DERMAL FORMULATIONS OF DP_2 RECEPTOR ANTAGONISTS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/230,585 entitled "DERMAL FORMULATIONS OF DP_2 RECEPTOR ANTAGONISTS" filed on July 31, 2009, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are pharmaceutical compositions for topical administration to the skin of a mammal that include at least one DP_2 receptor antagonist compound and methods of use thereof in the treatment or prevention of dermal diseases or conditions.

BACKGROUND OF THE INVENTION

[0003] Dermal diseases or conditions include, but are not limited to, dermatitis, psoriasis, eczema, urticaria, rosacea, burns, scarring and cutaneous mucinoses. In certain instances, dermal conditions result from an over-production of prostaglandin D_2 and/or cytokines.

SUMMARY OF THE INVENTION

[0004] Prostaglandins have a diverse range of activities and have a well recognized role in inflammation. Prostaglandin D_2 (PGD_2) is produced by mast cells, macrophages and Th2 lymphocytes in response to local tissue damage and/or inflammation and/or infection related to dermal diseases or conditions. PGD_2 binds to a number of receptors, which include the thromboxane-type prostanoid (TP) receptor, PGD_2 receptor (DP, also known as DP_1) and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2; also known as DP_2). In Th2 lymphocytes, IL-4, IL-5 and IL-13 cytokine production is stimulated. These cytokines have been implicated in numerous biological actions including, by way of example only, inflammation, and/or eosinophil recruitment. Topical administration of a DP_2 receptor antagonist compound is used to treat or prevent dermal diseases or conditions. Topical dermal formulations of DP_2 receptor antagonists, administered to any dermal site of a mammal, are used to prevent, ameliorate or treat DP_2-dependent or DP_2-mediated diseases or conditions.

[0005] Described herein, in certain embodiments, are topical formulations for treating a dermatological disease or condition (i.e., an abnormal state of the epidermis, dermis, and/or subcutaneous tissues). Described herein, in certain embodiments, are topical formulations

for treating or preventing dermal immune diseases or conditions (e.g. autoimmune diseases or conditions (e.g., eczema, psoriasis)); dermal proliferative diseases or conditions (e.g., melanoma); contact with an allergen, and/or an irritant; scarring; a burn (e.g., first degree, second degree, third degree, or fourth degree); cutaneous mucinoses; dermal inflammatory diseases or conditions or combinations thereof. In some embodiments, a topical formulation disclosed herein comprises a therapeutically-effective amount of a DP_2 receptor antagonist compound. In some embodiments, a topical formulation disclosed herein is administered before or after contact with an allergen and/or irritant. In some embodiments, a topical formulation disclosed herein is administered before or after a physical trauma (e.g., surgery).

[0006] Provided herein, in some embodiments, is a topical formulation comprising a DP_2 receptor antagonist in an amount effective for the treatment of a dermal disease or condition, and at least one pharmaceutically acceptable excipient to provide an ointment, cream, lotion, paste, gel, stick, a film, a patch or wound dressing, wherein the topical formulation is suitable for administration to the skin of a mammal.

[0007] Provided herein, in some embodiments, is a topical formulation comprising a DP_2 receptor antagonist in an amount effective for antagonizing dermal DP_2 receptors, and at least one suitable pharmaceutically acceptable excipient to provide an ointment, cream, lotion, paste, gel, stick, a film, a patch or wound dressing.

[0008] In some embodiments, the dermal disease or condition is scarring, dermatitis, a proliferative disease or condition, a mast cell diseases or conditions, a burn, contact with an allergen and/or an irritant, or an inflammatory disease or condition. In some embodiments, the dermal disease or condition is atopic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, contact dermatitis, eczema, urticaria, rosacea, hypertrophic scarring, keloid scar formation, scleroderma, Folliculitis keloidalis nuchae, Kawasaki Disease, Sjogren-Larsso Syndrome, Grover's disease, a first degree burn, a second degree burn, a third degree burn, a fourth degree burn, cutaneous mucinosis, solar keratosis, squamous cell carcinoma or melanoma.

[0009] In some embodiments, the dermal disease or condition is dermatitis. In some embodiments, the dermal disease or condition is eczema. In some embodiments, the dermal disease or condition is uticaria. In some embodiments, the dermal disease or condition is psoriasis.

[0010] In some embodiments, the dermal disease or condition results from surgery. In some embodiments, the dermal disease or condition is cutaneous mucinosis.

[0011] In some embodiments, the DP_2 receptor antagonist is a compound of Formula (I), Formula (II), Formula (III), or Formula (IV), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, metabolite, or prodrug thereof. In some embodiments, the DP_2 receptor antagonist is a compound of Formula (I), or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, metabolite, or prodrug thereof. In some embodiments, the DP_2 receptor antagonist is a DP_2 receptor antagonist disclosed herein.

[0012] In some embodiments, a topical formulation described herein further comprises a second therapeutic agent. In some embodiments, the second therapeutic agent is an antibiotic, anti-fungal agent, steroid anti-inflammatory agent, non-steroidal anti-inflammatory agent, antihistamine, antiviral agent, mast cell stabilizer, cyclosporine, or a leukotriene modulator. In some embodiments, the second therapeutic agent is a leukotriene modulator selected from 5-lipoxygenase (5-LO) inhibitors, 5-lipoxygenase activating protein (FLAP) inhibitors, and leukotriene receptor antagonists.

[0013] Also provided herein is a method of treating a prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition, comprising administering to a mammal in need thereof a therapeutically-effective amount of a topical formulation described above.

[0014] Also provided herein is a method of antagonizing dermal DP_2 receptors in a mammal in need thereof, comprising administering to the mammal a therapeutically-effective amount of a topical formulation described above.

[0015] In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is scarring, dermatitis, a proliferative disease or condition, a mast cell disease or condition, a burn, contact with an allergen and/or an irritant, or an inflammatory disease or condition.

[0016] In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is atopic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, contact dermatitis, eczema, urticaria, rosacea, hypertrophic scarring, keloid scar formation, scleroderma, Folliculitis keloidalis nuchae, Kawasaki Disease, Sjogren-Larsso Syndrome, Grover's disease, a first degree burn, a second degree burn, a third degree burn, a fourth degree burn, cutaneous mucinosis, solar keratosis, squamous cell carcinoma or melanoma.

[0017] In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is dermatitis. In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is atopic dermatitis or allergic dermatitis. In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is eczema. In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is uticaria. In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is psoriasis. In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition results from surgery. In some embodiments of the methods, the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is cutaneous mucinosis.

[0018] Also provided herein is a method of increasing the dermal concentration of a DP_2 receptor antagonist compound in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of a topical formulation described herein. In some embodiments of the method, the mammal has at least one symptom of a prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition. In some embodiments of the method, the dermatological disease or condition results from surgery. In some embodiments of the method, the topical formulation is administered before surgery. In some embodiments of the method, the topical formulation is administered after surgery. In some embodiments of the method, the topical formulation is administered before contact with an irritant and/or allergen. In some embodiments of the method, the topical formulation is administered after contact with an irritant and/or allergen.

[0019] In one aspect, provided is a method for the treatment or prevention of itching in a mammal comprising administering to the mammal a therapeutically-effective amount of a topical formulation described herein comprising a DP2 receptor antagonist. In some embodiments, the itching is a symptom of any of the diseases or conditions described herein. In some embodiments, the itching is a symptom of any of the PGD_2-dependent or PGD_2-mediated diseases or conditions described herein. In some embodiments, the itching is caused by contact with an irritant, allergen, or combination thereof. In some embodiments, the itching is a symptom of dermatitis, eczema, urticaria, or psoriasis. In some embodiments, the itching is a symptom of atopic dermatitis or allergic dermatitis.

[0020] In one aspect, provided herein is a method for the treatment or prevention of a rash in a mammal comprising administering to the mammal a therapeutically-effective amount of a topical formulation described herein comprising a DP2 receptor antagonist. In some embodiments, the rash is a symptom of any of the diseases or conditions described herein. In some embodiments, the rash is a symptom of any of the PGD_2-dependent or PGD_2-mediated diseases or conditions described herein. In some embodiments, the rash is caused by contact with an irritant, allergen, or combination thereof. In some embodiments, the rash is a symptom of dermatitis, eczema, urticaria, or psoriasis. In some embodiments, the rash is a symptom of atopic dermatitis or allergic dermatitis.

[0021] In one aspect, provided herein is a method for the treatment or prevention of skin inflammation in a mammal comprising administering to the mammal a therapeutically-effective amount of a topical formulation described herein comprising a DP2 receptor antagonist. In some embodiments, the skin inflammation is a symptom of any of the diseases or conditions described herein. In some embodiments, the skin inflammation is a symptom of any of the PGD_2-dependent or PGD_2-mediated diseases or conditions described herein. In some embodiments, the skin inflammation is caused by contact with an irritant, allergen, or combination thereof. In some embodiments, the skin inflammation is a symptom of dermatitis, eczema, urticaria, or psoriasis. In some embodiments, the skin inflammation is a symptom of atopic dermatitis or allergic dermatitis.

[0022] In one aspect, provided herein is a method for the treatment or prevention of blisters, redness, swelling, scabbing, scaling, or combinations thereof in a mammal comprising administering to the mammal a therapeutically-effective amount of a topical formulation described herein comprising a DP2 receptor antagonist. In some embodiments, the blisters, redness, swelling, scabbing, scaling, or combinations thereof is a symptom of any of the diseases or conditions described herein. In some embodiments, the blisters, redness, swelling, scabbing, scaling, or combinations thereof is a symptom of any of the PGD_2-dependent or PGD_2-mediated diseases or conditions described herein. In some embodiments, the blisters, redness, swelling, scabbing, scaling, or combinations thereof is caused by contact with an irritant, allergen, or combination thereof. In some embodiments, the blisters, redness, swelling, scabbing, scaling, or combinations thereof is a symptom of dermatitis, eczema, urticaria, or psoriasis. In some embodiments, the blisters, redness, swelling, scabbing, scaling, or combinations thereof is a symptom of atopic dermatitis or allergic dermatitis.

[0023] In one aspect is the use of a DP_2 receptor antagonist compound in the manufacture of a topical formulation for application to the skin. In one aspect is the use of a combination of a DP_2 receptor antagonist compound and a second therapeutic agent (e.g. a FLAP inhibitor compound) in the manufacture of a topical formulation for application to the skin.

[0024] In one aspect is the use of a DP_2 receptor antagonist compound in the treatment or prevention of a dermal disease or condition in a mammal. In one aspect is the use of a DP_2 receptor antagonist compound in the treatment or prevention of a dermal disease or condition in a mammal, wherein the DP_2 receptor antagonist compound is in a form suitable for topical administration to the skin of a mammal.

[0025] In one aspect is the use of DP_2 receptor antagonist compound in the manufacture of a topical formulation for the treatment of a dermal disease or condition. In one aspect is the use of a DP_2 receptor antagonist compound and a second therapeutic agent (e.g., a FLAP inhibitor compound) in the manufacture of a topical formulation for the treatment of a dermal disease or condition.

[0026] 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

BRIEF DESCRIPTION OF THE FIGURES

[0027] **Figure 1** illustrates the effect of DP_2 receptor antagonism, alone or in combination with FLAP inhibition, on the number of total cells, neutrophils and lymhocytes present in BALF in a mouse subchronic smoke model

[0028] **Figure 2** illustrates the effect of a DP_2 receptor antagonist, alone or in combination with a FLAP inhibitor, on the presence of mucin in BALF

DETAILED DESCRIPTION OF THE INVENTION

[0029] Prostaglandin D_2 (PGD_2) is an acidic lipid derived from the metabolism of arachidonic acid by cyclooxygenases and PGD_2 synthases. PGD_2 is produced by mast cells, macrophages and Th2 lymphocytes in response to local tissue damage as well as in response allergic inflammation and/or infection. PGD_2 exerts a variety of biologic actions in the skin; these include scarring, mucinosis and inflammatory effects.

[0030] Activation of DP_2 is associated with chemotaxis and activation of Th2 lymphocytes, eosinophils and basophils. PGD_2 binds to DP_2 receptors and mediates many of its effects through a G_i-dependent elevation of intracellular calcium levels and reduction of cyclic AMP. In Th2 lymphocytes, IL-4, IL-5 and IL-13 cytokine production are also stimulated by DP_2 receptor activation. These cytokines have been implicated in numerous biological actions including, by way of example only, immunoglobulin E production, mucous secretion and/or accumulation, and eosinophil recruitment.

[0031] DP_2 receptors provide a target for the treatment of PGD_2-dependent or PGD_2-mediated dermal diseases, disorders or conditions, including, by way of example, immune diseases or conditions, (e.g. an autoimmune diseases or conditions (e.g., eczema, psoriasis)); proliferative conditions (e.g., melanoma); contact with an allergen and/or an irritant; a mast cell diseases or conditions; scarring (e.g., scarring after a trauma (e.g., surgery)); burns; cutaneous mucinosis; inflammatory diseases or conditions affecting the skin, or combinations thereof.

[0032] Disclosed herein is the use of DP_2 receptor antagonist compounds in the manufacture of medicaments suitable for topical administration to the skin of a mammal for use in the treatment or prevention of prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal diseases or conditions.

[0033] Described herein are pharmaceutical compositions suitable for topical administration, methods for treating, methods for formulating topical formulations, methods for producing, methods for manufacturing, and treatment strategies using DP_2 receptor antagonist compounds.

[0034] Described herein, in certain embodiments, are topical formulations that include a DP_2 receptor antagonist compound for treating or preventing a dermatological disease or condition. In one aspect, topical administration of a DP_2 receptor antagonist compound to a mammal minimizes systemic absorption of the DP_2 receptor antagonist compound. In one aspect, topical administration of a DP_2 receptor antagonist compound allows for local treatment of dermal conditions. In one aspect, local treatment of dermal conditions with a DP_2 receptor antagonist compound reduces possible side effects associated with systemic administration of a DP_2 receptor antagonist compound.

[0035] In one aspect, the dermatological condition is a result of the over-production of PGD_2 and/or cytokines. In one aspect, the dermatological disease or condition includes, but is not limited to, dermatological immune diseases or conditions, dermatological

proliferative conditions, a dermatological disease or condition resulting from contact with an allergen and/or an irritant, a dermatological mast cell diseases or conditions, a burn, a cutaneous mucinosis, an inflammatory disease or condition affecting the skin, or combinations thereof. Allergens and/or irritants include, but are not limited to, uruishol, alcohol, xylene, turpentine, esters, acetone, ketones. Dermatological immune disorders include, but are not limited to, eczema, psoriasis. Dermatological proliferative disorders include, but are not limited to, melanoma. Dermatological mast cell disorders include but are not limited to, fibroblast disorders including scarring, such as the formation of keloid scars, hypertrophic scars, and/or acne scars. Dermatological burn disorders include, but are not limited to, a first degree burn, a second degree burn, a third degree burn, or a fourth degree burn.

[0036] Described herein, in certain embodiments, are topical formulations that include a DP_2 receptor antagonist compound for treating a chronic blistering disorder, psoriasis, dermatitis (e.g., contact or atopic), eczema, urticaria, rosacea, scarring (i.e. the formation of a scar (e.g., a keloid scar or a hypertrophic scar)), a first degree burn, a second degree burn, a third degree burn, a fourth degree burn, cutaneous mucinosis and/or melanoma. In some embodiments, a topical formulation disclosed herein comprises a therapeutically-effective amount of a DP_2 receptor antagonist. In some embodiments, a topical formulation disclosed herein is administered before or after contact with an allergen and/or irritant. In some embodiments, a topical formulation disclosed herein is administered before or after a physical trauma (e.g., surgery). In one aspect, a topical formulation disclosed herein that includes a DP_2 receptor antagonist compound is topically administered to treat and prevent scar formation following surgery. It is understood that the topical formulation is applied to the site of injury.

[0037] In certain instances, prostaglandin D_2 and/or cytokines are involved in scarring and/or the migration of eosinophils. In one aspect, inhibiting the activity of DP_2 receptors inhibits the activity of and/or migration of eosinophils, and/or treats scarring. In certain instances, inhibiting the activity of DP_2 receptors reduces or inhibits the deposition of mucin in the interstitial spaces of the dermis.

[0038] In one aspect, PGD_2 is involved in the pathogenesis of dermatological diseases or conditions described herein. In some instances, inhibition of binding of PGD_2 to DP_2 receptors will result in a decrease in the production of cytokines. In some instances, a

reduction of production of cytokines results in a decrease of inflammation and/or fibrosis and/or mucinosis.

Dermatological Diseases or Conditions

[0039] Described herein, in certain embodiments, are topical formulations for treating a dermatological disease or condition (e.g., dermatoses). As used herein, a dermatological disease or condition includes any abnormal state of the epidermis, dermis, and/or subcutaneous tissues. In certain instances, a dermatological disease or condition is caused by an immune disease or condition, (e.g. an autoimmune disease or condition); a proliferative disease or condition; contact with an allergen and/or an irritant; a mast cell disease or condition, scarring, a burn, cutaneous mucinosis, inflammatory disease or condition, or combinations thereof. Dermatological diseases or conditions include, but are not limited to, a chronic blistering (bullous) disorder, psoriasis, dermatitis (e.g., contact or atopic), eczema, urticaria, rosacea, scarring (i.e. the formation of a scar (e.g., a keloid scar or a hypertrophic scar)), a first degree burn, a second degree burn, a third degree burn, a fourth degree burn, cutaneous mucinosis and/or melanoma.

[0040] In some embodiments, a topical formulation disclosed herein is administered before or after contact with an allergen and/or irritant.

[0041] In some embodiments, treating or preventing any of the diseases or conditions described herein reduces the severity of or prevents the occurence of at least one symptom of the disease or condition. In some embodiments, dermatological diseases or conditions are accompanied by inflammation of the upper layers of the skin. In some embodiments, inflammation of the upper layers of the skin causes itching, blisters, redness, swelling, oozing, scabbing, and scaling. In some embodiments, inflammation of the upper layers of the skin results in a rash, blisters, pimples, open sores, oozing, crusting, and scaling.

Dermatitis

[0042] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is dermatitis. As used herein, dermatitis means an inflammatory condition of the skin. In certain instances, dermatitis is acute and results from contact with an offending agent (e.g., uruishol). In certain instances, dermatitis is chronic and results from hypersensitivity.

[0043] Types of dermatitis include, but are not limited to: spongiotic dermatitis (irritant dermatitis, seborrheic dermatitis, atopic dermatitis, allergic contact dermatitis, thermal induced dermatitis, and drug induced dermatitis); allergic contact dermatitis (contact

dermatitis can be due to external compounds, preservatives, fragrances, or plants); seborrhoeic dermatitis (seborrhoeic dermatitis is also known as dandruff); dyshidrotic dermatitis (also known as Pompholyx); vesicular or bullous dermatitis (can be caused by drug reaction, or auto immune diseases; examples includes Steven Johnson Syndrome, bullous erythema multiforme, bullous pemphigoid, and pemphigus vulgaris).

[0044] In certain instances, the symptoms of dermatitis (e.g., chronic or acute) result from a disorder of an immune system. In certain instances, the symptoms of dermatitis (e.g., chronic or acute) result from the exudation of plasma from vessels and capillaries into the epidermis, dermis, and/or subcutaneous tissues. In certain instances, cytokines cause inflammation associated with dermatitis. In certain instances, inhibiting DP_2 receptor activity reduces the concentration of cytokines associated with dermatitis. In certain instances, inhibiting DP_2 receptor activity reduces exudation of plasma from vessels and capillaries associated with dermatitis. In certain instances, antagonism of DP_2 receptors treats dermatitis.

[0045] In some embodiments, dermatitis is atopic dermatitis or allergic dermatitis. In some embodiments, dermatitis is atopic dermatitis. In some embodiments, dermatitis is allergic dermatitis.

Psoriasis

[0046] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is psoriasis. In certain instances, the symptoms of psoriasis result from influx of cytokines into the epidermis, dermis, and/or subcutaneous tissues. In certain instances, cytokines cause inflammation and subsequent psoriasis. In certain instances, inhibiting DP_2 activity reduces the concentration of cytokines associated with psoriasis. In certain instances, antagonism of DP_2 receptors treats psoriasis.

Eczema

[0047] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is eczema. As used herein, eczema is an inflammation of the epidermis. The symptoms of this persistent skin condition include dryness and recurring skin rashes which are characterized by one or more of inflammation (e.g., redness), skin edema (swelling), itching and dryness, crusting, flaking, blistering, cracking, oozing, or bleeding. In certain instances, inhibiting DP_2 receptor activity reduces the concentration of cytokines associated with eczema. In

certain instances, inhibiting DP_2 receptor activity reduces inflammation associated with eczema. In certain instances, antagonism of DP_2 receptors treats eczema.

Urticaria

[0048] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is urticaria. In certain instances, urticaria results from hypersensitivity or another immune disorder. In certain instances, the symptoms of urticaria result from influx of cytokines into the epidermis, dermis, and/or subcutaneous tissues. In certain instances, cytokines cause the inflammation and/or hypersensitivity associated with urticaria. In certain instances, inhibiting DP_2 receptor activity reduces the concentration of cytokines associated with uticaria. In certain instances, antagonism of DP_2 receptors treats urticaria.

[0049] In some embodiments, the uticaria is papular urticaria.

Type I hypersensitivity

[0050] In some embodiments, topical formulations disclosed herein are administered to mammal to treat or prevent type I hypersensitivity (or immediate hypersensitivity). Type I hypersensitivity is an allergic reaction provoked by exposure to an irritant or allergen or combination thereof. Exposure may be by ingestion, inhalation, injection, or direct contact. Non-limiting examples of type I hypersensitivity include allergic dermatitis, urticaria, and food allergy.

Itch

[0051] In some embodiments, a topical formulation disclosed herein is administered to treat or prevent itching in a mammal. In some embodiments, the itching is a symptom of any of the diseases or conditions disclosed herein. In some embodiments, the itching is a result of contact with an irritant, allergen, or combination thereof. In some embodiments, the itching is a result of the PGD_2-dependent or PGD_2-mediated diseases or conditions that are disclosed herein (e.g. atopic dermatitis, allergic contact dermatitis, urticaria, and the like). In some embodiments, the topical formulations disclosed herein reduce itching that is associated with contact with an irritant, allergen, or combination thereof. In some embodiments, the topical formulations disclosed herein reduce itching that is associated with dermatitis, psoriasis or uticaria.

Bullous Diseases or Conditions

[0052] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is a

bullous disease or condition. In certain instances, a bullous disease or condition is characterized by the formation of blisters (i.e., the accumulation of fluid between cells in the upper layers of the skin). In certain instances, bullous disease or condition are an immune disease or condition. In certain instances, PGD_2 and/or cytokines mediate the formation of blisters (e.g., induce the exudation of plasma from capillaries to the upper layers of the skin). In certain instances, inhibiting DP_2 receptor activity reduces the concentration of cytokines associated with bullous disease or condition, and, further, treats bullous diseases or conditions. Bullous diseases or conditions include, but are not limited to, bullous pemphigoid, pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceous, paraneoplastic pemphigus, mucous membrane pemphigoid, linear IgA bullous disease, dermatitis herpeti-formis, and epidermolysis bullosa acquisita.

Rosacea

[0053] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is rosacea. As used herein, rosacea refers to any of erythematotelangiectatic rosacea (ETR), Papulopustular rosacea, and/or Phymatous rosacea. In certain instances, inhibiting or reducing the binding of PGD_2 to DP_2 receptors treats rosacea.

Skin ulcers

[0054] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is skin ulcers. As used herein, an ulcer is a disease or condition of the skin characterized by degradation of the epidermis and often portions of the dermis and even subcutaneous fat. In certain instances, ulcers are areas of necrotic tissue. In certain instances, ulcers result from immune system dysfunction. In certain instances, ulcers result from immune system dysfunction such as, but not limited to, the improper functioning of neutrophils. In certain instances, PGD_2 and/or cytokines are chemotactic agents for eosinophils. In certain instances, inhibiting DP_2 receptor activity reduces the concentration of cytokines associated with skin ulcers. In certain instances, inhibiting DP_2 receptor activity reduces the chemotaxis of eosinophils associated with skin ulcers. In certain instances, antagonism of DP_2 receptors treats skin ulcers.

Scarring

[0055] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is

scarring. As used herein, scarring refers to the formation of a scar. In one aspect, the scar is a hypertrophic scar, or keloid scar, or a scar resulting from acne. In certain instances, a scar is an area of fibrous tissue that results from inflammation (e.g., the overproduction of cytokines and/or collagen). In certain instances a scar is a result of an infection (e.g. acne). In certain instances, cytokines modulate the inflammation associated with scarring. In certain instances, inhibiting the activity of DP_2 receptors reduces or inhibits the activity of mast cells and/or over-production of cytokines associated with scarring. In certain instances, inhibiting DP_2 receptors activity reduces the concentration of cytokines associated with scarring. In certain instances, antagonism of DP_2 receptors treats scarring.

Burns

[0056] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is a burn. As used herein, a burn refers to an injury to or the destruction of skin caused by heat, cold, electricity, chemicals, light (e.g. a sunburn caused by UV exposure), radiation, or friction. In one aspect, the burn is a first degree burn, a second degree burn, a third degree burn, or a fourth degree burn. In certain instances, a burn results in the formation of a scar. In certain instances, a burn results in inflammation. In certain instances, inhibiting the activity of DP_2 receptors inhibits the activity of mast cells and/or eosinophils associated with scarring and/or inflammation. In certain instances, inhibiting the binding of PGD_2 to DP_2 receptors reduces the concentration of cytokines associated with scarring and/or inflammation. In certain instances, inhibiting DP_2 receptor activity treats scarring and/or inflammation associated with burns.

Cutaneous Mucinoses

[0057] In some embodiments, a topical formulation disclosed herein is administered to treat a dermatological disease or condition, wherein the dermatological disease or condition is cutaneous mucinosis. Cutaneous mucinosis refers to diseases or conditions wherein mucin accumulates in the dermis. In some embodiments, accumulation of mucin occurs in the interstitial spaces of the dermis and within hair follicles. In certain instances, mucinosis results from a mast cell disorder. PGD_2 and/or cytokines released by mast cells upregulate the synthesis of mucin from fibroblasts. In certain instances, deposition of mucin causes papules or nodules within or outside skin lesions (e.g., in skin lesions associated with systemic lupus erythematosus, discoid lupus erythematosus, and/or subacute cutaneous lupus erythematosus). In certain instances, inhibiting the activity of DP_2 receptors inhibits

the activity of mast cells and/or fibroblasts associated with deposition of mucin and/or mucinoses. In certain instances, inhibiting the binding of PGD_2 to DP_2 receptors reduces the concentration of cytokines associated with mucinoses. In certain instances, inhibiting DP_2 receptor activity treats or prevents cutaneous mucinoses.

[0058] Cutaneous mucinoses are observed in diseases or conditions such as, but are not limited to, generalized myxedema, pretibial myxedema, reticular erythematous mucinosis, scleredema, scleromyxedema, papular mucinosis, acral persistent papular mucinosis, focal mucinosis, digital mucous cyst, mucocele, cutaneous myxoma, cutaneous mucinosis of infancy, nevus mucinosis, alopecia mucinosa (follicular mucinosis), mucopolysaccharidoses, Degos disease, dermatomyositis, granuloma annulare, Jessner's lymphocytic infiltrate, lupus erythematosus, papulonodular mucinosis associated with systemic lupus erythematosus (SLE), lichen-myxedematosus, , dysthyroidotic mucinoses (mucinoses associated with thyroid diseases), reticular erythematous mucinosis, acral persistent mucinosis, juvenile cutaneous mucinosis, cutaneous mucinosis of infancy, cutaneous toxic-oil mucinoses, neuropathy-related cutaneous mucinosis, urticaria-like mucinosis, hereditary mucinous histiocytosis and primary mucinous skin (sebaceous and sweat glands) carcinomas.

[0059] In some embodiments, any topical formulation described herein comprises a DP_2 receptor antagonist in combination with a second therapeutic agent (e.g., leukotriene modulator such as a FLAP inhibitor compound) and is administered to the skin for the treatment of any prostaglandin D_2-mediated or prostaglandin D_2-dependent disease or condition described herein. In some embodiments, the effects of a DP_2 receptor antagonist compound and the second therapeutic agent are additive, i.e., administration of a combination of a DP_2 receptor antagonist compound and the second therapeutic agent provides greater therapeutic benefit than administration of either compound alone.

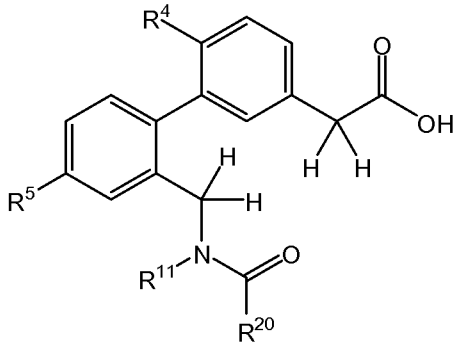
DP_2 Receptor Antagonists

[0060] In one aspect, the pharmaceutical compositions disclosed herein comprise at least one DP_2 receptor antagonist compound. In some embodiments, the DP_2 receptor antagonist is selected from compounds disclosed in International patent application no. PCT/US09/35174 (entitled Antagonists of Prostaglandin D_2 receptors); International patent application no. PCT/US08/82056 (entitled Antagonists of PG D_2 receptors (entitled Antagonists of PG D_2 receptors"); International patent application no. PCT/US08/82082 (entitled Antagonists of PG D_2 receptors (entitled Antagonists of PG D_2 receptors");

International patent application no. PCT/US0932495 (entitled N,N-disubstituted aminoalkylbiphenyl antagonists of prostaglandin D_2 receptors); International patent application no. PCT/US09/32499 (entitled "N,N-disubstituted aminoalkylbiphenyl antagonists of prostaglandin D_2 receptors"); International patent application no. PCT/US09/33961 (entitled "Cyclic diaryl ether compounds as antagonists of prostaglandin D_2 receptors"); International patent application no. PCT/US09/38291 (entitled "Aminoalkylphenyl antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/078,311 (entitled "Heteroalkyl antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/101,074 (entitled "Heteroaryl antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/054,093 (entitled "Tricyclic antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/107,638 (entitled "Tricyclic antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/075,242 (entitled "Cycloaklane[B]indole antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/101,964 (entitled "Heteroaryl antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/103,872 (entitled "Heteroalkyl biphenyl antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/115,259 (entitled "Heterocyclic antagonists of prostaglandin D_2 receptors"); US provisional application no. 61/112,044 (entitled "Cycloaklane[B]azaindole antagonists of prostaglandin D2 receptors"); US provisional application no. 61/147,437 (entitled "Indolozine compounds as prostaglandin D_2 receptor antagonists"); US provisional application no. 61/025,597; US provisional application no. 61/110,496; US application no. 12/362,439; International patent application no. PCT/US09/49621; International patent application no. PCT/US09/49631; US application no. 12/497,343; International patent application no. PCT/US09/58655; International patent application no. PCT/US09/58663; US application no. 12/568,571; International patent application no. PCT/US09/44219; International patent application no. PCT/US09/48327; International patent application no. PCT/US09/59256; International patent application no. PCT/US09/59891; International patent application no. PCT/US09/64630; International patent application no. PCT/US09/63439; International patent application no. PCT/US09/63438; US application no. 12/613,424; International patent application no. PCT/US2010/22145; or pharmaceutically acceptable salt; pharmaceutically acceptable solvate; metabolite, prodrug or N-oxide thereof, each disclosure is incorporated by reference for such compounds.

[0061] In some embodiments, the DP_2 receptor antagonist is ramatroban, AMG 009, AMG 853, Compound 14 of WO 09/085177, AZD1981, AZD8075, AZD5985, ARRY-005, ARRY-006, ARRY-063, ODC9101 (OC459), OC499, OC1768, OC2125, OC2184, QAV680, MLN6095, ACT-129968, ADC3680, SAR398171, S555739, AP768, [2'-(3-Benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid, {3-[2-tert-Butylsulfanylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-methoxy-phenyl}-acetic acid, TM30642, TM30643, TM30089, TM27632, and TM3170, {2'-[(N-cyclopropanecarbonyl-N-ethyl-amino)-methyl]-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl}-acetic acid, [2'-[(N-cyclopropanecarbonyl-N-ethyl-amino)-methyl]-4'-(6-ethoxy-pyridin-3-yl)-6-methoxy-biphenyl-3-yl]-acetic acid, (5-{2-[(N-benzyloxycarbonyl-N-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid, or {8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid, or pharmaceutically acceptable salt; pharmaceutically acceptable solvate; metabolite, prodrug or N-oxide thereof.

[0062] In some embodiments, the DP_2 receptor antagonist is a compound having the structure of Formula (I), pharmaceutically acceptable salt, pharmaceutically acceptable solvates, or prodrug thereof:



Formula (I)

wherein,

R^4 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl;

R^5 is H, halogen, -CN, $-NO_2$, -OH, $-OR^{13}$, $-SR^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-OCO_2R^{13}$, $-CH(R^{13})_2$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NHC(=O)NH(R^{13})$, $-NHC(=O)R^{12}$, $-NHC(=O)OR^{12}$, $-C(OH)(R^{13})_2$, -C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

or R^5 is C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted

or unsubstituted monocyclic heteroaryl, or a substituted or unsubstituted bicyclic heteroaryl, wherein if R^5 is substituted, then R^5 is substituted with 1, or 2 R^{21} groups

R^{20} is C_1-C_4alkyl, C_3-C_6cycloalkyl, -CH_2O-C_1-C_4alkyl, -CH_2O-(substituted or unsubstituted phenyl), -$CH(CH_3)$-O-(substituted or unsubstituted phenyl), -$C(CH_3)_2$-O-(substituted or unsubstituted phenyl), -CH_2OCH_2-(substituted or unsubstituted phenyl), -OC_1-C_4alkyl, –O-CH_2-(substituted or unsubstituted phenyl), –O-$CH(CH_3)$-(substituted or unsubstituted phenyl), -$NR^{16}C_1$-C_4alkyl, –NR^{16}-CH_2-(substituted or unsubstituted phenyl), or –NR^{16}-$CH(CH_3)$-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted, then the phenyl is substituted with 1, or 2 R^{21} groups;

each R^{21} is independently selected from halogen, -OH, -OC_1-C_4alkyl, C_1-C_4alkyl, and -CF_3;

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

R^{11} is C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_3-C_6cycloalkyl;

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

each R^{13} is independently selected from H, C_1-C_4alkyl, C_1-C_4heteroalkyl, and C_1-C_4fluoroalkyl.

[0063] In some embodiments, R^{11} is –CH_3, -CH_2CH_3, -CF_3, –CH_2CF_3, cyclopropyl, cyclobutyl, or cyclopentyl. In some embodiments, R^{11} is -CH_2CH_3 or –CH_2CF_3. In some embodiments, R^{11} is -CH_2CH_3.

[0064] In some embodiments, R^5 is H, halogen, -CN, -NO_2, -OH, -OR^{13}, -SR^{12}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, -$NHS(=O)_2R^{12}$, -C(=O)R^{12}, -OC(=O)R^{12}, -CO_2R^{13}, -OCO_2R^{13}, -$N(R^{13})_2$, -C(=O)$N(R^{13})_2$, -OC(=O)$N(R^{13})_2$, -NHC(=O)$NH(R^{13})$, -NHC(=O)R^{12}, -NHC(=O)OR^{12}, -$C(OH)(R^{13})_2$, -C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl; R^{12} is C_1-C_4alkyl; each R^{13} is independently selected from H, and C_1-C_4alkyl. In some embodiments, R^5 is H, -CF_3, -CO_2H, Br, -NH-C(=O)-CH_3, -NH-C(=O)-OCH_3, -NH-SO_2CH_3, -SCH_3, -SO_2CH_3, -NH-(C=O)-CH_3, -NH-SO_2-CH_3, or -$C(CH_3)_2$-(OH).

[0065] In some embodiments, R^{20} is C_1-C_4alkyl, C_3-C_6cycloalkyl, -CH_2O-C_1-C_4alkyl, -CH_2O-(substituted or unsubstituted phenyl), -$CH(CH_3)$-O-(substituted or unsubstituted phenyl), -$C(CH_3)_2$-O-(substituted or unsubstituted phenyl), -CH_2OCH_2-(substituted or unsubstituted phenyl), -OC_1-C_4alkyl, –O-CH_2-(substituted or unsubstituted phenyl), –O-$CH(CH_3)$-(substituted or unsubstituted phenyl), -$NR^{16}C_1$-C_4alkyl, –NR^{16}-CH_2-(substituted or unsubstituted phenyl), or –NR^{16}-$CH(CH_3)$-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted then the phenyl is substituted with 1 or 2 R^{21} groups.

[0066] In some embodiments, R^4 is H, F, Cl, Br, -OH, $-CH_3$, $-OCH_3$, $-CF_3$, or $-OCF_3$; R^5 is H, halogen, -CN, $-NO_2$, -OH, $-S(=O)_2CH_3$, $-NHS(=O)_2CH_3$, $-C(=O)CH_3$, $-OC(=O)CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-NH_2$, $-C(=O)NH_2$, $-NHC(=O)CH_3$, $-CH_3$, $-CF_3$, $-OCF_3$, $-OCH_3$, $-CH_2OH$, or $-C(CH_3)_2OH$.

[0067] In some embodiments, R^{20} is $-CH_3$, $-CH_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2OCH_3$, $-CH_2O$-(substituted or unsubstituted phenyl), $-CH(CH_3)$-O-(substituted or unsubstituted phenyl), $-C(CH_3)_2$-O-(substituted or unsubstituted phenyl), $-CH_2OCH_2$-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted then the phenyl is substituted with 1 or 2 R^{21} groups.

[0068] In some embodiments, each R^{21} is independently selected from F, Cl, Br, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2CH_3$, $-CH_3$, and $-CF_3$. In some embodiments, each R^{21} is independently selected from F, Cl, Br, -OH, $-OCH_3$, $-CH_3$, and $-CF_3$.

[0069] In some embodiments, R^4 is H, F, Cl, Br, $-CH_3$, $-OCH_3$, $-CF_3$, or $-OCF_3$; R^5 is halogen, $-CH_3$, $-CF_3$, $-OCF_3$, or $-OCH_3$.

[0070] In some embodiments, R^{20} is $-CH_3$, $-CH_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2OCH_3$, $-CH_2O$-(substituted or unsubstituted phenyl), $-CH(CH_3)$-O-(substituted or unsubstituted phenyl), $-C(CH_3)_2$-O-(substituted or unsubstituted phenyl), $-CH_2OCH_2$-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted, then the phenyl is substituted with 0, 1, or 2 R^{21} groups.

[0071] In some embodiments, R^{20} is $-CH_3$, cyclopropyl, $-CH_2OCH_3$, $-CH_2O$-(substituted or unsubstituted phenyl), $-CH_2OCH_2$-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted, then the phenyl is substituted with 1, or 2 R^{21} groups. In some embodiments, R^{20} is cyclopropyl.

[0072] In some embodiments, R^{20} is $-OC_1$-C_4alkyl, $-O-CH_2$-(substituted or unsubstituted phenyl), or $-O-CH(CH_3)$-(substituted or unsubstituted phenyl); wherein if the phenyl of R^{20} is substituted, then the phenyl is substituted with 1 or 2 R^{21} groups.

[0073] In some embodiments, R^{20} is $-O-CH_2$-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted, then the phenyl is substituted with 1 or 2 R^{21} groups.

[0074] In some embodiments, R^{20} is $-NR^{16}C_1$-C_4alkyl, $-NR^{16}-CH_2$-(substituted or unsubstituted phenyl), or $-NR^{16}-CH(CH_3)$-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted then the phenyl is substituted with 1, or 2 R^{21} groups; R^{16} is H, $-CH_3$, or $-CH_2CH_3$.

[0075] In some embodiments, R^{20} is–NH-CH_2-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted, then the phenyl is substituted with 1, or 2 R^{21} groups. In some embodiments, R^{20} is–NH-CH_2-phenyl.

[0076] In some embodiments, R^4 is F, Cl, Br, -CH_3, -OCH_3, -CF_3, or -OCF_3.

[0077] In some embodiments, R^5 is F, Cl, Br, -CH_3, -CF_3, -OCF_3, or -OCH_3.

[0078] In some embodiments, R^{11} is –CH_3, -CH_2CH_3, or –CH_2CF_3.

[0079] In some embodiments, each R^{21} is independently selected from F, Cl, Br, -OH, -OCH_3, -CH_3, and -CF_3. In some embodiments, each R^{21} is independently selected from F, Cl, Br, -OH, -OCH_3, -OCH_2CH_3, -CH_3, and -CF_3. In some embodiments, each R^{21} is independently selected from F, Cl, and Br.

[0080] In some embodiments, R^4 is -OCH_3. In some embodiments, R^5 is -CF_3.

[0081] In some embodiments, R^{11} is –CH_3, or -CH_2CH_3. In some embodiments, R^{11} is -CH_2CH_3.

[0082] In some embodiments, R^4 is H, F, Cl, Br, -OH, -CH_3, -OCH_3, -CF_3, or -OCF_3;

[0083] In some embodiments, R^{11} is cyclopropyl, cyclobutyl, or cyclopentyl.

[0084] In some embodiments, R^5 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, or a substituted or unsubstituted group selected from phenyl, naphthyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl, benzofuranyl, benzothienyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl, where if R^5 is substituted, then R^5 is substituted with 1, or 2 R^{21} groups.

[0085] In some embodiments, R^5 is a substituted or unsubstituted group selected from phenyl, naphthyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl, benzofuranyl, benzothienyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl, where if R^5 is substituted, then R^5 is substituted with 1 or 2 R^{21} groups.

[0086] In some embodiments, R^5 is a substituted or unsubstituted group selected from pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, indolyl,

benzofuranyl, benzothienyl, indazolyl, benzimidaolyl, benzthiazolyl, quinolinyl, isoquinolinyl, where if R^5 is substituted, then R^5 is substituted with 1 or 2 R^{21} groups.

[0087] In some embodiments, R^5 is a substituted or unsubstituted pyridinyl, where if R^5 is substituted, then R^5 is substituted with 1 or 2 R^{21} groups.

[0088] In some embodiments, R^4 is F, Cl, Br, $-CH_3$, $-OCH_3$, $-CF_3$, or $-OCF_3$; R^{11} is $-CH_3$, $-CH_2CH_3$, or $-CH_2CF_3$;

[0089] In some embodiments, R^4 is $-OCH_3$; R^{11} is $-CH_3$, or $-CH_2CH_3$.

[0090] In some embodiments, R^5 is a substituted or unsubstituted group selected from pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolinyl, and isoquinolinyl, where if R^5 is substituted, then R^5 is substituted with 1, or 2 R^{21} groups.

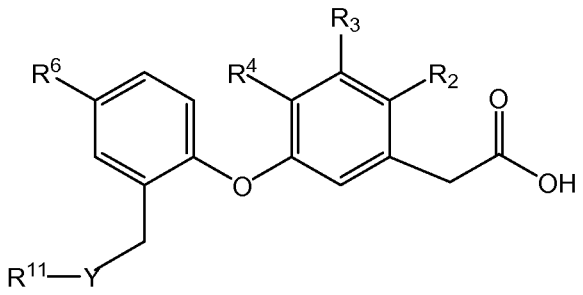
[0091] In some embodiments, R^5 is cyclopropyl, phenyl, pyrrolidin-1-yl, pyrazol-1-yl, 1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl, oxazol-2-yl, pyridin-2-yl, 6-ethoxy-pyridin-3-yl, 5-fluoro-pyridin-2-yl, 5-methoxy-pyrimidin-2-yl, or quinolin-7-yl.

[0092] In some embodiments, R^5 is pyrazol-1-yl, 1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl, oxazol-2-yl, pyridin-2-yl, 6-ethoxy-pyridin-3-yl, 5-fluoro-pyridin-2-yl, 5-methoxy-pyrimidin-2-yl, or quinolin-7-yl.

[0093] In some embodiments, R^5 is substituted or unsubstituted pyridin-2-yl, substituted or unsubstituted pyridin-3-yl, or substituted or unsubstituted pyridin-4-yl, where if R^5 is substituted, then R^5 is substituted with 1 or 2 R^{21} groups. In some embodiments, R^5 is pyridin-2-yl, 6-ethoxy-pyridin-3-yl, 5-fluoro-pyridin-2-yl, or 5-methoxy-pyrimidin-2-yl. In some embodiments, R^5 is pyridin-2-yl, 6-methyl-pyridin-3-yl, 6-ethyl-pyridin-3-yl, 6-methoxy-pyridin-3-yl, 6-ethoxy-pyridin-3-yl, 5-fluoro-pyridin-2-yl, 5-methyl-pyridin-2-yl, 5-ethyl-pyridin-2-yl, 5-methoxy-pyrimidin-2-yl or 5-ethoxy-pyrimidin-2-yl. In some embodiments, R^5 is 6-ethoxy-pyridin-3-yl.

[0094] In some embodiments, the DP_2 receptor antagonist is [2'-(3-benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid, {2'-[(N-cyclopropanecarbonyl-N-ethyl-amino)-methyl]-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl}-acetic acid, [2'-[(N-cyclopropanecarbonyl-N-ethyl-amino)-methyl]-4'-(6-ethoxy-pyridin-3-yl)-6-methoxy-biphenyl-3-yl]-acetic acid, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof.

[0095] In some embodiments, the DP_2 receptor antagonist is a compound having the structure of Formula (II), pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof:



Formula (II)

wherein,

each of R^2, R^3, and R^4 is independently H, F, Cl, Br, I, -CN, -OR^{12}, -C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

R^6 is F, Cl, Br, I, -CN, -NO_2, -OH, -O(C_1-C_6alkyl), -S(=O)$_2R^{12}$, -N(C_1-C_4alkyl)S(=O)$_2R^{12}$, -NHS(=O)$_2R^{12}$, -S(=O)$_2$N(R^{13})$_2$, -C(=O)R^{12}, -CO_2(C_1-C_6alkyl), -NH_2, -C(=O)NH(R^{13}), -C(=O)N(R^{13})$_2$, -OC(=O)NH(R^{13}), -OC(=O)N(R^{13})$_2$, -N(C_1-C_4alkyl)C(=O)N(R^{13})$_2$, -NHC(=O)N(R^{13})$_2$, -NHC(=O)NH(R^{13}), -N(C_1-C_4alkyl)C(=O)R^{12}, -NHC(=O)R^{12}, -NH-C_1-C_4alkyl-C(=O)R^{12}, -N(C_1-C_4alkyl)C(=O)OR^{12}, -NHC(=O)OR^{12}, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic or bicyclic heteroaryl containing 0-3 heteroatoms selected from N, O or S;

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted monocyclic or bicyclic heteroaryl containing 0-3 heteroatoms selected from N, O or S, a substituted or unsubstituted -C_1-C_4alkyl-phenyl, -C_1-C_6alkylene-N(R^{17})$_2$, -C_1-C_6alkylene-C(=O)O-R^{17}, or -C_1-C_6alkylene-C(=O)N(R^{17})$_2$;

R^{17} is H, or C_1-C_6alkyl;

R^{12} is C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted benzyl, a substituted or unsubstituted monocyclic heteroaryl containing 0-3 heteroatoms selected from N, O or S, a substituted or unsubstituted -C_1-C_4alkyl-C_3-C_{10}cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-phenyl, or a substituted or unsubstituted -C_1-C_4alkyl-(monocyclic heteroaryl containing 0 to 3 heteroatoms selected from N, O or S);

each R^{13} is independently selected from H, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted benzyl, a substituted or unsubstituted monocyclic heteroaryl containing 0-3 heteroatoms selected from N, O or S., a substituted or unsubstituted -C_1-C_4alkyl-C_3-C_{10}cycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted -C_1-C_4alkyl-phenyl, and a substituted or unsubstituted -C_1-C_4alkyl-(monocyclic heteroaryl containing 0 to 3 heteroatoms selected from N, O or S); or

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

Y is -S-, -S(=O)-, or -$S(=O)_2$-.

[0096] In some embodiments, R^6 is F, Cl, Br, I, -CN, -NO_2, -$S(=O)_2R^{12}$, -$N(C_1$-C_4alkyl)$S(=O)_2R^{12}$, -$NHS(=O)_2R^{12}$, -$S(=O)_2N(R^{13})_2$, -$C(=O)R^{12}$, -$CO_2(C_1$-C_6alkyl), -NH_2, -$C(=O)NH(R^{13})$, -$C(=O)N(R^{13})_2$, -$N(C_1$-C_4alkyl)$C(=O)N(R^{13})_2$, -$NHC(=O)N(R^{13})_2$, -$NHC(=O)NH(R^{13})$, -$N(C_1$-C_4alkyl)$C(=O)R^{12}$, -$NHC(=O)R^{12}$, -NH-C_1-C_4alkyl-$C(=O)R^{12}$, -$N(C_1$-C_4alkyl)$C(=O)OR^{12}$, -$NHC(=O)OR^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted monocyclic heteroaryl containing 0-3 heteroatoms selected from N, O or S.

[0097] In some embodiments, R^{11} is isopropyl, tert-butyl, -CH_2CF_3, -CH_2CO_2H, -$CH_2CH_2N(CH_3)_2$, phenyl, 4-chlorophenyl, benzyl, phenethyl, thiazol-2-yl, 5-methyl-[1,3,4]thiadiazol-2-yl, pyridin-2-yl, or quinolin-2-yl.

[0098] In some embodiments, R^6 is -NO_2, -$N(C_1$-C_4alkyl)$S(=O)_2R^{12}$, -$NHS(=O)_2R^{12}$, -$N(R^{13})_2$, -$N(C_1$-C_4alkyl)$C(=O)N(R^{13})_2$, -$NHC(=O)N(R^{13})_2$, -$N(C_1$-C_4alkyl)$C(=O)R^{12}$, -$NHC(=O)R^{12}$, -NH-C_1-C_4alkyl-$C(=O)R^{12}$, -$N(C_1$-C_4alkyl)$C(=O)OR^{12}$, or -$NHC(=O)OR^{12}$.

[0099] In some embodiments, R^6 is -$N(C_1$-C_4alkyl)$C(=O)R^{12}$ or -$NHC(=O)R^{12}$.

[00100] In some embodiments, each of R^2, R^3, and R^4 is independently H, F, Cl, Br, I, -CN, -OCH_3, -CH_3, -CH_2CH_3, -$CHCH_2$, -CHF_2, -CF_3, -$OCHF_2$, or -OCF_3.

[00101] In some embodiments, R^2 is H. In some embodiments, R^3 is H.

[00102] In some embodiments, R^4 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl; R^6 is –$NR^{13}S(=O)_2R^{12}$, -$S(=O)_2N(R^{12})(R^{13})$, -$N(R^{12})(R^{13})$, -$C(=O)N(R^{12})(R^{13})$, -$NHC(=O)N(R^{12})(R^{13})$, -$NR^{13}C(=O)R^{12}$, or -$NR^{13}C(=O)OR^{12}$; R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6heteroalkyl,

C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted or unsubstituted 5-membered heteroaryl, a substituted or unsubstituted 6-membered heteroaryl, or -C_1-C_4alkyl-(substituted or unsubstituted phenyl); R^{12} is C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted or unsubstituted benzyl, a substituted or unsubstituted 6-membered heteroaryl, or -C_1-C_4alkyl-(substituted or unsubstituted phenyl); R^{13} is H or C_1-C_4alkyl; or R^{12} and R^{13} attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted C_2-C_6heterocycloalkyl.

[00103] In some embodiments, R^4 is H, F, Cl, Br, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy.

[00104] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or -C_1-C_4alkyl-(substituted or unsubstituted phenyl).

[00105] In some embodiments, R^4 is H, F, Cl, Br, -OCH_3, -CH_3, -CH_2CH_3, -$CHCH_2$, -CHF_2, -CF_3, -$OCHF_2$, or -OCF_3.

[00106] In some embodiments, R^{12} is C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted benzyl, or -C_1-C_4alkyl-(substituted or unsubstituted phenyl); R^{13} is H or –CH_3.

[00107] In some embodiments, R^6 is –$NR^{13}S(=O)_2R^{12}$, -$N(R^{12})(R^{13})$, -$C(=O)N(R^{12})(R^{13})$, -$NHC(=O)N(R^{12})(R^{13})$, -$NR^{13}C(=O)R^{12}$, or -$NR^{13}C(=O)OR^{12}$.

[00108] In some embodiments, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, a substituted or unsubstituted phenyl, or -C_1-C_4alkyl-(substituted or unsubstituted phenyl).

[00109] In some embodiments, R^4 is F, Cl, Br, -OCH_3, -CH_3, -CH_2CH_3, -$CHCH_2$, -CHF_2, -CF_3, -$OCHF_2$, or -OCF_3. In some embodiments, R^4 is -OCH_3.

[00110] In some embodiments, R^6 is -$NR^{13}C(=O)R^{12}$.

[00111] In some embodiments, R^{12} is C_1-C_6alkyl, C_3-C_6cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted benzyl.

[00112] In some embodiments, R^{11} is –CH_2CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -CH_2CF_3, a susbtituted or unsubstituted phenyl, -C_1-C_2alkyl-(susbtituted or unsubstituted phenyl).

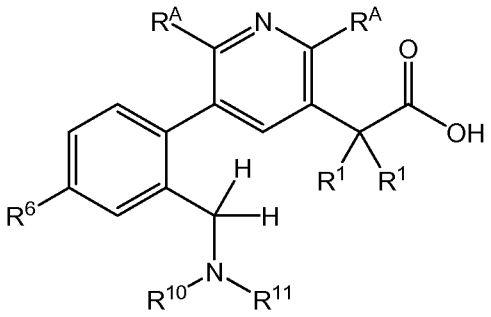
[00113] In some embodiments, R^{12} is –$CH(CH_3)_3$, -$C(CH_3)_3$, -$CH_2CH(CH_3)_2$, -$CH_2C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted benzyl.

[00114] In some embodiments, R^{11} is $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, or $-CH_2CF_3$; R^{12} is $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_3$, or a substituted or unsubstituted phenyl; R^{13} is H.

[00115] In some embodiments, R^4 is F, Cl, $-OCH_3$, $-CF_3$, or $-OCF_3$; R^{11} is $-C(CH_3)_3$; R^{12} is $-C(CH_3)_3$; R^{13} is H.

[00116] In some embodiments, the DP_2 receptor antagonist is {3-[2-tert-butylsulfanylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-methoxy-phenyl}-acetic acid, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof.

[00117] In some embodiments, the DP_2 receptor antagonist is a compound having the structure of Formula (III), pharmaceutically acceptable salt, pharmaceutically acceptable solvate, *N*-oxide, or prodrug thereof:



Formula (III)

wherein,

each R^1 is independently selected from H and $-CH_3$;

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

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

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

R^{14} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; or

R^{14} is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl;

R^{15} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; or

R^{15} is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl;

each R^{16} is independently H, -CN, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, or a C_3-C_6cycloalkyl; or two R^{16} groups attached to the same N atom are taken together with the N atom to which they are attached to form an optionally substituted heterocycloalkyl; or each R^{16} is independently H, C_1-C_6alkyl, C_1-C_6fluoroalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl;

R^{11} is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted -C_1-C_4alkyl-aryl, or a substituted or unsubstituted -C_1-C_4alkyl-heteroaryl; or

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl.

[00118] In some embodiments, each R^A is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4alkoxy; R^6 is H, halogen, -CN, tetrazolyl, -OH, -SR^{13}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$NHS(=O)_2R^{12}$, -$C(=O)R^{12}$, -$OC(=O)R^{12}$, -CO_2R^{13}, -$N(R^{13})_2$, -$C(=O)N(R^{13})_2$, -$NHC(=O)R^{12}$, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4alkoxy, or C_1-C_4heteroalkyl; R^{10} is –$C(=O)C_1$-C_4alkyl, –$C(=O)C_1$-C_4fluoroalkyl, –$C(=O)C_3$-C_6cycloalkyl, –C(=O)(a substituted or unsubstituted phenyl), –C(=O)(a substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom), –$C(=O)C_1$-C_2alkyl-(substituted or unsubstituted phenyl), –C(=O)-C_1-C_2alkyl-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom), –$C(=O)C_1$-C_2alkyl-O-C_1-C_4alkyl, –C(=O)-O-C_1-C_4alkyl, –C(=O)-O-C_1-C_2alkyl-(substituted or unsubstituted phenyl), –C(=O)–$NR^{16}C_1$-C_4alkyl, or –C(=O)–$NR^{16}C_1$-C_2alkyl-(substituted or unsubstituted phenyl); R^{11} is C_1-C_4alkyl, C_1-C_4haloalkyl, C_3-C_6cycloalkyl, or substituted or unsubstituted benzyl; R^{12} is C_1-C_4alkyl, C_1-C_4heteroalkyl, or C_1-C_4fluoroalkyl; each R^{13} is independently selected from H, C_1-C_4alkyl, C_1-C_4heteroalkyl, C_1-C_4fluoroalkyl, or substituted or unsubstituted benzyl; R^{16} is H or C_1-C_4alkyl; where each substituted phenyl or substituted heteroaryl is

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

[00119] In some embodiments, R^{10} is –C(=O)C_1-C_4alkyl, –C(=O)C_3-C_6cycloalkyl, –C(=O)C_1-C_2alkyl-(substituted or unsubstituted phenyl), –C(=O)-C_1-C_2alkyl-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom), –C(=O)-O-C_1-C_2alkyl-(substituted or unsubstituted phenyl), or –C(=O)–$NR^{16}C_1$-C_2alkyl-(substituted or unsubstituted phenyl).

[00120] In some embodiments, R^{10} is –C(=O)C_1-C_4alkyl, –C(=O)C_3-C_6cycloalkyl, –C(=O)CH_2-(substituted or unsubstituted phenyl), –C(=O)-CH_2-(substituted or unsubstituted 6-membered heteroaryl containing 1 or 2 N atom), –C(=O)-O-CH_2-(substituted or unsubstituted phenyl), or –C(=O)–$NHCH_2$-(substituted or unsubstituted phenyl). In some embodiments, R^{10} is –C(=O)C_1-C_4alkyl, –C(=O)C_3-C_6cycloalkyl, –C(=O)CH_2-(substituted or unsubstituted phenyl), –C(=O)-O-CH_2-(substituted or unsubstituted phenyl), or –C(=O)–$NHCH_2$-(substituted or unsubstituted phenyl). In some embodiments, R^{10} is –C(=O)-O-CH_2-(substituted or unsubstituted phenyl). In some embodiments, R^{10} is –C(=O)CH_3, –C(=O)CH_2CH_3, –C(=O)cyclopropyl, –C(=O)CH_2OCH_3, or –C(=O)$CH_2OCH_2CH_3$.

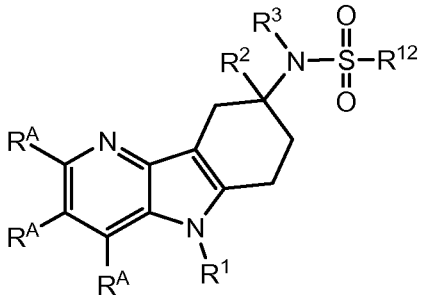
[00121] In some embodiments, each R^A is independently selected from H, F, Cl, Br, I, -CN, -OH, -OCH_3, -OCH_2CH_3, -CH_3, -CH_2CH_3, -CF_3, -CHF_2, -CH_2F, and -OCF_3.

[00122] In some embodiments, R^6 is H, -CF_3, -CO_2H, Br, -NH-C(=O)-CH_3, -NH-C(=O)-OCH_3, -NH-SO_2CH_3, -SCH_3, -SO_2CH_3, -NH-(C=O)-CH_3, -NH-SO_2-CH_3, or -$C(CH_3)_2$-(OH). In some embodiments, R^6 is F, Cl, -CH_3, -CF_3, -OCF_3, or -OCH_3. In some embodiments, R^6 is -CF_3.

[00123] In some embodiments, R^{11} is C_1-C_6alkyl. In some embodiments, R^{11} is –CH_2CH_3.

[00124] In some embodiments, the DP_2 receptor antagonist is (5-{2-[(N-benzyloxycarbonyl-N-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof.

[00125] In some embodiments, the DP_2 receptor antagonist is a compound having the structure of Formula (IV), pharmaceutically acceptable solvate, pharmaceutically acceptable salt, *N*-oxide, or prodrug thereof:



Formula (IV)

wherein,

R^1 is L^1-X^1; L^1 is C_1-C_6alkyl; X^1 is CO_2H, or $-CO_2(C_1$-C_6alkyl);

each R^A is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

R^2 is H or $-CH_3$;

R^3 is H or C_1-C_6alkyl;

R^{12} is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, an optionally substituted C_3-C_{10}cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted -C_1-C_6alkyl-cycloalkyl, an optionally substituted -C_1-C_6alkyl-phenyl, or an optionally substituted -C_1-C_6alkyl-heteroaryl.

[00126] In some embodiments, R^{12} is C_1-C_6alkyl, an optionally substituted phenyl, an optionally substituted naphthyl, or an optionally substituted heteroaryl containing 0-3 N atoms.

[00127] In some embodiments, R^{12} is an optionally substituted phenyl, an optionally substituted naphthyl, an optionally substituted monocyclic heteroaryl containing 0-3 N atoms or an optionally substituted bicyclic heteroaryl containing 0-3 N atoms.

[00128] In some embodiments, each R^A is independently selected from H, F, Cl, Br, I, -CN, -OH, $-OCH_3$, $-CH_3$, and $-CF_3$. In some embodiments, each R^A is H.

[00129] In some embodiments, L^1 is $-CH_2$-, $-CH(CH_3)$-, $-C(CH_3)_2$-, or $-CH_2CH_2$-. In some embodiments, L^1 is $-CH_2$- or $-CH_2CH_2$-. In some embodiments, L^1 is $-CH_2$-. In some embodiments, L^1 is $-CH_2CH_2$-.

[00130] In some embodiments, R^{12} is a substituted or unsubstituted phenyl, where if R^{12} is substituted then R^{12} is substituted with 1 or 2 groups selected from F, Cl, Br, I, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, R^{12} is a substituted or unsubstituted phenyl, where if R^{12} is substituted then R^{12} is substituted with 1

group selected from F, Cl, Br, I, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, R^{12} is 4-fluorophenyl.

[00131] In some embodiments, the DP_2 receptor antagonist is {8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid, (R)-{8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid, (S)-{8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof. In some embodiments, the DP_2 receptor antagonist is {8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof. In some embodiments, the DP_2 receptor antagonist is (R)-{8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof. In some embodiments, the DP_2 receptor antagonist is (S)-{8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof.

[00132] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[00133] In some embodiments, the DP_2 receptor antagonist compounds are included in the formulations described herein as pharmaceutically acceptable salts, and/or pharmaceutically acceptable solvates. In some embodiments, the DP_2 receptor antagonist compounds are included in the formulations described herein as pharmaceutically acceptable salts. In some embodiments, DP_2 receptor antagonist compounds are included in the formulations described herein in free acid form or free base form.

[00134] In some embodiments, the DP_2 receptor antagonist compounds described herein 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.

Combination therapy

[00135] In one aspect, pharmaceutical compositions and methods disclosed herein include an additional therapeutic agent. In one aspect, the additional therapeutic agent is a therapeutic agent other than a DP_2 receptor antagonist compound.

[00136] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same formulation) a therapeutic agent selected from: antibiotics (e.g., polymyxin B sulfate / bacitracin zinc, polymyxin B / neomycin / gramicidin, polymyxin B/trimethoprim, polymyxin B/bacitracin, fluoroquinolones (e.g., ciprofloxacin, moxifloxacin, ofloxacin, gatifloxacin, levofloxacin), aminoglycosides (e.g. tobramycin, azithromycin, gentamicin, erythromycin, bacitracin); anti-Fungal Agents (e.g., amphotericin B, intraconazole, fluconazole, voriconazole); steroid anti-inflammatory agents (e.g., fluorometholone acetate, prednisolone acetate, loteprednol etabonate, prednisolone sodium phosphate, prednisolone sodium, rimexolone, fluorometholone acetate); non-steroidal anti-inflammatory agents (e.g., nepafenac, ketorolac tromethamine, bromfenac, diclofenac sodium, ketorolac tromethamine, ketotifen fumarate); antihistamines (e.g., emedastine difumarate, olopatadine hydrochloride, epinastine HCl, azelastine hydrochloride, ketotifen fumarate); antivirals (e.g., acyclovir, vidarabine, trifluridine); mast cell stabilizers (e.g., lodoxamide tromethamine, nedocromil sodium, cromolyn sodium, pemirolast potassium), cyclosporine, and leukotriene modulators (e.g. 5-LO inhibitiors, FLAP inhibitor compounds, LTA_4 hydrolase inhibitors, leukotriene receptor antagonist (e.g. $CysLT_1$ receptor antagonists, BLT_1R antagonists)).

[00137] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same formulation) an antibiotic. Antibiotics include, but are not limited to, polymyxin B sulfate / bacitracin zinc, polymyxin B / neomycin / gramicidin, polymyxin B/trimethoprim, polymyxin B/bacitracin, fluoroquinolones (e.g., ciprofloxacin, moxifloxacin, ofloxacin, gatifloxacin, levofloxacin), aminoglycosides (e.g. tobramycin, azithromycin, gentamicin, erythromycin, bacitracin.

[00138] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same formulation) an anti-fungal agent. Anti-fungal agents include, but are not limited to, amphotericin B, intraconazole, fluconazole, voriconazole.

[00139] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same

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

[00140] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same formulation) a non-steroidal anti-inflammatory agent (NSAID). NSAIDs include, but are not limited to: aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, COX-2 specific inhibitors (such as, but not limited to, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, CS-502, JTE-522, L-745,337 and NS398).

[00141] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same formulation) an antihistamine. Antihistamines include, but are not limited to, amelexanox, astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, levocetirizine, efletirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine, and triprolidine.

[00142] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same formulation) an antiviral agent. Antiviral agents include, but are not limited to, acyclovir, vidarabine, trifluridine.

[00143] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same formulation) a mast cell stabilizer. Mast cell stabilizers include, but are not limited to, lodoxamide tromethamine, nedocromil sodium, cromolyn sodium, pemirolast potassium.

[00144] In one aspect, the dermal formulations disclosed herein that include a DP2 receptor antagonist compound are co-administered with (either separately or in the same formulation) cyclosporine.

[00145] In one aspect, the dermal formulations disclosed herein that include a DP_2 receptor antagonist compound are co-administered with (either separately or in the same formulation) a leukotriene modulator. Leukotriene modulators include, but are not limited to, 5-lipoxygenase inhibitors (5-LO) inhibitiors, 5-lipoxygenase activating protein (FLAP) inhibitor compounds, LTA_4 hydrolase inhibitors, leukotriene receptor antagonist (e.g. $CysLT_1$ receptor antagonists, BLT_1R antagonists).

[00146] In some embodiments, the second therapeutic agent is a leukotriene receptor antagonist selected from $CysLT_1/CysLT_2$ dual receptor antagonists, and $CysLT_1$ receptor anatagonists. $CysLT_1$ receptor antagonists include, but are not limited to, zafirlukast, montelukast, prankulast, and derivatives or analogs thereof.

[00147] In some embodiments, the second therapeutic agent is a FLAP inhibitor compound that is selected from FLAP inhibitor compounds disclosed herein or known in the art. In some embodiments, the FLAP inhibitor is selected from compounds described in U.S. patent application no. 11/538,762 (issued as US 7,405,302); U.S. patent application no. 12/131,828; U.S. patent application no. 11/553,946 (published as 2007/0105866); U.S. patent application no. 11/925,841; U.S. patent application no. 12/089,706; U.S. patent application no. 12/089,707; U.S. patent application no. 12/092,570; U.S. patent application no. 11/744,555 (published as 2007/0219206); U.S. patent application no. 11/746,010 (published as 2007/0225285); U.S. patent application no. 11/745,387 (published as 2007/0244128); U.S. patent application no. 12/257,876; U.S. patent application no. 61/055,887; U.S. patent application no. 61/055,899; International Patent Application no. PCT/US07/86188; WO 07/047207; WO07/056021; WO07/056220; WO07/056228;

International Patent Application no. PCT/US08/62310; International Patent Application no. PCT/US08/062793; International Patent Application no. PCT/US08/62580; International Patent Application no. PCT/US2008/052960; International Patent Application no. PCT/US08/81190; International Patent Application no. PCT/US08/76225; each of which is herein incorporated by reference in its entirety.

[00148] In some embodiments, the second therapeutic agent is a FLAP inhibitor is selected from: MK886 (also known as 3-[3-tert-butylsulfanyl-1-(4-chloro-benzyl)-5-isopropyl-1H-indol-2-yl]-2,2-dimethyl-propionic acid); MK591 (also known as 3-[3-tert-butylsulfanyl-1-(4-chloro-benzyl)-5-(quinolin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid); and DG031 (also known as BAY X1005; cyclopentyl-[4-(quinolin-2-ylmethoxy)-phenyl]-acetic acid), Compound A (3-[3-tert-Butylsulfanyl-1-[4-(5-methoxy-pyrimidin-2-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid); Compound B (3-[3-tert-Butylsulfanyl-1-[4-(5-methoxy-pyrimidin-2-yl)-benzyl]-5-(5-methyl-pyrazin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid); Compound C (3-{5-((S)-1-Acetyl-2,3-dihydro-1H-indol-2-ylmethoxy)-3-tert-butylsulfanyl-1-[4-(5-methoxy-pyrimidin-2-yl)-benzyl]-1H-indol-2-yl}-2,2-dimethyl-propionic acid); Compound D (3-[3-tert-Butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid); Compound E (3-[3-tert-Butylsulfanyl-1-[4-(6-ethoxy-pyridin-3-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid); Compound F (3-[3-tert-Butylsulfanyl-1-[4-(5-fluoro-pyridin-2-yl)-benzyl]-5-(quinolin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid); Compound G (2-[3-tert-Butylsulfanyl-1-[4-(5-methoxy-pyrimidin-2-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1H-indol-2-ylmethyl]-2-ethyl-butyric acid); Compound H (3-[3-tert-Butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid); Compound I (3-[5-((S)-1-Acetyl-pyrrolidin-2-ylmethoxy)-3-tert-butylsulfanyl-1-(4-chloro-benzyl)-1H-indol-2-yl]-2,2-dimethyl-propionic acid); Compound J (3-[3-tert-butylsulfanyl-1-[4-(5-fluoro-pyridin-2-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid), Compound K (3-{5-((S)-1-Acetyl-2,3-dihydro-1H-indol-2-ylmethoxy)-3-tert-butylsulfanyl-1-[4-(5-ethoxy-pyrimidin-2-yl)-benzyl]-1H-indol-2-yl}-2,2-dimethyl-propionic acid), or pharmaceutically acceptable salt or N-oxide thereof.

[00149] In another aspect, the FLAP inhibitor is selected from compounds described in U.S. Patent Nos. 4,929,626; 4970215; 5,081,138; 5,095,031; 5,204,344; 5,126,354; 5,221,678;

5,229,516; 5,272,145; 5,283,252; 5,288,743; 5,292,769; 5,304,563; 5,399,699; 5,459,150; 5,512,581; 5,597,833; 5,668,146; 5,668,150; 5,691,351; 5,714,488; 5,783,586; 5,795,900; and 5,843,968, each of which is herein incorporated by reference for the disclosure of such FLAP inhibitors).

[00150] In one aspect, a DP_2 receptor antagonist compound described herein is used in combination with a second therapeutic agent compound for the treatment of any dermal disease or condition described herein. In some instances, the ratio of the amount of a DP_2 receptor antagonist compound to a second therapeutic agent compound in any dermal formulation described herein is from about 10:1 to about 1: 10. In some instances, the ratio of the amount of a DP_2 receptor antagonist compound to a second therapeutic agent compound in any dermal formulation described herein is about 10:1, about 8:1, about 6:1, about 5:1, about 4:1, about 2:1, about 1:1, about 1:2, about 1:4, about 1:5, about 1:6, about 1:8, or about 1:10.

[00151] In some embodiments, the DP_2 receptor antagonist compound and the additional therapeutic agent are in the same pharmaceutical composition. In some embodiments, the DP_2 receptor antagonist compound and the additional therapeutic agent are in separate pharmaceutical compositions. In some embodiments, the DP_2 receptor antagonist compound and the additional therapeutic agent are in separate pharmaceutical compositions wherein the DP_2 receptor antagonist compound is administered topically and the additional therapeutic agent is administered by the same route or by a different route (e.g. oral administration). In some embodiments, the DP_2 receptor antagonist compound and the additional therapeutic agent are administered at the same time. In some embodiments, the DP_2 receptor antagonist compound and the additional therapeutic agent are administered at different times.

Further Forms of Compounds

[00152] In some embodiments, the therapeutic agent(s) (e.g. DP_2 receptor antagonist and/or second therapeutic agent) is present in the pharmaceutical composition as a pharmaceutically acceptable salt. In some embodiments, pharmaceutically acceptable salts are obtained by reacting the therapeutic agent(s) with an acid. In some other embodiments, pharmaceutically acceptable salts are obtained by reacting the therapeutic agent(s) with a base. In some embodiments, the therapeutic agents are used as pharmaceutically acceptable salts in the preparation of the pharmaceutical compositions described herein. In other embodiments, the therapeutic agents are used as free-acid or free-base form in the

manufacture of the pharmaceutical compositions described herein. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic 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, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion. In some cases, the therapuetic agent(s) is/are reacted with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, the therapeutic agent(s) form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. In some embodiments, a pharmaceutically acceptable salt of a compound disclosed herein is a sodium salt.

[00153] In some embodiments, the therapeutic agents disclosed herein 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.

[00154] In some embodiments, sites on the therapeutics agents disclosed herein are susceptible to various metabolic reactions Therefore incorporation of appropriate substituents at the places of metabolic reactions will reduce, minimize or eliminate the

metabolic pathways. 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, deuterium or an alkyl group.

[00155] In some embodiments, 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 some embodiments, compounds described herein are isotopically-labeled, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. In some embodiments, one or more hydrogen atoms are replaced with deuterium. In some embodiments, metabolic sites on the compounds described herein are deuterated. In some embodiments, substitution with deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

Certain Terminology

[00156] 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. 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.

[00157] "Alkoxy" refers to (alkyl)O-, where alkyl is as defined herein.

[00158] "Alkyl" refers to an aliphatic hydrocarbon group. The alkyl may be saturated or unsaturated. In one aspect, alkyl groups are selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

[00159] "Cycloalkyl" refers to a monocyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00160] "Halo", "halogen" or "halide" means fluoro, chloro, bromo or iodo.

[00161] "Fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoroalkyl is selected from $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$ and $-CF_2CF_3$.

[00162] "Fluoroalkoxy" refers to (fluoroalkyl)O-, where fluoroalkyl is as defined herein.

[00163] "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 (e.g. NH or Nalkyl), sulfur, or combinations thereof. In one aspect, heteroalkyl refers to an alkyl group in which one of the skeletal atoms of the alkyl is oxygen, nitrogen, or sulfur. In another aspect, heteroalkyl refers to an alkyl group in which one of the skeletal atoms of the alkyl is oxygen.

[00164] "6-Membered heteroaryl" includes pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

[00165] "Aryl" refers to phenyl or naphthalenyl. In some embodiments, an aryl is a phenyl.

[00166] The term "haloalkyl" refers to an alkyl group in which one or more hydrogen atoms are replaced by one or more halide atoms. In one aspect, a haloalkyl is a C_1-C_4haloalkyl.

[00167] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or *N*-attached where such is possible. In one aspect, the heteroaryl is a C_1-C_{10}heteroaryl. In another aspect, the heteroaryl is a C_2-C_9heteroaryl. In some cases, the heteroaryl includes at least one N atom in the ring. In some cases, the heteroaryl includes 1 or 2 N atom in the ring. In some cases, the heteroaryl includes 1 to 4 heteroatoms in the ring selected from O, N, and S. In one aspect, monocyclic heteroaryl is a C_1-C_5heteroaryl. In one aspect, bicyclic heteroaryl is a C_5-C_{10}heteroaryl.

[00168] A "heterocycloalkyl" or "heteroalicyclic" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. Examples of heterocycloalkyl groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl,

tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. In some embodiments, the heterocycloalkyl is selected from oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and indolinyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl. In some embodiments, a heterocycloalkyl includes 1 or 2 heteroatoms in the ring selected from O, S, and N.

[00169] 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 halogen, -OH, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, $-NH_2$, $-NH(C_1$-C_4alkyl), -N (C_1-C_4alkyl)$_2$, and C_1-C_4heteroalkyl. In some cases, substituted groups are substituted with one or more substituents selected from halogen, -OH, $-OC_1$-C_4alkyl, C_1-C_4alkyl, C_1-C_4heteroalkyl, C_1-C_4fluoroalkyl and $-OC_1$-C_4fluoroalkyl. For example, in some embodiments, a referenced substituted group is substituted with at least one group selected from halogen, -OH, -CN, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, $-OCH_2CH_3$, and $-OCF_3$. In some cases, the referenced substituted group is substituted with 1 or 2 of the aforementioned groups.

[00170] "Prodrug" refers to an agent that is converted into the parent drug *in vivo*. In some situations, prodrugs are often useful because 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 carboxylic acid containing compound which is administered as an ester (the "prodrug") and then is metabolically hydrolyzed to the carboxylic acid. In some embodiments, a prodrug is an alkyl ester prodrug. In some embodiments, a prodrug is a C_1-

C_4alkyl ester prodrug. In some embodiments, a prodrug is a methyl ester or ethyl ester prodrug. 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. 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. 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.

[00171] The terms "individual," "patient," or "subject" are used interchangeably and refer to any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human primate such as chimpanzee, and other apes and monkey species. In some embodiments, the mammal is a farm animal such as cattle, horse, sheep, goat, or swine. In some embodiments, the mammal is a domestic animal such as rabbit, dog, or cat. In some embodiments, the mammal is a laboratory animal, including rodents, such as rats, mice and guinea pigs, and the like.

[00172] The terms "treat," "treating" or "treatment," and other grammatical equivalents as used herein, include alleviating, abating, inhibiting, reducing, ameliorating, delaying the onset of, arresting the progression of, and/or inducing the regression of a disorder, disease or condition and/or the symptoms of a disorder, disease or condition. The terms also include prophylactic treatment of a disease or condition. The terms further include achieving any therapeutic benefit. Therapeutic benefit means the eradication or amelioration of the underlying disorder or disease or condition being treated, and/or the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder or disease or condition such that an improvement is observed in the individual.

[00173] The terms "prevent," "preventing" or "prevention," and other grammatical equivalents as used herein include inhibiting (arresting or stopping) the development of a disorder, disease or condition, and/or inhibiting (arresting or stopping) the further progression of a disorder, disease or condition. These terms are intended to include prophylaxis. For prophylactic benefit, the compositions are administered to an individual at risk of developing a particular disorder, disease or condition, or to an individual reporting one or more of the physiological symptoms of a disorder, disease or condition, or to an individual at risk of reoccurrence of the disorder, disease or condition.

[00174] The terms "effective amount" or "therapeutically effective amount" as used herein, refer to an amount of an agent (e.g. DP_2 receptor antagonist compound) being administered which achieves a desired result, e.g., to relieve to some extent one or more symptoms of a disease, disorder or condition being treated. In certain instances, the result is a reduction and/or alleviation of at least one sign, symptom, or cause of a disorder, disease or condition, or any other desired alteration of a biological system.

Topical formulations

[00175] In some embodiments, a topical formulation disclosed herein facilitates the delivery of a DP_2 receptor antagonist compound to the skin for a local effect (i.e., an effect that is limited to the skin). In certain instances, local administration of a DP_2 receptor antagonist compound reduces or eliminates side-effects that are associated with systemic administration of a DP_2 receptor antagonist compound.

[00176] Topical formulations include, but are not limited to, ointments, creams, lotions, solutions, pastes, gels, sticks, liposomes, nanoparticles, patches, bandages and wound dressings.

Creams and Lotions

[00177] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation is in the form of a cream. In certain instances, creams are semisolid (e.g., soft solid or thick liquid) formulations that include a DP_2 receptor antagonist compound dispersed in an oil-in-water emulsion or a water-in-oil emulsion. Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation is in the form of a lotion. In certain instances, lotions are fluid emulsions (e.g., oil-in-water emulsions or a water-in-oil emulsions). In some embodiments, the hydrophobic component of a lotion and/or cream is derived from an animal (e.g., lanolin, cod liver oil, and ambergris), plant (e.g., safflower oil,

castor oil, coconut oil, cottonseed oil, menhaden oil, palm kernel oil, palm oil, peanut oil, soybean oil, rapeseed oil, linseed oil, rice bran oil, pine oil, sesame oil, or sunflower seed oil), or petroleum (e.g., mineral oil, or petroleum jelly).

[00178] In certain instances, lotions and creams have a "drying" effect on dermatological diseases or conditions (e.g., some or all fluid exuded from the disorder is miscible in the ointment) and are thus useful for dermatological diseases or conditions characterized by the exudation of fluids.

Ointments

[00179] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation is in the form of an ointment. In certain instances, ointments are semisolid preparations that soften or melt at body temperature. In certain instances, ointments re-hydrate the skin and are thus useful for dermatological diseases or conditions characterized by loss of moisture.

Pastes

[00180] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation is in the form of a paste. In certain instances, pastes contain at least 20% solids. In certain instances, pastes are ointments that do not flow at body temperature. In certain instances, pastes re-hydrate the skin and are thus useful for dermatological diseases or conditions characterized by loss of moisture. In certain instances, pastes serve as protective coatings over areas to which they are applied.

Gels

[00181] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation is in the form of a gel. In certain instances, gels are semisolid (or semi-rigid) systems consisting of dispersions of large organic molecules dispersed in a liquid. In certain instances, gels are water-soluble and are removed using warm water or saline. In certain instances, gels re-hydrate the skin and are thus useful for dermatological diseases or conditions characterized by loss of moisture.

Sticks

[00182] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation is in the form of a stick. In certain instances, sticks are solid dosage forms that melt at body temperature. In some embodiments, a stick comprises a wax, a polymer, a resin, dry solids fused into a firm mass, and/or fused crystals. In some embodiments, a topical formulation of a DP_2 receptor

antagonist compound is in the form of a styptic pencil (i.e., a stick prepared by (1) heating crystals until they lose their water of crystallization and become molten, and (2) pouring the molten crystals into molds and allowing them to harden). In some embodiments, a topical formulation of a DP_2 receptor antagonist compound is in the form of stick wherein the stick comprises a wax (e.g., the wax is melted and poured into appropriate molds in which they solidify in stick form).

[00183] In some embodiments, a topical formulation of a DP_2 receptor antagonist compound is in the form of stick wherein the stick comprises a melting base (i.e., a base that softens at body temperature). Examples of melting bases include, but are not limited to, waxes, oils, polymers and gels. In some embodiments, a topical formulation of a DP_2 receptor antagonist compound is in the form of stick wherein the stick comprises a moisten base (i.e., a base that is activated by the addition of moisture).

Patches

[00184] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation is administered via a patch. In some embodiments, a topical formulation disclosed herein is dissolved and/or dispersed in a polymer or an adhesive. In some embodiments, a patch disclosed herein is constructed for continuous, pulsatile, or on demand delivery of a DP_2 receptor antagonist compound.

Wound Dressings

[00185] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation is administered with (or via) a wound dressing. Wound dressings include, but are not limited to gauzes, transparent film dressings, hydrogels, polyurethane foam dressings, hydrocolloids and alginates. In certain instances, wound dressings (1) maintain moisture in the wound, (2) are semipermeable, (3) are semiocclusive, (4) allow for autolytic debridement, (5) protect from external contaminants, (6) absorb exuded fluids, and/or (7) allow for wound visualization.

Dermatological Excipients

[00186] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation comprises a penetration enhancer. Penetration enhancers include, but are not limited to, hyaluronidase (e.g., PH-20), sodium lauryl sulfate, sodium laurate, polyoxyethylene-20-cetyl ether, laureth-9, sodium dodecylsulfate, dioctyl sodium sulfosuccinate, polyoxyethylene-9-lauryl ether (PLE), Tween 80, nonylphenoxypolyethylene (NP-POE), polysorbates, sodium glycocholate,

sodium deoxycholate, sodium taurocholate, sodium taurodihydrofusidate, sodium glycodihydrofusidate, oleic acid, caprylic acid, mono- and di-glycerides, lauric acids, acylcholines, caprylic acids, acylcarnitines, sodium caprates, EDTA, citric acid, salicylates, DMSO, decylmethyl sulfoxide, ethanol, isopropanol, propylene glycol, polyethylene glycol, glycerol, propanediol, diethylene glycol monoethyl ether, and alkyl glycosides (e.g., dodecyl maltoside).

[00187] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation comprises a gelling (or thickening) agent. In some embodiments, a topical formulation disclosed herein further comprises from about 0.1% to about 5%, more preferably from about 0.1% to about 3%, and most preferably from about 0.25% to about 2%, of a gelling agent. In certain embodiments, the viscosity of a topical formulation disclosed herein is in the range from about 100 to about 500,000 cP, about 100 cP to about 1,000 cP, about 500 cP to about 1500 cP, about 1000 cP to about 3000 cP, about 2000 cP to about 8,000 cP, about 4,000 cP to about 10,000 cP, about 10,000 cP to about 50,000 cP.

[00188] Suitable gelling agents for use in preparation of the gel topical formulation include, but are not limited to, celluloses, cellulose derivatives, cellulose ethers (e.g., carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose), guar gum, xanthan gum, locust bean gum, alginates (e.g., alginic acid), silicates, starch, tragacanth, carboxyvinyl polymers, carrageenan, paraffin, petrolatum, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium stearate, bladderwrack, bentonite, carbomer, carrageenan, carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), ceratonia, chondrus, dextrose, furcellaran, gelatin, ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, polyethylene glycol (e.g. PEG 200-4500), gum tragacanth, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, polygeline, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxyethoxyethyl methacrylate), hydroxypropyl cellulose, hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl-cellulose (CMC), silicon dioxide, polyvinylpyrrolidone (PVP: povidone), or combinations thereof.

[00189] Gels include a single-phase or a two-phase system. A single-phase gel consists of organic macromolecules distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Some single-phase gels are prepared from synthetic macromolecules (e.g., carbomer) or from natural gums, (e.g., tragacanth). In some embodiments, single-phase gels are generally aqueous, but will also be made using alcohols and oils. Two-phase gels consist of a network of small discrete particles.

[00190] Gels can also be classified as being hydrophobic or hydrophilic. In certain embodiments, the base of a hydrophobic gel consists of a liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, or aluminum or zinc soaps. In contrast, the base of hydrophobic gels usually consists of water, glycerol, or propylene glycol gelled with a suitable gelling agent (e.g., tragacanth, starch, cellulose derivatives, carboxyvinylpolymers, and magnesium-aluminum silicates).

[00191] Suitable agents for use in fomulations that are applied as liquids and gel upon application to the skin into a film include but are not limited to polymers composed of polyoxypropylene and polyoxyethylene that are known to form thermoreversible gels when incorporated into aqueous solutions. These polymers have the ability to change from the liquid state to the gel state at temperatures close to body temperature, therefore allowing useful formulations that are applied as gels and/or films to the affected area. Examples of polymers that gel at body temperature and are used in gels and/or films described herein include and are not limited to poloxamers (e.g., PLURONICS F68®, F88®, F108®, and F127®, which are block copolymers of ethylene oxide and propylene oxide). The liquid state-to-gel state phase transition is dependent on the polymer concentration and the ingredients in the solution.

[00192] In some embodiments, the formulations and compositions disclosed herein are administered as a dermal paint. As used herein, paints (also known as film formers) are solutions comprised of a solvent, a monomer or polymer, an active agent, and optionally one or more pharmaceutically-acceptable excipients. After application to a tissue, the solvent evaporates leaving behind a thin coating comprised of the monomers or polymers, and the active agent. The coating protects active agents and maintains them in an immobilized state at the site of application. This decreases the amount of active agent which may be lost and correspondingly increases the amount delivered to the affected area of the skin of an individual. By way of non-limiting example, paints include collodions (e.g.

Flexible Collodion, USP), and solutions comprising saccharide siloxane copolymers and a cross-linking agent. Collodions are ethyl ether/ethanol solutions containing pyroxylin (a nitrocellulose). After application, the ethyl ether/ethanol solution evaporates leaving behind a thin film of pyroxylin. In solutions comprising saccharide siloxane copolymers, the saccharide siloxane copolymers form the coating after evaporation of the solvent initiates the cross-linking of the saccharide siloxane copolymers.

[00193] In some instances, the topical formulations described herein comprise pressure sensitive adhesives (e.g., polyalkyloxazoline polymers) and allow for application of an adhesive film to an affected area of skin.

[00194] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation comprises an emollient. Emollients include, but are not limited to, castor oil esters, cocoa butter esters, safflower oil esters, cottonseed oil esters, corn oil esters, olive oil esters, cod liver oil esters, almond oil esters, avocado oil esters, palm oil esters, sesame oil esters, squalene esters, kikui oil esters, soybean oil esters, acetylated monoglycerides, ethoxylated glyceryl monostearate, hexyl laurate, isohexyl laurate, isohexyl palmitate, isopropyl palmitate, methyl palmitate, decyloleate, isodecyl oleate, hexadecyl stearate decyl stearate, isopropyl isostearate, methyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate, oleyl myristate, oleyl stearate, and oleyl oleate, pelargonic acid, lauric acid, myristic acid, palmitic acid, stearic acid, isostearic acid, hydroxystearic acid, oleic acid, linoleic acid, ricinoleic acid, arachidic acid, behenic acid, erucic acid, lauryl alcohol, myristyl alcohol, cetyl alcohol, hexadecyl alcohol, stearyl alcohol, isostearyl alcohol, hydroxystearyl alcohol, oleyl alcohol, ricinoleyl alcohol, behenyl alcohol, erucyl alcohol, 2-octyl dodecanyl alcohol, lanolin and lanolin derivatives, beeswax, spermaceti, myristyl myristate, stearyl stearate, carnauba wax, candelilla wax, lecithin, and cholesterol.

[00195] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation comprises abrasives, absorbents, anticaking agents, astringents, essential oils, fragrances, skin-conditioning agents, skin healing agents, skin protectants (e.g., sunscreens, or ultraviolet light absorbers or scattering agents), skin soothing agents, or combinations thereof.

[00196] Pharmaceutical topical formulations disclosed herein are formulated in any suitable manner. Any suitable technique, carrier, and/or excipient is contemplated for use with the

DP_2 receptor antagonist compounds disclosed herein. For a summary of pharmaceutical topical formulations described herein *see 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*, Eighth Ed. (Lippincott Williams & Wilkins 2004), Muller, R.H. et al. Advanced Drug Delivery Reviews 59 (2007) 522-530, which are herein incorporated by reference for such disclosures.

[00197] In some embodiments, any dermal formulation described herein comprises between about 0.1 to about 50%, between about 0.1 to about 25%, between about 0.1 to about 10%, between about 0.1 to about 5%, or between about 0.1 to about 1% of a DP_2 receptor antagonist by weight of the formulation.

Dosing

[00198] Disclosed herein, in certain embodiments, is a topical formulation of a DP_2 receptor antagonist compound wherein the topical formulation administered for prophylactic and/or therapeutic treatments. In certain instances, amounts effective for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the individual's health status and response to the drugs, and the judgment of the treating physician.

[00199] In some embodiments, where a dermatological disease or condition does not improve, a topical formulation disclosed herein is administered chronically (i.e., for an extended period of time, including throughout the duration of the individual's life). In some embodiments, where a dermatological disease or condition does improve, a topical formulation disclosed herein is given continuously; alternatively, the dose of active agent being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In some embodiments, a drug holiday lasts between 2 days and 1 year, including all integers in between. In some embodiments, the dose reduction during a drug holiday is from about 10% to about 100%, including all integers in between.

[00200] In some embodiments, where a dermatological disease or condition does improve, a topical formulation disclosed herein is administered as a maintenance dose. In some embodiments, where a dermatological disease or condition does improve, a topical formulation disclosed herein is administered with reduced frequency or at a reduced dose.

[00201] In one embodiment, a topical formulation disclosed herein is formulated for controlled release of a DP_2 receptor antagonist compound. In some embodiments, a DP_2 receptor antagonist compound is released over a time period exceeding 15 minutes, or 30 minutes, or 1 hour, or 4 hours, or 6 hours, or 12 hours, or 18 hours, or 1 day, or 2 days, or 3 days, or 4 days, or 5 days, or 6 days, or 7 days, or 10 days, or 12 days, or 14 days, or 18 days, or 21 days, or 25 days, or 30 days, or 45 days, or 2 months or 3 months or 4 months or 5 months or 6 months or 9 months or 1 year.

Examples

[00202] The following examples are illustrative and non-limiting to the scope of the formulations and methods described herein.

Example 1: Topical formulation of a DP_2 receptor antagonist compound

[00203] A topical formulation of a DP_2 receptor antagonist compound is prepared by mixing a DP_2 receptor antagonist compound with propylene glycol, transcutol and water. In one aspect, the topical formulation includes a DP_2 receptor antagonist compound (10 mg/mL) in a solution of 75% propylene glycol, 15% transcutol, 10% water.

Example 2: Lotion formulation of DP_2 receptor antagonist compound

[00204] A DP_2 receptor antagonist compound (15 g) is mixed ethanol. Tween 80 (5 mL) is added. Carbopol 974 is dispersed in 1 L water and the ethanol mixture is slowly added to the aqueous mixture. The mixture is stirred and the volume is adjusted to 1500 mL with purified water.

Example 3: Hydrogel formulation of DP_2 receptor antagonist compound

[00205] DP_2 receptor antagonist compound (150 g), benzyl alcohol (40 mL), and glycerin are added to about 3200 mL of purified water. Slowly add Pluronic F127 (45 g) into the mixture. Adjust pH to 7.0 with phosphate buffer. Add purified water to bring the volume to 4000 mL. Finally, add trolamine (dropwise) until a gel is formed.

Example 4: Stick formulation of DP_2 receptor antagonist compound

[00206] A mixture of melted beeswax (300 g), cocoa butter (50 g), paraffin (125 g) and lanolin (50 g) is added to a mixture of DP_2 receptor antagonist compound (50 g) and petrolatum (180 g). The mixture is stirred for 40 minutes and poured into molds.

Example 5: DP_2/CRTH2 binding assay

[00207] The ability of a compound to bind to the human DP_2 receptor is assessed via a radioligand binding assay using [^{3}H]PGD_2. HEK293 cells stably expressing recombinant human DP_2 are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT, lysed and

centrifuged at 75,000 xg to pellet the membranes. The membranes are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT and 10% glycerol to approximately 5 mg protein/ml. Membranes (2-10 μg protein/well) are incubated in 96-well plates with 1 nM [^{3}H]PGD_2 and test compound in Assay Buffer (50 mM Hepes, 10 mM $MnCl_2$, 1 mM EDTA, plus or minus 0.2% human serum albumin, pH 7.4) for 60 minutes at room temperature. The reactions are terminated by rapid filtration through Whatman GF/C glass fibre filter plates. The filter plates were pre-soaked in 0.33% polythylenimine for 30 minutes at room temperature then washed in Wash Buffer (50 mM Hepes, 0.5 M NaCl pH 7.4) prior to harvesting. After harvesting, the filter plates are washed 3 times with 1 ml cold Wash Buffer then dried. Scintillant is then added to the plates and the radioactivity retained on the filters is determined on a Packard TopCount (Perkin Elmer). Specific binding is determined as total radioactive binding minus non-specific binding in the presence of 10 μM PGD_2. IC_{50}s were determined using GraphPad prism analysis of drug titration curves.

Example 6: DP_1 binding assay

[00208] The ability of a compound to bind to the human DP1 receptor was evaluated via a radioligand membrane binding assay using the DP_1 selective synthetic ligand [^{3}H]BWA868C. Packed human platelets (Biological Specialty Corporation), were resuspended in 6 volumes of Hepes/HBSS buffer (10 mM Hepes, 1 mM DTT in Hanks Balanced Salt Solution (HBSS)), lysed and centrifuged at 75,000 xg to pellet the membranes. Membranes were resuspended in Hepes/HBSS buffer to approximately 12 mg protein/ml. Membranes (20 μg protein/well) are incubated in 96-well plates with 2 nM [^{3}H]BWA868C and test compound in Assay Buffer (50 mM Hepes, 10 mM $MnCl_2$, 1 mM EDTA, plus or minus 0.2% human serum albumin, pH 7.4) for 60 minutes at room temperature. The reactions are terminated by rapid filtration through Whatman GF/C glass fibre filter plates. The filter plates were pre-soaked in 0.33% polethylenimine for 30 minutes at room temperature then washed in Wash Buffer (50 mM Hepes, 0.5 M NaCl pH 7.4) prior to harvesting. After harvesting, the filter plates are washed 3 times with 1 ml cold Wash Buffer then dried. Scintillant is then added to the plates and the radioactivity retained on the filters is determined on a Packard TopCount (Perkin Elmer). Specific binding is determined as total radioactive binding minus non-specific binding in the presence of 10 μM BW A868C. IC_{50}s were determined using GraphPad prism analysis of drug titration curves.

[00209] Representative data for compounds tested in Example 5 and Example 6 is presented in the following table.

Table 1. Representative Biological Data

Compound	hDP2 μM	hDP1 μM
[2'-(3-Benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid	A	C
{3-[2-tert-Butylsulfanylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-methoxy-phenyl}-acetic acid	A	C
{2'-[(N-cyclopropanecarbonyl-N-ethyl-amino)-methyl]-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl}-acetic acid	A	C
[2'-[(N-cyclopropanecarbonyl-N-ethyl-amino)-methyl]-4'-(6-ethoxy-pyridin-3-yl)-6-methoxy-biphenyl-3-yl]-acetic acid	A	C
(5-{2-[(N-benzyloxycarbonyl-N-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid	A	C
{8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid	A	C
Ramatroban	B	C

A = less than 0.3 μM; B = greater than 0.3 μM but less than 1 μM; C= greater than 1 μM.

Example 7: Rabbit Wound Healing and Hypertrophic Scar Model

[00210] Following anesthesia, ear wounds are created in 10 young adult female New Zealand rabbits, 4 wounds per ear on each ear for a total of 8 wounds per animal. Wounds were created using a 7-mm biopsy punch with the wound created to go to bare cartilage. A dissecting microscope is used to ensure complete removal of the epidermis, dermis and perichondrium in each wound. For the hypertrophic scar model, it is the removal of the perichondrial layer and subsequent delay in reepithelialization of the defect that results in the elevated scar. Each wound heals independently and is considered a separate sample.

[00211] Two treatment groups are examined to study the early phase and a later phase of wound healing. The early treatment group (n=15 rabbits, 120 wounds) are treated with either the test compound formulated as a 0.05 - 1.5% by weight topical formulation (solution, cream, ointment or gel) or placebo using the topical vehicle formulation post-wounding on days 0, 1, 2, 3, 4, 5, 6 and 7 and harvested on day 28 after wounding. The later treatment group (n=15 rabbits, 120 wounds) are treated with either the test compound formulated as a 0.05 - 1.5% topical formulation (solution, cream, ointment or gel) or placebo using the topical vehicle formulation post-wounding on days 7, 8, 9, 10, 11, 12, 13 and 14 and harvested on day 28 after wounding. Half of the wounds in each group are treated with active compound and half are treated with placebo. Each wound is covered with a sterile dressing (Tegaderm; 3M) and dressings are changed daily following each treatment and as needed until the wound appears reepithelialized on gross examination. Wounds are excluded from analysis if there is evidence of infection, desiccation or necrosis.

[00212] At the end of each study wounds are harvested with a 5-mm margin of surrounding unwounded tissue. The scars are bisected and half of each wound is fixed in 4% neutral-buffered formaldehyde, dehydrated, embedded in paraffin, cut in 4-μm sections, and stained with Masson's trichrome or sirrus red. The other half of each wound is flash frozen in liquid nitrogen and stored for RNA extraction

Histologic Analysis

[00213] Light microscopy is used to examine each tissue section and the degree of wound healing and scar hypertrophy are measured with a calibrated lens reticle in a blinded fashion. Wound healing parameters: Relevant measurements are granulation tissue ingrowth volume and height, wound epithelialization, and wound closure. Each parameter is assessed twice and the results are averaged.

[00214] Scar hypertrophy parameters: The scar elevation index is determined as described by Lu *et al*, *J. Am. Coll. Surg.*, 2005, 201, p391-397. The values are determined twice by in a blinded fashion and the results averaged.

Example 8: Rat abraded skin model to test for acute irritancy and skin penetration following dermal administration:

[00215] Male Sprague Dawley Rats (n = 3 per group) are shaved on the back such that approximately 20% of the body area surface is exposed. The shaved skin is mildly abraded then 2 mL of a 10 mg/mL solution of the test compound in a formulation containing 75% propylene glycol, 15% transcutol, 10% water is applied to the abraded skin. The site of administration is occluded for 24 hours after which time the skin is cleansed of excess material (if any). Plasma samples are drawn from each rat at 2, 4, 24 and 72 hours.

[00216] Visual analysis of erythema, edema or other dermal findings are recorded prior to dosing then at 24, 48 and 72 hours. Scoring follows a Draize protocol. A Draize score of zero indicates no irritancy of the formulation. The plasma levels of the compounds are recorded at 24 h.

Example 9: Effects of DP2 Antagonist on Mucin Levels

[00217] BALB/c mice were divided into groups and acclimatized in cages for 24 hours (day 0). The control group was exposed to air and the test group was exposed to smoke from seven unfiltered cigarettes per day for 8 days (day 1 to day 8). Mice were divided into groups and are administered compound starting at day 1 and up to day 13. On day 14, bronchoalveolar lavage fluid (BALF) is tested for influx of cells, cytokines, chemokines (e.g., KC, MIP-2, IL-6), mucin, and/or proteins. Lung histology is also examined. One

group received treatment with DP_2 receptor antagonist 5-{2-[(N-Benzyloxycarbonyl-N-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid (Compound 1; 10 mg/kg qd), a second group received treatment with FLAP inhibitor compound H (3-(3-(tert-butylthio)-1-(4-(6-methoxypyridin-3-yl)benzyl)-5-((5-methylpyridin-2-yl)methoxy)-1H-indol-2-yl)-2,2-dimethylpropanoic acid) (30 mg/kg, b.i.d.); and the third group received treatment with a combination of DP_2 receptor antagonist Compound 1 (10 mg/kg qd) and FLAP inhibitor compound H (30 mg/kg, b.i.d.).

[00218] **Figure 1** illustrates the effect of DP_2 receptor antagonism and FLAP inhibition on the number of total cells, neutrophils and lymhocytes present in BALF. **Figure 2** illustrates the effect of a combination of a DP_2 receptor antagonist and a FLAP inhibitor on the presence of mucin in BALF. In the subchronic smoking mouse model, the effects of a combination of a DP_2 receptor antagonist compound and a FLAP inhibitor compound on mucin secretion in BALF were additive, i.e., a combination of Compound 1 and Compound H reduced the amount of mucin in BALF more than each compound alone. In one aspect, the effects of topical administration of a DP_2 receptor antagonist, either alone or in combination with a FLAP inhibitor compound, to the skin has similar effects (e.g., is mechanistically expected to) in dermal tissues as observed in the BALF.

Example 10: Mouse Epicutaneous Sensitization Model

[00219] Using the procedure described in Boehme *et al*, *Internat. Immunol.*, 2009, 21(1), p1-17 mice are anaesthetized and the dorsal skin shaved. Gauze (1X1 cm^2) soaked in either PBS or 1% ovalbumin (Fraction VI) solution in PBS is placed on the exposed skin surface. The gauze is held in place using a bioocclusive dressing (e.g. IV3000 MPV transparent dressing) and after 3 days the gauze is replaced with a fresh gauze patch kept in place for 4 days such that the total sensitization period is 7 days. The mice have a 2 week interval, then the 7 day patch protocol is repeated followed by a second 2 week interval and then a third 7 day patch protocol is carried out. One day following the last of the three sensitizations (day 50) the mice are sacrificed, serum and patched skin collected for analysis. Mice are dosed orally either with vehicle or with a DP2 antagonist compound in vehicle daily during the second and third sensitization periods. The patched skin is examined by histology, mRNA and for cytokine and chemokine levels.

Example 11: Effect of a DP_2 Receptor Antagonist Compound on the Treatment of Canine Atopic Dermatitis

[00220] The protocol described in Nuttall *et al*, *Vet Dermatol*., 2009, 20(3), 191-198 was followed with modifications. Dogs with a canine atopic dermatitis (AD) extent and severity index (CADESI-03) > or = 50 are randomly allocated to receive either vehicle solution or drug solution (n = 15 each group) as a spray. Animals receive two sprays from 10 cm distance once a day for 28 days. The area treated is 100 cm^2. CADESI score, pruritis and owner satisfaction (using a 5 point scale) is evaluated at day 28. Haematology and drug plasma concentrations are measured at baseline and at day 7, day 14, day 21, and day 28.

Example 12: Effect of a DP_2 Receptor Antagonist Compound on the Treatment of Atopic Dermatitis

[00221] This is a double-blind, placebo-controlled, randomized study to evaluate the safety, efficacy and tolerability of a topically applied DP_2 receptor antagonist in the treatment of subjects with atopic dermatitis.

[00222] Subjects are to read and sign an informed consent agreement and must be willing to comply with the protocol. Exclusion criteria include a diagnosis of an acute systemic illness; suspected viral, fungal or bacterial infection of the skin; severe hepatic disease or renal impairment; systemic treatment within the preceding thirty days and topical treatment within the preceding 30 days. Pregnant or lactating women are excluded and women of child-bearing potential must have a documented negative urine pregnancy test and must be practicing a medically proven form of contraception during the course of the study.

[00223] Two hundred patients with clinically diagnosed atopic dermatitis based on the evaluation of seven disease signs are randomly allocated to a placebo group and a drug-treated group (randomized 5:3 to drug treatment:placebo). The seven disease signs (infiltration, scaling, erythema, lichenification, vesicles, papules, and excoriation) are each given a ranking using a four-point scale: absent (0), mild (1), moderate (2) and severe (3). The disease severity is determined by the total score for the seven clinical signs with a score ≥ 6 being required for study enrollment. The drug treated group receive a dermal administration of a DP_2 receptor antagonist compound formulated to an appropriate concentration of between 0.05 to 1.5% by weight in a clinically acceptable and safe topical formulation (solution, cream, ointment or gel). The placebo group receive the same topical formulation absent the active drug. Patients receive treatment once daily for 14 days with the treatment areas covering approximately 15% of the body surface on the basis of location, extent of involvement and severity of signs. Treatment is excluded on the face, hands, groin or axillae. Follow up study visits are scheduled for days 3, 7 and 14.

[00224] **Clinical Assessment** . The seven disease signs (infiltration, scaling, erythema, lichenification, vesicles, papules, and excoriation) are each given a ranking using the four-point scale. The primary efficacy evaluation is based on the change from the baseline in the total severity score measured on days 3, 7 and 14. The efficacy of the drug treatment is also assessed by the investigator at day 14 based on overall improvement using the following scale: cleared (1), excellent (2), good (3), fair (4), poor (5), no effect (6), exacerbated (7). Patients also provide a self assessment on the final visit answering questions on: ease of application, lack of odor, and feeling on skin. Patients and investigators individually also provide an assessment of efficacy based on: excellent (1), good (2), fair (3), or poor (4).

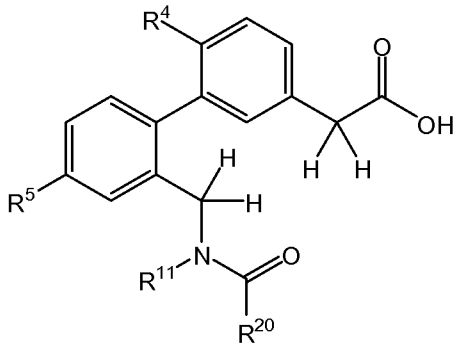
[00225] The examples and embodiments described herein are for illustrative purposes and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

CLAIMS

WHAT IS CLAIMED IS:

1. A topical formulation comprising a DP_2 receptor antagonist and at least one pharmaceutically acceptable excipient to provide an ointment, cream, lotion, paste, gel, stick, a film, a patch or wound dressing, wherein the topical formulation is suitable for administration to the skin of a mammal.

2. The topical formulation of claim 1, wherein the DP_2 antagonist is a compound having the structure of Formula (I), pharmaceutically acceptable salt, pharmaceutically acceptable solvates, or prodrug thereof:



Formula (I)

wherein,

R^4 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl;

R^5 is H, halogen, -CN, $-NO_2$, -OH, $-OR^{13}$, $-SR^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-NHS(=O)_2R^{12}$, $-C(=O)R^{12}$, $-OC(=O)R^{12}$, $-CO_2R^{13}$, $-OCO_2R^{13}$, $-CH(R^{13})_2$, $-N(R^{13})_2$, $-C(=O)N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NHC(=O)NH(R^{13})$, $-NHC(=O)R^{12}$, $-NHC(=O)OR^{12}$, $-C(OH)(R^{13})_2$, -C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

or R^5 is C_3-C_{10}cycloalkyl, a substituted or unsubstituted C_2-C_{10}heterocycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted or unsubstituted monocyclic heteroaryl, or a substituted or unsubstituted bicyclic heteroaryl, wherein if R^5 is substituted, then R^5 is substituted with 1 or 2 R^{21} groups;

R^{20} is C_1-C_4alkyl, C_3-C_6cycloalkyl, $-CH_2O$-C_1-C_4alkyl, $-CH_2O$-(substituted or unsubstituted phenyl), $-CH(CH_3)$-O-(substituted or unsubstituted phenyl), $-C(CH_3)_2$-O-(substituted or unsubstituted phenyl), $-CH_2OCH_2$-(substituted or unsubstituted phenyl), -OC_1-C_4alkyl, –O-CH_2-(substituted or unsubstituted

phenyl), –O-CH(CH_3)-(substituted or unsubstituted phenyl), -$NR^{16}$$C_1$-$C_4$alkyl, –$NR^{16}$-$CH_2$-(substituted or unsubstituted phenyl), or –NR^{16}-CH(CH_3)-(substituted or unsubstituted phenyl), wherein if the phenyl of R^{20} is substituted, then the phenyl is substituted with 1 or 2 R^{21} groups;

each R^{21} is independently selected from halogen, -OH, -OC_1-C_4alkyl, C_1-C_4alkyl, and -CF_3;

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

R^{11} is C_1-C_4alkyl, C_1-C_4fluoroalkyl, or C_3-C_6cycloalkyl;

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

each R^{13} is independently selected from H, C_1-C_4alkyl, C_1-C_4heteroalkyl, and C_1-C_4fluoroalkyl.

3. The topical formulation of claim 1, wherein the DP_2 antagonist is ramatroban, AMG 009, AMG 853, Compound 14 of WO 09/085177, AZD1981, AZD8075, AZD5985, ARRY-005, ARRY-006, ARRY-063, ODC9101 (OC459), OC499, OC1768, OC2125, OC2184, QAV680, MLN6095, ACT-129968, ADC3680, SAR398171, S555739, AP768, [2'-(3-Benzyl-1-ethyl-ureidomethyl)-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl]-acetic acid, {3-[2-tert-Butylsulfanylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-methoxy-phenyl}-acetic acid, TM30642, TM30643, TM30089, TM27632, and TM3170, {2'-[(N-cyclopropanecarbonyl-N-ethyl-amino)-methyl]-6-methoxy-4'-trifluoromethyl-biphenyl-3-yl}-acetic acid, [2'-[(N-cyclopropanecarbonyl-N-ethyl-amino)-methyl]-4'-(6-ethoxy-pyridin-3-yl)-6-methoxy-biphenyl-3-yl]-acetic acid, (5-{2-[(N-benzyloxycarbonyl-N-ethyl-amino)-methyl]-4-trifluoromethyl-phenyl}-pyridin-3-yl)-acetic acid, or {8-[(4-fluoro-benzenesulfonyl)-methyl-amino]-6,7,8,9-tetrahydro-pyrido[3,2-*b*]indol-5-yl}-acetic acid, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or prodrug thereof.

4. The topical formulation of any one of claims 1-3, wherein the topical formulation is used in the treatment of a prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition in a mammal.

5. The topical formulation of claim 4, wherein the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is scarring, a burn, dermal mucinosis, an immune disease or condition affecting the skin; a dermal proliferative disease or condition; an inflammatory disease or condition; a mast cell mediated

disease or condition; a Th2 lymphocyte mediated disease or condition; an infection or combinations thereof.

6. The topical formulation of claim 4, wherein the prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition is atopic dermatitis, allergic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, contact dermatitis, eczema, urticaria, rosacea, hypertrophic scarring, keloid scar formation, scleroderma, Folliculitis keloidalis nuchae, Kawasaki Disease, Sjogren-Larsso Syndrome, Grover's disease, a first degree burn, a second degree burn, a third degree burn, a fourth degree burn, cutaneous mucinosis, solar keratosis, squamous cell carcinoma or melanoma.

7. The topical formulation of any one of claims 1-3, wherein the topical formulation is used in the treatment of dermatitis, eczema, psoriasis, or cutaneous mucinosis.

8. The topical formulation of any one of claims 1-3, wherein the topical formulation is used for decreasing dermal mucin concentrations in a mammal.

9. The topical formulation of any one of claims 1-3, wherein the topical formulation is used in the treatment or prevention of itching in a mammal, in the treatment or prevention of a rash in a mammal, in the treatment or prevention of skin inflammation in a mammal.

10. The topical formulation of any one of claims 1-3, wherein the topical formulation is used in the treatment or prevention of blisters, redness, swelling, scabbing, scaling, or combinations thereof in a mammal.

11. The topical formulation of any one of claims 1-10, further comprising a second therapeutic agent.

12. Use of a DP_2 receptor antagonist compound in the treatment or prevention of a dermal disease or condition in a mammal.

13. The use of claim 12, wherein the DP_2 receptor antagonist compound is in a form suitable for topical administration to the skin of a mammal.

14. The use of claim 12 or claim 13, wherein the dermal disease or condition is a prostaglandin D_2-dependent or prostaglandin D_2-mediated dermal disease or condition.

15. The use of claim 12 or claim 13, wherein the dermal disease or condition is scarring, a burn, dermal mucinosis, an immune disease or condition affecting the skin; a dermal proliferative disease or condition; an inflammatory disease or condition; a

mast cell mediated disease or condition; a Th2 lymphocyte mediated disease or condition; an infection or combinations thereof.

16. The use of claim 12 or claim 13, wherein the dermal disease or condition is atopic dermatitis, allergic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, contact dermatitis, eczema, urticaria, rosacea, hypertrophic scarring, keloid scar formation, scleroderma, Folliculitis keloidalis nuchae, Kawasaki Disease, Sjogren-Larsso Syndrome, Grover's disease, a first degree burn, a second degree burn, a third degree burn, a fourth degree burn, cutaneous mucinosis, solar keratosis, squamous cell carcinoma or melanoma.
17. The use of claim 12 or claim 13, wherein the dermal disease or condition is dermatitis, eczema, psoriasis, or cutaneous mucinosis.
18. The use of claim 12 or claim 13, wherein the DP_2 receptor antagonist compound is used for decreasing dermal mucin concentrations in a mammal.
19. The use of claim 12 or claim 13, wherein the DP_2 receptor antagonist compound is used in treatment or prevention of itching in a mammal, in the treatment or prevention of a rash in a mammal, in the treatment or prevention of skin inflammation in a mammal.
20. The use of claim 12 or claim 13, wherein the DP_2 receptor antagonist compound is used in treatment or prevention of blisters, redness, swelling, scabbing, scaling, or combinations thereof in a mammal.
21. The use of any one of claims 12-20, further comprising a second therapeutic agent.
22. The use of claim 21, wherein the second therapeutic agent is an antibiotic, anti-fungal agent, steroid anti-inflammatory agent, non-steroidal anti-inflammatory agent, antihistamine, antiviral agent, mast cell stabilizer, cyclosporine, or a leukotriene modulator.
23. The use of claim 21, wherein the second therapeutic agent is a leukotriene modulator selected from 5-lipoxygenase (5-LO) inhibitors, 5-lipoxygenase activating protein (FLAP) inhibitors, and leukotriene receptor antagonists.