in numerous biological actions including, by way of example only, immunoglobulin E production, airway response, mucous secretion, and eosinophil recruitment.

SUMMARY

[0005] Described herein is [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1) including all pharmaceutically acceptable solvates (including hydrates), prodrugs, and metabolites thereof or a pharmaceutically acceptable salt of Compound 1 including (including hydrates), prodrugs, and metabolites thereof, and methods of uses thereof. Compound 1, as well as the pharmaceutically acceptable solvates thereof, are used in the manufacture of medicaments for the treatment or prevention of prostaglandin D_2 mediated and/or prostaglandin D_2 dependent diseases, disorders, or conditions. Also described are pharmacokinetic and pharmacodynamic properties of such formulations in mammals, including humans. Compound 1 is a DP2 antagonist.

[0006] Described herein are pharmaceutical compositions comprising Compound 1, or a pharmaceutically acceptable salt thereof (e.g. the sodium salt) as the active ingredient in the pharmaceutical composition; and at least one pharmaceutically acceptable inactive ingredient selected from among excipients, diluents, and carriers.

[0007] Disclosed is a pharmaceutically acceptable salt of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1), wherein the pharmaceutically acceptable salt is a calcium salt, potassium salt, sodium salt, magnesium salt, ammonium salt, L-arginine salt, L-lysine salt, or a N-methyl-D-glucamine salt. In some embodiments, the pharmaceutically acceptable salt is a sodium salt. In some embodiments, the pharmaceutically acceptable salt of Compound 1 is Compound 2.

[0007a] In one aspect, there is provided a pharmaceutically acceptable salt of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1), wherein the pharmaceutically acceptable salt is a calcium salt, potassium salt, sodium salt, ammonium salt, L-arginine salt, or a N-methyl-D-glucamine salt.

[0008] In some embodiments, Compound 2 is amorphous. In some embodiments, Compound 1 is amorphous.

[0009] In some embodiments, Compound 2 is hydrated.

[0010] In some embodiments, Compound 2 was obtained from a solution comprising heptane and ethanol. In some embodiments, Compound 2 comprises a detectable amount of heptane, ethanol or a combination of heptane and ethanol.

[0011] In some embodiments, a sample of Compound 1 comprises a detectable amount of palladium that is less than 20 ppm. In some embodiments, a sample of Compound 1 comprises a detectable amount of palladium that is less than 10 ppm. In some embodiments,

a sample of Compound 1 comprises a detectable amount of palladium that is less than 2 ppm. In some embodiments, a sample of Compound 1 does not include palladium. In some embodiments, a sample of Compound 2 comprises a detectable amount of palladium that is less than 20 ppm. In some embodiments, a sample of Compound 2 comprises a detectable amount of palladium that is less than 10 ppm. In some embodiments, a sample of Compound 2 comprises a detectable amount of palladium that is less than 2 ppm. In some embodiments, a sample of Compound 2 does not include palladium.

[0012] Described herein are pharmaceutical compositions comprising Compound 1 and/or pharmaceutically acceptable salts thereof. In some embodiments, the pharmaceutical compositions comprise Compound 1. In other embodiments, the pharmaceutical compositions comprise a pharmaceutically acceptable salt of Compound 1. In some embodiments, the pharmaceutically acceptable salt of Compound 1 is Compound 2. In some embodiments, the pharmaceutical compositions further comprise at least one pharmaceutically acceptable inactive ingredient selected from among excipients, diluents, and carriers.

[0013] Disclosed is a pharmaceutical composition comprising: a. Compound 1 or a pharmaceutically acceptable salt of Compound 1; and b. at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises Compound 1. In some embodiments, the pharmaceutical composition comprises Compound 2. Disclosed is a pharmaceutical composition comprising: a. a pharmaceutically acceptable salt of Compound 1; and b. at least one pharmaceutically acceptable excipient.

[0013a] In another aspect, there is provided a pharmaceutical composition comprising: a. [2′-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4′-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1) or a pharmaceutically acceptable salt of Compound 1; and b. at least one pharmaceutically acceptable excipient.

[0014] In some embodiments, Compound 1 is greater than 96% pure. In some embodiments, Compound 1 is greater than 97% pure. In some embodiments, Compound 1 is greater than 98% pure. In some embodiments, Compound 1 is greater than 99% pure. In some embodiments, Compound 2 is greater than 96% pure. In some embodiments, Compound 2 is greater than 97% pure. In some embodiments, Compound 2 is greater than 98% pure. In some embodiments, Compound 2 is greater than 99% pure.

[0015] In some embodiments the pharmaceutical compositions described herein comprise less than 10ppm of palladium. In some embodiments, the pharmaceutical compositions described herein comprise less than 5ppm of palladium. In some embodiments, the pharmaceutical compositions described herein comprise less than 2ppm of palladium. In some embodiments, the pharmaceutical compositions described herein comprise less than

1ppm of palladium. In some embodiments, the pharmaceutical compositions described herein do not include palladium.

[0016] In some embodiments, the pharmaceutical composition is in a form suitable for oral administration to a mammal. In some embodiments, the pharmaceutical composition is in the form of a pill, capsule, tablet, aqueous solution, aqueous suspension, non-aqueous solution, or non-aqueous suspension.

[0017] In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition is in the form of an immediate release tablet, an enteric coated tablet, or a sustained release tablet. In some embodiments, the pharmaceutical composition is in the form of a moisture barrier coated tablet.

[0018] In some embodiments, the pharmaceutical composition is in the form of a capsule.

[0019] In some embodiments, the pharmaceutical composition is in the form of an aqueous solution or aqueous suspension.

[0020] In some embodiments, a single dose of the pharmaceutical composition comprises about 0.3mg to about 600mg of Compound 1. In some embodiments, a single dose of the pharmaceutical composition comprises about 0.3mg to about 600mg of a pharmaceutically acceptable salt of Compound 1. In some embodiments, a single dose of the pharmaceutical composition comprises about 0.3mg to about 600mg of Compound 2.

[0021] In some embodiments, a single dose of the pharmaceutical composition when administered to healthy adult human subjects in the fasted state provides 80-100% inhibition of *ex vivo* PGD_2-stimulated eosinophil shape change in whole blood at C_{max}.

[0022] In some embodiments, a single dose of the pharmaceutical composition when administered to healthy adult human subjects in the fasted state provides about 25-100% inhibition of *ex vivo* PGD_2-stimulated eosinophil shape change in whole blood after about 24 hours following administration.

[0023] In some embodiments, a single dose of the pharmaceutical composition when administered to healthy adult human subjects in the fasted state provides about 30-70% inhibition of *ex vivo* PGD_2-stimulated eosinophil shape change in whole blood after about 24 hours following administration.

[0024] Disclosed is an oral solid dosage form pharmaceutical composition comprising: a) Compound 1 or a pharmaceutically acceptable salt of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1); and b) at least one inactive pharmaceutical ingredient. Disclosed is an oral solid

dosage form pharmaceutical composition comprising: a) Compound 1; and b) at least one inactive pharmaceutical ingredient. Disclosed is an oral solid dosage form pharmaceutical composition comprising: a) a pharmaceutically acceptable salt of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1), wherein the pharmaceutically acceptable salt is a calcium salt, potassium salt, sodium salt, magnesium salt, ammonium salt, L-arginine salt, L-lysine salt, or a N-methyl-D-glucamine salt; and b) at least one inactive pharmaceutical ingredient.

[0025] In some embodiments, the pharmaceutically acceptable salt of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1) is [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid, sodium salt (Compound 2).

[0026] In some embodiments, the oral solid dosage form is in the form of a tablet, pill or capsule.

[0027] In some embodiments, the pharmaceutical composition comprises about 1mg, about 3mg, about 10 mg, about 30 mg, about 60mg, about 100mg, about 200mg, about 250mg, about 300mg or about 600 mg of Compound 1 or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises about 1mg, about 3mg, about 10 mg, about 30 mg, about 60mg, about 100mg, about 200mg, about 250mg, about 300mg or about 600 mg of Compound 1. In some embodiments, the pharmaceutical composition comprises about 1mg, about 3mg, about 10 mg, about 30 mg, about 60mg, about 100mg, about 200mg, about 250mg, about 300mg or about 600 mg of Compound 2.

[0027a] In another aspect, there is provided an oral solid dosage form pharmaceutical composition comprising: a. about 1 mg, about 3 mg, about 10 mg, about 30 mg, or about 60 mg of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid, sodium salt; and b. at least one pharmaceutically acceptable excipient.

[0028] In some embodiments, the oral solid dosage form is in the form of a tablet. In some embodiments, the oral solid dosage form is in the form of an immediate release tablet, an enteric coated tablet, or a sustained release tablet. In some embodiments, the oral solid dosage form is in the form of an immediate release tablet. In some embodiments, the oral solid dosage form is in the form of a moisture barrier coated tablet.

[0029] In some embodiments, the oral solid dosage form pharmaceutical composition comprises from about 10% by weight to about 20% by weight of Compound 1 or a pharmaceutically acceptable salt thereof. In some embodiments, the oral solid dosage form pharmaceutical composition comprises from about 10% by weight to about 20% by weight of Compound 1. In some embodiments, the oral solid dosage form pharmaceutical composition comprises from about 10% by weight to about 20% by weight of Compound 2.

[0030] In some embodiments, the oral solid dosage form pharmaceutical composition is in the form of a capsule.

[0031] In some embodiments, the capsule is in the form of a hard gelatine capsule or hypromellose (HPMC) capsule. In some embodiments, the capsule comprises at least one excipient in addition to the hard gelatine capsule or hypromellose (HPMC) capsule.

[0032] Disclosed is a pharmaceutical composition that provides at least one metabolite of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1) after administration to a mammal. In some embodiments, the at least one metabolite is selected from among: 2-(2'-((ethylamino)methyl)-6-methoxy-4'-(trifluoromethyl)biphenyl-3-yl)acetic acid (M1); the acyl gluconuride of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (M2); [2'-(1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (M3); [2'-(3-benzyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (M6); [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-hydroxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid (M8); or combinations thereof. In some embodiments, the least one metabolite is the acyl gluconuride of [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid. In some embodiments, the pharmaceutical composition is a pharmaceutical composition as described herein.

[0033] Also provided is a method of treating or preventing a respiratory disease or condition, an inflammatory disease or condition or an allergic disease or condition, or combinations thereof, in a mammal comprising administering to the mammal an oral pharmaceutical composition as described herein.

[0034] In some embodiments, the respiratory disease or condition, inflammatory disease or condition or allergic disease or condition is asthma, adult respiratory distress syndrome, isocapnic hyperventilation, rhinitis, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, pulmonary hypertension, cystic fibrosis, an allergic ocular disease or condition, an inflammatory ocular disease or condition, an allergic skin disease or condition, or an inflammatory skin disease or condition.

[0035] In some embodiments, the respiratory disease or condition, inflammatory disease or condition or allergic disease or condition is asthma, rhinitis, dermatitis, ocular inflammation, or conjunctivitis.

[0036] Also provided is a method of treating or preventing asthma in a mammal comprising administering to the mammal an oral pharmaceutical composition as described herein. In

[0046] Also provided is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture of a medicament for the treatment or prevention of rhinitis in a human. In some embodiments, the rhinitis is allergic rhinitis.

[0047] Also provided is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease in a human

[0048] Also provided is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture of a medicament for the treatment of an ocular disease or condition in a human. In some embodiments, the ocular disease or condition is conjunctivitis.

[0049] Also provided is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture for the treatment of a skin disease or condition in a human. In some embodiments, the skin disease or condition is dermatitis.

[0050] Described in certain embodiments herein is a pharmaceutical composition comprising an active ingredient that antagonizes DP_2 receptors in a mammal and does not substantially inhibit at least one Cytochrome P450 enzyme selected from CYP 3A4, CYP 1A2, CYP 2A6, CYP 2B6, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 2E1 at doses up to 40μM or 50μM. In some embodiments, the pharmaceutical composition does not substantially induce Cytochrome P450 CYP 3A4, CYP 2C9, CYP 1A2, CYP 2C19, or CYP 2D6 at doses up to 40μM, or up to 50μM. In certain embodiments, the active ingredient is Compound 1, or a pharmaceutically acceptable salt thereof. In a specific embodiment, the active ingredient is Compound 1. In another specific embodiment, the active ingredient is Compound 2.

[0051] Described in certain embodiments herein is an oral solid dosage form pharmaceutical composition comprising: (a) Compound 2; and (b) optionally at least one inactive pharmaceutical ingredient. In specific embodiments, the oral solid dosage form pharmaceutical composition is in the form of a capsule. In more specific embodiments, the capsule is a hard gelatine capsule or hypromellose (HPMC) capsule. In various embodiments, the capsules described herein comprise at least one excipient or no excipients.

[0052] Disclosed are methods for treating PGD_2-dependent or PGD_2-mediated diseases or conditions in a mammal, comprising administering to the mammal at least once

an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2).

[0053] Disclosed are methods for treating mammals with an inflammatory and/or allergic condition comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2).

[0054] Disclosed is an oral pharmaceutical composition as described herein comprising Compound 1 or a pharmaceutically acceptable salt thereof as the active ingredient for use in the treatment or prevention of an inflammatory and/or allergic condition in a mammal. In some embodiments, the active ingredient is Compound 1. In other embodiments, the active ingredient is Compound 2.

[0055] Disclosed are methods for treating inflammation in a mammal comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2).

[0056] Disclosed are methods for treating respiratory diseases in a mammal comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2). 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, allergic rhinitis, vasomotor rhinitis, vascular responses, endotoxin shock, fibrogenesis, pulmonary fibrosis, allergic diseases, chronic inflammation, and adult respiratory distress syndrome. In a specific embodiment of this disclosure, the respiratory disease is asthma.

[0057] Disclosed are methods for treating or preventing rhinitis in a mammal comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2). Rhinitis includes: allergic rhinitis, non-allergic rhinitis, chronic rhinitis, allergen-induced rhinitis, aspirin-sensitive rhinitis, child-onset rhinitis, adult-onset rhinitis, occupational rhinitis, steroid-resistant rhinitis, seasonal rhinitis, perennial rhinitis, rhinosinusitis, and rhinopolyposis.

[0058] Disclosed are methods for treating chronic obstructive pulmonary disease in a mammal comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2). 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.

[0059] Disclosed are methods for preventing increased mucosal secretion and/or edema in a mammal comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2).

[0060] Disclosed are methods for preventing eosinophil and/or basophil and/or dendritic cell and/or neutrophil and/or monocyte recruitment in a mammal comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2).

[0061] Disclosed are methods for preventing ocular disease (for example, ocular inflammation, allergic conjunctivitis, vernal keratoconjunctivitis and papillary conjunctivitis) in a mammal comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2).

[0062] Disclosed are methods for preventing or treating acute or chronic disorders involving recruitment or activation of eosinophils in a mammal comprising administering to the mammal at least once an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2).

[0063] In any of the aforementioned disclosures, the mammal is a human. In any of the aforementioned disclosures, the mammal is a human, including embodiments wherein (a) 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, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, allergic rhinitis, non-allergic 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, rhinopolyposis, and chronic obstructive pulmonary disease.

[0064] In any of the aforementioned disclosures are further embodiments comprising single administrations of the effective amount of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2), including further embodiments in which Compound 1, or a

pharmaceutically acceptable salt thereof (e.g. Compound 2) is (i) administered once-a-day; (ii) is administered twice-a-day; or (iii) is administered multiple times over the span of one day.

[0065] In any of the aforementioned disclosures are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the time between multiple administrations is every 8 hours; (iv) the time between multiple administrations is every 12 hours.

[0066] In some embodiments, the pharmaceutical composition is administered daily to the mammal.

[0067] In some embodiments, the pharmaceutical composition is administered in treatment cycles comprising: (a) a first period during which Compound 2 is administered daily to the mammal; and (b) a second period of at least seven days during which the Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2) is administered to the mammal in a reduced amount as compared to (a).

[0068] In some embodiments, the methods of treatment or prevention disclosed herein comprise a drug holiday, wherein the administration of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2) is temporarily suspended or the dose being administered is temporarily reduced; at the end of the drug holiday dosing is resumed. In some embodiments, the length of the drug holiday varies from 2 days to 1 year.

[0069] In one disclosure, Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2) is used in the manufacture of medicaments for the treatment of a PGD_2-dependent or PGD_2-mediated respiratory disease or condition in a mammal whose symptoms of the respiratory disease or condition are not adequately controlled by corticosteroids. In a specific embodiment, the respiratory disease or condition is asthma.

[0070] Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for treating any of the diseases or conditions disclosed herein.

[0071] A pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for use in any of the uses and methods disclosed herein.

[0072] Use of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2) in the manufacture of a medicament for treating or preventing any of the diseases disclosed herein in a mammal. In one disclosure, Compound 1 or a pharmaceutically acceptable

salt thereof (e.g. Compound 2) is used in the treatment of a respiratory disease or condition in a mammal.

[0073] Disclosed is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture of a medicament for the treatment of asthma in a human. Disclosed is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture of a medicament for the treatment or prevention of allergic rhinitis in a human. Disclosed is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease in a human. Disclosed is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture of a medicament for the treatment of ocular disease in a human. Disclosed is the use of Compound 1 or a pharmaceutically acceptable salt thereof (e.g. Compound 2) for the manufacture of a medicament for the treatment of skin disease in a human.

[0074] In one disclosure, described herein is a method of increasing the bioavailability of an orally administered dose of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2) in healthy human patients comprising orally administering to a mammal: (1) a dose of Compound 1, or a pharmaceutically acceptable salt thereof (e.g. Compound 2); and (2) an inhibitor of a UDP-glucuronosyltransferase enzyme normally present in the mammal.

[0075] In any of the aforementioned disclosures 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; and/or (e) measuring inhibition of PGD_2-induced eosinophil shape change (ESC) in a mammal; and/or (f) measuring Th2 cytokine levels in a mammal.

[0076] Also described herein are process for the preparation of Compound 1 and pharmaceutically acceptable salts thereof. In one disclosure, the pharmaceutically acceptable salt of Compound 1 is Compound 2.

[0077] In one disclosure, described is a process for the preparation of amorphous Compound 2 comprising the steps of:

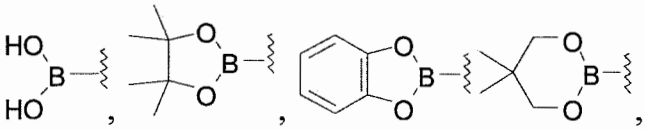
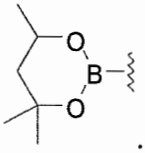
(1) concentrating Compound 2 from ethanol to obtain solids of Compound 2;

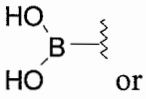
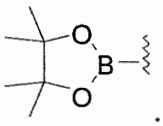
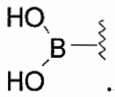
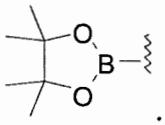
(2) adding heptane to Compound 2 of step (1) to form a filterable slurry; and

water, or combinations thereof. In some embodiments, the suitable solvent is tetrahydrofuran, dioxane, water, or combinations thereof.

[0085] In some embodiments, R is C_1-C_4alkyl. In some embodiments, R is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, or $-C(CH_3)_3$. In some embodiments, R is $-CH_3$ or $-CH_2CH_3$.

[0086] In some embodiments, X is halide or triflate. In some embodiments, X is Cl, Br, I, or $-OSO_2CF_3$.

[0087] In some embodiments, R^b is , or .

[0088] In some embodiments, R^b is  or . In some embodiments, R^b is . In some embodiments, R^b is .

[0089] The disclosed processes provide for the synthesis of Compound 1 and pharmaceutically acceptable salts thereof (e.g. Compound 2). The processes disclosed herein are particularly applicable to large scale chemical production of Compound 1 and pharmaceutically acceptable salts thereof. Also described herein are processes for the preparation of Compound 2, in good yield that have good solubility and good oral bioavailability.

[0090] Other objects, features and advantages of the 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 disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE FIGURES

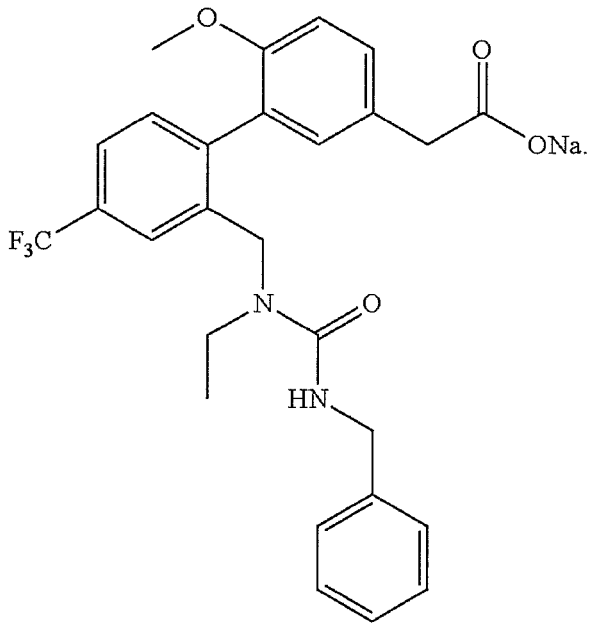
[0091] FIGURE 1 illustrates the *ex vivo* PGD_2-stimulated eosinophil shape change in whole blood after single dose administration of oral solutions of Compound 2 to humans.

What is claimed is:

1. A pharmaceutically acceptable salt of [2′-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4′-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1), wherein the pharmaceutically acceptable salt is a calcium salt, potassium salt, sodium salt, ammonium salt, L-arginine salt, or a N-methyl-D-glucamine salt.

2. The pharmaceutically acceptable salt of claim 1, wherein the pharmaceutically acceptable salt has the structure of Compound 2:

(Compound 2)



3. The pharmaceutically acceptable salt of claim 2, wherein Compound 2 is amorphous.

4. The pharmaceutically acceptable salt of claim 2, wherein the Compound 2 was obtained from a solution containing heptane and ethanol.

5. A pharmaceutical composition comprising:

a. [2′-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4′-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1) or a pharmaceutically acceptable salt of Compound 1; and

b. at least one pharmaceutically acceptable excipient.

6. The pharmaceutical composition of claim 5, wherein the pharmaceutical composition comprises [2′-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4′-trifluoromethyl-biphenyl-3-yl]-acetic acid, sodium salt (Compound 2).

7. The pharmaceutical composition of claim 6, wherein Compound 2 is greater than 96% pure.

8. The pharmaceutical composition of claim 6, wherein the pharmaceutical composition is in a form suitable for oral administration to a mammal.

9. The pharmaceutical composition of claim 8, wherein the pharmaceutical composition is in the form of a pill, capsule, tablet, aqueous solution, aqueous suspension, non-aqueous solution, or non-aqueous suspension.

10. The pharmaceutical composition of claim 9, wherein a single dose of the pharmaceutical composition comprises about 0.3 mg to about 600 mg of Compound 2.

11. The pharmaceutical composition of claim 9, wherein a single dose of the pharmaceutical composition when administered to a healthy adult human subject in the fasted state provides:

80-100% inhibition of ex vivo PGD_2-stimulated eosinophil shape change in whole blood at C_{max};

about 25-100% inhibition of ex vivo PGD_2-stimulated eosinophil shape change in whole blood after about 24 hours following administration; or

about 30-70% inhibition of ex vivo PGD_2-stimulated eosinophil shape change in whole blood after about 24 hours following administration.

12. The pharmaceutical composition according to claim 9, wherein the pharmaceutical composition is in the form of a tablet, pill, or capsule and the pharmaceutical composition comprises about 1 mg, about 3 mg, about 10 mg, about 30 mg, about 60 mg, about 100 mg, about 200 mg, about 250 mg, about 300 mg or about 600 mg of Compound 2.

13. The pharmaceutical composition of claim 5, wherein the pharmaceutical composition provides at least one metabolite of [2′-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4′-trifluoromethyl-biphenyl-3-yl]-acetic acid (Compound 1) after administration to a mammal.

14. An oral solid dosage form pharmaceutical composition comprising:

a. about 1 mg, about 3 mg, about 10 mg, about 30 mg, or about 60 mg of [2′-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4′-trifluoromethyl-biphenyl-3-yl]-acetic acid, sodium salt; and

b. at least one pharmaceutically acceptable excipient.

15. The pharmaceutical composition according to claim 14, wherein [2′-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4′-trifluoromethyl-biphenyl-3-yl]-acetic acid, sodium salt is greater than 96% pure.

16. The pharmaceutical composition according to claim 14, wherein the pharmaceutical composition is in the form of a pill, capsule, or tablet.

17. The pharmaceutical composition of claim 16, wherein a single dose of the pharmaceutical composition when administered to healthy adult human subjects in the fasted state provides:

80-100% inhibition of ex vivo PGD_2-stimulated eosinophil shape change in whole blood at C_{max};

about 25-100% inhibition of ex vivo PGD_2-stimulated eosinophil shape change in whole blood after about 24 hours following administration; or

about 30-70% inhibition of ex vivo PGD_2-stimulated eosinophil shape change in whole blood after about 24 hours following administration.

18. The pharmaceutical composition of claim 14, wherein the pharmaceutical composition provides at least one metabolite of [2′-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4′-trifluoromethyl-biphenyl-3-yl]-acetic acid after administration to a mammal.