 mmol) was added and stirred for 4 hours at ambient temperature. The reaction mixture was filtered through celite bed to afford the precipitated hexamine adduct. The adduct was then heated with Methanol (4 mL) and Conc. HCl (0.40 mL) for 16 h under reflux. The reaction mixture was cooled, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford 2-amino-1-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)ethan-1-one (91, 200 mg). LCMS Calcd. For $\text{C}_7\text{H}_9\text{F}_2\text{N}_3\text{O}$: [M] = 189.16, found $[\text{M}+\text{H}]^+ = 190.1$.

Example 56: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-2-(1-(o-tolyl)cyclopropyl)oxazole (Example 56)



Scheme 43

[0843] Synthesis of 1-(o-tolyl)cyclopropane-1-carboxylic acid, 92 [Step 1]: To a stirred solution of 1-(o-tolyl)cyclopropane-1-carbonitrile (10, 1.00 g, 6 mmol) in 4M LiOH·H₂O aq. solution (8.0 mL, 25 mmol) was refluxed at 100 °C for 24h with continue stirring. Reaction mixture was cooled at 0 °C, washed with ethyl acetate and aqueous layer was acidified by 5N HCl solution and extracted with ethyl acetate (thrice). Organic layer was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-(o-tolyl)cyclopropane-1-carboxylic acid (92, 600 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 12.19 (brs, 1H), 7.21-7.08 (m, 4H), 2.27 (s, 3H), 1.50 (d, 2H), 1.10-1.08 (m, 2H). Notes: Extra peak present in ¹H NMR.

[0844] Synthesis of 1-(o-tolyl)cyclopropane-1-carboxylic chloride, 93 [Step 2]: A stirred solution of 1-(o-tolyl)cyclopropane-1-carboxylic acid (92, 350 mg, 2 mmol) in SOCl₂ (6 mL, 80 mmol) was heated at 60 °C added and stirred for 2 h. After completion volatiles was evaporated under reduced pressure to afford 1-(o-tolyl)cyclopropanecarbonyl chloride (93, 350 mg) which was confirmed in next step.

[0845] Synthesis of N-(2-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-2-oxoethyl)-1-(o-tolyl)cyclopropane-1-carboxamide, 94 [Step 3]: To a stirred solution of 1-(o-tolyl)cyclopropane-1-carboxylic chloride (200 mg, 1.2 mmol) in 1,2 dichloromethane (4mL), triethyl amine (0.4 mL, 3 mmol) in 1,2 dichloromethane (2 ml) and 2-amino-1-[5-(difluoromethyl)-1-methyl-pyrazol-3-yl]ethanone (230 mg, 1.2 mmol) in 1,2 dichloromethane(2 ml) was added portionwise at 0 °C. The reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was concentrated under reduced pressure, diluted with water and extracted with 1,2 dichloromethane. The organic extracts were then separated and under reduced pressure. The product was purified by reverse phase prep HPLC purification to afford N-(2-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-2-oxoethyl)-1-(o-tolyl)cyclopropane-1-carboxamide (94, 120 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.44-6.81 (m, 7H), 4.39 (d, 2H), 3.99 (s, 3H), 2.39 (s, 3H), 1.42

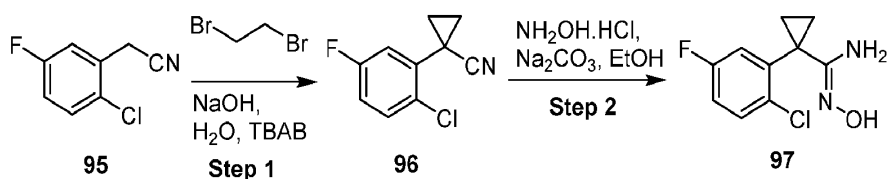
(d, 2H), 0.97 (d, 2H). LC/MS: calculated for $C_{18}H_{19}F_2N_3O_2$ [M]: 347.36, found $[M+H]^+$: 348.

Notes: 15mg of compound shipped. Rest amount were forwarded to next step.

[0846] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-2-(1-(o-tolyl)cyclopropyl)oxazole, Example 56 [Step 4]: In a round bottom flask, POCl₃ (1.5 mL, 15 mmol) was added in a stirred solution of N-(2-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-2-oxoethyl)-1-(o-tolyl)cyclopropane-1-carboxamide (94, 100 mg, 0.3 mmol) at 0 °C. The resulting reaction mixture was stirred for 16 h at 100 °C. The reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The organic extracts were then separated and dried under reduced pressure. The product was purified by reverse phase prep HPLC purification to afford 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-2-(1-(o-tolyl)cyclopropyl)oxazole (Example 56, 30 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.44-6.81 (m, 7H), 3.90 (s, 3H), 2.24 (s, 3H), 1.67-1.65 (m, 2H), 1.36-1.33 (m, 2H). LC/MS: calculated for C₁₈H₁₇F₂N₃O [M]: 329.34, found [M+H]⁺: 330.2.

Examples 57-64:

Synthesis of (Z)-1-(2-chloro-5-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide,
97



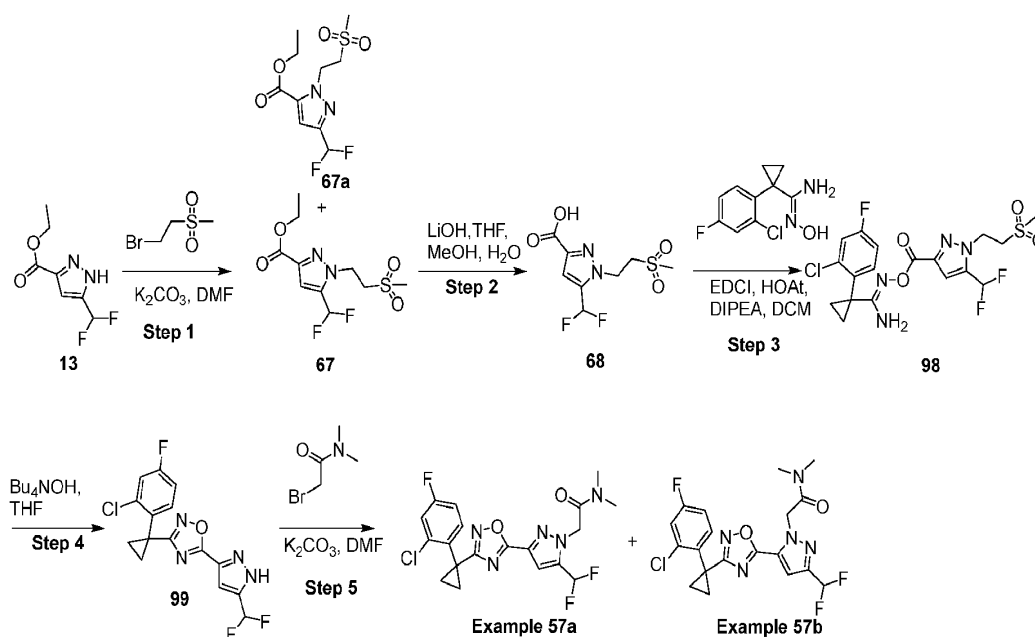
Scheme 44

[0847] Synthesis of 1-(2-chloro-5-fluorophenyl)cyclopropane-1-carbonitrile, 96 [Step 1]: To a stirred solution of NaOH (1.4 g, 35.4 mmol) in water (5 mL), 2-(2-chloro-5-fluorophenyl)acetonitrile (95, 500 mg, 3.0 mmol), TBAB (190 mg, 0.6 mmol) and 1,2-dibromoethane (2.2 mL, 14.7 mmol) were added and the reaction mixture was heated at 60 °C for 12h. After completion, the reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-(2-chloro-5-fluorophenyl)cyclopropane-1-carbonitrile (96, 510 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.63-7.59 (m, 1H), 7.50-7.47 (m, 1H), 7.34-7.29 (m, 1H), 1.99-1.69 (m, 2H), 1.52-1.41 (m, 2H).

[0848] Synthesis of (Z)-1-(2-chloro-5-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide, 97 [Step 2]: To a stirred solution of 1-(2-chloro-5-fluorophenyl)cyclopropane-1-carbonitrile (96, 500 mg, 2.6 mmol) in ethanol (2 5mL), sodium carbonate (540 mg, 5.1 mmol) and

hydroxylamine hydrochloride (355 mg, 5.1 mmol) were added and the reaction was heated at 70 °C for 12h. After completion, the volatiles were evaporated under reduced pressure, diluted with ethyl acetate and washed with water and brine. Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-1-(2-chloro-5-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (97, 550 mg). LCMS (ESI) Calcd for C₁₀H₁₀ClFN₂O: 228.6, found [M+H]⁺ = 229.2.

Examples 57a & 57b: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 57a)



Scheme 45

[0849] Synthesis of ethyl 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylate, 67 [Step 1]: To a stirred suspension of ethyl 5-(difluoromethyl)-1H-pyrazole-3-carboxylate (13, 1 g, 5.3 mmol) and potassium carbonate (2.9 g, 21.03 mmol) in dimethylformamide (60 mL) at 0 °C, 1-bromo-2-(methylsulfonyl)ethane (1.48 g, 7.89 mmol) was added. The resulting reaction mixture was allowed to stir at ambient temperature for 16 h, diluted with ethyl acetate and washed with ice-cold water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford ethyl 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylate (67, 420 mg). LCMS (ESI) calcd. for C₁₀H₁₄F₂N₂O₄S: 296.0 found [M+H]⁺ = 297.0, ¹H NMR (400 MHz, DMSO-

d_6): δ_H 7.38 (t, 1H), 7.09 (s, 1H), 4.70 (t, 2H), 4.32-4.27 (m, 2H), 3.78-3.74 (m, 2H), 3.07 (s, 3H), 1.29 (t, 3H). Note: Structure was confirmed based NOE experiment on compound 67a.

[0850] Synthesis of 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylic acid, 68 [Step 2]: To a cold solution of ethyl 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylate (67, 420 mg, 1.42 mmol) in tetrahydrofuran (6 mL) and methanol (1 mL), a solution of lithium hydroxide (119 mg, 2.84 mmol) in water (2 mL) was added drop-wise. The reaction mixture was stirred at ambient temperature for 16 h and volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous solution of hydrochloric acid to ~pH-5 and extracted with a mixture of dichloromethane and isopropyl alcohol (9:1). Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylic acid (68, 350 mg). The product was carried to next step without further purification. LCMS (ESI) Calcd. for $C_8H_{10}F_2N_2O_4S$: 268.03 found $[M+H]^+ = 269.09$.

[0851] Synthesis of (Z)-1-(4-chloro-2-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 98 [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylic acid (68, 600 mg, 2.2 mmol), and (Z)-1-(2-chloro-4-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (565 mg, 2.5 mmol) in dichloromethane (10 mL), *N,N*-diisopropylethylamine (1.9 mL, 11.2 mmol), 1-hydroxy-7-azabenzotriazole (60 mg, 0.5 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (645 mg, 3.4 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-1-(4-chloro-2-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (98, 500 mg). LCMS (ESI) Calcd. for $C_{18}H_{18}ClF_3N_4O_4S$: 478.1, found $[M+H]^+ = 479.1$.

[0852] Synthesis of 3-(1-(4-chloro-2-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 99 [Step 4]: To a stirred solution of (Z)-1-(4-chloro-2-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (98, 450 mg, 0.9 mmol) in tetrahydrofuran (8 mL), tetra butyl ammonium hydroxide (1.9 mL, 1.9 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 12 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over

anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 3-(1-(4-chloro-2-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (99, 250 mg). LCMS (ESI) Calcd. for C₁₅H₁₀ClF₃N₄O: 354.1, found [M+H]⁺ = 354.8.

[0853] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide, Example 57a [Step 5]: To a stirred suspension of 3-(1-(4-chloro-2-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (99, 130 mg, 0.4 mmol) and potassium carbonate (100 mg, 0.7 mmol) in THF (2 mL) at 0 °C, 2-bromo-*N,N*-dimethylacetamide (73 mg, 0.4 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with ice-cold water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product were purified by reverse phase prep HPLC to afford 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N,N*-dimethylacetamide (Example 57a, 35 mg). LCMS (ESI) Calcd. for C₁₉H₁₇ClF₃N₅O₂: 439.1, found [M+H]⁺ = 440.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.65-7.61 (m, 1H), 7.51-7.48 (dd, 1H), 7.34-7.08 (m, 3H), 5.44 (s, 2H), 3.05 (s, 3H), 2.86 (s, 3H), 1.73-1.70 (m, 2H), 1.49-1.46(m, 2H). Note: Example 57b was isolated as other regio-isomer.

[0854] Examples 58-64 were synthesized in a manner similar to Example 57 from the corresponding pyrazole carboxylic acid.

Example 58: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Examples 58)

[0855] 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 45 using 1-bromo-2-(methylsulfonyl)ethane. LCMS (ESI) Calcd. for C₁₈H₁₆ClF₃N₄O₃S: 460.1, found [M+H]⁺ = 461.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.65-7.61 (m, 1H), 7.55-7.42 (m, 2H), 7.32 (s, 1H), 7.29-7.23 (m, 1H), 4.78-4.74 (m, 2H), 3.82-3.78 (m, 2H), 3.06 (s, 3H), 1.71 (s, 2H), 1.48 (s, 2H).

Examples 59 & 60: Synthesis of (S)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide, (Example 59) and (R)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide (Example 60)

[0856] (S)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide and (R)-2-(3-(3-(1-(2-chloro-4-

fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide were synthesized following Scheme 45 using 2-bromopropanamide. The absolute stereochemistries were not determined and was arbitrarily assigned.

[0857] (S)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide, Example 59 (Peak 1): LCMS (ESI) Calcd. for $C_{18}H_{15}ClF_3N_5O_2$: 425.7, found $[M+H]^+$ = 426.2. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.63-7.25 (m, 7H), 5.26 (s, 1H), 1.73 (d, 5H), 1.47 (s, 2H).

[0858] (R)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanamide, Example 60 (Peak 2): LCMS (ESI) Calcd. for $C_{18}H_{15}ClF_3N_5O_2$: 425.7, found $[M+H]^+$ = 426.2. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.65-7.61 (m, 1H), 7.50-7.25 (m, 6H), 5.26 (d, 1H), 1.73 (d, 5H), 1.47 (s, 2H).

[0859] Chiral Prep HPLC method: HPLC SFC prep purification was performed on Pic Solution 175 instrument equipped with Knauer UV Detector 40D by using Chiralcel-*OX*-H (21.0 mm x 250 mm), 5 μ Column operating at 35 °C temperature, maintaining flow rate of 70 ml/min, using 80% CO₂ in super critical state & 20% of 100% methanol as mobile phase. Run this isocratic mixture up to 10 minutes and also maintained the isobaric condition of 100 bar at 254 nm wavelength.

Example 61: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(3-(methylsulfonyl)propyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 61)

[0860] 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(3-(methylsulfonyl)propyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 61) was synthesized following Scheme 45 using 1-bromo-3-(methylsulfonyl)propane. LCMS (ESI) Calcd. for $C_{19}H_{18}ClF_3N_4O_3S$: 474.1, found $[M+H]^+$ = 475.1. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.64-7.61 (m, 1H), 7.53-7.48 (m, 1H), 7.40-7.23 (m, 3H), 4.49-4.45 (t, 2H), 3.20-3.17 (t, 2H), 2.99 (s, 3H), 2.33-2.22 (m, 2H), 1.72 (brs, 2H), 1.47 (brs, 2H).

Example 62: Synthesis of 3-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide (Example 62)

[0861] 3-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)thietane 1,1-dioxide (Example 62) was synthesized following Scheme 45 using 3-bromothietane 1,1-dioxide. LCMS (ESI) Calcd for $C_{18}H_{14}ClF_3N_4O_3S$: 458.0, found $[M+H]^+$ = 459.0. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.65-7.61 (m, 1H), 7.53-7.24 (m, 4H), 5.65-5.61 (m, 1H), 4.84-4.82 (m, 4H), 1.73 (s, 2H), 1.48 (s, 2H).

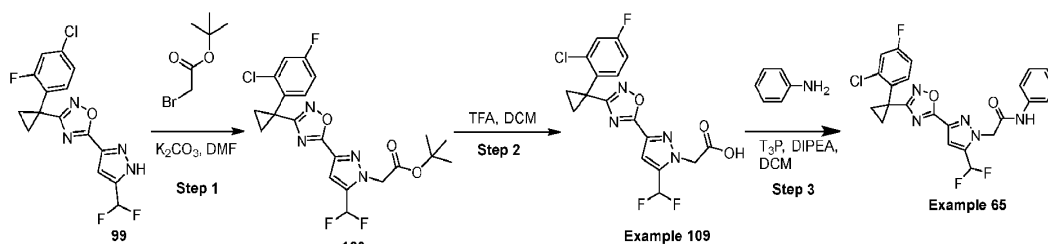
Example 63: Synthesis of 3-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)propanamide (Example 63)

[0862] 3-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)propanamide (Example 63) was synthesized following Scheme 45 using 3-bromopropanamide. LCMS (ESI) Calcd for $C_{18}H_{15}ClF_3N_5O_2$: 425.7; found $[M+H]^+$ = 426.3. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.64-7.60 (m, 1H), 7.56-7.24 (m, 5H), 6.97 (brs, 1H), 4.48 (t, 2H), 2.73 (t, 2H), 1.72-1.70 (m, 2H), 1.48-1.45 (m, 2H).

Example 64: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 64)

[0863] 2-(5-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 64) was synthesized following Scheme 45 using 3-2-bromoacetamide. LCMS (ESI) Calcd. for $C_{17}H_{13}ClF_3N_5O_2$: 411.1, found $[M+H]^+$ = 412.0. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.71 (s, 1H), 7.64-7.60 (m, 1H), 7.51-7.49 (dd, 1H), 7.42 (s, 1H), 7.34 (s, 1H), 7.26-6.97 (m, 2H), 5.25 (s, 2H), 1.74-1.72 (m, 2H), 1.50-1.47 (m, 2H).

Example 65: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-phenylacetamide (Example 65)



Scheme 46

[0864] Synthesis of *tert*-butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetate, 100 [step 1]: *tert*-Butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetate was synthesized following Scheme 45 using *tert*-butyl 2-bromoacetate. LCMS (ESI) Calcd. for $C_{21}H_{20}ClF_3N_4O_3$: 468.1, found $[M+H]^+$ = 469.2. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.65-7.61 (m, 1H), 7.51-7.48 (m, 1H), 7.46-7.19 (m, 3H) 5.26 (s, 2H), 1.74-1.71 (m, 2H), 1.49-1.46 (m, 2H), 1.40 (s, 9H).

[0865] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetic acid, Example 109 [Step 2]: To a stirred solution of *tert*-butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetate (100, 100 mg, 0.2 mmol) in dichloromethane (2 mL), trifluoroacetic acid

(16 equiv. 0.3 mL, 3.2 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 6 h and the volatiles were removed under reduced pressure and purified by reverse phase prep-HPLC to afford 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetic acid (Example 109, 23 mg). Structure was confirmed by NOE experiment. LCMS (ESI) Calcd for C₁₇H₁₂ClF₃N₄O₃: 412.1, found [M+H]⁺ = 413.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.65-7.61 (m, 1H), 7.50-7.47 (dd, 1H), 7.27-7.10 (m, 3H), 4.79 (s, 2H), 1.77-1.74 (m, 2H), 1.47-1.44 (m, 2H).

[0866] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-phenylacetamide, Example 65: [Step 3]: To a stirred solution of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetic acid (Example 109, 70 mg, 0.2 mmol) in dichloromethane (2 mL), aniline (0.023 mL, 0.3 mmol) and DIPEA (0.089 mL, 0.5 mmol) were added followed by addition of T₃P (50% in ethyl acetate) (3 equiv.). Resulting reaction mixture was stirred for 16 h at ambient temperature, diluted with dichloromethane and washed with water. Combined organic extracts were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-phenylacetamide (Example 65, 40 mg). LCMS (ESI) Calcd for C₂₃H₁₇ClF₃N₅O₂: 487.1, found [M-H]⁻: 486.2. ¹H NMR (400 MHz, DMSO-*d*₆, 100 °C): δ_H 10.13 (s, 1H), 7.64-7.60 (t, 1H), 7.55 (d, 2H), 7.42-16 (m, 6H), 7.11-7.09 (m, 1H), 5.29 (s, 2H), 1.75 (brs, 2H), 1.47 (brs, 2H).

[0867] Examples 66-92 were synthesized in a manner similar to Example 65.

Example 66: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(2,2,2-trifluoroethyl)acetamide (Example 66)

[0868] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(2,2,2-trifluoroethyl)acetamid (Example 66) was synthesized following Scheme 46 using 2,2,2-trifluoroethan-1-amine. LCMS Calcd. for C₁₉H₁₄ClF₆N₅O₂: 493.7, found [M+H]⁺ = 494. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.03-8.99 (m, 1H), 7.64-7.61 (m, 1H), 7.51-7.48 (m, 1H), 7.33-7.15 (m, 3H), 5.21 (s, 2H), 4.02-3.92 (brs, 2H), 1.73-1.70 (brs, 2H), 1.49-1.46 (brs, 2H).

Example 67: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(2-hydroxyethyl)acetamide (Example 67)

[0869] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(2-hydroxyethyl)acetamide (Example 67) was synthesized following Scheme

46 using 2-aminoethan-1-ol. LCMS (ESI) Calcd for $C_{19}H_{17}ClF_3N_5O_3$: 455.1, found $[M+H]^+$ = 456.1. 1H NMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 8.01 (brs, 1H), 7.62 (t, 1H), 7.39 (d, 1H), 7.23-7.19 (m, 2H), 5.07 (s, 2H), 4.39 (brs, 1H), 3.48-3.46 (m, 2H), 3.21 (q, 2H), 1.75 (s, 2H), 1.47-1.45 (m, 2H).

Example 68: Synthesis of *N*-(2-amino-2-oxoethyl)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide (Example 68)

[0870] *N*-(2-Amino-2-oxoethyl)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide (Example 68) was synthesized following Scheme 46 using 2-aminoacetamide. LCMS (ESI) Calcd for $C_{19}H_{16}ClF_3N_6O_3$: 468.1, found $[M+H]^+$ = 469.1. 1H NMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 8.24 (s, 1H), 7.64-7.60 (t, 1H), 7.39 (d, 1H), 7.24-6.96 (m, 5H), 5.16 (s, 2H), 3.73-3.72 (brs, 2H), 1.75 (s, 2H), 1.47 (s, 2H).

Example 69: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-hydroxyethyl)-*N*-methylacetamide (Example 69)

[0871] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-hydroxyethyl)-*N*-methylacetamide (Example 69) was synthesized following Scheme 46 using 2-(methylamino)ethan-1-ol. LCMS (ESI) Calcd for $C_{20}H_{19}ClF_3N_5O_3$: 469.1, found $[M+H]^+$ = 470.1. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.62 (d, 1H), 7.46 (d, 1H), 7.24-7.19 (m, 3H), 5.50 (s, 2H), 5.38 (s, 1H), 3.65 (d, 1H), 3.48-3.40 (m, 2H), 3.35-3.21 (m, 1H), 3.05 (s, 1H), 2.83 (s, 2H), 1.79 (t, 2H), 1.46 (t, 2H).

Example 70: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-(dimethylamino)ethyl)acetamide (Example 70)

[0872] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-(dimethylamino)ethyl)acetamide Example 70 was synthesized following Scheme 46 using *N*¹,*N*¹-dimethylethane-1,2-diamine. LCMS (ESI) Calcd. for $C_{21}H_{22}ClF_3N_6O_2$: 482.1, found $[M+H]^+$ = 483.1. 1HNMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 7.88 (s, 1H), 7.64-7.60 (t, 1H), 7.39-7.10 (m, 4H), 5.06 (s, 2H), 3.22-3.19 (brs, 2H), 2.37-2.34 (brs, 2H), 2.18 (s, 6H), 1.75 (s, 2H), 1.47 (s, 2H).

Example 71: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-methoxyethyl)acetamide (Example 71)

[0873] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-methoxyethyl)acetamide (Example 71) was synthesized following Scheme 3 using 2-methoxyethan-1-amine. LCMS (ESI) Calcd for $C_{20}H_{19}ClF_3N_5O_3$: 469.1, found $[M+H]^+$

= 470.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.43 (t, 1H), 7.62 (q, 1H), 7.49 (dd, 1H), 7.41-7.14 (m, 3H), 5.10 (s, 2H), 3.38-3.24 (m, 7H), 1.73-1.70 (m, 2H), 1.48-1.46 (m, 2H).

Example 72: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-methyl-*N*-(2,2,2-trifluoroethyl)acetamide (Example 72)

[0874] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-methyl-*N*-(2,2,2-trifluoroethyl)acetamide (Example 72) was synthesized following Scheme 46 using 2,2,2-trifluoro-*N*-methylethan-1-amine. LCMS (ESI) Calcd. for C₂₀H₁₆ClF₆N₅O₂: 507.1, found [M+H]⁺ = 508.1. ¹H NMR (400 MHz, DMSO-*d*₆ at 100 °C): δ_H 7.64-7.60 (t, 1H), 7.40 (d, 1H), 7.31-7.04 (m, 3H), 5.53 (s, 2H), 4.18 (s, 2H), 3.20 (s, 3H), 1.75 (s, 2H), 1.47 (s, 2H).

Example 73: Synthesis of (*R*)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamido)propanamide (Example 73)

[0875] (*R*)-2-(2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamido)propanamide (Example 73) was synthesized following Scheme 46 using (*R*)-2-aminopropanamide. LCMS (ESI) Calcd for C₂₀H₁₈ClF₃N₆O₃: 482.1, found [M+H]⁺ = 483.0. ¹H NMR (400 MHz, DMSO-*d*₆ at 100 °C): δ_H 8.20 (s, 1H), 7.63-7.62 (t, 1H), 7.40-7.37 (m, 1H), 7.22-6.93 (m, 5H), 5.14 (s, 2H), 4.27 (s, 1H), 1.75 (s, 2H), 1.47 (s, 2H), 1.27 (d, 3H).

Example 74: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-(dimethylamino)ethyl)-*N*-methylacetamide (Example 74)

[0876] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-(dimethylamino)ethyl)-*N*-methylacetamide (Example 74) was synthesized following Scheme 46 using *N*¹,*N*¹,*N*²-trimethylethane-1,2-diamine. LCMS (ESI) Calcd for C₂₂H₂₄ClF₃N₆O₂: 496.1, found [M+H]⁺ = 497.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.61 (t, 1H), 7.39-7.37 (m, 1H), 7.28-7.01 (m, 3H), 3.48-3.43 (m, 2H), 2.44 (brs, 1H), 2.21 (brs, 5H), 1.92 (s, 3H), 1.78-1.74 (m, 2H), 1.47-1.45 (m, 2H).

Example 75: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-methoxyethyl)-*N*-methylacetamide (Example 75)

[0877] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-methoxyethyl)-*N*-methylacetamide (Example 75) was synthesized following Scheme 46 using 2-methoxy-*N*-methylethan-1-amine. LCMS (ESI) Calcd for C₂₁H₂₁ClF₃N₅O₃: 483.2, found [M+H]⁺ = 484.1. ¹H NMR (400 MHz, DMSO-*d*₆ at 100 °C): δ_H 7.63-

7.60 (m, 1H), 7.37 (dd, 1H), 7.27-7.00 (m, 3H), 5.40 (s, 2H), 3.53 (brs, 4H), 3.31 (brs, 3H), 3.04-2.93 (m, 2H), 1.83-1.70 (m, 2H), 1.52-1.45 (m, 2H).

Example 76: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(2-hydroxy-2-methylpropyl)acetamide (Example 76)

[0878] 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(2-hydroxy-2-methylpropyl)acetamide (Example 76) was synthesized

following Scheme 46 using 1-amino-2-methylpropan-2-ol. LCMS (ESI) Calcd for

C₂₁H₂₁ClF₃N₅O₃: 483.1, found [M+H]⁺ = 484.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.82 (brs, 1H), 7.63-7.60 (m, 1H), 7.39-7.36 (m, 1H), 7.23-7.09 (m, 3H), 5.13 (s, 2H), 4.10 (s, 1H), 3.11 - 3.10 (brs, 2H), 1.77-1.75 (brs, 2H), 1.48-1.45 (brs, 2H), 1.10 (s, 6H).

Example 77: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-((1-methylpiperidin-4-yl)methyl)acetamide (Example 77)

[0879] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-((1-methylpiperidin-4-yl)methyl)acetamide (Example 77) was synthesized

following Scheme 46 using (1-methylpiperidin-4-yl)methanamine. LCMS (ESI) Calcd for

C₂₄H₂₆ClF₃N₆O₂: 522.1, found [M+H]⁺ = 523.1. ¹H NMR (400 MHz, DMSO-*d*₆ at 100 °C): δ_H 7.97 (brs, 1H), 7.63-7.60 (t, 1H), 7.39-7.09 (m, 4H), 5.06 (s, 2H), 3.04-3.01 (m, 2H), 2.73-2.67 (m, 2H), 2.15 (s, 3H), 1.88-1.82 (t, 2H), 1.76-1.75 (brs, 2H), 1.63-1.59 (m, 2H), 1.52-1.47 (brs, 2H), 1.43-1.38 (brs, 1H), 1.28-1.14 (m, 2H).

Example 78: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(1-cyanocyclopropyl)acetamide (Example 78)

[0880] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(1-cyanocyclopropyl)acetamide (Example 78) was synthesized following

Scheme 46 using 1-aminocyclopropane-1-carbonitrile. LCMS (ESI) Calcd for C₂₁H₁₆ClF₃N₆O₂:

476.1, found [M+H]⁺ = 477.2. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 9.27 (s, 1H), 7.65-7.61 (m, 1H), 7.50-7.48 (m, 1H), 7.40-7.14 (m, 3H), 5.12 (s, 2H), 1.73-1.71 (m, 2H), 1.52-1.46 (m, 4H), 1.18-1.14 (m, 2H).

Example 79: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(2-(methylamino)-2-oxoethyl)acetamide (Example 79)

[0881] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(2-(methylamino)-2-oxoethyl)acetamide (Example 79) was synthesized

following Scheme 46 using 2-amino-N-methylacetamide. LCMS (ESI) Calcd. for

C₂₀H₁₈ClF₃N₆O₂: 482.1, found [M-H]⁻ = 481.2. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.61 (t, 1H),

7.86 (d, 1H), 7.64-7.60 (m, 1H), 7.50-7.47 (m, 1H), 7.31-7.14 (m, 3H), 5.17 (s, 2H), 3.72 (d, 2H), 2.60 (d, 3H), 1.71 (s, 2H), 1.47 (s, 2H).

Example 80: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(cyclopropylmethyl)acetamide (Example 80)

[0882] 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(cyclopropylmethyl)acetamide (Example 80) was synthesized following Scheme 46 using cyclopropylmethanamine. LCMS (ESI) Calcd. For $C_{21}H_{19}ClF_3N_5O_2$: 465.2, found $[M+H]^+ = 466.2$. 1H NMR (400 MHz, DMSO- d_6): δ_H 8.42 (t, 1H), 7.64 (t, 1H), 7.50-7.48 (m, 1H), 7.41-7.14 (m, 3H), 5.08 (s, 2H), 2.99 (t, 2H), 1.71 (s, 2H), 1.47 (s, 2H), 0.90 (s, 1H), 0.43 (d, 2H), 0.17 (d, 2H).

Example 81: Synthesis of N-(2-amino-2-oxoethyl)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide (Example 81)

[0883] N-(2-Amino-2-oxoethyl)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide (Example 81) was synthesized following Scheme 46 using 2-(methylamino)acetamide. LCMS (ESI) Calcd. for $C_{20}H_{18}ClF_3N_6O_3$: 482.1, found $[M+H]^+ = 483.0$. 1H NMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 7.63-7.60 (m, 1H), 7.40-7.37 (m, 1H), 7.27-7.0 (m, 5H), 5.43 (brs, 2H), 4.04-3.91 (m, 2H), 3.09 (brs, 2H), 2.86 (brs, 1H), 1.76-1.73 (m, 2H), 1.48-1.45 (m, 2H).

Example 82: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(cyclobutylmethyl)acetamide (Example 82)

[0884] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(cyclobutylmethyl)acetamide was synthesized following Scheme 46 using cyclobutylmethanamine. LCMS (ESI) Calcd. for $C_{22}H_{21}ClF_3N_5O_2$: 479.1, found $[M+H]^+ = 480.1$. 1H NMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 7.93 (brs, 1H), 7.63-7.59 (m, 1H), 7.39-7.36 (m, 1H), 7.22-7.09 (m, 3H), 5.05 (s, 2H), 3.18-3.15 (m, 2H), 2.44-2.41 (m, 1H), 2.04-1.97 (m, 2H), 1.85-1.66 (m, 6H), 1.47-1.45 (m, 2H).

Example 83: Synthesis of (S)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-1-(3-methoxypyrrolidin-1-yl)ethan-1-one (Example 83)

[0885] (S)-2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-1-(3-methoxypyrrolidin-1-yl)ethan-1-one (Example 83) was synthesized following Scheme 46 using (S)-3-methoxypyrrolidine. LCMS (ESI) Calcd. for $C_{22}H_{21}ClF_3N_5O_3$: 495.1, found $[M+H]^+ = 496.1$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.64-7.60 (t,

1H), 7.39 (d, 1H), 7.33-7.06 (m, 3H), 5.36-5.28 (brs, 2H), 4.09-3.99 (m, 1H), 3.67-3.58 (m, 2H), 3.44 (s, 2H), 3.35-3.27 (m, 3H), 2.07 (s, 1H), 1.95 (s, 1H), 1.75 (s, 2H), 1.47-1.45 (brs, 2H).

Example 84: Synthesis of (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(3-methoxypyrrolidin-1-yl)ethan-1-one (Example 84)

[0886] (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(3-methoxypyrrolidin-1-yl)ethan-1-one (Example 84) was synthesized following Scheme 46 using (*R*)-3-methoxypyrrolidine. LCMS (ESI) Calcd. for $C_{22}H_{21}ClF_3N_5O_3$: 495.2, found $[M+H]^+ = 496.2$. 1H NMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 7.63-7.59 (m, 1H), 7.39-7.32 (m, 1H), 7.22-7.06 (m, 3H), 5.36-5.28 (m, 2H), 4.09-3.99 (m, 1H), 3.66-3.59 (m, 2H), 3.43-3.36 (m, 2H), 3.30-3.27 (m, 3H), 2.06-1.94 (m, 2H), 1.76-1.73 (m, 2H), 1.48-1.45 (m, 2H).

Example 85: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(3-methoxyazetidin-1-yl)ethan-1-one (Example 85)

[0887] 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(3-methoxyazetidin-1-yl)ethan-1-one (Example 85) was synthesized following Scheme 46 using 3-methoxyazetidine. LCMS (ESI) Calcd. for $C_{21}H_{19}ClF_3N_5O_3$: 481.8, found $[M+H]^+ = 482.2$. 1H NMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 7.62 (t, 1H), 7.40 (d, 1H), 7.35-7.08 (m, 3H), 5.16 (s, 2H), 4.39-4.28 (m, 3H), 4.09 (brs, 1H), 3.76 (brs, 1H), 3.26 (s, 3H), 1.74 (s, 2H), 1.47 (s, 2H).

Example 86: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(3,3-difluoropyrrolidin-1-yl)ethan-1-one (Example 86)

[0888] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(3,3-difluoropyrrolidin-1-yl)ethan-1-one (Example 86) was synthesized following Scheme 46 using 3,3-difluoropyrrolidine. LCMS (ESI) Calcd. for $C_{21}H_{17}ClF_5N_5O_2$: 501.8, found $[M+H]^+ = 502.4$. 1H NMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 7.62 (t, 1H), 7.39 (d, 1H), 7.32-7.06 (m, 3H), 5.36 (s, 2H), 4.07-3.62 (m, 4H), 2.32 (brs, 1H), 1.75-1.69 (m, 2H), 1.52-1.47 (m, 2H).

Example 87: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one (Example 87)

[0889] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one (Example 87) was synthesized following Scheme 46 using pyrrolidine. LCMS (ESI) Calcd. for $C_{21}H_{19}ClF_3N_5O_2$: 465.1, found $[M+H]^+ = 466.1$. 1H

NMR (400 MHz, DMSO-*d*₆): δ_{H} 7.65-7.61 (m, 1H), 7.51-7.48 (m, 1H), 7.36-7.09 (m, 3H), 5.35 (s, 2H), 3.54-3.51 (m, 2H), 3.31 (d, 2H), 1.96-1.90 (m, 2H), 1.83-1.76 (m, 2H), 1.71 (s, 2H), 1.47 (s, 2H).

Example 88: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(3,3-difluoroazetidin-1-yl)ethan-1-one (Example 88)

[0890] 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(3,3-difluoroazetidin-1-yl)ethan-1-one (Example 88) was synthesized following Scheme 46 using 3,3-difluoroazetidine. LCMS (ESI) Calcd. for C₂₀H₁₅ClF₅N₅O₂: 487.1, found [M+H]⁺ = 488.0. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 7.65-7.61 (m, 1H), 7.51-7.48 (m, 1H), 7.38-7.11 (m, 3H), 5.33 (s, 2H), 4.78-4.72 (m, 2H), 4.42-4.36 (m, 2H), 1.71 (s, 2H), 1.47 (brs, 2H).

Example 89: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-hydroxy-2-methylpropyl)-*N*-methylacetamide (Example 89)

[0891] 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(2-hydroxy-2-methylpropyl)-*N*-methylacetamide (Example 89) was synthesized following Scheme 46 using 2-methyl-1-(methylamino)propan-2-ol. LCMS (ESI) Calcd. for C₂₂H₂₃ClF₃N₅O₃: 497.1, found [M+H]⁺ = 498.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ_{H} 7.63-7.60 (t, 1H), 7.38 (d, 1H), 7.27-7.00 (m, 3H), 5.46 (s, 2H), 4.55-4.16 (brs, 1H), 3.34 (s, 2H), 3.17 (brs, 3H), 1.75 (s, 2H), 1.47 (s, 2H), 1.12 (s, 6H).

Examples 90 & 91: Synthesis of (S)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(tetrahydrofuran-3-yl)acetamide (Example 90) & (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(tetrahydrofuran-3-yl)acetamide (Example 91)

[0892] (S)-2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(tetrahydrofuran-3-yl)acetamide (Example 90) and (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(tetrahydrofuran-3-yl)acetamide (Example 91) were synthesized following Scheme 46 using tetrahydrofuran-3-amine. The absolute stereochemistries were assigned by matching the chiral HPLC SFC data of both peaks with the compound synthesized using chiral amine (*S*-isomer) with known absolute stereochemistry.

[0893] (S)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(tetrahydrofuran-3-yl)acetamide (Example 90) (Peak 1): ¹H

NMR (400 MHz, DMSO- d_6): δ_H 8.63 (d, 1H), 7.64-7.61 (m, 1H), 7.49 (dd, 1H), 7.31 (s, 1H), 7.27-7.23 (m, 2H), 5.08 (s, 2H), 4.24 (brs, 1H), 3.81-3.67 (m, 3H), 3.51-3.47 (m, 1H), 2.13-2.08 (m, 1H), 1.73 (d, 3H), 1.47 (s, 2H). LCMS (ESI) Calcd for $C_{21}H_{19}ClF_3N_5O_3$: 481.8, found $[M+H]^+$ = 482.1.

[0894] (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(tetrahydrofuran-3-yl)acetamide (Example 91) (Peak 2): LCMS (ESI) Calcd. for $C_{21}H_{19}ClF_3N_5O_3$: 481.8, found $[M+H]^+$ = 482.1. 1H NMR (400 MHz, DMSO- d_6): δ_H 8.63 (d, 1H), 7.64-7.61 (m, 1H), 7.49 (dd, 1H), 7.41-7.14 (m, 3H), 5.08 (s, 2H), 4.24 (brs, 1H), 3.81-3.67 (m, 3H), 3.51-3.47 (m, 1H), 2.13-2.08 (m, 1H), 1.73 (d, 3H), 1.47 (s, 2H).

[0895] Preparative chiral HPLC method: SFC preparative purification was performed on Pic Solution 175 instrument equipped with Knauer UV Detector 40D by using C Amylose A (30.0 mm x 250mm), 5 μ Column operating at 35 °C temperature, maintaining flow rate of 110 ml/min, using 75 % CO₂ in super critical state & 25% of methanol as mobile phase, Run this isocratic mixture up to 14.0 minutes and also maintained the isobaric condition of 100 bar at 254 nm wavelength.

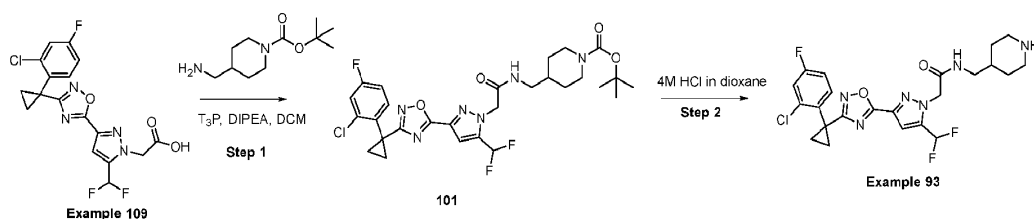
Example 92: Synthesis of (*S*)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamido)propanamide (Example 92)

[0896] (*S*)-2-(2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamido) propanamide (Example 92) was synthesized following Scheme 46 using 2-aminopropanamide. LCMS (ESI) Calcd for $C_{20}H_{18}ClF_3N_6O_3$: 482.1, found $[M+H]^+$ = 483.1. 1H NMR (400 MHz, DMSO- d_6): δ_H 8.53 (d, 1H), 7.65-7.61 (t, 1H), 7.51-7.50 (m, 1H), 7.48 (s, 1H), 7.43-7.13 (m, 3H), 7.06 (s, 1H), 5.21-5.11 (m, 2H), 4.24-4.21 (m, 1H), 1.72 (s, 2H), 1.47 (brs, 2H), 1.24-1.22 (m, 3H).

[0897] Preparative chiral HPLC method: SFC prepurative purification was performed on Pic Solution 175 instrument equipped with Knauer UV Detector 40D by using I Cullulose J (30.0 mm x 250 mm), 5 min column operating at 35 °C temperature, maintaining flow rate of 90 mL/min, using 85% CO₂ in super critical state and 15% of MeOH mobile phase. Run this isocratic mixture up to 14 min and also maintained the isobaric condition of 100 bar at 220 nm. Note: Reaction with (*2R*)-2-aminopropanamide was performed to obtain (*R*)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamido)propanamide (Example 92) with known absolute configuration. After comparing

the chiral HPLC of both isomers (Peak 1 & Peak 2) with this R-isomer, it is confirmed that Peak 1 is R-isomer and Peak 2 is S-isomer.

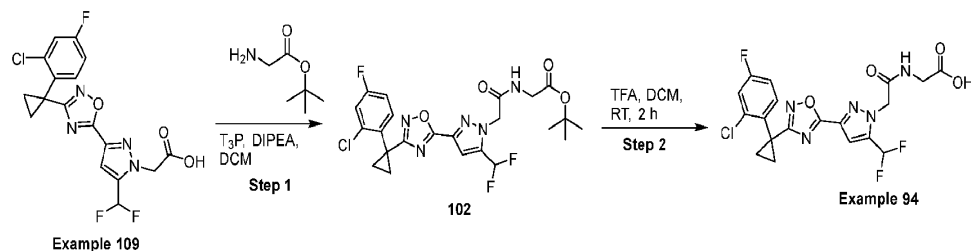
Example 93: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(piperidin-4-ylmethyl)acetamide (Example 93)



[0898] Synthesis of *tert*-butyl 4-((2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)methyl)piperidine-1-carboxylate, 101 [Step 1]: *tert*-Butyl 4-((2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)methyl)piperidine-1-carboxylate 101 was synthesized following Scheme 46 using *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate. LCMS (ESI) Calcd. for $C_{28}H_{32}ClF_3N_6O_4$: 608.2, found $[M+H]^+ = 609.1$.

[0899] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(piperidin-4-ylmethyl)acetamide, Example 93 [Step 2]: To a stirred solution of *tert*-butyl 4-((2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)methyl)piperidine-1-carboxylate (101, 150 mg, 0.2 mmol) in dichloromethane (4 mL), HCl (2.0 mL, 4M in Dioxane) was added dropwise at 0 °C and stirred at ambient temperature for 2h. After completion, the reaction mixture was concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC to afford 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(piperidin-4-ylmethyl)acetamide (Example 93, 80 mg). LCMS (ESI) Calcd. for $C_{23}H_{24}ClF_3N_6O_2$: 508.1, found $[M+H]^+ = 509.4$. 1H NMR (400 MHz, DMSO- d_6): δ_H 8.28 (s, 1H), 7.65-7.61 (m, 1H), 7.51-7.48 (m, 1H), 7.41-7.14 (m, 4H), 5.08 (s, 2H), 2.97-2.94 (m, 2H), 2.91-2.88 (m, 2H), 2.41-2.35 (m, 2H), 1.71 (s, 2H), 1.56-1.47 (m, 5H), 1.00-0.95 (m, 2H).

Example 94: Synthesis of (2-(3-(3-(1-(2-chloro-4-fluorophenyl) cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl) acetyl) glycine (Example 94)

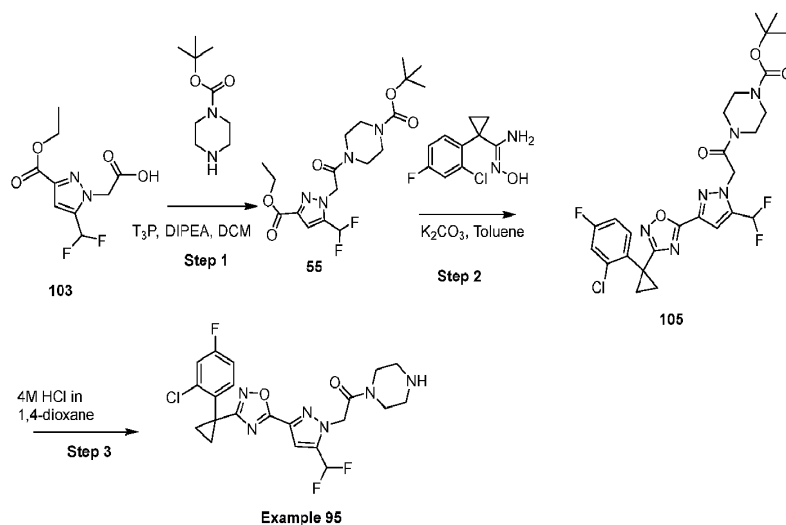


Scheme 48

[0900] Synthesis of *tert*-butyl (2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetyl)glycinate, 102 [Step 1]: *tert*-Butyl (2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetyl)glycinate 102 was synthesized following Scheme 46 using *tert*-butyl glycinate. The product was carried to next step without further purification. LCMS (ESI) Calcd. for $C_{23}H_{23}ClF_3N_5O_4$: 525.1, found $[M+H]^+ = 526.4$.

[0901] Synthesis of (2-(3-(3-(1-(2-chloro-4-fluorophenyl) cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl) acetyl) glycine, Example 94 [Step 2]: To a stirred solution of *tert*-butyl (2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetyl)glycinate (102, 170 mg, 0.3 mmol) in dichloromethane (4 mL), trifluoroacetic acid (0.3 mL, 3.9 mmol) was added dropwise at 0 °C and stirred at ambient temperature for 2h. After completion, the reaction mixture was concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford (2-(3-(3-(1-(2-chloro-4-fluorophenyl) cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl) acetyl) glycine (Example 94, 20 mg). LCMS (ESI) Calcd. for $C_{19}H_{15}ClF_3N_5O_4$: 469.1, found $[M+H]^+ = 470.0$. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 8.59 (s, 1H), 7.63 (t, 1H), 7.49 (d, 1H), 7.41-7.14 (m, 3H), 5.17 (s, 2H), 3.78 (s, 2H), 1.71 (s, 2H), 1.47 (s, 2H).

Example 95: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 95)



Scheme 49

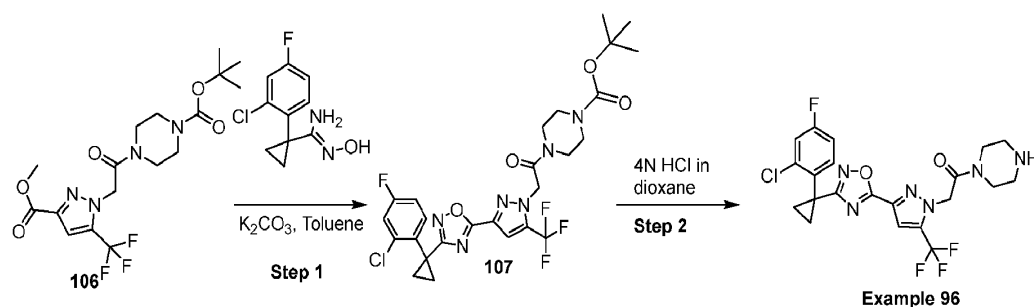
[0902] Synthesis of *tert*-butyl 4-(2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate, 104 [Step 1]: *tert*-Butyl 4-(2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate was synthesized following Scheme 46 using *tert*-butyl piperazine-1-carboxylate. LCMS (ESI) Calcd. for $C_{18}H_{26}F_2N_4O_5$: 416.2, found $[M+H]^+ = 417.1$.

[0903] Synthesis of *tert*-Butyl 4-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate, 105 [Step 2]: To a stirred solution of *tert*-butyl 4-(2-(5-(difluoromethyl)-3-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (55, 200 mg, 0.5 mmol) in toluene (5 mL), K_2CO_3 (172.5 mg, 1.2 mmol) and (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (228.6 mg, 0.6 mmol) were added and the resulting reaction mixture was allowed to stir at 90 °C for 16 h. After completion, volatiles were evaporated under reduced pressure, diluted with ethyl acetate and washed with water (twice). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford *tert*-butyl 4-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (105, 140 mg). LCMS (ESI) Calcd. for $C_{26}H_{28}ClF_3N_6O_4$: 580.2, found $[M+H]^+ = 581.4$.

[0904] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one, Example 95 [Step-3]: To a solution of *tert*-Butyl 4-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-

(difluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (105, 140 mg, 0.24 mmol) in dichloromethane (2 mL), 4M HCl in 1,4-dioxane (2 mL) was added at 0 °C and stirred for 2 h at ambient temperature. After completion, volatiles were evaporated under reduced pressure and the product was purified by reverse phase preparative HPLC to afford 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 95, 65 mg). LCMS (ESI) Calcd. for $C_{21}H_{20}ClF_3N_6O_2$: 480.1, found $[M+H]^+ = 481.1$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.65-7.61 (m, 1H), 7.51-7.49 (m, 1H), 7.35-7.08 (m, 3H), 5.45 (s, 2H), 3.40-3.31 (m, 4H), 2.74 (s, 2H), 2.65 (s, 2H), 1.71 (s, 2H), 1.47 (s, 2H).

Example 96: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 96)



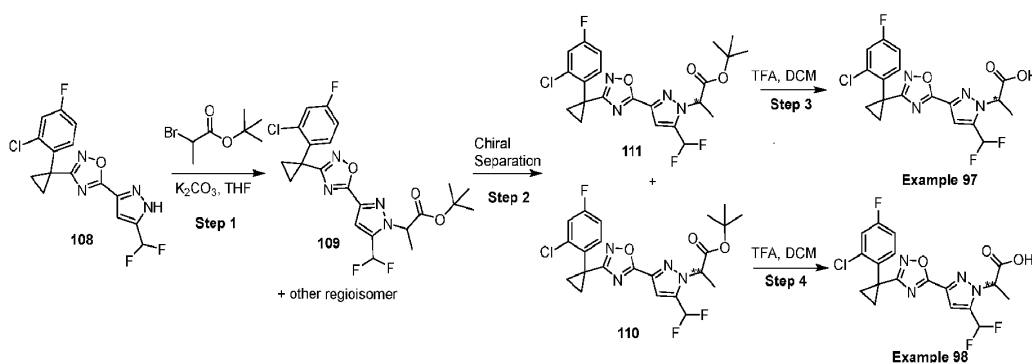
Scheme 50

[0905] Synthesis of *tert*-butyl 4-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate, 106 [Step 1]: *tert*-Butyl 4-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate was synthesized following Scheme 49 using *tert*-butyl 4-(2-(3-(methoxycarbonyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate. LCMS (ESI) Calcd for $C_{26}H_{27}ClF_4N_6O_4$: 598.1, found $[M+H]^+ = 599.3$.

[0906] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one, Example 96 [Step 2]: 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 96) was synthesized following Scheme 49 using *tert*-Butyl 4-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate. LCMS (ESI) Calcd for $C_{21}H_{19}ClF_4N_6O_2$: 498.1, found $[M+H]^+ = 499.2$. 1H NMR (400 MHz, DMSO- d_6 at 100 °C): δ_H 7.64-7.60 (t, 1H), 7.53 (s,

1H), 7.39 (d, 1H), 7.23-7.19 (t, 1H), 5.43 (s, 2H), 3.42 (s, 4H), 2.73 -2.64 (brs, 4H), 1.76 (s, 2H), 1.48-1.47 (brs, 2H).

Examples 97 & 98: Synthesis of (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid (Example 97) and (*S*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid (Example 98)



Scheme 51

[0907] Synthesis of *tert*-butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoate, 109 [Step 1]: *tert*-Butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoate was synthesized following Scheme 45 using *tert*-butyl 2-bromopropanoate. LCMS (ESI) Calcd for C₂₂H₂₂ClF₃N₄O₃: 482.8, found [M-H]⁻ = 481.2.

[0908] Synthesis of chiral *tert*-butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoate, 110 and 111 (Step 2): *Tert*-butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoate (109, 130 mg) was used for SFC chiral separation to afford chiral *tert*-butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoate (60 mg) as peak-1 and chiral *tert*-butyl 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoate (60 mg) as peak 2. LCMS (ESI) Calcd for C₂₂H₂₂ClF₃N₄O₃: 482.8, found [M-H]⁻ = 481.2. The absolute stereochemistry was not determined and was arbitrarily assigned.

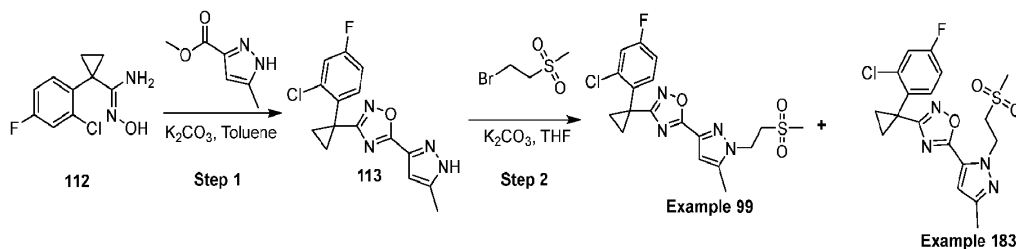
[0909] Chiral HPLC method: SFC PREP PURIFICATION was performed on Pic Solution 175 instrument equipped with Knauer UV Detector 40D by using Chiralpak IG (30.0mm x 250mm), 5μ Column operating at 35 °C temperature, maintaining flow rate of 70 ml/min ,using 60% CO₂

in super critical state & 40% MeOH as mobile phase, Run this isocratic mixture up to 5.0 minutes and also maintained the isobaric condition of 100 bar at 249 nm wavelength.

[0910] Synthesis of (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid, Example 97 (Step 3): To a stirred solution of *tert*-butyl (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoate (111, 60 mg, 0.1 mmol) in dichloromethane (2 mL), trifluoroacetic acid (0.2 mL, 2.5 mmol) was added drop wise under cold condition and the reaction mixture was stirred at ambient temperature for 4 h. After completion, the volatiles were removed under reduced pressure. The product was purified by reverse phase prep HPLC and lyophilized to afford (*R*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid (Example 97, 25 mg). LCMS (ESI) Calcd for $C_{18}H_{14}ClF_3N_4O_3$: 426.7, found $[M+H]^+ = 427.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.64-7.61 (m, 1H), 7.50-7.21 (m, 4H), 5.13 (t, 1H), 2.97 (s, 1H), 1.72 (s, 2H), 1.67 (d, 3H), 1.46 (s, 2H).

[0911] Synthesis of (*S*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid, Example 98 (Step 4): To a stirred solution of *tert*-butyl (*S*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoate (110, 60 mg, 0.1 mmol) in dichloromethane (2 mL), trifluoroacetic acid (0.2 mL, 2.5 mmol) was added drop wise under cold condition and the reaction mixture was stirred at ambient temperature for 12h. After completion, the volatiles were removed under reduced pressure. The product was purified by reverse phase prep HPLC and lyophilized to afford (*S*)-2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid (Example 98, 35 mg). LCMS (ESI) Calcd for $C_{18}H_{14}ClF_3N_4O_3$: 426.7, found $[M+H]^+ = 427.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.64-7.61 (m, 1H), 7.50-7.21 (m, 4H), 5.13 (t, 1H), 2.97 (s, 1H), 1.72 (s, 2H), 1.67 (d, 3H), 1.46 (s, 2H).

Example 99: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-methyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 99)



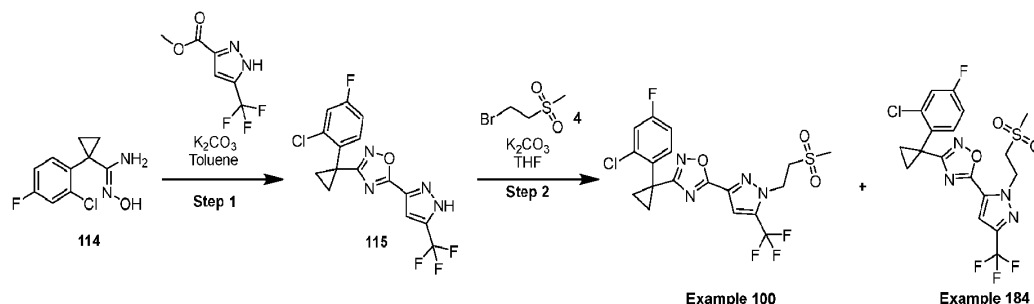
Scheme 52

[0912] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, 113 [Step 1]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(5-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole 113 was synthesized following Scheme 49 using methyl 5-methyl-1*H*-pyrazole-3-carboxylate. LCMS (ESI) Calcd. for $C_{15}H_{12}ClFN_4O$: 318.7, found $[M+H]^+ = 319.3$. 1H NMR (400 MHz, DMSO- d_6): δ_H 13.44 (brs, 1H), 7.61 (t, 1H), 7.48 (d, 1H), 7.24 (t, 1H), 6.65 (s, 1H), 2.29 (s, 3H), 1.69 (s, 2H), 1.43 (s, 2H).

[0913] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-methyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 99 [Step 2]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(5-methyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 99) was synthesized following Scheme 45 using 1-bromo-2-(methylsulfonyl)ethane. LCMS (ESI) Calcd. for $C_{18}H_{18}ClFN_4O_3S$: 424.8; found $[M+H]^+ = 425.2$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.63-7.59 (m, 1H), 7.50-7.47 (m, 1H), 7.27-7.21 (m, 1H), 6.74 (s, 1H), 4.56 (t, 2H), 3.74 (t, 2H), 2.96 (s, 3H), 2.38 (s, 3H), 1.68 (s, 2H), 1.46 (s, 2H).

Note: Structure of regio-isomer was confirmed by NOE.

Example 100: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 100)



Scheme 53

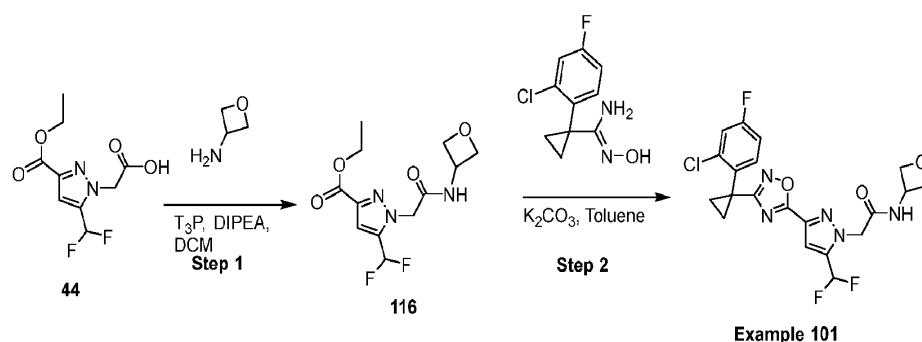
[0914] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, 115 [Step 1]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole 115 was synthesized following Scheme 49 using methyl 5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate. LCMS (ESI) Calcd for $C_{15}H_9ClF_4N_4O$: 372.7, found $[M-H]^- = 371.1$.

[0915] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 100 [Step 2]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 100) was synthesized following Scheme 45 using 1-bromo-2-

(methylsulfonyl)ethane. LCMS (ESI) Calcd for $C_{18}H_{15}ClF_4N_4O_3S$: 478.8; found $[M+H]^+ = 479.2$.

1H NMR (400 MHz, DMSO- d_6): δ_H 7.71 (s, 1H), 7.64-7.61 (m, 1H), 7.52-7.49 (m, 1H), 7.28-7.23 (s, 1H), 4.77 (t, 2H), 3.85 (t, 2H), 3.08 (s, 3H), 1.68 (s, 2H), 1.46 (s, 2H). Note: Structure was confirmed by HMBC & HSQC.

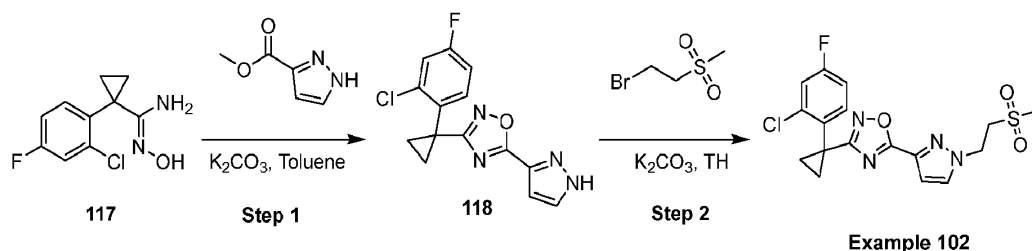
Example 101: Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(oxetan-3-yl)acetamide (Example 101)



[0916] Synthesis of ethyl 5-(difluoromethyl)-1-(2-(oxetan-3-ylamino)-2-oxoethyl)-1H-pyrazole-3-carboxylate, 116 (Step-1): Ethyl 5-(difluoromethyl)-1-(2-(oxetan-3-ylamino)-2-oxoethyl)-1H-pyrazole-3-carboxylate (116) was synthesized following Scheme 49 using oxetan-3-amine. LCMS (ESI) Calcd. for $C_{12}H_{15}F_2N_3O_4$: 303.1, found $[M+H]^+ = 304.0$.

[0917] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(oxetan-3-yl)acetamide, Example 101 [Step-2]: 2-(3-(3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-(oxetan-3-yl)acetamide (Example 101) was synthesized following Scheme 49. LCMS (ESI) Calcd. for $C_{20}H_{17}ClF_3N_5O_3$: 467.1, found $[M+H]^+ = 468.0$. 1H NMR (400 MHz, DMSO- d_6): δ_H 9.13 (d, 1H), 7.64-7.61 (m, 1H), 7.51-7.48 (m, 1H), 7.32-7.14 (m, 3H), 5.12 (s, 2H), 4.79-4.70 (m, 3H), 4.45-4.41 (t, 2H), 1.72-1.70 (m, 2H), 1.49-1.46 (m, 2H).

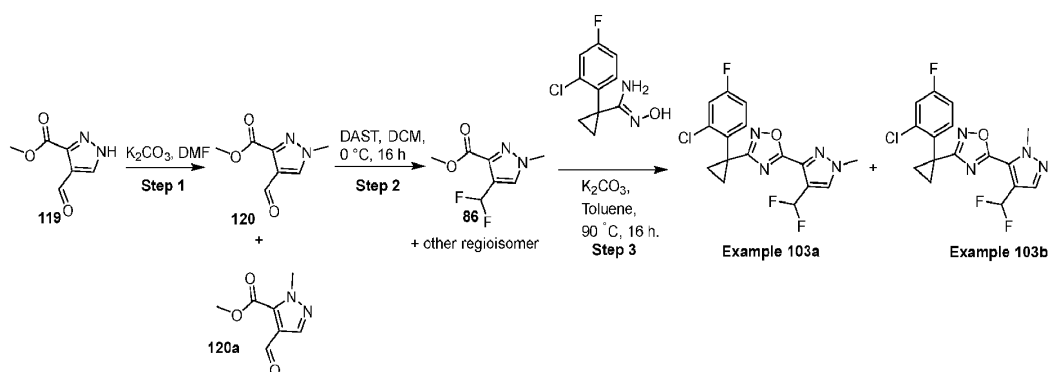
Example 102: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 102)

**Scheme 55**

[0918] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, 118 [Step 1]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (118) was synthesized following Scheme 49 using methyl 1*H*-pyrazole-3-carboxylate. LCMS (ESI) Calcd. for $C_{14}H_{10}ClFN_4O$: 304.7, found $[M+H]^+ = 305.2$. 1H NMR (400 MHz, DMSO- d_6): δ_H 13.76 (brs, 1H), 8.01 (s, 1H), 7.62 (t, 1H), 7.48 (d, 1H), 7.25 (t, 1H), 6.92 (s, 1H), 1.70 (s, 2H), 1.45 (s, 2H).

[0919] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 102 [Step 2]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 102) was synthesized following Scheme 45 using 1-bromo-2-(methylsulfonyl)ethane. LCMS (ESI) Calcd. for $C_{17}H_{16}ClFN_4O_3S$: 410.8; found $[M+H]^+ = 411.1$. 1H NMR (400 MHz, DMSO- d_6): δ_H 8.09 (d, 1H), 7.63-7.60 (m, 1H), 7.50-7.47 (m, 1H), 7.27-7.22 (m, 1H), 6.95 (d, 1H), 4.70 (t, 2H), 3.77 (t, 2H), 2.96 (s, 3H), 1.71-1.69 (m, 2H), 1.46-1.44 (m, 2H). Note: Structure was confirmed by NOE.

Examples 103a & 103b: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 103a)

**Scheme 56**

[0920] Synthesis of methyl 4-formyl-1-methyl-1*H*-pyrazole-3-carboxylate, 120 & 120a [Step 1]:

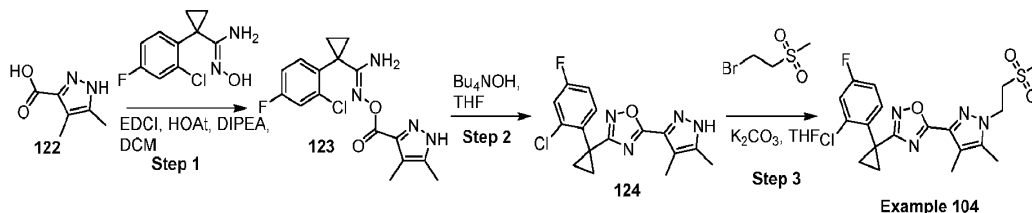
To a solution of methyl 4-formyl-1*H*-pyrazole-3-carboxylate (119, 700 mg, 4.5 mmol) in DMF (5 mL), K₂CO₃ (1.2 g, 9.0 mmol) was added and the reaction mixture was stirred for 15 minutes under nitrogen atmosphere. Iodomethane (0.5 mL, 8 mmol) was added and the reaction mixture was stirred at ambient temperature for 12 h. Ethyl acetate was added to the reaction mixture and washed with ice cold water. The organic extract was washed with brine for several times, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford methyl 4-formyl-1-methyl-1*H*-pyrazole-3-carboxylate as mixture of regioisomer (120 & 120a, 500 mg). LCMS (ESI) Calcd. For C₇H₈N₂O₃: 168.1, found [M+H]⁺ = 169.2.

[0921] Synthesis of methyl 4-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylate, 86 [Step 2]:

To a stirred solution of methyl 4-formyl-1-methyl-1*H*-pyrazole-3-carboxylate (along with other regioisomer) (120 & 120a, 350 mg, 2.0 mmol) in dichloromethane (5 mL), DAST (0.5 mL, 4.0 mmol) was added at 0 °C and stirred for 16 h. Dichloromethane was added to the reaction mixture and washed with water. Organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford methyl 4-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylate (along with other regioisomer) (86, 300 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 8.24 (s, 1H), 7.84 (s, 1H), 7.33-7.05 (m, 2H), 4.10-4.07 (m, 3H), 3.94-3.88 (m, 6H), 3.82-3.77 (m, 3H). Notes: Extra peak present in ¹H NMR.

[0922] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4-(difluoromethyl)-1-methyl-

1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 103a [Step 3]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 49 using methyl 4-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylate (86). LCMS (ESI) Calcd. for C₁₆H₁₂ClF₃N₄O: 368.7, found [M+H]⁺ = 369.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.39 (s, 1H), 7.62 (t, 1H), 7.49 (dd, 1H), 7.41-7.14 (m, 2H), 4.00 (s, 3H), 1.73 (s, 2H), 1.47 (s, 2H). Note: The exact structure of both the regioisomers was confirmed by NOE experiments.

Example 104: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4,5-dimethyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 104)

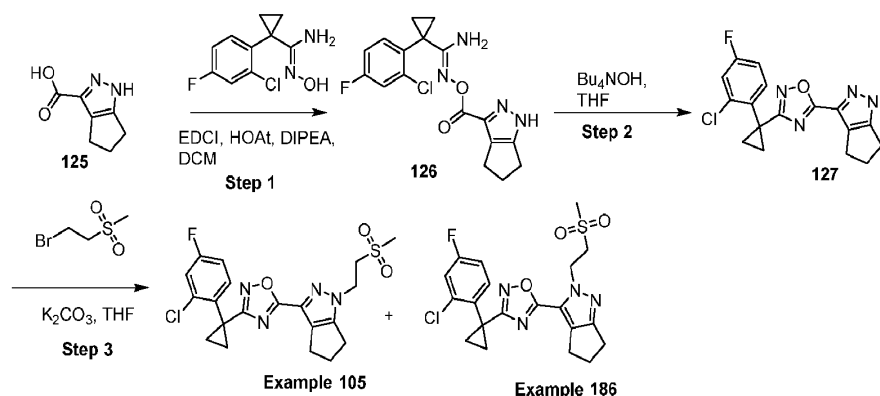
Scheme 57

[0923] Synthesis of (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-((4,5-dimethyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 123 [Step-1]: To a stirred solution of 4,5-dimethyl-1*H*-pyrazole-3-carboxylic acid (122, 120 mg, 0.9 mmol) and (Z)-1-(2-chloro-4-fluorophenyl)-*N*-hydroxycyclopropane-1-carboximidamide (215 mg, 0.9 mmol) in dichloromethane (2 mL), DIPEA (0.45 mL, 2.6 mmol), EDCI.HCl (245 mg, 1.3 mmol) and HOAt (24 mg, 0.2 mmol) were added and the reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-((4,5-dimethyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (123, 270 mg). LCMS (ESI) Calcd. for C₁₆H₁₆ClFN₄O₂: 350.1, found [M+H]⁺ = 351.0.

[0924] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4,5-dimethyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, 124 [Step-2]: To a stirred solution of (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-((4,5-dimethyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (123, 250 mg, 0.7 mmol) in THF (2 mL), tetrabutylammonium hydroxide (0.1 mL, 0.1 mmol, 1M in methanol) was added and the resulting reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water and dried over anhydrous Na₂SO₄, filtered and concentrated again under reduced pressure. The product was purified by reverse phase prep-HPLC and lyophilized to afford 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4,5-dimethyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (124, 160 mg). LCMS (ESI) Calcd. for C₁₆H₁₄ClFN₄O: 332.1, found [M+H]⁺ = 333.2. ¹H NMR (400 MHz, DMSO-*d*₆ at 100 °C): δ_H 13.01 (brs, 1H), 7.63-7.59 (t, 1H), 7.38 (d, 1H), 7.22-7.18 (t, 1H), 2.22 (s, 3H), 2.18 (s, 3H), 1.74 (s, 2H), 1.45 (s, 2H).

[0925] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4,5-dimethyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 104 [Step-3]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(4,5-dimethyl-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 2 using 1-bromo-2-(methylsulfonyl)ethane. LCMS (ESI) Calcd. for C₁₉H₂₀ClFN₄O₃S: 438.1, found [M+H]⁺ = 439.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.64-7.60 (t, 1H), 7.50-7.47 (dd, 1H), 7.27-7.22 (m, 1H), 4.57-4.53 (m, 2H), 3.73-3.70 (m, 2H), 2.96 (s, 3H), 2.30 (s, 3H), 2.19 (s, 3H), 1.71 (brs, 2H), 1.45 (brs, 2H). Note: The structure of the final compound was confirmed by NOE experiments.

Example 105: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-1,2,4-oxadiazole (Example 105)



Scheme 57

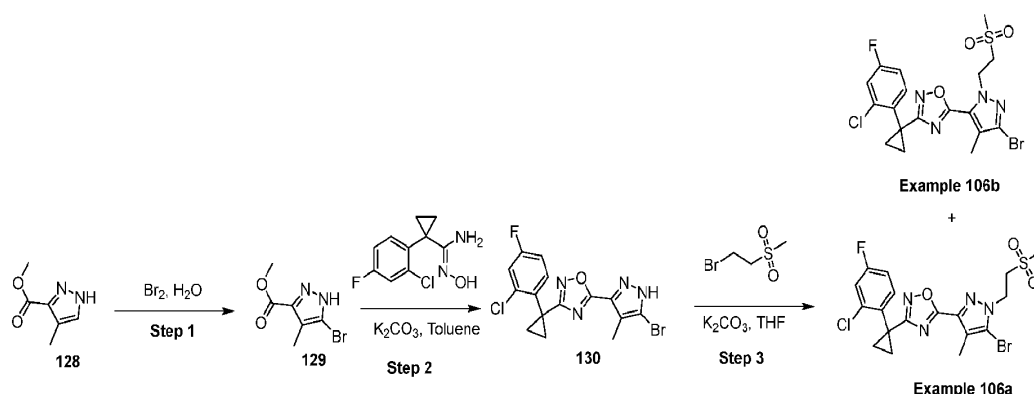
[0926] Synthesis of (Z)-1-(2-chloro-4-fluorophenyl)-N'-((1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 126 [Step-1]: To a stirred solution of 1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylic acid (125, 110 mg, 0.7 mmol) and (Z)-1-(2-chloro-4-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (180 mg, 0.8 mmol) in dichloromethane (2 mL), DIPEA (0.4 mL, 2.2 mmol), EDCI.HCl (210 mg, 1.1 mmol) and HOAt (20 mg, 0.15 mmol) were added and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (Z)-1-(2-chloro-4-fluorophenyl)-N'-((1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (126, 220 mg). LCMS (ESI) Calcd. for C₁₇H₁₆ClFN₄O₂: 362.1, found [M+H]⁺ = 363.2.

[0927] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-1,2,4-oxadiazole, 127 [Step-2]: To a stirred solution of (Z)-1-(2-chloro-4-fluorophenyl)-N'-((1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (126, 200 mg, 0.5 mmol) in THF (2 mL), tetrabutylammonium hydroxide (0.1 mL, 0.1 mmol, 1M in methanol) was added and the resulting reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated again under reduced pressure. The product was purified by reverse phase prep-HPLC and lyophilized to afford 3-(1-(2-chloro-

4-fluorophenyl)cyclopropyl)-5-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-1,2,4-oxadiazole (127, 114 mg). LCMS (ESI) Calcd. for $C_{17}H_{14}ClFN_4O$: 344.1, found $[M-H]^-$: 343.1. 1H NMR (400 MHz, $DMSO-d_6$, at 100 °C): δ_H 13.11 (brs, 1H), 7.62-7.59 (t, 1H), 7.38 (d, 1H), 7.22-7.18 (t, 1H), 2.74-2.67 (m, 4H), 2.50 (m, 2H), 1.73 (s, 2H), 1.44 (s, 2H).

[0928] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-1,2,4-oxadiazole, Example 105 [Step-3]: 3-(1-(2-Chloro-4-fluorophenyl)cyclopropyl)-5-(1-(2-(methylsulfonyl)ethyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 45 using 1-bromo-2-(methylsulfonyl)ethane. LCMS (ESI) Calcd. for $C_{20}H_{20}ClFN_4O_3S$: 450.1, found $[M+H]^+$ = 451.1. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 7.63-7.59 (m, 1H), 7.50-7.47 (m, 1H), 7.27-7.22 (m, 1H), 4.54-4.50 (t, 2H), 3.74-3.71 (t, 2H), 2.94 (s, 3H), 2.85-2.81 (m, 2H), 2.74-2.71 (m, 2H), 2.55-2.50 (m, 2H), 1.68 (brs, 2H), 1.44 (brs, 2H). Note: The structure of the final oxadiazoles were confirmed by NOE experiments.

Examples 106a & 106b: Synthesis of 5-(5-Bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (Example 106a) and 5-(3-bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-5-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (Example 106b)



Scheme 58

[0929] Synthesis of methyl 5-bromo-4-methyl-1H-pyrazole-3-carboxylate, 129 [Step 1]: To a solution of methyl 4-methyl-1H-pyrazole-3-carboxylate (128, 100 mg, 0.7 mmol) in water (1 mL), bromine (0.04 mL, 0.7 mmol) was added dropwise at 0 °C and reaction mixture was stirred for 3h at ambient temperature. After completion the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na_2SO_4 , filtered, concentrated and purified via column chromatography to afford methyl 5-

bromo-4-methyl-1H-pyrazole-3-carboxylate (129, 100 mg). LCMS (ESI) Calcd. for $C_6H_7BrN_2O_2$ [M]: 217.97, found $[M+H]^+$: 219.09

[0930] Synthesis of 5-(5-bromo-4-methyl-1H-pyrazol-3-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole, 130 [Step-2]: To a stirred solution of 1-(2-chloro-4-fluorophenyl)-*N'*-hydroxy-cyclopropanecarboxamidine (100 mg, 0.438 mmol) in toluene (4mL), K_2CO_3 (126 mg, 0.9 mmol) was added and stirred for 10 min. at ambient temperature. Methyl 5-bromo-4-methyl-1H-pyrazole-3-carboxylate (129, 80 mg, 0.37 mmol) was added to the reaction mixture and the resulting reaction mixture was heated at 100 °C for 16 h. After completion, volatiles were evaporated, diluted with ethyl acetate and washed with water (twice). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by prep-HPLC (reverse phase) to afford 5-(5-bromo-4-methyl-1H-pyrazol-3-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (130, 21 mg). LCMS (ESI) Calcd. for $C_{15}H_{11}BrClFN_4O$: 395.98, found $[M-H]^-$: 395.0. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 14.44 (brs, 1H), 7.64-7.61 (m, 1H), 7.51-7.48 (m, 1H), 7.28-7.24 (m, 1H), 2.22 (s, 3H), 1.73 (brs, 2H), 1.48 (brs, 2H).

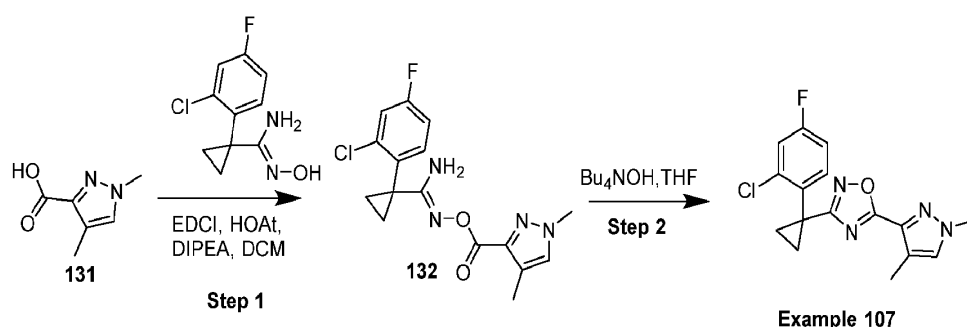
[0931] Synthesis of 5-(5-bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole, Example 106a & 5-(3-bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-5-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole, Example 106b [Step-3]: To a stirred suspension of 5-(5-bromo-4-methyl-1H-pyrazol-3-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (130, 100 mg, 0.25 mmol) in THF (3 mL), potassium carbonate (69 mg, 0.5 mmol) was added. After 15 min, 1-bromo-2-(methylsulfonyl)ethane (71 mg, 0.38 mmol) was added and the resulting reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with ice-cold water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product were purified by reverse phase preparative HPLC to afford 5-(5-bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (106a, 21 mg) as Peak-1 and 5-(3-bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-5-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (106b, 15 mg) as Peak-2.

[0932] Analytical data of 5-(5-bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole, 106a (Peak-1): LCMS (ESI) Calcd. for $C_{18}H_{17}BrClFN_4O_3S$: 501.99, found $[M+H]^+$ = 503.2. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.64-7.60

(m, 1H), 7.51-7.48 (dd, 1H), 7.28-7.23 (m, 1H), 4.69-4.66 (t, 2H), 3.77-3.74 (t, 2H), 3.03 (s, 3H), 2.23 (s, 3H), 1.73-1.71 (m, 2H), 1.49-1.46 (m, 2H).

[0933] Analytical data of 5-(3-bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-5-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole, 106b (Peak-2): LCMS (ESI) Calcd. for $C_{18}H_{17}BrClFN_4O_3S$: 501.99, found $[M+H]^+$ = 503.0. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.64-7.60 (m, 1H), 7.52-7.49 (dd, 1H), 7.28-7.24 (m, 1H), 4.99-4.96 (t, 2H), 3.71-3.68 (t, 2H), 3.00 (s, 3H), 2.22 (s, 3H), 1.81-1.79 (m, 2H), 1.51-1.48 (m, 2H).

Example 107: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1,4-dimethyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 107)



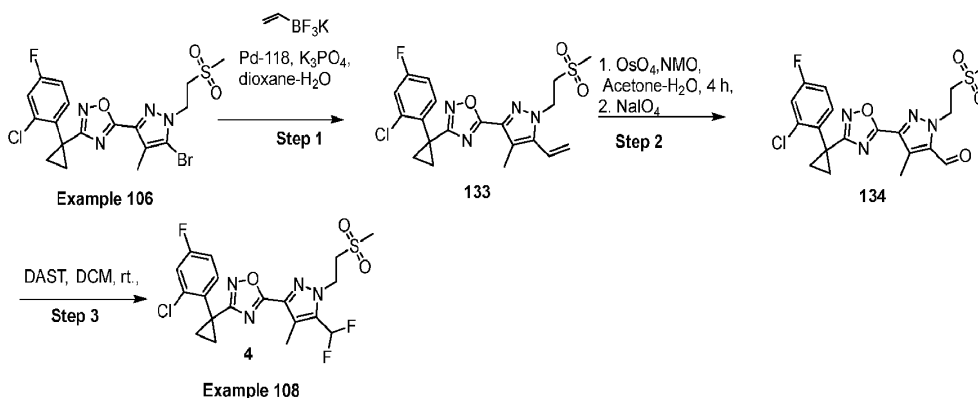
Scheme 59

[0934] Synthesis of (Z)-1-(2-chloro-4-fluorophenyl)-N'-((1,4-dimethyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 132 [Step 1]: To a solution of (Z)-1-(2-chloro-4-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (185 mg, 0.811 mmol) and 1,4-dimethyl-1H-pyrazole-3-carboxylic acid (131, 125 mg, 0.89 mmol) in dichloromethane (1 mL), DIPEA (0.39 mL, 2.21 mmol), EDCI.HCl (212 mg, 1.11 mmol) and HOAt (20 mg, 0.15 mmol) were added and reaction mixture was stirred for 16h at ambient temperature. The reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, concentrated. The product was purified by combiflash column chromatography to afford (Z)-1-(2-chloro-4-fluorophenyl)-N'-((1,4-dimethyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (132, 130 mg). LCMS (ESI) Calcd. for $C_{16}H_{16}ClFN_4O_2$: 350.7, found $[M+H]^+$: 351.2.

[0935] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1,4-dimethyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 107 [Step 2]: To a stirred solution of (Z)-1-(2-chloro-4-fluorophenyl)-N'-((1,4-dimethyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (132, 130 mg, 0.371 mmol) in THF (2 mL), tetrabutylammonium hydroxide (1M in methanol) (0.10 mL, 0.11 mmol) was added and the resulting reaction mixture was stirred for 60 min at ambient

temperature. The reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water (twice). Combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1,4-dimethyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 107, 20 mg). LCMS (ESI) Calcd for $\text{C}_{16}\text{H}_{14}\text{ClFN}_4\text{O}$: 332.1, found $[\text{M}+\text{H}]^+$: 333.1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 7.75 (s, 1H), 7.64-7.60 (m, 1H), 7.50-7.47 (dd, 1H), 7.27-7.22 (m, 1H), 3.90 (s, 3H), 2.24 (s, 3H), 1.72-1.69 (m, 2H), 1.46-1.43 (m, 2H).

Example 108: Synthesis of 3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-5-carbaldehyde (Example 108)



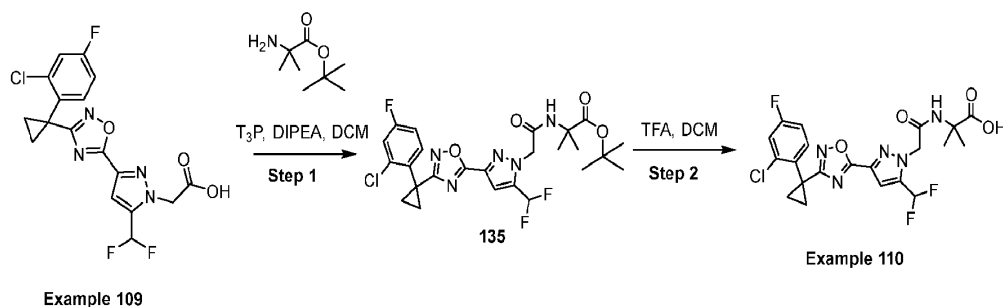
Scheme 60

[0936] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4-methyl-1-(2-(methylsulfonyl)ethyl)-5-vinyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 133 [Step 1]: To a stirred solution of 5-(5-bromo-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazole (Example 106, 300 mg, 0.6 mmol) in 1,4-Dioxane (4 mL) and water (1 mL), K_3PO_4 (379 mg, 1.8 mmol) and potassium vinyltrifluoroborate (80 mg, 0.6 mmol) were added and degassed for 10 min. Pd-118 (39 mg, 0.06 mmol) was added and the reaction mixture was heated at 100 °C for 12 h with continuous stirring. The reaction mixture was filtered through celite bed, washed with ethyl acetate, dried over anhydrous Na_2SO_4 , concentrated under reduced pressure. The product was purified by column chromatography to afford 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4-methyl-1-(2-(methylsulfonyl)ethyl)-5-vinyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (133, 2, 200 mg). LCMS (ESI) Calcd. for $\text{C}_{20}\text{H}_{20}\text{ClFN}_4\text{O}_3\text{S}$: 450.1, found $[\text{M}+\text{H}]^+$ = 451.2.

[0937] Synthesis of 3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-5-carbaldehyde, 134 [Step 2]: To a solution of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(4-methyl-1-(2-(methylsulfonyl)ethyl)-5-vinyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (133, 180 mg, 0.4 mmol) in acetone (5 mL) and water (1 mL) was added NMO (94 mg, 0.8 mmol) followed by the addition of OsO₄ (4% in water) (0.05 mL, 0.04 mmol) and stirred the reaction mixture at ambient temperature. After 4 h, NaIO₄ (128 mg, 0.6 mmol) was added, and the reaction mixture was stirred for another 16 h at ambient temperature. After completion, reaction mixture was concentrated under reduced pressure and dissolved in ethyl acetate. The organic layer was washed with water (twice), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford 3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-5-carbaldehyde (134, 130 mg). LCMS (ESI) Calcd. for C₁₉H₁₈ClFN₄O₄S: 452.1, found [M+H]⁺ = 453.2.

[0938] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 108 [Step-3]: To a solution of 3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-5-carbaldehyde (134, 100 mg, 0.22 mmol) in dichloromethane (3 mL), DAST (0.058 mL, 0.44 mmol) was added at 0 °C and stirred at ambient temperature for 12 h. After completion, the reaction mixture was quenched with saturated solution of NaHCO₃ at 0 °C and extracted with dichloromethane (twice). Combined organic extracts was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-4-methyl-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 108, 50 mg). LCMS (ESI) Calcd. for C₁₉H₁₈ClF₃N₄O₃S: 474.1, found [M+H]⁺ = 475.0. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.64-7.33 (m, 3H), 7.28-7.23 (m, 1H), 4.77-4.74 (t, 2H), 3.78-3.75 (t, 2H), 3.05 (s, 3H), 2.38 (s, 3H), 1.74-1.71 (m, 2H), 1.49-1.46 (m, 2H).

Example 110: Synthesis of 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-methylpropanoic acid (Example 110)

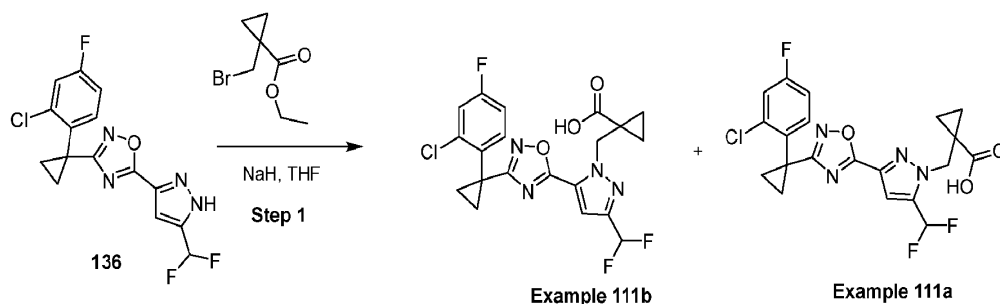


Scheme 61

[0939] Synthesis of tert-butyl 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-methylpropanoate, 135 [Step 1]: To a stirred solution of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetic acid (Example 109, 150 mg, 0.4 mmol) in 1,2 dichloromethane (2 mL), tert-butyl 2-amino-2-methylpropanoate (90 mg, 0.5 mmol) and DIPEA (0.3 mL, 1.2 mmol) were added followed by addition of T₃P (50% in ethyl acetate) (0.7 mL, 1.2 mmol). Reaction mixture was stirred for 16 h at ambient temperature. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in dichloromethane and washed with water (twice). Combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford tert-butyl 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-methylpropanoate (135, 150 mg). LCMS (ESI) Calcd. for C₂₅H₂₇ClF₃N₅O₄: 553.1, found [M+H]⁺: 554.1.

[0940] Synthesis of 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-methylpropanoic acid, Example 110 [Step 2]: To a stirred solution of tert-butyl 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-methylpropanoate (135, 150 mg, 0.3 mmol) in 1,2 dichloromethane (4mL), trifluoroacetic acid (0.3 mL, 3 mmol) was added dropwise at 0 °C and stirred for 2 h at ambient temperature. After completion, reaction mixture was concentrated under reduced pressure to afford product which was purified by reverse phase preparative HPLC to afford 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-methylpropanoic acid (Example 110, 110 mg). LCMS (ESI) Calcd. for C₂₁H₁₉ClF₃N₅O₄: 497.1, found [M+H]⁺: 498.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 12.36 (brs, 1H), 8.59 (s, 1H), 7.64-7.61 (m, 1H), 7.49 (dd, 1H), 7.34-7.07 (m, 3H), 5.10 (s, 2H), 1.71 (s, 2H), 1.47 (s, 2H), 1.37 (s, 6H).

Examples 111a & 111b: Synthesis of 1-((3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid (Example 111a) and 1-((5-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid (Example 111b)



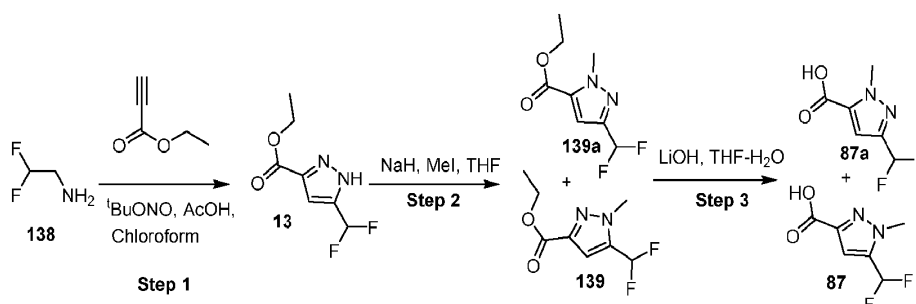
Scheme 62

[0941] Synthesis of 1-((3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid, Example 111a and 1-((5-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid, Example 111b [Step 1]: To a stirred solution of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (136, 300 mg, 0.8 mmol) in THF (10 mL) was added NaH (60%) (68 mg, 1.7 mmol) at 25 °C under nitrogen atmosphere. The reaction mixture was stirred for 15 min and ethyl 1-(bromomethyl) cyclopropanecarboxylate (210 mg, 1 mmol) was added. Resulting reaction mixture was stirred at ambient temperature for 16 h, quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by reverse phase preparative HPLC to afford 1-((3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid (Example 111a, 20 mg) as peak 2 and 1-((5-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)methyl)cyclopropane-1-carboxylic acid (Example 111b, 20mg) as peak 1. Formation of desired product was confirmed by nOe.

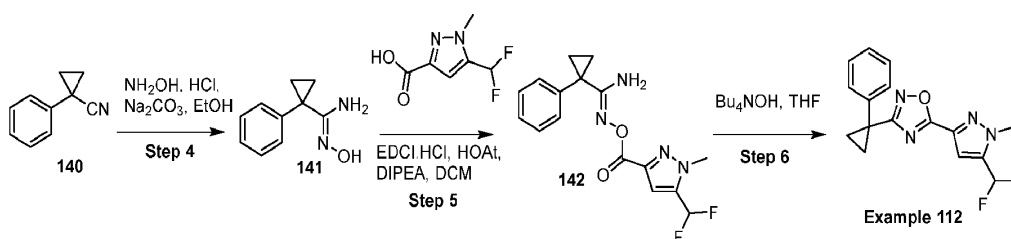
Example 111a: LCMS (ESI) Calcd. for $C_{20}H_{16}ClF_3N_4O_3$: 452.1, found $[M-H]^-$ = 451.0, 453.0. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.85-7.6 (m, 2H), 7.50-7.47 (dd, 1H), 7.27-7.22 (m, 1H), 7.20 (s, 1H), 4.47 (s, 2H), 1.71 (m, 2H), 1.47-1.44 (m, 2H), 1.11 (s, 2H), 1.02 (s, 2H).

Example 111b: LCMS (ESI) Calcd. for $C_{20}H_{16}ClF_3N_4O_3$ [M]: 452.81, found [M-H]⁻: 451, 453. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.64-7.61 (m, 1H), 7.52-7.49 (dd, 1H), 7.29 (s, 1H), 7.26 (dd, 1H), 7.21-6.94 (m, 1H), 4.82 (s, 2H), 1.72 (m, 2H), 1.51 (m, 2H), 1.04 (m, 2H), 0.80 (m, 2H).

Example 112: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-phenylcyclopropyl)-1,2,4-oxadiazole (Example 112)



Scheme 63



Scheme 64

[0942] Synthesis of ethyl 5-(difluoromethyl)-1H-pyrazole-3-carboxylate, 13 [Step-1]: 2,2-difluoroethan-1-amine (138, 5.0 g, 61.7 mmol), *tert*-Butyl nitrite (8.8 mL, 74.0 mmol) and acetic acid (0.4 mL, 6.2 mmol) was taken in chloroform (5 ml) and heated to 55 °C for 20 min. The resultant solution was cooled at ambient temperature, added dropwise into a reaction flask containing ethyl propiolate (3.2 mL, 30.8 mmol) in chloroform (10 ml) at 0 °C and stirred the reaction mixture at ambient temperature for 12 h. After completion, the reaction mixture was concentrated, partitioned with ethyl acetate and water. Combined organic layer was collected, washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford ethyl 5-(difluoromethyl)-1H-pyrazole-3-carboxylate (13, 3.2 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 14.46 (s, 1H), 7.18-6.91 (m, 2H), 4.35-4.19 (m, 2H), 1.33-1.24 (m, 3H).

[0943] Synthesis of ethyl 3-(difluoromethyl)-1-methyl-1H-pyrazole-5-carboxylate (139a) and ethyl 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxylate (139) [step-2]: To a solution of ethyl 5-(difluoromethyl)-1H-pyrazole-3-carboxylate (13, 3.0 g, 15.8 mmol) in DMF (2 mL), K₂CO₃ (4.4

g, 31.6 mmol) was added at 0 °C and the reaction mixture was stirred for 40 min under nitrogen atmosphere. Iodomethane (1.7 mL, 28.4 mmol) was then added to the reaction mixture and stirred for 12 h at ambient temperature. After completion, ethyl acetate was added to the reaction mixture and washed with ice cold brine (thrice). The organic layer was collected, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified through by column chromatography to afford ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (139a, 1.7 g) as peak 1 and ethyl 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylate (139, 1.1 g) as peak 2. NOTE: The actual structure of desired isomer ethyl 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylate (139, peak 2) was confirmed through NOE study of two peaks.

[0944] Analytical data of ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (139a): LCMS (ESI) Calcd for C₈H₁₀F₂N₂O₂: 204.1, found [M+H]⁺ = 205.0. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.16-6.89 (m, 2H), 4.34-4.29 (m, 2H), 4.12 (s, 3H), 1.33-1.29 (t, 3H).

[0945] Analytical data of ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (139): LCMS (ESI) Calcd for C₈H₁₀F₂N₂O₂: 204.1, found [M+H]⁺ = 205.0. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.45-7.19 (t, 1H), 7.05 (s, 1H), 4.30-4.25 (m, 2H), 3.99 (s, 3H), 1.30-1.27 (t, 3H).ss

[0946] Synthesis of 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (87) [Step 3]: To a stirred solution of ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (139, 450 mg, 2.2 mmol) in tetrahydrofuran (2 mL), methanol (1 mL) and water (0.5 mL), LiOH.H₂O (280 mg, 6.6 mmol) was added at 0 °C and the reaction mixture was stirred at ambient temperature for 12h. The reaction mixture was concentrated under reduced pressure, acidified with (1N) HCl up to pH 4-5 and extracted with ethyl acetate (thrice). The combined organic layer was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (87, 300 mg). ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 12.92 (s, 1H), 7.45-7.18 (t, 1H), 6.99 (s, 1H), 3.98 (s, 3H).

[0947] Synthesis of (Z)-*N'*-hydroxy-1-phenylcyclopropane-1-carboximidamide (141) (Step-4): To a stirred solution of 1-phenylcyclopropane-1-carbonitrile (140, 500 mg, 3.5 mmol) in ethanol (2 mL), Na₂CO₃ (740 mg, 7.0 mmol) was added followed by NH₂OH.HCl (485 mg, 7.0 mmol) and the reaction mixture was heated to reflux at 70 °C for 12h. After completion, the volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (thrice). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography

to afford (Z)-*N'*-hydroxy-1-phenylcyclopropane-1-carboximidamide (141, 450 mg). LCMS (ESI) Calcd for C₁₀H₁₂N₂O: 176.1, found [M+H]⁺ = 176.6.

[0948] Synthesis of (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-phenylcyclopropane-1-carboximidamide (142) (Step-5): To a stirred solution of 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (100 mg, 0.6 mmol) and (Z)-*N'*-hydroxy-1-phenylcyclopropane-1-carboximidamide (141, 150 mg, 0.9 mmol) in dichloromethane (4 mL), *N,N*-Diisopropylethylamine (0.2 mL, 1.1 mmol), EDCI.HCl (140 mg, 0.7 mmol) and HOAt (15 mg, 0.1 mmol) were added at 0 °C and reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was concentrated under reduced pressure, dissolved with ethyl acetate, washed with water (twice) and brine. The combined organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-phenylcyclopropane-1-carboximidamide (142, 150 mg). LCMS (ESI) Calcd for C₁₆H₁₆F₂N₄O₂: 334.1, found [M+H]⁺ = 335.3.

[0949] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-phenylcyclopropyl)-1,2,4-oxadiazole (Example 112) [Step-6]: To a stirred solution of (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-phenylcyclopropane-1-carboximidamide (142, 150 mg, 0.5 mmol) in THF (2 mL), tetrabutylammonium hydroxide (0.1 mL, 0.1 mmol, 1M in methanol) was added and resulting reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water (twice), dried over anhydrous Na₂SO₄, filtered and concentrated again under reduced pressure. The product was purified by reverse phase prep-HPLC and lyophilized to afford 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-phenylcyclopropyl)-1,2,4-oxadiazole (Example 112, 53 mg). LCMS (ESI) Calcd for C₁₆H₁₄F₂N₄O: 316.1, found [M+H]⁺ = 317.1. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.50-7.24 (m, 7H), 4.05 (s, 3H), 1.61-1.59 (m, 2H), 1.44-1.41 (m, 2H).

[0950] Examples 113-131 were synthesized in a manner similar to Example 112.

Example 113: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-fluoro-5-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 113)

[0951] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-fluoro-5-methylphenyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-fluoro-5-methylphenyl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₇H₁₅F₃N₄O: 348.1,

found $[M+H]^+ = 349.1$. ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 7.50-7.24 (m, 3H), 7.20-7.16 (m, 1H), 7.11-7.06 (m, 1H), 4.05 (s, 3H), 2.29 (s, 3H), 1.64-1.61 (m, 2H), 1.45-1.42 (m, 2H).

Example 114: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(pyridin-2-yl)cyclopropyl)-1,2,4-oxadiazole (Example 114)

[0952] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(pyridin-2-yl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(pyridin-2-yl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for $\text{C}_{15}\text{H}_{13}\text{F}_2\text{N}_5\text{O}$: 317.1, found $[M+H]^+ = 318.1$. ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 8.51 (d, 1H), 7.77-7.72 (m, 1H), 7.52-7.25 (m, 4H), 4.06 (s, 3H), 1.70-1.67 (m, 2H), 1.61-1.58 (m, 2H).

Example 115: Synthesis of 3-(1-(2-bromophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 115)

[0953] 3-(1-(2-bromophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-1-(2-bromophenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for $\text{C}_{16}\text{H}_{13}\text{BrF}_2\text{N}_4\text{O}$: 395.2, found $[M+H]^+ = 396.1$. ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 7.66 (d, 1H), 7.55 (dd, 1H), 7.50-7.24 (m, 4H), 4.05 (s, 3H), 1.74 (brs, 2H), 1.48-1.46 (m, 2H).

Example 116: Synthesis of 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 116)

[0954] 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-1-(2-chlorophenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for $\text{C}_{16}\text{H}_{13}\text{ClF}_2\text{N}_4\text{O}$: 350.8, found $[M+H]^+ = 351.1$. ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 7.58-7.56 (m, 1H), 7.50-7.48 (m, 1H), 7.41-7.24 (m, 4H), 4.04 (s, 3H), 1.73-1.70 (m, 2H), 1.48-1.45 (m, 2H).

Example 117: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(pyridin-3-yl)cyclopropyl)-1,2,4-oxadiazole (Example 117)

[0955] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(pyridin-3-yl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(pyridin-3-yl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for $\text{C}_{15}\text{H}_{13}\text{F}_2\text{N}_5\text{O}$: 317.1, found $[M+H]^+ = 318.1$. ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 8.67 (d, 1H), 8.53-8.51 (dd, 1H), 7.88-7.85 (m, 1H), 7.51-7.24 (m, 3H), 4.05 (s, 3H), 1.64-1.61 (m, 2H), 1.58-1.50 (m, 2H).

Example 118: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(pyridin-4-yl)cyclopropyl)-1,2,4-oxadiazole (Example 118)

[0956] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(pyridin-4-yl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(pyridin-4-yl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₅H₁₃F₂N₅O: 317.1, found [M+H]⁺ = 318.1. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 8.55-8.53 (m, 2H), 7.52-7.25 (m, 4H), 4.05 (s, 3H), 1.67-1.64 (m, 2H), 1.56-1.53 (m, 2H).

Example 119: Synthesis of 3-(1-(3-chloro-5-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 119)

[0957] 3-(1-(3-chloro-5-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-1-(3-chloro-5-fluorophenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₆H₁₂ClF₃N₄O: 368.1, found [M+H]⁺ = 369.0. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.51-7.24 (m, 5H), 4.05 (s, 3H), 1.61-1.58 (m, 2H), 1.55-1.52 (m, 2H).

Example 120: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(2-(5-fluoro-2-methylphenyl)propan-2-yl)-1,2,4-oxadiazole (Example 120)

[0958] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(2-(5-fluoro-2-methylphenyl)propan-2-yl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(3-fluoro-5-methylphenyl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₇H₁₅F₃N₄O: 348.1, found [M+H]⁺ = 349.1. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.51-7.24 (m, 2H), 7.10-6.96 (m, 3H), 4.05 (s, 3H), 2.32 (s, 3H), 1.58-1.55 (m, 2H), 1.46-1.44 (m, 2H).

Example 121: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*p*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 121)

[0959] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*p*-tolyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(*p*-tolyl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd. for C₁₇H₁₆F₂N₄O: 330.1, found [M+H]⁺ = 331.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.49-7.22 (m, 4H), 7.14 (d, 2H), 4.03 (s, 3H), 2.28 (s, 3H), 1.54-1.52 (m, 2H), 1.36-1.34 (m, 2H).

Example 122: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*m*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 122)

[0960] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(*m*-tolyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (*Z*)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(*m*-tolyl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd. for C₁₇H₁₆F₂N₄O: 330.1, found [M+H]⁺ = 331.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.50-7.10 (m, 6H), 4.05 (s, 3H), 2.31 (s, 3H), 1.57-1.55 (m, 2H), 1.41-1.39 (m, 2H).

Example 123: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(3-methylpyridin-2-yl)cyclopropyl)-1,2,4-oxadiazole (Example 123)

[0961] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(3-methylpyridin-2-yl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (*Z*)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(3-methylpyridin-2-yl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₆H₁₅F₂N₅O: 331.1, found [M+H]⁺ = 332.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 8.37(d, 1H), 7.65-7.24 (m, 4H), 4.05 (s, 3H), 2.25 (s, 3H), 1.68-1.65 (m, 2H), 1.58-1.55 (m, 2H).

Example 124: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 124)

[0962] 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (*Z*)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-(trifluoromethyl)phenyl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₇H₁₃F₅N₄O: 384.1, found [M+H]⁺ = 385.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.78-7.24 (m, 6H), 4.04 (s, 3H), 1.72 (brs, 2H), 1.55 (brs, 2H).

Example 125: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-methylpyridin-3-yl)cyclopropyl)-1,2,4-oxadiazole (Example 125)

[0963] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-methylpyridin-3-yl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (*Z*)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-methylpyridin-3-yl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₆H₁₅F₂N₅O: 331.1, found [M+H]⁺ = 332.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 8.41(d, 1H), 7.76(d, 1H), 7.50-7.23 (m, 4H), 4.05 (s, 3H), 2.45 (s, 3H), 1.71-1.68 (m, 2H), 1.48-1.45 (m, 2H).

Example 126: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2,5-difluorophenyl)cyclopropyl)-1,2,4-oxadiazole (Example 126)

[0964] 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2,5-difluorophenyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-*N*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2,5-difluorophenyl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₆H₁₂F₄N₄O: 352.1, found [M+H]⁺ = 353.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.51-7.37 (m, 2H), 7.30-7.24 (m, 3H), 4.05 (s, 3H), 1.66-1.63 (m, 2H), 1.52-1.49 (m, 2H).

Example 127: Synthesis of 3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 127)

[0965] 3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-1-(2-chloro-5-fluorophenyl)-*N*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₆H₁₂ClF₃N₄O: 368.0, found [M+H]⁺ = 369.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.52-7.49 (m, 1H), 7.45-7.18 (m, 4H), 4.05 (s, 3H), 1.75 (s, 2H), 1.51 (s, 2H).

Example 128: Synthesis of 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 128)

[0966] 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-1-(2-chloro-3-fluorophenyl)-*N*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd for C₁₆H₁₂ClF₃N₄O: 368.1, found [M+H]⁺ = 369.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.46-7.19 (m, 5H), 4.06 (s, 3H), 1.77 (s, 2H), 1.56 (s, 2H).

Example 129: Synthesis of (5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2,5-dimethylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 129)

[0967] (5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2,5-dimethylphenyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-*N*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2,5-dimethylphenyl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd. for C₁₈H₁₈F₂N₄O [M]: 344.36, found [M+H]⁺: 345.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.50-7.23 (m, 2H), 7.18 (s, 1H), 7.09 (d, 1H), 7.03 (d, 1H), 4.04 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H), 1.63 (d, 2H), 1.36 (d, 2H).

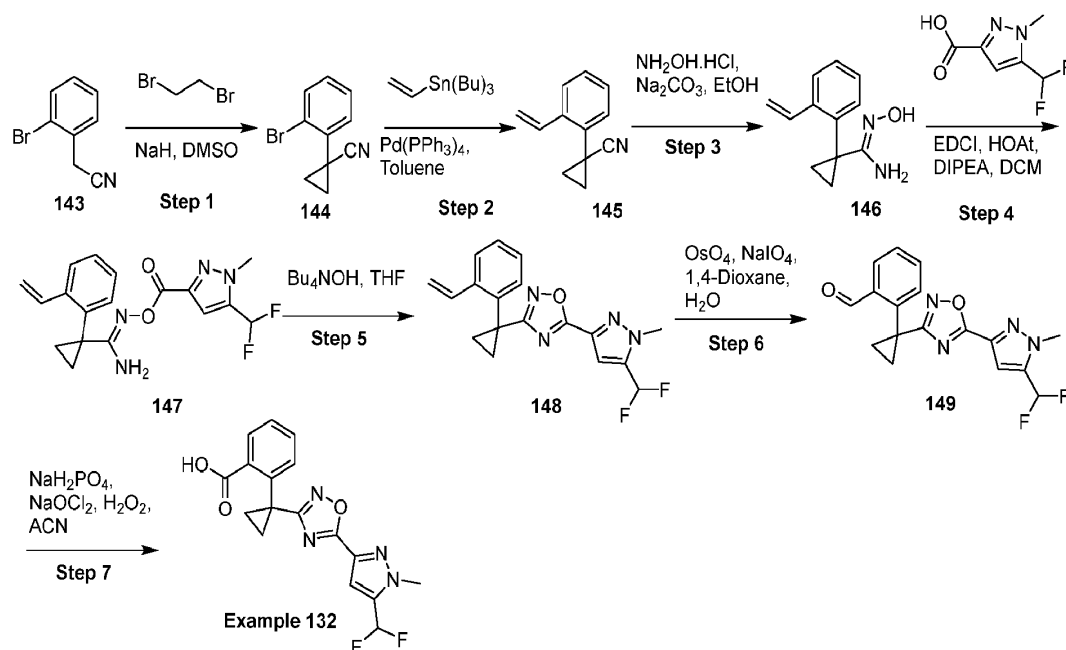
Example 130: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-methyl-5-(trifluoromethyl)phenyl)cyclopropyl)-1,2,4-oxadiazole (Example 130)

[0968] 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-methyl-5-(trifluoromethyl)phenyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-N'-((5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl)oxy)-1-(2-methyl-5-(trifluoromethyl)phenyl)cyclopropane-1-carboximidamide. LCMS (ESI) Calcd. for C₁₈H₁₅F₅N₄O : 398.3, found [M+H]⁺: 399.1. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H : 7.69 (s, 1H), 7.61 (d, 1H), 7.50-7.23 (m, 3H), 4.02 (d, 3H), 2.35 (s, 3H), 1.98-1.70 (m, 2H), 1.53-1.49 (m, 2H).

Example 131: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-phenoxyphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 131)

[0969] 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-phenoxyphenyl)cyclopropyl)-1,2,4-oxadiazole was synthesized following Scheme 64 using (Z)-N'-((5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl)oxy)-1-(2-phenoxyphenyl)cyclopropane-1-carboximidamide. ¹HNMR (400 MHz, DMSO-*d*₆) (at 100 °C) δ_H 7.45-7.32 (m, 4H), 7.20 (d, 2H), 7.15-7.10 (m, 2H), 7.03 (d, 2H), 6.92 (d, 1H), 4.06 (s, 3H), 1.61-1.58 (m, 2H), 1.45-1.42 (m, 2H). LCMS (ESI) Calcd for C₂₂H₁₈F₂N₄O₂: 408.4, found [M+H]⁺ = 409.2.

Example 132: Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzoic acid (Example 132)



Scheme 65

[0970] Synthesis of 1-(2-bromophenyl)cyclopropane-1-carbonitrile, 144 [Step 1]: To a stirred suspension of sodium hydride (920 mg, 38.3 mmol) in DMSO (50 mL) at 0 °C, 2-(2-bromophenyl) acetonitrile (143, 3.0 g, 15.3 mmol) was added. The reaction mixture was stirred at ambient temperature for 1 h and 1,2-dibromoethane (1.6 mL, 18.4 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford 1-(2-bromophenyl)cyclopropane-1-carbonitrile (144, 2.0 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.72 (d, 1H), 7.52 (d, 1H), 7.42 (t, 1H), 7.34 (t, 1H), 1.78-1.75 (m, 2H), 1.43-1.40 (m, 2H).

[0971] Synthesis of 1-(2-vinylphenyl)cyclopropane-1-carbonitrile, 145 [Step 2]: In a sealed tube, a solution of 1-(2-bromophenyl)cyclopropane-1-carbonitrile (144, 1.1 g, 4.9 mmol) and tributyl(vinyl)stannane (2.2 mL, 7.4 mmol) in toluene (10 mL) was purged with Argon gas for 15 min and tetrakis triphenyl phosphine Pd (0) (570 mg, 0.5 mmol) was added. The reaction mixture was stirred at 100 °C for 16 h and concentrated under reduced pressure. The product was purified by flash chromatography to afford 1-(2-vinylphenyl)cyclopropane-1-carbonitrile (145, 680 mg). LCMS (ESI) Calcd. for C₁₂H₁₁N: 169.0, found [M+H]⁺ = 169.9. ¹H NMR (400

MHz, DMSO- d_6) δ_H 7.68-7.66 (m, 1H), 7.40-7.37 (m, 2H), 7.33-7.31 (m, 1H), 7.27-7.20 (m, 1H), 5.89 (d, 1H), 5.51-5.48 (m, 1H), 1.76-1.73 (m, 2H), 1.38-1.30 (m, 2H).

[0972] Synthesis of (Z)-*N'*-hydroxy-1-(2-vinylphenyl)cyclopropane-1-carboximidamide 146, [Step 3]: To a stirred solution of 1-(2-vinylphenyl)cyclopropane-1-carbonitrile (145, 680 mg, 4.0 mmol) in ethanol (12 mL), sodium carbonate (1.1 g, 10.0 mmol) and hydroxyl amine hydrochloride (700 mg, 10.0 mmol) were added. The reaction mixture was heated at 70 °C for 16 h. After completion, the reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate and washed with water and by brine. The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-*N'*-hydroxy-1-(2-vinylphenyl)cyclopropane-1-carboximidamide (146, 580 mg). LCMS (ESI) Calcd. for $C_{12}H_{14}N_2O$: 202.3, found $[M+H]^+$ = 203.3.

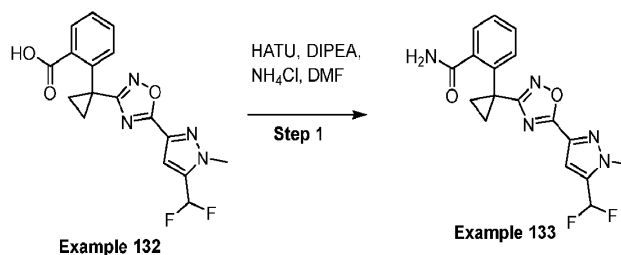
[0973] Synthesis of (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-vinylphenyl)cyclopropane-1-carboximidamide, 147 [Step 4]: To a stirred solution of (Z)-*N'*-hydroxy-1-(2-vinylphenyl)cyclopropane-1-carboximidamide (146, 580 mg, 2.9 mmol), and 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (200 mg, 1.1 mmol) in dichloromethane (10 mL), *N,N*-diisopropylethylamine (0.4 mL, 2.8 mmol), 1-hydroxy-7-azabenzotriazole (30 mg, 0.2 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (285 mg, 1.5 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-vinylphenyl)cyclopropane-1-carboximidamide (147, 940 mg). LCMS (ESI) Calcd. for $C_{18}H_{18}F_2N_4O_2$: 360.1, found $[M+H]^+$ = 361.4.

[0974] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-vinylphenyl)cyclopropyl)-1,2,4-oxadiazole, 148 [Step 5]: To a stirred solution of (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-vinylphenyl)cyclopropane-1-carboximidamide (147, 940 mg, 2.6 mmol) in THF (10 mL), tetra butyl ammonium hydroxide (205 mg, 0.8 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 4 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-vinylphenyl)cyclopropyl)-1,2,4-oxadiazole (148, 710 mg). LCMS (ESI) Calcd. for $C_{18}H_{16}F_2N_4O$: 342.2, found $[M+H]^+$ = 343.2.

[0975] Synthesis 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzaldehyde, 149 [Step 6]: To a stirred solution of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-vinylphenyl)cyclopropyl)-1,2,4-oxadiazole (148, 700 mg, 2.0 mmol) in 1,4-dioxane (15 mL) and water (8 mL) mixture at 0 °C, osmium tetroxide (50 mg, 0.20 mmol) and sodium periodate (855 mg, 4.0 mmol) were added. The reaction mixture was stirred at ambient temperature at for 16 h. After completion the reaction mixture was quenched with aqueous ammonium chloride, diluted with ethyl acetate and washed with water and brine. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography to afford 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzaldehyde (149, 680 mg). LCMS (ESI) Calcd. for C₁₇H₁₄F₂N₄O₂: 344.1, found [M+H]⁺ = 345.2.

[0976] Synthesis 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzoic acid, Example 132 [Step 7]: To a stirred solution of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzaldehyde (10, 700 mg, 2.0 mmol) in acetonitrile (20 mL) and water (10 mL), sodium chlorite (735 mg, 8.1 mmol), sodium dihydrogen phosphate (975 mg, 8.1 mmol) and hydrogen peroxide (1.1 mL, 40.7 mmol) were added. The reaction mixture was allowed to stir at ambient temperature for 16 h, diluted with ethyl acetate and washed with water and brine. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzoic acid (Example 132, 628 mg). LCMS (ESI) Calcd. for C₁₇H₁₄F₂N₄O₃: 360.1, found [M+H]⁺ = 361.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.74 (d, 1H), 7.52-7.26 (m, 5H), 4.04 (s, 3H), 1.61-1.60 (m, 2H), 1.37-1.36 (m, 2H). One carboxylic acid proton is exchangeable.

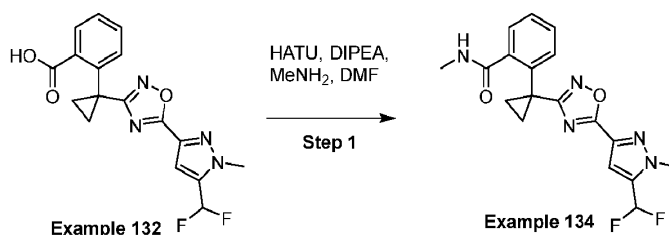
Example 133: Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzamide (Example 133)



Scheme 66

[0977] Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzamide, Example 133 [Step 1]: To a stirred solution of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzoic acid (Example 132, 100 mg, 0.3 mmol) in DMF (2 mL), *N,N*-diisopropylethylamine (0.2 mL, 1.1 mmol) and HATU (265 mg, 0.7 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min and ammonium chloride (45 mg, 0.8 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h and quenched with crushed ice. The precipitate was filtered, washed with ice-cold water and dried under vacuum. The product was purified by reverse phase prep HPLC to afford 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzamide (Example 133, 44 mg). LCMS (ESI) Calcd. for $\text{C}_{17}\text{H}_{15}\text{F}_2\text{N}_5\text{O}_2$: 359.1, found $[\text{M}+\text{H}]^+ = 360.2$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 7.55-7.24 (m, 8H), 4.04 (s, 3H), 1.59-1.57 (m, 2H), 1.39-1.36 (m, 2H).

Example 134: Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-*N*-methylbenzamide (Example 134)

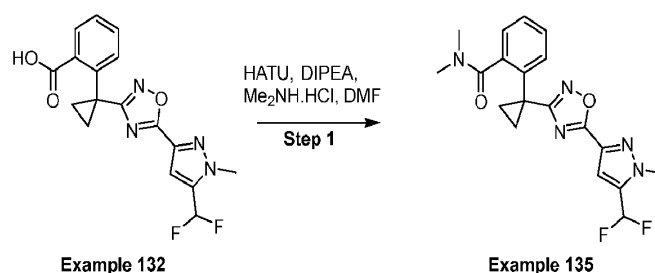


Scheme 67

[0978] Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-*N*-methylbenzamide, Example 134 [Step 1]: To a stirred solution of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzoic acid (Example 132, 100 mg, 0.3 mmol) in DMF (2 mL), *N,N*-diisopropylethylamine (0.2 mL, 1.1 mmol) and HATU (265 mg, 0.7 mmol) were added. The reaction mixture was stirred at 0 °C for

30 min and a solution of methyl amine in tetrahydrofuran (0.4 mL, 0.8 mmol, 2M) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h and quenched with crushed ice. The precipitate formed was filtered, washed with ice-cold water and dried under vacuum. The product was purified by reverse phase prep HPLC to afford 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-*N*-methylbenzamide (Example 134, 23 mg). LCMS (ESI) Calcd. for $C_{18}H_{17}F_2N_5O_2$: 373.1, found $[M+H]^+ = 374.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.99-7.98 (m, 1H), 7.55-7.51 (m, 1H), 7.47-7.43 (m, 1H), 7.41-7.36 (m, 3H), 7.27-7.24 (m, 1H), 4.05 (s, 3H), 2.66 (d, 3H), 1.57-1.54 (m, 2H), 1.34-1.31 (m, 2H).

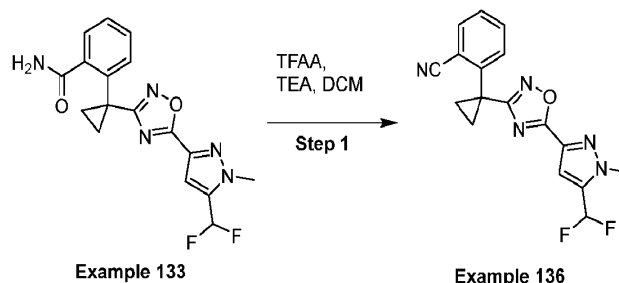
Example 135: Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-*N,N*-dimethylbenzamide (Example 135)



Scheme 68

[0979] Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-*N,N*-dimethylbenzamide, 135 [Step 1]: To a stirred solution of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzoic acid (**132**, 100 mg, 0.3 mmol) in DMF (2 mL), *N,N*-diisopropylethylamine (0.2 mL, 1.1 mmol) and HATU (265 mg, 0.7 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min and dimethylamine hydrochloride (30 mg, 0.4 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h and quenched with crushed ice. The precipitate was filtered, washed with ice-cold water and dried under vacuum. The product was purified by reverse phase preparative HPLC to afford 2-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-*N,N*-dimethylbenzamide (**135**, 29 mg). LCMS (ESI) Calcd. for $C_{19}H_{19}F_2N_5O_2$: 387.1, found $[M+H]^+ = 388.3$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.58 (d, 1H), 7.50-7.20 (m, 5H), 4.04 (s, 3H), 2.89 (s, 3H), 2.65 (s, 3H), 1.52 (m, 4H).

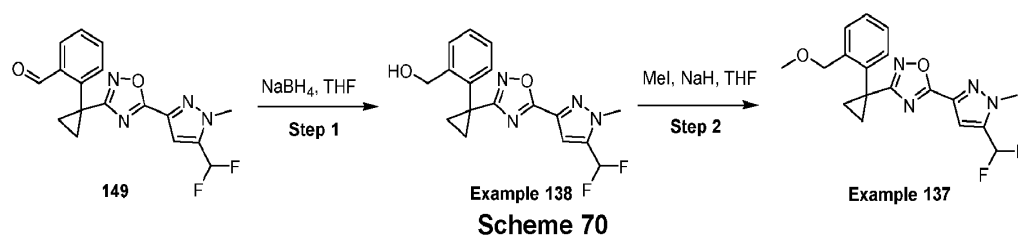
Example 136: Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzonitrile (Example 136)



Scheme 69

[0980] Synthesis of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzonitrile, 136 [Step 1]: To a solution of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzamide (**133**, 90 mg, 0.3 mmol) and triethylamine (0.25 mL, 1.5 mmol) in dry dichloromethane (5 mL) at 0 °C, trifluoroacetic acid anhydride (265 mg, 1.3 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate and washed with ice-cold water. The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford 2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzonitrile (**136**, 44 mg). LCMS (ESI) Calcd. for $C_{17}H_{13}F_2N_5O$: 341.1, found $[M+H]^+ = 342.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.89 (d, 1H), 7.76-7.68 (m, 2H), 7.56 (t, 1H), 7.51-7.24 (m, 2H), 4.05 (s, 3H), 1.77-1.74 (m, 2H), 1.61-1.58 (m, 2H).

Example 137: Synthesis of (2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)methanol (Example 137)



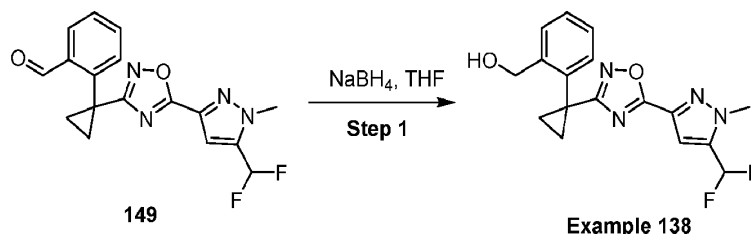
Scheme 70

[0981] Synthesis of (2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)methanol, Example 138 [Step 1]: To a stirred solution of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzaldehyde (**149**,

200 mg, 0.6 mmol) in THF (3 mL), sodium borohydride (45 mg, 1.2 mmol) was added at 0°C. The resulting reaction mixture was stirred at ambient temperature for 4 h. The reaction mixture was quenched with aqueous ammonium chloride, extracted with ethyl acetate and washed with brine. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography to afford (2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)methanol (Example 138, 165 mg). LCMS (ESI) Calcd. for C₁₇H₁₆F₂N₄O₂: 346.1, found [M+H]⁺ = 347.1. ¹H NMR (400 MHz, DMSO-d₆) δH 7.55-7.51 (m, 1H), 7.39-7.33 (m, 3H), 7.28-7.23 (m, 2H), 5.12 (t, 1H), 4.57 (d, 2H), 4.04 (s, 3H), 1.63-1.62 (m, 2H), 1.42-1.41 (m, 2H).

[0982] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-(methoxymethyl)phenyl)cyclopropyl)-1,2,4-oxadiazole, Example 137 [Step 2]: To a stirred solution of (2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)methanol (150, 140 mg, 0.4 mmol) in THF (3 mL) at 0 °C, sodium hydride (30 mg, 1.2 mmol) was added portion-wise and stirred for 1 h. Methyl iodide (0.05 mL, 0.6 mmol) was added and the resulting reaction mixture was stirred for at ambient temperature for 16 h. The reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate and washed with brine. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-(methoxymethyl)phenyl)cyclopropyl)-1,2,4-oxadiazole (Example 137, 28 mg). LCMS (ESI) Calcd. for C₁₈H₁₈F₂N₄O₂: 360.1, found [M+H]⁺ = 361.2. ¹H NMR (400 MHz, DMSO-d₆) δH 7.50-7.24 (m, 6H), 4.48 (s, 2H), 4.04 (s, 3H), 3.25 (s, 3H), 1.64 (brs, 2H), 1.43 (brs, 2H).

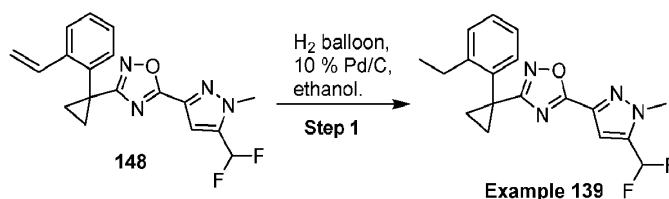
Example 138: Synthesis of (2-(1-(5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)methanol (Example 138)



Scheme 71

[0983] Synthesis of (2-(1-(5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)methanol, Example 138 [Step 1]: To a stirred solution of 2-(1-(5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)benzaldehyde (149, 30 mg, 0.1 mmol) in tetrahydrofuran (1 mL), sodium borohydride (6.6 mg, 0.2mmol) was added at 0 °C. The resulting reaction mixture was stirred at ambient temperature for 4 h. After completion, the reaction mixture was quenched with saturated solution of aqueous ammonium chloride. The aqueous phase was extracted with ethyl acetate (twice). The combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford (2-(1-(5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)phenyl)methanol, (Example 138, 8mg). LCMS (ESI) Calcd. for $C_{17}H_{16}F_2N_4O_2$: 346.1, found $[M+H]^+ = 347.1$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.55-7.53 (m, 1H), 7.50-7.25 (m, 5H), 5.11 (t, 1H), 4.58-4.57 (m, 2H), 4.04 (s, 3H), 1.63 (brs, 2H), 1.42 (brs, 2H).

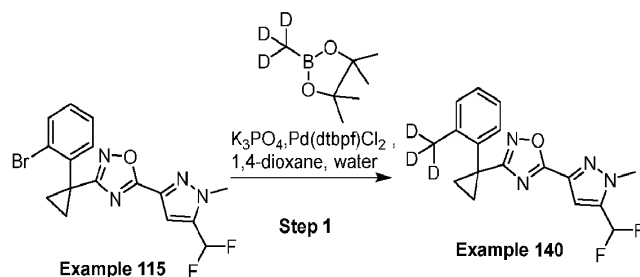
Example 139: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-ethylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 139)



Scheme 72

[0984] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-ethylphenyl)cyclopropyl)-1,2,4-oxadiazole, Example 139 [Step 6]: A stirred solution of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-vinylphenyl)cyclopropyl)-1,2,4-oxadiazole (148, 150 mg, 0.4 mmol) in ethanol (4 mL) was purged with Argon gas for 5 min. Pd on C (60 mg, 10 %) was added to the solution and the mixture was hydrogenated using a H_2 balloon for 2 h at ambient temperature. After completion, the mixture was passed through celite bed and concentrated under reduced pressure. The product was purified by RP prep HPLC purification to afford 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-ethylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 139, 75 mg). LCMS (ESI) Calcd for $C_{18}H_{18}F_2N_4O$: 344.3, found $[M+H]^+ = 345.2$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.50-7.17 (m, 6H), 4.04 (s, 3H), 2.66 (q, 2H), 1.66 (d, 2H), 1.39 (d, 2H), 1.12 (m, 3H).

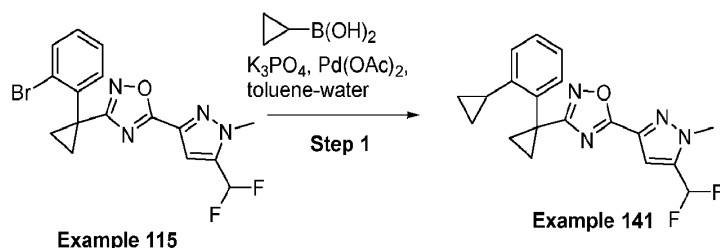
Example 140: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-(methyl-*d*₃)phenyl)cyclopropyl)-1,2,4-oxadiazole (Example 140)



Scheme 73

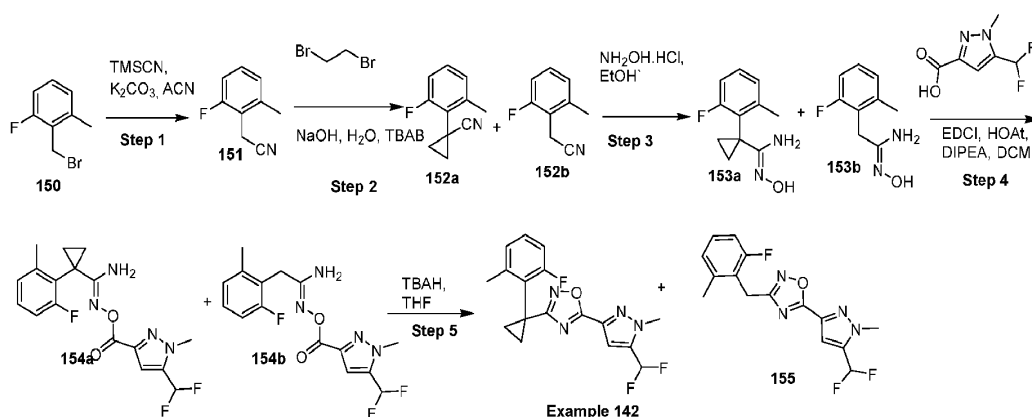
[0985] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-(methyl-*d*₃)phenyl)cyclopropyl)-1,2,4-oxadiazole, Example 140, (Step-1): To a stirred solution of 3-(1-(2-bromophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 115, 80 mg, 0.2 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) mixture, K₃PO₄ (115 mg, 0.6 mmol) and 4,4,5,5-tetramethyl-2-(methyl-*d*₃)-1,3,2-dioxaborolane (45 mg, 0.3 mmol) were added and the reaction mixture was degassed with nitrogen gas for 10 minutes. Pd(dtbpf)Cl₂ (15 mg, 0.02 mmol) was added to the reaction mixture and heated at 100 °C for 16h. After completion, the reaction mixture was filtered through celite bed, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified through reverse phase prep-HPLC to afford 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-(methyl-*d*₃)phenyl)cyclopropyl)-1,2,4-oxadiazole (Example 140, 7 mg). LCMS (ESI) Calcd for C₁₇H₁₃D₃F₂N₄O: 333.2, found [M+H]⁺ = 334.1. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.51-7.20 (m, 6H), 4.04 (s, 3H), 1.65 (brs, 2H), 1.39 (brs, 2H).

Example 141: Synthesis of 3-(1-(2-cyclopropylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 141)

**Scheme 74**

[0986] Synthesis of 3-(1-(2-cyclopropylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 141 [Step 1]: To a stirred solution of 3-(1-(2-bromophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 115, 100 mg, 0.3 mmol) in toluene (2 mL) and water (0.1 mL), cyclopropyl boronic acid (30 mg, 0.3 mmol) and K_3PO_4 (160 mg, 0.7 mmol) were added and degassed for 10 min. $Pd(OAc)_2$ (6.0 mg, 0.02 mmol) was added to the reaction mixture and heated at 100 °C for 12 h with continuous stirring. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water (twice). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product which was purified by reverse phase prep-HPLC to afford 3-(1-(2-cyclopropylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 141, 40 mg). 1H NMR (400 MHz, $DMSO-d_6$) δ : 7.50-7.18 (m, 4H), 7.16 (t, 1H), 6.89 (d, 1H), 4.04 (s, 3H), 2.07-2.01 (m, 1H), 1.70 (s, 2H), 1.44 (s, 2H), 0.82 (d, 2H), 0.62 (d, 2H). LCMS (ESI) Calcd for $C_{19}H_{18}F_2N_4O$: 356.3, found $[M+H]^+ = 357.2$.

Example 142: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(2-fluoro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 142)



Scheme 75

[0987] Synthesis of 2-(2-fluoro-6-methylphenyl)acetonitrile, 151 [Step 1]: To a stirred solution of 2-(bromomethyl)-1-fluoro-3-methylbenzene (150, 1.0 g, 4.9 mmol) in acetonitrile (10 mL), K_2CO_3 (1.4 g, 9.9 mmol) was added followed by trimethylsilylformonitrile (0.9 mL, 7.4 mmol) and the resulting reaction mixture was heated at 100 °C for 16h. After completion, the reaction mixture was dissolved in ethyl acetate, washed with water (thrice) and brine. The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford 2-(2-fluoro-6-methyl-phenyl)acetonitrile (151, 650 mg). GCMS Calcd for C_9H_8FN : 149.1, found $[M]^+ = 149.2$.

[0988] Synthesis of 1-(2-fluoro-6-methylphenyl)cyclopropane-1-carbonitrile & 2-(2-fluoro-6-methylphenyl)acetonitrile 152a & 152b, [Step 2]: To a stirred solution of NaOH (2.1 g, 52.3 mmol) in water (7 mL), 1,2-dibromoethane (3.3 mL, 21.8 mmol), TBAB (280 mg, 0.9 mmol) and 2-(2-fluoro-6-methyl-phenyl)acetonitrile (151, 650 mg, 4.4 mmol) were added and the reaction mixture was heated at 100 °C for 12h. After completion, the reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford 1-(2-fluoro-6-methylphenyl)cyclopropane-1-carbonitrile and 2-(2-fluoro-6-methylphenyl)acetonitrile (152a & 152b, 250 mg). GCMS Calcd for $C_{11}H_{10}FN$: 175.2, found $[M]^+ = 175.1$. GCMS Calcd for C_9H_8FN : 149.1, found $[M]^+ = 149.1$.

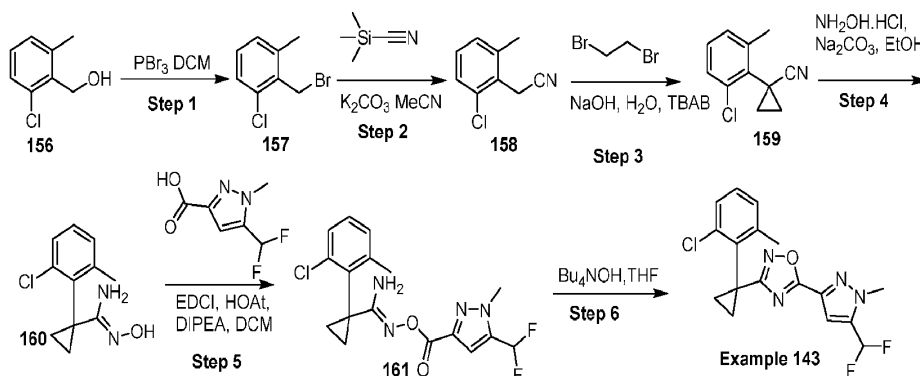
[0989] Synthesis of (Z)-1-(2-fluoro-6-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide & (Z)-2-(2-fluoro-6-methylphenyl)-*N'*-hydroxyacetimidamide, 153a & 153b [Step 3]: To a stirred solution of 1-(2-fluoro-6-methylphenyl)cyclopropane-1-carbonitrile and (Z)-2-(2-fluoro-6-methylphenyl)-*N'*-hydroxyacetimidamide (152a & 152b, 250 mg) in ethanol (2 mL), sodium carbonate (305 mg, 2.9 mmol) and hydroxylamine hydrochloride (200 mg, 2.9 mmol) were added and the reaction was heated at 70 °C for 12h. After completion, the volatiles were evaporated under reduced pressure, dissolved in water and extracted with ethyl acetate(thrice). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure and purified by combiflash column chromatography to afford (Z)-1-(2-fluoro-6-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide and (Z)-2-(2-fluoro-6-methylphenyl)-*N'*-hydroxyacetimidamide (153a & 153b, 270 mg). LCMS (ESI) Calcd for $C_{11}H_{13}FN_2O$: 208.2, found $[M+H]^+ = 209.3$. LCMS Calcd for $C_9H_{11}FN_2O$: 182.0, found $[M+H]^+ = 183.2$.

[0990] Synthesis of (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-fluoro-6-methylphenyl)cyclopropane-1-carboximidamide & (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-2-(2-fluoro-6-methylphenyl)acetimidamide, 154a & 154b [Step 4]: To a stirred solution of 5-(difluoromethyl)-1-methyl-pyrazole-3-carboxylic acid (150 mg, 0.9 mmol) and (Z)-1-(2-fluoro-6-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide & (Z)-2-(2-fluoro-6-methylphenyl)-*N'*-hydroxyacetimidamide (153a & 153b, 265 mg) in dichloromethane (3 mL), *N,N*-Diisopropylethylamine (0.5 mL, 2.6 mmol), EDC.HCl (210 mg, 1.1 mmol) and HOAt (25 mg, 0.2 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was concentrated, diluted with water and extracted with ethyl acetate (twice). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure and purified through combiflash column chromatography to afford (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-fluoro-6-methylphenyl)cyclopropane-1-carboximidamide and (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-2-(2-fluoro-6-methylphenyl)acetimidamide (154a & 154b, 200 mg). LCMS (ESI) Calcd for C₁₇H₁₇F₃N₄O₂: 366.3, found [M+H]⁺ = 367. LCMS (ESI) Calcd for C₁₅H₁₅F₃N₄O₂: 340.3, found [M+H]⁺ = 341.2.

[0991] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-fluoro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazole & 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(2-fluoro-6-methylbenzyl)-1,2,4-oxadiazole, Example 142 & 155 [Step 5]: (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(2-fluoro-6-methylphenyl)cyclopropane-1-carboximidamide and (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-2-(2-fluoro-6-methylphenyl)acetimidamide (Example 142 & 155, 200 mg) in THF (2 mL), tetrabutylammonium hydroxide (0.2 ml, 0.02 mmol) was added and the reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water (twice). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by reverse phase RP prep to afford 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-fluoro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 142, 15 mg) and 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(2-fluoro-6-methylbenzyl)-1,2,4-oxadiazole (155, 30 mg). ¹H NMR (400 MHz, DMSO-*d*₆) (Example 142): δ_H 7.51-7.22 (m, 3H), 7.09-7.02 (m, 2H), 4.05 (s, 3H), 2.33 (s, 3H), 1.74 (s, 2H), 1.42 (s, 2H). LCMS (ESI) Calcd for C₁₇H₁₅F₃N₄O: 348.3, found [M+H]⁺ = 349.2. ¹H NMR (400 MHz, DMSO-*d*₆) (155) δ_H 7.50-7.22 (m, 3H), 7.08-7.03 (m, 2H), 4.18 (s,

2H), 4.04 (s, 3H), 2.36 (s, 3H). LCMS (ESI) Calcd for $C_{15}H_{13}F_3N_4O$: 322.2, found $[M+H]^+ = 323.1$.

Example 143: Synthesis of 3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 143)



Scheme 76

[0992] Synthesis of 2-(bromomethyl)-1-chloro-3-methylbenzene, 157 [Step 1]: To a suspension of (2-chloro-6-methylphenyl)methanol (156, 600 mg, 3.8 mmol) in dichloromethane, PBr_3 (0.4 mL, 4.2 mmol) was added drop wise at $0^\circ C$ and the reaction mixture was stirred at same temperature for 45 min. After completion, the reaction mixture was quenched with $NaHCO_3$ solution and extracted with dichloromethane (thrice). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 2-(bromomethyl)-1-chloro-3-methyl-benzene (157, 700 mg). 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.51-7.22 (m, 5H), 4.05 (s, 3H), 2.36 (s, 3H), 1.91-1.77 (m, 2H), 1.48-1.46 (m, 2H).

[0993] Synthesis of 2-(2-chloro-6-methylphenyl)acetonitrile, 158 [Step 2]: To a stirred solution of 2-(bromomethyl)-1-chloro-3-methyl-benzene (157, 600 mg, 2.7 mmol) in acetonitrile (8 mL), K_2CO_3 (380 mg, 2.7 mmol) was added followed by trimethylsilylformonitrile (0.3 mL, 2.7 mmol) and the reaction mixture was heated at $100^\circ C$ for 16h. After completion, the reaction mixture was dissolved in ethyl acetate, washed with water (thrice) and brine. The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford 2-(2-chloro-6-methyl-phenyl)acetonitrile (158, 550 mg). IR spectra showed cyanide peak and also NMR consistent with desired product. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.39-7.37 (d, 1H), 7.31-7.25 (m, 2H), 4.04 (s, 2H), 2.40 (s, 3H).

[0994] Synthesis of 1-(2-chloro-6-methylphenyl)cyclopropane-1-carbonitrile, 159 [Step 3]: To a stirred solution of NaOH (1.7 g, 43.5 mmol) in water (10 mL), 2-(2-chloro-6-methyl-

phenyl)acetonitrile (158, 600 mg, 3.6 mmol), 1,2-dibromoethane (0.3 mL, 3.6 mmol) and TBAB (235 mg, 0.7 mmol) were added and the reaction mixture was heated at 60 °C for 12h. After completion, the reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic extract was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-(2-chloro-6-methylphenyl)cyclopropanecarbonitrile (159, 550 mg). ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.42-7.15 (m, 3H), 1.57 (s, 2H), 1.40 (s, 2H), 0.92 (s, 3H).

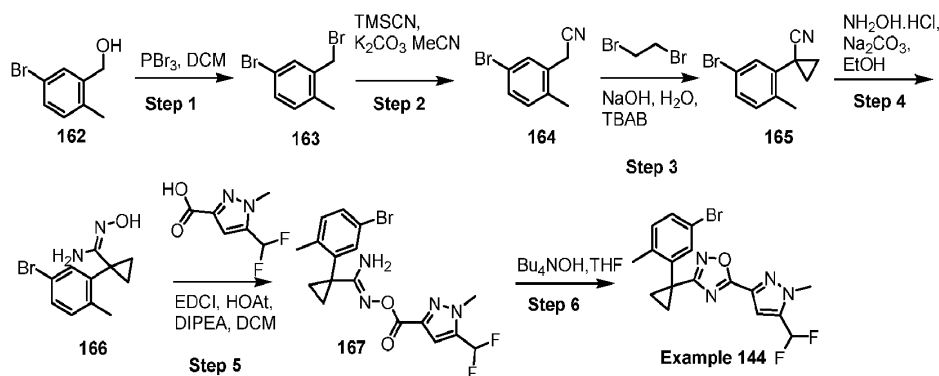
[0995] Synthesis of (Z)-1-(2-chloro-6-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide, 160 [Step 4]: To a stirred solution of 1-(2-chloro-6-methylphenyl)cyclopropanecarbonitrile (159, 700 mg, 3.6 mmol) in ethanol (10 mL), sodium carbonate (775 mg, 7.3 mmol) and hydroxylamine hydrochloride (510 mg, 7.3 mmol) were added and the reaction was heated at 70 °C for 12h. After completion, the volatiles were evaporated under reduced pressure, dissolved in water and extracted with ethyl acetate (thrice). Combined organic extract was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford 1-(2-chloro-6-methyl-phenyl)-*N'*-hydroxy-cyclopropanecarboxamidamide (160, 250 mg). LCMS (ESI) Calcd for C₁₁H₁₃ClN₂O: 224.1, found [M+H]⁺ = 225.2.

[0996] Synthesis of (Z)-1-(2-chloro-6-methylphenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 161 [Step 5]: To a solution of 5-(difluoromethyl)-1-methyl-pyrazole-3-carboxylic acid (150 mg, 0.8 mmol) and 1-(2-chloro-6-methyl-phenyl)-*N'*-hydroxy-cyclopropanecarboxamidine (160, 210 mg, 0.9 mmol) in dichloromethane (5 mL), DIPEA (0.5 mL, 2.6 mmol), EDCI.HCl (245 mg, 1.3 mmol) and HOAt (10 mg, 0.1 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by combiflash column chromatography to afford (Z)-1-(2-chloro-6-methylphenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (161, 130 mg). LCMS (ESI) Calcd for C₁₇H₁₇ClF₂N₄O₂: 382.1, found [M+H]⁺ = 383.1.

[0997] Synthesis of 3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 143 [Step 6]: To a stirred solution of (Z)-1-(2-chloro-6-methylphenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (161, 110 mg, 0.3 mmol) in THF (5 mL), tetrabutylammonium hydroxide (0.02

mL, 0.02 mmol, 1M in methanol) was added and the resulting reaction mixture was stirred for 12h at ambient temperature. Reaction was monitored by LCMS. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water (twice). The combined organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC to afford 3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 143, 13 mg). LCMS (ESI) Calcd for $\text{C}_{17}\text{H}_{15}\text{ClF}_2\text{N}_4\text{O}$: 364.1, found $[\text{M}+\text{H}]^+ = 365.2$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 7.51-7.22 (m, 5H), 4.05 (s, 3H), 2.36 (s, 3H), 1.90-1.86 (m, 1H), 1.79-1.78 (m, 1H), 1.48-1.45 (m, 2H).

Example 144: Synthesis of 3-(1-(5-bromo-2-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 144)



Scheme 77

[0998] Synthesis of 4-bromo-2-(bromomethyl)-1-methylbenzene, 163 [Step 1]: To a suspension of (5-bromo-2-methylphenyl) methanol (162, 1.5 g, 7.5 mmol) in dichloromethane (10 mL), PBr_3 (0.8 mL, 8.2 mmol) was added drop wise at 0°C and the reaction mixture was stirred at same temperature for 1h. After completion, the reaction mixture was quenched with aqueous NaHCO_3 solution and partitioned with dichloromethane. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 4-bromo-2-(bromomethyl)-1-methylbenzene (163, 1.1 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 7.63 (s, 1H), 7.42 (d, 1H), 7.18 (d, 1H), 4.68 (d, 2H), 2.31 (s, 3H). GCMS (ESI) Calcd. For $\text{C}_8\text{H}_8\text{Br}_2$: 263.6, found $[\text{M}]^+ = 264.0$.

[0999] Synthesis of 2-(5-bromo-2-methylphenyl) acetonitrile, 164 [Step 2]: To a stirred solution of 4-bromo-2-(bromomethyl)-1-methylbenzene (163, 1.1 g, 4.2 mmol) in acetonitrile (10 mL), K_2CO_3 (575 mg, 4.2 mmol) was added followed by trimethylsilyl formonitrile (0.5 mL, 4.2 mmol)

and the reaction mixture was heated at 100 °C for 16 h. After completion, the reaction mixture was dissolved in ethyl acetate, washed with water and brine. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 2-(5-bromo-2-methylphenyl) acetonitrile (164, 845 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.49 (s, 1H), 7.37 (d, 1H), 7.35 (d, 1H), 3.62 (s, 2H), 2.28 (d, 3H). GCMS (ESI) Calcd. For C₉H₈BrN: 209.0, found [M]⁺ = 209.0.

[1000] Synthesis of 1-(5-bromo-2-methylphenyl) cyclopropane-1-carbonitrile, 165 [Step 3]: To a stirred solution of NaOH (1.9 g, 48.3 mmol) in water (4 mL), 2-(5-bromo-2-methylphenyl) acetonitrile (164, 845 mg, 4.0 mmol), TBAB (260 mg, 0.8 mmol) and 1,2-dibromoethane (3.0 mL, 20.1 mmol) were added and the resultant reaction mixture was heated at 60 °C for 12 h. After completion, the reaction mixture was poured into cold water and extracted with ethyl acetate. Combined organic extract was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-(5-bromo-2-methylphenyl) cyclopropane-1-carbonitrile (165, 930 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.59 (s, 1H), 7.49 (t, 1H), 7.24 (d, 1H), 2.30 (s, 3H), 1.73-1.63 (m, 2H), 1.46-1.41 (m, 2H). GCMS (ESI) Calcd. for C₁₁H₁₀BrN: 236.1, found [M]⁺ = 237.1.

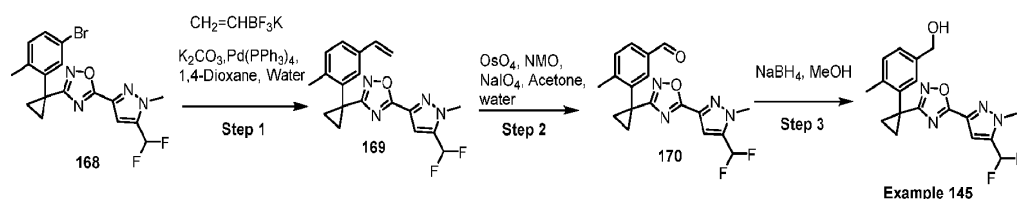
[1001] Synthesis of 1-(5-bromo-2-methylphenyl)-*N*-hydroxycyclopropane-1-carboximidamide, 166 [Step 4]: To a stirred solution of 1-(5-bromo-2-methylphenyl) cyclopropane-1-carbonitrile (165, 930 mg, 3.9 mmol) in ethanol (10 mL), sodium carbonate (835 mg, 7.9 mmol) and hydroxylamine hydrochloride (545 mg, 7.9 mmol) were added and the reaction was heated at 70 °C for 16 h. After completion, the volatiles were evaporated under reduced pressure, dissolve in water and extracted with ethyl acetate. Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by combi flash column chromatography to afford 1-(5-bromo-2-methylphenyl)-*N*'-hydroxycyclopropane-1-carboximidamide (166, 775 mg). LCMS (ESI) Calcd. for C₁₁H₁₃BrN₂O: 269.1, found [M+H]⁺ = 269.0.

[1002] Synthesis of 1-(5-bromo-2-methylphenyl)-*N*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 167 [Step 5]: To a stirred solution of 5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (150 mg, 0.9 mmol) and 1-(5-bromo-2-methylphenyl)-*N*'-hydroxycyclopropane-1-carboximidamide (166, 252 mg, 0.9 mmol) in dichloromethane (4 mL), DIPEA (0.5 mL, 2.6 mmol), EDCI.HCl (245 mg, 1.3 mmol) and HOAt (10 mg, 0.1 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was diluted with dichloromethane

and partitioned with water. Combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by combi flash column chromatography to afford 1-(5-bromo-2-methylphenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (167, 360 mg). LCMS (ESI) Calcd. For $\text{C}_{17}\text{H}_{17}\text{BrF}_2\text{N}_4\text{O}_2$: 427.2, found $[\text{M}+\text{H}]^+ = 427.1$.

[1003] Synthesis of 3-(1-(5-bromo-2-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 144 [Step 6]: To a stirred solution of 1-(5-bromo-2-methylphenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (167, 235 mg, 0.55 mmol) in THF (5 mL), tetrabutylammonium hydroxide (29 mg, 0.1 mmol, 1M in methanol) was added and the resulting reaction mixture was stirred at ambient temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water. The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC to afford 3-(1-(5-bromo-2-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 144, 30 mg). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 7.54 (d, 1H), 7.44-7.39 (m, 3H), 7.28-7.18 (m, 1H), 4.04 (s, 3H), 2.22 (s, 3H), 1.65 (d, 2H), 1.45-1.42 (q, 2H). LCMS (ESI) Calcd. For $\text{C}_{17}\text{H}_{15}\text{BrF}_2\text{N}_4\text{O}$: 409.2, found $[\text{M}-\text{H}]^- = 408.9$.

Example 145: Synthesis of (3-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylphenyl)methanol (Example 145)



Scheme 78

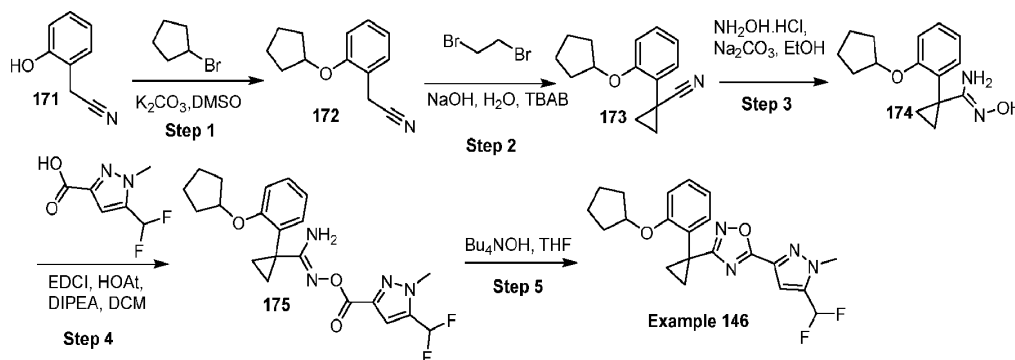
[1004] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-methyl-5-vinylphenyl)cyclopropyl)-1,2,4-oxadiazole, 169 [Step 1]: To a stirred solution of potassium vinyl trifluoroborate (2, 80 mg, 0.6 mmol) in 1,4-dioxane (8 mL):Water (2mL) mixture, K_2CO_3 (255 mg, 1.8 mmol) and 3-(1-(5-bromo-2-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (168, 250 mg, 0.6 mmol) were added and degassed for 10 min. $\text{Pd}(\text{PPh}_3)_4$ (70 mg, 0.1 mmol) was then added to the reaction mixture and heated at 100 °C for

12 h. After completion, reaction mixture was filtered through celite bed, washed with ethyl acetate, dried over anhydrous Na₂SO₄, concentrated under reduced pressure and purified by combi flash column chromatography to afford 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-methyl-5-vinylphenyl)cyclopropyl)-1,2,4-oxadiazole (169, 185 mg). LCMS (ESI) Calcd. For C₁₉H₁₈F₂N₄O: 356.3, found [M+H]⁺ = 357.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.50-7.46 (m, 2H), 7.35 (d, 1H), 7.27 (s, 1H), 7.23-7.18 (m, 1H), 6.75-6.68 (m, 1H), 5.79 (t, 1H), 5.22 (d, 1H), 4.04 (s, 3H), 2.25 (s, 3H), 1.66 (s, 2H), 1.42 (s, 2H).

[1005] Synthesis of 3-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylbenzaldehyde, 170 [Step 2]: To a solution of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(2-methyl-5-vinylphenyl) cyclopropyl)-1,2,4-oxadiazole (169, 130 mg, 0.4 mmol) in acetone (8 mL) and water (2 mL) mixture, was added NMO (85 mg, 0.7 mmol) followed by the addition of OsO₄ (0.4 mL, 0.04 mmol, 4% in water) and continue to stir at 0 °C for 2h. Then NaIO₄ (385 mg, 1.8 mmol) was added to the reaction mixture at ice cold condition and the reaction mixture was stirred at ambient temperature for 3h. TLC showed full conversion of starting material with formation of new nonpolar spot. The reaction mixture was diluted with EtOAc and washed with water and brine. It was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford 3-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylbenzaldehyde (170, 120 mg). LCMS (ESI) Calcd. For C₁₈H₁₆F₂N₄O₂: 358.3, found [M+H]⁺ = 359.0.

[1006] Synthesis of (3-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylphenyl)methanol, Example 145 [Step 3]: To a stirred solution of 3-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylbenzaldehyde (170, 140 mg, 0.4 mmol) in methanol (6 mL), sodium borohydride (30 mg, 0.78 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. It was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC to afford (3-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylphenyl)methanol (Example 145, 85 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.50 (s, 1H), 7.37-7.23 (m, 2H), 7.16 (t, 2H), 5.12 (t, 1H), 4.46 (d, 2H), 4.04 (s, 3H), 2.24 (s, 3H), 1.65 (d, 2H), 1.38-1.36 (q, 2H). LCMS (ESI) Calcd. For C₁₈H₁₈F₂N₄O₂: 360.3, found [M+H]⁺: 361.2.

Example 146: Synthesis of 3-(1-(2-(cyclopentyloxy)phenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 146)



Scheme 79

[1007] Synthesis of 2-(2-(cyclopentyloxy)phenyl)acetonitrile, 172 [Step 1]: To a stirred solution of 2-(2-hydroxyphenyl)acetonitrile (171, 500 mg, 4 mmol) and bromocyclopentane (840 mg, 5.5 mmol) in DMSO (5 mL), K_2CO_3 was added (1.0 g, 7.5 mmol). The reaction mixture was heated at 60 °C for 16 h. After completion, the reaction mixture was diluted with ethyl acetate, washed with water (thrice), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 2-(2-(cyclopentyloxy)phenyl)acetonitrile (3, 500 mg). 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.32-7.28 (m, 2H), 7.03 (d, 1H), 6.91 (t, 1H), 4.92-4.89 (m, 2H), 1.90-1.86 (m, 2H), 1.75 (s, 4H), 1.60 (brs, 2H).

[1008] Synthesis of 1-(2-(cyclopentyloxy)phenyl)cyclopropane-1-carbonitrile, 173 [Step 2]: To a stirred solution of NaOH (1.3 g, 32 mmol) in water (3 mL), 2-(2-(cyclopentyloxy)phenyl)acetonitrile (172, 500 mg, 3.0 mmol), TBAB (180 mg, 0.5 mmol) and 1,2-dibromoethane (1.5 mL, 10 mmol) were added and the reaction mixture was heated at 60 °C for 12h. After completion, the reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford 1-(2-(cyclopentyloxy)phenyl)cyclopropane-1-carbonitrile (173, 400 mg). GCMS Calcd. For $C_{15}H_{17}NO$: 227.3, $[M/Z] = 227.1$.

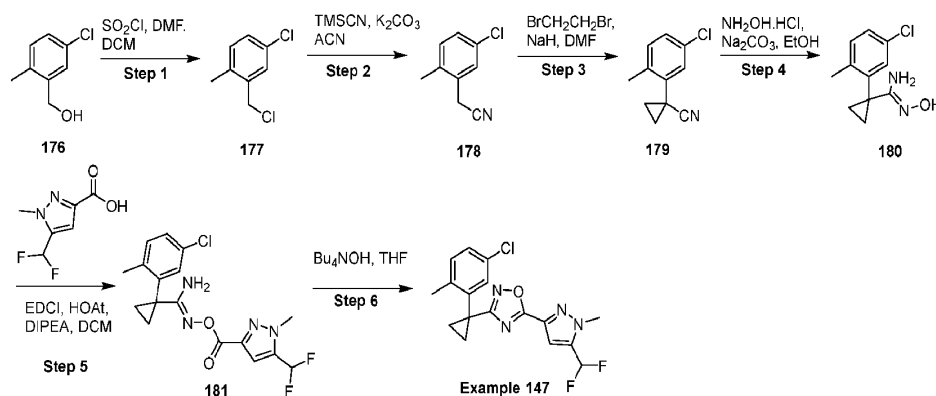
[1009] Synthesis of (Z)-1-(2-(cyclopentyloxy)phenyl)-N'-hydroxycyclopropane-1-carboximidamide, 174 [Step 3]: To a stirred solution of 1-(2-(cyclopentyloxy)phenyl)cyclopropane-1-carbonitrile (173, 300 mg, 1.3 mmol) in ethanol (2 mL), hydroxylamine hydrochloride (180 mg, 2.5 mmol) and sodium carbonate (280 mg, 2.5 mmol) were added and the reaction was heated at 70 °C for 12h. After completion, the volatiles were

evaporated under reduced pressure, dissolved in water and extracted with ethyl acetate (thrice). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified through column chromatography to afford (Z)-1-(2-(cyclopentyloxy)phenyl)-N'-hydroxycyclopropane-1-carboximidamide (174, 130 mg). LCMS (ESI) Calcd for C₁₅H₂₀N₂O₂: 260.3, found [M+H]⁺ = 261.3.

[1010] Synthesis of (Z)-1-(2-(cyclopentyloxy)phenyl)-N'-((5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 175 [Step 4]: To a solution of (Z)-1-(2-(cyclopentyloxy)phenyl)-N'-hydroxycyclopropane-1-carboximidamide (174, 130 mg, 0.5 mmol) and 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxylic acid (80 mg, 0.4 mmol) in 1,2-dichloromethane (4 mL), DIPEA (0.3 mL, 1.4 mmol), EDCI.HCl (135 mg, 0.7 mmol) and HOAt (7 mg, 0.05 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (Z)-1-(2-(cyclopentyloxy)phenyl)-N'-((5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (175, 120 mg). LCMS (ESI) Calcd for C₂₁H₂₄F₂N₄O₃: 418.4, found [M+H]⁺ = 419.4.

[1011] Synthesis of 3-(1-(2-(cyclopentyloxy)phenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 146 [Step 5]: To a stirred solution of (Z)-1-(2-(cyclopentyloxy)phenyl)-N'-((5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (175, 100 mg, 0.2 mmol) in THF (2 mL), tetrabutylammonium hydroxide (12 mg, 0.05 mmol, 1 M in methanol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC purification to afford 3-(1-(2-(cyclopentyloxy)phenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 146, 65 mg). ¹H NMR (400 MHz, DMSO-*d*₆) (at 100 °C) δ_H 7.44-7.17 (m, 4H), 6.97-6.88 (m, 2H), 4.82 (brs, 1H), 4.04 (s, 3H), 1.77 (brs, 2H), 1.63-1.57 (m, 4H), 1.48 (s, 4H), 1.28 (s, 2H). LCMS (ESI) Calcd for C₂₁H₂₂F₂N₄O₂: 400.4, found [M-H]⁺ = 401.2.

Example 147: Synthesis of 3-(1-(5-chloro-2-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 147)



Scheme 80

[1012] Synthesis of 4-chloro-2-(chloromethyl)-1-methylbenzene, 177 [Step 1]: To a stirred solution of 5-chloro-2-methylphenylmethanol (176, 1.5 g, 9.6 mmol) in dry dichloromethane (10 mL), thionyl chloride (2.1 mL, 28.7 mmol) and DMF (2.3 mL, 28.7 mmol) were added at 0 °C. Resulting reaction mixture was stirred at ambient temperature for 16 h, diluted with dichloromethane and washed with saturated solution of sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford 4-chloro-2-(chloromethyl)-1-methylbenzene (177, 1.5 g). ¹H NMR (400 MHz, CDCl₃): δ_H 7.30-7.29 (m, 1H), 7.21-7.18 (m, 1H), 7.12-7.10 (m, 1H), 4.53 (s, 2H), 2.37 (s, 3H).

[1013] Synthesis of 2-(5-chloro-2-methylphenyl)acetonitrile, 178 [Step 2]: To a stirred solution of 4-chloro-2-(chloromethyl)-1-methylbenzene (177, 3.0 g, 17.1 mmol) in acetonitrile (20 mL), potassium carbonate (2.3 g, 17.1 mmol) and trimethylsilylformonitrile (2.1 mL, 17.1 mmol) were added. Resulting reaction mixture was stirred at 90 °C for 16 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 2-(5-chloro-2-methylphenyl)acetonitrile (178, 2.5 g). LCMS (ESI) Calcd. for C₉H₈ClN: 165.0, found [M-H]⁻ = 164.2. ¹H NMR (400 MHz, CDCl₃): δ_H 7.35 (s, 1H), 7.23-7.21 (m, 1H), 7.14 (d, 1H), 3.63 (s, 2H), 2.30 (s, 3H).

[1014] Synthesis of 1-(5-chloro-2-methylphenyl)cyclopropane-1-carbonitrile, 179 [Step 3]: To a stirred solution of 2-(5-chloro-2-methylphenyl)acetonitrile (178, 1.5 g, 9.1 mmol) in DMF (40 mL), sodium hydride (1.0 g, 27.2 mmol) was added at 0 °C. The resulting suspension was allowed to stir at ambient temperature for 1 h, cooled to 0 °C and a solution of 1,2-dibromoethane (2.3 mL, 27.2 mmol) in DMF (10 mL) was added. The reaction mixture was

allowed to stir at ambient temperature for 16 h, quenched with ice cold water and extracted with ethyl acetate. Combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 1-(5-chloro-2-methylphenyl)cyclopropanecarbonitrile (179, 2.1 g). The product was carried to next step without further purification.

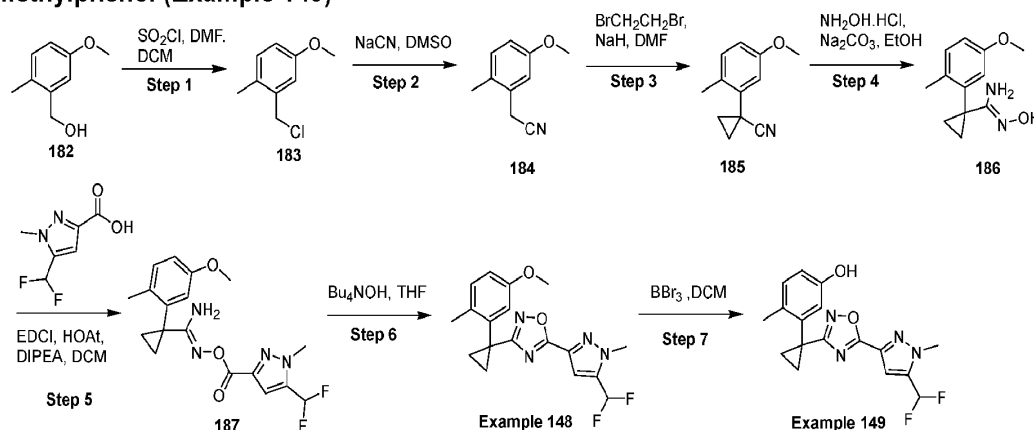
[1015] Synthesis of (Z)-1-(5-chloro-2-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide, 180 [Step 4]: To a stirred solution of 1-(5-chloro-2-methylphenyl)cyclopropanecarbonitrile (179, 2.0 g, 10.4 mmol) in ethanol (20 mL), hydroxylamine hydrochloride (1.4 g, 20.9 mmol) and sodium carbonate (2.2 g, 20.9 mmol) were added. The reaction mixture was stirred at 80 °C for 16 h and volatiles were evaporated. The residue was diluted with ethyl acetate and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography to afford (Z)-1-(5-chloro-2-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (180, 980 mg). LCMS (ESI) Calcd. for C₁₁H₁₃ClN₂O: 224.1, found [M+H]⁺ = 225.2.

[1016] Synthesis of (Z)-1-(5-chloro-2-methylphenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 181 [Step 5]: To a stirred solution of (Z)-1-(5-chloro-2-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (180, 200 mg, 0.9 mmol) in dry dichloromethane (8 mL), DIPEA (0.4 mL, 2.2 mmol), EDC.HCl (205 mg, 1.1 mmol), HOAt (24 mg, 0.2 mmol) and 5-(difluoromethyl)-1-methyl-pyrazole-3-carboxylic acid (157 mg, 0.9 mmol) were added. Resulting reaction mixture was stirred at ambient temperature for 16 h, diluted with dichloromethane and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-1-(5-chloro-2-methylphenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (181, 350 mg). LCMS (ESI) Calcd. for C₁₇H₁₇ClF₂N₄O₂: 382.1, found [M + H]⁺ = 383.3. The product was carried to next step without further purification.

[1017] Synthesis of 3-(1-(5-chloro-2-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 147 [Step 6]: A solution of (Z)-1-(5-chloro-2-methylphenyl)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (181, 470 mg, 1.2 mmol) and tetra butyl ammonium hydroxide (0.16 mL, 0.25 mmol) in THF (10 mL) was stirred at ambient temperature for 16 h and volatiles were evaporated under reduced pressure. The product was purified by reverse phase preparative-

HPLC to give 3-(1-(5-chloro-2-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 147, 147 mg). LCMS (ESI) Calcd. for $C_{17}H_{15}ClF_2N_4O$: 364.1, found $[M+H]^+ = 365.1$. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 7.42-7.27 (m, 5H), 4.05 (s, 3H), 2.24 (s, 3H), 1.66 (brs, 2H), 1.44 (brs, 2H).

Examples 148 & 149: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(5-methoxy-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 148) and 3-(1-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylphenol (Example 149)



Scheme 81

[1018] Synthesis of 2-(chloromethyl)-4-methoxy-1-methylbenzene, 183 [Step 1]: To a stirred solution of (5-methoxy-2-methylphenyl)methanol (182, 1.1 g, 6.8 mmol) in dry dichloromethane (10 mL), thionyl chloride (1.4 mL, 19.7 mmol) and DMF (1.6 mL, 19.7 mmol) were added at 0 °C. Resulting reaction mixture was stirred at ambient temperature for 16 h, diluted with dichloromethane and washed with saturated solution of sodium bicarbonate followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford 2-(chloromethyl)-4-methoxy-1-methylbenzene (183, 1.1 g). 1H NMR (400 MHz, $DMSO-d_6$): δ_H 7.13 (d, 1H), 6.98 (d, 1H), 6.84-6.81 (m, 1H), 4.73 (s, 2H), 3.72 (s, 3H), 2.29 (s, 3H).

[1019] Synthesis of 2-(5-methoxy-2-methylphenyl)acetonitrile, 184 [Step 2]: To a stirred solution of 2-(chloromethyl)-4-methoxy-1-methylbenzene (183, 1.3 g, 7.6 mmol) in DMSO (5 mL), sodium cyanide (560 mg, 11.4 mmol) was added. Resulting reaction mixture was stirred at ambient temperature for 6 h, quenched with saturated solution of ferrous sulfate. The resulting aqueous solution was extracted with ethyl acetate and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and

concentrated under reduced pressure to afford 2-(5-methoxy-2-methylphenyl)acetonitrile (184, 1 g). ¹H NMR (400 MHz, CDCl₃): δ_H 7.10 (d, 1H), 6.91 (brs, 1H), 6.79-6.77 (m, 1H), 3.79 (s, 3H), 3.62 (s, 2H), 2.25 (s, 3H).

[1020] Synthesis of 1-(5-methoxy-2-methylphenyl)cyclopropane-1-carbonitrile, 185 [Step 3]: To a stirred solution of 2-(5-methoxy-2-methylphenyl)acetonitrile (184, 500 mg, 3.1 mmol) in DMF (15 mL), sodium hydride (370 mg, 9.3 mmol) was added at 0 °C. The resulting suspension was allowed to stir at ambient temperature for 1 h, cooled to 0 °C and a solution of 1,2-dibromoethane (0.8 mL, 9.3 mmol) in DMF (5 mL) was added. The reaction mixture was allowed to stir at ambient temperature for 16 h, quenched with ice cold water and extracted with ethyl acetate. Combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 1-(5-methoxy-2-methylphenyl)cyclopropane-1-carbonitrile (185, 800 mg). The product was carried to next step without further purification.

[1021] Synthesis of (Z)-*N'*-hydroxy-1-(5-methoxy-2-methylphenyl)cyclopropane-1-carboximidamide, 186 [Step 4]: To a stirred solution of 1-(5-methoxy-2-methylphenyl)cyclopropane-1-carbonitrile (185, 800 mg) in ethanol (20 mL), hydroxylamine hydrochloride (650 mg, 9.4 mmol) and sodium carbonate (996 mg, 9.4 mmol) were added. The reaction mixture was stirred at 80 °C for 16 h and volatiles were evaporated. The residue was diluted with ethyl acetate and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography to afford (Z)-*N'*-hydroxy-1-(5-methoxy-2-methylphenyl)cyclopropane-1-carboximidamide (186, 300 mg). LCMS (ESI) Calcd. for C₁₂H₁₆N₂O₂: 220.1, found [M+H]⁺ = 221.2.

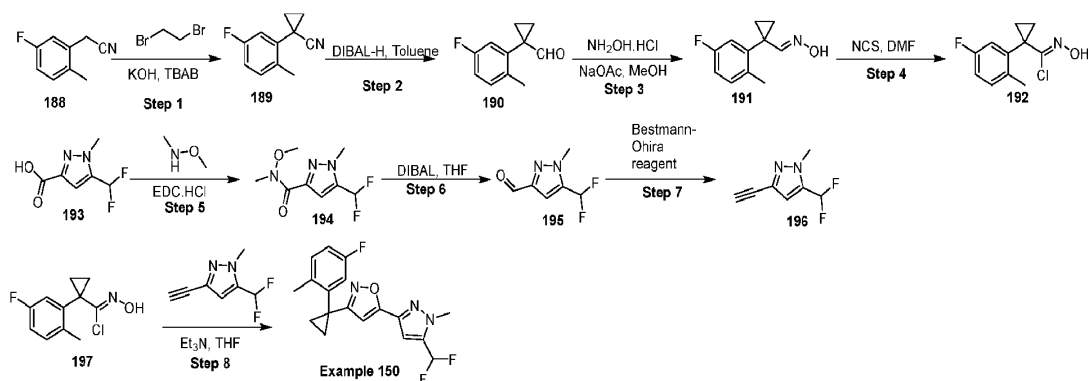
[1022] Synthesis of (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(5-methoxy-2-methylphenyl)cyclopropane-1-carboximidamide, 187 [Step 5]: To a stirred solution of (Z)-1-(5-chloro-2-methylphenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (186, 300 mg, 1.4 mmol) in dry dichloromethane (10 mL), DIPEA (0.6 mL, 3.4 mmol), EDC.HCl (313 mg, 1.6 mmol), HOAt (37 mg, 0.2 mmol) and 5-(difluoromethyl)-1-methyl-pyrazole-3-carboxylic acid (239 mg, 1.4 mmol) were added. Resulting reaction mixture was stirred at ambient temperature for 16 h, diluted with dichloromethane and washed with water followed by brine wash. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(5-methoxy-2-methylphenyl)cyclopropane-1-carboximidamide (187, 450 mg). LCMS (ESI)

Calcd. for $C_{18}H_{20}F_2N_4O_3$: 378.1, found $[M + H]^+ = 379.2$ The product was carried to next step without further purification.

[1023] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(5-methoxy-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole, Example 148 [Step 6]: A solution of (Z)-*N'*-((5-(difluoromethyl)-1-methyl-1*H*-pyrazole-3-carbonyl)oxy)-1-(5-methoxy-2-methylphenyl)cyclopropane-1-carboximidamide (187, 640 mg, 1.6 mmol) and tetra butyl ammonium hydroxide (0.2 mL, 0.33 mmol) in THF (10 mL) was stirred at ambient temperature for 16 h and volatiles were evaporated under reduced pressure. The product was purified by reverse phase preparative HPLC to give 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(5-methoxy-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 148, 140 mg). LCMS (ESI) Calcd. for $C_{18}H_{18}F_2N_4O_2$: 360.1, found $[M+H]^+ = 361.2$. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.50-7.24 (m, 2H), 7.12 (d, 1H), 6.93 (d, 1H), 6.83-6.80 (m, 1H), 4.05 (s, 3H), 3.74 (s, 3H), 2.18 (s, 3H), 1.59-1.57 (m, 2H), 1.34-1.32 (s, 2H).

[1024] Synthesis of 3-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylphenol, Example 149 [Step 7]: To a stirred solution of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(5-methoxy-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 148, 100 mg) in dichloromethane (5 mL) was cooled to -78 °C, boron tribromide (1M in dichloromethane) (1.6 mL, 1.7 mmol) was added dropwise and the reaction mixture was stirred at -78 °C. After 4 h, the reaction mixture was quenched saturated solution of sodium bicarbonate, extracted with dichloromethane, washed with water and brine. Combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to give 3-(1-(5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)cyclopropyl)-4-methylphenol (Example 149, 25 mg). LCMS (ESI) Calcd. for $C_{17}H_{16}F_2N_4O_2$: 346.1, found $[M+H]^+ = 347.2$. 1H NMR (400 MHz, DMSO- d_6): δ_H 9.17 (s, 1H), 7.50-7.24 (m, 2H), 6.98 (d, 1H), 6.77 (s, 1H), 6.63 (d, 1H), 4.04 (s, 3H), 2.13 (s, 3H), 1.61 (brs, 2H), 1.33 (brs, 2H).

Example 150: Synthesis of 5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)isoxazole (Example 150)



Scheme 82

[1025] Synthesis of 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonitrile, 189 [Step 1]: To a stirred solution of KOH (6.77 g, 121 mmol) in water (10 mL), 2-(5-fluoro-2-methylphenyl)acetonitrile (188, 1.5 g, 10.1 mmol) was added portion wise under inert atmosphere and stirred for 10 min. TBAB (648 mg, 2.0 mmol) and 1,2-dibromoethane (4.4 mL, 50.3 mmol) were added to the reaction mixture and stirred at 60 °C for 12 h. After completion (detected by TLC), the reaction mixture was poured into cold water and extracted with ethyl acetate. The combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to afford 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonitrile (1.20 g, 61% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 7.30 (t, 1H), 7.22 - 7.19 (m, 1H), 7.15 - 7.10 (m, 1H), 2.43 (s, 3H), 1.69 - 1.67 (m, 2H), 1.41 - 1.38 (m, 2H).

[1026] Synthesis of 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbaldehyde, 190 [Step 2]: A two neck round bottom flask was charged with 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonitrile (189, 500 mg, 2.9 mmol) in Toluene (5 mL) at -78 °C under inert atmosphere. DIBAL-H 1M solution in Toluene (3.7 mL, 3.7 mmol) was added dropwise to the reaction mixture and stirred for 2 h at -78 °C. After completion (detected by TLC), the reaction mixture was quenched with saturated NH_4Cl and warmed up to ambient temperature. The reaction mixture was extracted with EtOAc. The combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to afford 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbaldehyde (190, 300 mg, 58.9 % yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.23-7.22 (m, 1H), 7.12 - 6.97 (m, 2H), 2.25 (s, 3H), 1.66 - 1.65 (m, 2H), 1.45-1.41 (m, 2H).

[1027] Synthesis of (E)-1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbaldehyde oxime, 191 [Step 3]: A round bottom flask was charged with 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbaldehyde (190, 300 mg, 1.7 mmol), NaOAc (276 mg, 3.4 mmol) and $\text{NH}_2\text{OH} \cdot \text{HCl}$ (234 mg, 3.4 mmol) in Methanol (5 mL). The reaction mixture was stirred at ambient temperature for 12 h.

After completion (detected by TLC), the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extract was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford (E)-1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbaldehyde oxime (191, 320 mg, 98 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.39 (s, 1H), 7.16-7.13 (m, 1H), 7.02-6.93 (m, 3H), 2.25 (s, 3H), 1.23-1.19 (m, 2H), 1.17-1.07 (m, 2H).

[1028] Synthesis of (Z)-1-(5-fluoro-2-methylphenyl)-N-hydroxycyclopropane-1-carbimidoxy chloride, 192 [Step 4]: To a stirred solution of (E)-1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbaldehyde oxime (191, 100 mg, 0.5 mmol) in DMF (3mL) was added NCS (76 mg, 0.6 mmol) at ambient temperature and stirred for 1 h. After completion (monitored by TLC), the reaction mixture was quenched with water and extracted with EtOAc. The combined EtOAc extract was washed with iced water, brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude was used for next step without any purification.

[1029] Synthesis of 5-(difluoromethyl)-N-methoxy-N,1-dimethyl-1H-pyrazole-3-carboxamide, 194 [Step 5]: To a stirred solution of 5-(difluoromethyl)-1-methyl-pyrazole-3-carboxylic acid (193, 300 mg, 1.7 mmol) in dichloromethane (3mL), N-methoxymethanamine;hydrochloride (183 mg, 1.9 mmol), N-Methylmorpholine (0.21 mL, 1.9 mmol), and EDC.HCl (359 mg, 1.9 mmol) were added subsequently under inert atmosphere and stirred at ambient temperature for 12 h. After completion, the reaction mixture was quenched with water and extracted with dichloromethane. The combined organic extract was dried over Na₂SO₄ and concentrated under reduced pressure to afford 5-(difluoromethyl)-N-methoxy-N,1-dimethyl-1H-pyrazole-3-carboxamide (194, 290 mg, 77% yield). ¹H NMR (400 MHz, CDCl₃) δ 6.95 (s, 1H), 6.72 (t, 1H), 4.04 (s, 3H), 3.74 (s, 3H), 3.41 (s, 3H).

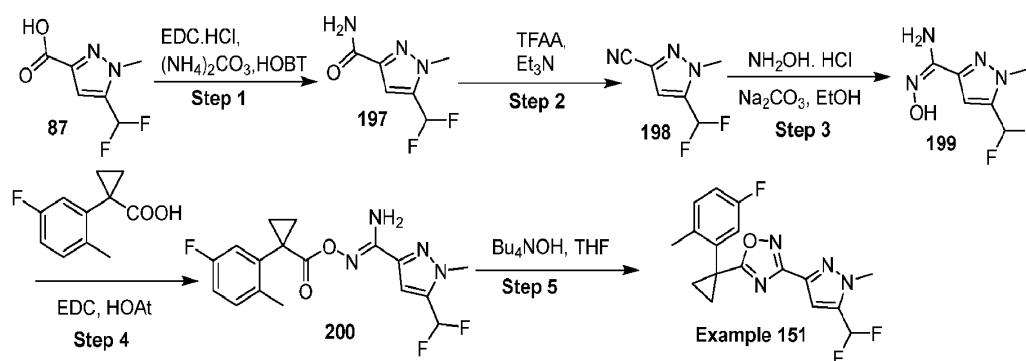
[1030] Synthesis of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbaldehyde, 195 [Step 6]: A stirred solution of 5-(difluoromethyl)-N-methoxy-N,1-dimethyl-pyrazole-3-carboxamide (194, 350 mg, 1.6 mmol) in toluene (10mL), was added DIBAL-H 1M solution in toluene (568 mg, 3.4 mmol) dropwise at -78 °C under inert atmosphere and stirred for 2 h. After completion (monitored by TLC), the reaction mixture was quenched with saturated NH₄Cl solution at -78 °C and warmed up to ambient temperature. The reaction mixture was extracted with EtOAc. The combined organic extract was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbaldehyde (195, 290 mg, 96 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.88 (s, 1H), 7.33 (t, 1H), 7.06 (s, 1H), 4.04 (s, 3H).

[1031] Synthesis of 5-(difluoromethyl)-3-ethynyl-1-methyl-1H-pyrazole, 196 [Step 7]: To a stirred solution of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbaldehyde (195, 60 mg, 0.4

mmol) in methanol (5mL), 1-diazo-1-dimethoxyphosphoryl-propan-2-one (94 mg, 0.5 mmol) and K_2CO_3 (104 mg, 0.8 mmol) were added at 0 °C and the resulting yellow suspension was stirred at ambient temperature for 16 h. After completion, (analyzed by TLC), the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to afford desired product 5-(difluoromethyl)-3-ethynyl-1-methyl-1H-pyrazole (196, 40 mg, 41% yield). 1H NMR (400 MHz, $DMSO-d_6$) δ 7.28 (t, 1H), 6.81 (s, 1H), 4.22 (s, 1H), 3.89 (s, 3H).

[1032] Synthesis of 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)isoxazole, Example 150 [Step 8]: A round bottom flask was charged with (1Z)-1-(5-fluoro-2-methyl-phenyl)-N-hydroxy-cyclopropanecarboximidoyl chloride (192, 150 mg, 0.7 mmol) and 5-(difluoromethyl)-3-ethynyl-1-methyl-pyrazole (103 mg, 0.7 mmol) in THF (2mL) followed by Et_3N (0.2 mL, 1.3 mmol) was added at ambient temperature and stirred for 16 h. After completion (monitored by TLC), the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and purified by reverse phase HPLC to afford 5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)isoxazole (Example 150, 18 mg, 7.8 % yield). 1H NMR (400 MHz, $DMSO-d_6$): δ 7.34 (t, 1H), 7.22-7.19 (m, 2H), 7.08-7.03 (m, 2H), 6.48 (s, 1H), 3.95 (s, 3H), 2.20 (s, 3H), 1.52-1.49 (m, 2H), 1.36-1.23 (m, 2H). LC/MS: calculated for $C_{18}H_{16}F_3N_3O$ [M]: 347.33, found, $[M + H]^+$: 348.1.

Example 151: Synthesis of 3-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-5-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 151)



Scheme 83

[1033] Synthesis of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxamide, 197 [Step 1: To a stirred solution of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxylic acid (87, 200 mg, 1.2

mmol) in THF (2mL) and DMF (1mL) were added HOBt (230 mg, 1.70 mmol), EDC.HCl (330 mg, 1.70 mmol) and DIPEA (0.62 mL, 4.6 mmol) followed by (NH₄)₂CO₃ (440 mg, 4.6 mmol) and stirred the reaction mixture at ambient temperature for 17 h. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extract was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxamide (197, 100 mg). LCMS (ESI) Calcd. for C₆H₇F₂N₃O : 175.17; found : [M+H]⁺ : 175.9.

[1034] Synthesis of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonitrile, 198 [Step 2]: To a stirred solution 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxamide (197, 100 mg, 0.6 mmol) and triethylamine (0.20 mL, 1.6 mmol) in dichloromethane (2mL), was added Trifluoroacetic anhydride (0.1 mL, 0.8 mmol) at 0°C. The mixture was stirred at 0°C for 1 h and then the reaction mixture was stirred at ambient temperature for 2 h. After completion, the solvent was concentrated under reduce pressure and the residue was purified by silica gel column chromatography to afford 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonitrile (198, 45 mg). GCMS (ESI) Calcd. for C₆H₅F₂N₃: 157.12; found: [M]⁺ : 157.1.

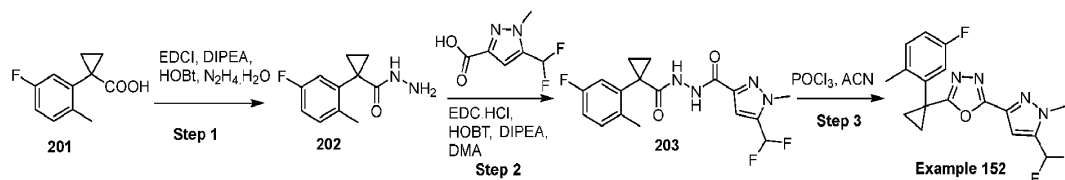
[1035] Synthesis of (E)-5-(difluoromethyl)-N'-hydroxy-1-methyl-1H-pyrazole-3-carboximidamide, 199 [Step 3]: To a stirred suspension of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonitrile (198, 0.20 g, 1.3 mmol) and NH₂OH.HCl (0.15 g, 1.9 mmol) in Water (1mL) was added NaHCO₃ (0.16 g, 1.9 mmol) and the reaction mixture was refluxed for 6 h. After completion, concentrated the reaction mixture under reduced pressure. Dilute the residue with cold water (200 mL). Filter the resulting precipitate. Wash the resulting precipitate with cold water (50 mL) and dried under vacuum to obtain (E)-5-(difluoromethyl)-N'-hydroxy-1-methyl-1H-pyrazole-3-carboximidamide (199, 130 mg). LCMS (ESI) Calcd. for C₆H₈F₂N₄O : 190.15; found: [M+H]⁺ : 191.0.

[1036] Synthesis of (Z)-5-(difluoromethyl)-N'-((1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonyl)oxy)-1-methyl-1H-pyrazole-3-carboximidamide, 200 [Step 4]: To a stirred solution of 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carboxylic acid (120 mg, 0.65 mmol) in DMA (2mL), DIPEA (0. mL, 1.3 mmol) was added followed by EDC.HCl (120 mg, 0.65 mmol) and HOBt (85 mg, 0.65 mmol) and the reaction mixture was allowed to stir for 10 min at 0°C. After that (E)-5-(difluoromethyl)-N'-hydroxy-1-methyl-1H-pyrazole-3-carboximidamide (199, 120 mg, 0.65 mmol) was added to the reaction mixture and the reaction mixture was allowed to stir at ambient temperature for 3 h. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was dried with anhydrous Na₂SO₄ and purified

by combi flash chromatography to afford (Z)-5-(difluoromethyl)-N'-((1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonyl)oxy)-1-methyl-1H-pyrazole-3-carboximidamide (200, 100 mg). LCMS (ESI) Calcd. for $C_{17}H_{17}F_3N_4O_2$: 366.3; found $[M+H]^+$ = 367.2.

[1037] Synthesis of 3-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-5-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole, Example 151 [Step 5]: To a stirred solution of (Z)-5-(difluoromethyl)-N'-((1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonyl)oxy)-1-methyl-1H-pyrazole-3-carboximidamide (200, 90 mg, 0.25 mmol) in acetonitrile (5mL) was added Tetrabutylammonium hydroxide (7 mg, 0.03 mmol) and the reaction mixture was allowed to stir at 120°C for 3 h. After completion, the reaction mixture was concentrated under reduced pressure and submitted for Prep-HPLC purification. After prep-purification followed by lyophilization to afford 3-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-5-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,2,4-oxadiazole (Example 151, 30 mg) .LCMS (ESI) Calcd. for $C_{17}H_{15}F_3N_4O$: 348.32; found $[M]^+$: 349.30. 1H NMR (400 MHz, DMSO- d_6): δ_H 7.46-7.27 (m, 3H), 7.16-7.13 (m, 1H), 7.04 (brs, 1H), 3.99 (s, 3H), 2.19 (s, 3H), 1.88-1.85 (t, 2H), 1.65-1.62 (t, 2H).

Example 152: Synthesis of 2-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-5-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,3,4-oxadiazole (Example 152)



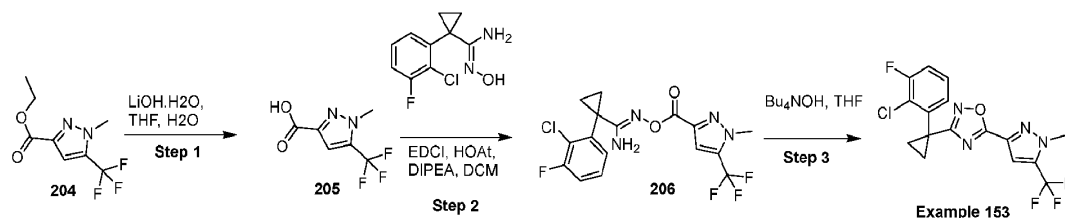
Scheme 84

[1038] Synthesis of 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbohydrazide, 202 [Step 1]: To a stirred solution of 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carboxylic acid (201, 500 mg, 2.6 mmol) in DMA (2mL) was added DIPEA (0.9 mL, 5.2 mmol) followed by EDC.HCl (494 mg, 2.6 mmol) and HOBT (348 mg, 2.6 mmol) and stirred at 0 °C for 15 mins. $N_2H_4.H_2O$ (0.1 mL, 2.8 mmol) was added to the reaction mixture and the reaction mixture was allowed to stir at ambient temperature for 4 h. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was collected, washed with brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbohydrazide (202, 200 mg). LCMS (ESI): Calcd for $C_{11}H_{13}FN_2O$: 208.23; found $[M+H]^+$ = 209.1.

[1039] Synthesis of 5-(difluoromethyl)-N'-(1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonyl)-1-methyl-1H-pyrazole-3-carbohydrazide, 203 [Step 2]: To a stirred solution of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxylic acid (169 mg, 0.960 mmol) in DMA (2mL), was added DIPEA (0.3 mL, 1.9 mmol) followed by EDC.HCl (184 mg, 1.0 mmol) and HOBT (130 mg, 1.0 mmol) at 0 °C and stirred the reaction mixture for 15 mins. 1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbohydrazide (202, 200 mg, 1.0 mmol) was added and the reaction mixture was allowed to stir at ambient temperature for 4 h. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was collected, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by column chromatography to afford 5-(difluoromethyl)-N'-(1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonyl)-1-methyl-1H-pyrazole-3-carbohydrazide (203, 70 mg) as brown liquid. LCMS (ESI): Calcd for C₁₇H₁₇F₃N₄O₂: 366.34; found [M+H]⁺ = 367.3.

[1040] Synthesis of 2-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-5-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,3,4-oxadiazole, Example 152 [Step 3]: To a stirred solution of 5-(difluoromethyl)-N'-(1-(5-fluoro-2-methylphenyl)cyclopropane-1-carbonyl)-1-methyl-1H-pyrazole-3-carbohydrazide (203, 120 mg, 0.3 mmol) in MeCN (5mL), POCl₃ (0.1 mL, 1.3 mmol) was added and the reaction mixture was allowed to stir at 120 °C for 3 h. After completion, the reaction mixture was concentrated under reduced pressure and the product was purified by reverse phase Prep-HPLC and isolated compound was lyophilized to afford 2-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-5-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-1,3,4-oxadiazole (Example 152, 20 mg). LCMS (ESI) Calcd. for C₁₇H₁₅F₃N₄O: [M] = 348.32; [M]⁺ = 348.7. ¹H NMR (VT, 400 MHz, DMSO-d₆): δ_H 7.42-7.22 (m, 3H), 7.09-7.06 (m, 2H), 4.00 (s, 3H), 2.28 (s, 3H), 1.80-1.77 (m, 2H), 1.52-1.49 (m, 2H).

Example 153: Synthesis of 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 153)



Scheme 85

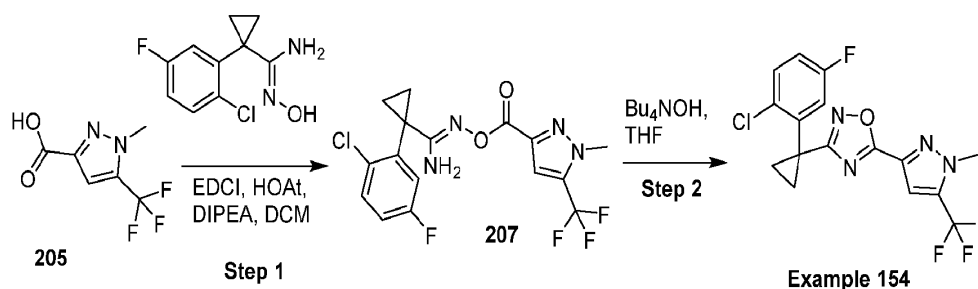
[1041] Synthesis of 1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid, 205 [Step 1] : To a stirred solution of ethyl 1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (204, 450 mg, 2.20 mmol) in THF(2 mL), methanol(1 mL) and water (0.5 mL), LiOH.H₂O (278 mg, 6.61 mmol) was added at 0 °C and the reaction mixture was stirred for 12h at ambient temperature. The reaction mixture was concentrated under reduced pressure, acidified with (1N) HCl up to pH 4-5 and extracted with ethyl acetate (thrice). The combined organic layer was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (205, 300 mg). ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 13.02 (s, 1H), 7.28(s, 1H), 4.03 (s, 3H).

[1042] Synthesis of (Z)-1-(2-chloro-3-fluorophenyl)-N'-((1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 206 [Step 2]: To a stirred solution of 1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (205, 110 mg, 0.57 mmol) and (Z)-1-(2-chloro-3-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (Int. 5 of Example 128, 143 mg, 0.62 mmol) in dichloromethane (2 mL), DIPEA (0.3 mL, 1.42 mmol), EDCI.HCl (163 mg, 0.85 mmol) and HOAt (15 mg, 0.11 mmol) were added and reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (Z)-1-(2-chloro-3-fluorophenyl)-N'-((1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (206, 150 mg). LCMS (ESI) Calcd for C₁₆H₁₃ClF₄N₄O₂: 404.1, found [M+H]⁺ = 405.1

[1043] Synthesis of 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 153 [Step 3]: To a stirred solution of (Z)-1-(2-chloro-3-fluorophenyl)-N'-((1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (206, 150 mg, 0.4 mmol) in THF (1 mL), tetrabutylammonium hydroxide (0.04 mL, 0.04 mmol, 1M in methanol) was added and the reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water (twice). The combined organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified through prep-HPLC (reverse phase) to afford 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 153, 14 mg). LCMS (ESI) Calcd for C₁₆H₁₁ClF₄N₄O: 386.1, found [M+H]⁺ = 387.0. ¹H

NMR (400 MHz, DMSO- d_6) δ_H 7.66 (s, 1H), 7.44 (d, 3H), 4.11 (s, 3H), 1.74 (brs, 2H), 1.52 (brs, 2H).

Example 154: Synthesis of 3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 154)

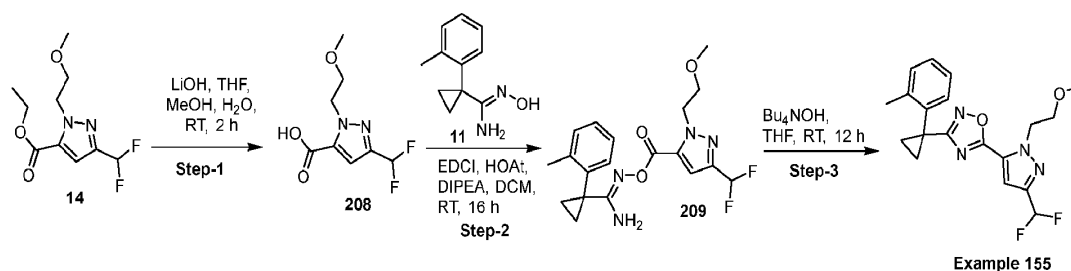


[1044] Synthesis of (Z)-1-(2-chloro-5-fluorophenyl)-N'-((1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 207 [Step 1]: To a stirred solution of 1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (205, 110 mg, 0.6 mmol) and (Z)-1-(2-chloro-5-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (Int. 4 of Example 127, 145 mg, 0.6 mmol) in dichloromethane (2 mL), DIPEA (0.3 mL, 1.42 mmol), EDCI.HCl (163 mg, 0.85 mmol) and HOAt (15 mg, 0.11 mmol) were added and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford (Z)-1-(2-chloro-5-fluorophenyl)-N'-((1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (207, 170 mg). LCMS (ESI) Calcd for $\text{C}_{16}\text{H}_{13}\text{ClF}_4\text{N}_4\text{O}_2$: 404.1, found $[\text{M}+\text{H}]^+ = 405.3$.

[1045] Synthesis of 3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 154 [Step 2]: To a stirred solution of (Z)-1-(2-chloro-5-fluorophenyl)-N'-((1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (207, 150 mg, 0.4 mmol) in THF (1 mL), tetrabutylammonium hydroxide (0.04 mL, 0.04 mmol, 1M in methanol) was added and the reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water (twice). The combined organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified through reverse phase prep-HPLC to afford 3-(1-(2-chloro-5-

fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 154, 67 mg). LCMS (ESI) Calcd for $C_{16}H_{11}ClF_4N_4O$: 386.1, found $[M+H]^+ = 387.0$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.66 (s, 1H), 7.57-7.53 (m, 1H), 7.50-7.47 (m, 1H) 7.30-7.25(m, 1H), 4.11 (s, 3H), 1.73-1.70 (m, 2H), 1.54-1.52 (m, 2H).

Example 155: Synthesis of 5-(3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 155)



Scheme 87

[1046] Synthesis of 3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-5-carboxylic acid, 208 [Step 1]: To an ice cold solution of ethyl 3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-5-carboxylate (14, 550 mg, 2.2 mmol) in THF (4 mL) and methanol (1 mL), an aqueous solution of lithium hydroxide (185 mg, 4.4 mmol) in water (2 mL) was added drop-wise. The reaction mixture was stirred at ambient temperature for 2 h. After completion, the volatiles were evaporated under reduced pressure. The aqueous phase was acidified with 1 N aqueous hydrochloric acid to ~pH-5 and extracted with a mixture of dichloromethane and isopropyl alcohol (9:1). Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-5-carboxylic acid (208, 400 mg). LCMS (ESI) Calcd. for $C_8H_{10}F_2N_2O_3$: 220.0, found $[M+H]^+ = 221.0$.

[1047] Synthesis of (Z)-*N'*-((3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-5-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide, 209 [Step 2]: To a stirred solution of 3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-5-carboxylic acid (208, 400 mg, 1.8 mmol) and (Z)-*N'*-hydroxy-1-(*o*-tolyl)cyclopropane-1-carboximidamide (11, 345.6 mg, 1.8 mmol) in dichloromethane (20 mL), *N,N*-diisopropylethylamine (585.9 mg, 4.5 mmol), 1-hydroxy-7-azabenzotriazole (49.6 mg, 0.4 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (455 mg, 2.4 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h, diluted with ethyl acetate and washed with water and brine. Combined

organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-*N'*-((3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-5-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (209, 440 mg). LCMS (ESI) Calcd. for $C_{19}H_{22}F_2N_4O_3$: 392.2, found $[M+H]^+ = 393.4$.

[1048] Synthesis of 5-(3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, Example 155 [Step 3]: To a stirred solution of (Z)-*N'*-((3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazole-5-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (209, 416.4 mg, 1.0 mmol) in THF (10 mL), tetra butyl ammonium hydroxide (39.6 mg, 0.2 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 12 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC to afford 5-(3-(difluoromethyl)-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (Example 155, 287.2 mg). LCMS (ESI) Calcd. for $C_{19}H_{20}F_2N_4O_2$: 374.1, found $[M+H]^+ = 375.3$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.39-7.37 (m, 2H), 7.27-6.97 (m, 4H), 4.77 (t, 2H), 3.73 (t, 2H), 3.16 (s, 3H), 2.29 (s, 3H), 1.70-1.67 (m, 2H), 1.45-1.42 (m, 2H).

Example 156: Synthesis of 2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 156)

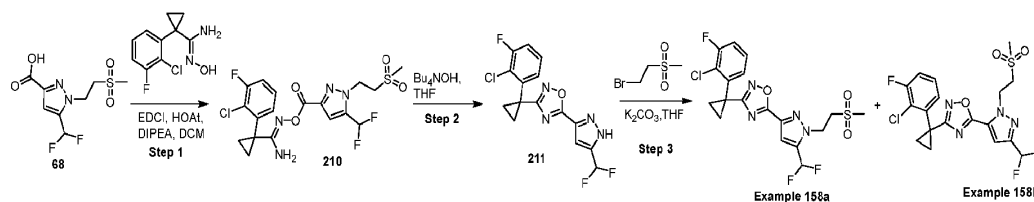
[1049] 2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one was synthesized following Scheme 87 using tert-butyl 4-(2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate. LCMS (ESI) Calcd. for $C_{21}H_{20}ClF_3N_6O_2$: 480.1, found $[M+H]^+ = 481.1$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.56-7.53 (m, 1H), 7.50-7.47 (m, 1H), 7.35-7.08 (m, 3H), 5.45 (s, 2H), 3.40-3.29 (m, 4H), 2.75-2.73 (m, 2H), 2.66-2.63 (m, 2H), 1.73-1.70 (m, 2H), 1.53-1.51 (m, 2H)

Example 157: Synthesis of 2-(3-(3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 157)

[1050] 2-(3-(3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one was synthesized following Scheme 87 using *tert*-

butyl 4-(2-(3-(3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate. LCMS (ESI) Calcd. for $C_{21}H_{20}ClF_3N_6O_2$: 480.1, found $[M+H]^+ = 481.1$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.44-7.08 (m, 5H), 5.45 (s, 2H), 3.49-3.33 (m, 4H), 2.74 (brs, 2H), 2.65 (brs, 2H), 1.74 (brs, 2H), 1.51 (brs, 2H).

Examples 158a & 158b: Synthesis of 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 158a) and 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(3-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-5-yl)-1,2,4-oxadiazole (Example 158b)



Scheme 88

[1051] Synthesis of (Z)-1-(2-chloro-3-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 210 [Step-1]: To a stirred solution of 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylic acid (along with other regioisomer) (68, 550 mg, 2.05 mmol), and (Z)-1-(2-chloro-3-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (516 mg, 2.26 mmol) in dichloromethane (10 mL), *N,N*-diisopropylethylamine (1.1 mL, 6.15 mmol), 1-hydroxy-7-azabenzotriazole (56 mg, 0.41 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (590 mg, 3.08 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (Z)-1-(2-chloro-3-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (along with other regioisomer) (210, 550 mg). LCMS (ESI) Calcd. for $C_{18}H_{18}ClF_3N_4O_4S$: 478.1, found $[M+H]^+ = 479.3$.

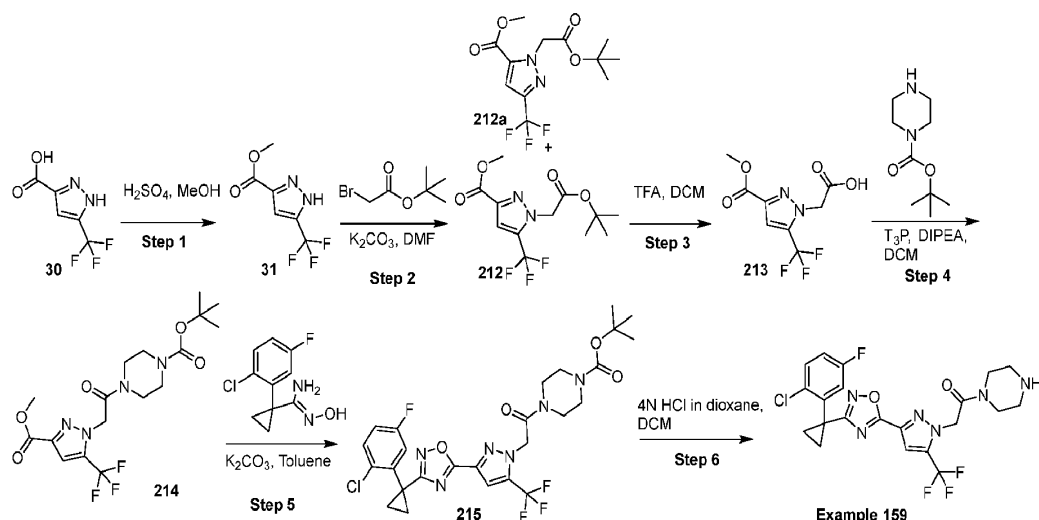
[1052] Synthesis of 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 211 [Step-2]: To a stirred solution of (Z)-1-(2-chloro-3-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (along with other regioisomer) (210, 500 mg, 1.04 mmol) in tetrahydrofuran (10 mL), tetra butyl ammonium hydroxide (1 mL, 1.04 mmol) was added. The resulting reaction

mixture was stirred at ambient temperature for 12 h. After completion the reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water (thrice). Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (211, 250 mg). LCMS (ESI) Calcd. for $C_{15}H_{10}ClF_3N_4O$: 354.1, found $[M-H]^- = 352.8$.

[1053] Synthesis 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 158a [Step-3]: To a stirred suspension of 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (211, 250 mg, 0.7 mmol) and potassium carbonate (195 mg, 1.4 mmol) in tetrahydrofuran (5 mL) at 0 °C, 1-bromo-2-(methylsulfonyl)ethane (198 mg, 1.06 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with ice-cold water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product were purified by reverse phase preparative HPLC to afford the first product as 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 158a, 95 mg) as Peak-1 and the second product as 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(3-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-5-yl)-1,2,4-oxadiazole (Example 158b, 32 mg) as Peak-2.

[1054] 3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 158a (Peak-1): LCMS (ESI) Calcd. for $C_{18}H_{16}ClF_3N_4O_3S$: 460.1, found $[M+H]^+ = 461.1$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.55-7.29 (m, 5H), 4.78-4.74 (t, 2H), 3.82-3.78 (t, 2H), 3.07 (s, 3H), 1.74 (s, 2H), 1.51 (s, 2H). Note: The structure of the compound was confirmed by NOE experiments.

Example 159: Synthesis of 2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 159)



Scheme 89

[1055] Synthesis of methyl 5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate, 31 [Step 1]: To a solution of 5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid (30, 1.5 g, 8.3 mmol) in methanol (10 mL), sulfuric acid (1.8 mL, 25.0 mmol) was added drop wise at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h. After completion, the reaction mixture was quenched with NaHCO₃ solution and extracted with ethyl acetate (thrice). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford methyl 5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate (31, 1.3 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 14.89 (s, 1H), 7.32 (s, 3H), 3.88 (s, 3H).

[1056] Synthesis of methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate and methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (212 and 212a) [Step 2]: To a stirred solution of methyl 5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate (31, 500 mg, 2.6 mmol) in THF (15 mL), K₂CO₃ (535 mg, 3.9 mmol) was added at 0 °C under nitrogen atmosphere and the reaction mixture was stirred for 30 minutes at same condition. Then *tert*-butyl 2-bromoacetate (0.5 mL, 3.1 mmol) was added and the reaction mixture was stirred at ambient temperature for 12h. After completion, the reaction mixture was diluted with ethyl acetate and washed with ice cold brine (thrice). The combined organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (212a, 200 mg) as Peak1 and methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate (212, 450 mg) as Peak2. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.46 (s, 1H), 5.25(s, 2H), 3.85 (s, 3H), 1.41(s, 9H). NOTE: The

actual structure was confirmed through 2D & NOE experiments of two spots with batch Id 'CR620-SB-2023-09-80-PEAK-1' and 'CR620-SB-2023-09-80-PEAK-2'.

[1057] Synthesis of 2-(3-(methoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetic acid, 213 [Step 3]: To a stirred solution of methyl 1-(2-*tert*-butoxy-2-oxo-ethyl)-5-(trifluoromethyl)pyrazole-3-carboxylate (212, 450 mg, 1.5 mmol) in dichloromethane (10 mL), trifluoroacetic acid (1.3 mL, 17.5 mmol) was added dropwise at 0 °C and stirred at ambient temperature for 2h. After completion, the volatiles were evaporated under reduced pressure to afford 2-(3-(methoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetic acid (213, 450 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 13.64 (s, 1H), 7.46 (s, 1H), 5.24 (s, 2H), 3.85 (s, 3H).

[1058] Synthesis of *tert*-butyl 4-(2-(3-(methoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate, 214 [Step 4]: To a stirred solution of DIPEA (1.4 mL, 7.9 mmol) in dichloromethane (10 mL), 2-(3-(methoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetic acid (213, 400 mg, 1.6 mmol) was added followed by *tert*-butyl piperazine-1-carboxylate (445 mg, 2.4 mmol) at 0 °C. After 10 min, T₃P (2.4 mL, 4.0 mmol, 50% in ethyl acetate) was added to the reaction mixture at 0°C and stirred at ambient temperature for 16 h. After completion, the reaction mixture was quenched with ice water and extracted with dichloromethane (twice). Combined organic extract was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography to afford *tert*-butyl 4-(2-(3-(methoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (214, 450 mg). LCMS (ESI) Calcd for C₁₇H₂₃F₃N₄O₅: 420.1, found [M+H]⁺ = 421.4.

[1059] Synthesis of *tert*-butyl 4-(2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate, 215 [Step 5]: To a stirred solution of *tert*-butyl 4-(2-(3-(methoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (214, 170 mg, 0.4 mmol) in toluene (4 mL), were added K₂CO₃ (110 mg, 0.9 mmol) and 1-(2-chloro-5-fluoro-phenyl)-*N'*-hydroxy-cyclopropanecarboxamidine (110 mg, 0.5 mmol). The resulting reaction mixture was heated at 90 °C for 16 h. After completion, the volatiles were concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water followed by brine. The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by combi-flash chromatography to afford *tert*-butyl 4-(2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1*H*-

pyrazol-1-yl)acetyl)piperazine-1-carboxylate (215, 120 mg). LCMS (ESI) Calcd for

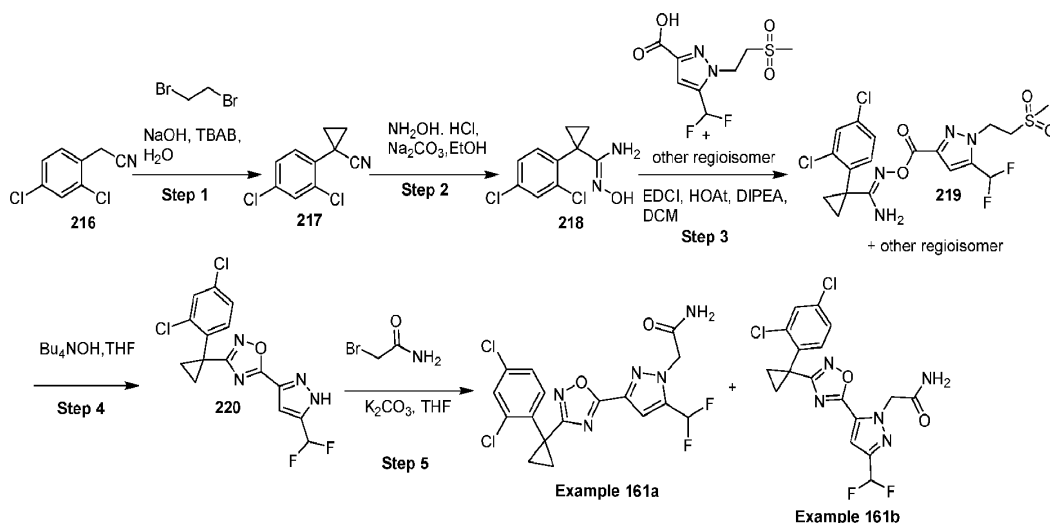
C₂₆H₂₇ClF₄N₆O₄: 598.1, found [M+H]⁺ = 599.3.

[1060] Synthesis of 2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one, Example 159 [Step 6]: To a solution of *tert*-butyl 4-(2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (215, 100 mg, 0.2 mmol) in dichloromethane (4 mL), HCl in dioxane (0.6 mL, 2.50 mmol, 4M) was added at 0 °C and stirred for 2h at ambient temperature. After completion, the reaction mixture was concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC to afford 2-(3-(3-(1-(2-chloro-5-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 159, 35 mg). LCMS (ESI) Calcd for C₂₁H₁₉ClF₄N₆O₂: 498.8, found [M+H]⁺ = 499.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.70 (s, 1H), 7.57-7.53 (m, 1H), 7.50-7.48 (m, 1H), 7.28-7.27(m, 1H), 5.51(s, 2H), 3.42-3.34 (m, 2H), 3.31-3.29 (m, 3H), 2.72-2.71 (m, 2H), 2.66-2.62 (m, 2H), 1.74-1.71 (m, 2H), 1.55-1.52 (m, 2H).

Example 160: Synthesis of 2-(3-(3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (Example 160)

[1061] 2-(3-(3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one was synthesized following Scheme 89 using *tert*-butyl 4-(2-(3-(3-(1-(2-chloro-3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate. LCMS (ESI) Calcd for C₂₁H₁₉ClF₄N₆O₂: 498.8, found [M+H]⁺ = 499.0. ¹H NMR (400 MHz, DMSO-*d*₆) (at 100 °C) δ_H 7.52 (s, 1H), 7.44-7.34 (m, 3H), 5.42 (s, 2H), 3.42 (t, 4H), 2.96-2.73 (m, 4H), 1.80-1.77 (m, 2H), 1.53-1.51 (m, 2H).

Examples 161a & 161b: Synthesis of 2-(3-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 161a) and 2-(5-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)acetamide, Example 161b



Scheme 90

[1062] Synthesis of 1-(2,4-dichlorophenyl)cyclopropane-1-carbonitrile, 217 [Step 1]: To a stirred solution of NaOH (5.16 g, 129 mmol) in water (10 mL), 2-(2,4-dichlorophenyl)acetonitrile (216, 2.00 g, 10.8 mmol) and TBAB (690 mg, 2.15 mmol) were added at 0 °C. After 5 min 1,2-dibromoethane (8.1 mL, 53.8 mmol) was added dropwise and the resulting reaction mixture was heated at 60 °C for 12 hr. After completion, reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(2,4-dichlorophenyl)cyclopropane-1-carbonitrile (217, 2.1 g). ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.74 (brs, 1H), 7.56 (d, 1H), 7.48-7.45 (m, 1H), 1.80-1.73 (m, 2H), 1.44-1.41 (m, 2H).

[1063] Synthesis of (Z)-1-(2,4-dichlorophenyl)-N'-hydroxycyclopropane-1-carboximidamide, 218 [Step 2]: To a stirred solution of 1-(2,4-dichlorophenyl)cyclopropane-1-carbonitrile (217, 2.00 g, 9.43 mmol) in Ethanol (10 mL), Na₂CO₃ (2.00 g, 18.9 mmol) was added followed by NH₂OH·HCl (1.31 g, 18.9 mmol) and the reaction mixture was heated at 70 °C for 12h. After completion, volatiles are evaporated under reduced pressure, diluted with water and extracted with ethyl acetate (thrice). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (Z)-1-(2,4-dichlorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (218, 1.8 g). LCMS (ESI) calculated for C₁₀H₁₀Cl₂N₂O [M]: 244.0, found [M+H]⁺: 245.2.

[1064] Synthesis of (Z)-1-(2,4-dichlorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 219, [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-

carboxylic acid (along with other regioisomer) (900 mg, 3.4 mmol) and (Z)-1-(2,4-dichlorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (218, 905 mg, 3.7 mmol) in dichloromethane (10 mL), N,N-Diisopropylethylamine (1.8 mL, 10.1 mmol), EDCI.HCl (965 mg, 5.0 mmol) and HOAt (90 mg, 0.7 mmol) were added at 0 °C and reaction mixture was stirred for 16h at ambient temperature. After completion the reaction mixture was concentrated under reduced pressure, dissolved with ethyl acetate, washed with water (twice) and brine. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-1-(2,4-dichlorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (along with other regioisomer) (219, 600mg). LCMS (ESI) Calcd for C₁₈H₁₈Cl₂F₂N₄O₄S [M]: 494.0, found [M+H]⁺: 495.1.

[1065] Synthesis of 3-(1-(2,4-dichlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 220 [Step 4]: To a stirred solution of (Z)-1-(2,4-dichlorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (along with other regioisomer) (219, 550 mg, 0.4 mmol) in THF (2mL), tetrabutylammonium hydroxide(1M in methanol, 1 mL, 1.1 mmol) was added and resulting reaction mixture was stirred for 12 h at ambient temperature. After completion Reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water (thrice), dried over anhydrous Na₂SO₄, filtered and concentrated again under reduced pressure. Product was purified through column chromatography to afford 3-(1-(2,4-dichlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (220, 210 mg). LCMS (ESI) calculated for C₁₅H₁₀Cl₂F₂N₄O [M]: 370.0, found [M+H]⁺: 371.2.

[1066] Synthesis of 2-(3-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide, Example 161a and 2-(5-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)acetamide, Example 161b (Step 5): To a stirred suspension of 3-(1-(2,4-dichlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (220, 200 mg, 0.4 mmol) and potassium carbonate (149 mg, 1.08 mmol) in THF (2 mL) at 0 °C, 2-bromoacetamide (89 mg, 0.65 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with ice-cold water and brine. Combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to afford 2-(3-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-

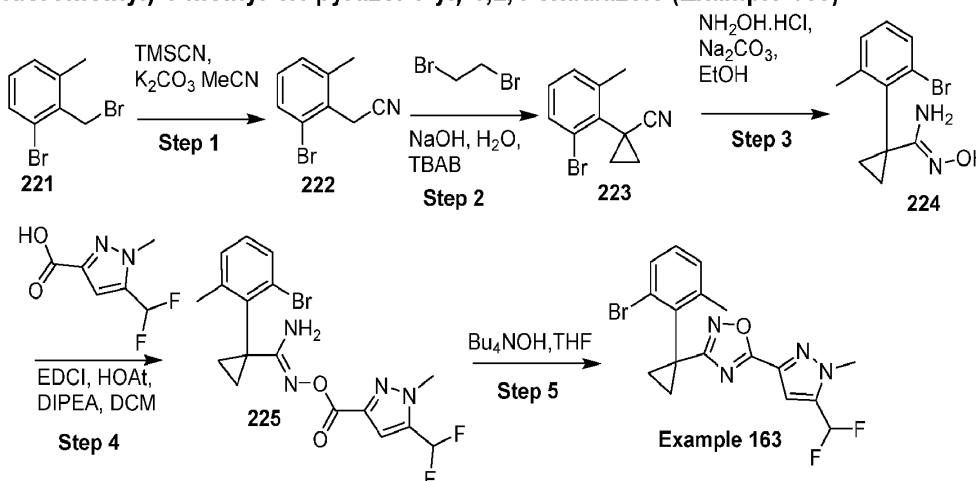
(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 161a, 30 mg) as Peak-1 and 2-(5-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 161b, 17 mg) as Peak-2.

[1067] 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide, Example 161a (Peak-1): LCMS (ESI) Calcd. for $C_{17}H_{13}Cl_2F_2N_5O_2$: 427.0, found $[M+H]^+ = 428.0$. 1H NMR (400 MHz, DMSO- d_6) δ_H 7.72 (brs, 1H), 7.67 (d, 1H), 7.60 (d, 1H), 7.48-7.45 (m, 1H), 7.41-7.14 (m, 3H), 5.05 (s, 2H), 1.75-1.71 (m, 2H), 1.50-1.47 (m, 2H). Note: The structure of the final products was confirmed by NOE data analysis.

Example 162: Synthesis of 2-(3-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide (Example 162)

[1068] 2-(3-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide was synthesized following Scheme 90 using 2-bromo-N-methylacetamide. LCMS (ESI) Calcd for $C_{18}H_{15}Cl_2F_2N_5O_2$: 441.0, found $[M+H]^+ = 442.1$. 1H NMR (400 MHz, DMSO- d_6 at 100 °C) δ_H 7.94 (brs, 1H), 7.60-7.59 (m, 2H), 7.44 (d, 1H), 7.38-7.11 (m, 2H), 5.04 (s, 2H), 2.66 (s, 3H), 1.75 (s, 2H), 1.48 (s, 2H).

Example 163: Synthesis of 3-(1-(2-bromo-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 163)



Scheme 91

[1069] Synthesis of 2-(2-bromo-6-methylphenyl)acetonitrile, 222 [Step 1]: To a stirred solution of 1-bromo-2-(bromomethyl)-3-methylbenzene (221, 800 mg, 3 mmol) in MeCN (10mL), K_2CO_3 (420 mg, 3 mmol) was added followed by trimethylsilylformonitrile (0.4 mL, 3 mmol) and the

reaction mixture was heated at 100 °C for 16h. After completion, the reaction mixture was dissolved in ethyl acetate, washed with water(thrice) and brine. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 2-(2-bromo-6-methylphenyl)acetonitrile (222, 600 mg). LCMS (ESI) Calcd for C₉H₈BrN: 210.07, found [M-2H]⁻: 208.0.

[1070] Synthesis of 1-(2-bromo-6-methylphenyl)cyclopropane-1-carbonitrile, 223 [Step 2]: To a stirred solution of NaOH (1.1 g, 28 mmol) in Water (4mL), 2-(2-bromo-6-methylphenyl)acetonitrile (222, 500 mg, 2.3 mmol), TBAB (155 mg, 0.5 mmol) and 1,2-dibromoethane (2 mL, 12 mmol) were added and the reaction mixture was heated at 100 °C for 24 h. After completion, reaction mixture was poured into cold water and extracted with ethyl acetate(thrice). Combined organic layered was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-(2-bromo-6-methylphenyl)cyclopropane-1-carbonitrile (223, 400 mg). GCMS Calcd. For C₁₁H₁₀BrN: = 236.11, [M/Z] = 236.

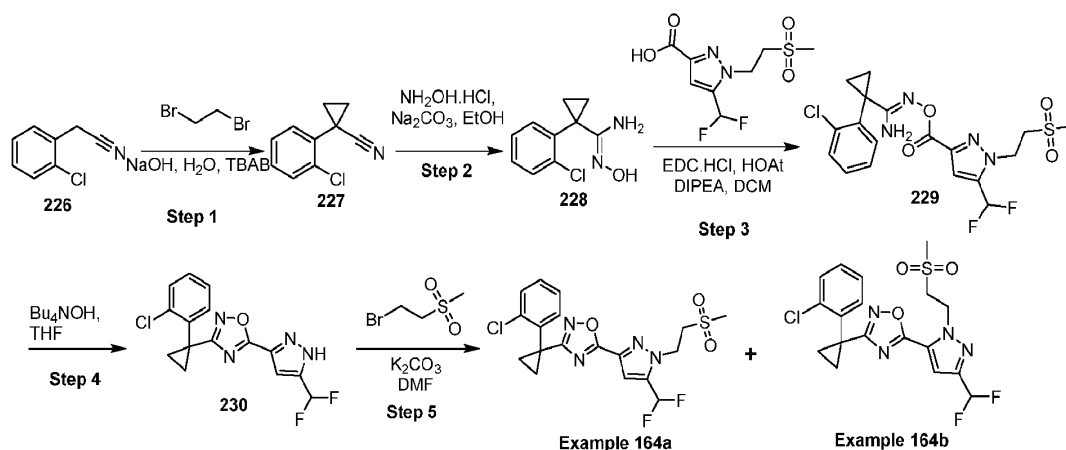
[1071] Synthesis of (Z)-1-(2-bromo-6-methylphenyl)-N'-hydroxycyclopropane-1-carboximidamide, 224 [Step 3]: To a stirred solution of 1-(2-bromo-6-methylphenyl)cyclopropane-1-carbonitrile (223, 400 mg, 1.7 mmol) in ethanol (8 mL), hydroxylamine hydrochloride (240 mg, 3.5 mmol) and sodium carbonate (360 mg, 3.5 mmol) were added and the reaction was heated at 70 °C for 12 h. After completion volatiles were evaporated under reduced pressure, dissolved in water and extracted with ethyl acetate(thrice). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the product which was purified through column chromatography(50% ethyl acetate in hexane as eluent) to afford (Z)-1-(2-bromo-6-methylphenyl)-N'-hydroxycyclopropane-1-carboximidamide (224, 120 mg). LCMS (ESI) Calcd for C₁₁H₁₃BrN₂O: 269.1, found [M+2H]⁺: 272.0.

[1072] Synthesis of (Z)-1-(2-bromo-6-methylphenyl)-N'-((5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 225 [Step 4]: To a stirred solution of 5-(difluoromethyl)-1-methyl-pyrazole-3-carboxylic acid (80 mg, 0.4 mmol) and (Z)-1-(2-bromo-6-methylphenyl)-N'-hydroxycyclopropane-1-carboximidamide (224, 135 mg, 0.5 mmol) in DCM (4mL), DIPEA (0.3 mL, 1.4 mmol), EDCI.HCl (130 mg, 0.7 mmol) and HOAt (7 mg, 0.05 mmol) were added at 0 °C and reaction mixture was stirred for 16 h at ambient temperature. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na₂SO₄, filtered

and concentrated under reduced pressure to afford (Z)-1-(2-bromo-6-methylphenyl)-N'-((5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (225, 120 mg) as sticky liquid. LCMS (ESI) Calcd for $C_{17}H_{17}BrF_2N_4O_2$: 427.2, found $[M+2H]^+$: 429.0.

[1073] Synthesis of 3-(1-(2-bromo-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 163 [Step 5]: To a stirred solution of (Z)-1-(2-bromo-6-methylphenyl)-N'-((5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (7, 90 mg, 0.2 mmol) in THF (2mL), Tetrabutylammonium hydroxide (0.05 mmol/1 M) was added. The resulting reaction mixture was stirred for 16 h at ambient temperature. The reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford product which was purified by reverse phase prep HPLC purification to afford 3-(1-(2-bromo-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 163, 28 mg). 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.50-7.16 (m, 5H), 4.05 (s, 3H), 2.37 (s, 3H), 1.92-1.90 (m, 1H), 1.81-1.80 (m, 1H), 1.50-1.45 (m, 2H). LCMS: Calcd for $C_{17}H_{15}BrF_2N_4O$: 409.2, found $[M+2H]^+$: 411.0.

Examples 164a & 164b: Synthesis of 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 164a) and 3-(1-(2-chlorophenyl)cyclopropyl)-5-(3-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazol-5-yl)-1,2,4-oxadiazole (Example 165b)



Scheme 92

[1074] Synthesis of 1-(2-chlorophenyl)cyclopropane-1-carbonitrile, 227 [Step 1]: To a stirred solution of NaOH (7.9 g, 200.0 mmol) in water (15 mL), 2-(2-chlorophenyl)acetonitrile (1, 2.5 g, 16.5 mmol), TBAB (1.1 g, 3.3 mmol) and 1,2-dibromoethane (12 mL, 82.5 mmol) were added and the reaction mixture was heated at 60 °C for 12h. After completion, the reaction mixture was

poured into cold water and extracted with ethyl acetate (thrice). Combined organic extract was collected, washed with brine, dried over anhydrous Na₂SO₄, filtered and, concentrated under reduced pressure to afford 1-(2-chlorophenyl)cyclopropane-1-carbonitrile (227, 2.5 g). ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 7.56-7.51 (m, 2H), 7.44-7.35 (m, 2H), 1.75-1.72 (m, 2H), 1.42-1.35 (m, 2H).

[1075] Synthesis of (Z)-1-(2-chlorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide, 228 [Step 2]: To a stirred solution of 1-(2-chlorophenyl)cyclopropane-1-carbonitrile (227, 2.5 g, 14.1 mmol) in ethanol (30 mL) was added sodium carbonate (3.0 g, 28.1 mmol) followed by hydroxylamine hydrochloride (2.0 g, 28.1 mmol) and the reaction was heated at 70 °C for 12 h. After completion, the volatiles were removed under reduced pressure, dissolved in water and extracted with ethyl acetate. Combined organic extract was collected, washed with brine, dried over anhydrous Na₂SO₄ and, concentrated under reduced pressure and triturated with pentane to afford (Z)-1-(2-chlorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (228, 2.6 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 9.11 (s, 1H), 7.44-7.40 (m, 1H), 7.38-7.30 (m, 1H), 7.28-7.20 (m, 2H), 1.46-1.39 (m, 2H), 0.98-0.91 (m, 2H).

[1076] Synthesis of (Z)-1-(2-chlorophenyl)-*N'*-((5-(difluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 229 [Step 3]: To a stirred solution of (Z)-1-(2-chlorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (228, 500 mg, 2.4 mmol) and 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazole-3-carboxylic acid (700 mg, 2.6 mmol) in dichloromethane (8 mL) were added DIPEA (1.2 mL, 7.1 mmol), EDC.HCl (905 mg, 4.7 mmol) and HOAt (50 mg, 0.5 mmol) at 0 °C and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was diluted with dichloromethane and washed with water. Organic extracts was collected, washed with brine, dried over anhydrous Na₂SO₄ and, concentrated under reduce pressure to afford (Z)-1-(2-chlorophenyl)-*N'*-((5-(difluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (229, 700 mg). LCMS (ESI) Calcd for C₁₈H₁₉ClF₂N₄O₄S: 460.8; found [M+H]⁺ = 461.0.

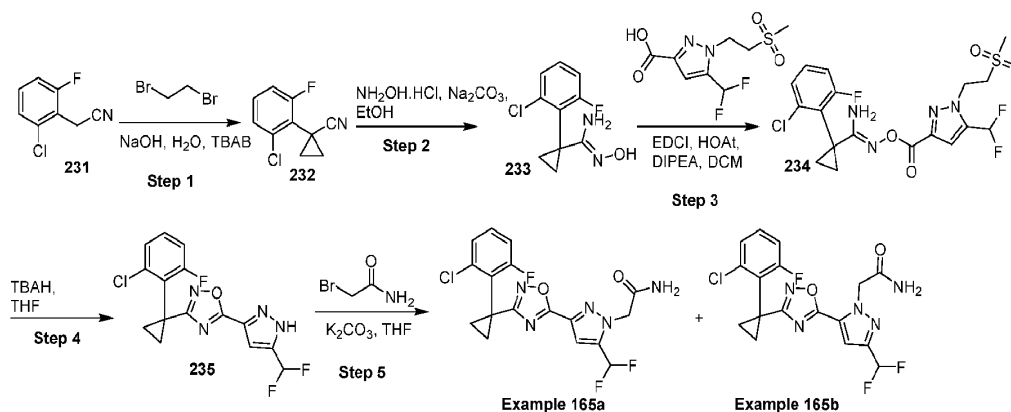
[1077] Synthesis of 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, 230 [Step 4]: To a stirred solution of (Z)-1-(2-chlorophenyl)-*N'*-((5-(difluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (229, 700 mg, 1.5 mmol) in THF (10 mL), tetrabutylammonium hydroxide (0.2 mL, 0.3 mmol, 40% in water) was added and the resulting reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with ethyl acetate and washed with water (thrice). The combined organic extract was collected, washed with brine, dried over anhydrous Na₂SO₄, filtered and,

concentrated under reduced pressure to afford 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (230, 300 mg). LCMS (ESI) Calcd for $C_{15}H_{11}ClF_2N_4O$: 336.7; found $[M+H]^+ = 337.0$.

[1078] Synthesis of 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole & 3-(1-(2-chlorophenyl)cyclopropyl)-5-(3-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-5-yl)-1,2,4-oxadiazole, Examples 164a & 164b [Step 5]: To a stirred solution of 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (230, 200 mg, 0.6 mmol) in THF (4 mL) was added K_2CO_3 (328 mg, 2.4 mmol) at 0 °C. After 15 min, 1-bromo-2-methylsulfonyl-ethane (222 mg, 1.2 mmol) was added to the reaction mixture and stirred at ambient temperature for 16 h. The reaction mixture was diluted with ethyl acetate and washed with water. The combined organic extracts was collected, washed with brine, dried over anhydrous Na_2SO_4 and, concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC and isolated compound was lyophilized to afford 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 164a, 17 mg) and 3-(1-(2-chlorophenyl)cyclopropyl)-5-(3-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-5-yl)-1,2,4-oxadiazole (Example 164b, 12 mg). Note: Structure was confirmed by NOE.

[1079] Analytical data of 3-(1-(2-chlorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole, Example 164a: LCMS (ESI) Calcd for $C_{18}H_{17}ClF_2N_4O_3S$: 442.8; found $[M+H]^+ = 443.3$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.58-7.55 (m, 1H), 7.50-7.48 (m, 1H), 7.41-7.28 (m, 4H), 4.75 (t, 2H), 3.80 (t, 2H), 3.06 (s, 3H), 1.73-1.70 (m, 2H), 1.48-1.45 (m, 2H).

Examples 165a & 165b: Synthesis of 2-(3-(3-(1-(2-chloro-6-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide (Example 165a) and 2-(5-(3-(1-(2-chloro-6-fluoro-phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)pyrazol-1-yl)acetamide (Example 165b)



Scheme 93

[1080] Synthesis of 1-(2-chloro-6-fluorophenyl)cyclopropane-1-carbonitrile, 232 [Step 1]: To a stirred solution of NaOH (2.8 g, 70.8 mmol) in water (10 mL), 2-(2-chloro-6-fluorophenyl)acetonitrile (231, 1.0 g, 5.9 mmol), TBAB (0.4 g, 1.2 mmol) and 1,2-dibromoethane (4.6 mL, 29.5 mmol) were added and the reaction mixture was heated at 60 °C for 12h. After completion, reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford as a 1-(2-chloro-6-fluorophenyl)cyclopropanecarbonitrile (232, 1.0 g). ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.53-7.47 (m, 1H), 7.44-7.42 (m, 1H), 7.35-7.30 (m, 1H), 1.89-1.86 (t, 2H), 1.47-1.45 (t, 2H).

[1081] Synthesis of (Z)-1-(2-chloro-6-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide, 233 [Step 2]: To a stirred solution of 1-(2-chloro-6-fluorophenyl)cyclopropanecarbonitrile (232, 1.0 g, 5.1 mmol) in ethanol (15 mL), sodium carbonate (1.1 g, 10.2 mmol) and hydroxylamine hydrochloride (0.7 g, 10.2 mmol) were added and the reaction was heated at 70 °C for 12h. After completion, the volatiles were evaporated under reduced pressure, dissolved in water and extracted with ethyl acetate (thrice). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (Z)-1-(2-chloro-6-fluorophenyl)-*N'*-hydroxy-cyclopropanecarboximidine (233, 900 mg). ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 7.53-7.47 (m, 1H), 7.44-7.42 (m, 1H), 7.35-7.30 (m, 1H), 1.89-1.86 (t, 2H), 1.47-1.45 (t, 2H).

[1082] Synthesis of (Z)-1-(2-chloro-6-fluorophenyl)-*N'*-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 234 [Step 3]: To a solution of 5-(difluoromethyl)-1-(2-methylsulfonyl)pyrazole-3-carboxylic acid (500 mg, 1.9 mmol) (along with other regioisomer) and (Z)-1-(2-chloro-6-fluorophenyl)-*N'*-

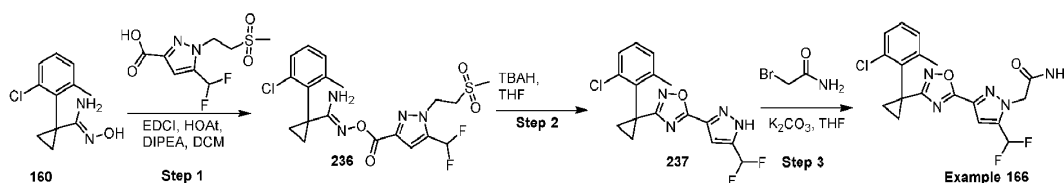
hydroxycyclopropane-1-carboximidamide (233, 500 mg, 1.4 mmol) in dichloromethane (10mL), DIPEA (1.0 mL, 5.6 mmol), EDCI.HCl (535 mg, 2.8 mmol) and HOAt (50 mg, 0.4 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-1-(2-chloro-6-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (234, 350 mg) along with other regioisomer. LCMS (ESI) Calcd for C₁₈H₁₈ClF₃N₄O₄S: 478.0, found [M+H]⁺ = 479.3.

[1083] Synthesis of 3-(1-(2-chloro-6-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 235 [Step 4]: To a stirred solution of (Z)-1-(2-chloro-6-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (234, 300 mg, 0.6 mmol) in THF (10 mL), Tetrabutylammonium hydroxide (2.0 mL, 1M in methanol) was added and the resulting reaction mixture was stirred at ambient temperature for 12 h. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water (twice). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford 3-(1-(2-chloro-6-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (235, 200 mg). LCMS (ESI) Calcd for C₁₅H₁₀ClF₃N₄O: 354.0, found [M+H]⁺ = 355.3.

[1084] Synthesis of 2-(3-(3-(1-(2-chloro-6-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide, Example 165a and Example 165b [Step 5]: To a stirred solution of 3-(1-(2-chloro-6-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (235, 200 mg, 0.6 mmol) in THF (5 mL), K₂CO₃ (155 mg, 1.1 mmol) was added at 0 °C. After 15 min, 2-bromoacetamide (95 mg, 0.7 mmol) was added to the reaction mixture and stirred at ambient temperature for 16 h. After completion, the reaction mixture was dissolved in ethyl acetate and washed with water (twice). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by prep-HPLC purification to afford the first product as 2-(3-(3-(1-(2-chloro-6-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)pyrazol-1-yl)acetamide (Example 165a, 20 mg) as Peak 1 and the second product as 2-(5-(3-(1-(2-chloro-6-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)pyrazol-1-yl)acetamide (Example 165b, 10 mg) as Peak 2.

[1085] Analytical data of 2-(3-(3-(1-(2-chloro-6-fluoro-phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)pyrazol-1-yl)acetamide, Example 165a : ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 7.41(s, 1H), 7.49-7.14 (m, 6H), 5.05(s, 2H), 1.89(s, 2H), 1.75(s, 2H). LCMS (ESI) Calcd for $\text{C}_{19}\text{H}_{16}\text{ClF}_3\text{N}_4\text{O}$: 408.1, found $[\text{M}+\text{H}]^+ = 412.0$. NOTE: The actual structure was confirmed through 2D &NOE experiments.

Example 166: Synthesis of 2-(3-(3-(1-(2-chloro-6-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 166)



Scheme 94

[1086] Synthesis of (Z)-1-(2-chloro-6-methylphenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 236 [Step 1]: To a solution of 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)pyrazole-3-carboxylic acid (700 mg, 2.6 mmol) and 1-(2-chloro-6-methyl-phenyl)-N'-hydroxy-cyclopropanecarboximidine (160, 645 mg, 2.8 mmol) in dichloromethane (20 mL), DIPEA (1.4 mL, 7.8 mmol), EDCI.HCl (750 mg, 3.9 mmol) and HOAt (70 mg, 0.5 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-1-(2-chloro-6-methylphenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (236, 600 mg). LCMS (ESI) Calcd for $\text{C}_{19}\text{H}_{21}\text{ClF}_2\text{N}_4\text{O}_4\text{S}$: 474.0, found $[\text{M}+\text{H}]^+ = 474.7$.

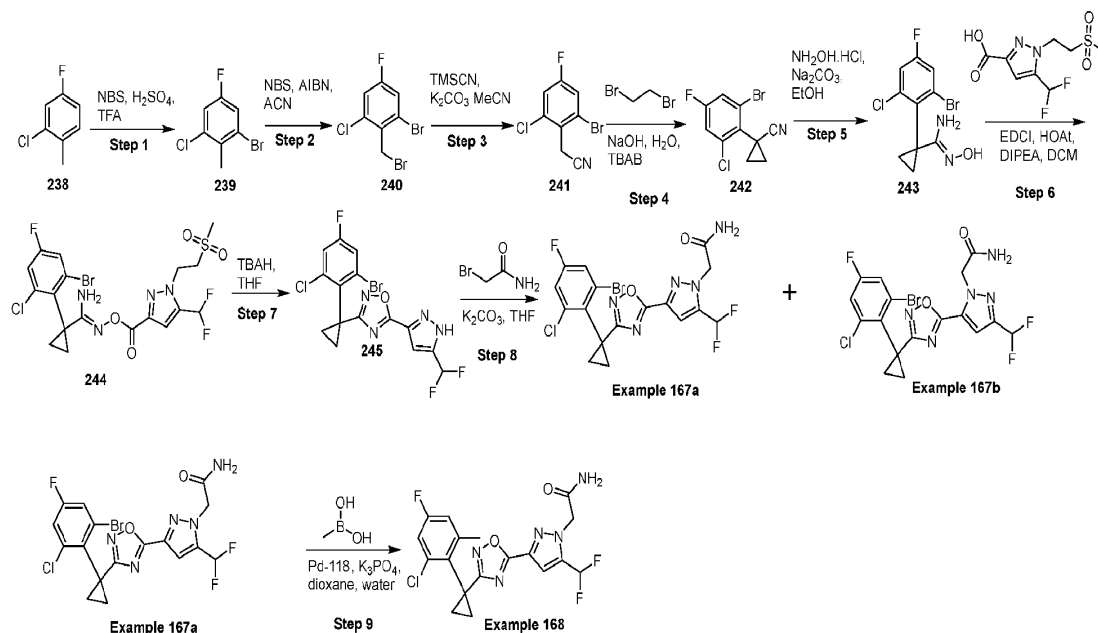
[1087] Synthesis of 3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 237 [Step 2]: To a stirred solution of (Z)-1-(2-chloro-6-methylphenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (236, 600 mg, 1.3 mmol) in THF (10 mL), tetrabutylammonium hydroxide (4.0 mL, 4.0 mmol, 1M in methanol) was added and the resulting reaction mixture was stirred at ambient temperature for 12 h. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate and washed with water (twice). The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and

concentrated under reduced pressure to afford 3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (237, 350 mg). LCMS (ESI) Calcd for $C_{16}H_{13}ClF_2N_4O$: 350.0, found $[M+H]^+$ = 351.0.

[1088] Synthesis of 2-(3-(3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide, Example 166 [Step 3]: To a stirred solution of 3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (237, 150 mg, 0.4 mmol) in THF (4 mL), K_2CO_3 (120 mg, 0.8 mmol) was added at 0 °C. After 15 min, 2-bromoacetamide (70 mg, 0.5 mmol) was added to the reaction mixture and stirred at ambient temperature for 16 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water (twice). The combined organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by reverse phase prep-HPLC to afford 2-(3-(3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide (Example 166, 5 mg) as Peak-1 and 2-(5-(3-(1-(2-chloro-6-methyl-phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)pyrazol-1-yl)acetamide (3.0 mg) as Peak-2.

[1089] Analytical data of 2-(3-(3-(1-(2-chloro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide, Example 166 (Peak 1): 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.71 (brs, 1H), 7.42 (brs, 1H), 7.33-7.24 (m, 5H), 5.06 (s, 2H), 2.36 (s, 3H), 1.88 (brs, 1H), 1.80 (brs, 1H), 1.47 (t, 2H). LCMS (ESI) Calcd for $C_{18}H_{16}ClF_2N_5O_2$: 407.1, found $[M+H]^+$ = 408.1. Note: NOTE: The actual structure was confirmed through HNMR study of two spots with batch Id 'CR620-SB-2023-10-40-P-F-Peak-1' and 'CR620-SB-2023-10-40-P-F-Peak-2'. Peak-2 HNMR consistent with desired product along with other impurities.

Examples 167a, 167b, & 168: Synthesis of 2-(3-(3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide (Example 167a), 2-(5-(3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide (Example 167b), and 2-(3-(3-(1-(2-chloro-4-fluoro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)acetamide (Example 168)



Scheme 95

[1090] Synthesis of 1-bromo-3-chloro-5-fluoro-2-methylbenzene, 239 [Step 1]: Sulfuric Acid (0.6 mL) and NBS (700 mg, 4 mmol) are added to a solution of 2-chloro-4-fluoro-1-methylbenzene (238, 500 mg, 3.5 mmol) in TFA (2.0 mL, 25 mmol). The reaction mixture was allowed to stir at ambient temperature for 18 h. Reaction mixture was quenched with saturated NaHCO₃ solution and extracted with ethyl acetate. Organic extracts were evaporated under reduced pressure to afford product which was purified by combiflash chromatography to afford 1-bromo-3-chloro-5-fluoro-2-methylbenzene (239, 600 mg). ¹HNMR (400 MHz, DMSO-d₆) δ_H 7.75 (d, 1H), 7.59 (d, 1H), 2.29 (s, 3H).

[1091] Synthesis of 1-bromo-2-(bromomethyl)-3-chloro-5-fluorobenzene, 240 [Step 2]: AIBN (90 mg, 0.5 mmol) and NBS (580 mg, 3 mmol) were added to a solution of 1-bromo-3-chloro-5-fluoro-2-methylbenzene (239, 600 mg, 3 mmol) in MeCN (15mL). The reaction mixture was allowed to stir at 80 °C for 16 h. After stirring for 16 h at reflux the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 1-bromo-2-(bromomethyl)-3-chloro-5-fluorobenzene (240, 750 mg). GCMS Calcd. for C₇H₄Br₂ClF: [M] = 302.37, [M/Z] = 301.9.

[1092] Synthesis of 2-(2-bromo-6-chloro-4-fluorophenyl)acetonitrile, 241[Step 3]: To a stirred solution of 1-bromo-2-(bromomethyl)-3-chloro-5-fluorobenzene (240, 750 mg, 2.5 mmol) in MeCN (10mL), K₂CO₃ (350 mg, 2.5 mmol) was added followed by trimethylsilylformonitrile (0.4 mL, 2.5 mmol) and the reaction mixture was heated at 100 °C for 16 h. After completion, the

reaction mixture was dissolved in ethyl acetate, washed with water(thrice) and brine. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford product as 2-(2-bromo-6-chloro-4-fluorophenyl)acetonitrile (241, 600 mg). GCMS Calcd. for C₈H₄BrClFN: [M] = 248.48, [M/Z] = 249.

[1093] Synthesis of 1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropane-1-carbonitrile, 242 [Step 4]: To a stirred solution of NaOH (1.1 g, 30 mmol) in Water (5mL), 2-(2-bromo-6-chloro-4-fluorophenyl)acetonitrile (241, 600 mg, 2.5 mmol), TBAB (160 mg, 0.5 mmol) and 1,2-dibromoethane (2 mL, 12 mmol) were added and the reaction mixture was heated at 100 °C for 12h. After completion reaction mixture was poured into cold water and extracted with ethyl acetate(thrice). Combined organic layered was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropane-1-carbonitrile (242, 650 mg). GCMS Calcd. For C₁₀H₆BrClFN: [M] = 274.52, [M/Z] = 274.

[1094] Synthesis of (Z)-1-(2-bromo-6-chloro-4-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide, 243 [Step 5]: To a stirred solution of 1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropane-1-carbonitrile (242, 600 mg, 2 mmol) in Ethanol (10mL), sodium carbonate (460 mg, 4 mmol) and Hydroxylamine hydrochloride (305 mg, 4 mmol) were added and the reaction was heated at 70 °C for 12h. After completion volatiles were evaporated under reduced pressure, dissolved in water and extracted with ethyl acetate(thrice). Combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford product as (Z)-1-(2-bromo-6-chloro-4-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (243, 350 mg). LCMS (ESI) calculated for C₁₀H₉BrClFN₂O [M]: 307.55, found [M+2]⁺: 309.14.

[1095] Synthesis of (Z)-1-(2-bromo-6-chloro-4-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 244 [Step 6]: To a solution of 5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carboxylic acid (250 mg, 1 mmol)(along with other regioisomer) and (Z)-1-(2-bromo-6-chloro-4-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (243, 320 mg, 2 mmol) in 1,2-dichloromethane (5mL), DIPEA (0.5 mL, 3 mmol), EDCI.HCl (270 mg, 1.5 mmol) and HOAt (30 mg, 0.2 mmol) were added at 0 °C and the reaction mixture was stirred for 16h at ambient temperature. After completion the reaction mixture was diluted with dichloromethane and partitioned with water. Combined organic layer was dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure to afford (Z)-1-(2-bromo-6-chloro-4-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-

(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (244, 300 mg) along with other regioisomer. LCMS (ESI) calculated for $C_{18}H_{17}BrClF_3N_4O_4S$ [M]: 557.77, found $[M+H]^+$: 558.8.

[1096] Synthesis of 3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, 245 [Step 7]: To a stirred solution of (Z)-1-(2-bromo-6-chloro-4-fluorophenyl)-N'-((5-(difluoromethyl)-1-(2-(methylsulfonyl)ethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (244, 300 mg, 0.6 mmol) in THF (6mL), Tetrabutylammonium hydroxide(1 M) (15 mg, 0.05 mmol) was added. The resulting reaction mixture was stirred for 16 h at ambient temperature. The mixture was passed through celite bed, washed with water then brine solution and extracted with ethyl acetate. The organics were then separated and dried under reduced pressure to afford product. Product was purified through prep-HPLC(RP) to afford 3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (245, 200 mg). 1H NMR (at 100 °C) (400 MHz, DMSO- d_6) δ H 7.89 (d, 1H), 7.59 (d, 1H), 7.20-6.93 (m, 2H), 1.78-1.75 (m, 2H), 1.52 (s, 2H). LC/MS: calculated for $C_{15}H_9BrClF_3N_4O$ [M]: 433.61, found $[M+2]^+$:435. Notes: 6 mg of int 10 was shipped. Rest amount were forwarded to next step.

[1097] Synthesis of 2-(3-(3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide, Example 167a and 2-(5-(3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)acetamide, Example 168b [Step 8]: To a stirred solution of 3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (245, 100 mg, 0.2 mmol) in THF (4mL), Cs_2CO_3 (150 mg, 0.4 mmol) was added at 0 °C. After 15 min, 2-bromoacetamide (50 mg, 0.3 mmol) was added to the reaction mixture and stirred at ambient temperature for 16 h. After completion, the mixture was diluted partitioned with ethyl acetate and water. The combined organic layer was collected, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford mixture which was purified and separated through RP prep chromatography to afford as 2-(3-(3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 167a, 10 mg) as peak 1 and 2-(5-(3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 167b, 10 mg) as peak 2.

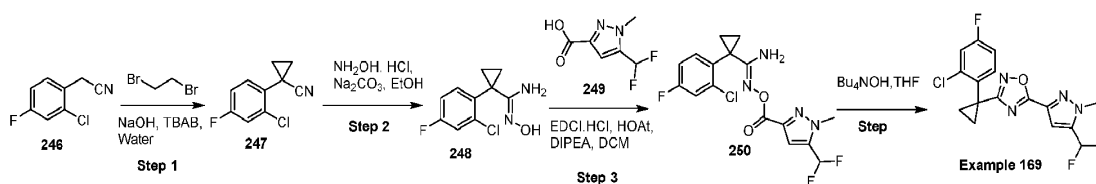
[1098] Analytical data for peak 1: 1H NMR (at 100 °C) (400 MHz, DMSO- d_6) δ H 7.89 (d, 1H), 7.58 (d, 1H), 7.36-7.09 (m, 2H), 5.04 (s, 2H), 3.64 (s, 2H), 1.75 (s, 2H), 1.53 (s, 2H). LC/MS:

calculated for $C_{17}H_{12}BrClF_3N_5O_2$: 490.6, found $[M+H]^+ = 491.8$. Notes: 10 mg of compound was shipped. Rest amount were forwarded to next step. Extra peak present in 1H NMR.

[1099] Analytical data for peak 2: 1H NMR (400 MHz, DMSO- d_6) δ H 7.94 (d, 1H), 7.72 (d, 1H), 7.43 (s, 1H), 7.34-6.97 (m, 1H), 5.25 (s, 2H), 1.73 (s, 2H), 1.55 (s, 2H). LC/MS: calculated for $C_{17}H_{12}BrClF_3N_5O_2$ [M]: 490.66, found $[M+H]^+ = 475$.

[1100] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluoro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide, Example 168 [Step 5]: To a stirred solution of 2-(3-(3-(1-(2-bromo-6-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (50 mg, 0.1 mmol) in 1,4-Dioxane (2mL) and Water (0.2mL), K_3PO_4 (60 mg, 0.3 mmol) and Methyl boronic acid (1.50 eq, 9.1 mg, 0.153 mmol) were added at ambient temperature. It was then degassed with nitrogen for 10 minutes and $PdCl_2(dtbpf)$ (10 mg, 0.01 mmol) was added to it and the reaction mass was heated to 100 °C for 16h. After completion, the mixture was diluted partitioned with ethyl acetate and water. The combined organic layer was collected, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford mixture which was purified and separated through reverse phase prep chromatography to afford 2-(3-(3-(1-(2-chloro-4-fluoro-6-methylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 168, 10 mg). 1H NMR (400 MHz, DMSO- d_6) (at 100 °C) δ H 7.49 (d, 1H), 7.36-7.02 (m, 5H), 2.26 (s, 3H), 1.74 (d, 2H), 1.47 (d, 2H). LC/MS: calculated for $C_{18}H_{15}ClF_3N_5O_2$ [M]: 425.79, found $[M+H]^+ = 426$.

Examples 169: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 169)



Scheme 96

[1101] Synthesis of 1-(2-chloro-4-fluorophenyl)cyclopropane-1-carbonitrile, 247 [Step 1]: To a stirred solution of NaOH (850 mg, 21.2 mmol) in water (5 mL), 2-(2-chloro-4-fluorophenyl)acetonitrile (246, 300 mg, 1.8 mmol) and TBAB (115 mg, 0.4 mmol) were added at 0 °C. After 5 min, 1,2-dibromoethane (1.3 mL, 8.9 mmol) was added dropwise and the resulting reaction mixture was heated at 60 °C for 12 h. After completion, the reaction mixture was poured into cold water and extracted with ethyl acetate (thrice). Combined organic layer was dried over

anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(2-chloro-4-fluorophenyl)cyclopropane-1-carbonitrile (247, 300 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H 7.62-7.55 (m, 2H), 7.29-7.24 (m, 1H), 1.76-1.73 (m, 2H), 1.43-1.40 (m, 2H) [Note: HNMR contain extra peak.]

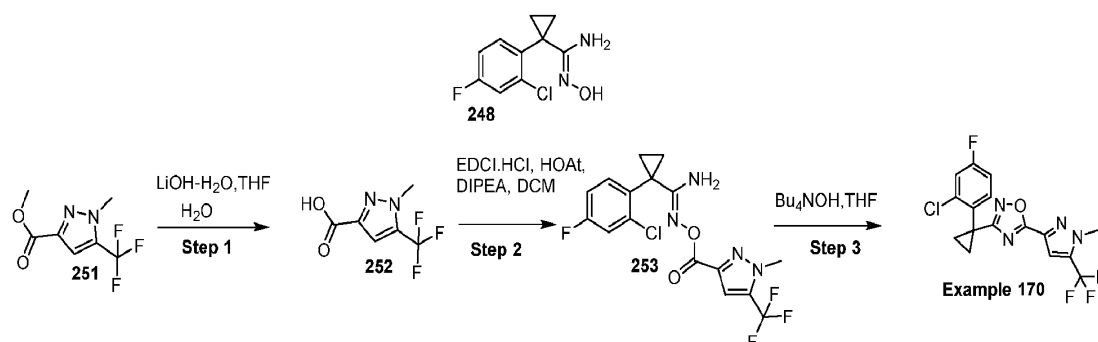
[1102] Synthesis of (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide, 248 [Step 2]: To a stirred solution of 1-(2-chloro-4-fluorophenyl)cyclopropane-1-carbonitrile (247, 250 mg, 1.3 mmol) in ethanol (2mL), Na₂CO₃ (270 mg, 2.6 mmol) was added followed by NH₂OH.HCl (180 mg, 2.6 mmol) and the reaction mixture was heated to reflux at 70 °C for 12h. After completion, the volatiles were evaporated under reduced pressure, diluted with water and extracted with ethyl acetate (thrice). The combined organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (248, 250 mg). LCMS (ESI) Calcd for C₁₀H₁₀ClFN₂O: 228.1, found [M+H]⁺ = 228.9.

[1103] Synthesis of (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-((5-(difluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 250 [Step 3]: To a stirred solution of 5-(difluoromethyl)-1-methyl-1H-pyrazole-3-carboxylic acid (249, 85 mg, 0.5 mmol) and (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (248, 140 mg, 0.6 mmol) in dichloromethane (1 mL), *N,N*-Diisopropylethylamine (2 mL, 1.2 mmol), EDCI.HCl (120 mg, 0.6 mmol) and HOAt (15 mg, 0.1 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was concentrated under reduced pressure, dissolved with ethyl acetate, washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by column chromatography to (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-((5-(difluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (250, 140 mg). LCMS (ESI) Calcd for C₁₆H₁₄ClF₃N₄O₂: 386.1, found [M+H]⁺ = 387.1.

[1104] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 169 (Step-4): To a stirred solution of (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-((5-(difluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (250, 140 mg, 0.4 mmol) in THF (2 mL), tetrabutylammonium hydroxide (0.1 mL, 0.1 mmol, 1M in methanol) was added and resulting reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, dried over anhydrous Na₂SO₄, filtered

and concentrated again under reduced pressure. The product was purified by reverse phase prep-HPLC and lyophilized to afford 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 169, 27 mg). LCMS (ESI) Calcd for C₁₆H₁₂ClF₃N₄O: 368.1, found [M+H]⁺ = 369.0. ¹HNMR (400 MHz, DMSO-*d*₆, 100 °C) δ_H 7.63-7.59 (m, 1H), 7.44-7.18 (m, 4H), 4.05 (s, 3H), 1.76-1.73 (m, 2H), 1.50-1.45 (m, 2H).

Examples 170: Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-1,2,4-oxadiazole (Example 170)



Scheme 97

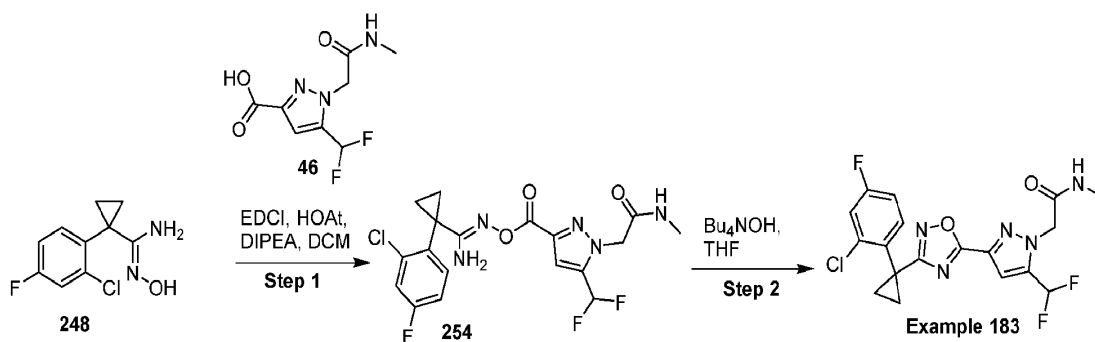
[1105] Synthesis of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid, 252 [Step 1]: To a stirred solution of methyl 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate (251, 250 mg, 1.2 mmol) in THF (2 mL) and water (0.5 mL), LiOH·H₂O (250 mg, 6.0 mmol) was added at 0 °C and the reaction mixture was stirred at ambient temperature for 12h. The reaction mixture was concentrated under reduced pressure, acidified with (1N) HCl up to pH- 4 to 5 and extracted with ethyl acetate (thrice). The combined organic extract was washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid (252, 200 mg). ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 13.19 (s, 1H), 7.29 (s, 1H), 4.02 (d, 3H).

[1106] Synthesis of (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-((1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 253 [Step 2]: To a stirred solution of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid (252, 80 mg, 0.4 mmol) and (Z)-1-(2-chloro-4-fluorophenyl)-*N'*-hydroxycyclopropane-1-carboximidamide (248, 125 mg, 0.5 mmol) in dichloromethane (1 mL), *N,N*-Diisopropylethylamine (0.2 mL, 0.8 mmol), EDCI·HCl (105 mg, 0.5 mmol) and HOAt (6.0 mg, 0.04 mmol) were added at 0 °C and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was concentrated under reduced pressure, dissolved with ethyl acetate, washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by column

chromatography to (Z)-1-(2-chloro-4-fluorophenyl)-N'-((1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (253, 150 mg). LCMS (ESI) Calcd for $C_{16}H_{13}ClF_4N_4O_2$: 404.1, found $[M+H]^+ = 405.2$.

[1107] Synthesis of 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 170 (Step-3): To a stirred solution of (Z)-1-(2-chloro-4-fluorophenyl)-N'-((1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (253, 120 mg, 0.3 mmol) in THF (2 mL), tetrabutylammonium hydroxide (0.06 mL, 0.06 mmol, 1M in methanol) was added and the resulting reaction mixture was stirred at ambient temperature for 60 min. After completion, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, dried over anhydrous Na_2SO_4 , filtered and concentrated again under reduced pressure. The product was purified by reverse phase prep-HPLC and lyophilized to afford 3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-5-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 170, 70 mg). LCMS (ESI) Calcd for $C_{16}H_{11}ClF_4N_4O$: 386.1, found $[M+H]^+ = 387.1$. 1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.65-7.61 (m, 2H), 7.51-7.48 (dd, 1H), 7.26-7.25 (m, 1H), 4.11 (s, 3H), 1.73-1.70 (m, 2H), 1.49-1.47 (m, 2H).

Examples 183: Synthesis of 2-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide (Example 183)



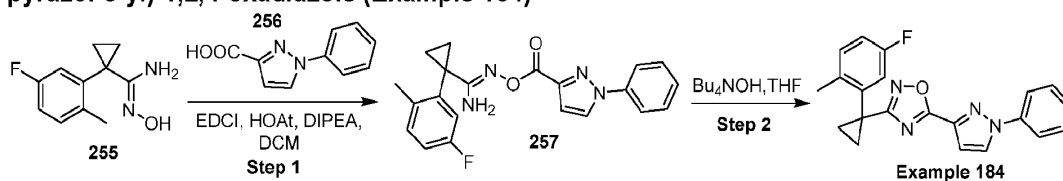
Scheme 98

[1108] Synthesis of (Z)-2-(3-(((amino(1-(2-chloro-4-fluorophenyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide, 254 [Step-1]: To a stirred solution of 5-(difluoromethyl)-1-(2-(methylamino)-2-oxoethyl)-1H-pyrazole-3-carboxylic acid (46, 140 mg, 0.6 mmol.) and (Z)-1-(2-chloro-5-fluorophenyl)-N'-hydroxycyclopropane-1-carboximidamide (248, 151 mg, 0.66 mmol) in dichloromethane (1mL), N,N-Diisopropylethylamine (0.3 ml, 1.5 mmol.), EDCI.HCl (173 mg, 0.9 mmol.) and HOAt (16 mg, 0.12 mmol.) were added at 0 °C and reaction mixture was stirred for

16h at ambient temperature. The reaction mixture was concentrated under reduced pressure, dissolved with ethyl acetate, washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by column chromatography to afford (Z)-2-(3-((((amino(1-(2-chloro-4-fluorophenyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide (254, 100 mg). LCMS (ESI) calculated for C₁₈H₁₇ClF₃N₅O₃ [M]: 443.1, found [M+H]⁺: 443.9.

[1109] Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide, Example 183 [Step-2]: To a stirred solution of (Z)-2-(3-((((amino(1-(2-chloro-4-fluorophenyl)cyclopropyl)methylene)amino)oxy)carbonyl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide (254, 100 mg, 0.2 mmol.) in THF (2mL), tetrabutylammonium hydroxide(1M in methanol, 0.04 mL, 0.04 mmol.) was added and resulting reaction mixture was stirred for 60 min at ambient temperature. After completion Reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated again under reduced pressure. Product was purified through prep-HPLC (Reverse phase) and lyophilized to afford Synthesis of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)-N-methylacetamide (Example 183, 33 mg). LCMS (ESI) calculated for C₁₈H₁₅ClF₃N₅O₂ [M]: 425.1, found [M-H]⁻: 426.1. ¹HNMR (400 MHz, DMSO-*d*₆) δ_H 8.21 (d, 1H), 7.64-7.61 (m, 1H), 7.51-7.48 (dd, 1H) 7.42-7.15(m, 3H), 5.06 (s, 2H), 2.66-2.62 (m, 3H), 1.73-1.70 (m, 2H), 1.49-1.46 (m, 2H).

Examples 184: Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-phenyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 184)



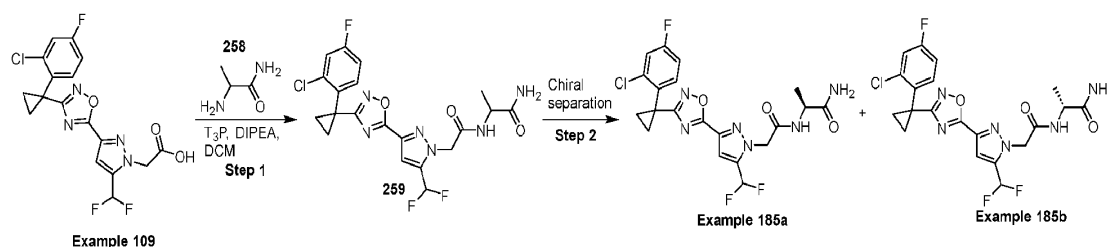
Scheme 99

[1110] Synthesis of (Z)-1-(5-fluoro-2-methylphenyl)-N'-((1-phenyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide, 257 (Step 1): To a stirred solution of 1-phenylpyrazole-3-carboxylic acid (256, 150 mg, 0.8 mmol) and 1-(5-fluoro-2-methyl-phenyl)-N'-hydroxy-cyclopropanecarboximidine (255, 150 mg, 0.7 mmol) in dichloromethane (5 mL), DIPEA (0.4 mL, 2.2 mmol), EDC.HCl (275 mg, 1.4 mmol) and HOAt (15 mg, 0.1 mmol) were added at 0 °C and reaction mixture was stirred at ambient temperature. After completion, the

reaction mixture was diluted with water and extracted with dichloromethane. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford (Z)-1-(5-fluoro-2-methylphenyl)-N'-((1-phenyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (257, 130 mg). LCMS Calcd for $\text{C}_{21}\text{H}_{19}\text{FN}_4\text{O}_2$: 378.4, found $[\text{M}+\text{H}]^+ = 379.2$.

[1111] Synthesis of 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-phenyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole, Example 184 (Step 2): To a stirred solution of (Z)-1-(5-fluoro-2-methylphenyl)-N'-((1-phenyl-1H-pyrazole-3-carbonyl)oxy)cyclopropane-1-carboximidamide (257, 300 mg, 0.8 mmol) in THF (5 mL), tetrabutylammonium hydroxide (0.05 mL, 0.1 mmol) was added and the reaction mixture was stirred at ambient temperature for 2h. After completion, the reaction mixture was diluted with ethyl acetate and washed with water (thrice). The combined organic extract was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The product was purified by reverse phase prep HPLC and lyophilized to afford 3-(1-(5-fluoro-2-methylphenyl)cyclopropyl)-5-(1-phenyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (Example 184, 165 mg). LCMS (ESI) Calcd for $\text{C}_{21}\text{H}_{17}\text{FN}_4\text{O}$: 360.3, found $[\text{M}+\text{H}]^+ = 361.2$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} 8.78 (d, 1H), 7.39 (d, 2H), 7.56 (t, 2H), 7.42 (t, 1H), 7.27-7.22 (m, 3H), 7.11-7.06 (m, 1H), 2.24 (s, 3H), 1.68 (s, 2H), 1.46-1.43 (m, 2H).

Examples 185a & 185b: Synthesis of (R)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide (Example 185a) and (S)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide (Example 185b)



Scheme 100

[1112] Synthesis of 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide, 259, [Step 1]: To a stirred solution of 2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetic acid (Example 109, 250 mg, 0.6 mmol) in dichloromethane (2 mL), 2-aminopropanamide (258, 80 mg, 0.9 mmol) and DIPEA (0.3 mL, 1.8 mmol) were added followed by T₃P (1.1 mL, 1.8 mmol, 50% in ethyl acetate) and the reaction mixture was stirred at ambient temperature for 16h. After completion, the reaction mixture was diluted with dichloromethane

and partitioned with water. Combined organic layer was dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure and purified by reverse phase prep-HPLC to afford 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide (259, 80 mg). LCMS (ESI) Calcd for C₂₀H₁₈ClF₃N₆O₃: 482.1, found [M+H]⁺ = 483.1.

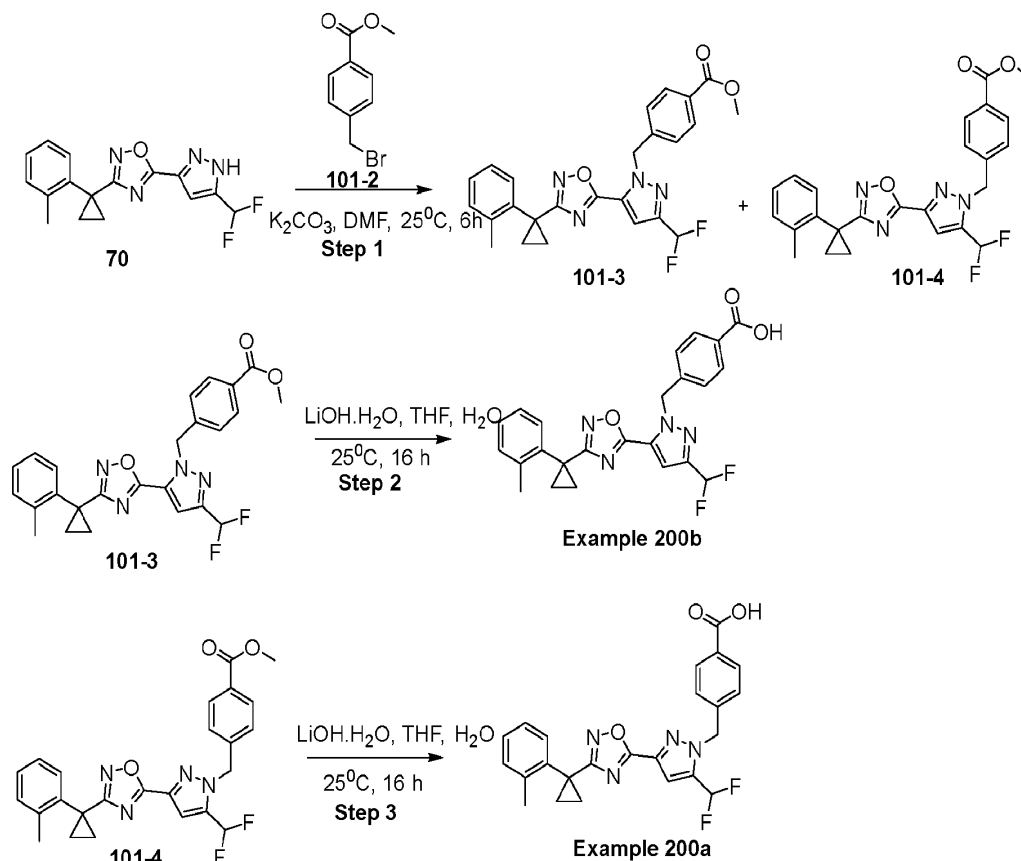
[1113] Synthesis of (S)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide, Example 185 [Step 1]: Racemic 2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide (259, 80 mg, 0.2 mmol) was separated by chiral separation to afford the first product as (R)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide (Example 185, 25 mg) as peak 1 and the second product as (S)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide (Example 186, 32 mg) as peak 2. Absolute stereochemistry known.

[1114] Note: A reaction with (2R)-2-aminopropanamide was attempted to obtain (R)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide with known absolute configuration. After comparing the chiral HPLC of both isomers (PEAK1 & PEAK2) with this R-isomer, it was confirmed that PEAK1 is R-isomer and PEAK2 is S-isomer. Analytical data of (S)-2-(2-(3-(3-(1-(2-chloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)propanamide, Example 185b: LCMS (ESI) Calcd for C₂₀H₁₆ClF₃N₄O₃: 452.09, found [M-H]⁻ = 451.1. ¹HNMR (400 MHz, DMSO-d₆) δ_H 8.53 (d, 1H), 7.65-7.61 (t, 1H), 7.51-7.50 (m, 1H), 7.48 (s, 1H), 7.43-7.13 (m, 3H), 7.06 (s, 1H), 5.21-5.11 (m, 2H), 4.24-4.21 (m, 1H), 1.72 (s, 2H), 1.47 (brs, 2H), 1.24-1.22 (m, 3H).

[1115] Chiral prep HPLC procedure: HPLC SFC Prep Purification has been completed on Pic Solution 175 instrument equipped with Knauer UV Detector 40D by using I Cellulose J (30.0 mm x 250mm), 5 min Column operating at 35 °C temperature, maintaining flow rate of 90 ml/min, using 85% CO₂ in super critical state & 15% of (100% MeOH) as Mobile phase, Run this isocratic mixture up to 14.0 minutes and also maintained the isobaric condition of 100 bar at 220 nm wavelength.

Examples 200a & 200b: Synthesis of 4-((5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoic acid (Example 200a) and 4-((3-

(difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoic acid (Example 200b)



Scheme 101

[1116] Synthesis of methyl 4-((3-(difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoate, 101-3 and methyl 4-((5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoate, 101-4 [Step 1]: To a stirred solution of 5-(5-(difluoromethyl)-1H-pyrazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (70, 200 mg, 0.632 mmol) in DMF (7 mL) was added K_2CO_3 (175 mg, 1.26 mmol) followed by addition of methyl 4-(bromomethyl)benzoate (101-2, 174 mg, 0.75 mmol) at ambient temperature and stirred for 16 h. The reaction mixture was diluted with ethyl acetate and washed by water (thrice) and brine, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography to give methyl 4-((3-(difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoate as peak 1 (101-3, 220 mg) and methyl 4-((5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-

pyrazol-1-yl)methyl)benzoate as peak 2 (101-4, 90 mg). LCMS (ESI) Calcd. for $C_{25}H_{22}F_2N_4O_3$: 464.17, found $[M+H]^+ = 465.4$.

[1117] Compound 101-4: LCMS (ESI) Calcd. for $C_{25}H_{22}F_2N_4O_3$: 464.17, found $[M+H]^+ = 465.4$.

1H NMR (400 MHz, d_6 -DMSO) δ_H : 7.94 (d, 2H), 7.55-7.29 (m, 5H), 7.24-7.19 (m, 3H), 5.27 (s, 2H), 3.84 (s, 3H), 2.26 (s, 3H), 1.75-1.65 (m, 2H), 1.45-1.39 (m, 2H).

[1118] Compound 101-3: LCMS (ESI) Calcd. for $C_{25}H_{22}F_2N_4O_3$: 464.17, found $[M+H]^+ = 465.4$.

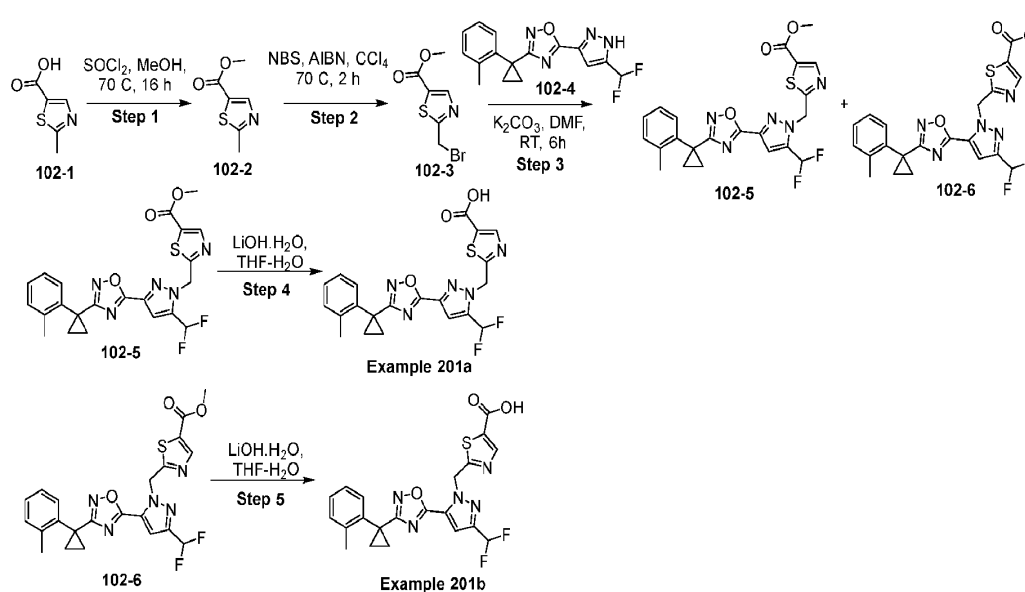
1H NMR (400 MHz, d_6 -DMSO) δ_H : 7.91 (d, 2H), 7.48 (s, 1H), 7.36-7.01 (m, 7H), 5.89 (s, 2H), 3.84 (s, 3H), 2.21 (s, 3H), 1.59 (m, 2H), 1.40 (m, 2H).

[1119] Synthesis of 4-((5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoic acid, Example 200a [Step 3]: To a stirred solution of methyl 4-((5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoate (101-4, 90 mg, 0.20 mmol) in THF (5 mL) and water (2 mL) was added LiOH.H₂O (24 mg, 0.58 mmol) at 0 °C and stirred at ambient temperature for 16 h. The reaction mixture was cooled to 0C and acidified with saturated aqueous KHSO₄ solution (pH: 4) and extracted with ethyl acetate (twice). The combined organic extract was washed with water, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by Prep HPLC and lyophilised to give 4-((5-(difluoromethyl)-3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoic acid (Example 200a, 55 mg). LCMS (ESI) Calcd. for $C_{24}H_{20}F_2N_4O_3$: 450.15, found $[M+H]^+ = 451.2$. 1H NMR (400 MHz, d_6 -DMSO) δ_H : 7.90 (d, 2H), 7.55-7.36 (m, 3H), 7.28-7.17 (m, 5H), 5.68 (s, 2H), 2.26 (s, 3H), 1.65-1.63 (m, 2H), 1.39-1.38 (m, 2H).

[1120] Synthesis of 4-((3-(difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoic acid, Example 200b [Step 2]: To a stirred solution of methyl 4-((3-(difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoate (101-3, 200 mg, 0.43 mmol) in THF (6 mL) and water (2 mL) was added LiOH.H₂O (90 mg, 2.15 mmol) at 0 °C and stirred at ambient temperature for 16 h. The reaction mixture was cooled to 0C and acidified with saturated aqueous KHSO₄ solution (pH: 4) and extracted with ethyl acetate (twice). The combined organic extract was washed with water, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by Prep HPLC and lyophilised to give 4-((3-(difluoromethyl)-5-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)methyl)benzoic acid (Example 200b, 82 mg). LCMS (ESI) Calcd. for $C_{24}H_{20}F_2N_4O_3$: 450.15, found $[M-H]^- = 449.3$. 1H NMR (400 MHz, d_6 -

DMSO) δ _H: 7.88 (d, 2H), 7.48 (s, 1H), 7.37-7.35 (d, 1H), 7.28-7.01 (m, 6H), 5.88 (s, 2H), 2.22 (s, 3H), 1.60-1.58 (m, 2H), 1.41-1.40 (m, 2H).

Examples 201a & 201b: Synthesis of 2-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylic acid (Example 201a) and 2-((3-(difluoromethyl)-5-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylic acid (Example 201b)



Scheme 102

[1121] Synthesis of methyl 2-methylthiazole-5-carboxylate, 2 [Step 1]: To a stirred solution of 2-methylthiazole-5-carboxylic acid (102-1, 2 g, 14.0 mmol) in methanol (25 mL) was added thionyl chloride (3.0 mL, 42 mmol) dropwise at 0 °C and stirred at 70 °C for 16 h. Volatiles were removed under reduced pressure and partitioned between EtOAc and water. The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by combi flash chromatography to afford methyl 2-methylthiazole-5-carboxylate (102-2, 1.8 g). LCMS (ESI) Calcd. for $\text{C}_6\text{H}_7\text{NO}_2\text{S}$: 157.02, found $[\text{M}+\text{H}]^+ = 158.0$.

[1122] Synthesis of methyl 2-(bromomethyl)thiazole-5-carboxylate, 102-3 (Step 2): To a stirred solution of methyl 2-methylthiazole-5-carboxylate (102-2, 1 g, 6.4 mmol) in carbon tetrachloride (15 mL) was added NBS (1.4 g, 7.6 mmol) followed by AIBN (313 mg, 1.9 mmol) and stirred the reaction mixture at 80 °C for 16 h. Volatiles were removed under reduced pressure and partitioned between ethyl acetate and water. Organic layer was washed with saturated NaHCO_3 , dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude

product was purified by combi flash chromatography to afford methyl 2-(bromomethyl)thiazole-5-carboxylate (102-3, 700 mg). LCMS (ESI) Calcd. for $C_6H_6BrNO_2S$: 234.93, found $[M+H]^+$ = 236.0.

[1123] Synthesis of methyl 2-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylate, 102-5, and methyl 2-((3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylate, 102-6 [Step 3]: To a stirred solution of 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (102-4, 300 mg, 0.9 mmol) in DMF (5 mL) was added K_2CO_3 (262 mg, 1.9 mmol) followed by methyl 2-(bromomethyl)thiazole-5-carboxylate (102-3, 448 mg, 1.9 mmol) and stirred at ambient temperature for 2 h. The reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by combi flash chromatography to afford methyl 2-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylate (102-5, 120 mg) and methyl 2-((3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylate (102-6, 250 mg).

[1124] Compound 102-5: LCMS (ESI) Calcd. for $C_{22}H_{19}F_2N_5O_3S$: 471.12, found $[M+H]^+$ = 472.32. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 8.39 (s, 1H), 7.57-7.17 (m, 6H), 6.07 (s, 2H), 3.81 (s, 3H), 2.26 (s, 3H), 1.66 (m, 2H), 1.40 (m, 2H).

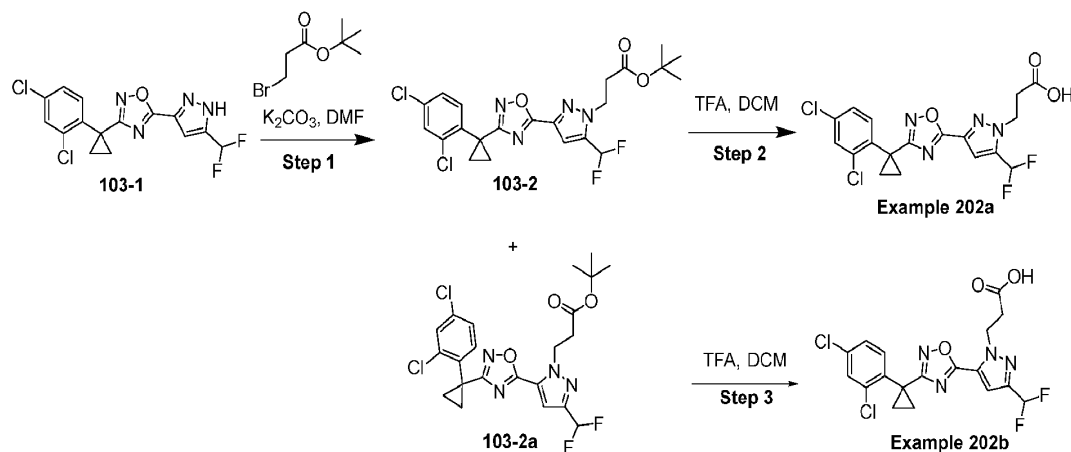
[1125] Compound 102-6: LCMS (ESI) Calcd. for $C_{22}H_{19}F_2N_5O_3S$: 471.12, found $[M+H]^+$ = 472.32. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 8.33 (s, 1H), 7.52 (s, 1H), 7.34 (d, 1H), 7.29-7.04 (m, 4H), 6.23 (s, 2H), 3.84 (s, 3H), 2.21 (s, 3H), 1.58 (m, 2H), 1.39 (m, 2H).

[1126] Synthesis of 2-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylic acid, Example 201a [Step 4]: To a stirred solution of methyl 2-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylate (102-5, 120 mg, 0.3 mmol) in THF (5 mL) and water (1 mL) was added $LiOH \cdot H_2O$ (43 mg, 1 mmol) at 0 °C and stirred at ambient temperature for 2 h. Volatiles were removed under reduced pressure. It was diluted with water and washed with ethyl acetate. The aqueous extract was acidified with saturated aqueous $NaHSO_4$ solution (pH: ~3) and extracted with ethyl acetate. The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by prep HPLC, lyophilized to afford 2-((5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylic acid (Example 201a, 55 mg). LCMS (ESI) Calcd. for

$C_{21}H_{17}F_2N_5O_3S$: 457.10, found $[M+H]^+ = 458.2$, 1H NMR (400 MHz, $DMSO-d_6$): δ_H 7.89 (bs, 1H), 7.56-7.30 (m, 3H), 7.23-7.19 (m, 4H), 5.93 (s, 2H), 2.26 (s, 3H), 1.66 (m, 2H), 1.38 (m, 2H).

[1127] Synthesis of 2-((3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylic acid, Example 201b [Step 5]: To a stirred solution of methyl 2-((3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylate (102-6, 280 mg, 0.5 mmol) in THF (6 mL) and water (1.5 mL) was added LiOH. H_2O (90 mg, 2.1 mmol) at 0 °C and stirred the reaction mixture at ambient temperature for 2 h. Volatiles were removed under reduced pressure, diluted with minimum amount of water and washed with ethyl acetate. The aqueous extract was acidified with aqueous $NaHSO_4$ solution until pH 2~3 and extracted with ethyl acetate. The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by prep HPLC, lyophilized to afford 2-((3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)methyl)thiazole-5-carboxylic acid (Example 201b, 135 mg). LCMS (ESI) Calcd. for $C_{21}H_{17}F_2N_5O_3S$: 457.10, found $[M+H]^+ = 458.2$, 1H NMR (400 MHz, $DMSO-d_6$): δ_H 7.78 (s, 1H), 7.49 (s, 1H), 7.35 (d, 1H), 7.28-7.01 (m, 5H), 6.10 (s, 2H), 2.23 (s, 3H), 1.62 (m, 2H), 1.39 (m, 2H).

Examples 202a & 202b: Synthesis of 3-(3-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid (Example 202a) and 3-(5-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)propanoic acid (Example 202b)



Scheme 103

[1128] Synthesis of *tert*-butyl 3-[3-[3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-5-(difluoromethyl)pyrazol-1-yl]propanoate, 103-2 & 103-2a [Step 1]: To the stirred solution of 3-[1-(2,4-dichlorophenyl)cyclopropyl]-5-[5-(difluoromethyl)-1*H*-pyrazol-3-yl]-1,2,4-oxadiazole (103-1,

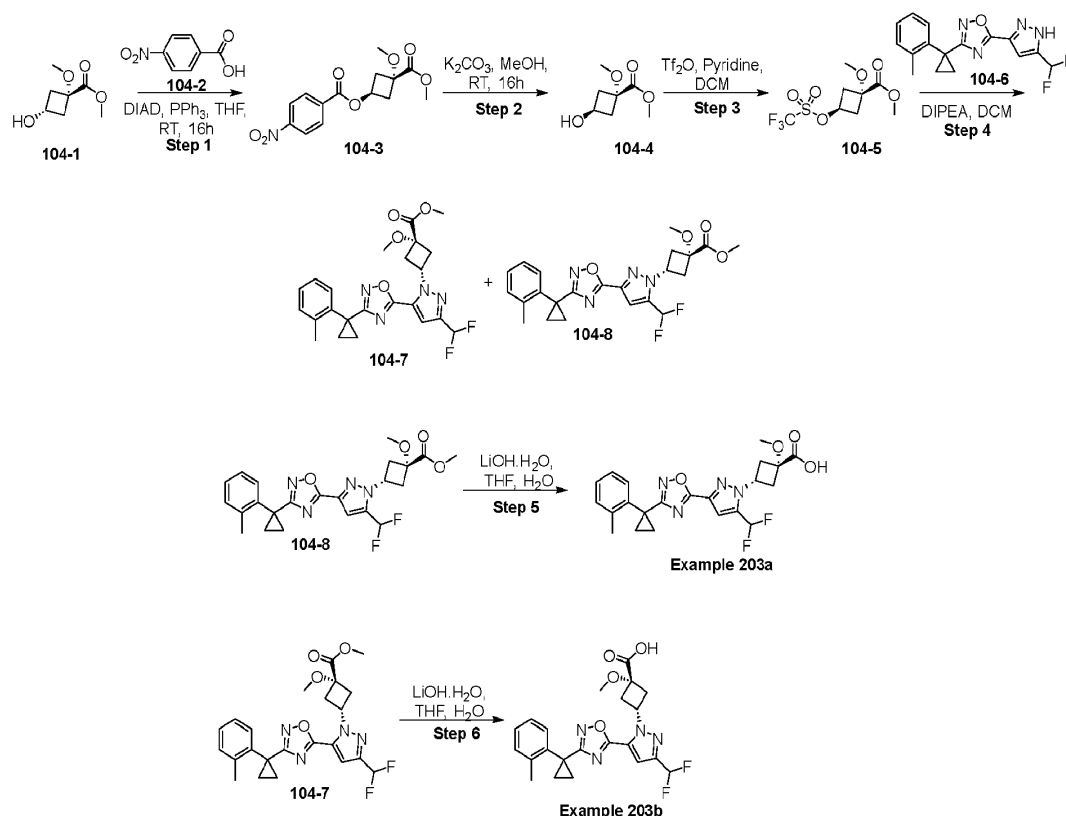
400 mg, 1.08 mmol) in DMF (4 mL), anhydrous K_2CO_3 (596 mg, 4.31 mmol) followed by *tert*-butyl 3-bromopropanoate (451 mg, 2.16 mmol) were added. Then the reaction mixture was heated at 100°C for 16 h. Reaction was diluted with cold water and extracted with ethyl acetate. Organic extract was washed with brine, dried over anhydrous Na_2SO_4 , concentrated under reduced pressure to obtain crude. The product was purified by combi flash column chromatography to afford *tert*-butyl 3-[3-[3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-5-(difluoromethyl)pyrazol-1-yl]propanoate (103-2, 100 mg, 0.190 mmol) as the first fraction and *tert*-butyl 3-[5-[3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-3-(difluoromethyl)pyrazol-1-yl]propanoate (103-2a, 250 mg, 0.476 mmol) as the second fraction. LCMS (ESI) calcd for $C_{22}H_{22}Cl_2F_2N_4O_3$: = 498.10, found $[M+H]^+$ = 499.0.

[1129] Synthesis of 3-(3-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5-(difluoromethyl)-1H-pyrazol-1-yl)propanoic acid, Example 202a [Step 2]: To the stirred solution of *tert*-butyl 3-[3-[3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-5-(difluoromethyl)pyrazol-1-yl]propanoate (103-2, 72 mg, 0.144 mmol) in dichloromethane (3 mL), TFA (0.038 mL, 0.501 mmol) was added dropwise at 0°C. Reaction mixture was continued to stir at ambient temperature for 16 h. Solvent and TFA were evaporated under reduced pressure to get crude which was purified by reverse phase preparative HPLC to afford 3-[3-[3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-5-(difluoromethyl)pyrazol-1-yl]propanoic acid (Example 202a, 45 mg). LCMS (ESI) calcd for $C_{18}H_{14}Cl_2F_2N_4O_3$: = 442.04, found $[M+H]^+$ = 443.2. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 7.66(d, 1H), 7.60-7.35 (m, 3H), 7.23 (s, 1H), 4.49 (t, 2H), 2.79 (t, 2H), 1.73-1.72 (m, 2H), 1.48-1.45 (m, 2H).

[1130] Synthesis of 3-(5-(3-(1-(2,4-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-3-(difluoromethyl)-1H-pyrazol-1-yl)propanoic acid, Example 202b [Step 3]: To the stirred solution of *tert*-butyl 3-[5-[3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-3-(difluoromethyl)pyrazol-1-yl]propanoate (103-2a, 215 mg, 0.431 mmol) in dichloromethane (3 mL), TFA (0.038 mL, 0.501 mmol) was added dropwise at 0°C and the reaction was continued to stir at ambient temperature for 16 h. Solvent and TFA were evaporated under reduced pressure and the crude was purified by reverse phase preparative HPLC to afford 3-[5-[3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl]-3-(difluoromethyl)pyrazol-1-yl]propanoic acid (Example 202b, 123 mg). LCMS (ESI) calcd for $C_{18}H_{14}Cl_2F_2N_4O_3$: = 442.04, found $[M+H]^+$ = 443.2. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 7.67 (d, 1H), 7.60-7.58 (s, 1H), 7.48-7.45 (m, 1H), 7.37 (s, 1H), 4.80 (t, 2H), 2.82 (t, 2H), 1.76 (t, 2H), 1.52-1.49 (m, 2H).

Examples 203a & 203b: Synthesis of (1s,3s)-3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl)-1-methoxycyclobutane-1-

carboxylic acid (Example 203a) and (1*s*,3*s*)-3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylic acids (Example 203b)



Scheme 104

[1131] Synthesis of (1*r*,3*r*)-3-methoxy-3-(methoxycarbonyl)cyclobutyl 4-nitrobenzoate, 104-3
[Step 1]: To a stirred solution of methyl (1*s*,3*s*)-3-hydroxy-1-methoxycyclobutane-1-carboxylate (1, 500 mg, 3.1 mmol) in THF (7 mL) was added 4-nitrobenzoic acid (104-2, 1.1 g, 6.3 mmol) followed by triphenylphosphine (1.6 g, 6.2 mmol). Diisopropyl azodicarboxylate (1.2 mL, 6.2 mmol) was added at 0 °C and stirred at ambient temperature for 16 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by combi flash chromatography to afford (1*r*,3*r*)-3-methoxy-3-(methoxycarbonyl)cyclobutyl 4-nitrobenzoate (104-3, 700 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 8.37-8.35 (d, 2H), 8.21-8.18 (d, 2H), 5.30-5.26 (m, 1H), 3.71 (s, 3H), 3.19 (s, 3H), 2.76-2.70 (m, 2H), 2.65-2.60 (m, 2H).

[1132] Synthesis of methyl (1*r*,3*r*)-3-hydroxy-1-methoxycyclobutane-1-carboxylate, 104-4 (Step 2): To a stirred solution of (1*r*,3*r*)-3-methoxy-3-(methoxycarbonyl)cyclobutyl 4-nitrobenzoate (104-3, 600 mg, 1.9 mmol) in methanol (5 mL) was added K₂CO₃ (402 mg, 2.9 mmol) and stirred at ambient temperature for 30 min. The reaction mixture was filtered, and volatiles were removed under reduced pressure. The crude product was purified by combi flash chromatography to afford methyl (1*r*,3*r*)-3-hydroxy-1-methoxycyclobutane-1-carboxylate (104-4, 260 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 5.28 (d, 1H), 4.21-4.15 (m, 1H), 3.67 (s, 3H), 3.10 (s, 3H), 2.44-2.39 (m, 2H), 2.19-2.14 (m, 2H).

[1133] Synthesis of methyl (1*r*,3*r*)-1-methoxy-3-(((trifluoromethyl)sulfonyl)oxy)cyclobutane-1-carboxylate, 104-5 [Step 3]: To a stirred solution of trifluoromethanesulfonic anhydride (0.3 mL, 1.8 mmol) in DCM (2 mL) was added pyridine (0.2 mL, 2 mmol) dropwise at 0 °C and stirred for 5 min. To this reaction mixture was added a solution of methyl (1*r*,3*r*)-3-hydroxy-1-methoxycyclobutane-1-carboxylate (104-4, 260 mg, 1.6 mmol) in DCM (1 mL) at 0 °C and stirred for 30 min. The reaction mixture was diluted with DCM and washed with water. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford methyl (1*r*,3*r*)-1-methoxy-3-(((trifluoromethyl)sulfonyl)oxy)cyclobutane-1-carboxylate (104-5, 460 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 4.93-4.87 (m, 1H), 3.72 (s, 3H), 3.17 (s, 3H), 2.98-2.93 (m, 2H), 2.43-2.38 (m, 2H).

[1134] Synthesis of methyl (1*s*,3*s*)-3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylate and methyl (1*s*,3*s*)-3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylate, 104-7 and 104-8 [Step 4]: To a stirred solution of 5-(5-(difluoromethyl)-1*H*-pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (104-6, 180 mg, 0.6 mmol) in DCM (5 mL) was added *N,N*-diisopropylethylamine (0.4 mL, 2.3 mmol) and stirred for 5 min. A solution of methyl (1*r*,3*r*)-1-methoxy-3-(((trifluoromethyl)sulfonyl)oxy)cyclobutane-1-carboxylate (5, 460 mg, 1.6 mmol) in DCM (0.5 mL) was added dropwise to the reaction mixture and stirred at the ambient temperature for 16 h. Volatiles were removed under reduced pressure. The crude product was purified by combi flash chromatography to afford methyl (1*s*,3*s*)-3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylate (104-7, 200 mg) as peak 1 and methyl (1*s*,3*s*)-3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylate (104-8, 70 mg) assign as peak 2. N1 and N2 linked compound was confirmed by nOe analysis.

[1135] Compound 104-7: LCMS (ESI) Calcd. for $C_{23}H_{24}F_2N_4O_4$: 458.18, found $[M+H]^+$: 459.0; 1H NMR (400 MHz, DMSO- d_6): δ_H 7.41-7.37 (m, 2H), 7.29-7.02 (m, 4H), 5.75 (s, 1H), 5.65-5.61 (m, 1H), 3.80 (s, 3H), 3.20 (s, 3H), 2.99-2.94 (m, 2H), 2.79-2.74 (m, 2H), 2.30 (s, 3H), 1.71 (m, 2H), 1.46 (m, 2H).

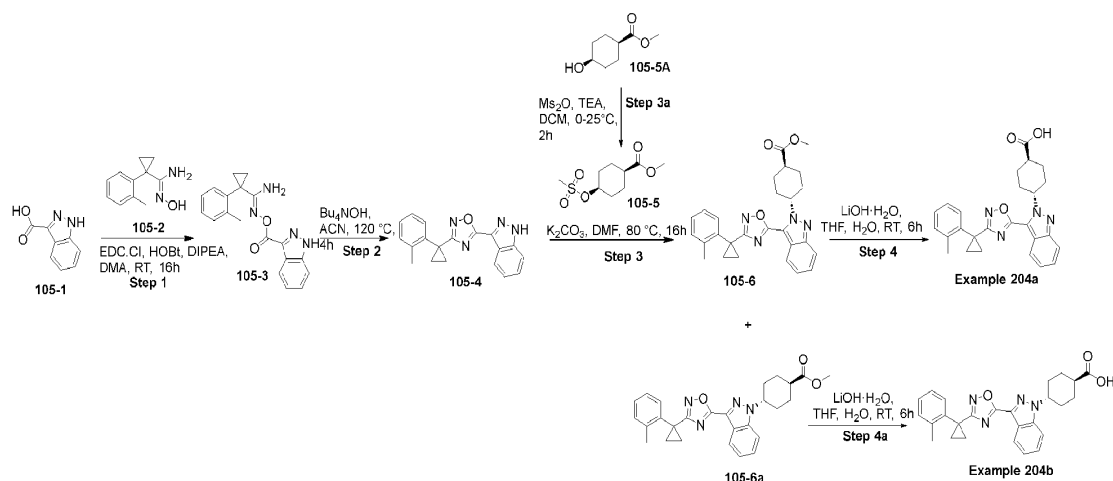
[1136] Compound 104-8: LCMS (ESI) Calcd. for $C_{23}H_{24}F_2N_4O_4$: 458.18, found $[M+H]^+$: 459.2; 1H NMR (400 MHz, DMSO- d_6): δ_H 7.56-7.20 (m, 6H), 4.97-4.93 (m, 1H), 3.78 (s, 3H), 3.20 (s, 3H), 3.02-2.97 (m, 2H), 2.84-2.79 (m, 2H), 2.27 (s, 3H), 1.68 (m, 2H), 1.40 (m, 2H).

[1137] Synthesis of (1s,3s)-3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylic acid, Example 203a [Step 5]: To a stirred solution of methyl (1s,3s)-3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylate (104-8, 65 mg, 0.2 mmol) in THF (3 mL) and water (1.5 mL) was added LiOH.H₂O (18 mg, 0.4 mmol) at 0 °C and stirred at ambient temperature for 2 h. The reaction mixture was diluted with water, acidified with saturated aqueous solution of KHSO₄ (pH: ~3) and extracted with ethyl acetate. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by Prep HPLC and lyophilized to afford (1s,3s)-3-(5-(difluoromethyl)-3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylic acid (Example 203a, 32 mg). LCMS (ESI) Calcd. For $C_{22}H_{22}F_2N_4O_4$: 444.16; found $[M+H]^+$: 445.3. 1H NMR (400 MHz, DMSO- d_6): δ_H : 13.18 (bs, 1H), 7.56-7.20 (m, 6H), 4.98-4.94 (m, 1H), 3.21 (s, 3H), 2.98-2.93 (m, 2H), 2.80-2.75 (m, 2H), 2.27 (s, 3H), 1.70-1.68 (m, 2H), 1.41-1.38 (m, 2H).

[1138] Synthesis of (1s,3s)-3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylic acids, Example 203b [Step 6]: To a stirred solution of methyl (1s,3s)-3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylate (104-7, 200 mg, 0.4 mmol) in THF (4 mL) and water (1 mL) was added LiOH.H₂O (73 mg, 1.7 mmol) at 0 °C and stirred at ambient temperature for 2 h. The reaction mixture was diluted with minimum amount of water, acidified with saturated aqueous solution of KHSO₄ (pH: ~3) and extracted with ethyl acetate. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by prep HPLC and lyophilized to afford (1s,3s)-3-(3-(difluoromethyl)-5-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1*H*-pyrazol-1-yl)-1-methoxycyclobutane-1-carboxylic acid (Example 203b, 135 mg). LCMS

(ESI) Calcd. for $C_{22}H_{22}F_2N_4O_4$: 444.2, found $[M+H]^+$ = 445.3, 1H NMR (400 MHz, $DMSO-d_6$): δ_H 7.38-7.35 (m, 2H), 7.27-7.00 (m, 4H), 5.59 (m, 1H), 3.17 (s, 3H), 2.91-2.86 (m, 2H), 2.66-2.59 (m, 2H), 2.29 (s, 3H), 1.72-1.70 (m, 2H), 1.43-1.40 (m, 2H).

Examples 204a & 204b: Synthesis of (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-2H-indazol-2-yl)cyclohexane-1-carboxylic acid (Example 204a) and (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-indazol-1-yl)cyclohexane-1-carboxylic acid (Example 204b)



Scheme 105

[1139] Synthesis of (Z)-N'-((1H-indazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide, 105-3 [Step 1]: To a stirred solution of 1H-indazole-3-carboxylic acid (105-1, 1.00 g, 6.15 mmol) in DMA (10 mL) were added DIPEA (3.20 mL, 18.4 mmol), EDCI.HCl (1.91 g, 12.3 mmol) and HOBT (1.66 g, 12.3 mmol). The reaction mixture was stirred at RT for 15 min. To the resulting mixture was added N'-hydroxy-1-(*o*-tolyl)cyclopropanecarboximidamide (105-2, 1.17 g, 6.15 mmol) and it was stirred at 25 °C for 16h. After completion, reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude product which was purified by combi flash column chromatography to afford (Z)-N'-((1H-indazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (105-3, 1.50 g,) as gummy substance. LCMS (ESI) calculated for $C_{19}H_{18}N_4O_2$: 334.14, found $[M+H]^+$: 335.4. 1H NMR (400 MHz, $DMSO-d_6$): δ_H 13.82 (s, 1H), 8.03 (d, 1H), 7.65 (d, 1H), 7.45-7.41 (m, 2H), 7.31-7.27 (m, 1H), 7.213-7.18 (m, 3H), 5.92 (s, 2H), 2.46 (s, 3H), 1.51-1.48 (m, 2H), 1.05-1.03 (m, 2H).

[1140] Synthesis of 5-(1H-indazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole, 105-4 [Step 2]: To a stirred solution of (Z)-N'-((1H-indazole-3-carbonyl)oxy)-1-(o-tolyl)cyclopropane-1-carboximidamide (105-3, 1.30 g, 3.89 mmol) in MeCN (15 mL), was added TBAH (121 mg, 0.47 mmol) at 25 °C. The reaction mixture was heated at 110 °C for 3h. Upon completion, the reaction mixture was cooled to room temperature, diluted with water and ethyl acetate. Organic layer was separated, washed with brine, dried over anhydrous sodium sulphate, concentrated under reduced pressure to get crude which was purified by combi flash column chromatography (using 20-25% EtOAc/Hexane) to afford 5-(1H-indazol-3-yl)-3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazole (105-4, 600 mg) as off white solid. LCMS (ESI) calculated for C₁₉H₁₆N₄O: 316.13, found [M+H]⁺: 317.4. ¹H NMR (400 MHz, CDCl₃): δ_H 8.24 (d, 1H), 7.59 (d, 1H), 7.52-7.48 (m, 1H), 7.44 (d, 1H), 7.38-7.35 (m, 1H), 7.27-7.22 (m, 3H), 2.39 (s, 3H), 1.87-1.84 (m, 2H), 1.49-1.45 (m, 2H).

[1141] Synthesis of methyl (1s,4s)-4-((methylsulfonyl)oxy)cyclohexane-1-carboxylate, 105-5 [Step 3A]: To a solution of methyl (1s,4s)-4-hydroxycyclohexane-1-carboxylate (105-5A, 1.00 g, 6.32 mmol) in DCM (10 mL) cooled to 0 °C, was added triethylamine (1.8 mL, 12.6 mmol) followed by the addition of methanesulfonic anhydride (1.65 g, 9.48 mmol) portion wise at ice cool condition. The reaction mixture was stirred from 0 °C to 25 °C for 2h. After completion, the reaction mixture was diluted with DCM and water, organic layer was separated and washed with saturated NaHCO₃ solution and brine, dried over sodium sulphate, concentrated under reduced pressure to get methyl (1s,4s)-4-((methylsulfonyl)oxy)cyclohexane-1-carboxylate (105-5, 1.10 g) as oil. ¹H NMR (400 MHz, CDCl₃): δ_H 4.91-4.90 (m, 1H), 3.68 (s, 3H), 3.00 (s, 3H), 2.43-2.36 (m, 1H), 2.06-2.00 (m, 2H), 1.97-1.87 (m, 2H), 1.81-1.73 (m, 4H).

[1142] Synthesis of methyl (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-2H-indazol-2-yl)cyclohexane-1-carboxylate, 6 & methyl (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-indazol-1-yl)cyclohexane-1-carboxylate, 105-6a [Step 3]: To a solution of 5-(1H-indazol-3-yl)-3-[1-(o-tolyl)cyclopropyl]-1,2,4-oxadiazole (105-4, 400 mg, 1.26 mmol) in DMF (4 mL) was added K₂CO₃ (523 mg, 3.79 mmol) and the mixture was heated at 80 °C for 1h. To the resulting mixture was added a solution of methyl (1s,4s)-4-((methylsulfonyl)oxy)cyclohexane-1-carboxylate (1.20 g, 5.06 mmol) in DMF (0.50 mL) dropwise and the mixture stirred at 80 °C for 16 h. After completion, the reaction mixture was cooled to room temperature and extracted with EtOAc. The combined organic layer was washed with excess water, brine, dried over anhydrous sodium sulphate and concentrated to give crude product. The crude product was purified by combiflash column chromatography to afford two regio-isomers: methyl

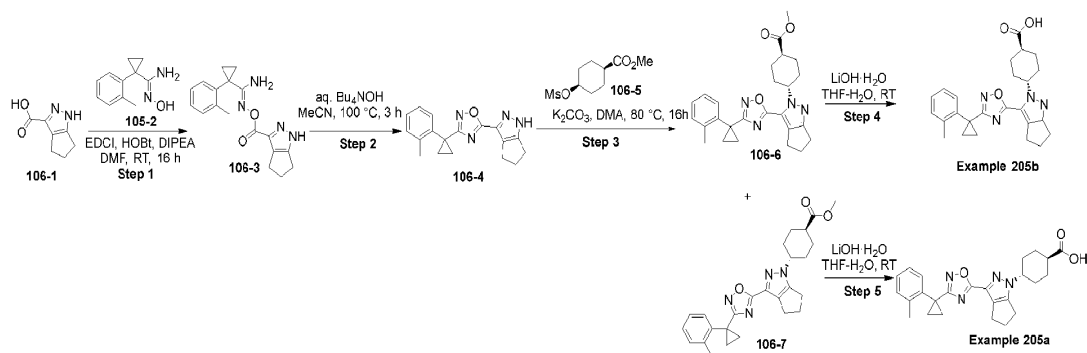
(1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-2H-indazol-2-yl)cyclohexane-1-carboxylate (105-6, 160 mg) with impurities as gummy solid. LCMS (ESI) calculated for C₂₇H₂₈N₄O₃: Exact Mass: 456.22, found [M+H]⁺: 457.5 and methyl (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-indazol-1-yl)cyclohexane-1-carboxylate (105-6a, 150 mg) as gummy solid. LCMS (ESI) calculated for C₂₇H₂₈N₄O₃: Exact Mass: 456.22, found [M+H]⁺: 457.5.

[1143] Synthesis of (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-2H-indazol-2-yl)cyclohexane-1-carboxylic acid, Example 204a [Step 5]: Methyl (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-2H-indazol-2-yl)cyclohexane-1-carboxylate (105-6, 160 mg, 0.350 mmol) was taken in THF (4mL) and Water (2mL). Then was added LiOH.H₂O (59 mg, 1.40 mmol) at 25 °C and the reaction mixture was stirred at 25 °C for 6h. After completion, the reaction mixture was concentrated under reduced pressure and the residue was acidified with aqueous 1 (N) HCl solution and extracted with 5% MeOH/DCM. The combined organic layer washed with brine, dried over anhydrous Na₂SO₄, concentrated under reduced pressure to get crude. The crude was purified by RP-PREP HPLC to afford (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-2H-indazol-2-yl)cyclohexane-1-carboxylic acid, (Example 204a, 43 mg) as white solid. LCMS (ESI) calcd. for C₂₆H₂₆N₄O₃: 442.20, found [M+H]⁺: 443.3, ¹H NMR (400 MHz, DMSO-d₆): δ_H 12.22 (brs, 1H), 8.02 (d, 1H), 7.85 (d, 1H), 7.45-7.36 (m, 3H), 7.24-7.20 (m, 3H), 5.41-5.37 (m, 1H), 2.37-2.34 (m, 4H), 2.16-2.02 (m, 6H), 1.77-1.74 (m, 2H), 1.54-1.47 (m, 4H).

[1144] Synthesis of (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-indazol-1-yl)cyclohexane-1-carboxylic acid, Example 204b [Step 5a]: To a solution of methyl (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-indazol-1-yl)cyclohexane-1-carboxylate (105-6a, 150 mg, 0.33 mmol) in THF (4 mL) and water (2mL) was added LiOH.H₂O (55 mg, 1.31 mmol) at 25 °C and the reaction mixture was stirred at 25 °C for 6 h. After completion, the reaction mixture was concentrated under reduced pressure and the residue was acidified with aqueous 1 (N) HCl solution and extracted with 5% MeOH/DCM. The combined organic layer washed with brine, dried over anhydrous Na₂SO₄, concentrated under reduced pressure to get crude. The crude was purified by RP-PREP HPLC to afford (1r,4r)-4-(3-(3-(1-(o-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-1H-indazol-1-yl)cyclohexane-1-carboxylic acid (Example 204b, 101 mg) as white solid. LCMS (ESI) calcd. for C₂₆H₂₆N₄O₃: 442.20, found [M+H]⁺: 443.3, ¹H NMR (400 MHz, DMSO-d₆): δ_H 12.18 (brs, 1H), 8.12 (d, 1H), 7.99 (d, 1H), 7.57-7.54

(m, 1H), 7.44-7.40 (m, 2H), 7.25-7.21 (m, 3H), 4.87-4.85 (m, 1H), 2.49-2.38 (m, 1H), 2.30 (s, 3H), 2.09-1.99 (m, 6H), 1.78-1.75 (m, 2H), 1.71-1.64 (m, 2H), 1.43-1.41 (m, 2H).

Examples 205a & 205b: Synthesis of (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[*c*]pyrazol-2(4*H*)-yl) cyclohexane-1-carboxylic acid (Example 205a) and (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[*c*]pyrazol-1(4*H*)-yl) cyclohexane-1-carboxylic acid (Example 205b)



Scheme 106

[1145] Synthesis of *N'*-((1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide, 106-3 [Step 1]: To a solution of 1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carboxylic acid (106-1, 500 mg, 3.29 mmol), EDCI·HCl (1.26 g, 6.58 mmol) and HOBt (889 mg, 6.58 mmol) in DMF (10 mL) was added DIPEA (2.3 mL, 13.2 mmol) at ambient temperature. After 15 min, *N'*-hydroxy-1-(*o*-tolyl) cyclopropane-1-carboximidamide (105-2, 625 mg, 3.29 mmol) was added, and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was diluted with ethyl acetate and washed with cold brine (three times). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford *N'*-((1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carbonyl) oxy)-1-(*o*-tolyl) cyclopropane-1-carboximidamide (106-3, 1.00 g) which was used for the next step without further purification. LCMS (ESI) calcd. for C₁₈H₂₀N₄O₂: 324.16, found [M+H]⁺: 325.4.

[1146] Synthesis of 5-(1,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole, 106-4 [Step 2]: To a solution of *N'*-((1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole-3-carbonyl)oxy)-1-(*o*-tolyl)cyclopropane-1-carboximidamide (106-3, 1.0 g, 3.08 mmol) in MeCN (15 mL) was added tetrabutylammonium hydroxide (0.24 mL, 40% in water, 0.37 mmol) and the reaction mixture was stirred at 100 °C for 3 h. The reaction mixture was concentrated under reduced pressure and purified on a silica gel column using 0-30% ethyl acetate in hexanes to

afford 5-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-(1-(*o*-tolyl) cyclopropyl)-1,2,4-oxadiazole (106-4, 600 mg). LCMS (ESI) calcd. for C₁₈H₁₈N₄O: 306.15, found [M+H]⁺: 307.4.

[1147] Synthesis of methyl (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[c]pyrazol-2(4*H*)-yl)cyclohexane-1-carboxylate, 6 and methyl (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[c]pyrazol-1(4*H*)-yl)cyclohexane-1-carboxylate, 106-7 [Step 3]: A solution of 5-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazole (106-4, 600 mg, 1.96 mmol) in DMA (10 mL) was heated to 80 °C. After 10 min, a solution of methyl (1*s*,4*s*)-4-((methylsulfonyl)oxy) cyclohexane-1-carboxylate (106-5, 1.85 g, 7.83 mmol) in DMA (6 mL) was added dropwise in two portions one hour apart. The reaction mixture was stirred at the same temperature for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and washed with cold brine (two times). The reaction mixture was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification on a silica gel column afforded two regioisomers. The faster eluting compound was methyl (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl) cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[c]pyrazol-2(4*H*)-yl)cyclohexane-1-carboxylate (106-6, 310 mg). LCMS (ESI) calcd. for C₂₆H₃₀N₄O₃: 446.23, found [M+H]⁺: 447.2. The slower eluting compound was methyl (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl) cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[c]pyrazol-1(4*H*)-yl) cyclohexane-1-carboxylate (106-7, 120 mg, 0.269 mmol). LCMS (ESI) calcd. for C₂₆H₃₀N₄O₃: 446.23, found [M+H]⁺: 447.2.

[1148] Synthesis of (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[c] pyrazol-2(4*H*)-yl) cyclohexane-1-carboxylic acid, Example 205b [Step 4]: To a solution of methyl (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl) cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta [c] pyrazol-2(4*H*)-yl) cyclohexane-1-carboxylate (106-6, 310 mg, 0.69 mmol) in THF (4 mL) and water (2 mL) was added LiOH·H₂O (117 mg, 2.78 mmol) and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was concentrated under reduced pressure, the residue was acidified (pH 1) with 1N aqueous HCl solution and extracted with 10% MeOH in DCM. The COMBINED organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to get the crude. The crude product was purified by reverse phase preparative HPLC to afford (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl) cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[c]pyrazol-2(4*H*)-yl) cyclohexane-1-carboxylic acid (Example 205b, 160 mg) as white solid. LCMS (ESI) calcd. for C₂₅H₂₈N₄O₃: 432.22, found [M+H]⁺: 433.6. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 12.20 (brs, 1H), 7.38-7.36 (m,

1H), 7.25-7.19 (m, 3H), 4.93-4.87 (m, 1H), 2.77 (t, 2H), 2.66 (t, 2H), 2.42-2.35 (m, 2H), 2.30-2.24 (m, 4H), 2.04-1.96 (m, 4H), 1.88-1.80 (m, 2H), 1.70-1.63 (m, 2H), 1.47-1.38 (m, 4H).

[1149] Synthesis of (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta [c] pyrazol-1(4*H*)-yl) cyclohexane-1-carboxylic acid, Example 205a [Step 5]: To a solution of methyl (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl) cyclopropyl) -1,2,4-oxadiazol-5-yl) -5,6-dihydrocyclopenta [c]pyrazol-1(4*H*)-yl) cyclohexane-1-carboxylate (106-7, 120 mg, 0.27 mmol) in THF (3 mL) and water (1.5 mL) was added LiOH·H₂O (45 mg, 1.07 mmol) and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was concentrated under reduced pressure, the residue was acidified (pH 1) with 1N aqueous HCl solution and extracted with 10% MeOH in DCM. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to get the crude. The crude product was purified by reverse phase preparative HPLC afforded (1*r*,4*r*)-4-(3-(3-(1-(*o*-tolyl) cyclopropyl)-1,2,4-oxadiazol-5-yl)-5,6-dihydrocyclopenta[c]pyrazol-1(4*H*)-yl) cyclohexane-1-carboxylic acid (Example 205a, 35 mg) as white solid. LCMS (ESI) calcd. for C₂₅H₂₈N₄O₃: 432.22, found [M+H]⁺: 433.4. ¹H NMR (400 MHz, DMSO-*d*₆): δ_H 12.05 (brs, 1H), 7.36 (d, 1H), 7.23-7.17 (m, 3H), 4.19-4.13 (m, 1H), 2.82 (t, 2H), 2.70 (t, 2H), 2.54-2.50 (m, 2H), 2.33-2.25 (m, 4H), 2.03-2.00 (m, 4H), 1.82-1.74 (m, 2H), 1.63-1.62 (m, 2H), 1.54-1.45 (m, 2H), 1.37-1.34 (m, 2H).

BIOLOGICAL/ BIOCHEMICAL EVALUATION

[1150] General protocol for in vitro analysis of compounds

[1151] The inhibitory activity of the compounds of the present invention against POLRMT were determined by assays based on Bergbrede, T., et al., "An adaptable high-throughput technology enabling the identification of specific transcription modulators," SLAC Discov., 22, 378–386 (2017).

[1152] The ability of some compounds of the present invention to inhibit POLRMT were determined in a homogeneous TR-FRET Assay using high-throughput screening in a 384- well plate format. This method is used to monitor the activity of mitochondrial transcription through measurement of its product, a 407 bp long RNA transcript. Detection of the product is facilitated by hybridization of two DNA-oligonucleotide probes to specific and adjacent sequences within the RNA product sequence. Upon annealing of the probes, two fluorophores are coupled directly to an acceptor nucleotide probe (ATTO647, 5'), or introduced via a coupled streptavidin with a biotinylated donor nucleotide probe (Europium cryptate) that is brought into sufficient

proximity to serve as a fluorescence-donor-acceptor pair. Thus, a FRET signal at 665 nm is generated upon excitation at 340 nm.

[1153] Proteins used as transcription factors (POLRMT: NP_005026.3, TFAM: NP_003192.1, TFB2M: NP_071761.1) are diluted from their stocks to working concentrations of 1 μ M, 20 μ M and 4 μ M respectively, in a dilution buffer containing 20 mM Tris-HCl (pH 8.0), 200 mM NaCl, 10% (v/v) glycerol, 1 mM Dithiothreitol (DTT), 0.5 mM EDTA.

[1154] DNA template is a pUC18 plasmid with the mitochondrial light strand promotor sequence (1-477) cloned between HindIII and BamHI sites. The DNA template is restriction linearized proximal to the promotor 3'-end (pUC-LSP).

[1155] The reaction mixture (10 μ L) containing 7.5 nM POLRMT, 15 nM of TFB2M, 30 nM of TFAM, 0.5 nM of DNA template and 500 μ M nucleotide triphosphate mix (NTPs) in a reaction buffer (containing 10 mM Tris-HCl (pH 7.5), 10 mM MgCl₂, 40 mM NaCl, 10 mM DTT, 0.005% (w/v) Tween-20, 160 units/ml Rnase inhibitor and 0.1 mg/mL BSA) are dispensed to compounds in microplates, using a Thermo Multidrop® dispenser, and incubated at 37 °C in a VWR INCU-Line incubator for 60 minutes after mixing. No nucleotide triphosphate mix is added to negative control samples. Microplates with compounds to be tested in the assay are prepared from 10 mM compound stocks in 100% DMSO, equal amounts of DMSO without any compound are added to positive control and negative control samples.

[1156] During the incubation, a mix of the detection reagents is prepared in a buffer such that the enzymatic reaction is terminated due to chelating of Mg-ions and increased ionic strength, containing 50 mM Tris-HCl (pH 7.5), 700 mM NaCl, 20 mM EDTA, and 0.01% (w/v) Tween-20. Europium-streptavidin is pre-incubated with a 200-fold molar excess of a random sequence oligonucleotide to block unspecific binding of oligo, for two hours at ambient temperature in the dark. Afterwards, the blocked Europium-streptavidin is kept on ice until use.

[1157] At the end of the enzymatic reaction time, 5 μ L detection oligo mix in the detection buffer is added, and assay plates are mixed and kept at ambient temperature for one hour, protected from light. The concentration of the Acceptor nucleotide oligo (e.g., ATTO647N-5' - ACAAAGAACCCTAACACCAG-3') and Donor nucleotide oligo (e.g., bio-5'-AACACATCTCT(-bio)GCCAAACCCCA-bio-3') in each assay well is 1 nM, and 3 nM, respectively. 0430 After incubation with oligo mix, 5 μ L of pre-blocked Europium-streptavidin reagent is dispensed to each assay well, assay plates are again mixed and kept at ambient temperature for one hour, protected from light.

[1158] The generated signal is measured with BMG Pherastar microtiter plate reader with a TRF light unit, using excitation at 340 nm, an integration time of 200 μ s, and a delay time of 100 μ s, before detection at 620 nm and 665 nm. The ratio of donor- and acceptor- fluorescence is used as a measure of the generated transcript product (i.e. enzymatic activity).

Table 2. IC₅₀ values for compounds.

Example Number	Compound ID	POLRMT HUMAN IC ₅₀ (μ M)
203b	Compound 1	0.66
203a	Compound 2	0.02
-	Compound 3	4.08
-	Compound 4	0.39
-	Compound 5	2.36
-	Compound 6	0.05
-	Compound 7	2.89
-	Compound 8	0.69
-	Compound 9	4.43
-	Compound 10	0.66
-	Compound 11	0.84
-	Compound 12	0.06
-	Compound 13	0.53
-	Compound 14	3.35
-	Compound 15	0.04
-	Compound 16	3.16
-	Compound 17	6.65
-	Compound 18	10.00
-	Compound 19	0.09
-	Compound 20	0.19
-	Compound 21	1.33
-	Compound 22	0.04
-	Compound 23	1.71
-	Compound 24	5.49
-	Compound 25	0.05
-	Compound 26	11.74
-	Compound 27	0.11
-	Compound 28	3.56
-	Compound 29	0.30
-	Compound 30	1.04
-	Compound 31	1.10
-	Compound 32	0.50

-	Compound 33	2.59
42	Compound 34	0.09
-	Compound 35	>10
-	Compound 36	1.27
-	Compound 37	0.06
-	Compound 38	0.06
-	Compound 39	2.36
-	Compound 40	3.68
-	Compound 41	0.19
-	Compound 42	2.94
-	Compound 43	1.24
-	Compound 44	0.01
-	Compound 45	3.67
-	Compound 46	0.09
-	Compound 47	0.68
-	Compound 48	0.01
-	Compound 49	0.03
-	Compound 50	0.03
-	Compound 51	0.03
-	Compound 52	1.61
202b	Compound 53	7.14
202a	Compound 54	1.66
-	Compound 55	6.93
-	Compound 56	1.50
-	Compound 57	1.62
-	Compound 58	0.15
-	Compound 59	1.13
-	Compound 60	4.59
-	Compound 61	0.52
-	Compound 62	0.07
-	Compound 63	0.03
-	Compound 64	2.53
98	Compound 65	0.48
97	Compound 66	0.28
-	Compound 67	0.97
23	Compound 68	0.26
-	Compound 69	1.26
39	Compound 70	0.02
-	Compound 71	0.37
25	Compound 72	2.42

109	Compound 73	0.45
44	Compound 74	0.29
35	Compound 75	0.24
168	Compound 76	1.30
167b	Compound 77	2.07
167a	Compound 78	1.33
166	Compound 79	0.01
-	Compound 80	4.48
63	Compound 81	0.08
149	Compound 82	3.43
165b	Compound 83	0.64
165a	Compound 84	0.09
89	Compound 85	0.07
60	Compound 86	0.06
59	Compound 87	0.59
94	Compound 88	0.20
110	Compound 89	0.09
185	Compound 90	0.07
88	Compound 91	0.12
87	Compound 92	0.03
86	Compound 93	0.16
93	Compound 94	0.10
-	Compound 95	2.99
24	Compound 96	0.14
-	Compound 97	2.74
-	Compound 98	2.71
162	Compound 99	0.15
85	Compound 100	0.15
84	Compound 101	0.06
83	Compound 102	0.10
-	Compound 103	>100
-	Compound 104	>100
-	Compound 105	2.73
81	Compound 106	0.26
82	Compound 107	>100
-	Compound 108	>100
80	Compound 109	0.44
79	Compound 110	1.05
78	Compound 111	0.61
77	Compound 112	0.44

76	Compound 113	0.78
161b	Compound 114	29.60
161a	Compound 115	1.31
75	Compound 116	0.05
74	Compound 117	0.53
-	Compound 118	48.13
160	Compound 119	0.06
54	Compound 120	0.49
53	Compound 121	0.05
52	Compound 122	0.03
96	Compound 123	0.17
91	Compound 124	0.11
90	Compound 125	0.13
73	Compound 126	0.12
72	Compound 127	0.04
159	Compound 128	0.22
71	Compound 129	0.62
70	Compound 130	2.86
69	Compound 131	0.29
68	Compound 132	0.65
51	Compound 133	0.07
50	Compound 134	0.06
-	Compound 135	75.92
95	Compound 136	0.09
157	Compound 137	0.04
156	Compound 138	0.07
67	Compound 139	1.03
66	Compound 140	0.89
45	Compound 141	1.17
43	Compound 142	0.55
49	Compound 143	0.54
47	Compound 144	0.16
-	Compound 145	3.87
64	Compound 146	0.16
101	Compound 147	0.22
48	Compound 148	0.11
65	Compound 149	0.71
46	Compound 150	0.05
-	Compound 151	16.72
31	Compound 152	0.20

33	Compound 153	0.08
37	Compound 154	0.06
57b	Compound 155	9.82
57a	Compound 156	0.11
30	Compound 157	0.11
32	Compound 158	0.35
183	Compound 159	0.10
-	Compound 160	3.04
18	Compound 161	0.06
29	Compound 162	0.12
27	Compound 163	0.23
28	Compound 164	0.09
92	Compound 165	>100
41	Compound 166	4.43
36b	Compound 167	26.37
36a	Compound 168	0.33
108	Compound 169	0.10
106b	Compound 170	14.85
106a	Compound 171	0.68
-	Compound 172	2.04
105	Compound 173	0.02
104	Compound 174	0.98
164b	Compound 175	2.70
164a	Compound 176	0.01
-	Compound 177	64.69
61	Compound 178	0.89
102	Compound 179	1.43
-	Compound 180	49.39
100	Compound 181	0.08
-	Compound 182	19.56
99	Compound 183	0.09
-	Compound 184	>100
26	Compound 185	0.13
-	Compound 186	>100
22	Compound 187	0.98
158b	Compound 188	2.96
158a	Compound 189	0.01
20	Compound 190	0.11
19	Compound 191	0.75
21	Compound 192	0.05

-	Compound 193	3.65
58	Compound 194	0.04
-	Compound 195	1.17
34	Compound 196	0.02
201b	Compound 197	3.24
201a	Compound 198	0.04
-	Compound 199	2.60
-	Compound 200	0.04
200b	Compound 201	4.97
200a	Compound 202	0.08
-	Compound 203	2.07
-	Compound 204	0.02
8	Compound 205	1.07
184	Compound 206	>100
-	Compound 207	0.15
-	Compound 208	2.48
-	Compound 209	0.30
-	Compound 210	0.32
-	Compound 211	0.14
-	Compound 212	1.04
-	Compound 213	0.03
-	Compound 214	0.27
-	Compound 215	1.41
-	Compound 216	1.08
-	Compound 217	0.16
-	Compound 218	0.24
-	Compound 219	0.17
-	Compound 220	10.00
-	Compound 221	10.00
-	Compound 222	0.11
-	Compound 223	0.05
-	Compound 224	0.11
-	Compound 225	6.12
-	Compound 226	>100
-	Compound 227	11.01
-	Compound 228	>100
-	Compound 229	2.61
-	Compound 230	>100
-	Compound 231	8.60
-	Compound 232	>100

-	Compound 233	2.89
-	Compound 234	>100
-	Compound 235	>100
-	Compound 236	0.16
-	Compound 237	0.16
-	Compound 238	0.12
-	Compound 239	8.30
-	Compound 240	0.19
-	Compound 241	18.25
111b	Compound 242	4.55
111a	Compound 243	0.07
38	Compound 244	0.13
17	Compound 245	0.05
155	Compound 246	18.72
-	Compound 247	>100
148	Compound 248	>100
147	Compound 249	3.62
163	Compound 250	0.24
55b	Compound 251	>100
55a	Compound 252	3.32
103	Compound 253	13.74
146	Compound 254	>100
145	Compound 255	>100
141	Compound 256	34.86
144	Compound 257	13.96
143	Compound 258	0.09
107	Compound 259	>100
16	Compound 260	6.81
131	Compound 261	>100
130	Compound 262	>100
129	Compound 263	7.99
153	Compound 264	1.41
128	Compound 265	0.25
127	Compound 266	0.58
154	Compound 267	2.36
142	Compound 268	0.23
56	Compound 269	12.25
15	Compound 270	26.63
139	Compound 271	7.29
126	Compound 272	5.86

140	Compound 273	0.46
170	Compound 274	6.74
136	Compound 275	3.26
132	Compound 276	42.27
133	Compound 277	25.46
135	Compound 278	>100
134	Compound 279	>100
137	Compound 280	>100
125	Compound 281	13.99
138	Compound 282	2.64
124	Compound 283	4.42
123	Compound 284	>100
169	Compound 285	1.18
122	Compound 286	>100
151	Compound 287	0.51
121	Compound 288	>100
150	Compound 289	6.39
120	Compound 290	>100
119	Compound 291	49.91
118	Compound 292	>100
117	Compound 293	>100
152	Compound 294	39.52
116	Compound 295	1.11
115	Compound 296	0.77
114	Compound 297	>100
5	Compound 298	36.06
4	Compound 299	5.77
113	Compound 300	38.82
1	Compound 301	4.71
14	Compound 302	0.37
13	Compound 303	0.91
-	Compound 304	5.13
3	Compound 305	30.22
112	Compound 306	3.61
2	Compound 307	2.15
12	Compound 308	1.34
11	Compound 309	21.08
-	Compound 310	23.11
40b	Compound 311	0.98
40a	Compound 312	0.14

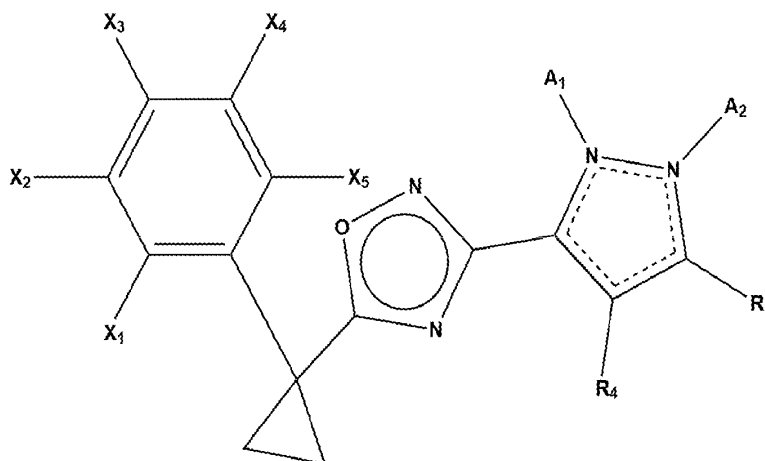
-	Compound 313	4.57
62	Compound 314	0.45
7	Compound 315	>100
-	Compound 316	3.11
-	Compound 317	0.02
-	Compound 318	0.05
-	Compound 319	0.05
-	Compound 320	0.05
-	Compound 321	0.02
-	Compound 322	3.49
-	Compound 323	0.02
-	Compound 324	0.02
-	Compound 325	1.44
-	Compound 326	0.04
-	Compound 327	2.18
-	Compound 328	0.04
-	Compound 329	0.46
-	Compound 330	1.09
-	Compound 331	0.06
-	Compound 332	0.03
-	Compound 333	0.51
-	Compound 334	0.05
-	Compound 335	0.56
-	Compound 336	0.02
-	Compound 337	0.75
-	Compound 338	0.06
-	Compound 339	0.01
-	Compound 340	1.09
-	Compound 341	0.02
-	Compound 342	1.17
-	Compound 343	0.01
-	Compound 344	0.89
-	Compound 345	0.02
-	Compound 346	2.49
-	Compound 347	0.04
-	Compound 348	2.52
-	Compound 349	0.05
-	Compound 350	1.40
-	Compound 351	0.77
-	Compound 352	0.84

-	Compound 353	0.54
-	Compound 354	1.28
-	Compound 355	0.57
-	Compound 356	0.01
-	Compound 357	0.57
-	Compound 358	0.02
-	Compound 359	0.25
-	Compound 360	1.13
-	Compound 361	0.03
-	Compound 362	0.03
-	Compound 363	0.03
-	Compound 364	0.53
-	Compound 365	0.04
-	Compound 366	2.38
-	Compound 367	0.02
-	Compound 368	2.27
-	Compound 369	0.18
-	Compound 370	0.61
-	Compound 371	0.31
204a	Compound 372	3.09
204b	Compound 373	0.02
205b	Compound 374	0.02
205a	Compound 375	>10

CLAIMS

What is claimed is:

1. A compound, or a pharmaceutically acceptable salt thereof, according to Formula (III):



Formula (III);

wherein

X_1 - X_5 are each independently a hydrogen, a halogen, a hydroxy, a cyano, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_1 - C_6 alkoxy, optionally substituted with an aryl, a C_3 - C_{10} cycloalkyl, $-C(O)NH_2$, $-C(O)NHY^1$, $-C(O)NY^1Y^2$, $-COOH$, $-C(O)OY^1$, $-Y^1COOH$, or $-Y^1OY^2$;

Y^1 and Y^2 are each independently a C_1 - C_6 alkyl optionally substituted with one or more halogen or hydroxy;

A_1 and A_2 are each independently a hydrogen, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, an aryl, substituted aryl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, a C_3 - C_6 heterocyclyl, substituted C_3 - C_6 heterocyclyl, or absent;

wherein A_1 and A_2 may be optionally substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, $-C(O)NH_2$, $-CS(O)_2Y^3$, a $-CY^1S(O)_2Y^3$;

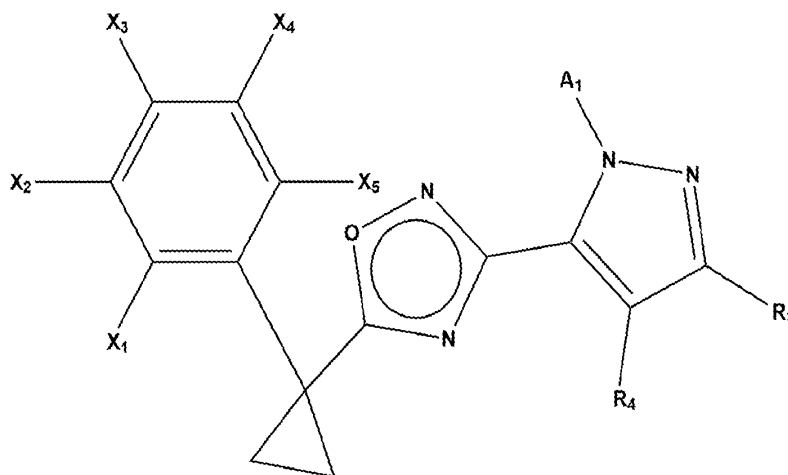
Y^3 is independently a hydrogen or a C_1 - C_4 alkyl optionally substituted with one or more groups selected from the group consisting of a halogen, a hydroxyl, a C_1 - C_4 haloalkoxyl, and a C_1 - C_4 alkoxy;

R₃ is a halogen, a hydrogen, a C₁-C₆ alkyl, a C₁-C₆ alkyl substituted with one or more halogen, or a C₃-C₆ cycloalkyl; and

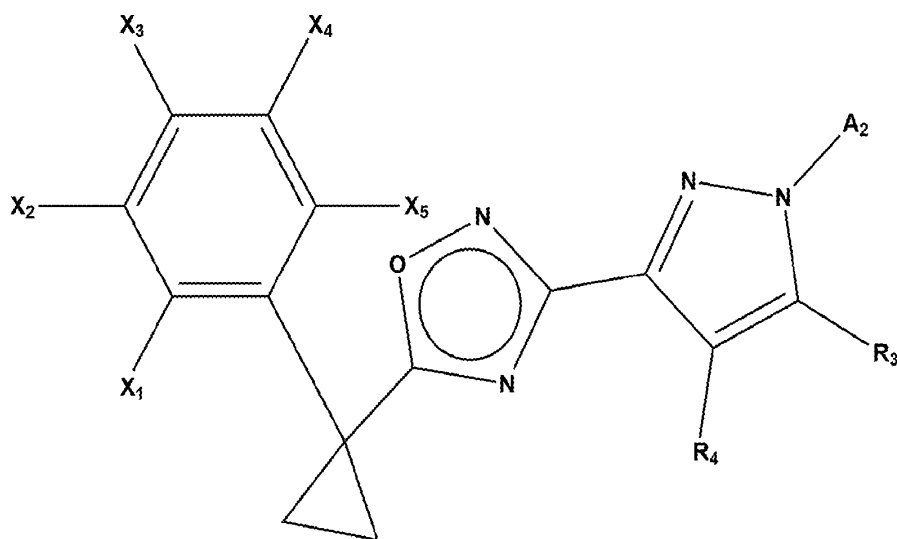
R₄ is a hydrogen, a C₁-C₆ alkyl, or a C₁-C₆ alkyl substituted with one or more halogen;

if R₃ and R₄ are optionally interconnected they form a C₃-C₆ cycloalkyl, a substituted C₃-C₆ cycloalkyl, 5-membered heterocyclic ring, a substituted 5-membered heterocyclic ring, 6-membered heterocyclic ring, a substituted 6-membered heterocyclic ring, a phenyl ring, or a substituted phenyl ring.

2. The compound of claim 1, according to any one of Formulae (IIIa) or (IIIb):



Formula (IIIa); or



Formula (IIIb);

wherein

X_1 is C_1 - C_6 alkyl;

X_2 , X_3 , and X_5 are hydrogen;

X_4 is hydrogen or fluorine;

A_1 and A_2 are each independently a hydrogen, a C_1 - C_6 alkyl, a substituted C_1 - C_6 alkyl, an aryl, substituted aryl, a C_3 - C_6 cycloalkyl, a substituted C_3 - C_6 cycloalkyl, or a C_3 - C_6 heterocyclyl, substituted C_3 - C_6 heterocyclyl;

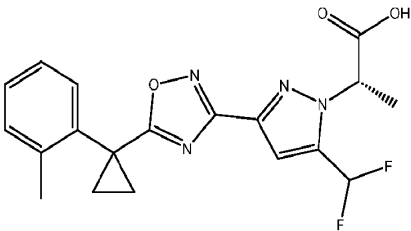
wherein A_1 and A_2 may be optionally substituted with one or more members selected from the group consisting of halogen, ester, ether, carboxylic acid, $-C(O)NH_2$, $-CS(O)_2Y^3$, a $-CY^1S(O)_2Y^3$;

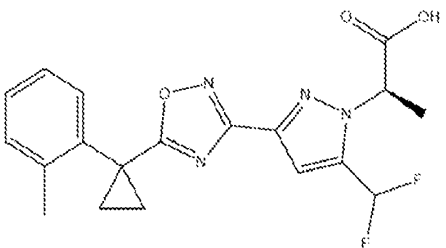
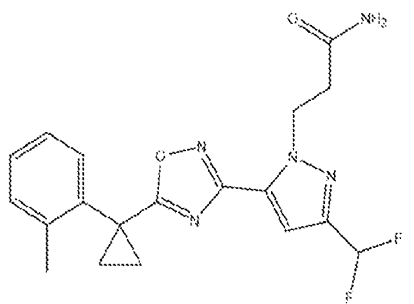
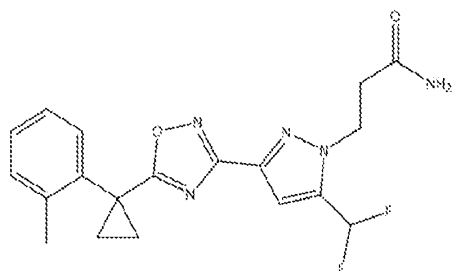
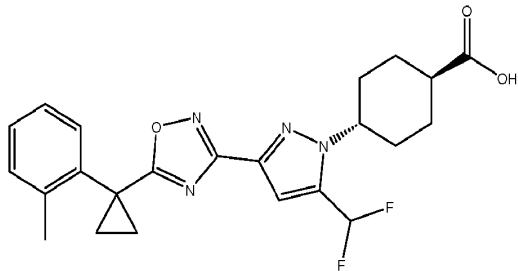
R_3 is C_1 - C_6 alkyl substituted with one or more halogen; and

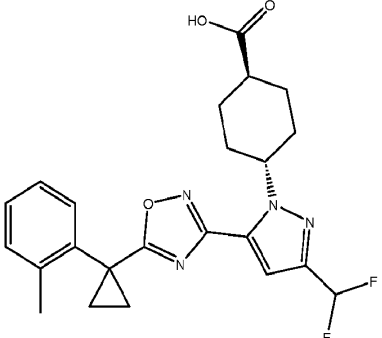
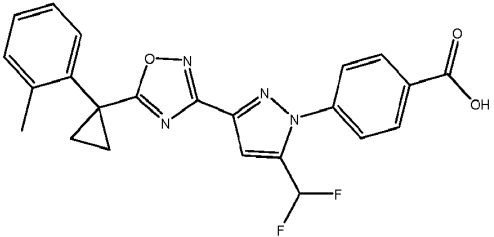
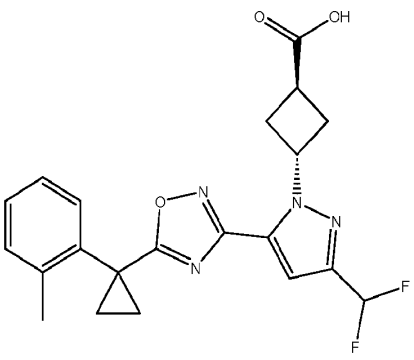
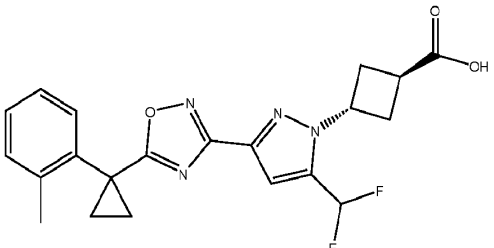
R_4 is a hydrogen.

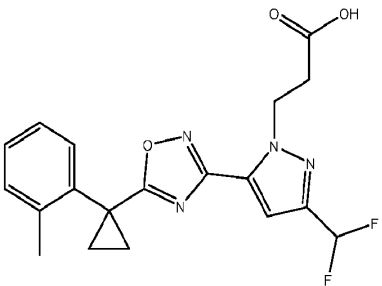
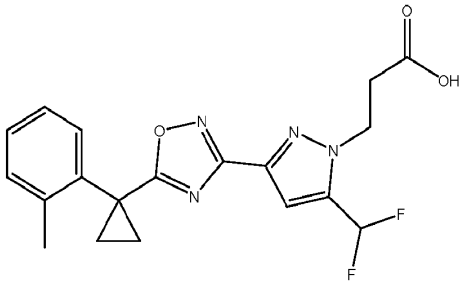
3. The compound of claim 2, wherein X_1 is methyl.
4. The compound of claim 2, X_4 is hydrogen or fluorine.
5. The compound of claim 1, wherein at least two of X_2 - X_5 are hydrogen.
6. The compound of claim 1, wherein at least three of X_2 - X_5 are hydrogen.
7. The compound of claim 2, wherein A_1 and A_2 are substituted C_1 - C_6 alkyl.

8. The compound of claim 7, wherein A₁ and A₂ are substituted ethyl.
9. The compound of claim 8, wherein the ethyl is substituted with carboxylic acid or amide.
10. The compound of claim 7, wherein A₁ and A₂ are -CH(CH₃)COOH.
11. The compound of claim 7, wherein A₁ and A₂ are -CH₂CH₃COOH.
12. The compound of claim 7, wherein A₁ and A₂ are -CH₂CH₃CONH₂.
13. The compound of claim 7, wherein A₁ and A₂ are substituted C₃-C₆ cycloalkyl.
14. The compound of claim 13, wherein the substituted C₃-C₆ cycloalkyl is a cyclobutyl or cyclohexyl substituted with one or more carboxylic acid.
15. The compound of claim 7, wherein A₁ and A₂ are substituted phenyl.
16. The compound of claim 15, the phenyl is substituted with one or more carboxylic acid.
17. The compound of claim 2, wherein R₃ is -CHF₂ or -CF₃.
18. The compound of claim 1, wherein X₁-X₅ are each independently hydrogen, halogen, or methyl.
19. A composition comprising one of the following compounds:

Compound	Structure
Compound 318	

Compound 321	
Compound 322	
Compound 323	
Compound 339	

Compound 340	
Compound 341	
Compound 342	
Compound 343	

Compound 344	
Compound 345	
Compound 287	