ANTAGONISTS OF PROSTAGLANDIN D2 RECEPTORS

Inventors: John Howard Hutchinson, San Diego, CA (US); Thomas Jon Seiders, San Diego, CA (US); Bowei Wang, Westfield, NJ (US); Jeannie M. Arruda, San Diego, CA (US); Brian Andrew Stearns, Encinitas, CA (US)

Assignee: Amira Pharmaceuticals, Inc., San Diego, CA (US)

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ABSTRACT

Described herein are compounds that are antagonists of PGD2 receptors. Also described are pharmaceutical compositions that include the compounds described herein, and methods of using such antagonists of PGD2 receptors, alone or in combination with other compounds, for treating respiratory, cardiovascular, and other PGD2-dependent or PGD2-mediated conditions or diseases.
Figure 1

Compound 1

Compound 4

Compound 7

Compound 2

Compound 5

Compound 8

Compound 3

Compound 6

Compound 9
Figure 2

Compound 10

Compound 11

Compound 12

Compound 13

Compound 14

Compound 15

Compound 16

Compound 17

Compound 18
Figure 4

Compound 29

Compound 30

Compound 31

Compound 32

Compound 33

Compound 34

Compound 35

Compound 36

Compound 37
Figure 6

Compound 49

Compound 53

Compound 57

Compound 50

Compound 54

Compound 58

Compound 51

Compound 55

Compound 59

Compound 52

Compound 56
Figure 7

Compound 60

Compound 63

Compound 66

Compound 61

Compound 64

Compound 67

Compound 62

Compound 65

Compound 68
Figure 8

Compound 69

Compound 70

Compound 71

Compound 72

Compound 73

Compound 74

Compound 75

Compound 76
ANTAGONISTS OF PROSTAGLANDIN D2 RECEPTORS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional patent application No. 61/078,311 entitled “HETEROCYCLIC ANTAGONISTS OF PROSTAGLANDIN D2 RECEPTORS” filed on Jul. 3, 2008, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases or conditions associated with prostaglandin D2.

BACKGROUND OF THE INVENTION

[0003] Prostaglandins have a diverse range of activities and have a well recognized role in pain and inflammation. Prostaglandin D2 (PGD2) is produced by mast cells, macrophages and Th2 lymphocytes in response to local tissue damage as well as allergic inflammation in diseases such as asthma, rhinitis, and atopic dermatitis. PGD2 binds to a number of receptors, which include the thromboxane-type prostaglandin (TP) receptor, PGD2 receptor (DP, also known as DP2), and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2; also known as DP3).

SUMMARY OF THE INVENTION

[0004] Presented herein are compounds, pharmaceutical compositions, and methods, for (a) diagnosing, preventing, or treating allergic and non-allergic inflammation, (b) mitigating adverse signs and symptoms that are associated with inflammation, and/or (c) controlling immunological, proliferative disorders. These disorders may arise from one or more of a genetic, iatrogenic, immunological, infectious, oncological, toxic, surgical, and/or traumatic etiology. In one aspect, the methods, compounds, pharmaceutical compositions, and medicaments described herein comprise antagonists of PGD2 receptors. In one aspect, the methods, compounds, pharmaceutical compositions, described herein comprise antagonists of DP2.

[0005] In one aspect provided herein are compounds of Formula (I), pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, which are antagonists of DP2, and are used to treat mammals suffering from one or more PGD2-dependent conditions or diseases, including, but not limited to, asthma, rhinitis, allergic conjunctivitis, atopic dermatitis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, interstitial lung fibrosis, arthritis, allergy, psoriasis, inflammatory bowel disease, adult respiratory distress syndrome, myocardial infarction, aneurysm, stroke, cancer, wound healing, endotoxic shock, pain, inflammatory conditions, eosinophilic esophagitis, eosinophil-associated gastrointestinal disorders (EGID), idiopathic hypertrophic pyloric stenosis, otitis, airway constriction, mucus secretion, nasal congestion, increased microvascular permeability and recruitment of eosinophils, urticaria, sinusitis, angioedema, anaphylaxis, chronic cough and Chung Strauss syndrome.

[0006] In one aspect, provided is a compound having the structure of Formula (I), or pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof:

[0007] wherein,
[0008] R4 is H or C1-Calkyl;
[0009] R4 is H, halogen, —CN, —OH, C1-Calkyl, C1-Cfluoroalkyl, C1-Cfluoroalkoxy, C1-Calkoxy, or C1-Calkylheteroalkyl;
[0010] R5 is —NR1SR2(═O)R32, —S(═O)NR2(═O)R32, —C(═O)NR2(═O)R32, —NH(═O)NR2(═O)R32, or —NR2C(═O)R32;
[0011] R3 is —C1-Calkyl, —C1-Calkoxycarbonyl, —C1-Calkoxy, —C1-Calkylheteroalkyl, —C1-Calkylcyloalkyl, —C1-Calkylcyloalkyl, 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 —C1-Calkyl(—substituted or unsubstituted phenyl);
[0012] R3 is C1-Calkyl, C1-Calkoxy, C1-Calkylcyloalkyl, C1-Calkoxy, —C1-Calkylcyloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted naphthyl, a substituted or unsubstituted benzyl, a substituted or unsubstituted 6-membered heteroaryl, or —C1-Calkyl(—substituted or unsubstituted phenyl);
[0013] R1 is H or C1-Calkyl; or
[0014] R2 is —C1-Calkyl and R3 is attracted to the same N atom to which they are attached to form a substituted or unsubstituted C2-C3-heterocycloalkyl;
[0015] x is 0, 1, or 2.

[0016] In one aspect, presented herein are the compounds of Formula (I) presented in Table 1, or pharmaceutically acceptable salts, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof.

[0017] Compounds of Formula (I) are antagonists of DP2.

[0018] In one aspect, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I). In some embodiments, the pharmaceutical compositions comprise at least one inactive pharmaceutically acceptable inactive ingredient selected from excipients, diluents, and carriers.

[0019] In certain embodiments, presented herein are methods for treating a PGD2-dependent condition or disease in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of Formula (I).

[0020] In another aspect, compounds of Formula (I) are used to treat or prevent inflammatory diseases or conditions. Inflammatory conditions include, but are not limited to, asthma, rhinitis, chronic obstructive pulmonary disease, pul-
monary hypertension, interstitial lung fibrosis, atherosclerosis, aortic aneurysm, myocardial infarction, and stroke.

[0021] In a specific aspect, provided herein is a method for treating asthma in a mammal comprising administering a therapeutically effective amount of a compound provided herein to the mammal in need.

[0022] In another aspect, compounds of Formula (I) are used to treat or prevent immunological disorders, including, but are not limited to, allergy or to excessive or inappropriate response to an endogenous or exogenous antigen. In certain embodiments, the immunological disorder that is characterized by immune dysregulation that is not accompanied by inflammation.

[0023] In additional aspects, such diseases or conditions are atopic and increases in, or abnormal localization of, PGD₂ is induced by other therapies or medical or surgical procedures. In other embodiments, the PGD₂-dependent or PGD₂ mediated condition or disease is caused by surgery.

[0024] In another aspect are methods for treating respiratory diseases or conditions in a mammal comprising administering to the mammal at least once an effective amount of at least one compound of Formula (I). In a further embodiment of this aspect, the respiratory disease is asthma. In a further embodiment of this aspect, the respiratory disease includes, but is not limited to, asthma, adult respiratory distress syndrome, allergic (extrinsic) asthma, non-allergic ( intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, neutrophilic asthma, ischemic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

[0025] In another aspect compounds described herein are used for treating rhinitis in a mammal. In a further embodiment of this aspect, compounds described herein are used for treating allergic (extrinsic) rhinitis, non-allergic (intrinsic) rhinitis, chronic rhinitis, allergen-induced rhinitis, aspirin-sensitive rhinitis, child-onset rhinitis, adult-onset rhinitis, occupational rhinitis, steroid-resistant rhinitis, seasonal rhinitis, perennial rhinitis, rhinosinusitis, and rhinopolyposis.

[0026] In another aspect are methods for treating chronic obstructive pulmonary disease comprising administering to the mammal at least once an effective amount of a compound of Formula (I). In a further embodiment of this aspect, chronic obstructive pulmonary disease includes, but is not limited to, chronic bronchitis and/or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis.

[0027] In another aspect are methods for preventing increased mucosal secretion and/or edema in mammals comprising administering to the mammal at least once an effective amount of a compound of Formula (I).

[0028] In another aspect are methods for preventing eosinophil and/or basophil and/or dendritic cell and/or neutrophil and/or monocyte or Th2 cell recruitment comprising administering to the mammal an effective amount of a compound of Formula (I).

[0029] In another aspect are methods for treating or preventing ocular inflammation, conjunctivitis, retinitis, scleritis, uveitis, allergic conjunctivitis, vernal keratoconjunctivitis, and papillary conjunctivitis comprising administering to the mammal at least once an effective amount of a compound of Formula (I).

[0030] In another aspect, compounds of Formula (I) are used to treat or prevent pain.

[0031] In another aspect are methods for preventing or treating acute or chronic disorders involving recruitment or activation of eosinophils comprising administering to the mammal at least once an effective amount of a compound of Formula (I).

[0032] In another aspect are methods for treating inflammatory responses of the skin comprising administering to the mammal at least once an effective amount of at least one compound of Formula (I). Such inflammatory responses of the skin include, by way of example, psoriasis, dermatitis, atopic dermatitis, contact dermatitis, eczema, urticaria, rhusce, bullous disorders, collagenoses, Kawasaki Disease, Sjogren-Larsen Syndrome, wound healing and scarring. In another aspect are methods for reducing psoriatic lesions in the skin, joints, or other tissues or organs, comprising administering to the mammal an effective amount of a compound of Formula (I). In another aspect are methods for reducing psoriatic lesions in the skin, joints, or other tissues or organs, comprising administering at least once to the mammal an effective amount of a compound of Formula (I).

[0033] In a further aspect are methods to modulate the immune response to endogenous or exogenous antigens. In a further aspect are methods to treat acute or chronic allergic responses to exogenous substances that have been ingested such as foods (e.g., peanuts) or drugs (e.g., penicillin, non-steroidal anti-inflammatory drugs or the like).

[0034] In another aspect is the use of a compound of Formula (I) in the manufacture of a medicament for treating an inflammatory disease or condition in a mammal in which the activity of at least one PGD₂-associated protein contributes to the pathology and/or symptoms of the disease or condition. In one embodiment of this aspect, the PGD₂-associated protein is DP2. In another further embodiment of this aspect, the inflammatory disease or conditions are respiratory, cardiovascular, or proliferative diseases.

[0035] “Cardiovascular disease or conditions,” refers to diseases affecting the heart or blood vessels or both, including but not limited to: arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis; stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure; shock; vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue.

[0036] In any of the aforementioned aspects are further embodiments in which: (a) the effective amount of the compound is systemically administered to the mammal; and/or (b) the effective amount of the compound is administered orally to the mammal; and/or (c) the effective amount of the compound is intravenously administered to the mammal; and/or (d) the effective amount of the compound administered by inhalation; and/or (e) the effective amount of the compound is administered by nasal administration; and/or (f) the effective amount of the compound is administered by injection to the mammal; and/or (g) the effective amount of
the compound is administered topically (dermal) to the mamma-
mal; and/or (b) the effective amount of the compound is
administered by ophthalmic administration; and/or (i) the
effective amount of the compound is administered rectally to
the mammal.
[0037] In any of the aforementioned aspects are further
embodiments comprising single administrations of the effec-
tive amount of the compound, including further embodi-
ments in which (i) the compound is administered once; (ii)
the compound is administered to the mammal multiple times
over the span of one day; (iii) continually; or (iv) continually.
[0038] In any of the aforementioned aspects are further
embodiments comprising multiple administrations of the
effective amount of the compound, including further embodi-
ments in which (i) the compound is administered once daily;
(ii) the compound is administered twice daily; (iii) the com-
pound is administered in cycles that include daily adminis-
tration for a period of time followed by at least 1 day without
administration; (iv) the compound is administered in cycles
that include daily administration for a period of time followed
by at least 1 day that includes a dose reduction in the daily
amount of compound that is administered.
[0039] In any of the aforementioned aspects involving
the treatment of PGD₂, dependent diseases or conditions are fur-
ther embodiments comprising administering at least one
additional agent in addition to the administration of a com-
pound having the structure of Formula (I).
[0040] In any of the aforementioned aspects involving the
prevention or treatment of inflammation are further embodi-
ments comprising: (a) monitoring inflammation in a mamma-
mal; (b) measuring bronchoconstriction in a mammal; (c)
measuring eosinophil and/or basophil and/or dendritic cell
and/or neutrophil and/or monocyte and/or lymphocyte
recruitment in a mammal; (d) monitoring mucosal secretion
in a mammal; (e) measuring mucosal edema in a mammal.
[0041] Other objects, features and advantages of the com-
pounds, 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 embodi-
ments, 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
[0042] FIG. 1. Illustrative examples of compounds
described herein.
[0043] FIG. 2. Illustrative examples of compounds
described herein.
[0044] FIG. 3. Illustrative examples of compounds
described herein.
[0045] FIG. 4. Illustrative examples of compounds
described herein.
[0046] FIG. 5. Illustrative examples of compounds
described herein.
[0047] FIG. 6. Illustrative examples of compounds
described herein.
[0048] FIG. 7. Illustrative examples of compounds
described herein.
[0049] FIG. 8. Illustrative examples of compounds
described herein.

DETAILED DESCRIPTION OF THE INVENTION
[0050] Prostaglandin D₂ (PGD₂) is an acidic lipid derived
from the metabolism of arachidonic acid by cyclooxygenases
and PGD₂ synthases. PGD₂ is produced by mast cells, mac-
rophages and Th2 lymphocytes in response to local tissue
damage as well as in response allergic inflammation observed
in diseases such as asthma, rhinitis, and atopic dermatitis.
Exogenous PGD₂ applied to bronchial airways elicits many
responses that are characteristic of acute asthma.
[0051] Activation of DP₂ is associated with chemotaxis
and activation of Th2 lymphocytes, eosinophils and basophils.
PGD₂ binds to DP₂ and mediates many of its effects through
a G₂- 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 DP₂
activation. These cytokines have been implicated in numerous
biological actions including, by way of example only, immuno-
globulin E production, airway response, mucous secretion,
and eosinophil recruitment.
[0052] In the brain and central nervous system, PGD₂ is
produced and thought to function in pain perception and sleep
regulation. In other tissues, PGD₂ is produced primarily in
immunoglobulin E (IgE)T-activated mast cells and to a lesser
extent, in macrophages, dendritic cells, T helper 2 (Th2)
lymphocytes and other leukocytes. In the cell, PGD₂ is rap-
idly metabolized and converted to other downstream effectors
including 13,14-dihydro-15-keto-PGD₂, and 15-deoxy-Δ12,14-PGD₂.
[0053] Most-cell-derived PGD₂ is produced in high con-
centrations in response to an allergen challenge. Studies in
preclinical species have observed the following features
when PGD₂ is applied in vivo preparations, or its overpro-
duction is engineered by genetic manipulation: vasodilatation
leading to erythema (flare) and potentiation of oedema (deal)
recruitment of eosinophils and Th2 lymphocytes, modulation of
Th2-cytokine production, bronchoconstriction.
[0054] Injection of PGD₂ into human skin has been shown
to produce a long lasting erythema, to potentiate the effects of
other mediators on induction and leukocyte infiltration in
human skin and to enhance oedema formation in rat skin. It
is most likely that these effects of PGD₂, like those of other
vasodilator prostaglandins, are due to an increased blood flow
to the inflamed lesion and are, therefore, most likely to be
mediated predominantly by the DP₂ receptor. Although these
observations make it clear that DP₂ mediates the vascular
effects of PGD₂, the capacity of PGD₂ to promote the cellular
changes associated with inflammation is not due to an action
on DP₂.
[0055] Much of PGD₂’s pro-inflammatory activity is
through interaction with DP₂, DP₂ is a G-protein coupled
receptor and is typically highly expressed in Th2 lympho-
cytes, eosinophils and basophils. DP₂ activation functions
to directly activate and recruit Th2 lymphocytes and eosino-
phils. Activated Th2 lymphocytes produce and secrete
inflammatory cytokines including IL-4, IL-5, and IL-13.
Despite binding PGD₂ with a similar affinity as DP₂, DP₂ is
not structurally related to DP₂, and signals through a different
mechanism—the effects of DP₂ are mediated through G₂-
dependent elevation in intracellular calcium levels and reduc-
tion in intracellular levels of cyclic AMP. DP₂ activation
is important in eosinophil recruitment in response to allergi-
challenge in such tissues as nasal mucosa, bronchial airways,
and skin. The application of either PGD₂ or selective DP₂
agonists both exacerbate and enhance allergic responses in lung and skin. DP2 activation appears to have a crucial role in mediating allergic responses. The use of antagonists of PGD2 activation of the DP2 receptor is an approach to treat the inflammatory component of inflammatory diseases or conditions, respiratory diseases or conditions, allergic diseases or conditions, such as asthma, rhinitis, and dermatitis, among others.

Compounds

[0056] Compounds of Formula (I) have the following structure:

![Formula (I)](image)

[0057] wherein,

[0058] R1 is H or C1-Calkyl;

[0059] R2 is H, halogen, —CN, —OH, C1-Calkyl, C1-Calkoxy, or C1-Calkylsilyl;

[0060] R3 is —NR1(S(==O)2)R12, —N(S(==O)2)N(R12)(R13), —N(==O)N(R12)(R13), —NHC(==O)N(R12)(R13), —NR1C(==O)R12, or —NR1C(==O)OR12;

[0061] R11 is C1-Calkyl, C1-Calkoxy, C1-Calkylsilyl, or C1-Calkylsilylalkyl, 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 —C1-Calkyl(—substituted or unsubstituted phenyl);

[0062] R7 is C1-Calkyl, C1-Calkylsilyl, C1-Calkoxy, C1-Calkylsilylalkyl, a substituted or unsubstituted naphthyl, a substitutted or unsubstituted benzy1, a substituted or unsubstituted 6-membered heteroaryl, or —C1-Calkyl(—substituted or unsubstituted phenyl);

[0063] R12 is H or C1-Calkyl; or

[0064] R12 and R13 attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted C1-Calkylsilylalkyl;

[0065] x is 0, 1, or 2.

[0066] For any and all of the embodiments, substituents can be selected from among from a subset of the listed alternatives.

[0067] For example, in some embodiments, R1 is H or C1-Calkyl. In other embodiments, R1 is H, —CH3, or —CH3CH3. In some embodiments, R2 is H.

[0068] In some embodiments, x is 0 (sulfide). In some embodiments, x is 1 (sulfoxide). In some embodiments, x is 2 (sulfone).

[0069] In some embodiments, R4 is H, F, Cl, Br, —OH, C1-Calkyl, C1-Calkoxy, C1-Calkylsilylalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted 5-membered heteroaryl, or —C1-Calkyl(—substituted or unsubstituted phenyl).

[0070] In some embodiments, R2 is C1-Calkyl, C1-Calkoxy, C1-Calkylsilylalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted 5-membered heteroaryl, or —C1-Calkyl(—substituted or unsubstituted phenyl); a substituted or unsubstituted phenyl; or —C1-Calkyl(—substituted or unsubstituted phenyl);

[0071] In some embodiments, the compound of Formula (I) has the structure of Formula (II):

![Formula (II)](image)

[0072] In some embodiments, R11 is C1-Calkyl, C1-Calkoxy, C1-Calkylsilylalkyl, a substituted or unsubstituted phenyl, or —C1-Calkyl(—substituted or unsubstituted phenyl);

[0073] In some embodiments, R4 is H, F, Cl, Br, —OCH3, —CH3, —CH2CH3, —CH2CH2CH3, —CHF2, —CF3, —OCH2F2, —OCH2CH3, or —OCH2CH2CH3. In some embodiments, R4 is F, Cl, Br, —OCH3, —CH3, —CH2CH3, —CH2CH2CH3, —CHF2, —CF3, —OCH2F2, —OCH2CH3, or —OCH2CH2CH3. In some embodiments, R4 is —OCH3.

[0074] In some embodiments, R12 is C1-Calkyl, C1-Calkoxy, C1-Calkylsilylalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted 6-membered heteroaryl, or —C1-Calkyl(—substituted or unsubstituted phenyl).

[0075] In some embodiments, R13 is H or —CH3. In some embodiments, R13 is H.

[0076] In some embodiments, R3 is —NR1(S(==O)2)R12, —N(S(==O)2)N(R12)(R13), —N(==O)N(R12)(R13), —NHC(==O)N(R12)(R13), —NR1C(==O)R12, or —NR1C(==O)OR12.

[0077] In some embodiments, R3 is —N(R12)(R13), —C(==O)N(R12)(R13), —NHC(==O)N(R12)(R13), —NR1C(==O)R12, or —NR1C(==O)OR12.

[0078] In some embodiments, R1 is C1-Calkyl, C1-Calkoxy, C1-Calkylsilylalkyl, a substituted or unsubstituted phenyl, or —C1-Calkyl(—substituted or unsubstituted phenyl). In some embodiments, R1 is C1-Calkyl or C1-Calkoxy, C1-Calkylsilylalkyl. In some embodiments, R1 is C1-Calkyl or C1-Calkoxy, C1-Calkylsilylalkyl. In some embodiments, R1 is C1-Calkyl. In some embodiments, R1 is C1-Calkyl. In some embodiments, R1 is C1-Calkyl.
In some embodiments, R12 is C1-C3 alkyl, C1-C6 cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted benzyl. In some embodiments, R12 is C1-C3 alkyl or C1-C6 cycloalkyl. In some embodiments, R12 is C1-C3 alkyl.

In some embodiments, R11 is —CH2CH3, —CH(CH3)2, —C(CH3)3, —CH2CF3, a substituted or unsubstituted phenyl, —C1-C6 alkyl-(substituted or unsubstituted phenyl). In some embodiments, R11 is —CH2CH3, —CH(CH3)2, —C(CH3)3, or —CH2CF3.

In some embodiments, R12 is —CH(CH3)3, —C(CH3)3, —CH2CH(CH3)2, —CH2C(CH3)3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted benzyl. In some embodiments, R12 is —CH(CH3)3, —C(CH3)3, —CH2CH(CH3)2, —CH2C(CH3)3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or a substituted or unsubstituted phenyl. In some embodiments, R12 is —C(CH3)3, or a substituted or unsubstituted phenyl. In some embodiments, R12 is —C(CH3)3.

In some embodiments, R12 is a substituted or unsubstituted phenyl. In some embodiments, R12 is a substituted phenyl, where the phenyl is substituted in the 4-position. In some embodiments, R12 is a substituted or unsubstituted phenyl, where the substituted phenyl is substituted with 1 or 2 groups selected from halogen, —OH, —CN, —CH2Cl, —CH2CH2Cl, —CF3, —OCF3, —OCH2CH3, and —OCF3.

In some embodiments, R12 is —NR1(O—OR1)R12 and x is 0. In some embodiments, the compound of Formula (I) or Formula (II) has the structure of Formula (III):

![Chemical structure diagram]

**TABLE 1**

<table>
<thead>
<tr>
<th>Compd #</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>x</th>
<th>R11</th>
<th>M+H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>OCH3</td>
<td>4-Chloro-benzoylamino</td>
<td>0</td>
<td>CH2CF3</td>
<td>540</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>OCH3</td>
<td>2,2-Dimethyl-propionylamino</td>
<td>0</td>
<td>CH2CF3</td>
<td>486</td>
</tr>
<tr>
<td>3</td>
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Further Forms of Compounds

In certain embodiments, compounds of Formula (1) are prepared as pharmaceutically acceptable salts by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluene sulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, aroylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoctonic 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, hydroxyanphthoic acid, salicylic acid, stearic acid, and mucinic acid.

Pharmaceutically acceptable salts are also obtained by reacting a compound of Formula (1) with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

In other embodiments, compounds of Formula (1) are prepared as pharmaceutically acceptable salts by reacting the free acid form of the compound with pharmaceutically acceptable inorganic or organic base, including, but not limited to organic bases such as ethanamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like, or with an inorganic base such as aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

Reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are optionally formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, and alcoholates are formed when the solvent is alcohol. Solvates of compounds of Formula (1) are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of compounds of Formula (1) are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, ethanol, or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

In some embodiments, compounds of Formula (1) are prepared as prodrugs. A “prodrug” refers to an agent that is converted into the parent drug in vivo.

In yet another embodiment, the compounds of Formula (1) 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. Stereoisomers are obtained, if desired, by methods such as, the separation of stereoisomers by chiral chromatographic columns or stereoselective synthesis.

The methods and formulations described herein include the use of N-oxides (if appropriate), crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having the structure of Formula (1), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds exist as tautomers.

In some embodiments, the compounds described herein exist as tautomers. All tautomers are intended to be within the scope of the molecular formulas described herein.

In 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.

DEFINITIONS

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” and “and” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other terms, such as “include”, “includes,” and “included,” is not limiting.

0099 “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, isopropyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl, and neo-pentyl.

0100 “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.

0102 “ Halo”, “halogen” or “halide” means fluoro, chloro, bromo or iodo.

0103 “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 —CF₃, —CH₂CF₂, —CH₂CF₃, —CH₂CF₂CF₂ and —CF₂CF₂.

0104 “Fluoroalkoxy” refers to —(fluoroalkyl)O—, where fluoroalkyl is as defined herein.

0105 “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. In one aspect, 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.

0106 “Heterocycloalkyl” refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. A heterocycloalkyl is a 5-membered ring or a 6-membered ring. In some embodiments, a heterocycloalkyl includes at least one N atom in the ring. Heterocycloalkyls include oxazolidinone, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophanyl, tetrahydropropyranyl, pipеридинил, morpholinyl, thiomorpholinyl, and пiperазинил.

0107 “5-Membered heteroaryle” include imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furyl, thiienyl, isoazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, oxadiazolyl, thiadiazolyl, and furazanyl. In one aspect, a heteroaryle contains 0-3 N atoms.

0108 “6-Membered heteroaryle” includes pyridinyl, pyridazinyl, pyrimidinyl, piperazinyl and triazinyl.

0109 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, C₁-C₄ fluoroalkyl, C₁-C₅ alkoxycarbonyl, C₁-C₄ fluoroalkoxycarbonyl, —NH₂, —NH(C₁-C₅ alkyl), —N(C⁰-C₅ alkyl), and C₁-C₅ heteroalkyl. In some cases, the referenced substituted group is substituted with 1 or 2 of the aforementioned groups. For example, in some embodiments, a referenced substituted group is substituted with at least one group selected from halogen, —OH, —CN, —CH₃, —CH₂CH₃, —CF₃, —OCH₃, —OCH₂CH₃, and —OCF₃.

0110 A “metabolite” of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term “active metabolite” refers to a biologically active derivative of a compound that is formed when the compound is metabolized.

0111 “PGD₂-dependent” refers to conditions or disorders that would not occur, or would not occur to the same extent, in the absence of PGD₂. “PGD₂-mediated” refers to refers to conditions or disorders that might occur in the presence of PGD₂.

0112 “Effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. An appropriate effective amount in any individual case may be determined using techniques, such as a dose escalation study.

0113 The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic cause of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

0114 The term “subject” or “patient” encompasses mammals and non-mammals. In one aspect, the “subject” or “patient” is a mammal. In one embodiment, the mammal is a human.

Pharmaceutical Composition/Forulation

0115 Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, intramuscular injection, subcutaneous injection, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramurary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intrathymic, and intramuscular injections.

0116 In certain embodiments, a compound as described herein is administered in a local rather than systemic manner. In other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

0117 In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington’s Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. 1975; Liberman, H. A. and Lachman, I.,

[0118] A pharmaceutical composition refers to a mixture of a compound of Formula (I) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to a mammal.

[0119] In some embodiments, compounds described herein are formulated for oral administration. The compounds described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

[0120] In one embodiment, compounds of Formula (I) are formulated in an aqueous solution. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer.

[0121] In other embodiments, compounds of Formula (I) are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated.

[0122] In still other embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions.

[0123] In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or pills. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked carboxymethylcelllose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0124] Oral dosage forms also include push-fit capsule made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oils, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

[0125] In still other embodiments, the compounds of Formula (I) are administered topically. TOPICALLY ADMINISTRABLE COMPOSITIONS include solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments.

[0126] In other embodiments, the compounds of Formula (I) are formulated for administration by inhalation. Various forms suitable for administration by inhalation include, but are not limited to, aerosols, mists or powders.

[0127] The active ingredient in the pharmaceutical compositions is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

[0128] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient’s health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[0129] In prophylactic applications, compositions comprising the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. In this use, the precise amounts also depend on the patient’s state of health, weight, and the like.

[0130] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, existent condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the mammal being treated. Doses employed for adult human treatment are typically in the range of 0.02-5000 mg per day, 0.5-1500 mg per day, or 1-500 mg per day. In one embodiment, the dose is presented in a single dose or in divided doses administered at appropriate intervals, for example as two, three, four or more subdoses per day.

[0131] In one embodiment, the daily dosages appropriate for the compound of Formula (I) are from about 0.01 mg to about 10 mg/kg per body weight. In certain embodiments, suitable unit dosage forms for oral administration comprise from about 1 to 500 mg active ingredient. In other embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein.

[0132] In certain instances, it is appropriate to administer at least one compound of Formula (I) in combination with another therapeutic agent. In combination therapies, the mul-
multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills).

[0133] In some embodiments, compounds of Formula (I) are administered chronically. In some embodiments, compounds of Formula (I) are administered intermittently (e.g., drug holiday that includes a period of time in which the compound is not administered or is administered in a reduced amount). In some embodiments, compounds of Formula (I) are administered in cycles that include: (a) a first period that includes daily administration of the compound of Formula (I); followed by (b) a second period that includes a dose reduction of the daily amount of compound of Formula (I) that is administered. In some embodiments, the compound of Formula (I) is not administered in the second period. In some embodiments, the duration of the first and second periods, as well as the dose amounts are determined using methods described herein or known in the art.

EXAMPLES

[0134] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1

General Oxidation Procedure for the Preparation of Sulfoxide Compounds

[0135] To the sulfide compound (0.06 mmol) in CH₂Cl₂ (2 mL) was added 3-chloroperbenzoic acid (0.027 g, 0.12 mmol), and the reaction was stirred at room temperature for 20 minutes. The mixture was concentrated and purified by preparative HPLC to give the sulfone compound.

Example 2

General Oxidation Procedure for the Preparation of Sulfoxide Compounds

[0136] To the sulfide compound (0.06 mmol) in CH₂Cl₂ (2 mL) was added 3-chloroperbenzoic acid (0.014 g, 0.06 mmol), and the reaction was stirred at room temperature for 20 minutes. The mixture was concentrated and purified by preparative HPLC to give the sulfoxide compound.

Example 3

Synthesis of [3-[4-(4-Chloro-benzyloami-no)-2-(2,2,2-trifluoro-ethylsulfanyl-methyl]-phenox-y]-4-methoxy-phenyl]-acetic acid ethyl ester

Step 1: [3-(2-Formyl-4-nitro-phenoxy)-4-methoxy-phenyl]-acetic acid ethyl ester

[0137] To 3-hydroxy-4-methoxyphenylacetic acid (5.0 g, 27.4 mmol) in EtOH (100 mL) was added sulfuric acid (1 mL), and the mixture was stirred overnight at room temperature. Once no starting material was seen by analytical TLC, the solution was concentrated and dried under high vacuum to give (3-hydroxy-4-methoxy-phenyl)-acetic acid ethyl ester. A solution of (3-hydroxy-4-methoxy-phenyl)-acetic acid ethyl ester (1 equivalent), 2-fluoro-5-nitrobenzaldehyde (1 equivalent), and potassium carbonate (2 equivalents) in 1,4-dioxane was heated overnight at 70°C. The mixture was partitioned between EtOAc and H₂O and acidified with IN aqueous HCl to pH 1, and then extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography (EtOAc in hexane gradient) to give the title compound.

Step 2: [3-(2-Hydroxymethyl-4-nitro-phenox-y)-4-methoxy-phenyl]-acetic acid ethyl ester

[0138] To [3-(2-formyl-4-nitro-phenox-y)-4-methoxy-phenyl]-acetic acid ethyl ester (1 equivalent) in methanol was added sodium borohydride (1.2 equivalents), and the reaction was stirred at room temperature for 15 minutes. The mixture was then concentrated and partitioned between EtOAc and H₂O. The aqueous layer was saponified and then extracted with EtOAc, and the combined organic layers were dried over MgSO₄, filtered, and concentrated to give the title compound.

Step 3: [3-(2-Bromomethyl-4-nitro-phenox-y)-4-methoxy-phenyl]-acetic acid ethyl ester

[0139] To a solution of [3-(2-hydroxymethyl-4-nitro-phenox-y)-4-methoxy-phenyl]-acetic acid ethyl ester (15.14 g, 41.9 mmol) in DME was added phosphorus tribromide (5.92 mL, 62.8 mmol), and the reaction was stirred at room temperature overnight. After cooling to 0°C, the mixture was quenched with saturated aqueous NaHCO₃ and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give the title compound.

Step 4: [4-Methoxy-3-[4-nitro-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-phenox-y]-4-methoxy-phenyl]-acetic acid ethyl ester

[0140] To [3-(2-bromomethyl-4-nitro-phenox-y)-4-methoxy-phenyl]-acetic acid ethyl ester (2.0 g, 4.72 mmol) and 2,2,2-trifluoroethanol (0.46 mL, 5.18 mmol) in 1,4-dioxane (40 mL) at 0°C was added sodium hydride (60% in mineral oil, 0.207 g, 5.18 mmol), and the reaction was stirred at 0°C for 30 minutes. The mixture was partitioned between EtOAc and H₂O. The aqueous layer was separated and acidified, and then extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography to give the title compound.

Step 5: [3-[4-Amino-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-phenox-y]-4-methoxy-phenyl]-acetic acid ethyl ester

[0141] A solution of [4-methoxy-3-[4-nitro-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-phenox-y]-phenyl]-acetic acid ethyl ester (1.46 g, 3.18 mmol), ferric chloride (0.026 g, 0.16 mmol), 1,1-dimethylhydrazine (1.69 mL, 22.27 mmol), and DARCO (0.300 g) in EtOH (30 mL) was stirred overnight at 65°C. The mixture was partitioned between EtOAc and H₂O and extracted three times with EtOAc. The combined organic layers were washed with H₂O and brine, and then dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (EtOAc in hexanes gradient) to give the title compound.

Step 6: [3-[4-(4-Chloro-benzyloami-no)-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-phenox-y]-4-methoxy-phenyl]-acetic acid ethyl ester

[0142] To [3-[4-amino-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-phenox-y]-4-methoxy-phenyl]-acetic acid ethyl ester
(0.200 g, 0.47 mmol) and triethylamine (0.08 mL, 0.56 mmol) in CH₂Cl₂, was added 4-chlorobenzoyl chloride (0.07 mL, 0.56 mmol), and the reaction was stirred at room temperature for 1 hour. The mixture was concentrated and used directly in the hydrolysis step.

Step 7: [3-[4-(4-Chloro-benzoylamo)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid

[0143] To [3-[4-(4-chloro-benzoylamino)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester (0.47 mmol) in MeOH and H₂O was added 1N aqueous lithium hydroxide. The reaction was stirred overnight at 65°C, and then acidified and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by preparative HPLC to give the title compound.

[0144] Following the procedures of Example 3, [3-[4-amino-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester was reacted with:

[0154] Pivaloyl chloride to provide [3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to provide [3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 2);

[0146] Benzyl isocyanate to provide [3-[4-(3-benzyl-ureido)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[4-(3-benzyl-ureido)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 3);

[0147] Cyclopropene carbonyl chloride to provide [3-[4-(cyclopropene carbonyl-amino)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[4-(cyclopropene-carbonyl-amino)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 14);

[0148] Isobutyl chloride to provide [3-[4-isobutyl-uramino-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[4-isobutyl-amino-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 15);

[0149] tert-Butyloacetyl chloride to provide [3-[4-(3,3-Dimethyl-butylamino)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[4-(3,3-Dimethyl-butylamino)-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 16);

[0150] 3-(trifluoromethyl) benzoyl chloride to provide [4-methoxy-3-[2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-4-[3-trifluoromethyl-benzoylamino]-phenoxy]-acetic acid ethyl ester, which was hydrolyzed to [4-methoxy-3-[2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-4-[3-trifluoromethyl-benzoylamino]-phenoxy]-phenyl]-acetic acid (Compound 68);

[0151] 4-(trifluoromethyl) benzoyl chloride to provide [4-methoxy-3-[2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-4-[4-trifluoromethyl-benzoylamino]-phenoxy]-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [4-methoxy-3-[2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-4-[4-trifluoromethyl-benzoylamino]-phenoxy]-phenyl]-acetic acid (Compound 69);

[0152] Nicotinyl chloride hydrochloride to provide [4-methoxy-3-[4-{(pyridine-3-carbonyl)-amino}-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [4-methoxy-3-[4-{(pyridine-3-carbonyl)-amino}-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-phenyl]-acetic acid (Compound 70);

[0153] Isonicotinyl chloride hydrochloride to provide [4-methoxy-3-[4-{(pyridine-4-carbonyl)-amino}-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [4-methoxy-3-[4-{(pyridine-4-carbonyl)-amino}-2-(2,2,2-trifluoro-ethyl)sulfanyl-methyl]-phenoxy]-phenyl]-acetic acid (Compound 71).

Example 4

Synthesis of [3-[4-(4-Chloro-benzoylamino)-2-(4-chloro-phenyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 4)

[0154] Following the procedure described in Example 3, Step 4, [3-[2-(4-chloro-phenyl)sulfanyl-methyl]-4-nitro-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester was obtained from [3-[2-(bromomethyl)-4-nitro-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester and 4-chlorobenzene-thiol. [3-[2-(4-Chloro-phenyl)sulfanyl-methyl]-4-nitro-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester was then reduced to [3-[4-amino-2-(4-chloro-phenyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester according to Example 3, Step 5. Treatment of the amine with 4-chlorobenzyl chloride according to the procedure of Example 3, Step 6 to provide [3-[4-(4-chloro-benzoylamino)-2-(4-chloro-phenyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester according to the procedure described in Example 3, Step 7 provided the acid.

[0155] Following the procedures described in Example 3, [3-[4-amino-2-(4-chloro-phenyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester was reacted with:

[0156] Pivaloyl chloride to provide [3-[2-(4-Chloro-phenyl)sulfanyl-methyl]-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-(4-chloro-phenyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 5);

[0157] Benzyl isocyanate to provide [3-[4-(3-benzyl-ureido)-2-(4-chloro-phenyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[4-(3-benzyl-ureido)-2-(4-chloro-phenyl)sulfanyl-methyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 6).

Example 5

Synthesis of [3-[2-tert-Butylsulfanyl-methyl]-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 7)

Step 1: [3-[2-tert-Butylsulfanyl-methyl]-4-nitro-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester

[0158] Prepared according to the procedure described in Example 3, Step 4, using the following starting materials:
[3-(2-bromomethyl-4-nitro-phenoxyl)-4-methoxy-phenyl]-
ceamic acid ethyl ester and 2-methyl-2-propanethiol.

Step 2: [3-(4-Amino-2-tert-butylsulfinylmethyl-phenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester

[0159] Prepared according to the procedure described in Example 3, Step 5, using the following starting materials: [3-(2-tert-butylsulfinylmethyl-4-nitro-phenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester.

Step 3: [3-(2-tert-Butylsulfinylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester

[0160] Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: [3-(4-amino-2-tert-butylsulfinylmethyl-phenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester and pivotal chloride.

Step 4: [3-(2-tert-Butylsulfinylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxyl)-4-methoxy-phenyl]-acetic acid

[0161] Prepared according to the procedure described in Example 3, Step 7, using the following starting materials: [3-(2-tert-butylsulfinylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester.

[0162] Following the procedures described for Example 3, [3-(4-amino-2-tert-butylsulfinylmethyl-phenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester was reacted with:

[0163] 4-chlorobenzoyl chloride to provide [3-(2-tert-butylsulfinylmethyl-4-(4-chloro-benzoxy-laminophenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-(2-tert-butylsulfinylmethyl-4-(4-chloro-benzoxy-laminophenoxyl)-4-methoxy-phenyl]-acetic acid (Compound 8).

[0164] benzoyl isocyanate to provide [3-[4-(3-benzyl-ureido)-2-tert-butylsulfinylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[4-(3-benzyl-ureido)-2-tert-butylsulfinylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 13);

[0165] cyclopropanecarbonyl chloride to provide [3-[2-tert-butyrsulfinylmethyl-4-(cyclopropanecarbonyl-amino)-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-tert-butyrsulfinylmethyl-4-(cyclopropanecarbonyl-amino)-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 35);

[0166] isobutyryl chloride to provide [3-[2-tert-butyrsulfinylmethyl-4-isobutyramino-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-tert-butyrsulfinylmethyl-4-isobutyramino-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 36);

[0167] tert-butylacetyl chloride to provide [3-[2-tert-butylsulfinylmethyl-4-(3,3-dimethyl-buturylaminophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-tert-butylsulfinylmethyl-4-(3,3-dimethyl-buturylaminophenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 37);

[0168] benzoyl chloride to provide [3-(4-benzoamino-2-tert-butylsulfinylmethyl-phenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-(4-benzoamino-2-tert-butylsulfinylmethyl-phenoxyl)-4-methoxy-phenyl]-acetic acid (Compound 58);

[0169] 3-fluorobenzoyl chloride to provide [3-[2-tert-butyrsulfinylmethyl-4-(3-fluoro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-tert-butyrsulfinylmethyl-4-(3-fluoro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 62);

[0170] 4-fluorobenzoyl chloride to provide [3-[2-tert-butyrsulfinylmethyl-4-(4-fluoro-benzoylaminophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-tert-butyrsulfinylmethyl-4-(4-fluoro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 63);

[0171] 2-fluorobenzoyl chloride to provide [3-[2-tert-butyrsulfinylmethyl-4-(2-fluoro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-tert-butyrsulfinylmethyl-4-(2-fluoro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 64);

[0172] 2,4-dichlorobenzoyl chloride to provide [3-[2-tert-butyrsulfinylmethyl-4-(2,4-dichloro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-tert-butyrsulfinylmethyl-4-(2,4-dichloro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 65);

[0173] 3,5-dichlorobenzoyl chloride to provide [3-[2-tert-butyrsulfinylmethyl-4-(3,5-dichloro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester [3-[2-tert-Butylsulfinylmethyl-4-(3,5-dichloro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 67);

[0174] 3,5-difluorobenzoyl chloride to provide [3-[2-tert-butyrsulfinylmethyl-4-(3,5-difluoro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to [3-[2-tert-Butylsulfinylmethyl-4-(3,5-difluoro-benzoxy-laminophenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 68);

[0175] danyl chloride to provide [3-[2-tert-Butylsulfanyl-methyl-4-(5-dimethylaminono-naphthalene-1-sulfonylaminophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester (the crude material was purified by silica gel chromatography), which was hydrolyzed to [3-[2-tert-butyrsulfinylmethyl-4-(5-dimethylaminono-naphthalene-1-sulfonylaminophenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 72).

Example 6

Synthesis of [3-(4,2,2-Dimethyl-propionylamino)-2-isopropylsulfinylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 9).

[0176] [3-(2-Bromomethyl-4-nitro-phenoxyl)-4-methoxy-phenyl]-acetic acid ethyl ester (0.4 g, 0.94 mmol), 2-propanethiol (0.11 mL, 1.13 mmol), and sodium hydride (60% in mineral oil; 0.05 g, 1.13 mmol) were combined in 1.4-dioxane and stirred at room temperature for 30 minutes. The mixture was worked-up to give [3-(4,2-isopropylsulfinylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester, which was then reduced to the amine as described in Example 3, Step 5 to provide [3-(4-amino-2-isopropylsulfinylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester. The amine was then treated with pivotal chloride according to Example 3, Step 6 to provide [3-[4-(2,2-dimethyl-propionylamino)-2-isopropylsulfinylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester.
noxyl]-4-methoxy-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester according to the procedure described in Example 3, Step 7 provided the acid.

Example 7

Synthesis of [3-[4-(2,2-Dimethyl-propionylamino)-2-(propane-2-sulfamoylmethyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 10)

[0177] Prepared according to the procedure described in Example 1 using [3-[4-(2,2-dimethyl-propionylamino)-2-isopropylsulfamoylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid.

Example 8

Synthesis of [3-[4-(2,2-Dimethyl-propionylamino)-2-(propane-2-sulfamoylmethyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 11)

[0178] Prepared according to the procedure described in Example 2 using [3-[4-(2,2-dimethyl-propionylamino)-2-isopropylsulfamoylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid.

Example 9

Synthesis of [3-[4-(2,2-Dimethyl-propionylamino)-2-(trifluoro-ethanesulfamoylmethyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 12)

[0179] Prepared according to the procedure described in Example 1 using [3-[4-(2,2-dimethyl-propionylamino)-2-(2,2-trifluoro-ethanesulfamoylmethyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid.

Example 10

Synthesis of [3-[4-Benzylsulfamoylmethyl-4-chlorophenoxyl]-4-methoxy-phenyl]-acetic acid

Step 1: [3-[4-Chloro-2-formyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester

[0180] (3-Hydroxy-4-methoxy-phenyl]-acetic acid ethyl ester (0.75 g, 4.8 mmol), 5-chloro-2-fluorobenzaldehyde (1.0 g, 4.8 mmol), and potassium carbonate (1.0 g, 7.5 mmol) were combined in 1,4-dioxane (30 mL) and heated to 100 °C. for 3 days. After work-up, the crude material was purified by gel chromatography (90% EtOAc in hexanes) to give the title compound.

Step 2: [3-[4-Chloro-2-hydroxymethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester

[0181] To [3-[4-Chloro-2-formyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester (0.9 g, 2.6 mmol) in MeOH (30 mL) was added sodium borohydride (0.11 g, 2.9 mmol), and the mixture was stirred at room temperature for 10 minutes. The mixture was worked-up to give the title compound.

Step 3: [3-[4-Chloro-2-bromomethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester

[0182] To [3-[4-Chloro-2-hydroxymethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester (0.9 g, 2.6 mmol) in DME was added phosphorus tribromide (0.37 mL, 3.9 mmol), and the reaction was stirred for 3 hours at room temperature. The mixture was worked-up to give the title compound.

Step 4: [3-(2-Benzylsulfonylmethyl-4-chlorophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester

[0183] To [3-[2-bromomethyl-4-chlorophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester (0.15 g, 0.36 mmol) and benzyl mercaptan (0.06 mL, 0.4 mmol) in 1,4-dioxane (10 mL) was added sodium hydride (60% in mineral oil, 0.05 g, 1.25 mmol), and the reaction was stirred for 1 hour at room temperature. After work-up, the crude material was purified by preparative HPLC to give the title compound.

Step 5: [3-[4-Benzylsulfamoylmethyl-4-chlorophenoxyl]-4-methoxy-phenyl]-acetic acid

[0184] [3-[2-Benzylsulfonylmethyl-4-chlorophenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester was hydrolyzed with lithium hydroxide in MeOH and H₂O to give the title compound.

Example 11

Synthesis of [3-[4-(4-Chloro-benzoylamino)-2-phenylsulfamoylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 17)

Step 1: [4-Methoxy-3-(4-nitro-phenylsulfonylmethyl-phenoxyl)-acetic acid ethyl ester

[0185] Prepared according to the procedure described in Example 10, Step 4, using the following starting materials: [3-[2-bromomethyl-4-nitro-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester and thiophenol.

Step 2: [3-[4-Amino-2-phenylsulfamoylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester

[0186] [4-Methoxy-3-(4-nitro-phenylsulfonylmethyl-phenoxyl)-phenyl]-acetic acid ethyl ester (0.4 g, 0.9 mmol) and tri(bromomethyl) chloride (0.6 g, 2.7 mmol) were combined in EtOH (20 mL) and stirred overnight at 70 °C. CH₂Cl₂, H₂O, and sodium bicarbonate were added, and the mixture was filtered through Celite. The organic layer was separated and concentrated to give the title compound.

Step 3: [3-[4-(4-Chloro-benzoylamino)-2-phenylsulfamoylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester

[0187] [3-[4-Amino-2-phenylsulfamoylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester (0.4 g, 0.9 mmol) and triethylamine (1 mL) were combined in CH₂Cl₂ (30 mL). 4-Chlorobenzoyl chloride (0.29 mL, 2.3 mmol) was added, and the reaction was stirred at room temperature for 20 minutes. The mixture was concentrated to give the title compound, which was used directly in the hydrolysis step.

Step 4: [3-[4-(4-Chloro-benzoylamino)-2-phenylsulfamoylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid

[0188] To [3-[4-(4-Chloro-benzoylamino)-2-phenylsulfamoylmethyl-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester (0.9 mmol) was added lithium hydroxide (0.3 g), H₂O (5
mL), and MeOH (20 mL). The reaction was stirred at 60°C, and then worked up and purified by preparative HPLC to give the title compound.

Example 12
Synthesis of [3-[2-Benzylsulfanylmethyl-4-(4-
chloro-benzylamino)-phenoxy]-4-methoxy-phen-
yl]-acetic acid (Compound 18)

[0189] As described for Example 10, [3-(2-bromomethyl-
4-nitro-phenoxo)-4-methoxy-phenyl]-acetic acid ethyl ester and benzyl mercaptan were reacted to provide [3-(2-benzy-
sulfanylmethyl-4-nitro-phenoxo)-4-methoxy-phenyl]-acetic acid ethyl ester, which was reduced to [3-(4-amino-2-benzy-
sulfanylmethyl-4-chloro-benzylamino)-phenoxo]-4-methoxy-phenyl]-acetic acid ethyl ester and then treated with 4-chlorobenzyl chloride to provide [3-[2-benzylsulfanylmethyl-4-chloro-benzylamino]-phenoxo]-4-methoxy-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester provided Compound 18.

Example 13
Synthesis of [3-[4-(4-Chloro-benzylamino)-2-(5-
methyl-1,3,4-thiadiazole-2-ylsulfanylmethyl)-phen-
oxo]-4-methoxy-phenyl]-acetic acid (Compound 19)

[0190] As described for Example 10, [3-(2-bromomethyl-
4-nitro-phenoxo)-4-methoxy-phenyl]-acetic acid ethyl ester and 5-methyl-1,3,4-thiadiazole-2-thiol were reacted to form [4-methoxy-3-[2-(5-methyl-1,3,4-thiadiazole-2-ylsulfanylmethyl)-4-nitro-phenoxo]-phenyl]-acetic acid ethyl ester, which was reduced to [3-[4-amino-2-(5-methyl-1,3,4-thia-
diazole-2-ylsulfanylmethyl)-phenoxo]-4-methoxy-phenyl]-acetic acid ethyl ester and then treated with 4-chlorobenzyl chloride to provide [3-[4-(4-chloro-benzylamino)-2-(5-methyl-1,3,4-thia-
diazole-2-ylsulfanylmethyl)-phenoxo]-4-methoxy-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester to the acid provided Compound 19.

Example 14
Synthesis of [3-[4-(4-Chloro-benzylamino)-2-isopropylsulfanylmethyl-phenoxo]-4-methoxy-phenyl]-acetic acid (Compound 20)

[0191] [3-(2-isopropylsulfanylmethyl-4-nitro-phenoxo)-
4-methoxy-phenyl]-acetic acid ethyl ester was reduced to the amine according to the procedure described in Example 11, Step 2. The amine was treated with 4-chlorobenzyl chloride to provide [3-[4-(4-Chloro-benzylamino)-2-isopropylsulfanylmethyl-phenoxo]-4-methoxy-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester as outlined in Example 11, Step 4 provided the acid.

Example 15
Synthesis of [3-(4-Bromo-2-bromomethyl-phenoxo)-
4-methoxy-phenyl]-acetic acid ethyl ester

Step 1: (3-Hydroxy-4-methoxy-phenyl)-acetic acid ethyl ester

[0192] To 3-hydroxy-4-methoxyphenylacetic acid (5.0 g, 23.8 mmol) in EtOH (100 mL) was added sulfuric acid (1 ml.), and the reaction was stirred overnight at room tempora-
ture. Once no starting material was seen by analytical tlc, the mixture was concentrated to give the desired product.

Step 2: [3-(4-Bromo-2-formyl-phenoxo)-4-methoxy-
phenyl]-acetic acid ethyl ester

[0193] (3-Hydroxy-4-methoxy-phenyl)-acetic acid ethyl ester (2.0 g, 9.5 mmol), 5-bromo-2-fluorobenzaldehyde (2.0 g, 9.5 mmol), and potassium carbonate (2.0 g, 14.3 mmol) were combined in 1,4-dioxane and heated to 90°C overnight. After work-up, the crude material was purified by silica gel chromatography (0-25% EtOAc in hexanes) to give the desired product (1.8 g).

Step 3: [3-(4-Bromo-2-hydroxymethyl-phenoxo)-4-
methoxy-phenyl]-acetic acid ethyl ester

[0194] Prepared according to the procedure described in Example 10, Step 2, using the following starting material: [3-(4-bromo-2-formyl-phenoxo)-4-methoxy-phenyl]-acetic acid ethyl ester.

Step 4: [3-(4-Bromo-2-bromomethyl-phenoxo)-4-
methoxy-phenyl]-acetic acid ethyl ester

[0195] Prepared according to the procedure described in Example 10, Step 3, using the following starting material: [3-(4-bromo-2-hydroxymethyl-phenoxo)-4-methoxy-phenyl]-acetic acid ethyl ester.

Step 5: [3-(4-Bromo-2-isopropylsulfanylmethyl-
phenoxo)-4-methoxy-phenyl]-acetic acid ethyl ester

[0196] [3-(4-Bromo-2-bromomethyl-phenoxo)-4-meth-
 oxy-phenyl]-acetic acid ethyl ester (0.4 g, 0.087 mmol) and 2-propanethiol (0.08 g, 1.0 mmol) were combined in 1,4-
dioxane (20 mL). Sodium hydride (60% in mineral oil; 0.04 g, 1.0 mmol) was added, and the reaction was stirred at room temperature for 20 minutes. The mixture was worked up to give the title compound.

Example 16
Synthesis of [3-[4-(4-Chloro-benzylamino)-2-(pro-
pene-2-sulfanyl)methyl]-phenoxo]-4-methoxy-
phenyl]-acetic acid (Compound 21) and [3-[4-(4-
Chloro-benzylamino)-2-(propane-2-
sulfanyl)methyl]-phenoxo]-4-methoxy-phenyl]-acetic acid (Compound 22)

[0197] To [3-[4-(4-Chloro-benzylamino)-2-isopropylsulfanylmethyl-phenoxo]-4-methoxy-phenyl]-acetic acid (0.17 g, 0.34 mmol) in CHCl₃ (20 mL) was added 3-chloroperbenzoic acid (77%; 0.076 g, 0.34 mmol), and the reaction was stirred for 10 minutes at room temperature. Additional 3-chloroperbenzoic acid (77%; 0.025 g, 0.11 mmol) was added to increase the production of the sulfone product, and then the mixture was concentrated and purified by preparative HPLC to give the title sulfone and sulfone compounds.

Example 17
Synthesis of [3-[2-Benzensulfanyl methyl-4-(4-
chloro-benzylamino)-phenoxo]-4-methoxy-phen-
yl]-acetic acid (Compound 23) and [3-[2-Benzene-
sulfonylmethyl-4-(4-chloro-benzylamino)-phenoxo]-4-methoxy-phenyl]-acetic acid (Compound 24)

[0198] To [3-[4-(4-chloro-benzylamino)-2-phenylsulfanyl-
methyl-phenoxo]-4-methoxy-phenyl]-acetic acid (0.16
mmol) in CH₂Cl₂ (3 mL) was added 3-chloroperbenzoic acid (77%; 0.036 g, 0.16 mmol), and the reaction was stirred at room temperature for 1 hour. The mixture was concentrated and purified by preparative HPLC to give the title sulfone and sulfone compounds.

Example 18

Synthesis of [3-(4-Ethylcarbamoyl-2-isopropylsulfanylphenyl-4-methoxy-phenyl)-acetic acid (Compound 25)

Step 1: [3-(4-Bromo-2-isopropylsulfanylphenyle)-4-methoxy-phenyl]-acetic acid ethyl ester

[0199] To [3-(4-bromo-2-bromophenyl-4-methoxy-phenyl)-4-methoxy-phenyl]-acetic acid ethyl ester and 2-propanethiol in 1,4-dioxane was added sodium hydroxide (60% in mineral oil), and the reaction was stirred for 1 hour at room temperature. After work-up, the crude material was purified by silica gel chromatography (20-20% EtOAc in hexanes) to give the title compound.

Step 2: 4-(5-Ethoxycarbonylmethyl-2-methoxy-phenyl)-3-isopropylsulfanylphenylbenzoic acid methyl ester

[0200] [3-(4-Bromo-2-isopropylsulfanylphenyl-4-methoxy-phenyl)-4-methoxy-phenyl]-acetic acid ethyl ester (0.5 g, 1.1 mmol) and triethylamine (0.5 mL) were dissolved in DMF (10 mL) and MeOH (10 mL) and degassed for 10 minutes with N₂. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.09 g, 0.11 mmol) was added, and then carbon monoxide was bubbled through the solution for 10 minutes. The reaction was stirred under a balloon of carbon monoxide at 65°C overnight, and then concentrated and purified by silica gel chromatography to give the title compound.

Step 3: 4-(5-Ethoxycarbonylmethyl-2-methoxy-phenyl)-3-isopropylsulfanylbenzoic acid

[0201] 4-(5-Ethoxycarbonylmethyl-2-methoxy-phenyl)-3-isopropylsulfanylbenzoic acid methyl ester (0.5 g, 1.16 mmol) and sodium methylthiolate (0.16 g, 2.3 mmol) were combined in DMF (20 mL) and stirred at 65°C for 1 hour. After an acidic work-up, the crude material was purified by preparative HPLC to give the title compound.

Step 4: [3-(4-Ethylcarbamoyl-2-isopropylsulfanyl-ethyl-phenyl)-4-methoxy-phenyl]-acetic acid ethyl ester

[0202] To 4-(5-ethoxycarbonylmethyl-2-methoxy-phenyl)-3-isopropylsulfanyl-benzoic acid (0.07 g, 0.17 mmol) in CH₂Cl₂ (10 mL) and DMF (1 drop) was added oxalyl chloride (0.04 mL, 0.5 mmol), and the reaction was stirred at room temperature for 30 minutes. After concentrating to dryness, ethylamine (2M in THF; 0.25 mL, 0.5 mmol) was added, followed by CH₂Cl₂ (10 mL) and diisopropylethylamine (0.5 mL), and the reaction was stirred at room temperature for 15 minutes. The mixture was worked up to give the title compound.

Step 5: [3-(4-Ethylcarbamoyl-2-isopropylsulfanyl-ethyl-phenyl)-4-methoxy-phenyl]-acetic acid

[0203] Prepared according to the procedure described in Example 11, Step 4, using the following starting material:

[3-(4-ethylcarbamoyl-2-isopropylsulfanylphenyl-4-methoxy-phenyl)-4-methoxy-phenyl]-acetic acid

Example 19

Synthesis of [3-(4-(4-Chloro-benzylcarbamoyl)-2-isopropylsulfanylphenyl-4-methoxy-phenyl]-acetic acid (Compound 26)

[0204] Following the procedure described in Example 18, Step 4, [3-(4-(4-Chloro-benzylcarbamoyl)-2-isopropylsulfanylphenyl-4-methoxy-phenyl]-acetic acid ethyl ester was obtained from 4-(5-ethoxy carbonylmethyl-2-methoxy-phenyl)-3-isopropylsulfanylbenzoic acid and 4-chlorobenzylamine. Hydrolysis of the ester according to the procedure described in Example 11, Step 4 provided the acid.

Example 20

Synthesis of [3-(4-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-2-isopropylsulfanylphenyl-4-methoxy-phenyl]-acetic acid (Compound 27)

[0205] Following the procedure described in Example 18, Step 4, [3-(4-[2-(4-Fluoro-phenyl)-ethylcarbamoyl]-2-isopropylsulfanylphenyl-4-methoxy-phenyl]-acetic acid ethyl ester was obtained from 4-(5-ethoxy carbonylmethyl-2-methoxy-phenyl)-3-isopropylsulfanylbenzoic acid and 4-fluorophenylamine. Hydrolysis of the ester according to the procedure described in Example 11, Step 4 provided the acid.

Example 21

Synthesis of [3-Chloro-5-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethyl)sulfanylphenyl]-phenyl]-acetic acid (Compound 28)

Step 1: 1-Benzzyloxy-3-bromo-5-chloro-benzene

[0206] To 1-bromo-3-chloro-5-fluorobenzene (25 g, 112 mmol) and benzyl alcohol (25 mL, 239 mmol) in NMP (200 mL) at room temperature was added sodium hydroxide (60% in mineral oil: 10.5 g, 263 mmol), and the reaction was heated to 120°C for 10 hours. The mixture was acidified with 10% aqueous HCl and extracted with EtOAc to give the title compound.

Step 2: 2-(3-Benzzyloxy-5-chloro-phenyl)-malonic acid dimethyl ester

[0207] To a solution of 1-benzzyloxy-3-bromo-5-chloro-benzene (31 g, 101.7 mmol), dimethylmalonate (25.7 mL, 223.8 mmol), and copper(I) bromide (32 g, 223.8 mmol) in 1,4-dioxane (300 mL) at 0°C under N₂ was added sodium hydroxide (60% in mineral oil: 9 g, 223.9 mmol) portionwise. After 10 minutes, the reaction was heated to 100°C and stirred for 6 hours. Analytical LCMS indicated that starting material remained, so the reaction was stirred at 100°C for 24 hours, 50% Aqueous NH₄OH (1 L) was added to break up the solid, and the mixture was extracted three times with CH₂Cl₂ (3 L total). The organic layer was washed with brine,
dried over MgSO₄, filtered, and concentrated, and the residue was purified by silica gel chromatography to give the title compound.

Step 3: (3-Benzyl-2,5-chloro-phenyl)-2-acetic acid methyl ester

[0208] A mixture of 2-(3-benzyl-5-chloro-phenyl)-3-malic acid dimethyl ester (21 g, 60.2 mmol) and lithium chloride (3.06 g, 72.2 mmol) in DMAPO:H₂O (10:1; 200 mL) was stirred at 150°C for 5 hours. After cooling to room temperature, H₂O (500 mL) was added, and the mixture was extracted with EtOAc:hexanes (1:10; 1.5 L total) to give the title compound.

Step 4: (3-Chloro-5-hydroxy-phenyl)-2-acetic acid methyl ester

[0209] To (3-benzyl-5-chloro-phenyl)-2-acetic acid methyl ester (8 g, 28 mmol) in CH₂Cl₂ (100 mL) at 0°C was added boron trifluoride (1M in CH₂Cl₂; 56 mL, 56 mmol). The reaction mixture was warmed to room temperature over 30 minutes and stirred for 2 hours. Once no starting material was seen by analytical LC/MS and TLC, the mixture was cooled to 0°C and quenched with H₂O (50 mL). The volume was reduced, and the residue was diluted with EtOAc (500 mL). The solid material was filtered, and the organic layer was separated and concentrated. The crude material was purified by silica gel chromatography to give the title compound.

Step 5: (3-Chloro-5-(2-formyl-4-nitro-phenoxy)-phenyl)-2-acetic acid methyl ester

[0210] To (3-chloro-5-hydroxy-phenyl)-2-acetic acid methyl ester (2.9 g, 14.5 mmol), 2-fluoro-5-nitrobenzaldehyde (2.7 g, 15.9 mmol), and potassium carbonate (4.0 g, 28.9 mmol) were combined in 1,4-dioxane (20 mL) and stirred at 100°C overnight. Once no starting material was seen by analytical LC/MS and TLC, the mixture was worked up with EtOAc and 10% aqueous HCl and the crude material was purified by silica gel chromatography to give the title compound.

Step 6: (3-Chloro-5-(2-hydroxymethyl-4-nitro-phenoxy)-phenyl)-2-acetic acid methyl ester

[0211] To (3-chloro-5-(2-formyl-4-nitro-phenoxy)-phenyl)-2-acetic acid methyl ester (3.7 g, 10.6 mmol) in MeOH (30 mL) was added sodium borohydride (0.52 g, 13.8 mmol), and the reaction was stirred at room temperature for 20 minutes. After work-up with EtOAc and H₂O, the crude material was purified by silica gel chromatography to give the title compound.

Step 7: (3-(2-Bromomethyl-4-nitro-phenoxy)-5-chloro-phenyl)-2-acetic acid methyl ester

[0212] To a solution of (3-chloro-5-(2-hydroxymethyl-4-nitro-phenoxy)-phenyl)-2-acetic acid methyl ester (2.4 g, 6.8 mmol) in DMF (20 mL) was added phosphorus tribromide (0.97 mL, 10.2 mmol), and the reaction was stirred for 1 hour at room temperature. After work-up with EtOAc and H₂O, the crude material was purified by silica gel chromatography to give the title compound.

Step 8: (3-Chloro-5-(2-nitro-2,2,2-trifluoro-ethyl-sulfanyl)methyl)-phenyl)-2-acetic acid methyl ester

[0213] To (3-(2-cromomethyl-4-nitro-phenoxy)-5-chloro-phenyl)-2-acetic acid methyl ester (0.5 g, 1.25 mmol) and 2,2,2-trifluoroethanethiol (0.13 mL, 1.38 mmol) in 1,4-dioxane (6 mL) was added sodium hydride (60% in mineral oil; 0.055 g, 1.38 mmol), and the reaction was stirred at room temperature overnight. After work-up with EtOAc and 10% aqueous HCl, the crude material was purified by silica gel chromatography to give the title compound.

Step 9: (3-[4-Amino-2-(2,2,2-trifluoro-ethyl-sulfanyl)methyl]-phenyl)-2-acetic acid methyl ester

[0214] To a solution of (3-[4-nitro-2-(2,2,2-trifluoro-ethyl-sulfanyl)methyl]-phenyl)-2-acetic acid methyl ester (0.07 g, 0.16 mmol), 1,1-dimethylydrazine (0.08 mL, 1.09 mmol), ferric chloride (0.003 g, 0.02 mmol), and DARCO (0.016 g) were combined in EtOH and stirred at 65°C for 30 hours. After work-up with EtOAc and H₂O, the crude material was purified by silica gel chromatography to give the title compound.

Step 10: (3-Chloro-5-[4-(2,2,2-trifluoro-ethyl-sulfanyl)methyl]-phenyl)-2-acetic acid methyl ester

[0215] To a solution of (3-[4-amino-2-(2,2,2-trifluoro-ethyl-sulfanyl)methyl]-phenyl)-2-acetic acid methyl ester (0.058 g, 0.14 mmol) in CH₂Cl₂ (2 mL) was added triethylamine (0.04 mL, 0.28 mmol), followed by pivalyl chloride (0.02 mL, 0.17 mmol), and the reaction was stirred at room temperature for 10 minutes. After work-up with CH₂Cl₂ and H₂O, the crude material was purified by silica gel chromatography to give the title compound.

Step 11: (3-Chloro-5-[4-(2,2,2-dimethyl-propionyl)-aminolino]-2-(2,2,2-trifluoro-ethyl-sulfanyl)methyl]-phenyl)-2-acetic acid methyl ester

[0216] To a solution of (3-[4-(2,2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethyl-sulfanyl)methyl]-phenyl)-2-acetic acid methyl ester (0.038 g, 0.08 mmol) in THF:H₂O:MeOH (2:1:2; 2 mL) was added 1N aqueous lithium hydroxide, and the mixture was stirred at room temperature overnight. The mixture was acidified to pH 5 with 10% aqueous HCl, and extracted with EtOAc. The crude material was purified by preparative HPLC to give the title compound.

Example 22

Synthesis of (3-Chloro-5-[4-(2,2-dimethyl-propionylamino)-2-(trifluoro-ethanesulfanyl)methyl]-phenyl)-2-acetic acid (Compound 29)

[0217] To a solution of (3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethyl-sulfanyl)methyl]-phenyl)-2-acetic acid (0.02 g, 0.04 mmol) in CH₂Cl₂ (5 mL) was added 3-chloroperbenzoic acid (77%; 0.046 g, 0.2 mmol), and the reaction was stirred for 3 hours at room temperature. After work-up with CH₂Cl₂ and H₂O, the crude material was purified by silica gel chromatography to give the title compound.

Example 23

Synthesis of (3-Chloro-5-[4-(2,2-dimethyl-propionylamino)-2-isopropylsulfanyl)methyl]-phenyl)-2-acetic acid (Compound 30)

[0218] Following the procedures described in Example 21, Step 8 (starting from [3-(2-bromomethyl-4-nitro-phenoxy)-]
5-chloro-phenyl]-acetic acid methyl ester and 2-propanethiol, Example 21, Step 9, and Example 21, Step 10 (using pivaloyl chloride), [3-Chloro-5-[4-(2,2-dimethyl-propionylamino)-2-isopropylsulfanyl(methyl)-phenyl]-acetic acid methyl ester was obtained. Hydrolysis of the ester according to the procedure described in Example 21, Step 11 provided the acid.

**Example 24**

**Synthesis of 3-Chloro-5-[4-(2,2-dimethyl-propionylamino)-2-(propane-2-sulfonylmethyl)-phenoxyl]-acetic acid (Compound 31)**

**0219** To 3-chloro-5-[4-(2,2-dimethyl-propionylamino)-2-(propane-2-sulfonylmethyl)-phenyl]-acetic acid methyl ester (0.05 g, 0.29 mmol) in CH₂Cl₂ (3 mL) was added 3-chloroperbenzoic acid (77%; 0.12 g, 1.45 mmol), and the reaction was stirred for 1 hour at room temperature. After work-up with EtOAc and brine, the crude material was purified by silica gel chromatography to give 3-Chloro-5-[4-(2,2-dimethyl-propionylamino)-2-(propane-2-sulfonylmethyl)-phenyl]-acetic acid methyl ester. Hydrolysis of the ester according to the procedure described in Example 21, Step 11 provided the acid.

**Example 25**

**Synthesis of 3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid (Compound 32)**

**0220** To benzyl alcohol (1.1 g, 10 mmol) in NMP (20 mL) was added sodium hydride (60% in mineral oil; 0.44 g, 11 mmol), and the mixture was stirred for 30 minutes at room temperature. The mixture was then added to a vial containing 3-fluoro-5-( trifluoromethyl)phenolic acid (1 g, 4.5 mmol), and the reaction was stirred at 120°C for 3 hours. Acidic work-up gave 3-benzyloxy-5-(trifluoromethyl-phenyl)-acetic acid ethyl ester.

**0221** To 3-benzyloxy-5-trifluoromethyl-phenyl]-acetic acid ethyl ester (1.7 g, 5.6 mmol) was dissolved in EtOH (30 mL) and degassed with N₂. 5% Palladium on carbon (1 g) was added, and the mixture was purged with H₂ and then stirred under an H₂ balloon at 50°C overnight. The mixture was filtered and concentrated to give 3-Benzylx-5-trifluoromethyl-phenyl]-acetic acid ethyl ester.

**0222** (3-Benzoxyl-5-trifluoromethyl-phenyl]-acetic acid ethyl ester (1.7 g, 5.6 mmol) was dissolved in EtOH (30 mL) and degassed with N₂. 5% Palladium on carbon (1 g) was added, and the mixture was purged with H₂ and then stirred under an H₂ balloon at 50°C overnight. The mixture was filtered and concentrated to give 3-Hydroxy-5-trifluoromethyl-phenyl]-acetic acid ethyl ester.

**0223** (3-Hydroxy-5-trifluoromethyl-phenyl]-acetic acid ethyl ester and 2-fluoro-5-nitrobenzaldehyde were reacted according to the procedure described in Example 21, Step 5, to give 3-[2-(formyl-4-nitro-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester.

**0224** (3-[2-(Formyl-4-nitro-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester was reduced to 3-[2-(hydroxymethyl-4-nitro-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester according to the procedure described in Example 21, Step 6 and then brominated as described in Example 21, Step 7 and then treated with 2,2,2-trifluoroethanethiol to give 3-[4-Nitro-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester. The amine was reduced as described in Example 21, Step 9, and then treated with pivaloyl chloride as described in Example 21, Step 10 to provide 3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester as described in Example 21, Step 11 provided the acid.

**Example 26**

**Synthesis of 3-[4-(2,2-Dimethyl-propionylamino)-2-(trifluoro-ethanesulfanyl(methyl)-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid (Compound 33)**

**0225** Prepared according to the procedure described in Example 24 using 3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester.

**Example 27**

**Synthesis of 3-[4-(2,2-Dimethyl-propionyl)-methyl-aminol]-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid (Compound 34)**

**0226** To 3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid (0.128 g, 0.26 mmol) in MeCN (3 mL) was added iodomethane (0.03 mL, 0.53 mmol), followed by sodium hydride (60% in mineral oil; 0.021 g, 0.53 mmol). The reaction was stirred at room temperature, but only starting material was seen by analytical LCMS, so the reaction was heated to 60°C for 2 hours, and then cooled to room temperature and stirred for 2 days under N₂. The mixture was used directly in the hydrolysis step. To a solution of 3-[4-(2,2-dimethyl-propionyl)-methyl-aminol]-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid methyl ester (0.026 mmol) in MeCN was added H₂O, MeOH, and lithium hydroxide, and the reaction was heated to 65°C for 1 hour to give the title compound.

**Example 28**

**Synthesis of 4-Methoxy-3-[4-(2-oxo-oxazolidin-3-yl]-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid (Compound 38)**

**Step 1**: 3-[4-(2-Chloro-ethoxycarbonylamino)-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester

**0227** Prepared according to the procedure described in Example 3, Step 6, using the following starting materials: 3-[4-amino-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester and 2-chloroethyl chlorofomate.

**Step 2**: 2-[4-Methoxy-3-[4-(2-oxo-oxazolidin-3-yl]-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid

**0228** To 3-[4-(2-Chloro-ethoxycarbonylamino)-2-(2,2,2-trifluoro-ethoxysulfanyl(methyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester (0.100 g, 0.19 mmol) in EtOH (5 mL) was added sodium ethoxide (21 wt% in EtOH; 4.61 mL, 0.37 mmol), and the reaction was stirred at 65°C overnight. The mixture was partitioned between EtOAc and H₂O, and the aqueous layer was extracted with EtOAc. The combined
organic layers were dried over MgSO₄, filtered, and concentrated, and the residue was purified by preparative HPLC to give the title compound.

Example 29
Synthesis of 3-[4-(tert-Butylcarbamoyl)-2-tert-butylsulfonylmethyl-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 39)

Step 1: 3-[4-(Bromo-2-tert-butylsulfonylmethyl-phenox)-4-methoxy-phenyl]-acetic acid ethyl ester

[0229] Prepared according to the procedure described in Example 15, Step 5, using the following starting materials: 3-[4-(bromomethyl-phenox)-4-methoxy-phenyl]-acetic acid ethyl ester and 2-methyl-2-propanethiol.

Step 2: 2-tert-Butylsulfonylmethyl-4-(5-ethoxy-carbonylmethyl-2-methoxy-phenox)-benzoic acid

[0230] 3-[4-(Bromo-2-tert-butylsulfonylmethyl-phenox)-4-methoxy-phenyl]-acetic acid ethyl ester (2.0 g, 4.3 mmol) and triethylamine (5.9 mL, 43 mmol) were combined in H₂O (5 mL) and DMF (50 mL) and degassed with carbon monoxide for 20 minutes. 1,1’-Bis(diphenylphosphino)ferrocene/dichloropalladium(II) (0.35 g, 0.43 mmol) was added, and the reaction was heated to 80°C for 4 hours. The mixture was acidified and extracted with EtOAc to give the title compound.

Step 3: 3-[4-(tert-Butylcarbamoyl)-2-tert-butylsulfonylmethyl-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester

[0231] 3-tert-Butylsulfonylmethyl-4-(5-ethoxy-carbonylmethyl-2-methoxy-phenox)-benzoic acid (0.2 g, 0.46 mmol), tert-butylamine (0.15 mL, 13.9 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodimide (0.11 g, 0.55 mmol), and N-hydroxybenzotriazole (0.074 g, 0.55 mmol) were combined in CH₂Cl₂ (8 mL) and stirred overnight. The mixture was concentrated and purified by preparative HPLC to give the title compound.

Step 4: 3-[4-(tert-Butylcarbamoyl)-2-tert-butylsulfonylmethyl-phenox]-4-methoxy-phenyl]-acetic acid

[0232] 3-[4-(tert-Butylcarbamoyl)-2-tert-butylsulfonylmethyl-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester (0.46 mmol) was treated with lithium hydroxide in MeOH and H₂O at 60°C for 20 minutes to give the title compound.

[0233] Following the procedures outlined in Example 29, 3-tert-butylsulfonylmethyl-4-(5-ethoxy-carbonylmethyl-2-methoxy-phenox)-benzoic acid was reacted with:

[0234] 2-aminoacetophenone hydrochloride to provide 3-[4-(tert-butylsulfonylmethyl)-2-(2-oxo-2-phenyl-ethylcarbamoyl)-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to 3-[4-(tert-butylsulfonylmethyl)-4-(2-oxo-2-phenyl-ethylcarbamoyl)-phenox]-4-methoxy-phenyl]-acetic acid (Compound 40);

[0235] 1-(4-fluorophenyl)-2-methyl-2-propylamine to provide 3-[4-(tert-butylsulfonylmethyl)-4-[2-(4-fluorophenyl)-1,1-dimethyl-ethylcarbamoyl]-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to 3-[4-(tert-butylsulfonylmethyl)-4-[2-(4-fluorophenyl)-1,1-dimethyl-ethylcarbamoyl]-phenox]-4-methoxy-phenyl]-acetic acid (Compound 41);

[0236] piperidine to provide 3-[4-(tert-Butylsulfonylmethyl-4-(piperidine-1-carbonyl)-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to 3-[4-(tert-butylsulfonylmethyl)-4-(piperidine-1-carbonyl)-phenox]-4-methoxy-phenyl]-acetic acid (Compound 42);

[0237] 5-amino-2-methoxy pyridine to provide 3-[4-(tert-Butylsulfonylmethyl)-4-(6-methoxy-pyridin-3-ylcarbamoyl)-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to 3-[4-(tert-butylsulfonylmethyl)-4-(6-methoxy-pyridin-3-ylcarbamoyl)-phenox]-4-methoxy-phenyl]-acetic acid (Compound 43);

[0238] 2,2,2-trifluoroethylamine hydrochloride to provide 3-[4-(tert-Butylsulfonylmethyl)-4-[2,2,2-trifluoroethylcarbamoyl]-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to 3-[4-(tert-butylsulfonylmethyl)-4-[2,2,2-trifluoroethylcarbamoyl]-phenox]-4-methoxy-phenyl]-acetic acid (Compound 44);

[0239] N-methylisopropylamine to provide 3-[4-(tert-Butylsulfonylmethyl)-4-(isopropyl-methylcarbamoyl)-phenox]-4-methoxy-phenyl]-acetic acid ethyl ester, which was hydrolyzed to 3-[4-(tert-butylsulfonylmethyl)-4-(2,2-dimethylpropylcarbamoyl)-phenox]-4-methoxy-phenyl]-acetic acid (Compound 45).

Example 30
Synthesis of 3-[4-(tert-Butylsulfonylmethyl)-4-(2,2-dimethyl-propionylamino)-phenox]-5-chloro-phenyl]-acetic acid

[0241] 3-[4-(tert-Butylsulfonylmethyl)-4-nitro-phenox]-5-chloro-phenyl]-acetic acid methyl ester was prepared according to the procedure described in Example 21, Step 8, using 3-[4-(bromomethyl-4-nitro-phenox)-5-chloro-phenyl]-acetic acid methyl ester and 2-methyl-2-propanethiol, which was reduced to 3-[4-(amino-2-tert-butylsulfonylmethyl-ethylcarbamoyl)-5-chloro-phenyl]-acetic acid methyl ester as described in Example 21, Step 9. The amine was treated with pivaloyl chloride as described in Example 21, Step 10 to provide 3-[4-(tert-butylsulfonylmethyl)-4-(2,2-dimethyl-propionylamino)-phenox]-5-chloro-phenyl]-acetic acid methyl ester. Hydrolysis of the ester to the acid was carried out as outlined in Example 21, Step 11.

Example 31
Synthesis of 3-Chloro-5-[4-(2,2-dimethyl-propionylamino)-2-(methyl-propionate-2-sulfonylmethyl)-phenox]-phenyl]-acetic acid

[0242] Prepared according to the procedure described in Example 22 using 3-[4-(tert-butylsulfonylmethyl)-4-(2,2-dimethyl-propionylamino)-phenox]-5-chloro-phenyl]-acetic acid.

Example 32
Synthesis of 4-Difluoromethoxy-3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoroethylsulfonylmethyl)-phenox]-phenyl]-acetic acid

[0243] 4-[Methoxy-3-[4-nitro-2-(2,2,2-trifluoroethylsulfonylmethyl)-phenox]-phenyl]-acetic acid ethyl ester (1.5
g. 3.6 mmol) was treated with 48% hydrogen bromide in acetic acid (1:1; 20 mL) at 100°C overnight. After work-up with EtOAc and H₂O, the crude material was purified by preparative HPLC to give [4-hydroxy-3-[4-nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid. [0244] [4-Hydroxy-3-[4-nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid (3.6 mmol) and hydrogen chloride (4N in 1,4-dioxane) were combined in EtOH and stirred at 80°C for 3 hours. After concentrating to dryness, the residue was purified by silica gel chromatography to give [4-hydroxy-3-[4-nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid methyl ester. [0245] [4-Hydroxy-3-[4-nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid methyl ester (0.40 g, 0.92 mmol), sodium chlorodifluoroacetate (0.282 g, 1.86 mmol), and potassium carbonate (0.14 g, 1.02 mmol) were combined in DMF:H₂O (8:5:1; 4.6 mL) and degassed with N₂ for 15 minutes. The reaction was then stirred at 100°C for 4 hours. After work-up with EtOAc and 1N aqueous HCl, the residue was purified by silica gel chromatography to give [4-difluoromethoxy-3-[4-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid methyl ester. [0246] [4-Difluoromethoxy-3-[4-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid methyl ester was reduced to [3-[4-amino-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)]-4-difluoromethoxy-phenyl]-acetic acid methyl ester as described in Example 21, Step 9, which was treated with pivaloyl chloride as described in Example 21, Step 10 to provide [4-difluoromethoxy-3-[4-(2,2-dimethyl-propionyloxy)-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid methyl ester. Hydrolysis of the ester to the acid was carried out as described in Example 21, Step 11.

Example 33
Synthesis of [4-Chloro-3-[4-(2,2-dimethyl-propionyloxy)-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid (Compound 50)

[0247] Prepared according to the procedure described in Example 22 using [4-difluoromethoxy-3-[4-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid (Compound 50).

[0248] To [4-hydroxy-3-[4-nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid methyl ester (0.50 g, 1.16 mmol) in DMF (10 mL) was added N-phenylbis(trifluoromethanesulfonylimidate) (0.455 g, 1.27 mmol) and cesium carbonate (0.755 g, 2.32 mmol), and the reaction was stirred at room temperature for 2 hours. After work-up with EtOAc and H₂O, the crude material was purified by silica gel chromatography to give [3-[4-nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)]-4-difluoromethanesulfonyloxy-phenyl]-acetic acid methyl ester. [0249] [3-[4-Nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-4-trifluoromethanesulfonyloxy-phenyl]-acetic acid methyl ester (0.20 g, 0.35 mmol), trimethylboroxine (0.07 mL, 0.53 mmol), potassium carbonate (0.125 g, 0.89 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.041 g, 0.035 mmol) were combined in DME:H₂O (2:1; 4 mL) and degassed with N₂ for 8 minutes. The reaction was stirred at 90°C for 2 hours, and then worked up with EtOAc and 10% aqueous HCl. The residue was purified by silica gel chromatography to give [4-methyl-3-[4-nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid methyl ester.

[0250] Following the procedures described for Example 21, [4-methyl-3-[4-nitro-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid methyl ester was reduced to [3-[4-amino-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-4-methyl-phenyl]-acetic acid methyl ester and then treated with pivaloyl chloride to provide [3-[4-(2,2-dimethyl-propionyloxy)-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-4-methyl-phenyl]-acetic acid methyl ester. Hydrolysis of the ester provided the acid.

Example 35
Synthesis of [4-Chloro-3-[4-(2,2-dimethyl-propionyloxy)-2-(2,2,2-trifluoro-ethyl)sulfanyl(methyl)-phenoxyl]-phenyl]-acetic acid (Compound 52)

[0251] To 4-chloro-3-thiophenecarboxylic acid (5 g, 26.5 mmol) and benzyl alcohol (5.5 mL, 53.0 mmol) in NMP (50 mL) at 0°C was added sodium hydride (60% in mineral oil; 2.3 g, 58.3 mmol), and the reaction was then heated to 120°C and stirred overnight. The mixture was acidified to pH 4 and extracted with EtOAc to give [3-benzyloxy-4-chloro-phenyl]-acetic acid.

[0252] [3-Benzyloxy-4-chloro-phenyl]-acetic acid (8 g) was treated with hydrogen chloride (4 N in 1,4-dioxane; 6 mL) in EtOH (100 mL) at 80°C for 3 hours. After concentrating to dryness, the residue was purified by silica gel chromatography to give [3-benzyloxy-4-chloro-phenyl]-acetic acid ethyl ester.

[0253] [3-Benzyloxy-4-chloro-phenyl]-acetic acid ethyl ester was reneutralized as outlined in Example 21, Step 4 to provide [4-chloro-3-hydroxy-phenyl]-acetic acid ethyl ester.

[0254] [4-Chloro-3-hydroxy-phenyl]-acetic acid ethyl ester was reacted with 2-thiophene-5-benzoic acid as outlined in Example 21, Step 5, to provide [4-chloro-3-[2-formyl-4-nitro-phenoxy]-phenyl]-acetic acid ethyl ester.

[0255] [4-Chloro-3-[2-formyl-4-nitro-phenoxy]-phenyl]-acetic acid ethyl ester was reduced to [4-chloro-3-[2-hydroxymethyl-4-nitro-phenoxy]-phenyl]-acetic acid ethyl ester as described in Example 21, Step 6 and then brominated to provide [3-[2-bromomethyl-4-nitro-phenoxy]-4-chlorophenyl]-acetic acid ethyl ester as outlined in Example 21, Step 7.

[0256] [3-[2-Bromomethyl-4-nitro-phenoxy]-4-chlorophenyl]-acetic acid ethyl ester was treated with 2-propanethiol as described in Example 21, Step 8 to provide [4-chloro-3-[2-(2-isopropylsulfanyl)methyl-4-nitro-phenoxy]-phenyl]-acetic acid ethyl ester, which was reduced to [3-[4-amino-2-(2-isopropylsulfanyl)methyl-phenoxyl]-4-chlorophenyl]-acetic acid ethyl ester as described in Example 21, Step 9. Treatment of the amine with pivaloyl chloride as described in Example 21, Step 10 provided [3-[4-chloro-3-[2-(2,2-dimethyl-propionyloxy)-2-(2-isopropylsulfanyl)methyl-phenoxyl]-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester to the acid was carried out as described in Example 21, Step 11.
Example 36
Synthesis of 3-[4-Chloro-3-[2,2,2-trifluoro-ethylsulfonylmethyl]-phenoxyl]-phenyl]-acetic acid (Compound 53)

[0257] As described for Example 21, 3-[2-bromomethyl-4-nitro-phenoxyl]-4-chloro-phenyl]-acetic acid ethyl ester and 2,2,2-trifluoroethanethiol were reacted to provide 3-[4-chloro-3-[4-nitro-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-phenyl]-acetic acid ethyl ester, which was reduced to the amine and then treated with pivaloyl chloride to provide 3-[4-chloro-3-[2,2,2-trifluoro-ethylsulfonylmethyl]-phenoxyl]-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester provided the acid.

Example 37
Synthesis of 3-[4-(2,2-Dimethyl-propionylamino)-2-isopropylsulfonylmethyl-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid (Compound 54)

[0258] As described for Example 21, 3-[2-bromomethyl-4-nitro-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester and 2-propanethiol were reacted to provide 3-[2-isopropylsulfonylmethyl-4-nitro-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester. Reduction to amine and then treatment of the amine with pivaloyl chloride was carried out to provide 3-[4-(2,2-dimethyl-propionylamino)-2-isopropylsulfonylmethyl-phenoxyl]-5-trifluoromethyl-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester provided the acid.

Example 38
Synthesis of 3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethylsulfonylmethyl-phenoxyl]-4-vinyl-phenyl]-acetic acid (Compound 55) and 3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethylsulfonylmethyl-phenoxyl]-4-ethyl-phenyl]-acetic acid (Compound 56)

[0259] 3-[4-Nitro-2-(2,2,2-trifluoro-ethylsulfonylmethyl-phenoxyl]-4-trifluoromethanesulfonyl-phenyl]-acetic acid methyl ester (0.920 g, 1.63 mmol), trimethylsilyl acetate (0.34 mL, 2.45 mmol), dichlorobis (triethylphosphine)palladium (H) (0.1155, 0.16 mmol), and copper iodide (0.031 g, 0.16 mmol) were combined in triethylamine (8 mL) and degassed for 5 minutes. The reaction was heated for 8 hours, and then worked-up with CH$_2$Cl$_2$ and H$_2$O. The crude material was purified by silica gel chromatography to give 3-[4-nilro-2-(2,2,2-trifluoro-ethylsulfonylmethyl-phenoxyl]-4-trimethylsilyl-phenyl]-acetic acid methyl ester.

[0260] To a solution of 3-[4-nitro-2-(2,2,2-trifluoro-ethylsulfonylmethyl-phenoxyl]-4-trimethylsilyl-phenyl]-acetic acid methyl ester (0.410 g, 0.8 mmol) in THF (3 mL) was added tetraethylammonium fluoride (1M in THF; 1.2 mL, 1.2 mmol), and the reaction was stirred for 30 minutes at room temperature. Once no starting material was seen by analytical tlc, the mixture was worked-up with EtOAc and H$_2$O, and the residue was purified by silica gel chromatography to give 3-[4-(Ethynyl)-3-[4-nilro-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-phenyl]-acetic acid methyl ester.

[0261] 3-[4-(Ethynyl)-3-[4-nilro-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-phenyl]-acetic acid methyl ester (0.170 g, 0.39 mmol) was hydrogenated with 10% palladium on carbon in EtOH under 50 psi H$_2$, using the Parr apparatus, overnight. The mixture was filtered through Celite, and the filtrate was concentrated to give a 1:1 mixture of 3-[4-Amino-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-4-vinyl-phenyl]-acetic acid methyl ester and 3-[4-Amino-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-4-ethyl-phenyl]-acetic acid methyl ester.

Example 39
Synthesis of 3-[4-Methoxy-3-[4-(2-oxo-imidazolidin-1-yl)-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-phenyl]-acetic acid (Compound 57)

[0263] 3-[4-Amino-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester and 2-chloroethyl isocyanate were reacted as described for Example 3, Step 6. The crude material was purified by silica gel chromatography.

[0264] Sodium ethoxide (20% w/v; 2.27 mL, 0.187 mmol) was added to a solution of 3-[4-[3-(2-chloro-ethyl)-ureido]-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-4-methoxy-phenyl]-acetic acid ethyl ester (0.050 g, 0.049 mmol) in EtOH (5 mL). The reaction was stirred at 65°C overnight, and then partitioned between EtOAc and H$_2$O. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated. The residue was purified by preparative HPLC to give Compound 57.

Example 40
Synthesis of 3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethylsulfonylmethyl)-phenoxyl]-4-chloro-phenyl]-acetic acid (Compound 59)

[0265] As described for Example 21, 3-[2-bromomethyl-4-nitro-phenoxyl]-4-chloro-phenyl]-acetic acid ethyl ester and 2-methyl-2-propanethiol were reacted to provide 3-[2-tert-butylsulfanyl methyl-4-nitro-phenoxyl]-4-chloro-phenyl]-acetic acid ethyl ester, which was reduced to 3-[4-amino-2-tert-butylsulfanyl methyl-phenoxyl]-4-chloro-phenyl]-acetic acid ethyl ester. The amine was treated with trimethylacetyl chloride to provide 3-[4-(2-tert-Butylsulfanyl methyl)-phenoxyl]-4-(2,2-dimethyl-propionylamino)-phenoxyl]-4-chloro-phenyl]-acetic acid ethyl ester. Hydrolysis of the ester provided the acid.

Example 41
Synthesis of 3-[4-(2-tert-Butylsulfanyl methyl)-4-(4-chloro-benzoylamin o)-phenoxyl]-4-chloro-phenyl]-acetic acid (Compound 60)

[0266] Following the procedures described for Example 21, 3-[2-tert-butylsulfanyl methyl-4-(4-chloro-benzoy-
lamino)-4-chloro-phenyl]-acetic acid ethyl ester was obtained from [3-(4-amino-2-tert-butylsulfanilylmethyl-phenoxo)-4-chloro-phenyl]-acetic acid ethyl ester and 4-chlorobenzoyl chloride. Hydrolysis of the ester provided the acid.

Example 42
Synthesis of [3-(2-tert-Butylsulfanilylmethyl-4-isobutyrylamino-phenoxo)-4-chloro-phenyl]-acetic acid (Compound 61)

[0267] Following the procedures described for Example 21, [3-(2-tert-butylsulfanilylmethyl-4-isobutyrylamino-phenoxo)-4-chloro-phenyl]-acetic acid ethyl ester was obtained from [3-(4-amino-2-tert-butylsulfanilylmethyl-phenoxo)-4-chloro-phenyl]-acetic acid ethyl ester and isobutyl chloride. Hydrolysis of the ester provided the acid.

Example 43
Synthesis of [3-(4-(2,2-Dimethyl-propionylamino)-2-(methyl-propane-2-sulfonylmethyl)-phenoxo)-4-methoxy-phenyl]-acetic acid (Compound 73)

[0268] Prepared according to the procedure described in Example 2 using [3-(2-tert-butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-methoxy-phenyl]-acetic acid and 3-chloroperbenzoic acid (1 equivalent).

Example 44
Synthesis of [3-(4-(2,2-Dimethyl-propionylamino)-2-(methyl-propane-2-sulfonylmethyl)-phenoxo]-4-methoxy-phenyl]-acetic acid (Compound 74)

[0269] Prepared according to the procedure described in Example 1 using [3-(2-tert-butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-methoxy-phenyl]-acetic acid and 3-chloroperbenzoic acid (2 equivalents).

Example 45
Synthesis of [3-(2-tert-Butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-hydroxy-phenyl]-acetic acid (Compound 75)

[0270] [3-(2-tert-Butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-methoxy-phenyl]-acetic acid (0.953 g, 2.07 mmol) in CHCl₃, 2.61 mL, 6.21 mmol) was added, and the reaction was stirred at room temperature for 2 hours. The reaction was quenched, and after aqueous work-up, the crude material was purified by preparative HPLC to give the title compound.

Example 46
Synthesis of [3-(4-(2,2-Dimethyl-propionylamino)-2-(methyl-propane-2-sulfonylmethyl)-phenoxo]-4-hydroxy-phenyl]-acetic acid (Compound 76)

[0271] Prepared according to the procedure described in Example 2 using [3-(2-tert-butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-hydroxy-phenyl]-acetic acid and 3-chloroperbenzoic acid (1 equivalent).

Example 47
Synthesis of (2R,3R,4R,5S,6S)-6-(2-[3-(2-tert-Butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-methoxy-phenyl]-acetoxy)-3,4,5-trihydroxy-tetrahydro-pyrano-2-carboxylic acid (Compound 77)

[0272] [3-(2-tert-Butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-methoxy-phenyl]-acetic acid (0.200 g, 0.44 mmol), (2R,3R,4R,5S,6S)-3,4,5,6-tetrahydro-tetrahydro-pyrano-2-carboxylic acid benzyl ester (0.200 g, 0.7 mmol), prepared according to the procedure described in Tetrahedron 2007, 63, 7896), HATU (0.266 g, 0.7 mmol), N,N-dimethylformamide (0.1 mL, 0.7 mmol) were combined in MeCN, and the reaction was stirred overnight at room temperature. The mixture was concentrated, and the residue was purified by preparative HPLC to give (2R,3R,4R,5S,6S)-6-(2-[3-(2-tert-Butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-methoxy-phenyl]-acetoxy)-3,4,5-trihydroxy-tetrahydro-pyrano-2-carboxylic acid benzyl ester, which was subsequently treated with palladium hydroxide on carbon and stirred under an atmosphere of H₂ overnight. The crude material was purified by preparative HPLC to give (2R,3R,4R,5S,6S)-6-(2-[3-(2-tert-Butylsulfanilylmethyl-4-(2,2-dimethyl-propionylamino)-phenoxo]-4-methoxy-phenyl]-acetoxy)-3,4,5-trihydroxy-tetrahydro-pyrano-2-carboxylic acid.

[0273] Mass spectrometric data (M+H) for compounds are displayed in Table 1.

Example 48
CRT1H2 Assays

Example 48a
DP₂/CRT1H2 Binding Assay

[0274] The ability of a compound to bind to the human DP₂ receptor is assessed via a radioligand binding assay using [³⁵S]PGD₂. HEK293 cells stably expressing recombinant human DP₂ are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT, lysed and centrifuged at 75,000g 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 [³⁵S]PGD₂, and test compound in assay buffer (50 mM Hepes, 10 mM MgCl₂, 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 0.35% polyethyleneimine 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 PGD₂. IC₅₀'s were determined using Graphpad prism...
analysis of drug titration curves. Compounds tested had an IC\textsubscript{50} of less than 20 micromolar in this assay.

**Example 48b**
GTP\textsubscript{S} Binding Assay

**[0275]** The ability of a compound to inhibit binding of GTP to DP\textsubscript{2} is assessed via a membrane GTP\textsubscript{S} assay. CHO cells stably expressing the recombinant human CTR12 receptor are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT, lysed and centrifuged at 75,000g to pellet the membranes. The membranes are resuspended in 10 mM Hepes, 7.4 containing 1 mM DTT and 10% glycerol. Membranes (~12.5 mg per well) are incubated in 96-well plates with 0.05 nM [\textsuperscript{35}S]-GTP\textsubscript{S}, 80 nM PGP\textsubscript{D2}, 5 \mu M GDP, and test compound in Assay Buffer (50 mM Hepes, pH 7.4, 100 mM NaCl, 5 mM MgCl\textsubscript{2} and 0.2% human serum albumin) for 60 minutes at 30\degree C. The reactions are terminated by rapid filtration through Whatman GF/C glass fibre filter plates. The filter plates are washed 3 times with 1 ml cold Assay Buffer and dried. Scintillant is then added to the plates and the radioactivity retained on the filters is determined on a Packard TopCount (Perkin Elmer). Specific binding is determined as total radioactive binding minus non-specific binding in the absence of the ligand (80 nM PGP\textsubscript{D2}). IC\textsubscript{50} were determined using Graphpad prism analysis of drug titration curves.

**Example 48c**
Whole Blood Eosinophil Shape Change Assay

**[0276]** Blood is drawn from consenting human volunteers in EDTA vacutainer tubes and used within 1 hr of draw. A 98 \mu l aliquot of blood is mixed with 2 \mu l of test compound (in 50% DMSO) in 1.2 ml polypropylene tubes. The blood is vortexed and incubated at 37\degree C for 15 minutes. 5 \mu l of 1 mM PGP\textsubscript{D2} in PHS is added for a final concentration of 50 nM and the tubes briefly vortexed. The reactions are incubated for exactly 5 minutes at 37\degree C and then terminated by placing the tubes on ice and immediately adding 250 \mu l of ice-cold 1:4 diluted Cytofix (BD Biosciences). The reactions are transferred to 12x75 mm polypropylene round bottom tubes and the red blood cells lysed by the addition of 3 ml ammonium chloride lysing solution (150 mM NaCl, 10 mM KH\textsubscript{2}CO\textsubscript{3}, 0.1 mM EDTA disodium salt) and incubated at room temperature for 15 minutes. The cells are pelleted by spinning at 1300 rpm for 5 minutes at 4\degree C and washed once with 3 ml ice-cold PBS. The cells are resuspended in 0.2 ml of ice-cold 1:4 diluted Cytofix (BD Biosciences) and analyzed on a FACSCalibur (BD Biosciences) within 2 hours. Eosinophils were gated on the basis of auto-fluorescence in the FL2 channel and shape change on 500 eosinophils was assayed by forward scatter and side scatter analysis. The specific change in shape induced by PGP\textsubscript{D2} was calculated as the difference between the percentage of high forward scatter eosinophils in the presence and absence of PGP\textsubscript{D2}. IC\textsubscript{50} were determined using Graphpad Prism\textregistered analysis of drug titration curves.

**Example 48d**
DP\textsubscript{1} Binding Assay

**[0277]** The ability of a compound to bind to the human DP\textsubscript{1} receptor was evaluated via a radioligand membrane binding assay using the DP\textsubscript{1} selective synthetic ligand [\textsuperscript{3}H] BWA868C. Packed human platelets (Biological Speciality 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 75,000g to pellet the membranes. Membranes were resuspended in Hepes/HBSS buffer to approximately 12 mg protein/ml. Membranes (20 nM protein/well) are incubated in 96-well plates with 2 nM [\textsuperscript{3}H]BWA868C and test compound in Assay Buffer (50 mM Hepes, 10 mM MnCl\textsubscript{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/B glass fibre filter plates. The filter plates were pre-soaked in 0.33% polyethyleneimine 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 nM BW A868C. IC\textsubscript{50} were determined using Graphpad prism analysis of drug titration curves.

**Example 49**
Mouse Allergic Rhinitis Model

**[0278]** The compounds ability to inhibit allergen-induced sneezing and nasal rubbing is assessed using a mouse model of allergic rhinitis. Methods were adapted from those detailed in Nakayama, M., et al. 2006, Laboratory Investigation, 86:917-926. Female BALB/c mice (20-25 g) are immunized by an intraperitoneal injection (i.p.) of 2 \mu g ovalbumin (OVA) complexed with alum in a volume 0.2 ml on days 0 and 14. Seven days later (day 21) mice are challenged intranasally with 20 \mu l of a 10 mg/ml solution of OVA. The challenge period occurs daily from days 21 to day 25. Mice (5-7/group) are randomly assigned to receive either compound or vehicle and are treated by oral gavage 1-2 hour prior to each OVA challenge. The number of sneezes and nasal rubs are counted by an independent blind observer during a period of 8 minutes immediately following OVA challenge on days 21, 23 and 25. A significant increase in allergen-induced sneezing and nasal rubbing occurs over the 5-day challenge period. Inhibition of this effect by select compounds is determined statistically using Graphpad prism.

**Example 50**
Guinea Pig IV-DKPGD2-Induced Peripheral Blood Leukocyte Influx

**[0279]** The compounds ability to inhibit leukocyte migration in vivo was assessed using intravenous injection of 13,14-dihydro-15-keto-prostaglandin D\textsubscript{2} (DK-PGD\textsubscript{2}). Methods were adapted from those detailed Shichijo et al., 2003, Journal of Pharmacology and Experimental Therapeutics, 307:518-525. Male Hartley guinea pigs were immunized with ovalbumin (OVA) on day 0 by intraperitoneal (IP) injection of 1 ml of a 100 \mu g/ml solution in imunogen mixture which was then used in the DK-PGD\textsubscript{2} procedure between days 14 and 21. Subjects were randomly assigned to receive either vehicle (0.5% methyl cellulose, 4 ml/kg, oral (PO)) or one of three to four doses of test compound. Two hours or eighteen hours after dosing, animals were anesthetized with ketamine and challenged with DK-PGD\textsubscript{2} (1 mg/kg, iv). Thirty minutes
after IV administration, blood was collected via the marginal ear vein into EDTA tubes for cell analysis. 10 µl blood was lysed in 190 µl water followed by a further 20-fold dilution in PBS. A 10 µM fraction was mixed with equal parts trypan blue and loaded on a hemocytometer. Cells were visualized at a magnification of 40x using a LabPro light microscope and totals counted and recorded. Cells are expressed as total cells x 10^6 per ml of blood. Inhibition of this effect by select compounds is determined statistically using Graphpad prism.

The compounds that were tested in Table 2 had IC_{50} below 40 µM in the CTH12 binding assay.

**TABLE 2**

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<tr>
<td>Compound 58</td>
<td>A</td>
<td>A</td>
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</tbody>
</table>

A = less than 0.3 µM; B = greater than 0.3 µM and less than 1 µM; C = greater than 1 µM. ND = Not determined

**Example 51**

**Clinical Trials in Humans**

**Study 1: Clinical Trial Evaluating Effect of Compound of Formula (I) on Ex Vivo PGD2-Induced Blood Eosinophil Shape Change**

In this double-blind, randomized, placebo-controlled, single ascending dose study of Compound of Formula (I) in healthy volunteers the inhibition of ex vivo PGD2-induced blood eosinophil shape change is determined to show proof of biochemical mechanism of DP2 receptor antagonism. Eight subjects (6 active, 2 placebo) per dose level are used. Pre dose blood is drawn and challenged with PGD2 to determine baseline shape change as described above in Example 48. At varying times after dosing blood is drawn for both pharmacokinetic analyses of drug concentration in blood, and also for PGD2 challenge and eosinophil shape change determination. The extent of receptor blockade is determined from the relationship between drug blood concentration and percentage inhibition of eosinophil shape change.

**Study 2: Clinical Trial Evaluating Effect of Compound of Formula (I) on Allergen-Induced Nasal Symptoms and Inflammatory and Allergic Biomarkers**

In this double-blind, randomized, placebo-controlled study of Compound of Formula (I) in individuals with allergic rhinitis the inhibition of nasal symptoms and allergic biomarkers is determined following nasal challenge with appropriate allergen. Fifteen subjects (10 active, 5 placebo) are used. Subjects are dosed for 7 days with either placebo or an amount of compound of formula (I) that results in complete DP2 receptor block in an ex vivo PGD2-induced blood eosinophil shape change pharmacodynamic study as described above. On day 7 subjects undergo nasal allergen challenge (2 hours post-dose) and early allergic response (0.25-1.0 hr) and late allergic response (4-24 hr) are evaluated.
as an increase from baseline for treated vs placebo. In addition, changes in inflammatory cell differentials, Th2 cytokines and other inflammatory markers are determined as increase from baseline for treated vs. placebo.

Compound of Formula (I) Assay


Study 3—Vienna Challenge Chamber Study

[0284] Study design: The study is a randomised, double blind, placebo controlled, two way crossover evaluation of compound of Formula (I), given orally for eight days. There is a screening period of one week and a washout period of three weeks between the two treatment periods.

[0285] There is a follow up one week after the last dose of study drug. The group of patients who receive the study drug for the first treatment period and placebo for the second are designated group A, while the group of patients who receive placebo for the first treatment period and the study drug for the second treatment period are designated group B.

[0286] Treatment plan and methods: The subjects undergo a complete screening assessment to determine a baseline response to allergens. This screening assessment takes place one week prior to the start of dosing.

[0287] Subjects commence dosing with compound of Formula (I) or placebo on Day 1 of each treatment period of the study. Adverse events, total nasal symptom score and concomitant medications are noted.

[0288] Subjects report back to the clinic on Day 2 of each treatment period for a 6 hour allergen challenge. The following measurements are obtained:

[0289] Total nasal symptom score (TNSS) (obstruction, rhinorrhea, itch, sneeze) with each symptom scored on a categorical scale from 0 to 3 pre-challenge, every 15 mins from 0 to 6 h post-start of challenge.

[0290] Eye symptom score (watery eyes, itchy eyes, red eyes) with each symptom scored on a categorical scale from 0 to 3 pre-challenge, every 15 mins from 0 to 6 h post-start of challenge.

[0291] Other symptoms (cough, itchy throat, itchy ears) with each symptom scored on a categorical scale from 0 to 3 pre-challenge and every 15 mins from 0 to 6 h post-start of challenge.

[0292] Subjects report back to the clinic on Day 8 of each treatment period for a 6 hour allergen challenge and the measurements obtained on Day 2 are repeated.

[0293] A final follow-up visit is conducted one after the last dose of test article in Treatment Period 2.

Example 52a

Parenteral Composition

[0294] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a watersoluble salt of a compound of Formula (I) is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Example 52b

Oral Composition

[0295] To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula (I) is mixed with 750 mg of starch. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

Example 52c

Sublingual (Hard Lozenge) Composition

[0296] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a compound of Formula (I) with 420 mg of powdered sugar mixed with 1.6 mL of light corn syrup, 2.4 mL distilled water, and 0.42 mL mint extract. The mixture is gently blended and poured into a mold to form a lozenge suitable for buccal administration.

Example 52d

Fast-Disintegrating Sublingual Tablet

[0297] A fast-disintegrating sublingual tablet is prepared by mixing 48.5% by weight of a compound of Formula (I), 44.5% by weight of microcrystalline cellulose (KRG-802), 5% by weight of low-substituted hydroxypropyl cellulose (50 μm), and 2% by weight of magnesium stearate. Tablets are prepared by direct compression (AAPS PharmSciTech, 2006; 7(2):E41). The total weight of the compressed tablets is maintained at 150 mg. The formulation is prepared by mixing the amount of compound of Formula (I) with the total quantity of microcrystalline cellulose (MCC) and two-thirds of the quantity of low-substituted hydroxypropyl cellulose (L-HPC) by using a three dimensional manual mixer (Inversinar®, Bioengineering AG, Switzerland) for 4.5 minutes. All of the magnesium stearate (MS) and the remaining one-third of the quantity of L-HPC are added 30 seconds before the end of mixing.

Example 52e

Inhalation Composition

[0298] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula (I) is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Example 52f

Rectal Gel Composition

[0299] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound of Formula (I) is mixed with 2.5 g of methylcellulose (1500 mPa.s), 100 mg of methylparaben, 5 g of glycerin and 100 mL of purified water. The result-
Example 52g

Topical Gel Composition

[0300] To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula (I) is mixed with 0.75 g of hydroxypropyl cellulose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

Example 52h

Ophthalmic Solution Composition

[0301] To prepare a pharmaceutical ophthalmic solution composition, 100 mg of a compound of Formula (I) is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

Example 52i

Nasal Spray Solution

[0302] To prepare a pharmaceutical nasal spray solution, 10 g of a compound of Formula (I) is mixed with 30 mL of a 0.05 M phosphate buffer solution (pH 4.4). The solution is placed in a nasal atomizer designed to deliver 100 µg of spray for each application.

[0303] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

1. A compound having the structure of Formula (I), or pharmaceutically acceptable salt thereof:

![Formula (I)](image)

wherein,

- R¹ is H or C₁₋₅ alkyl;
- R² is halogen, —CN, —OH, C₁₋₅ alkyl, C₁₋₅ fluoroalkyl, C₁₋₅ haloalkyl, or C₁₋₅ heteroaryl;
- R⁶ is —NR¹₂S(═O)R¹₂, —S(═O)₂NR¹₂(R¹₂), —NR¹₂(R¹₂), —C(═O)NR¹₂(R¹₂)₂, —NE(═O)₂N(R¹₂)₂, or —NR¹₂(C(═O)OR¹₂)₂, or —NR¹₂(C(═O)OR¹₂)₂;
- R¹₁ is C₁₋₅ alkyl, C₁₋₅ haloalkyl, C₁₋₅ heteroaryl, C₁₋₅ cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted napthyl, a substituted or unsubstituted 5-membered heteroaryl, a substituted or unsubstituted 6-membered heteroaryl, or —C₁₋₅ alkyl (substituted or unsubstituted phenyl);
- R¹₂ is C₁₋₅ alkyl, C₁₋₅ heteroaryl, C₁₋₅ fluoroalkyl, C₁₋₅ cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted napthyl, a substituted or unsubstituted benzy1, a substituted or unsubstituted 6-membered heteroaryl, or —C₁₋₅ alkyl (substituted or unsubstituted phenyl);
- R¹³ is H or C₁₋₅ alkyl; or
- R¹² and R¹³ attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted C₂₋₅ heterocycloalkyl; x is 0, 1, or 2.

2. The compound of claim 1, wherein:
- R² is H, —CH₃, or —CH₂CH₃;
- R¹ is H, F, Cl, Br, —OCH₃, —CH₃, —CH₂CH₃, —CH₂—CH₂—CH₃, —CF₃, —OCH₂F₂, or —OCF₃.

3. The compound of claim 2, wherein:
- R¹₁ is C₁₋₅ alkyl, C₁₋₅ haloalkyl, C₁₋₅ cycloalkyl, a substituted or unsubstituted phenyl, or —C₁₋₅ alkyl (substituted or unsubstituted phenyl);

4. The compound of claim 3, wherein the compound of Formula (I) has the structure of Formula (II):

![Formula (II)](image)

5. The compound of claim 4, wherein:
- R² is H, F, Cl, Br, —OCH₃, —CH₃, —CH₂CH₃, —CH₂—CH₂—CH₃, —CF₃, —OCH₂F₂, or —OCF₃.

6. The compound of claim 5, wherein:
- R¹ is C₁₋₅ alkyl, C₁₋₅ heteroaryl, C₁₋₅ fluoroalkyl, C₁₋₅ cycloalkyl, a substituted or unsubstituted phenyl, a substituted or unsubstituted benzy1, or —C₁₋₅ alkyl (substituted or unsubstituted phenyl);
- R¹³ is H or —CH₃.

7. The compound of claim 6, wherein:
- R² is —NR¹₂S(═O)R¹₂, —S(═O)₂NR¹₂(R¹₂), —NR¹₂(R¹₂), —C(═O)NR¹₂(R¹₂)₂, —NE(═O)₂N(R¹₂)₂, —NR¹₂(C(═O)OR¹₂)₂, or —NR¹₂(C(═O)OR¹₂)₂.

8. The compound of claim 7, wherein:
- R¹₁ is C₁₋₅ alkyl, C₁₋₅ haloalkyl, a substituted or unsubstituted phenyl, or —C₁₋₅ alkyl (substituted or unsubstituted phenyl).

9. The compound of claim 8, wherein:
- R² is H, F, Cl, Br, —OCH₃, —CH₃, —CH₂CH₃, —CH₂—CH₂—CH₃, —CF₃, —OCH₂F₂, or —OCF₃.

10. The compound of claim 9, wherein:
- R² is —NR¹₂(C(═O)OR¹₂)₂.

11. The compound of claim 10, wherein:
- R¹₂ is C₁₋₅ alkyl, C₁₋₅ cycloalkyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted benzy1.

12. The compound of claim 11, wherein:
- R¹ is —CH₂CH₃, —CH(CH₃)₂, —C(CH₃)₃, —CH₂CF₃, a substituted or unsubstituted phenyl, or —C₁₋₅ alkyl (substituted or unsubstituted phenyl).
13. The compound of claim 12, wherein:

R¹₂ is \(-\text{CH(CH}_3\text{)}_2\), \(-\text{CH}_2\text{CH}(\text{CH}_3)\), \(-\text{CH}_2\text{C(CH}_3\text{)}_3\), cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, a substituted or unsubstituted phenyl, or a substituted or unsubstituted benzyl.

14. The compound of claim 1, wherein the compound of Formula (I) has the structure of Formula (III):

\[
\text{Formula (II)}
\]

15. The compound of claim 14, wherein:

R¹₁ is \(-\text{CH}_2\text{CH}(\text{CH}_3)\), \(-\text{CH}_2\text{Cl}\), \(-\text{CH}_2\text{CF}_2\), \(-\text{OCH}_3\), \(-\text{OCH}_2\text{CH}_3\), or \(-\text{OCF}_3\);

R¹₂ is \(-\text{CH}(\text{CH}_3)\), \(-\text{CH}_2\text{CH}(\text{CH}_3)\), \(-\text{CH}_2\text{C(CH}_3\text{)}_3\), or a substituted or unsubstituted phenyl;

R² is \(\text{H}\).

16. The compound of claim 15, wherein:

R² is F, Cl, \(-\text{OCH}_3\), \(-\text{CF}_3\), or \(-\text{OCF}_3\);

R¹₂ is \(-\text{CH}(\text{CH}_3)\);

R² is \(\text{H}\).

17. The compound of claim 1 selected from among: [3-[4-(4-Chloro-benzoylamino)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 1); [3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 2); [3-[4-(3-Benzyl-ureido)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 3); [3-[4-(4-Chloro-benzoylamino)-2-(4-chloro-phenyl-sulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 4); [3-[4-(4-Chloro-phenoxy)-2-(2,2-dimethyl-propionylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 5); [3-[4-(3-Benzyl-ureido)-2-(4-chloro-phenyl-sulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 6); [3-[4-[2-tert-Butylsulfonyl]-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 7); [3-[4-[2-tert-Butylsulfonyl]-4-(4-chloro-benzoylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 8); [3-[4-[2,2-Dimethyl-propionylamino]-2-isopropylsulfonyl]-4-methoxy-phenyl]-acetic acid (Compound 9); [3-[4-[2,2-Dimethyl-propionylamino]-2-(propene-2-sulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 10); [3-[4-[2,2-Dimethyl-propionylamino]-2-(propene-2-sulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 11); [3-[4-[2,2-Dimethyl-propionylamino]-2-(2-trifluoro-ethanesulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 12); [3-[4-(3-Benzyl-ureido)-2-tert-butylsulfonyl]-4-methoxy-phenyl]-acetic acid (Compound 13); [3-[4-[3-Cyclopropane-carbonylamino]-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 14); [3-[4-Isobutylazolino)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 15); [3-[4-(3,3-Dimethyl-butyrylamino)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 16); [3-[4-(4-Chloro-benzoylamino)-2-phenyl sulfonyl]-4-methoxy-phenyl]-acetic acid (Compound 17); [3-[2-Benzylsulfonyl]-4-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 18); [3-[4-(4-Chloro-benzoylamino)-2-(5-methyl-[1,3,5]-thiadiazol-2-yl-sulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 19); [3-[4-(4-Chloro-benzoylamino)-2-isopropylsulfonyl]-4-methoxy-phenyl]-acetic acid (Compound 20); [3-[4-(4-Chloro-benzoylamino)-2-(propene-2-sulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 21); [3-[4-(4-Chloro-benzoylamino)-2-(propene-2-sulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 22); [3-[2-Benzesulfonyl]-4-(4-chloro-benzoylamino)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 23); [3-[2-Benzesulfonyl]-4-(4-chloro-benzoylamino)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 24); [3-[4-(4-Chloro-benzoylamino)-2-isopropylsulfonyl]-4-methoxy-phenyl]-acetic acid (Compound 25); [3-[4-(4-Chloro-benzoylamino)-2-isopropylsulfonyl]-4-methoxy-phenyl]-acetic acid (Compound 26); [3-[4-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 27); [3-[4-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 28); [3-[4-(4,4-dimethyl-propiionylamino)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 29); [3-[4-(4,4-dimethyl-propiionylamino)-2-isopropylsulfonyl]-4-methoxy-phenyl]-acetic acid (Compound 30); [3-[4-(2,2-Dimethyl-propionylamino)-2-(propene-2-sulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 31); [3-[4-(4,4-dimethyl-propiionylamino)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-5-trifluoromethyl]-phenyl]-acetic acid (Compound 32); [3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-5-trifluoromethyl]-phenyl]-acetic acid (Compound 33); [3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 34); [3-[2-tert-Butylsulfonyl]-4-(cy clopropane-carbonylamino)-4-methoxy-phenyl]-acetic acid (Compound 35); [3-[2-tert-Butylsulfonyl]-4-isobutylazolino)-2,4-methoxy-phenyl]-acetic acid (Compound 36); [3-[2-tert-Butylsulfonyl]-4-(3,3-dimethyl-butyramino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 37); [4-Methoxy-3-[4-(2-oxo-oxazolidin-3-yl)-2-(2,2,2-trifluoro-ethylsulfonyl)phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 38); [3-[4-(4,4-dimethyl-butyrylamino)-2-tert-butylsulfonyl]-4-methoxy-phenyl]-acetic acid (Compound 39); [3-[2-tert-Butylsulfonyl]-4-(2-oxo-2-phenyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 40); [3-[2-tert-Butylsulfonyl]-4-(2-fluoro-2-phenyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 41); [3-[2-tert-Butylsulfonyl]-4-(1,1-dimethyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 42); [3-[2-tert-Butylsulfonyl]-4-(6-methoxy-pyridin-3-ylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 43); [3-[2-tert-Butylsulfonyl]-4-(1,1-dimethyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 44); [3-[2-tert-Butylsulfonyl]-4-(6-methoxy-pyridin-3-ylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 45); [3-[2-tert-Butylsulfonyl]-4-(1,1-dimethyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 46); [3-[2-tert-Butylsulfonyl]-4-(1,1-dimethyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 47); [3-[2-tert-Butylsulfonyl]-4-(1,1-dimethyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 48); [3-[2-tert-Butylsulfonyl]-4-(1,1-dimethyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 49); [3-[2-tert-Butylsulfonyl]-4-(1,1-dimethyl-ethylcarbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 50).
acetic acid (Compound 43); [3-[2-tert-Butylsulfanyl-1-methyl-1,2,2-trifluoro-ethyl-carbamoyl]-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 44); [3-[2-tert-Butylsulfanyl-methyl]-4-(isopropyl-methyl-carbamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 45); [3-[2-tert-Butylsulfanyl-methyl]-4-(2,2-dimethyl-propylcar- bamoyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 46); [3-[2-tert-Butylsulfanyl-methyl]-4-(2,2-dimethyl-propionylamino)-phenoxy]-5-chloro-phenyl]-acetic acid (Compound 47); [3-Chloro-5-[4-(2,2-dimethyl-propiony- lamino)-2-(2-methyl-propyl-2-sulfonylmethyl)-phenoxy]-phenyl]-acetic acid (Compound 48); [4-Difluoroethoxy-3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro- ethylsulfanyl-methyl)-phenoxy]-phenoxy]-phenyl]-acetic acid (Compound 49); [4-Difluoroethoxy-3-[4-(2,2-dimethyl-propionylamino)-2-(trifluoro-ethanesulfanyl-methyl)-phenoxy]-phenyl]-acetic acid (Compound 50); [3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro- ethylsulfanyl-methyl)-phenoxy]-phenyl]-acetic acid (Compound 51); [4-Chloro-3-[4-(2,2-dimethyl-propionylamino)-2-isopropylsulfanyl-methyl-phenoxy]-phenyl]-acetic acid (Compound 52); [4-Chloro-3-[4-(2,2-dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)- phenox]-phenyl]-acetic acid (Compound 53); [3-[4-(2,2-Dimethyl-propionylamino)-2-isopropylsulfanyl-methyl- phenox]-5-trifluoromethyl-phenyl]-acetic acid (Compound 54); [3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-triflu- oro-ethylsulfanyl-methyl)-phenoxy]-phenyl]-acetic acid (Compound 55); [3-[4-(2,2-Dimethyl-propionylamino)-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-phenoxy]-4-ethyl-phenyl]-acetic acid (Compound 56); [4-Methoxy-3-[4-(2-oxo-imidazolidin-1-yl)-2-(2,2,2-trifluoro- ethylsulfanyl-methyl)-phenoxy]-phenyl]-acetic acid (Compound 57); [3-[4-Benzoylaminio-2-tert-Butylsulfanyl-methyl-phenox]-4-methoxy-phenyl]-acetic acid (Compound 58); [3-[2-tert-Butylsulfanyl-methyl]-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-chloro-phenyl]-acetic acid (Compound 59); [3-[2-tert-Butylsulfanyl-methyl]-4-(4-chloro-benzylamino)-phenoxy]-4-chloro-phenyl]-acetic acid (Compound 60); [3-[2-tert-Butylsulfanyl-methyl]-4-(isobutyramino-phenox)-4-chloro-phenyl]-acetic acid (Compound 61); [3-[2-tert-Butylsulfanyl-methyl]-4-(3-fluoro-benzylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 62); [3-[2-tert-Butylsulfanyl-methyl]-4-(4-fluoro-benzylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 63); [3-[2-tert-Butylsulfanyl-methyl]-4-(2-fluoro-benzylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 64); [3-[2-tert-Butylsulfanyl-methyl]-4-(2,4-dichloro-benzylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 65); [3-[2-tert-Butylsulfanyl-methyl]-4-(3,5-dichloro-benzylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 66); [3-[2-tert-Butylsulfanyl-methyl]-4-(3,5-difluoro-benzylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 67); [4-Methoxy-3-[2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-4-(3-fluoro-benzylamino)-phenoxy]-phenyl]-acetic acid (Compound 68); [4-Methoxy-3-[2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-4-(3-trifluoromethyl-benzylamino)-phenoxy]-phenyl]-acetic acid (Compound 69); [4-Methoxy-3-[4-(pyridine-3-carbonyl)-amino]-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-phenoxy]-phenyl]-acetic acid (Compound 70); [4-Methoxy-3-[4-(pyridine-4-carbonyl)-amino]-2-(2,2,2-trifluoro-ethylsulfanyl-methyl)-phenoxy]-phenyl]-acetic acid (Compound 71); [3-[2-tert-Butylsulfanyl-methyl]-4-(5-dimethylamino-naphthalene-1-sulfonylamino)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 72); [3-[4-(2,2-Dimethyl-propionylamino)-2-(2-methyl-propyl-2-sulfonylmethyl)-phenoxy]-4-methoxy-phenyl]-acetic acid (Compound 73); [3-[4-(2,2-Dimethyl-propionylamino)-2-(2-methyl-propyl-2-sulfonylmethyl)-phenox]-4-methoxy-phenyl]-acetic acid (Compound 74); [3-[2-tert-Butylsulfanyl-methyl]-4-(2,2-dimethyl-propionylamino)-phenoxy]-4-hydroxy-phenyl]-acetic acid (Compound 75); and [3-[4-(2,2-Dimethyl-propionylamino)-2-(2-methyl-propyl-2-sulfonylmethyl)-phenoxy]-4-hydroxy-phenyl]-acetic acid (Compound 76); or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable inactive ingredient selected from pharmaceutically acceptable diluents, pharmaceutically acceptable excipients, and pharmaceutically acceptable carriers.

19. The pharmaceutical composition of claim 18, wherein the pharmaceutical composition is formulated for intravenous injection, oral administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration.

20. The pharmaceutical composition of claim 18, wherein the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

21. (canceled)
22. (canceled)
23. (canceled)
24. (canceled)
25. (canceled)