Abstract: Substituted phenyl acetic acid compounds of formula (I), pharmaceutical compositions, methods for their preparation and methods are provided that are useful in the treatment and prevention of disorders or conditions responsive to DP 2 receptor modulation, in particular, inflammatory and immune related disorders and conditions, such as asthma, allergic rhinitis and atopic dermatitis.
SUBSTITUTED PHENYL ACETIC ACIDS AS DP-2 ANTAGONISTS

BACKGROUND OF THE INVENTION

Prostaglandin D$_2$ (PGD$_2$) is the major proinflammatory mediator abundantly secreted by mast cells activated by allergen exposure of a previously sensitized host. PGD$_2$ is capable of eliciting a multitude of pathobiological responses relevant to inflammatory disorders including constriction of the airways, leukocyte influx, increase in vascular permeability, edema, and mucus secretion. The biological actions of PGD$_2$ are mediated by at least 3 distinct G-protein coupled receptors: The high affinity receptors DP-I (formerly known as DP) and DP-2 (formerly known as orphan receptor "G-protein receptor 44", GPR44 and "chemoattractant receptor homologue expressed in Th2 cells", CRTH2 (See Hirai, H., et al. J. Exp. Med. 2001, 193(2): 255-61; Nagata, K., J. Biol. Regul. Homeost. Agents 2003, 17(4):334-7) and the thromboxane A2 receptor, TP, to which PGD$_2$ binds with low affinity.

Accordingly, pharmaceuticals that target this receptor are likely to be therapeutically beneficial for a host of disorders, specifically inflammatory conditions that have an allergic component, such as asthma (See Huang, J., J. Microbiol. Immunol. Infect 2005, 38(3): 158-63). DP-2 is selectively expressed in Eosinophils, Basophils, and highly polarized Th2 cells in humans. These cell types are well known contributors to inflammatory disorders and other conditions. Activation of DP-2, a chemoattractant receptor, stimulates chemotaxis of human Th2 cells, eosinophils, and basophils both in vitro and in vivo and may mediate recruitment of relevant cell types to diseased sites and exacerbate end organ damage.

DP-2 agonists are capable of directly activating inflammatory cells and DP-2-mediated activation and mediator release from Eosinophils and Basophils has been reported (see Gervais, F. G. et al., J Allergy Clin Immunol (2004), 108 (6):982-8; Yoshimura-Uchiyama, C. et al., CHn Exp Allergy 2004, 34(8):1283-90). Furthermore, Th2 effector T lymphocytes will elaborate inflammatory cytokines IL-4, IL-5 and IL-13 in response to DP-2 stimulation (See Xue, L. et al, J. Immunol. 2005, 175(10): 6531-6). These cytokines in turn act as important regulators of inflammatory responses and support Th2 cell differentiation, mast cell growth, differentiation and IgE synthesis, and the differentiation, infiltration and survival of eosinophils.
This suggests that the PGD$_2$/DP-2 pathway acts as a positive feedback loop and augments pathologic responses in disorders associated with excessive or dysregulated PGD$_2$ production. Therefore, pharmaceutical agents that interfere with this pathway may have utility in the treatment of a broad array of allergic and inflammatory conditions and other disorders.

The utility of PGD$_2$ antagonists in the treatment of inflammatory disorders is supported by clinical studies with Ramatroban$^\text{®}$ (Baynas, BAY u3405). Clinical studies have demonstrated a beneficial effect of Ramatroban$^\text{®}$ on rhinitis symptoms as well as inflammatory markers in nasal lavages, suggesting anti-inflammatory activity. Ramatroban$^\text{®}$ was initially described as a TP selective antagonist, and its clinical effects on rhinitis were believed to be TP mediated. Recent discoveries, however, revealed that Ramatroban$^\text{®}$ possesses dual specificity and antagonizes both TP and DP-2 receptors (See Sugimoto, H., et al., J. Pharmacol. Exp. Ther. 2003, 305(1): 347-52). In light of the presence of DP-2 on pivotal inflammatory cells involved in allergic rhinitis, and the stimulatory effects of PGD$_2$ and other DP-2 agonists on theses cells, it is reasonable to postulate that the clinical benefit of Ramatroban$^\text{®}$ in allergic rhinitis is to a large extent due to its activity against the DP-2 receptor. It can be inferred therefore that DP-2 selective antagonists may be useful in the treatment of allergic rhinitis, other inflammatory conditions, other conditions where the PGD$_2$ pathway is deregulated, as well as other disorders where the utility of Ramatroban$^\text{®}$ has been established.


Numerous compounds have been reported as modulators of PGD$_2$ receptors and/or useful for the treatment of allergic and inflammatory disorders. WO 2006021418 discloses a series of sulfamyl-benzoimidazole-1-yl-acetic acid compounds with DP-2 or PGD$_2$ antagonist activity. WO 2006021759 discloses a series of biphenyloxyacetic acid derivatives with PGD$_2$ and DP-2 modulating activity said to be useful for the treatment of respiratory disorders.

[0008] Even so, there is a relative paucity of drugs that selectively modulate non-aminergic liganded G-protein-coupled receptors on the market (see Beaumont K et al., Bioorg Med Chem Lett, 2005, 15 (16): 3658-64).

**SUMMARY OF THE INVENTION**

[0009] It has now surprisingly been found that certain phenyl acetic acids are potent DP-2 receptor antagonists. In certain embodiments, the phenyl acetic acids are selective DP-2 receptor antagonists over other PGD₂ receptors. The phenyl acetic acid compounds of the invention are expected to be potentially useful for the treatment or prevention of medical conditions or disorders responsive to DP-2 antagonism, or symptoms associated with such
medical conditions or disorders, such as those having an allergic or inflammatory component. Examples conditions or disorders treatable or preventable with compounds and compositions of the invention are provided below.

[0010] Amongst several aspects of the present invention, the invention provides compounds, pharmaceutical compositions and methods useful for treating or preventing conditions and disorders associated with inflammation and/or allergic processes. In particular, the invention provides compounds, pharmaceutical compositions and methods useful for treating or preventing asthma, allergic conditions, inflammatory conditions, cancer and viral infection.

[0011] The compounds of the invention have the general structure (I):

![Chemical Structure](image)

[0012] Within the above formula, L is selected from the group consisting of a CR\textsuperscript{6}R\textsuperscript{7}, CO, CNR\textsuperscript{6} and CS.

[0013] A is a 5-14-membered heterocyclic ring having 1-4 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen and sulfur, the heterocyclic ring being moncyclic or polycyclic, optionally substituted with 1-3 R\textsuperscript{8} substituents.

[0014] Q\textsuperscript{1} is selected from the group consisting of: a bond, -C\textsubscript{1}-C\textsubscript{4} alkylene-,

- C\textsubscript{1}-C\textsubscript{4} heteroalkylene-, -CO-, -NH-, -O-, -SO\textsubscript{q}-, -C(O)O-, -OC(O)-, -CONH-, -NHCO-, -NHCONH-, -NHSO\textsubscript{q}-, -SO\textsubscript{q}NH- and -COCH\textsubscript{2}HNSO\textsubscript{q}.

[0015] Each R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, R\textsuperscript{6} and R\textsuperscript{7} is independently selected from the group consisting of H, C\textsubscript{i}-6 alkyl, C\textsubscript{o}-6 alkylaryl and C\textsubscript{o}-6 alkylheteroaryl; wherein the aryl or heteroaryl portions are optionally substituted with C\textsubscript{i}-6 alkyl, CN, OR, C\textsubscript{i}-6 haloalkyl, C\textsubscript{i}-6 heteroalkyl, NR\textsubscript{2}, NO\textsubscript{2}, halo, C(O)R, CO\textsubscript{2}R, CONR\textsubscript{2}, SO\textsubscript{q}R, SO\textsubscript{q}NR\textsubscript{2}, OC(O)OR, OC(O)R, OC(O)NR\textsubscript{2}, NRC(O)NR\textsubscript{2}, NRC(O)R and NRC(O)OR.
Each R^4 is independently selected from the group consisting of C_{1-6} alkyl, Co-alkylC_{3-6} cycloalkyl, Co-alkylaryl, Co-alkylheteroaryl, C_{2-4} alkenylaryl, C_{2-4} alkynylaryl, Co-alkylheterocyclyl, CN, amino, NHCOR, hydroxy, d-alkoxy, OC(O)R, -OC(O)alkylaryl, OCo-alkylheteroaryl, -OC_{6-4} alkylC_{3-6} cycloalkyl, OCo-alkylC_{3-6} ioheterocyclyl, OCo-alkylINR, nitro, halo and haloC_{1-6} alkyl; or are combined together or with R^6 to form an aryl or heterocyclyl ring system having 1-2 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the alkyl, aryl and heterocyclyl portions are each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of C_{1-6} alkyl, CN, CONHR, CO_2R, amino, C_{1-6} alkoxy, halo, haloC_{1-6} alkyl and SO_4R.

Each R^5 is selected from the group consisting of C_{1-6} alkyl, C_{0-4} alkylaryl, C_{2-4} alkenylaryl, C_{2-4} alkynylaryl and Co-alkylheteroaryl, each of which is optionally substituted with 1-3 R^9 substituents.

Each R^8 is independently selected from the group consisting of C_{1-6} alkyl, Co-alkylC_{3-6} cycloalkyl, Co-alkylaryl, Co-alkylheteroaryl, oxo, C_{1-6} alkyl, CN, OR, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, NR_2, NO_2, halo, C(O)R, CO_2R, CONR_2, SO_4R, SO_4NR_2, OC(O)OR, OC(O)R, OC(O)NR_2, NRC(O)NR_2, and NRC(O)OR.

Each R^9 is independently selected from the group consisting of C_{1-6} alkyl, CN, OR, oxo, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, NR_2, NO_2, halo, C(O)R, CO_2R, CONR_2, SO_4R, SO_4NR_2, OC(O)OR, OC(O)R, OC(O)NR_2, NRC(O)NR_2, and NRC(O)OR.

Each R is independently selected from the group consisting of H, C_{1-6} alkyl, Co-4 alkylheteroaryl, Co-4 heterocyclyl, C_{3-8} cycloalkyl and Co-4 alkylaryl or when attached to the same nitrogen atom may be combined to form a 5-8 membered ring having 1-4 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen and sulfur.

The subscript n is independently 0, 1, 2, 3 or 4.

Each subscript q is independently 0, 1 or 2.

The invention also provides pharmaceutically acceptable salts, hydrates, solvates and prodrugs of compounds of structure I. Examples of prodrugs are compounds wherein R^1 is C_{1-6} alkyl, Co-6 alkyaryl or Co-6 alkylheteroaryl wherein the aryl or heteroaryl portions are optionally substituted as described herein.
[0024] The invention also provides pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, excipient or diluent.

[0025] The invention also provides methods for antagonizing a DP-2 receptor comprising contacting a DP-2 receptor with a compound of structure I as well as methods of selectively agonizing a DP-2 receptor over one or more PGD$_2$ receptors.

[0026] The invention also provides methods for treating or preventing a disorder or condition responsive to the antagonizing a DP-2 receptor as well as methods of treating or preventing a disorder or condition associated with elevated levels of PGD$_2$ or a metabolite thereof comprising administering to a subject in need thereof a therapeutically effective amount of a compound of structure I.

[0027] The invention further provides methods for treating or preventing an inflammatory disorder or condition with an inflammation or allergic component as provided herein.

[0028] The invention also provides methods for treating or preventing a condition or disorder mediated by DP-2 and/or one or more other PGD$_2$ receptors, e.g., DP-I, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I.

[0029] The invention also provides methods for selectively modulating DP-2 in the presence of one or more other PGD$_2$ receptors, e.g., DP-I, comprising contacting a cell with a compound of structure I.

[0030] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

**DETAILED DESCRIPTION OF THE INVENTION**

**Abbreviations and Definitions**

[0031] The abbreviations used herein are conventional, unless otherwise defined. The following abbreviations are used: EtOAc = Ethylacetate, DMF = N,N-Dimethyl formamide, NMP = N-methylpyrrolidine, THF = tetrahydrofuran, RT = room temperature, TFA = trifluoroacetic acid, LDA = lithium diisopropylamide, n-BuLi = n-butyl lithium, Na$_2$CO$_3$ = sodium carbonate, DME = dimethyl ether, K$_2$PO$_4$ = potassium phosphate, CH$_2$Cl$_2$ or DCM = dichloromethane, Et$_3$N = triethylamine, DIEA = Hunig's base or diisopropyl ethylamine,
KOH = potassium hydroxide, NaOH = sodium hydroxide, TMS = trimethylsilyl, Tf = trifluoromethylsulfonyl, Boc = t-butyloxycarbonyl, Bz - benzyl, IPA = isopropyl alcohol, NBS = N-bromosuccinimide, AIBN = azobisisobutyronitrile (also azobisisobutylonitrile), Pin = pinacolato, Cs₂CO₃ = cesium carbonate, HIV = human immunodeficiency virus, RLV = Raucher leukemia virus, IgE = immunoglobulin E.

[0032] It is noted here that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0033] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which is fully saturated, having the number of carbon atoms designated (i.e., C₁₋₈ means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopentylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like.

[0034] The term "alkenyl", by itself or as part of another substituent, means a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e., C₂₋₈ means two to eight carbons) and one or more double bonds. Examples of alkenyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl) and higher homologs and isomers thereof.

[0035] The term "alkynyl", by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e., C₂₋₈ means two to eight carbons) and one or more triple bonds. Examples of alkynyl groups include ethynyl, 1- and 3-propynyl, 3-butylnyl and higher homologs and isomers thereof.

[0036] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from alkyl, as exemplified by -CH₂CH₂CH₂CH₂-. Typically, an alkyl (or alkyne) group will have 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkyne" is a shorter chain alkyl or alkyne group, generally having eight or fewer carbon atoms.
[0037] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively. Similarly, the term dialkylamino refers to an amino group having two attached alkyl groups that can be the same or different.

[0038] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include

-CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂- -CH₃,
-CH₂-CH₂, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃,
-CH₂=CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms maybe consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. When a prefix such as (C₂-C₈) is used to refer to a heteroalkyl group, the number of carbons (2-8, in this example) is meant to include the heteroatoms as well. For example, a C₂-heteroalkyl group is meant to include, for example, -CH₂OH (one carbon atom and one heteroatom replacing a carbon atom) and -CH₂SH. The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by -CH₂-CH₂-S-CH₂CH₂- - and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alklynedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[0039] The terms "cycloalkyl", "heterocycl" and "heterocyclic ring", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Thus, the terms "cycloalkyl" and "heterocyclic ring" are meant to be included in the terms "alkyl" and "heteroalkyl", respectively. Additionally, for a heterocyclic ring, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of a heterocyclic ring
include pyrrolidinyl, pyrrolyl, piperadiny1, tetrahydropyridinyl, piperaziny1, pyrizin-1-oxide, morpholiny1, thiomorpholiny1, azepiny1, azepiny1, oxazepane, thiazepane, azocany1, azociny1, indolyl, azaindole, tetrahydroquinoliny1, decahydroquinoliny1, tetrahydrobenzooxazepiny1 dihydrodibenzooxepiny1, and the like.

[0040] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include alkyl substituted with halogen atoms which can be the same or different, in a number ranging from one to (2m'+l), where m' is the total number of carbon atoms in the alkyl group. For example, the term "haloCi-oalkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

Thus, the term "haloalkyl" includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl substituted with halogen atoms in a number ranging from two to (2m'+l) halogen atoms). The term "perhaloalkyl" means, unless otherwise stated, alkyl substituted with (2m'+l) halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example, the term "perhaloCi-oalkyl", is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like.

[0041] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from the group consisting of N, O and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazinyl, 4-pyridazinyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, IH-indazole, carbazole, \( \alpha \)-carboline, \( \beta \)-carboline, \( \gamma \)-carboline, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl and 8-quinolyl.
In some embodiments, the term "aryl" refers to a phenyl or naphthyl group which is unsubstituted or substituted. In some embodiments, the term "heteroaryl" refers to a pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, indolyl, isoquinolyl, quinoxaliny1 or quinolyl group which is unsubstituted or substituted.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxyethyl, 2-pyridyloxymethyl, 3-(1-naphthoxy)propyl, and the like).

Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl" and "heteroaryl") is meant to include both substituted and unsubstituted forms of the indicated radical, unless otherwise indicated. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (as well as those groups referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocyclyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR R", -SR', halogen, -SiR" R"", -OC(O)R', -C(O)R', -CO 2R', -CONR'R", -OC(O)NR R", -NR-C(O)R".

-NR'-(O)NR"R"", -NR'-SO 2NR"R"", -NR'-CO 2R', -NH-C(NH 2)=NH, -NR'C(NH 2)=NH, -NH-C(NH 2)=NR', -S(O)R', -SO 2R', -SO 2NR R", -NR'SO 2R, -CN and -NO 2, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R" and R" each independently refer to hydrogen, unsubstituted C 1 6 alkyl and heteroalkyl, aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-C 1 6 alkyl groups. When R" and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. For example, -NR R" is meant to include 1-pyrrolidinyl and 4-morpholiny1. Typically, an alkyl or heteroalkyl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the present invention. More preferably, an alkyl or heteroalkyl radical will be unsubstituted or monosubstituted. Most preferably, an alkyl or heteroalkyl radical will be unsubstituted. From
the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as trihaloalkyl (e.g., -CF₃ and -CH₂CF₃).

[0046] In some embodiments, substituents for the alkyl and heteroalkyl radicals are selected from: -OR, =0, -NR R", -SR, halogen, -SiR R" R", -OC(O)R', -C(O)R', -CO₂R', -CONR'R", -OC(O)NR R", -NR·C(O)R', -NR·CO₂R', -NR·SO₂R, -NR·SO₂R"R\', -S(O)R', -SO₂R', -SO₂NR R", -NR·SO₂R, -CN and -NO₂, where R' and R" are as defined above. In some embodiments, substituents are selected from: -OR, =0, -NR R", halogen, -OC(O)R', -CO₂R', -CONR'R", -OC(O)NR R", -NR·C(O)R', -NR·CO₂R', -NR·SO₂NR"R\', -SO₂R', -SO₂NR R", -NR·SO₂R, -CN and -NO₂.

[0047] Similarly, substituents for the aryl and heteroaryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR R", -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R"', -C(O)R', -OC(O)NR R", -NR·C(O)R', -NR·CO₂R', -NR·SO₂R, -NR·SO₂R"R\', -NH-C(NH₂)=NH, -NR·C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR R", -N₃, -CH(Ph)₂, perfluoroC₆H₅alkoxy, and perfluoroC₆H₅alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R" are independently selected from hydrogen, C₆H₅alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-C₆H₅alkyl, and (unsubstituted aryl)oxy-C₆H₅alkyl.

[0048] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)ₗq-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is 0, 1 or 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)ₗ-B-, wherein A and B are independently -CH₂-, -0-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR-, or a single bond, and r is 1, 2 or 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond.

Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)ₗ-X-(CH₂)ₗ-, where s and t are independently integers of from 0 to 3, and X is -0-, -NR-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR-. The substituent R¹ in -NR²- and -S(O)₂NR¹ is selected from hydrogen or unsubstituted C₆H₅alkyl. Otherwise, R¹ is as defined above.

[0049] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).
The term "pharmaceutically acceptable salts" or "pharmaceutically acceptable carrier" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrgencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge et al., Journal of Pharmaceutical Science 66:1-19 (1977)).

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the invention.

In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of formula I which are antagonists of the DP-2 receptor. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an *ex vivo* environment.
For example, prodrugs can be slowly converted to the compounds of the invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the invention which is administered as an ester (e.g. wherein $R^1$ is substituted or unsubstituted $C_{1-6}$ alkyl, $C_{0-6}$ alkylaryl or $C_{0-6}$ alkylheteroaryl, the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid (e.g. wherein $R^1$ is H, the "active entity"). Additional examples include peptidyl derivatives of a compound of the invention.

[0053] Certain compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the invention. Certain compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the invention and are intended to be within the scope of the invention.

[0054] Certain compounds of the invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the invention. These isomers can be resolved or asymmetrically synthesized using conventional methods to render the isomers "optically pure", i.e., substantially free of its other isomers. If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxilliary, where the resulting diastereomeric mixture is separated and the auxilliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diasteromers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.
The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). Radiolabeled compounds are useful as therapeutic or prophylactic agents, e.g., cancer therapeutic agents, research reagents, e.g., DP-2 assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention.

An "antagonist" or "inhibitor" refers to an agent or molecule that inhibits or binds to, partially or totally blocks stimulation or activity, decreases, closes, prevents, delays activation or enzymatic activity, inactivates, desensitizes, or down regulates the activity of a receptor of the invention. As used herein, "antagonist" also includes a reverse or inverse agonist.

An "agonist" or "activator" refers to an agent or molecule that binds to a receptor of the invention, stimulates, increases, opens, activates, facilitates, enhances activation or enzymatic activity, sensitizes or up regulates the activity of a receptor of the invention.

"Modulators" of activity are used to refer to "ligands", "antagonists" and "agonists" identified using in vitro and in vivo assays for activity and their homologs and mimetics. Modulators include naturally occurring and synthetic ligands, antagonists, agonists, molecules and the like. Assays to identify antagonists and agonists include, e.g., applying putative modulator compounds to cells, in the presence or absence of a receptor of the invention and then determining the functional effects on a receptor of the invention activity. Samples or assays comprising a receptor of the invention that are treated with a potential activator, inhibitor, or modulator are compared to control samples without the inhibitor, activator, or modulator to examine the extent of effect. Control samples (untreated with modulators) are assigned a relative activity value of 100%. Inhibition is achieved when the activity value of a receptor of the invention relative to the control is about 80%, optionally 50% or 25-1%. Activation is achieved when the activity value of a receptor of the invention relative to the control is 110%, optionally 150%, optionally 200-500%, or 1000-3000% higher.

The terms "treat", "treating", "treatment" and grammatical variations thereof as used herein, includes partially or completely delaying, alleviating, mitigating or reducing the
intensity of one or more attendant symptoms of a disorder or condition and/or alleviating, mitigating or impeding one or more causes of a disorder or condition. Treatments according to the invention may be applied preventively, prophylactically, pallatively or remedially.

[0060] The terms "prevent", "preventing", "prevention" and grammatical variations thereof as used herein, refers to a method of partially or completely delaying or precluding the onset or recurrence of a disorder or condition and/or one or more of its attendant symptoms or barring a subject from acquiring or reacquiring a disorder or condition or reducing a subject's risk of acquiring or reacquiring a disorder or condition or one or more of its attendant symptoms.

[0061] The term "therapeutically effective amount" or "therapeutically effective dose" refers to the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The term "therapeutically effective amount" includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective amount will vary depending on the compound, the disorder or condition and its severity and the age, weight, etc., of the mammal to be treated.

[0062] The phrase "selectively" or "specifically" when referring to binding to a receptor, refers to a binding reaction that is determinative of the presence of the receptor, often in a heterogeneous population of receptors and other biologies. Thus, under designated conditions, the compounds bind to a particular receptor at least two times the background and more typically more than 10 to 100 times background. Specific binding of a compound under such conditions requires a compound that is selected for its specificity for a particular receptor. For example, small organic molecules can be screened to obtain only those compounds that specifically or selectively bind to a selected receptor and not with other receptors or proteins. A variety of assay formats may be used to select compounds that are selective for a particular receptor. For example, High-throughput screening assays are routinely used to select compounds that are selective for a particular a receptor.

[0063] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.
As used herein, the term "DP-2" refers to a DP-2 receptor protein (RefSeq Accession No. NP-007469) or a variant thereof that is capable of mediating a cellular response to PGD$_2$ \textit{in vitro} or \textit{in vivo}. DP-2 variants include proteins substantially homologous to native DP-2, i.e., proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (e.g., DP-2 derivatives, homologs and fragments). The amino acid sequence of DP-2 variant preferably is at least about 80% identical to a native DP-2, more preferably at least about 90% identical, and most preferably at least about 95% identical.

As used herein, the terms "other PGD$_2$ receptor", "another PGD$_2$ receptor" and the like refer to a prostanoid receptor protein other than DP-2, or variant thereof, that is capable of mediating a cellular response to PGD$_2$ \textit{in vitro} or \textit{in vivo}. Another PGD$_2$ receptor may be selective for PGD$_2$, e.g., DP-I (RefSeq Accession No. NP-000944), or may also interact with one or more other prostanoids (e.g., EP1, EP2, EP3 and EP4, FP, IP and TP). Other PGD$_2$ receptor variants include proteins substantially homologous to a corresponding native prostanoid receptor other than DP-2, i.e., proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (e.g., derivatives, homologs and fragments of another PGD$_2$ receptor). The amino acid sequence of other PGD$_2$ receptor variants preferably is at least about 80% identical to the corresponding native other PGD$_2$ receptors, more preferably at least about 90% identical, and most preferably at least about 95% identical. Preferably, another PGD$_2$ receptor is DP-I.

As used herein, the term "DP-I" refers to a DP-I receptor protein (RefSeq Accession No. NP-000944) or a variant thereof that is capable of mediating a cellular response to PGD$_2$ \textit{in vitro} or \textit{in vivo}. DP-I variants include proteins substantially homologous to native DP-I, i.e., proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (e.g., DP-I derivatives, homologs and fragments). The amino acid sequence of DP-I variant preferably is at least about 80% identical to a native DP-I, more preferably at least about 90% identical, and most preferably at least about 95% identical.

As used herein, the term "TP" refers to a TP receptor protein (RefSeq Accession No. NP-963998) or a variant thereof that is capable of mediating a cellular response to PGD$_2$ \textit{in vitro} or \textit{in vivo}. TP variants include proteins substantially homologous to native TP, i.e., proteins having one or more naturally or non-naturally occurring amino acid deletions,
insertions or substitutions (e.g., TP derivatives, homologs and fragments). The amino acid sequence of TP variant preferably is at least about 80% identical to a native TP, more preferably at least about 90% identical, and most preferably at least about 95% identical.

[0068] The terms "modulate", "modulation" and the like refer to the ability of a compound to increase or decrease the function and/or expression of DP-2 and/or one or more other PGD_2 receptors, e.g., DP-I, where such function may include transcription regulatory activity and/or protein-binding. Modulation may occur in vitro or in vivo. Modulation, as described herein, includes the inhibition, antagonism, partial antagonism, activation, agonism or partial agonism of a function or characteristic associated with DP-2 and/or one or more other PGD_2 receptors, either directly or indirectly, and/or the upregulation or downregulation of the expression of DP-2 and/or one or more other PGD_2 receptors, either directly or indirectly. In a preferred embodiment, the modulation is direct. Inhibitors or antagonists are compounds that, e.g., bind to, partially or totally block stimulation, decrease, prevent, inhibit, delay activation, inactivate, desensitize, or downregulate signal transduction. Activators or agonists are compounds that, e.g., bind to, stimulate, increase, open, activate, facilitate, enhance activation, activate, sensitize or upregulate signal transduction. The ability of a compound to inhibit the function of DP-2 and/or one or more other PGD_2 receptors can be demonstrated in a biochemical assay, e.g., binding assay, or a cell-based assay, e.g., a transient transfection assay.

[0069] As used herein, the term "condition or disorder responsive to modulation of PGD_2 or a PGD_2 receptor" and related terms and phrases refer to a condition or disorder associated with inappropriate, e.g., less than or greater than normal, activity of a PGD_2 receptor and at least partially responsive to or affected by modulation of a PGD_2 receptor (e.g., a PGD_2 receptor antagonist or agonist results in some improvement in patient well-being in at least some patients). Inappropriate functional activity of a PGD_2 receptor might arise as the result of expression of a PGD_2 receptor in cells which normally do not express the receptor, greater than normal production of PGD_2, or slower than normal metabolic inactivation or elimination of PGD_2 or its active metabolites, increased expression of a PGD_2 receptor or degree of intracellular activation (leading to, e.g., inflammatory and immune-related disorders and conditions) or decreased expression of a PGD_2 receptor. A condition or disorder associated with a PGD_2 receptor may include a "DP-2-mediated condition or disorder".
As used herein, the phrases "condition or disorder responsive to the antagonizing a DP-2 receptor", and related phrases and terms refer to a condition or disorder characterized by inappropriate, e.g., greater than normal, DP-2 activity. Inappropriate DP-2 functional activity might arise as the result of DP-2 expression in cells which normally do not express DP-2 or increased DP-2 expression or degree of intracellular activation (leading to, e.g., inflammatory and immune-related disorders and conditions). A condition or disorder responsive to the antagonizing a DP-2 receptor may be completely or partially mediated by inappropriate DP-2 functional activity. However, a condition or disorder responsive to the antagonizing a DP-2 receptor is one in which modulation of DP-2 results in some effect on the underlying condition or disorder (e.g., an DP-2 antagonist results in some improvement in patient well-being in at least some patients).

Embodiments of the Invention

A class of compounds that antagonize DP-2 has been discovered. Depending on the biological environment (e.g., cell type, pathological condition of the host, etc.), these compounds can antagonize DP-2 and/or one or more other PGD₂ receptors (e.g., ligand binding). By antagonizing DP-2 and/or one or more other PGD₂ receptors, the compounds will find use as therapeutic agents capable of modulating disorders and conditions responsive to modulation of DP-2 and/or one or more other PGD₂ receptors and/or mediated by DP-2 and/or one or more other PGD₂ receptors. Examples of such conditions and disorders are provided below.

While the compounds of the invention are believed to exert their effects by selectively interacting with DP-2, the mechanism of action by which the compounds act is not a limiting embodiment of the invention. For example, compounds of the invention may interact with PGD₂ receptor subtypes other than DP-2. However, as noted herein, the present invention specifically contemplates the activity of the disclosed compounds to selectively antagonize DP-2 receptor over e.g. DP-1 receptor, and/or other prostanoid receptors, e.g., TP receptor.

Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein.
Compounds of the Invention

In one embodiment, the present invention provides compounds of the general structure (I):

\[
\begin{align*}
\text{R}^3 & \text{R}^2 \\
\text{A} & \text{L} \\
\text{R}^1 & \text{Q}^1 \\
\text{R}^5 & \\
\end{align*}
\]

Within the above formula, \( L \) is selected from the group consisting of \( \text{CR}^6\text{R}^7 \), CO, CNR\(^6\) and CS.

A is a 5-14-membered heterocyclic ring having 1-4 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen and sulfur, the heterocyclic ring being monocyclic or polycyclic, optionally substituted with 1-3 \( \text{R}^8 \) substituents.

\( \text{Q}^1 \) is selected from the group consisting of: a bond, \( \text{-C}|-\text{C}_4\text{alkylene}- \), \( \text{-C}_n\text{-heteroalkylene}- \), \( \text{-CO}- \), \( \text{-NH}- \), \( \text{-SO}_q^- \), \( \text{-C(O)O}- \), \( \text{-OC(O)}- \), \( \text{-CONH}- \), \( \text{-NHCO}- \), \( \text{-NHCONH}- \), \( \text{-NHSO}_q^- \), \( \text{-SO}_q^-\text{NH}- \) and \( \text{-COCH}_2\text{HNSO}_q^- \).

Each \( \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^6 \) and \( \text{R}^7 \) is independently selected from the group consisting of H, \( \text{C}_1\text{-alkyl}, \text{Co}_4\text{-alkylaryl and Co}_6\text{-alkylheteroaryl} \); wherein the aryl or heteroaryl portions are optionally substituted with \( \text{C}_1\text{-alkyl}, \text{CN, OR, Ci}_6\text{haloalkyl, Ci}_6\text{heteroalkyl, NR}_2, \text{NO}_2, \text{halo, C(O)R, CO}_2\text{R, CONR}_2, \text{SO}_q\text{R, SO}_q\text{NR}_2, \text{OC(O)OR, OC(O)R, OC(O)NR}_2, \text{NRC(O)NR}_2, \text{NRC(O)OR and NRC(O)OR.}

Each \( \text{R}^4 \) is independently selected from the group consisting of \( \text{Cl}_{-6}\text{alkyl}, \text{Co}_{-4}\text{alkylC}_{3}\text{-iocycloalkyl, C}_{0-3}\text{alkylaryl, Co}_{-4}\text{alkylheteroaryl, C}_{2-4}\text{alkenylaryl, C}_{2-4}\text{alkynylaryl, Co}_{-4}\text{alkylheterocyclyl, CN, amino, NHCOR}^1 \), \( \text{hydroxy, Ci}_6\text{alkoxy, OC(O)R}^1, \text{-OC}_{0-4}\text{alkylaryl, OCo}_{-4}\text{alkylheteroaryl, -OC}_{-4}\text{alkylC}_{3}\text{-iocycloalkyl, OCo}_{-4}\text{alkylC}_5\text{-ioheterocyclyl, OCo}_{-4}\text{alkylINR}^8, \text{nitro, halo and haloCi}_{-6}\text{alkyl; or are combined together or with R}^6 \text{to form an aryl or heterocyclyl ring system having 1-2 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the alkyl, aryl and heterocyclyl portions are each optionally substituted with 1 to 3 substituents each independently selected from the group} \).
consisting of Ci-alkyl, CN, CONHR, CO₂R, amino, Ci-alkoxy, halo, haloCi-alkyl, and SO₉R².

[0080] R⁵ is selected from the group consisting of Ci-alkyl, Co₂alkylaryl, C₆alkenylaryl, C₆alkynylaryl and Co₄alkylheteroaryl, each of which is optionally substituted with 1-3 R⁹ substituents.

[0081] Each R⁸ is independently selected from the group consisting of Ci-alkyl, C₆alkylC₃-cycloalkyl, Co₆alkylaryl, Co₆alkylheteroaryl, oxo, Ci-alkyl, CN, OR, Ci-6-ialoalkyl, Ci₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO₂R, SO₉NR₂, OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R² and NRC(O)OR.

[0082] Each R⁹ is independently selected from the group consisting of Ci-alkyl, CN, OR, oxo, Ci₆haloalkyl, Ci₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO₂R, SO₉NR₂, OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R² and NRC(O)OR.

[0083] Each R is independently selected from the group consisting of H, Ci-alkyl, C₆alkylheteroaryl, Co₄heterocyclyl, C₃-cycloalkyl and Co₄alkylaryl or when attached to the same nitrogen atom may be combined to form a 5-8 membered ring having 1-4 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen and sulfur.

[0084] The subscript n is independently o, 1, 2, 3 or 4;

[0085] Each subscript q is independently o, 1 or 2.

[0086] In another embodiment, the present invention provides pharmaceutically acceptable derivatives thereof.

[0087] In another embodiment, L is CR⁶R⁷. In another embodiment, L is CO. In another embodiment, L is CNR⁶. In another embodiment, L is CS.

[0088] In another embodiment, R¹, R², R³, R⁶ and R⁷ are each independently selected from the group consisting of H, Ci-alkyl and Co₆alkylaryl. In one embodiment, R¹, R², R³, R⁶ and R⁷ are each independently selected from the group consisting of H, CH₃ and phenyl. In one embodiment, R¹ is H. In another embodiment, R² and R³ are H.

[0089] In another embodiment, A has the structure (II):
wherein

Y is selected from the group consisting of a bond, CH₂, N, O, NO and SO₂;  

R¹⁰ and R¹¹ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;  

the subscript p is independently 0, 1 or 2;  

each dashed ring bond independently indicates the presence of a single, double or normalized bond;

the dotted line indicates the point of attachment to Q¹ and the wavy line indicates the point of attachment to L.

[0090] In another embodiment, A is selected from the group consisting of pyrrolidinyl, pyrrolyl, piperadiny1, tetrahydropyridinyl, piperazinyl, piperazin-1-oxide, morpholinyl, thiomorpholinyl, azepanyl, azepinyl, oxazepane, thiazepane, azocan1, azocinyl, indolyl, azaindole, tetrahydroquinolinyl and decahydroquinoliny.

[0091] In another embodiment, A has a formula selected from the group consisting of:
m is an integer from 0 to 3; and

the dashed line indicates the point of attachment to $Q^1$ and the wavy line indicates the point of attachment to $L$.

[0092] In another embodiment, $Q^1$ is selected from a bond, $-\text{C}^n\text{alkylene}-$, $-\text{C}_4\text{heteroalkylene}-$, $-\text{CO}-$, $-\text{NH}-$, $-\text{O}-$, $-\text{SCy}$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-\text{CONH}-$, $-\text{NHCO}-$, $-\text{NHCONH}-$, $-\text{NH}_q\text{SO}-$, $-\text{SO}_q\text{NH}$ and $-\text{COCH}_2\text{HNSO}_q$. In another embodiment, $Q^1$ is a bond. In another embodiment, $Q^1$ is $-\text{C}_1\text{C}_4\text{alkylene}-$. In another embodiment, $Q^1$ is $-\text{C}_1\text{heteroalkylene}-$. In another embodiment, $Q^1$ is $-\text{CO}-$. In another embodiment, $Q^1$ is a $-\text{NH}-$. In another embodiment, $Q^1$ is a $-\text{O}-$. In another embodiment, $Q^1$ is $-\text{SO}_q-$. In another embodiment, $Q^1$ is $-\text{C}(\text{O})\text{O}-$. In another embodiment, $Q^1$ is $-\text{OC}(\text{O})-$. In another embodiment, $Q^1$ is $-\text{CONH}-$. In another embodiment, $Q^1$ is $-\text{NHCO}-$. In another embodiment, $Q^1$ is $-\text{NHCONH}-$. In another embodiment, $Q^1$ is $-\text{NH}_q\text{SO}-$. In another embodiment, $Q^1$ is $-\text{SO}_q\text{NH}-$. In another embodiment, $Q^1$ is $-\text{COCH}_2\text{HNSO}_q$.

[0093] In another embodiment, the compound has a structure (III):
wherein

Y is selected from the group consisting of a bond, CH₂, N, O, NO and SO₄⁻;

R₁⁰ and R₁¹ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;

the subscript m is independently 0, 1, 2 or 3;

the subscript p is independently 0, 1 or 2; and

each dashed ring bond independently indicates the presence of a single, double or normalized bond.

In another embodiment, L is CR₆R₇. In another embodiment, L is CO. In another embodiment, L is CS.

In another embodiment, the compound has a structure (IV):

wherein

Y is selected from the group consisting of a bond, CH₂, N, O, NO and SO₄⁻;

R₁⁰ and R₁¹ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;

the subscript m is independently 0, 1, 2 or 3;
the subscript \( p \) is independently 0, 1 or 2; and

each dashed ring bond independently indicates the presence of a single, double or normalized bond.

[0096] In another embodiment, \( Y \) is CH\(_2\) and \( p \) is 0.

[0097] In another embodiment, \( L \) is CR\(^6\)R\(^7\).

[0098] In another embodiment, \( Q^1 \) is a bond.

[0099] In another embodiment, \( Y \) is SOq and \( p \) is 0.

[0100] In another embodiment, the compound is selected from the group consisting of:

- [4-(4-Chloro-benzyloxy)-3-thiomorpholin-4-ylmethyl -phenyl]-acetic acid;

[0101] In another embodiment, \( Y \) is O and \( p \) is 0.

[0102] In another embodiment, the compound is

- [4-(4-Chloro-benzyloxy)-3-(1,1-dioxo-1\(\lambda^6\)-thiomorpholin-4-ylmethyl)-phenyl] -acetic acid;

10 and [4-(4-Fluoro-benzyloxy)-3-(1,1-dioxo- \( 1\lambda^6\)-thiomorpholin-4-ylmethyl)-phenyl] -acetic acid.

[0103] In another embodiment, \( Y \) is N and \( p \) is 0.

[0104] In another embodiment, the compound is selected from the group consisting of:

- [4-(4-Chloro-benzyloxy)-3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl]-acetic acid;

[0105] In another embodiment, \( Q^1 \) is -CO-.

[0106] In another embodiment, the compound is selected from the group consisting of:

- [4-(4-Chloro-benzyloxy)-3-[4-[2-(4-methoxy-phenyl)-acetyl]-piperazin-1-ylmethyl]-phenyl]-acetic acid;

25 -acetic acid;

- [4-(4-Chloro-benzyloxy)-3-[4-(2-p-tolyl-acetyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;

- [4-(4-Chloro-benzyloxy)-3-[4-[2-(4-chloro-phenyl)-acetyl]-piperazin-1-ylmethyl]-phenyl]-acetic acid;

[3-(4-Benzyl-piperazin-1-ylmethyl)-4-(4-chloro-benzyloxy)-phenyl] -acetic acid;

[4-[5-Carboxymethyl-2-(4-chloro-benzyloxy)-benzyl]-piperazin-1-yl]-oxo-acetic acid
methyl ester; and
{4-(4-Chloro-benzyloxy)-3-[4-(2-hydroxy-2-phenyl-acetyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid.

[0107] In another embodiment, Q¹ is -C(O)O-.

[0108] In another embodiment, the compound is selected from the group consisting of:
4-[5-Carboxymethyl-2-(4-chloro-benzyloxy)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester; 4-[5-Carboxymethyl-2-(4-chloro-benzyloxy)-benzyl]-piperazine-1-carboxylic acid methyl ester; 4-[5-Carboxymethyl-2-(4-chloro-benzyloxy)-benzyl]-piperazine-1-carboxylic acid isopropyl ester;

[0109] In another embodiment, the compound is selected from the group consisting of:
4-[5-Carboxymethyl-2-(4-chloro-benzyloxy)-benzyl]-piperazine-1-carboxylic acid ethyl ester.

[0110] In another embodiment, the compound is selected from the group consisting of:
{4-(2,6-Difluoro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-2-fluoro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(2-Fluoro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; [3-(4-Benzenesulfonyl-piperazin-1-ylmethyl)-4-(4-chloro-benzyloxy)-phenyl]-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
[3-[4-(4-Chloro-benzenesulfonyl)-piperazin-1-ylmethyl]-4-(4-chloro-benzyloxy)-phenyl]-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(3-Methoxy)-benzyloxy]-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3,5-bis-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-Cyclopent oxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; 
{2-[4-(Toluene-4-sulfonyl)-piperazin-1-ylmethyl]-biphenyl-4-yl}-acetic acid; 
{4-Benzyl oxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-Cyclopropylmethoxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-Phenylethynyl-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(4-methoxy-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(3,4-dichloro-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; 5 {4-(4-Chloro-benzyloxy)-3-[4-(3,4-dichloro-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; [3-[4-(2-Chloro-benzenesulfonyl)-piperazin-1-ylmethyl]-4-(4-chloro-benzyloxy)-phenyl]-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(toluene-3-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(quinoline-8-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4'-Methyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-biphenyl-4-yl} -acetic acid; 10 {4'-Chloro-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-biphenyl-4-yl} -acetic acid; [3-[4-(Toluene-4-sulfonyl)-piperazin-1-ylmethyl]-4-(4-trifluoromethyl-benzyloxy)-phenyl]-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(2,4-dichloro-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; 15 {4-(4-Chloro-benzyloxy)-3-[4-(quinoline-8-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-Phenethyl-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4'-Methyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-biphenyl-4-yl} -acetic acid; 20 {4'-Chloro-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-biphenyl-4-yl} -acetic acid; [3-[4-(4-tert-Butyl-benzenesulfonyl)-piperazin-1-ylmethyl]-4-(4-chloro-benzyloxy)-phenyl]-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(3,5-dimethyl-isoxazole-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; 25 {4-(4-Chloro-benzyloxy)-3-[4-(naphthalene-2-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(pyridine-3-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(3,5-dichloro-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; 30 {4-(4-Chloro-benzyloxy)-3-[4-(4-ethyl-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(naphthalene-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
[3-{4-(4-Bromo-benzenesulfonyl)-piperazin-1-ylmethyl]-4-(4-chloro-benzyloxy)-phenyl]-acetic acid;
{4-(4-Methoxy-benzyloxy)-3-{4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
5 {4-(4-Methyl-benzyloxy)-3-{4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid; {4-Cyclohexylmethoxy-3-{4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
[4-(4-Chloro-benzyloxy)-3-{4-phenylmethanesulfanyl-piperazin-1-ylmethyl]-phenyl]-acetic acid;
[4-(4-Chloro-benzyloxy)-3-{4-(to 4-(t oluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid; [4-(2,4-Dichloro-benzyloxy)-3-{4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
4-{4-Carboxymethyl-2-{4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenoxymethyl]-benzoic acid;
[4-(4-Fluoro-benzyloxy)-3-{4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
6 [4-(4-Chloro-benzyloxy)-3-{4-(thiophene-3-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
[4-(3,4-Dichloro-benzyloxy)-3-{4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid; {4-(4-Nitro-benzyloxy)-3-{4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
[4-(4-Chloro-benzyloxy)-3-{2-oxo-4-(toluene-4-sulfanyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid.
[0111] In another embodiment, the compound is selected from the group consisting of:
(4-Hydroxy-3-{phenyl-[4-(toluene-4-sulfanyl)-piperazin-1-yl]-methyl]-phenyl}-acetic acid;
(3-{(2-Hydroxy-phenyl)-[4-(toluene-4-sulfanyl)-piperazin-1-yl]-methyl]-phenyl}-acetic acid;
(3-{Phenyl-[4-(toluene-4-sulfonyl)-piperazin-l-yl]-methyl}-phenyl)-acetic acid;
(3-{[4-(4-Fluoro-benzenesulfonyl)-piperazin-l-yl]-phenyl-methyl}-phenyl)-acetic acid;
{3-{[(4-Benzenesulfonyl-piperazin-l-yl)-phenyl-methyl]-phenyl}} -acetic acid;
{3-{[4-Methanesulfonyl-piperazin-l-yl]-phenyl-methyl]-phenyl}-acetic acid;
{3-{[(4-Benzenesulfonyl-piperazin-l-yl)-phenyl-methyl]-5-chloro-phenyl}} -acetic acid;
(3-{[4-(4-Fluoro-benzenesulfonyl)-piperazin-l-yl]-p-tolyl-methyl}-4-hydroxy-phenyl)-acetic acid;
(3-{[4-(4-Fluoro-benzenesulfonyl)-piperazin-l-yl]-p-tolyl-methyl}-phenyl)-acetic acid;
(3-{(4-Chloro-phenyl)-[4-(4-fluoro-benzenesulfonyl)-piperazin-l-yl]-methyl}-phenyl)-acetic acid;
and (3-{[4-(4-Fluoro-benzenesulfonyl)-piperazin-l-yl]-phenyl-methyl}-phenyl)-acetic acid.

[0112] In another embodiment, R^4 and R^6 are combined together to form an aryl or heterocyclyl ring system.

[0113] In another embodiment, the compound has the structure IVa:

![IVa](image)

wherein Y^2 is selected from the group consisting of N, O and S; each R^12 is independently selected from the group consisting of C_1-6 alkyl, CN, CONHR, CO_2R, amino, C_i^alkoxy, halo, haloC_1-6 alkyl and SO_q R’ or is are combined together to form an aryl or heteroaryl ring; and the subscript u is independently 1, 2 or 3.

[0114] In another embodiment, the compound is selected from the group consisting of: 2-(11-(4-tosylpiperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(1 l-(4-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-1 l-(4-tosylpiperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-1 l-(4-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-1 l-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-1 l-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-1 l-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-1 l-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-1 l-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-1 l-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid.
In another embodiment, the compound is 1-(5-(carboxymethyl)-2-(2,4-dichlorobenzyloxy)benzyl)-4-tosylpiperazine N-oxide.

In another embodiment, \( Q^1 \) is -C(O)O-.

In another embodiment, the compound is selected from the group consisting of:

- 4-[5-Carboxymethyl-2-(4-chloro-benzyloxy)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester.
- 4-(4-Chloro-benzyloxy)-3-(4-phenylcarbamoyl-piperazin-1-ylmethyl)-phenyl]-acetic acid;
- [4-(4-Chloro-benzyloxy)-3,5-bis-(4-phenylcarbamoyl-piperazin-1-ylmethyl)-phenyl]-acetic acid;
- [4-(4-Chloro-benzyloxy)-3-piperidin-1-ylmethyl-phenyl]-acetic acid;
- [4-(4-Chloro-benzyloxy)-3-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-acetic acid.

In another embodiment, \( Y \) is CH₂ and \( p \) is 0.

In another embodiment, the compound is selected from the group consisting of:

- 4-(4-Chloro-benzyloxy)-3-piperidin-1-ylmethyl-phenyl]-acetic acid; and
- 4-(4-Chloro-benzyloxy)-3-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-acetic acid.

In another embodiment, \( Q^1 \) is -NHSO₂⁻.

In another embodiment, the compound is selected from the group consisting of:

- 4-(4-Chloro-benzyloxy)-3-[2-oxo-3-(toluene-4-sulfonylamino)-pyrrolidin-1-ylmethyl]-phenyl]-acetic acid;
- 4-(4-Chloro-benzyloxy)-3-[2-oxo-3-(toluene-4-sulfonylamino)-piperidin-1-ylmethyl]-phenyl]-acetic acid;
- 4-(4-Chloro-benzyloxy)-3-[2-oxo-3-(toluene-4-sulfonylamino)-azepan-1-ylmethyl]-phenyl]-acetic acid; and
- 4-(4-Chloro-benzyloxy)-3-[2-oxo-3-(toluene-4-sulfonylamino)-3,4,7,8-tetrahydro-2H-azoci...
n-1-ylmethyl]-phenyl} -acetic acid; and
{4-(4-Chloro-benzyloxy)-3-{2-oxo-3-(toluene-4-sulfonylamino)-azocan-1-ylmethyl]-phenyl} -acetic acid.

[0124] In another embodiment, L is CO.

[0125] In another embodiment, the compound is selected from the group consisting of:
{4-(4-Chloro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazine-1-carbonyl]-phenyl} -acetic acid; and
{4-(4-Chloro-benzyloxy)-3-(4-methanesulfonyl-piperazine-1-carbonyl)-phenyl} -acetic acid.

[0126] In another embodiment, the compound has a structure (V):

![Chemical Structure](image)

wherein

Y is selected from the group consisting of a bond, CH₂, N, O, NO and SO₂;
R¹₀ and R¹¹ are H or are combined together to form an aryl, heteroaryl, or cycloalkyl ring;
the subscript m is independently 0, 1, 2 or 3;
the subscript p is independently 0, 1 or 2; and
each dashed ring bond independently indicates the presence of a single, double or normalized bond.

[0127] In another embodiment, L is CR⁶R⁷. In another embodiment, L is CO. In another embodiment, L is CS.

[0128] In another embodiment, Q¹ is a bond. In another embodiment, Q¹ is -Ci-C₄-alkylene-. In another embodiment, Q¹ is -Ci-Qheteroalkylene-. In another embodiment, Q¹ is -CO-. In another embodiment, Q¹ is a -NH-. In another embodiment, Q¹
is a -O-. In another embodiment, Q\(^1\) is -SO\(_q\) -. In another embodiment, Q\(^1\) is -C(O)O-. In another embodiment, Q\(^1\) is -OC(O) -. In another embodiment, Q\(^1\) is -CONH-. In another embodiment, Q\(^1\) is -NHCONH-. In another embodiment, Q\(^1\) is -NHSO\(_q\) -. In another embodiment, Q\(^1\) is -SO\(_q\) NH-. In another embodiment, Q\(^1\) is -COCT\(^1\)HNSO\(_q\).  


[0130] The invention encompasses novel compounds, novel pharmaceutical compositions and/or novel methods of use. While some compounds disclosed herein are available from commercial sources, the pharmaceutical compositions or methods of using these compounds are novel. Unless otherwise indicated, it is to be understood that the invention includes those compounds that are novel, as well as pharmaceutical compositions, various methods (e.g., methods of treating or preventing certain conditions and disorders mediated by DP-2 and/or one or more other PGD\(_2\) receptors), and the like which include both the novel compounds of the invention and compounds that are commercially available.

**Preparation of the Compounds**

[0131] Synthetic routes to the compounds provided herein are also described below in Schemes A-I and in the Examples. One of skill in the art will understand that the synthetic routes can be modified to use different starting materials and/or alternate reagents to accomplish the desired transformations. Additionally, one of skill in the art will recognize that protecting groups may be necessary for the preparation of certain compounds and will be aware of those conditions compatible with a selected protecting group. Accordingly, the methods and reagents described herein are all expressed as non-limiting embodiments.
In some embodiments, as shown in Scheme A, an alkyl phenyl acetate of formula A is mixed to a solution of para formaldehyde and a substituted heterocycle, such as a piperidine or a substituted piperazine, in a solvent system such as isopropyl alcohol for 1 to 12 hours at reflux to give B. If the phenyl ring of the alkyl phenyl acetate A is substituted with a hydroxyl group (as shown), alkylation of the phenol using an appropriate alkyl or aryl halide, in the presence of a base such as K$_2$CO$_3$, or CsCO$_3$ in a solvent such as DMF at temperatures ranging from 20 to 60 $^\circ$C, or acetone at temperatures ranging from 20 to 80 $^\circ$C, leads to further substituted compounds C. Saponification with a base such as potassium hydroxide (KOH) or sodium hydroxide (NaOH) in a solvent system such as methanol: water, for a period of 1-6 hours at temperatures between 35-65 $^\circ$C, leads to a carboxylic acid of formula D. Alternatively, treatment of B with triflic anhydride in DCM, followed by a palladium (0) mediated cross coupling with an aryl boronic acid in a solvent such as dioxane or DME, at temperatures ranging from 20 to 90 $^\circ$C, with a base such as sodium carbonate, leads to compounds with general formula E. Saponification with a base such as lithium hydroxide (LiOH), potassium hydroxide (KOH) or sodium hydroxide (NaOH) in a solvent system such as THF: water or methanol: water, for a period of 1-6 hours at temperatures between 35-65 $^\circ$C, leads to a carboxylic acid of formula F.
In some embodiments, as shown in Scheme B1, treatment of benzaldehyde H with a suitably protected heterocycle and an aryl boronic acid in a solvent such as dioxane at a temperature varying from 20 to 100 °C for a period of 1 to 12 hours leads to I. Saponification of I using reaction conditions described in Scheme A leads to J. Compound I can also be treated with triflic anhydride or N-phenyl triflimide in DCM at temperatures varying from room temperature to 50 °C. Treatment with a source of palladium (O) in the presence of formic acid, followed by a saponification as outlined in Scheme A leads to K. As shown in Scheme B2, Benzaldehyde GGG was obtained by treatment a halotoluene with N-bromosuccinimide and AIBN in a solvent such as carbon tetrachloride, followed by addition of trimethylamine N-oxide in a solvent such as acetonitrile, at temperatures ranging from
room temperature to 80 °C, over 15 hours. Oxidation of F with Jones' reagent in a solvent such as acetone, followed by the Arndt-Eistert reaction leads to G. Aryl bromide G can be converted to the corresponding benzaldehyde via a palladium (0) mediated reaction in a solvent such as toluene in the presence of carbon monoxide.

Scheme C

[0134] In some embodiments, as shown in Scheme C, ketone I was treated with sodium borohydride in a solvent such as methanol at temperatures varying from -10 to 35 °C, followed by treatment with thionyl chloride in DCM at room temperature over a period of 12 hours, to give J. Treatment of J with a suitably protected heterocycle in a solvent such as AcCN at temperatures ranging from 20 to 95 °C, over a period of 2 to 13 hours, followed by a saponification as described in Scheme A leads to K.

Scheme D

[0135] In some embodiments, as shown in Scheme D, substituted benzaldehyde L can be treated with an alkyl or aryl Grignard reagent in a solvent system such as THF at temperatures ranging from -20 to 20 °C over a period of a few hours to give secondary alcohol M. An in situ chloride formation, upon treatment of M with thionyl chloride in a
solvent such as DCM, for a few hours at ambient temperature, followed by a modified Finkelstein reaction in the presence of a suitably protected heterocycle in a solvent system such as AcCN for a few hours at temperatures ranging from -10 to 80 °C, leads to N. Aryl bromide N is then transformed into a boronate ester O using standard palladium (0) coupling conditions. Further palladium (0) coupling of O with ethyl-2-bromo acetate in the presence of a base such as K₂CO₃, in a solvent system such as dioxane or DME, at temperatures ranging from 15 to 85 °C leads to phenyl acetate P. Saponification of P using conditions described in Scheme A leads to K.

Scheme E

[0136] In some embodiments, as shown in Scheme E, phenyl acetate A is treated with paraformaldehyde in AcCN at temperatures ranging from 25 to 100 °C, and leads to Q. Oxidation of Q with potassium permanganate for example in a solvent system such as acetone/water for a few hours under reflux conditions leads to benzoic acid R. This acid S can then be coupled to a substituted heterocycle, such as a piperidine or piperazine using for example HATU and a base such as Et₃N or DIEA in a solvent such as AcCN, at ambient temperatures for a period of 2 to 12 hours.

Scheme F
[0137] In some embodiments, as shown in Scheme F, alkylation of phenol A with a commercially available benzyl bromide using a base such as K₂CO₃ or Cs₂CO₃ in a solvent such as acetone or DMF at temperatures ranging from 20 to 100 °C, followed by a saponification using standard conditions described in Scheme A leads to phenyl acetic acid T. A Friedel Craft reaction catalyzed by polyphosphoric acid in a solvent such as acetic anhydride at temperatures ranging from 30 to 90 °C for a few hours, followed by an in situ esterification with hydrochloric acid in a solvent such as methanol leads to tricyclic U. Reduction of U under standard reaction conditions using sodium borohydride (NaBH₄) in methanol for a few hours, followed by treatment with thionyl chloride in a solvent such as DCM, as described in Scheme C or D, leads to V. Compound V is then evolved to W using reaction conditions previously described in Scheme C or D.

Scheme G
In some embodiments, as shown in Scheme G, benzaldehyde X is reacted with an amino acid such as Boc-Lysine or Boc-Ornithine, using sodium cyanoborohydride in the presence of zinc chloride in a solvent such as methanol for up to 30 min. to give amino acid Z. Cyclization of Z to AA takes place under standard coupling conditions such as hydroxybenzotriazole (HOBT) and 1-[3-(dimethylamino)propoyl]-3-ethylcarbodiimide hydrochloride (EDCI) in a solvent system such as DCM or DMF, at temperatures ranging from -30 to 50 °C, for up to 12 hours. Saponification as described in Scheme A leads to heterocycle BB.

In some embodiments, as shown in Scheme H, benzyl bromide CC can be reacted with a heterocycle such as DD in the presence of a base such as Cs$_2$CO$_3$ or K$_2$CO$_3$ in a solvent system such as AcCN/DMF at temperatures ranging from 10 to 75 °C over a few hours, followed by protecting group removal and alkylation as described in Schemes G and A. Saponification of EE leads to compound FF using standard reaction conditions as described in Scheme A.
[0140] In some embodiments, as shown in Scheme H, reductive amination of benzaldehyde GG with an alken-1-amine under standard conditions described in Scheme G leads to HH. Coupling of amine HH to a protected amino acid such as 2-(tert-butoxycarbonylamino)pent-4-enoic acid in the presence of HATU and a base such as triethylamine or DIEA in a solvent such as AcCN or DMF for a few hours leads to II. Ring closure catalyzed by Grubb's first generation catalyst in a solvent such as DCM for a few hours at temperatures ranging from 20 to 90 °C leads to seven membered lactam JJ. Protecting group removal followed by sulfonylation and saponification using reaction conditions described in Scheme A leads to lactam MM. Hydrogenation of JJ under 1 atmosphere of hydrogen in a solvent such as benzene in the presence of a rhodium catalyst such as RhCl(PPh₃)₃, for a few days leads to unsaturated heterocycle KK. Once again, protecting group removal under acidic conditions followed by sulfonylation and saponification as described in Scheme A leads to LL.
Analysis of the Compounds

[0141] In yet another aspect, the invention includes methods to evaluate putative specific agonists or antagonists of DP-2 and/or one or more other PGD₂ receptors. Accordingly, the invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the function of DP-2 and/or one or more other PGD₂ receptors. For example, the compounds of this invention are useful for DP-2 mutants and/or one or more other PGD₂ receptor mutants, which are excellent screening tools for potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to DP-2 and/or one or more other PGD₂ receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of DP-2 over one or more other PGD₂ receptors. One of skill in the art will appreciate that thorough evaluation of specific antagonists of PGD₂ receptors has been hampered by the lack of availability of specific, non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. The compounds provided herein are particularly useful in this context.

[0142] The above and other assays described herein are designed to be amenable to a high throughput format to detect or quantify the presence, absence, quantification, or other properties of particular compounds individually or as library containing a large number of potential therapeutic compounds (potential modulator compounds). Any of the assay steps may be automated and compounds from any convenient source may be provided to the assay. Assays are typically run in parallel (e.g., in microtiter formats on microtiter plates in robotic assays). Preferred assays detect enhancement or inhibition of DP-2, DP-2 and/or one or more other PGD₂ receptors function.

[0143] High throughput screening systems are commercially available (see e.g., Zymark Corp., Hopkinton Mass.; Air Technical Industries, Mentor Ohio; Beckman Instruments, Inc., Fullerton Calif; Precision Systems, Inc., Natick Mass.; etc.). These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing, timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start-up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, for example, Zymark Corp.
provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

**Methods of Use**

5  **[0144]** The present invention relates to the identification of phenylacetic acid derivatives and their use as functional antagonists of the DP-2 receptor for the treatment of conditions or disorders mediated by PGD$_2$, to pharmaceutical compositions containing these derivatives and to processes for their preparation.

10  **[0145]** In particular, compounds and derivatives of the general formula I have activity as modulators of DP-2 receptor activity, and therefore may be used in the treatment of conditions or disorders which are caused by the excessive, unbalanced or deregulated expression of PGD$_2$ and its metabolites. Non-limiting example of such conditions and disorders include:

15  **[0146]** 1) Respiratory system conditions or disorders such as Obstructive airway diseases such as: asthma, e.g., intermittent and persistent asthma, extrinsic (allergic) asthma, intrinsic (non-allergic) asthma, mixed extrinsic-intrinsic asthma, exercise induced asthma, nocturnal asthma, bronchial asthma, seasonal asthma, occupational asthma, cough variant asthma, chronic severe corticosteroid-dependent asthma, steroid-resistant asthma, allergic bronchopulmonary aspergillosis, asthma triad (including asthma nasal polyps, and aspirin sensitivity), and allergic airway syndrome; bronchitis, e.g., acute and chronic bronchitis, allergic rhinobronchitis, eosinophilic bronchitis, and chronic obstructive pulmonary disease (COPD)); rhinitis, including acute and chronic rhinitis, atrophic rhinitis, allergic and non-allergic rhinitis, seasonal (e.g., rhinitis nervosa, hay fever, and vasomotor rhinitis), perennial, and vasomotor rhinitis, nasal polyposis, nasal congestion, rhinitis medicamentosa; sarcoidosis; fanners lung and related diseases; fibroid lung; cystic fibrosis; idiopathic interstitial fibrosis; chronic cough associated with inflammation; and sinusitis, e.g., allergic, acute, sub-acute, and chronic sinusitis;

20  **[0147]** 2) Skin and Eyes conditions or disorders such as dermatitis, e.g., allergic contact dermatitis, atopic dermatitis (eczema), contact (and irritant contact) dermatitis, excematos dermatitis, neurodermatitis, perennial dermatitis, seborrheic dermatitis, statsis dermatitis, diaper dermatitis, dyshidrotic dermatitis (pompholyx), nummular dermatitis,
autosenstitization dermatitis, lichen simplex chronicus, and urticaria; conjunctivitis, e.g.,
viral, allergic, bacterial, and chemical/toxic conjunctivitis; psoriasis; urticaria; erythemas;
cutaneous eosinophilia; and chronic skin ulcers;

[0148] 3) Gastrointestinal System conditions or disorders such as food-induced allergies
(e.g., those that have effects remote form the gut such as migraine, rhinitis and eczema);

[0149] 4) Central nervous system conditions or disorders such as inflammatory pain, neuropathic pain;

[0150] 5) Conditions or disorders relating to other systems: e.g., eosinophilic fascitis;
hyper IgE syndrome; systemic mast cell disorder; Idopathic thrombocytopenia purpura;
atherosclerosis; lupus erythematosus; systemic lupus erythematosus; sepsis; reperfusion
injury; glomerulonephritis; allergic nephritis; nephritic syndrome; eosinophil related disorders
such as Churg-Strauss syndrome; basophilic leukocytosis and basophilic leukemia and
acquired immunodeficiency syndrome;

[0151] 6) Conditions or disorders relating to skeletal and joints systems, e.g., arthritis
and conditions associated therewith, e.g., osteoarthritis (OA), osteonecrosis, psoriatic
arthritis, Reiter's syndrome (reactive arthritis), tendonitis, bursitis, inflammation of joint
lining, ankylosing spondylitis, Behcet's disease, childhood arthritis, diffuse idiopathic
skeletal hyperostosis (DISH), Ehlers-Danlos syndrome, rheumatoid arthritis, Felty's
syndrome, fibromyalgia, gout, pseudo gout, infectious arthritis, lupus, mixed connective
tissue disease, osteoarthritis, Paget's disease, polymyalgia rheumatica, polyarteritis nodossa,
Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), psoriatic arthritis,
Raynoud's phenomenon, and Still's disease;

[0152] 7) Autoimmune conditions or disorders, e.g., systemic lupus erythematosis, anti-
phospholipid syndrome, rheumatoid arthritis, Sjogren's syndrome, scleroderma, systemic
vasculitis, e.g., giant cell (temporal) arteritis, takayasu's arteritis, polyarteritis nodosa,
Kawasaki disease, Wegner's granulomatosis, Churg Strauss syndrome, microscopic
polyangiitis, Henoch-Schonlein purpura, essential cryoglobulinemic vasculitis, cutaneous
lekocytoclastic angiitis, autoimmune hemolytic anemia, idiopathic thrombocytopenic
purpura, autoimmune neutropenia, Diabetes millitus, Hashimoto's disease, Grave's disease,
autoimmune polyglandular syndromes, multiple sclerosis, myathenia gravis, Behcet's
syndrome, pernicious anemia, primary biliary sclerosis, autoimmune hepatitis, autoimmune myocarditis, Goodpasture's syndrome, glomerular nephritis, and tubulointerstitial nephritis; and

[0153] 8) Other conditions or disorders associated with raised levels of PGD$_2$ or its metabolites.

[0154] In yet another aspect, the invention provides methods of treating or preventing a disorder or condition associated with DP-2 and/or one or more other PGD$_2$ receptors by administering to a subject having such a condition or disorder, a therapeutically effective amount of a compound or composition of the invention. In one group of embodiments, disorders and conditions, including chronic conditions and disorders of humans or other species, can be treated with modulators, or antagonists, of DP-2 and/or one or more other PGD$_2$ receptors. These disorders and conditions include (1) inflammatory or allergic diseases such as systemic anaphylaxis and hypersensitivity disorders, atopic dermatitis, urticaria, drug allergies, insect sting allergies, food allergies (including celiac disease and the like) and mastocytosis, (2) inflammatory bowel diseases such as Crohn's disease, ulcerative colitis, ileitis and enteritis, (3) vasculitis, Behcet's syndrome, (4) psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria, viral cutaneous pathologies such as those derived from human papillomavirus, HIV or RLV infection, bacterial, fungal and other parasitical cutaneous pathologies, and cutaneous lupus erythematosus, (5) asthma and respiratory allergic diseases such as allergic asthma, allergic rhinitis, otitis media, allergic conjunctivitis, hypersensitivity lung diseases, chronic obstructive pulmonary disease and the like, (6) autoimmune diseases, such as arthritis (including rheumatoid and psoriatic), systemic lupus erythematosus, type I diabetes, myasthenia gravis, multiple sclerosis, Graves' disease, glomerulonephritis, scleroderma, including, e.g., systemic scleroderma, fasciitis, including, e.g., eosinophilia fasciitis (Schulman's syndrome), Sjogren's syndrome, hyper IgE syndrome, soft tissue disease, and inflammatory myopathies and the like, (7) graft rejection (including, e.g., allograft rejection and graft-v-host disease), e.g., skin graft rejection, solid organ transplant rejection, bone marrow transplant rejection, (8) fever, (9) cardiovascular disorders such as acute heart failure, hypotension, hypertension, angina pectoris, myocardial infarction, cardiomyopathy, congestive heart failure, atherosclerosis, coronary artery disease, restenosis, thrombosis and vascular stenosis, (10) cerebrovascular disorders such as traumatic brain injury, stroke, ischemic reperfusion injury and aneurysm, (11) cancers of the breast, skin, prostate, cervix,
uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract
(e.g., esophagus, stomach, pancreas), brain, thyroid, blood and lymphatic system, (12)
fibrosis, connective tissue disease and sarcoidosis, (13) genital and reproductive conditions
such as erectile dysfunction, (14) gastrointestinal disorders such as gastritis, ulcers, nausea,
pancreatitis and vomiting; (15) neurologic disorders, such as Alzheimer’s disease, (16) sleep
disorders such as insomnia, narcolepsy, sleep apnea syndrome and Pickwick Syndrome, (17)
pain, (18) renal disorders, (19) ocular disorders such as glaucoma, (20) infectious diseases,
viral infections such as HIV, and bacterial infections such as sepsis, (21) inflammation, (22)
flushing and (23) nasal congestion.

[0155] In yet another aspect, the invention provides methods of treating or preventing a
condition or disorder mediated, regulated or influenced by Th2 cells, eosinophils, basophils,
platelets, Langerhans cells, dendritic cells or mast cells, comprising administering to a subject
having such as condition or disorder a therapeutically effective amount of one or more of the
subject compounds or compositions.

[0156] In yet another aspect, the invention provides methods of treating or preventing a
condition or disorder mediated, regulated or influenced by PGD₂ and metabolites thereof,
such as 13,14-dihydro-15-keto-PGD₂ and 15-deoxy-Δ12-14PGJ₂, comprising administering to a subject
having such as condition or disorder a therapeutically effective amount of one or
more of the subject compounds or compositions.

[0157] In yet another aspect, the invention provides methods of treating or preventing a
condition or disorder responsive to modulation of DP-2 and/or one or more other PGD₂
receptors comprising administering to a subject having such a condition or disorder, a
therapeutically effective amount of one or more of the subject compounds or compositions.

[0158] In yet another aspect, the invention provides methods of treating or preventing a
condition or disorder mediated by DP-2 and/or one or more other PGD₂ receptors comprising
administering to a subject having such a condition or disorder, a therapeutically effective
amount of one or more of the subject compounds or compositions.

[0159] In yet another aspect, the invention provides methods of modulating DP-2 and/or
one or more other PGD₂ receptors comprising contacting a cell with one or more of the
subject compounds or compositions.
Depending on the disorder to be treated and the subject’s condition, the compounds of the invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracysternal injection or infusion, subcutaneous injection or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal, local) routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. The invention also contemplates administration of the compounds of the invention in a depot formulation, in which the active ingredient is released over a defined time period.

In the treatment or prevention of various conditions and disorders according to the invention associated with DP-2 and/or one or more other PGD₂ receptors, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Compositions

In another aspect, the invention provides pharmaceutical compositions suitable for pharmaceutical use comprising one or more compounds of the invention and a
pharmaceutically acceptable carrier, excipient or diluent. The term "composition" as used herein is intended to encompass a product comprising the specified ingredients (and in the specified amounts, if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant that the carrier or excipient is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0164] Formulation may improve one or more pharmacokinetic properties (e.g., oral bioavailability, membrane permeability) of a compound of the invention (herein referred to as the active ingredient).

[0165] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process, condition or disorder.

[0166] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the
gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Pat. Nos. 4,256,108; 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release.

> [0167] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil-medium, for example peanut oil, liquid paraffin, or olive oil.

> [0168] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

> [0169] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example-beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

> [0170] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting
agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0171] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0172] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0173] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0174] The pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0175] For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the invention are employed. As used herein, topical application is also meant to include the use of mouthwashes and gargles.
Pulmonary Administration

Inhalable Powder

[0176] In some embodiments, the agents are administered directly to the lung by inhalation. Accordingly, the agents for use according to the invention may be formulated as inhalable powders in admixture with suitable physiologically acceptable excipients (see, U.S. Patent Publication No. 20060034776 which is incorporated herein by reference with respect to suitable methods of administering pharmaceutical agents by inhalation).

[0177] For aerosol delivery in humans or other primates and mammals, the aerosol is generated by a medical nebulizer system that delivers the aerosol through a mouthpiece, facemask, etc. from which the mammalian host can draw the aerosol into the lungs. Various nebulizers are known in the art and can be used in the method of the present invention. The selection of a nebulizer system depends on whether alveolar or airway delivery (i.e., trachea, primary, secondary or tertiary bronchi, etc.), is desired. The composition is formulated as to not be too irritating at the required dosage.

[0178] Nebulizers useful for airway delivery include those typically used in the treatment of asthma. Such nebulizers are also commercially available. A therapeutic amount of the agent is a sufficient amount to prevent, treat, or palliate asthma following administration of the composition to the host mammal's lung, particularly the alveoli or bronchopulmonary and bronchiolopulmonary smooth muscle and epithelial cells of the trachea, bronchi, bronchia, bronchioli, and alveoli. Thus, an effective amount of the aerosolized compound of the invention, is a dose sufficient to effect treatment, that is, to cause alleviation or reduction of symptoms, to inhibit the worsening of symptoms, to prevent the onset of symptoms, and the like. The dosages of the preset compositions that constitute an effective amount can be determined in view of this disclosure by one of ordinary skill in the art by running routine trials with appropriate controls. Comparison of the appropriate treatment groups to the controls will indicate whether a particular dosage is effective in preventing or reducing particular symptoms.

[0179] The total amount of compound delivered to a mammalian host will depend upon many factors, including the total amount aerosolized, the type of nebulizer, the particle size,
breathing patterns of the mammalian host, severity of lung disease, concentration of the compound composition in the aerosolized solution, and length of inhalation therapy.

[0180] Despite the interacting factors described above, one of ordinary skill in the art will be able readily to design effective protocols, particularly if the particle size of the aerosol is optimized. Based on estimates of nebulizer efficiency, an effective dose delivered usually lies in the range of about 1 mg/treatment to about 500 mg/treatment, although more or less may be found to be effective depending on the subject, agent, dosage regimen, and desired result. It is generally desirable to administer higher doses when treating more severe conditions. If the treatment is repeated, the mammalian host can be monitored to ensure that there is no adverse response to the treatment. The frequency of treatments depends upon a number of factors, such as the amount of the agent administered per dose, as well as the health and history of the subject.

Propellant Gas-Driven Inhalation Aerosols

[0181] Inhalation aerosols containing propellant gas according to the invention may contain the agents for use according to the invention dissolved in the propellant gas or in dispersed form. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are halogenated alkane derivatives selected from TGl 34a, TG227, and mixtures thereof. The propellant-driven inhalation aerosols according to the invention may also contain other ingredients such as cosolvents, stabilizers, surfactants, antioxidants, lubricants, preservatives and pH adjusters. All these ingredients are known in the art. When in dispersed form, the agents can, for instance, be formulated to have an average particle size of up to 10 microns or preferably from 0.1 to 5 microns, or from 1 to 5 microns.

[0182] The propellant-driven inhalation aerosols according to the invention mentioned above may be administered using inhalers known in the art, such as metered dose inhalers. Accordingly, in another aspect, the present invention relates to pharmaceutical compositions
in the form of propellant gas-containing aerosols as hereinbefore described combined with one or more inhalers suitable for administering these aerosols.

C. Propellant-Free Inhalable Solutions or Suspensions

5 [0183] Propellant-free inhalable solutions and suspensions of the agents for use according to the invention are contemplated. The solvent used may be an aqueous or alcoholic, preferably an ethanolic solution. The solvent may be water on its own or a mixture of water and ethanol. The relative proportion of ethanol compared with water is not limited but the maximum is up to 70 percent by volume, more particularly up to 60 percent by volume and most preferably up to 30 percent by volume. The remainder of the volume is made up of water.

Combination Therapy

[0184] The pharmaceutical compositions and methods of the invention may further comprise other therapeutically active compounds, as noted herein, useful in the treatment of asthma, allergic diseases, inflammatory conditions and cancer and pathologies associated therewith (e.g., cardiovascular disease) or other adjuvant. In many instances, compositions which include a compounds of the invention and an alternative agent have additive or synergistic effects when administered.

[0185] The compounds of the invention can be combined or used in combination with other agents useful in the treatment, prevention, suppression or amelioration of the disorder or conditions for which compounds of the invention are useful, including inflammatory conditions, immune disorders, asthma, allergic rhinitis, eczema, psoriasis, atopic dermatitis, fever, sepsis, systemic lupus erythematosus, diabetes, rheumatoid arthritis, multiple sclerosis, atherosclerosis, transplant rejection, inflammatory bowel disease, cancer, viral infection, thrombosis, fibrosis, flushing, Crohn's disease, ulcerative colitis, chronic obstructive pulmonary disease, inflammation, pain, conjunctivitis, nasal congestion, urticaria and those pathologies noted above.

[0186] Such other agents, or drugs, may be administered, by a route and in an amount commonly used therefor, simultaneously or sequentially with a compound of the invention.
When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the invention include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound of the invention.

[0187] Examples of other therapeutic agents that may be combined with a compound of the invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists, (b) corticosteroids, such as beclomethasone, methylprednisolone, betamethasone, prednisone, prenisolone, triamcinolone, dexamethasone, fluticasone, flunisolide and hydrocortisone, and corticosteroid analogs such as budesonide; (c) immunosuppressants such as cyclosporine (cyclosporine A, Sandimmune®, Neoral®), tacrolimus (FK-506, Prograil®), rapamycin (sirolimus, Rapamune®) and other FK-506 type immunosuppressants, and mycophenolate, e.g., mycophenolate mofetil (CellCept®); (d) antihistamines (H1-histamine antagonists) such as brompheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine, pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, desacboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β2-agonists (e.g., terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, salmeterol, bitolterol and pirbuterol) and β2-agonist-corticosteroid combinations (e.g., salmeterol-fluticasone (Advair®), formoterol-budesonid (Symbicort®)), theophylline, cromolyn, cromolyn sodium, nedocromil, atropine, ipratropium, ipratropium bromide, leukotriene antagonists (e.g., zafirlukast, montelukast, montelukast sodium (Singulair®), pranlukast, irlukast, pobilukast and SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (e.g., alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid and toloprofen), acetic acid derivatives (e.g., indomethacin, acemetacin, alclofenac, clidacin, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin and zomepirac), fenamic acid derivatives (e.g., flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (e.g., diflunisal and flufenusal),
oxicams (e.g., isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (e.g., acetyl salicylic acid and sulfasalazine) and the pyrazolones (e.g., apazone, beziprylon, feprazone, mofebutazone, oxyphenbutazone and phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex®) and rofecoxib (Vioxx®); (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) other PGD₂ receptor antagonists, especially DP-I antagonists; (j) opioid analgesics such as codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, propoxyphene, buprenorphine, butorphanol, dezocine, nalbuphine and pentazocine; (k) cholesterol lowering agents such as HMG-CoA reductase inhibitors (e.g., lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and other statins), bile acid sequestrants (e.g., cholestyramine and colestipol), vitamin B3 (also known as nicotinic acid, or niacin), vitamin B6 (pyridoxine), vitamin B12 (cyanocobalamin), fibric acid derivatives (e.g., gemfibrozil, clofibrate, fenofibrate and benzafibrate), probucol, nitroglycerin, and inhibitors of cholesterol absorption (e.g., beta-sitosterol and acylCoA-cholesterol acyltransferase (ACAT) inhibitors such as melinamide), HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthetase inhibitors; (1) antithrombotic agents, such as thrombolytic agents (e.g., streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, O-blockers (e.g., atenolol), O-adrenergic agonists (e.g., isoproterenol), ACE inhibitors and vasodilators (e.g., sodium nitroprusside, nicardipine hydrochloride, nitroglycerin and enalaprilat); (m) anti-diabetic agents such as insulin and insulin mimetics, sulfonylureas (e.g., glyburide, meglitinide), biguanides, e.g., metformin (Glucophage®), α-glucosidase inhibitors (acarbose), thiazolidinone compounds, e.g., rosiglitazone (Avandia®), troglitazone (Rezulino), ciglitazone, pioglitazone (Actos®) and englitazone; (n) preparations of interferon beta (interferon β - 1 α, interferon β - 1 β); (O) gold compounds such as auranofin and aurothioglucone, (p) TNF inhibitors, e.g., etanercept (Enbrel®), antibody therapies such as orthoclone (0KT3), daclizumab (Zenapax®), basiliximab (Simulect®), infliximab (Remicade®) and D2E6 TNF antibody, (q) lubricants or emollients such as petrolatum and lanolin, keratolytic agents, vitamin D3 derivatives (e.g., calcipotriene and calcipotriol (Dovonex®), PUVA, anthralin (Drithrocreme®), etretinate (Tegison®) and isotretinoin; (r) multiple sclerosis therapeutic agents such as interferon β - 1 β (Betaseron®), interferon β - 1 α (Avonex®, azathioprine (Imurek®, Imuran®), glatiramer acetate (Capoxone®), a glucocorticoid (e.g., prednisolone) and cyclophosphamide; (s) other compounds such as 5-aminosalicylic acid and prodrugs thereof; (t) DNA-alkylating agents (e.g.,
cyclophosphamide, ifosfamide), antimetabolites (e.g., azathioprine, 6-mercaptopurine, methotrexate, a folate antagonist, and 5-fluorouracil, a pyrimidine antagonist), microtubule disruptors (e.g., vincristine, vinblastine, paclitaxel, colchicine, nocodazole and vinorelbine), DNA intercalators (e.g., doxorubicin, daunomycin and cisplatin), DNA synthesis inhibitors such as hydroxyurea, DNA cross-linking agents, e.g., mitomycin C, hormone therapy (e.g., tamoxifen, and flutamide), cytostatic agents, e.g., imatinib (STI 571, Gleevec®) and rituximab (Rituxan®), FLAP inhibitors, and PLA₂ inhibitors. The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the invention is combined with an NSAID, the weight ratio of the compound of the invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

Diagnosis of Asthma

[0188] Methods of diagnosing asthma and other respiratory inflammatory and obstructive disorders or conditions are well known to persons of ordinary skill in the art. For example, spirometry can be used to assess lung function. The diagnosis of asthma, in particular, may be made in part based upon family history or personal history of a severe and sudden episode or recurrent episodes of wheezing, coughing or shortness of breath which may be associated with exposure to an allergen or exacerbated or precipitated by moderate exercise. Typically a physical exam is involved to detect the disorder or condition.

[0189] Using a nasal speculum, the nose may be examined for signs of allergic disorder or condition such as increased nasal secretions, swelling or polyps which may be triggering asthma. A stethoscope may be used to listen to the sounds the lungs make during breathing. Wheezing sounds are one of the main indicators of the obstructed airways associated with asthma. In addition, allergic conditions such as eczema or hives, are often associated with asthma.

[0190] Pulmonary function tests are particularly useful in confirming the diagnosis of respiratory disorders or conditions. These tests include spirometry to determine vital capacity, the maximum amount of air that you can inhale and exhale; the peak expiratory
flow rate, also known as the peak flow rate, which is the maximum flow rate you can generate during a forced exhalation; and forced expiratory volume, which is the maximum amount of air you can exhale in one second.

[0191] If the measurements are below normal for a person your age, a bronchodilator drug used in asthma treatment can be administered to open obstructed air passages and the spirometry repeated. If the measurements improve significantly, asthma is likely.

[0192] In addition, asthma may be diagnosed by challenging the individual with exercise, or by inhaling an airway-constricting chemical or taking several breaths of cold air. After the challenge with a symptom-producing substance or activity, the spirometry test is readministered. If the spirometry measurements fall significantly, asthma is indicated.

[0193] The following examples are offered by way of illustration and are not intended to limit the scope of the invention. Those of skill in the art will readily recognize a variety of noncritical parameters that could be modified to yield essentially similar results.

EXAMPLES

General Methods:

[0194] The invention will now be illustrated by the following non-limiting examples. The title and sub-titled compounds of the examples and methods were named using the ChemDraw Ultra (version 7.0) from CambridgeSoft Inc. Flash column chromatography refers to normal phase silica chromatography. Reagents and solvents used can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wis., USA). Solvents were dried with MgSO₄ or Na₂SO₄. Evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration. Unless otherwise stated, operations were carried out at ambient temperature that is in the range 18-25 °C and under an atmosphere of an inert gas such as argon or nitrogen. Yields are given for illustration only and are not necessarily the maximum attainable. The structures of the end-products of the structure (1) were confirmed by nuclear (generally proton) magnetic resonance PMR) and mass spectral techniques. ¹H NMR spectra were recorded on a Varian™ 400 MHz NMR spectrometer. Proton magnetic resonance chemical shift values were measured on the delta scale, δ, in parts per million (ppm). Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q,
quartet; m, multiplet; br s, broad singlet), coupling constant(s) in Hertz (Hz) and number of protons. Intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TILC), high-performance liquid chromatography (BPLC), mass spectrometry (MS), infra-red (IR) or NMR analysis. Mass spectra were recorded by one of the three Liquid Chromatographic/Mass Spectrometry (LC/MS) methods:

**Method A:**

[0195] Run on an Agilent 1100 HPLC over a phenomenex Luna C18 3micron 30x2.0mm id column at a flow rate of 0.300mL/min. The column, at 35 °C, was eluted with a gradient comprised of increasing AcCN (modified with 0.05% formic acid) and water (modified with 0.05% formic acid) as described in the table* below. The analytes were monitored at 214nm and 254nm. The analytes were vaporized in an Agilent electrospray source charged to 80V and detected after passing through a single quadrupole.

**Gradient**

<table>
<thead>
<tr>
<th>Time</th>
<th>% organic</th>
<th>Organic Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>10</td>
<td>AcCN</td>
</tr>
<tr>
<td>0.2</td>
<td>10</td>
<td>AcCN</td>
</tr>
<tr>
<td>3.8</td>
<td>95</td>
<td>AcCN</td>
</tr>
<tr>
<td>4.1</td>
<td>95</td>
<td>AcCN</td>
</tr>
<tr>
<td>4.4</td>
<td>10</td>
<td>AcCN</td>
</tr>
<tr>
<td>6.0</td>
<td>10</td>
<td>AcCN</td>
</tr>
</tbody>
</table>

**Method B:**

[0196] Run on an Agilent 1100 HPLC over a phenomenex Luna C18 3micron 30x2.0mm id column at a flow rate of 0.300mL/min. The column, at 35 °C, was eluted with a gradient comprised of increasing AcCN (modified with 0.05% formic acid) and water (modified with 0.05% formic acid) as described in the table below. The analytes were monitored at 214nm and 254nm. The analytes were vaporized in an Agilent multi-mode source in electrospray mode charged to 80V and detected after passing through a single quadrupole.

**Gradient**

<table>
<thead>
<tr>
<th>Time</th>
<th>% organic</th>
<th>Organic Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>10</td>
<td>AcCN</td>
</tr>
<tr>
<td>0.2</td>
<td>10</td>
<td>AcCN</td>
</tr>
<tr>
<td>3.8</td>
<td>95</td>
<td>AcCN</td>
</tr>
<tr>
<td>4.1</td>
<td>95</td>
<td>AcCN</td>
</tr>
<tr>
<td>4.4</td>
<td>10</td>
<td>AcCN</td>
</tr>
<tr>
<td>6.0</td>
<td>10</td>
<td>AcCN</td>
</tr>
</tbody>
</table>
Method C:

[0197] Run on an Agilent 1100 HPLC over a phenomenex Luna C18 3micron 30x2.0mm id column at a flow rate of 0.300mL/min. The column, at 35 °C, was eluted with a gradient comprised of increasing methanol (modified with 0.05% formic acid) and water (modified with 0.05% formic acid) as described in the table below. The analytes were monitored at 214nm and 254nm. The analytes were vaporized in an Agilent multi-mode source in atmospheric chemical ionization mode charged to 80V and detected after passing through a single quadrupole.

Gradient

<table>
<thead>
<tr>
<th>Time</th>
<th>% organic</th>
<th>Organic Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>35</td>
<td>methanol</td>
</tr>
<tr>
<td>0.2</td>
<td>35</td>
<td>methanol</td>
</tr>
<tr>
<td>3.6</td>
<td>98</td>
<td>methanol</td>
</tr>
<tr>
<td>4.1</td>
<td>98</td>
<td>methanol</td>
</tr>
<tr>
<td>4.4</td>
<td>35</td>
<td>methanol</td>
</tr>
<tr>
<td>6.0</td>
<td>35</td>
<td>methanol</td>
</tr>
</tbody>
</table>

Examples 1-53

Method IA:

[0198] To tert-butyl 4-(2-hydroxy-5-(2-methoxy-2-oxoethyl) benzyl) piperazine-1-carboxylate (0.41mmol, 0.150g) in DMF (1mL) was added K₂CO₃ (0.82mmol, 0.113g), alkyl halide, R⁴aX (0.58mmol) and catalytic KI. The reaction was stirred at 100 °C until the absence of starting material was observed. Once complete, the reaction mixture was
worked up by quenching with water then extracted several times into EtOAc. The combined organics were washed with brine and dried over Na₂SO₄. The material was filtered, dried and used without further purification.

<table>
<thead>
<tr>
<th>Example</th>
<th>Syn. Method</th>
<th>R²</th>
<th>R¹a</th>
<th>Avg. MW</th>
<th>m/z</th>
<th>LC/MS Method</th>
<th>Rt (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>5</td>
<td><img src="image" alt="R²" /></td>
<td><img src="image" alt="R¹a" /></td>
<td>447</td>
<td>447.2, 449.2</td>
<td>A</td>
<td>2.60</td>
</tr>
<tr>
<td>28</td>
<td>5</td>
<td><img src="image" alt="R²" /></td>
<td><img src="image" alt="R¹a" /></td>
<td>461</td>
<td>461.2, 463.2</td>
<td>A</td>
<td>2.70</td>
</tr>
<tr>
<td>29</td>
<td>5</td>
<td><img src="image" alt="R²" /></td>
<td><img src="image" alt="R¹a" /></td>
<td>475</td>
<td>475.2, 477.2</td>
<td>A</td>
<td>2.78</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td><img src="image" alt="R²" /></td>
<td><img src="image" alt="R¹a" /></td>
<td>489</td>
<td>489.2, 491.2</td>
<td>A</td>
<td>2.55</td>
</tr>
<tr>
<td>31</td>
<td>5</td>
<td><img src="image" alt="R²" /></td>
<td><img src="image" alt="R¹a" /></td>
<td>503</td>
<td>503.2, 505.2</td>
<td>A</td>
<td>2.60</td>
</tr>
<tr>
<td>32</td>
<td>5</td>
<td><img src="image" alt="R²" /></td>
<td><img src="image" alt="R¹a" /></td>
<td>489</td>
<td>489.1, 491.1</td>
<td>A</td>
<td>2.59</td>
</tr>
<tr>
<td>33</td>
<td>5</td>
<td><img src="image" alt="R²" /></td>
<td><img src="image" alt="R¹a" /></td>
<td>475</td>
<td>475.1, 477.1</td>
<td>A</td>
<td>2.69</td>
</tr>
<tr>
<td>34</td>
<td>7</td>
<td><img src="image" alt="R²" /></td>
<td><img src="image" alt="R¹a" /></td>
<td>459</td>
<td>460.2, 462.2</td>
<td>A</td>
<td>2.46</td>
</tr>
</tbody>
</table>
To the piperazine (0.12 mmol) in 2mL methylene chloride was added DIEA (0.15mmol) and acid chloride (0.12 mmol). The reaction stirred at RT until judged complete by LC/MS. The product was purified by reverse phase HPLC (Rainin) using a 1:3 CH₃CN/H₂O/0.1% formic acid gradient to 9:1 CH₃CN/H₂O/0.1% formic acid gradient, over a 23 min. period.
<table>
<thead>
<tr>
<th>Example</th>
<th>Syn. Method</th>
<th>$Q^1R^5$</th>
<th>$R^{4B}$</th>
<th>Avg. MW</th>
<th>m/z</th>
<th>LC/MS method</th>
<th>Rt (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>433</td>
<td>433.1, 435.1</td>
<td>A</td>
<td>2.44</td>
</tr>
<tr>
<td>41</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>447</td>
<td>447.2, 449.1</td>
<td>A</td>
<td>2.57</td>
</tr>
<tr>
<td>42</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>461</td>
<td>461.2, 463.2</td>
<td>A</td>
<td>2.63</td>
</tr>
<tr>
<td>43</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>523</td>
<td>523.2, 525.2</td>
<td>A</td>
<td>2.70</td>
</tr>
<tr>
<td>44</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>507</td>
<td>507.2, 509.2</td>
<td>A</td>
<td>2.76</td>
</tr>
<tr>
<td>45</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>528</td>
<td>527.1, 529.1, 531.1</td>
<td>A</td>
<td>2.79</td>
</tr>
<tr>
<td>46</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>509</td>
<td>509.2, 511.2</td>
<td>A</td>
<td>2.54</td>
</tr>
<tr>
<td>47</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>522</td>
<td>522.2, 524.2</td>
<td>A</td>
<td>2.14</td>
</tr>
<tr>
<td>48</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>460</td>
<td>461.1, 463.1</td>
<td>A</td>
<td>2.47</td>
</tr>
</tbody>
</table>
Example 54

4-[5-Carboxymethyl-2-(4-chloro-benzyloxy)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (Compound 54).

\[
\begin{array}{|c|c|c|c|c|c|}
\hline
\text{No.} & \text{R}^4 & \text{R}^4 & \text{R}^4 & \text{R}^4 & \text{R}^4 \\
\hline
49 & - & - & - & - & - \\
50 & - & - & - & - & - \\
51 & - & - & - & - & - \\
52 & - & - & - & - & - \\
53 & - & - & - & - & - \\
\hline
\end{array}
\]

[0200] To tert-butyl 4-(2-hydroxy-5-(2-methoxy-2-oxoethyl) benzyl) piperazine-1-carboxylate (0.41mmol, 0.150g) in DMF (ImL) was added K\textsubscript{2}CO\textsubscript{3} (0.82mmol, 0.1 13g), alkyl halide, R\textsuperscript{4a}X (0.58mmol) and catalytic KI. The reaction was stirred at 100 °C until the absence of starting material was observed. Once complete, the reaction mixture was worked up by quenching with water then extracted several times into EtOAc. The combined
organics were washed with brine and dried over Na$_2$SO$_4$. The material was filtered, dried and used without further purification.

Example 55

5 Methyl 2-(4-(4-chlorobenzyloxy)-3-(4-(pyrimidin-2-yl)piperazine-1-ylmethyl)phenyl)acetate (Compound 55A) and 2-(4-(4-chlorobenzyloxy)-3-(4-(pyrimidin-2-yl)piperazine-1-ylmethyl)phenyl)acetic acid (Compound 55B).

Methyl 2-(4-(4-chlorobenzyloxy)-3-(4-(pyrimidin-2-yl)piperazine-1-ylmethyl)phenyl)acetate (Compound 55A)

![Molecular structure of Compound 55A]

[0201] To methyl 2-(4-(4-chlorobenzyloxy)-3-(piperazine-1-ylmethyl)phenyl)acetate (O.Dmmol) in AcCN with TEA (0.3 lmmol, 0.043mL) was added 2-chloropyrimidine (0.13mmol, 0.015g). The mixture was heated to 80 °C for 72 hours, then dried over MgSO$_4$. The desired material was used without further purification. LC/MS (Method A) Rt =2.66 min., MS m/z (M+H) 467.2.

2-(4-(4-chlorobenzyloxy)-3-(4-(pyrimidin-2-yl)piperazine-1-ylmethyl)phenyl)acetic acid (Compound 55B)
The title material was prepared from methyl 2-(4-(4-chlorobenzyloxy)-3-(4-(pyrimidin-2-yl)piperazine-1-ylmethyl)phenyl)acetate using Method 2. MS m/z 453.2 (M+H). LC/MS (Method A), Rt= 2.55 min.

Examples 56
Methyl 2-(4-(3,4-dichlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 56A) and 2-(4-(3,4-dichlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 56B)

The title compounds were prepared according to General Methods IA through 2 using 1,2-dichloro-4-(chloromethyl)benzene and 4-methyl phenyl sulfonyl chloride. Compound 56B LC/MS: (Method A), Rt=2.975 min. MS (m/z) 563 (M+H).

Example 57
2-(4-(4-fluorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 57A) and 2-(4-(4-fluorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 57B)

[0204] The title compounds were prepared according to General Methods IA to 2 using 1-(chloromethyl)-4-fluorobenzene and 4-methyl phenyl sulfonyl chloride; however after hydrolysis the final product was isolated as an HCl salt upon acidification of reaction mixture with LON aq. HCl with no further purification. Compound 57B LC/MS: (Method A), Rt=2.763 min. MS (m/z) 513 (M+H).

Example 58

Methyl 2-(4-(4-nitrobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 58A) and

2-(4-(4-nitrobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 58B)

[0205] The compounds were prepared according to Methods IA to 2 using 1-(chloromethyl)-4-nitrobenzene and 4-methyl phenyl sulfonyl chloride. Compound 58B
MS (m/z) 540 (M+H). \( ^1 \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 8.29 (2H, d), 7.6 (5H, m), 7.35 (3H, m), 6.95 (IH, d), 5.22 (2H, s), 4.28 (2H, s), 3.61 (2H, d), 3.45 (4H, br. s), 3.18 (4H, br. s), 2.43 (3H, s).

Example 59

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(3,5-dichlorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 59A)

Example 60

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(4-ethylphenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 60A) and
2-(4-(4-chlorobenzyloxy)-3-((4-(4-ethylphenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 60B)

[0207] The title compounds were prepared according to standard Methods 1A to 2 using 4-ethylbenzene-1-sulfonyl chloride and 1-chloromethyl-4-chlorobenzene. Compound 60B- same MS (m/z) 544 (M+H). 1H NMR (300 MHz, DMSO-d₆) δ : 8.21 (IH, s), 7.61 (2H, d), 7.42 (4H, dd), 7.23 (2H, s), 7.14-6.92 (2H, m), 5.09 (2H, s), 4.2 (2H, br. s), 3.81-3.51 (8H, v. br. s), 3.5 (2H, s), 2.7 (2H, dq), 1.19 (3H, t).

Example 61

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(naphthalen-1-ylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 61A)

2-(4-(4-chlorobenzyloxy)-3-((4-(naphthalen-1-ylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 61B)

[0208] The title compounds were prepared according to General Methods 1A to 2 using naphthalene-1-sulfonyl chloride and 1-chloromethyl-4-chlorobenzene. Compound 61B MS (m/z) 566 (M+H). 1H NMR (300 MHz, DMSOd₆) δ : 8.62 (IH, d), 8.3 (IH, d), 8.14 (2H,
m), 7.69 (3H, m), 7.43 (4H, dd), 7.23 (2H, s), 7.04 (IH, d), 5.09 (2H, s), 4.24 (2H, br. s), 3.96-3.53 (4H, br. m), 3.41 (2H, s), 3.1 (2H, br. s), 2.8 (2H, br. s).

Example 62

5 Methyl

(E)-2-(4-(4-chlorobenzyloxy)-3-((4-(styrylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate

(Compound 62A)

(E)-2-(4-(4-chlorobenzyloxy)-3-((4-(styrylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid

(Compound 62B)

[0209] The title compounds were prepared according to General Methods IA to 2 using (E)-2-phenylethenesulfonyl chloride and 1-chloromethyl-4-chlorobenzene. Compound 62B

LC/MS: (Method A), Rt = 2.838 min. MS (m/z)542 (M+H).

Example 63

Methyl

2-(3-((4-(4-chloro-3-(trifluoromethyl)phenylsulfonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyl)oxy)phenyl)acetate (Compound 63A) and

2-(3-((4-(4-chloro-3-(trifluoromethyl)phenylsulfonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyl)oxy)phenyl)acetic acid (Compound 63B)
The title compounds were prepared according to General Methods IA to 2 using 4-chloro-3-(trifluoromethyl)benzene-1-sulfonyl chloride and 1-chloromethyl-4-chloro benzene. **Compound 63B** LC/MS: (Method A) R$_t$ = 3.229 min. MS (m/z) 618 (M+H).

**Example 64**

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(phenethylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 64A) and

**Compound 64B**

LC/MS: (Method A), R$_t$ = 2.854 min. MS (m/z) 544 (M+H).

The title compound(s) were prepared according to General Methods IA to 2 using 2-phenylethanesulfonyl chloride and 1-chloromethyl-4-chloro benzene. Upon acidification of reaction mixture with 1.0N HCl, a white solid crashed out. The solid was collected by filtration, washed with water, and dried under high vacuum yielding pure compound 64B. LC/MS: (Method A), R$_t$ = 2.854 min. MS (m/z) 544 (M+H).

Examples 65-68
General Method 65 Step A:

[0212] Intermediate A1 (100 mg, 0.32 mmol) was dissolved in 5 ml of DMF. To the solution was added the alkyl bromide (0.35 mmol, 1.1 equivalents) and K$_2$CO$_3$ (0.48 mmol, 1.5 equivalents). The reaction was heated to 85°C and stirred for 20-24 hours. Reaction was then allowed to cool to room temperature, was diluted with water and extracted with EtOAc. Organic extracts were washed with brine, dried over sodium sulfate, concentrated. The crude residue was purified via reverse phase HPLC (Column: Phenomenex, 250 X 10 mm, 10 micro, Luna 10 µ; Gradient: 90%:10%:0.05% H$_2$O/CH$_3$CN/TFA (or formic acid) to 10%/90%/0.05% H$_2$O/CH$_3$CN/TFA (or formic acid) over 20 min).

Step B:

[0213] The fractions containing intermediate B1 from HPLC purification in step A were pooled and 5-8 ml of 1.0N aqueous KOH was added. The resulting mixture was stirred until reaction was complete as confirmed by LC/MS analysis. Reaction was then acidified to pH 2-4 with 1.0N HCl and extracted with EtOAc/isopropyl alcohol. Organic extracts were washed with brine, dried over sodium sulfate and concentrated yielding the desired product.

Example 65

Methyl 2-(4-isopropoxy-3-(S,S-dioxo - thiomorpholine methyl)phenyl)acetate (Compound 65A) and 2-(4-isopropoxy-3-(S,S-dioxo - thiomorpholine methyl)phenyl)acetic acid (Compound 65B)
The title compound(s) were prepared according to General Method 65 Steps A-B using 2-bromo propane. LC/MS: Method C, Rt = 5.59 min. MS (m/z) 342 (M+H).

Example 66

2-(4-isopentyloxy-3-(S,S-dioxo-thiomorpholine methyl)phenyl)acetic acid (Compound 66A) and

2-(4-isopentyloxy-3-(S,S-dioxo-thiomorpholine methyl)phenyl)acetic acid (Compound 66B)

The title compound(s) were prepared according to General Method 65 Steps A-B using 1-bromo-3-methylbutane. LC/MS Method C, Rt= 6.370 min. MS (m/z)370 (M+H).

Example 67

Methyl (S)-2-(4-(2-methylbutoxy)-3-(S,S-dioxo thiomorpholine methyl)phenyl)acetate (Compound 67A)

(S)-2-(4-(2-methylbutoxy)-3-(S,S-dioxo thiomorpholine methyl)phenyl)acetic acid (Compound 67B)
[0216] The title compound(s) were prepared according to General Method 65 Steps A-B using (S)-1-bromo-2-methylbutane. LC/MS: Method C, Rt= 6.290 min. MS (m/z) 370 (M+H).

Example 68

2-(4-isobutoxy-3-(thiomorpholine 1,1'-dioxidemethyl)phenyl)acetic acid (Compound 68A) and 2-(4-isobutoxy-3-(thiomorpholine 1,1'-dioxidemethyl)phenyl)acetic acid (Compound 68B)

[0217] The title compound(s) were prepared according to General Method 65 Steps A-B using 1-bromo-2-methylpropane, however the product recovered from step B was insufficiently pure and was subjected to HPLC purification. Compound 68B LC/MS: (Method A), Rt= 2.744 min. MS (m/z) 356 (M+H).

Example 69

2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 69D)
Step A: t-butyl
4-(2-(isopentyloxy)-5-(2-methoxy-2-oxoethyl)benzyl)piperazine-1-carboxylate (Compound 69A)

Solid K$_2$CO$_3$ (379 mg, 2.74 mmol) and 1-chloro-3-methylbutane (107 mg, 1.51 mmol) were added to a stirring solution of t-butyl 4-(2-hydroxy-5-(2-methoxy-2-oxoethyl)benzyl)piperazine-1-carboxylate (500 mg, 1.37 mmol) in DMF (5 mL) at 80 °C. The resulting suspension was cooled after 16 h, then diluted with ethyl acetate (20 mL). The organic layer was washed with H$_2$O (30 mL), dried over Na$_2$SO$_4$, and concentrated to give the crude ether (492 mg) as a brown oil. The compound was carried to the next step without purification.

Step B: Methyl 2-(4-(isopentyloxy)-3-(piperazin-1-ylmethyl)phenyl)acetate (Compound 69B).

TFA (0.21 mL) was added to a stirring solution of crude ether t-butyl 4-(2-(isopentyloxy)-5-(2-methoxy-2-oxoethyl)benzyl)piperazine-1-carboxylate above (492 mg) in CH$_2$Cl$_2$ (5 mL) at RT. The reaction mixture was stirred overnight then quenched with satd. NaHCO$_3$ (20 mL). The aqueous was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine (20 mL), dried over Na$_2$SO$_4$, and concentrated to give crude piperazine (300 mg) as brown oil. The compound was carried to the next step without purification.
Step C: Methyl 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 69C)

[DIEA (0.156 mL, 0.897 mmol) and TsCl (94 mg, 0.493 mmol) were added to a stirring solution of crude piperazine methyl 2-(4-(isopentyloxy)-3-(piperazin-1-ylmethyl)phenyl)acetate above (150 mg, 0.448 mmol) in CH₂Cl₂ (5 mL) at RT. The resulting suspension was quenched with satd. NaHCO₃ (20 mL) after 16 h and the aqueous was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄ then concentrated to give crude sulfonamide. The compound was carried to the next step without purification.

Step D: 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 69D)

[Solid LiOH (64 mg, 1.53 mmol) was added to a stirring solution of methyl 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl) (187 mg, 0.383 mmol) in THF/MeOH/H₂O (5 mL, 3:1:1) at RT. After stirring over night the resulting mixture was quenched with 1 N HCl (<pH 1). The aqueous was extracted with EtOAc (3 X 20 mL), dried over Na₂SO₄, and concentrated to give crude acid (226 mg) as a brown oil. HPLC purification afforded pure compound: ES/MS, m/z 476 (M+H).]
Example 70

2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid
(Compound 70B)

Step A: Methyl

2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetate
(Compound 70A)

[0222] DIEA (0.156 mL, 0.897 mmol) and PhNCO (0.054 mL, 0.493 mmol) were added to a stirring solution of piperazine methyl

2-(4-(isopentyloxy)-3-(piperazin-1-ylmethyl)phenyl)acetate (150 mg, 0.448 mmol) in CH₂Cl₂ (5 mL) at RT. The resulting solution was quenched with satd. NaHCO₃ (20 mL) after stirring for over night. The aqueous was extracted with CH₂Cl₂ (3 X 20 mL), dried over Na₂SO₄, and concentrated to give urea as a brown oil (183 mg). The compound was carried to the next step without purification.

Step B: 2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 70B).

[0223] Solid LiOH (67 mg, 1.61 mmol) was added to a stirring solution of methyl

2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetate (183 mg,
0.403 mmol) in THF/MeOH/H₂O (5 mL, 3:1:1) at RT. After stirring over night the resulting mixture was quenched with 1 N HCl (pH 1). The aqueous was extracted with EtOAc (3 X 20 mL), dried over Na₂SO₄, and concentrated to give crude acid (226 mg) as a brown oil. HPLC purification afforded pure compound: ES/MS m/z 440.2 (M+H); LC/MS (Method C) Rt = 2.58 min.

Example 71

Methyl 2-(4-(cyclopentyl)oxy)-3-((4-tosylpiperazin-1-yl)methyl)phenylacetate, (Compound 71A) and 2-(4-(cyclopentyl)oxy)-3-((4-tosylpiperazin-1-yl)methyl)phenylacetic acid, (Compound 71B):

![Structural formula of Compound 71A]

[0224] The title compound(s) were obtained using bromo cyclopentane and 4-methyl phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyl)oxy)-3-((4-tosylpiperazin-1-yl)methyl)phenylacetic acid. Compound 71B ES/MS, m/z 473.3 (M+H); LC/MS (Method C) Rt = 2.65 min.

Example 72

Methyl 2-(4-(cyclopentyl)oxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenylacetate (Compound 72A) and 2-(4-(cyclopentyl)oxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenylacetic acid (Compound 72B):
The title compound(s) were obtained using bromo cyclopentane and phenyl isocyanate using the Method described for 2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid.

Example 72

Methyl (4-(4-Chloro-benzyloxy)-3,5-bis-(4-phenylcarbamoyl-piperazin-1-ylmethyl)-phenyl)-acetate, (Compound 72A) and (4-(4-Chloro-benzyloxy)-3,5-bis-(4-phenylcarbamoyl-piperazin-1-ylmethyl)-phenyl)-acetic acid, (Compound 72B) ES/MS, m/z 438.3 (M+H); LC/MS (Method C) Rt= 2.50 min.

Example 73

Methyl 2-(4-(cyclopropylmethoxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 73A) and

Example 74

Methyl 2-(4-(cyclopropylmethoxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 74A) and
2-(4-(cyclopropylmethoxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 74B):

![Chemical Structure Image]

The title compound(s) were obtained using bromo methyl cyclopropane and 4-methyl phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 74B: ES/MS, m/z 459.3 (M+H); LC/MS (Method C) Rt = 2.62 min.

Example 75

Methyl 2-(4-(cyclopropylmethoxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 75A) and 2-(4-(cyclopropylmethoxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 75B):

![Chemical Structure Image]

The title compound(s) were obtained using bromo methyl cyclopropane and phenyl isocyanate using the Method described for 2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid. Compound 75B: ES/MS m/z 424.3 (M+H); LC/MS (Method C) Rt = 2.46 min.

Example 76
Methyl 2-(4-methoxy-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 76A) and 2-(4-methoxy-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 76B):

[0229] The title compound(s) were obtained using iodomethane and 4-methyl phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 76B: ES/MS m/z 419.2 (M+H); LC/MS (Method C) Rt = 2.50 min.

Example 77

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(4-methoxyphenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 77A) and 2-(4-(4-chlorobenzyloxy)-3-((4-(4-methoxyphenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 77B):

[0230] The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 4-methoxy phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 77B: ES/MS, m/z 545.1 (M+H); LC/MS: (Method A) Rt = 2.79 min.

Example 78
Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(3,4-dichlorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 78A) and
2-(4-(4-chlorobenzyloxy)-3-((4-(3,4-dichlorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 78B):

![Chemical Structure](image)

[0231] The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 3,4-di chloro phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 78B:

ES/MS m/z 585.2 (M+H); LC/MS (Method C) Rt = 3.12 min.

Example 79

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(2-chlorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 79A) and
2-(4-(4-chlorobenzyloxy)-3-((4-(2-chlorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 79B):

![Chemical Structure](image)

[0232] The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 2-chloro phenyl sulfonyl chloride, using the Method described for
2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 79B:** ES/MS, m/z 549.2 (M+H); LC/MS (Method C) Rt = 2.85 min.

Example 80

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(m-tolylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 80A) and 2-(4-(4-chlorobenzyloxy)-3-((4-(m-tolylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 80B):

![Chemical Structure](image)

[0233] The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 3-methyl phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 80B:** ES/MS, m/z 529.3 (M+H); LC/MS (Method C) Rt = 2.85 min.

Example 81

2-(4-(4-chlorobenzyloxy)-3-((4-(quinolin-8-ylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 81A) and 2-(4-(4-chlorobenzyloxy)-3-((4-(quinolin-8-ylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 81B):
The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and quinoline-8-sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 81B:**

- ES/MS, m/z 529.3 (M+H); LC/MS (Method C) Rt = 2.65 min.

**Example 82**

Methyl 2-(3-((4-tosylpiperazin-1-yl)methyl)-4-(4-(trifluoromethyl)benzylloxy)phenyl)acetate (**Compound 82A**) and 2-(3-((4-tosylpiperazin-1-yl)methyl)-4-(4-(trifluoromethyl)benzylloxy)phenyl)acetic acid (**Compound 82B**):

- ES/MS, m/z 563.3 (M+H); LC/MS (Method C) Rt = 3.04 min.

The title compound(s) were obtained using 1-chloromethyl 4-trifluoromethyl benzene and 4-methyl-sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 82B:**

- ES/MS, m/z 563.3 (M+H); LC/MS (Method C) Rt = 3.04 min.

**Example 83**
4-((4-(carboxymethyl)-2-((4-tosylpiperazin-1-yl)methyl)phenoxy)methyl)benzoic acid (Compound 83):

[0236] The title compound(s) were obtained using 1-bromomethyl 4-cyano benzene and 4-methyl-sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, followed by hydrolysis using the method described in Biorg. Med. Chem. Letters, 2005, 15: 5247-5252. ES/MS m/z 539.3 (M+H); LC/MS (Method C) Rt = 2.46 min.

Example 84

Methyl {4-(2,4-Dichloro-benzyloxy)-3-[1-oxy-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl} -acetate (Compound 84A) and {4-(2,4-Dichloro-benzyloxy)-3-[1-oxy-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl} -acetic acid (Compound 84B):

[0237] The title compound was obtained using 2,4-dichloro benzyl chloride and 4-methyl-sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, followed by treatment with mCPBA in CH$_2$Cl$_2$. Compound 84B: ES/MS m/z 580.1 (M+H).
Examples 85-£

Scheme 2

5 Example 85

2-(2-((4-tosylpiperazin-l-yl)methyl)biphenyl-4-yl)acetic acid (Compound 85C).

Step A: tert-butyl

4-(5-(2-methoxy-2-oxoethyl)-2-(trifluoromethylsulfonyloxy)benzyl)piperazine-l-carboxylate

(Compound 85A)

[0238] Trifluoromethanesulfonic anhydride (0.691 mL, 4.12 mmol), DIEA (0.718 mL, 4.12 mmol), and DMAP (33 mg, 0.274 mmol) were added to a stirring solution of tert-butyl 4-(2-hydroxy-5-(2-methoxy-2-oxoethyl)benzyl)piperazine-l-carboxylate (Ig, 2.74 mmol) in CH₂Cl₂ (20 mL) at 0°C. The resulting suspension was warm to rt and stirred overnight.
followed by addition of satd. NaHCO₃ (30 mL). The aqueous was extracted with CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄, then concentrated to give crude (1.945 g) as yellow oil. A flash chromatography on silica gel (3:1, hexanes/EtOAc) afforded pure material (0.85 g, 62%).

![Chemical Structure](image)

**Step B: tert-butyl**

4-((4-(2-methoxy-2-oxoethyl)biphenyl-2-yl)methyl)piperazine-1-carboxylate (Compound 85B)

[0239] Palladium tetrakis (22 mg, 0.0191 mmol) and phenyl boronic acid (51 mg, 0.421 mmol) were added to a stirring solution of tert-butyl 4-(5-(2-methoxy-2-oxoethyl)-2-(trifluoromethylsulfonyloxy)benzyl)piperazine-1-carboxylate (190 mg, 0.383 mmol) in dimethoxy methane/2 M Na₂CO₃ (2:1, 9 mL). After refluxing for 3 days, the resulting suspension was cooled, then the organic layer was concentrated. Water (10 mL) was added to a mixture and the aqueous was extracted with ether (3 X 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude material (342 mg). The compound was earned to the next step without purification.

**Step C: 2-(2-((4-tosylpiperazin-1-yl)methyl)biphenyl-4-yl)acetic acid (Compound 85C).**

[0240] The compound was prepared using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, Steps A-D: ES/MS m/z 465.1 (M+H); LC/MS (Method C) Rt = 3.12 min.
Example 86

Methyl 2-(4'-methyl-2-((4-tosylpiperazin-l-yl)methyl)biphenyl-4-yl)acetic acid (Compound 86A) and 2-(4'-methyl-2-((4-tosylpiperazin-l-yl)methyl)biphenyl-4-yl)acetate (Compound 86B)

[0241] The compound was prepared using the method described for 2-(2-((4-tosylpiperazin-l-yl)methyl)biphenyl-4-yl)acetic acid, using 4-methyl boronic acid. Compound 86B: ES/MS m/z 479.3 (M+H); LC/MS (Method C) Rt = 3.04 min.

Example 87

Methyl 2-(4'-chloro-2-((4-tosylpiperazin-l-yl)methyl)biphenyl-4-yl)acetate (Compound 87A) and 2-(4'-chloro-2-((4-tosylpiperazin-l-yl)methyl)biphenyl-4-yl)acetic acid (Compound 87B):

[0242] The compound was prepared using the Method described for 2-(2-((4-tosylpiperazin-l-yl)methyl)biphenyl-4-yl)acetic acid, using 4-chloro boronic acid. Compound 87B: ES/MS, m/z 499.3 (M+H); LC/MS (Method C) Rt = 3.27 min.

Example 88
Methyl 2-(4'-chloro-2-(thiomorpholindioxy-methyl)biphenyl-4-yl)acetate (Compound 88A) and 2-(4'-chloro-2-(thiomorpholindioxy-methyl)biphenyl-4-yl)acetic acid (Compound 88B).

[0243] The compound was prepared using the similar Method as described for 2-(4'-chloro-2-((4-tosylpiperazin-1-yl)methyl)biphenyl-4-yl)acetic acid starting with methyl 2-(4-hydroxy-3-(S,S-dioxo thiomorpholine-methyl)phenyl)acetate. Compound 88B: ES/MS, m/z 394.1 (M+H); LC/MS: (Method A) Rt = 3.31 min.

Example 89

2-(4-(phenylethynyl)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 89B)

Step A: tert-butyl

4-(5-(2-methoxy-2-oxoethyl)-2-(phenylethynyl)benzyl)piperazine-1-carboxylate (Compound 89A).

[0244] Palladium tetrakis (5 mg, 0.43 μmol), CuI (0.2 mg, 0.86 μmol), Et₃N (0.12 mL, 0.86 mmol), and phenyl acetylene (0.06 mL, 0.52 mmol) were added to a solution of tert-butyl 4-(5-(2-methoxy-2-oxoethyl)-2-(trifluoromethylsulfonyloxy)benzyl)piperazine-1-carboxylate (215 mg, 0.43 mmol) in DMF (1 mL) in a sealed tube. Argon gas was bubbled through the solution for 2 min. then the reaction vessel was sealed. The tube was heated to 110 ⁰C for overnight followed by addition of satd. Na₂HCO₃ (5 mL) after cooling. The aqueous was extracted with EtOAc (3 X 10 mL) and the combined organic was washed with H₂O (10 mL),
dried over Na₂SO₄, and concentrated to give crude (324 mg) as brown oil. A flash chromatography on silica gel (3:1, hexanes/EtOAc) afforded pure title material (65 mg, 33 %) as a light yellow oil.

![Chemical structure](image)

5 **Step B:** 2-(4-(phenylethynyl)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 89B).

[0245] The compound was prepared using a similar Method as described for
2-(2-((4-tosylpiperazin-1-yl)methyl)biphenyl-4-yl)acetic acid: ES/MS, m/z 489.3 (M+H); LC/MS (Method C) Rt = 3.19 min.

Example 90

2-(4-phenethyl-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 90).

![Chemical structure](image)

[0246] Palladium on carbon (5 % w/w, 0.1 mg, 0.11 µmol) was added to solution of
2-(4-(phenylethynyl)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (5.4 mg, 1.1 µmol) in acetic acid (1 mL). The reaction vessel was attached to a balloon (H₂) and stirred for 2 h. The resulting suspension was filtered through CELITE and the filter cake was washed with MTBE (20 mL). The combined organic was concentrated to give crude product. HPLC purification afforded the pure product: ES/MS, m/z 493.3 (M+H); LC/MS (Method C) Rt= 3.35 min.
Examples 91-92

Scheme 3

Example 91

2-(4-(4-chlorobenzyloxy)-3-((3-oxo-4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 91D):

Step A: Methyl 2-(4-hydroxy-3-((3-oxopiperazin-1-yl)methyl)phenyl)acetate (Compound 91A).

Para formaldehyde (89 mg, 2.95 mmol) and piperazin-2-one (500 mg, 2.68 mmol) were added to a stirring solution of 4-hydroxy methyl phenyl acetate (408 mg, 2.68 mmol) in z-PrOH (10 mL). The resulting mixture was refluxed over night, cooled, then concentrated. The residue was redissolved in EtOAc (20 mL) and organic layer was washed with H₂O (20 mL), dried over Na₂SO₄, and concentrated to give crude product. The compound was carried to the next step without purification.
Step B: Methyl 2-(4-(4-chlorobenzyloxy)-3-(3-oxopiperazin-1-yl)methyl)phenylacetate (Compound 91B).

[0248] Solid $\text{K}_2\text{CO}_3$ (567 mg, 4.1 mmol) and 4-chlorobenzyl bromide (463 mg, 2.26 mmol) were added to a stirring solution of methyl 2-(4-hydroxy-3-(3-oxopiperazin-1-yl)methyl)phenylacetate (570 mg, 2.05 mmol) in DMF (10 mL) at RT. The mixture was stirred over night then diluted with EtOAc (20 mL). The organic was washed with $\text{H}_2\text{O}$ (20 mL), dried over $\text{Na}_2\text{SO}_4$, and concentrated to give the desired crude material (601 mg) as a yellow oil. The compound was carried to the next step without purification.

Step C: Methyl 2-(4-(4-chlorobenzyloxy)-3-(3-oxo-4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)phenylacetate (Compound 91C)

[0249] Solid $\text{K}_2\text{CO}_3$ (192 mg, 1.39 mmol), CuI (13 mg, 0.07 mmol), ethyl diamine (0.005 mL, 0.07 mmol), and 4-trifluoromethyl iodobenzene (0.122 mL, 0.834 mmol) were added to a stirring solution of methyl 2-(4-(4-chlorobenzyloxy)-3-(3-oxopiperazin-1-yl)methyl)phenylacetate (280 mg, 0.695 mmol) in dioxane (2 mL). The mixture was degassed (argon gas) and the reaction vessel was
sealed, and then heated to 110 °C for overnight. After cooling, the suspension was filtered through a plug of silica gel and the filter cake was washed with EtOAc (40 mL). The combined organic was concentrated to give crude product that was carried to next step without further purification.

Step D:
2-(4-(4-chlorobenzyloxy)-3-((3-oxo-4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 91D)

[0250] The compound was prepared by using the similar Method as Step D of the method to make 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. ES/MS, m/z 533.3 (M+H); LC/MS (Method C) Rt = 3.35 min.

Example 92
Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(phenylsulfonyl)piperidin-1-yl)methyl)phenyl)acetate (Compound 92A) and
2-(4-(4-chlorobenzyloxy)-3-((4-(phenylsulfonyl)piperidin-1-yl)methyl)phenyl)acetic acid (Compound 92B).
The compound was prepared using the similar Method described for 2-(4-(4-chlorobezzyloxy)-3-((3-oxo-4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)phenyl)acetic acid except for using 4-(phenylsulfonyl)piperidine. **Compound 92B:** ES/MS, m/z 514.1 (M+H); LC/MS (Method C) R<sub>t</sub> = 2.58 min.

Example 93

2-(3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 93)

Scheme 4

---

DIEA (0.61 mL, 3.51 mmol) and 1-tosylpiperazine (420 mg, 1.75 mmol) were added to a stirring solution of methyl 2-(-3(-bromo methyl) phenyl) acetate (300 mg, 1.17 mmol) in CH<sub>3</sub>CN (10 mL) at 50 °C. The mixture was stirred over night, cooled, and then quenched with H<sub>2</sub>O (10 mL). The aqueous was extracted with EtOAc (3 X 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give crude ester (695 mg) as yellow oil. A flash chromatography on silica gel (3:1, hexanes/EtOAc) afforded pure ester (178 mg, 37%) which was hydrolyzed using NaOH in MeOH:water to give crude acid. HPLC purification afforded pure product: ES/MS, m/z 389.1 (M+H); LC/MS: (Method A) R<sub>t</sub> = 2.317 min.

Examples 94-96

Scheme 5
Example 94

2-(4-hydroxy-3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 94B)

Step A: Methyl 2-(4-hydroxy-3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 94A).

[0253] Phenyl boronic acid (188 mg, 1.54 mmol) and 1-tosylpiperazine (371 mg, 1.54 mmol) was added to a stirring solution of methyl 2-(3-formyl-4-hydroxyphenyl)acetate (300 mg, 1.54 mmol) in dioxane (10 mL) at 90°C. After stirring for 16 h, the reaction mixture was
cooled then quenched with \( H_2O \) (10 mL) and the aqueous was extracted with \( CH_2Cl_2 \) (3 X 10 mL). The combined organic was dried over \( Na_2SO_4 \) and concentrated to give crude ester (1.3 g) as yellow solid. The flash chromatography on silica gel (3:1, hexanes/EtOAc) afforded the desired material (567 mg, 74%) as a white solid.

**Step B:** 2-(4-hydroxy-3-(phenyl(4-tosylpipеразин-1-yl)methyl)phenyl)acetic acid (Compound 94B)

[0254] Solid LiOH (161 mg, 3.84 mmol) was added to a stirring solution of Methyl 2-(4-hydroxy-3-(phenyl(4-tosylpipеразин-1-yl)methyl)phenyl)acetate (190 mg, 0.384 mmol) in THF/MeOH/H\(_2\)O (5 mL, 3:1:1) at RT. After stirring over night the resulting mixture was quenched with 1 N HCl (<pH 1). The aqueous was extracted with EtOAc (3 x 20 mL), dried over \( Na_2SO_4 \), and concentrated to give crude acid (85 mg) as a brown oil. HPLC purification afforded pure Compound 94B: ES/MS m/z 481.2 (M+H); LC/MS: (Method A) Rt = 3.43 min.

Example 95

Methyl 2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(p-tolyl)methyl)-4-hydroxyphenyl)acetate (Compound 95A) and 2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(p-tolyl)methyl)-4-hydroxyphenyl)acetic acid (Compound 95B).
The compound was prepared using the Method described for 2-(4-hydroxy-3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with 4-methyl phenyl boronic acid. **Compound 95B:** ES/MS m/z 499.2 (M+H); LC/MS (Method B) Rt = 3.535 min.

Example 96

**Methyl**

2-(3-((4-chlorophenyl)(4-(4-fluorophenylsulfonyl)piperazin-1-yl)methyl)-4-hydroxyphenyl)acetic acid (Compound 96A) and 2-(3-((4-chlorophenyl)(4-(4-fluorophenylsulfonyl)piperazin-1-yl)methyl)-4-hydroxyphenyl)acetic acid (Compound 96B):

The compound was prepared using the Method described for 2-(4-hydroxy-3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with 4-chloro phenyl boronic acid. **Compound 96B:** ES/MS m/z 519.1 (M+H); LC/MS (Method B) Rt = 3.767 min.

Example 97
2-(3-((2-hydroxyphenyl)(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 97B).

**Step A:** 2-((3-(hydroxymethyl)phenyl)(4-tosylpiperazin-1-yl)methyl)phenol.

[0257] 3-(hydroxymethyl)benzaldehyde (0.35 mL, 3.29 mmol) and 1-tosylpiperazine (790 mg, 3.29 mmol) were added to a stirring solution of 2-phenol boronic acid in dioxane (30 mL) at 90 °C. After stirring for 16h, the reaction mixture was cooled then quenched with H₂O (40 mL) and the aqueous was extracted with CH₂Cl₂ (3 X 20 mL). The combined organic was dried over Na₂SO₄ and concentrated to give crude material (1.53 g) that was used in the subsequent step with no further purification.

**Step B:** 2-(3-((2-hydroxyphenyl)(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid

[0258] 2-((3-(hydroxymethyl)phenyl)(4-tosylpiperazin-1-yl)methyl)phenol was converted to the benzyl chloride using SOCl₂ followed by treatment with KCN. A hydrolysis of benzyl nitrile afforded the desired material, using the Method of Biorg. Med. Chem. Letters., 2005, 15, 5247-5252, which was then purified with HPLC: ES/MS m/z 481.2 (M+H); LC/MS (Method B) Rt= 3.33 min.

Example 97

2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(p-tolyl)methyl)phenyl)acetic acid (Compound 97).
DIEA (0.346 mL, 1.99 mmol), Tf₂O (0.335 mL, 1.99 mmol), and DMAP (16 mg, 0.132) was added to a stirring solution of methyl 2-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(p-tolyl)methyl)-4-hydroxyphenyl)acetate (700 mg, 1.32 mmol) in CH₂Cl₂ (10 mL) at RT. After stirring for 1.5 h, the resulting mixture was quenched with satd. NaHCO₃ (10 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give crude triflate (1.07 g) as brown oil. A chromatography on silica gel (3:1, hexanes/EtOAc) afforded triflate (760 mg, 86%) as white solid. The triflate (100 mg, 0.155 mmol) was dissolved in DMF (2 mL). To this solution formic acid (15 µL, 0.434 mmol), Et₃N (91 µL, 0.65 mmol), PdCl₂(PPh₃)₂, and dppp (10 mg, 0.023 mmol) was added. The resulting suspension was degassed under Ar, sealed, and heated to 90 °C for 17 h. After cooling to RT, the reaction mixture was poured into H₂O (10 mL) and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with IN HCl (15 mL), brine (15 mL), dried over Na₂SO₄, and concentrated to give the crude deoxygenated product (262 mg). A saponification of the methyl ester as described for 2-(4-hydroxy-3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, led to the desired material. ES/MS, m/z 483.2 (M+H); LC/MS (Method B) Rt = 3.33 min.

Example 98

Methyl 2-((4-chlorophenyl)(4-(4-fluorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 98A) and 2-((4-chlorophenyl)(4-(4-fluorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 98B).
The compound was prepared using the Method described for 2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(p-tolyl)methyl)phenyl)acetic acid, starting with methyl 2-(3-((4-chlorophenyl)(4-(4-fluorophenylsulfonyl)piperazin-1-yl)methyl)-4-hydroxyphenyl)acetate. Compound 98B: ES/MS, m/z 503.1 (M+H); LC/MS (Method B) Rt = 3.33 min.

Example 99

R-2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid and S-2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid (Compound 99B and C)

Scheme 6

Step A: Methyl 2-(3-(chloro(phenyl)methyl)phenyl)acetate (Compound 99A)
Solid NaBH$_4$ (505 mg, 13.3 mmol) was added to a solution of 2-(3-benzoylphenyl)acetic acid (850 mg, 3.34 mmol) in MeOH (30 mL) at 0°C. The resulting solution was quenched with NaHCO$_3$ (30 mL) after 5 min. and the aqueous was extracted with EtOAc (3 X 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na$_2$SO$_4$, and concentrated. The residue was redissolved in CH$_2$Cl$_2$ (20 mL) and SOCl$_2$ (1.2 mL, 16.7 mmol) was added. The resulting mixture was concentrated after stirring overnight to give crude chloride. A flash chromatography (3:1, hexanes/EtOAc) afforded pure material.

Step B: R-2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid and S-2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid (Compound 99B and C)

Step B:

I-(4-fluorophenylsulfonyl)piperazine (320 mg, 1.31 mmol), DIEA (0.57 mL, 3.28 mmol), and NaI (16 mg, 0.109 mmol) were added to a stirring solution of methyl 2-(3-(chloro(phenyl)methyl)phenyl)acetate in CH$_3$CN (15 mL). The resulting suspension was warmed to 80°C and stirred overnight. After cooling reaction mixture was quenched with satd. NaHCO$_3$ (20 mL) and the aqueous was extracted with EtOAc (3 X 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na$_2$SO$_4$, and concentrated. The resulting ester was hydrolyzed using the similar Method as preparation of 2-(4-hydroxy-3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. HPLC purification afforded pure material. Both enantiomers were also separated by chiral HPLC (Chiralpak AD-H, 4.6 x 250 mm, 80% Heptanes: 20% IPA: 0.1% TFA, 40°C, 1.0 mL/min). 98B Rt = 14.479 min., 98 C Rt = 22.119 min. ES/MS, m/z 469.2 (M+H); LC/MS (Method B) Rt = 3.673 min.
Methyl 2-(3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 10OA) and 2-(3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 10OB)

The title compound(s) were prepared using the methodology described for 2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid starting with 1-(4-methylphenylsulfonyl)piperazine. Compound 10OB: $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.31 (IH, brs) 7.61 (2H, dd, $J = 0.9$, 8.1 Hz) 7.48 (2H, dd, $J = 0.7$, 7.7 Hz) 7.34 (2H, d, $J = 8.2$ Hz) 7.26-7.14 (6H, m) 7.05 (IH, dd, $J = 1.1$, 7.3 Hz) 4.28 (IH, s) 3.49 (2H, s) 2.88 (4H, brm) 2.44 (3H, s) 2.35 (4H, brm); ES/MS, m/z 465.2 (M+H); LC/MS (Method B) $R_t$ = 3.750 min.

Example 101

Methyl 2-(3-(phenyl(4-(phenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 101A) and 2-(3-(phenyl(4-(phenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 101B):

The title compound(s) were prepared using the methodology described for 2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid starting with (phenylsulfonyl)piperazine. Compound 101B: ES/MS, m/z 451.2 (M+H); LC/MS (Method B) $R_t$ = 3.594 min.

Example 102
Methyl 2-((3-((4-(methylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetate (Compound 102A) and 2-((3-((4-(methylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid (Compound 102B)

The title compound(s) were prepared using the methodology described for
2-((3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid starting with (methylsulfonyl)piperazine. Compound 102B: ES/MS, m/z 389.1 (M+H); LC/MS (Method B) R_t = 2.686 min.

Example 103

2-((3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)propanoic acid (Compound 103A) and

2-((3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)propanoic acid (Compound 103B)

The compound was prepared via a similar Method as preparation of
2-((3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(phenyl)methyl)phenyl)acetic acid starting from s-ketoprofen: Compound 103B: ES/MS, m/z 483.2 (M+H); LC/MS (Method B) R_t = 3.9 min.

Example 104
2-(3-chloro-5-(phenyl(4-(phenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 104E).

Scheme 7

Step A: (3-bromo-5-chlorophenyl)(phenyl)methanol (Compound 104A)

[0267] 1.0 M (in THF) PhMgBr (4.1 mL, 4.1 mmol) was slowly added to a stirring solution of 3-bromo-5-chloro benzaldehyde (600 mg, 2.73 mmol) in THF (20 mL) at 0 °C. The resulting mixture was stirred for 1.5h then quenched with satd. NH₄Cl (20 mL) and the aqueous was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give crude alcohol (1.02 g). A flash chromatography on silica gel (3:1, hexanes/EtOAc) afforded pure material (512 mg, 63%).
Step B: f-Butyl 4-((3-bromo-5-chlorophenyl)(phenyl)methyl)piperazine-1-carboxylate
(Compound 104B).

\[ \text{SOCl}_2 (0.61 \text{ mL}, 8.4 \text{ mmol}) \text{ was added to a stirring solution of} \]
(3-bromo-5-chlorophenyl)(phenyl)methanol (500 mg, 1.68 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at RT. After stirring for 4 h solution was concentrated. The residue was redissolved in CH\(_3\)CN (15 mL) and DIEA (0.878 mL, 5.04 mmol), NaI (25 mg, 0.168 mmol), and /-butyl piperazine-1-carboxylate (470 mg, 2.52 mmol) were added. The resulting mixture was warmed to 80 °C and stirred over night. After cooling to rt satd. Na\(_2\)CO\(_3\) (20 mL) was added and the aqueous was extracted with EtOAc (3 X 15 mL). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated. A flash chromatography on silica gel (3:1, hexanes/EtOAc) afforded pure material.

Step C: tert-butyl

4-((3-chloro-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)(phenyl)methyl)piperazine-1-carboxylate (Compound 104C)

AcOK (160 mg, 1.62 mmol) and pinacolborane (165 mg, 0.65 mmol) were added to a solution of f-Butyl 4-((3-bromo-5-chlorophenyl)(phenyl)methyl)piperazine-1-carboxylate. (250 mg, 0.54 mmol) in dioxane (5 mL). The resulting solution was degassed using argon followed by addition of PdCl\(_2\)(dppf) (20 mg, 0.027 mmol) and dppf (15 mg, 0.027 mmol). The reaction mixture was warmed to 80 °C for 4 h, cooled, and then concentrated. The residue was dissolved in hexanes and activated charcoal was added then filtered through
CELITE. The combined organic was concentrated to give crude material. A flash chromatography on silica gel (9:1, hexanes/EtOAc) afforded pure material (189 mg, 69%).

**Step D:** f-Butyl

4-((3-chloro-5-(2-ethoxy-2-oxoethyl)phenyl)(phenyl)methyl)piperazine-1-carboxylate (Compound 104D).

![Chemical Structure](image)

**[0270]** Solid K$_2$CO$_3$ (160 mg, 1.16 mmol) and 1-bromoethyl ester (0.039 mL, 0.351 mmol) were added to a solution of tert-butyl

4-((3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(phenyl)methyl)piperazin e-1-carboxylate (180 mg, 0.351 mmol) in toluene (5 mL). The resulting solution was degassed using argon followed by addition of Pd(PPh$_3$)$_4$ (13 mg, 0.011 mmol) and Cu$_2$O (1.5 mg, 0.011 mmol). The reaction mixture was warmed to 80 °C for 16 h, cooled, and then concentrated to give crude ester (80 mg). A flash chromatography on silica gel (3:1, hexanes/EtOAc) afforded pure material (36 mg, 22%).

**Step E:** 2-(3-chloro-5-(phenyl(4-(phenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 104E)

![Chemical Structure](image)

**[0271]** The compound was prepared via a similar Method as described for the preparation of 2-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid: ES/MS, m/z 485.2 (M+H); LC/MS (Method B) Rt = 3.9 min.
Example 105

Methyl 2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(pyridin-3-yl)methyl)-4-hydroxyphenyl)acetate (Compound 105A) and 2-(3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)(pyridin-3-yl)methyl)-4-hydroxyphenyl)acetic acid (Compound 105B)

![Chemical Structure](image)

[0272] The compound was prepared using the Method described for 2-(4-hydroxy-3-(phenyl(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with 3-pyridyl boronic acid and 4-fluorophenyl sulfonyl chloride. Compound 105B: LC/MS Rt = 2.61 min. (Method A); MS (m/z) 486.1(M^+ + H).

Example 106

2-(4-(4-chlorobenzyloxy)-3-(4-tosylpiperazine-1-carbonyl)phenyl)acetic acid (Compound 106B)

![Chemical Structure](image)

Scheme 8
Step A: 2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzoic acid (Compound 106A)

[0273] To a suspension of methyl 4-hydroxyphenyl acetate (11.6g, 70 mmol, 1.0 equivalent), magnesium chloride (10g, 105 mmol, 1.5 equivalents) and triethyl amine (36.6 mL, 265.5 mmol) in AcCN (200 mL) was added powdered paraformaldehyde (15.3g, 472.5 mmol, 7 equivalents). The resulting white suspension was then transferred to an oil-bath, a reflux condenser attached and refluxed at 82 °C for 2 hours. The reaction mixture was cooled to room temperature and neutralized with 1.0M hydrochloric acid (to pH 4) and then extracted with EtOAc (400 mL). The extract was dried with NaSO₄ and concentrated to give an aldehyde intermediate methyl 2-(3-formyl-4-hydroxyphenyl)acetate (6.2g). LC/MS: (method A) MS m/z 195.10 (M+H), (Rt = 3.47 min).

[0274] The crude aldehyde (3g, 9.43mmol) was placed in a 500-mL reaction flask and dissolved in acetone (40mL) then transferred to oil bath at 40 °C. A hot solution of potassium permanganate (2.61g, 16.5mmol) in acetone-L^O (60mL, 5:1) was then added and stirred at 40 °C overnight. An acid base workup gave 3.06g of crude product, 2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzoic acid. LC/MS method A, MS m/z 333.0 (M+H), Rt = 3.58 min.

Step B: 2-(4-(4-chlorobenzyloxy)-3-(4-tosylpiperazine-1-carbonyl)phenyl)acetic acid (Compound 106B)
2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzoic acid (100mg, 0.299mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HATU, 113.5mg, 0.299mmol) and N,N-diisopropylethylamine (0.067mL, 0.389mmol) were dissolved in AcCN (2mL) in a reaction vial and stirred for 10 minutes. 1-(tosyl)piperazine (71.8mg, 0.299mmol) was then added and the resulting solution stirred for 10h. The product precipitated out of solution and was filtered and washed to give 110mg of pure ester, methyl 2-(4-(4-chlorobenzyloxy)-3-(4-tosylpiperazine-1-carbonyl)phenyl)acetate. LC/MS: (Method A), MS m/z 557.1 (M+H), (Rt = 4.02 min).

The ester (100mg, 0.18mmol) and lithium hydroxide (100mg, excess) were suspended in MeOH-H₂O mixture (2:1) and stirred for 8 hours. The mixture was then diluted with EtOAc (60mL), washed with 1.0M HCl (50mL) and with brine. The solution was then dried and concentrated to give product (109.7mg). LC/MS: (Method A), MS m/z 543.1 (M+H), (Rt = 3.71 min).

Example 107

Methyl 2-(4-(4-chlorobenzyloxy)-3-(4-(methylsulfonyl)piperazine-1-carbonyl)phenyl)acetate (Compound 107A) and 2-(4-(4-chlorobenzyloxy)-3-(4-(methylsulfonyl)piperazine-1-carbonyl)phenyl)acetic acid (Compound 107B)
The title material(s) were prepared from methyl 2-(4-(4-chlorobenzyloxy)-3-formylphenyl)acetate and 1-(methylsulfonyl)piperazine according to Method described for 2-(4-(4-chlorobenzyloxy)-3-(4-tosylpiperazine-1-carbonyl)phenyl)acetic acid. **Compound 107B:** LC/MS: (Method A), MS m/z 467.1 (M+H), (Rt = 3.19 min).

Example 108

Methyl 2-(4-(4-chlorobenzyloxy)-3-(S,S-dioxo thiomorpholine-4-carbonyl)phenyl) acetate (**Compound 108A**) and 2-(4-(4-chlorobenzyloxy)-3-(S,S-dioxo thiomorpholine-4-carbonyl)phenyl) acetic acid (**Compound 108B**)

The compound(s) were prepared from methyl 2-(4-(4-chlorobenzyloxy)-3-formylphenyl)acetate and thiomorpholine dioxide according to Method described for 2-(4-(4-chlorobenzyloxy)-3-(4-tosylpiperazine-1-carbonyl)phenyl)acetic acid. LC/MS: (Method A), MS m/z 438.1 (M+H), (Rt = 3.1 min).

Example 109-1 10

**Scheme 9**
Example 109

(S, Z)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxo-3,4,7,8-tetrahydroazocin-l(2H)-yl)methyl)phenyl)acetic acid (Compound 109D)

**Step A:** methyl 2-(3-((but-3-enylamino)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 109A)
To a vigorously stirred suspension of but-3-en-l-amine hydrochloride (202mg, 1.89mmol) in brine (3mL) and CH₂Cl₂ (3mL) was added 2M NaOH to pH=14. The organic layer was separated, dried (Na₂SO₄) and added directly to a flask, under inert atmosphere, containing methyl 2-(4-(4-chlorobenzyloxy)-3-formylphenyl)acetate (200mg, 0.63mmol). In a separate flask, sodium cyanoborohydride (40mg, 0.63mmol) was carefully added in one portion to a solution of zinc chloride (315µL, IM) in ImL of MeOH as the mixture resulted in effervescence. The mixture was allowed to stir for 10 min. then the whole was added via cannular to the flask containing the stirred solution of 2-(4-(4-chlorobenzyloxy)-3-formylphenyl)acetate and but-3-en-l-amine. The mixture was stirred for 10 min. then quenched with NaHCO₃ (10mL), then extracted with CH₂Cl₂ (2x10mL), dried (Na₂SO₄) and concentrated in vacuo to give methyl 2-(3-((but-3-enylamino)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (300mg) as colorless oil. LC/MS (Rt =2.35 min., (Method A), m/z 374 M+H)

**Step B:** (S)-methyl
2-(3-((N-(but-3-enyl)-2-(?r-butoxycarbonylamino)pent-4-enamido)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 109B)

To a solution of (S)-2-(ter?-butoxycarbonylamino)pent-4-enoic acid (409mg, 2.67mmol), methyl 2-(3-((but-3-enylamino)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Ig, 2.67mmol) and Hunigs base (0.98mL, 5.34mmol) in DMF (10mL) was added HATU
(Ig, 2.67mmol). The reaction was stirred for 1h then poured into 200mL of water and extracted with EtOAc (3x20mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Column chromatography (silica gel, 20-40% EtOAc / hexane), furnished (S)-methyl 2-((N-(but-3-enyl)-2-(fer^-butoxycarbonylamino)pent-4-enamido)methyl)-4-(4-chlorobenz yloxy)phenyl)acetate as a colorless oil (0.8g, 1.4mmol, 52%); LC/MS (Rt=4.35 min., (Method A), 571 M+H).

**Step C:** (S,Z)-methyl 2-(3-((3-(tert-butoxycarbonylamino)-2-oxo-3,4,7,8-tetrahydroazocin-l(2H)-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 109C)

A solution of (S)-methyl 2-((N-(but-3-enyl)-2-(3-tert-butoxycarbonylamino)pent-4-enamido)methyl)-4-(4-chlorobenz yloxy)phenyl)acetate (100mg, 0.175mmol) and Grubb's first generation catalyst (34mg, 0.032mmol) in CH$_2$Cl$_2$ (35mL) was heated at 50°C for 8h. The mixture was concentrated and subjected to column chromatography (silica gel, 20-40% EtOAc / hexane) to furnish (S, Z)-methyl 2-((3-((3-fer?-butoxycarbonylamino)-2-oxo-3,4,7,8-tetrahydroazocin-l(2H)-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate as a colorless oil (70mg, 1.4 mmol, 74%); $^1$H NMR (300MHz, CDCl$_3$) 7.4-7.3 (m, 4H), 7.15-7.1 (m., 2H), 6.85 (d, IH), 5.9 (d, IH), 5.7 (m, IH), 5.4(m, IH), 5.1(s, 2H), 4.9(d, IH), 4.8(m,IH), 4.3 (d, IH), 3.8(m, IH), 3.7 (s, 3H), 3.5 (s, 2H), 3.2 (m, IH), 2.8 (m, IH), 2.4 (m, 3H), 1.45 (s, 9H).

**Step D:**

(S,Z)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxo-3,4,7,8-tetrahydro azocin-l(2H)-yl)methyl)phenyl)acetic acid (Compound 109D)
To a solution of (S)-methyl 2-(3-((3-(tert-butoxycarbonylamino)-2-oxoazocan-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (100mg, 0.183mmol) in CH₂Cl₂ (2mL) was added TFA (1mL). The solution was stirred for 1h then neutralized (sat. NaHCO₃), extracted with CH₂Cl₂ (2x1OmL), dried (Na₂SO₄) and concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (2mL) to which was added triethylamine (63µL, 0.44mmol) and p-toluene sulfonyl chloride (52mg, 0.27mmol). The solution was stirred for 2h and concentrated in vacuo. The residue was dissolved in THF (3mL) and H₂O (2mL) to which was added LiOH (75mg, 1.76mmol). The solution was vigorously stirred for 1h then acidified with HCl (2M), extracted with EtOAc (3X1OmL), dried (Na₂SO₄) and concentrated in vacuo. The crude residue was subjected to preparative HPLC purification followed by lyophilization of the fractions to give (S,Z)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)methyl)phenyl)acetic acid as a colorless solid, (75mg, 0.13mmol, 70%); H NMR (300MHz, CDCl₃) 12.2(br s, IH), 7.9 (d, IH), 7.7 (d., 2H), 7.45(s,4H), 7.3 (d, 2H), 7.1 (dd, IH), 6.95(d, IH), 6.85(d,IH), 5.5 (m, IH), 5.35(m, IH), 5.1(s,2H), 4.5-4.4 (m, IH), 4.35(d, IH), 4.1 (d, IH), 3.55 (m, 2H), 3.4 (s, 2H), 3.2-3.1 (m, IH), 2.3 (m, 6H).

Example 110

(R)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazocan-1-yl)methyl)phenyl)acetic acid (Compound HOA) and (S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazocan-1-yl)methyl)phenyl)acetic acid (Compound HOB)
Step A: (S)-methyl

2-(3-((3-(tert-butoxycarbonylamino)-2-oxoazocan-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 110AA)

[0283] A solution of (S,Z)-methyl 2-((3-(tert-butoxycarbonylamino)-2,3,4,7,8-pentahydroazocin-1(2H)-yl)methyl)-4-(4-chlorobenzyloxy)phenyl acetate (50 mg, 0.092 mmol) and RhCl(PPh₃)₃ (16.6 mg, 0.018 mmol) in benzene (2 mL) under an atmosphere of hydrogen was stirred for 48 h. The mixture was concentrated and subjected to column chromatography (silica gel, 20-50% EtOAc / hexane) to furnish (S)-methyl 2-(3-((3-(tert-butoxycarbonylamino)-2-oxoazocan-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate as a colorless oil (45 mg, 0.082 mmol, 89%); ¹H NMR (300 MHz, d₆-DMSO) 7.4-7.3 (m, 4H), 7.15-7.10 (m, 2H), 6.85 (d, IH), 5.7 (d, IH), 5.1 (d, IH), 5.0 (s, 2H), 4.7 (m, IH), 4.2 (d, IH), 3.7 (m, IH), 3.65 (s, 3H), 3.55 (s, 2H), 3.2 (m, IH), 1.7-1.5 (m, 6H), 1.4 (m, 10H).

Step B:

(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxazocan-1-yl)methyl)phenyl)acetic acid (Compound 110AB)
To a solution of (S)-methyl 2-((3-(fe^butoxycarbonylamino)-2-oxoazocan-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (100 mg, 0.18 mmol) in CH₂Cl₂ (2 mL) was added TFA (1 mL). The solution was stirred for 1 h then neutralized (sat. NaHCO₃), extracted with CH₂Cl₂ (2x1 mL), dried (Na₂SO₄) and concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (2 mL) to which was added triethylamine (63 µL, 0.44 mmol) and p-toluene sulfonyl chloride (52 mg, 0.27 mmol). The solution was stirred for 2 h and concentrated in vacuo. The residue was dissolved in THF (3 mL) and H₂O (2 mL) to which was added LiOH (75 mg, 1.76 mmol). The solution was vigorously stirred for 1 h then acidified with HCl (2 M), extracted with EtOAc (3 X 10 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude residue was subjected to preparative HPLC purification followed by lyophilization of the fractions to give (S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazocan-1-yl)methyl)phenyl)acetic acid as a colorless solid, (40 mg, 0.068 mmol, 40%); ¹H NMR (300 MHz, d₆-DMSO) 12.3 (br s, 1H), 7.85 (d, 1H), 7.7 (d., 2H), 7.45 (s, 4H), 7.3 (d., 2H), 7.0 (m, 2H), 5.1 (s, 2H), 4.5 (d, 1H), 4.4 (m, 1H), 4.2 (d, 1H), 3.55 (m, 2H), 3.1-3.0 (m, 1H), 2.3 (s, 3H), 1.5-1.0 (m, 8H).

Example 111

Methyl

(R,Z)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)methyl)phenyl)acetate (Compound 111) and (R,Z)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)methyl)phenyl)acetic acid (Compound 111)

The title materials were obtained using the Method described for (S,Z)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxo-3,4,7,8-tetrahydroazocin-1(2H)-yl)methyl)phenyl)acetic acid, starting with (R)-2-(terZ-butoxycarbonylamino)pent-4-enoic acid. Compound HIB: ¹H NMR (300 MHz, CDC13) 12.2 (br s, 1H), 7.9 (d, 1H), 7.7 (d., 2H), 7.45 (s, 4H), 7.3 (d, 2H), 7.1 (dd, 1H), 6.95 (d, 1H), 6.85 (d, 1H), 5.5 (m, 1H), 5.35 (m, 1H), 5.1 (s, 2H), 4.5-4.4 (m, 1H), 4.35 (d, 1H), 4.1 (d, 1H), 3.55 (m, 2H), 3.4 (s, 2H), 3.2-3.1 (m, 1H), 2.3 (m, 6H).
Example 112

Methyl
(R)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazocan-1-yl)methyl) phenyl)acetate (Compound 112A) and
(R)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazocan-1-yl)methyl) phenyl)acetic acid (Compound 112B)

[0286] The title material was obtained using the Method described for
(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazocan-1-yl)methyl) phenyl)acetic acid, starting with (R)-2-(tert-butoxycarbonylamino)pent-4-enoic acid.

Compound 112B: 1H NMR (300MHz, d6-DMSO) 12.3 (br s, 1H), 7.85 (d, IH), 7.7 (d, 2H), 7.45(s,4H), 7.3 (d, 2H), 7.0 (m, 2H), 5.1(s,2H), 4.5(d,IH), 4.4 (m, IH), 4.2(d, IH), 3.55 (m, 2H), 3.1-3.0 (m, IH), 2.3 (s, 3H), 1.5-1.0(m, 8H).

Example 113

(R)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazepan-1-yl)methyl) phenyl)acetic acid (Compound 113A) and
(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazepan-1-yl)methyl) phenyl)acetic acid (Compound 113B)

Scheme 10
**Step A**: (S)-2-(tert-butoxycarbonylamino)-6-(2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzylamino) hexanoic acid (Compound 113A)

To a solution of methyl 2-(4-(4-chlorobenzyloxy)-3-formylphenyl) acetate (250mg, 0.78mmol) in methanol (3mL) was added Boc-L-Lysine (386mg, 1.57mmol). The mixture was stirred for 20 min. In a separate flask, zinc chloride (400µL, IM) was added to 3mL of methanol followed by sodium cyanoborohydride (50.2mg, 0.78mmol) carefully added in one portion as the mixture resulted in effervescence. The mixture was allowed to stir for 10 min. then the whole was added via cannular to the flask containing the stirred solution of methyl 2-(4-(4-chlorobenzyloxy)-3-formylphenyl) acetate and Boc-L-Lysine. The reaction was stirred for 10 min. then quenched with brine (5mL), extracted with EtOAc (3x1 5mL), dried (Na₂SO₄), and concentrated *in vacuo*. The crude residue was passed through a plug of silica (CH₂Cl₂/MeOH 10%-20%) to give (S)-2-(tert-butoxycarbonylamino)-6-(2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzylamino) hexanoic acid as colorless oil (250mg, 0.45mmol, 58%). LC/MS (Rt= 2.510 min., (Method A), m/z 549 M+H).

**Step B**: (S)-methyl 2-(3-((3-(fert-butoxycarbonylamino)-2-oxazepan-l-yl)methyl)-4-(4-chlorobenzyloxy)phenylacetate (Compound 113B)
To a solution of (S)-2-(tert-butoxycarbonylamino)-6-(2-(methoxy-2-oxoethyl)benzylamino) hexanoic acid (250 mg, 0.45 mmol) and triethylamine (0.2 mL, 1.3 mmol) in DMF (25 mL) was added HOBT (73.7 mg, 0.55 mmol) and 1-[3-(dimethylamino)propoyl]-3-ethylcarbodiimide hydrochloride (104 mg, 0.546 mmol). The solution was stirred for 18 h then concentrated in vacuo. The residue was diluted with EtOAc (20 mL) and washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was passed through a plug of silica (EtOAc) to give (S)-methyl 2-(3-((3-tert-butoxycarbonylamino)-2-oxoazepan-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl acetate as a colorless oil (150 mg, 0.28 mmol, 62%). LC/MS Rt = 4.23 min., (Method A), MS m/z 531 M+H).

**Step C:**

(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazepan-1-yl)methyl)phenyl)acetic acid (Compound 113C)

To a solution of (S)-methyl 2-(3-((3-tert-butoxycarbonylamino)-2-oxoazepan-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl acetate (150 mg, 0.28 mmol) in CH$_2$Cl$_2$ (2 mL) was added TFA (1 mL). The solution was stirred for 1 h then neutralized (sat. NaHCO$_3$), extracted with CH$_2$Cl$_2$ (2 x 10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was dissolved in pyridine (1.5 mL) to which was added p-toluene sulfonyl chloride (50 mg, 0.27 mmol). The solution was stirred for 18 h and concentrated in vacuo. The residue was dissolved in THF (3 mL) and H$_2$O (2 mL) to which was added LiOH (55 mg, 1.36 mmol). The solution was vigorously stirred for 24 h then acidified with HCl (2 M), extracted with EtOAc (3 x 10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude residue was subjected to preparative HPLC purification followed by lyophilization of the fractions to give (S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazepan-1-yl)methyl)phenyl)acetic acid (Compound 113C).
phenyl)acetic acid as a colorless solid, (20mg, 0.035mmol, 12.5%); $^1$H NMR (300MHz, d$_6$-DMSO) 7.7 (d, 2H), 7.55 (d., IH), 7.35(d,2H), 7.2 (t, IH), 7.15 (d, IH), 7.05(s, IH), 6.85(d,IH), 4.6(d, IH), 4.25 (d, IH), 4.1 (m, IH), 3.5(s, 2H), 3.4-3.3 (m, IH), 3.2-3.1 (m, IH), 2.4 (s, 3H), 1.7-1.4(m, 5H), 1.3-1.0 (m, IH).

5

(R)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazepan-1-yl)methyl)phenyl)acetic acid (Compound 113B)

[0290] The title material was obtained using Boc-R-lysine, following the Method described for

(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazepan-1-yl)methyl)phenyl)acetic acid. $^1$H NMR (300MHz, d$_6$-DMSO) 7.7 (d, 2H), 7.55 (d., IH), 7.35(d,2H), 7.2 (t, IH), 7.15 (d, IH), 7.05(s, IH), 6.85(d,IH), 4.6(d, IH), 4.25 (d, IH), 4.1 (m, IH), 3.5(s, 2H), 3.4-3.3 (m, IH), 3.2-3.1 (m, IH), 2.4 (s, 3H), 1.7-1.4(m, 5H), 1.3-1.0 (m, IH).

15 Example 114

(R)

(R)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazepan-1-yl)methyl)phenyl)acetic acid (Compound 114A) and

(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopyrrolidin-1-yl)methyl)phenyl)acetic acid (Compound 114B)

Scheme 11
Step A: (S)-methyl

2-(4-(4-chlorobenzoyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxypyrrolidin-1-yl)methyl)phenyl)acetate (Compound 114A)

[0291] A mixture of methyl 2-(3-(bromomethyl)-4-(4-chlorobenzoyloxy)phenyl)acetate (0.7g, 1.82mmol), (S)-tert-butyloxypyrrolidin-3-ylcarbamate (439mg, 2.19mmol) and Cs₂CO₃ (1.92g, 5.97mmol) in CH₃CN (3mL) and DMF (1mL) was heated to 55 oC for 12h.

[0292] The reaction was diluted with H₂O (20mL) and extracted with EtOAc (3X5mL), dried (Na₂SO₄) and concentrated in vacuo. A solution of the residue in CH₂Cl₂ (4mL) was treated with TFA (4mL) and stirred for 30 min. then concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (4mL) to which was added triethylamine (228µL, 1.64mmol) and p-toluene sulfonyl chloride (117mg, 0.61mmol). The reaction was stirred for 12h the diluted with H₂O (20mL) and extracted with CH₂Cl₂ (2x10mL). Column chromatography (silica gel, 1:1 EtOAc / hexane), furnished (S)-methyl
2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopyrrolidin-1-yl)methyl)phenyl)acetate as a colorless oil (191mg, 0.34mmol, 15%); \( ^1H \) NMR (300MHz, CDCl\(_3\)) 7.8 (d, 2H), 7.4-7.4 (m., 6H), 7.15 ( dd, IH), 7.05(m, IH), 6.85 (d, IH), 5.2(s, IH), 5.0(s, 2H), 4.5(m, 2H), 3.7-3.6(m, 4H), 3.3-3.1 (m, 2H), 2.6-2.5(m, IH), 2.4 (s, 3H), 2.0 (m, IH).

**Step B:**

(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopyrrolidin-1-yl)methyl)phenyl)acetic acid (114B)

![Chemical structure](image)

To a solution of (S)-methyl 2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopyrrolidin-1-yl)methyl)phenyl)acetate (190mg, 0.34mmol) in THF (1mL) was LiOH (1.0mL, IM). The reaction was stirred for 12h and the the THF was removed under vacuum. To the remaining aqueous mixture was added 5mL of HCl (IM) and the resulting precipitate was filtered and washed with H\(_2\)O (15mL) to give

(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopyrrolidin-1-yl)methyl)phenyl)acetic acid as a colorless solid (130mg, 0.24mmol, 70%); \( ^1H \) NMR (300MHz, d\(_6\)-DMSO) 8.1(d, IH), 7.75 (d, 2H), 7.5-7.4( m, 4H), 7.35 (d, 2H), 7.1(d, IH), 7.00(m,2H), 5.1(s, 2H), 4.3 (m, 2H), 4.0 (m, IH), 3.4(s, 2H), 3.0 (m, 2H), 2.3 (s, 3H), 2.0-1.9(m, IH), 1.5-1.4 (m, IH).

(R)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopyrrolidin-1-yl)methyl)phenyl)acetic acid (Compound 114A)

To the solution of the title material was made starting with (R)-fcr^-butyl 2-oxopyrrolidin-3-ylcarbamate, using the Method disclosed for

(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopyrrolidin-1-yl)methyl)phenyl)acetic acid.
yl)phenyl)acetic acid. $^1$H NMR (300MHz, d$_6$-DMSO) 8.1(d, 1H), 7.75 (d, 2H), 7.5-7.4( m, 4H), 7.35 (d, 2H), 7.1(d, 1H), 7.00(m,2H), 5.1(s, 2H), 4.3 (m, 2H), 4.0 (m, IH), 3.4(s, 2H), 3.0 (m, 2H), 2.3 (s, 3H), 2.0-1.9(m, IH), 1.5-1.4 (m, IH).

Example 115

(R) -2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopiperidin-l-yl)methyl)phenyl)acetic acid (Compound 115A) and (S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopiperidin-l-yl)methyl)phenyl)acetic acid (Compound 115B)

Scheme 12

Step A:

(S)-2-(tert-butoxycarbonylamino)-5-(2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzylamino)pentanoic acid (Compound 115AA)
Using identical Method as described for the preparation of (S)-2-(tert-butoxycarbonylamino)-6-(2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzylamino)hexanoic acid with the following reagents: 4-(4-chlorobenzyloxy)-3-formylphenyl (422mg, 1.32mmol); Boc-L-Ornithine (461mg, 1.98mmol); zinc chloride (622µL, 1M); sodium cyanoborohydride (83.1mg, 1.32mmol); to give (S)-2-(tert-butoxycarbonylamino)-5-(2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzylamino)pentanoic acid as colorless oil (680mg, 1.27mmol, 96%). LC/MS Rt = 2.613 min., (Method A), MS m/z 535 M+H.

**Step B:** (S)-methyl 2-(3-((3-(tert-butoxycarbonylamino)-2-oxopiperidin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 115AB)

Using identical Method as described for the preparation (S)-methyl 2-(3-((3-(tert-butoxycarbonylamino)-2-oxazepan-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate with the following reagents: (S)-2-(tert-butoxycarbonylamino)-5-(2-(4-chlorobenzyloxy)-5-(2-methoxy-2-oxoethyl)benzylamino)pentanoic acid (800mg, 1.49mmol); triethylamine (0.62mL, 4.48mmol); HOBT (242mg, 1.79mmol); 1-[3-(dimethylamino)propoyl]-3-ethylcarbodiimide hydrochloride (344mg, 1.79mmol); gives (S)-methyl
2-(3-((3-(tert-butoxycarbonylamino)-2-oxopiperidin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate as a colorless oil (380mg, 0.74mmol, 50%). LC/MS Rt = 4.081 min., (Method A), MS m/z 517 M+H.

5 Step C:
(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxoazepan-1-yl)methyl)phenyl)acetic acid (Compound 115B)

Using identical Method as described for the preparation of (S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopiperidin-1-yl)methyl)phenyl)acetic acid; (S)-methyl 2-(3-((3-(tert-butoxycarbonylamino)-2-oxopiperidin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (742mg, 1.43mmol); TFA (5mL); p-toluene sulfonyl chloride (330mg, 1.57mmol); LiOH (92mg, 4mmol). Column chromatography (silica gel, 0-100% EtOAc / hexane) furnished (S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopiperidin-1-yl)methyl)phenyl)acetic acid as a colorless solid, (400mg, 0.7mmol, 49%); $^1$H NMR (300MHz, d$_6$-DMSO): 12.2 (brs, IH), 7.85 (d, IH), 7.75 (d., 2H), 7.5-7.4(m,4H), 7.35( d, IH), 7.1 1 (dd, IH), 7.00(d, IH), 7.05(d,IH), 5.1(s, 2H), 4.55 (d, IH), 4.35 (d, IH), 3.8(m, IH), 3.1 (m, IH), 2.4 (s, 3H), 1.9-1.7(m, 3H).

(R)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopiperidin-1-yl)methyl)phenyl)acetic acid (Compound 115B)
The title material was obtained using the chemistry outlined for
(S)-2-(4-(4-chlorobenzyloxy)-3-((3-(4-methylphenylsulfonamido)-2-oxopiperidin-1-yl)methyl)phenyl)acetic acid, starting with Boc-D-ornithine. $^1$H NMR (300MHz, d$_6$-DMSO); 12.2 (brs, 1H), 7.85 (d, 1H), 7.75 (d., 2H), 7.5-7.4(m,4H), 7.35 (d, IH), 7.11 (dd, IH), 7.00(d, IH), 7.05(d,IH), 5.1(s, 2H), 4.55 (d, IH), 4.35 (d, IH), 3.8(m, IH), 3.1 (m, IH), 2.4 (s, 3H), 1.9-1.7(m, 3H).

Example 116

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate(Compound 116A) and 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 116B)

[0299] The title compound(s) were obtained using l-chloromethyl-4-chlorobenzene and 4-methyl phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 116B:
LC/MS Rt = 2.77 min. (Method A); MS (m/z) 529.26(M$^+$ + H).
Example 117

Methyl {4-(4-Chloro-benzyloxy)-3,5-bis-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetate (Compound 117A) and {4-(4-Chloro-benzyloxy)-3,5-bis-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid (Compound 117B)

[0300] The title compound(s) were obtained using 1-chloromethyl-4-chlorobenzene and 4-methyl phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 117B: M+H 782.

Example 118

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(phenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 118A) and 2-(4-(4-chlorobenzyloxy)-3-((4-(phenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 118B)
The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-l-yl)methyl)phenyl)acetic acid. Compound 118B: LC/MS Rt = 2.73 min. (Method A); MS (m/z) 515.21(M+H).

Example 119

Methyl

2-(4-(4-chlorobenzyloxy)-3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 119A) and 2-(4-(4-chlorobenzyloxy)-3-((4-(4-fluorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 119B)

The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 4-fluoro phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-l-yl)methyl)phenyl)acetic acid. Compound 119B: LC/MS Rt = 2.73 min. (Method A); MS (m/z) 533.23(M+ H).

Example 120

Methyl

2-(4-(4-chlorobenzyloxy)-3-((4-(4-chlorophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 120A) and 2-(4-(4-chlorobenzyloxy)-3-((4-(4-chlorophenylsulfonyl)piperazin-l-yl)methyl)phenyl)acetic acid (Compound 120B)
The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 4-chloro phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 120B:**

$R_t = 2.85$ min. (Method A); $MS (m/z) \ 549.21(M^+ + H)$.

**Example 121**

*Example 121*

Methyl

2-(3-((4-(4-bromophenylsulfonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl) acetate (Compound **121A**) and 2-(3-((4-(4-bromophenylsulfonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl) acetic acid (Compound **121B**)

The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 4-bromo phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 120B:**

$\text{LC/MS } R_t = 2.83$ min. (Method A); $MS (m/z) \ 595(M^+ + H)$. 
Example 122

Methyl
2-(4-(4-chlorobenzyloxy)-3-((4-(thiophen-2-y1sulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 122A) and
2-(4-(4-chlorobenzyloxy)-3-((4-(thiophen-2-y1sulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 122B)

[0305] The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 2-thiophene sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 122B: LC/MS Rt = 2.73 min. (Method A); MS (m/z) 521.16(M+ + H).

Example 123

Methyl
2-(4-(4-chlorobenzyloxy)-3-((4-(thiophen-3-y1sulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound 123A) and
2-(4-(4-chlorobenzyloxy)-3-((4-(thiophen-3-y1sulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound 123B)
The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 3-thiophene sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 123B:**

\[ \text{LC/MS } R_t = 2.73 \text{ min. (Method A); } M_S (m/z) \ 521.15(M^+ + H). \]

Example 124

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(4-nitrophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate (Compound **124A**) and 2-(4-(4-chlorobenzyloxy)-3-((4-(4-nitrophenylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid (Compound **124B**)

The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 4-nitro phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 124B:**

\[ \text{LC/MS } R_t = 2.92 \text{ min. (Method A); } M_S (m/z) \ 561.0(M^+ + H). \]
Example 125

Methyl 2-((4-(4-chlorobenzyloxy)-3-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate

(Compound 125A) and 2-((4-(4-chlorobenzyloxy)-3-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid

(Compound 125B)

[0308] The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and methyl sulfonyle chloride, using the Method described for 2-(4-(isopentyl)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 125B: LC/MS Rt = 2.50 min. (Method A); MS (m/z) 453.21(M+H).

Example 126

Methyl 2-((4-(4-chlorobenzyloxy)-3-((4-(isopropylsulfonyl)piperazin-1-yl)methyl)phenyl)acetate

(Compound 126A) and 2-((4-(4-chlorobenzyloxy)-3-((4-(isopropylsulfonyl)piperazin-1-yl)methyl)phenyl)acetic acid

(Compound 126B)
The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and isopropyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 126B:**

\[
\text{LC/MS } R_t = 2.62 \text{ min. (Method A); MS (m/z) } 481.24(M^+ + H).
\]

Example 127

Methyl 2-(3-((4-(butylsulfonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 127A) and 2-(3-((4-(butylsulfonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetic acid (Compound 127B)

The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and butyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. **Compound 127B:**

\[
\text{LC/MS } R_t = 2.69 \text{ min. (Method A); MS (m/z) } 495.24(M^+ + H).
\]

Example 128
Methyl 2-(4-(4-methoxybenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 128A) and 2-(4-(4-methoxybenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 128B)

[0311] The title compound(s) were obtained using 1-chloromethyl 4-methoxybenzene and 4-methyl phenyl sulfonyl chloride, using the Method described for 2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 128B: LC/MS Rt = 2.69 min. (Method A); MS (m/z) 525.30(M+ + H).

Example 129

Methyl 2-(4-(4-methylbenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 129A) and 2-(4-(4-methylbenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 129B)

[0312] The title compound(s) were obtained using 1-chloromethyl 4-methylbenzene and 4-methyl phenyl sulfonyl chloride, using the Method described for
2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 129B:
LC/MS R_t = 2.85 min. (Method A); MS (m/z) 509.31(M^+ + H).

Example 130

Methyl 2-(4-(benzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetate (Compound 130A) and 2-(4-(benzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 130B)

[0313] The title compound(s) were obtained using benzyl bromide and 4-methyl phenyl sulfonyl chloride, using the Method described for

2-(4-(isopentyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid. Compound 130B:
LC/MS R_t = 2.81 min. (Method A); MS (m/z) 495.32(M^+ + H).

Example 131

Methyl
2-(3-((4-(benzylcarbamoyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 131A) and
2-(3-((4-(benzylcarbamoyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetic acid (Compound 131B)
The title compound(s) were obtained using 1-chloromethyl 4-chlorophenyl and benzyl isocyanate using the Method described for 2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid.

**Compound 131B**: \( \text{Rt} = 2.67 \text{ min. (Method A); MS (m/z) 508.2 (M}^+ + \text{H).} \)

Example 132

Methyl 2-(3-((4-benzylpiperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 132A) and

2-(3-((4-benzylpiperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetic acid (Compound 132B)

The title compound(s) were obtained using the same experimental Method described for 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with N-Benzyl piperazine. **Compound 132B**: LC/MS \( \text{Rt} = 2.70 \text{ min. (Method A); MS (m/z) 465.2(M}^+ + \text{H).} \)

Example 133
Methyl 2-(3-((4-benzoylpiperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate 
(Compound 133A) and
2-(3-((4-benzoylpiperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetic acid
(Compound 133B)

[0316] The title compound(s) were obtained using 1- chloromethyl 4-chlorophenyl and 
benzoyl chloride using the Method described for
2-(3-((4-benzoylpiperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate. 

Example 134

Methyl 
2-(4-(4-chlorobenzyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetate 
(Compound 134A) and
2-(4-(4-chlorobenzyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid 
(Compound 134B)
[0317] The title compound(s) were obtained using 1-chloromethyl 4-chlorophenyl and phenyl isocyanate using the Method described for 2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid.

**Compound 134B:** \( \text{Rt} = 2.58 \text{ min. (Method A); MS (m/z) 494.17(M}^+ + \text{H).} \)

Example 135

Methyl 2-(3-((4-(benzyloxycarbonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (**Compound 135A**) and 2-(3-((4-(benzyloxycarbonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetic acid (**Compound 135B**)

[0318] The title compound(s) were obtained using 1-chloromethyl 4-chlorophenyl and benzyloxy chloroformate using the Method described for 2-(4-(isopentyloxy)-3-((4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic acid.

**Compound 135B:** \( \text{Rt} = 2.81 \text{ min. (Method A); MS (m/z) 509.16(M}^+ + \text{H).} \)

Example 136

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(2-phenylacetyl)piperazin-1-yl)methyl)phenyl)acetate (**Compound 136A**) and 2-(4-(4-chlorobenzyloxy)-3-((4-(2-phenylacetyl)piperazin-1-yl)methyl)phenyl)acetic acid (**Compound 136B**)

\[ \text{Example 135} \]

Methyl 2-(3-((4-(benzyloxycarbonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetate (**Compound 135A**) and 2-(3-((4-(benzyloxycarbonyl)piperazin-1-yl)methyl)-4-(4-chlorobenzyloxy)phenyl)acetic acid (**Compound 135B**)

\[ \text{Example 136} \]

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-(2-phenylacetyl)piperazin-1-yl)methyl)phenyl)acetate (**Compound 136A**) and 2-(4-(4-chlorobenzyloxy)-3-((4-(2-phenylacetyl)piperazin-1-yl)methyl)phenyl)acetic acid (**Compound 136B**)

134
The title compound(s) were obtained using 1-chloromethyl 4-chlorophenyl and 2-phenyl acetyl chloride using the Method described for 2-(4-(isopentyloxy)-3-(4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic.

**Compound 136B:** LC/MS $R_t = 2.62$ min. (Method A); MS (m/z) 493.15(M$^+$ + H).

Example 137

Methyl (4-(4-Chloro-benzyloxy)-3-[4-(2-hydroxy-2-phenyl-acetyl)-piperazin-1-ylmethyl]-phenyl)-acetate (Compound 137A) and (4-(4-Chloro-benzyloxy)-3-[4-(2-hydroxy-2-phenyl-acetyl)-piperazin-1-ylmethyl]-phenyl)-acetic acid (Compound 137B)

The title compound(s) were obtained using 1-chloromethyl 4-chlorobenzene and 2-phenyl acetyl chloride using the method described for 2-(4-(isopentyloxy)-3-(4-(phenylcarbamoyl)piperazin-1-yl)methyl)phenyl)acetic.

**Compound 137B:** MS (m/z) 509(M$^+$ + H).

Example 138
2-(4-(4-chlorobenzyloxy)-3-((2-oxo-4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid
(Compound 138D)

Scheme 13

Step A : Methyl 2-(3-formyl-4-hydroxyphenyl)acetate

[0321] A solution of methyl 2-(4-hydroxyphenyl)acetate (10g, 60.2mmol) in TFA (50ml) was refluxed with hexamethylenetetramine (8.44g, 60.2mmol) overnight; the solution was concentrated to remove excess TFA. The residue was suspended in H₂O (50ml), after being made alkaline with Na₂CO₃, the mixture was extracted with EtAc (3 X 100ml). The extract was washed with IN HCl (3 X 20ml). The combined organic layers were dried over Na₂SO₄. The product was used without further purification.

Step B : Methyl 2-(4-(4-chlorobenzyloxy)-3-formylphenyl)acetate

[0322] To the crude aldehyde (549mg, 2.83mmol) above in CH₃CN (15ml) were added 1-chloro methyl-4-(chlorobenzene) (500mg, 3.11mmol) and K₂CO₃ (781mg, 5.66mmol). The reaction was heated at 85 °C overnight. The solid was filtered off through CELITE. The product was used without further purification. LC/MS Rt = 4.01 min. (Method A); MS (m/z) 341.1(M⁺ + 23).

Step C : Methyl 2-(3-(bromomethyl)-4-(4-chlorobenzyloxy)phenyl)acetate (Compound 138C)
To methyl 2-(4-(4-chlorobenzyloxy)-3-formylphenyl)acetate (901 mg, 2.83 mmol) in MeOH (10ml) were added NaBH₄ (537mg, 14.16mmol) at 0°C. The reaction was run at RT overnight. H₂O was added to quench the reaction, extracted with EtOAc (3 X 20ml). The product was obtained after flash chromatography on silica gel. LC/MS Rt = 3.70 min. (Method A); MS (m/z) 343.1(M+ + 23).

To the alcohol (241 mg, 0.75mmol) in CH₃CN (10ml) were added TMSCl (0.238 ml, 1.88 mmol) and LiBr (131mg, 1.50 mmol). The solution was heated at 85°C overnight. The product (173mg, 60%) was obtained after flash chromatography on silica gel. LC/MS Rt = 3.69 min. (Method A); MS (m/z) 384.1(M+ + H).

**Step D**: 2-(4-(4-chlorobenzyloxy)-3-((2-oxo-4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid (Compound 138D)

[0325] To methyl 2-(3-(bromomethyl)-4-(4-chlorobenzyloxy)phenyl)acetate (92.7mg, 0.24mmol) in CH₃CN (5ml) were added 4-tosylpiperazin-2-one (92.2 mg, 0.36 mmol) and Cs₂CO₃ (118mg, 0.36mmol). The reaction was heated at 85°C overnight. The solid was filtered off through CELITE. The product was collected after flash chromatography on silica gel. MS (m/z) 557.1(M+ + 23).

[0326] To this product (16.2mg, 0.03mmol) in THF (1ml) was added IN LiOH (1ml). The reaction was monitored by TLC until the starting material was consumed. Diluted with EtOAc (10ml), washed with IN HCl (3 X 5ml). The organic layer was dried over Na₂SO₄, and concentrated to afford the desired product (10.4mg, 64%). MS (m/z) 543.1(M+ + H).
Methyl 2-(4-(4-chlorobenzyloxy)-3-(thiomorpholinomethyl)phenyl)acetate (Compound 139A) and 2-(4-(4-chlorobenzyloxy)-3-(thiomorpholinomethyl)phenyl)acetic acid (Compound 139B)

[0327] The title compound(s) were obtained using the same experimental method described for 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with thiomorpholine. Compound 139B: LC/MS Rt = 2.52 min. (Method A); MS (m/z) 392.1(M⁺ + H).

Example 140

Methyl 2-(4-(4-chlorobenzyloxy)-3-((4-hydroxypiperidin-1-yl)methyl)phenyl)acetate (Compound 140A) and 2-(4-(4-chlorobenzyloxy)-3-((4-hydroxypiperidin-1-yl)methyl)phenyl)acetic acid (Compound 140B)

[0328] The title compound(s) were obtained using the same experimental Method described for 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid,
starting with 4-hydroxy piperidine. **Compound 140B**: LC/MS 

\[ \text{R}_t = 2.38 \text{ min. (Method A)}; \]

\[ \text{MS (m/z) 390.1(M}^+ + \text{H).} \]

Example 141

Methyl 2-((4-(4-chlorobenzyloxy)-3-(morpholinomethyl)phenyl)acetate (Compound 141A) and 2-(4-(4-chlorobenzyloxy)-3-(morpholinomethyl)phenyl)acetic acid (Compound 141B)

[0329] The title compound(s) were obtained using the same experimental Method described for 2-(4-(4-chlorobenzyloxy)-3-(4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with morpholine. **Compound 141B**: LC/MS 

\[ \text{R}_t = 2.42 \text{ min. (Method A)}; \]

\[ \text{MS (m/z) 376.1(M}^+ + \text{H).} \]

Example 142

Methyl 2-((4-(4-chlorobenzyloxy)-3-(piperidin-1-ylmethyl)phenyl)acetate (Compound 142A) and 2-(4-(4-chlorobenzyloxy)-3-(piperidin-1-ylmethyl)phenyl)acetic acid (Compound 142B)
The title compound(s) were obtained using the same experimental Method described for 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with piperidine. **Compound 142B**: LC/MS Rt = 2.53 min. (Method A); MS (m/z) 374.1(M⁺ + H).

Example 143

Methyl 2-(4-(4-chlorobenzyloxy)-3-(thiomorpholine 1-oxidemethyl)phenyl)acetate (Compound 143A) and 2-(4-(4-chlorobenzyloxy)-3-(thiomorpholine 1-oxidemethyl)phenyl)acetic acid (Compound 143B)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{S}=\text{O} \\
\text{Cl} & \quad \text{C}
\end{align*}
\]

The title compound(s) were obtained using the same experimental Method described for 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with S-oxo thiomorpholine. **Compound 143B**: LC/MS Rt = 2.39 min. (Method A); MS (m/z) 408.09(M⁺ + H).

Example 144

Methyl 2-(4-(4-chlorobenzyloxy)-3-(thiomorpholine 1,1'-dioxidemethyl)phenyl)acetate (Compound 144A) and 2-(4-(4-chlorobenzyloxy)-3-(thiomorpholine 1,1'-dioxidemethyl)phenyl)acetic acid (Compound 144B)
[0332] The title compound(s) were obtained using the same experimental Method described for 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with S, S-dioxo thiomorpholine. Compound 144B: LC/MS Rt = 3.05 min. (Method A); MS (m/z) 424.31(M+ + H).

Example 148

Methyl 2-(4-(4-fluorobenzyloxy)-3-(thiomorpholine 1,1'-dioxidemethyl)phenyl)acetate (Compound 145A) and 2-(4-(4-fluorobenzyloxy)-3-(thiomorpholine 1,1'-dioxidemethyl)phenyl)acetic acid (Compound 145B)

[0333] The title compound(s) were obtained using the same experimental Method described for 2-(4-(4-chlorobenzyloxy)-3-((4-tosylpiperazin-1-yl)methyl)phenyl)acetic acid, starting with S, S-dioxo thiomorpholine and 1-bromomethyl-4-fluorobenzene. Compound 145B: LC/MS Rt = 2.90 min. (Method A); MS (m/z) 408.1(M+ + H).

Example 146
(1R)/(1S)-2-(1-(4-tosylpiperazin-1-yl)-6,1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid (Compound 146D and E)

Scheme 14

Step A: 2-((4-(carboxymethyl)phenoxy)methyl)benzoic acid (Compound 146A)

[0334] Solid K$_2$CO$_3$ (14.3 g, 104 mmol), NaI (390 mg, 2.6 mmol), and ethyl 2-(bromomethyl)benzoate (6.3 g, 26 mmol) were added to a stirring solution of methyl 4-hydroxy phenylacetate (4.3 g, 26 mmol) in 2-propanone (100 mL). The resulting mixture was refluxed over night, cooled, filtered through filter paper, and concentrated. The residue was redissolved in EtOH/H$_2$O (10:1, 150 mL) and solid KOH (14 g, 260 mmol) was added followed by refluxing over night. After concentration the residue was dissolved in H$_2$O (100 mL) and the aqueous was washed with ether (100 mL) and acidified with cone. HCl (1 < pH).
A filtration gave crude acid (9.8 g) which was used in subsequent reaction with no further purification.

**Step B:** Methyl 2-(1-oxo-6,1 1-dihydrop[ene][b,e]o[epin-2-yl]acetate (Compound 146B)

[0335] Polyphosphoric acid (50 g) was added to a stirring solution of 2-((4-(carboxymethyl)phenoxy)methyl)benzoic acid (9.8 g) in acetic acid (17 mL) at 90 °C. After stirring for 5 h, the resulting mixture was cooled, and H₂O (150 mL) was added. The aqueous was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, and concentrated. The residue was redissolved in MeOH (150 mL) and HCl (g) was bubbled through for 5 min. The resulting solution was stirred over night and concentrated to give crude ester. A flash chromatography on silica gel (3:1, hexanes/EtOAc) afforded the desired material.

**Step C:** Methyl 2-(1-chloro-6,1 1-dihydrop[ene][b,e]o[epin-2-yl]acetate (Compound 146C)

[0336] NaBH₄ (430 mg, 11.3 mmol) was added to a stirring solution of methyl 2-(1-oxo-6,1 1-dihydrop[ene][b,e]o[epin-2-yl]acetate (800 mg, 2.83 mmol) in MeOH (20 mL). After stirring for 5 min, reaction mixture was quenched with satd. NaHCO₃ (20 mL) and the aqueous was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The residue was redissolved in
CH₂Cl₂ (20 mL) and SOCl₂ (1.03 mL, 14.15 mmol) was added. After stirring for 1 h reaction mixture was concentrated to give the crude material that was used in subsequent reaction without further purification.

5 Step D:
(1R)/(1S)-2-(1-(4-tosylpiperazin-1-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid (Compound 146D/146E)

[0337] DIEA (1.1 mL, 6.35 mmol) and 1-tosylpiperazine (607 mg, 2.5 mmol) were added to a stirring solution of methyl 2-(1-chloro-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetate (640 mg, 2.11 mmol) in CH₂Cl₂ (20 mL). The reaction mixture was quenched with satd. NaHCO₃ (20 mL) after stirring over night and the aqueous was extracted with CH₂Cl₂ (3 X 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was redissolved in THF/MeOH/H₂O (3:1:1, 15 mL) and LiOH (621 mg, 14.8 mmol) was added. After stirring over night the resulting mixture was quenched with 1 N HCl (<pH 1). The aqueous was extracted with EtOAc (3 X 20 mL), dried over Na₂SO₄, and concentrated to give crude acid (411 mg) as light yellow oil. HPLC purification afforded pure title material. Both enantiomers (146A/146B) were also separated by chiral HPLC: ES/MS, m/z 493.2 (M+H); LC/MS (Method B) Rt = 3.602 min. Chiral LC (Chiralpak OD-H, 4.6 x 250 mm, 80 % Hexanes: 20 % IPA, 40 °C, 1.0 mL/min.) 146A Rt = 12.148 min, 146B Rt = 25.056 min.

Example 147

Methyl

2-(1-(4-(4-fluorophenylsulfonyl)piperazin-1-yl)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl)acetate (Compound 147A) and
2-(1l-(4-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,l l-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid (Compound 147B)

[0338] The title material was obtained using the Method described for 2-(1l-(4-tosylpiperazin-l-yl)-6,l l-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid using 4-fluorophenyl sulfonyl piperazine: Compound 147B: $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 12.24 (IH, brs) 7.75 (2H, dd, $J = 5.5, 7.87$ Hz) 7.46 (2H, t, $J = 8.8$ Hz) 7.32 (4H, m) 7.06 (2H, d, $J = 8.0$ Hz) 6.66 (IH, d, $J = 7.9$ Hz) 6.37 (IH, d, $J = 11.5$ Hz) 4.65 (IH, d, $J = 11.5$ Hz) 4.03 (IH, s) 3.45 (2H, s) 2.83 (4H, brs) 2.36 (4H, m); ES/MS, m/z 497.2 (M+H); LC/MS (Method B) Rt = 3.560 min.

Example 148

Methyl 2-(9-chloro-l-(4-tosylpiperazin-l-yl)-6,l l-dihydrodibenzo[b,e]oxepin-2-yl)acetate (Compound 148A) and 2-(9-chloro-l-(4-tosylpiperazin-l-yl)-6,l l-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid (Compound 148B)

[0339] The title material was obtained using the Method described for 2-(1l-(4-tosylpiperazin-l-yl)-6,l l-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid using 4-methyl phenyl sulfonyl piperazine and 5-chloro-2-(bromomethyl)benzoate. Compound 148B: ES/MS, m/z 527.1 (M+H); LC/MS (Method B) Rt = 4.105 min.
Example 149

Methyl 2-(9-chloro-1-1-(4-(4-fluorophenylsulfonyl)piperazin-1-yl)-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetate (Compound 149A) and 2-(9-chloro-11-(4-(4-fluorophenylsulfonyl)piperazin-1-yl)-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid (Compound 149B)

[0340] The title material was obtained using the Method described for 2-(11-(4-tosylpiperazin-1-yl)-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid using 4-fluoro phenyl sulfonfyl piperazine and 5-chloro-2-(bromomethyl)benzoate. Compound 149B: ES/MS, m/z 531.1 (M+H); LC/MS (Method B) Rt = 3.996 min.

Example 150

Methyl 2-(1-(2-oxo-4-tosylpiperazin-1-yl)-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetate (Compound 150A) and 2-(1-(2-oxo-4-tosylpiperazin-1-yl)-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid (Compound 150B)

[0341] The title material was obtained using the Method described for 2-(1-(4-tosylpiperazin-1-yl)-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetic acid using 4-tosyl piperazin-2-one and 2-(bromomethyl)benzoate. Compound 150B: ES/MS, m/z 507.2 (M+H); LC/MS (Method B) Rt = 3.52 min.
Pharmacological Data:

Receptor Interaction Assay

Cell culture:

[0342] Human Jurkat cells transfected with DP 2, DP 1 or TP receptors were maintained in culture in a humidified atmosphere at 37 °C (5% CO 2) in RPMI 1640 media (Gibco®, Invitrogen, USA) with 10% fetal bovine serum (Hyclone, Logan, UT, USA) plus penicillin streptomycin (Gibco®), L Glutamine (Gibco®), sodium pyruvate and 100ug/ml G418. Cells were grown in T225 flasks (Corning®) and harvested by centrifugation. Cell pellets were collected from approximately 200 ml of cell suspension, pelleted by centrifugation and stored at 20 °C until processed into membranes.

Preparation of cell membranes:

[0343] Frozen Jurkat cell pellets expressing either DP-2, DP-I or TP were thawed on ice. Each pellet was suspended in membrane buffer (25mM Hepes® pH7.2, 6mM MgC12, ImM EDTA) plus Complete® protease inhibitor cocktail tablets (Roche Mannheim Germany). The pellets were dounce homogenized and centrifuged at 1900 for 10 min. in a table top centrifuge (Beckman Coulter Allegra™ 6R). Supernatants were collected and pellets resuspended in 10mls of membrane buffer, dounced again and centrifuged as above. Supernatants were pooled and centrifuged in a Beckman J2-21M centrifuge using a JA20 rotor at 20,000 RPM for 1.5 hours at 4 °C. The supernatants were discarded and the pellets suspended in membrane buffer and pooled. Protein concentration was determined and membranes adjusted to approximately 1.5mgs/ml.

DP-2 Binding Assay:

[0344] Compound interactions with the DP-2 receptors were determined by means of competitive radioligand binding assays using membranes prepared from DP-2 expressing cells (prepared as above) and 3[H] PGD 2 (166Ci/mmol) as a radioactive tracer. Assays were performed in a final volume of 150μl of assay buffer (10mM Hepes®, 10mM MnCl 2 , ImM EDTA and 1% DMSO). Test article serially diluted in assay buffer was incubated with ImM radioactive tracer and 10µg/well of the membranes prepared from DP-2 expressing cells in a 96 well polystyrene plate for one hour at room temperature. The reaction mixture was then...
transferred to a Millipore (Bedford, MA) MultiScreen \textsuperscript{\textregistered}, FC MAFCNOB glass fiber filter plate. The plate was vacuum aspirated, and washed 2 times with 200ul of binding buffer vacuum aspirating between each wash. The plate was allowed to dry and 50ul of Optiphase 'Super Mix' (Wallac Oy Turku, Finland) scintillation cocktail was added to each well. The plate was counted on a Wallac \textsuperscript{\textreg}(Wallac Oy Turku, Finland) 1450 micro beta liquid scintillation counter.

**DP-2 Chemotaxis Assay**

[0345] The ability of compounds of the invention to antagonize DP-2 receptor function was examined in chemotaxis assays using DP-2 transfected Jurkat cells. Compounds were serially diluted into complete media containing InM PGD\textsubscript{2} as a chemoattractant, and 600ul of this mixture were transferred into the bottom wells of a Costar Transwell \textsuperscript{\textreg} plate (8 \textmu m pore size). DP-2 transfected Jurkat cells were harvested, re-suspended at 7.5x10\textsuperscript{6} cells/ml complete media, and 100 \textmu L of this cell suspension was added into the pore filter inserts. After equilibration of all the components to 37 \textdegree C in a cell incubator for 15 min, chemotaxis was initiated by transfer of the filter inserts onto the bottom wells. Following 2 hr incubation in a 37 \textdegree C incubator the filter inserts were removed, the media with cells were collected from lower wells and transferred to FACS tubes. Cells in each sample were then enumerated on FACScan using CellQuest software.

Selectivity assay

**DP-I binding assay**

[0346] DP-I binding assays were performed in a manner substantially identical to the DP-2 binding assay, except that DP-I transfected cell membranes were used.

**Human TP binding assay**

[0347] TP receptor interaction was assessed in competition binding assays using membranes from TP receptor transfected cells (prepared as above) and \textsuperscript{3}H SQ29,548 (48.2\textmu Ci/mmol) as a TP-selective tracer. Assays were performed in a final volume of 150ul of binding buffer (10mM Hepes, 10mM MnCl\textsubscript{2}, 1mM EDTA and 1\% DMSO. Duplicate samples of serially diluted test compound were incubated with 10ug/well of TP membranes
in the presence of 3nM $^3$H SQ 29,548. Following a one hour incubation at room
temperature the reaction mixture was transferred to a Millipore® (Bedford, MA)
MultiScreen®, FC MAFCN OB glass fiber filter plate. The mixture was vacuum aspirated,
and washed 2 times with 200ul of binding buffer vacuum aspirating between each wash.
After air drying 50ul of Optiphase Super Mix® (Wallac Oy Turku, Finland) scintillation
cocktail was added to each well and radioactivity was quantified on a Wallac® (Wallac Oy
Turku, Finland) 1450 micro beta liquid scintillation counter.

[0348] All of the acid compounds of the Examples that were tested in the assay exhibited
IC$_{50}$ values less than 2.5 µM, for example the acid compounds of examples 1, 2, 3, 4, 5, 7, 6, 8,
9, 10, 11, 13, 27, 40, 41, 42, 43, 44, 45, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 69, 70, 71,
72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 89, 90, 91, 106, 109, 109, 107,
110, 113, 114, 115, 116, 117, 119, 120, 121, 123, 124, 125, 126, 127, 128, 129, 130, 131,
132, 133, 134, 135, 136, 137 and 140. In some embodiments, the acid compounds of the
invention exhibited IC$_{50}$ values less than 10 µM, for example the acid compounds of examples
1, 2, 3, 4, 5, 7, 6, 8, 9, 10, 11, 13, 27, 40, 41, 42, 43, 44, 45, 54, 55, 56, 57, 58, 59, 60, 61, 62,
63, 64, 69, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 89, 90, 91, 106, 109,
107, 110, 113, 114, 115, 116, 117, 119, 120, 121, 123, 124, 125, 126, 127, 128, 129, 130,
131, 133, 134, 135, 136, 138 and 140. In some embodiments, the acid compounds of the
invention exhibited IC$_{50}$ values less than 1 µM. In some embodiments, the compounds of the
invention exhibited IC$_{50}$ values less than 0.1 µM.

[0349] All of the acid compounds of the Examples that were tested in the above-described
ligand binding assays exhibited an average IC$_{50}$ value which was least 2-fold lower for DP-2
over DP-I and TP, for example the acid compounds of examples 1, 25, 26, 27, 40, 43, 44, 45,
55, 58, 62, 63, 95, 96, 97, 98, 99, 100, 103, 106, 107, 109, 110, 113, 114, 115, 118, 119, 120,
123, 131, 134, 137, 141, 143 and 144. In some embodiments, the acid compounds of the
invention exhibited an average IC$_{50}$ value which was least 10-fold lower for DP-2 over DP-I
and TP, for example the acid compounds of examples 1, 25, 26, 27, 40, 43, 44, 45, 55, 58, 62,
63, 95, 96, 97, 98, 99, 100, 103, 106, 107, 109, 110, 113, 114, 115, 118, 119, 120, 123, 131,
134, 137, 143 and 144 In some embodiments, the acid compounds of the invention exhibited
an average IC$_{50}$ value which was least 50-fold lower for DP-2 over DP-I and TP, for example
the acid compounds of 1, 27, 58, 62, 63, 95, 96, 97, 98, 99, 100, 103, 106, 107, 110, 113, 114,
115, 118, 119, 120, 123, 131, 134, 137, 143 and 144.
All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.
WHAT I S CLAIMED IS:

1. A compound having the structure (I):

   [Chemical structure image]

   (I)

   wherein:

   A is a 5-14-membered heterocyclic ring having 1-4 ring heteroatoms each
   independently selected from the group consisting of nitrogen, oxygen and
   sulfur, the heterocyclic ring being monocyclic or polycyclic, optionally
   substituted with 1-3 R₈ substituents;

   L is selected from the group consisting of a CR₆R₇, CO, CNR₆ and CS;

   Q¹ is selected from the group consisting of: a bond, -Ci-C₄alkylene-,
   -Ci-C₄heteroalkylene-, -CO-, -NH-, -O-, -SO₆-, -C(O)O-, -OC(O)-, -CONH-,
   -NHCO-, -NHCONH-, -NHSO₆-, -SO₆NH- and -COCH₂HNSO₆;

   each R¹, R², R₃, R₆ and R₇ is independently selected from the group consisting of H,
   Ci₆alkyl, Co₆alkylaryl and Co₆alkylheteroaryl; wherein the aryl or heteroaryl
   portions are optionally substituted with Ci₆alkyl, CN, OR, Ci₆haloalkyl,
   Ci₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO₆R, SO₁₆NR₂,
   OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R and NRC(O)OR;

   each R₄ is independently selected from the group consisting of Ci₆alkyl,
   Co₆alkylC₃-iocycloalkyl, C₀₄₆alkylaryl, Co₆alkylheteroaryl, C₂₆alkenylaryl,
   C₂₆alkynylaryl, C₀₄₆alkylheterocyclyl, CN, amino, NHCOR₁, hydroxy,
   Ci₆alkoxy, OC(O)R₁, -OC₆₀₄alkylaryl, OC₀₄₆alkylheteroaryl,
   -OC₀₄₆alkylC₃-iocycloalkyl, OCo₆alkylC₃-iocycloalkyl, OC₀₄₆alkylheterocyclyl, OC₀₄₆alkylNR₈, nitro,
   halo and haloCi₆alkyl; or are combined together or with R₆ to form an aryl or
   heterocyclyl ring system having from 1-2 heteroatoms selected from the group
   consisting of nitrogen, oxygen and sulfur; wherein the alkyl, aryl and
   heterocyclyl portions are each optionally substituted with 1 to 3 substituents
each independently selected from the group consisting of \( \text{C}_1-\text{C}_6 \) alkyl, CN,
CONHR, CO\(_2\)R, amino, \( \text{C}_1-\text{C}_6 \) alkoxy, halo, haloh\( \text{C}_1-\text{C}_6 \) alkyl and SO\(_q\)R;
\( R^5 \) is selected from the group consisting of \( \text{Cl}_1-\text{C}_6 \) alkyl, \( \text{C}_0-4 \) alkylaryl, \( \text{C}_2-4 \) alkenylaryl,
\( \text{C}_2-4 \) alkynylaryl and \( \text{Co}_1-4 \) alkylheteroaryl, each of which is optionally substituted
with 1-3 \( R^9 \) substituents;
each \( R^8 \) is independently selected from the group consisting of \( \text{C}_1-\text{C}_6 \) alkyl,
\( \text{Co}_1-3 \) cycloalkyl, \( \text{Co}_1-4 \) alkylaryl, \( \text{Co}_1-4 \) heterocyclyl, \( \text{C}_1-6 \) heteroalkyl,
\( \text{N}R_2 \), \( \text{N}O_2 \), halo, C(OR), \( \text{C}_1-6 \) haloalkyl, \( \text{C}_1-6 \) heteroalkyl,
\( \text{SO}_q\)R, \( \text{SO}_q\)NR\(_2\), OC(OR), OC(OR), OC(O)NR\(_2\), NRC(O)NR\(_2\), NRC(O)R
and NRC(O)OR;
each \( R^9 \) is independently selected from the group consisting of \( \text{C}_1-\text{C}_6 \) alkyl, CN, OR,
\( \text{oxo}, \text{Cl}_1-\text{C}_6 \) haloalkyl, \( \text{C}_1-\text{C}_6 \) heteroalkyl, \( \text{NR}_2, \text{NO}_2, \text{halo}, \text{C}(\text{OR}), \text{CO}_2\text{R}, \text{CONR}_2, \text{SO}_q\)R,
\( \text{SO}_q\)NR\(_2\), OC(OR), OC(OR), OC(O)NR\(_2\), NRC(O)NR\(_2\), NRC(O)R
and NRC(O)OR;
each \( R \) is independently selected from the group consisting of \( \text{H}, \text{Cl}_1-\text{C}_6 \) alkyl, \( \text{C}_0-4 \)
heterocyclyl, \( \text{C}_3-8 \) cycloalkyl and \( \text{Co}_1-4 \) alkylaryl or when
attached to the same nitrogen atom may be combined to form a 5-8 membered
ring having 1-4 ring heteroatoms each independently selected from the group
consisting of nitrogen, oxygen and sulfur;
the subscript \( n \) is independently \( 0, 1, 2, 3 \) or \( 4 \);
each subscript \( q \) is independently \( 0, 1 \) or \( 2 \); and
the compound of claim 1, wherein \( A \) has the structure (II):

\[
\begin{array}{c}
\text{N} \\
\text{R}^1 \\
\text{R}^{10} \\
\text{Y} \\
\text{R}^{11}
\end{array}
\]

(II)

wherein
\( Y \) is selected from the group consisting of a bond, \( \text{CH}_2, \text{N}, \text{O}, \text{NO} \) and \( \text{SO}_q^1 \);
\( R^{10} \) and \( R^{11} \) are \( \text{H} \) or are combined together to form an aryl, heteroaryl or cycloalkyl
ring;
the subscript \( p \) is independently \( 0, 1 \) or \( 2 \);
each dashed ring bond independently indicates the presence of a single, double or normalized bond;
the dotted line indicates the point of attachment to $Q^1$ and the wavy line indicates the point of attachment to $L$.

3. A compound of claim 1 having a structure (III):

\[
\begin{align*}
\text{wherein} \\
Y & \text{ is selected from the group consisting of a bond, CH}_2, N, O, NO \text{ and SO}_q; \\
R^{10} \text{ and } R^{11} & \text{ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;} \\
\text{the subscript } m & \text{ is independently 0, 1, 2 or 3;} \\
\text{the subscript } p & \text{ is independently 0, 1 or 2;} \text{ and} \\
\text{each dashed ring bond independently indicates the presence of a single, double or normalized bond.}
\end{align*}
\]

4. A compound of claim 1 having a structure (IV):

\[
\begin{align*}
\text{wherein} \\
Y & \text{ is selected from the group consisting of a bond, CH}_2, N, O, NO \text{ and SO}_q; \\
R^{10} \text{ and } R^{11} & \text{ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;} \\
\text{the subscript } m & \text{ is independently 0, 1, 2 or 3;}
\end{align*}
\]
the subscript \( p \) is independently 0, 1 or 2; and

each dashed ring bond independently indicates the presence of a single, double or
normalized bond.

5. A compound of claim 1 selected from the group consisting of:

\[ [\text{4-(4-Chloro-benzyloxy)-3-thiomorpholin-4-ylmethyl-phenyl]-acetic acid;} \]
\[ [\text{4-(4-Chloro-benzyloxy)-3-(1,1-dioxo-1,6-thiomorpholin-4-ylmethyl)-phenyl]-acetic acid;} \]
\[ [\text{4-(4-Fluoro-benzyloxy)-3-(1,1-dioxo-1,6-thiomorpholin-4-ylmethyl)-phenyl]-acetic acid;} \]
\[ [\text{4-(4-Chloro-benzyloxy)-3-morpholin-4-ylmethyl-phenyl]-acetic acid;} \]
\[ [\text{4-(4-Chloro-benzyloxy)-3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl]-acetic acid;} \]
\[ [\text{4-(4-Chloro-benzyloxy)-3-{4-(2-(4-methoxy-phenyl)-acetyl)-piperazin-1-ylmethyl}-phenyl]-acetic acid;} \]
\[ [\text{3-(4-Benzyl-piperazin-1-ylmethyl)-4-(4-chloro-benzyloxy)-phenyl]-acetic acid;} \]
\[ [\text{(4-(4-Chloro-benzyloxy)-3-{4-[2-(4-chloro-phenyl)-acetyl]-piperazin-1-ylmethyl}-phenyl)-acetic acid;} \]
\[ [\text{4-(4-Chloro-benzyloxy)-3-\{4-(4-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl\}-phenyl]-acetic acid;} \]
\[ [\text{4-(4-Chloro-benzyloxy)-3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl]-acetic acid;} \]
\[ [\text{4-(4-Chloro-benzyloxy)-3-(4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl)-phenyl]-acetic acid;} \]
\[ [\text{4-(2,6-Difluoro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;} \]
\[ [\text{4-(4-Chloro-2-fluoro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;} \]
\[ [\text{4-(2-Fluoro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;} \]
WO 2007/143745

31 {4-(4-Chloro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; [3-(4-Benzesulfonyl-piperazin-1-ylmethyl)-4-(4-chloro-benzyloxy)-phenyl]-acetic acid;
34 {4-(4-Chloro-benzyloxy)-3-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; [3-[4-(4-Chloro-benzenesulfonyl)-piperazin-1-ylmethyl]-4-(4-chloro-benzyloxy)-phenyl]-acetic acid; {4-(4-Methoxy-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
37 {4-(4-Chloro-benzyloxy)-3,5-bis-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-Cyclopentylmethoxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; [2-[4-(Toluene-4-sulfonyl)-piperazin-1-ylmethyl]-biphenyl-4-yl]-acetic acid; {4-Benzyloxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-Cyclopropylmethoxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-Phenylethynyl-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(4-methoxy-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; [3-[4-(Toluene-4-sulfonyl)-piperazin-1-ylmethyl]-4-(4-trifluoromethyl-benzyloxy)-phenyl]-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(quinoline-8-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-Phenethylmethoxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; [4'-Methyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-biphenyl-4-yl]-acetic acid; [3-[4-(Toluene-4-sulfonyl)-piperazin-1-ylmethyl]-4-(4-trifluoromethyl-benzyloxy)-phenyl]-acetic acid; {4-(4-Chloro-benzyloxy)-3-[4-(2,4-dichloro-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-(4-Cyano-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; {4-Phenethyloxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid; [3-[4-(4-tert-Butyl-benzenesulfonyl)-piperazin-1-ylmethyl]-4-(4-chloro-benzyloxy)-phenyl]-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(3,5-dimethyl-isoxazole-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(naphthalene-2-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(pyridine-3-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(3,5-dichloro-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(4-ethyl-benzenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(naphthalene-1-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{3-[4-(4-Bromo-benzenesulfonyl)-piperazin-1-ylmethyl]-4-(4-chloro-benzyloxy)-phenyl]-acetic acid;
{4-(4-Methoxy-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Methyl-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-Cyclohexylmethoxy-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3-(4-phenylmethanesulfonyl-piperazin-1-ylmethyl)-phenyl}-acetic acid;
{4-(2,4-Dichloro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
{4-[Carboxymethyl-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenoxyethyl]-benzoic acid;
{4-(4-Fluoro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(thiophene-3-sulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
{4-(3,4-Dichloro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
{4-(4-Nitro-benzyloxy)-3-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-phenyl]-acetic acid;
{4-(4-Chloro-benzyloxy)-3-[4-(2-phenylethenesulfonyl)-piperazin-1-ylmethyl]-phenyl}-acetic acid;
6. A compound of claim 1 having a structure IVa:

![Structure IVa](image_url)

wherein Y^2 is selected from the group consisting of N, O and S;
each R\textsuperscript{12} is independently selected from the group consisting of C\textsubscript{1-6} alkyl, CN, CONHR\textsuperscript{1}, CO\textsubscript{2}R\textsuperscript{1}, amino, C\textsubscript{1-6} alkoxy, halo, haloC\textsubscript{1-6} alkyl and SO\textsubscript{q}R\textsuperscript{1} or is combined together to form an aryl or heteroaryl ring; and

the subscript u is independently 1, 2 or 3.

7. A compound of claim 1 selected from the group consisting of: 2-(1-l-(4-tosylpiperazin-l-yl)-6,l 1-diarylbenzene[b,e]oxepin-2-yl)acetic acid; 2-(1 l-(4-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,l 1-diarylbenzene[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-l l-(4-tosylpiperazin-l-yl)-6,l 1-diarylbenzene[b,e]oxepin-2-yl)acetic acid; 2-(9-chloro-l l-(4-(4-fluorophenylsulfonyl)piperazin-l-yl)-6,l 1-diarylbenzene[b,e]oxepin-2-yl)acetic acid; and 2-(l l-(2-oxo-4-tosylpiperazin-l-yl)-6,l 1-diarylbenzene[b,e]oxepin-2-yl)acetic acid; 1-(5-(carboxymethyl)-2-(2,4-dichlorobenzyl)benzyl)-4-tosylpiperazine N-oxide; 4-[5-Carboxymethyl-2-(4-chloro-benzyloxy)-benzyl] Piperazine-l-carboxylic acid tert-butyl ester;

[4-(4-Chloro-benzyloxy)-3-(4-phenylcarbamoyl-piperazin-l-ylmethyl)-phenyl]-acetic acid;
[4-[4-(3-Methyl-butoxy)-benzyloxy]-3-(4-phenylcarbamoyl-piperazin-l-ylmethyl)-phenyl]-acetic acid;

[4-(4-Chloro-benzyloxy)-3,5-bis-(4-phenylcarbamoyl-piperazin-l-ylmethyl)-phenyl]-acetic acid; [4-Cyclopropyloxy-3-(4-phenylcarbamoyl-piperazin-l-ylmethyl)-phenyl]-acetic acid; [4-Cyclopropyloxy-3-(4-phenylcarbamoyl-piperazin-l-ylmethyl)-phenyl]-acetic acid; and [3-(4-Benzylcarbamoyl-piperazin-l-ylmethyl)-4-(4-chloro-benzyloxy)-phenyl]-acetic acid; and [4-(4-Chloro-benzyloxy)-3-piperidin-l-ylmethyl-phenyl]-acetic acid;

[4-(4-Chloro-benzyloxy)-3-(4-hydroxy-piperidin-l-ylmethyl)-phenyl]-acetic acid;

[4-(4-Chloro-benzyloxy)-3-[2-oxo-3-(toluene-4-sulfonylamino)pyrrolidin-1-ylmethyl]-phenyl]-acetic acid;

[4-(4-Chloro-benzyloxy)-3-[2-oxo-3-(toluene-4-sulfonylamino)-azepan-l-ylmethyl]-phenyl]-acetic acid;
8. A compound of claim 1 having a structure (V):

\[
\begin{align*}
\text{(V)} \quad \text{wherein} \\
Y \text{ is selected from the group consisting of a bond, CH}_2, N, O, NO \text{ and SO}_4^2; \\
R^{10} \text{ and } R^{11} \text{ are } H \text{ or are combined together to form an aryl, heteroaryl or cycloalkyl} \\
\text{ring; } \\
\text{the subscript } m \text{ is independently } 0, 1, 2 \text{ or } 3; \\
\text{the subscript } p \text{ is independently } 0, 1 \text{ or } 2; \text{ and} \\
\text{each dashed ring bond independently indicates the presence of a single, double or} \\
\text{normalized bond.}
\end{align*}
\]

9. A pharmaceutical composition comprising a compound of any one of 
claims 1 to 8 and a pharmaceutically acceptable carrier, excipient, diluent or delivery system.

10. A method of antagonizing a DP-2 receptor comprising contacting a 
DP-2 receptor with a compound of any one of claims 1 to 8.

11. A use of a compound of any one of claims 1 to 8 or a pharmaceutically 
acceptable derivative thereof to prepare a medicament treating or preventing a disorder or 
condition responsive to modulation of PGD\(_2\) or a PGD\(_2\) receptor.

12. A use of a compound of any one of claims 1 to 8 or a pharmaceutically 
acceptable derivative thereof to prepare a medicament for treating or preventing a disorder or 
condition responsive to antagonizing a DP-2 receptor.
13. A use of a compound of any one of claims 1 to 8 or a pharmaceutically acceptable derivative thereof to prepare a medicament for treating or preventing a disorder or condition associated with elevated levels of PGD₂ or a metabolite thereof.

14. The use of any one of claims 11 to 13 wherein the disorder or condition is selected from the group consisting of: Obstructive airway diseases; bronchitis, chronic obstructive pulmonary disease; rhinitis; fibroid lung; cystic fibrosis; idiopathic interstitial fibrosis; chronic cough associated with inflammation; and sinusitis; conjunctivitis; dermatitis; psoriasis; urticaria; erythemas; cutaneous eosinophilia; chronic skin ulcers; food-induced allergies; eosinophilic gastroenteritis; mastocytosis; ulcerative colitis; Crohn's disease; irritable bowel syndrome; celiac disease; inflammatory pain, neuropathic pain; eosinophilic fascitis; hyper IgE syndrome; systemic mast cell disorder; Idopathic thrombocytopenia purpura; atherosclerosis; lupus erythematosus; systemic lupus erythematosus; sepsis; reperfusion injury; glomerulonephritis; allergic nephritis; nephritic syndrome; eosinophil related disorders such as Churg-Strauss syndrome; basophilic leukocytosis and basophilic leukemia; acquired immunodeficiency syndrome; arthritis and conditions associated therewith and other conditions or disorders associated with raised levels of PGD₂ or its metabolites.

15. The use of any one of claims 11 to 13 wherein said compound is used in combination with a second therapeutic agent.

16. The use of claim 15 wherein said second therapeutic agent is useful for preventing or treating a disorder or condition selected from the group consisting of: asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer's lung, fibroid lung, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behcet's disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, pain, osteoarthritis (OA), osteonecrosis,
psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendonitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, systemic diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fascitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury, transplant rejection, graft versus host disease, eczema, psoriasis, fever, cancer, viral invention, thrombosis, fibrosis, flushing, inflammation, nasal congestion, urticaria, contact hypersensitivity (including contact dermatitis), food allergies, eosinophilic gastroenteritis, mastocytosis, acne, colitis ulcerosa, pruritus, angioedema, excematous dermatides, erytherma, cutaneous eosinophilia, chronic skin ulcers, celiac disease, systemic mast cell disorder; idiopathic thromboytopenia purpura, Churg-Stauss syndrome, basophilic leukocytosis, basophilic leukemia and acquired immunodeficiency syndrome (AIDS).

17. The use of claim 15 wherein said second therapeutic agent is selected from the group consisting of: a corticosteroid, a corticosteroid analog, an antihistamine, a β2-agonist, a cromolyn, a leukotriene antagonist, an anti-IgE antibody therapy, an anti-infective, an anti-fungal, an immunosuppressant, a PGD₂ or DP antagonist, a PDE4 inhibitor, a cytokine modulator, a PPAR-γ agonist, a 5-lipoxygenase inhibitor, a FLAP inhibitor, and a PLA₂ inhibitor.