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(54) **Title**: HETEROARYL ANTAGONISTS OF PROSTAGLANDIN D_2 RECEPTORS

(57) **Abstract**: Described herein are compounds that are antagonists of PGD_2 receptors. Also described are pharmaceutical compositions and medicaments that include the compounds described herein, as well as methods of using such antagonists of PGD_2 receptors, alone and in combination with other compounds, for treating respiratory, cardiovascular, and other PGD_2-dependent or PGD_2-mediated conditions or diseases.

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HETEROARYL ANTAGONISTS OF PROSTAGLANDIN D_2 RECEPTORS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/101,074 entitled "HETEROARYL ANTAGONISTS OF PROSTAGLANDIN D_2 RECEPTORS" filed on September 29, 2008, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases, disorders or conditions associated with prostaglandin D_2.

BACKGROUND OF THE INVENTION

[0003] Prostaglandins are acidic lipids derived from the metabolism of arachidonic acid by the action of cyclooxygenase enzymes and downstream synthases. Prostaglandins have a diverse range of activities and have a well recognized role in pain and inflammation. Prostaglandin D_2 (PGD_2) is an acidic lipid mediator derived from the metabolism of arachidonic acid by cyclooxygenases and PGD_2 synthases. PGD_2 is produced by mast cells, macrophages and Th2 lymphocytes in response to local tissue damage as well as allergic inflammation in diseases such as asthma, rhinitis, and atopic dermatitis. Exogenous PGD_2 applied to bronchial airways elucidates many characteristics of an asthmatic response suggesting that PGD_2 plays an important pro-inflammatory role in allergic diseases.

[0004] PGD_2 binds to a number of receptors, which include the thromboxane-type prostanoid (TP) receptor, PGD_2 receptor (DP, also known as DP_1) and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2; also known as DP_2). DP_2 is associated with promoting chemotaxis and activation of Th2 lymphocytes, eosinophils and basophils. In particular, PGD_2 binds to DP_2, and mediates its effects through a G_i-dependant elevation in calcium levels and reduction of intracellular cyclic AMP. In Th2 lymphocytes, IL4, IL5 and IL13 cytokine production is stimulated. These cytokines have been implicated in numerous biological actions including, by way of example only, immunoglobulin E production, airway response, mucous secretion, and eosinophil recruitment.

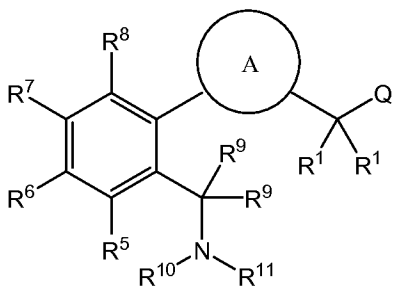
SUMMARY OF THE INVENTION

[0005] Presented herein are compounds, pharmaceutical compositions and medicaments, methods, for (a) diagnosing, preventing, or treating allergic and non-allergic inflammation, (b) mitigating adverse signs and symptoms that are associated with inflammation, and/or (c)

controlling immunological, proliferative or disorders. These disorders may arise from one or more of a genetic, iatrogenic, immunological, infectious, metabolic, oncological, toxic, surgical, and/or traumatic etiology. In one aspect, the methods, compounds, pharmaceutical compositions, and medicaments described herein comprise antagonists of PGD_2 receptors. In one aspect, the methods, compounds, pharmaceutical compositions, and medicaments described herein comprise antagonists of DP_2

[0006] In one aspect provided herein are compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, which are anatgonists of DP_2, and are used to treat patients suffering from one or more PGD_2-dependent conditions or diseases, including, but not limited to, asthma, rhinitis, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung fibrosis, arthritis, allergy, psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, cancer, endotoxic shock, proliferative disorders and inflammatory conditions. In some embodiments, PGD_2-dependent conditions or diseases include those wherein an absolute or relative excess of PGD_2 is present and/or observed.

[0007] In one aspect is a compound having the structure of Formula (I), pharmaceutically acceptable salt, pharmaceutically acceptable solvate, *N*-oxide, or pharmaceutically acceptable prodrug thereof:



Formula (I)

wherein,

Q is tetrazolyl, or -C(=O)-Q^1;

Q^1 is –OH, –OR^B, -$NHSO_2R^{12}$, -$N(R^{13})_2$, -NH-OH, or –NH-CN; R^B is H or C_1-C_6alkyl;

ring A represents a substituted or unsubstituted monocyclic heteroaryl, wherein if ring A is substituted, then ring A is subtituted with 1 to 4 R^A;

each R^1 is independently selected from H, F, C_1-C_4alkyl, and C_1-C_4fluoroalkyl;

each of R^A, R^5, R^6, R^7, and R^8 is independently selected from H, halogen, -CN, -NO_2, -OH, -OR^{12}, -SR^{12}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$N(R^{13})S(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -$NHCH_2CO_2R^{13}$, -$OCH_2CO_2R^{13}$, -$SCH_2CO_2R^{13}$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NR^{13}C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, -

NR^{13}-C_1-C_4alkyl-C(=O)R^{12}, -C_1-C_4alkyl-N(R^{13})$_2$, -C_1-C_4alkyl-NR^{13}C(=O)R^{12}, -C_1-C_4alkyl-NR^{13}S(=O)$_2R^{12}$, -NR^{13}C(=O)OR^{12}, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), and -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl);

each R^9 is H;

R^{10} is –C(=O)R^{14}, –C(=O)OR^{15}, –C(=O)N(R^{16})$_2$, –S(=O)$_2$N(R^{16})$_2$ or –S(=O)$_2R^{14}$;

R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl) or -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl); or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_6alkyl or a substituted or unsubstituted aryl;

X^3 is a bond, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -NR^{13}S(=O)$_2$-, or –NR^{13}-;

Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), or C_1-C_4alkyl-(substituted or unsubstituted heteroaryl);

R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), or -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl);

each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-

(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), or -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl); or

two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted C_2-C_{10}heterocycloalkyl;

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl), -C_1-C_6alkylene-O-R^{17}, -C_1-C_6alkylene-S-R^{17}, -C_1-C_6alkylene-S(=O)-R^{17}, -C_1-C_6alkylene-S(=O)$_2$-R^{17}, -C_1-C_6alkylene-N(R^{17})$_2$, -C_1-C_6alkylene-C(=O)-R^{17}, -C_1-C_6alkylene-C(=O)O-R^{17}-, -C_1-C_6alkylene-OC(=O)-R^{17}, -C_1-C_6alkylene-NR^{17}C(=O)-R^{17} or -C_1-C_6alkylene-C(=O)N(R^{17})$_2$;

each R^{17} is independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, and a substituted or unsubstituted heteroaryl; or

two R^{17} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted C_2-C_{10}heterocycloalkyl; or

R^{10} and R^{11} are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle;

R^{12} is C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), or -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl);

each R^{13} is independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), and -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl); or

two R^{13} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted C_2-C_{10}heterocycloalkyl.

[0008] For any and all of the embodiments, substituents can be selected from among from a subset of the listed alternatives. For example, in some embodiments, Q is -C(=O)-Q^1; Q^1 is –OR^B; R^B is H or C_1-C_6alkyl. In other embodiments, Q is -C(=O)-OH. In some embodiments, Q^1 is –OH. In some embodiments, R^B is H or C_1-C_4alkyl. In some embodiments, R^B is H.

[0009] In some embodiments, each R^1 is independently selected from H, F, and $–CH_3$. In some other embodiments, each R^1 is H.

[0010] In some embodiments, ring A is a substituted or unsubstituted 5-membered or 6-membered heteroaryl, wherein if ring A is substituted, then ring A is subtituted with 1 to 4 R^A.

[0011] In some embodiments, ring A is a substituted or unsubstituted 5-membered heteroaryl or a substituted or unsubstituted 6-membered heteroaryl, wherein ring A includes 0 or 1 O atoms, 0 or 1 S atoms, 0-3 N atoms, and at least 2 carbon atoms, wherein if ring A is substituted, then ring A is substituted with 1 to 3 R^A.

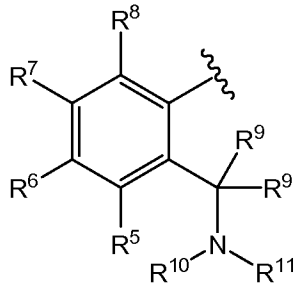
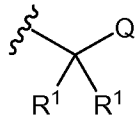
[0012] In some embodiments, ring A is a substituted or unsubstituted 5-membered or 6-membered heteroaryl selected from among furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, wherein if ring A is substituted then ring A is substituted with 1 to 3 R^A.

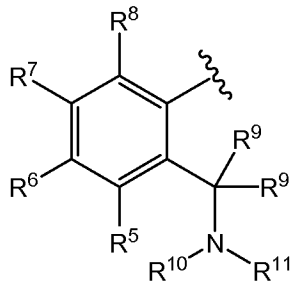
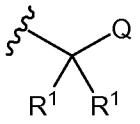
[0013] In some embodiments, ring A is a substituted or unsubstituted 5-membered heteroaryl, wherein ring A includes 0 or 1 O atoms, 0 or 1 S atoms, 1-3 N atoms, and at least 2 carbon atoms, wherein if ring A is substituted then ring A is substituted with 1 to 3 R^A.

[0014] In some embodiments, ring A is a substituted or unsubstituted 5-membered heteroaryl selected from among pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, wherein if ring A is substituted then ring A is substituted with 1 to 3 R^A.

[0015] In some embodiments, ring A is a substituted or unsubstituted 6-membered heteroaryl containing 1-3 N atoms in the ring, wherein if ring A is substituted then ring A is substituted with 1 to 3 R^A.

[0016] In some embodiments, ring A is a substituted or unsubstituted 6-membered heteroaryl selected from among pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, wherein if ring A is substituted then ring A is substituted with 1 or 2 R^A.

[0017] In some embodiments, the groups  and  are attached to ring A on non-adjacent atoms of ring A.

[0018] In some embodiments, the groups  and  are attached to ring A on non-adjacent carbon atoms of ring A.

[0019] In some embodiments, each R^A is independently selected from H, halogen, -CN, -OH, -OR^{12}, -$S(=O)_2R^{12}$, -$C(=O)R^{12}$, -CO_2R^{13}, -$N(R^{13})_2$, -$C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; each of R^5, R^6, R^7, and R^8 is independently selected from H, halogen, -CN, -NO_2, -OH, -OR^{12}, -SR^{12}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$N(R^{13})S(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -$NHCH_2CO_2R^{13}$, -$OCH_2CO_2R^{13}$, -$SCH_2CO_2R^{13}$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NR^{13}C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, -NR^{13}-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, -$NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, and a substituted or unsubstituted monocyclic heteroaryl.

[0020] In some embodiments, each of R^5, R^7, and R^8 is independently selected from H, halogen, -CN, -OH, -OR^{12}, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

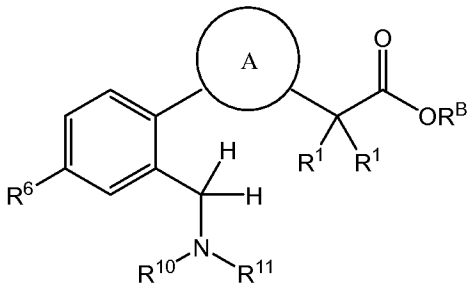
[0021] In some embodiments, each of R^5, R^7, and R^8 is independently selected from H, F, Cl, Br, I, -CN, -OH, -OCH_3, -OCH_2CH_3, -CH_3, -CH_3CH_3, -CF_3, CHF_2, CH_2F, and -OCF_3.

[0022] In some embodiments, at least one of R^5, R^7, and R^8 is H.

[0023] In some embodiments, at least two of R^5, R^7, and R^8 is H.

[0024] In some embodiments, each of R^5, R^7, and R^8 is H.

[0025] In some embodiments, the compound of Formula (I) has the structure of Formula (II):



Formula (II).

[0026] In some embodiments, R^B is H; each R^1 is independently selected from H and $-CH_3$.

[0027] In some embodiments, ring A is a substituted or unsubstituted 6-membered heteroaryl selected from among pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, wherein if ring A is substituted then ring A is substituted with 1 or 2 R^A. In some embodiments, ring A is a substituted or unsubstituted pyridinyl, wherein if ring A is substituted then ring A is substituted with 1 or 2 R^A.

[0028] In some embodiments, ring A is a substituted or unsubstituted pyridinyl, wherein if ring A is substituted then ring A is substituted with 1 or 2 R^A; each R^A is independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy; R^{10} is $-C(=O)R^{14}$, $-C(=O)OR^{15}$, or $-C(=O)N(R^{16})_2$; R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0029] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0030] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0031] In some embodiments, R^{10} is $-C(=O)R^{14}$; R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(C_3-C_6cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl) or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is $-L^3$-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-, -S-, -S(=O)-, or $-S(=O)_2$-; Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0032] In some embodiments, R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or

unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-; Q^3 is a C_1-C_6alkyl, a substituted or unsubstituted phenyl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl). In some embodiments, R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl). In some embodiments, R^{14} is C_1-C_4alkyl, C_3-C_6cycloalkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl). In some embodiments, R^{14} is C_1-C_4alkyl, or C_3-C_6cycloalkyl. In some embodiments, R^{14} is C_1-C_4alkyl. In some embodiments, R^{14} is C_3-C_6cycloalkyl. In some embodiments, R^{14} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl). In some embodiments, R^{14} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl). In some embodiments, R^{14} is -L^3-X^3-Q^3.

[0033] In some embodiments, R^{11} is C_1-C_6alkyl, C_3-C_6cycloalkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-; Q^3 is a C_1-C_6alkyl.

[0034] In some embodiments, R^{11} is C_1-C_6alkyl, C_3-C_6cycloalkyl; R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-; Q^3 is a C_1-C_6alkyl.

[0035] In some embodiments, R^{11} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl; or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-; Q^3 is a C_1-C_6alkyl.

[0036] In some embodiments, R^{10} is –C(=O)OR^{15}; R^{15} is C_1-C_6alkyl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0037] In some embodiments, R^{10} is –C(=O)OR^{15}; R^{15} is C_1-C_4alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl).

[0038] In some embodiments, R^{10} is –C(=O)OR^{15}; R^{11} is C_1-C_6alkyl; R^{15} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl). In some embodiments, R^{10} is –C(=O)OR^{15}; R^{11} is C_1-C_4alkyl; R^{15} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl).

[0039] In some embodiments, R^{10} is $-C(=O)N(R^{16})_2$; each R^{16} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0040] In some embodiments, R^{10} is $-C(=O)N(R^{16})_2$; one R^{16} is C_1-C_6alkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); and the other R^{16} is H or C_1-C_6alkyl.

[0041] In some embodiments, R^{10} is $-C(=O)N(R^{16})_2$; R^{11} is C_1-C_6alkyl; one R^{16} is C_1-C_6alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl); and the other R^{16} is H or C_1-C_6alkyl. In some embodiments, R^{10} is $-C(=O)N(R^{16})_2$; R^{11} is C_1-C_4alkyl; one R^{16} is C_1-C_4alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl); and the other R^{16} is H or C_1-C_4alkyl.

[0042] In some embodiments, R^6 is selected from H, halogen, -CN, $-NO_2$, -OH, $-OR^{12}$, $-SR^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-N(R^{13})S(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-OCO_2R^{13}$, $-N(R^{13})_2$, $-NHCH_2CO_2R^{13}$, $-OCH_2CO_2R^{13}$, $-SCH_2CO_2R^{13}$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{12}$, $-NR^{13}$-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, $-NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl.

[0043] In some embodiments, R^6 is H, halogen, -OH, $-SR^{13}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl.

[0044] In some embodiments, R^6 is halogen, -CN, -OH, $-SR^{13}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl.

[0045] In some embodiments, R^6 is halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy.

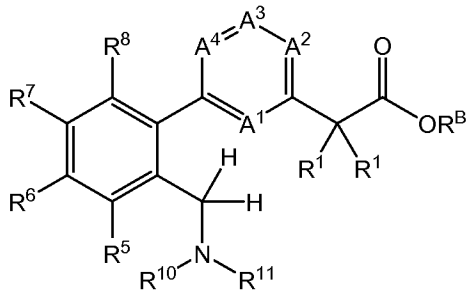
[0046] In some embodiments, R^6 is selected from a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, and a substituted or unsubstituted monocyclic heteroaryl.

[0047] In some embodiments, R^6 is selected from a substituted or unsubstituted C_3-C_6cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, and a substituted or unsubstituted monocyclic heteroaryl.

[0048] In some embodiments, R^6 is C_3-C_6cycloalkyl. In some embodiments, R^6 is a substituted or unsubstituted C_2-C_{10}heterocycloalkyl. In some embodiments, R^6 is a substituted or unsubstituted C_3-C_6heterocycloalkyl. In some embodiments, R^6 is a substituted or unsubstituted

phenyl, or a substituted or unsubstituted monocyclic heteroaryl. In some embodiments, R^6 is a substituted or unsubstituted phenyl. In some embodiments, R^6 is a substituted or unsubstituted monocyclic heteroaryl.

[0049] In some embodiments, the compound of Formula (I) has the structure of Formula (III):



Formula (III)

wherein

each of A^1, A^2, A^3, and A^4 is independently selected from among –N-, $-N^+(-O^-)-$ and $-C(R^A)-$, where one or two of A^1, A^2, A^3, and A^4 is –N- or $-N^+(-O^-)-$.

[0050] In some embodiments, each R^A is independently selected from H, halogen, -CN, -OH, $-OR^{12}$, $-N(R^{13})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

[0051] In some embodiments, each R^A is independently selected from H, halogen, -CN, -OH, $-OR^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, and C_1-C_4heteroalkyl; A^1 is –N-, $-N^+(-O^-)-$ or -CH-; each of A^2, A^3, and A^4 is independently selected from among –N-, $-N^+(-O^-)-$ and $-C(R^A)-$, where one or two of A^1, A^2, A^3, and A^4 is –N- or $-N^+(-O^-)-$

[0052] In some embodiments, each R^A is independently selected from H, halogen, -CN, -OH, $-OR^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, and C_1-C_4heteroalkyl.

[0053] In some embodiments, one of A^1, A^2, A^3, and A^4 is –N- or $-N^+(-O^-)-$.

[0054] In some embodiments, A^1 is –N- or $-N^+(-O^-)-$.

[0055] In some embodiments, A^2 is –N- or $-N^+(-O^-)-$.

[0056] In some embodiments, A^3 is –N- or $-N^+(-O^-)-$.

[0057] In some embodiments, A^4 is -N- or $-N^+(-O^-)-$.

[0058] In some embodiments, A^1 is –CH-.

[0059] In some embodiments, A^1 is CH; A^3 is –N- or $-N^+(-O^-)-$; and each of A^2 and A^4 is $-C(R^A)-$; each R^A is independently selected from H, F, Cl, Br, I, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, and $-OCF_3$.

[0060] In some embodiments, each R^1 is independently selected from H and $–CH_3$.

[0061] In some embodiments, R^B is H, methyl, ethyl, propyl, or butyl.

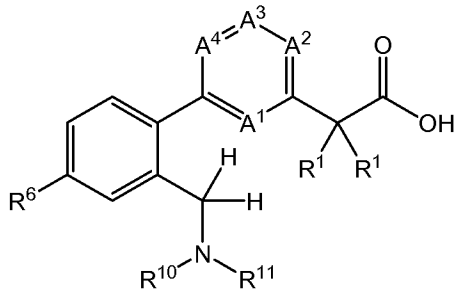
[0062] In some embodiments, each R^1 is H; R^B is H.

[0063] In some embodiments, each of R^5, R^7, and R^8 is independently selected from H, F, Cl, Br, I, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CH_3CH_3$, $-CF_3$, CHF_2, CH_2F, and $-OCF_3$.

[0064] In some embodiments, at least one of R^5, R^7, and R^8 is H.

[0065] In some embodiments, each of R^5, R^7, and R^8 is H.

[0066] In some embodiments, the compound of Formula (III) has the structure of Formula (IV):



Formula (IV).

[0067] In some embodiments, each R^1 is independently selected from H and $-CH_3$; A^1 is CH; A^3 is –N- or $-N^+(-O^-)$-; and each of A^2 and A^4 is $-C(R^A)$-; each R^A is independently selected from H, halogen, -CN, -OH, $-OR^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, and C_1-C_4heteroalkyl.

[0068] In some embodiments, each R^1 is H; each R^A is independently selected from H, F, Cl, Br, I, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, and $-OCF_3$.

[0069] In some embodiments, at least one R^A is H.

[0070] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(C_3-C_6cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0071] In some embodiments, R^{10} is $-C(=O)R^{14}$, $-C(=O)OR^{15}$, or $-C(=O)N(R^{16})_2$.

[0072] In some embodiments, R^{10} is $-C(=O)R^{14}$, $-C(=O)OR^{15}$, or $-C(=O)N(R^{16})_2$; R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl) or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is $-L^3$-X^3-Q^3; L^3 is a C_1-C_4alkylene or a substituted or unsubstituted phenyl; X^3 is a bond, -O-, -S-, -S(=O)-, or $-S(=O)_2$-; Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted

phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); or two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted C_2-C_{10}heterocycloalkyl.

[0073] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl.

[0074] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl.

[0075] In some embodiments, R^{11} is C_1-C_6alkyl or C_3-C_6cycloalkyl.

[0076] In some embodiments, R^{11} is a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0077] In some embodiments, R^{11} is -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0078] In some embodiments, R^{10} is –C(=O)R^{14}, –C(=O)OR^{15}, or –C(=O)N(R^{16})$_2$; R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; each R^{16} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; or two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl.

[0079] In some embodiments, R^{10} is –C(=O)R^{14}; R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(C_3-C_6cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl) or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-, -S-, -S(=O)-, or -S(=O)$_2$-; Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0080] In some embodiments, R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or

unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-; Q^3 is a C_1-C_6alkyl, a substituted or unsubstituted phenyl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0081] In some embodiments, R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-; Q^3 is a C_1-C_6alkyl.

[0082] In some embodiments, R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-; Q^3 is a C_1-C_6alkyl.

[0083] In some embodiments, R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl; or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_4alkyl; X^3 is -O-; Q^3 is a C_1-C_6alkyl. In some embodiments, R^{14} is C_1-C_6alkyl, or C_3-C_6cycloalkyl.

[0084] In some embodiments, R^{10} is –C(=O)OR^{15}; R^{15} is C_1-C_6alkyl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0085] In some embodiments, R^{10} is –C(=O)OR^{15}; R^{15} is C_1-C_4alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl).

[0086] In some embodiments, R^{10} is –C(=O)OR^{15}; R^{15} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl).

[0087] In some embodiments, R^{10} is –C(=O)N(R^{16})$_2$; each R^{16} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl).

[0088] In some embodiments, R^{10} is –C(=O)N(R^{16})$_2$; one R^{16} is C_1-C_6alkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); and the other R^{16} is H or C_1-C_6alkyl.

[0089] In some embodiments, R^{10} is –C(=O)N(R^{16})$_2$; one R^{16} is C_1-C_6alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl); and the other R^{16} is H or C_1-C_6alkyl.

[0090] In some embodiments, R^{10} is –C(=O)N(R^{16})$_2$; one R^{16} is C_1-C_4alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl); and the other R^{16} is H or C_1-C_4alkyl. In some embodiments, R^{10} is –C(=O)N(R^{16})$_2$; one R^{16} is C_1-C_4alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl); and the other R^{16} is H.

[0091] In some embodiments, R^6 is selected from halogen, -CN, -NO_2, -OH, -OR^{12}, -SR^{12}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$N(R^{13})S(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -$NHCH_2CO_2R^{13}$, -$OCH_2CO_2R^{13}$, -$SCH_2CO_2R^{13}$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NR^{13}C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, -NR^{13}-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, -$NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_6cycloalkyl, a substituted or unsubstituted C_2-C_6heterocycloalkyl.

[0092] In some embodiments, R^6 is selected from halogen, -CN, -NO_2, -OH, -OR^{12}, -SR^{12}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$NHS(=O)_2R^{12}$, -$N(C_1$-C_4alkyl$)S(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NHC(=O)N(R^{13})_2$, -$N(C_1$-C_4alkyl$)C(=O)N(R^{13})_2$, -$NHC(=O)R^{12}$, -$N(C_1$-C_4alkyl$)C(=O)R^{12}$, -NHC_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NHC(=O)R^{12}$, -C_1-C_4alkyl-$NHS(=O)_2R^{12}$, -$NHC(=O)OR^{12}$, -$N(C_1$-C_4alkyl$)C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_6cycloalkyl, and a substituted or unsubstituted C_2-C_6heterocycloalkyl.

[0093] In some embodiments, R^6 is selected from halogen, -CN, -NO_2, -OH, -OR^{12}, -$S(=O)_2R^{12}$, -$NHS(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -CO_2R^{13}, -$N(R^{13})_2$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NHC(=O)N(R^{13})_2$, -$N(C_1$-C_6alkyl$)C(=O)N(R^{13})_2$, -$NHC(=O)R^{12}$, -$N(C_1$-C_6alkyl$)C(=O)R^{12}$, -NHC_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NHC(=O)R^{12}$, -C_1-C_4alkyl-$NHS(=O)_2R^{12}$, -$NHC(=O)OR^{12}$, -$N(C_1$-C_6alkyl$)C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

[0094] In some embodiments, R^6 is selected from -$NHS(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -CO_2R^{13}, -$N(R^{13})_2$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NHC(=O)N(R^{13})_2$, -$N(C_1$-C_6alkyl$)C(=O)N(R^{13})_2$, -$NHC(=O)R^{12}$, -$N(C_1$-C_6alkyl$)C(=O)R^{12}$, -NHC_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -$NHC(=O)OR^{12}$, -$N(C_1$-C_6alkyl$)C(=O)OR^{12}$.

[0095] In some embodiments, R^6 is selected from halogen, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy.

[0096] In some embodiments, R^6 is C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted napthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic heteroaryl.

[0097] In some embodiments, R^6 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or a substituted or unsubstituted group selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, phenyl, naphthyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl,

pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl, benzofuranyl, benzothienyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl.

[0098] In some embodiments, R^6 is a substituted or unsubstituted group selected from phenyl, naphthyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl, benzofuranyl, benzothienyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl.

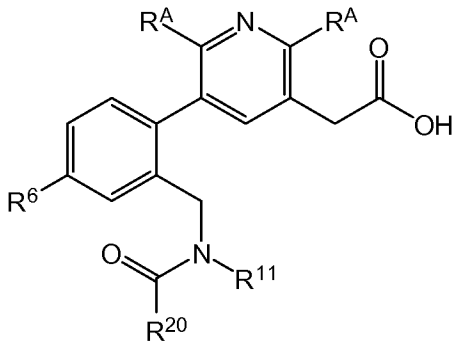
[0099] In some embodiments, R^6 is a substituted or unsubstituted group selected from pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl.

[00100] In some embodiments, R^6 is a substituted or unsubstituted group selected from pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolinyl, and isoquinolinyl.

[00101] In some embodiments, R^6 is a substituted or unsubstituted group selected from pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, and pyrimidinyl.

[00102] In some embodiments, the compound of Formula (I) has the structure of Formula (V). In some embodiments, R^{10} is $-C(=O)R^{20}$, where R^{20} is as defined herein.

[00103] In one aspect, described herein is a compound having the structure of Formula (V), pharmaceutically acceptable salt or *N*-oxide thereof:



Formula (V)

wherein,

each R^A is independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy;

R^6 is H, halogen, -CN, tetrazolyl, -OH, $-SR^{13}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl;

R^{20} is C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom), -C_1-C_2alkyl-O-C_1-C_4alkyl, -O-C_1-C_4alkyl, -O-C_1-C_2alkyl-(substituted or unsubstituted phenyl), $-NR^{16}$-C_1-C_4alkyl, or $-NR^{16}$-C_1-C_2alkyl-(substituted or unsubstituted phenyl);

R^{11} is C_1-C_4alkyl, C_1-C_4haloalkyl, C_3-C_6cycloalkyl, or substituted or unsubstituted benzyl;

R^{12} is C_1-C_4alkyl, C_1-C_4heteroalkyl, or C_1-C_4fluoroalkyl;

each R^{13} is independently selected from H, C_1-C_4alkyl, C_1-C_4heteroalkyl, C_1-C_4fluoroalkyl, or substituted or unsubstituted benzyl;

R^{16} is H or C_1-C_4alkyl;

where each substituted phenyl or substituted heteroaryl is substituted with 1 or 2 R^C, where each R^C is independently selected from halogen, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4alkoxy.

[00104] In some embodiments, each R^A is independently R^A is H, F, Cl, Br, -CN, -OH, $-CH_3$, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-OCH_3$ or $-OCH_2CH_3$; R^6 is H, F, Cl, Br, -CN, -OH, $-SR^{13}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-CO_2R^{13}$, $-C(=O)NH(R^{13})$, $-NHC(=O)R^{12}$, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$; R^{12} is C_1-C_4alkyl; R^{13} is H, C_1-C_4alkyl, or substituted or unsubstituted benzyl.

[00105] In some embodiments, R^{20} is C_1-C_4alkyl, C_3-C_6cycloalkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom), -C_1-C_2alkyl-O-C_1-C_4alkyl, -O-C_1-C_4alkyl, -O-C_1-C_2alkyl-(substituted or unsubstituted phenyl), $-NR^{16}C_1$-C_4alkyl, or $-NR^{16}C_1$-C_2alkyl-(substituted or unsubstituted phenyl); R^{11} is C_1-C_4alkyl, C_3-C_6cycloalkyl or substituted or unsubstituted benzyl.

[00106] In some embodiments, R^{20} is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom); where each substituted phenyl or substituted heteroaryl is substituted with 1 or 2 R^C, where each R^C is independently selected from halogen, -OH, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, and $-CF_3$; R^{11} is $-CH_3$, $-CH_2CH_3$, or cyclopropyl.

[00107] In some embodiments, at least one R^A is H; R^6 is F, Cl, Br, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$; R^{20} is $-CH_3$, cyclopropyl, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$.

[00108] In some embodiments, at least one R^A is H; R^{11} is $-CH_2CH_3$.

[00109] In some embodiments, R^{20} is C_1-C_4alkyl, or C_3-C_6cycloalkyl; R^{11} is substituted or unsubstituted benzyl.

[00110] In some embodiments, at least one R^A is H; R^6 is F, Cl, Br, -CN, -OH, $-SR^{13}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-CO_2R^{13}$, $-C(=O)NH(R^{13})$, $-NHC(=O)R^{12}$, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$; R^{20} is $-CH_3$, or cyclopropyl; R^{11} is substituted or unsubstituted benzyl.

[00111] In some embodiments, R^{20} is -O-C_1-C_4alkyl or -O-C_1-C_2alkyl-(substituted or unsubstituted phenyl).

[00112] In some embodiments, R^{20} is $-O-CH_2$-(substituted or unsubstituted phenyl) or $-O-CH(CH_3)$-(substituted or unsubstituted phenyl); where each substituted phenyl is substituted with 1 or 2 R^C, where each R^C is independently selected from halogen, -OH, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, and $-CF_3$; R^{11} is C_1-C_4alkyl or C_3-C_6cycloalkyl.

[00113] In some embodiments, at least one R^A is H; R^6 is F, Cl, Br, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$; R^{20} is $-O-CH_2$-(substituted or unsubstituted phenyl), where the substituted phenyl is substituted with 1 or 2 R^C, where each R^C is independently selected from F, Cl, Br, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$; R^{11} is C_1-C_4alkyl.

[00114] In some embodiments, one R^A is H, F, Cl, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$, and the other R^A is H; R^6 is $-CF_3$; R^{11} is $-CH_2CH_3$.

[00115] In some embodiments, R^{20} is $-NR^{16}C_1$-C_4alkyl, or $-NR^{16}C_1$-C_2alkyl-(substituted or unsubstituted phenyl); R^{16} is H, $-CH_3$ or $-CH_2CH_3$.

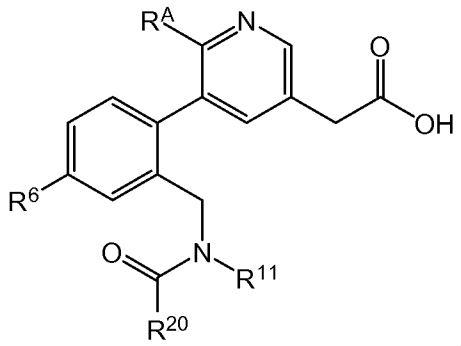
[00116] In some embodiments, R^{20} is $-NR^{16}-CH_2$-(substituted or unsubstituted phenyl) or $-NR^{16}-CH(CH_3)$-(substituted or unsubstituted phenyl), where the substituted phenyl is substituted with 1 or 2 R^C, where each R^C is independently selected from F, Cl, Br, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$; R^{11} is C_1-C_4alkyl or C_3-C_6cycloalkyl; R^{16} is H, $-CH_3$ or $-CH_2CH_3$.

[00117] In some embodiments, at least one R^A is H; R^6 is F, Cl, Br, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$;

[00118] R^{20} is $-NR^{16}-CH_2$-(substituted or unsubstituted phenyl); where the substituted phenyl is substituted with 1 or 2 R^C, where each R^C is independently selected from F, Cl, Br, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$; R^{11} is C_1-C_4alkyl.

[00119] In some embodiments, one R^A is H, F, Cl, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$, and the other R^A is H; R^6 is $-CF_3$; R^{11} is $-CH_2CH_3$.

[00120] In some embodiments, compounds presented herein have the following structure:



[00121] Any combination of the groups described above for the various variables is contemplated herein.

[00122] In certain embodiments presented herein, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), and Formula (V) are antagonists of DP_2. In specific embodiments, the antagonist of DP_2 is selective for DP_2. In other embodiments, the antagonist of DP_2 is also an antagonist of DP_1. In some embodiments, the antagonist of DP_2 is also an antagonist of TP (thromboxane receptor).

[00123] In other embodiments, presented herein are compounds selected from active metabolites, solvates, pharmaceutically acceptable salts or pharmaceutically acceptable prodrugs of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00124] In one aspect, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein. In some embodiments, the pharmaceutical composition also contains a pharmaceutically acceptable excipient.

[00125] In certain embodiments, presented herein are methods for treating a PGD_2-dependent condition or disease in a patient comprising administering to the patient a therapeutically effective amount of an antagonist of DP_2 having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00126] In certain aspects, provided herein is a method for treating inflammation in a mammal comprising administering a therapeutically effective amount of a compound provided herein to the mammal in need.

[00127] In a specific aspect, provided herein is a method for treating asthma in a mammal comprising administering a therapeutically effective amount of a compound provided herein to the mammal in need. In a further or alternative embodiment, provided herein is a method for treating asthma in a mammal comprising administering a therapeutically effective amount of a compound provided herein, such as, for example, a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), to the mammal in need.

[00128] In another aspect are compounds presented in Table 1, Table 2 and Table 3 or pharmaceutically acceptable salts, pharmaceutically active metabolites, pharmaceutically

acceptable prodrugs, and pharmaceutically acceptable solvates thereof, which antagonize DP_2 and are used to treat patients suffering from one or more PGD_2-dependent conditions or diseases, including, but not limited to, asthma, rhinitis, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung fibrosis, arthritis, allergy, psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, cancer, endotoxic shock, proliferative disorders and inflammatory conditions.

[00129] In one aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), including pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, are antagonists of CRTH2. In various embodiments presented herein, these compounds are used to treat patients suffering from one or more PGD_2-dependent conditions or diseases, including, but not limited to, asthma, rhinitis, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung fibrosis, rhinitis, allergy, and adult respiratory distress syndrome.

[00130] In one aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are antagonists of DP_2. In still further or alternative embodiments such antagonists of DP_2 also antagonize other related PGD_2 receptors. Related PGD_2 receptors include, but are not limited to, DP_1 and TP.

[00131] In one aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered with a TP antagonist. TP antagonists inhibit bronchoconstriction, vasoconstriction, and platelet aggregation. In one aspect, co-administration of a TP antagonist with a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) inhibits bronchoconstrictor effects of PGD_2 and other prostanoids.

[00132] In further or alternative embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are included into pharmaceutical compositions or medicaments used for treating a PGD_2-dependent or PGD_2 mediated condition or disease in a patient.

[00133] Pharmaceutical formulations described herein are administerable to a subject in a variety of by multiple administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00134] In some embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered orally.

[00135] In some embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered topically. In such embodiments, the compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, shampoos, scrubs, rubs, smears, medicated sticks, medicated bandages, balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[00136] In another aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered by intranasal administration.

[00137] In another aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are formaulted for intranasal adminstration. Such formulations include nasal sprays, nasal mists, and the like.

[00138] In another aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are formulated as eye drops.

[00139] In one aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered topically to the skin.

[00140] In another aspect, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are used to treat or prevent inflammatory conditions. Inflammatory conditions include, but are not limited to, asthma, rhinitis, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung fibrosis, atherosclerosis, aortic aneurysm, myocardial infarction, and stroke.

[00141] In another aspect, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are used to treat or prevent immunological disorders. In one aspect the immunological disorders include, but are not limited to, allergy or to excessive or inappropriate response to an endogenous or exogenous antigen. In certain embodiments, the immunological disorder that is characterized by immune dysregulation that is not accompanied by inflammation.

[00142] In another aspect, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are used to treat or prevent proliferative disorders. In one aspect the proliferative disorders include, but are not limited to, cancer and noncancerous disorders, including, but not limited to, those involving the skin or lymphatic tissues.

[00143] In additional aspects, such conditions are iatrogenic and increases in, or abnormal localization of, PGD_2 is induced by other therapies or medical or surgical procedures. In other embodiments, the PGD_2-dependent or PGD_2 mediated condition or disease is caused by surgery.

[00144] In other aspects, the methods, compounds, pharmaceutical compositions, and medicaments described herein are used to prevent the cellular activity of PGD_2. In other aspects, such methods, compounds, pharmaceutical compositions, and medicaments comprise DP_2 antagonists disclosed herein for the treatment of asthma by modulating the activity of enzymes or proteins in a patient wherein such enzymes or proteins are involved in the PGD_2 pathway such as, by way of example, DP_2. In yet other aspects, the methods, compounds, pharmaceutical compositions, and medicaments described herein are used in combination with other medical treatments or surgical modalities.

[00145] In one aspect are methods for reducing/antagonizing the PGD_2 activation of DP_2 in a mammal comprising administering to the mammal at least once an effective amount of a compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00146] In another aspect are methods for modulating, including reducing and/or antagonizing the activation of DP_2, directly or indirectly, in a mammal comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00147] In another aspect, presented herein are methods for modulating, including reducing and/or antagonizing the activity of PGD_2 in a mammal, directly or indirectly, comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00148] In another aspect are methods for treating PGD_2 -dependent or PGD_2 mediated conditions or diseases, comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00149] In another aspect are methods for treating inflammation comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00150] In another aspect are methods for treating immunological abnormalities comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00151] In another aspect are methods for treating respiratory diseases comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). In a further embodiment of this aspect, the respiratory disease is asthma. In a further embodiment of this aspect, the respiratory disease includes, but is not limited to, adult respiratory distress syndrome and allergic

(extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, neutrophilic asthma, occupational asthma, steroid-resistant asthma, seasonal asthma.

[00152] In another aspect are methods for treating respiratory diseases comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). In a further embodiment of this aspect, the respiratory disease is rhinitis. In a further embodiment of this aspect, the respiratory disease includes, but is not limited to, allergic (extrinsic) rhinitis, non-allergic (intrinsic) rhinitis, chronic rhinitis, allergen-induced rhinitis, aspirin-sensitive rhinitis, child-onset rhinitis, adult-onset rhinitis, occupational rhinitis, steroid-resistant rhinitis, seasonal rhinitis, perennial rhinitis, rhinosinusitis, and rhinopolyposis.

[00153] In another aspect are methods for treating chronic obstructive pulmonary disease comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). In a further embodiment of this aspect, chronic obstructive pulmonary disease includes, but is not limited to, chronic bronchitis and/or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis.

[00154] In another aspect are methods for preventing increased mucosal secretion and/or edema in a disease or condition comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00155] In another aspect are methods for treating vasoconstriction, atherosclerosis and its sequelae, myocardial ischemia, myocardial infarction, aortic aneurysm, vasculitis, cardiac arrhythmia, and stroke comprising administering to the mammal an effective amount of a compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00156] In another aspect are methods for treating organ reperfusion injury following organ ischemia and/or endotoxic shock comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00157] In another aspect are methods for reducing the constriction of blood vessels in a mammal comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00158] In another aspect are methods for lowering or preventing an increase in blood pressure of a mammal comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00159] In another aspect are methods for preventing eosinophil and/or basophil and/or dendritic cell and/or neutrophil and/or monocyte or TH2 cell recruitment comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00160] A further aspect are methods for the prevention or treatment of abnormal bone remodeling, loss or gain, including diseases or conditions as, by way of example, osteopenia, osteoporosis, Paget's disease, cancer, trauma, surgery, and other diseases comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00161] In another aspect are methods for preventing ocular inflammation and allergic conjunctivitis, vernal keratoconjunctivitis, and papillary conjunctivitis comprising administering to the mammal at least once an effective amount of at least one having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00162] In another aspect are methods for treating CNS disorders comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). CNS disorders include, but are not limited to, multiple sclerosis, Parkinson's disease, Alzheimer's or other degenerative disease, stroke, cerebral ischemia, retinal ischemia, post-surgical cognitive dysfunction, migraine, peripheral neuropathy/neuropathic pain, spinal cord injury, cerebral edema and head injury.

[00163] A further aspect are methods for the treatment of cancer comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). The type of cancer includes, but is not limited to, pancreatic cancer and other solid or hematological tumors.

[00164] In another aspect are methods for treating endotoxic shock and septic shock comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00165] In another aspect are methods for treating rheumatoid arthritis and osteoarthritis comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00166] In another aspect are methods for treating or preventing increased gastrointestinal diseases comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). Such diseases include, by way of example only, chronic gastritis, eosinophilic gastroenteritis, and gastric motor dysfunction.

[00167] A further aspect are methods for treating kidney diseases comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). Such diseases include, by way of example only, acute tubular necrosis, glomerulonephritis, cyclosporine nephrotoxicity, renal ischemia, and reperfusion injury.

[00168] In another aspect are methods for preventing or treating acute or chronic renal insufficiency comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00169] In another aspect are methods for treating pain including neuropathic pain comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00170] In another aspect are methods to diminish the inflammatory aspects of acute infections within one or more solid organs or tissues such as the kidney with acute pyelonephritis.

[00171] In another aspect are methods for preventing or treating acute or chronic disorders involving recruitment or activation of eosinophils comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00172] In another aspect are methods for preventing or treating acute or chronic erosive disease or motor dysfunction of the gastrointestinal tract caused by non-steroidal anti-inflammatory drugs (including selective or non-selective cyclooxygenase –1 or –2 inhibitors) comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00173] A further aspect are methods for the prevention or treatment of rejection or dysfunction in a transplanted organ or tissue comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00174] In another aspect are methods for treating inflammatory responses of the skin comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). Such

inflammatory responses of the skin include, by way of example, dermatitis, contact dermatitis, eczema, urticaria, rosacea, and scarring. In another aspect are methods for reducing psoriatic lesions in the skin, joints, or other tissues or organs, comprising administering to the mammal an effective amount of a first compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00175] A further aspect are methods for the treatment of cystitis, including, by way of example only, interstitial cystitis, comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00176] A further aspect are methods for the treatment of Familial Mediterranean Fever comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00177] In a further aspect are methods to treat hepatorenal syndrome comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00178] In a further aspect are methods to modulate the immune response to endogenous or exogenous antigens.

[00179] In a further aspect are methods to treat acute or chronic allergic responses to exogenous substances that have been ingested such as foods (e.g., peanuts) or drugs (e.g., penicillin, non-steroidal anti-inflammatory drugs or the like).

[00180] In another aspect is the use of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) in the manufacture of a medicament for treating an inflammatory disease or condition in an animal in which the activity of at least one PGD_2-associated protein contributes to the pathology and/or symptoms of the disease or condition. In one embodiment of this aspect, the PGD_2 pathway protein is CRTH2. In another or further embodiment of this aspect, the inflammatory disease or conditions are respiratory, cardiovascular, or proliferative diseases.

[00181] In any of the aforementioned aspects are further embodiments in which: (a) the effective amount of the compound is systemically administered to the mammal; and/or (b) the effective amount of the compound is administered orally to the mammal; and/or (c) the effective amount of the compound is intravenously administered to the mammal; and/or (d) the effective amount of the compound administered by inhalation; and/or (e) the effective amount of the compound is administered by nasal administration; or and/or (f) the effective amount of the compound is administered by injection to the mammal; and/or (g) the effective amount of the compound is

administered topically (dermal) to the mammal; and/or (h) the effective amount of the compound is administered by ophthalmic administration; and/or (i) the effective amount of the compound is administered rectally to the mammal.

[00182] In any of the aforementioned aspects are further embodiments in which the mammal is a human, including embodiments wherein the human has an asthmatic condition or one or more other condition(s) selected from the group consisting of allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, neutrophilic asthma, occupational asthma, steroid-resistant asthma, or seasonal asthma, or chronic obstructive pulmonary disease, or pulmonary hypertension or interstitial lung fibrosis. In any of the aforementioned aspects are further embodiments in which the mammal is an animal model for pulmonary inflammation, examples of which are provided herein.

[00183] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[00184] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[00185] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once daily; (ii) the compound is administered twice daily; (iii) the compound is administered in cycles that include daily administration for a period of time followed by at least 1 day without administration; (iv) the compound is administered in cycles that include daily administration for a period of time followed by at least 1 day that includes a dose reduction in the daily amount of compound that is administered.

[00186] In any of the aforementioned aspects involving the treatment of PGD_2 dependent diseases or conditions are further embodiments comprising administering at least one additional agent in

addition to the administration of a compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). In various embodiments, each agent is administered in any order, including simultaneously. In certain embodiments, the at least one additional agent is, by way of example only, an anti-inflammatory agent, a different compound having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), a DP_1 receptor antagonist, a TP receptor antagonist, or a different DP_2 receptor antagonist.

[00187] In other embodiments, a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is combined with an additional agent that is a respiratory agent, including, but not limited to antihistamines (e.g., Zyrtec®), bronchodilators, LABAs (e.g., salmeterol), theophylline, IgE modulators (e.g., Xolair® and omalizumab), steroids (e.g., fluticasone).

[00188] In further or alternative embodiments, the anti-inflammatory agent is, by way of example only, a leukotriene pathway modulator such as a CysLT1 receptor antagonists (e.g., montelukast), a CysLT2 receptor antagonist, a 5-lipoxygenase inhibitor (e.g., zileuton), a 5-lipoxygenase-activating protein inhibitor (e.g., MK-0591, MK-886, DG-031 (BAY X1005), 3-[3-*tert*-butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1*H*-indol-2-yl]-2,2-dimethyl-propionic acid, 3-[3-*tert*-butylsulfanyl-1-[4-(6-ethoxy-pyridin-3-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1*H*-indol-2-yl]-2,2-dimethyl-propionic acid), a LTA4 hydrolase inhibitor, a LTC_4 synthase inhibitor, a BLT1 receptor antagonist or a BLT2 receptor antagonist.

[00189] In any of the aforementioned aspects involving the treatment of proliferative disorders, including cancer, are further embodiments comprising administering at least one additional agent, including by way of example only alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, Paclitaxel™, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues), interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

[00190] In any of the aforementioned aspects involving the therapy of an immunogical disorder requiring immunosuppression or involving the therapy of transplanted organs or tissues or cells are further embodiments comprising administering at least one additional agent, including by way of example only azathioprine, a corticosteroid, cyclophosphamide, cyclosporin, dacluzimab, mycophenolate mofetil, OKT3, rapamycin, tacrolimus, or thymoglobulin.

[00191] In any of the aforementioned aspects involving the therapy of interstitial cystitis are further embodiments comprising administering at least one additional agent selected from, e.g., dimethylsulfoxide, omalizumab, and pentosan polysulfate.

[00192] In any of the aforementioned aspects involving the therapy of disorders of bone are further embodiments comprising administering at least one additional agent such as, by way of example only, minerals, vitamins, bisphosphonates, anabolic steroids, parathyroid hormone or analogs, and cathepsin K inhibitors dronabinol.

[00193] In any of the aforementioned aspects involving the prevention or treatment of inflammation are further embodiments comprising: (a) monitoring inflammation in a mammal; (b) measuring bronchoconstriction in a mammal; (c) measuring eosinophil and/or basophil and/or dendritic cell and/or neutrophil and/or monocyte and/or lymphocyte recruitment in a mammal; (d) monitoring mucosal secretion in a mammal; (e) measuring mucosal edema in a mammal.;

[00194] In any of the aforementioned aspects the PGD_2 -dependent or PGD_2 mediated diseases or conditions include, but are not limited to, asthma, rhinitis, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung fibrosis, arthritis, allergy, inflammatory bowel disease, adult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, cancer, and endotoxic shock.

[00195] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[00196] Prostaglandin D_2 (PGD_2) is an acidic lipid derived from the metabolism of arachidonic acid by cyclooxygenases and PGD_2 synthases. PGD_2 is produced by mast cells, macrophages and Th2 lymphocytes in response to local tissue damage as well as in response allergic inflammation observed in diseases such as asthma, rhinitis, and atopic dermatitis. More specifically, exogenous PGD_2 applied to bronchial airways elicits many responses that are characteristic of acute asthma.

[00197] PGD_2 is a major mast cell product that acts via two receptors, the D-type prostanoid (DP, also known as DP_1) and the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2, also known as DP_2) receptors. DP_2 mediates the chemotaxis of eosinophils, basophils, and Th2 lymphocytes, and DP_1 receptor plays an important role in eosinophil trafficking. DP_1 antagonists do not inhibit the release of eosinophils when induced by the DP_2-selective agonists. However, eosinophils in human bone marrow specimens express DP_1 and DP_2

receptors at similar levels and human peripheral blood expresses both DP_1 and DP_2, but the DP_1 receptor is expressed at lower levels. In agreement with this, the chemotaxis of human peripheral blood eosinophils is inhibited by both DP_1 and DP_2 antagonists. Accordingly, DP_1, DP_2 and dual DP_1/DP_2 antagonists are useful in the treatment of allergic inflammation.

[00198] Activation of DP_2 is associated with chemotaxis and activation of Th2 lymphocytes, eosinophils and basophils. In particular, PGD_2 binds to DP_2 and mediates many of its effects through a G_i-dependent elevation of intracellular calcium levels and reduction of cyclic AMP. In Th2 lymphocytes, IL4, IL5 and IL13 cytokine production are also stimulated by DP_2 activation. These cytokines have been implicated in numerous biological actions including, by way of example only, immunoglobulin E production, airway response, mucous secretion, and eosinophil recruitment.

[00199] The terms CRTH2 and DP_2, refer to the same receptor and are used interchangeably herein. Likewise, another common name for DP is DP_1, and the two terms are used interchangeably herein.

Illustrative Biological Activity

[00200] Prostaglandins (PGs) are recognized physiological lipid acid mediators produced by the release of arachidonic acid from cell membrane phospholipids and converted to prostaglandins by the action of COX_1 and COX_2 cyclooxygenases and PG synthases. The cyclooxygenases sequentially convert arachidonic acid to cyclic endoperoxide prostaglandin G_2 (PGG_2) and subsequently, prostaglandin H_2 (PGH_2). Depending on the tissue, physiological signal, and/or synthase type, PGH_2 can be converted to numerous different prostaglandins, such as PGE_2, PGD_2, $PGF_2\alpha$, and PGI_2 as well as thromboxane A_2, another eicosanoid signaling molecule. These mediators then elicit a wide variety of physiological responses including vasoconstriction or dilation, platelet aggregation, calcium transport, pain sensitization, hormone release, inflammatory and immune response, and cellular growth.

[00201] Prostaglandin D_2 is a major metabolite produced from the PGH_2 intermediate via hematopoietic PGD_2 synthase or lipocalin PGD_2 synthase. In the brain and central nervous system, PGD_2 is produced and thought to function in pain perception and sleep regulation. In other tissues, PGD_2 is produced primarily in immunoglobulin E (IgE) activated mast cells and to a lesser extent, in macrophages, dendritic cells, T helper 2 (Th2) lymphocytes and other leukocytes. In the cell, PGD_2 is rapidly metabolized and converted to other downstream effectors including $\Delta^{12}PGJ_2$, $9\alpha 11\beta PGF_2$, 13,14-dihydro-15-keto-PGD_2, and 15-deoxy-$\Delta^{12,14}PGD_2$..

[00202] Mast-cell-derived PGD_2 is produced in high concentrations in response to an allergen challenge. Studies in preclinical species have observed the following features when PGD_2 is applied to *in vivo* preparations, or its overproduction is engineered by genetic manipulation:

-Vasodilatation leading to erythema (flare) and -potentiation of oedema (wheal).

-Recruitment of eosinophils and Th2 lymphocytes.

-Modulation of Th2-cytokine production.

-Bronchoconstriction.

[00203] Injection of PGD_2 into human skin has been shown to produce a long lasting erythema, to potentiate the effects of other mediators on induration and leukocyte infiltration in human skin and to enhance oedema formation in rat skin. It is most likely that these effects of PGD_2, like those of other vasodilator prostaglandins, are due to an increased blood flow to the inflamed lesion and are, therefore, most likely to be mediated predominantly by the DP_1 receptor. Although these observations make it clear that DP_1 mediates the vascular effects of PGD_2, the capacity of PGD_2 to promote the cellular changes associated with inflammation is not due to an action on DP_1.

[00204] The main receptors that are activated by PGD_2 or its metabolites and mediate its effects are DP_1, CRTH2 (or DP_2) and TP.

[00205] DP_1 (or DP) is a G-protein coupled seven-transmembrane receptor that, upon activation by PGD_2 binding, leads to an increase in intracellular cAMP levels. DP_1 is expressed in the brain, bronchial smooth muscle, vascular and airway smooth muscle, dendritic cells, and platelets and induces PGD_2 dependent bronchodilation, vasodilation, platelet aggregation inhibition, and suppression of cytokine production. Genetic analysis of DP_1 function using knock-out mice has shown that mice lacking DP do not develop asthmatic responses in an ovalbumin-induced asthma model. Analysis of selective DP anatgonists in guinea pig allergic rhinitis models demonstrated dramatic inhibition of early nasal responses, as assessed by sneezing, mucosal plasma exudation and eosinophil infiltration. DP antagonism alleviate allergen-induced plasma exudation in the conjunctiva in a guinea pig allergic conjuctivitis model and antigen-induced esinophil infiltration into the lung in a guinea pig asthma model.

[00206] Much of the pro-inflammatory activity of PGD_2 is through interaction with DP_2 (or CRTH2). DP_2 is a G-protein coupled receptor and is typically highly expressed in Th2 lymphocytes, eosinophils and basophils. DP_2 activation functions to directly activate and recruit Th2 lymphocytes and eosinophils. Activated Th2 lymphocytes produce and secrete inflammatory cytokines including IL4, IL5, and IL13. Despite binding PGD_2 with a similar affinity as DP_1, DP_2 is not structurally related to DP_1 and signals through a different mechanism- the effects of DP_2 are mediated through Gi-dependent elevation in intracellular calcium levels and reduction in intracellular levels of cyclic AMP. DP_2 activation is important in eosinophil recruitment in response to allergic challenge in such tissues as nasal mucosa, bronchial airways, and skin. The application of either PGD_2 or selective DP_2 agonists both exacerbate and enhance allergic

responses in lung and skin. DP_2 activation appears to have a crucial role in mediating allergic responses, and thus the use of antagonists of PGD_2 activation of the DP_2 receptor are an attractive approach to treat the inflammatory component of allergic diseases such as asthma, rhinitis, and dermatitis.

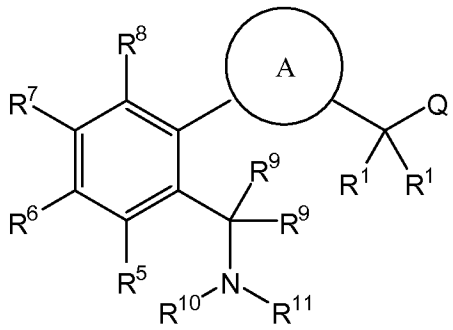
[00207] TP receptors primarily function to antagonize DP_1 receptor's effects such as promoting bronchoconstriction, vasoconstriction, and platelet aggregation. While TP receptor's main ligand is thromboxane A_2, it also binds and is activated by the PGD_2 derivative, $9\alpha 11\beta PGF_2$. TP is a Gq-coupled prostanoid receptor that binds thromboxane with high affinity, promoting platelet aggregation and constriction of both vascular and airway smooth muscle. PGD_2 activates the TP receptor in human bronchial muscle, probably through the formation of the 11-ketoreductase metabolite 9α11βPGF2. The bronchoconstrictor effects of TP dominate over the bronchodilator effects of DP_1 in the airways.

[00208] DP_1 and DP_2 have crucial, and complementary, roles in the physiological response of animals to PGD_2 and blockade of either one or both of these receptors may prove beneficial in alleviating allergic diseases or conditions triggered by PGD_2, such as, but not limited to, allergic rhinitis, asthma, dermatitis, and allergic conjunctivitis. In one aspect, blockade of DP_2 and TP activity is beneficial in alleviating allergic diseases or conditions triggered by PGD_2, such as, but not limited to, allergic rhinitis, asthma, dermatitis, and allergic conjunctivitis. In another aspect, blockade of DP_1, DP_2 and TP activity is beneficial in alleviating allergic diseases or conditions triggered by PGD_2, such as, but not limited to, allergic rhinitis, asthma, dermatitis, and allergic conjunctivitis.

Compounds

[00209] Compounds of Formula (I), Formula (II), Formula (III), Formula (IV), and Formula (V), including pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, antagonize or modulate DP_2 and are used to treat patients suffering from PGD_2-dependent or PGD_2 mediated conditions or diseases, including, but not limited to, asthma, rhinitis, dermatitis, and inflammatory conditions.

[00210] In one aspect is a compound having the structure of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable solvates, *N*-oxides, or pharmaceutically acceptable prodrugs thereof:



Formula (I)

wherein,

Q is tetrazolyl, -C(=O)-Q^1, or a carboxylic acid bioisostere;

Q^1 is –OH, –OR^B, -$NHSO_2R^{12}$, -$N(R^{13})_2$, -NH-OH, or –NH-CN; R^B is H or C_1-C_6alkyl;

ring A represents a substituted or unsubstituted heteroaryl, wherein if ring A is substituted, then each substituent on ring A is independently selected from H and R^A;

each R^1 is independently selected from H, F, C_1-C_4alkyl, and C_1-C_4fluoroalkyl;

each of R^A, R^5, R^6, R^7, and R^8 is independently selected from H, halogen, -CN, -NO_2, -OH, -OR^{12}, -SR^{12}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$N(R^{13})S(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -$NHCH_2CO_2R^{13}$, -$OCH_2CO_2R^{13}$, -$SCH_2CO_2R^{13}$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NR^{13}C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, -NR^{13}-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, -$NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, and a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl;

each R^9 is each independently selected from H, F, C_1-C_4alkyl, and C_1-C_4haloalkyl; or

both R^9 groups are taken together with the carbon atom to which they are attached to form a C_3-C_6cycloalkyl;

R^{10} is –$C(=O)R^{14}$, –$C(=O)OR^{15}$, –$C(=O)N(R^{16})_2$, –$S(=O)_2N(R^{16})_2$ or –$S(=O)_2R^{14}$;

R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_6alkylene or a substituted or unsubstituted aryl;

X^3 is a bond, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -NR^{13}S(=O)$_2$-, or –NR^{13}-;

Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted C_1-C_4alkyl-C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted C_1-C_4alkyl-aryl, or a substituted or unsubstituted C_1-C_4alkyl-heteroaryl;

R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl;

each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; or

two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl;

R^{11} is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl, -C_1-C_6alkylene-O-R^{17}, -C_1-C_6alkylene-S-R^{17}, -C_1-C_6alkylene-S(=O)-R^{17}, -C_1-C_6alkylene-S(=O)$_2$-R^{17}, -C_1-C_6alkylene-N(R^{17})$_2$, -C_1-C_6alkylene-C(=O)-R^{17}, -C_1-C_6alkylene-C(=O)O-R^{17}-, -C_1-C_6alkylene-OC(=O)-R^{17}, -C_1-C_6alkylene-NR^{17}C(=O)-R^{17} or -C_1-C_6alkylene-C(=O)N(R^{17})$_2$;

each R^{17} is independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, and a substituted or unsubstituted heteroaryl; or

two R^{17} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycloalkyl; or

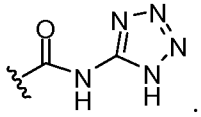
R^{10} and R^{11} are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle;

R^{12} is C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl;

each R^{13} is independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, and a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; or

two R^{13} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycloalkyl.

[00211] For any and all of the embodiments, substituents can be selected from among from a subset of the listed alternatives.

[00212] In some embodiments, Q is –C(=O)-Q^1, or tetrazolyl. In other embodiments, Q is selected from –CO_2H, -CO_2Me, -CO_2Et, -C(=O)NH_2, -C(=O)NHOH, -C(=O)NH-CN, tetrazolyl, –C(=O)-$NHSO_2R^{12}$, or  . In some other embodiments, Q is selected from –CO_2H, -CO_2Me, -CO_2Et, -C(=O)NH_2, –C(=O)-$NHSO_2CH_3$, –C(=O)-$NHSO_2CH_2CH_3$. In other embodiments, Q is –C(=O)-Q^1. In yet some other embodiments, Q is –CO_2H.

[00213] In some embodiments, Q^1 is –OH, -OR^{13}, -$NHSO_2R^{12}$, or -$N(R^{13})_2$. In some other embodiments, Q^1 is –OH, -OCH_3, -OCH_2CH_3, or -$NHSO_2CH_3$. In some other embodiments, Q^1 is –OH, -OCH_3, or -OCH_2CH_3.

[00214] In some embodiments, Q is tetrazolyl or -C(=O)-Q^1; Q^1 is –OH, -OR^B, -$NHSO_2R^{12}$, or -$N(R^{13})_2$.

[00215] In some embodiments, Q is -C(=O)-Q^1; Q^1 is –OH or –OR^B. In some embodiments, R^B is H, –CH_3 or –CH_2CH_3. In other embodiments, R^B is H.

[00216] In one aspect, each R^1 is independently selected from H, F, or C_1-C_4alkyl; or both R^1 groups are taken together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclophenyl, or cyclohexyl.

[00217] In some embodiments, each R^1 is independently selected from H, F, and $-CH_3$. In one aspect, each R^1 is H.

[00218] In some embodiments, Q is -C(=O)-Q^1; Q^1 is –OH, or $-OR^B$; R^B is H or C_1-C_6alkyl.

[00219] In some embodiments, each R^1 is independently selected from H, F, and C_1-C_4alkyl; each R^9 is each independently selected from H and $-CH_3$.

[00220] In some embodiments, ring A is a substituted or unsubstituted monocyclic heteroaryl, wherein if ring A is substituted then each substituent on ring A is independently selected from among H and R^A.

[00221] In some embodiments, each R^1 is independently selected from H and C_1-C_4alkyl.

[00222] In some embodiments, each R^9 is H.

[00223] In some embodiments, ring A is a substituted or unsubstituted 5-membered heteroaryl or a substituted or unsubstituted 6-membered heteroaryl, wherein ring A includes 0 or 1 O atoms, 0 or 1 S atoms, 0-3 N atoms, and at least 2 carbon atoms, wherein if ring A is substituted then each substituent on ring A is independently selected from among H and R^A.

[00224] In some embodiments, ring A is a substituted or unsubstituted 5-membered or 6-membered heteroaryl selected from among furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, wherein if ring A is substituted then each substitutuent on ring A is independently selected from H and R^A.

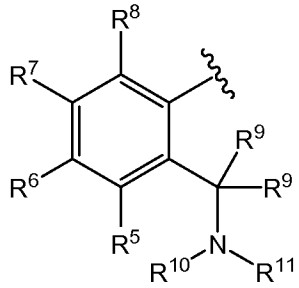
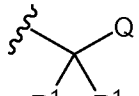
[00225] In some embodiments, ring A is a substituted or unsubstituted 5-membered heteroaryl, wherein ring A includes 0 or 1 O atoms, 0 or 1 S atoms, 1-3 N atoms, and at least 2 carbon atoms, wherein if ring A is substituted then each substituent on ring A is independently selected from among H and R^A.

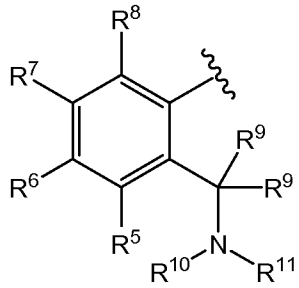
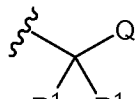
[00226] In some embodiments, ring A is a substituted or unsubstituted 5-membered heteroaryl selected from among pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, wherein if ring A is substituted then each substitutuent on ring A is independently selected from H and R^A.

[00227] In some embodiments, ring A is a substituted or unsubstituted 6-membered heteroaryl containing 1-3 N atoms in the ring, wherein if ring A is substituted then each substitutuent on ring A is independently selected from among H and R^A.

[00228] In some embodiments, ring A is a substituted or unsubstituted 6-membered heteroaryl selected from among pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, wherein if ring

A is substituted then each substitutuent on ring A is independently selected from among H and R^A.

[00229] In one aspect, the groups  and  are attached to ring A on non-adjacent atoms of ring A.

[00230] In one aspect, the groups  and  are attached to ring A on non-adjacent carbon atoms of ring A.

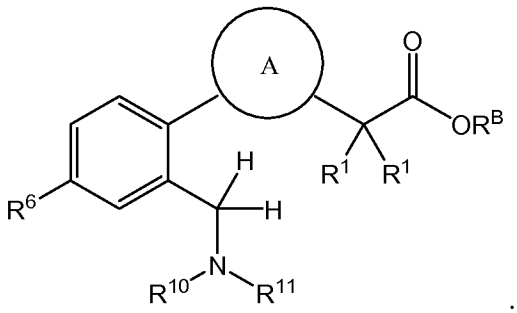
[00231] In some embodiments, each of R^5, R^6, R^7, and R^8 is independently selected from H, halogen, -CN, -NO_2, -OH, -OR^{12}, -SR^{12}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$N(R^{13})S(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -$NHCH_2CO_2R^{13}$, -$OCH_2CO_2R^{13}$, -$SCH_2CO_2R^{13}$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NR^{13}C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, -NR^{13}-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, -$NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocycloalkyl.

[00232] In some embodiments, each of R^5, R^7, and R^8 is independently selected from H, halogen, -CN, -OH, -OR^{12}, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

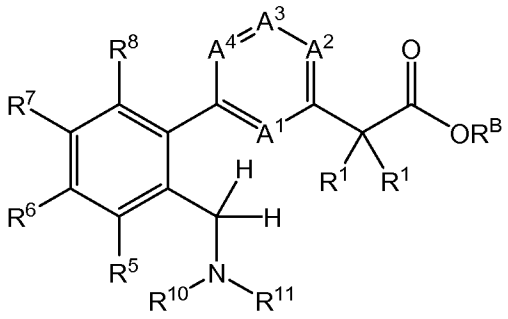
[00233] In some embodiments, each of R^5, R^7, and R^8 is independently selected from H, F, Cl, Br, I, -CN, -OH, -OCH_3, -OCH_2CH_3, -CH_3, -CH_3CH_3, -CF_3, CHF_2, CH_2F, and -OCF_3.

[00234] In some embodiments, at least one of R^5, R^7, and R^8 is H. In some embodiments, at least two of R^5, R^7, and R^8 is H. In some embodiments, each of R^5, R^7, and R^8 is H.

[00235] In one aspect, the compound of Formula (I) has the following structure:



[00236] In another aspect, the compound of Formula (I) has the structure of Formula (III):



Formula (III)

wherein

each of A^1, A^2, A^3, and A^4 is independently selected from among -N-, $-N^+(-O^-)-$ and -$C(R^A)$-, where one or two of A^1, A^2, A^3, and A^4 is -N- or $-N^+(-O^-)-$.

[00237] In some embodiments, each R^A is independently selected from H, halogen, -CN, -OH, -OR^{12}, -$S(=O)_2R^{12}$, -$C(=O)R^{12}$, -CO_2R^{13}, -$N(R^{13})_2$, -$C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

[00238] In some embodiments, each R^A is independently selected from H, halogen, -CN, -OH, -OR^{12}, -$N(R^{13})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

[00239] In some embodiments, each R^A is independently selected from H, F, Cl, Br, I, -CN, -OH, -OCH_3, -OCH_2CH_3, -CH_3, -CH_2CH_3, -CF_3, -CHF_2, -CH_2F, and -OCF_3.

[00240] In some embodiments, one of A^1, A^2, A^3, and A^4 is -N- or $-N^+(-O^-)-$. In some embodiments, two of A^1, A^2, A^3, and A^4 is -N- or $-N^+(-O^-)-$. In some embodiments, two of A^1, A^2, A^3, and A^4 is -N-.

[00241] In some embodiments, A^1 is -N- or $-N^+(-O^-)-$. In some embodiments, A^1 is N. In some embodiments, A^2 is -N- or $-N^+(-O^-)-$. In some embodiments, A^2 is N. In some embodiments, A^3 is -N- or $-N^+(-O^-)-$. In some embodiments, A^3 is N. In some embodiments, A^4 is -N- or $-N^+(-O^-)-$. In some embodiments, A^4 is N.

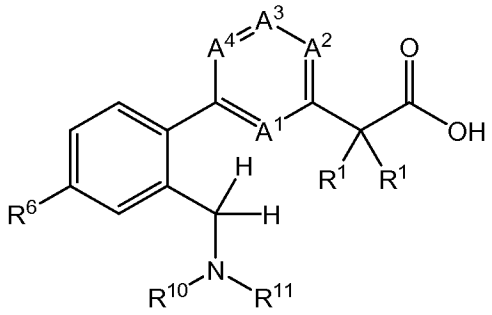
[00242] In some embodiments, A^4 is -C(H)-.

[00243] In some embodiments, A^1 is CH; A^3 is -N- or $-N^+(-O^-)-$; and each of A^2 and A^4 is -$C(R^A)$-.

[00244] In some embodiments, each R^1 is independently selected from H and $-CH_3$. In some embodiments, each R^1 is H.

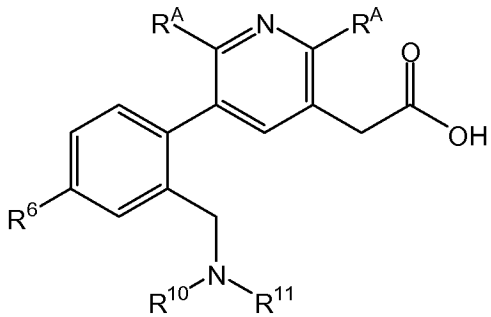
[00245] In some embodiments, R^B is H, methyl, ethyl, propyl, or butyl. In some embodiments, R^B is H.

[00246] In one aspect, the compound of Formula (I) has the structure of Formula (IV):



Formula (IV).

[00247] In one aspect, the compound of Formula (I) has the structure of Formula (V):



Formula (V), or N-oxide thereof.

[00248] In some embodiments, R^{10} is $-C(=O)-R^{20}$, where R^{20} is $-R^{14}$, $-OR^{15}$, or $-N(R^{16})_2$. In some embodiments, R^{20} is $-R^{14}$. In some embodiments, R^{20} is $-OR^{15}$. In some embodiments, R^{20} is $-N(R^{16})_2$.

[00249] In some embodiments, R^6 is selected from halogen, -CN, $-NO_2$, -OH, $-OR^{12}$, $-SR^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-N(R^{13})S(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-OCO_2R^{13}$, $-N(R^{13})_2$, $-NHCH_2CO_2R^{13}$, $-OCH_2CO_2R^{13}$, $-SCH_2CO_2R^{13}$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{12}$, $-NR^{13}-C_1$-C_4alkyl-$C(=O)R^{12}$, $-C_1$-C_4alkyl-$N(R^{13})_2$, $-C_1$-C_4alkyl-$NR^{13}C(=O)R^{12}$, $-C_1$-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, $-NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl.

[00250] In some embodiments, R^6 is selected from halogen, -CN, $-NO_2$, -OH, $-OR^{12}$, $-SR^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-N(C_1$-C_6alkyl$)S(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-OCO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NHC(=O)N(R^{13})_2$, $-N(C_1$-C_6alkyl$)C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, $-N(C_1$-C_6alkyl$)C(=O)R^{12}$, $-NHC_1$-C_4alkyl-$C(=O)R^{12}$, $-C_1$-C_4alkyl-$N(R^{13})_2$, $-C_1$-C_4alkyl-$NHC(=O)R^{12}$, $-C_1$-C_4alkyl-$NHS(=O)_2R^{12}$, $-NHC(=O)OR^{12}$, $-N(C_1$-C_6alkyl$)C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocycloalkyl.

[00251] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl, -C_1-C_6alkylene-O-R^{17}, -C_1-C_6alkylene-N(R^{17})$_2$, -C_1-C_6alkylene-C(=O)-R^{17}, -C_1-C_6alkylene-OC(=O)-R^{17}, or -C_1-C_6alkylene-C(=O)N(R^{17})$_2$.

[00252] In some embodiments, R^{10} is –C(=O)R^{14}, –C(=O)OR^{15}, or –C(=O)N(R^{16})$_2$.

[00253] In some embodiments, R^{10} is –C(=O)R^{14}, –C(=O)OR^{15}, or –C(=O)N(R^{16})$_2$; R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_6alkylene or a substituted or unsubstituted aryl; X^3 is a bond, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -NR^{13}S(=O)$_2$-,or –NR^{13}-; Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted C_1-C_4alkyl-C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted C_1-C_4alkyl-aryl, or a substituted or unsubstituted C_1-C_4alkyl-heteroaryl; R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; or two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl; R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, -C_1-C_6alkylene-O-R^{17}, -C_1-C_6alkylene-N(R^{17})$_2$, -C_1-C_6alkylene-C(=O)-R^{17}, -C_1-C_6alkylene-C(=O)O-R^{17}-, or -C_1-C_6alkylene-C(=O)N(R^{17})$_2$; each R^{17} is independently selected from H, C_1-C_6alkyl, C_1-

C_6heteroalkyl, C_1-C_6haloalkyl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocycloalkyl; or two R^{17} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycloalkyl.

[00254] In some embodiments, R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl.

[00255] In some embodiments, R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl.

[00256] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl.

[00257] In some embodiments, R^{11} is C_1-C_6alkyl, or C_1-C_6haloalkyl.

[00258] In some embodiments, R^{10} is $-C(=O)R^{14}$, $-C(=O)OR^{15}$, or $-C(=O)N(R^{16})_2$; R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; or two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl; R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl, -C_1-C_6alkylene-O-R^{17}, -C_1-C_6alkylene-N(R^{17})$_2$, -C_1-C_6alkylene-C(=O)-R^{17}, -C_1-C_6alkylene-C(=O)O-R^{17}-, or -C_1-C_6alkylene-C(=O)N(R^{17})$_2$.

[00259] In some embodiments, R^{11} is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl.

[00260] In some embodiments, R^{11} is a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl.

[00261] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl.

[00262] In some embodiments, R^{11} is C_1-C_6alkyl, or a C_1-C_6haloalkyl.

[00263] In some embodiments, R^{10} is $-C(=O)R^{14}$, $-C(=O)OR^{15}$, or $-C(=O)N(R^{16})_2$; R^{14} is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; or R^{14} is -L^3-X^3-Q^3; L^3 is a C_1-C_6alkylene or a substituted or unsubstituted aryl; X^3 is a bond, -O-, -S-, -S(=O)-, -$S(=O)_2$-, -$NR^{13}S(=O)_2$-,or $-NR^{13}$-; Q^3 is a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted C_1-C_4alkyl-C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted C_1-C_4alkyl-aryl, or a substituted or unsubstituted C_1-C_4alkyl-heteroaryl; R^{15} is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; or two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl; R^{11} is C_1-C_6alkyl, or C_1-C_6haloalkyl.

[00264] In some embodiments, R^{14} is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; R^{15} is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; each R^{16} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; R^{11} is C_1-C_6alkyl, or C_1-C_6haloalkyl.

[00265] In some embodiments, R^6 is selected from halogen, -CN, $-NO_2$, -OH, $-OR^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NHC(=O)N(R^{13})_2$, $-N(C_1$-C_6alkyl$)C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, $-N(C_1$-C_6alkyl$)C(=O)R^{12}$, -NHC_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NHC(=O)R^{12}$, -C_1-C_4alkyl-$NHS(=O)_2R^{12}$, $-NHC(=O)OR^{12}$, $-N(C_1$-C_6alkyl$)C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

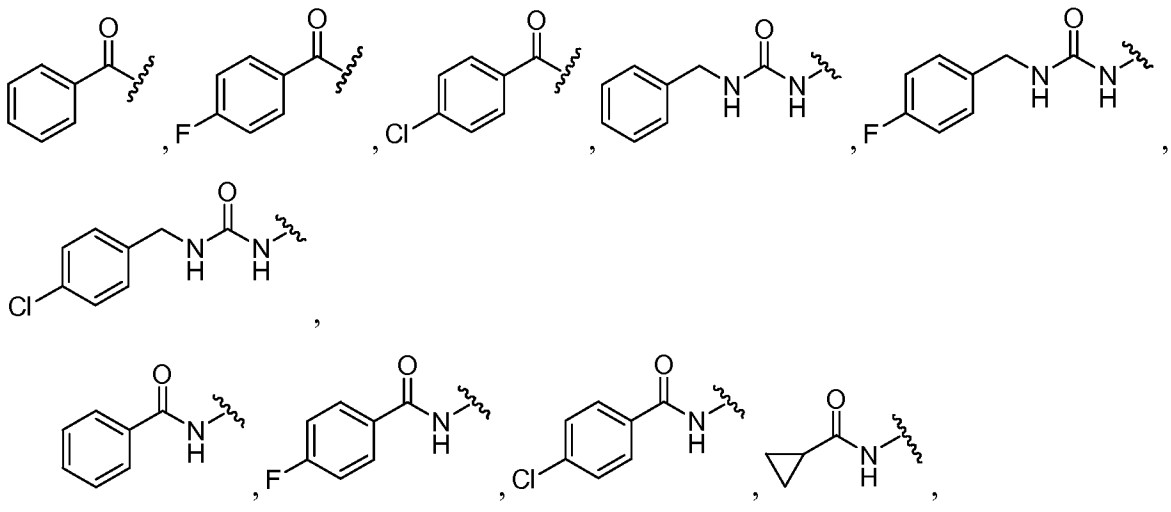
[00266] In some embodiments, R^6 is selected from $-NHS(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NHC(=O)N(R^{13})_2$, $-N(C_1$-C_6alkyl$)C(=O)N(R^{13})_2$, -

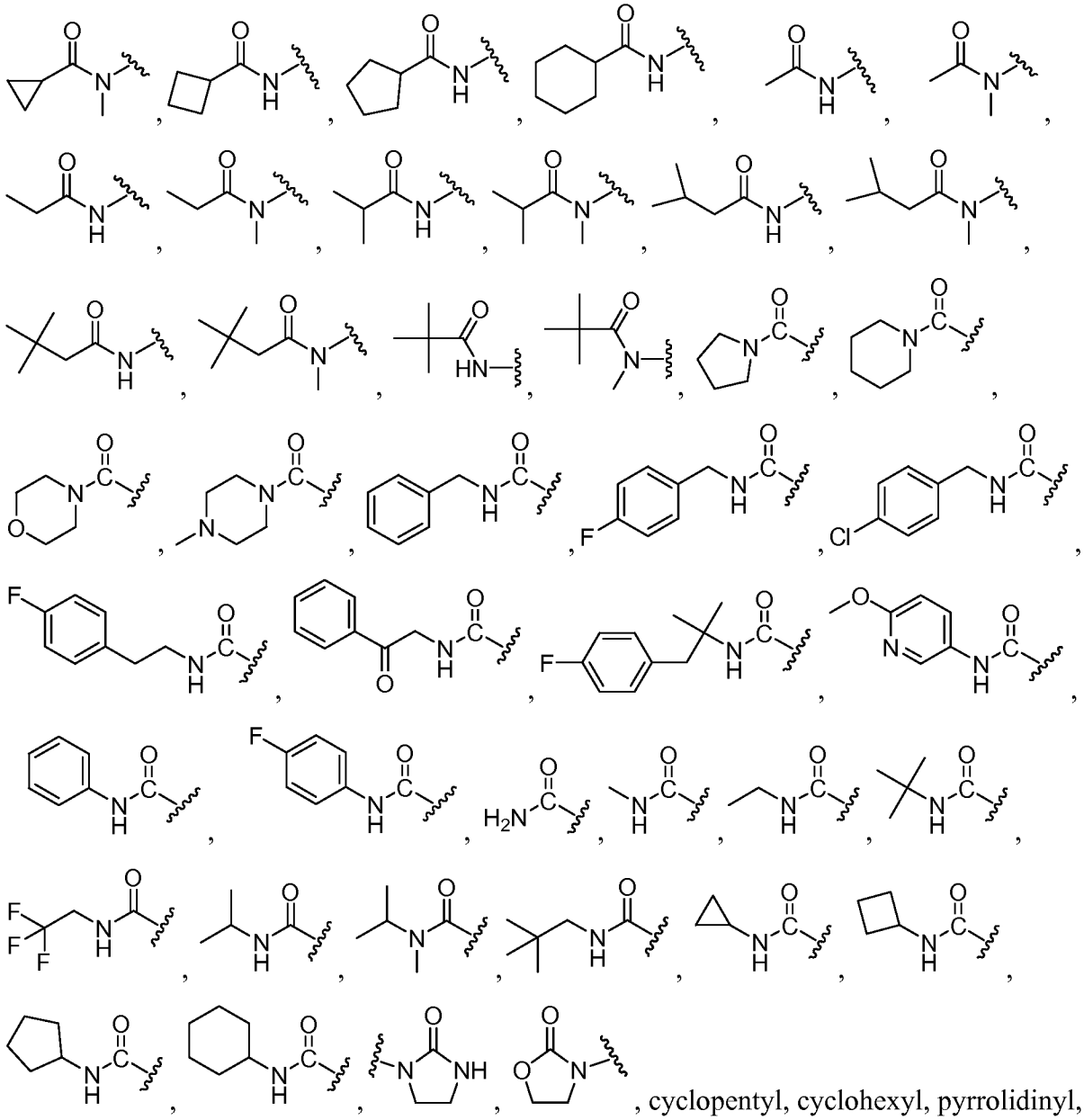
$NHC(=O)R^{12}$, $-N(C_1\text{-}C_6alkyl)C(=O)R^{12}$, $-NHC_1\text{-}C_4alkyl\text{-}C(=O)R^{12}$, $-C_1\text{-}C_4alkyl\text{-}N(R^{13})_2$, $-NHC(=O)OR^{12}$, $-N(C_1\text{-}C_6alkyl)C(=O)OR^{12}$.

[00267] In one aspect, R^6 is $-NO_2$, $-N(C_1\text{-}C_4alkyl)S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-N(R^{13})_2$, $-N(C_1\text{-}C_4alkyl)C(=O)N(R^{13})_2$, $-NHC(=O)N(R^{13})_2$, $-N(C_1\text{-}C_4alkyl)C(=O)R^{12}$, $-NHC(=O)R^{12}$, $-NH\text{-}C_1\text{-}C_4alkyl\text{-}C(=O)R^{12}$, $-N(C_1\text{-}C_4alkyl)C(=O)OR^{12}$, or $-NHC(=O)OR^{12}$.

[00268] In one aspect, R^6 is F, Cl, Br, I, -CN, $-NO_2$, -OH $-CH_3$, $-CH_2CH_3$, i-propyl, -tert-butyl, $-CF_3$, $-CH_2CF_3$, $-OCH_3$, $-OCHF_2$, $-OCF_3$, $-S(=O)_2(C_1\text{-}C_6alkyl)$, $-S(=O)_2$(substituted or unsubstituted phenyl), $-C(=O)\text{-}(C_1\text{-}C_6alkyl)$, -C(=O)-(substituted or unsusbtituted phenyl), -C(=O)-(substituted or unsusbtituted heteroaryl contianing 0-3 N atoms), -C(=O)-(substituted or unsusbtituted $C_2\text{-}C_{10}$heterocycloalkyl), $-C(=O)\text{-}$(substituted or unsusbtituted $C_3\text{-}C_6$cycloalkyl), $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-NH_2$, $-NH(R^{13})$, $-C(=O)N(C_1\text{-}C_6alkyl)_2$, $-C(=O)NH(C_1\text{-}C_6alkyl)$, $-C(=O)NH(C_1\text{-}C_6$fluoroalkyl), $-C(=O)NH(C_1\text{-}C_6$heteroalkyl), -C(=O)NH(substituted or unsubstituted phenyl), $-C(=O)N(C_1\text{-}C_6alkyl)$(substituted or unsubstituted phenyl), -C(=O)NH(substituted or unsubstituted $-C_1\text{-}C_4$alkyl-phenyl), -C(=O)NH(substituted or unsubstituted monocyclic heteroaryl), -C(=O)NH(substituted or unsubstituted $C_2\text{-}C_{10}$heterocycloalkyl), -C(=O)NH(substituted or unsubstituted $C_3\text{-}C_6$cycloalkyl), $-NHC(=O)(C_1\text{-}C_6alkyl)$, -NHC(=O)(substituted or unsubstituted phenyl), $-NH\text{-}C_1\text{-}C_4alkyl\text{-}C(=O)\text{-}$(substituted or unsubstituted phenyl), $-NHC(=O)NH_2$, -NHC(=O)NH(substituted or unsusbtituted phenyl), -NHC(=O)NH(substituted or unsusbtituted benzyl), or a substituted or unsubstituted group selected from benzyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl.

[00269] In one aspect, R^6 is Cl, Br, $-CF_3$, $-CH_3$, NO_2, $-NH_2$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-C(=O)CH_3$, $-C(=O)CH_3CH_3$, $-C(=O)CH(CH_3)_2$, $-C(=O)(CH_3)_3$, $-C(=O)CH_2(CH_3)_3$, $-C(=O)NHCH_3$, $-C(=O)NHCH_2CH_3$,





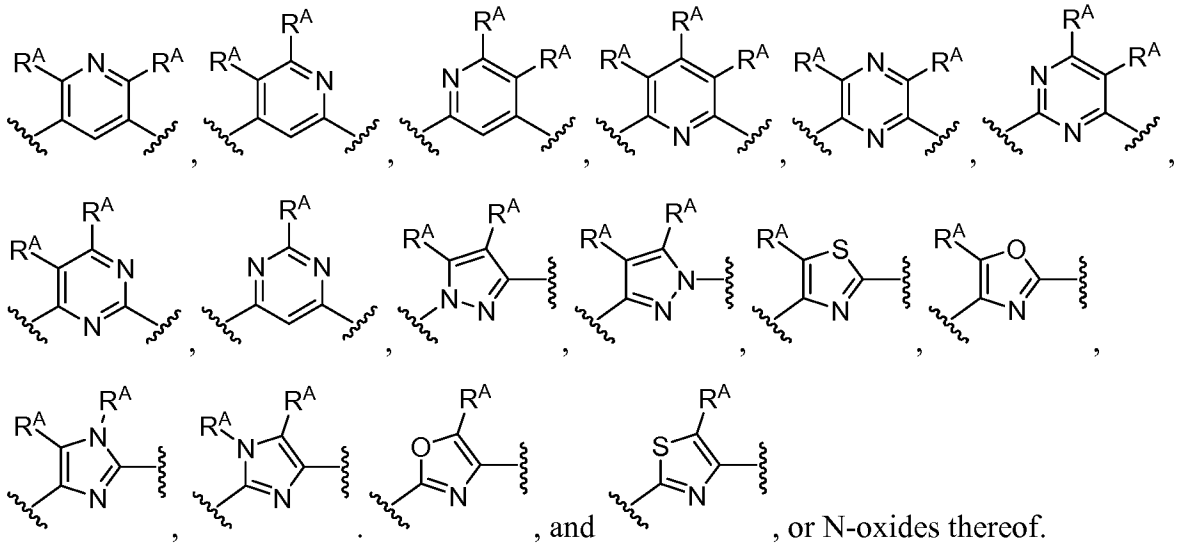
, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl.

[00270] In one aspect, R^{10} is $-C(=O)R^{14}$.

[00271] In one aspect, R^{10} is $-C(=O)OR^{15}$.

[00272] In one aspect, R^{10} is $-C(=O)N(R^{16})_2$.

[00273] In one aspect, ring A is selected from:



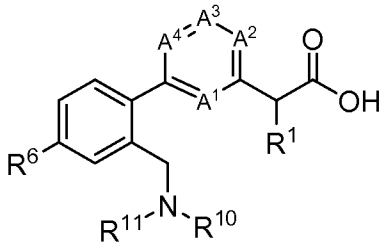
, and , or N-oxides thereof.

[00274] In one aspect, R^1 is as defined in Table 1. In one aspect, R^{11} is as defined in Table 1. In one aspect, R^{10} is as defined in Table 1. In one aspect, R^6 is as defined in Table 1. In one aspect, A^1 is as defined in Table 1. In one aspect, A^2 is as defined in Table 1. In one aspect, A^3 is as defined in Table 1. In one aspect, A^4 is as defined in Table 1.

[00275] Any combination of the groups described above for the various variables is contemplated herein.

[00276] In one aspect, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) include, but are not limited to, those described in Table 1:

Table 1:



Cpmd #	A^1	A^2	A^3	A^4	R^1	R^6	R^{11}	R^{10}	M+H*
1-1	CH	CH	N	CH	H	$-CO_2H$	$-CH_2CH_3$	$-C(=O)-OCH_2$-phenyl	449
1-2	CH	CH	N	CH	H	$-CO_2H$	$-CH_2CH_3$	-C(=O)-cyclopropyl	383
1-3	CH	CH	N	CH	H	-CN	Benzyl	-C(=O)-cyclopropyl	426
1-4	CH	CH	N	CH	H	2*H*-Tetrazol-5-yl	Benzyl	-C(=O)-cyclopropyl	469
1-5	CH	CH	N	CH	H	Benzyl-carbamoyl	Benzyl	-C(=O)-cyclopropyl	534
1-6	CH	CH	N	CH	H	Methyl-carbamoyl	Benzyl	-C(=O)-cyclopropyl	458
1-7	CH	CH	N	CH	H	*tert*-Butylcarbamoyl	Benzyl	-C(=O)-cyclopropyl	500
1-8	CH	CH	N	C	H	Pyrrolidine-1-carbonyl	Benzyl	-C(=O)-cyclopropyl	498

Cpmd #	A^1	A^2	A^3	A^4	R^1	R^6	R^{11}	R^{10}	M+H*
1-9	CH	CH	N	C	H	Acetylamino-methyl	Benzyl	-C(=O)-cyclopropyl	472
1-10	CH	CH	N	CH	H	Methane-sulfonyl-amino-methyl-	Benzyl	-C(=O)-cyclopropyl	508
1-11	CH	CH	N	CH	CH_3	-F	Benzyl	-C(=O)-OCH_2phenyl	437
1-12	CH	CH	N	CH	CH_3	-F	Benzyl	C(O)NH-Benzyl	436
1-13	CH	CH	N	CH	CH_3	-F	$-CH_2CH_3$	-C(=O)-cyclopropyl	371
1-14	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	407
1-15	CH	C(Cl)	N	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	441
1-16	CH	CH	N	$C(OCH_3)$	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	437
1-17	CH	CH	N	C(Cl)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	441
1-18	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-OCH_2phenyl	473
1-19	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	*tert*-Butoxycarbonyl	439
1-20	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	C(O)NH-Benzyl	472
1-21	CH	CH	N-O	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-OCH_2phenyl	489
1-22	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)CH_2$-(phenyl)	457
1-23	CH	CH	N	CH	H	$-CF_3$	Benzyl	-C(=O)-cyclopropyl	469
1-24	CH	CH	N	CH	H	$-CF_3$	Indan-2-yl	-C(=O)-cyclopropyl	495
1-25	CH	CH	N	CH	H	$-CF_3$	Benzyl	$-C(=O)CH_3$	443
1-26	CH	CH	N	CH	H	$-CF_3$	Phenethyl	-C(=O)-cyclopropyl	483
1-27	CH	CH	N	CH	H	$-CF_3$	Phenethyl	$-C(=O)CH_3$	457
1-28	CH	CH	N	C(Cl)	H	$-CF_3$	Benzyl	$-C(=O)CH_3$	477
1-29	CH	C(Cl)	N	CH	H	$-CF_3$	Benzyl	$-C(=O)CH_3$	477
1-30	CH	CH	N	CH	H	$-SCH_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	385
1-31	CH	CH	N	CH	H	4-*tert*-Butylsulfanyl	$-CH_2CH_3$	-C(=O)-cyclopropyl	427
1-32	CH	CH	N	CH	H	-F	$-CH_2CH_3$	-C(=O)-cyclopropyl	357
1-33	CH	CH	N	CH	H	-SH	$-CH_2CH_3$	-C(=O)-cyclopropyl	
1-34	CH	CH	CH	N	H	$-CF_3$	$-CH_2CH_3$	C(O)NH-Benzyl	472
1-35	CH	CH	CH	N	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	407
1-36	CH	CH	CH	N	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	421
1-37	CH	CH	CH	N	H	$-CF_3$	$-CH_2CH_3$	-C(=O)phenyl	443
1-38	N	CH	CH	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)O-(*tert*-butyl)	439
1-39	N	CHH	CH	CH	H	$-CF_3$	$-CH_2CH_3$	C(O)NH-Benzyl	472

Cpmd #	A^1	A^2	A^3	A^4	R^1	R^6	R^{11}	R^{10}	M+H*
1-40	N	CH	CH	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	407
1-41	N	CH	$C(CF_3)$	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclobutyl	489
1-42	N	CH	$C(CF_3)$	CH	H	$-CF_3$	$-CH_2CH_3$	C(O)NH-Benzyl	540
1-43	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)-CH_2CH_2-$(phenyl)	471
1-44	CH	CH	N	C(OH)	H	$-CF_3$	Benzyl	$-C(=O)CH_3$	459
1-45	CH	CH	N	$C(OCH_3)$	H	$-CF_3$	$-CH_2CH_3$	C(O)NH-Benzyl	502
1-46	CH	CH	N	$C(OCH_3)$	H	4-Pyrazol-1-yl	$-CH_2CH_3$	-C(=O)-cyclopropyl	435
1-47	CH	CH	N	$C(OCH_3)$	H	$-CF_3$	Benzyl	$-C(=O)CH_3$	473
1-48	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-(pyrazin-2-yl)	445
1-49	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-(2,4-dimethoxy-pyrimidin-5-yl)	505
1-50	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)CH_2-$(6-chloro-pyridin-3-yl)	492
1-51	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)CH_2-$(4,6-diethoxy-pyrimidin-2-yl)	547
1-52	CH	CH	N	CH	H	$-CF_3$	Pyridin-2-ylmethyl	-C(=O)-cyclopropyl	470
1-53	CH	CH	N	CH	H	$-CF_3$	Pyridin-2-ylmethyl	$-C(=O)CH_3$	444
1-54	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)CH_2-$(pyridin-2-yl)	458
1-55	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)CH_2OCH_3$	411
1-56	CH	C	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)-CH_2OCH_2CH_3$	425
1-57	CH	C	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)-CH_2CH_2-$(pyridin-3-yl)	472
1-58	CH	C	N	CH	H	$-CF_3$	5-Methyl-pyrazin-2-ylmethyl	-C(=O)-cyclopropyl	485
1-59	CH	C	N	CH	H	$-CF_3$	6-Trifluoromethyl-pyridin-3-ylmethyl	-C(=O)-cyclopropyl	538
1-60	CH	C	N	CH	H	$-CF_3$	5-Methyl-pyrazin-2-ylmethyl	$-C(=O)-CH_2OCH_3$	489
1-61	CH	C	N	CH	H	$-CF_3$	5-Methyl-pyrazin-2-ylmethyl	$-C(=O)CH_3$	459
1-62	CH	C	N	CH	H	$-CF_3$	6-Trifluoromethyl-pyridin-3-ylmethyl	$-C(=O)CH_3$	512
1-63	CH	C	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)CH_2-$(6-Methyl-pyridin-3-yl)	472
1-64	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_2-$	-C(=O)-	484

Cpmd #	A^1	A^2	A^3	A^4	R^1	R^6	R^{11}	R^{10}	M+H*
							pyridin-2-yl	cyclopropyl	
1-65	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_2$-pyridin-3-yl	-C(=O)-cyclopropyl	484
1-66	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_2$-pyridin-4-yl	-C(=O)-cyclopropyl	484
1-67	CH	CH	N	C(OH)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	423
1-68	CH	CH	N	C(OBn)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	513
1-69	CH	CH	N	C(OCH_2-cyclopropyl)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	477
1-70	CH	CH	N	C(OCH_2-2-methylthiazol-4-yl)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	534
1-71	CH	CH	N	C(OCH_2CF_3)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	505
1-72	CH	CH	N	C(OCH_3)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-OCH_2phenyl	503
1-73	CH	CH	N	C(OCH_3)	H	$-CF_3$	$-CH_2CH_3$	$-C(=O)CH_3$	411
1-74	CH	CH	N	C(OCH_3)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-CH_2OCH_3	441
1-75	CH	CH	N	C(OCH_3)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-OCH_2CH_3	441
1-76	CH	CH	N	C(Ph)	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	483
1-77	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	$-S(=O)_2$-(5-dimethylamino-naphthalen-1-yl)	572
1-78	CH	CH	N	CH	H	$-CF_3$	$-CH_2CH_3$	H	339
1-79	N	CH	CH	N	H	$-CF_3$	$-CH_2CH_3$	-C(=O)-cyclopropyl	

* mass spectrometric data

[00277] Compounds in Table 1 are named:

3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-carboxymethyl-pyridin-3-yl)-benzoic acid (Compound 1-1);

4-(5-Carboxymethyl-pyridin-3-yl)-3-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-benzoic acid (Compound 1-2);

(5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-cyano-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-3);

{5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(2*H*-tetrazol-5-yl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-4);

(5-{4-Benzylcarbamoyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-5);

(5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-methylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-6);

(5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-*tert*-butylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-7);

{5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-8);

(5-{4-(Acetylamino-methyl)-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-9);

{5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(methanesulfonylamino-methyl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-10);

2-(5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid (Compound 1-11);

2-{5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-fluoro-phenyl]-pyridin-3-yl}-propionic acid (Compound 1-12);

2-(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid (Compound 1-13);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-14);

(2-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-15);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-16);

(6-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-17);

(5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-18);

(5-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-19);

{5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-20);

(5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-1-oxy-pyridin-3-yl)-acetic acid (Compound 1-21);

(5-{2-[(*N*-Ethyl-*N*-phenylacetyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-22);

(5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-23);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-indan-2-yl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-24);

(5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-25);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-phenethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-26);

(5-{2-[(*N*-Acetyl-*N*-phenethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-27);

(5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-chloro-pyridin-3-yl)-acetic acid (Compound 1-28);

(5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-2-chloro-pyridin-3-yl)-acetic acid (Compound 1-29);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-methylsulfanyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-30);

(5-{4-*tert*-Butylsulfanyl-2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-31);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-32);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-mercapto-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-33);

{2-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-4-yl}-acetic acid (Compound 1-34);

(2-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-35);

(2-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-36);

(2-{2-[(*N*-Benzoyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-37);

(6-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid (Compound 1-38);

{6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-2-yl}-acetic acid (Compound 1-39);

(6-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid (Compound 1-40);

(6-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-4-trifluoromethyl-pyridin-2-yl)-acetic acid (Compound 1-41);

{6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-pyridin-2-yl}-acetic acid (Compound 1-42);

[5-(2-{[*N*-Ethyl-*N*-(3-phenyl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-43);

(5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid (Compound 1-44);

{5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-6-methoxy-pyridin-3-yl}-acetic acid (Compound 1-45);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-pyrazol-1-yl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-46);

(5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-47);

[5-(2-{[*N*-Ethyl-*N*-(pyrazine-2-carbonyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-48);

[5-(2-{[*N*-(2,4-Dimethoxy-pyrimidine-5-carbonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-49);

{5-[2-({*N*-[2-(6-Chloro-pyridin-3-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-50);

{5-[2-({*N*-[2-(4,6-Diethoxy-pyrimidin-2-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-51);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-52);

(5-{2-[(*N*-Acetyl- *N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-53);

[5-(2-{[*N*-Ethyl-*N*-(2-pyridin-2-yl-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-54);

[5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-55);

[5-(2-{[*N*-(2-Ethoxy-acetyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-56);

[5-(2-{[*N*-Ethyl-*N*-(3-pyridin-3-yl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-57);

[5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-58);

[5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-59);

[5-(2-{[*N*-(2-Methoxy-acetyl)-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-60);

[5-(2-{[*N*-Acetyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-61);

[5-(2-{[*N*-Acetyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-62);

{5-[2-({*N*-Ethyl-*N*-[2-(6-methyl-pyridin-3-yl)-acetyl]-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-63);

[5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-2-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-64);

[5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-3-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-65);

[5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-4-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-66);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid (Compound 1-67);

(6-Benzyloxy-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-68);

(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-cyclopropylmethoxy-pyridin-3-yl)-acetic acid (Compound 1-69);

[5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2-methyl-thiazol-4-ylmethoxy)-pyridin-3-yl]-acetic acid (Compound 1-70);

[5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-acetic acid (Compound 1-71);

(5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-72);

(5-{2-[(*N*-Acetyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-73);

[5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid (Compound 1-74);

(5-{2-[*N*-(Ethoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-75);

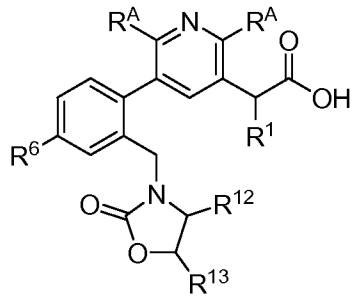
(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-phenyl-pyridin-3-yl)-acetic acid (Compound 1-76);

[5-(2-{[*N*-(5-Dimethylamino-naphthalene-1-sulfonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-77);

[5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-78); and

(2-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrimidin-4-yl)-acetic acid (Compound 1-79).

Table 2:



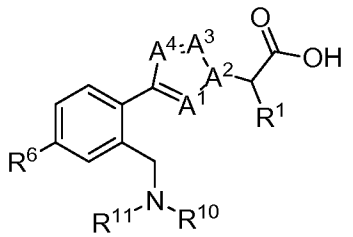
Cpmd #	R^1	R^A	R^3	R^4	R^6	R^{12}	R^{13}	M+H*
2-1	H	H	H	H	CF_3	CH_3	Phenyl	471

* mass spectrometric data

[00278] Compounds in Table 2 are named:

{5-[2-((4S,5R)-4-Methyl-2-oxo-5-phenyl-oxazolidin-3-ylmethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 2-1).

Table 3:



Cpmd #	A^1	A^2	A^3	A^4	R^1	R^6	R^{11}	R^{10}	M+H*
3-1	CH	N	N	CH	H	CF_3	CH_2CH_3	-C(=O)-cyclopropyl	395
3-2	$C(CH_3)$	N	N	$C(CH_3)$	H	CF_3	CH_2CH_3	-C(=O)-cyclopropyl	
3-3	$C(CH_3)$	N	N	$C(CH_3)$	H	CF_3	Benzyl	-C(=O)-cyclopropyl	

* mass spectrometric data

[00279] Compounds in Table 3 are named:

(4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrazol-1-yl)-acetic acid (Compound 3-1); (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid (Compound 3-2); and (4-{2-[(*N*-

Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid (Compound 3-3).

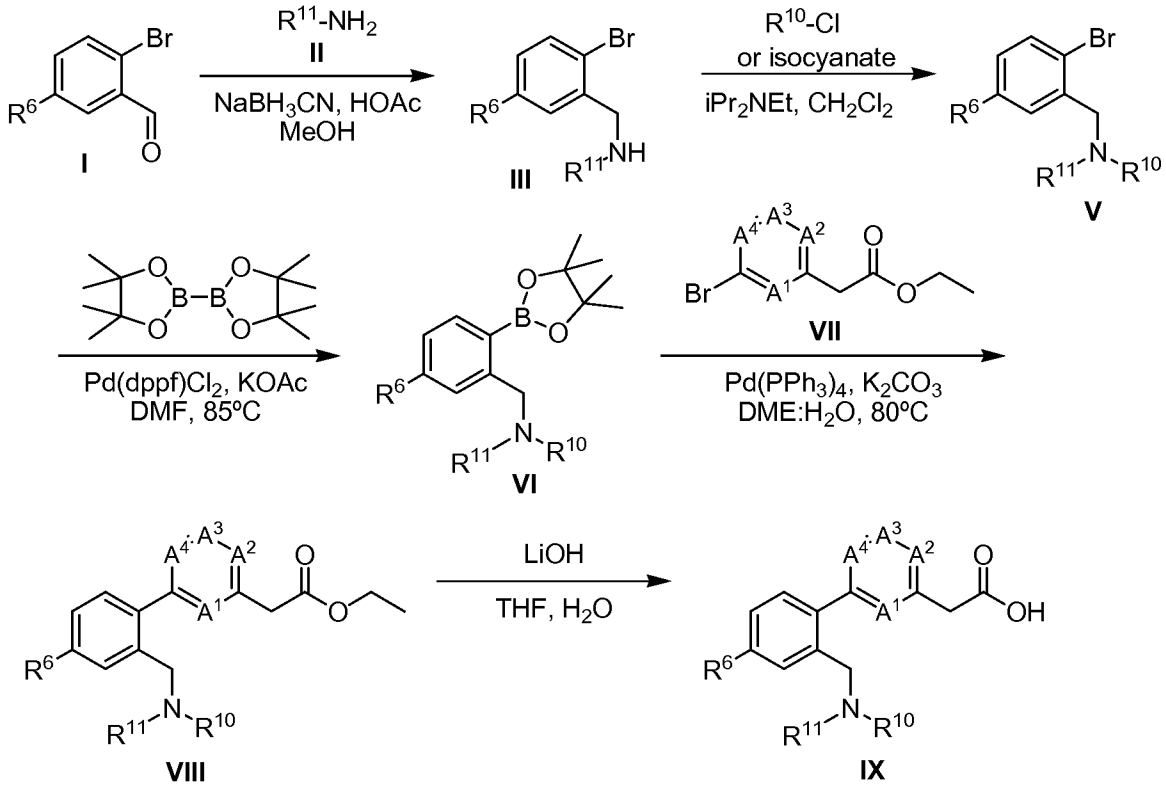
Synthesis of Compounds

[00280] Compounds of Formula (I) described in the prior section are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein. In additions, solvents, temperatures and other reaction conditions presented herein may vary.

[00281] The starting material used for the synthesis of the compounds of Formula (I) described in the prior section are either synthesized or obtained from commercial sources, such as, but not limited to, Aldrich Chemical Co. (Milwaukee, Wis.), or Sigma Chemical Co. (St. Louis, Mo.). The compounds described herein, and other related compounds having different substituents are synthesized using known techniques and materials, including those found in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999). General methods for the preparation of compounds can be modified by the use of appropriate reagents and conditions for the introduction of the various moieties found in the formulae as provided herein.

[00282] In one aspect, compounds described herein are prepared according to Scheme 1 (where A^1, A^2, A^3, A^4, R^B, R^6, R^{10}, R^{11} and R^{13} are as described herein).

Scheme 1:



[00283] In one aspect, 2-halo-benzaldehydes, such as 2-bromobenzaldehydes of structure **I** are reacted with amines of structure **II** under reductive amination conditions to provide secondary amines of structure **III**. Secondary amines of structure **III** are then reacted with acid chlorides, chloroformates, isocyantes, sulfonylchlorides and the like, to provide 2-bromobenzylamines of structure **V**. In some embodiments, amines of structure **III** are reacted with, but not limited to, a carboxylic acid and coupling reagent such as EDC, DCC, BOP, HATU or the like, or a carboxylic acid activated ester or an acid halide, alkylchloroformates, arylchloroformates, benzylchloroformates, alkylisocyanates, benzylisocyanates, arylisocyanates, alkylsulfonyl chlorides, arylsulfonyl chlorides, heteroarylsulfonyl chlorides, or the like in dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like in the presence of a hindered base such as triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine or the like, to afford compounds of structure **V**.

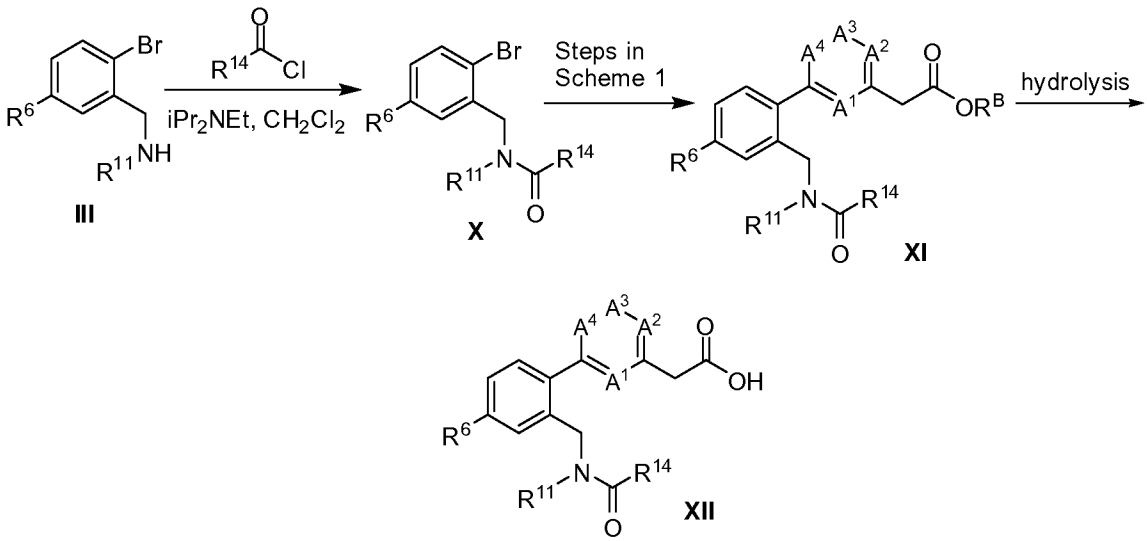
[00284] 2-Bromobenzylamines of structure **V** are converted to boronic esters of structure **VI** via metal-mediated reactions with boranes. Other methods of borylation are known, including but not limited to the Miyaura borylation reaction and other magnesium, lithium, copper, irridium and palladium mediated reactions of triflates or halides with boranes (T. Ishiyama, et al., *J. Org. Chem.*, 1995, 60, 7508-7510; X.-J. Wang, et al., *Org. Lett.*, 2006, 8, 305-307; M. Murata, et al., *Synlett*, 2006, 1867-1870; W. Zhu, D. Ma, *Org. Lett.*, 2006, 8, 261-263).

[00285] Boronic esters of structure **VI** are coupled to halogen containing heteroaryl compounds of structure **VII** under palladium mediated coupling conditions to provide esters of structure **VIII**. Other metal mediated coupling reactions to form phenyl-heteroaryl compounds of structure **VIII** include, but are not limited to Suzuki reactions, Stille cross couplings, Negishi couplings, Kumada couplings, Ullmann reactions, Hiyama Coupling, and variants thereof (Metal-Catalyzed Cross-Coupling Reactions, Armin de Meijere (Editor), François Diederich (Editor), John Wiley & Sons; 2nd edition, 2004; Özdemir, *et al.*, *Tetrahedron*, 2005, 61, 9791-9798; Ackermann, *et al., Org. Lett.*, 2006, 8, 3457-3460; Blakey, *et al., J. Am. Chem. Soc.*, 2003, 125, 6046-6047; Dai, *et al., Org. Lett.*, 2004, 6, 221-224; Yoshikai, *et al, J. Am. Chem. Soc.*, 2005, 127, 17978-17979; Tang, *et al, J. Org. Chem.*, 2006, 71, 2167-2169; Murata, *et al., Synthesis*, 2001, 2231-2233).

[00286] The ester group of amides of structure **VIII** is then hydrolyzed to form carboxylic acid compounds of structure **IX**.

[00287] In one aspect, amides of structure **XII** are prepared as outlined in Scheme 2.

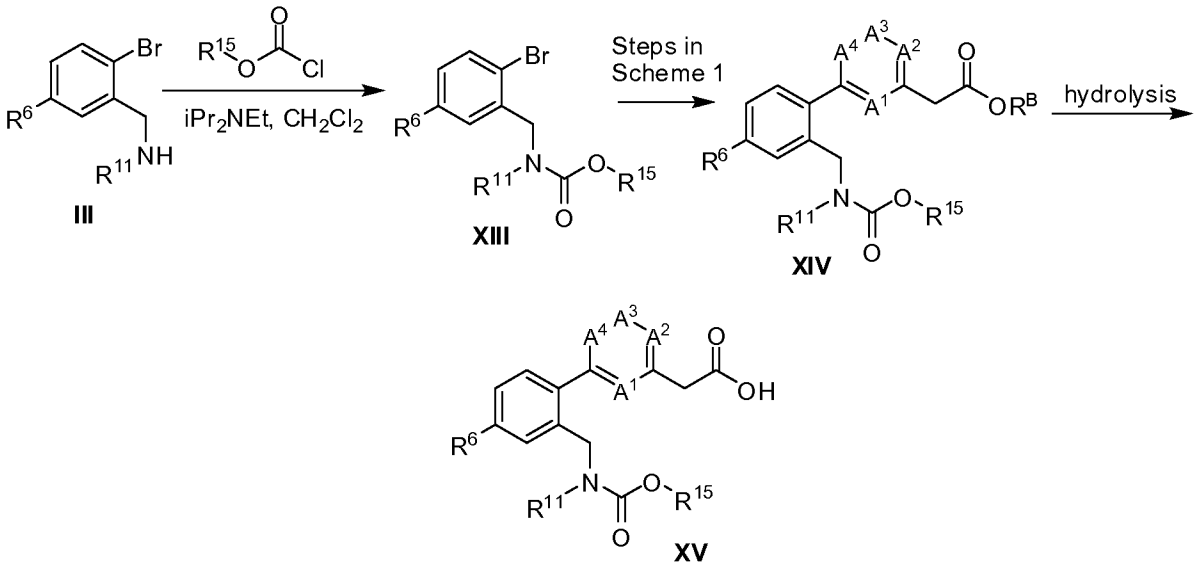
Scheme 2.



[00288] In one aspect, benzylamines of structure **III** are reacted with acid clorides to provide amides of structure **X**. Amides of structure **X** are used in the synthesis of compounds of Formula (I) as oultined in Scheme 1.

[00289] Carbamates of structure **XV** are prepared as outlined in Scheme 3:

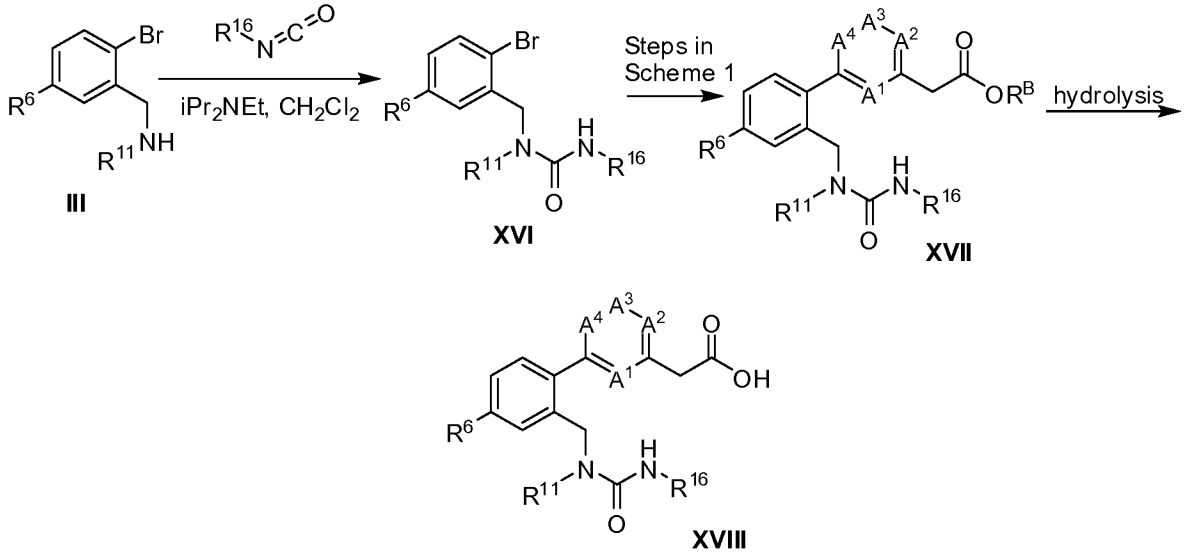
Scheme 3.



[00290] Reaction of benzylamines of structure **III** with chloroformates provides carbamates of structure **XIII**, which are used in the synthesis of compounds of Formula (I) as outlined in Scheme 1. Methods for the preparation of carbamates are known, such as described herein or in reference texts such as, but not limited to, Greene, T.W. and Wuts, P.G.M "Protective Groups in Organic Synthesis", 3rd Edition, p.549, New York:Wiley, 1999. In one aspect, benzylamines (compounds of structure **V**) are treated with phosgene or a phosgene equivalent, such as, for example, trichloromethyl chloroformate or carbonyldiimidazole, to yield an intemediate, which is then treated with a hydroxy containing compound R^{15}-OH to provide carbamates of structure **XIII**.

[00291] In one aspect, ureas of structure **XVIII** are prepared as depicted in Scheme 4:

Scheme 4.

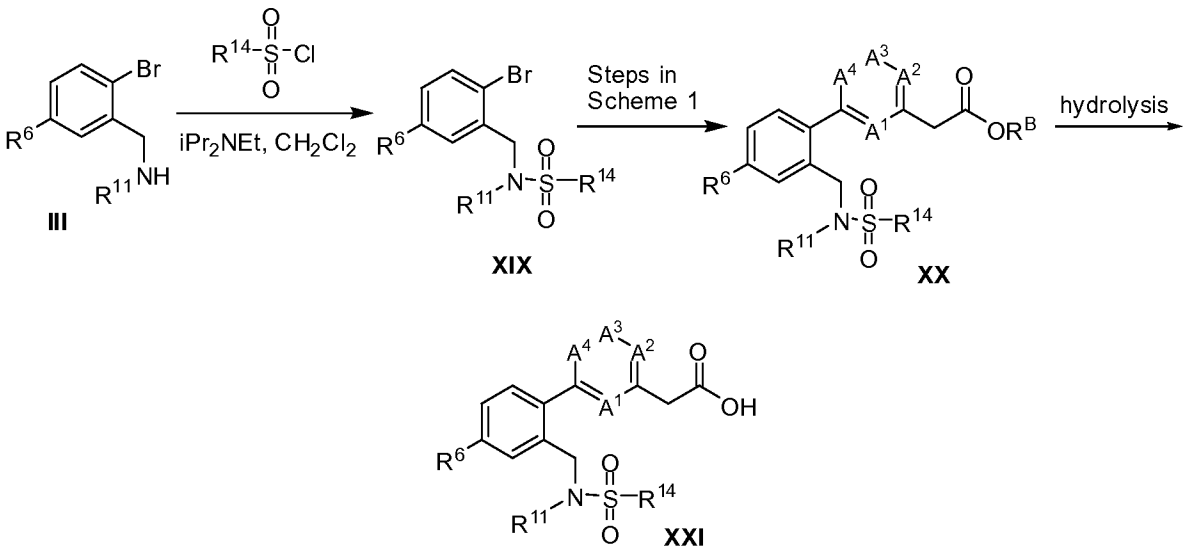


[00292] Reaction of benzylamines of structure **III** with isocyanates provides ureas of structure **XVI**. Ureas of structure **XVI** are used in the synthesis of compounds of Formula (I) as outlined in Scheme 1.

[00293] Common methods for the synthesis of isocyanates include the Curtius rearrangement of acyl azides and the Lossen rearrangement of hydroxamic acids. The synthesis of ureas include the following procedures: C. Han, J. A. Porco, Jr, *Org. Lett.*, 2007, 9, 1517-1520; H. Lebel, O. Leogane, *Org. Lett.*, 2006, 8, 5717-5720; M. B. Bertrand, J. P. Wolfe, *Tetrahedron*, 2005, 61, 6447-6459; M. McLaughlin, M. Palucki, I. W. Davies, *Org. Lett.*, 2006, 8, 3311-3314; J. A. Fritz, et al., *Org. Lett.*, 2006, 8, 2531-2534; L. Marinescu, et al., *J. Org. Chem.*, 2003, 68, 9453-9455; S.-H. Lee, et al., *Tetrahedron*, 2004, 60, 3439-3443.

[00294] In one aspect, sulfonamides of structure **XXI** are prepared as depicted in Scheme 5:

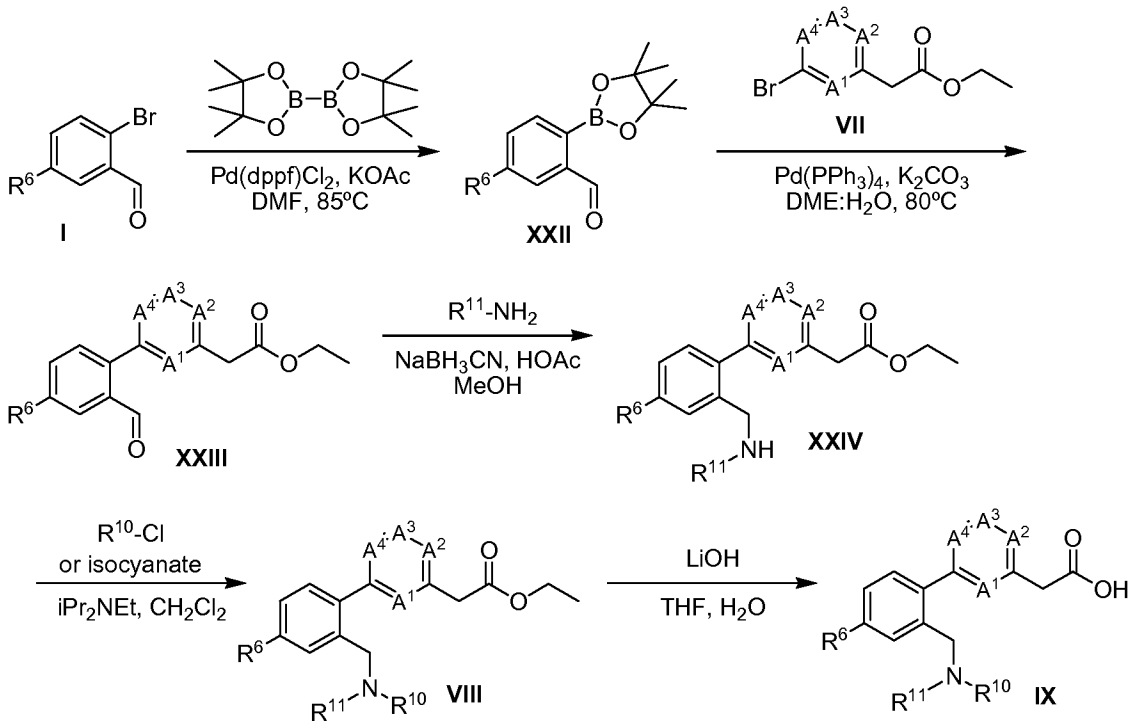
Scheme 5.



[00295] Reaction of benzylamines of structure **III** with sulfonyl chlorides provides sulfonamides of structure **XIX**. Sulfonamides of structure **XIX** are used in the synthesis of compounds of Formula (I) as outlined in Scheme 1.

[00296] In another aspect, compounds of Formula (I) are synthesized as outlined in Scheme 6.

Scheme 6:



[00297] In one aspect, 2-bromobenzaldehydes of structure **I** are converted to boronic esters of structure **XXII** via palladium metal-mediated reactions with boranes. Boronic esters of structure **XXII** are coupled with halogen containing heteroaryl compounds of structure **VII** under palladium mediated coupling conditions to provide phenyl-heteroaryl compounds of structure **XXIII**. Other metal mediated coupling reactions to form phenyl-heteroaryl compounds are known in the art. The aldehyde group of the phenyl-heteroaryl compounds of structure **XXIII** are reacted with amines (i.e. R^{11}-NH_2) under reductive amination conditions to provide secondary amines of structure **XXIV**. Secondary amines of structure **XXIV** are then reacted with a variety of acid chlorides, chloroformates, isocyantes, sulfonyl chlorides and the like, to provide compounds of structure **VIII**. Compounds of structure **VIII** are then treated with base to provide the free acid compounds of structure **IX**.

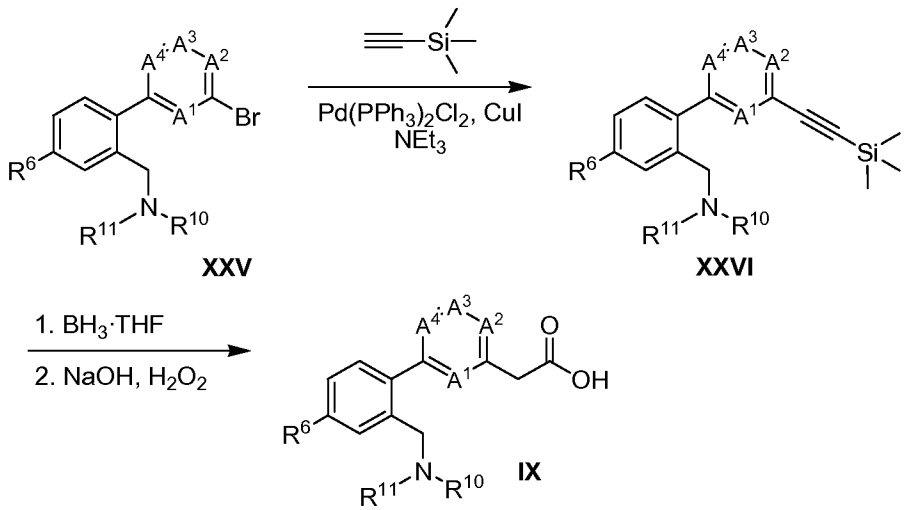
[00298] In cases where R^6 is a halide or other leaving group, metal mediated coupling reactions may be used to introduce other groups at R^6. Metal mediated coupling reactions include, but are not limited to Suzuki reactions, Stille cross couplings, Negishi couplings, Kumada couplings, Ullmann reactions, Hiyama Coupling, and variants thereof (Metal-Catalyzed Cross-Coupling Reactions, Armin de Meijere (Editor), François Diederich (Editor), John Wiley & Sons; 2nd edition, 2004; Özdemir, *et al.*, *Tetrahedron*, 2005, 61, 9791-9798; Ackermann, *et al., Org. Lett.*,

2006, 8, 3457-3460; Blakey, *et al., J. Am. Chem. Soc.*, 2003, 125, 6046-6047; Dai, *et al., Org. Lett.*, 2004, 6, 221-224; Yoshikai, *et al, J. Am. Chem. Soc.*, 2005, 127, 17978-17979; Tang, *et al, J. Org. Chem.*, 2006, 71, 2167-2169; Murata, *et al., Synthesis*, 2001, 2231-2233).

[00299] In one aspect, R^6 in any of Schemes 1 to 8 is a nitro group ($-NO_2$). Reduction of the nitro group provides the amine (i.e. R^6 is $-NH_2$). Typical reaction conditions for the reduction of nitro groups include treatment of the the nitro compound with iron trichloride in the presence of hydrazine. Other reaction conditions exist for the reduction of nitrobenzenes to anilines such as, but not limited to, catalytic hydrogenation using palladium-on-carbon (Bavin, P. M. G. (1973). Org. Synth.; Coll. Vol. 5: 30), platinum oxide, or Raney nickel (Allen, C. F. H.; VanAllan, J. (1955)). Org. Synth.; Coll. Vol. 3: 63), iron in acidic media (Fox, B. A.; Threlfall, T. L. (1973). Org. Synth.; Coll. Vol. 5: 346), sodium hydrosulfite (Redemann, C. T.; Redemann, C. E. (1955). Org. Synth.; Coll. Vol. 3: 69), sodium sulfide (or hydrogen sulfide and base), tin(II) chloride, titanium(III) chloride, and zinc. In one embodiment, when R^6 is $-NH_2$, such compounds are: (1) reacted with acyl halides to provide amides (i.e. R^6 is $-NHC(=O)R^{12}$); (2) reacted with chloroformates to provide carbamates (i.e. R^6 is $-NHC(=O)OR^{12}$); (3) reacted with isocyanates to provide ureas (i.e. R^6 is $-NHC(=O)N(R^{13})_2$; (4) reacted with sulfonyl chlorides to provide sulfonamides (i.e. R^6 is $-SO_2R^{12}$); or reacted with a variety of other electrophiles to provide derivatized amino groups.

[00300] In one aspect, the acetic acid moiety of compounds of Formula (I) are introduced using the chemistry outlined in Scheme 7.

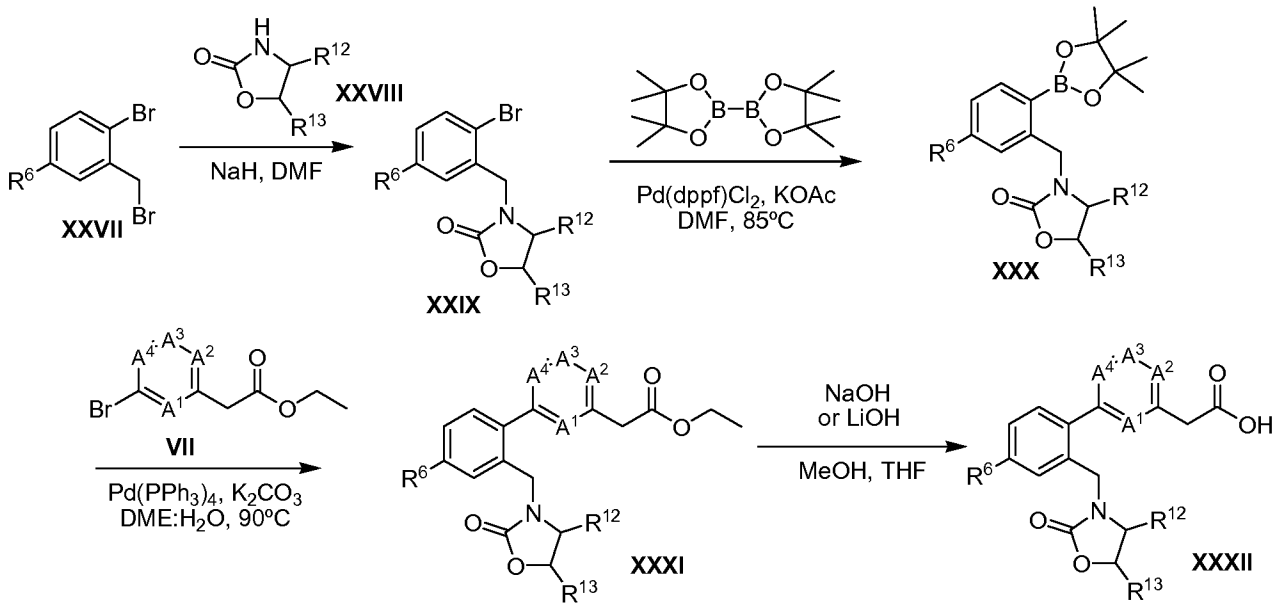
Scheme 7:



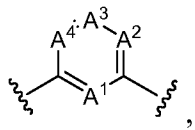
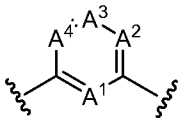
[00301] Phenyl-heteroaryl compounds of structure **XXV** that contain a halide are coupled with trimethylsilylacetylene in the presence of a palladium catalyst and a copper co-catalyst to provide acetylene compounds of structure **XXVI**. Hydroboration of acetylene compounds of structure **XXVI** is followed by treatment with sodium hydroxide and hydrogen peroxide to provide the compounds of Formula (I).

[00302] In certain embodiments, compounds described herein are prepared according to Scheme 8.

Scheme 8.



[00303] In one aspect, benzyl halides of structure **XXVII** are reacted with heterocycles of structure **XXVIII** to form benzyl heterocycles of structure **XXIX**. Boronate compounds of structure **XXX** are reacted with bromo heterocycles of structure **VII** under palladium mediated coupling conditions to form phenyl-heteroaryl compounds of structure **XXXI**. The ester group of the phenyl-heteroaryl compounds of structure **XXXI** is then hydrolyzed to form carboxylic acid compounds of structure **XXXII**. Each R13 in Scheme 8 is independently defined as described herein.

[00304] The preceding Schemes have exemplified the synthesis of compounds of Formula (I) where the ring A of the compounds of Formula (I) is represented by the structure  , where each of A^1, A^2, A^3 and A^4 are independently selected from N, N(-O) and C(R^A). It will be understood that the preceding Schemes are applicable to cases where ring A is as defined herein. In one case,  is replaced by a 5-membered heteroaryl ring.

[00305] In one aspect, compounds of Formula (I) are synthesized as outlined in the Examples.

Formation of Covalent Linkages by Reaction of an Electrophile with a Nucleophile

[00306] In certain embodiments, the compounds described herein are modified using various electrophiles or nucleophiles to form new functional groups or substituents. Table 4 entitled "Examples of Covalent Linkages and Precursors Thereof" lists selected, non-limiting examples

of covalent linkages and precursor functional groups that are used to prepare the modified compounds. Precursor functional groups are shown as electrophilic groups and nucleophilic groups.

Table 4: Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	amines/anilines
Carboxamides	acyl azides	amines/anilines
Carboxamides	acyl halides	amines/anilines
Esters	acyl halides	alcohols/phenols
Esters	acyl nitriles	alcohols/phenols
Carboxamides	acyl nitriles	amines/anilines
Imines	Aldehydes	amines/anilines
Hydrazones	aldehydes or ketones	Hydrazines
Oximes	aldehydes or ketones	Hydroxylamines
Alkyl amines	alkyl halides	amines/anilines
Esters	alkyl halides	carboxylic acids
Thioethers	alkyl halides	Thiols
Ethers	alkyl halides	alcohols/phenols
Thioethers	alkyl sulfonates	Thiols
Esters	alkyl sulfonates	carboxylic acids
Ethers	alkyl sulfonates	alcohols/phenols
Esters	Anhydrides	alcohols/phenols
Carboxamides	Anhydrides	amines/anilines
Thiophenols	aryl halides	Thiols
Aryl amines	aryl halides	Amines
Thioethers	Azindines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	carboxylic acids	amines/anilines
Esters	carboxylic acids	Alcohols
hydrazines	Hydrazides	carboxylic acids
N-acylureas or Anhydrides	carbodiimides	carboxylic acids
Esters	diazoalkanes	carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	haloacetamides	Thiols
Ammotriazines	halotriazines	amines/anilines
Triazinyl ethers	halotriazines	alcohols/phenols
Amidines	imido esters	amines/anilines
Ureas	Isocyanates	amines/anilines
Urethanes	Isocyanates	alcohols/phenols
Thioureas	isothiocyanates	amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	phosphoramidites	Alcohols
Silyl ethers	silyl halides	Alcohols
Alkyl amines	sulfonate esters	amines/anilines
Thioethers	sulfonate esters	Thiols
Esters	sulfonate esters	carboxylic acids
Ethers	sulfonate esters	Alcohols
Sulfonamides	sulfonyl halides	amines/anilines
Sulfonate esters	sulfonyl halides	phenols/alcohols

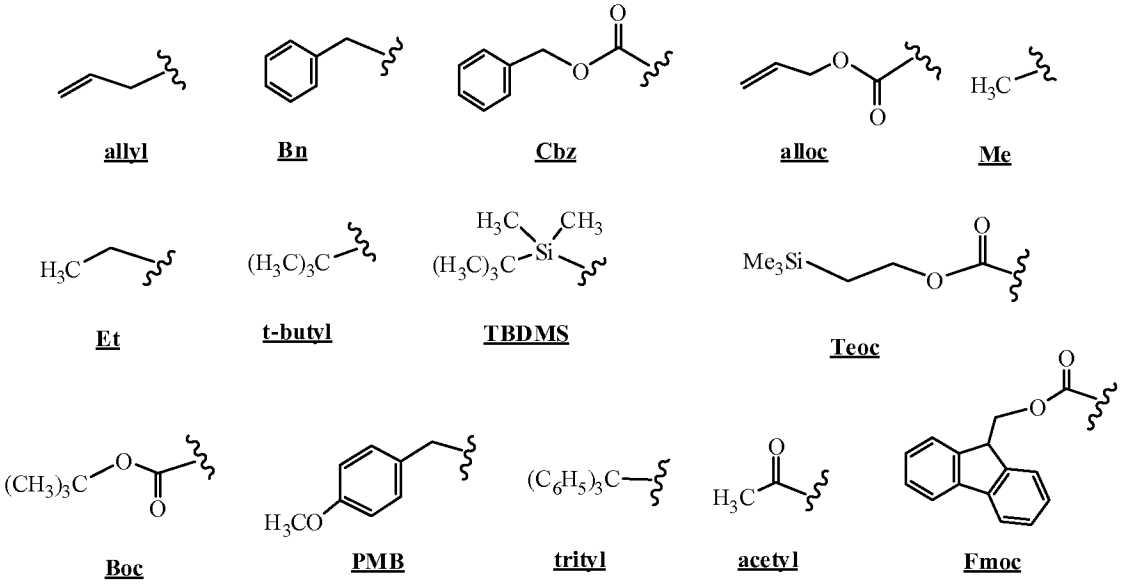
Use of Protecting Groups

[00307] In the reactions described, it is necessary in certain embodiments to protect reactive functional groups, for example hydroxy, amino, thiol or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Protecting groups are used to block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. In one embodiment, each protective group is removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. In some embodiments, protective groups are removed by acid, base, and/or hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and are used in certain embodiments to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and/or Fmoc groups, which are base labile. In other embodiments, carboxylic acid and hydroxy reactive moieties are blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

[00308] In another embodiment, carboxylic acid and hydroxy reactive moieties are blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids are blocked with base labile groups such as Fmoc. In another embodiment, carboxylic acid reactive moieties are protected by conversion to simple ester compounds as exemplified herein, or they are, in yet another embodiment, blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups are blocked with fluoride labile silyl carbamates.

[00309] Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd(0)-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate is attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

[00310] Typically blocking/protecting groups are, by way of example only:



[00311] Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure.

Further Forms of Compounds

[00312] In certain embodiments, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are prepared as a pharmaceutically acceptable acid addition salt (which is a type of a pharmaceutically acceptable salt) by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[00313] By "pharmaceutically acceptable," as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material may be administered to an individual without causing

undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00314] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutically acceptable salts are also obtained by reacting a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[00315] In other embodiments, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are prepared as a pharmaceutically acceptable salts by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base, including, but not limited to organic bases such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like, or with an inorganic base such as aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[00316] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are optionally formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, ethanol, or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms

are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[00317] In yet other embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are prepared in various forms, including but not limited to, amorphous forms, milled forms and nano-particulate forms. In addition, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) include crystalline forms, also known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[00318] In some embodiments, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[00319] Prodrugs are generally drug precursors that, following administration to a subject and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by a metabolic pathway. Some prodrugs have a chemical group present on the prodrug that renders it less active and/or confers solubility or some other property to the drug. Once the chemical group has been cleaved and/or modified from the prodrug the active drug is generated. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. In certain embodiments, the prodrug of a compound described herein is bioavailable by oral administration whereas the parent is not. Furthermore, in some embodiments, the prodrug of a compound described herein has improved solubility in pharmaceutical compositions over the parent drug.

[00320] In other embodiments, prodrugs are designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. In specific embodiments, the design

of prodrugs to date is to increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent. Fedorak *et al.*, *Am. J. Physiol.*, 269:G210-218 (1995); McLoed *et al.*, *Gastroenterol*, 106:405-413 (1994); Hochhaus *et al.*, *Biomed. Chrom.,* 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics,* 37, 87 (1987); J. Larsen *et al., Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula *et al.*, *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Prodrugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987.

[00321] Additionally, prodrug derivatives of compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are prepared, if desired (e.g., for further details see Saulnier *et al.*, (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). By way of example only, in one aspect appropriate prodrugs are prepared by reacting a non-derivatized compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with a suitable carbamylating agent, such as, but not limited to, 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like. Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth herein are included within the scope of the claims. Indeed, some of the herein-described compounds are a prodrug for another derivative or active compound.

[00322] In some embodiments, sites on the aromatic ring portion of compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are susceptible to various metabolic reactions Therefore incorporation of appropriate substituents on the aromatic ring structures will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00323] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00324] In yet another embodiment, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) possess one or more stereocenters and each center exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. In certain embodiments, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some

embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In other embodiments, dissociable complexes are utilized (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are, in specific embodiments, separated by taking advantage of these dissimilarities. In these embodiments, the diastereomers are separated by chiral chromatography or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that does not result in racemization. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981.

[00325] Additionally, in certain embodiments, the compounds provided herein exist as geometric isomers. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. In some embodiments, the compounds described herein exist as tautomers. All tautomers are intended to be within the scope of the molecular formulas described herein. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are envisioned.

Certain Terminology

[00326] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. In this application, the use of "or" or "and" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[00327] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl moiety may be a saturated alkyl group (which means that it does not contain any units of unsaturation, e.g. carbon-carbon double bonds or carbon-carbon triple bonds) or the the alkyl moiety may be an unsaturated alkyl group (which means that it contains at least one unit of unsaturation). The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or include a cyclic portion. The point of attachment of an alkyl is at a carbon atom that is not part of a ring.

[00328] The "alkyl" moiety may have 1 to 10 carbon atoms (whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon

atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group of the compounds described herein may be designated as "C_1-C_6 alkyl" or similar designations. By way of example only, "C_1-C_6 alkyl" indicates that there are one, two , three, four, five, or six carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary butyl, pentyl, neopentyl, hexyl, allyl, but-2-enyl, but-3-enyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, and the like. In one aspect, an alkyl is a C_1-C_6 alkyl.

[00329] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00330] The term "alkylamine" refers to the $-N(alkyl)_xH_y$ group, where x and y are selected from the group x=1, y=1 and x=2, y=0. In some embodiments, when x=2 and y=0, the alkyl groups taken together with the ntrogen atom to which they are attached form a cyclic ring system.

[00331] An "amide" is a chemical moiety with formula -C(=O)NHR or -NHC(=O)R, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). An amide may be an amino acid or a peptide molecule attached to a compound of Formula (I), thereby forming a prodrug. Any amine, or carboxyl side chain on the compounds described herein is optionally amidified, as desired. See, e.g., Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, is incorporated herein by reference for such disclosure.

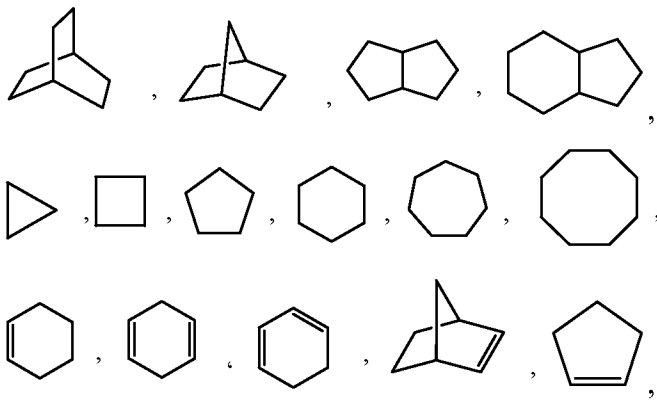
[00332] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, ten, or more than ten atoms. Aromatics are optionally substituted. The term "aromatic" includes both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00333] The term "carbocyclic" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon.

[00334] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings are formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups are optionally substituted. In one aspect, an aryl is a phenyl

or a naphthalenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group). In one aspect, an aryl is a C_6-C_{10}aryl.

[00335] The term "cycloalkyl" refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:



, and the like. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In some embodiments, bicyclic cycloalkyl groups are selected from among indanyl, indenyl, and 1,2,3,4-tetrahydronaphthalenyl. Cycloalkyl groups may be substituted or unsubstituted. Depending on the structure, a cycloalkyl group can be a monoradical or a diradical (i.e., an cycloalkylene group, such as, but not limited to, cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, cyclopentan-1,1-diyl, cyclohexan-1,1-diyl, cyclohexan-1,4-diyl, cycloheptan-1,1-diyl, and the like).

[00336] The term "ester" refers to a chemical moiety with formula -COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). Any hydroxy, or carboxyl side chain on the compounds described herein is esterified, if desired. Examples of procedures and specific groups to make such esters are found in sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999.

[00337] The term "halo" or, alternatively, "halogen" or "halide" means fluoro, chloro, bromo or iodo.

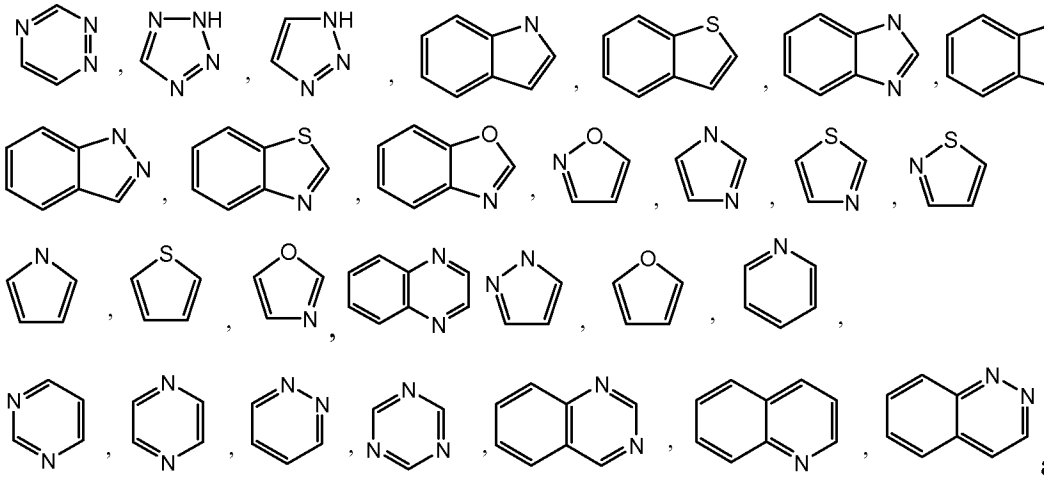
[00338] The term "haloalkyl" refers to an alkyl group in which one or more hydrogen atoms are replaced by one or more halide atoms. In one aspect, a haloalkyl is a C_1-C_4haloalkyl.

[00339] The term "fluoroalkyl" refers to a alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoralkyl is a C_1-C_4fluoroalkyl.

[00340] The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl.

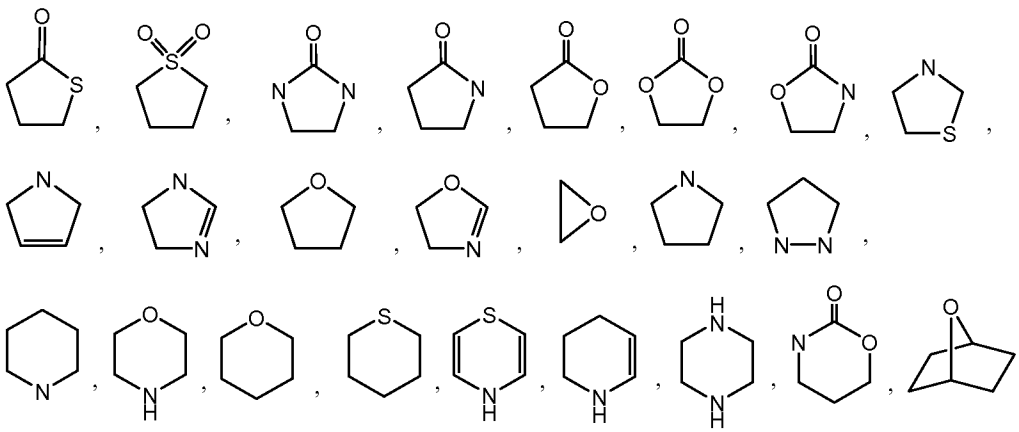
[00341] The term "heterocycle" or "heterocyclic" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include groups having only 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3-membered heterocyclic group is aziridinyl. An example of a 4-membered heterocyclic group is azetidinyl. An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups may be C-attached or *N*-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles may ber substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one.

[00342] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryl groups include the following moieties:



and the like. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. In one aspect, a heteroaryl contains 0-3 N atoms. In another aspect, a heteroaryl contains 1-3 N atoms. In another aspect, a heteroaryl contains 0-3 N atoms, 0-1 O atoms, and 0-1 S atoms. In another aspect, a heteroaryl is a monocyclic or bicyclic heteroaryl. In some embodiments, a heteroaryl is a C_1-C_9 heteroaryl. In some embodiments, a heteroaryl is a C_1-C_5 heteroaryl. In some embodiments, a heteroaryl is a C_6-C_9 heteroaryl.

[00343] A "heterocycloalkyl" or "heteroalicyclic" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



and the like. In some embodiments, the heterocycloalkyl is selected from oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and indolinyl. The term heteroalicyclic

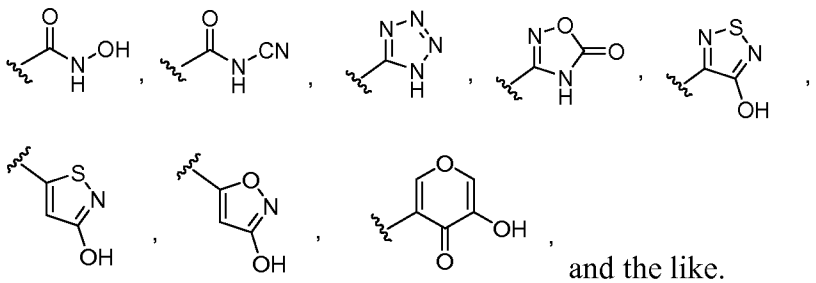
also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_3-C_6heterocycloalkyl. In one aspect, a heterocycloalkyl contains 0-2 N atoms. In another aspect, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms or 0-1 S atoms.

[00344] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[00345] The term "membered ring" includes any cyclic structure. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, cyclohexyl, pyridinyl, pyranyl and thiopyranyl are 6-membered rings and cyclopentyl, pyrrolyl, furanyl, and thienyl are 5-membered rings.

[00346] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00347] As used herein, "carboxylic acid bioisostere" refers to a functional group or moiety that exhibits similar physical and/or chemical properties as a carboxylic acid moiety. In one aspect, a carboxylic acid bioisostere has similar biological properties to that of a carboxylic acid group. A compound with a carboxylic acid moiety can have the carboxylic acid moiety exchanged with a carboxylic acid bioisostere and have similar physical and/or biological properties when compared to the carboxylic acid-containing compound. For example, in one embodiment, a carboxylic acid bioisostere would ionize at physiological pH to roughly the same extent as a carboxylic acid group. Examples of bioisoteres of a carboxylic acid include, but are not limited to,



and the like.

[00348] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, carbonyl, thiocarbonyl, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino groups, and

the protected derivatives thereof. By way of example an optional substituents may be halide, -CN, -NO_2, or L_sR_s, wherein each L_s is independently selected from a bond, -O-, -C(=O)-, -C(=O)O-, -S-, -S(=O)-, -S(=O)$_2$-, -NH-, -NHC(=O)-, -C(=O)NH-, S(=O)$_2$NH-, -NHS(=O)$_2$, -OC(=O)NH-, -NHC(=O)O-, or -(C_1-C_6 alkyl)-; and each R_s is selected from H, alkyl, fluoroalkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. The protecting groups that may form the protective derivatives of the above substituents may be found in sources such as Greene and Wuts, above. In one aspect, optional substituents are selected from halogen, -CN, -NH_2, -OH, -N(CH_3)$_2$, alkyl, fluoroalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, an optional substituents is halogen, -CN, -NH_2, -OH, -NH(CH_3), -N(CH_3)$_2$, alkyl, fluoroalkyl, heteroalkyl, alkoxy, -S-alkyl, or –S(=O)$_2$alkyl. In some embodiments, substituted groups are substituted with one or more substituents selected from halogen, -OH, -OC_1-C_4alkyl, C_1-C_4alkyl, C_1-C_4heteroalkyl, C_1-C_4fluoroalkyl and -OC_1-C_4fluoroalkyl. In yet other embodiments, substituted groups are substituted with one or more substituents selected from F, Cl, Br, -OH, -OCH_3, -CH_3, and -CF_3. In one aspect, substituted groups are substituted with one or two of the preceding groups. The protecting groups that may form the protective derivatives of the above substituents may be found in sources such as Greene and Wuts, above

[00349] In certain embodiments, the compounds presented herein possess one or more stereocenters and each center independently exists in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers are obtained, if desired, by methods such as, the separation of stereoisomers by chiral chromatographic columns.

[00350] The methods and formulations described herein include the use of *N*-oxides (if appropriate), crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having the structure of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In specific embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In other embodiments, the compounds described herein exist in unsolvated form.

Certain Pharmaceutical and Medical Terminology

[00351] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00352] The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00353] The term "modulator," as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist and antagonist. In one embodiment, a modulator is an antagonist.

[00354] The term "agonist," as used herein, refers to a molecule such as a compound, a drug, an enzyme activator or a hormone modulator that binds to a specific receptor and triggers a response in the cell. An agonist mimics the action of an endogenous ligand (such as prostaglandin, hormone or neurotransmitter) that binds to the same receptor.

[00355] The term "antagonist," as used herein, refers to a molecule such as a compound, which diminishes, inhibits, or prevents the action of another molecule or the activity of a receptor site. Antagonists include, but are not limited to, competitive antagonists, non-competitive antagonists, uncompetitive antagonists, partial agonists and inverse agonists.

[00356] Competitive antagonists reversibly bind to receptors at the same binding site (active site) as the endogenous ligand or agonist, but without activating the receptor.

[00357] Non-competitive antagonists (also known as allosteric antagonists) bind to a distinctly separate binding site from the agonist, exerting their action to that receptor via the other binding site. Non-competitive antagonists do not compete with agonists for binding. The bound antagonists may result in a decreased affinity of an agonist for that receptor, or alternatively may prevent conformational changes in the receptor required for receptor activation after the agonist binds.

[00358] Uncompetitive antagonists differ from non-competitive antagonists in that they require receptor activation by an agonist before they can bind to a separate allosteric binding site.

[00359] Partial agonists are defined as drugs which, at a given receptor, might differ in the amplitude of the functional response that they elicit after maximal receptor occupancy. Although they are agonists, partial agonists can act as a competitive antagonist if co-administered with a full agonist, as it competes with the full agonist for receptor occupancy and producing a net decrease in the receptor activation observed with the full agonist alone.

[00360] An inverse agonist can have effects similar to an antagonist, but causes a distinct set of downstream biological responses. Constitutively active receptors which exhibit intrinsic or basal activity can have inverse agonists, which not only block the effects of binding agonists like a classical antagonist, but inhibit the basal activity of the receptor.

[00361] The term "PGD_2-dependent", as used herein, refers to conditions or disorders that would not occur, or would not occur to the same extent, in the absence of PGD_2.

[00362] The term "PGD_2-mediated", as used herein, refers to refers to conditions or disorders that might occur in the absence of PGD_2 but can occur in the presence of PGD_2.

[00363] The term "asthma" as used herein refers to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever cause (intrinsic, extrinsic, or both; allergic or non-allergic). The term asthma may be used with one or more adjectives to indicate cause.

[00364] The term "rhinitis" as used herein refers to any disorder of the nose in which there is inflammation of the mucous lining of the nose by whatever cause (intrinsic, extrinsic or both; allergic or non-allergic).

[00365] The term "bone disease,' as used herein, refers to a disease or condition of the bone, including, but not limited to, inapproriate bone remodeling, loss or gain, osteopenia, osteomalacia, osteofibrosis, and Paget's disease.

[00366] The term "cardiovascular disease," as used herein refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue;endotoxic, surgical, or traumaticshock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue..

[00367] The term "cancer," as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, lymhatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma) or hematological tumors (such as the leukemias).

[00368] The term "carrier," as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[00369] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00370] The term "dermatological disorder," as used herein refers to a skin disorder. Such dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsso Syndrome, urticaria.

[00371] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution.

[00372] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00373] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00374] The terms "fibrosis" or "fibrosing disorder," as used herein, refers to conditions that follow acute or chronic inflammation and are associated with the abnormal accumulation of cells and/or collagen and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, joints, lung, or skin, and includes such disorders as idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis.

[00375] The term "iatrogenic" means a PGD_2-dependent or PGD_2-mediated condition, disorder, or disease created or worsened by medical or surgical therapy.

[00376] The term "inflammatory disorders" refers to those diseases or conditions that are characterized by one or more of the signs of pain, heat, redness, swelling, and loss of function (temporary or permanent). Inflammation takes many forms and includes, but is not limited to, inflammation that is one or more of the following: acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous,

hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative. Inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis, temporal arteritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter's); gastrointestinal tract (colitis); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

[00377] The term "immunological disorders" refers to those diseases or conditions that are characterized by inappropriate or deleterious response to an endogenous or exogenous antigen that may result in cellular dysfunction or destruction and consequently dysfunction or destruction of an organ or tissue and which may or may not be accompanied by signs or symptoms of inflammation.

[00378] The terms "kit" and "article of manufacture" are used as synonyms.

[00379] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Metabolites of the compounds disclosed herein are optionally identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

[00380] The terms "neurogenerative disease" or "nervous system disorder," as used herein, refers to conditions that alter the structure or function of the brain, spinal cord or peripheral nervous system, including but not limited to Alzheimer's Disease, cerebral edema, cerebral ischemia, multiple sclerosis, neuropathies, Parkinson's Disease, those found after blunt or surgical trauma (including post-surgical cognitive dysfunction and spinal cord or brain stem injury), as well as the neurological aspects of disorders such as degenerative disk disease and sciatica. The acronym "CNS" refers to disorders of the central nervous system, i.e., brain and spinal cord.

[00381] The terms "ocular disease" or "ophthalmic disease," as used herein, refer to diseases which affect the eye or eyes and potentially the surrounding tissues as well. Ocular or ophthalmic

diseases include, but are not limited to, conjunctivitis, retinitis, scleritis, uveitis, allergic conjuctivitis, vernal conjunctivitis, papillary conjunctivitis.

[00382] The term "interstitial cystitis" refers to a disorder characterized by lower abdominal discomfort, frequent and sometimes painful urination that is not caused by anatomical abnormalites, infection, toxins, trauma or tumors.

[00383] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00384] The term "pharmaceutical composition" refers to a mixture of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

[00385] The term "respiratory disease," as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, eustachian tubes, trachea, bronchi, lungs, related muscles (e.g., diaphram and intercostals) and nerves. Respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, neutrophilic asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

[00386] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one embodiment, the mammal is a human.

[00387] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Routes of Administration

[00388] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00389] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

Pharmaceutical Composition/Formulation

[00390] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the

route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Fo*rms *and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

[00391] Provided herein are pharmaceutical compositions comprising a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) and a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s). In certain embodiments, the compounds described are administered as pharmaceutical compositions in which a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is mixed with other active ingredients, as in combination therapy. Encompassed herein are all combinations of actives set forth in the combination therapies section below and throughout this disclosure. In specific embodiments, the pharmaceutical compositions include one or more compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V).

[00392] A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered in a pharmaceutical composition to a mammal having a disease or condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

[00393] In one embodiment, one or more compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is formulated in an aqueous solution. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, one or more compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other

embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

[00394] In another embodiment, compounds described herein are formulated for oral administration. Compounds described herein, including compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), are formulated by combining the active compounds with, e.g., pharmaceutically acceptable carriers or excipients. In various embodiments, the compounds described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

[00395] In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00396] In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

[00397] In certain embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and,

optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

[00398] In other embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated for buccal or sublingual administration. Formulations suitable for buccal or sublingual administration include, by way of example only, tablets, lozenges, or gels. In still other embodiments, the compounds described herein are formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (*e.g.*, in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical composition of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are formulated in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, suspensions of the active compounds are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[00399] In one aspect, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are prepared as solutions for parenteral injection as described herein or known in the art and administered with an automatic injector. Automatic injectors, such as those disclosed in U.S. Patent Nos. 4,031,893, 5,358,489; 5,540,664; 5,665,071, 5,695,472 and WO/2005/087297 (each of which are incorporated herein by reference for such disclosure) are known. In general, all automatic injectors contain a volume of solution that includes a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) to be injected. In general, automatic injectors include a reservoir for holding the solution, which is in fluid communication with a

needle for delivering the drug, as well as a mechanism for automatically deploying the needle, inserting the needle into the patient and delivering the dose into the patient. Exemplary injectors provide about 0.3 mL of solution at about a concentration of 0.5 mg to 10 mg of compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) per 1 mL of solution. Each injector is capable of delivering only one dose of the compound.

[00400] In still other embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered topically. The compounds described herein are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compositions optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[00401] In yet other embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are formulated for transdermal administration. In specific embodiments, transdermal formulations employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In various embodiments, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In additional embodiments, the transdermal delivery of the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is accomplished by means of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). In specific embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. In alternative embodiments, absorption enhancers are used to increase absorption. Absorption enhancers or carriers include absorbable pharmaceutically acceptable solvents that assist passage through the skin. For example, in one embodiment, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[00402] Transdermal formulations described herein may be administered using a variety of devices which have been described in the art. For example, such devices include, but are not limited to, U.S. Pat. Nos. 3,598,122, 3,598,123, 3,710,795, 3,731,683, 3,742,951, 3,814,097, 3,921,636, 3,972,995, 3,993,072, 3,993,073, 3,996,934, 4,031,894, 4,060,084, 4,069,307, 4,077,407, 4,201,211, 4,230,105, 4,292,299, 4,292,303, 5,336,168, 5,665,378, 5,837,280, 5,869,090, 6,923,983, 6,929,801 and 6,946,144.

[00403] The transdermal dosage forms described herein may incorporate certain pharmaceutically acceptable excipients which are conventional in the art. In one embodiment, the transdermal formulations described herein include at least three components: (1) a formulation of a compound of Formula (I); (2) a penetration enhancer; and (3) an aqueous adjuvant. In addition, transdermal formulations can include additional components such as, but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulation further include a woven or non-woven backing material to enhance absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein maintain a saturated or supersaturated state to promote diffusion into the skin.

[00404] In other embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are formulated for administration by inhalation. Various forms suitable for administration by inhalation include, but are not limited to, aerosols, mists or powders. Pharmaceutical compositions of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In specific embodiments, the dosage unit of a pressurized aerosol is determined by providing a valve to deliver a metered amount. In certain embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator are formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00405] Intranasal formulations are known in the art and are described in, for example, U.S. Pat. Nos. 4,476,116, 5,116,817 and 6,391,452, each of which is specifically incorporated by reference. Formulations, which include a compound of Formula (I), which are prepared according to these and other techniques well-known in the art are prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, for example, Ansel, H. C. et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, Sixth Ed. (1995). Preferably these compositions and formulations are prepared with suitable nontoxic pharmaceutically acceptable ingredients. These ingredients are found in sources such as REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 21st edition, 2005, a standard reference in the field. The choice of suitable carriers is highly dependent upon the exact nature of the nasal dosage form desired, e.g., solutions, suspensions, ointments, or gels. Nasal dosage forms generally contain large amounts of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters,

emulsifiers or dispersing agents, preservatives, surfactants, gelling agents, or buffering and other stabilizing and solubilizing agents may also be present. Preferably, the nasal dosage form should be isotonic with nasal secretions.

[00406] For administration by inhalation, the compounds described herein, may be in a form as an aerosol, a mist or a powder. Pharmaceutical compositions described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound described herein and a suitable powder base such as lactose or starch.

[00407] In still other embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[00408] In certain embodiments, pharmaceutical compositions are formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients is optionally used as suitable and as understood in the art. Pharmaceutical compositions comprising a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) may be manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00409] Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds

having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

[00410] Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[00411] In some embodiments, pharmaceutical composition comprising at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

[00412] In certain embodiments, pharmaceutical aqueous suspensions include one or more polymers as suspending agents. Polymers include water-soluble polymers such as cellulosic polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein include a mucoadhesive polymer, selected from, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00413] Pharmaceutical compositions also, optionally include solubilizing agents to aid in the solubility of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula

(V). The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

[00414] Furthermore, pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[00415] Additionally, pharmaceutical compositions optionally include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[00416] Other pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[00417] Still other pharmaceutical compositions include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40.

[00418] Still other pharmaceutical compositions may include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

[00419] In certain embodiments, pharmaceutical aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

[00420] In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers herein. In certain embodiments, organic solvents such as *N*-methylpyrrolidone are also employed. In additional embodiments, the compounds described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some

embodiments, sustained-release capsules release the compounds for a few hours up to over 24 hours. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[00421] In certain embodiments, the formulations described herein include one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

Methods of Dosing and Treatment Regimens

[00422] In one embodiment, the compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are used in the preparation of medicaments for the treatment of PGD_2-dependent or PGD_2-mediated diseases or conditions. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or a pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[00423] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00424] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the severity and course of the

disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[00425] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00426] In certain embodiments wherein a patient's status does improve, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00427] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00428] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment are typically in the range of 0.02mg-5000 mg per day, preferably 1-1500 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00429] In some embodiments, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered chronically. In some embodiments, compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered intermittently (e.g. drug holiday that includes a period of time in which the compound is not administered or is administered in a reduced amount). In some embodiments, compounds of

Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are administered in cycles that include: (a) a first period that includes daily administration of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V); followed by (b) a second period that includes a dose reduction of the daily amount of the compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) that is administered. In some embodiments, the compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is not administered in the second period. In some embodiments, the duration of the first and second periods, as well as the dose amounts are determined using methods described herein or known in the art. By way of example only, a drug holiday or a dose reduction period is appropriate depending on the pharmacodynamic profile of the active agent, e.g., the 'off' rate of the active agent is significantly slower than the 'off' rate of prostaglandin D_2 from the DP_2 receptor.

[00430] In certain embodiments, the pharmaceutical composition described herein is in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. In specific embodiments, the unit dosage is in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions are optionally packaged in single-dose non-re-closeable containers. Alternatively, multiple-dose re-closeable containers are used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection are, in some embodiments, presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[00431] In one embodiment, the daily dosages appropriate for the compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) described herein are from about 0.01 to about 10 mg/kg per body weight. In specific embodiments, an indicated daily dosage in a large mammal, including, but not limited to, humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered in divided doses, including, but not limited to, up to four times a day. In one embodiment, the daily dosage is administered in extended release form. In certain embodiments, suitable unit dosage forms for oral administration comprise from about 1 to 500 mg active ingredient. In other embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the

requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00432] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

Use of DP_2 Anatagonists to Prevent and/or Treat PGD_2-Dependent or PGD_2 Mediated Diseases or Conditions

[00433] The therapy of PGD_2-dependent or PGD_2-mediated diseases or conditions is designed to modulate the activity of DP_2, DP_1 and/or TP. Such modulation includes, in some embodiments, antagonizing DP_2 activity. In other embodiments, such modulation includes antagonizing DP_2 and DP_1. For example, in one embodiment, a DP_2 antgonist is administered in order to decrease signal transduction initiated by PGD_2 within the individual.

[00434] In accordance with one aspect, compositions and methods described herein include compositions and methods for treating, preventing, reversing, halting or slowing the progression of PGD_2-dependent or PGD_2 mediated diseases or conditions once it becomes clinically evident, or treating the symptoms associated with or related to PGD_2-dependent or PGD_2 mediated diseases or conditions, by administering to the subject a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof. In certain embodiments, the subject already has a PGD_2-dependent or PGD_2 mediated disease or condition at the time of administration, or is at risk of developing a PGD_2-dependent or PGD_2 mediated disease or condition.

[00435] In certain aspects, the activity of DP_2 in a mammal is directly or indirectly modulated by the administration of (at least once) an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof to a mammal. Such modulation includes, but is not limited to, reducing and/or inhibiting the activity of DP_2. In additional aspects, the activity of PGD_2 in a mammal is

directly or indirectly modulated, including reducing and/or inhibiting, by the administration of (at least once) an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof to a mammal. Such modulation includes, but is not limited to, reducing and/or inhibiting the activity of DP_2.

[00436] In one embodiment, prevention and/or treatment of PGD_2-dependent or PGD_2 mediated diseases or conditions comprises administering to a mammal at least once a therapeutically effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof. In specific embodiments, the compound administered to the mammal is a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V). In some embodiments, there is provided a method of treating PGD_2-dependent or PGD_2 mediated diseases or conditions that include, but are not limited to, bone diseases and disorders, cardiovascular diseases and disorders, inflammatory diseases and disorders, immunological diseases or disorders, dermatological diseases and disorders, ocular diseases and disorders, cancer and other proliferative diseases and disorders, respiratory diseases and disorder, and non-cancerous disorders.

[00437] By way of example only, included in the prevention/treatment methods described herein are methods for treating respiratory diseases comprising administering to the mammal at least once an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof. By way of example, in some embodiments, the respiratory disease is asthma. Other respiratory diseases include, but are not limited to, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, neutrophilic asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, allergic rhinitis, vascular responses, endotoxin shock, fibrogenesis, pulmonary fibrosis, allergic diseases, chronic inflammation, and adult respiratory distress syndrome.

[00438] By way of example only, included in such treatment methods are methods for preventing chronic obstructive pulmonary disease comprising administering to the mammal at least once an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof. In addition, chronic obstructive pulmonary disease includes, but is not limited to, chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis.

[00439] By way of example only, included in such treatment methods are methods for preventing increased mucosal secretion and/or edema in a disease or condition comprising administering to the mammal at least once an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00440] By way of example only, included in the prevention/treatment methods described herein are methods for preventing or treating vasoconstriction, atherosclerosis and its sequelae myocardial ischemia, myocardial infarction, aortic aneurysm, vasculitis and stroke comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00441] By way of example only, included in the prevention/treatment methods described herein are methods for reducing cardiac reperfusion injury following myocardial ischemia and/or endotoxic shock comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00442] By way of example only, included in the prevention/treatment methods described herein are methods for reducing the constriction of blood vessels in a mammal comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00443] By way of example only, included in the prevention/treatment methods described herein are methods for lowering or preventing an increase in blood pressure of a mammal comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00444] By way of example only, included in the prevention/treatment methods described herein are methods for preventing or treating eosinophil and/or basophil and/or dendritic cell and/or neutrophil and/or monocyte and/or T-cell recruitment comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00445] By way of example only, included in the prevention/treatment methods described herein are methods for the prevention or treatment of abnormal bone remodeling, loss or gain, including diseases or conditions as, by way of example, osteopenia, osteoporosis, Paget's disease, cancer and other diseases comprising administering at least once to the mammal an effective amount of

at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00446] By way of example only, included in the prevention/treatment methods described herein are methods for preventing ocular inflammation and allergic conjunctivitis, vernal keratoconjunctivitis, and papillary conjunctivitis comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00447] By way of example only, included in the prevention/treatment methods described herein are methods for preventing otitis, otitis media comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00448] By way of example only, included in the prevention/treatment methods described herein are methods for preventing CNS disorders comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof. CNS disorders include, but are not limited to, multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke, cerebral ischemia, retinal ischemia, post-surgical cognitive dysfunction, migraine, peripheral neuropathy/neuropathic pain, spinal cord injury, cerebral edema and head injury.

[00449] By way of example only, included in the prevention/treatment methods described herein are methods for the treatment of cancer comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof. The type of cancer may include, but is not limited to, pancreatic cancer and other solid or hematological tumors.

[00450] By way of example only, included in the prevention/treatment methods described herein are methods for preventing or reducing the chances of endotoxic shock and septic shock comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00451] By way of example only, included in the prevention/treatment methods described herein methods for preventing, treating or alleviating rheumatoid arthritis and osteoarthritis comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00452] By way of example only, included in the prevention/treatment methods described herein are methods for preventing increased, reducing the incidences of or treating gastrointestinal diseases comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof. Such gastrointestinal diseases include, by way of example only, inflammatory bowel disease (IBD), colitis and Crohn's disease.

[00453] By way of example only, included in the prevention/treatment methods described herein are methods for the reduction or treatment of inflammation and/or preventing, reducing the incidences of or treating acute or chronic transplant rejection (including any vascular abnormality associated with acute or chronic rejection) or preventing or treating tumors or accelerating the healing of wounds comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00454] By way of example only, included in the prevention/treatment methods described herein are methods for the prevention or treatment of rejection or dysfunction in a transplanted organ or tissue comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00455] By way of example only, included in the prevention/treatment methods described herein are methods for treating inflammatory responses of the skin comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof. Such inflammatory responses of the skin include, by way of example, psoriasis, dermatitis, contact dermatitis, eczema, urticaria, rosacea, wound healing and scarring. In another aspect are methods for reducing psoriatic lesions in the skin, joints, or other tissues or organs, comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00456] By way of example only, included in the prevention/treatment methods described herein are methods for the treatment of cystitis, including, e.g.,interstitial cystitis, comprising administering at least once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00457] By way of example only, included in the prevention/treatment methods described herein are methods for the treatment of Familial Mediterranean Fever comprising administering at least

once to the mammal an effective amount of at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof.

[00458] Compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are DP_2 antagonists. In one aspect, compounds of Formula (I) are used in the treatment of PGD_2-dependent or PGD_2-mediated diseases, disorders or conditions as disclosed herein. In one aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) show higher selectivity for DP_2 versus other receptors, such as for example DP_1, CETP and/or PPAR receptors. In one aspect, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) show higher affinity for DP_2 versus other receptors, such as for example DP_1, CETP and/or PPAR receptors.

Combination Treatments

[00459] In certain instances, it is appropriate to administer at least one compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is inflammation, then it may be appropriate to administer an anti-inflammatory agent in combination with the initial therapeutic agent. Or, in one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant may have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit of experienced by a patient is increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. In one specific embodiment, the therapeutic benefit of treating asthma by administering at least one of the compounds described herein is increased by also providing the patient with other therapeutic agents or therapies for asthma. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[00460] In certain embodiments, different therapeutically-effective dosages of the compounds disclosed herein will be utilized in formulating pharmaceutical composition and/or in treatment regimens when the compounds disclosed herein are administered in combination with one or more additional agent, such as an additional therapeutically effective drug, an adjuvant or the like. Therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens can be determined by means similar to those set forth hereinabove for the actives themselves. Furthermore, the methods of prevention/treatment described herein

encompasses the use of metronomic dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects. In some embodiments, a combination treatment regimen encompasses treatment regimens in which administration of a DP_2 antagonist described herein is initiated prior to, during, or after treatment with a second agent described above, and continues until any time during treatment with the second agent or after termination of treatment with the second agent. It also includes treatments in which a DP_2 antagonist described herein and the second agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient. For example, in one embodiment, a DP_2 antagonist described herein in the combination treatment is administered weekly at the onset of treatment, decreasing to biweekly, and decreasing further as appropriate.

[00461] Compositions and methods for combination therapy are provided herein. In accordance with one aspect, the pharmaceutical compositions disclosed herein are used to treat PGD_2-dependent or PGD_2 mediated conditions. In accordance with another aspect, the pharmaceutical compositions disclosed herein are used to treat respiratory diseases (e.g., asthma), where treatment with a DP_2 antagonist is indicated and to induce bronchodilation in a subject. In one embodiment, the pharmaceutical compositions disclosed herein are used to treat airways or nasal inflammation diseases such as asthma and rhinitis.

[00462] In one embodiment, pharmaceutical compositions disclosed herein are used to treat a subject suffering from a vascular inflammation-driven disorder. In one embodiment, the pharmaceutical compositions disclosed herein are used to treat skin inflammation diseases such as atopic dermatitis.

[00463] In certain embodiments, combination therapies described herein are used as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of a DP_2 described herein and a concurrent treatment. It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors. These factors include the type of respiratory disorder and the type of bronchoconstriction or inflammation from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, in some instances, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

[00464] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In additional embodiments, when co-administered with

one or more biologically active agents, the compound provided herein is administered either simultaneously with the biologically active agent(s), or sequentially. If administered sequentially, the attending physician decides on the appropriate sequence of administering protein in combination with the biologically active agent(s).

[00465] In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills). In one embodiment, one of the therapeutic agents is given in multiple doses, and in another, two (or more if present) are given as multiple doses. In some embodiments of non-simultaneous administration, the timing between the multiple doses vary from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents; the use of multiple therapeutic combinations is also envisioned.

[00466] In additional embodiments, the compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are used in combination with procedures that provide additional or synergistic benefit to the patient. By way of example only, patients are expected to find therapeutic and/or prophylactic benefit in the methods described herein, wherein pharmaceutical composition of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) and/or combinations with other therapeutics are combined with genetic testing to determine whether that individual is a carrier of a mutant gene that is known to be correlated with certain diseases or conditions.

[00467] The compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) and combination therapies are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, in one embodiment, the compounds described herein are used as a prophylactic and are administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In another embodiment, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the compounds are initiated within the first 48 hours of the onset of the symptoms, preferably within the first 48 hours of the onset of the symptoms, more preferably within the first 6 hours of the onset of the symptoms, and most preferably within 3 hours of the onset of the symptoms. The initial administration is accomplished via any practical route, such as, for example, by intravenous injection, a bolus injection, infusion over 5 minutes to about 5 hours, a pill, a capsule, transdermal patch, buccal

delivery, and the like, or combination thereof. In specific embodiments, a compound described herein is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. In some embodiments, the length required for effective treatment varies, and the treatment length is adjusted to suit the specific needs of each subject. For example, in specific embodiments, a compound described herein or a formulation containing the compound is administered for at least 2 weeks, about 1 month to about 5 years, or from about 1 month to about 3 years.

[00468] By way of example, therapies which combine compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with inhibitors of PGD_2 synthesis or PGD_2 receptor antagonists, either acting at the same or other points in the PGD_2 synthesis pathway, are encompassed herein for treating PGD_2-dependent or PGD_2 mediated diseases or conditions. In addition, by way of example, encompassed herein are therapies that combine compounds of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with inhibitors of inflammation for treating PGD_2-dependent or PGD_2 mediated diseases or conditions.

Anti-Inflammatory Agents

[00469] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases include administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with an anti-inflammatory agent including, but not limited to, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (glucocorticoids). Anti-inflammatory agents include, but are not limited to: arthrotec, mesalamine, auralglan, sulfasalazine, daypro, etodolac, ponstan, and solumedrol; non-steroidal anti-inflammatory agents; corticosteroids; and leukotriene pathway modulators (e.g. montelukast, zilueton).

[00470] By way of example only, asthma is a chronic inflammatory disease characterized by pulmonary eosinophilia and airway hyperresponsiveness. In patients with asthma, PGD_2 is released from mast cells, eosinophils, and basophils. PGD_2 is involved in contraction of airway smooth muscle, an increase in vascular permeability and mucus secretions, and has been reported to attract and activate inflammatory cells in the airways of asthmatics. Thus, in another embodiment described herein, the methods for treatment of respiratory diseases include administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with an anti-inflammatory agent.

[00471] NSAIDs include, but are not limited to: aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium,

flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, COX-2 specific inhibitors (such as, but not limited to, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, CS-502, JTE-522, L-745,337 and NS398).

[00472] Corticosteroids, include, but are not limited to: betamethasone (Celestone), prednisone (Deltasone), alclometasone, aldosterone, amcinonide, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, cortisone, cortivazol, deflazacort, deoxycorticosterone, desonide, desoximetasone, desoxycortone, dexamethasone, diflorasone, diflucortolone, difluprednate, fluclorolone, fludrocortisone, fludroxycortide, flumetasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin, fluocortolone, fluorometholone, fluperolone, fluprednidene, fluticasone, formocortal, halcinonide, halometasone, hydrocortisone/cortisol, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone butyrate, loteprednol, medrysone, meprednisone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, paramethasone, prednicarbate, prednisone/prednisolone, rimexolone, tixocortol, triamcinolone, and ulobetasol.

[00473] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases include administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination in combination with NSAIDs and NO-donors or NSAIDs and proton-pump inhibitors.

PGD_2 Receptor Antagonists

[00474] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases includes administering to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with other PGD_2 receptor antagonists including, but are not limited to, DP_1 receptor antagonists and TP receptor antagonists. In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases includes administered to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with a DP_1 receptor antagonist. DP_1 receptor antagonists include, but are not limited to, BWA868C (Sharif *et al., Br. J. Pharmacol.*, 2000 Nov;131(6):1025-38), MK-0524 (Sturino *et al*, *J. Med. Chem.*, 2007, 50, 794-806 and Cheng *et al*, PNAS, 2006 Apr 25;103(17):6682-7.) and S-5751 (Arimura *et al., J. Pharmacol. Exp. Ther.,* 2001 Aug; 298(2):411-9). For some patients, the most appropriate formulation or method of use of such combination treatments depends on the type of PGD_2-dependent or PGD_2 mediated disorder, the time period in which the DP_2 antagonist acts to treat the disorder and/or the time period in which the DP_1 receptor antagonist acts to prevent DP_1

receptor activity. By way of example only, some embodiments described herein provide for such combination treatments that are used for treating a patient suffering from respiratory disorders such as asthma and rhinitis.

[00475] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases includes administering to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with a TP receptor antagonist. TP receptor antagonists include, but are not limited to, Ramatroban ("Bayer™"), GR32191 (Beasley *et al., J. Appl. Physiol.*, 1989 Apr;66(4):1685-93), ICI192605 (Boersma *et al., Br. J. Pharmacol.*, 1999 Dec;128(7):1505-12) and derivatives or analogs thereof. Such combinations may be used to treat PGD_2-dependent or PGD_2 mediated disorders, including respiratory disorders.

[00476] In one embodiment, the co-administration of a DP_2 receptor antagonist with a DP_1 receptor antagonist or a TP receptor antagonist has therapeutic benefit over and above the benefit derived from the administration of a either a DP_2 antagonist, DP_1 antagonist or a TP antagonist alone. In the case that substantial inhibition of PGD_2 activity has undesired effects, partial inhibition of this pathway through the amelioration of the effects of the proinflammatory agonists combined with the block of the DP_1 receptor, TP receptor and/or DP_2 receptor may afford substantial therapeutic benefits, particularly for respiratory diseases.

Other Combination Therapies

[00477] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases, such as proliferative disorders, including cancer, comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected, by way of example only, alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, Paclitaxel™, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

[00478] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of transplanted organs or tissues or cells, comprises administration to a patient compounds, pharmaceutical compositions, or

medicaments described herein in combination with at least one additional agent selected from, by way of example only, azathioprine, a corticosteroid, cyclophosphamide, cyclosporin, dacluzimab, mycophenolate mofetil, OKT3, rapamycin, tacrolimus,thymoglobulin.

[00479] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases, such as atherosclerosis, comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected, by way of example only, HMG-CoA reductase inhibitors (e.g., statins in their lactonized or dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof, including but not limited to lovastatin; simvastatin; dihydroxy open-acid simvastatin, particularly the ammonium or calcium salts thereof; pravastatin, particularly the sodium salt thereof; fluvastatin, particularly the sodium salt thereof; atorvastatin, particularly the calcium salt thereof; nisvastatin, also referred to as NK-104; rosuvastatin); agents that have both lipid-altering effects and other pharmaceutical activities; HMG-CoA synthase inhibitors; cholesterol absorption inhibitors such as ezetimibe; cholesterol ester transfer protein (CETP) inhibitors, for example JTT-705 and CP529, 414; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors); acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT-1 and-2; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPARγ) agonists, including the compounds commonly referred to as glitazones, for example troglitazone, pioglitazone and rosiglitazone and including those compounds included within the structural class known as thiazolidinediones as well as those PPARγ agonists outside the thiazolidinedione structural class; PPARα agonists such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil ; PPAR dual α/γ agonists such as 5-[(2, 4-dioxo-5-thiazolidinyl)methyl]-2-methoxy-N-[[4-(trifluoromethyl)phenyl]methyl]-benzamide, known as KRP-297; vitamin B6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B12 (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as vitamin C and E and beta carotene; beta-blockers; angiotensin II antagonists such as losartan; angiotensin converting enzyme inhibitors such as enalapril and captopril ; calcium channel blockers such as nifedipine and diltiazam; endothelian antagonists; agents that enhance ABC1 gene expression; FXR and LXR ligands

including both inhibitors and agonists; bisphosphonate compounds such as alendronate sodium; and cyclooxygenase-2 inhibitors such as rofecoxib and celecoxib.

[00480] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of stroke, comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from, by way of example only, COX-2 inhibitors; nitric oxide synthase inhibitors, such as N-(3-(aminomethyl)benzyl) acetamidine; Rho kinase inhibitors, such as fasudil; angiotension II type-1 receptor antagonists, including candesartan, losartan, irbesartan, eprosartan, telmisartan and valsartan; glycogen synthase kinase 3 inhibitors; sodium or calcium channel blockers, including crobenetine; p38 MAP kinase inhibitors, including SKB 239063; thromboxane AX- synthetase inhibitors, including isbogrel, ozagrel, ridogrel and dazoxiben; statins (HMG CoA reductase inhibitors), including lovastatin, simvastatin, dihydroxy open-acid simvastatin, pravastatin, fluvastatin, atorvastatin, nisvastatin, and rosuvastatin; neuroprotectants, including free radical scavengers, calcium channel blockers, excitatory amino acid antagonists, growth factors, antioxidants, such as edaravone, vitamin C, TROLOX™, citicoline and minicycline, and reactive astrocyte inhibitors, such as (2R)-2-propyloctanoic acid; beta andrenergic blockers, such as propranolol, nadolol, timolol, pindolol, labetalol, metoprolol, atenolol, esmolol and acebutolol; NMDA receptor antagonists, including memantine; NR2B antagonists, such as traxoprodil; 5-HTlA agonists; receptor platelet fibrinogen receptor antagonists, including tirofiban and lamifiban; thrombin inhibitors; antithrombotics, such as argatroban; antihypertensive agents, such as enalapril; vasodilators, such as cyclandelate; nociceptin antagonists; DPIV antagonists; CETP inhibitors; GABA 5 inverse agonists; and selective androgen receptor modulators.

[00481] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of pulmonary fibrosis, comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from, by way of example only, anti- inflammatory agents, such as corticosteroids, azathioprine or cyclophosphamide.

[00482] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of interstitial cystitis, comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from, by way of example only, dimethylsulfoxide, omalizumab, and pentosan polysulfate.

[00483] In another embodiment described herein, methods for treatment of PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of disorders of bone, comprises

administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from the, by way of example only, minerals, vitamins, bisphosphonates, anabolic steroids, parathyroid hormone or analogs, and cathepsin K inhibitors.

[00484] In yet another embodiment described herein, methods for treating PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of respiratory disorders (e.g., asthma, COPD and rhinitis), comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one respiratory agent. Respiratory agents include, but are not limited to, bronchodilators (e.g., sympathomimetic agents and xanthine derivatives), leukotriene receptor antagonists, leukotriene formation inhibitors, leukotriene modulators, nasal decongestants, respiratory enzymes, lung surfactants, antihistamines (e.g., Mepyramine (pyrilamine), Antazoline, Diphenhydramine, Carbinoxamine, Doxylamine, Clemastine, Dimenhydrinate, Pheniramine, Chlorphenamine (chlorpheniramine), Dexchlorpheniramine, Brompheniramine, Triprolidine, cetirizine, Cyclizine, Chlorcyclizine, Hydroxyzine, Meclizine, loratadine, desloratidine, Promethazine, Alimemazine (trimeprazine), Cyproheptadine, Azatadine, Ketotifen, Acrivastine, Astemizole, Cetirizine, Mizolastine, Terfenadine, Azelastine, Levocabastine, Olopatadine, Levocetirizine, Fexofenadine), mucolytics, corticosteroids, glucocorticoids, anticholinergics, antitussives, analgesics, expectorants, albuterol, ephedrine, epinephrine, fomoterol, metaproterenol, terbutaline, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone propionate, triamcinolone acetonide, ipratropium bromide, pseudoephedrine, theophylline, montelukast, zafirlukast, pranlukast, tomelukast, ambrisentan, bosentan, enrasentan, sitaxsentan, tezosentan, iloprost, treprostinil, pirfenidone, FLAP inhibitors, FLAP modulators, 5-LO inhibitors, BLT1 receptor antagonists and BLT2 receptor antagonists.

[00485] In a specific embodiment described herein, methods for treating PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of asthma and/or COPD, comprises administration to a patient anti-inflammatory agents. In certain embodiments, methods for treating PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of asthma and/or COPD, comprise administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from, but not limited to, epinephrine, isoproterenol, orciprenaline, bronchodilators, glucocorticoids, leukotriene modifiers, mast-cell stabilizers, xanthines, anticholinergics, β-2 agonists, FLAP inhibitors, FLAP modulators or 5-LO inhibitors. β-2 agonists include, but are not limited to, short-acting β-2 agonists (e.g., salbutamol (albuterol), levalbuterol, terbutaline, pirbuterol, procaterol, metaproterenol, fenoterol and bitolterol mesylate) and long-acting β-2 agonists (e.g.,

salmeterol, formoterol, bambuterol and clenbuterol). FLAP inhibitors and/or FLAP modulators include, but are not limited to, 3-[3-tert-butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid, 3-[3-*tert*-butylsulfanyl-1-[4-(6-ethoxy-pyridin-3-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1*H*-indol-2-yl]-2,2-dimethyl-propionic acid, MK-886, MK-0591, DG-031 (BAY-x1005) and compounds found in US 2007/0225285, US 2007/0219206, US 2007/0173508, US 2007/0123522 and US 2007/0105866 (each of which are hereby incorporated by reference). Glucocorticoids include, but are not limited to, beclometasone, budesonide, ciclesonide, fluticasone and mometasone. Anticholinergics include, but are not limited to, ipratropium and tiotropium. Mast cell stabilizers include, but are not limited to, cromoglicate and nedocromil. Xanthines include, but are not limited to, amminophylline, theobromine and theophylline. Leukotriene antagonists include, but are not limited to, montelukast, tomelukast, pranlukast and zafirlukast. 5-LO inhibitors include, but are not limited to, zileuton, VIA-2291 (ABT761), MK-0633, CJ-13,610 (PF-4191834), AZ-4407 and ZD-2138 and compounds found in US 2007/0149579, WO2007/016784.

[00486] In another specific embodiment described herein, methods for treating PGD_2-dependent or PGD_2 mediated conditions or diseases, such as the therapy of rhinitis, comprises administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from, by way of example only, antihistamines, leukotriene antagonists, corticosteroids and decongestants. Leukotriene antagonists include, but are not limited to, montelukast, tomelukast, pranlukast and zafirlukast.

[00487] In another aspect, methods for treating PGD_2-dependent or PGD_2 mediated conditions or diseases, iclude administering a DP_2 antagonist described herein in combination with other agents to treat respiratory diseases or conditions. Therapeutic agents used in the treatment of respiratory conditions and disorders, such as, but not limited to asthma, include: glucocorticoids, such as, ciclesonide, beclomethasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone; leukotriene modifiers, such as, montelukast, zafirlukast, pranlukast, and zileuton; mast cell stabilizers, such as, cromoglicate (cromolyn), and nedocromil; antimuscarinics/anticholinergics, such as, ipratropium, oxitropium, and tiotropium; methylxanthines, such as, theophylline and aminophylline; antihistamine, such as, mepyramine (pyrilamine), antazoline, diphenhydramine, carbinoxamine, doxylamine, clemastine, dimenhydrinate, pheniramine, chlorphenamine (chlorpheniramine), dexchlorphenamine, brompheniramine, triprolidine, cyclizine, chlorcyclizine, hydroxyzine, meclizine, promethazine, alimemazine (trimeprazine), cyproheptadine, azatadine, ketotifen, acrivastine, astemizole, cetirizine, loratadine, mizolastine, terfenadine, fexofenadine, levocetirizine, desloratadine, fexofenadine; omalizumab, an IgE blocker; beta2-adrenergic receptor agonists, such as: short

acting beta2-adrenergic receptor agonists, such as, salbutamol (albuterol), levalbuterol, terbutaline, pirbuterol, procaterol, metaproterenol, fenoterol, bitolterol mesylate; and long-acting beta2-adrenergic receptor agonists, such as, salmeterol, formoterol, bambuterol.

[00488] In one aspect, DP_2 anatogonists described herein are admistered in combination with one or more agents used to treat used to treat asthma, including, but not limited to: combination inhalers (fluticasone and salmeterol oral inhalation (e.g. Advair)); inhaled Beta-2 agonists (albuterol inhaler; albuterol nebulizer solution; formoterol; isoproterenol oral inhalation; levalbuterol; metaproterenol inhalation; pirbuterol acetate oral inhalation; salmeterol aerosol inhalation; salmeterol powder inhalation; terbutaline inhaler); inhaled corticosteroids (beclomethasone oral inhalation; budesonide inhalation solution; budesonide inhaler; flunisolide oral inhalation; fluticasone inhalation aerosol; fluticasone powder for oral inhalation; mometasone inhalation powder; triamcinolone oral inhalation); leukotriene modifiers (montelukast; zafirlukast; pranlukast; tomelukast; zileuton); mast cell stabilizers (cromolyn inhaler; nedocromil oral inhalation); monoclonal antibodies (omalizumab); oral Beta-2 agonists (albuterol oral syrup; albuterol oral tablets; metaproterenol; terbutaline); bronchodilator (aminophylline; oxtriphylline; theophylline).

[00489] In one aspect, DP_2 anatogonists described herein are admistered in combination with one or more agents used to treat allergy, including, but not limited to: antihistamine and decongestant combinations (cetirizine and pseudoephedrine; desloratadine and pseudoephedrine ER; fexofenadine and pseudoephedrine; loratadine and pseudoephedrine); antihistamines (azelastine nasal spray; brompheniramine; brompheniramine oral suspension; carbinoxamine; cetirizine; chlorpheniramine; clemastine; desloratadine; dexchlorpheniramine ER; dexchlorpheniramine oral syrup; diphenhydramine oral; fexofenadine; loratadine; promethazine); decongestants (pseudoephedrine); leukotriene modifiers (montelukast; montelukast granules); nasal anticholinergics (ipratropium); nasal corticosteroids (beclomethasone nasal inhalation; budesonide nasal inhaler; flunisolide nasal inhalation; fluticasone nasal inhalation; mometasone nasal spray; triamcinolone nasal inhalation; triamcinolone nasal spray); nasal decongestants (phenylephrine); nasal mast cell stabilizers (cromolyn nasal spray).

[00490] In one aspect, DP_2 anatogonists described herein are admistered in combination with one or more agents used to treat chronic obstructive pulmonary disease (COPD), including, but not limited to: anticholinergics - ipratropium bromide oral inhalation); combination Inhalers (albuterol and ipratropium (e.g. Combivent, DuoNeb); fluticasone and salmeterol oral inhalation (e.g. Advair)); corticosteroids (dexamethasone tablets; fludrocortisone acetate; hydrocortisone tablets; methylprednisolone; prednisolone liquid; prednisone oral; triamcinolone oral); inhaled Beta-2 Agonists (albuterol inhaler; albuterol nebulizer solution; formoterol; isoproterenol oral

inhalation; levalbuterol; metaproterenol inhalation; pirbuterol acetate oral inhalation; salmeterol aerosol inhalation; salmeterol powder inhalation; terbutaline inhaler); inhaled Corticosteroids (beclomethasone oral inhalation; budesonide inhalation solution; budesonide inhaler; flunisolide oral inhalation; fluticasone inhalation aerosol; fluticasone powder for oral inhalation; triamcinolone oral inhalation); mukolytics (guaifenesin); oral Beta-2 agonists (albuterol oral syrup; albuterol oral tablets; metaproterenol; terbutaline); bronchodilator (aminophylline; oxtriphylline; theophylline).

[00491] In one embodiment, DP_2 anatogonists described herein are administered to a patient in combination with inhaled corticosteroids.

[00492] In one embodiment, DP_2 anatogonists described herein are administered to a patient in combination with beta2-adrenergic receptor agonists. In one embodiment, DP_2 anatogonists described herein are administered to a patient in combination with short acting beta2-adrenergic receptor agonists. In one embodiment, DP_2 anatogonists described herein are administered to a patient in combination with long-acting beta2-adrenergic receptor agonists.

[00493] As discussed herein, the administration of compounds of any of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is designed to anatagonize the activity of DP_2. For example, in specific embodiments, the administration of a DP_2 inhibitor decreases signal transduction initiated by PGD_2 within the individual.

[00494] Thus, in accordance with one aspect, methods described herein include the diagnosis or determination of whether or not a patient is suffering from a PGD_2-dependent or PGD_2 mediated disease or condition by administering to the subject a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) or pharmaceutical composition or medicament thereof and determining whether or not the patient responds to the treatment.

Kits/Articles of Manufacture

[00495] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from any acceptable material including, e.g., glass or plastic.

[00496] For example, the container(s) can comprise one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits

optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

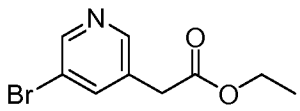
[00497] A kit will typically comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[00498] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

EXAMPLES

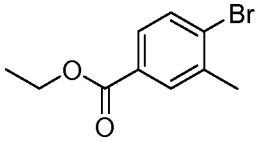
These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1: Synthesis of 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-carboxymethyl-pyridin-3-yl)-benzoic acid (Compound 1-1)



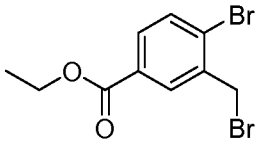
Step 1: (5-Bromo-pyridin-3-yl)-acetic acid ethyl ester

[00499] 5-Bromo-3-pyridylacetic acid was treated with 5% concentrated sulfuric acid in EtOH at reflux overnight to give the title compound.



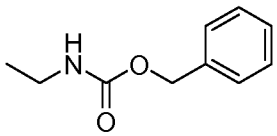
Step 2: 4-Bromo-3-methyl-benzoic acid ethyl ester

[00500] To 4-bromo-3-methylbenzoic acid (16.27g, 75.7mmol) in EtOH (500mL) was added concentrated sulfuric acid (0.5mL), and the reaction was stirred at 95°C overnight. Additional sulfuric acid (2mL) was added to push the reaction to completion, and then the mixture was quenched with the slow addition of sodium carbonate. The mixture was filtered and concentrated, and the residue was diluted and washed with H_2O twice, saturated aqueous $NaHCO_3$, brine, and H_2O to give the title compound.



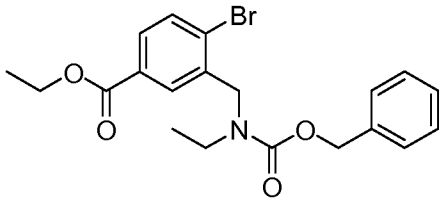
Step 3: 4-Bromo-3-bromomethyl-benzoic acid ethyl ester

[00501] 4-Bromo-3-methyl-benzoic acid ethyl ester (18.24g, 75.4mmol), N-bromosuccinimide (14.1g, 79.2mmol), and benzoyl peroxide (0.9g, 3.77mmol) were combined in CCl_4, and the reaction was heated to 80°C and stirred with a halogen desk lamp shining on it for 6 hours. The mixture was concentrated and partitioned between CH_2Cl_2 and H_2O. The organic layer was separated and washed with H_2O and brine, and then dried and concentrated. The residue was triturated with hexane (3x50mL) and dried to give the title compound.



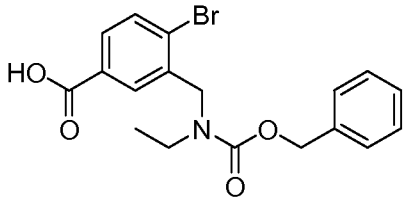
Step 4: Ethyl-carbamic acid benzyl ester

[00502] Ethylamine (1.3mL, 20.0mmol) and diisopropylethylamine (7mL, 40.0mmol) were combined in CH_2Cl_2 (200mL) and cooled to 0°C. Benzyl chloroformate (2.86mL, 20.0mmol) was added dropwise, and the reaction was stirred at 0°C for 30 minutes. Once no starting material was seen by analytical tlc, the mixture was warmed to room temperature and washed with H_2O, 0.1N aqueous HCl, and H_2O, and then dried and concentrated to give the title compound.



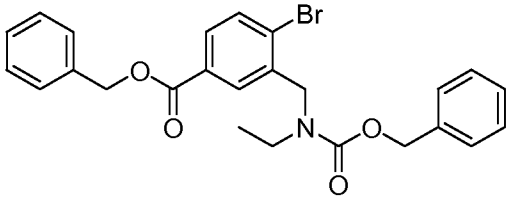
Step 5: 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-bromo-benzoic acid ethyl ester

[00503] 4-Bromo-3-bromomethyl-benzoic acid ethyl ester (2.95g, 9.2mmol) and ethyl-carbamic acid benzyl ester (3.30g, 18.4mmol) were combined in DMF (100mL) and cooled to 0°C. Sodium hydride (60% in mineral oil; 0.772g, 19.3mmol) was added slowly, and the reaction was stirred at room temperature for 10 minutes. The mixture was quenched with H_2O and 1N aqueous HCl (20mL), and then extracted with 1:1 EtOAc:hexanes three times. The organic layer was washed with brine, and then dried and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound, as well as the hydrolyzed product, which was combined with the product from the next step.



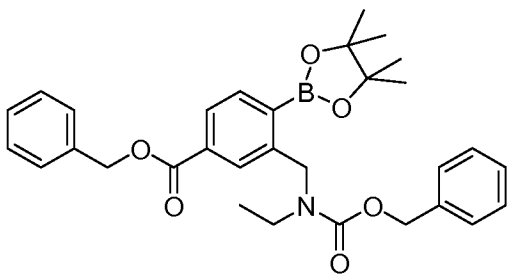
Step 6: 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-bromo-benzoic acid

[00504] 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-bromo-benzoic acid ethyl ester (3.62g, 7.2mmol) was dissolved in MeOH (40mL) and cooled to 0°C. 1N Aqueous LiOH (22mL, 22mmol) was added, and the reaction was stirred at room temperature for 3 hours. The mixture was quenched with 1N aqueous HCl (22mL) and extracted three times with EtOAc. The combined organic layers were washed with brine, dried, and concentrated to give the title compound, which was combined with the hydrolyzed product isolated in step 5.



Step 7: 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-bromo-benzoic acid benzyl ester

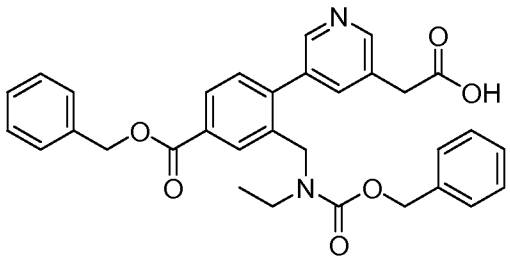
[00505] To 3-[(*N*-benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-bromo-benzoic acid (8.9g, 22.6mmol) in MeCN (400mL) was added cesium carbonate (18.4g, 56.5mmol), followed by benzyl bromide (2.95mL, 24.9mmol), and the reaction was stirred at room temperature overnight. The mixture was filtered and extracted with EtOAc and washed with H_2O. The organic layer was dried and concentrated, and the residue was purified by silica gel chromatography (0-25% EtOAc in hexanes) to give the title compound.



Step 8: 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid benzyl ester

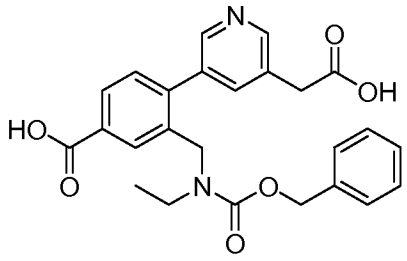
[00506] 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-bromo-benzoic acid benzyl ester (5.5g, 11.4mmol), bis(pinacolato)diboron (4.35g, 17.1mmol), and potassium acetate (4.1g, 45.6mmol) were combined in 1,4-dioxane (200mL), and the solution was purged with N_2 for 10 minutes. (1,1'-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.466g, 0.57mmol) was added, and the reaction was stirred at 80°C for 4 hours. Analytical LCMS indicated that starting

material was still present, so additional bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.466g, 0.57mmol) was added, and the reaction was stirred at 80°C overnight. The mixture was filtered over silica gel with 1:1 EtOAc:hexanes, and the filtrate was extracted with EtOAc three times and washed with brine. The organic layer was concentrated and purified by silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound.



Step 9: 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-carboxymethyl-pyridin-3-yl)-benzoic acid benzyl ester

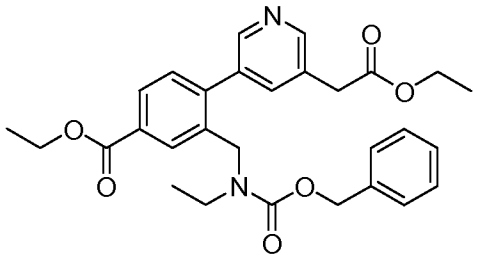
[00507] 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid benzyl ester (1.96g, 3.7mmol), (5-bromo-pyridin-3-yl)-acetic acid ethyl ester (0.99g, 4.1mmol), and potassium carbonate (1.79g, 13.0mmol) were combined in DME (40mL) and H_2O (30mL), and the solution was purged with N_2 for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.427g, 0.37mmol) was added, and the reaction was stirred at 70°C overnight. Analytical LCMS indicated that the ethyl ester had been hydrolyzed during the reaction, so the mixture was quenched with 1N aqueous HCl (13mL) and extracted with EtOAc. The combined organic layers were washed with H_2O, and then dried and concentrated to give the title compound.



Step 10: 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-carboxymethyl-pyridin-3-yl)-benzoic acid

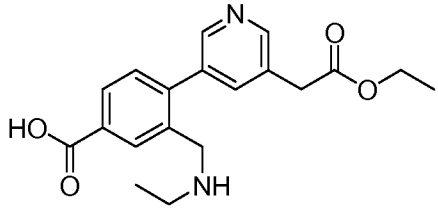
[00508] 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-carboxymethyl-pyridin-3-yl)-benzoic acid benzyl ester (0.369g, 0.68mmol) was dissolved in MeOH (4mL) and cooled to 0°C. 1N Aqueous LiOH (3mL, 3mmol) was added, and the reaction was stirred at room temperature for 1 hour. The mixture was quenched with 1N aqueous HCl (3mL) and extracted with EtOAc. The combined organic layers were washed with H_2O and concentrated, and the residue was purified by preparative HPLC to give the title compound.

Example 2: Synthesis of 4-(5-Carboxymethyl-pyridin-3-yl)-3-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-benzoic acid (Compound 1-2)



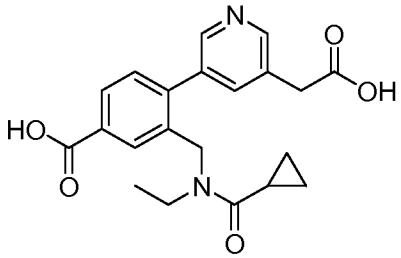
Step 1: 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-ethoxycarbonylmethyl-pyridin-3-yl)-benzoic acid ethyl ester

[00509] 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-carboxymethyl-pyridin-3-yl)-benzoic acid benzyl ester (1.74g, 3.2mmol) in EtOH (200mL) was treated with sulfuric acid (2mL), and the reaction was stirred at 95°C for 2 hours. The mixture was cooled to room temperature and concentrated, and the residue was partitioned between EtOAc and H_2O. The solution was extracted with EtOAc, and the combined organic layers were washed with 1N aqueous HCl and concentrated. The crude material was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.



Step 2: 4-(5-Ethoxycarbonylmethyl-pyridin-3-yl)-3-ethylaminomethyl-benzoic acid

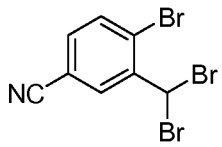
[00510] 3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-ethoxycarbonylmethyl-pyridin-3-yl)-benzoic acid ethyl ester (0.5g, 1mmol) was dissolved in MeOH (20mL), and the solution was purged with N_2 for 10 minutes. 10% Palladium on carbon (0.2g) was added, and the reaction was stirred under an atmosphere on H_2 at room temperature for 3 hours. Analytical LCMS indicated that starting material remained, so additional 10% palladium on carbon (0.1g) was added, and the reaction was stirred under H_2 overnight. Once no starting material was seen by analytical LCMS, the mixture was purged with N_2 and filtered over Celite. After washing with MeOH, the filtrate was concentrated to give the title compound.



Step 3: 4-(5-Carboxymethyl-pyridin-3-yl)-3-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-benzoic acid

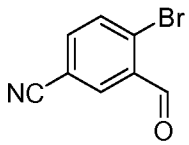
[00511] 4-(5-Ethoxycarbonylmethyl-pyridin-3-yl)-3-ethylaminomethyl-benzoic acid (0.347g, 1.0mmol) and diisopropylethylamine (0.44mL, 2.5mmol) were combined in CH_2Cl_2 (75mL). Cyclopropanecarbonyl chloride (0.12mL, 1.3mmol) was added slowly, and the reaction was stirred at room temperature for 10 minutes. The mixture was quenched with H_2O (100mL), and the product was extracted with CH_2Cl_2. The combined organic layers were washed with brine and concentrated. The crude material was dissolved in MeOH (75mL), and 1N aqueous LiOH (5mL) was added. The reaction was stirred at room temperature for 3 hours. Analytical LCMS indicated that starting material was still present, so additional 1N aqueous LiOH (1mL) was added, and the reaction was stirred at room temperature for 3 days. The mixture was quenched with 1N aqueous HCl (5mL) and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, and then concentrated to give the title compound.

Example 3: Synthesis of (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-cyano-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-3)



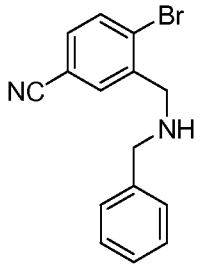
Step 1: 4-Bromo-3-dibromomethyl-benzonitrile

[00512] 4-Bromo-3-methylbenzonitrile (6.19g, 31.6mmol), N-bromosuccinimide (11.81g, 66.4mmol), and benzoyl peroxide (1.52g, 6.3mmol) were combined in CCl_4 (500mL) and stirred at 80°C for 3 days. The mixture was filtered over silica gel, diluted with H_2O, and extracted with EtOAc. The combined organic layers were dried and concentrated, and the residue was purified by silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound.



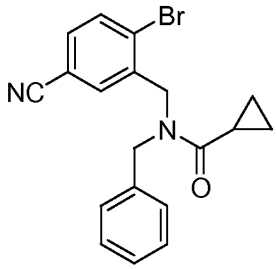
Step 2: 4-Bromo-3-formyl-benzonitrile

[00513] 4-Bromo-3-dibromomethyl-benzonitrile (5.66g, 16mmol) was dissolved in EtOH (150mL) and heated to 60°C. Silver nitrate (6.80g, 40mmol), prepared as a solution in H_2O (40mL), was added dropwise, and the reaction was heated to 75°C and stirred overnight. The organic layer was decanted, concentrated, and filtered, and the residue was partitioned between EtOAc and H_2O. The product was extracted with EtOAc, and the combined organic layers were concentrated and purified by silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound.



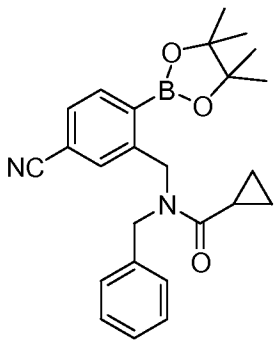
Step 3: 3-(Benzylamino-methyl)-4-bromo-benzonitrile

[00514] To 4-bromo-3-formyl-benzonitrile (2.42g, 11.5mmol) in MeOH (450mL) was added benzylamine (1.88mL, 17.3mmol) and sodium cyanoborohydride (1.09g, 17.3mmol). Acetic acid (0.99mL, 17.3mmol) was added dropwise, and the reaction was stirred at room temperature overnight. The mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried, concentrated, and purified by silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound.



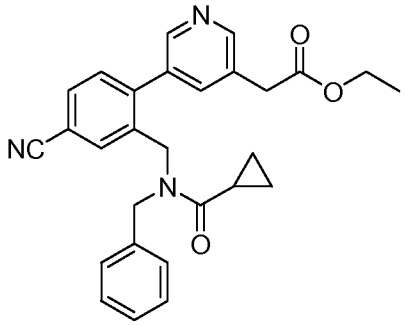
Step 4: Cyclopropanecarboxylic acid benzyl-(2-bromo-5-cyano-benzyl)-amide

[00515] Prepared according to the procedure described in Example 2, Step 3, using the following starting materials: 3-(benzylamino-methyl)-4-bromo-benzonitrile and cyclopropanecarbonyl chloride.



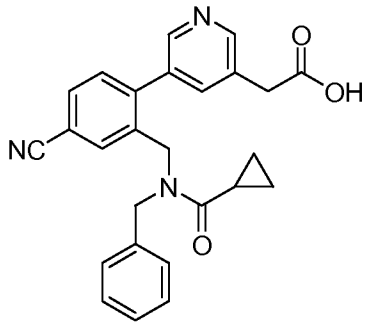
Step 5: Cyclopropanecarboxylic acid benzyl-[5-cyano-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-amide

[00516] Prepared according to the procedure described in Example 1, Step 8, using the following starting materials: cyclopropanecarboxylic acid benzyl-(2-bromo-5-cyano-benzyl)-amide and bis(pinacolato)diboron.



Step 6: (5-{2-[(Benzyl-cyclopropanecarbonyl-amino)-methyl]-4-cyano-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

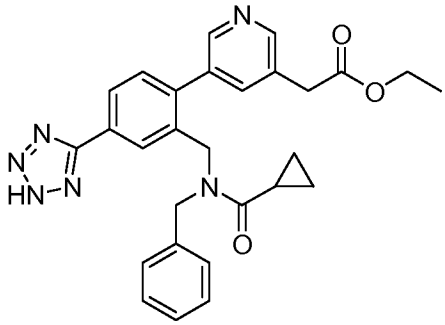
[00517] Cyclopropanecarboxylic acid benzyl-[5-cyano-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-amide (1.33g, 3.2mmol), (5-bromo-pyridin-3-yl)-acetic acid ethyl ester (1.02g, 4.2mmol), and potassium carbonate (1.55g, 11.2mmol) were combined in DME (40mL) and H_2O (30mL), and the solution was purged with N_2 for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.370g, 0.35mmol) was added, and the reaction was stirred at 70°C for 1 hour. Once no starting material was present by analytical LCMS, the mixture was diluted with H_2O and 1N aqueous HCl (15mL), and extracted with EtOAc. The combined organic layers were concentrated and purified by preparative HPLC to give the title compound, as well as the some of the hydrolyzed ester product.



Step 7: (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-cyano-phenyl}-pyridin-3-yl)-acetic acid

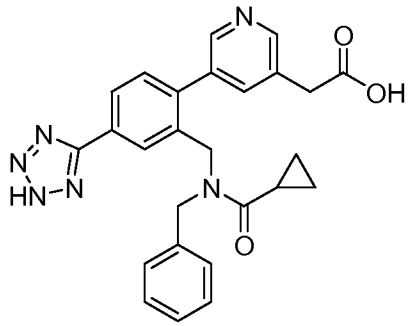
[00518] (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-cyano-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.1g, 0.22mmol) was dissolved in MeOH (10mL) and treated with 1N aqueous LiOH (1mL) dropwise. The reaction was stirred at room temperature for 1 hour, and then quenched with 1N aqueous HCl (1ml) and extracted with EtOAc. The combined organic layers were dried and concentrated to give the title compound.

Example 4: Synthesis of {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(2H-tetrazol-5-yl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-4)



Step 1: {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(2*H*-tetrazol-5-yl)-phenyl]-pyridin-3-yl}-acetic acid ethyl ester

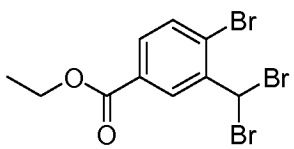
[00519] (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-cyano-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.253g, 0.56mmol) was dissolved in toluene (10mL). Dibutyltin oxide (0.014g, 0.06mmol) was added, followed by azidotrimethylsilane (0.09mL, 0.67mmol), and the reaction was stirred at 80°C for 5 hours, and at 100°C overnight. Although the reaction was only 50% complete, the mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were concentrated and purified by preparative HPLC to give the title compound.



Step 2: {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(2*H*-tetrazol-5-yl)-phenyl]-pyridin-3-yl}-acetic acid

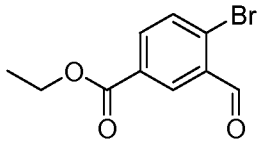
[00520] Prepared according to the procedure described in Example 1, Step 10, using the following starting material: {5-[2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(2*H*-tetrazol-5-yl)-phenyl]-pyridin-3-yl}-acetic acid ethyl ester.

Example 5: Synthesis of (5-{4-Benzylcarbamoyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-5)



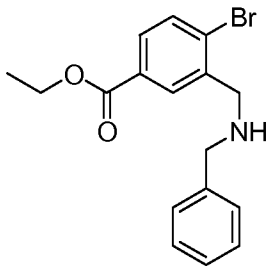
Step 1: 4-Bromo-3-dibromomethyl-benzoic acid ethyl ester

[00521] Prepared according to the procedure described in Example 3, Step 1, using the following starting material: 4-bromo-3-methyl-benzoic acid ethyl ester.



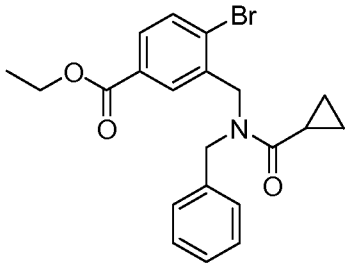
Step 2: 4-Bromo-3-formyl-benzoic acid ethyl ester

[00522] 4-Bromo-3-dibromomethyl-benzoic acid ethyl ester (6.4g, 16mmol) was dissolved in EtOH (200mL) and heated to 60°C. Silver nitrate (6.80g, 40mmol), prepared as a solution in H_2O (50mL), was added dropwise, resulting in a precipitate. After 1 hour, the mixture was decanted, and the precipitate was washed with EtOH (3x50mL) and decanted after each wash. The combined EtOH solution was treated with 1N aqueous HCl (40mL), which resulted in additional precipitate formation. The mixture was filtered, and the filtrate was concentrated and partitioned between EtOAc and H_2O. The aqueous layer was separated and extracted with EtOAc, and the combined organic layers were concentrated to give a mixture of the title compound and the diethyl acetal product. The mixture was dissolved in MeOH (100mL) and treated with 2N aqueous H_2SO_4 (15mL) for 1 hour at room temperature. After work-up, the crude material was purified by silica gel chromatography to give a mixture of the title compound and the dimethyl acetal. The mixture was dissolved in 1,4-dioxane and treated with 2N aqueous H_2SO_4 (80mL), and stirred overnight at room temperature. The solution was diluted with EtOAc and H_2O, and the organic layer was separated, dried, and concentrated to give the title compound.



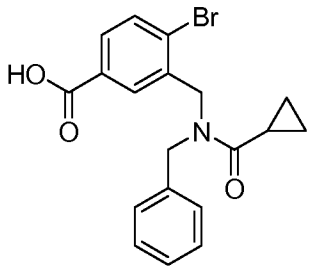
Step 3: 3-(Benzylamino-methyl)-4-bromo-benzoic acid ethyl ester

[00523] 4-Bromo-3-formyl-benzoic acid ethyl ester (3.3g, 12.9mmol) and benzylamine (2.1mL, 19.3mmol) were combined in EtOH (150mL) with 4Å molecular sieves. Sodium cyanoborohydride (1.21g, 19.3mmol) was added, followed by acetic acid (1.1mL, 19.3mmol), and the reaction was stirred at room temperature for 1 hour. Aqueous work-up provided the title compound.



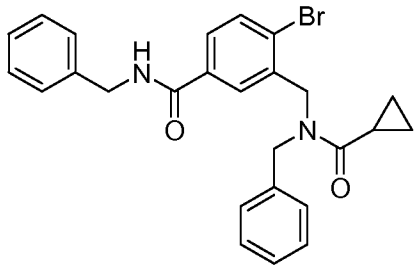
Step 4: 3-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzoic acid ethyl ester

[00524] 3-(Benzylamino-methyl)-4-bromo-benzoic acid ethyl ester (5.0g, 12.9mmol) and diisopropylethylamine (6.7mL, 38.7mmol) were combined in CH_2Cl_2 (100mL) at room temperature. Cyclopropanecarbonyl chloride (1.77mL, 19.4mmol) was added dropwise, and the reaction was stirred at room temperature until no starting material was seen by analytical LCMS. The mixture was worked-up and purified by silica gel chromatography to give the title compound.



Step 5: 3-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzoic acid

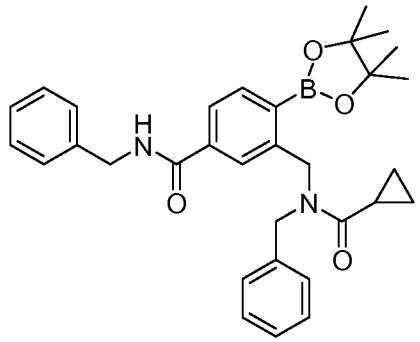
[00525] 3-[(*N*-Benzyl- *N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzoic acid ethyl ester (2.03g, 4.9mmol) was treated with 1N aqueous LiOH (10mL) in MeOH (60mL) and THF (10mL). After stirring for 1 hour at room temperature, additional 1N aqueous LiOH (10mL) was added, and the reaction was stirred for another 2 hours. The mixture was poured into H_2O (200mL) and neutralized with 1N aqueous HCl (50mL). The solution was extracted three times with EtOAc to give the title compound.



Step 6: *N*-Benzyl-3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzamide

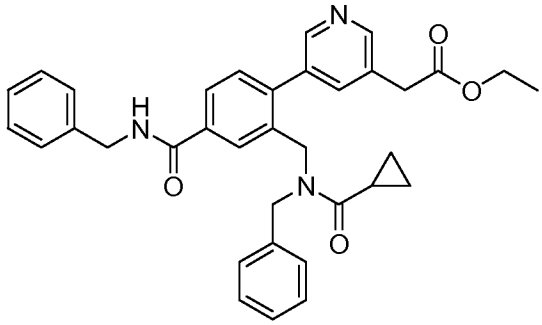
[00526] 3-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzoic acid (0.1g, 0.26mmol) and catalytic DMF (0.01mL) were combined in CH_2Cl_2 (4mL) at room temperature. Oxalyl chloride (0.03mL, 0.33mmol) was added, and the reaction was stirred for 30 minutes. The solution was concentrated and dried under vacuum, and then NMP (3mL) and diisopropylethylamine (0.14mL, 0.78mmol) were added. Benzylamine (0.04mL, 0.39mmol) was then added, and the reaction was stirred for 5 minutes. No starting material was observed by analytical LCMS and tlc, so the mixture was poured into H_2O and partitioned with 1:1

EtOAc:hexanes. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O, and dilute brine, and then dried, filtered, and concentrated to give the title compound.



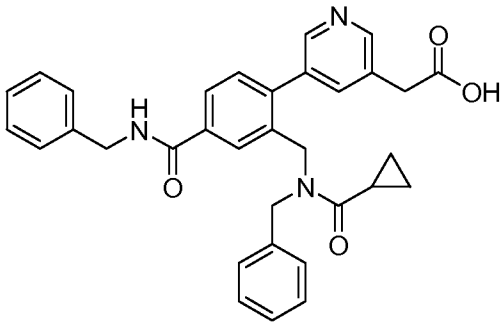
Step 7: *N*-Benzyl-3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide

[00527] Prepared according to the procedure described in Example 1, Step 8, using the following starting materials: *N*-benzyl-3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzamide and bis(pinacolato)diboron.



Step 8: (5-{4-Benzylcarbamoyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

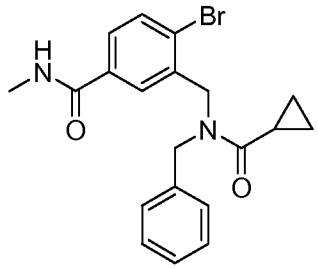
[00528] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: *N*-benzyl-3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.



Step 9: (5-{4-Benzylcarbamoyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid

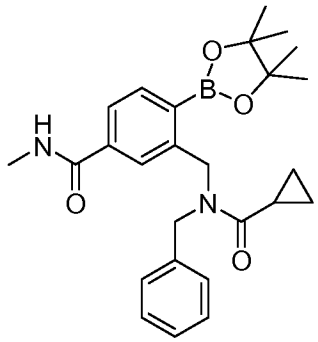
[00529] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (5-{4-benzylcarbamoyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 6: Synthesis of (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-methylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-6)



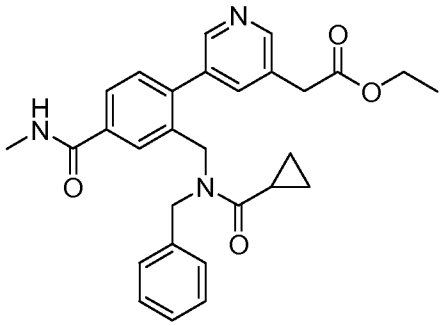
Step 1: 3-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-*N*-methyl-benzamide

[00530] Prepared according to the procedure described in Example 5, Step 6, using the following starting materials: 3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzoic acid and methylamine (2M in THF).



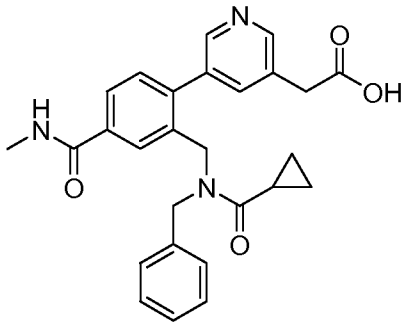
Step 2: 3-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-*N*-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide

[00531] Prepared according to the procedure described in Example 1, Step 8, using the following starting materials: 3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-*N*-methyl-benzamide and bis(pinacolato)diboron.



Step 3: (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-methylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

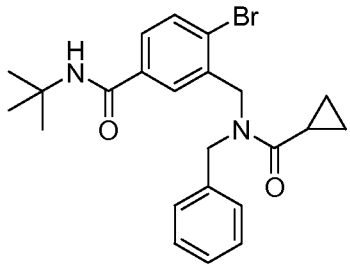
[00532] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: 3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-*N*-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.



Step 4: (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-methylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid

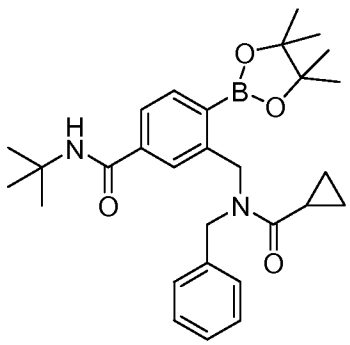
[00533] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (5-{2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-methylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 7: Synthesis of (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-*tert*-butylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-7)



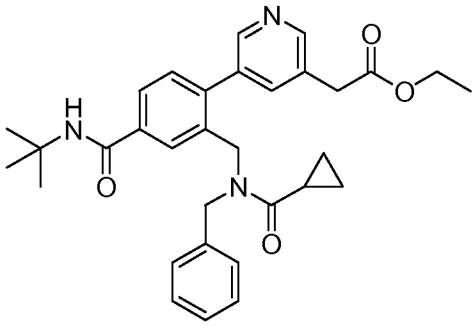
Step 1: 3-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-*N*-*tert*-butyl-benzamide

[00534] Prepared according to the procedure described in Example 5, Step 6, using the following starting materials: 3-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzoic acid and *tert*-butylamine.



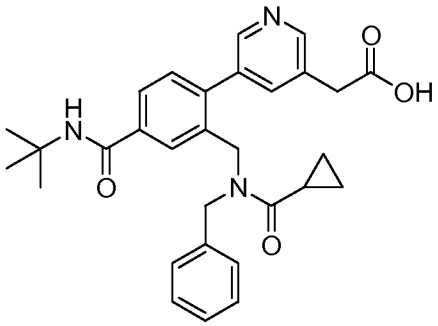
Step 2: 3-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-*N*-*tert*-butyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide

[00535] Prepared according to the procedure described in Example 1, Step 8, using the following starting materials: 3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-bromo-*N*-*tert*-butyl-benzamide and bis(pinacolato)diboron.



Step 3: (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-*tert*-butylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

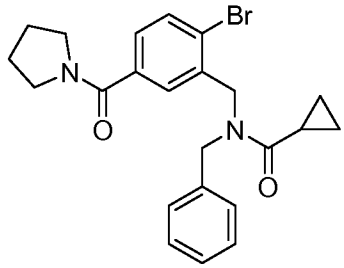
[00536] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: 3-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-*N*-*tert*-butyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.



Step 4: (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-*tert*-butylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid

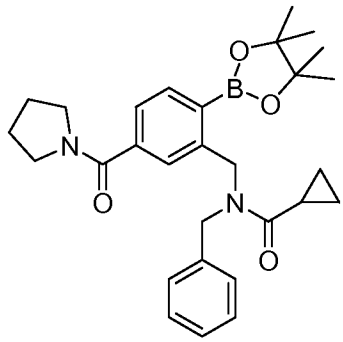
[00537] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (5-{2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-*tert*-butylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 8: Synthesis of {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-8)



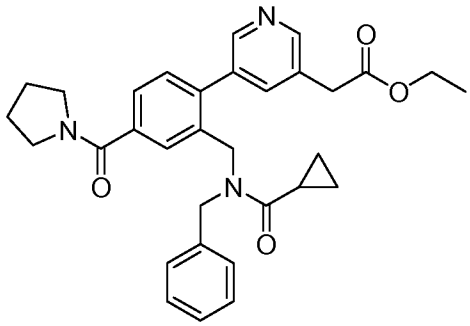
Step 1: Cyclopropanecarboxylic acid benzyl-[2-bromo-5-(pyrrolidine-1-carbonyl)-benzyl]-amide

[00538] Prepared according to the procedure described in Example 5, Step 6, using the following starting materials: 3-[(benzyl-cyclopropanecarbonyl-amino)-methyl]-4-bromo-benzoic acid and pyrrolidine.



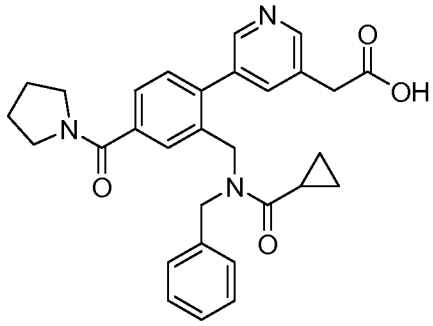
Step 2: Cyclopropanecarboxylic acid benzyl-[5-(pyrrolidine-1-carbonyl)-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-amide

[00539] Prepared according to the procedure described in Example 1, Step 8, using the following starting materials: cyclopropanecarboxylic acid benzyl-[2-bromo-5-(pyrrolidine-1-carbonyl)-benzyl]-amide and bis(pinacolato)diboron.



Step 3: {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yl}-acetic acid ethyl ester

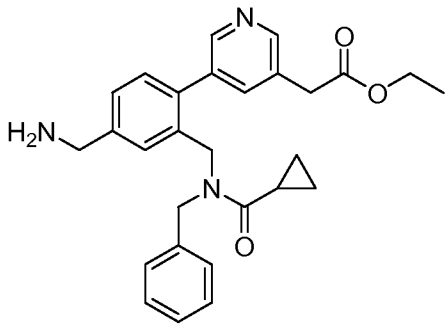
[00540] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: cyclopropanecarboxylic acid benzyl-[5-(pyrrolidine-1-carbonyl)-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-amide and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.



Step 4: {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yl}-acetic acid

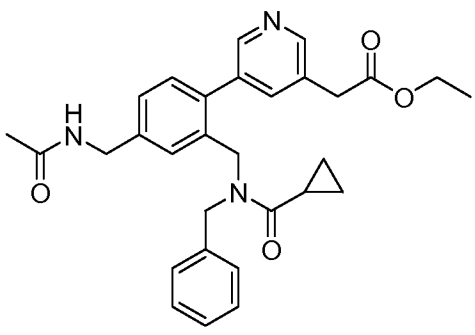
[00541] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: {5-[2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yl}-acetic acid ethyl ester.

Example 9: Synthesis of (5-{4-(Acetylamino-methyl)-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-9)



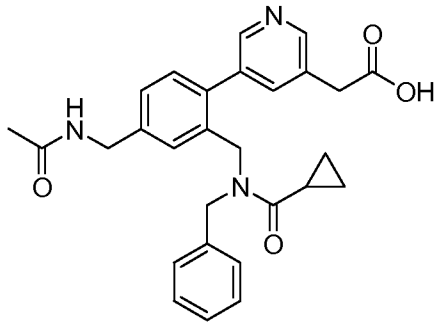
Step 1: (5-{4-Aminomethyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

[00542] To a solution of (5-{2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-cyano-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.335g, 0.78mmol) and cobalt chloride hexahydrate (0.351g, 1.48mmol) in MeOH (20mL) and THF (8mL) was added sodium borohydride (0.286g, 1.55mmol), and the reaction was stirred at room temperature for 30 minutes. The mixture was quenched with 1N aqueous HCl (2mL) and extracted with CH_2Cl_2. The combined organic layers were washed with aqueous NH_4Cl and brine, dried, and concentrated to give the title compound.



Step 2: (5-{4-(Acetylamino-methyl)-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

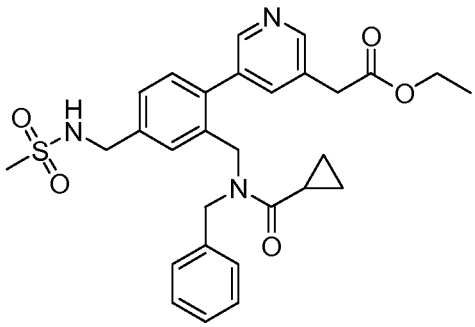
[00543] Prepared according to the procedure described in Example 2, Step 3, using the following starting materials: (5-{4-aminomethyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid ethyl ester and acetyl chloride.



Step 3: (5-{4-(Acetylamino-methyl)-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid

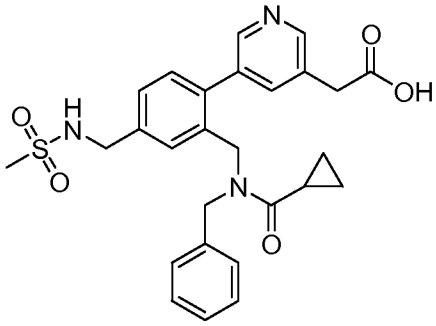
[00544] Prepared according to the procedure described in Example 2, Step 4, using the following starting material: (5-{4-(acetylamino-methyl)-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 10: Synthesis of {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(methanesulfonylamino-methyl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-10)



Step 1: {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(methanesulfonylamino-methyl)-phenyl]-pyridin-3-yl}-acetic acid ethyl ester

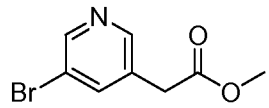
[00545] Prepared according to the procedure described in Example 2, Step 3, using the following starting materials: (5-{4-aminomethyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid ethyl ester and methanesulfonyl chloride.



Step 2: {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(methanesulfonylamino-methyl)-phenyl]-pyridin-3-yl}-acetic acid

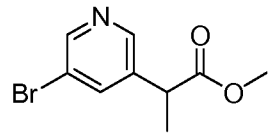
[00546] Prepared according to the procedure described in Example 2, Step 4, using the following starting material: {5-[2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(methanesulfonylamino-methyl)-phenyl]-pyridin-3-yl}-acetic acid ethyl ester.

Example 11: Synthesis of 2-(5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid (Compound 1-11)



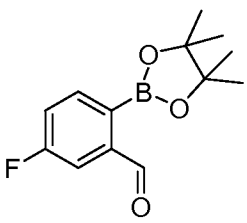
Step 1: (5-Bromo-pyridin-3-yl)-acetic acid methyl ester

[00547] To 5-bromo-3-pyridylacetic acid (0.9g, 4.2mmol) in MeOH (75mL) was added concentrated sulfuric acid (0.5mL), and the reaction was stirred at reflux overnight. The mixture was concentrated and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to give the title compound.



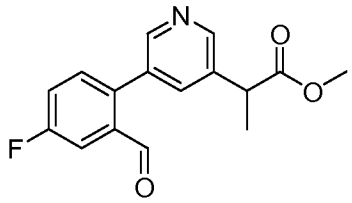
Step 2: 2-(5-Bromo-pyridin-3-yl)-propionic acid methyl ester

[00548] (5-Bromo-pyridin-3-yl)-acetic acid methyl ester (1.57g, 6.8mmol) was dissolved in THF (80mL) and cooled to -78°C in an oven-dried round bottom flask. Lithium hexamethyldisilazide (1M in toluene; 8.16mL, 8.2mmol) was added slowly, and the mixture was stirred for 1 hour. Iodomethane (0.53mL, 8.5mmol) was added slowly, and the reaction was allowed to warm to room temperature. The mixture was worked-up with EtOAc and H_2O, and the crude material was purified by silica gel chromatography (0-35% EtOAc in hexanes) to give the title compound.



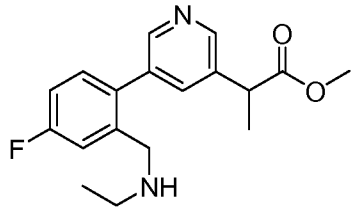
Step 3: 5-Fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde

[00549] Prepared according to the procedure described in Example 1, Step 8, using the following starting materials: 2-bromo-5-fluorobenzaldehyde and bis(pinacolato)diboron.



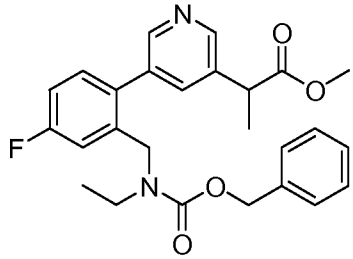
Step 4: 2-[5-(4-Fluoro-2-formyl-phenyl)-pyridin-3-yl]-propionic acid methyl ester

[00550] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: 2-(5-bromo-pyridin-3-yl)-propionic acid methyl ester and 5-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde.



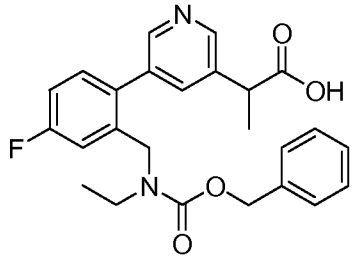
Step 5: 2-[5-(2-Ethylaminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-propionic acid methyl ester

[00551] Prepared according to the procedure described in Example 5, Step 3, using the following starting materials: 2-[5-(4-fluoro-2-formyl-phenyl)-pyridin-3-yl]-propionic acid methyl ester and ethylamine (2M in THF).



Step 6: 2-(5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid methyl ester

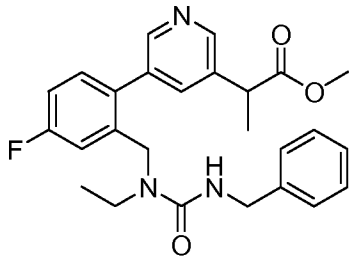
[00552] Prepared according to the procedure described in Example 2, Step 3, using the following starting materials: 2-[5-(2-ethylaminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-propionic acid methyl ester and benzyl chloroformate.



Step 7: 2-(5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid

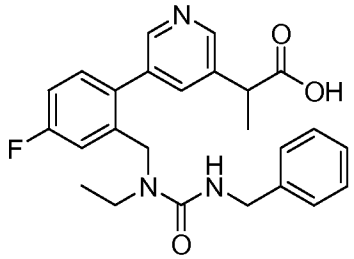
[00553] Prepared according to the procedure described in Example 2, Step 4, using the following starting material: 2-(5-{2-[(*N*-benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid methyl ester.

Example 12: Synthesis of 2-{5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-fluoro-phenyl]-pyridin-3-yl}-propionic acid (Compound 1-12)



Step 1: 2-{5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-fluoro-phenyl]-pyridin-3-yl}-propionic acid methyl ester

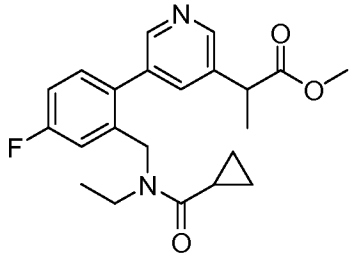
[00554] Prepared according to the procedure described in Example 2, Step 3, using the following starting materials: 2-[5-(2-ethylaminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-propionic acid methyl ester and benzyl isocyanate.



Step 2: 2-{5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-fluoro-phenyl]-pyridin-3-yl}-propionic acid

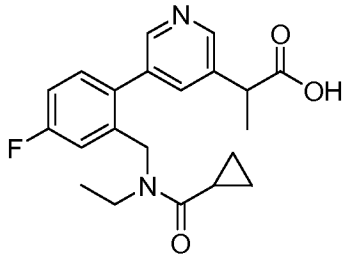
[00555] Prepared according to the procedure described in Example 2, Step 4, using the following starting material: 2-{5-[2-(3-benzyl-1-ethyl-ureidomethyl)-4-fluoro-phenyl]-pyridin-3-yl}-propionic acid methyl ester.

Example 13: Synthesis of 2-(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid (Compound 1-13)



Step 1: 2-(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid methyl ester

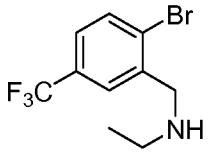
[00556] Prepared according to the procedure described in Example 2, Step 3, using the following starting materials: 2-[5-(2-Ethylaminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-propionic acid methyl ester and cyclopropanecarbonyl chloride.



Step 2: 2-(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid

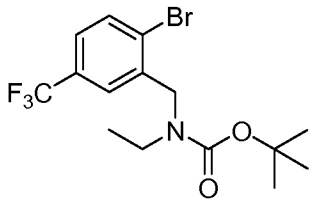
[00557] Prepared according to the procedure described in Example 2, Step 4, using the following starting material: 2-(5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid methyl ester.

Example 14: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-14)



Step 1: (2-Bromo-5-trifluoromethyl-benzyl)-ethyl-amine

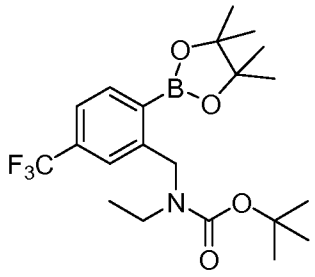
[00558] To 2-bromo-5-(trifluoromethyl)benzaldehyde (7.5g, 29.6mmol) in MeOH (80mL) was added ethylamine (2M in MeOH; 30mL, 60mmol), sodium cyanoborohydride (3.7g, 58.9mmol), and acetic acid (1.7mL, 26.2mmol), and the reaction was stirred at room temperature for 4 days. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by silica gel chromatography (0-4% MeOH in CH_2Cl_2) to give the title compound.



Step 2: (2-Bromo-5-trifluoromethyl-benzyl)-ethyl-carbamic acid *tert*-butyl ester

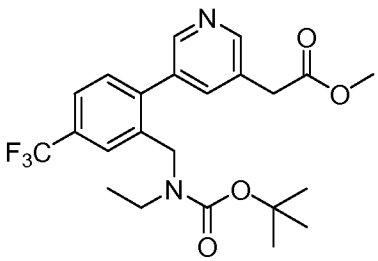
[00559] (2-Bromo-5-trifluoromethyl-benzyl)-ethyl-amine (3.6g, 12.8mmol) and di-*tert*-butyl dicarbonate (3.74g, 17.1mmol) were combined in CH_2Cl_2 (30mL) and stirred at room temperature for 1 hour. The mixture was quenched with saturated aqueous $NaHCO_3$ and

extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the title compound.



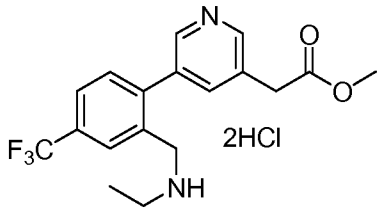
Step 3: Ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid *tert*-butyl ester

[00560] (2-Bromo-5-trifluoromethyl-benzyl)-ethyl-carbamic acid *tert*-butyl ester (3.23g, 8.5mmol), bis(pinacolato)diboron (2.57g, 10.1mmol), potassium acetate (2.5g, 25.5mmol), and bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.390g, 0.5mmol) were combined in 1,4-dioxane (30mL). The solution was purged with N_2, and then the reaction was stirred at 85°C for 14 hours. Once no starting material was seen by analytical LCMS, the mixture was concentrated and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was filtered through a plug of silica gel (20% EtOAc in hexanes) to give the title compound.



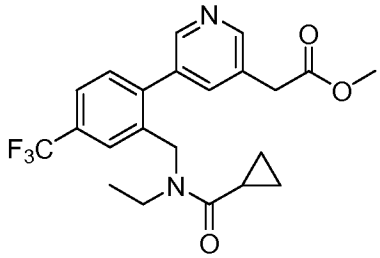
Step 4: (5-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester

[00561] Ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid *tert*-butyl ester (1.0g, 2.33mmol), (5-bromo-pyridin-3-yl)-acetic acid methyl ester (0.535g, 2.33mmol), potassium carbonate (0.807g, 5.8mmol), and tetrakis(triphenylphosphine)palladium(0) (0.100g, 0.09mmol) were combined in DME (8mL) and H_2O (4mL). The solution was purged with N_2, and then the reaction was stirred at 80°C for 12 hours. The mixture was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography to give the title compound.



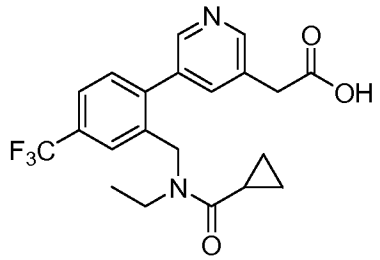
Step 5: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid methyl ester, dihydrochloride

[00562] To (5-{2-[(*N*-*tert*-butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester (0.742g, 1.6mmol) in CH_2Cl_2 (3mL) was added 4N HCl in 1,4-dioxane (4mL), and the reaction was stirred at room temperature until no starting material was seen by analytical LCMS. The mixture was then concentrated to give the title compound.



Step 6: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester

[00563] [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid methyl ester, dihydrochloride (0.108g, 0.25mmol), cyclopropanecarboxylic acid (0.02mL, 0.30mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.073g, 0.38mmol), 1-hydroxybenzotriazole hydrate (0.051g, 0.38mmol), and triethylamine (0.16mL, 1.14mmol) were combined in CH_2Cl_2 (1mL) and stirred at room temperature for 45 minutes. Once no starting material was seen by analytical LCMS, the mixture was diluted with aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.

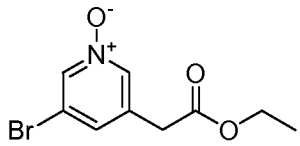


Step 7: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

[00564] (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester (0.069g, 0.16mmol) was dissolved in THF (1mL) and

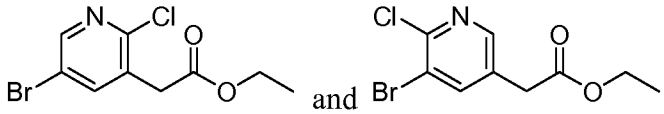
MeOH (0.8mL) and treated with 1N aqueous NaOH (0.5mL). The reaction was stirred at room temperature for 1 hour, until no starting material was seen by analytical LCMS. The mixture was neutralized with 1N aqueous HCl and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the title compound.

Example 15: Synthesis of (2-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-15)



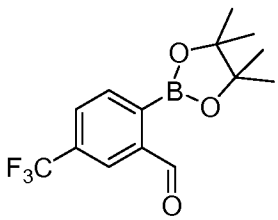
Step 1: (5-Bromo-1-oxy-pyridin-3-yl)-acetic acid ethyl ester

[00565] To (5-bromo-pyridin-3-yl)-acetic acid ethyl ester (5.0g, 20.5mmol) in CH_2Cl_2 (50mL) was added meta-chloroperoxybenzoic acid (77 wt%; 7.03g, 30.7mmol), and the reaction was stirred overnight at room temperature. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and 1N aqueous NaOH to give the title compound.



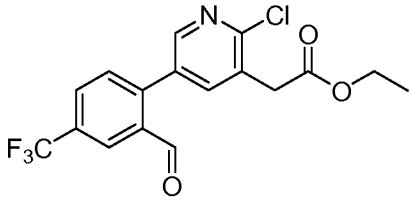
Step 2: (5-Bromo-2-chloro-pyridin-3-yl)-acetic acid ethyl ester and (5-Bromo-6-chloro-pyridin-3-yl)-acetic acid ethyl ester

[00566] (5-Bromo-1-oxy-pyridin-3-yl)-acetic acid ethyl ester (4.28g, 16.5mmol) was treated with phosphorus oxychloride (20mL) and stirred at 90°C for 1.5 hours. After cooling to room temperature, the reaction was quenched by pouring into saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the separated title compounds.



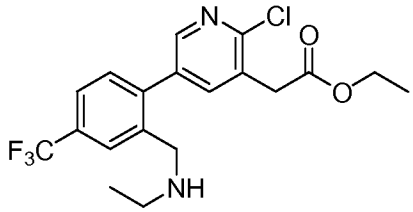
Step 3: 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzaldehyde

[00567] Prepared according to the procedure described in Example 1, Step 8, using the following starting materials: 2-bromo-5-(trifluoromethyl)benzaldehyde and bis(pinacolato)diboron.



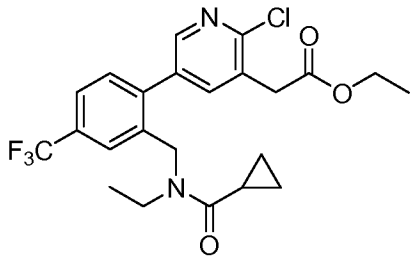
Step 4: [2-Chloro-5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

[00568] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: (5-bromo-2-chloro-pyridin-3-yl)-acetic acid ethyl ester and 2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzaldehyde.



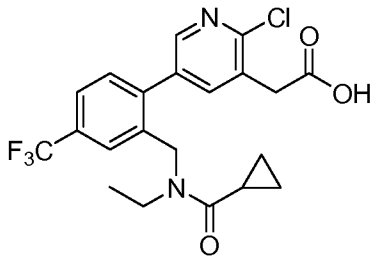
Step 5: [2-Chloro-5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

[00569] Prepared according to the procedure described in Example 3, Step 3, using the following starting materials: [2-chloro-5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and ethylamine (2M in THF).



Step 6: (2-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

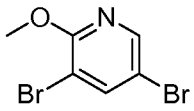
[00570] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [2-chloro-5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and cyclopropanecarboxylic acid.



Step 7: (2-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

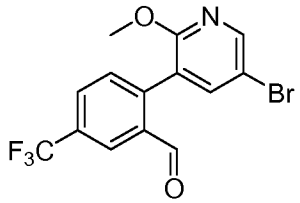
[00571] Prepared according to the procedure described in Example 14, Step 7, using the following starting material: (2-chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 16: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-16)



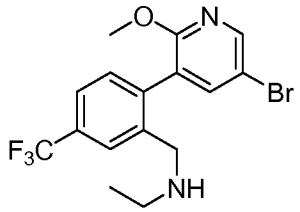
Step 1: 3,5-Dibromo-2-methoxy-pyridine

[00572] To 5-bromo-2-methoxypyridine (0.564g, 3.0mmol) and sodium acetate (0.246g, 3.0mmol) in acetic acid (3mL) was added bromine (0.27mL, 5.25mmol), and the mixture was stirred at 80°C for 3 hours, and then at room temperature overnight. The mixture was diluted with H_2O and extracted with EtOAc, and the combined organic layers were washed with saturated aqueous Na_2CO_3 and saturated aqueous $Na_2S_2O_3$. The organic layer was concentrated and dried under high vacuum to give the title compound.



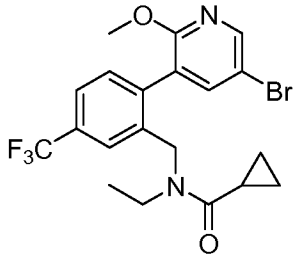
Step 2: 2-(5-Bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzaldehyde

[00573] 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzaldehyde (1.59g, 4.4mmol), 3,5-dibromo-2-methoxy-pyridine (1.19g, 4.4mmol), and potassium carbonate (2.17g, 15.6mmol) were combined in DME (13mL) and H_2O (6mL). The solution was purged with N_2 for 30 minutes, and dichlorobis(triphenylphosphine)palladium(II) (0.156g, 0.22mmol) was added. The reaction was stirred at 85°C overnight, and then cooled to room temperature and worked-up with EtOAc and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound, which was repurified by preparative HPLC.



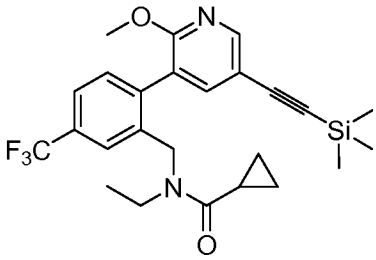
Step 3: [2-(5-Bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-ethyl-amine

[00574] Prepared according to the procedure described in Example 3, Step 3, using the following starting materials: 2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzaldehyde and ethylamine (2M in THF).



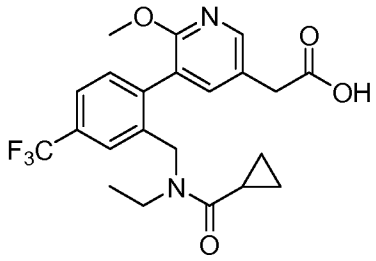
Step 4: Cyclopropanecarboxylic acid [2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-ethyl-amide

[00575] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-ethyl-amine and cyclopropanecarboxylic acid.



Step 5: Cyclopropanecarboxylic acid ethyl-[2-(2-methoxy-5-trimethylsilanylethynyl-pyridin-3-yl)-5-trifluoromethyl-benzyl]-amide

[00576] Cyclopropanecarboxylic acid [2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-ethyl-amide (0.215g, 0.47mmol), (trimethylsilyl)acetylene (0.07mL, 0.47mmol), and copper iodide (0.012g, 0.05mmol) were combined in triethylamine (2mL), and the solution was purged with N_2 for 25 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.039g, 0.05mmol) was added, and the reaction was stirred at room temperature overnight. The mixture was worked-up with CH_2Cl_2 and H_2O, and the combined organic layers were dried, filtered, and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.

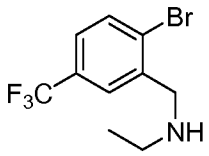


Step 5: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid

[00577] To cyclopropanecarboxylic acid ethyl-[2-(2-methoxy-5-trimethylsilanylethynyl-pyridin-3-yl)-5-trifluoromethyl-benzyl]-amide (0.205g, 0.42mmol) in THF (2mL) at 0°C was added borane tetrahydrofuran complex (1M in THF; 0.48mL, 0.48mmol), and the reaction was stirred

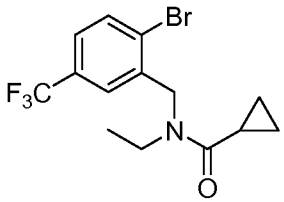
for 2 hours. Once no starting material was seen by analytical LCMS, MeOH (0.22mL), hydrogen peroxide (0.04mL, 0.43mmol), and 3M aqueous sodium hydroxide (0.22ml) was added, and the reaction was stirred for 1 hour. Additional hydrogen peroxide (0.1mL) was added, and the reaction was stirred for another hour. The mixture was then acidified and extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative HPLC to give the title compound.

Example 17: Synthesis of (6-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-17)



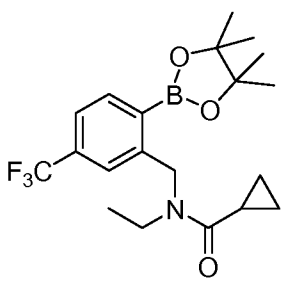
Step 1: (2-Bromo-5-trifluoromethyl-benzyl)-ethyl-amine

[00578] 2-Bromo-5-(trifluoromethyl)benzaldehyde (20g, 79.1mmol), ethylamine (2M in MeOH; 59.3mL, 118.6mmol), and sodium cyanoborohydride (7.45g, 118.6mmol) were combined in MeOH (200mL). Acetic acid (6.79mL, 118.6mmol) was added, and the reaction was stirred at room temperature overnight. The mixture was concentrated and partitioned between CH_2Cl_2 and H_2O. The aqueous layer was separated and extracted twice with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated to give the title compound.



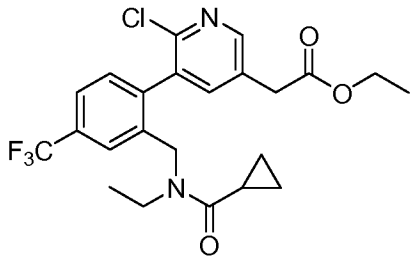
Step 2: Cyclopropanecarboxylic acid (2-bromo-5-trifluoromethyl-benzyl)-ethyl-amide

[00579] To (2-bromo-5-trifluoromethyl-benzyl)-ethyl-amine (22.3g, 79.1mmol) and triethylamine (16.53mL, 118.6mmol) in CH_2Cl_2 (200mL) was added cyclopropanecarbonyl chloride (8.68mL, 94.9mmol) dropwise over 15 minutes, and the reaction was stirred at room temperature for 2 hours. The mixture was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were dried and concentrated, and the residue was purified by silica gel chromatography (10-30% EtOAc in hexanes) to give the title compound.



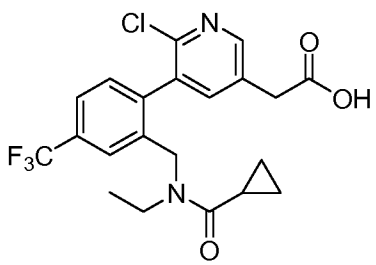
Step 3: Cyclopropanecarboxylic acid ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide

[00580] Cyclopropanecarboxylic acid (2-bromo-5-trifluoromethyl-benzyl)-ethyl-amide (22.1g, 63.1mmol), bis(pinacolato)diboron (17.6g, 69.5mmol), and potassium acetate (15.5g, 157.9mmol) were combined in 1,4-dioxane, and the solution was purged with N_2. (1,1'-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (2.58 g, 3.2mmol) was added, and the reaction was stirred at 100°C overnight. After cooling to room temperature, the mixture was filtered through Celite and rinsed with EtOAc and H_2O. The filtrate was worked up with brine and EtOAc, and the organic layer was separated, dried and concentrated. The residue was purified by silica gel chromatography (10-20% EtOAc in hexanes) to give the title compound.



Step 4: (6-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

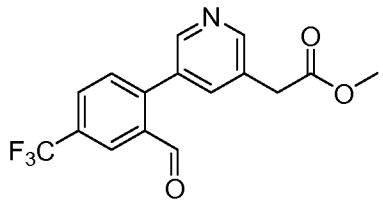
[00581] (5-Bromo-6-chloro-pyridin-3-yl)-acetic acid ethyl ester (0.549g, 1.97mmol), cyclopropanecarboxylic acid ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide (0.787g, 1.97mmol), and potassium carbonate (0.824g, 5.91mmol) were combined in DME (6mL) and H2O (3mL), and the solution was purged with N_2 for 40 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.338g, 0.20mmol) was added, and the reaction was stirred at 85°C for 2 hours. After cooling to room temperature, the mixture was worked-up with EtOAc, H_2O, and brine, and the organic layer was separated, dried, filtered, and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.



Step 5: (6-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

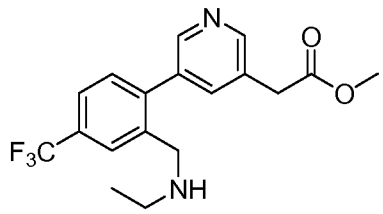
[00582] Prepared according to the procedure described in Example 14, Step 7, using the following starting material: (6-chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 18: Synthesis of (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-18)



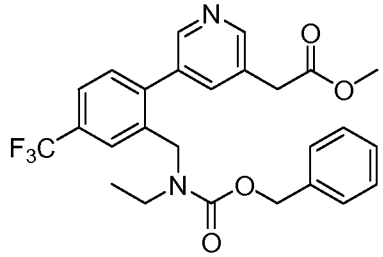
Step 1: [5-(2-Formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid methyl ester

[00583] Prepared according to the procedure described in Example 14, Step 4, using the following starting materials: 2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzaldehyde and (5-bromo-pyridin-3-yl)-acetic acid methyl ester.



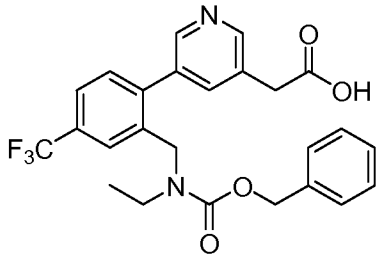
Step 2: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid methyl ester

[00584] Prepared according to the procedure described in Example 14, Step 1, using the following starting materials: [5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid methyl ester and ethylamine (2M in MeOH).



Step 3: (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester

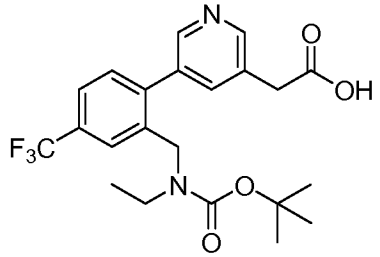
[00585] Prepared according to the procedure described in Example 17, Step 2, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid methyl ester and benzyl chloroformate.



Step 4: (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

[00586] (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester (0.1g, 0.2mmol) in THF (2mL), MeOH (0.5mL), and H_2O (0.5mL) was treated with lithium hydroxide (0.03g) and stirred at room temperature until no starting material was seen by analytical LCMS. The reaction was neutralized with citric acid to pH 4 and extracted with EtOAc, and the combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated to give the title compound.

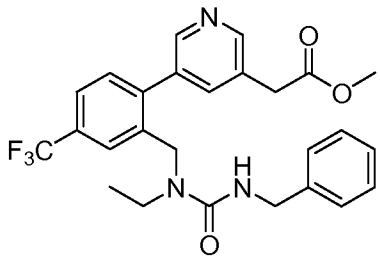
Example 19: Synthesis of (5-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-19)



Step 1: (5-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

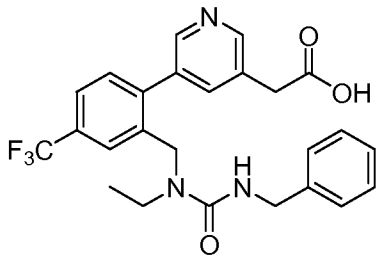
[00587] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: (5-{2-[(*N*-*tert*-butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester.

Example 20: Synthesis of {5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-20)



Step 1: {5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid methyl ester

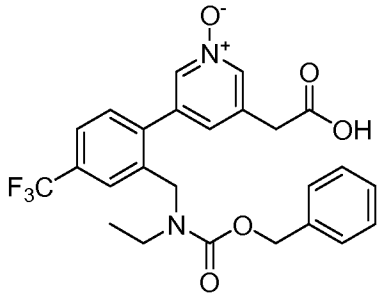
[00588] Prepared according to the procedure described in Example 2, Step 3, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid methyl ester, dihydrochloride and benzyl isocyanate.



Step 2: {5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid

[00589] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: {5-[2-(3-benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid methyl ester.

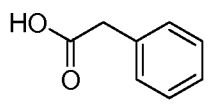
Example 21: Synthesis of (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-1-oxy-pyridin-3-yl)-acetic acid (Compound 1-21)



Step 1: (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-1-oxy-pyridin-3-yl)-acetic acid

[00590] (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (0.1g, 0.2mmol) and meta-chloroperoxybenzoic acid (77 wt%; 0.05g, 0.2mmol) were combined in CH_2Cl_2 (2mL) and stirred at room temperature until no starting material was seen by analytical LCMS. The mixture was concentrated and purified by preparative HPLC to give the title compound.

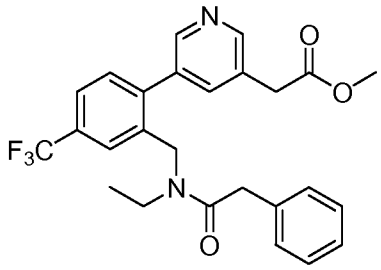
Example 22: Synthesis of (5-{2-[(*N*-Ethyl-*N*-phenylacetyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-22)



Step 1: Phenyl-acetic acid

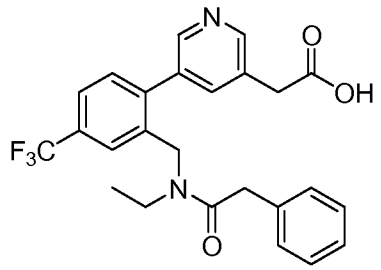
[00591] Methyl phenylacetate (5.03g, 33.5mmol) was treated with 1N aqueous NaOH (22mL, 22mmol) in THF (40mL) and MeOH (4mL), and stirred overnight at room temperature.

Additional 1N aqueous NaOH (22mL, 22mmol) was added, and the reaction was stirred for 6 hours at room temperature, until no starting material was seen by analytical LCMS. The mixture was acidified with 1N aqueous HCl to pH 3-4 and extracted with EtOAc three times. The combined organic layers were dried and concentrated to give the title compound.



Step 2: (5-{2-[(*N*-Ethyl-*N*-phenylacetyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester

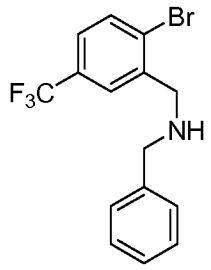
[00592] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid methyl ester, dihydrochloride and phenyl-acetic acid.



Step 3: (5-{2-[(*N*-Ethyl-*N*-phenylacetyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

[00593] Prepared according to the procedure described in Example 14, Step7, using the following starting material: (5-{2-[(*N*-ethyl-*N*-phenylacetyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid methyl ester.

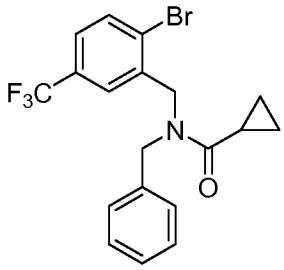
Example 23: Synthesis of (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-23)



Step 1: Benzyl-(2-bromo-5-trifluoromethyl-benzyl)-amine

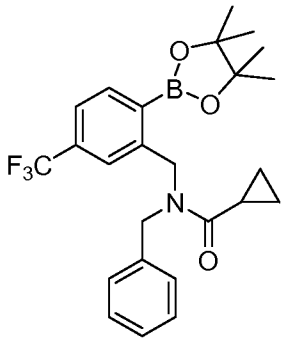
[00594] 2-Bromo-5-(trifluoromethyl)benzaldehyde (3g, 11.9mmol), benzylamine (1.94mL, 17.8mmol), and sodium cyanoborohydride (1.12g, 17.8mmol) were combined in MeOH (30mL). Acetic acid (1.02mL, 17.8mmol) was added, and the reaction was stirred at room temperature for

2 hours. The mixture was concentrated, and the residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was separated and extracted twice with CH_2Cl_2, and the combined organic layers were dried, concentrated, and purified by silica gel chromatography (10-40% EtOAc in hexanes) to give the title compound.



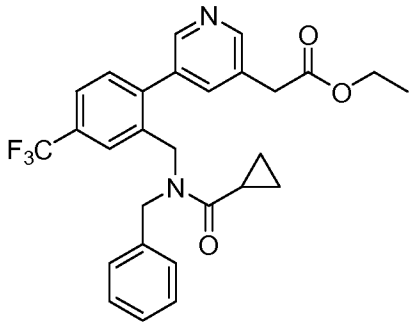
Step 2: Cyclopropanecarboxylic acid benzyl-(2-bromo-5-trifluoromethyl-benzyl)-amide

[00595] Prepared according to the procedure described in Example 17, Step 2, using the following starting materials: benzyl-(2-bromo-5-trifluoromethyl-benzyl)-amine and cyclopropanecarbonyl chloride.



Step 3: Cyclopropanecarboxylic acid benzyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide

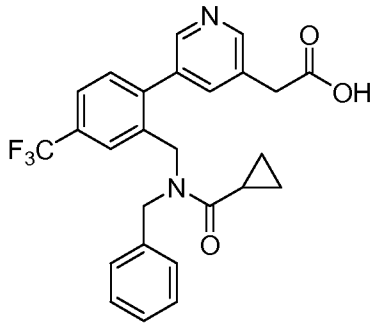
[00596] Prepared according to the procedure described in Example 17, Step 3, using the following starting materials: cyclopropanecarboxylic acid benzyl-(2-bromo-5-trifluoromethyl-benzyl)-amide and bis(pinacolato)diboron.



Step 4: (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

[00597] Cyclopropanecarboxylic acid benzyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide (60% pure; 1.07g, 1.4mmol), (5-bromo-pyridin-3-yl)-acetic acid

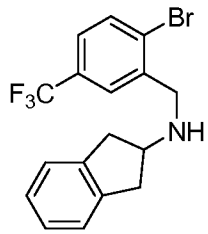
ethyl ester (0.375g, 1.5mmol), and potassium carbonate (0.484g, 3.5mmol) were combined in DME (8mL) and H_2O (4mL), and the solution was purged with N_2 for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.162g, 0.14mmol) was added, and the reaction was stirred at 90°C overnight. Analytical LCMS indicated that some of the ester had been hydrolyzed during the coupling reaction, so the mixture was diluted with saturated aqueous NH_4Cl and EtOAc. The aqueous layer was separated and extracted twice with EtOAc, and the combined organic layers were dried and concentrated. The residue was purified by preparative HPLC to give the title compound, which was then hydrolyzed in the following step, as well as the hydrolyzed product.



Step 5: (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

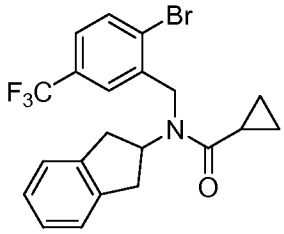
[00598] To (5-{2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.043g, 0.09mmol) in THF (3mL) and MeOH (0.3mL) was added 1N aqueous LiOH (3mL), and the reaction was stirred at room temperature. The mixture was neutralized with 1N aqueous HCl to pH 4-5 and extracted three times with EtOAc. The combined organic layers were dried and concentrated, and the residue was purified by preparative HPLC to give the title compound.

Example 24: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-indan-2-yl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-24)



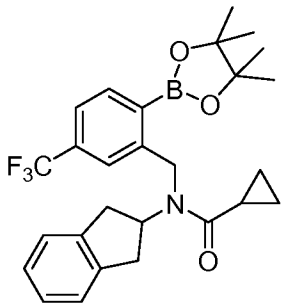
Step 1: (2-Bromo-5-trifluoromethyl-benzyl)-indan-2-yl-amine

[00599] Prepared according to the procedure described in Example 23, Step 1, using the following starting materials: 2-bromo-5-(trifluoromethyl)benzaldehyde and 2-aminoindan hydrochloride.



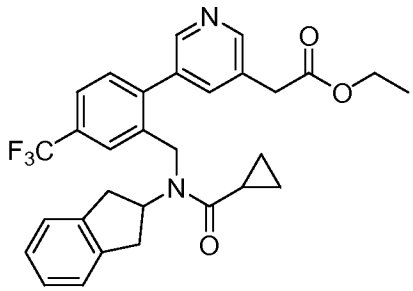
Step 2: Cyclopropanecarboxylic acid (2-bromo-5-trifluoromethyl-benzyl)-indan-2-yl-amide

[00600] Prepared according to the procedure described in Example 17, Step 2, using the following starting materials: (2-Bromo-5-trifluoromethyl-benzyl)-indan-2-yl-amine and cyclopropanecarbonyl chloride.



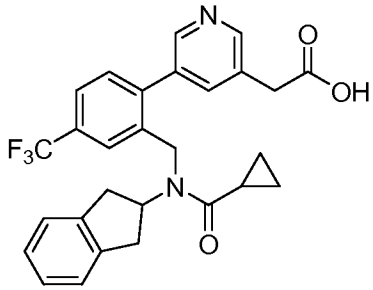
Step 3: Cyclopropanecarboxylic acid indan-2-yl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide

[00601] Prepared according to the procedure described in Example 17, Step 3, using the following starting materials: cyclopropanecarboxylic acid (2-bromo-5-trifluoromethyl-benzyl)-indan-2-yl-amide and bis(pinacolato)diboron.



Step 4: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-indan-2-yl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

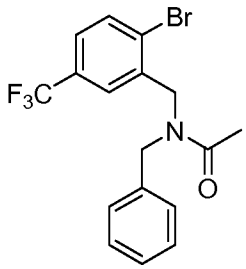
[00602] Prepared according to the procedure described in Example 17, Step 4, using the following starting materials: cyclopropanecarboxylic acid indan-2-yl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.



Step 5: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-indan-2-yl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

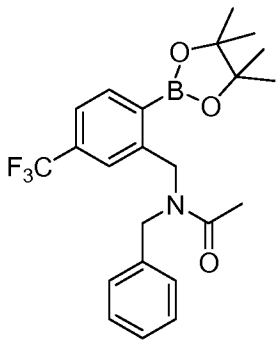
[00603] Prepared according to the procedure described in Example 23, Step 5, using the following starting material: (5-{2-[(*N*-cyclopropanecarbonyl- *N*-indan-2-yl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 25: Synthesis of (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-25)



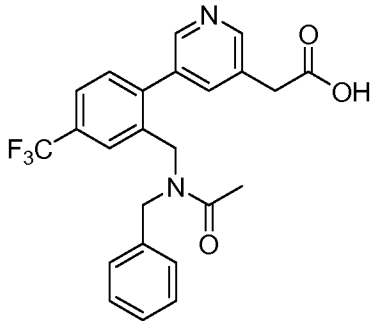
Step 1: *N*-Benzyl-*N*-(2-bromo-5-trifluoromethyl-benzyl)-acetamide

[00604] Prepared according to the procedure described in Example 17, Step 2, using the following starting materials: benzyl-(2-bromo-5-trifluoromethyl-benzyl)-amine and acetyl chloride.



Step 2: *N*-Benzyl-*N*-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-acetamide

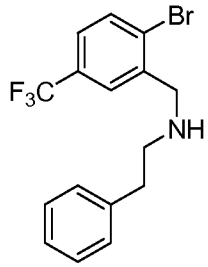
[00605] Prepared according to the procedure described in Example 17, Step 3, using the following starting materials: *N*-benzyl-*N*-(2-bromo-5-trifluoromethyl-benzyl)-acetamide and bis(pinacolato)diboron.



Step 3: (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

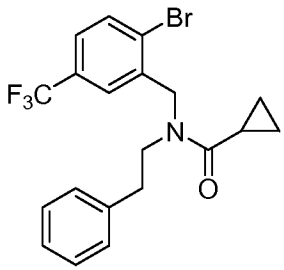
[00606] Prepared according to the procedure described in Example 23, Step 4, using the following starting materials: *N*-benzyl-*N*-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-acetamide and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.

Example 26: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-phenethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-26)



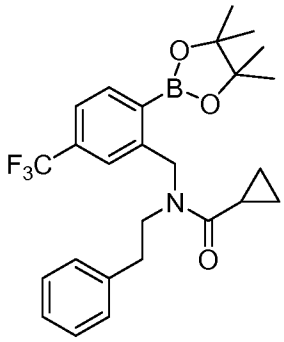
Step 1: (2-Bromo-5-trifluoromethyl-benzyl)-phenethyl-amine

[00607] Prepared according to the procedure described in Example 23, Step 1, using the following starting materials: 2-bromo-5-(trifluoromethyl)benzaldehyde and 2-phenylethylamine



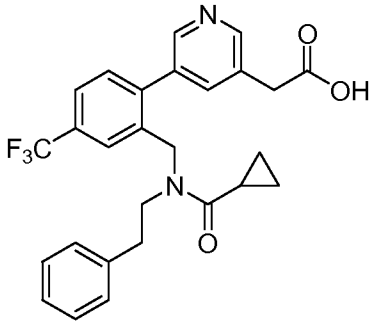
Step 2: Cyclopropanecarboxylic acid (2-bromo-5-trifluoromethyl-benzyl)-phenethyl-amide

[00608] Prepared according to the procedure described in Example 17, Step 2, using the following starting materials: (2-bromo-5-trifluoromethyl-benzyl)-phenethyl-amine and cyclopropanecarbonyl chloride.



Step 3: Cyclopropanecarboxylic acid phenethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide

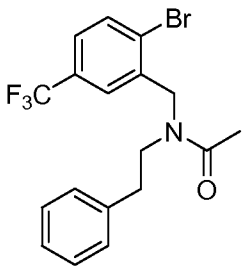
[00609] Prepared according to the procedure described in Example 17, Step 3, using the following starting materials: cyclopropanecarboxylic acid (2-bromo-5-trifluoromethyl-benzyl)-phenethyl-amide and bis(pinacolato)diboron.



Step 4: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-phenethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

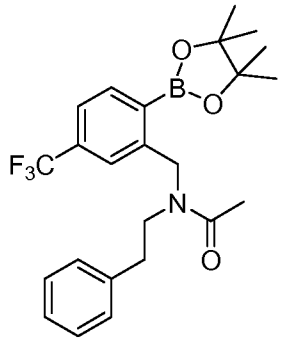
[00610] Prepared according to the procedure described in Example 23, Step 4, using the following starting materials: cyclopropanecarboxylic acid phenethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.

Example 27: Synthesis of (5-{2-[(*N*-Acetyl-*N*-phenethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-27)



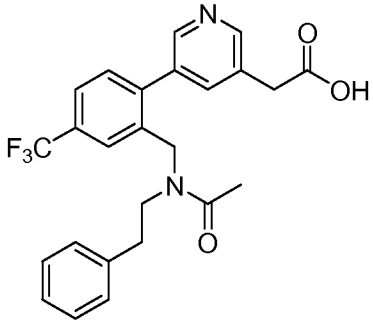
Step 1: *N*-(2-Bromo-5-trifluoromethyl-benzyl)-*N*-phenethyl-acetamide

[00611] Prepared according to the procedure described in Example 17, Step 2, using the following starting materials: (2-bromo-5-trifluoromethyl-benzyl)-phenethyl-amine and acetyl chloride.



Step 2: *N*-Phenethyl-*N*-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-acetamide

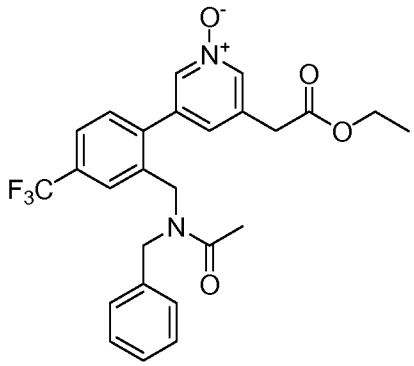
[00612] Prepared according to the procedure described in Example 17, Step 3, using the following starting materials: *N*-(2-bromo-5-trifluoromethyl-benzyl)-*N*-phenethyl-acetamide and bis(pinacolato)diboron.



Step 3: (5-{2-[(*N*-Acetyl-*N*-phenethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

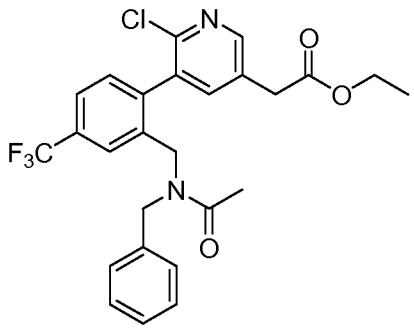
[00613] Prepared according to the procedure described in Example 23, Step 4, using the following starting materials: *N*-phenethyl-*N*-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-acetamide and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.

Example 28: Synthesis of (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-chloro-pyridin-3-yl)-acetic acid (Compound 1-28)

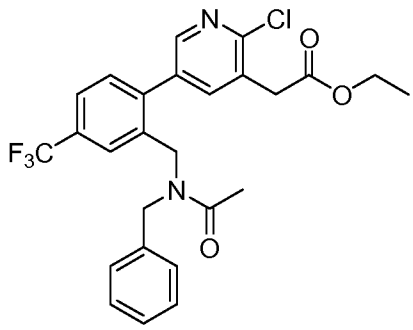


Step 1: (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-1-oxy-pyridin-3-yl)-acetic acid ethyl ester

[00614] Prepared according to the procedure described in Example 15, Step 1, using the following starting material: (5-{2-[(*N*-acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

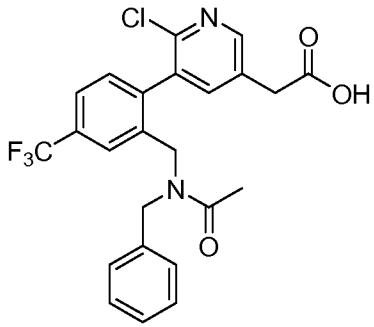


and



Step 2: (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-chloro-pyridin-3-yl)-acetic acid ethyl ester and (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-2-chloro-pyridin-3-yl)-acetic acid ethyl ester

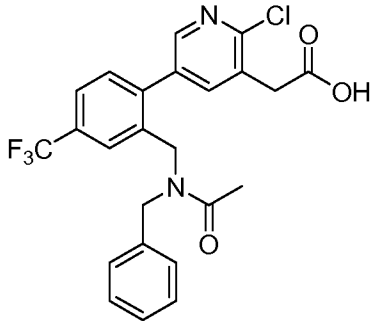
[00615] Prepared according to the procedure described in Example 15, Step 2, using the following starting material: (5-{2-[(*N*-acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-1-oxy-pyridin-3-yl)-acetic acid ethyl ester.



Step 3: (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-chloro-pyridin-3-yl)-acetic acid

[00616] Prepared according to the procedure described in Example 23, Step 5, using the following starting material: a mixture of (5-{2-[(*N*-acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-chloro-pyridin-3-yl)-acetic acid ethyl ester and (5-{2-[(*N*-acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-2-chloro-pyridin-3-yl)-acetic acid ethyl ester.

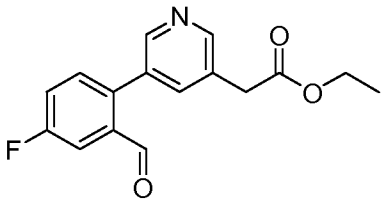
Example 29: Synthesis of (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-2-chloro-pyridin-3-yl)-acetic acid (Compound 1-29)



Step 1: (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-2-chloro-pyridin-3-yl)-acetic acid

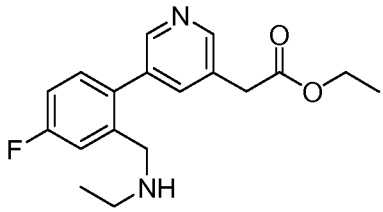
[00617] Prepared according to the procedure described in Example 23, Step 5, using the following starting material: a mixture of (5-{2-[(*N*-acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-chloro-pyridin-3-yl)-acetic acid ethyl ester and (5-{2-[(*N*-acetyl- *N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-2-chloro-pyridin-3-yl)-acetic acid ethyl ester.

Example 30: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-methylsulfanyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-30) and (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-mercapto-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-33)



Step 1: [5-(4-Fluoro-2-formyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

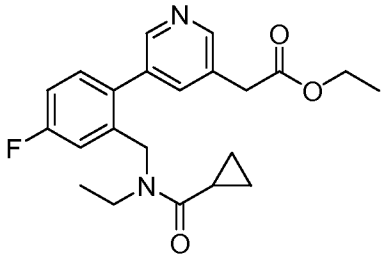
[00618] (5-Bromo-pyridin-3-yl)-acetic acid ethyl ester (1.91g, 7.8mmol), 5-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (50% pure; 2.94g, 11.75mmol), and potassium carbonate (3.25g, 23.5mmol) were combined in 2:1 DME:H_2O, and the solution was purged with N_2 for 20 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.45g, 0.39mmol) was added, and the reaction was purged with N_2 for another 25 minutes and then stirred at 75°C for 2 hours. The mixture was worked up with EtOAc and H_2O, and the residue was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.



Step 2: [5-(2-Ethylaminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

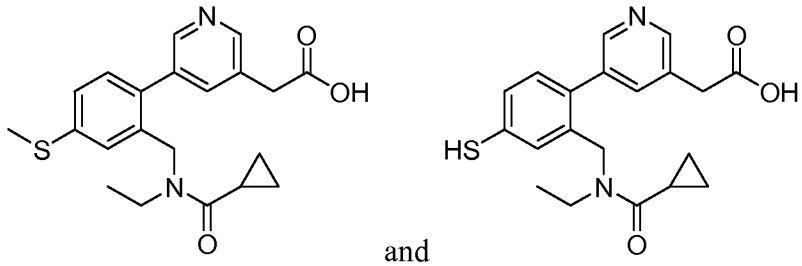
[00619] To [5-(4-fluoro-2-formyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester (1.2g, 4.18mmol) in MeOH was added sodium cyanoborohydride (0.394g, 6.26mmol) and ethylamine (2M in THF;

3.13mL, 6.26mmol). Acetic acid (0.36mL, 6.26mmol) was added, and the reaction was stirred for 2 hours at room temperature. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by silica gel chromatography (0-10% MeOH in CH_2Cl_2) to give the title compound.



Step 3: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

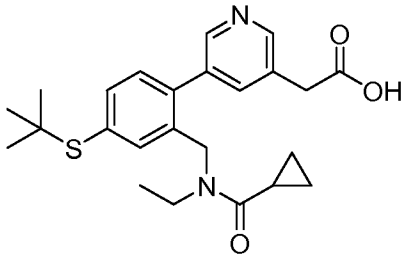
[00620] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-ethylaminomethyl-4-fluoro-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and cyclopropanecarboxylic acid.



Step 4: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-methylsulfanyl-phenyl}-pyridin-3-yl)-acetic acid and (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-mercapto-phenyl}-pyridin-3-yl)-acetic acid

[00621] (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.154g, 0.42mmol) and sodium thiomethoxide (0.067g, 0.95mmol) were combined in DMF (4.2mL), and the reaction was stirred at 100°C overnight. Analytical LCMS indicated that the ester hydrolyzed during the reaction, and that some of the thiomethoxy group was demethylated. The mixture was diluted with H_2O, acidified with 2N aqueous HCl to pH 4, and extracted with EtOAc. The combined organic layers were concentrated, and then dissolved in CH_2Cl_2 and concentrated. The residue was purified by preparative HPLC to give the title compounds as separated products.

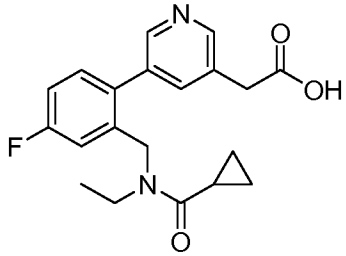
Example 31: Synthesis of (5-{4-*tert*-Butylsulfanyl-2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-31)



Step 1: (5-{4-*tert*-Butylsulfanyl-2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid

[00622] Sodium hydride (60% in mineral oil; 0.042g, 1.04mmol) was suspended in DMF (5mL). After stirring for 10 minutes, 2-methyl-2-propanethiol (0.13mL, 1.15mmol) was added, and the mixture was stirred for 30 minutes. (5-{2-[(*N*-Cyclopropanecarbonyl- *N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.20g, 0.52mmol) was added, and the reaction was stirred at 90°C overnight. Analytical LCMS indicated that some of the ester was hydrolyzed during the reaction. The mixture was diluted with H_2O, and N_2 was bubbled through the solution into a bleach trap until all odor was removed. The aqueous layer was washed with EtOAc, and then acidified to pH 4 and extracted with EtOAc. The combined organic layers were concentrated, and the residue was purified by preparative HPLC to give the title compound.

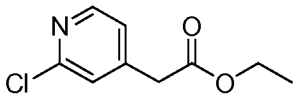
Example 32: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-32)



Step 1: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-acetic acid

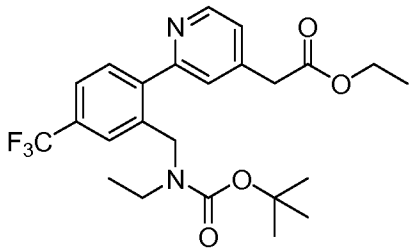
[00623] (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.202g, 0.53mmol) was dissolved in THF (5.25mL) and treated with 1N aqueous LiOH (2.63mL, 2.63mmol) and a small amount of MeOH. The reaction was stirred at 35°C for 30 minutes, until no starting material was seen by analytical tlc. The mixture was concentrated, and the residue was diluted with H_2O and washed with EtOAc. The aqueous layer was acidified with 1N aqueous HCl to pH 6 and extracted with EtOAc, and the combined organic layers were washed with H_2O and brine, and then dried over Na_2SO_4, filtered, and concentrated to give the title compound.

Example 33: Synthesis of {2-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-4-yl}-acetic acid (Compound 1-34)



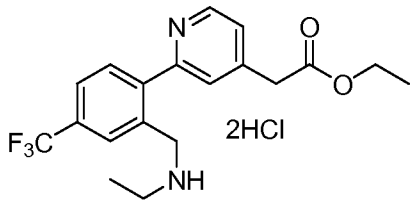
Step 1: (2-Chloro-pyridin-4-yl)-acetic acid ethyl ester

[00624] To diisopropylamine (16.2mL, 115.6mmol) in THF (40mL) at 0°C was added n-butyllithium (2.5M in hexanes; 46mL, 115mmol). After cooling the solution to -78°C, 2-chloro-4-methylpyridine (7.16g, 56.1mmol) was added slowly, and the mixture was stirred for 1 hour at -78°C. Diethyl carbonate (8.15mL, 67.3mmol) was added, and the reaction was stirred at -78°C overnight and then slowly warmed to room temperature. The mixture was quenched with saturated aqueous NH_4Cl, and after standard work-up, the residue was purified by silica gel chromatography to give the title compound.



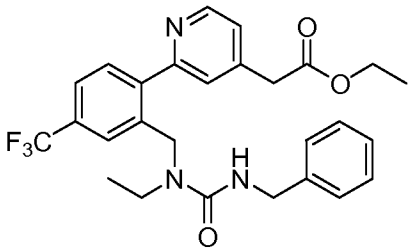
Step 2: (2-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid ethyl ester

[00625] Prepared according to the procedure described in Example 14, Step 4, using the following starting materials: (2-chloro-pyridin-4-yl)-acetic acid ethyl ester and ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid *tert*-butyl ester.



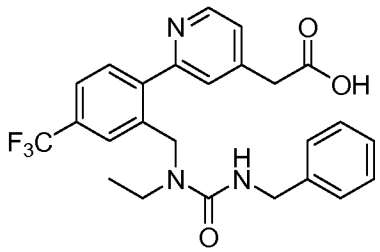
Step 3: [2-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-4-yl]-acetic acid ethyl ester, dihydrochloride

[00626] Prepared according to the procedure described in Example 14, Step 5, using the following starting material: (2-{2-[(*tert*-butoxycarbonyl-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid ethyl ester.



Step 4: {2-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-4-yl}-acetic acid ethyl ester

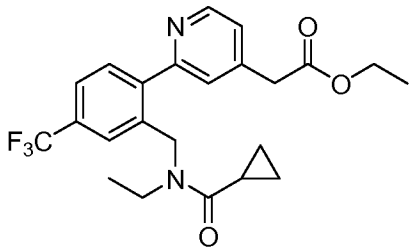
[00627] [2-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-4-yl]-acetic acid ethyl ester, dihydrochloride (0.15g, 0.34mmol), benzyl isocyanate (0.05mL, 0.39mmol), and diisopropylethylamine (1mL) were combined in CH_2Cl_2 (3mL) and stirred at room temperature until no starting material was seen by analytical LCMS. The mixture was concentrated and purified by silica gel chromatography (0-60% EtOAc in hexanes) to give the title compound.



Step 5: {2-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-4-yl}-acetic acid

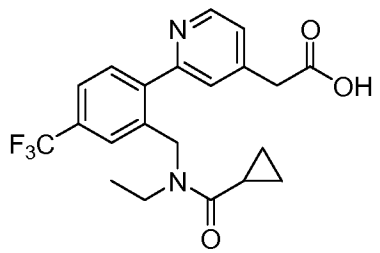
[00628] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: {2-[2-(3-benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-4-yl}-acetic acid ethyl ester.

Example 34: Synthesis of (2-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-35)



Step 1: (2-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid ethyl ester

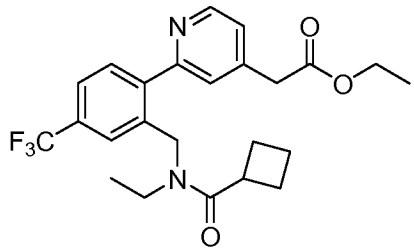
[00629] Prepared according to the procedure described in Example 33, Step 4, using the following starting materials: [2-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-4-yl]-acetic acid ethyl ester, dihydrochloride and cyclopropanecarbonyl chloride.



Step 2: (2-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid

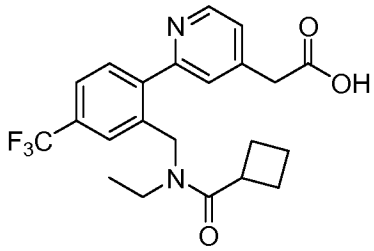
[00630] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: (2-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid ethyl ester.

Example 35: Synthesis of (2-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-36)



Step 1: (2-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid ethyl ester

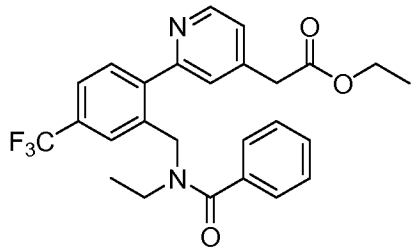
[00631] Prepared according to the procedure described in Example 33, Step 4, using the following starting materials: [2-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-4-yl]-acetic acid ethyl ester, dihydrochloride and cyclobutanecarbonyl chloride.



Step 2: (2-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid

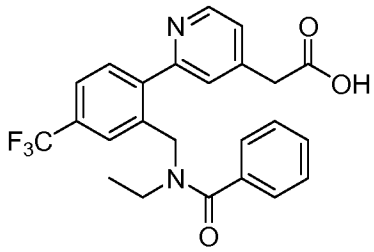
[00632] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: (2-{2-[(*N*-cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid ethyl ester.

Example 36: Synthesis of (2-{2-[(*N*-Benzoyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-37)



Step 1: (2-{2-[(*N*-Benzoyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid ethyl ester

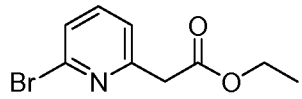
[00633] Prepared according to the procedure described in Example 33, Step 4, using the following starting materials: [2-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-4-yl]-acetic acid ethyl ester, dihydrochloride and benzoyl chloride.



Step 2: (2-{2-[(*N*-Benzoyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid

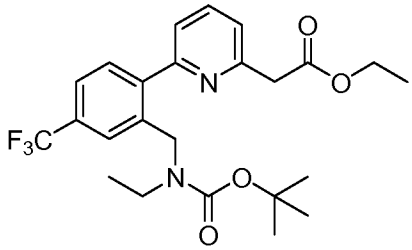
[00634] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: (2-{2-[(*N*-benzoyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid ethyl ester.

Example 37: Synthesis of (6-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid (Compound 1-38)



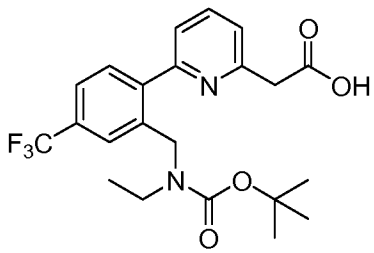
Step 1: (6-Bromo-pyridin-2-yl)-acetic acid ethyl ester

[00635] Prepared according to the procedure described in Example 33, Step 1, using the following starting materials: 2-bromo-6-methylpyridine and diethyl carbonate.



Step 2: (6-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid ethyl ester

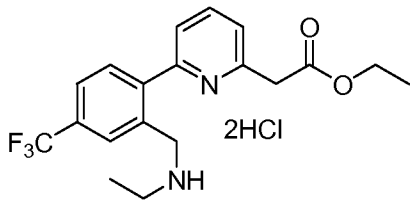
[00636] Prepared according to the procedure described in Example 14, Step 4, using the following starting materials: (6-bromo-pyridin-2-yl)-acetic acid ethyl ester and ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid *tert*-butyl ester.



Step 3: (6-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid

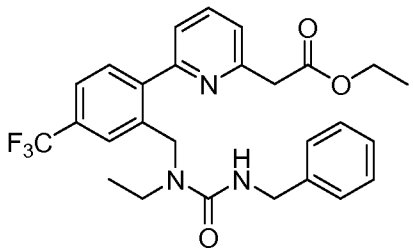
[00637] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: (6-{2-[(*N*-*tert*-butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid ethyl ester.

Example 38: Synthesis of {6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-2-yl}-acetic acid (Compound 1-39)



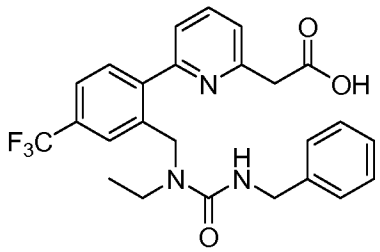
Step 1: [6-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-2-yl]-acetic acid ethyl ester, dihydrochloride

[00638] Prepared according to the procedure described in Example 14, Step 5, using the following starting material: (6-{2-[(*N*-*tert*-butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid ethyl ester.



Step 2: {6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-2-yl}-acetic acid ethyl ester

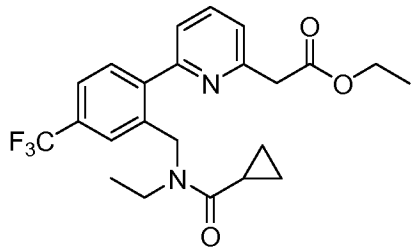
[00639] Prepared according to the procedure described in Example 33, Step 4, using the following starting materials: [6-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-2-yl]-acetic acid ethyl ester, dihydrochloride and benzyl isocyanate.



Step 3: {6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-2-yl}-acetic acid

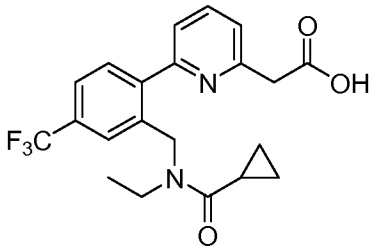
[00640] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: {6-[2-(3-benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-2-yl}-acetic acid ethyl ester.

Example 39: Synthesis of (6-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid (Compound 1-40)



Step 1: (6-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid ethyl ester

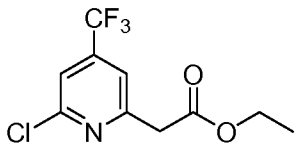
[00641] Prepared according to the procedure described in Example 33, Step 4, using the following starting materials: [6-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-2-yl]-acetic acid ethyl ester, dihydrochloride and cyclopropanecarbonyl chloride.



Step 2: (6-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid

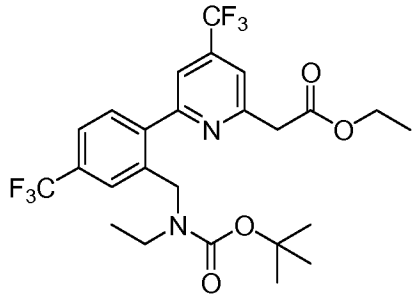
[00642] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: (6-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid ethyl ester.

Example 40: Synthesis of (6-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-4-trifluoromethyl-pyridin-2-yl)-acetic acid (Compound 1-41)



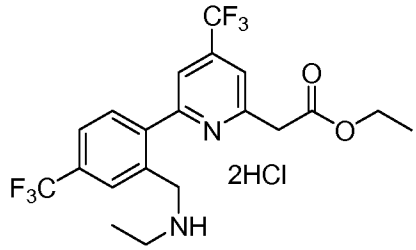
Step 1: (6-Chloro-4-trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester

[00643] Prepared according to the procedure described in Example 33, Step 1, using the following starting materials: 2-chloro-6-methyl-4-(trifluoromethyl)pyridine and diethyl carbonate.



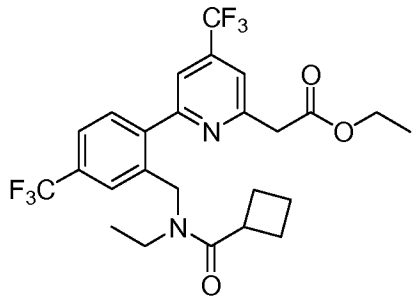
Step 2: (6-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-4-trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester

[00644] Prepared according to the procedure described in Example 14, Step 4, using the following starting materials: (6-chloro-4-trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester and ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid *tert*-butyl ester.



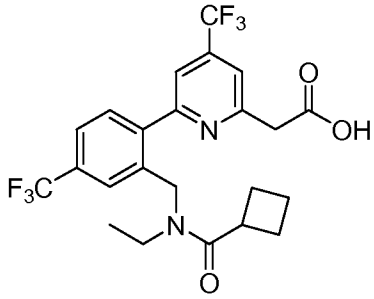
Step 3: [6-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-pyridin-2-yl]-acetic acid ethyl ester, dihydrochloride

[00645] Prepared according to the procedure described in Example 14, Step 5, using the following starting material: (6-{2-[(*N*-*tert*-butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-4-trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester.



Step 4: (6-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-4-trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester

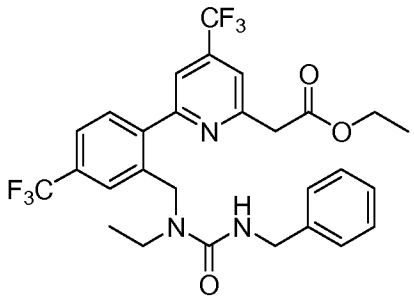
[00646] Prepared according to the procedure described in Example 33, Step 4, using the following starting materials: [6-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-pyridin-2-yl]-acetic acid ethyl ester, dihydrochloride and cyclobutanecarbonyl chloride.



Step 5: (6-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-4-trifluoromethyl-pyridin-2-yl)-acetic acid

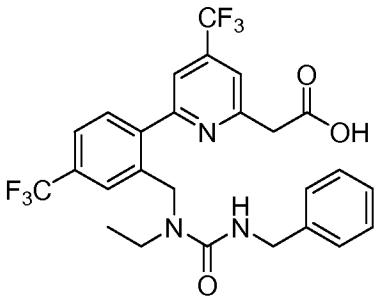
[00647] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: (6-{2-[(*N*-cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-4-trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester.

Example 41: Synthesis of {6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-pyridin-2-yl}-acetic acid (Compound 1-42)



Step 1: {6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-pyridin-2-yl}-acetic acid ethyl ester

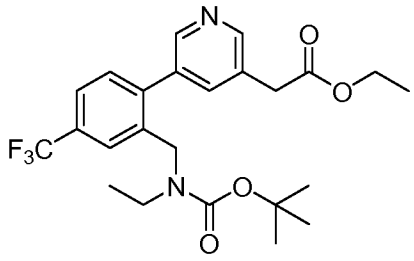
[00648] Prepared according to the procedure described in Example 33, Step 4, using the following starting materials: [6-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-pyridin-2-yl]-acetic acid ethyl ester, dihydrochloride and benzyl isocyanate.



Step 2: {6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-pyridin-2-yl}-acetic acid

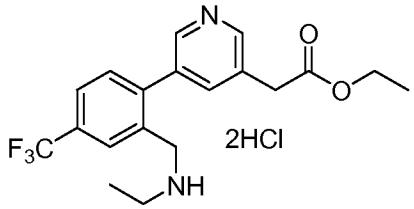
[00649] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: {6-[2-(3-benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-pyridin-2-yl}-acetic acid ethyl ester.

Example 42: Synthesis of [5-(2-{[*N*-Ethyl-*N*-(3-phenyl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-43)



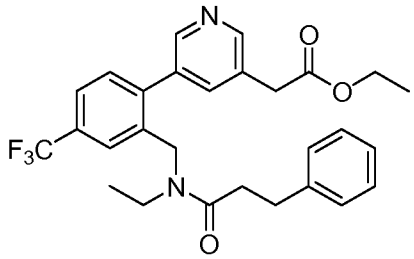
Step 1: (5-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

[00650] Prepared according to the procedure described in Example 14, Step 4, using the following starting materials: ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid *tert*-butyl ester and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.



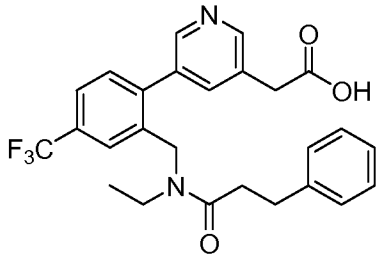
Step 2: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester, dihydrochloride

[00651] Prepared according to the procedure described in Example 14, Step 5, using the following starting material: (5-{2-[(*N*-*tert*-butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.



Step 3: [5-(2-{[*N*-Ethyl-*N*-(3-phenyl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

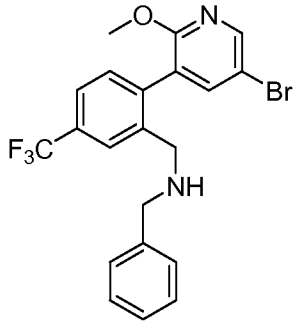
[00652] Prepared according to the procedure described in Example 14, Step 6, using the following starting material: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester, dihydrochloride and hydrocinnamic acid.



Step 4: [5-(2-{[*N*-Ethyl-*N*-(3-phenyl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

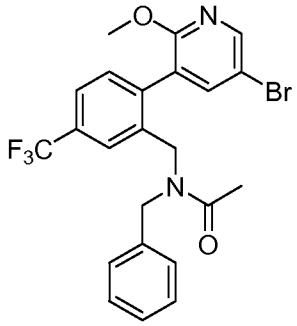
[00653] Prepared according to the procedure described in Example 18, Step 4, using the following starting material: [5-(2-{[*N*-ethyl-*N*-(3-phenyl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 43: Synthesis of (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid (Compound 1-44)



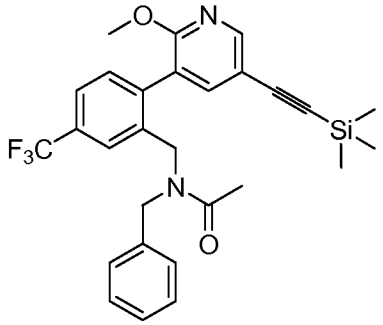
Step 1: Benzyl-[2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-amine

[00654] Prepared according to the procedure described in Example 23, Step 1, using the following starting materials: 2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzaldehyde and benzylamine.



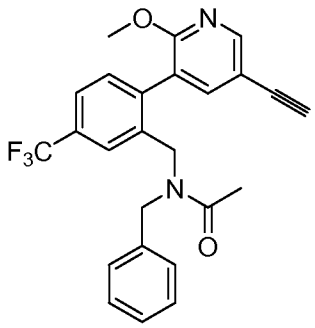
Step 2: *N*-Benzyl-*N*-[2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-acetamide

[00655] Prepared according to the procedure described in Example 17, Step 2, using the following starting materials: benzyl-[2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-amine and acetyl chloride.



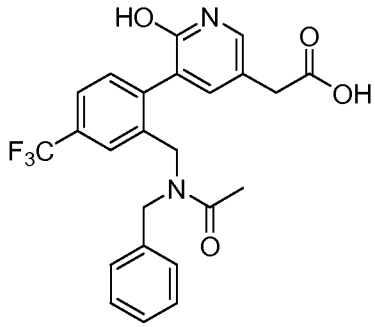
Step 3: *N*-Benzyl-*N*-[2-(2-methoxy-5-trimethylsilanylethynyl-pyridin-3-yl)-5-trifluoromethyl-benzyl]-acetamide

[00656] *N*-Benzyl-*N*-[2-(5-bromo-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-acetamide (0.288g, 0.58mmol), (trimethylsilyl)acetylene (0.08mL, 0.58mmol), and copper iodide (0.011g, 0.06mmol) were combined in triethylamine (3.5mL), and the solution was purged with N_2 for 25 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.042g, 0.06mmol) was added, and the reaction was stirred at room temperature overnight. Anatlyical LCMS indicated that starting material was still present, so a few drops of DMF was added, and the reaction was stirred at 50°C for 5 hours, and at 60°C for 3 hours. The mixture was worked-up with CH_2Cl_2 and H_2O, and the combined organic layers were dried, filtered, and concentrated. The residue was purified by silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound.



Step 4: *N*-Benzyl-*N*-[2-(5-ethynyl-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-acetamide

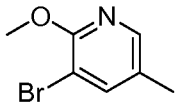
[00657] To cyclohexene (0.12mL, 1.14mmol) in THF (0.3mL) at 0°C was added borane tetrahydrofuran complex (1M in THF; 0.53mL, 0.53mmol), and the reaction was stirred for 1.5 hours. *N*-Benzyl-*N*-[2-(2-methoxy-5-trimethylsilanylethynyl-pyridin-3-yl)-5-trifluoromethyl-benzyl]-acetamide (0.084g, 0.15mmol) in THF (2mL) was added dropwise, and the reaction was stirred for 1 hour at room temperature. The mixture was cooled to 0°C, and MeOH (0.9mL) was added, followed by 1N aqueous NaOH (0.53mL, 0.53mmol) and hydrogen peroxide (30%; 0.16mL, 1.55mmol), and the reaction was stirred for 1 hour at 0°C and 1.5 hours at 40°C. The mixture was acidified with 1N aqueous HCl and extracted with EtOAc to give the title compound.



Step 5: (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid

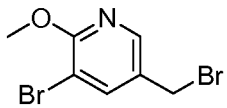
[00658] To cyclohexene (0.20mL, 1.98mmol) at room temperature was added borane tetrahydrofuran complex (1M in THF; 1.01mL, 1.01mmol), and the reaction was stirred for 45 minutes. *N*-Benzyl-*N*-[2-(5-ethynyl-2-methoxy-pyridin-3-yl)-5-trifluoromethyl-benzyl]-acetamide (0.126g, 0.29mmol) in THF (2mL) was added dropwise, and the reaction was stirred for 2 hours at room temperature. The mixture was cooled to 0°C, and MeOH (1mL) and 1N aqueous NaOH (1.01mL, 1.01mmol) were added, followed by hydrogen peroxide (30%; 0.31mL, 3.00mmol), and the reaction was stirred for 1 hour at 0°C. The mixture was acidified with 1N aqueous HCl and extracted with EtOAc, and the combined organic layers were dried, filtered, and concentrated. The residue was purified by preparative HPLC to give the title compound.

Example 44: Synthesis of {5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-6-methoxy-pyridin-3-yl}-acetic acid (Compound 1-45)



Step 1: 3-Bromo-2-methoxy-5-methyl-pyridine

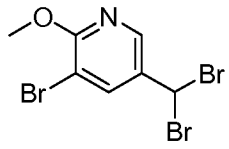
[00659] 3-Bromo-2-hydroxy-5-methylpyridine (5.012g, 26.7mmol), silver carbonate (9.58g, 34.7mmol), and iodomethane (5mL, 80.0mmol) were combined in $CHCl_3$ (75mL) and stirred at 55°C for 3 hours. Once no starting material was seen by analytical LCMS, the mixture was cooled and filtered through Celite, and the filtrate was concentrated and purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.



Step 2: 3-Bromo-5-bromomethyl-2-methoxy-pyridine

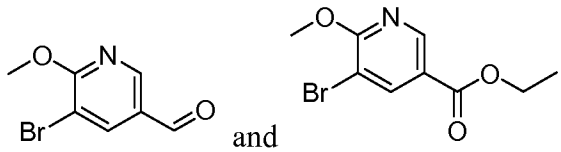
[00660] 3-Bromo-2-methoxy-5-methyl-pyridine (4.0g, 19.8mmol), N-bromosuccinimide (4.45g, 23.8mmol), and azobisisobutyronitrile (0.163g, 0.99mmol) were combined in benzene (40mL) and stirred overnight at 80°C. Analytical LCMS indicated the starting material was still present, so the reaction was stirred for another 24 hours at 80°C, and then additional N-bromosuccinimide

(1.8g, 10.1mmol), and azobisisobutyronitrile (catalytic) were added. After stirring for another 2 hours at 80°C, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The residue was purified by silica gel chromatography to give the title compound.



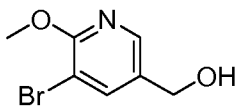
Step 3: 3-Bromo-5-dibromomethyl-2-methoxy-pyridine

[00661] 3-Bromo-5-bromomethyl-2-methoxy-pyridine (6.03g, 21.5mmol), N-bromosuccinimide (4.09g, 23.0mmol), and azobisisobutyronitrile (one scoop) were combined in benzene (40mL) and stirred at 80°C for 4 hours. After cooling, the mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the title compound.



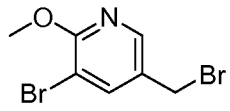
Step 4: 5-Bromo-6-methoxy-pyridine-3-carbaldehyde and 5-Bromo-6-methoxy-nicotinic acid ethyl ester

[00662] To 3-bromo-5-dibromomethyl-2-methoxy-pyridine (7.1g, 19.7mmol) in EtOH (200mL) was added silver nitrate (8.38g, 49.3mmol) in H2O (40mL) slowly, and the reaction was stirred at 75°C overnight. Analytical LCMS indicated that the diethyl acetal product may have formed, so the mixture was cooled, diluted with brine, filtered, and concentrated. 1,4-Dioxane (70mL) and 1N aqueous HCl (70mL) was added, and the reaction was stirred overnight. Analytical LCMS showed that two products were present. The mixture was neutralized and extracted with EtOAc, and the combined organic layers were dried, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compounds, which were combined and reduced together in the next step.



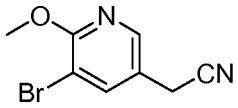
Step 5: (5-Bromo-6-methoxy-pyridin-3-yl)-methanol

[00663] A mixture of 5-bromo-6-methoxy-pyridine-3-carbaldehyde and 5-bromo-6-methoxy-nicotinic acid ethyl ester (3g, 13.9mmol) was dissolved in THF (30mL) and cooled to 0°C, and lithium triethylborohydride (1M in THF; 42mL, 42mmol) was added. The reaction was stirred for 5 minutes, and then quenched with EtOH, acidified with 1N aqueous HCl, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the title compound.



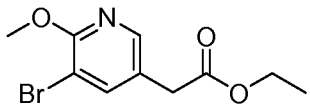
Step 6: 3-Bromo-5-bromomethyl-2-methoxy-pyridine

[00664] To (5-bromo-6-methoxy-pyridin-3-yl)-methanol (2.86g, 13.1mmol) in DME (30mL) was added phosphorus tribromide (1.9mL, 19.7mmol), and the reaction was stirred for 15 minutes. The mixture was worked up with EtOAc and saturated aqueous $NaHCO_3$, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the title compound.



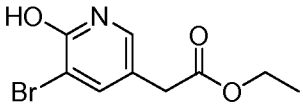
Step 7: (5-Bromo-6-methoxy-pyridin-3-yl)-acetonitrile

[00665] To 3-bromo-5-bromomethyl-2-methoxy-pyridine (1.42g, 5.05mmol) in EtOH (14mL) and H_2O (1.5mL) was added sodium cyanide (0.25g, 5.05mmol), and the reaction was stirred at 50°C overnight. The mixture was cooled to room temperature and worked up with CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic layers were dried, filtered, and concentrated to give the title compound.



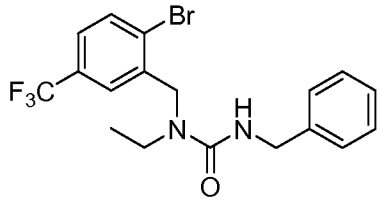
Step 8: (5-Bromo-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester

[00666] To (5-bromo-6-methoxy-pyridin-3-yl)-acetonitrile (1.139g, 5.02mmol) in EtOH (11ml) was added acetyl chloride (3.6mL, 50.54mmol), and the reaction was stirred at 50°C for 24 hours, and at room temperature for 2 days. The reaction was worked up with CH_2Cl_2 and saturated aqueous $NaHCO_3$, and then reacidified and extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated to give the title compound.



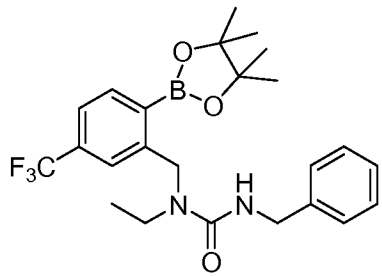
Step 9: (5-Bromo-6-hydroxy-pyridin-3-yl)-acetic acid ethyl ester

[00667] (5-Bromo-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester (5.02mmol) was dissolved in $CHCl_3$ (17mL). Silver carbonate (1.58g, 5.7mmol) and iodomethane (0.82mL, 13.14mmol) were added, and the reaction was stirred at 55°C for 2.5 hours. The mixture was filtered through Celite, and the filtrate was concentrated and purified by silica gel chromatography (0-60% EtOAc in hexanes) to give the title compound.



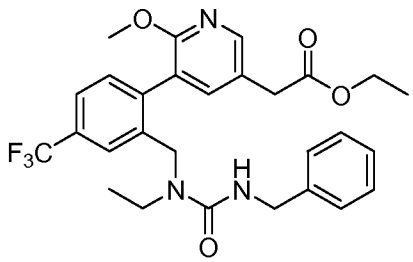
Step 10: 3-Benzyl-1-(2-bromo-5-trifluoromethyl-benzyl)-1-ethyl-urea

[00668] To (2-bromo-5-trifluoromethyl-benzyl)-ethyl-amine (2.35g, 8.33mmol) in CH_2Cl_2 (24mL) was added triethylamine (1.8mL, 12.5mmol), followed by benzyl isocyanate (1.22mL, 10.0mmol), and the reaction was stirred at room temperature for 50 minutes. The mixture was worked up with CH_2Cl_2 and H_2O, and the combined organic layers were dried, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 and filtered to remove solids, and the filtrate was purified by silica gel chromatography to give the title compound.



Step 11: 3-Benzyl-1-ethyl-1-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-urea

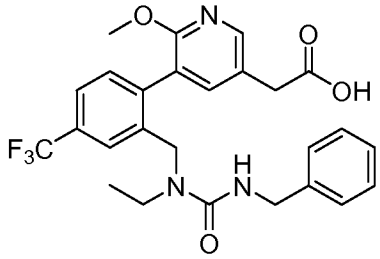
[00669] Prepared according to the procedure described in Example 17, Step 3, using the following starting materials: 3-benzyl-1-(2-bromo-5-trifluoromethyl-benzyl)-1-ethyl-urea and bis(pinacolato)diboron.



Step 12: {5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-6-methoxy-pyridin-3-yl}-acetic acid ethyl ester

[00670] Prepared according to the procedure described in Example 17, Step 4, using the following starting materials:

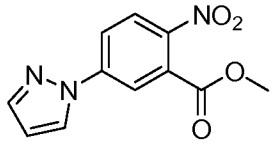
[00671] 3-benzyl-1-ethyl-1-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-urea and (5-bromo-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester.



Step 13: {5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-6-methoxy-pyridin-3-yl}-acetic acid

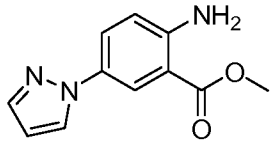
[00672] Prepared according to the procedure described in Example 14, Step 7, using the following starting material: {5-[2-(3-benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-6-methoxy-pyridin-3-yl}-acetic acid ethyl ester.

Example 45: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-pyrazol-1-yl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-46)



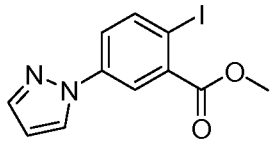
Step 1: 2-Nitro-5-pyrazol-1-yl-benzoic acid methyl ester

[00673] 2-Nitro-5-fluorobenzoic acid methyl ester (3.2g, 16.1mmol), pyrazole (1.2g, 17.7mmol), and potassium carbonate (3.33g, 24.1mmol) were combined in DMF (25mL) and stirred at 100°C overnight. The mixture was worked up with EtOAc and H_2O, and the organic layer was separated and washed three times with H_2O to remove DMF, then dried over $MgSO_4$, filtered, and concentrated to give the title compound.



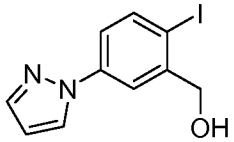
Step 2: 2-Amino-5-pyrazol-1-yl-benzoic acid methyl ester

[00674] 2-Nitro-5-pyrazol-1-yl-benzoic acid methyl ester (3.59g, 14.5mmol) and 10% palladium on carbon (0.36g) were combined in EtOH (50mL). The reaction was stirred under 45psi H_2 using the Parr appartus overnight. Analytical LCMS indicated that no starting material remained, so the mixture was filtered through Celite. The Celite was washed with EtOH, and the filtrate was concentrated and purified by silica gel chromatography (0-40% EtOAc in hexanes) to give the title compound.



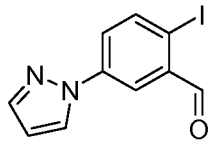
Step 3: 2-Iodo-5-pyrazol-1-yl-benzoic acid methyl ester

[00675] 2-Amino-5-pyrazol-1-yl-benzoic acid methyl ester (2.81g, 12.9mmol) and 6M aqueous HCl (0.19mL) were combined in a round bottom flask and cooled to 0°C. Sodium nitrite (1.07g, 15.5mmol) in H_2O (3.2mL) was added, and the mixture was stirred for 2 hours at 0°C. Potassium iodide (3.22g, 19.4mmol) in H_2O (12mL) was cooled and then added to the mixture at 0°C, and the reaction was stirred for 10 minutes. CH_2Cl_2 (120mL) was added at 0°C, and the reaction was stirred overnight. The mixture was diluted with H_2O and extracted three times with CH_2Cl_2. The combined organic layers were filtered to remove suspended solids, and then dried and concentrated. The residue was purified by silica gel chromatography (0-20% EtOAc in hexanes) to give the title compound.



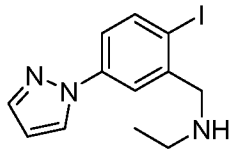
Step 4: (2-Iodo-5-pyrazol-1-yl-phenyl)-methanol

[00676] To 2-iodo-5-pyrazol-1-yl-benzoic acid methyl ester (0.95g, 2.9mmol) in THF (10mL) at -10°C was added lithium triethylborohydride (1M in THF; 4.34mL, 4.34mmol), and the reaction was stirred for 20 minutes at -5°C. Additional lithium triethylborohydride (1M in THF; 4.34mL, 4.34mmol) was added at -5°C, and the reaction was stirred for 5 minutes, until no starting material was seen by analytical LCMS. The mixture was quenched with MeOH (2mL) and acidified with 1N aqueous HCl to pH 3-4, and then extracted three times with EtOAc. The combined organic layers were dried and concentrated to give the title compound.



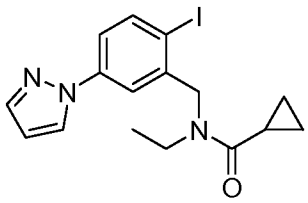
Step 5: 2-Iodo-5-pyrazol-1-yl-benzaldehyde

[00677] (2-Iodo-5-pyrazol-1-yl-phenyl)-methanol (1.19g, 3.97mmol) and N-methylmorpholine-N-oxide (0.933g, 7.94mmol) were combined in 95:5 CH_2Cl_2:MeCN. Tetrapropylammonium perruthenate (0.014g, 0.04mmol) was added, and the reaction was stirred at room temperature for 2 hours. Additional tetrapropylammonium perruthenate (0.015g, 0.04mmol) was added, and the reaction was stirred for 2 hours. Analytical LCMS indicated that starting material was still present, so additional tetrapropylammonium perruthenate (0.02g, 0.06mmol) was added, and the reaction was stirred for 20 minutes. The mixture was concentrated and purified by silica gel chromatography (0-20%-70% EtOAc in hexanes) to give the title compound, as well as recovered starting material.



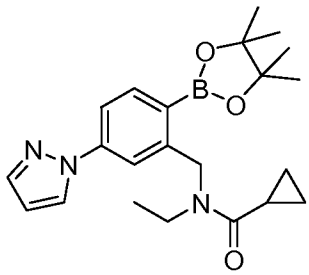
Step 6: Ethyl-(2-iodo-5-pyrazol-1-yl-benzyl)-amine

[00678] Prepared according to the procedure described in Example 23, Step 1, using the following starting materials: 2-iodo-5-pyrazol-1-yl-benzaldehyde and ethylamine (2M in MeOH).



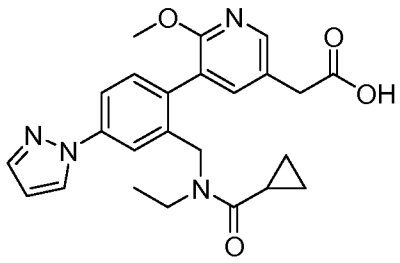
Step 7: Cyclopropanecarboxylic acid ethyl-(2-iodo-5-pyrazol-1-yl-benzyl)-amide

[00679] Prepared according to the procedure described in Example 17, Step 2, using the following starting materials: ethyl-(2-iodo-5-pyrazol-1-yl-benzyl)-amine and cyclopropanecarbonyl chloride.



Step 8: Cyclopropanecarboxylic acid ethyl-[5-pyrazol-1-yl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-amide

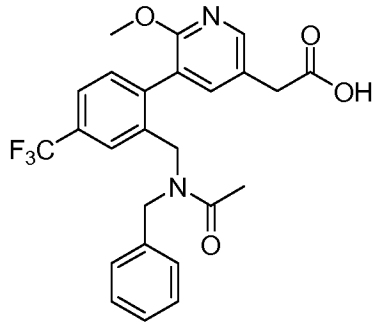
[00680] Prepared according to the procedure described in Example 17, Step 3, using the following starting materials: cyclopropanecarboxylic acid ethyl-(2-iodo-5-pyrazol-1-yl-benzyl)-amide and bis(pinacolato)diboron.



Step 9: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-pyrazol-1-yl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid

[00681] Prepared according to the procedure described in Example 23, Step 4, using the following starting materials: cyclopropanecarboxylic acid ethyl-[5-pyrazol-1-yl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-amide and (5-bromo-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester.

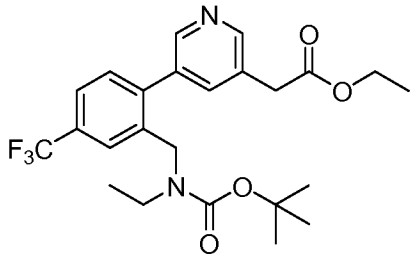
Example 46: Synthesis of (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-47)



Step 1: (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid

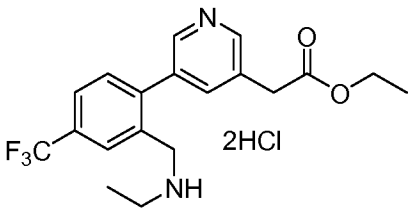
[00682] Prepared according to the procedure described in Example 23, Step 4, using the following starting materials: *N*-benzyl-*N*-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-acetamide and (5-bromo-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester.

Example 47: Synthesis of [5-(2-{[*N*-Ethyl-*N*-(pyrazine-2-carbonyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-48)



Step 1: (5-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

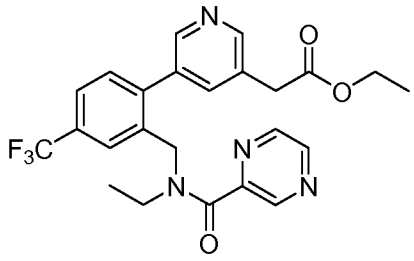
[00683] Prepared according to the procedure described in Example 17, Step 4, using the following starting materials: ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid *tert*-butyl ester and (5-bromo-pyridin-3-yl)-acetic acid ethyl ester.



Step 2: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester, dihydrochloride

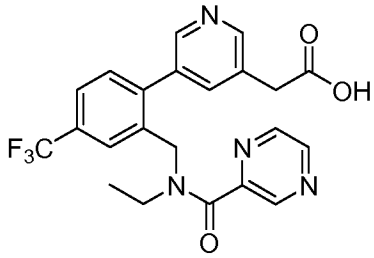
[00684] To (5-{2-[(*N*-*tert*-butoxycarbonyl- *N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.375g, 0.8mmol) in EtOAc (4mL) was added 4N HCl in 1,4-dioxane (0.8mL), and the reaction was stirred at 50°C for 1 hour. Additional 4N HCl in 1,4-

dioxane (0.8mL) was added, and the reaction was stirred for 1 hour at 70°C. The mixture was concentrated to give the title compound.



Step 3: [5-(2-{[*N*-Ethyl-*N*-(pyrazine-2-carbonyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

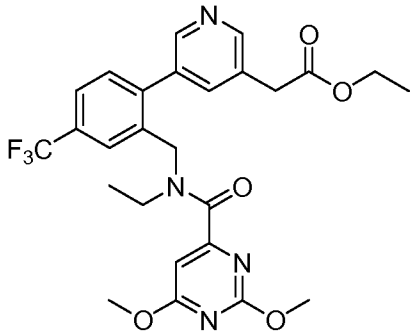
[00685] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester, dihydrochloride and pyrazinecarboxylic acid.



Step 4: [5-(2-{[*N*-Ethyl-*N*-(pyrazine-2-carbonyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

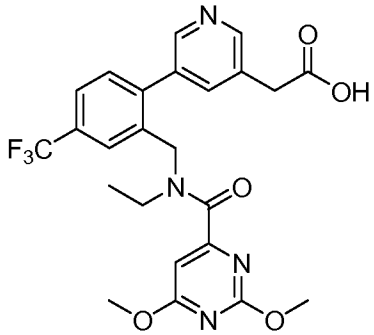
[00686] Prepared according to the procedure described in Example 14, Step 7, using the following starting material: [5-(2-{[ethyl-(pyrazine-2-carbonyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 48: Synthesis of [5-(2-{[*N*-(2,4-Dimethoxy-pyrimidine-5-carbonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-49)



Step 1: [5-(2-{[*N*-(2,6-Dimethoxy-pyrimidine-4-carbonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

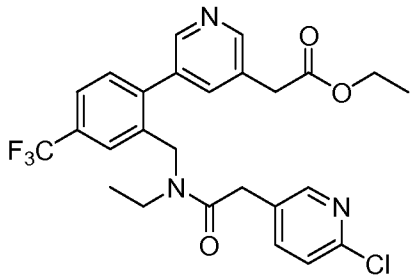
[00687] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester, dihydrochloride and 2,4-dimethoxypyrimidine-6-carboxylic acid.



Step 2: [5-(2-{[*N*-(2,6-Dimethoxy-pyrimidine-4-carbonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

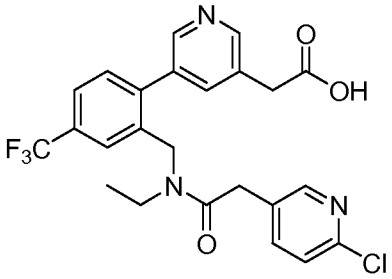
[00688] Prepared according to the procedure described in Example 14, Step 7, using the following starting material: [5-(2-{[*N*-(2,6-dimethoxy-pyrimidine-4-carbonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 49: Synthesis of {5-[2-({*N*-[2-(6-Chloro-pyridin-3-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-50)



Step 1: {5-[2-({*N*-[2-(6-Chloro-pyridin-3-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid ethyl ester

[00689] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester, dihydrochloride and 2-chloropyridine-5-acetic acid.

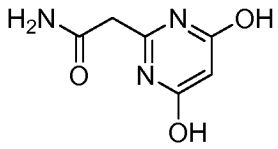


Step 2: {5-[2-({*N*-[2-(6-Chloro-pyridin-3-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid

[00690] To {5-[2-({*N*-[2-(6-chloro-pyridin-3-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid ethyl ester (0.085g, 0.16mmol) in THF (2mL) was added 1N aqueous LiOH (2mL), and the reaction was stirred at 50°C. The mixture was

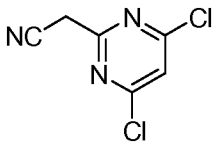
neutralized with 1N aqueous HCl to pH 3-4 and extracted three times with EtOAc. The combined organic layers were dried and concentrated to give the title compound.

Example 50: Synthesis of {5-[2-({*N*-[2-(4,6-Diethoxy-pyrimidin-2-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-51)



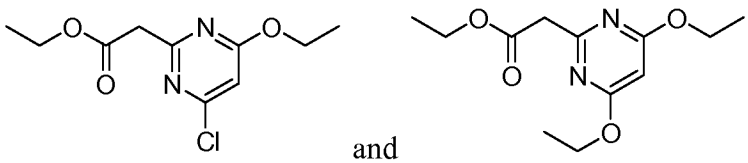
Step 1: 2-(4,6-Dihydroxy-pyrimidin-2-yl)-acetamide

[00691] Diethyl malonate and malonamamidine hydrochloride were combined in EtOH (50mL) with stirring. Sodium ethoxide was added dropwise via addition funnel over 10 minutes. The reactino was stirred overnight at room temperature to give the title compound.



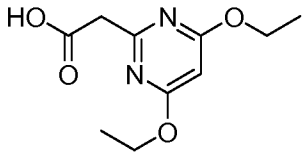
Step 2: (4,6-Dichloro-pyrimidin-2-yl)-acetonitrile

[00692] N,N-Diethylaniline (1.51mL, 0.95mmol) was added carefully to a slurry of (2-(4,6-dihydroxy-pyrimidin-2-yl)-acetamide (1.0g, 0.59mmol) in phosphorus oxychloride (3.0mL, 32.54mmol) through a reflux condenser. The reaction was heated for 10 minutes and then poured onto ice (50mL) and extracted twice with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc in hexanes) to give the title compound.



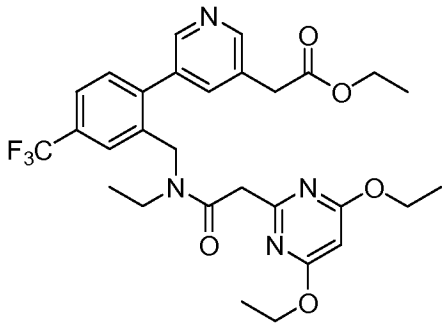
Step 3: (4-Chloro-6-ethoxy-pyrimidin-2-yl)-acetic acid ethyl ester and (4,6-Diethoxy-pyrimidin-2-yl)-acetic acid ethyl ester

[00693] Acetyl chloride (15.12mL, 212.8mmol) was slowly added to EtOH (50mL) at 0°C. (4,6-Dichloro-pyrimidin-2-yl)-acetonitrile (2.0g, 10.6mmol) was then added to this solution, and the reaction was stirred at 60°C for 12 hours. The mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4, decanted, and concentrated to give a mixture of the title compounds.



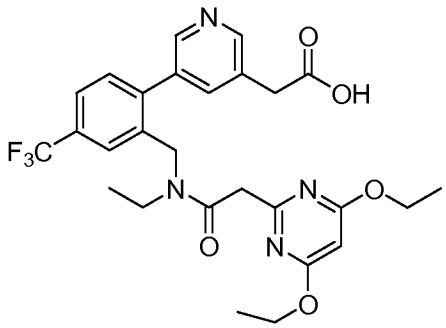
Step 4: (4,6-Diethoxy-pyrimidin-2-yl)-acetic acid

[00694] To (4,6-diethoxy-pyrimidin-2-yl)-acetic acid ethyl ester (0.218g, 0.86mmol) in THF (3mL) was added 1N aqueous LiOH (2.58mL, 2.58mmol), and the reaction was stirred at 50°C for 1 hour, and then at room temperature overnight. The mixture was acidified with 1N aqueous HCl and extracted three times with EtOAc. The combined organic layers were dried, filtered, and concentrated to give the title compound.



Step 5: {5-[2-({*N*-[2-(4,6-Diethoxy-pyrimidin-2-yl)-acetyl]- *N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid ethyl ester

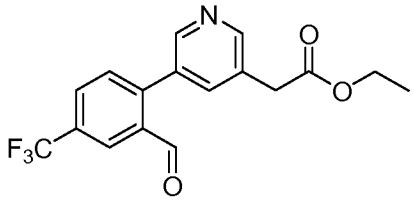
[00695] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester, dihydrochloride and (4,6-diethoxy-pyrimidin-2-yl)-acetic acid.



Step 6: {5-[2-({*N*-[2-(4,6-Diethoxy-pyrimidin-2-yl)-acetyl]- *N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid

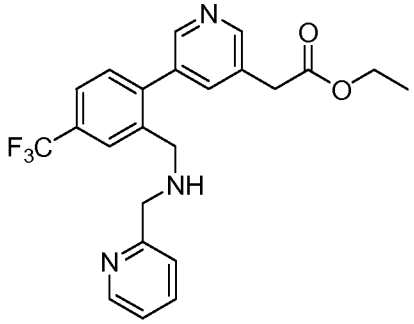
[00696] Prepared according to the procedure described in Example 49, Step 2, using the following starting material: {5-[2-({*N*-[2-(4,6-diethoxy-pyrimidin-2-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid ethyl ester.

Example 51: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-52)



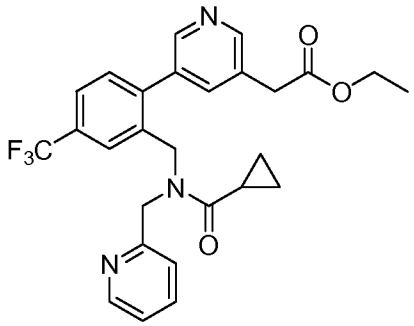
Step 1: [5-(2-Formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

[00697] 2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzaldehyde (2.14g, 5.0mmol), (5-bromo-pyridin-3-yl)-acetic acid ethyl ester (1.73g, 7.1mmol), and potassium carbonate (2.41g, 17.5mmol) were combined in DME (50mL) and H_2O (30mL), and the solution was purged with N_2 for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.058g, 0.05mmol) was added, and the reaction was stirred at 70°C overnight. The mixture was quenched with H_2O and extracted with EtOAc. The combined organic dried and concentrated, and the residue was purified by silica gel chromatography to give the title compound.



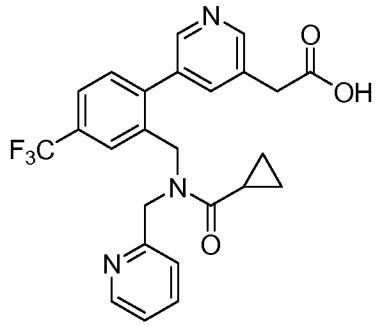
Step 2: [5-(2-{[(Pyridin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

[00698] To [5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester (0.70g, 2.07mmol) in dichloroethane (100mL) was added molecular sieves, followed by 2-(aminomethyl)pyridine (1.06mL, 10.35mmol) and acetic acid (0.59mL, 10.35mmol). MeOH (20mL) was added to solubilize the reaction, and the mixture was stirred for 1 hour. Sodium cyanoborohydride (0.650g, 10.35mmol) was added, and the reaction was stirred for 3 days. The mixture was quenched with H_2O and filtered to remove the molecular sieves, and the filtrate was extracted with EtOAc. The combined organic layers were dried and concentrated, and the residue was purified by silica gel chromatography to give the title compound.



Step 3: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

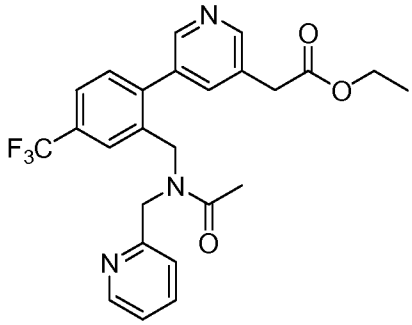
[00699] To [5-(2-{[(pyridin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester (0.100g, 0.23mmol) in CH_2Cl_2 (5mL) was added triethylamine (0.08mL, 0.58mmol), followed by cyclopropanecarbonyl chloride (0.02mL, 0.25mmol) dropwise. The reaction was stirred for 10 minutes, and then quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to give the title compound.



Step 4: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

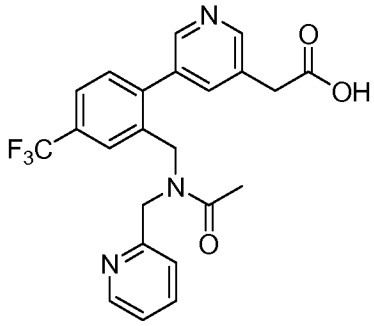
[00700] To (5-{2-[(*N*-cyclopropanecarbonyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester (0.23mmol) in MeOH (5mL) was added 1N aqueous LiOH (1mL), and the reaction was stirred overnight at room temperature. The mixture was diluted with H_2O and extracted with EtOAc to give the title compound.

Example 52: Synthesis of (5-{2-[(*N*-Acetyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-53)



Step 1: (5-{2-[(*N*-Acetyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

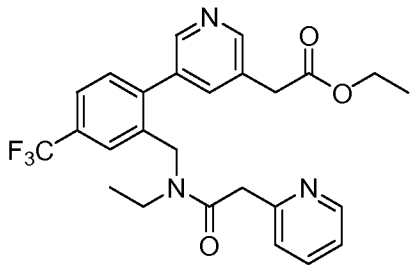
[00701] Prepared according to the procedure described in Example 51, Step 3, using the following starting materials: [5-(2-{[(pyridin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and acetyl chloride.



Step 2: (5-{2-[(*N*-Acetyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

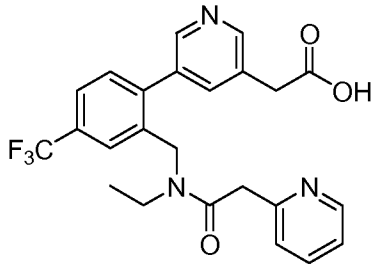
[00702] Prepared according to the procedure described in Example 51, Step 4, using the following starting material: (5-{2-[(*N*-acetyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 53: Synthesis of [5-(2-{[*N*-Ethyl-*N*-(2-pyridin-2-yl-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-54)



Step 1: [5-(2-{[*N*-Ethyl-*N*-(2-pyridin-2-yl-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

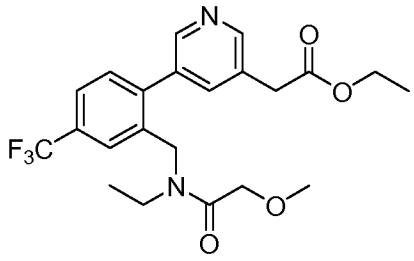
[00703] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and 2-pyridylacetic acid hydrochloride.



Step 2: [5-(2-{[*N*-Ethyl-*N*-(2-pyridin-2-yl-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

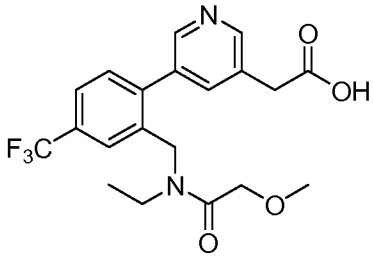
[00704] Prepared according to the procedure described in Example 49, Step 2, using the following starting material: [5-(2-{[*N*-ethyl-*N*-(2-pyridin-2-yl-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 54: Synthesis of [5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-55)



Step 1: [5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

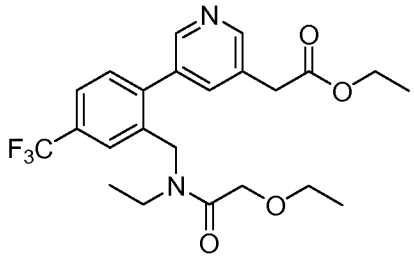
[00705] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and methoxyacetic acid.



Step 2: [5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

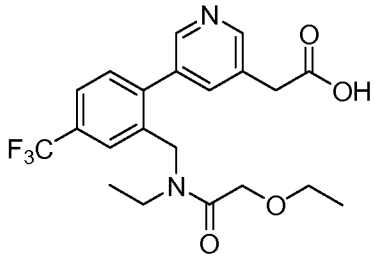
[00706] Prepared according to the procedure described in Example 49, Step 2, using the following starting material: [5-(2-{[*N*-ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 55: Synthesis of [5-(2-{[*N*-(2-Ethoxy-acetyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-56)



Step 1: [5-(2-{[*N*-(2-Ethoxy-acetyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

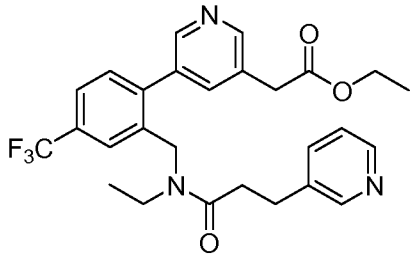
[00707] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and ethoxyacetic acid.



Step 2: [5-(2-{[*N*-(2-Ethoxy-acetyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

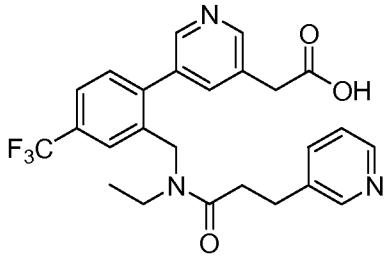
[00708] Prepared according to the procedure described in Example 49, Step 2, using the following starting material: [5-(2-{[*N*-(2-ethoxy-acetyl)- *N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

Example 56: Synthesis of [5-(2-{[*N*-Ethyl-*N*-(3-pyridin-3-yl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-57)



Step 1: [5-(2-{[*N*-Ethyl-*N*-(3-pyridin-3-yl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

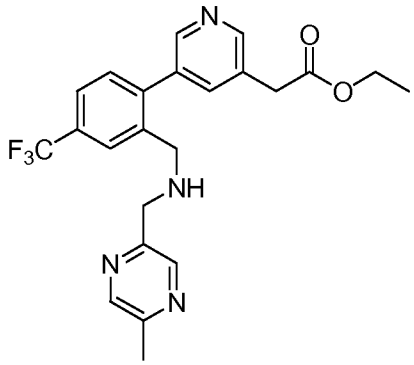
[00709] Prepared according to the procedure described in Example 14, Step 6, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and 3-pyridinepropionic acid.



Step 2: [5-(2-{[*N*-Ethyl-*N*-(3-pyridin-3-yl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

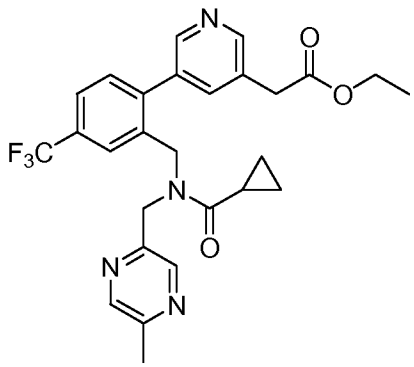
[00710] Prepared according to the procedure described in Example 49, Step 2, using the following starting material: [5-(2-{[*N*-ethyl-*N*-(3-pyridin-3-yl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 57: Synthesis of [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-58)



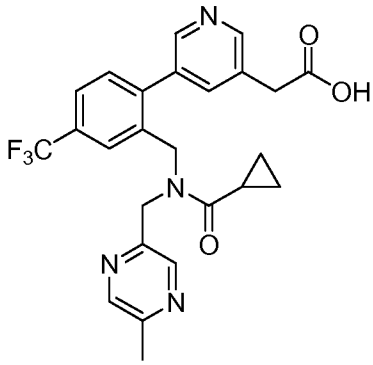
Step 1: [5-(2-{[(5-Methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

[00711] To [5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester (0.954g, 2.82mmol) in dichloroethane (30mL) was added 2-(aminomethyl)-5-methylpyrazine (0.416g, 3.38mmol) and acetic acid (0.02mL, 0.28mmol), followed by molecular sieves, and the mixture was stirred for 1 hour. Sodium triacetoxyborohydride (0.897g, 4.23mmol) was added, and the reaction was stirred overnight. The mixture was quenched with H_2O and filtered to remove the molecular sieves, and the filtrate was extracted with EtOAc. The combined organic layers were dried and concentrated, and the residue was purified by preparative HPLC to give the title compound.



Step 2: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

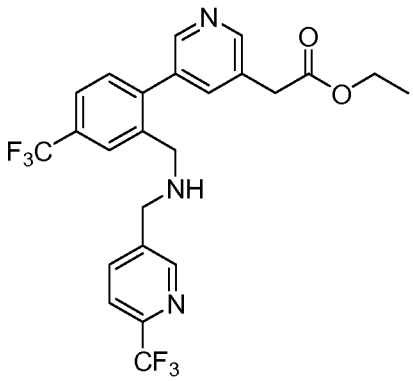
[00712] Prepared according to the procedure described in Example 51, Step 3, using the following starting materials: [5-(2-{[(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and cyclopropanecarbonyl chloride.



Step 3: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

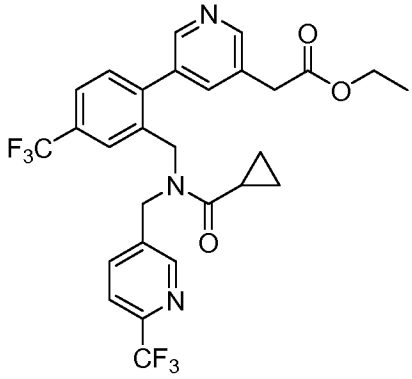
[00713] Prepared according to the procedure described in Example 51, Step 4, using the following starting material: [5-(2-{[*N*-cyclopropanecarbonyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 58: Synthesis of [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-59)



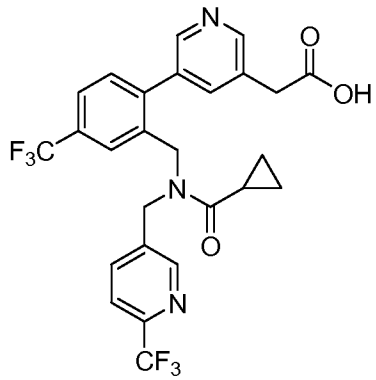
Step 1: [5-(4-Trifluoromethyl-2-{[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

[00714] Prepared according to the procedure described in Example 57, Step 1, using the following starting materials: [5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and 3-aminomethyl-6-(trifluoromethyl)pyridine.



Step 2: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

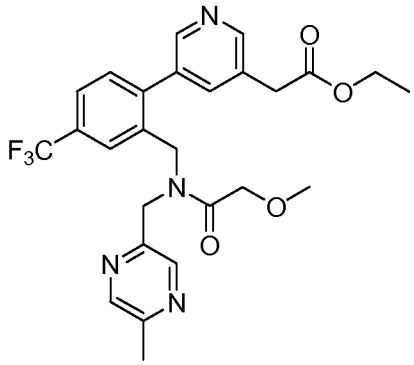
[00715] Prepared according to the procedure described in Example 51, Step 3, using the following starting materials: [5-(4-Trifluoromethyl-2-{[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and cyclopropanecarbonyl chloride.



Step 3: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

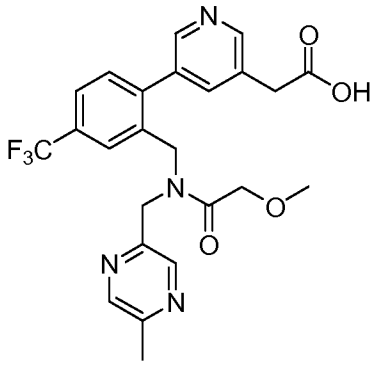
[00716] Prepared according to the procedure described in Example 51, Step 4, using the following starting material: [5-(2-{[*N*-cyclopropanecarbonyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 59: Synthesis of [5-(2-{[*N*-(2-Methoxy-acetyl)-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-60)



Step 1: [5-(2-{[*N*-(2-Methoxy-acetyl)-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

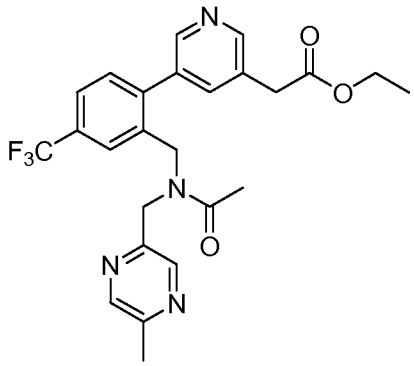
[00717] Prepared according to the procedure described in Example 51, Step 3, using the following starting materials: [5-(2-{[(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and methoxyacetyl chloride.



Step 2: [5-(2-{[*N*-(2-Methoxy-acetyl)-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

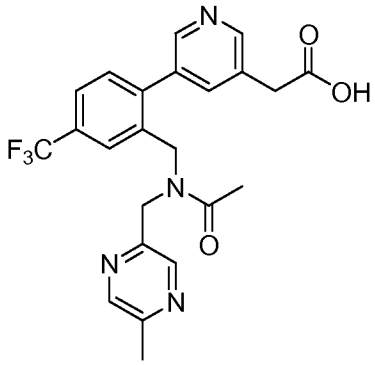
[00718] Prepared according to the procedure described in Example 51, Step 4, using the following starting material: [5-(2-{[*N*-(2-methoxy-acetyl)-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 60: Synthesis of [5-(2-{[*N*-Acetyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-61)



Step 1: [5-(2-{[*N*-Acetyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

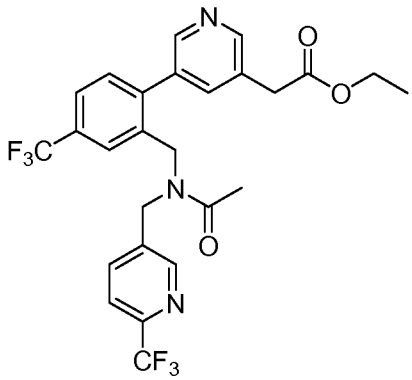
[00719] Prepared according to the procedure described in Example 51, Step 3, using the following starting materials: [5-(2-{[(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and acetyl chloride.



Step 2: [5-(2-{[*N*-Acetyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

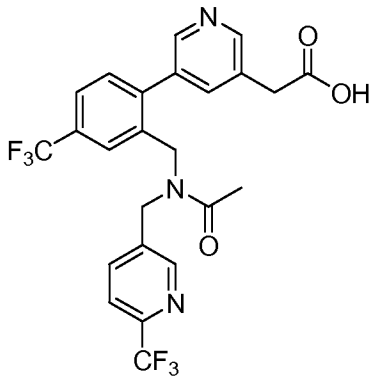
[00720] Prepared according to the procedure described in Example 51, Step 4, using the following starting material: [5-(2-{[*N*-acetyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 61: Synthesis of [5-(2-{[*N*-Acetyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-62)



Step 1: [5-(2-{[*N*-Acetyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

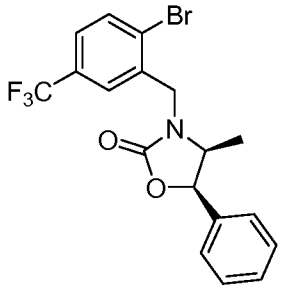
[00721] Prepared according to the procedure described in Example 51, Step 3, using the following starting materials: [5-(4-trifluoromethyl-2-{[(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and acetyl chloride.



Step 2: [5-(2-{[*N*-Acetyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

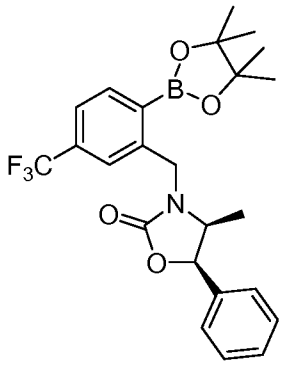
[00722] Prepared according to the procedure described in Example 51, Step 4, using the following starting material: [5-(2-{[*N*-acetyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 62: Synthesis of {5-[2-((4S,5R)-4-Methyl-2-oxo-5-phenyl-oxazolidin-3-ylmethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 2-1)



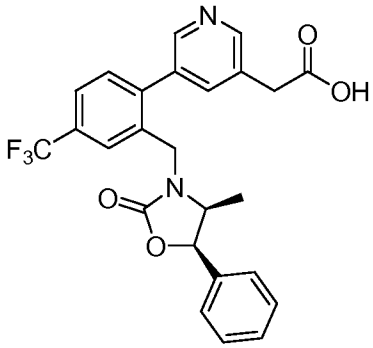
Step 1: (4S,5R)-3-(2-Bromo-5-trifluoromethyl-benzyl)-4-methyl-5-phenyl-oxazolidin-2-one

[00723] To a solution of (4S,5R)-(-)-4-methyl-5-phenyl-2-oxazolidinone (0.5g, 2.82mmol) in DMF (10mL) at 0°C was added sodium hydride (60% in mineral oil; 0.124g, 3.1mmol). After stirring for 10 minutes, 2-bromo-5-(trifluoromethyl)benzyl bromide (0.9g, 2.82mmol) was added, and the reaction was stirred for 30 minutes at 0°C. Once no starting material was seen by analytical tlc, the mixture was worked-up with EtOAc and H_2O, and the crude material was purified by silica gel chromatography to give the title compound.



Step 2: (4S,5R)-4-Methyl-5-phenyl-3-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-oxazolidin-2-one

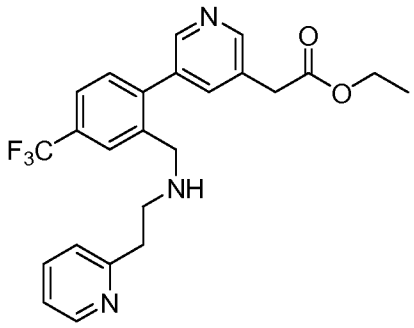
[00724] (4S,5R)-3-(2-Bromo-5-trifluoromethyl-benzyl)-4-methyl-5-phenyl-oxazolidin-2-one (0.7g, 1.69mmol), bis(pinacolato)diboron (0.644g, 2.52mmol), and potassium acetate (0.498g, 5.07mmol) were combined in DMF (10mL), and the solution was purged with N_2 for 10 minutes. (1,1'-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.138g, 0.17mmol) was added, and the reaction was stirred at 80°C for 5 hours, until no starting material was seen by analytical LCMS. After work-up with EtOAc and H_2O, the crude material was purified by silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound.



Step 3: {5-[2-((4S,5R)-4-Methyl-2-oxo-5-phenyl-oxazolidin-3-ylmethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid

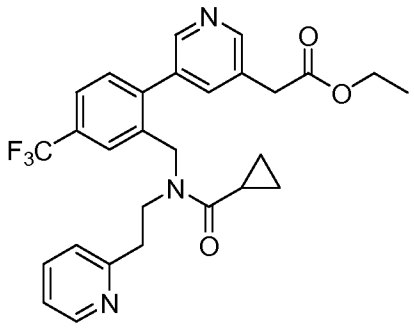
[00725] 5-Bromo-3-pyridylacetic acid (0.061g, 0.26mmol), (4S,5R)-4-methyl-5-phenyl-3-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-oxazolidin-2-one (0.08g, 0.17mmol), potassium carbonate (0.084g, 0.61mmol), and tetrakis(triphenylphosphine)palladium(0) (0.021g, 0.02mmol) were combined in DME (2mL) and H_2O (1mL), and the reaction was purged with N_2 for 5 minutes and then stirred at 90°C overnight. The mixture was worked-up with EtOAc and brine, and the crude material was purified by silica gel chromatography to give the title compound.

Example 63: Synthesis of [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-2-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-64)



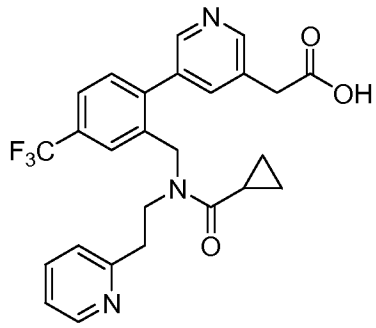
Step 1: (5-{2-[(2-Pyridin-2-yl-ethylamino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

[00726] To a solution of [5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester (0.682g, 2.01mmol) in dichloroethane (30mL) was added 2-(2-aminoethyl)pyridine (0.286mL, 2.4mmol), acetic acid (0.02mL, 0.2mmol), and molecular seives. The solution was stirred for 1 hour, and then sodium triacetoxyborohydride (0.638g, 3.01mmol) was added, and the reaction was stirred at room temperature for 4.5 hours. MeOH (2mL) was added to increase solubility, and the reaction was stirred at room temperature overnight. The mixture was filtered and quenched with H_2O, and then extracted with EtOAc. The crude material was purified by preparative HPLC to give the title compound.



Step 2: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-2-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

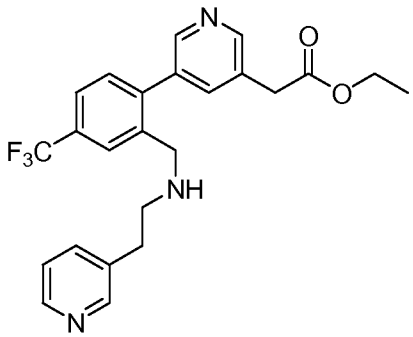
[00727] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: (5-{2-[(2-pyridin-2-yl-ethylamino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester and cyclopropanecarbonyl chloride.



Step 3: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-2-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

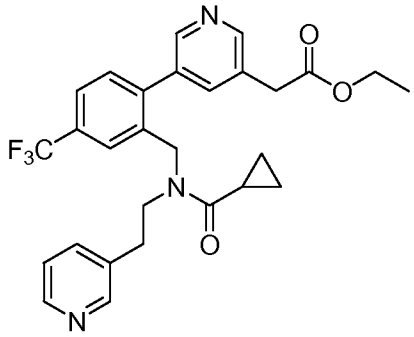
[00728] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: [5-(2-{[*N*-cyclopropanecarbonyl-*N*-(2-pyridin-2-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 64: Synthesis of [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-3-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-65)



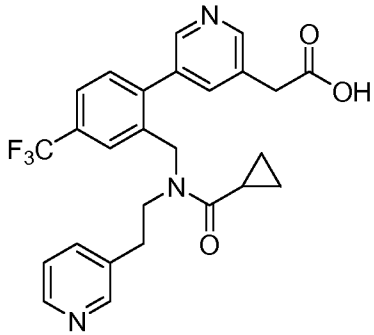
Step 1: (5-{2-[(2-Pyridin-3-yl-ethylamino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

[00729] Prepared according to the procedure described in Example 63, Step 1, using the following starting materials: [5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and 3-(2-aminoethyl)pyridine.



Step 3: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-3-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

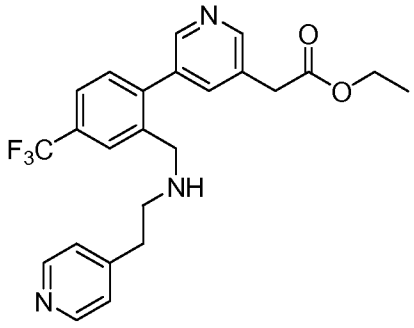
[00730] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: (5-{2-[(2-pyridin-3-yl-ethylamino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester and cyclopropanecarbonyl chloride.



Step 4: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-3-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

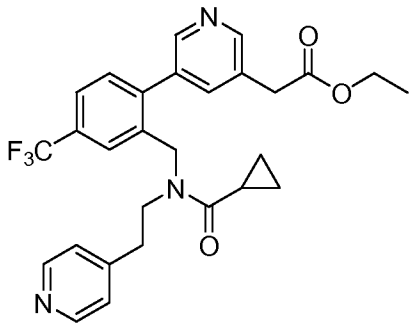
[00731] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: [5-(2-{[*N*-cyclopropanecarbonyl-*N*-(2-pyridin-3-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 65: Synthesis of [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-4-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-66)



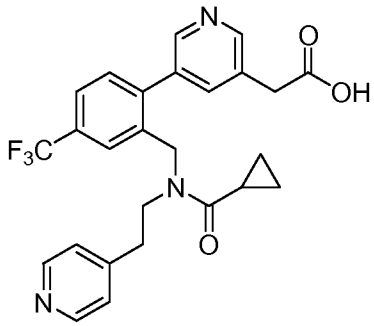
Step 1: (5-{2-[(2-Pyridin-4-yl-ethylamino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

[00732] Prepared according to the procedure described in Example 63, Step 1, using the following starting materials: [5-(2-formyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and 4-(2-aminoethyl)pyridine.



Step 2: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-4-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

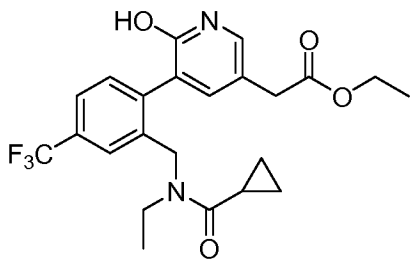
[00733] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: (5-{2-[(2-pyridin-4-yl-ethylamino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester and cyclopropanecarbonyl chloride.



Step 3: [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-4-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

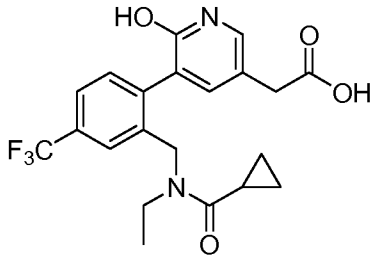
[00734] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: [5-(2-{[*N*-cyclopropanecarbonyl-*N*-(2-pyridin-4-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

Example 66: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid (Compound 1-67)



Step 1: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid ethyl ester

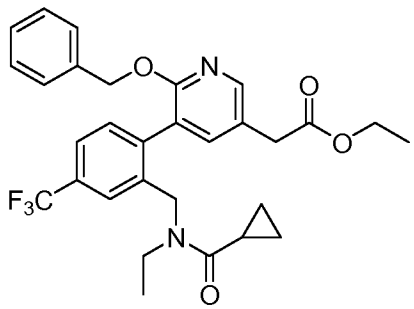
[00735] To a solutin of (5-{2-[(cyclopropanecarbonyl-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (0.099g, 0.22mmol) in EtOH (1mL) was added thionyl chloride (0.16mL, 2.19mmol), and the reaction was stirred at 80°C overnight. The mixture was diluted with CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the title compound.



Step 2: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid

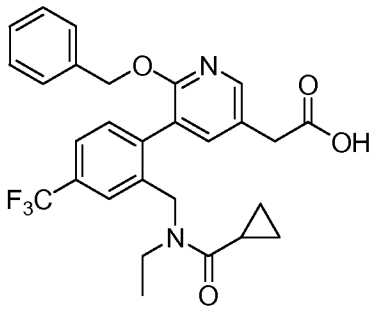
[00736] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (5-{2-[(cyclopropanecarbonyl-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid ethyl ester.

Example 67: Synthesis of (6-Benzyloxy-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-68)



Step 1: (6-Benzyloxy-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester

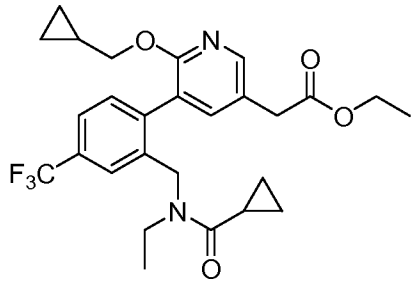
[00737] (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid ethyl ester (0.048g, 0.11mmol), benzyl bromide (0.02mL, 0.16mmol), and silver carbonate (0.039g, 0.14mmol) were combined in $CHCl_3$ (1mL) and stirred at 50°C for 3 hours. The mixture was cooled to room temperature and filtered, and the filtrate was concentrated and purified by silica gel chromatography to give the title compound.



Step 2: (6-Benzyloxy-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid

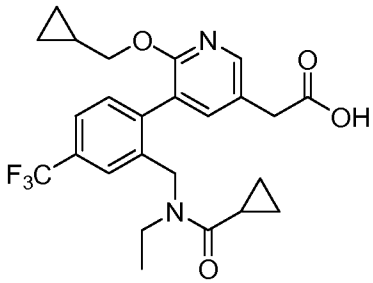
[00738] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (6-benzyloxy-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid ethyl ester.

Example 68: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-cyclopropylmethoxy-pyridin-3-yl)-acetic acid (Compound 1-69)



Step 1: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-cyclopropylmethoxy-pyridin-3-yl)-acetic acid ethyl ester

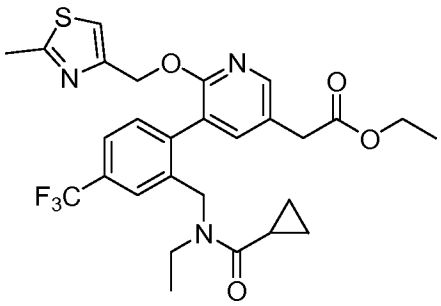
[00739] Prepared according to the procedure described in Example 67, Step 1, using the following starting materials: (5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid ethyl ester and (bromomethyl)cyclopropane.



Step 2: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-cyclopropylmethoxy-pyridin-3-yl)-acetic acid

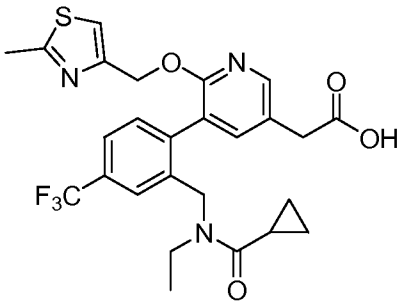
[00740] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-cyclopropylmethoxy-pyridin-3-yl)-acetic acid ethyl ester.

Example 69: Synthesis of [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2-methyl-thiazol-4-ylmethoxy)-pyridin-3-yl]-acetic acid (Compound 1-70)



Step 1: [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2-methyl-thiazol-4-ylmethoxy)-pyridin-3-yl]-acetic acid ethyl ester

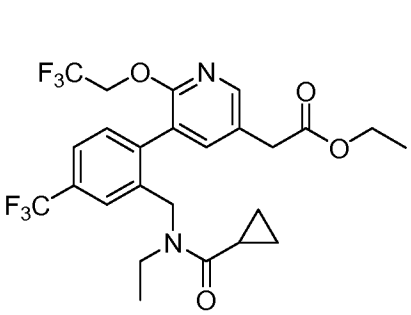
[00741] Prepared according to the procedure described in Example 67, Step 1, using the following starting materials: (5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid ethyl ester and 4-chloromethyl-2-methylthiazole hydrochloride.



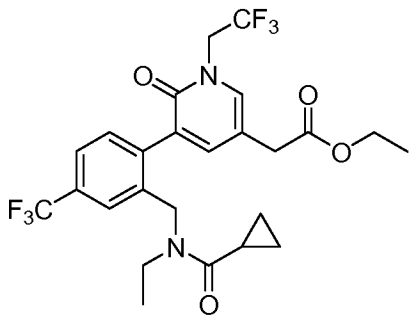
Step 2: [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2-methyl-thiazol-4-ylmethoxy)-pyridin-3-yl]-acetic acid

[00742] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: [5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2-methyl-thiazol-4-ylmethoxy)-pyridin-3-yl]-acetic acid ethyl ester.

Example 70: Synthesis of [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-acetic acid (Compound 1-71)

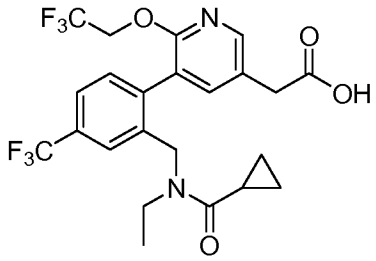


and



Step 1: [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-acetic acid ethyl ester and [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-oxo-1-(2,2,2-trifluoro-ethyl)-1,6-dihydro-pyridin-3-yl]-acetic acid ethyl ester

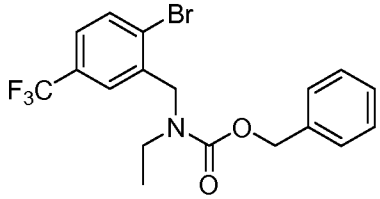
[00743] (5-{2-[(*N*-Cyclopropanecarbonyl- *N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid ethyl ester (0.175g, 0.39mmol), 2,2,2-trifluoroethyl tosylate (0.151g, 0.58mmol), and potassium carbonate (0.070g, 0.51mmol) were combined in DMF (1.8mL) and stirred at 55°C overnight. Additional 2,2,2-trifluoroethyl tosylate and potassium carbonate were added, and the reaction was stirred at 75°C overnight. After cooling, the crude material was used directly in the hydrolysis step as a mixture of two compounds.



Step 2: [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-acetic acid

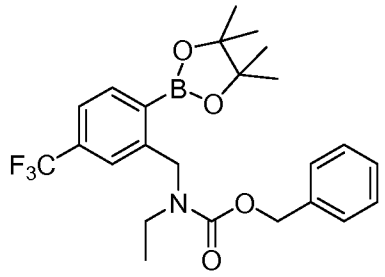
[00744] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: a mixture of [5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-acetic acid ethyl ester and [5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-oxo-1-(2,2,2-trifluoro-ethyl)-1,6-dihydro-pyridin-3-yl]-acetic acid ethyl ester; the desired product was separated from the secondary product, [5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-oxo-1-(2,2,2-trifluoro-ethyl)-1,6-dihydro-pyridin-3-yl]-acetic acid, via preparative HPLC.

Example 71: Synthesis of (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-72)



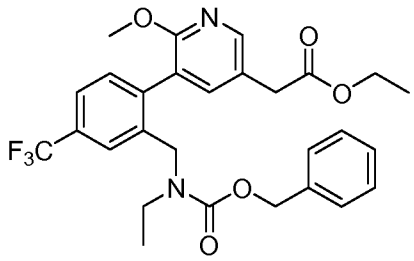
Step 1: (2-Bromo-5-trifluoromethyl-benzyl)-ethyl-carbamic acid benzyl ester

[00745] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: (2-bromo-5-trifluoromethyl-benzyl)-ethyl-amine and benzyl chloroformate.



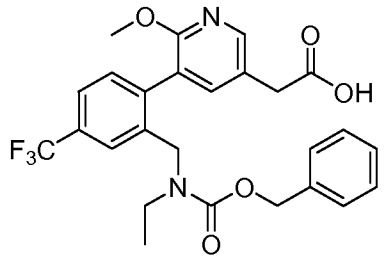
Step 2: Ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid benzyl ester

[00746] Prepared according to the procedure described in Example 1, Step 8, using the following starting materials: (2-bromo-5-trifluoromethyl-benzyl)-ethyl-carbamic acid benzyl ester and bis(pinacolato)diboron.



Step 3: (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester

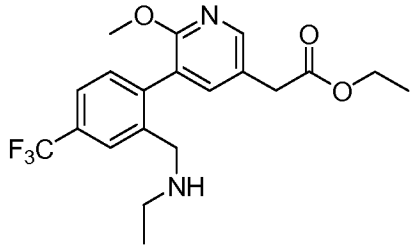
[00747] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-carbamic acid benzyl ester and (5-bromo-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester.



Step 4: (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid

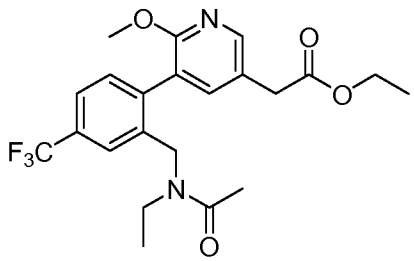
[00748] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (5-{2-[(*N*-benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester.

Example 72: Synthesis of (5-{2-[(*N*-Acetyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-73)



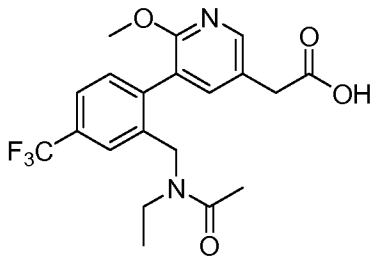
Step 1: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid ethyl ester

[00749] (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester (0.700g, 1.3mmol), ammonium formate (0.164g, 2.6mmol), and palladium on carbon (10%; 0.138g) were combined in an evacuated flask that was backfilled with N_2. MeOH (10mL) was added, and the resulting suspension was stirred at room temperature for 3 hours. No product was observed via analytical LCMS, so a balloon of H_2 was added, and the reaction was stirred under an atmosphere of H_2 overnight at room temperature. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in EtOAc and washed with H_2O and brine, and then dried over $Na2SO_4$, filtered, and concentrated. The crude material was purified by silica gel chromatography (0-5% MeOH in CH_2Cl_2) to give the title compound.



Step 2: (5-{2-[(*N*-Acetyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester

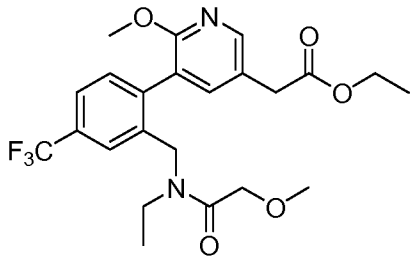
[00750] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid ethyl ester and acetyl chloride.



Step 3: (5-{2-[(*N*-Acetyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid

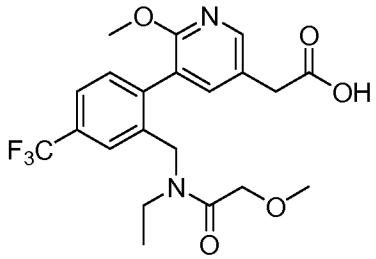
[00751] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (5-{2-[(*N*-acetyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester.

Example 73: Synthesis of [5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid (Compound 1-74)



Step 1: [5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid ethyl ester

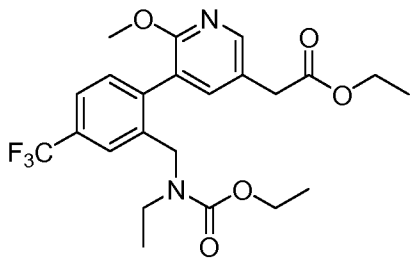
[00752] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid ethyl ester and methoxyacetyl chloride.



Step 2: [5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid

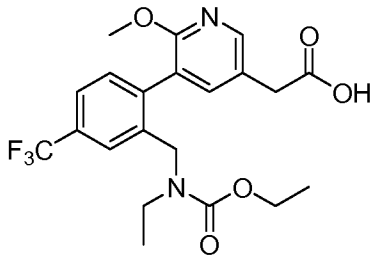
[00753] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: [5-(2-{[*N*-ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid ethyl ester.

Example 74: Synthesis of (5-{2-[(*N*-Ethoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-75)



Step 1: (5-{2-[(*N*-Ethoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester

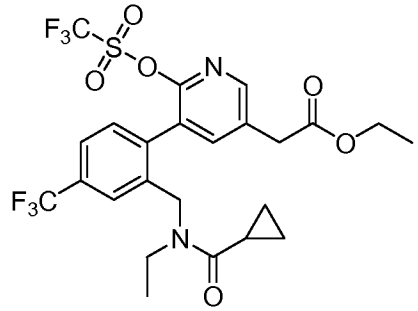
[00754] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid ethyl ester and ethyl chloroformate.



Step 2: (5-{2-[(*N*-Ethoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid

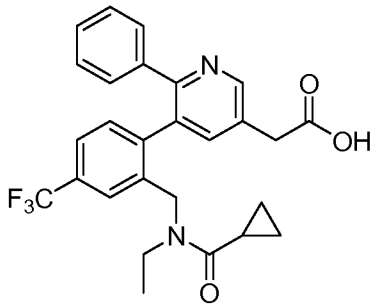
[00755] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (5-{2-[(ethoxycarbonyl-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid ethyl ester.

Example 75: Synthesis of (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-phenyl-pyridin-3-yl)-acetic acid (Compound 1-76)



Step 1: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-trifluoromethanesulfonyloxy-pyridin-3-yl)-acetic acid ethyl ester

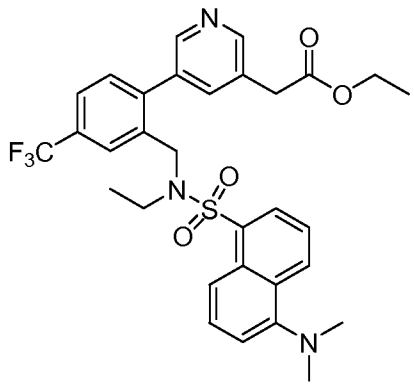
[00756] (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid ethyl ester (0.166g, 0.37mmol), N-phenyl-bis(trifluoromethanesulfonimide) (0.145g, 0.41mmol), and cesium carbonate (0.180g, 0.55mmol) were combined in MeCN (4mL) and stirred at room temperature for 3 hours. The mixture was diluted with EtOAc and H_2O, and the organic layer was separated, washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (20-40% EtOAc in hexanes) to give the title compound.



Step 2: (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-phenyl-pyridin-3-yl)-acetic acid

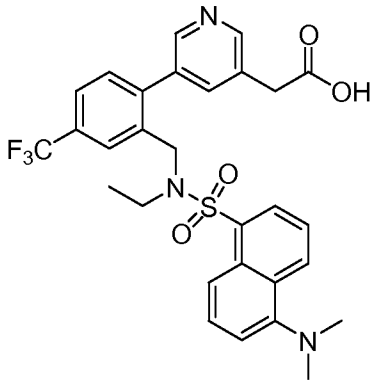
[00757] (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-trifluoromethanesulfonyloxy-pyridin-3-yl)-acetic acid ethyl ester (0.045g, 0.08mmol), phenylboronic acid (0.010g, 0.08mmol), and sodium bicarbonate (0.017g, 0.20mmol) were combined in DME (2mL) and H_2O (1mL). The mixture was purged with N_2 for 16 minutes, and then [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007g, 0.01mmol) was added, and the reaction was stirred at 85°C overnight in a sealed tube. Once no starting material was seen by analytical LCMS, 1N aqueous NaOH (1mL) and MeOH (1mL) were added, and the reaction was stirred overnight at room temperature. The mixture was worked up with EtOAc and 1N aqueous HCl, and the organic layer was separated, dried, and concentrated. The crude material was purified by preparative HPLC to give the title compound.

Example 76: Synthesis of [5-(2-{[*N*-(5-Dimethylamino-naphthalene-1-sulfonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-77)



Step 1: [5-(2-{[*N*-(5-Dimethylamino-naphthalene-1-sulfonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester

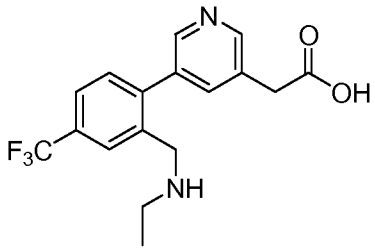
[00758] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: [5-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester and dansyl chloride.



Step 2: [5-(2-{[*N*- (5-Dimethylamino-naphthalene-1-sulfonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

[00759] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: [5-(2-{[*N*-(5-dimethylamino-naphthalene-1-sulfonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid ethyl ester.

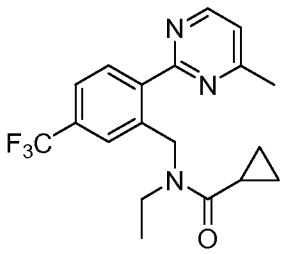
Example 77: Synthesis of [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-78)



Step 1: [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid

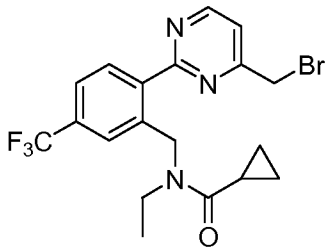
[00760] Prepared according to the procedure described in Example 72, Step 1, using the following starting material: (5-{2-[(*N*-benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid.

Example 78: Synthesis of (2-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrimidin-4-yl)-acetic acid (Compound 1-79)



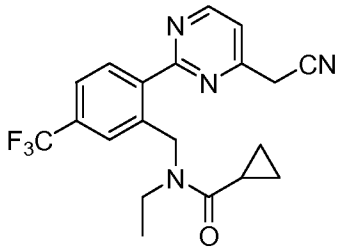
Step 1: Cyclopropanecarboxylic acid ethyl-[2-(4-methyl-pyrimidin-2-yl)-5-trifluoromethyl-benzyl]-amide

[00761] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: cyclopropanecarboxylic acid ethyl-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trifluoromethyl-benzyl]-amide and 2-chloro-4-methylpyrimidine.



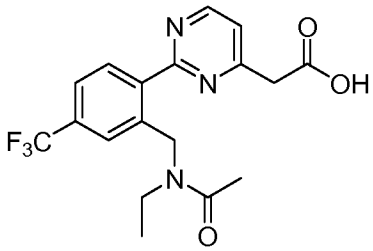
Step 2: Cyclopropanecarboxylic acid [2-(4-bromomethyl-pyrimidin-2-yl)-5-trifluoromethyl-benzyl]-ethyl-amide

[00762] Prepared according to the procedure described in Example 44, Step 2, using the following starting materials: cyclopropanecarboxylic acid ethyl-[2-(4-methyl-pyrimidin-2-yl)-5-trifluoromethyl-benzyl]-amide and N-bromosuccinimide.



Step 3: Cyclopropanecarboxylic acid [2-(4-cyanomethyl-pyrimidin-2-yl)-5-trifluoromethyl-benzyl]-ethyl-amide

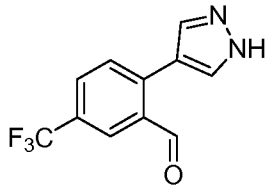
[00763] To a solution of cyclopropanecarboxylic acid [2-(4-bromomethyl-pyrimidin-2-yl)-5-trifluoromethyl-benzyl]-ethyl-amide (0.130g, 0.29mmol) in EtOH (2mL) was added H_2O (0.2mL), followed by potassium cyanide (0.019g, 0.29mmol), and the reaction was stirred at 55°C overnight. Once no starting material was seen by analytical LCMS, the crude mixture was used directly in the hydrolysis step.



Step 4: (2-{2-[(*N*-Acetyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrimidin-4-yl)-acetic acid

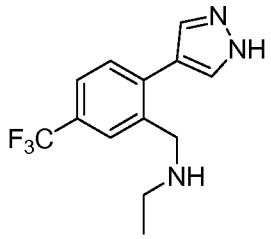
[00764] A solution of cyclopropanecarboxylic acid [2-(4-cyanomethyl-pyrimidin-2-yl)-5-trifluoromethyl-benzyl]-ethyl-amide (0.29mmol) in EtOH and H_2O was treated with 3N aqueous NaOH (1mL) and stirred at 60°C overnight. After work-up with EtOAc and 1N aqueous HCl, the crude material was purified by preparative HPLC to give the title compound.

Example 79: Synthesis of (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrazol-1-yl)-acetic acid (Compound 3-1)



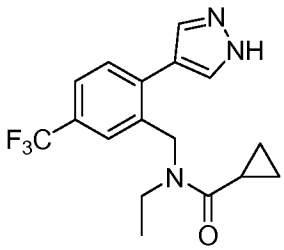
Step 1: 2-(1*H*-Pyrazol-4-yl)-5-trifluoromethyl-benzaldehyde

[00765] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: 2-bromo-5-(trifluoromethyl)benzaldehyde and 1*H*-pyrazol-4-yl boronic acid.



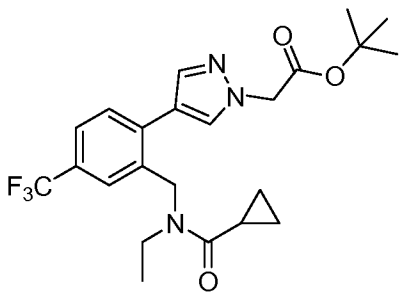
Step 2: Ethyl-[2-(1*H*-pyrazol-4-yl)-5-trifluoromethyl-benzyl]-amine

[00766] Prepared according to the procedure described in Example 3, Step 3, using the following starting materials: 2-(1*H*-pyrazol-4-yl)-5-trifluoromethyl-benzaldehyde and ethylamine (2M in THF).



Step 3: Cyclopropanecarboxylic acid ethyl-[2-(1*H*-pyrazol-4-yl)-5-trifluoromethyl-benzyl]-amide

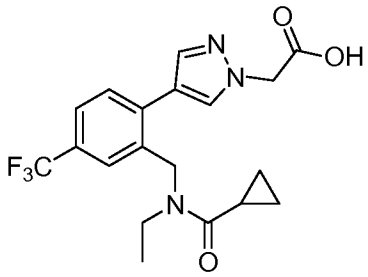
[00767] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: ehyl-[2-(1*H*-pyrazol-4-yl)-5-trifluoromethyl-benzyl]-amine and cyclopropanecarbonyl chloride.



Step 4: (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrazol-1-yl)-acetic acid *tert*-butyl ester

[00768] Cyclopropanecarboxylic acid ethyl-[2-(1*H*-pyrazol-4-yl)-5-trifluoromethyl-benzyl]-amide (0.187g, 0.55mmol), *tert*-butyl bromoacetate (0.07mL, 0.66mmol), and cesium carbonate

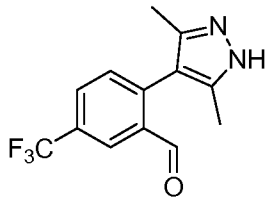
(0.360g, 1.1mmol) were combined in MeCN (10mL) at room temperature. Tetrabutylammonium iodide (10%) was added, and the reaction was stirred at room temperature overnight. After aqueous work-up, the crude material was purified by silica gel chromatography to give the title compound.



Step 5: (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrazol-1-yl)-acetic acid

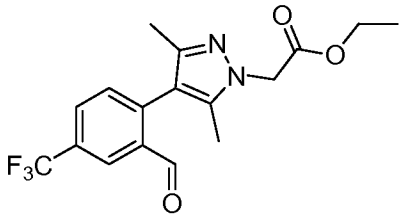
[00769] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (4-{2-[(*N*-cylopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrazol-1-yl)-acetic acid *tert*-butyl ester.

Example 80: Synthesis of (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid (Compound 3-2)



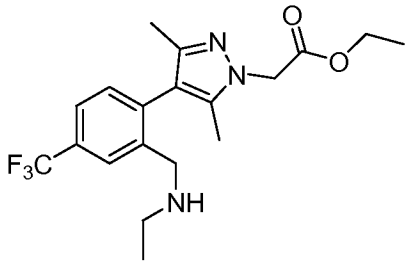
Step 1: 2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-5-trifluoromethyl-benzaldehyde

[00770] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: 2-bromo-5-(trifluoromethyl)benzaldehyde and 3,5-dimethylpyrazole-4-boronic acid, pinacol ester.



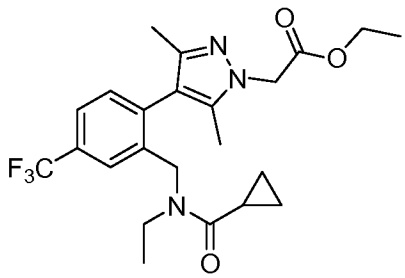
Step 2: [4-(2-Formyl-4-trifluoromethyl-phenyl)-3,5-dimethyl-pyrazol-1-yl]-acetic acid ethyl ester

[00771] Prepared according to the procedure described in Example 79, Step 4, using the following starting materials: 2-(3,5-dimethyl-1*H*-pyrazol-4-yl)-5-trifluoromethyl-benzaldehyde and ethyl bromoacetate.



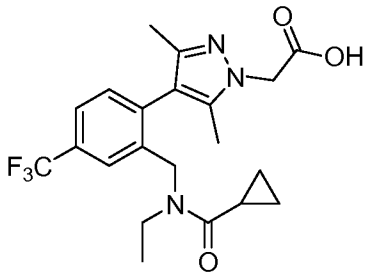
Step 3: [4-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-3,5-dimethyl-pyrazol-1-yl]-acetic acid ethyl ester

[00772] Prepared according to the procedure described in Example 3, Step 3, using the following starting materials: [4-(2-formyl-4-trifluoromethyl-phenyl)-3,5-dimethyl-pyrazol-1-yl]-acetic acid ethyl ester and ethylamine (2M in THF).



Step 4: (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid ethyl ester

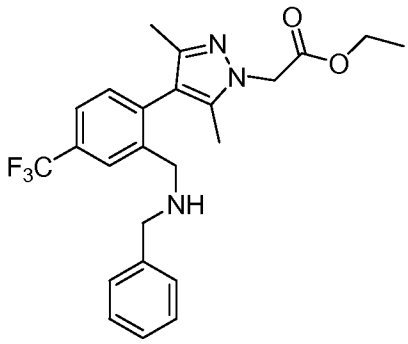
[00773] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: [4-(2-ethylaminomethyl-4-trifluoromethyl-phenyl)-3,5-dimethyl-pyrazol-1-yl]-acetic acid ethyl ester and cyclopropanecarbonyl chloride.



Step 5: (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid

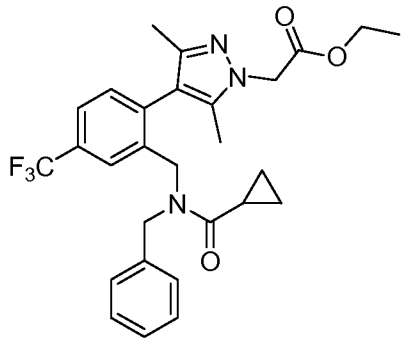
[00774] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (4-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid ethyl ester.

Example 81: Synthesis of (4-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid (Compound 3-3



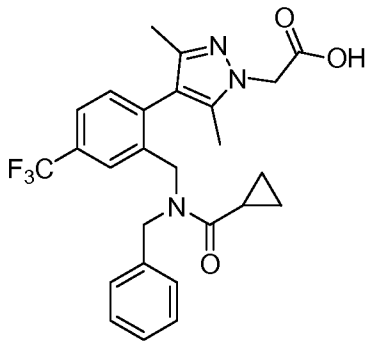
Step 1: {4-[2-(Benzylamino-methyl)-4-trifluoromethyl-phenyl]-3,5-dimethyl-pyrazol-1-yl}-acetic acid ethyl ester

[00775] Prepared according to the procedure described in Example 3, Step 3, using the following starting materials: [4-(2-formyl-4-trifluoromethyl-phenyl)-3,5-dimethyl-pyrazol-1-yl]-acetic acid ethyl ester and benzylamine.



Step 2: (4-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid ethyl ester

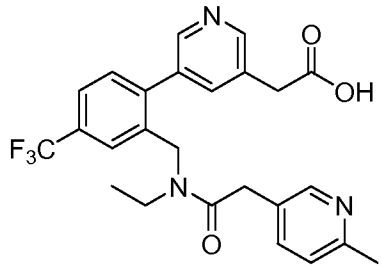
[00776] Prepared according to the procedure described in Example 5, Step 4, using the following starting materials: {4-[2-(benzylamino-methyl)-4-trifluoromethyl-phenyl]-3,5-dimethyl-pyrazol-1-yl}-acetic acid ethyl ester and cyclopropanecarbonyl chloride.



Step 3: (4-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid

[00777] Prepared according to the procedure described in Example 3, Step 7, using the following starting material: (4-{2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid ethyl ester.

Example 82: Synthesis of {5-[2-({*N*-Ethyl-*N*-[2-(6-methyl-pyridin-3-yl)-acetyl]-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid



Step 1: {5-[2-({*N*-Ethyl-*N*-[2-(6-methyl-pyridin-3-yl)-acetyl]-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid

[00778] {5-[2-({*N*-[2-(6-chloro-pyridin-3-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid ethyl ester ester (0.120g, 0.23mmol), methylboronic acid (0.060g, 0.25mmol), and sodium bicarbonate (0.049g, 0.58mmol) were combined in DME (2mL) and H_2O (1mL). The mixture was purged with N_2 for 15 minutes, and then [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.019g, 0.023mmol) was added, and the reaction was stirred at 85°C in a sealed tube for 5 hours. No desired product was seen by analytical LCMS, so the reaction was heated at 100°C overnight. The reaction was diluted with MeOH, and solid material was removed by filtration. The filtrate was purified by preparative HPLC to give the title compound.

[00779] Mass spectrometric data for compounds described in the Examples are displayed in Table 1, Table 2 and Table 3.

Example 83: CRTH2 Assays

Example 83a: DP_2/CRTH2 binding assay

[00780] The ability of a compound to bind to the human DP_2 receptor is assessed via a radioligand binding assay using [^{3}H]PGD_2. HEK293 cells stably expressing recombinant human DP_2 are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT, lysed and centrifuged at 75,000 xg to pellet the membranes. The membranes are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT and 10% glycerol to approximately 5 mg protein/ml. Membranes (2-10 μg protein/well) are incubated in 96-well plates with 1 nM [^{3}H]PGD_2 and test compound in Assay Buffer (50 mM Hepes, 10 mM $MnCl_2$, 1 mM EDTA, plus or minus 0.2% human serum albumin, pH 7.4) for 60 minutes at room temperature. The reactions are terminated by rapid filtration through Whatman GF/C glass fibre filter plates. The filter plates were pre-soaked in 0.33% polythylenimine for 30 minutes at room temperature then washed in Wash Buffer (50 mM Hepes, 0.5 M NaCl pH 7.4) prior to harvesting. After harvesting, the filter plates are washed 3 times with 1 ml cold Wash Buffer then dried. Scintillant is then added to the plates and the radioactivity retained on the filters is determined on a Packard TopCount (Perkin Elmer). Specific binding is determined as

total radioactive binding minus non-specific binding in the presence of 10 μM PGD_2. IC_{50}s were determined using GraphPad prism analysis of drug titration curves. Compounds tested had an IC_{50} of less than 100 micromolar in this assay.

Example 83b: GTPγS Binding Assay

[00781] The ability of a compound to inhibit binding of GTP to DP_2 is assessed via a membrane GTPγS assay. CHO cells stably expressing the recombinant human CRTH2 receptor are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT, lysed and centrifuged at 75,000 xg to pellet the membranes. The membranes are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT and 10% glycerol. Membranes (~12.5 μg per well) are incubated in 96-well plates with 0.05 nM [^{35}S]-GTPγS, 80 nM PGD_2, 5 μM GDP, and test compound in Assay Buffer (50 mM Hepes, pH 7.4, 100 mM NaCl, 5 mM $MgCl_2$ and 0.2% human serum albumin) for 60 minutes at 30°C. The reactions are terminated by rapid filtration through Whatman GF/B glass fibre filter plates. The filter plates are washed 3 times with 1 ml cold Assay Buffer and dried. Scintillant is then added to the plates and the radioactivity retained on the filters is determined on a Packard TopCount (Perkin Elmer). Specific binding is determined as total radioactive binding minus non-specific binding in the absence of the ligand (80 nM PGD_2). IC_{50}s were determined using Graphpad prism analysis of drug titration curves.

Example 83c: Whole Blood Esoinophil Shape Change Assay

[00782] Blood is drawn from consenting human volunteers in EDTA vacutainer tubes and used within 1 hr of draw. A 98 μl aliquot of blood is mixed with 2 μl of test compound (in 50% DMSO) in 1.2 ml polypropylene tubes. The blood is vortexed and incubated at 37°C for 15 minutes. 5 μl of 1 μM PGD_2 in PBS is added for a final concentration of 50 nM and the tubes briefly vortexed. The reactions are incubated for exactly 5 minutes at 37°C and then terminated by placing the tubes on ice and immediately adding 250 μl of ice-cold 1:4 diluted Cytofix (BD Biosciences). The reactions are transferred to 12 x 75 mM polystyrene round bottom tubes and the red blood cells lysed by the addition of 3 ml ammonium chloride lysing solution (150 mM NH_4Cl, 10 mM $KHCO_3$, 0.1 mM EDTA disodium salt) and incubation at room temperature for 15 minutes. The cells are pelleted by spinning at 1300 rpm for 5 minutes at 4°C and washed once with 3 ml ice-cold PBS. The cells are resuspended in 0.2 ml of ice-cold 1:4 diluted Cytofix (BD Biosciences) and analyzed on a FACSCalibur (BD Biosciences) within 2 hours. Eosinophils were gated on the basis of autofluorescence in the FL2 channel and shape change on 500 eosinophils was assayed by forward scatter and side scatter analysis. The specific change in shape induced by PGD_2 was calculated as the difference between the percentage of high forward scatter eosinophils in the presence and absence of PGD_2. IC_{50}s were determined using Graphpad Prism® analysis of drug titration curves.

Example 83d: DP_1 binding assay

[00783] The ability of a compound to bind to the human DP1 receptor was evaluated via a radioligand membrane binding assay using the DP_1 selective synthetic ligand [^{3}H]BWA868C. Packed human platelets (Biological Specialty Corporation), were resuspended in 6 volumes of Hepes/HBSS buffer (10 mM Hepes, 1 mM DTT in Hanks Balanced Salt Solution (HBSS)), lysed and centrifuged at 75,000 xg to pellet the membranes. Membranes were resuspended in Hepes/HBSS buffer to approximately 12 mg protein/ml. Membranes (20 μg protein/well) are incubated in 96-well plates with 2 nM [^{3}H]BWA868C and test compound in Assay Buffer (50 mM Hepes, 10 mM $MnCl_2$, 1 mM EDTA, plus or minus 0.2% human serum albumin, pH 7.4) for 60 minutes at room temperature. The reactions are terminated by rapid filtration through Whatman GF/C glass fibre filter plates. The filter plates were pre-soaked in 0.33% polethylenimine for 30 minutes at room temperature then washed in Wash Buffer (50 mM Hepes, 0.5 M NaCl pH 7.4) prior to harvesting. After harvesting, the filter plates are washed 3 times with 1 ml cold Wash Buffer then dried. Scintillant is then added to the plates and the radioactivity retained on the filters is determined on a Packard TopCount (Perkin Elmer). Specific binding is determined as total radioactive binding minus non-specific binding in the presence of 10 μM BW A868C. IC_{50}s were determined using GraphPad prism analysis of drug titration curves.

Example 84: *In vivo* assays

Mouse Allergic Rhinitis Model

[00784] The compounds ability to inhibit allergen-induced sneezing and nasal rubbing is assessed using a mouse model of allergic rhinitis. Methods were adapted from those detailed in Nakaya, M., *et al*.. 2006. Noninvasive system for evaluating allergen-induced nasal hypersensitivity in murine allergic rhinitis. *Laboratory Investigation*, 86:917-926. Female BALB/c mice (20-25g) are immunized by an intraperitoneal injection (i.p.) of 2 μg ovalbumin (OVA) complexed with alum in a volume 0.2 ml on days 0 and 14. Seven days later (day 21) mice are challenged intranasally with 20 μl of a 10mg/ml solution of OVA. The challenge period occurs daily from days 21 to day 25. Mice (5-7/group) are randomly assigned to receive either compound or vehicle and are treated by oral gavage 1-2 hour prior to each OVA challenge. The number of sneezes and nasal rubs are counted by an independent blind observe during a period of 8 minutes immediately following OVA challenge on days 21, 23 and 25. A significant increase in allergen-induced sneezing and nasal rubbing occurs over the 5-day challenge period. Inhibition of this effect by select compounds is determined statistically using Graphpad prism.

Example 85: Guinea Pig IV-DKPGD2-induced peripheral blood leukocyte influx

[00785] The compounds ability to inhibit leukocyte migration in vivo was assessed using intravenous injection of 13,14-dihydro-15-keto-prostaglandin D2 (DK-PGD2). Methods were adapted from those detailed Shichijo *et al*., 2003, Chemoattractant receptor-homologous molecule expressed on Th2 cells activation *in vivo* increases blood leukocyte counts and its blockade abrogates 13, 14-dihydro-15-keto-prostaglandin D2-induced eosinophilia in rats. *Journal of Pharmacology and Experimental Therapeutics*, 307:518-525. Male Hartley guinea pigs were immunized with ovalbumin (OVA) on day 0 by intraperitoneal (IP) injection of 1 ml of a 100 μg/ml solution in Imject Alum. They were then used in the DK-PGD2 procedure between days 14 and 21. Subjects were randomly assigned to receive either vehicle (0.5% methyl cellulose, 4 ml/kg, oral (PO)) or one of three to four doses of test compound. Two hours or eighteen hours after dosing, animals were anesthetized with ketamine and challenged with DK-PGD2 (1 mg/kg, IV). Thirty minutes after IV administration, blood was collected via the marginal ear vein into EDTA tubes for cell analysis. 10 μl blood was lysed in 190μl water followed by a further 20-fold dilution in PBS. A 10 μl fraction was mixed with equal parts trypan blue and loaded on a hemocytometer. Cells were visualized at a magnification of 40X using a LabPro light microscope and totals counted and recorded. Cells are expressed as total cells x 10^8 per ml of blood. Inhibition of this effect by select compounds is determined statistically using Graphpad prism.

[00786] The compounds that were tested in Table 1 had IC_{50} below 40 μM in the hDP2 (CRTH2) binding assay.

Table 5. Representative Biological Data

Compound Number	hDP2 (μM)
Compound 1-1	A
Compound 1-2	A
Compound 1-3	A
Compound 1-4	A
Compound 1-5	A
Compound 1-6	B
Compound 1-7	B
Compound 1-8	B
Compound 1-9	C
Compound 1-10	C
Compound 1-11	A
Compound 1-12	B
Compound 1-13	C
Compound 1-14	A
Compound 1-15	B
Compound 1-16	A
Compound 1-17	B
Compound 1-18	A
Compound 1-19	A

Compound Number	hDP2 (μM)
Compound 1-20	A
Compound 1-21	A
Compound 1-22	A
Compound 1-23	A
Compound 1-24	A
Compound 1-25	A
Compound 1-26	A
Compound 1-27	A
Compound 1-28	A
Compound 1-29	A
Compound 1-30	A
Compound 1-31	A
Compound 1-32	B
Compound 1-33	A
Compound 1-34	C
Compound 1-35	C
Compound 1-36	C
Compound 1-37	C
Compound 1-38	C
Compound 1-39	C
Compound 1-40	C
Compound 1-41	A
Compound 1-42	A
Compound 1-43	A
Compound 1-44	A
Compound 1-45	A
Compound 1-46	A
Compound 1-47	A
Compound 1-48	B
Compound 1-49	C
Compound 1-50	A
Compound 1-51	A
Compound 1-52	A
Compound 1-53	A
Compound 1-54	A
Compound 1-55	B
Compound 1-56	B
Compound 1-57	B
Compound 1-58	A
Compound 1-59	A
Compound 1-60	B
Compound 1-61	A
Compound 1-62	A
Compound 1-63	A
Compound 2-1	A
Compound 1-64	C
Compound 1-65	B
Compound 1-66	C
Compound 1-67	B
Compound 1-68	A

Compound Number	hDP2 (μM)
Compound 1-69	A
Compound 1-70	A
Compound 1-71	A
Compound 1-72	A
Compound 1-73	B
Compound 1-74	A
Compound 1-75	A
Compound 1-76	C
Compound 1-77	A
Compound 1-78	C
Compound 1-79	C
Compound 3-1	A
Compound 3-2	C
Compound 3-3	A
Ramatroban	B

A = less than 0.3 μM; B = greater than 0.3 μM and less than 1 μM; C= greater than 1 μM.

Example 86: Clinical Trials in Humans

Study 1: Clinical Trial Evaluating Effect of Compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) on ex vivo PGD_2-induced blood eosinophil shape change

In this double-blind, randomized, placebo-controlled, single ascending dose study of Compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) in healthy volunteers the inhibition of ex vivo PGD_2-induced blood eosinophil shape change is determined to show proof of biochemical mechanism of DP2 receptor antagonism. Eight subjects (6 active, 2 placebo) per dose level are used. Pre dose blood is drawn and challenged with PGD_2 to determine baseline shape change as described above in example 83. At varying times after dosing blood is drawn for both pharmacokinetic analyses of drug concentration in blood, and also for PGD_2 challenge and eosinophil shape change determination. The extent of receptor blockage is determined from the relationship between drug blood concentration and percentage inhibition of eosinophil shape change.

Study 2: Clinical Trial Evaluating Effect of Compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) on Allergen-induced Nasal symptoms and inflammatory and allergic biomarkers

In this double-blind, randomized, placebo-controlled study of Compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) in individuals with allergic rhinitis the inhibition of nasal symptoms and allergic biomarkers is determined following nasal challenge with appropriate allergen. Fifteen subjects (10 active, 5 placebo) are used. Subjects are dosed for 7 days with either placebo or an amount of compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) that results in complete DP2 receptor block in an ex vivo PGD_2-

induced blood eosinophil shape change pharmacodynamic study as described above. On day 7 subjects undergo nasal allergen challenge (2 hours post-dose) and early allergic response (0.25-1.0hr) and late allergic response (4-24hr) are evaluated as an increase from baseline for treated vs placebo. In addition changes in inflammatory cell differentials, Th2 cytokines and other inflammatory markers are determined as increase from baseline for treated vs placebo.

Compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) assay

[00787] The plasma concentrations of compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) are determined by gas chromatography, giving a detection limit of 1 ng·ml-1 (Ritter W. Determination of BAY u 3405, a novel thromboxane antagonist, in plasma and urine by HPLC and GC. In: Reid E, Wilson ID, eds. Bioanalytical Approaches for Drugs, Including Anti-asthmatics and Metabolites. Methodological Surveys in Biochemistry and Analysis, 1992; 22: 211–216).

Study 3 - Vienna Challenge Chamber Study

[00788] Study design: The study is a randomised, double blind, placebo controlled, two way crossover evaluation of compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), given orally for eight days. There is a screening period of one week and a washout period of three weeks between the two treatment periods.

[00789] There is a follow up one week after the last dose of study drug. The group of patients who receive the study drug for the first treatment period and placebo for the second are designated group A, while the group of patients who receive placebo for the first treatment period and the study drug for the second treatment period are designated group B.

[00790] Treatment plan and methods: The subjects undergo a complete screening assessment to determine a baseline response to allergens. This screening assessment takes place one week prior to the start of dosing.

[00791] Subjects commence dosing with compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), or placebo on Day 1 of each treatment period of the study. Adverse events, total nasal symptom score and concomitant medications are noted.

[00792] Subjects report back to the clinic on Day 2 of each treatment period for a 6 hour allergen challenge. The following measurements are obtained:

[00793] - Total nasal symptom score (TNSS) (obstruction, rhinorrhoea, itch, sneeze) with each symptom scored on a categorical scale from 0 to 3 pre-challenge, every 15 mins from 0 to 6h post-start of challenge

[00794] - Eye symptom score (watery eyes, itchy eyes, red eyes) with each symptom scored on a categorical scale from 0 to 3 pre-challenge, every 15mins from 0 to 6h post-start of challenge

[00795] - Other symptoms (cough, itchy throat, itchy ears) with each symptom scored on a categorical scale from 0 to 3 pre-challenge and every 15mins from 0 to 6h post-start of challenge

[00796] Subjects report back to the clinic on Day 8 of each treatment period for a 6 hour allergen challenge and the measurements obtained on Day 2 are repeated.

[00797] A final follow-up visit is conducted one week after the last dose of test article in Treatment Period 2.

Example 87: Pharmaceutical Compositions

Example 87a: Parenteral Composition

[00798] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Example 87b: Oral Composition

[00799] To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is mixed with 750 mg of starch. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

Example 87c: Sublingual (Hard Lozenge) Composition

[00800] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with 420 mg of powdered sugar mixed, with 1.6 mL of light corn syrup, 2.4 mL distilled water, and 0.42 mL mint extract. The mixture is gently blended and poured into a mold to form a lozenge suitable for buccal administration.

Example 87d: Fast-Disintegrating Sublingual Tablet

[00801] A fast-disintegrating sublingual tablet is prepared by mixing 48.5% by weigh of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V), 44.5% by weight of microcrystalline cellulose (KG-802), 5% by weight of low-substituted hydroxypropyl cellulose (50 μm), and 2% by weight of magnesium stearate. Tablets are prepared by direct compression (*AAPS PharmSciTech.* 2006;7(2):E41). The total weight of the compressed tablets is maintained at 150 mg. The formulation is prepared by mixing the amount of compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) with the total quantity of microcrystalline cellulose (MCC) and two-thirds of the quantity of low-substituted hydroxypropyl cellulose (L-HPC) by using a three dimensional manual mixer (Inversina ®,

Bioengineering AG, Switzerland) for 4.5 minutes. All of the magnesium stearate (MS) and the remaining one-third of the quantity of L-HPC are added 30 seconds before the end of mixing.

Example 87e: Inhalation Composition

[00802] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Example 87f: Rectal Gel Composition

[00803] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is mixed with 2.5 g of methylcelluose (1500 mPa), 100 mg of methylparapen, 5 g of glycerin and 100 mL of purified water. The resulting gel mixture is then incorporated into rectal delivery units, such as syringes, which are suitable for rectal administration.

Example 87g: Topical Gel Composition

[00804] To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is mixed with 1.75 g of hydroxypropyl celluose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topicl administration.

Example 87h: Ophthalmic Solution Composition

[00805] To prepare a pharmaceutical opthalmic solution composition, 100 mg of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is mixed with 0.9 g of NaCl in 100 mL of purified water and filterd using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

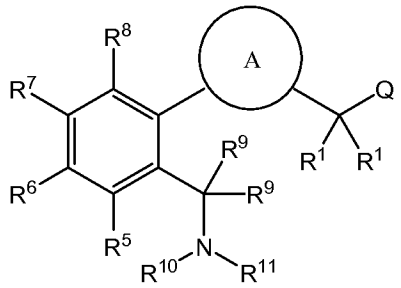
Example 87i: Nasal spray solution

[00806] To prepare a pharmaceutical nasal spray solution, 10 g of a compound of Formula (I), Formula (II), Formula (III), Formula (IV), or Formula (V) is mixed with 30 mL of a 0.05M phosphate buffer solution (pH 4.4). The solution is placed in a nasal administrator designed to deliver 100 μl of spray for each application.

[00807] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula (I), pharmaceutically acceptable salt, pharmaceutically acceptable solvate, *N*-oxide, or pharmaceutically acceptable prodrug thereof:



Formula (I)

wherein,

Q is tetrazolyl, or -C(=O)-Q^1;

Q^1 is –OH, –OR^B, -$NHSO_2R^{12}$, -$N(R^{13})_2$, -NH-OH, or –NH-CN; R^B is H or C_1-C_6alkyl;

ring A represents a substituted or unsubstituted monocyclic heteroaryl, wherein if ring A is substituted, then ring A is subtituted with 1 to 4 R^A;

each R^1 is independently selected from H, F, C_1-C_4alkyl, and C_1-C_4fluoroalkyl;

each of R^A, R^5, R^6, R^7, and R^8 is independently selected from H, halogen, -CN, -NO_2, -OH, -OR^{12}, -SR^{12}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$N(R^{13})S(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -$NHCH_2CO_2R^{13}$, -$OCH_2CO_2R^{13}$, -$SCH_2CO_2R^{13}$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NR^{13}C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, -NR^{13}-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, -$NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), and -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl);

each R^9 is H;

R^{10} is –$C(=O)R^{14}$, –$C(=O)OR^{15}$, –$C(=O)N(R^{16})_2$, –$S(=O)_2N(R^{16})_2$ or –$S(=O)_2R^{14}$;

R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-

C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl) or -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl); or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_6alkyl or a substituted or unsubstituted aryl;

X^3 is a bond, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -NR^{13}S(=O)$_2$-, or –NR^{13}-;

Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), or C_1-C_4alkyl-(substituted or unsubstituted heteroaryl);

R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), or -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl);

each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), or -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl); or

two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted C_2-C_{10}heterocycloalkyl;

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl), -C_1-C_6alkylene-O-R^{17}, -C_1-C_6alkylene-S-R^{17}, -C_1-C_6alkylene-S(=O)-R^{17}, -C_1-C_6alkylene-S(=O)$_2$-R^{17}, -C_1-C_6alkylene-N(R^{17})$_2$, -C_1-C_6alkylene-C(=O)-R^{17}, -C_1-C_6alkylene-C(=O)O-R^{17}-, -C_1-C_6alkylene-OC(=O)-R^{17}, -C_1-C_6alkylene-NR^{17}C(=O)-R^{17} or -C_1-C_6alkylene-C(=O)N(R^{17})$_2$;

each R^{17} is independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6haloalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, and a substituted or unsubstituted heteroaryl; or

two R^{17} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted C_2-C_{10}heterocycloalkyl; or

R^{10} and R^{11} are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle;

R^{12} is C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), or -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl);

each R^{13} is independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted benzyl, a substituted or unsubstituted heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted aryl), and -C_1-C_4alkyl-(substituted or unsubstituted heteroaryl); or

two R^{13} groups attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted C_2-C_{10}heterocycloalkyl.

2. The compound of claim 1, wherein:

Q is -C(=O)-Q^1;

Q^1 is –OR^B; R^B is H or C_1-C_6alkyl;

each R^1 is independently selected from H, F, and –CH_3.

3. The compound of claim 2, wherein:

ring A is a substituted or unsubstituted 5-membered or 6-membered heteroaryl, wherein if ring A is substituted, then ring A is subtituted with 1 to 4 R^A.

4. The compound of claim 3, wherein:

ring A is a substituted or unsubstituted 5-membered heteroaryl or a substituted or unsubstituted 6-membered heteroaryl, wherein ring A includes 0 or 1 O atoms, 0 or 1 S atoms, 0-3 N atoms, and at least 2 carbon atoms, wherein if ring A is substituted, then ring A is substituted with 1 to 3 R^A.

5. The compound of claim 3, wherein:

ring A is a substituted or unsubstituted 5-membered or 6-membered heteroaryl selected from among furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, wherein if ring A is substituted then ring A is substituted with 1 to 3 R^A.

6. The compound of claim 3, wherein:

ring A is a substituted or unsubstituted 5-membered heteroaryl, wherein ring A includes 0 or 1 O atoms, 0 or 1 S atoms, 1-3 N atoms, and at least 2 carbon atoms, wherein if ring A is substituted then ring A is substituted with 1 to 3 R^A.

7. The compound of claim 6, wherein:

ring A is a substituted or unsubstituted 5-membered heteroaryl selected from among pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,3,4-thiadiazolyl, wherein if ring A is substituted then ring A is substituted with 1 to 3 R^A.

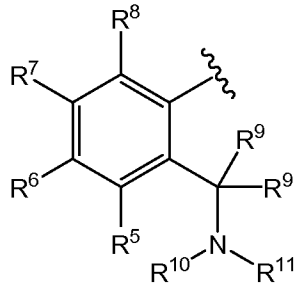
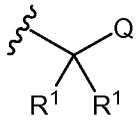
8. The compound of claim 3, wherein:

ring A is a substituted or unsubstituted 6-membered heteroaryl containing 1-3 N atoms in the ring, wherein if ring A is substituted then ring A is substituted with 1 to 3 R^A.

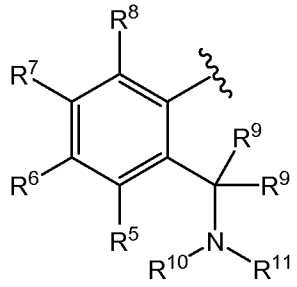
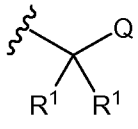
9. The compound of claim 8, wherein:

ring A is a substituted or unsubstituted 6-membered heteroaryl selected from among pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, wherein if ring A is substituted then ring A is substituted with 1 or 2 R^A.

10. The compound of claim 3, wherein:

the groups  and  are attached to ring A on non-adjacent atoms of ring A.

11. The compound of claim 10, wherein:

the groups  and  are attached to ring A on non-adjacent carbon atoms of ring A.

12. The compound of claim 3, wherein:

each R^A is independently selected from H, halogen, -CN, -OH, $-OR^{12}$, $-S(=O)_2R^{12}$, $-C(=O)R^{12}$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each of R^5, R^6, R^7, and R^8 is independently selected from H, halogen, -CN, $-NO_2$, -OH, $-OR^{12}$, $-SR^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-N(R^{13})S(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-OCO_2R^{13}$, $-N(R^{13})_2$, $-NHCH_2CO_2R^{13}$, $-OCH_2CO_2R^{13}$, $-SCH_2CO_2R^{13}$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{12}$, $-NR^{13}$-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, $-NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, and a substituted or unsubstituted monocyclic heteroaryl.

13. The compound of claim 12, wherein:

each of R^5, R^7, and R^8 is independently selected from H, halogen, -CN, -OH, $-OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

14. The compound of claim 12, wherein:

each of R^5, R^7, and R^8 is independently selected from H, F, Cl, Br, I, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CH_3CH_3$, $-CF_3$, CHF_2, CH_2F, and $-OCF_3$.

15. The compound of claim 14, wherein:

at least one of R^5, R^7, and R^8 is H.

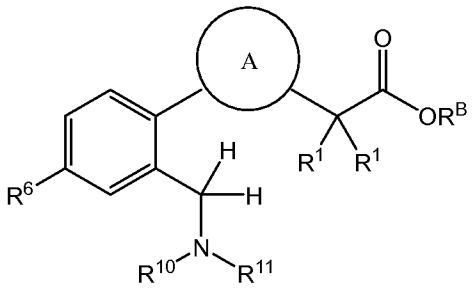
16. The compound of claim 14, wherein:

at least two of R^5, R^7, and R^8 is H.

17. The compound of claim 14, wherein:

each of R^5, R^7, and R^8 is H.

18. The compound of claim 17, wherein the compound of Formula (I) has the structure of Formula (II):



Formula (II).

19. The compound of claim 18, wherein:

R^B is H;

each R^1 is independently selected from H and $-CH_3$.

20. The compound of claim 19, wherein:

ring A is a substituted or unsubstituted 6-membered heteroaryl selected from among pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl, wherein if ring A is substituted then ring A is substituted with 1 or 2 R^A.

21. The compound of claim 19, wherein:

ring A is a substituted or unsubstituted pyridinyl, wherein if ring A is substituted then ring A is substituted with 1 or 2 R^A;

each R^A is independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy;

R^{10} is $-C(=O)R^{14}$, $-C(=O)OR^{15}$, or $-C(=O)N(R^{16})_2$;

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

22. The compound of claim 21, wherein:

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl).

23. The compound of claim 22, wherein:

R^{10} is $-C(=O)R^{14}$;

R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(C_3-C_6cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl) or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is $-L^3$-X^3-Q^3;

L^3 is a C_1-C_4alkyl;

X^3 is -O-, -S-, -S(=O)-, or -$S(=O)_2$-;

Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

24. The compound of claim 23, wherein:

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_4alkyl;

X^3 is -O-;

Q^3 is a C_1-C_6alkyl, a substituted or unsubstituted phenyl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

25. The compound of claim 23, wherein:

R^{11} is C_1-C_6alkyl, C_3-C_6cycloalkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl);

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_4alkyl;

X^3 is -O-;

Q^3 is a C_1-C_6alkyl.

26. The compound of claim 23, wherein:

R^{11} is C_1-C_6alkyl, C_3-C_6cycloalkyl;

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_4alkyl;

X^3 is -O-;

Q^3 is a C_1-C_6alkyl.

27. The compound of claim 23, wherein:

R^{11} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl);

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl; or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_4alkyl;

X^3 is -O-;

Q^3 is a C_1-C_6alkyl.

28. The compound of claim 22, wherein:

R^{10} is –C(=O)OR^{15};

R^{15} is C_1-C_6alkyl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

29. The compound of claim 22, wherein:

R^{10} is –C(=O)OR^{15};

R^{15} is C_1-C_4alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl).

30. The compound of claim 22, wherein:

R^{10} is –C(=O)OR^{15};

R^{11} is C_1-C_6alkyl;

R^{15} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl).

31. The compound of claim 22, wherein:

R^{10} is –C(=O)N(R^{16})$_2$;

each R^{16} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl).

32. The compound of claim 31, wherein:

R^{10} is –C(=O)N(R^{16})$_2$;

one R^{16} is C_1-C_6alkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); and the other R^{16} is H or C_1-C_6alkyl.

33. The compound of claim 31, wherein:

R^{10} is –C(=O)N(R^{16})$_2$;

R^{11} is C_1-C_6alkyl;

one R^{16} is C_1-C_6alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl); and the other R^{16} is H or C_1-C_6alkyl.

34. The compound of any one of claims 18-33, wherein:

R^6 is selected from H, halogen, -CN, -NO_2, -OH, -OR^{12}, -SR^{12}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$N(R^{13})S(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -$NHCH_2CO_2R^{13}$, -$OCH_2CO_2R^{13}$, -$SCH_2CO_2R^{13}$, -$C(=O)N(R^{13})_2$, -$OC(=O)N(R^{13})_2$, -$NR^{13}C(=O)N(R^{13})_2$, -$NR^{13}C(=O)R^{12}$, -NR^{13}-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, -$NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl.

35. The compound of claim 34, wherein:

R^6 is H, halogen, -OH, -SR^{13}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$NHS(=O)_2R^{12}$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -$N(R^{13})_2$, -$C(=O)N(R^{13})_2$, -$NHC(=O)R^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl.

36. The compound of claim 34, wherein:

R^6 is halogen, -CN, -OH, -SR^{13}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$NHS(=O)_2R^{12}$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -$N(R^{13})_2$, -$C(=O)N(R^{13})_2$, -$NHC(=O)R^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl.

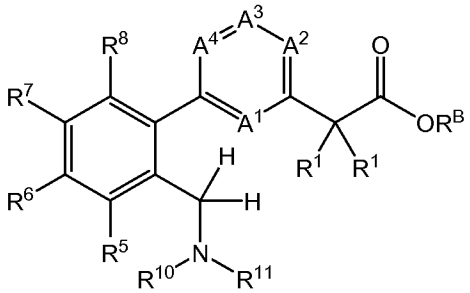
37. The compound of claim 34, wherein:

R^6 is halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy.

38. The compound of any one of claims 18-33, wherein:

R^6 is selected from a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, and a substituted or unsubstituted monocyclic heteroaryl.

39. The compound of claim 3, wherein the compound of Formula (I) has the structure of Formula (III):



Formula (III)

wherein

each of A^1, A^2, A^3, and A^4 is independently selected from among –N-, -$N^+(-O^-)$- and -$C(R^A)$-, where one or two of A^1, A^2, A^3, and A^4 is –N- or -$N^+(-O^-)$-.

40. The compound of any one of claims 39, wherein:

each R^A is independently selected from H, halogen, -CN, -OH, $-OR^{12}$, $-N(R^{13})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

41. The compound of claim 39, wherein:

each R^A is independently selected from H, halogen, -CN, -OH, $-OR^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, and C_1-C_4heteroalkyl;

A^1 is –N-, $-N^+(-O^-)$- or -CH-;

each of A^2, A^3, and A^4 is independently selected from among –N-, $-N^+(-O^-)$- and $-C(R^A)$-, where one or two of A^1, A^2, A^3, and A^4 is –N- or $-N^+(-O^-)$-

42. The compound of claim 41, wherein:

one of A^1, A^2, A^3, and A^4 is –N- or $-N^+(-O^-)$-.

43. The compound of claim 42, wherein:

A^1 is –N- or $-N^+(-O^-)$-.

44. The compound of claim 42, wherein:

A^2 is –N- or $-N^+(-O^-)$-.

45. The compound of claim 42, wherein:

A^3 is –N- or $-N^+(-O^-)$-.

46. The compound of claim 42, wherein:

A^4 is -N- or $-N^+(-O^-)$-.

47. The compound of claim 42, wherein:

A^1 is –CH-.

48. The compound of claim 47, wherein:

A^1 is CH;

A^3 is –N- or $-N^+(-O^-)$-; and

each of A^2 and A^4 is $-C(R^A)$-;

each R^A is independently selected from H, F, Cl, Br, I, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, and $-OCF_3$.

49. The compound of claim 48, wherein:

each R^1 is independently selected from H and $–CH_3$.

50. The compound of claim 49, wherein:

R^B is H, methyl, ethyl, propyl, or butyl.

51. The compound of claim 48, wherein:

each R^1 is H;

R^B is H.

52. The compound of claim 51, wherein:

each of R^5, R^7, and R^8 is independently selected from H, F, Cl, Br, I, -CN, -OH, -OCH_3, -OCH_2CH_3, -CH_3, -CH_3CH_3, -CF_3, CHF_2, CH_2F, and -OCF_3.

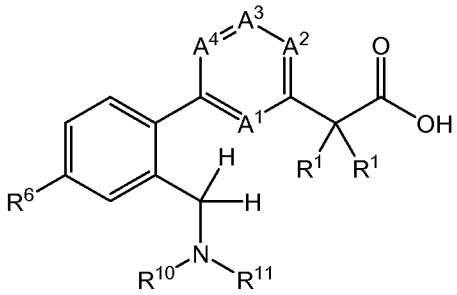
53. The compound of claim 52, wherein:

at least one of R^5, R^7, and R^8 is H.

54. The compound of claim 52, wherein:

each of R^5, R^7, and R^8 is H.

55. The compound of claim 39, wherein the compound has the structure of Formula (IV):



Formula (IV).

56. The compound of claim 55, wherein:

each R^1 is independently selected from H and –CH_3;

A^1 is CH;

A^3 is –N- or -N^+(-O^-)-; and

each of A^2 and A^4 is -$C(R^A)$-;

each R^A is independently selected from H, halogen, -CN, -OH, -OR^{12}, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, and C_1-C_4heteroalkyl.

57. The compound of claim 56, wherein:

each R^1 is H;

each R^A is independently selected from H, F, Cl, Br, I, -CN, -OH, -OCH_3, -OCH_2CH_3, -CH_3, -CH_2CH_3, -CF_3, -CHF_2, -CH_2F, and -OCF_3.

58. The compound of claim 57, wherein:

at least one R^A is H.

59. The compound of any one of claims 39-58, wherein:

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(C_3-C_6cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

60. The compound of claim 59, wherein:

R^{10} is –C(=O)R^{14}, –C(=O)OR^{15}, or –C(=O)N(R^{16})$_2$.

61. The compound of claim 60, wherein:

R^{10} is –C(=O)R^{14}, –C(=O)OR^{15}, or –C(=O)N(R^{16})$_2$;

R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl) or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_4alkylene or a substituted or unsubstituted phenyl;

X^3 is a bond, -O-, -S-, -S(=O)-, or -S(=O)$_2$-;

Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl);

R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl);

each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted C_2-C_{10}heterocycloalkyl.

62. The compound of claim 61, wherein:

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, or C_3-C_6cycloalkyl.

63. The compound of claim 61, wherein:

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl.

64. The compound of claim 61, wherein:

R^{11} is C_1-C_6alkyl or C_3-C_6cycloalkyl.

65. The compound of claim 61, wherein:

R^{11} is a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

66. The compound of claim 61, wherein:

R^{11} is -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

67. The compound of any one of claims 62-66, wherein:

R^{10} is –C(=O)R^{14}, –C(=O)OR^{15}, or –C(=O)N(R^{16})$_2$;

R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl;

R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl;

each R^{16} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; or

two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl.

68. The compound of any one of claims 62-66, wherein:

R^{10} is –C(=O)R^{14};

R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(C_3-C_6cycloalkyl), -C_1-C_4alkyl-(substituted or unsubstituted phenyl) or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_4alkyl;

X^3 is -O-, -S-, -S(=O)-, or -S(=O)$_2$-;

Q^3 is a C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

69. The compound of any one of claims 62-66, wherein:

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is -L^3-X^3-Q^3;

L^3 is a C_1-C_4alkyl;

X^3 is -O-;

Q^3 is a C_1-C_6alkyl, a substituted or unsubstituted phenyl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

70. The compound of any one of claims 62-66, wherein:

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is $-L^3-X^3-Q^3$;

L^3 is a C_1-C_4alkyl;

X^3 is -O-;

Q^3 is a C_1-C_6alkyl.

71. The compound of any one of claims 62-66, wherein:

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl) or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); or

R^{14} is $-L^3-X^3-Q^3$;

L^3 is a C_1-C_4alkyl;

X^3 is -O-;

Q^3 is a C_1-C_6alkyl.

72. The compound of any one of claims 62-66, wherein:

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl; or

R^{14} is $-L^3-X^3-Q^3$;

L^3 is a C_1-C_4alkyl;

X^3 is -O-;

Q^3 is a C_1-C_6alkyl.

73. The compound of any one of claims 62-66, wherein:

R^{10} is $-C(=O)OR^{15}$;

R^{15} is C_1-C_6alkyl, -C_1-C_4alkyl-(substituted or unsubstituted phenyl), or -C_1-C_4alkyl-(substituted or unsubstituted monocyclic heteroaryl).

74. The compound of any one of claims 62-66, wherein:

R^{10} is $-C(=O)OR^{15}$;

R^{15} is C_1-C_4alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl).

75. The compound of any one of claims 62-66, wherein:

R^{10} is $-C(=O)OR^{15}$;

R^{15} is -C_1-C_2alkyl-(substituted or unsubstituted phenyl).

76. The compound of any one of claims 62-66, wherein:

R^{10} is $-C(=O)N(R^{16})_2$;

each R^{16} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic heteroaryl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl).

77. The compound of any one of claims 62-66, wherein:

R^{10} is $-C(=O)N(R^{16})_2$;

one R^{16} is C_1-C_6alkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), or -C_1-C_2alkyl-(substituted or unsubstituted monocyclic heteroaryl); and the other R^{16} is H or C_1-C_6alkyl.

78. The compound of any one of claims 62-66, wherein:

R^{10} is $-C(=O)N(R^{16})_2$;

one R^{16} is C_1-C_6alkyl, or -C_1-C_2alkyl-(substituted or unsubstituted phenyl); and the other R^{16} is H or C_1-C_6alkyl.

79. The compound of any one of claims 39-78, wherein:

R^6 is selected from halogen, -CN, $-NO_2$, -OH, $-OR^{12}$, $-SR^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-N(R^{13})S(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-OCO_2R^{13}$, $-N(R^{13})_2$, $-NHCH_2CO_2R^{13}$, $-OCH_2CO_2R^{13}$, $-SCH_2CO_2R^{13}$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{12}$, $-NR^{13}$-C_1-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NR^{13}C(=O)R^{12}$, -C_1-C_4alkyl-$NR^{13}S(=O)_2R^{12}$, $-NR^{13}C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_6cycloalkyl, a substituted or unsubstituted C_2-C_6heterocycloalkyl.

80. The compound of any one of claims 39-78, wherein:

R^6 is selected from halogen, -CN, $-NO_2$, -OH, $-OR^{12}$, $-SR^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-N(C_1$-C_4alkyl$)S(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-OCO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NHC(=O)N(R^{13})_2$, $-N(C_1$-C_4alkyl$)C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, $-N(C_1$-C_4alkyl$)C(=O)R^{12}$, $-NHC_1$-C_4alkyl-$C(=O)R^{12}$, -C_1-C_4alkyl-$N(R^{13})_2$, -C_1-C_4alkyl-$NHC(=O)R^{12}$, -C_1-C_4alkyl-$NHS(=O)_2R^{12}$, $-NHC(=O)OR^{12}$, $-N(C_1$-C_4alkyl$)C(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_3-C_6cycloalkyl, and a substituted or unsubstituted C_2-C_6heterocycloalkyl.

81. The compound of any one of claims 39-78, wherein:

R^6 is selected from halogen, -CN, $-NO_2$, -OH, $-OR^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NHC(=O)N(R^{13})_2$, $-N(C_1\text{-}C_6alkyl)C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, $-N(C_1\text{-}C_6alkyl)C(=O)R^{12}$, $-NHC_1\text{-}C_4alkyl\text{-}C(=O)R^{12}$, $-C_1\text{-}C_4alkyl\text{-}N(R^{13})_2$, $-C_1\text{-}C_4alkyl\text{-}NHC(=O)R^{12}$, $-C_1\text{-}C_4alkyl\text{-}NHS(=O)_2R^{12}$, $-NHC(=O)OR^{12}$, $-N(C_1\text{-}C_6alkyl)C(=O)OR^{12}$, $C_1\text{-}C_6$alkyl, $C_1\text{-}C_6$fluoroalkyl, $C_1\text{-}C_6$fluoroalkoxy, $C_1\text{-}C_6$alkoxy, and $C_1\text{-}C_6$heteroalkyl.

82. The compound of any one of claims 39-78, wherein:

R^6 is selected from $-NHS(=O)_2R^{12}$, $-S(=O)_2N(R^{13})_2$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NHC(=O)N(R^{13})_2$, $-N(C_1\text{-}C_6alkyl)C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, $-N(C_1\text{-}C_6alkyl)C(=O)R^{12}$, $-NHC_1\text{-}C_4alkyl\text{-}C(=O)R^{12}$, $-C_1\text{-}C_4alkyl\text{-}N(R^{13})_2$, $-NHC(=O)OR^{12}$, $-N(C_1\text{-}C_6alkyl)C(=O)OR^{12}$.

83. The compound of any one of claims 39-78, wherein:

R^6 is selected from halogen, -OH, $C_1\text{-}C_4$alkyl, $C_1\text{-}C_4$fluoroalkyl, $C_1\text{-}C_4$fluoroalkoxy, or $C_1\text{-}C_4$alkoxy.

84. The compound of any one of claims 39-78, wherein:

R^6 is $C_3\text{-}C_{10}$cycloalkyl, substituted or unsubstituted $C_2\text{-}C_{10}$heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted napthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic heteroaryl.

85. The compound of any one of claims 39-78, wherein:

R^6 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or a substituted or unsubstituted group selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, phenyl, naphthyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl, benzofuranyl, benzothienyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl.

86. The compound of any one of claims 39-78, wherein:

R^6 is a substituted or unsubstituted group selected from phenyl, naphthyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl, benzofuranyl, benzothienyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl.

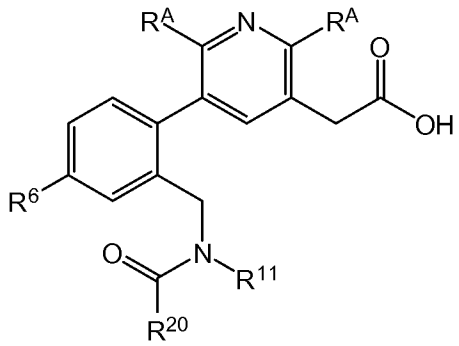
87. The compound of any one of claims 39-78, wherein:

R^6 is a substituted or unsubstituted group selected from pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl.

88. The compound of any one of claims 39-78, wherein:

R^6 is a substituted or unsubstituted group selected from pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolinyl, and isoquinolinyl.

89. A compound having the structure of Formula (V), pharmaceutically acceptable salt or *N*-oxide thereof:



Formula (V)

wherein,

each R^A is independently H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy;

R^6 is H, halogen, -CN, tetrazolyl, -OH, $-SR^{13}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-NHC(=O)R^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl;

R^{20} is C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom), -C_1-C_2alkyl-O-C_1-C_4alkyl, -O-C_1-C_4alkyl, -O-C_1-C_2alkyl-(substituted or unsubstituted phenyl), $-NR^{16}$-C_1-C_4alkyl, or $-NR^{16}$-C_1-C_2alkyl-(substituted or unsubstituted phenyl);

R^{11} is C_1-C_4alkyl, C_1-C_4haloalkyl, C_3-C_6cycloalkyl, or substituted or unsubstituted benzyl;

R^{12} is C_1-C_4alkyl, C_1-C_4heteroalkyl, or C_1-C_4fluoroalkyl;

each R^{13} is independently selected from H, C_1-C_4alkyl, C_1-C_4heteroalkyl, C_1-C_4fluoroalkyl, or substituted or unsubstituted benzyl;

R^{16} is H or C_1-C_4alkyl;

where each substituted phenyl or substituted heteroaryl is substituted with 1 or 2 R^C, where each R^C is independently selected from halogen, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and C_1-C_4alkoxy.

90. The compound of claim 89, wherein:

each R^A is independently R^A is H, F, Cl, Br, -CN, -OH, $-CH_3$, $-CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-OCH_3$ or $-OCH_2CH_3$;

R^6 is H, F, Cl, Br, -CN, -OH, $-SR^{13}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-CO_2R^{13}$, $-C(=O)NH(R^{13})$, $-NHC(=O)R^{12}$, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$;

R^{12} is C_1-C_4alkyl;

R^{13} is H, C_1-C_4alkyl, or substituted or unsubstituted benzyl.

91. The compound of claim 90, wherein:

R^{20} is C_1-C_4alkyl, C_3-C_6cycloalkyl, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom), -C_1-C_2alkyl-O-C_1-C_4alkyl, -O-C_1-C_4alkyl, -O-C_1-C_2alkyl-(substituted or unsubstituted phenyl), $–NR^{16}C_1$-C_4alkyl, or $–NR^{16}C_1$-C_2alkyl-(substituted or unsubstituted phenyl);

R^{11} is C_1-C_4alkyl, C_3-C_6cycloalkyl or substituted or unsubstituted benzyl.

92. The compound of claim 91, wherein:

R^{20} is $–CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, -C_1-C_2alkyl-(substituted or unsubstituted phenyl), -C_1-C_2alkyl-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom); where each substituted phenyl or substituted heteroaryl is substituted with 1 or 2 R^C, where each R^C is independently selected from halogen, -OH, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, and $-CF_3$;

R^{11} is $–CH_3$, $-CH_2CH_3$, or cyclopropyl.

93. The compound of claim 92, wherein:

at least one R^A is H;

R^6 is F, Cl, Br, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$;

R^{20} is $–CH_3$, cyclopropyl, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$.

94. The compound of claim 93, wherein:

at least one R^A is H;

R^{11} is $-CH_2CH_3$.

95. The compound of claim 89, wherein:

R^{20} is C_1-C_4alkyl, or C_3-C_6cycloalkyl;

R^{11} is substituted or unsubstituted benzyl.

96. The compound of claim 95, wherein:

at least one R^A is H;

R^6 is F, Cl, Br, -CN, -OH, $-SR^{13}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-CO_2R^{13}$, $-C(=O)NH(R^{13})$, $-NHC(=O)R^{12}$, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$;

R^{20} is $-CH_3$, or cyclopropyl;

R^{11} is substituted or unsubstituted benzyl.

97. The compound of claim 90, wherein:

R^{20} is -O-C_1-C_4alkyl or -O-C_1-C_2alkyl-(substituted or unsubstituted phenyl).

98. The compound of claim 97, wherein:

R^{20} is $-O-CH_2$-(substituted or unsubstituted phenyl) or $-O-CH(CH_3)$-(substituted or unsubstituted phenyl); where each substituted phenyl is substituted with 1 or 2 R^C, where each R^C is independently selected from halogen, -OH, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, and $-CF_3$;

R^{11} is C_1-C_4alkyl or C_3-C_6cycloalkyl.

99. The compound of claim 98, wherein:

at least one R^A is H;

R^6 is F, Cl, Br, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$;

R^{20} is $-O-CH_2$-(substituted or unsubstituted phenyl), where the substituted phenyl is substituted with 1 or 2 R^C, where each R^C is independently selected from F, Cl, Br, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$;

R^{11} is C_1-C_4alkyl.

100. The compound of claim 99, wherein:

one R^A is H, F, Cl, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$, and the other R^A is H;

R^6 is $-CF_3$;

R^{11} is $-CH_2CH_3$.

101. The compound of claim 90, wherein:

R^{20} is $-NR^{16}C_1$-C_4alkyl, or $-NR^{16}C_1$-C_2alkyl-(substituted or unsubstituted phenyl);

R^{16} is H, $-CH_3$ or $-CH_2CH_3$.

102. The compound of claim 101, wherein:

R^{20} is $-NR^{16}-CH_2$-(substituted or unsubstituted phenyl) or $-NR^{16}-CH(CH_3)$-(substituted or unsubstituted phenyl), where the substituted phenyl is substituted with 1 or 2 R^C, where each R^C is independently selected from F, Cl, Br, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$;

R^{11} is C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{16} is H, $-CH_3$ or $-CH_2CH_3$.

103. The compound of claim 102, wherein:

at least one R^A is H;

R^6 is F, Cl, Br, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$;

R^{20} is $-NR^{16}-CH_2-$(substituted or unsubstituted phenyl); where the substituted phenyl is substituted with 1 or 2 R^C, where each R^C is independently selected from F, Cl, Br, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$;

R^{11} is C_1-C_4alkyl.

104. The compound of claim 103, wherein:

one R^A is H, F, Cl, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$, and the other R^A is H;

R^6 is $-CF_3$;

R^{11} is $-CH_2CH_3$.

105. A compound selected from among:

3-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-(5-carboxymethyl-pyridin-3-yl)-benzoic acid (Compound 1-1); 4-(5-Carboxymethyl-pyridin-3-yl)-3-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-benzoic acid (Compound 1-2); (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-cyano-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-3); {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(2*H*-tetrazol-5-yl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-4); (5-{4-Benzylcarbamoyl-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-5); (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-methylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-6); (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-*tert*-butylcarbamoyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-7); {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-8); (5-{4-(Acetylamino-methyl)-2-[(*N*-benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-9); {5-[2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-(methanesulfonylamino-methyl)-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-10); 2-(5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid (Compound 1-11); 2-{5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-fluoro-phenyl]-pyridin-3-yl}-propionic acid (Compound 1-12); 2-(5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-propionic acid (Compound 1-13); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-14); (2-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-15); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-16); (6-Chloro-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-

amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-17); (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-18); (5-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-19); {5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-20); (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-1-oxy-pyridin-3-yl)-acetic acid (Compound 1-21); (5-{2-[(*N*-Ethyl-*N*-phenylacetyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-22); (5-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-23); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-indan-2-yl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-24); (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-25); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-phenethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-26); (5-{2-[(*N*-Acetyl-*N*-phenethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-27); (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-chloro-pyridin-3-yl)-acetic acid (Compound 1-28); (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-2-chloro-pyridin-3-yl)-acetic acid (Compound 1-29); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-methylsulfanyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-30); (5-{4-*tert*-Butylsulfanyl-2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-31); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-fluoro-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-32); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-mercapto-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-33); {2-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-4-yl}-acetic acid (Compound 1-34); (2-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-35); (2-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-36); (2-{2-[(*N*-Benzoyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-4-yl)-acetic acid (Compound 1-37); (6-{2-[(*N*-*tert*-Butoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid (Compound 1-38); {6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-pyridin-2-yl}-acetic acid (Compound 1-39); (6-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-2-yl)-acetic acid (Compound 1-40); (6-{2-[(*N*-Cyclobutanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-4-trifluoromethyl-pyridin-2-yl)-acetic acid (Compound 1-41); {6-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-pyridin-2-yl}-acetic acid (Compound 1-42); [5-(2-{[*N*-

Ethyl-*N*-(3-phenyl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-43); (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid (Compound 1-44); {5-[2-(3-Benzyl-1-ethyl-ureidomethyl)-4-trifluoromethyl-phenyl]-6-methoxy-pyridin-3-yl}-acetic acid (Compound 1-45); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-pyrazol-1-yl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-46); (5-{2-[(*N*-Acetyl-*N*-benzyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-47); [5-(2-{[*N*-Ethyl-*N*-(pyrazine-2-carbonyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-48); [5-(2-{[*N*-(2,4-Dimethoxy-pyrimidine-5-carbonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-49); {5-[2-({*N*-[2-(6-Chloro-pyridin-3-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-50); {5-[2-({*N*-[2-(4,6-Diethoxy-pyrimidin-2-yl)-acetyl]-*N*-ethyl-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-51); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-52); (5-{2-[(*N*-Acetyl- *N*-pyridin-2-ylmethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-53); [5-(2-{[*N*-Ethyl-*N*-(2-pyridin-2-yl-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-54); [5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-55); [5-(2-{[*N*-(2-Ethoxy-acetyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-56); [5-(2-{[*N*-Ethyl-*N*-(3-pyridin-3-yl-propionyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-57); [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-58); [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-59); [5-(2-{[*N*-(2-Methoxy-acetyl)-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-60); [5-(2-{[*N*-Acetyl-*N*-(5-methyl-pyrazin-2-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-61); [5-(2-{[*N*-Acetyl-*N*-(6-trifluoromethyl-pyridin-3-ylmethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-62); {5-[2-({*N*-Ethyl-*N*-[2-(6-methyl-pyridin-3-yl)-acetyl]-amino}-methyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 1-63); [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-2-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-64); [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-3-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-65); [5-(2-{[*N*-Cyclopropanecarbonyl-*N*-(2-pyridin-4-yl-ethyl)-amino]-methyl}-4-trifluoromethyl-

phenyl)-pyridin-3-yl]-acetic acid (Compound 1-66); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-hydroxy-pyridin-3-yl)-acetic acid (Compound 1-67); (6-Benzyloxy-5-{2-[(*N*-cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1-68); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-cyclopropylmethoxy-pyridin-3-yl)-acetic acid (Compound 1-69); [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2-methyl-thiazol-4-ylmethoxy)-pyridin-3-yl]-acetic acid (Compound 1-70); [5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl]-acetic acid (Compound 1-71); (5-{2-[(*N*-Benzyloxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-72); (5-{2-[(*N*-Acetyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-73); [5-(2-{[*N*-Ethyl-*N*-(2-methoxy-acetyl)-amino]-methyl}-4-trifluoromethyl-phenyl)-6-methoxy-pyridin-3-yl]-acetic acid (Compound 1-74); (5-{2-[*N*-(Ethoxycarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-methoxy-pyridin-3-yl)-acetic acid (Compound 1-75); (5-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-6-phenyl-pyridin-3-yl)-acetic acid (Compound 1-76); [5-(2-{[*N*-(5-Dimethylamino-naphthalene-1-sulfonyl)-*N*-ethyl-amino]-methyl}-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-77); [5-(2-Ethylaminomethyl-4-trifluoromethyl-phenyl)-pyridin-3-yl]-acetic acid (Compound 1-78); (2-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrimidin-4-yl)-acetic acid (Compound 1-79); {5-[2-((4S,5R)-4-Methyl-2-oxo-5-phenyl-oxazolidin-3-ylmethyl)-4-trifluoromethyl-phenyl]-pyridin-3-yl}-acetic acid (Compound 2-1); (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyrazol-1-yl)-acetic acid (Compound 3-1); (4-{2-[(*N*-Cyclopropanecarbonyl-*N*-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid (Compound 3-2); and (4-{2-[(*N*-Benzyl-*N*-cyclopropanecarbonyl-amino)-methyl]-4-trifluoromethyl-phenyl}-3,5-dimethyl-pyrazol-1-yl)-acetic acid (Compound 3-3).

106. The compound of any of claim 1-105, wherein the compound is an antagonist of DP_2.

107. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-105, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable inactive ingredient selected from pharmaceutically acceptable diluents, pharmaceutically acceptable excipients, and pharmaceutically acceptable carriers.

108. The pharmaceutical composition of claim 107, wherein the pharmaceutical composition is formulated for intravenous injection, oral administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration.

109. The pharmaceutical composition of claim 107, wherein the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

110. The pharmaceutical composition of any of claims 107-109 further comprising one or more additional therapeutically active agents selected from 5-lipoxygenase activating protein inhibitors, 5-lipoxygenase inhibitors, CYSLTR1 antagonists, thromboxane antagonists, DP_1 receptor antagonists, DP_1 receptor agonists, IP receptor agonists, chemokine receptor antagonists, IL5 antibody, bronchodilators, leukotriene receptor antagonists, leukotriene formation inhibitors, decongestants, antihistamines, mucolytics, corticosteroids, glucocorticoids, anticholinergics, antitussives, analgesics, expectorants, and β-2 agonists.

111. A medicament for treating a PGD_2-dependent condition or disease in a patient comprising a therapeutically effective amount of a compound of any of claims 1-105.

112. Use of a compound of any of claims 1-105 in the manufacture of a medicament for the treatment of a PGD_2-dependent condition or disease.

113. A method for treating a PGD_2-dependent condition or disease in a patient comprising administering to the patient a therapeutically effective amount of a compound of any of claims 1-105.

114. The method of claim 113, wherein the PGD_2-dependent condition or disease is selected from asthma, rhinitis, allergic conjuctivitis, atopic dermatitis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, interstitial lung fibrosis, arthritis, allergy, psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, cancer, wound healing, endotoxic shock, pain, inflammatory conditions, eosinophilic esophagitis, eosinophil-associated gastrointestinal disorders (EGID), idiopathic hypereosinophilic syndrome, otitis, airway constriction, mucus secretion, nasal congestion, increased microvascular permeability and recruitment of eosinophils, urticaria, sinusitis, angioedema, anaphylaxia, chronic cough and Churg Strauss syndrome.

115. The method of claim 113, wherein the PGD_2-dependent condition or disease is a respiratory disorder.

116. The method of claim 113, wherein the respiratory disorder is asthma, rhinitis or chronic obstructive pulmonary disease (COPD).

117. The method of any of claims 113-116, wherein the method further comprises administering to the patient a second therapeutic agent selected from 5-lipoxygenase-

activating protein inhibitors, 5-lipoxygenase inhibitors, CYSLTR1 antagonists, CYSLTR2 antagonists, thromboxane antagonists, DP1 receptor antagonists, DP1 receptor agonists, IP receptor agonists, anti-IgE, chemokine receptor antagonists, IL5 antibody, bronchodilators, theophylline, leukotriene receptor antagonists, leukotriene formation inhibitors, decongestants, antihistamines, mucolytics, corticosteroids, glucocorticoids, anticholinergics, antitussives, analgesics, expectorants, and β-2 agonists.

118. A compound of any of claims 1-105 for use in treating a disease or condition mediated by prostaglandin D_2.

119. The compound of claim 118, wherein the disease or condition is a respiratory disease or condition or an allergic disease or condition.

120. The compound of claim 118, wherein the disease or condition is asthma.

121. A compound of any of claims 1-105 for use in treating or preventing asthma in a mammal.

122. A compound of any of claims 1-105 for use in treating or preventing rhinitis in a rhinitis in a mammal.

123. A compound of any of claims 1-105 for use in treating chronic obstructive pulmonary disease (COPD) in a mammal.

124. A method for treating asthma in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of any of claims 1-105.

125. A method for treating rhinitis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of any of claims 1-105.

126. A method for treating chronic obstructive pulmonary disease (COPD) in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of any of claims 1-105.