

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 May 2009 (14.05.2009)

PCT

(10) International Publication Number
WO 2009/061676 A2

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61K 31/41* (2006.01)

(21) International Application Number:
PCT/US2008/082056

(22) International Filing Date: 31 October 2008 (31.10.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/985,919 6 November 2007 (06.11.2007) US

(71) Applicant (for all designated States except US): **AMIRA PHARMACEUTICALS, INC.** [US/US]; 9535 Waples Street Suite 100, San Diego, California 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **STEARNS, Brian Andrew** [US/US]; 3339 32nd Street, San Diego, California 92104 (US). **TRUONG, Yen Pham** [US/US]; 9175 Judicial Drive #6407, San Diego, California 92122 (US). **HUTCHINSON, John Howard** [US/US]; 5948 Via Zurita, La Jolla, California 92037 (US).

(74) Agents: **HOSTETLER, Michael, J.** et al.; WILSON SONSINI GOODRICH & ROSATI, 650 Page Mill Road, Palo Alto, California 94304-1050 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

(54) Title: ANTAGONISTS OF PGD₂ RECEPTORS

(57) Abstract: Described herein are compounds and pharmaceutical compositions containing such compounds that antagonize the PGD₂ activated chemoattractant receptor-homologous molecule expressed on TH2 cells (CRTH2). Also described herein are methods of using such CRTH2 antagonists, alone and in combination with other compounds, for treating respiratory, cardiovascular, and other PGD₂-dependent or PGD₂ mediated conditions or diseases.



WO 2009/061676 A2

ANTAGONISTS OF PGD₂ RECEPTORS

RELATED APPLICATIONS

[0001] This patent application claims the benefit of U.S. Provisional Application Ser. No. 60/985,919, entitled "ANTAGONISTS OF PGD₂ RECEPTORS" filed November 6, 2007, herein 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 or conditions associated with prostaglandin D₂.

BACKGROUND OF THE INVENTION

[0003] Prostaglandins have a diverse range of activities and have a well recognized role in pain and inflammation. Prostaglandin D₂ (PGD₂) is an acidic lipid mediator derived from the metabolism of arachidonic acid by cyclooxygenases and PGD₂ synthases. PGD₂ is produced by mast cells, macrophages and T_H2 lymphocytes in response to local tissue damage as well as allergic inflammation in diseases such as asthma, rhinitis, and atopic dermatitis. Exogenous PGD₂ applied to bronchial airways elucidates many characteristics of an asthmatic response suggesting that PGD₂ plays an important pro-inflammatory role in allergic diseases.

[0004] PGD₂ binds to a number of receptors, which include the thromboxane-type prostanoid (TP) receptor, PGD₂ receptor (DP, also known as DP₁) and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2; also known as DP₂). DP₂ is associated with promoting chemotaxis and activation of T_H2 lymphocytes, eosinophils and basophils. In particular, PGD₂ binds to DP₂, and mediates its effects through a G_i-dependant elevation in calcium levels and reduction of intracellular cyclic AMP. In T_H2 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.

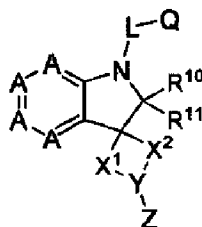
SUMMARY OF THE INVENTION

[0005] Presented herein are methods, compounds, pharmaceutical compositions, and medicaments 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 metabolic 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 CRTH2 modulators.

[0006] In one aspect provided herein are compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, and Formula 9, pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically acceptable prodrugs, and pharmaceutically

acceptable solvates thereof. In one aspect, such compounds antagonize CRTH2 and are used to treat patients suffering from one or more PGD₂-dependent conditions or diseases. In one aspect, such PGD₂-dependent conditions or diseases include, but not limited to, asthma, rhinitis, allergic conjunctivitis, 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, proliferative disorders, 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, anaphylaxis, chronic cough and Churg Strauss syndrome. In some embodiments, PGD₂-dependent conditions or diseases include those wherein an absolute or relative excess of PGD₂ is present and/or observed. In one aspect are 2,3-dihydrospiro[(2-oxo)-indole] compounds. In a further aspect, such compounds antagonize CRTH2 and are used to treat patients suffering from one or more PGD₂-dependent conditions or diseases.

[0007] In one aspect is a compound of Formula 1:



Formula 1

wherein,

X¹ is -(CR^AR^B)_m-; m is 0, 1, 2 or 3;

X² is -(CR^AR^B)_n-; n is 0, 1, 2 or 3; and the sum of m + n ≥ 2;

each R^A is independently selected from H, OH, halogen, -C≡N, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

each R^B is independently selected from H, OH, halogen and alkyl; or

R^A and R^B on the same carbon atom are taken together to form an oxo (=O); or

R^A and R^B taken together form an unsubstituted or substituted 4-, 5-, 6-, 7- or 8-membered ring;

Y is N or >CH(CH₂)_oNH-, wherein o is 0, 1, 2 or 3;

Z is selected from alkyl, substituted alkyl, fluoroalkyl, substituted fluoroalkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, -COR³, -CO₂R³, -SO₂R³, -SOR³, -CON(R²)₂, -SO₂N(R²)₂, -C(=NSO₂R³)N(R²)₂, and -C(=CH-CN)N(R²)₂;

each A is CR¹ or N; provided that at least two A groups are CR¹;

each R¹ is independently selected from H, OH, halogen, -C≡N, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, -N(R²)₂, -OR², -C(=O)R³, -CO₂R², -CON(R²)₂, -NR²COR³, -S(=O)R³, -S(=O)₂R³, -SO₂N(R²)₂, -N(R²)SO₂R³, -N(R²)SO₂N(R²)₂, -NR²CO₂R³, -NR²CON(R²)₂, -OCO₂R³ and -OCON(R²)₂; or

two R^1 groups on adjacent carbons taken together form an unsubstituted or substituted 5-, 6-, 7- or 8-membered ring;

each R^2 is independently selected from H, alkyl, substituted alkyl, fluoroalkyl, substituted fluoroalkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, and substituted -alkyl-heteroaryl; or

two R^2 groups on the same nitrogen atom are taken together with the nitrogen atom to form an unsubstituted or substituted 4-, 5-, 6-, 7- or 8-membered ring;

each R^3 is independently selected from alkyl, substituted alkyl, fluoroalkyl, substituted fluoroalkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, and $-R^4-L^3-R^5$;

R^4 is an unsubstituted or substituted group selected from alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

L^3 is a bond, -O-, -S-, -NH-, -C(=O)-, -NHC(=O)O-, -NHC(=O)NH-, -OC(=O)O-, -OC(=O)NH-, -NHC(=O)-, -C(=O)NH-, -C(=O)O-, or -OC(=O)-;

R^5 is H or a unsubstituted or substituted group selected from alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R^{10} is H or $-CH_3$;

R^{11} is H or $-CH_3$; or

R^{10} and R^{11} are taken together to form an oxo (=O);

-L- is $-(CR^C R^D)_p$, where p is 1 or 2;

R^C is independently selected from H, halogen, and alkyl;

R^D is independently selected from H, halogen, and alkyl; or

R^C and R^D taken together with the carbon atom to which they are attached to form a 3-, 4-, 5-, or 6-membered ring;

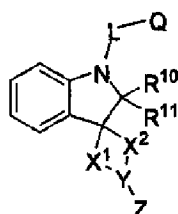
Q is selected from -OH, $-CO_2H$, $-CO_2R^3$ or a carboxylic acid bioisostere;

or a pharmaceutically acceptable solvate, pharmaceutically acceptable salt or pharmaceutically acceptable prodrug thereof.

[0008] For any and all of the embodiments, substituents are optionally selected from among from a subset of the listed alternatives. For example, in some embodiments, each A is CR^1 or N; provided that at least two A groups are CR^1 . In other embodiments, each A is CR^1 or N; provided that at least three A groups are CR^1 . In yet other embodiments, each A is CR^1 . In some embodiments, one A is N. In other embodiments, two A are N. In some embodiments, each R^1 is independently selected from H, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, OR^2 , $C(=O)R^3$, CO_2R^2 , and $CON(R^2)_2$. In some embodiments, each R^1 is independently selected from H, halogen, $-C\equiv N$, alkyl, and fluoroalkyl. In some embodiments, at least one R^1 is H. In other embodiments, at least two R^1 are H. In some embodiments, each R^1 is H. In some embodiments, each A is CR^1 ; and each R^1 is H.

[0009] In one aspect, R^{10} is H; R^{11} is H; or R^{10} and R^{11} taken together form an oxo (=O).

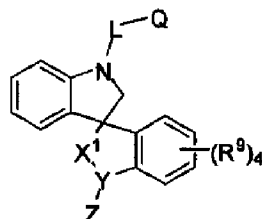
[0010] In another aspect, provided herein is a compound of Formula 2:



Formula 2.

[0011] In some embodiments, R^{10} and R^{11} are both H.

[0012] In one aspect, provided herein is a compound of Formula 3:



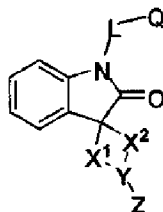
Formula 3

wherein,

each R^9 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $N(R^2)_2$, OR^2 , $C(=O)R^3$, CO_2R^2 , $CON(R^2)_2$, NR^2COR^3 , $S(=O)R^3$, $S(=O)_2R^3$, $SO_2N(R^2)_2$, $N(R^2)SO_2R^3$, $N(R^2)SO_2N(R^2)_2$, $NR^2CO_2R^3$, $OCO(NR^2)_2$, $NR^2CON(R^2)_2$ or OCO_2R^3 ; or two R^9 groups on adjacent carbons taken together form a 5-, 6-, 7- or 8-membered ring.

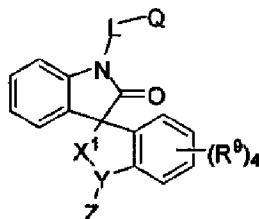
[0013] In some embodiments, R^{10} and R^{11} are taken together to form an oxo ($=O$).

[0014] In one aspect, provided herein is a compound of Formula 4:



Formula 4.

[0015] In another aspect, provided herein is a compound of Formula 5:



Formula 5

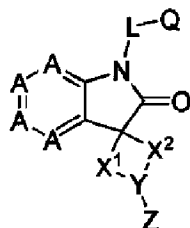
each R^9 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $N(R^2)_2$, OR^2 , $C(=O)R^3$, CO_2R^2 , $CON(R^2)_2$, NR^2COR^3 , $S(=O)R^3$, $S(=O)_2R^3$, $SO_2N(R^2)_2$,

$N(R^2)SO_2R^3$, $N(R^2)SO_2N(R^2)_2$, $NR^2CO_2R^3$, $OCO(NR^2)_2$, $NR^2CON(R^2)_2$ or OCO_2R^3 ; or two R^9 groups on adjacent carbons taken together form a 5-, 6-, 7- or 8-membered ring.

[0016] In some embodiments, each R^9 is selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, and OR^2 .

In some embodiments, each R^9 is H.

[0017] In another aspect, provided herein is a compound of Formula 6:



Formula 6.

[0018] In one aspect, $-L-$ is $-(CR^C R^D)_p$, where p is 1 or 2; R^C is independently selected from H, F, and $-CH_3$; R^D is independently selected from H, F, and $-CH_3$; or R^C and R^D taken together with the carbon atom to which they are attached to form a cyclopropyl, cyclobutyl or cyclohexyl.

[0019] In some embodiments, Q is selected from $-OH$, $-CO_2H$, and $-CO_2R^3$.

[0020] In other embodiments, $-L-$ is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)-$, , or $-CH_2CH_2-$.

[0021] In some embodiments, Q is selected from $-OH$, $-CO_2H$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In other embodiments, Q is selected from $-OH$, and $-CO_2H$. In some embodiments, Q is $-CO_2H$.

[0022] In some other embodiments, $-L-$ is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)-$, or $-CH_2CH_2-$. In some embodiments, $-L-$ is $-CH_2-$ or $-CH_2CH_2-$. In some embodiments, $-L-$ is $-CH_2-$.

[0023] In some embodiments, Y is N or $>CHNH-$. In some embodiments, Y is $>CHNH-$. In some embodiments, Y is N.

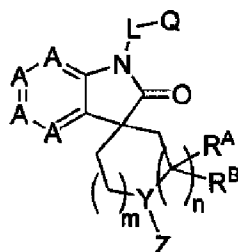
[0024] In some embodiments, X^1 is $-(CR^A R^B)_m-$; m is 1, 2 or 3; X^2 is $-(CR^A R^B)_n-$; n is 1, 2 or 3; each R^A is independently selected from H, halogen, and alkyl; each R^B is independently selected from H, halogen or alkyl; or R^A and R^B on the same carbon atom are taken together form an oxo ($=O$).

[0025] In some embodiments, X^1 is $-(CR^A R^B)_m-$; m is 1, 2 or 3; X^2 is $-(CR^A R^B)_n-$; n is 1, 2 or 3; each R^A is independently selected from H, F, and $-CH_3$; each R^B is independently selected from H, F or $-CH_3$; or R^A and R^B on the same carbon atom are taken together form an oxo ($=O$).

[0026] In some embodiments, m is 1 or 2; n is 1, 2 or 3. In some embodiments, m is 2; n is 2. In some embodiments, m is 1; n is 3. In some embodiments, m is 1; n is 2.

[0027] In some embodiments, both X^1 and X^2 are $-CH_2-$. In some embodiments, both X^1 and X^2 groups are $-CH_2CH_2-$. In some embodiments, X^1 is $-CH_2-$ and X^2 is $-CH_2CH_2CH_2-$. In some embodiments, X^1 is a $-CH_2-$ and X^2 is a $-CH_2CH_2-$.

[0028] In one aspect, provided herein is a compound having the structure of Formula 7:

**Formula 7.**

[0029] In some embodiments, provided herein is a compound having the structure of Formula 7 wherein m is 0 or 1; n is 1 or 2; each R^A is independently selected from H, halogen, and alkyl; each R^B is independently selected from H, halogen, and alkyl; or R^A and R^B on the same carbon atom are taken together to form an oxo (=O); Y is N or $>CHNH$.

[0030] In some embodiments, each R^A is H; each R^B is H; Y is $>CHNH$.

[0031] In some embodiments, each R^A is H; each R^B is H; Y is $>CHNH$, m is 0; n is 2.

[0032] In some embodiments, each R^A is H; each R^B is H; Y is $>CHNH$, m is 1; n is 1.

[0033] In some embodiments, each R^A is H; each R^B is H; or R^A and R^B on the same carbon atom are taken together to form an oxo (=O); Y is N.

[0034] In some embodiments, m is 1; n is 1; each R^A is H; each R^B is H; or R^A and R^B on the same carbon atom are taken together to form an oxo (=O); Y is N.

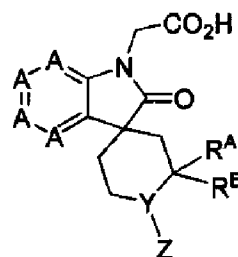
[0035] In some embodiments, each A is CR^1 . In some embodiments, one A is N. In some embodiments, two A are N.

[0036] In some embodiments, each R^1 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $-N(R^2)_2$, $-OR^2$, $-C(=O)R^3$, $-CO_2R^2$, $-CON(R^2)_2$, $-NR^2COR^3$, and $-S(=O)_2R^3$.

[0037] In some embodiments, each R^1 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, $-N(R^2)_2$, $-OR^2$, $-C(=O)R^3$, $-CO_2R^2$, $-CON(R^2)_2$, and $-S(=O)_2R^3$. In some embodiments, each R^1 is independently selected from H, OH, F, Cl, Br, $-C\equiv N$, $-CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, each R^1 is H.

[0038] In some embodiments, $-L-$ is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)-$, or $-CH_2CH_2-$; and Q is $-CO_2H$. In some embodiments, $-L-$ is $-CH_2-$ or $-CH_2CH_2-$; and Q is $-CO_2H$. In some embodiments, $-L-$ is $-CH_2-$; and Q is $-CO_2H$.

[0039] In one aspect, provided herein is a compound having the structure of Formula 8:

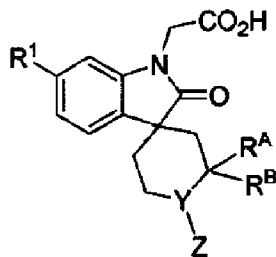
**Formula 8**

[0040] In some embodiments, provided herein is a compound having the structure of Formula 8 wherein: each R^A is independently selected from H, halogen, and alkyl; each R^B is independently selected from H,

halogen, and alkyl; or R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$); each A is CR^1 or N; provided that at least two A groups are CR^1 ; Y is N.

[0041] In some embodiments, one A is N. In some embodiments, two A are N.

[0042] In one aspect, the compound of Formula 1 has the structure of Formula 9:



Formula 9

[0043] In some embodiments, provided herein is a compound having the structure of Formula 9 wherein: each R^A is independently selected from H, halogen, and alkyl; each R^B is independently selected from H, halogen, and alkyl; or R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$); Y is N.

[0044] In some embodiments, R^A is H; R^B is H; or R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$); Y is N.

[0045] In some embodiments, R^A is H; R^B is H; Y is N.

[0046] In some embodiments, R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$); Y is N.

[0047] In some embodiments, R^1 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, $-N(R^2)_2$, $-OR^2$, $-C(=O)R^3$, $-CO_2R^2$, $-CON(R^2)_2$, and $-S(=O)_2R^3$. In some embodiments, each R^1 is independently selected from H, OH, F, Cl, Br, $-C\equiv N$, $-CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$.

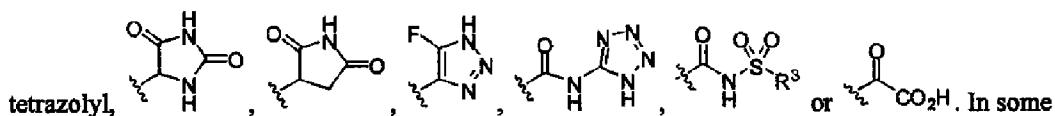
[0048] In some embodiments, Z is selected from cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, $-COR^3$, $-CO_2R^3$, $-SO_2R^3$, and $-CON(R^2)_2$.

[0049] In some embodiments, Z is selected from aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, $-COR^3$, and $-SO_2R^3$.

[0050] In some embodiments, R^3 is independently selected from aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, and $-R^4-L^3-R^5$; R^4 is a unsubstituted or substituted group selected from aryl, and heteroaryl; L^3 is a bond, -O-, -S-, and -NH-; R^5 is a unsubstituted or substituted group selected from aryl, and heteroaryl;

[0051] In some embodiments, Z is selected from phenyl, substituted phenyl, naphthyl, substituted naphthyl, $-CH_2$ -phenyl, substituted $-CH_2$ -phenyl, monocyclic or bicyclic heteroaryl heteroaryl, substituted monocyclic or bicyclic heteroaryl heteroaryl, $-CH_2$ -(monocyclic or bicyclic heteroaryl heteroaryl), substituted $-CH_2$ -(monocyclic or bicyclic heteroaryl heteroaryl), $-COR^3$, and $-SO_2R^3$; R^3 is independently selected from phenyl, substituted phenyl, naphthyl, substituted naphthyl, monocyclic or bicyclic heteroaryl, substituted monocyclic or bicyclic heteroaryl, and $-R^4-L^3-R^5$; R^4 is an unsubstituted or substituted group selected from phenyl, naphthyl, and (monocyclic or bicyclic heteroaryl); L^3 is a bond, -O-, -S-, and -NH-; R^5 is an unsubstituted or substituted group selected from phenyl, naphthyl, and (monocyclic or bicyclic heteroaryl).

[0052] In other embodiments, Q is selected from OH, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{Me}$, $-\text{CO}_2\text{Et}$, $\text{C}(=\text{O})\text{NHOH}$, CH_2SH ,



embodiments, Q is $-\text{OH}$ or $-\text{CO}_2\text{H}$. In some other embodiments, Q is $-\text{CO}_2\text{H}$

[0053] In certain embodiments, Z is COR^3 , CO_2R^3 , SO_2R^3 , $\text{CON}(\text{R}^2)_2$, $\text{SO}_2\text{N}(\text{R}^2)_2$, $-\text{C}(=\text{NSO}_2\text{R}^3)\text{N}(\text{R}^2)_2$, or $-\text{C}(=\text{CH-CN})\text{N}(\text{R}^2)_2$. In certain other embodiments, Z is COR^3 or SO_2R^3 . In yet embodiments, Z is COR^3 . In yet some other embodiments, Z is SO_2R^3 .

[0054] In certain embodiments, R^3 is independently selected from alkyl, fluoroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-\text{R}^4-\text{L}^3-\text{R}^5$; R^4 is a unsubstituted or substituted group selected from heterocycloalkyl, aryl, and heteroaryl; L^3 is a bond, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, or $-\text{C}(=\text{O})-$; R^5 is a unsubstituted or substituted group selected from aryl and heteroaryl.

[0055] In certain other embodiments, R^3 is selected from alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-\text{R}^4-\text{L}^3-\text{R}^5$; R^4 is a unsubstituted or substituted group selected from heterocycloalkyl, aryl, and heteroaryl; L^3 is a bond, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, or $-\text{C}(=\text{O})-$; R^5 is a unsubstituted or substituted group selected from aryl and heteroaryl. In certain other embodiments, R^3 is selected from alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-\text{R}^4-\text{L}^3-\text{R}^5$; R^4 is a unsubstituted or substituted group selected from aryl and heteroaryl; L^3 is a bond, $-\text{O}-$, $-\text{S}-$, or $-\text{NH}-$; R^5 is a unsubstituted or substituted group selected from aryl and heteroaryl. In certain other embodiments, R^3 is selected from alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-\text{R}^4-\text{L}^3-\text{R}^5$; R^4 is a unsubstituted or substituted aryl; L^3 is a bond, $-\text{O}-$, $-\text{S}-$, or $-\text{NH}-$; R^5 is a unsubstituted or substituted group selected from aryl and heteroaryl.

[0056] Any of the 3-, 4-, 5-, 6-, 7- or 8- membered rings described herein include substituted and unsubstituted heterocyclic and carbocyclic rings.

[0057] Any combination of the groups described above for the various variables is contemplated herein.

[0058] In certain embodiments presented herein, a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, is a modulator of DP_2 . In certain embodiments presented herein, a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, is an antagonist of DP_2 . In specific embodiments, the antagonist of DP_2 is selective for DP_2 . In other embodiments, the modulator of DP_2 is also a modulator of DP_1 . In some embodiments, the modulator of DP_2 is also a modulator of TP (thromboxane receptor).

[0059] In other embodiments, presented herein are compounds selected from active metabolites, solvates, pharmaceutically acceptable salts or pharmaceutically acceptable prodrugs of a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0060] 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 includes a pharmaceutically acceptable excipient.

[0061] 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 a modulator of DP_2 having the structure of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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.

[0062] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, to the mammal in need.

[0063] In another aspect are compounds presented in Table 1 or pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, which antagonize CRTH2 and may be used to treat patients suffering from one or more PGD₂-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, pain, endotoxic shock, proliferative disorders and inflammatory conditions.

[0064] In a specific aspect, presented herein are the following compounds:

1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(4-Bromo-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(2-Trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(3-Trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(3,5-Bis-trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(4-*tert*-Butyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(2,5-Dimethoxy-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(Naphthalene-2-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(Naphthalene-1-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(Biphenyl-4-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-[4-(5-Fluoro-pyrimidin-2-yl)-benzenesulfonyl]-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(4-(1*H*-Pyrazol-4-yl)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(4-(3-Methyl-anilino)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(4-Chloro-benzoyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(4-Chloro-phenyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid; 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid; 1-(4-Chloro-benzenesulfonylamino)-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid; 3-(1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid; 1'-(4-Chloro-benzenesulfonyl)-1-(2-hydroxy-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]; and 2-(1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid.

[0065] In another aspect are compounds presented in Tables 1 to 9.

[0066] Also provided are pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable

solvates thereof, which antagonize CRTH2. In various embodiments presented herein, these compounds are used to treat patients suffering from one or more PGD₂-dependent conditions or diseases, including, but not limited to, asthma, rhinitis, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung fibrosis, rhinitis, arthritis, allergy, psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, cancer, endotoxic shock, proliferative disorders and inflammatory conditions.

[0067] In further or alternative embodiments, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are antagonists of CRTH2. In even further or alternative embodiments, such inhibitors have an IC₅₀ below 100 μ M in the CRTH2 binding assay. In still further or alternative embodiments such antagonists antagonize CRTH2 and other related PGD₂ receptors. Related PGD₂ receptors include, but are not limited to, DP₁ and TP.

[0068] In one aspect, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, inhibits bronchoconstrictor effects of PGD₂ and other prostanoids.

[0069] In further or alternative embodiments, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are included into pharmaceutical compositions or medicaments used for treating a PGD₂-dependent or PGD₂ mediated condition or disease in a patient.

[0070] The pharmaceutical formulations described herein are administered to a subject 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.

[0071] In some embodiments, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are administered orally.

[0072] In some embodiments, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are administered topically. In such embodiments, the compound of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0073] In another aspect, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are administered by intranasal administration.

[0074] In another aspect, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are formulated for intranasal administration. Such formulations include nasal sprays, nasal mists, and the like.

[0075] In another aspect, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are formulated as eye drops.

[0076] In one aspect, the compounds of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are administered topically to the skin.

[0077] In another aspect, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[0078] In another aspect, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[0079] In another aspect, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[0080] In another aspect, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are used to treat or prevent metabolic disorders. In one aspect the metabolic disorders include, but are not limited to, bone remodeling, loss or gain.

[0081] 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.

[0082] 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 CRTH2 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, CRTH2. In yet other aspects, the methods, compounds, pharmaceutical compositions, and medicaments described herein are used in combination with other medical treatments or surgical modalities.

[0083] In one aspect are methods for reducing/antagonizing the PGD_2 activation of CRTH2 in a mammal comprising administering to the mammal at least once an effective amount of a compound having the structure of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0084] In another aspect are methods for modulating, including reducing and/or antagonizing the activation of CRTH2, 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0085] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0086] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0087] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0088] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0089] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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, occupational asthma, steroid-resistant asthma, seasonal asthma.

[0090] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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 rhinopolypsis.

[0091] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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.

[0092] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0093] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0094] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0095] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0096] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0097] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0098] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[0099] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00100] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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.

[00101] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. The type of cancer includes, but is not limited to, pancreatic cancer and other solid or hematological tumors.

[00102] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00103] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00104] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. Such diseases include, by way of example only, chronic gastritis, eosinophilic gastroenteritis, and gastric motor dysfunction.

[00105] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. Such diseases include, by way of example only, acute tubular necrosis, glomerulonephritis, cyclosporine nephrotoxicity, renal ischemia, and reperfusion injury.

[00106] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00107] In another aspect are methods for treating type II diabetes comprising administering to the mammal at least once an effective amount of at least one compound having the structure of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00108] 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.

[00109] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00110] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00111] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00112] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00113] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00114] A further aspect are methods for the treatment of metabolic syndromes such as Familial Mediterranean Fever comprising administering to the mammal at least once an effective amount of at least one compound having the structure of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00115] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00116] In a further aspect are methods to modulate the immune response to endogenous or exogenous antigens.

[00117] 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).

[00118] In another aspect is the use of a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, in the manufacture of a medicament for treating an inflammatory disease or condition in an animal in which the activity of at least one PGD₂-associated protein contributes to the pathology and/or symptoms of the disease or condition. In one embodiment of this aspect, the PGD₂ pathway protein is CRTH2. In another or further embodiment of this aspect, the inflammatory disease or conditions are respiratory, cardiovascular, or proliferative diseases.

[00119] In any of the aforementioned aspects are further embodiments in which administration is enteral, parenteral, or both, and wherein (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.

[00120] 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, 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.

[00121] 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.

[00122] 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 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.

[00123] 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 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, a DP_1 receptor antagonist, a TP receptor antagonist, or a different CRTH_2 receptor antagonist.

[00124] In other embodiments, a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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).

[00125] In further or alternative embodiments, the anti-inflammatory agent includes, but is not limited to, non-steroidal anti-inflammatory drugs such as a cyclooxygenase inhibitor (COX-1 and/or COX-2), and steroids such as prednisone or dexamethasone. In further or alternative embodiments, the anti-inflammatory agent is, by way of example only, Arthrotec®, Asacol, Auralgan®, Azulfidine, Daypro, etodolac, Ponstan,

Salofalk, Solu-Medrol®, aspirin, indomethacin (Indocin™), rofecoxib (Vioxx™), celecoxib (Celebrex™), valdecoxib (Bextra™), diclofenac, etodolac, ketoprofen, Lodine®, Mobic®, nabumetone, naproxen, piroxicam, Celestone®, prednisone, Deltasone®, or any generic equivalent thereof.

[00126] 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; VIA2291 (ABT761)), a 5-lipoxygenase-activating protein inhibitor (e.g., MK-0591, 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 LTC4 synthase inhibitor or a BLT1 receptor antagonist.

[00127] 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 gefitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

[00128] In any of the aforementioned aspects involving the therapy of an immunological 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.

[00129] 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.

[00130] 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.

[00131] 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.;

[00132] In any of the aforementioned aspects the PGD₂-dependent or PGD₂ 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.

[00133] 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

[00134] Prostaglandin D₂ (PGD₂) is an acidic lipid derived from the metabolism of arachidonic acid by cyclooxygenases and PGD₂ synthases. PGD₂ is produced by mast cells, macrophages and T_H2 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 PGD₂ applied to bronchial airways elicits many responses that are characteristic of acute asthma.

[00135] PGD₂ is a major mast cell product that acts via two receptors, the D-type prostanoid (DP, DP₁) and the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2, DP₂) receptors. CRTH2 mediates the chemotaxis of eosinophils, basophils, and Th2 lymphocytes, and DP receptor plays an important role in eosinophil trafficking. DP antagonists do not inhibit the release of eosinophils when induced by the CRTH2-selective agonists. However, eosinophils in human bone marrow specimens express DP and CRTH2 receptors at similar levels and human peripheral blood expresses both DP and CRTH2, but the DP receptor is expressed at lower levels. In agreement with this, the chemotaxis of human peripheral blood eosinophils is inhibited by both DP and CRTH2 antagonists. Accordingly, DP, CRTH2 and dual DP/CRTH2 antagonists are useful in the treatment of allergic inflammation.

[00136] Activation of CRTH2 is associated with chemotaxis and activation of T_H2 lymphocytes, eosinophils and basophils. In particular, PGD₂ binds to CRTH2 and mediates many of its effects through a G_i-dependent elevation of intracellular calcium levels and reduction of cyclic AMP. In T_H2 lymphocytes, IL4, IL5 and IL13 cytokine production are also stimulated by CRTH2 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.

[00137] Another common name for CRTH2 is DP₂, and the two terms are used interchangeably herein. Likewise, another common name for DP is DP₁, and the two terms are used interchangeably herein.

Illustrative Biological Activity

[00138] 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 COX1 and COX2 cyclooxygenases and PG synthases. The cyclooxygenases sequentially convert arachidonic acid to cyclic endoperoxide prostaglandin G₂ (PGG₂) and subsequently, prostaglandin H₂ (PGH₂). Depending on the tissue, physiological signal, and/or synthase type, PGH₂ can be converted to numerous different prostaglandins, such as PGE₂, PGD₂, PGF₂α, and PGI₂ as well as thromboxane A₂, 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.

[00139] Prostaglandin D₂ is a major metabolite produced from the PGH₂ intermediate via hematopoietic PGD₂ synthase or lipocalin PGD₂ synthase. In the brain and central nervous system, PGD₂ is produced and thought to function in pain perception and sleep regulation. In other tissues, PGD₂ is produced primarily in immunoglobulin E (IgE) activated mast cells and to a lesser extent, in macrophages, dendritic cells, T helper 2 (T_H2) lymphocytes and other leukocytes. In the cell, PGD₂ is rapidly metabolized and converted to other downstream effectors including Δ^{12} PGJ₂, 9 α 11 β PGF₂, 13,14-dihydro-15-keto-PGD₂, and 15-deoxy- $\Delta^{12,14}$ PGD₂.

[00140] Mast-cell-derived PGD₂ is produced in high concentrations in response to an allergen challenge. Studies in preclinical species have observed the following features when PGD₂ 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.

[00141] Injection of PGD₂ 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 PGD₂, 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 DP₁ receptor. Although these observations make it clear that DP₁ mediates the vascular effects of PGD₂, the capacity of PGD₂ to promote the cellular changes associated with inflammation is not due to an action on DP₁.

[00142] The main receptors that are activated by PGD₂ or its metabolites and mediate its effects are DP₁, CRTH2 (or DP₂) and TP.

[00143] DP₁ (or DP) is a G-protein coupled seven-transmembrane receptor that, upon activation by PGD₂ binding, leads to an increase in intracellular cAMP levels. DP₁ is expressed in the brain, bronchial smooth muscle, vascular and airway smooth muscle, dendritic cells, and platelets and induces PGD₂ dependent bronchodilation, vasodilation, platelet aggregation inhibition, and suppression of cytokine production. Genetic analysis of DP₁ 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 antagonists 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 conjunctivitis model and antigen-induced eosinophil infiltration into the lung in a guinea pig asthma model.

[00144] Much of PGD₂'s pro-inflammatory activity is through interaction with CRTH2 (or DP₂). CRTH2 is also a G-protein coupled receptor and is typically highly expressed in T_H2 lymphocytes, eosinophils and basophils. CRTH2 activation functions to directly activate and recruit T_H2 lymphocytes and eosinophils. Activated T_H2 lymphocytes produce and secrete inflammatory cytokines including IL4, IL5, and IL13. Despite binding PGD₂ with a similar affinity as DP₁, CRTH2 is not structurally related to DP₁ and signals

through a different mechanism- the effects of CRTH2 are mediated through Gi-dependent elevation in intracellular calcium levels and reduction in intracellular levels of cyclic AMP. CRTH2 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 PGD₂ or selective CRTH2 agonists both exacerbate and enhance allergic responses in lung and skin. CRTH2 activation appears to have a crucial role in mediating allergic responses, and thus the use of antagonists of PGD₂ activation of the CRTH2 receptor would be an attractive approach to treat the inflammatory component of allergic diseases such as asthma, rhinitis, and dermatitis.

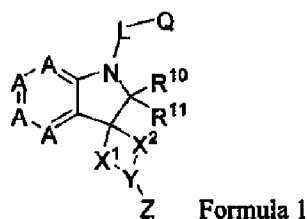
[00145] TP receptors primarily function to antagonize DP1 receptor's effects such as promoting bronchoconstriction, vasoconstriction, and platelet aggregation. While TP receptor's main ligand is thromboxane A₂, it also binds and is activated by the PGD₂ derivative, 9α,11βPGF₂. TP is a Gq-coupled prostanoid receptor that binds thromboxane with high affinity, promoting platelet aggregation and constriction of both vascular and airway smooth muscle. PGD₂ activates the TP receptor in human bronchial muscle, probably through the formation of the 11-ketoreductase metabolite 9α,11βPGF₂. The bronchoconstrictor effects of TP dominate over the bronchodilator effects of DP1 in the airways.

[00146] DP₁ and CRTH2 have crucial, and complementary, roles in the physiological response of animals to PGD₂ and blockade of either one or both of these receptors may prove beneficial in alleviating allergic diseases or conditions triggered by PGD₂, such as, but not limited to, allergic rhinitis, asthma, dermatitis, and allergic conjunctivitis.

Compounds

[00147] Compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, antagonize CRTH2 and are used to treat patients suffering from PGD₂-dependent or PGD₂ mediated conditions or diseases, including, but not limited to, asthma, rhinitis, dermatitis, and inflammatory conditions.

[00148] In one aspect is a compound of Formula 1:



wherein,

X¹ is (CR^AR^B)_m; m is 0, 1, 2 or 3;

X² is (CR^AR^B)_n; n is 0, 1, 2 or 3; and the sum of m + n ≥ 2;

each R^A is independently selected from H, OH, halogen, -C≡N, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

each R^B is independently selected from H, OH, halogen or lower alkyl; or

R^A and R^B taken together form an oxo; or

R^A and R^B taken together form a 4-, 5-, 6-, 7- or 8-membered ring;

Y is N or $>\text{CH}(\text{CH}_2)_o\text{NH}-$, wherein o is 0, 1, 2 or 3;

Z is selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,

COR^3 , CO_2R^3 , SO_2R^3 , SOR^3 , $\text{CON}(\text{R}^2)_2$, $\text{SO}_2\text{N}(\text{R}^2)_2$, $-\text{C}(=\text{NSO}_2\text{R}^3)\text{N}(\text{R}^2)_2$, or $-\text{C}(=\text{CH-CN})\text{N}(\text{R}^2)_2$;

each A is CR^1 or N; provided that at least two A groups are CR^1 ;

each R^1 is independently selected from H, OH, halogen, $-\text{C}\equiv\text{N}$, alkyl, fluoroalkyl, cycloalkyl,

heteroalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, substituted

heteroaryl, $\text{N}(\text{R}^2)_2$, OR^2 , $\text{C}(=\text{O})\text{R}^3$, CO_2R^2 , $\text{CON}(\text{R}^2)_2$, NR^2COR^3 , $\text{S}(=\text{O})\text{R}^3$, $\text{S}(=\text{O})_2\text{R}^3$, $\text{SO}_2\text{N}(\text{R}^2)_2$,

$\text{N}(\text{R}^2)\text{SO}_2\text{R}^3$, $\text{N}(\text{R}^2)\text{SO}_2\text{N}(\text{R}^2)_2$, $\text{NR}^2\text{CO}_2\text{R}^3$, $\text{NR}^2\text{CON}(\text{R}^2)_2$, OCO_2R^3 or $\text{OCON}(\text{R}^2)_2$; or

two R^1 groups on adjacent carbons taken together form a 5-, 6-, 7- or 8-membered ring;

each R^2 is independently selected from H, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl,

alkenyl, alkynyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl; or two R^2 groups on the same nitrogen taken together form a 4-, 5-, 6-, 7- or 8-membered ring;

each R^3 is independently selected from alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl,

alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-\text{R}^4-\text{L}^3-\text{R}^5$;

R^4 is a unsubstituted or substituted group selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

L^3 is a bond, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{C}(=\text{O})-$, $-\text{NHC}(=\text{O})\text{O}$, $-\text{NHC}(=\text{O})\text{NH}-$, $-\text{OC}(=\text{O})\text{O}-$, $-\text{OC}(=\text{O})\text{NH}-$, $-\text{NHC}(=\text{O})-$, $-\text{C}(=\text{O})\text{NH}-$, $-\text{C}(=\text{O})\text{O}-$, or $-\text{OC}(=\text{O})-$;

R^5 is a unsubstituted or substituted group selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R^{10} is H;

R^{11} is H; or R^{10} and R^{11} taken together form an oxo;

L is $(\text{CR}^{\text{C}}\text{R}^{\text{D}})_p$, where p is 1 or 2;

R^{C} is independently selected from H, OH, halogen, $-\text{C}\equiv\text{N}$, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R^{D} is selected from H, OH, halogen or lower alkyl; or

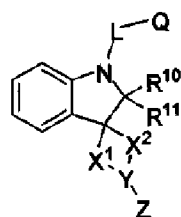
R^{C} and R^{D} taken together form a 3-, 4-, 5-, 6-, 7- or 8-membered ring;

Q is selected from $-\text{OH}$, CO_2H , CO_2R^3 or a carboxylic acid bioisostere;

or an active metabolite, solvate, pharmaceutically acceptable salt or pharmaceutically acceptable prodrug thereof.

[00149] For any and all of the embodiments, substituents are optionally selected from among from a subset of the listed alternatives. For example, in some embodiments, each A is CR^1 or N; provided that at least two A groups are CR^1 . In other embodiments, each A is CR^1 or N; provided that at least three A groups are CR^1 . In yet other embodiments, each A is CR^1 . In some embodiments, each R^1 is independently selected from H, halogen, $-\text{C}\equiv\text{N}$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, OR^2 , $\text{C}(=\text{O})\text{R}^3$, CO_2R^2 , or $\text{CON}(\text{R}^2)_2$. In some embodiments, each R^1 is independently selected from H, halogen, $-\text{C}\equiv\text{N}$, alkyl, fluoroalkyl, cycloalkyl, aryl, and substituted aryl. In some embodiments, each R^1 is H. In some embodiments, each A is CR^1 ; and each R^1 is H.

[00150] In another aspect, provided herein is a compound of Formula 2:

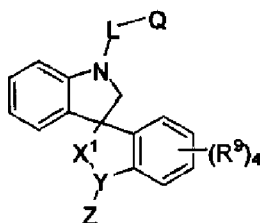


Formula 2.

wherein the substituents for Formula 2 are as described herein.

[00151] In some embodiments, R^{10} and R^{11} are both H.

[00152] In one aspect, provided herein is a compound of Formula 3:



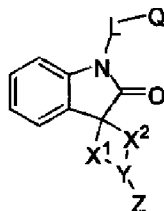
Formula 3

wherein,

each R^9 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $N(R^2)_2$, OR^2 , $C(=O)R^3$, CO_2R^2 , $CON(R^2)_2$, NR^2COR^3 , $S(=O)R^3$, $S(=O)_2R^3$, $SO_2N(R^2)_2$, $N(R^2)SO_2R^3$, $N(R^2)SO_2N(R^2)_2$, $NR^2CO_2R^3$, $OCO(NR^2)_2$, $NR^2CON(R^2)_2$ or OCO_2R^3 ; or two R^9 groups on adjacent carbons taken together form a 5-, 6-, 7- or 8-membered ring.

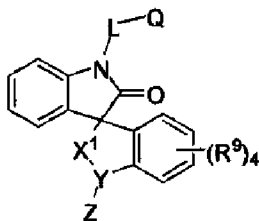
[00153] In some embodiments, R^{10} and R^{11} taken together form oxo ($=O$).

[00154] In one aspect, provided herein is a compound of Formula 4:



Formula 4.

[00155] In another aspect, provided herein is a compound of Formula 5:



Formula 5

each R^9 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $N(R^2)_2$, OR^2 , $C(=O)R^3$, CO_2R^2 , $CON(R^2)_2$, NR^2COR^3 , $S(=O)R^3$, $S(=O)_2R^3$, $SO_2N(R^2)_2$, $N(R^2)SO_2R^3$, $N(R^2)SO_2N(R^2)_2$, $NR^2CO_2R^3$, $OCO(NR^2)_2$, $NR^2CON(R^2)_2$ or OCO_2R^3 ; or two R^9 groups on adjacent carbons taken together form a 5-, 6-, 7- or 8-membered ring.

[00156] In some embodiments, m is 1, 2, or 3. In other embodiments, m is 1 or 2. In some other embodiments, m is 2, or 3. In some embodiments, n is 1, 2, or 3. In other embodiments, n is 1 or 2. In some other embodiments, n is 2 or 3.

[00157] In some embodiments, X^1 and X^2 are each independently selected from $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

[00158] In one aspect, both X^1 and X^2 are $-\text{CH}_2-$. In more specific embodiments, presented herein are compounds of Formulas 1, 2 and 4 wherein both X^1 and X^2 are $-\text{CH}_2-$. In other embodiments, compounds of Formulas 1, 2 and 4, wherein both X^1 and X^2 groups are $-\text{CH}_2\text{CH}_2-$ are provided. In still other embodiments, compounds of Formulas 1, 2 and 4, wherein X^1 is $-\text{CH}_2-$ and X^2 is $-\text{CH}_2\text{CH}_2\text{CH}_2-$ are provided. In yet other embodiments, presented herein are compounds of Formulas 1, 2 and 4 wherein X^1 is a $-\text{CH}_2-$ and X^2 is a $-\text{CH}_2\text{CH}_2-$. In other embodiments, compounds of Formulas 1, 2 and 4, wherein m is equal to 0 and X^2 is $-\text{CH}_2\text{CH}_2\text{CH}_2-$ are provided.

[00159] In one aspect, L is $(\text{CR}^{\text{C}}\text{R}^{\text{D}})_p$, where p is 1 or 2; R^{C} is independently selected from H and alkyl; R^{D} is selected from H and alkyl; or R^{C} and R^{D} taken together form a 3-, 4-, 5-, or 6-membered ring.

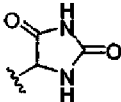
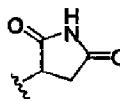
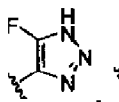
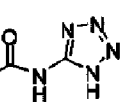
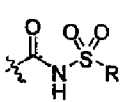
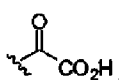
[00160] In one aspect, L is $(\text{CR}^{\text{C}}\text{R}^{\text{D}})_p$, where p is 1 or 2; R^{C} is independently selected from H and alkyl; R^{D} is selected from H and alkyl; or R^{C} and R^{D} taken together form a 3-membered ring.

[00161] In certain embodiments, L is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$ or . In certain embodiments, L is $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$. In certain embodiments, L is $-\text{CH}_2-$. In other embodiments, L is

selected from $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$ or .

[00162] In some embodiments, each R^9 is selected from H, OH, halogen, $-\text{C}\equiv\text{N}$, alkyl, fluoroalkyl, and OR^2 . In some embodiments, each R^9 is H.

[00163] In other embodiments, Q is selected from OH, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{Me}$, $-\text{CO}_2\text{Et}$, $\text{C}(=\text{O})\text{NHOH}$, CH_2SH ,

tetrazolyl, , , , ,  or . In some embodiments, Q is $-\text{OH}$ or $-\text{CO}_2\text{H}$. In some other embodiments, Q is $-\text{CO}_2\text{H}$

[00164] In some embodiments, Y is N or $>\text{CH}(\text{CH}_2)_o\text{NH}-$, wherein o is 0 or 1. In some other embodiments, Y is N or $>\text{CH}-\text{NH}-$. In some other embodiments, Y is N. In yet other embodiments, Y is $>\text{CH}-\text{NH}-$.

[00165] In certain embodiments, Z is COR^3 , CO_2R^3 , SO_2R^3 , $\text{CON}(\text{R}^2)_2$, $\text{SO}_2\text{N}(\text{R}^2)_2$, $-\text{C}(=\text{NSO}_2\text{R}^3)\text{N}(\text{R}^2)_2$, or $-\text{C}(=\text{CH}-\text{CN})\text{N}(\text{R}^2)_2$. In certain other embodiments, Z is COR^3 or SO_2R^3 . In yet embodiments, Z is COR^3 . In yet some other embodiments, Z is SO_2R^3 .

[00166] In certain embodiments, R^3 is independently selected from alkyl, fluoroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-\text{R}^4-\text{L}^3-\text{R}^5$; R^4 is a unsubstituted or substituted group selected from heterocycloalkyl, aryl, and heteroaryl; L^3 is a bond, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, or $-\text{C}(=\text{O})-$; R^5 is a unsubstituted or substituted group selected from aryl and heteroaryl.

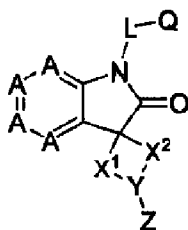
[00167] In certain other embodiments, R^3 is selected from alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-\text{R}^4-\text{L}^3-\text{R}^5$; R^4 is a unsubstituted or substituted group selected from heterocycloalkyl, aryl, and heteroaryl; L^3 is a bond, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, or $-\text{C}(=\text{O})-$; R^5 is a unsubstituted or

substituted group selected from aryl and heteroaryl. In certain other embodiments, R^3 is selected from alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-R^4-L^3-R^5$; R^4 is a unsubstituted or substituted group selected from aryl and heteroaryl; L^3 is a bond, $-O-$, $-S-$, or $-NH-$; R^5 is a unsubstituted or substituted group selected from aryl and heteroaryl. In certain other embodiments, R^3 is selected from alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-R^4-L^3-R^5$; R^4 is a unsubstituted or substituted aryl; L^3 is a bond, $-O-$, $-S-$, or $-NH-$; R^5 is a unsubstituted or substituted group selected from aryl and heteroaryl.

[00168] Any of the 3-, 4-, 5-, 6-, 7- or 8- membered rings described herein include substituted and unsubstituted heterocyclic and carbocyclic rings.

[00169] In some embodiments, each R^9 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $N(R^2)_2$, OR^2 , $C(=O)R^2$, CO_2R^2 , and $CON(R^2)$. In some embodiments, each R^9 is selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, and $-CH_3$. In some embodiments, each R^9 is H.

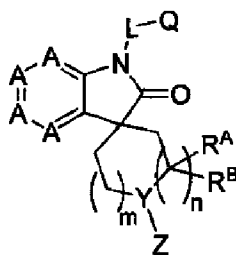
[00170] In another aspect, provided herein is a compound of Formula 6:



Formula 6.

[00171] In some embodiments, Y is N or $>CHNH-$. In one aspect, Y is $>CHNH-$. In some embodiments, Y is N.

[00172] In another aspect, provided herein is a compound having the structure of Formula 7:



Formula 7.

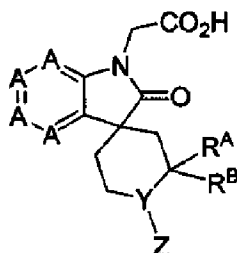
[00173] In some embodiments, provided herein is a compound having the structure of Formula 7 wherein m is 0 or 1; n is 1 or 2; each R^A is independently selected from H, halogen, and alkyl; each R^B is independently selected from H, halogen, and alkyl; or R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$); Y is N or $>CHNH-$.

[00174] In some embodiments, each R^A is H; each R^B is H; Y is $>CHNH-$. In some embodiments, each R^A is H; each R^B is H; Y is $>CHNH-$, m is 0; n is 2. In some embodiments, each R^A is H; each R^B is H; Y is $>CHNH-$, m is 1; n is 1.

[00175] In some embodiments, each R^A is H; each R^B is H; or R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$); Y is N. In some embodiments, m is 1; n is 1; each R^A is H; each R^B is H; or R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$); Y is N.

[00176] In some embodiments, each A is CR¹. In some embodiments, one A is N. In some embodiments, two A are N.

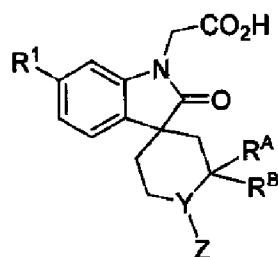
[00177] In one aspect, provided herein is a compound having the structure of Formula 8:



Formula 8

[00178] In some embodiments, provided herein is a compound having the structure of Formula 8 wherein: each R^A is independently selected from H, halogen, and alkyl; each R^B is independently selected from H, halogen, and alkyl; or R^A and R^B on the same carbon atom are taken together to form an oxo (=O); each A is CR¹ or N; provided that at least two A groups are CR¹; Y is N.

[00179] In one aspect, the compound of Formula 1 has the structure of Formula 9:



Formula 9

[00180] In some embodiments, provided herein is a compound having the structure of Formula 9 wherein: each R^A is independently selected from H, halogen, and alkyl; each R^B is independently selected from H, halogen, and alkyl; or R^A and R^B on the same carbon atom are taken together to form an oxo (=O); Y is N.

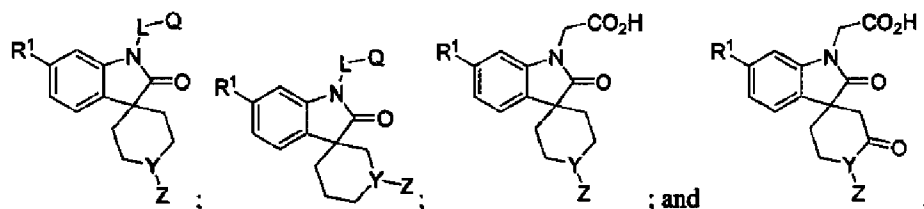
[00181] In some embodiments, R^A is H; R^B is H; or R^A and R^B on the same carbon atom are taken together to form an oxo (=O); Y is N. In some embodiments, R^A is H; R^B is H; Y is N. In some embodiments, R^A and R^B on the same carbon atom are taken together to form an oxo (=O); Y is N.

[00182] In some embodiments, Z is selected from cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, -COR³, -CO₂R³, -SO₂R³, and -CON(R²)₂.

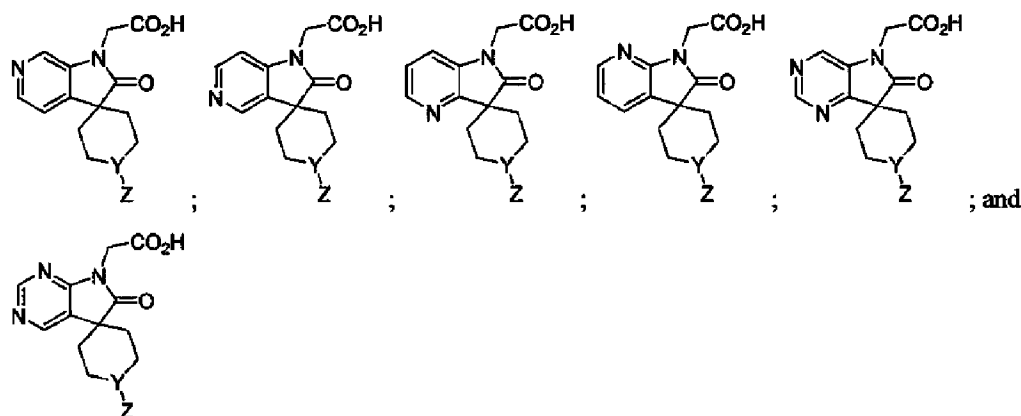
[00183] In some embodiments, Z is selected from aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, -COR³, and -SO₂R³.

[00184] In some embodiments, R³ is independently selected from aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, and -R⁴-L³-R⁵; R⁴ is a unsubstituted or substituted group selected from aryl, and heteroaryl; L³ is a bond, -O-, -S-, and -NH-; R⁵ is a unsubstituted or substituted group selected from aryl, and heteroaryl;

[00185] In one aspect, the compound of Formula 1 has a structure selected from:



[00186] In another aspect, the compound of Formula 1 has a structure selected from:

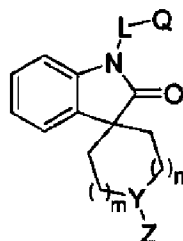


[00187] In one aspect, Y is as defined in Tables 1 to 9. In one aspect, Z is as defined in Tables 1 to 9. In one aspect, Q is -OH or -CO₂H. In another aspect, Q is -CO₂H. In one aspect, R¹ is as defined in Tables 1 to 9.

[00188] Any combination of the groups described above for the various variables is contemplated herein.

[00189] In one aspect, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, include, but are not limited to, those described in Tables 1 to 9:

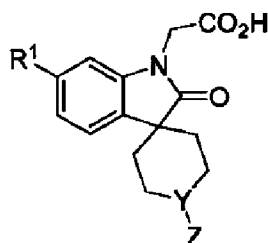
Table 1:



Cmpd #	L	Q	Y	n	m	Z	M+H
1-1	-CH ₂ -	CO ₂ H	N	1	1	4-Chloro-benzenesulfonyl	435
1-2	-CH ₂ -	CO ₂ H	N	1	1	4-Bromo-benzenesulfonyl	480
1-3	-CH ₂ -	CO ₂ H	N	1	1	2-Trifluoromethyl-benzenesulfonyl	469
1-4	-CH ₂ -	CO ₂ H	N	1	1	3-Trifluoromethyl-benzenesulfonyl	469
1-5	-CH ₂ -	CO ₂ H	N	1	1	3,5-Bis-trifluoromethyl-benzenesulfonyl	537
1-6	-CH ₂ -	CO ₂ H	N	1	1	4- <i>tert</i> -Butyl-benzenesulfonyl	457
1-7	-CH ₂ -	CO ₂ H	N	1	1	2,5-Dimethoxy-benzenesulfonyl	461
1-8	-CH ₂ -	CO ₂ H	N	1	1	Naphthalene-2-sulfonyl	451
1-9	-CH ₂ -	CO ₂ H	N	1	1	Naphthalene-1-sulfonyl	451
1-10	-CH ₂ -	CO ₂ H	N	1	1	Biphenyl-4-sulfonyl	477
1-11	-CH ₂ -	CO ₂ H	N	1	1	4-(5-Fluoro-pyrimidin-2-yl)-benzenesulfonyl	497
1-12	-CH ₂ -	CO ₂ H	N	1	1	4-(1 <i>H</i> -Pyrazol-4-yl)-benzenesulfonyl	467
1-13	-CH ₂ -	CO ₂ H	N	1	1	4-(3-Methyl-anilino)-benzenesulfonyl	506

1-14	-CH ₂ -	CO ₂ H	N	1	1	4-Chloro-benzoyl	399
1-15	-CH ₂ -	CO ₂ H	N	1	1	4-Chloro-phenyl	371
1-16	-CH ₂ -	CO ₂ H	N	2	0	4-Chloro-benzenesulfonyl	435
1-17	-CH ₂ -	CO ₂ H	>CH-NH-	2	0	4-Chloro-benzenesulfonyl	449
1-18	-CH ₂ CH ₂ -	CO ₂ H	N	1	1	4-Chloro-benzenesulfonyl	449
1-19	-CH ₂ CH ₂ -	OH	N	1	1	4-Chloro-benzenesulfonyl	421
1-21	-CH(CH ₃)-	CO ₂ H	N	1	1	4-Chloro-benzenesulfonyl	449

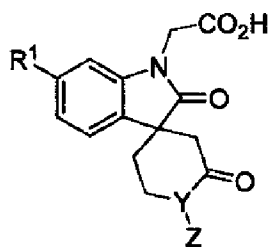
Table 2



Cmpd #	R ¹	Y	Z
2-1	H	N	2-fluoro-benzenesulfonyl
2-2	H	N	3-fluoro-benzenesulfonyl
2-3	H	N	4-fluoro-benzenesulfonyl
2-4	H	N	2-chloro-benzenesulfonyl
2-5	H	N	3-chloro-benzenesulfonyl
2-6	H	N	2,5-difluoro-benzenesulfonyl
2-7	H	N	3,5-difluoro-benzenesulfonyl
2-8	H	N	2,3-difluoro-benzenesulfonyl
2-9	H	N	3,5-dichloro-benzenesulfonyl
2-10	H	N	2-fluoro-5-dichloro-benzenesulfonyl
2-11	Cl	N	2-fluoro-benzenesulfonyl
2-12	Cl	N	3-fluoro-benzenesulfonyl
2-13	Cl	N	4-fluoro-benzenesulfonyl
2-14	Cl	N	2-chloro-benzenesulfonyl
2-15	Cl	N	3-chloro-benzenesulfonyl
2-16	Cl	N	4-chloro-benzenesulfonyl
2-17	Cl	N	2,5-difluoro-benzenesulfonyl
2-18	Cl	N	3,5-difluoro-benzenesulfonyl
2-19	Cl	N	2,3-difluoro-benzenesulfonyl
2-20	Cl	N	3,5-dichloro-benzenesulfonyl
2-21	Cl	N	2-fluoro-5-dichloro-benzenesulfonyl
2-22	H	N	pyridin-2-yl
2-23	H	N	pyrimidin-2-yl
2-24	H	N	pyrazin-2-yl
2-25	H	N	pyridazin-2-yl
2-26	H	N	quinolin-2-yl
2-27	H	N	quinolin-4-yl
2-28	H	N	quinolin-5-yl
2-29	H	N	quinolin-8-yl
2-30	Cl	N	pyridin-2-yl
2-31	Cl	N	pyrimidin-2-yl
2-32	Cl	N	pyrazin-2-yl
2-33	Cl	N	pyridazin-2-yl

Cmpd #	R ¹	Y	Z
2-34	Cl	N	quinolin-2-yl
2-35	Cl	N	quinolin-4-yl
2-36	Cl	N	quinolin-5-yl
2-37	Cl	N	quinolin-8-yl
2-38	H	N	pyridin-2-ylmethyl
2-39	H	N	pyrimidin-2-ylmethyl
2-40	H	N	pyrazin-2-ylmethyl
2-41	H	N	pyridazin-2-ylmethyl
2-42	H	N	quinolin-2-ylmethyl
2-43	H	N	quinolin-4-ylmethyl
2-44	H	N	quinolin-5-ylmethyl
2-45	H	N	quinolin-8-ylmethyl
2-46	Cl	N	pyridin-2-ylmethyl
2-47	Cl	N	pyrimidin-2-ylmethyl
2-48	Cl	N	pyrazin-2-ylmethyl
2-49	Cl	N	pyridazin-2-ylmethyl
2-50	Cl	N	quinolin-2-ylmethyl
2-51	Cl	N	quinolin-4-ylmethyl
2-52	Cl	N	quinolin-5-ylmethyl
2-53	Cl	N	quinolin-8-ylmethyl

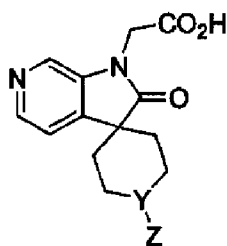
Table 3



Cmpd #	R ¹	Y	Z
3-1	H	N	2-fluorophenyl
3-2	H	N	3-fluorophenyl
3-3	H	N	4-fluorophenyl
3-4	H	N	2-chlorophenyl
3-5	H	N	3-chlorophenyl
3-6	H	N	4-chlorophenyl
3-7	H	N	2,5-difluorophenyl
3-8	H	N	3,5-difluorophenyl
3-9	H	N	2,3-difluorophenyl
3-10	H	N	3,5-dichlorophenyl
3-11	H	N	2-fluoro-5-dichloro
3-12	Cl	N	2-fluorophenyl
3-13	Cl	N	3-fluorophenyl
3-14	Cl	N	4-fluorophenyl
3-15	Cl	N	2-chlorophenyl
3-16	Cl	N	3-chlorophenyl
3-17	Cl	N	4-chlorophenyl
3-18	Cl	N	2,5-difluorophenyl
3-19	Cl	N	3,5-difluorophenyl
3-20	Cl	N	2,3-difluorophenyl

Cmpd #	R ¹	Y	Z
3-21	Cl	N	3,5-dichlorophenyl
3-22	Cl	N	2-fluoro-5-dichloro
3-23	H	N	pyridin-2-yl
3-24	H	N	pyrimidin-2-yl
3-25	H	N	pyrazin-2-yl
3-26	H	N	pyridazin-2-yl
3-27	H	N	quinolin-2-yl
3-28	H	N	quinolin-4-yl
3-29	H	N	quinolin-5-yl
3-30	H	N	quinolin-8-yl
3-31	Cl	N	pyridin-2-yl
3-32	Cl	N	pyrimidin-2-yl
3-33	Cl	N	pyrazin-2-yl
3-34	Cl	N	pyridazin-2-yl
3-35	Cl	N	quinolin-2-yl
3-36	Cl	N	quinolin-4-yl
3-37	Cl	N	quinolin-5-yl
3-38	Cl	N	quinolin-8-yl
3-39	H	N	pyridin-2-ylmethyl
3-40	H	N	pyrimidin-2-ylmethyl
3-41	H	N	pyrazin-2-ylmethyl
3-42	H	N	pyridazin-2-ylmethyl
3-43	H	N	quinolin-2-ylmethyl
3-44	H	N	quinolin-4-ylmethyl
3-45	H	N	quinolin-5-ylmethyl
3-46	H	N	quinolin-8-ylmethyl
3-47	Cl	N	pyridin-2-ylmethyl
3-48	Cl	N	pyrimidin-2-ylmethyl
3-49	Cl	N	pyrazin-2-ylmethyl
3-50	Cl	N	pyridazin-2-ylmethyl
3-51	Cl	N	quinolin-2-ylmethyl
3-52	Cl	N	quinolin-4-ylmethyl
3-53	Cl	N	quinolin-5-ylmethyl
3-54	Cl	N	quinolin-8-ylmethyl

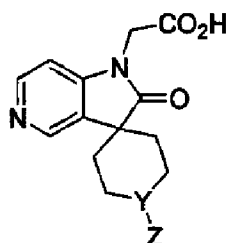
Table 4



Cmpd #	Y	Z
4-1	N	2-fluoro-benzenesulfonyl
4-2	N	3-fluoro-benzenesulfonyl
4-3	N	4-fluoro-benzenesulfonyl
4-4	N	2-chloro-benzenesulfonyl
4-5	N	3-chloro-benzenesulfonyl

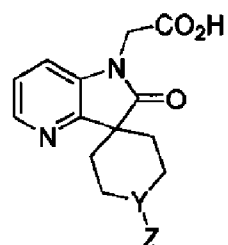
Cmpd #	Y	Z
4-6	N	4-chloro-benzenesulfonyl
4-7	N	2,5-difluoro-benzenesulfonyl
4-8	N	3,5-difluoro-benzenesulfonyl
4-9	N	2,3-difluoro-benzenesulfonyl
4-10	N	3,5-dichloro-benzenesulfonyl
4-11	N	2-fluoro-5-dichloro-benzenesulfonyl

Table 5



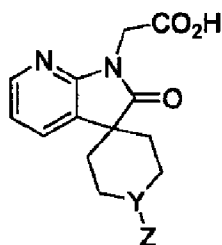
Cmpd #	Y	Z
5-1	N	2-fluoro-benzenesulfonyl
5-2	N	3-fluoro-benzenesulfonyl
5-3	N	4-fluoro-benzenesulfonyl
5-4	N	2-chloro-benzenesulfonyl
5-5	N	3-chloro-benzenesulfonyl
5-6	N	4-chloro-benzenesulfonyl
5-7	N	2,5-difluoro-benzenesulfonyl
5-8	N	3,5-difluoro-benzenesulfonyl
5-9	N	2,3-difluoro-benzenesulfonyl
5-10	N	3,5-dichloro-benzenesulfonyl
5-11	N	2-fluoro-5-dichloro-benzenesulfonyl

Table 6



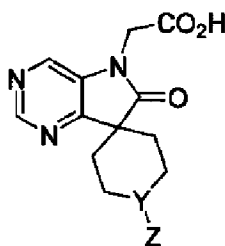
Cmpd #	Y	Z
6-1	N	2-fluoro-benzenesulfonyl
6-2	N	3-fluoro-benzenesulfonyl
6-3	N	4-fluoro-benzenesulfonyl
6-4	N	2-chloro-benzenesulfonyl
6-5	N	3-chloro-benzenesulfonyl
6-6	N	4-chloro-benzenesulfonyl
6-7	N	2,5-difluoro-benzenesulfonyl
6-8	N	3,5-difluoro-benzenesulfonyl
6-9	N	2,3-difluoro-benzenesulfonyl
6-10	N	3,5-dichloro-benzenesulfonyl
6-11	N	2-fluoro-5-dichloro-benzenesulfonyl

Table 7



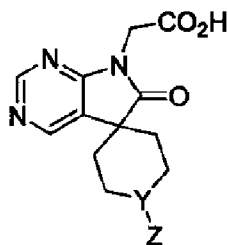
Cmpd #	Y	Z
7-1	N	2-fluoro-benzenesulfonyl
7-2	N	3-fluoro-benzenesulfonyl
7-3	N	4-fluoro-benzenesulfonyl
7-4	N	2-chloro-benzenesulfonyl
7-5	N	3-chloro-benzenesulfonyl
7-6	N	4-chloro-benzenesulfonyl
7-7	N	2,5-difluoro-benzenesulfonyl
7-8	N	3,5-difluoro-benzenesulfonyl
7-9	N	2,3-difluoro-benzenesulfonyl
7-10	N	3,5-dichloro-benzenesulfonyl
7-11	N	2-fluoro-5-dichloro-benzenesulfonyl

Table 8



Cmpd #	Y	Z
8-1	N	2-fluoro-benzenesulfonyl
8-2	N	3-fluoro-benzenesulfonyl
8-3	N	4-fluoro-benzenesulfonyl
8-4	N	2-chloro-benzenesulfonyl
8-5	N	3-chloro-benzenesulfonyl
8-6	N	4-chloro-benzenesulfonyl
8-7	N	2,5-difluoro-benzenesulfonyl
8-8	N	3,5-difluoro-benzenesulfonyl
8-9	N	2,3-difluoro-benzenesulfonyl
8-10	N	3,5-dichloro-benzenesulfonyl
8-11	N	2-fluoro-5-dichloro-benzenesulfonyl

Table 9



Cmpd #	Y	Z
9-1	N	2-fluoro-benzenesulfonyl
9-2	N	3-fluoro-benzenesulfonyl
9-3	N	4-fluoro-benzenesulfonyl
9-4	N	2-chloro-benzenesulfonyl
9-5	N	3-chloro-benzenesulfonyl
9-6	N	4-chloro-benzenesulfonyl
9-7	N	2,5-difluoro-benzenesulfonyl
9-8	N	3,5-difluoro-benzenesulfonyl
9-9	N	2,3-difluoro-benzenesulfonyl
9-10	N	3,5-dichloro-benzenesulfonyl
9-11	N	2-fluoro-5-dichloro-benzenesulfonyl

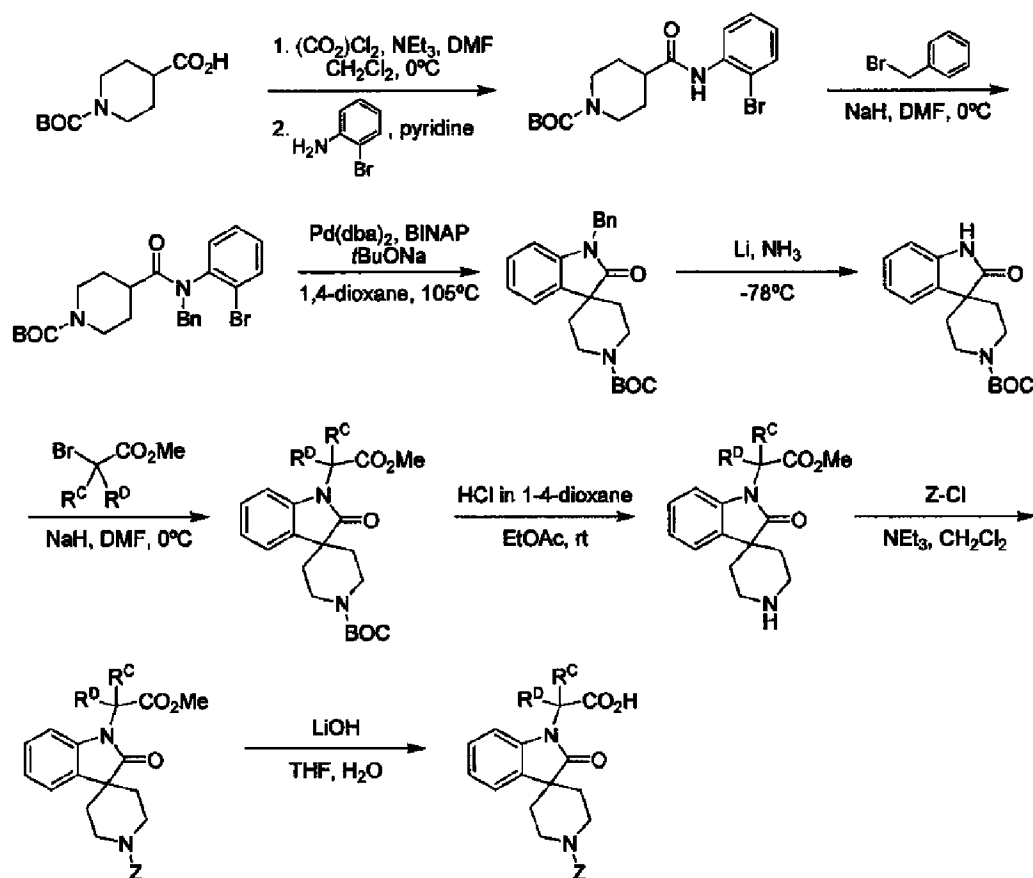
Synthesis of Compounds

[00190] Compounds described in the prior section may be 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.

[00191] The starting material used for the synthesis of the compounds described in the prior section may be synthesized or can be 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.

[00192] In certain embodiments, compounds described herein are prepared according to Scheme 1.

Scheme 1:



[00193] In one aspect, the synthesis of compounds of Formula 1 begins with the reaction of a 2-haloaniline with N-protected 4-carboxypiperidine. In one aspect, 2-halo-3-amino-pyridine is reacted with N-protected 4-carboxypiperidine to form amides that are then used to prepare compounds of Formula 1 where one A is N. In one aspect, other pyridine compounds, as well as pyrimidine, pyrazine and pyridazine compounds and that substituted with at least one halogen and amino group, are used in place of 2-haloaniline as outlined in Scheme 1 to prepare compounds of Formula 1 where one or two A are N.

[00194] The substituents in Scheme 1 are as described herein.

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

[00195] In certain embodiments, the compounds described herein are modified using various electrophiles or nucleophiles to form new functional groups or substituents. Table 10 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 10: 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
<i>N</i> -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

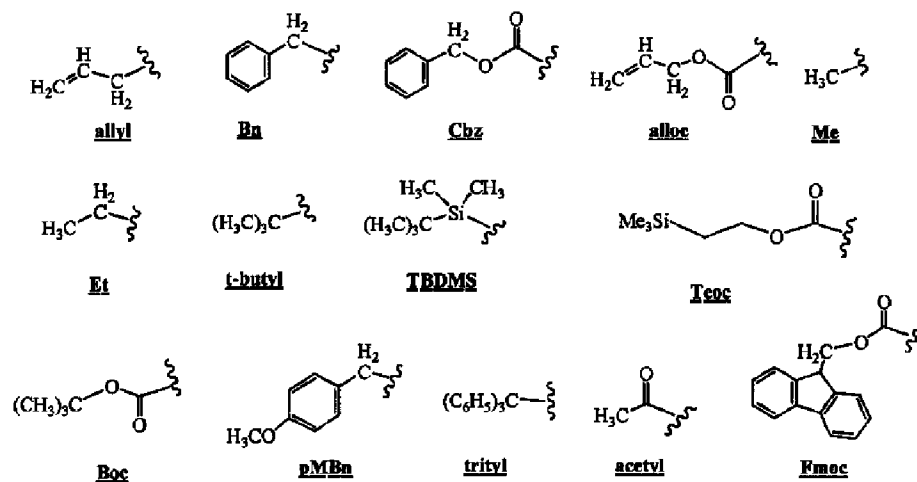
[00196] In the reactions described, it is necessary in certain embodiments to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Protecting groups are used 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.

[00197] 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.

[00198] 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.

[00199] Typically blocking/protecting groups are, by way of example only:



[00200] 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.

[00201] In certain embodiments, indole containing compounds are prepared using standard procedures such as those found in Katritzky, *Handbook of Heterocyclic Chemistry* Pergamon Press, Oxford, 1986; Pindur *et al*, *J. Heterocyclic Chem.*, vol 25, 1, 1987, and Robinson *"The Fisher Indole Synthesis"*, John Wiley & Sons, Chichester, New York, 1982, are incorporated herein by reference for such disclosure.

Further Forms of Compounds

[00202] In certain embodiments, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00203] Alternatively, in other embodiments, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are prepared as a pharmaceutically acceptable base addition salts (which is a type of a pharmaceutically acceptable salt) 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 and inorganic bases such as aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[00204] In still other embodiments, the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are prepared as a pharmaceutically acceptable salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, for example an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. In addition, the salt forms of the disclosed compounds are optionally prepared using salts of the starting materials or intermediates.

[00205] 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 may be 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 any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are optionally prepared or formed during the processes described herein. By way of example only, hydrates of compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are optionally prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran 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.

[00206] In yet other embodiments, the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are prepared in various forms, including but not limited to, amorphous forms, milled forms and nano-particulate forms. In addition, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9,

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.

[00207] In some embodiments, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, in unoxidized form are prepared from N-oxides of compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, by treating with a reducing agent, such as, but not limited to, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like in a suitable inert organic solvent, such as, but not limited to, acetonitrile, ethanol, aqueous dioxane, or the like at 0 to 80°C.

[00208] In some embodiments, compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are prepared as prodrugs. 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.

[00209] 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, are all incorporated herein by reference for such disclosure.

[00210] Additionally, prodrug derivatives of compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are optionally prepared (e.g., for further details see Saulnier et al., (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). By way of example only, appropriate prodrugs are prepared by reacting a non-derivatized compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00211] In some embodiments, sites on the aromatic ring portion of compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00212] 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. In yet another embodiment, the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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, is hereby incorporated herein by reference for such disclosure.

[00213] 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 Chemical Terminology

[00214] 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. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00215] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00216] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl moiety may be saturated, which means that it does not contain any carbon-carbon double bonds or carbon-carbon triple bonds. The alkyl moiety may also be unsaturated, which means that it contains at least one carbon-carbon double bonds or carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, or straight chain.

[00217] 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 "C₁-C₄ alkyl" or similar designations. A "lower alkyl" is used to designate a C₁-C₄alkyl. By way of example only, "C₁-C₄ alkyl" indicates that there are one to four carbon atoms in the alkyl chain. In one aspect, the alkyl 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, tertiary butyl, pentyl, hexyl, allyl, but-2-enyl, but-3-enyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, and the like. In one aspect, an alkyl is a C₁-C₆ alkyl.

[00218] 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 nitrogen atom to which they are attached form a cyclic ring system.

[00219] The term "alkenyl" refers to a type of alkyl group in which the first two atoms of the alkyl group form a double bond that is not part of an aromatic group. That is, an alkenyl group begins with the atoms -C(R)=C-R, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. Non-limiting examples of an alkenyl group include -CH=CH₂, -C(CH₃)=CH₂, -CH=CHCH₃ and -C(CH₃)=CHCH₃. The alkenyl moiety may be branched, straight chain, or cyclic (in which case, it would also be known as a "cycloalkenyl" group). In one aspect, an alkenyl is a C₂-C₆alkenyl.

[00220] The term "alkynyl" refers to a type of alkyl group in which the first two atoms of the alkyl group form a triple bond. That is, an alkynyl group begins with the atoms -C≡C-R, wherein R refers to the remaining portions of the alkynyl group, which may be the same or different. Non-limiting examples of an alkynyl group include -C≡CH, -C≡CCH₃ and -C≡CCH₂CH₃. In one aspect, an alkynyl is a C₂-C₆alkynyl.

[00221] 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 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, thereby forming a prodrug. Any amine, or carboxyl side chain on the compounds described

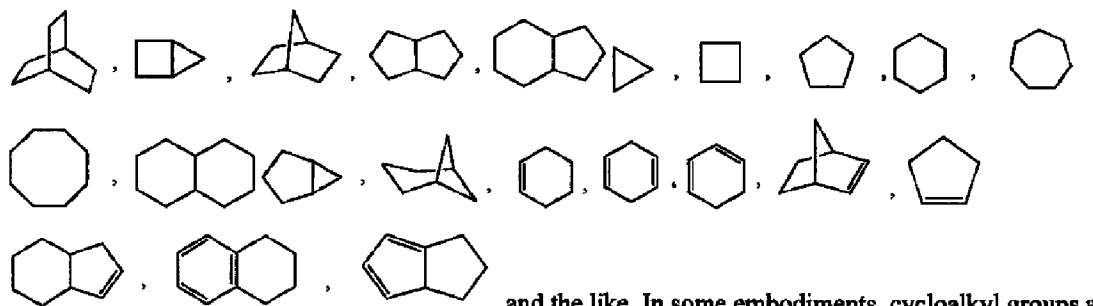
herein can be amidified. See, e.g., Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, is incorporated herein by reference for such disclosure.

[00222] 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 can be 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.

[00223] 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.

[00224] 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 can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthalenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

[00225] 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.

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, cycloheptan-1,1-diyl, and the like).

[00226] 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 can be esterified. Examples of procedures and specific groups to make such esters can be found in sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference for such disclosure.

[00227] The term “halo” or, alternatively, “halogen” or “halide” means fluoro, chloro, bromo or iodo.

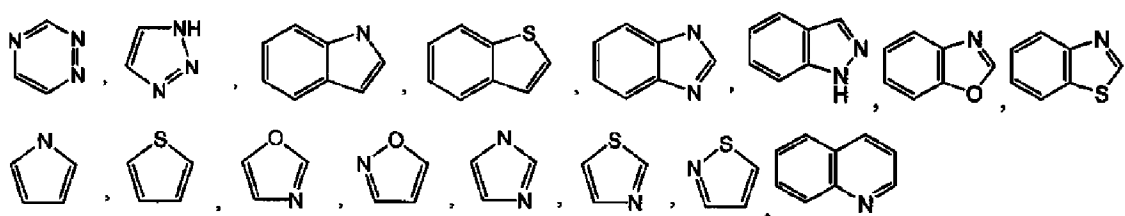
[00228] The term "haloalkyl" refers to an alkyl group in which one or more hydrogen atoms are replaced by one or more halide atoms. In one aspect, a haloalkyl is a C₁-C₄haloalkyl.

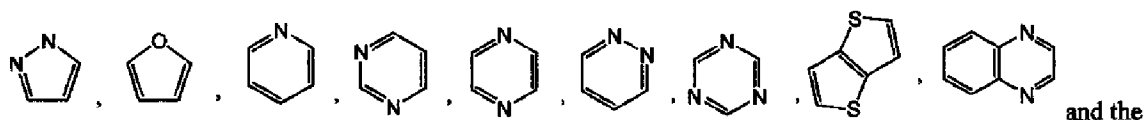
[00229] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoroalkyl is a C₁-C₄fluoroalkyl.

[00230] 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 C₂-C₆ heteroalkyl.

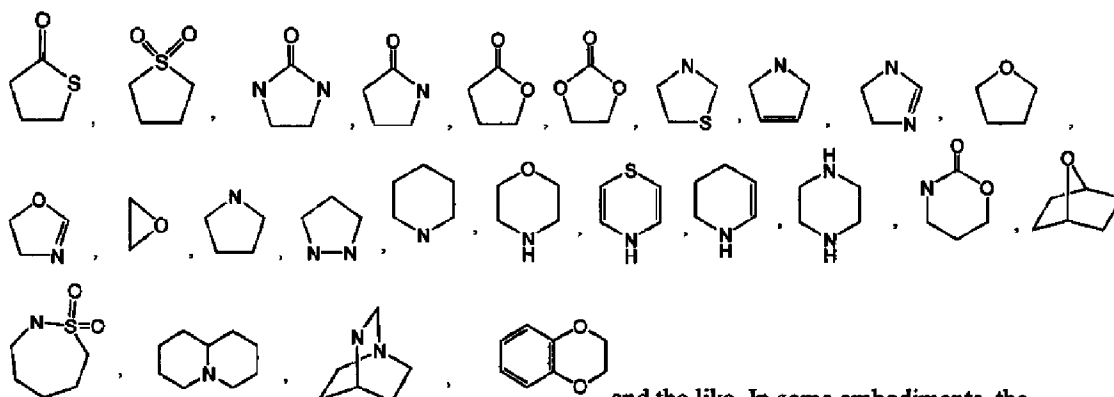
[00231] The term "heterocycle" refers to heteroaromatic and heteroalicyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 4 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 4-membered heterocyclic group is azetidiny (derived from azetidine). 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, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridiny, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinoliziny. Examples of aromatic heterocyclic groups are pyridiny, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyraziny, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, puriny, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxaliny, naphthyridiny, and furopyridiny. The foregoing groups, as derived from the groups listed above, 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 and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one.

[00232] 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:





[00233] A "heteroalicyclic" group or "heterocycloalkyl" 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:



[00234] 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.

[00235] A "cyano" group refers to a -CN group.

[00236] 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, pyranlyl and thiopyranlyl are 6-membered rings and cyclopentyl, pyrrolyl, furanyl, and thiophenyl are 5-membered rings.

[00237] 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.

[00238] A "sulfonyl" group refers to a -S(=O)₂-.

[00239] 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, mercapto, 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 L_sR_s, wherein each L_s is independently selected from a bond, -O-, -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -NH-, -NHC(O)-, -C(O)NH-, S(=O)₂NH-, -

NHS(=O)₂, -OC(O)NH-, -NHC(O)O-, -(C₁-C₆ alkyl), or -(C₂-C₆ alkenyl); and each R_x is independently selected from H, alkyl, fluoroalkyl, cycloalkyl, aryl, heteroaryl, or heteroalkyl. In some embodiments, optional substituents are selected from alkyl, hydroxy, alkoxy, cyano, halo, nitro, haloalkyl, fluoroalkyl, amino, methylamino, and dimethylamino. In yet other embodiments, optional substituents are selected from methyl, hydroxy, methoxy, cyano, fluoro, chloro, bromo, nitro, trifluoromethyl, trifluoromethoxy, amino, methylamino, and dimethylamino. The protecting groups that may form the protective derivatives of the above substituents may be found in sources such as Greene and Wuts, above.

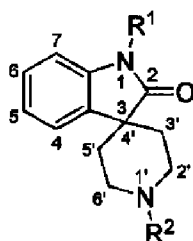
[00240] In certain embodiments, the compounds presented herein possess one or more stereocenters and each center independently exists in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers are obtained, if desired, by methods such as, the separation of stereoisomers by chiral chromatographic columns.

[00241] The methods and formulations described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having the structure of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

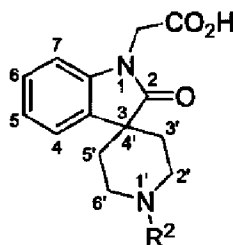
Naming Convention:

[00242] The following conventions were used to name the spiro compounds described herein:

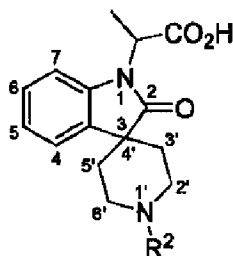
[00243] 1-(R¹)-1'-(R²)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] corresponds to the following structure:



[00244] 1'-(R²)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid corresponds to the following structure:



[00245] 2-(1'-(R²)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid corresponds to the following structure:



Certain Terminology

[00246] 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.

[00247] 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.

[00248] 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.

[00249] 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.

[00250] 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.

[00251] 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.

[00252] 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).

[00253] The term “bone disease,” as used herein, refers to a disease or condition of the bone, including, but not limited to, inappropriate bone remodeling, loss or gain, osteopenia, osteomalacia, osteofibrosis, and Paget’s disease.

[00254] 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 traumatic shock; 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..

[00255] 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, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma) or hematological tumors (such as the leukemias).

[00256] 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.

[00257] 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.

[00258] 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-Larsson Syndrome, urticaria.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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.

[00263] The term “iatrogenic” means a PGD₂-dependent or PGD₂-mediated condition, disorder, or disease created or worsened by medical or surgical therapy.

[00264] The term “inflammatory disorders” refers to those diseases or conditions that are characterized by one or more of the signs of pain (*dolor*, from the generation of noxious substances and the stimulation of nerves), heat (*calor*, from vasodilatation), redness (*rubor*, from vasodilatation and increased blood flow),

swelling (*tumor*, from excessive inflow or restricted outflow of fluid), and loss of function (*functio laesa*, which may be partial or complete, 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 (Disease,); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

[00265] 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.

[00266] The term "PGD₂-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 PGD₂.

[00267] The term "PGD₂-mediated", as used herein, refers to conditions or disorders that might occur in the absence of PGD₂ but can occur in the presence of PGD₂.

[00268] The terms "kit" and "article of manufacture" are used as synonyms.

[00269] 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 sulphhydryl groups. Metabolites of the compounds disclosed herein can be 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.

[00270] 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.

[00271] 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 conjunctivitis, vernal conjunctivitis, pappillary conjunctivitis.

[00272] The term “interstitial cystitis” refers to a disorder characterized by lower abdominal discomfort, frequent and sometimes painful urination that is not caused by anatomical abnormalities, infection, toxins, trauma or tumors.

[00273] By “pharmaceutically acceptable,” as used herein, refers 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.

[00274] 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. Pharmaceutically acceptable salts may be obtained by reacting a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 may also be obtained by reacting a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00275] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00276] The term “pharmaceutical composition” refers to a mixture of a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00277] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00278] 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., diaphragm 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, 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.

[00279] The term "subject" or "patient" encompasses mammals and non-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. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[00280] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of 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

[00281] Suitable routes of administration include, but are not limited to, intravenous, oral, 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.

[00282] 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 drug 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.

Pharmaceutical Composition/Formulation

[00283] 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 Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999), are hereby incorporated herein by reference for such disclosure.

[00284] Provided herein are pharmaceutical compositions comprising a compound of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, and a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s). In certain embodiments, the compounds described are administered as pharmaceutical compositions in which compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are 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 1, compounds of Formula 2, compounds of Formula 3, compounds of Formula 4 and/or compounds of Formula 5.

[00285] A pharmaceutical composition, as used herein, refers to a mixture of a compound of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, provided herein 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.

[00286] In one embodiment, one or more compound of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, is formulated in an aqueous solutions. 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 any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00287] In another embodiment, compounds described herein are formulated for oral administration. Compounds described herein, including compounds of any of Formula 1, Formula 2, Formula 3, Formula 4 Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00288] 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.

[00289] 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.

[00290] 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.

[00291] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00292] In still other embodiments, the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00293] In yet other embodiments, the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, is accomplished by means of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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.

[00294] 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.

[00295] 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 1; (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.

[00296] In other embodiments, the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00297] 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 for such disclosure. Formulations, which include a compound of Formula 1, 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. 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.

[00298] 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.

[00299] In still other embodiments, the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00300] 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 may be used as suitable and as understood in the art. Pharmaceutical compositions comprising a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00301] Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and at least one compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00302] 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.

[00303] In some embodiments, pharmaceutical composition comprising at least one compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00304] In certain embodiments, useful aqueous suspension contain one or more polymers as suspending agents. Useful 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 comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00305] Useful pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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, can be useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

[00306] Furthermore, useful 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.

[00307] Additionally, useful compositions also, 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.

[00308] Other useful 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.

[00309] Still other useful 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.

[00310] Still other useful 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.

[00311] In certain embodiments, 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.

[00312] In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful 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 weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[00313] In certain embodiments, the formulations described herein comprise 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

[00314] In one embodiment, the compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, are used in the preparation of medicaments for the treatment of PGD₂-dependent or PGD₂-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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[00315] 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.

[00316] 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.

[00317] 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.

[00318] In certain embodiments wherein a patient's status does improve, administration of the compounds are given continuously; or, alternatively, 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%.

[00319] 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.

[00320] 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) 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 0.02-5000 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.

[00321] 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.

[00322] In one embodiment, the daily dosages appropriate for the compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 or 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.

[00323] 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 LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (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 LD₅₀ and ED₅₀. 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 ED₅₀ 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 CRTH2 Modulators to Prevent and/or Treat PGD₂-Dependent or PGD₂ Mediated Diseases or Conditions

[00324] The therapy of PGD₂-dependent or PGD₂ mediated diseases or conditions is designed to modulate the activity of CRTH2, DP₁ and/or TP. Such modulation includes, in some embodiments, antagonizing CRTH2 activity. In other embodiments, such modulation includes antagonizing CRTH2 and DP₁. For example, in specific embodiments, a CRTH2 inhibitor is administered in order to decrease signal transduction of PGD₂ within the individual, or to down-regulate or decrease the expression or availability of

the CRTH2 mRNA or specific splicing variants of the CRTH2 mRNA. In other specific embodiments, down-regulation or decreasing expression or availability of a native CRTH2 mRNA or of a particular splicing variant minimizes the expression or activity of a defective nucleic acid or the particular splicing variant and thereby minimizes the impact of the defective nucleic acid or the particular splicing variant.

[00325] In accordance with one aspect, compositions and methods described herein include compositions and methods for treating, preventing, reversing, halting or slowing the progression of PGD₂-dependent or PGD₂ mediated diseases or conditions once it becomes clinically evident, or treating the symptoms associated with or related to PGD₂-dependent or PGD₂ mediated diseases or conditions, by administering to the subject a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. In certain embodiments, the subject already has a PGD₂-dependent or PGD₂ mediated disease or condition at the time of administration, or is at risk of developing a PGD₂-dependent or PGD₂ mediated disease or condition.

[00326] In certain aspects, the activity of CRTH2 in a mammal is directly or indirectly modulated by the administration of (at least once) an effective amount of at least one compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, to a mammal. Such modulation includes, but is not limited to, reducing and/or inhibiting the activity of CRTH2. In additional aspects, the activity of PGD₂ 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, to a mammal. Such modulation includes, but is not limited to, reducing and/or inhibiting the activity of CRTH2.

[00327] In one embodiment, prevention and/or treatment of PGD₂-dependent or PGD₂ mediated diseases or conditions comprises administering to a mammal at least once a therapeutically effective amount of at least one compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. In specific embodiments, the compound administered to the mammal is a compound of Formula 1, a compound of Formula 2, a compound of Formula 3, a compound of Formula 4 and/or a compound of Formula 5. In some embodiments, there is provided a method of treating PGD₂-dependent or PGD₂ 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.

[00328] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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, 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.

[00329] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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.

[00330] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00331] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00332] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00333] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00334] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00335] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00336] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00337] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00338] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00339] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which

includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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.

[00340] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. The type of cancer may include, but is not limited to, pancreatic cancer and other solid or hematological tumors.

[00341] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00342] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00343] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. Such gastrointestinal diseases include, by way of example only, inflammatory bowel disease (IBD), colitis and Crohn's disease.

[00344] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00345] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00346] By way of example only, included in the prevention/treatment methods described herein are methods for treating type II diabetes comprising administering at least once to the mammal an effective amount of at least one compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00347] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9. 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00348] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

[00349] By way of example only, included in the prevention/treatment methods described herein are methods for the treatment of metabolic syndromes such as Familial Mediterranean Fever comprising administering at least once to the mammal an effective amount of at least one compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9.

Combination Treatments

[00350] In certain instances, it is appropriate to administer at least one compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 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.

[00351] 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 CRTH2 modulator (*e.g.* 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 CRTH2 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 CRTH2 antagonist described herein in the combination treatment is administered weekly at the onset of treatment, decreasing to biweekly, and decreasing further as appropriate.

[00352] Compositions and methods for combination therapy are provided herein. In accordance with one aspect, the pharmaceutical compositions disclosed herein are used to treat PGD₂-dependent or PGD₂ 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 CRTH2 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.

[00353] 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.

[00354] 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 CRTH2 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.

[00355] 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).

[00356] 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.

[00357] In additional embodiments, the compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, , 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.

[00358] The compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, 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.

[00359] By way of example, therapies which combine compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, with inhibitors of PGD₂ synthesis or PGD₂ receptor antagonists, either acting at the same or other points in the PGD₂ synthesis pathway, are encompassed herein for treating PGD₂-dependent or PGD₂ mediated diseases or conditions. In addition, by way of example, encompassed herein are therapies that combine compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, with inhibitors of inflammation for treating PGD₂-dependent or PGD₂ mediated diseases or conditions.

Anti-Inflammatory Agents

[00360] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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, arthrotec, asacol, auralgan, azulfidine, daypro, etodolac, ponstan, salofalk, and solumedrol; non-steroidal anti-inflammatory agents, by way of example, aspirin (Bayer™, Bufferin™), indomethacin (Indocin™), rofecoxib (Vioxx™), celecoxib (Celebrex™), valdecoxib (Bextra™), diclofenac, etodolac, ketoprofen, lodine, mobic, nabumetone, naproxen, piroxicam; and corticosteroids, by way of example, celestone, prednisone, and deltasone, or leukotriene pathway modulators such as montelukast (Singulair™) or zileuton (Zyflo™).

[00361] By way of example only, asthma is a chronic inflammatory disease characterized by pulmonary eosinophilia and airway hyperresponsiveness. In patients with asthma, PGD₂ is released from mast cells, eosinophils, and basophils. PGD₂ 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.

PGD₂ Receptor Antagonists

[00362] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ mediated conditions or diseases includes administering to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with other PGD₂ receptor antagonists including, but are not limited to, DP₁ receptor antagonists and TP receptor antagonists. In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ mediated conditions or diseases includes administered to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with a DP₁ receptor antagonist. DP₁ 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 PGD₂-dependent or PGD₂ mediated disorder, the time period in which the CRTH2 antagonist acts to treat the disorder and/or the time period in which the DP₁ receptor antagonist acts to prevent DP₁ 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.

[00363] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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 PGD₂-dependent or PGD₂ mediated disorders, including respiratory disorders.

[00364] In one embodiment, the co-administration of a CRTH2 inhibitor with a DP₁ receptor antagonist or a TP receptor antagonist has therapeutic benefit over and above the benefit derived from the administration of either a CRTH2, DP₁ or a TP antagonist alone. In the case that substantial inhibition of PGD₂ 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 DP₁ receptor, TP receptor and/or CRTH2 receptor may afford substantial therapeutic benefits, particularly for respiratory diseases.

Other Combination Therapies

[00365] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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.

[00366] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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.

[00367] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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 (PPAR γ) 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 PPAR γ agonists outside the thiazolidinedione structural class; PPAR α 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; endothelial 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.

[00368] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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; angiotensin 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 adrenergic blockers, such as propranolol, nadolol, timolol, pindolol, labetalol, metoprolol, atenolol, esmolol and acebutolol; NMDA receptor antagonists, including memantine; NR2B antagonists, such as traxoprodil; 5-HT1A 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; GABA 5 inverse agonists; and selective androgen receptor modulators.

[00369] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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.

[00370] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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.

[00371] In another embodiment described herein, methods for treatment of PGD₂-dependent or PGD₂ 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.

[00372] In yet another embodiment described herein, methods for treating PGD₂-dependent or PGD₂ 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, nasal decongestants, respiratory enzymes, lung surfactants, antihistamines (e.g., ethanolamines, alkylamines, phenothiazines, piperidines, and ethylenediamines), mucolytics, corticosteroids, glucocorticoids, anticholinergics, antitussives, analgesics, expectorants, albuterol, ephedrine, epinephrine, formoterol, metaproterenol, terbutaline, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone propionate, triamcinolone acetonide, ipratropium bromide, pseudoephedrine, theophylline, montelukast, zafirlukast, ambrisentan, bosentan, enrasentan, sitaxsentan, tezosentan, iloprost, treprostinil, pirfenidone, FLAP inhibitors, FLAP modulators and 5-LO inhibitors

[00373] In a specific embodiment described herein, methods for treating PGD₂-dependent or PGD₂ 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 PGD₂-dependent or PGD₂ 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)-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, MK-0591, 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 for such disclosure). 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, aminophylline, 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), AZ-4407 and ZD-2138 and compounds found in US 2007/0149579, WO2007/016784.

[00374] 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. Antihistamines include, but are not limited to, ethanolamines, alkylamines, phenothiazines, piperidines, and ethylenediamines.

Use of CRTH2 Modulators to Diagnose a Patient with a PGD_2 -Dependent or PGD_2 Mediated Disease or Condition

[00375] As discussed herein, the administration of compounds of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, is designed to modulate the activity of CRTH2. Such modulation includes, in some embodiments, antagonizing CRTH2 activity. For example, in specific embodiments, the administration of a CRTH2 inhibitor decreases signal transduction of PGD_2 within the individual, or down-regulates or decreases the expression or availability of the CRTH2 mRNA or specific splicing variants of the CRTH2 mRNA.

[00376] 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 any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, or pharmaceutical composition or medicament which includes a compound of any of Formula 1, Formula 2, Formula 3, Formula 4, Formula 5, Formula 6, Formula 7, Formula 8, or Formula 9, and determining whether or not the patient responds to the treatment.

Kits/Articles of Manufacture

[00377] 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.

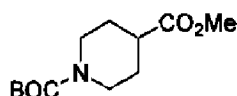
[00378] For example, the container(s) can comprise one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial 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.

[00379] 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.

[00380] 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.

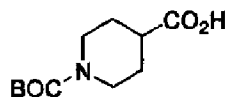
EXAMPLES

[00381] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1: Synthesis of Compounds of Formula 1, Formula 2, Formula 3, Formula 4 and Formula 5**Example 1a: Synthesis of 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-1)****Step 1: Piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester**

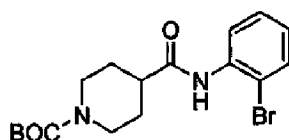
[00382] To methyl isonipecotate (18.9mL, 14.0mmol) in CH₂Cl₂ (200mL) was added di-*tert*-butyl dicarbonate (36.6g, 16.8mmol), followed by triethylamine (23.4mL, 16.8mmol) dropwise, and the mixture was stirred at room temperature overnight. The solution was then diluted with saturated aqueous NH₄Cl and extracted with CH₂Cl₂, and the combined organic layers were dried over MgSO₄, filtered, and concentrated.

The residue was purified by silica gel chromatography (50-80% EtOAc in hexanes) to give the desired product as an oil (24.8g).



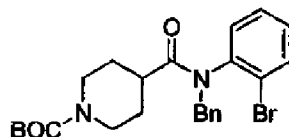
Step 2: Piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester

[00383] To piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-methyl ester (1.34g, 5.51mmol) in THF (7mL) was added lithium hydroxide (1.16g, 27.57mmol) and H₂O (7mL), and the reaction was stirred at room temperature overnight. The mixture was then acidified with aqueous 1N HCl to pH 3-4 and extracted with EtOAc three times. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give the desired product as a white solid (1.28g).



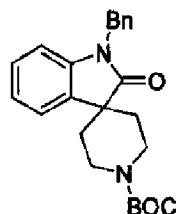
Step 3: 4-(2-Bromo-phenylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

[00384] Piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester (1.25g, 5.46mmol) and triethylamine (0.91mL, 6.55mmol) were dissolved in CH₂Cl₂ (12.5mL) and cooled to 0°C under N₂. Oxalyl chloride (0.57mL, 6.55mmol) was added, followed by DMF (0.1mL), and the mixture was stirred at 0°C for 2 hours. The solution was concentrated and dried under vacuum, and the crude acid chloride was then dissolved in pyridine (15mL). 2-Bromoaniline (0.68mL, 6.0mmol) was added, and the reaction was stirred at room temperature overnight. The mixture was diluted with aqueous 1N HCl and EtOAc, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with aqueous 1N HCl three times, and then dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (20-40% EtOAc in hexanes) to give the desired product (1.68g).



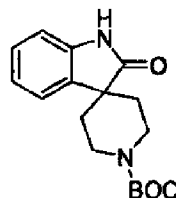
Step 4: 4-[Benzyl-(2-bromo-phenyl)-carbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester

[00385] 4-(2-Bromo-phenylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester (1.68g, 4.38mmol) was dissolved in DMF (16.8mL) and cooled to 0°C under N₂. Sodium hydride (60% in mineral oil; 0.263g, 6.57mmol) was added portionwise, followed by benzyl bromide (0.62mL, 5.26mmol). DMF (3mL) was added to facilitate stirring, and the reaction was warmed to room temperature and stirred for 2 hours, until no starting material was seen by analytical LCMS. The mixture was quenched with H₂O and extracted twice with EtOAc, and the combined organic layers were washed with H₂O three times. The organic layer was dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography (10-30% EtOAc in hexanes) to give the desired product (1.51g).



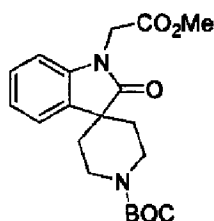
Step 5: 1-Benzyl-1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]

[00386] 4-[Benzyl-(2-bromo-phenyl)-carbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester (1.51g, 3.19mmol) was dissolved in 1,4-dioxane (10mL) under N₂. Sodium *tert*-butoxide (0.460g, 4.79mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.299g, 0.48mmol), and bis(dibenzylideneacetone)palladium(0) (0.183g, 0.32mmol) were added, and the reaction was purged with N₂ for 10 minutes. The solution was then heated to 105°C and stirred overnight under N₂. No starting material was seen by analytical LCMS, so the mixture was diluted with saturated aqueous NH₄Cl and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography (10-30% EtOAc in hexanes) to give the desired product as a yellow solid (0.905g).



Step 6: 1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]

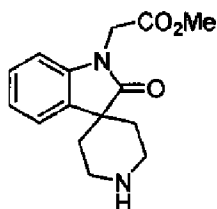
[00387] To liquid ammonia (17.5mL) collected at -78°C was added lithium metal (0.097g, 14.0mmol), and the solution turned dark blue. 1-Benzyl-1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] (0.686g, 1.75mmol) in THF (4mL) was added dropwise, and the reaction was stirred for 10 minutes. The mixture was quenched with solid NH₄Cl and warmed to room temperature. EtOAc was added to facilitate stirring, followed by H₂O. The organic layer was separated, dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography (10-30% EtOAc in hexanes) to give the desired product (0.340g).



Step 7: 1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

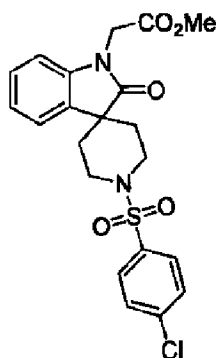
[00388] To 1'-(*tert*-butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] (0.340g, 1.13mmol) in DMF (5.1mL) at 0°C was added sodium hydride (60% in mineral oil; 0.077g, 1.92mmol) portionwise. After stirring for 20 minutes, methyl bromoacetate (0.15mL, 1.58mmol) was added, and the reaction was warmed to room temperature and stirred overnight. The mixture was diluted with H₂O and extracted twice with EtOAc. The combined organic layers were washed twice with H₂O, dried over MgSO₄, filtered, and

concentrated, and the residue was purified by silica gel chromatography (20-30% EtOAc in hexanes) to give the desired product (0.352g).



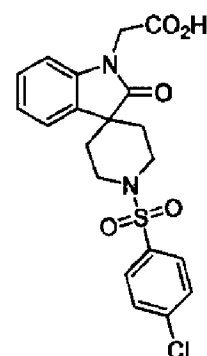
Step 8: 2,3-Dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

[00389] 1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester (0.333g, 0.89mmol) was dissolved in EtOAc (4mL) and treated with HCl (4N in 1,4-dioxane; 6mL, 24mmol) at room temperature for 2 hours. Once no starting material was seen by analytical LCMS, the mixture was concentrated and dried under vacuum, and the crude material was used directly in the next step.



Step 9: 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

[00390] 2,3-Dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester (0.049g, 0.18mmol) and 4-chlorobenzenesulfonyl chloride (0.041g, 0.20mmol) were dissolved in CH₂Cl₂ (1mL). Triethylamine (0.05mL, 0.36mmol) was added, and the reaction was stirred for 15 minutes. Once no starting material was seen by analytical LCMS, the mixture was concentrated and dried under vacuum, and the crude material was used directly in the next step.

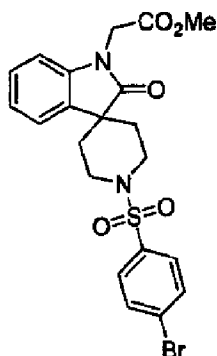


Step 10: 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

[00391] 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester (~0.08g, 0.18mmol) was dissolved in THF (2mL). Lithium hydroxide (1N; 2mL) was added, and the mixture was stirred at room temperature for 45 minutes. Once no starting material was seen by

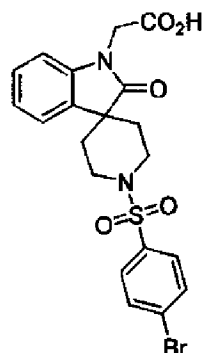
analytical LCMS, the mixture was acidified with aqueous 1N HCl to pH 3-4 and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography (30-50% EtOAc in hexanes) to give the desired product (0.050g).

Example 1b: Synthesis of 1'-(4-Bromo-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-2)



Step 1: 1'-(4-Bromo-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

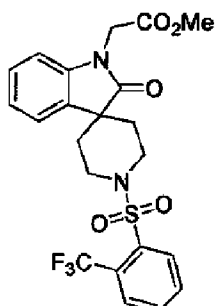
[00392] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 4-bromobenzenesulfonyl chloride.



Step 2: 1'-(4-Bromo-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

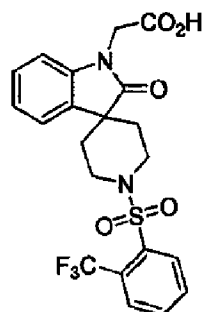
[00393] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(4-bromo-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1c: Synthesis of 1'-(2-Trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-3)



Step 1: 1'-(2-Trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

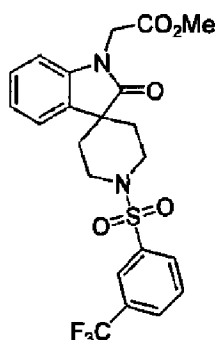
[00394] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 2-(trifluoromethyl)benzenesulfonyl chloride.



Step 2: 1'-(2-Trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

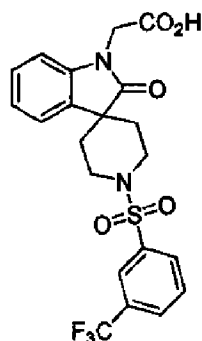
[00395] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(2-trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1d: Synthesis of 1'-(3-Trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-4)



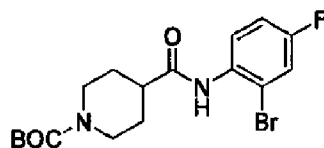
Step 1: 1'-(3-Trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

[00396] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 3-(trifluoromethyl)benzenesulfonyl chloride.

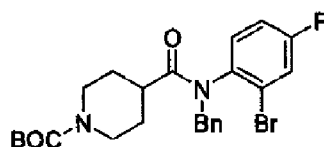


Step 2: 1'-(3-Trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

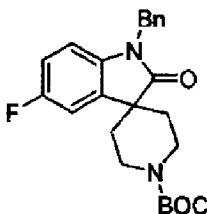
[00397] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(3-trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1e: Synthesis of 1'-(3,5-Bis-trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-5)**Step 1: 4-(2-Bromo-4-fluoro-phenylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester**

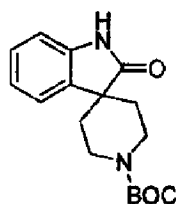
[00398] Prepared according to the procedure described in Example 1a, Step 3, using the following starting materials: piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester and 2-bromo-4-fluoroaniline.

**Step 2: 4-[Benzyl-(2-bromo-4-fluoro-phenyl)-carbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester**

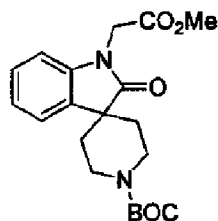
[00399] Prepared according to the procedure described in Example 1a, Step 4, using the following starting materials: 4-(2-bromo-4-fluoro-phenylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester and benzyl bromide.

**Step 3: 1-Benzyl-1'-(*tert*-Butoxycarbonyl)-5-fluoro-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]**

[00400] Prepared according to the procedure described in Example 1a, Step 5, using the following starting material: 4-[benzyl-(2-bromo-4-fluoro-phenyl)-carbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester.

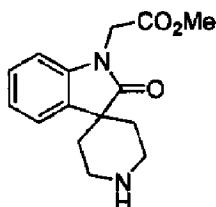
**Step 4: 1'-(*tert*-Butoxycarbonyl)- 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]**

[00401] Prepared according to the procedure described in Example 1a, Step 6, using the following starting material: 1-Benzyl-1'-(*tert*-Butoxycarbonyl)-5-fluoro-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine].



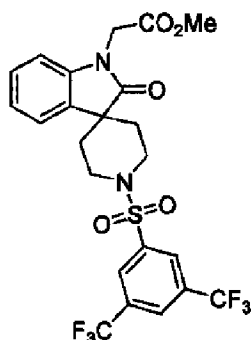
Step 5: 1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

[00402] Prepared according to the procedure described in Example 1a, Step 7, using the following starting materials: 1'-(*tert*-butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] and methyl bromoacetate.



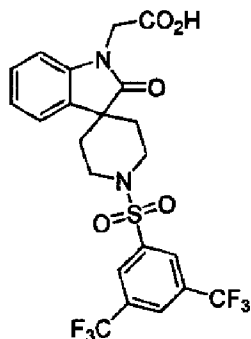
Step 6: 2,3-Dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

[00403] Prepared according to the procedure described in Example 1a, Step 8, using the following starting material: 1'-(*tert*-butoxycarbonyl)-5-fluoro-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.



Step 7: 1'-(3,5-Bis-trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

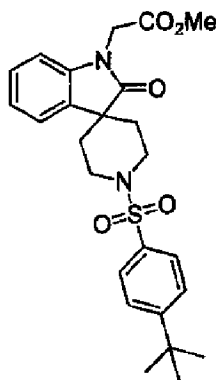
[00404] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 3,5-bis-(trifluoromethyl)benzenesulfonyl chloride.



Step 8: 1'-(3,5-Bis-trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

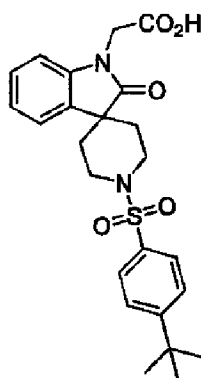
[00405] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(3,5-Bis-trifluoromethyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1f: Synthesis of 1'-(4-*tert*-Butyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-6)



Step 1: 1'-(4-*tert*-Butyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

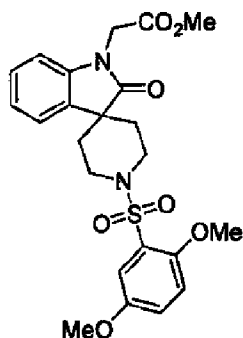
[00406] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 4-*tert*-butylbenzenesulfonyl chloride.



Step 2: 1'-(4-*tert*-Butyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

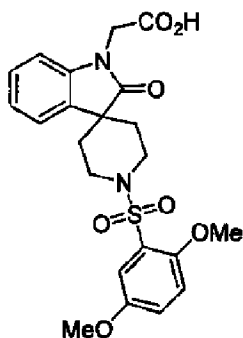
[00407] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(4-*tert*-butyl-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1g: Synthesis of 1'-(2,5-Dimethoxy-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-7)



Step 1: 1'-(2,5-Dimethoxy-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

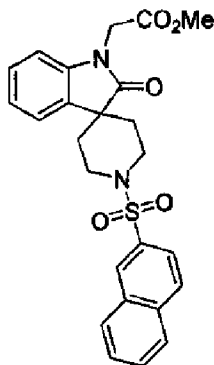
[00408] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 2,5-dimethoxybenzenesulfonyl chloride.



Step 2: 1'-(2,5-Dimethoxy-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

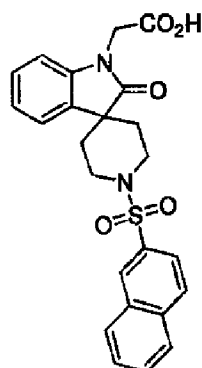
[00409] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(2,5-dimethoxy-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1h: Synthesis of 1'-(Naphthalene-2-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-8)



Step 1: 1'-(Naphthalene-2-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

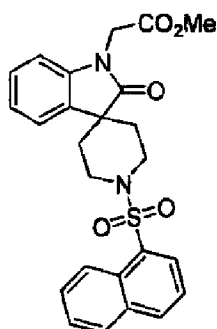
[00410] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 2-naphthalenesulfonyl chloride.



Step 2: 1'-(Naphthalene-2-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

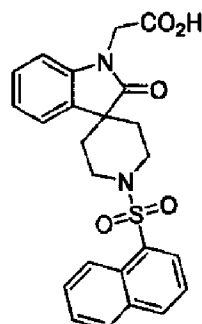
[00411] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(naphthalene-2-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1i: Synthesis of 1'-(Naphthalene-1-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-9)



Step 1: 1'-(Naphthalene-1-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

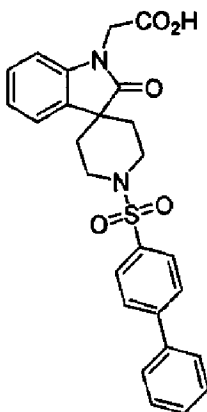
[00412] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 1-naphthalenesulfonyl chloride.



Step 2: 1'-(Naphthalene-1-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

[00413] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(naphthalene-1-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

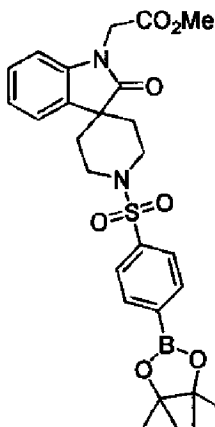
Example 1i: Synthesis of 1'-(Biphenyl-4-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-10)



Step 1: 1'-(Biphenyl-4-sulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

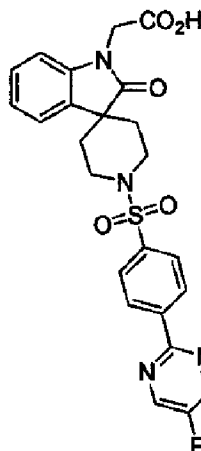
[00414] 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester (0.105g, 0.23mmol), phenylboronic acid (0.033g, 0.26mmol), and potassium carbonate (0.079g, 0.58mmol) were dissolved in DME (2mL) and H₂O (1mL), and the mixture was purged with N₂ for 10 minutes. Tetrakis(triphenylphosphine)palladium (0.027g, 0.02mmol) was added, and the mixture was purged with N₂ for an additional 5 minutes and then heated to 90°C overnight. Analytical LCMS indicated that the methyl ester had been hydrolyzed to the acid, and both hydrolyzed starting material and product were observed. The reaction was stirred for another 24 hours at 90°C and then cooled to room temperature. The mixture was diluted with H₂O and extracted with EtOAc, and the combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by preparative HPLC to give the desired product.

Example 1k: Synthesis of 1'-[4-(5-Fluoro-pyrimidin-2-yl)-benzenesulfonyl]-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-11)



Step 1: 1'-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonyl]-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

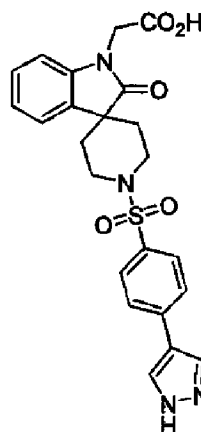
[00415] 1'-(4-Bromo-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester (0.330g, 0.67mmol), bis(pinacolato)diboron (0.260g, 1.0mmol), and potassium acetate (0.196g, 2.0mmol) were combined in 1,4-dioxane (7.4mL) and purged with N₂ for 10 minutes. (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (0.056g, 0.07mmol) was added, and the reaction was heated to 110°C for 8 hours and then stirred at room temperature for 2 days. The mixture was diluted with saturated aqueous NH₄Cl and extracted twice with EtOAc, and the combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (30-40% EtOAc in hexanes) to give the desired product (0.270g).



Step 2: 1'-(4-(5-Fluoro-pyrimidin-2-yl)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

[00416] Prepared according to the procedure described in Example 1j, Step 1, using the following starting materials: 1'-(4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 2-chloro-5-fluoropyrimidine.

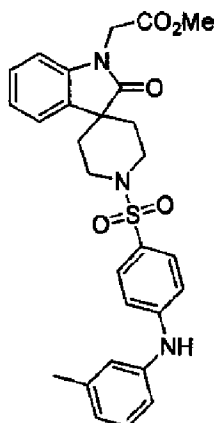
Example 1l: Synthesis of 1'-(4-(1H-Pyrazol-4-yl)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-12)



Step 1: 1'-(4-(1H-Pyrazol-4-yl)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

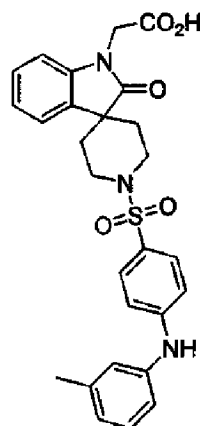
[00417] Prepared according to the procedure described in Example 1j, Step 1, using the following starting materials: 1'-(4-bromo-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

Example 1m: Synthesis of 1'-(4-(3-Methyl-anilino)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-13)



Step 1: 1'-(4-(3-Methyl-anilino)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

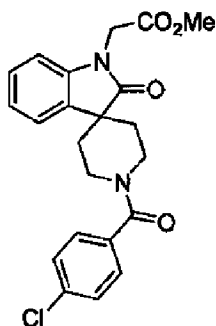
[00418] 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester (0.150g, 0.33mmol), m-toluidine (0.04mL, 0.40mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.010g, 0.02mmol), bis(dibenzylideneacetone)palladium(0) (0.037g, 0.04mmol), and cesium carbonate (0.538g, 1.65mmol) were combined in 1,4-dioxane (3mL) and purged with N₂ for 15 minutes. The reaction was heated to 60°C and stirred overnight under N₂. Some starting material was still observed by analytical LCMS after 18 hours, so the temperature was increased to 80°C for 3 hours. The product began to decompose at 80°C, so the reaction was cooled to room temperature and filtered through a pad of Celite. The filtrate was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography to give the desired product.



Step 2: 1'-(4-(3-Methyl-anilino)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

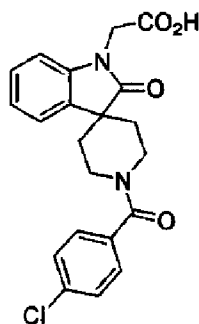
[00419] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(4-(3-methyl-anilino)-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1n: Synthesis of 1'-(4-Chloro-benzoyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-14)



Step 1: 1'-(4-Chloro-benzoyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester

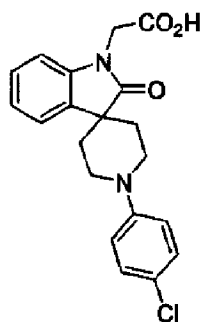
[00420] To 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester (0.175g, 0.47mmol) in CH_2Cl_2 (5mL) was added pyridine (5mL), followed by 4-chlorobenzoyl chloride. After 45 minutes, no starting material was seen by analytical LCMS, so the mixture was diluted with H_2O and extracted twice with CH_2Cl_2 . The combined organic layers were washed three times with aqueous 1N HCl, and then dried over MgSO_4 , filtered, and concentrated. The residue was purified by silica gel chromatography (20-50% EtOAc in hexanes) to give the desired product (0.146g).



Step 2: 1'-(4-Chloro-benzoyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

[00421] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(4-chloro-benzoyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester.

Example 1c: Synthesis of 1'-(4-Chloro-phenyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (Compound 1-15)

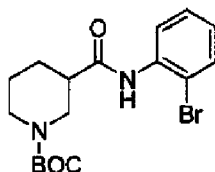


Step 1: 1'-(4-Chloro-phenyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid

[00422] 2,3-Dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid methyl ester (0.129g, 0.47mmol) and 4-bromochlorobenzene (0.108g, 0.56mmol) were dissolved in toluene (4mL) and 1,4-dioxane (1mL) under N_2 . Sodium *tert*-butoxide (0.068g, 0.71mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.004g,

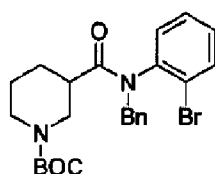
0.007mmol), and bis(dibenzylideneacetone)palladium(0) (0.002g, 0.002mmol) were added, and the reaction was purged with N₂ for 15 minutes. The solution was then heated to 80°C and stirred overnight under N₂. Analytical LCMS showed that no starting material remained and that the methyl ester of the product had been hydrolyzed to the acid, so the mixture was diluted with aqueous 1N HCl and extracted twice with EtOAc. The organic layer was dried over MgSO₄, filtered, and concentrated, and the residue was purified by preparative HPLC give the desired product (0.030g).

Example 1p: Synthesis of 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid (Compound 1-16)



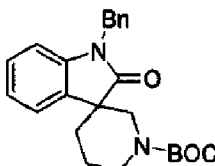
Step 1: 3-(2-Bromo-phenylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester

[00423] Prepared according to the procedure described in Example 1a, Step 3, using the following starting materials: 1-(*tert*-butoxycarbonyl)-3-piperidinecarboxylic acid and 2-bromoaniline.



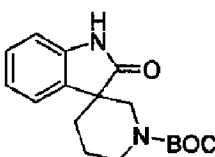
Step 2: 3-[Benzyl-(2-bromo-phenyl)-carbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester

[00424] Prepared according to the procedure described in Example 1a, Step 4, using the following starting materials: 3-(2-bromo-phenylcarbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester and benzyl bromide.



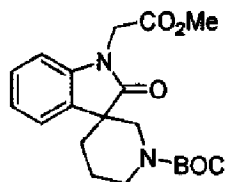
Step 3: 1-Benzyl-1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]

[00425] Prepared according to the procedure described in Example 1a, Step 5, using the following starting material: 3-[benzyl-(2-bromo-phenyl)-carbamoyl]-piperidine-1-carboxylic acid *tert*-butyl ester.



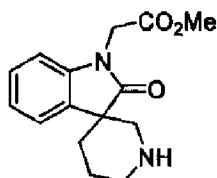
Step 4: 1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]

[00426] Prepared according to the procedure described in Example 1a, Step 6, using the following starting material: 1-benzyl-1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine].



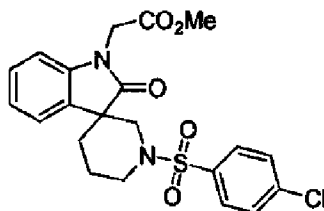
Step 5: 1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid methyl ester

[00427] Prepared according to the procedure described in Example 1a, Step 7, using the following starting materials: 1'-(*tert*-butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine] and methyl bromoacetate.



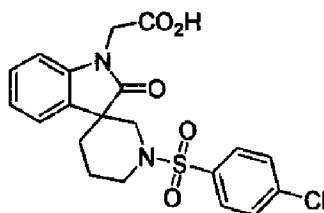
Step 6: 2,3-Dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid methyl ester

[00428] Prepared according to the procedure described in Example 1a, Step 8, using the following starting material: 1'-(*tert*-butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid methyl ester.



Step 7: 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid methyl ester

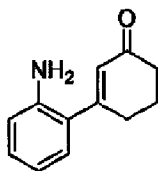
[00429] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid methyl ester and 4-chlorobenzenesulfonyl chloride.



Step 8: 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid

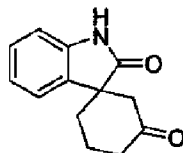
[00430] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1'-(4-chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,3'-piperidine]-1-yl-acetic acid methyl ester.

Example 1q: Synthesis of 1-(4-Chloro-benzenesulfonylamino)-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid (Compound 1-17)



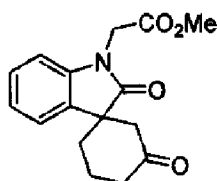
Step 1: 3-(2-Amino-phenyl)-cyclohex-2-enone

[00431] 2-Bromoaniline (11.0g, 50.2mmol), 2-cyclohexen-1-one (5.3mL, 55.3mmol), tri(o-tolyl)phosphine (1.5g, 5.0mmol), palladium(II) acetate (0.564g, 2.5mmol), and triethylamine (14.0mL, 100.4mmol) were combined in MeCN, and the mixture was purged with N₂ for 10 minutes. The reaction was then heated at 90°C for 24 hours. After cooling to room temperature, the mixture was diluted with H₂O and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography (10-40% EtOAc in hexanes) to give the desired product as an oil (2.15g).



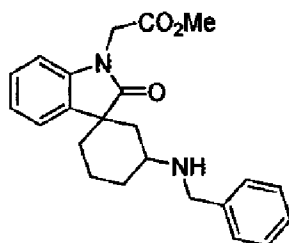
Step 2: 2',3'-Dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]

[00432] To 3-(2-amino-phenyl)-cyclohex-2-enone (0.391g, 2.09mmol) in THF (10.5mL) was added triethylamine (0.64mL, 4.60mmol), and the mixture was cooled to 0°C under N₂. Phosgene (20% in toluene; 1.47mL, 2.80mmol) was added over 5 minutes, and the reaction was stirred for 30 minutes. The mixture was concentrated to give a red solid, which was taken up in Et₂O (70mL) and filtered through a pad of Celite. The Celite was washed with additional Et₂O (70mL), and the filtrate was concentrated. The crude material was dissolved in THF (60mL) and *t*BuOH (0.20mL, 2.09mmol), and the mixture was cooled to -78°C and purged with N₂ for 10 minutes. In a separate flask, lithium chloride (0.752g, 17.75mmol) and samarium iodide (0.10mL, 12.54mmol) were combined at room temperature, and the mixture was stirred for 10 minutes and then added dropwise to the reaction at -78°C via an addition funnel over 30 minutes. After stirring for 30 minutes at -78°C, the reaction was quenched with saturated aqueous NH₄Cl, and the dry ice bath was removed. Once the mixture had warmed to room temperature, H₂O was added, and the solution was extracted twice with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography (30-50% EtOAc in hexanes) to give the desired product as a brown oil (0.263g).



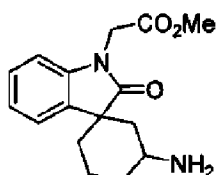
Step 3: 2',3'-Dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid methyl ester

[00433] Prepared according to the procedure described in Example 1a, Step 7, using the following starting materials: 2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole] and methyl bromoacetate.



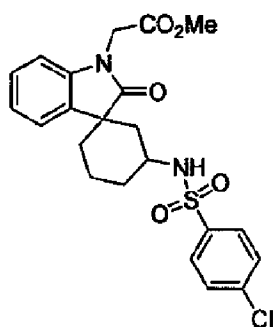
Step 4: 1-(Benzyl-amino)-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid methyl ester

[00434] 2',3'-Dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid methyl ester (0.115g, 0.40mmol) and benzylamine (0.05mL, 0.44mmol) were combined in benzene (4mL) and treated with powdered molecular sieves. The reaction was stirred overnight at 85°C, during which time the solvent evaporated. The residue was dissolved in MeOH (3mL), and sodium borohydride (0.025g, 0.64mmol) was added. The solution was stirred at room temperature for 4 hours, and then quenched with H₂O and extracted twice with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by preparative HPLC to give the desired product (0.019g).



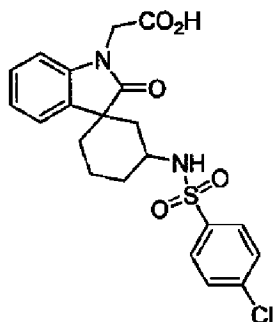
Step 5: 1-Amino-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid methyl ester

[00435] 1-(Benzyl-amino)-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid methyl ester (0.019g, 0.05mmol), ammonium formate (0.019g), and 10% palladium on carbon (0.014g) were combined in DMF (3mL) and heated to 160°C for 1 hour. After cooling to room temperature, the mixture was filtered through a pad of Celite, and the filter cake was washed with EtOAc. The filtrate was diluted with H₂O and EtOAc, and the product was basified with aqueous 1N NaOH to pH 10-11. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over MgSO₄, filtered, and concentrated to give the crude material, which was used directly in the next step.



Step 6: 1-(4-Chloro-benzenesulfonylamino)-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid methyl ester

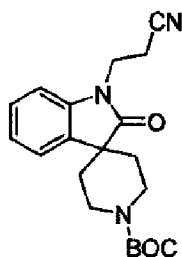
[00436] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 1-amino-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid methyl ester and 4-chlorobenzenesulfonyl chloride.



Step 7: 1-(4-Chloro-benzenesulfonylamino)-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid

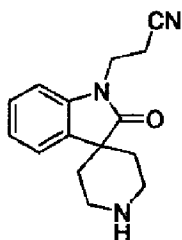
[00437] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 1-(4-chloro-benzenesulfonylamino)-2',3'-dihydrospiro[cyclohexanone-3,3'-(2'-oxo)-indole]-1'-yl-acetic acid methyl ester.

Example 1r: Synthesis of 1'-(4-Chloro-benzenesulfonyl)-1-(2-cyano-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] (Compound 1-20)



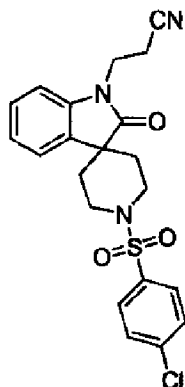
Step 1: 1'-(tert-Butoxycarbonyl)-1-(2-cyano-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]

[00438] To 1'-(tert-butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] (0.202g, 0.66mmol) in DMF (3mL) at 0°C was added sodium hydride (60% in mineral oil; 0.040g, 0.99mmol). The reaction was warmed to room temperature, and acrylonitrile (0.18mL, 2.67mmol) was added, resulting in an exothermic reaction. After stirring the solution overnight at room temperature, starting material was still seen by analytical LCMS, so additional acrylonitrile (0.18mL, 2.67mmol) was added at room temperature. 2 hours later, an additional portion of acrylonitrile (0.09mL, 1.33mmol) was added to try to push the reaction to completion. After 2 hours, the mixture was quenched with H₂O and diluted with EtOAc. The solution was filtered, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography (30-50% EtOAc in hexanes) to give the desired product (0.162g).



Step 2: 1-(2-Cyano-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]

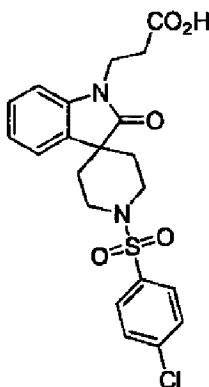
[00439] Prepared according to the procedure described in Example 1a, Step 8, using the following starting material: 1'-(tert-butoxycarbonyl)-1-(2-cyano-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine].



Step 3: 1'-(4-Chloro-benzenesulfonyl)- 1-(2-cyano-ethyl)- 2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]

[00440] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 1-(2-cyano-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] and 4-chlorobenzenesulfonyl chloride.

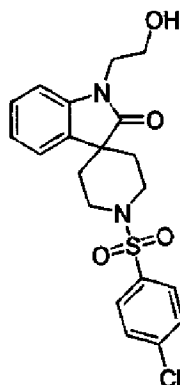
Example 1s: Synthesis of 3-(1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid (Compound 1-18)



Step 1: 3-(1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid

[00441] To 1'-(4-chloro-benzenesulfonyl)- 1-(2-cyano-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] (0.100g, 0.23mmol) in *i*PrOH (4mL) was added 10% aqueous KOH (2mL), and the reaction was heated to 85°C overnight. No starting material was seen by analytical LCMS, so the solution was poured over ice and acidified with concentrated HCl to pH 3-4. The mixture was extracted with EtOAc three times, and the combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by preparative HPLC to give the desired product (0.055g).

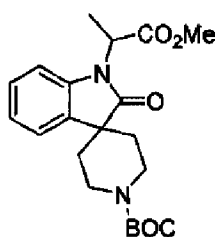
Example 1t: Synthesis of 1'-(4-Chloro-benzenesulfonyl)-1-(2-hydroxy-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] (Compound 1-19)



Step 1: 1'-(4-Chloro-benzenesulfonyl)-1-(2-hydroxy-ethyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]

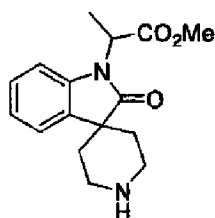
[00442] 1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl-acetic acid (0.097g, 0.22mmol) was dissolved in THF (2mL) and cooled to 0°C under N₂. Borane (1M in THF; 0.45mL, 0.45mmol) was added, and the reaction was stirred for 1 hour. No reaction was observed by analytical LCMS, so an additional portion of borane (1M in THF; 0.45mL, 0.45mmol) was added, and the reaction was stirred at room temperature for 2 days. Starting material was still observed by analytical LCMS, so an additional portion of borane (1M in THF; 0.45mL, 0.45mmol) was added at 0°C. After 6 hours, starting material was still observed, and so additional borane was added (1M in THF, 1.0mL, 1.0mmol). After 3 hours, no change was seen by analytical tlc, and so the reaction was diluted with H₂O and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography to give the desired product (0.063g).

Example 1u: Synthesis of 2-(1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid (Compound 1-21)



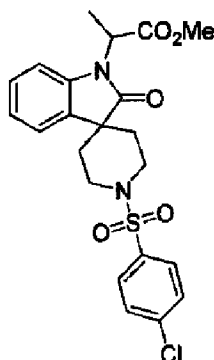
Step 1: 2-(1'-(*tert*-Butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid methyl ester

[00443] Prepared according to the procedure described in Example 1a, Step 7, using the following starting materials: 1'-(*tert*-butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine] and methyl 2-bromopropionate.



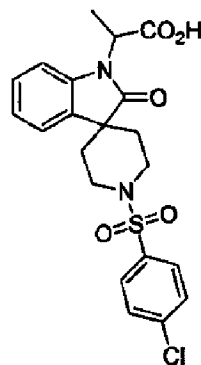
Step 2: 2-(2,3-Dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid methyl ester

[00444] Prepared according to the procedure described in Example 1a, Step 8, using the following starting material: 2-(1'-(*tert*-butoxycarbonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid methyl ester.



Step 3: 2-(1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid methyl ester

[00445] Prepared according to the procedure described in Example 1a, Step 9, using the following starting materials: 2-(2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid methyl ester and 4-chlorobenzenesulfonyl chloride.



Step 4: 2-(1'-(4-Chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid

[00446] Prepared according to the procedure described in Example 1a, Step 10, using the following starting material: 2-(1'-(4-chloro-benzenesulfonyl)-2,3-dihydrospiro[(2-oxo)-indole-3,4'-piperidine]-1-yl)-propionic acid methyl ester.

Example 2: CRTH2 Assays

Example 2a: DP2/CRTH2 binding assay

[00447] The ability of a compound to bind to the human DP₂ receptor is assessed via a radioligand binding assay using [³H]PGD₂. HEK293 cells stably expressing recombinant human DP₂ 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 [³H]PGD₂ and test compound in Assay Buffer (50 mM Hepes, 10 mM MnCl₂, 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 μ M PGD₂. IC₅₀s were determined using GraphPad prism analysis of drug titration curves. Compounds tested had an IC₅₀ of less than 100 micromolar in this assay.

Example 2b: GTP γ S Binding Assay

[00448] The ability of a compound to inhibit binding of GTP to DP₂ is assessed via a membrane GTP γ S 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 μ g per well) are incubated in 96-well plates with 0.05 nM [³⁵S]-GTP γ S, 80 nM PGD₂, 5 μ M GDP, and test compound in Assay Buffer (50 mM Hepes, pH 7.4, 100 mM NaCl, 5 mM MgCl₂ 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 PGD₂). IC₅₀s were determined using Graphpad prism analysis of drug titration curves.

Example 2c: Whole Blood Eosinophil Shape Change Assay

[00449] Blood is drawn from consenting human volunteers in EDTA vacutainer tubes and used within 1 hr of draw. A 98 μ l aliquot of blood is mixed with 2 μ l 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 μ l of 1 μ M PGD₂ 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 μ l of ice-cold 1:4 diluted Cytotfix (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 NH₄Cl, 10 mM KHCO₃, 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 Cytotfix (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 PGD₂ was calculated as the difference between the percentage of high forward scatter eosinophils in the presence and absence of PGD₂. IC₅₀s were determined using Graphpad Prism® analysis of drug titration curves.

Example 2d: DP₁ binding assay

[00450] The ability of a compound to bind to the human DP₁ receptor was evaluated via a radioligand membrane binding assay using the DP₁ selective synthetic ligand [³H]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 [³H]BWA868C and test compound in Assay Buffer (50 mM Hepes, 10 mM MnCl₂, 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% polyethylenimine 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. IC₅₀s were determined using GraphPad prism analysis of drug titration curves.

Example 3: In vivo assays

Mouse Allergic Rhinitis Model

[00451] 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 4: Guinea Pig IV-DKPGD₂-induced peripheral blood leukocyte influx

[00452] 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 190 µl 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.

Example 5: Clinical Trials in Humans

Study 1: Clinical Trial Evaluating Effect of Compound of Formula 1 on ex vivo PGD₂-induced blood eosinophil shape change

[00453] In this double-blind, randomized, placebo-controlled, single ascending dose study of Compound of Formula 1 in healthy volunteers the inhibition of ex vivo PGD₂-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 PGD₂ to determine baseline shape change as described above in example 2. At varying times after dosing blood is drawn for both pharmacokinetic analyses of drug concentration in blood, and also for PGD₂ 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 1 on Allergen-induced Nasal symptoms and inflammatory and allergic biomarkers

[00454] In this double-blind, randomized, placebo-controlled study of Compound of Formula 1 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 1 that results in complete DP₂ receptor block in an ex vivo PGD₂-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 1 assay

[00455] The plasma concentrations of compound of Formula 1 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).

Example 6: Pharmaceutical Compositions

Example 6a: Parenteral Composition

[00456] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula 1 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 6b: Oral Composition

[00457] To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula 1 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 6c: Sublingual (Hard Lozenge) Composition

[00458] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a compound of Formula 1 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 6d: Fast-Disintegrating Sublingual Tablet

[00459] A fast-disintegrating sublingual tablet is prepared by mixing 48.5% by weight of a compound of Formula 1, 44.5% by weight of microcrystalline cellulose (KG-802), 5% by weight of low-substituted hydroxypropyl cellulose (50 μ m), 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 1 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 $\text{\textcircled{C}}$, 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 6e: Inhalation Composition

[00460] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula 1 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 6f: Rectal Gel Composition

[00461] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound of Formula 1 is mixed with 2.5 g of methylcellulose (1500 mPa), 100 mg of methylparaben, 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 6g: Topical Gel Composition

[00462] To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula 1 is mixed with 1.75 g of hydroxypropyl cellulose, 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 topical administration.

Example 6h: Ophthalmic Solution Composition

[00463] To prepare a pharmaceutical ophthalmic solution composition, 100 mg of a compound of Formula 1 is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered 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.

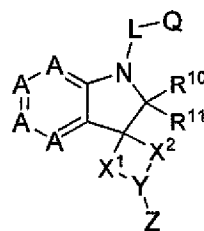
Example 6i: Nasal spray solution

[00464] To prepare a pharmaceutical nasal spray solution, 10 g of a compound of Formula 1 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 μ L of spray for each application.

[00465] 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.

We claim:

1. A compound of Formula 1:



Formula 1

wherein,

X^1 is $-(CR^A R^B)_m-$; m is 0, 1, 2 or 3;

X^2 is $-(CR^A R^B)_n-$; n is 0, 1, 2 or 3; and the sum of $m + n \geq 2$;

each R^A is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

each R^B is independently selected from H, OH, halogen and alkyl; or

R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$); or

R^A and R^B taken together form an unsubstituted or substituted 4-, 5-, 6-, 7- or 8-membered ring;

Y is N or $>CH(CH_2)_oNH-$, wherein o is 0, 1, 2 or 3;

Z is selected from alkyl, substituted alkyl, fluoroalkyl, substituted fluoroalkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, $-COR^3$, $-CO_2R^3$, $-SO_2R^3$, $-SOR^3$, $-CON(R^2)_2$, $-SO_2N(R^2)_2$, $-C(=NSO_2R^3)N(R^2)_2$, and $-C(=CH-CN)N(R^2)_2$;

each A is CR^1 or N; provided that at least two A groups are CR^1 ;

each R^1 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $-N(R^2)_2$, $-OR^2$, $-C(=O)R^3$, $-CO_2R^2$, $-CON(R^2)_2$, $-NR^2COR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-SO_2N(R^2)_2$, $-N(R^2)SO_2R^3$, $-N(R^2)SO_2N(R^2)_2$, $-NR^2CO_2R^3$, $-NR^2CON(R^2)_2$, $-OCO_2R^3$ and $-OCON(R^2)_2$; or

two R^1 groups on adjacent carbons taken together form an unsubstituted or substituted 5-, 6-, 7- or 8-membered ring;

each R^2 is independently selected from H, alkyl, substituted alkyl, fluoroalkyl, substituted fluoroalkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, and substituted -alkyl-heteroaryl; or

two R^2 groups on the same nitrogen atom are taken together with the nitrogen atom to form an unsubstituted or substituted 4-, 5-, 6-, 7- or 8-membered ring;

each R^3 is independently selected from alkyl, substituted alkyl, fluoroalkyl, substituted fluoroalkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted

heterocycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, and $-R^4-L^3-R^5$;

R^4 is an unsubstituted or substituted group selected from alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

L^3 is a bond, -O-, -S-, -NH-, -C(=O)-, -NHC(=O)O-, -NHC(=O)NH-, -OC(=O)O-, -OC(=O)NH-, -NHC(=O)-, -C(=O)NH-, -C(=O)O-, or -OC(=O)-;

R^5 is H or an unsubstituted or substituted group selected from alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

R^{10} is H or $-CH_3$;

R^{11} is H or $-CH_3$; or

R^{10} and R^{11} are taken together to form an oxo (=O);

-L- is $-(CR^C R^D)_p$ -, where p is 1 or 2;

R^C is independently selected from H, halogen, and alkyl;

R^D is independently selected from H, halogen, and alkyl; or

R^C and R^D taken together with the carbon atom to which they are attached to form a 3-, 4-, 5-, or 6-membered ring;

Q is selected from -OH, $-CO_2H$, $-CO_2R^3$, tetrazolyl, or a carboxylic acid bioisostere;

or a pharmaceutically acceptable solvate, pharmaceutically acceptable salt or pharmaceutically acceptable prodrug thereof.

2. The compound of claim 1, wherein:

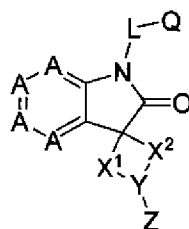
R^{10} is H; R^{11} is H; or

R^{10} and R^{11} taken together form an oxo (=O).

3. The compound of claim 2, wherein:

R^{10} and R^{11} taken together form an oxo (=O).

4. The compound of claim 3, wherein the compound of Formula 1 has the structure of Formula 6:



Formula 6.

5. The compound of any one of claims 1-4, wherein:

-L- is $-(CR^C R^D)_p$ -, where p is 1 or 2;

R^C is independently selected from H, F, and $-CH_3$;

R^D is independently selected from H, F, and $-CH_3$; or

R^C and R^D taken together with the carbon atom to which they are attached to form a cyclopropyl, cyclobutyl or cyclohexyl;

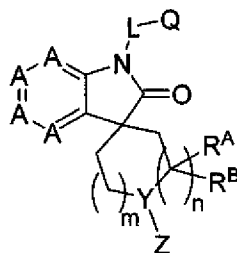
Q is selected from -OH, $-CO_2H$, and $-CO_2R^3$.

6. The compound of any one of claims 1-5, wherein:

-L- is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)-$, , or $-\text{CH}_2\text{CH}_2-$;
 Q is selected from $-\text{OH}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, and $-\text{CO}_2\text{CH}_2\text{CH}_3$.

7. The compound of any one of claims 1-6, wherein:
 -L- is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)-$, or $-\text{CH}_2\text{CH}_2-$; and
 Q is selected from $-\text{OH}$, and $-\text{CO}_2\text{H}$.
8. The compound of any one of claims 1-7, wherein:
 -L- is $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$.
9. The compound of any one of claims 1-8, wherein:
 -L- is $-\text{CH}_2-$.
10. The compound of any one of claims 1-9, wherein:
 Q is $-\text{CO}_2\text{H}$.
11. The compound of any one of claims 1-10, wherein:
 Y is N or $>\text{CHNH}-$.
12. The compound of any one of claims 1-11, wherein:
 Y is N.
13. The compound of any one of claims 1-12, wherein:
 X^1 is $-(\text{CR}^{\text{A}}\text{R}^{\text{B}})_m-$; m is 1, 2 or 3;
 X^2 is $-(\text{CR}^{\text{A}}\text{R}^{\text{B}})_n-$; n is 1, 2 or 3;
 each R^{A} is independently selected from H, halogen, and alkyl;
 each R^{B} is independently selected from H, halogen or alkyl; or
 R^{A} and R^{B} on the same carbon atom are taken together form an oxo ($=\text{O}$).
14. The compound of any one of claims 1-13, wherein:
 X^1 is $-(\text{CR}^{\text{A}}\text{R}^{\text{B}})_m-$; m is 1, 2 or 3;
 X^2 is $-(\text{CR}^{\text{A}}\text{R}^{\text{B}})_n-$; n is 1, 2 or 3;
 each R^{A} is independently selected from H, F, and $-\text{CH}_3$;
 each R^{B} is independently selected from H, F or $-\text{CH}_3$; or
 R^{A} and R^{B} on the same carbon atom are taken together form an oxo ($=\text{O}$).
15. The compound of any one of claims 1-14, wherein
 m is 1 or 2; n is 1, 2 or 3.
16. The compound of claim 15, wherein:
 both X^1 and X^2 are $-\text{CH}_2-$.
17. The compound of claim 15, wherein:
 m is 2; n is 2.
18. The compound of claim 17, wherein:
 both X^1 and X^2 groups are $-\text{CH}_2\text{CH}_2-$.
19. The compound of claim 15, wherein
 m is 1; n is 3.
20. The compound of claim 19, wherein:
 X^1 is $-\text{CH}_2-$ and X^2 is $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

21. The compound of 1 claim 15, wherein
m is 1; n is 2.
22. The compound of claim 21, wherein:
 X^1 is a $-\text{CH}_2-$ and X^2 is a $-\text{CH}_2\text{CH}_2-$.
23. The compound of claim 1, wherein the compound of Formula 1 has the structure of Formula 7:

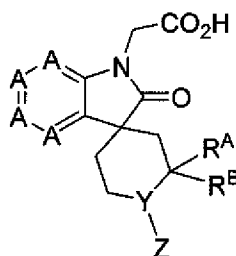


Formula 7

wherein:

- m is 0 or 1; n is 1 or 2;
each R^A is independently selected from H, halogen, and alkyl;
each R^B is independently selected from H, halogen, and alkyl; or
 R^A and R^B on the same carbon atom are taken together to form an oxo ($=\text{O}$);
Y is N or $>\text{CHNH}-$;
or a pharmaceutically acceptable solvate, pharmaceutically acceptable salt or pharmaceutically acceptable prodrug thereof.
24. The compound of claim 23, wherein:
each R^A is H; each R^B is H;
Y is $>\text{CHNH}-$.
25. The compound of claim 24, wherein:
m is 0; n is 2.
26. The compound of claim 24, wherein:
m is 1; n is 1.
27. The compound of claim 23, wherein:
each R^A is H;
each R^B is H; or
 R^A and R^B on the same carbon atom are taken together to form an oxo ($=\text{O}$);
Y is N.
28. The compound of claim 27, wherein:
m is 1; n is 1.
29. The compound of any one of claims 1-28, wherein:
each A is CR^1 .
30. The compound of any one of claims 1-28, wherein:
one A is N.
31. The compound of any one of claims 1-28, wherein:
two A are N.

32. The compound of any one of claims 1-31, wherein:
each R^1 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $-N(R^2)_2$, $-OR^2$, $-C(=O)R^3$, $-CO_2R^2$, $-CON(R^2)_2$, $-NR^2COR^3$, and $-S(=O)_2R^3$.
33. The compound of any one of claims 1-32, wherein:
each R^1 is independently selected from H, OH, halogen, $-C\equiv N$, alkyl, fluoroalkyl, $-N(R^2)_2$, $-OR^2$, $-C(=O)R^3$, $-CO_2R^2$, $-CON(R^2)_2$, and $-S(=O)_2R^3$.
34. The compound of any one of claims 1-33, wherein:
each R^1 is independently selected from H, OH, F, Cl, Br, $-C\equiv N$, $-CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$.
35. The compound of any one of claim 1-34, wherein:
each R^1 is H.
36. The compound of any one of claims 23-35, wherein:
 $-L-$ is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)-$, , or $-CH_2CH_2-$;
Q is selected from $-OH$, $-CO_2H$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$.
37. The compound of any one of claims 23-36, wherein:
 $-L-$ is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)-$, or $-CH_2CH_2-$; and
Q is selected from $-OH$, and $-CO_2H$.
38. The compound of any one of claims 23-37, wherein:
 $-L-$ is $-CH_2-$ or $-CH_2CH_2-$.
39. The compound of any one of claims 23-38, wherein:
 $-L-$ is $-CH_2-$.
40. The compound of any one of claims 23-39, wherein:
Q is $-CO_2H$.
41. The compound of claim 1, wherein the compound of Formula 1 has the structure of Formula 8:



Formula 8

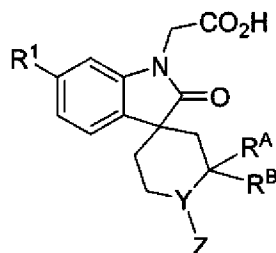
wherein:

- each R^A is independently selected from H, halogen, and alkyl;
each R^B is independently selected from H, halogen, and alkyl; or
 R^A and R^B on the same carbon atom are taken together to form an oxo ($=O$);
each A is CR^1 or N; provided that at least two A groups are CR^1 ;
Y is N.
42. The compound of claim 41, wherein:
one A is N.

43. The compound of claim 41, wherein:

two A are N.

44. The compound of claim 41, wherein the compound has the structure of Formula 9:



Formula 9

wherein:

each R^A is independently selected from H, halogen, and alkyl;

each R^B is independently selected from H, halogen, and alkyl; or

R^A and R^B on the same carbon atom are taken together to form an oxo (=O);

Y is N.

45. The compound of any one of claims 41-44, wherein:

R^A is H; R^B is H; or

R^A and R^B on the same carbon atom are taken together to form an oxo (=O);

Y is N.

46. The compound of claim 45, wherein:

R^A is H; R^B is H;

Y is N.

47. The compound of claim 45, wherein:

R^A and R^B on the same carbon atom are taken together to form an oxo (=O);

Y is N.

48. The compound of any one of claims 41-47, wherein:

R¹ is independently selected from H, OH, halogen, -C≡N, alkyl, fluoroalkyl, -N(R²)₂, -OR², -C(=O)R³, -CO₂R², -CON(R²)₂, and -S(=O)₂R³.

49. The compound of claim 48, wherein:

each R¹ is independently selected from H, OH, F, Cl, Br, -C≡N, -CH₃, -CF₃, -OCH₃, and -OCF₃.

50. The compound of any one of claims 1-49, wherein:

Z is selected from cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, -COR³, -CO₂R³, -SO₂R³, and -CON(R²)₂;

51. The compound of any one of claims 1-50, wherein:

Z is selected from aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, -COR³, and -SO₂R³.

52. The compound of any of claims 1-51, wherein

R³ is independently selected from aryl, substituted aryl, -alkyl-aryl, substituted -alkyl-aryl, heteroaryl, substituted heteroaryl, -alkyl-heteroaryl, substituted -alkyl-heteroaryl, and -R⁴-L³-R⁵;

- R^4 is a unsubstituted or substituted group selected from aryl, and heteroaryl;
 L^3 is a bond, -O-, -S-, and -NH-;
 R^5 is a unsubstituted or substituted group selected from aryl, and heteroaryl;
53. The compound of any of claims 1-52, wherein
 Z is selected from phenyl, substituted phenyl, naphthyl, substituted naphthyl, -CH₂-phenyl, substituted -CH₂-phenyl, monocyclic or bicyclic heteroaryl heteroaryl, substituted monocyclic or bicyclic heteroaryl heteroaryl, -CH₂-(monocyclic or bicyclic heteroaryl heteroaryl), substituted -CH₂-(monocyclic or bicyclic heteroaryl heteroaryl), -COR³, and -SO₂R³
 R^3 is independently selected from phenyl, substituted phenyl, naphthyl, substituted naphthyl, monocyclic or bicyclic heteroaryl, substituted monocyclic or bicyclic heteroaryl, and -R⁴-L³-R⁵;
 R^4 is an unsubstituted or substituted group selected from phenyl, naphthyl, and (monocyclic or bicyclic heteroaryl);
 L^3 is a bond, -O-, -S-, and -NH-;
 R^5 is an unsubstituted or substituted group selected from phenyl, naphthyl, and (monocyclic or bicyclic heteroaryl).
54. The compound of any of claim 1-53, wherein the compound is an antagonist of DP₂.
55. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-54, 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.
56. The pharmaceutical composition of claim 55, wherein the pharmaceutical composition is formulated for intravenous injection, oral administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration.
57. The pharmaceutical composition of claim 55, 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.
58. The pharmaceutical composition of any of claims 55-57 further comprising one or more additional therapeutically active agents selected from 5-lipoxygenase activating protein inhibitors, 5-lipoxygenase inhibitors, CYSLTR1 antagonists, thromboxane antagonists, DP₁ receptor antagonists, DP₁ 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.
59. A medicament for treating a PGD₂-dependent condition or disease in a patient comprising a therapeutically effective amount of a compound of any of claims 1-54.
60. Use of a compound of any of claims 1-54 in the manufacture of a medicament for the treatment of a PGD₂-dependent condition or disease.
61. A method for treating a PGD₂-dependent condition or disease in a patient comprising administering to the patient a therapeutically effective amount of a compound of any of claims 1-54.
62. The method of claim 61, wherein the PGD₂-dependent condition or disease is selected from asthma,

rhinitis, allergic conjunctivitis, 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, anaphylaxis, chronic cough and Churg Strauss syndrome.

63. The method of claim 61, wherein the PGD₂-dependent condition or disease is a respiratory disorder.
64. The method of claim 63, wherein the respiratory disorder is asthma, rhinitis or chronic obstructive pulmonary disease (COPD).
65. The method of any of claims 61-64, 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.
66. A compound of any of claims 1-54 for use in treating a disease or condition mediated by prostaglandin D₂.
67. The compound of claim 66, wherein the disease or condition is a respiratory disease or condition or an allergic disease or condition.
68. The compound of claim 66, wherein the disease or condition is asthma.