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(71) Applicant (*for all designated States except US*): **ICOS CORPORATION** [US/US]; 22021 20th Avenue S.E., Bothell, Washington 98021 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DUDLER, Thomas** [CH/US]; 13410 NE 36th Street, Bellevue, Washington 98005 (US). **FAROUZ, Francine** [FR/US]; 4222 93rd Ave SE, Mercer Island, Washington 98040 (US). **FOWLER, Kerry** [US/US]; 6534 4th Ave NW, Seattle, Washington 98117 (US). **HAWTHORN, Nataly** [US/US]; 15629 NE 106th Way, Redmond, Washington 98052 (US). **HUANG, Danwen** [US/US]; 1924 235th Ct. NE, Sammamish, Washington 98074 (US). **BOHAN, Jin** [CN/US]; 37101

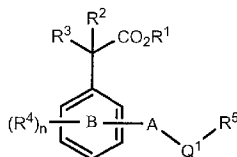
SE Stewart Street, Snoqualmie, Washington 98065 (US). **KIM, Musong** [US/US]; 2610 194th St SE, Bothell, Washington 98012 (US). **LOVER, Andrew** [US/US]; 6053 25th Ave NE, Seattle, Washington 98115 (US). **ODINGO, Joshua** [US/US]; 20117 84th Pl NE, Bothell, Washington 98011 (US). **OLIVER, Amy** [US/US]; 3312 189th Pl SE, Bothell, Washington 98012 (US). **REED, Mark** [GB/US]; 4301 Lake Washington Blvd, Apt 1105, Kirkland, Washington 98033 (US). **RUAN, Fuqiang** [US/US]; 16701 SE 63rd Pl, Bellevue, Washington 98006 (US). **THORSETT, Eugene** [US/US]; 410 2nd Ave S, Unit 304, Kirkland, Washington 98033 (US).

(74) Agents: **HOPKINS, Mark, H.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, Eighth Floor, San Francisco, California 94111 (US).

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[Continued on next page]

(54) Title: SUBSTITUTED PHENYL ACETIC ACIDS AS DP-2 ANTAGONISTS



(I)

(57) 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.

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SUBSTITUTED PHENYL ACETIC ACIDS AS DP-2 ANTAGONISTS

BACKGROUND OF THE INVENTION

[0001] Prostaglandin D₂ (PGD₂) is the major proinflammatory mediator abundantly
5 secreted by mast cells activated by allergen exposure of a previously sensitized host. PGD₂ 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 PGD₂ are mediated by
at least 3 distinct G-protein coupled receptors: The high affinity receptors DP-1 (formerly
10 known as DP) and DP-2 (formerly known as orphan receptor 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 PGD₂ binds with low affinity.

[0002] DP-2 receptor is a major contributor to the pathophysiological actions of PGD₂.

15 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
20 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.

[0003] DP-2 agonists are capable of directly activating inflammatory cells and
DP-2-mediated activation and mediator release from Eosinophils and Basophils has been
25 reported (see Gervais, F. G. *et al.*, *J Allergy Clin Immunol* (2004), 108 (6):982-8;
Yoshimura-Uchiyama, C. *et al.*, *Clin 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
30 differentiation, mast cell growth, differentiation and IgE synthesis, and the differentiation,
infiltration and survival of eosinophils.

[0004] This suggests that the PGD₂/DP-2 pathway acts as a positive feedback loop and augments pathologic responses in disorders associated with excessive or dysregulated PGD₂ 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.

[0005] The utility of PGD₂ antagonists in the treatment of inflammatory disorders is supported by clinical studies with Ramatroban[®] (Baynas, BAY u3405). Clinical studies have demonstrated a beneficial effect of Ramatroban[®] on rhinitis symptoms as well as inflammatory markers in nasal lavages, suggesting anti-inflammatory activity. Ramatroban[®] 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[®] 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 PGD₂ and other DP-2 agonists on these cells, it is reasonable to postulate that the clinical benefit of Ramatroban[®] 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 PGD₂ pathway is deregulated, as well as other disorders where the utility of Ramatroban[®] has been established.

[0006] Minami et al. have demonstrated the effectiveness of Ramatroban[®] on edema in experimental allergic conjunctivitis (*See Minami, K., et al. Int. Immunopharmacol.* 2004, **4**(12):1531-5). It has been demonstrated that DP-2 exerts an essential role in allergic disorders, specifically, IgE-mediated cutaneous responses that occur in chronic contact hypersensitivity (*See Mitsumori, S., Curr. Pharm. Des.*, 2004, **10**(28):3533-8); Moroi, R., et al. *30th Annu. Meet. Jpn. Soc. Invest. Dermatol.* (Apr 20-Apr 22, Yokohama) 2005, Abst. 48).

[0007] Numerous compounds have been reported as modulators of PGD₂ receptors and/or useful for the treatment of allergic and inflammatory disorders. WO 2006021418 discloses a series of sulfamyl-benzimidazole-1-yl-acetic acid compounds with DP-2 or PGD₂ antagonist activity. WO 2006021759 discloses a series of biphenyloxyacetic acid derivatives with PGD₂ and DP-2 modulating activity said to be useful for the treatment of respiratory disorders.

WO 2005019171, WO 2004106302 and WO 2005054232 disclose a series of Acetic acid-indole, -indazole and -benzimidazole compounds said to be useful for the treatment of respiratory disorders. WO 2005105727 discloses phenoxy acetic acid compounds with DP-2 antagonistic activity. WO 2005018529 discloses phenoxy acetic acid compounds said to be useful for the treatment of asthma and rhinitis. WO 2005040114 and WO 2005040112 discloses a series of compounds with DP-2 or PGD₂ antagonist activity said to be useful for the treatment of allergy, asthma and atopic dermatitis. WO 2004058164, U.S. Patent publication No. 2005038070 and WO 2005007094 disclose a series of compounds said to be useful for the treatment of allergy, asthma, cancer and inflammation. WO 2004096777 discloses a series of pyrimidine derivatives useful for the treatment of conditions mediated by DP-2, including asthma conjunctivitis, dermatitis, atopic rhinitis, allergic sinusitis. WO 2004078719 discloses a series of indole compounds said to be useful for the treatment of asthma and allergic rhinitis. U.S. Patent publication No. 2004132772 discloses a series of tetrahydroquinoline compounds as DP-2 antagonists said to be useful for the treatment of allergic asthma and allergic rhinitis. WO 2003066046, WO 2003066047, WO 2003101961, WO 2003101981, WO 2004007451 discloses a series of indole-acetic acids said to be useful in the treatment of asthma, chronic obstructive pulmonary disease (COPD), rhinitis and other conditions. WO 2003097598 discloses a series of compounds said to exhibit PGD₂ receptor antagonism. U.S. Patent No. 4,656,192 discloses a series of Tropolone compounds said to be useful as anti-tumor agents. EP 1170594 discloses methods for the identification of compounds useful for the treatment of conditions mediated by prostaglandin D₂, a ligand for orphan receptor DP-2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity.

[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

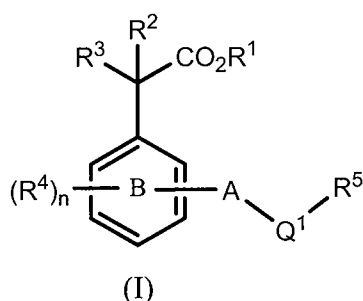
[0009] It has now surprisingly been found that certain phenyl acetic acids are potent DP-2 receptor antagonists. In certain embodiments, the phenyl acetic acids are selective DP-2 receptor antagonists over other PGD₂ receptors. The phenyl acetic acid compounds of the invention are expected to be potentially 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

- 5 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.

- 10 **[0011]** The compounds of the invention have the general structure (I):



- [0012]** A is a 5-14-membered heterocyclic ring fused or bonded to phenyl ring B 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.
- 15

[0013] Q¹ is selected from the group consisting of: a bond, -C₁-C₄alkylene-, -C₁-C₄heteroalkylene-, -CO-, -NH-, -O-, -SO_q-, -C(O)O-, -OC(O)-, -CONH-, -NHCO-, -NHCONH-, -NHSO_q-, -SO_qNH- and -COCH₂HNSO_q.

- 20 **[0014]** Each R¹, R² and R³ is independently selected from the group consisting of H, C₁₋₆alkyl, C₀₋₆alkylaryl and C₀₋₆alkylheteroaryl; wherein the aryl or heteroaryl portions are optionally substituted with C₁₋₆alkyl, CN, OR, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO_qR, SO_qNR₂, OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R and NRC(O)OR.

- 25 **[0015]** Each R⁴ is independently selected from the group consisting of C₁₋₆alkyl, C₀₋₄alkylC₃₋₁₀cycloalkyl, C₀₋₄alkylaryl, C₀₋₄alkylheteroaryl, C₂₋₄alkenylaryl, C₂₋₄alkynylaryl,

C₀₋₄alkylheterocyclyl, CN, amino, NHCOR¹, hydroxy, C₁₋₆alkoxy, OC(O)R¹, -OC₀₋₄alkylaryl, OC₀₋₄alkylheteroaryl, -OC₀₋₄alkylC₃₋₁₀cycloalkyl, OC₀₋₄alkylC₃₋₁₀heterocycloalkyl, OC₀₋₄alkylNR⁸, nitro, halo and haloC₁₋₆alkyl; or are combined together to form an aryl or heterocyclyl ring 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 C₁₋₆alkyl, CN, CONHR¹, CO₂R¹, amino, C₁₋₆alkoxy, halo, haloC₁₋₆alkyl and SO_qR¹.

[0016] R⁵ is selected from the group consisting of C₁₋₆alkyl, C₀₋₄alkylaryl, C₂₋₄alkenylaryl, C₂₋₄alkynylaryl, C₀₋₄alkylheteroaryl, each of which is optionally substituted with 1-3 R⁹ substituents.

[0017] Each R⁸ is independently selected from the group consisting of C₁₋₆alkyl, C₀₋₆alkylC₃₋₆cycloalkyl, C₀₋₆alkylaryl, C₀₋₆alkylheteroaryl, oxo, C₁₋₆alkyl, CN, OR, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO_qR, SO_qNR₂, OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R and NRC(O)OR.

[0018] Each R⁹ is independently selected from the group consisting of C₁₋₆alkyl, CN, OR, oxo, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO_qR, SO_qNR₂, OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R and NRC(O)OR.

[0019] Each R is independently selected from the group consisting of H, C₁₋₆alkyl, C₀₋₄alkylheteroaryl, C₀₋₄heterocyclyl, C₃₋₈cycloalkyl and C₀₋₄alkylaryl 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.

[0020] The subscript n is independently 0, 1, 2, 3 or 4.

[0021] Each subscript q is independently 0, 1 or 2.

[0022] The invention also provides pharmaceutically acceptable salts, hydrates, solvates and prodrugs of compounds of structure I. Examples of prodrugs are compounds wherein R¹ is C₁₋₆alkyl, C₀₋₆alkylaryl or C₀₋₆alkylheteroaryl wherein the aryl or heteroaryl portions are optionally substituted as described herein.

[0023] The invention also provides pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, excipient or diluent.

[0024] 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 PGD₂ receptors.

[0025] 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 PGD₂ or a metabolite thereof comprising administering to a subject in need thereof a therapeutically effective amount of a compound of structure I.

[0026] The invention further provides methods for treating or preventing an inflammatory disorder or condition with an inflammation or allergic component as provided herein.

[0027] The invention also provides methods for treating or preventing a condition or disorder mediated by DP-2 and/or one or more other PGD₂ receptors, e.g., DP-1, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I.

[0028] The invention also provides methods for selectively modulating DP-2 in the presence of one or more other PGD₂ receptors, e.g., DP-1, comprising contacting a cell with a compound of structure I.

[0029] 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

[0030] 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 diisopropylamine, n-BuLi = n-butyl lithium, Na₂CO₃ = sodium carbonate, DME = dimethyl ether, K₂PO₄ = potassium phosphate, CH₂Cl₂ or DCM = dichloromethane, Et₃N = triethylamine, DIEA = Hunig's base or diisopropyl ethylamine, KOH = potassium hydroxide, NaOH = sodium hydroxide, TMS = trimethylsilyl, Tf = trifluoromethylsulfonyl, Boc = t-butylcarbonyl, Bz = benzyl, IPA = isopropyl alcohol, NBS = N-bromosuccinamide, AIBN = azobisisobutyronitrile (also azobisisobutyronitrile), Pin =

pinacolato, Cs_2CO_3 = cesium carbonate, HIV = human immunodeficiency virus, RLV = Raucher leukemia virus, IgE = immunoglobulin E.

[0031] 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.

[0032] 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., C_{1-8} 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, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like.

[0033] 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., $\text{C}_2\text{-C}_8$ 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.

[0034] 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., $\text{C}_2\text{-C}_8$ means two to eight carbons) and one or more triple bonds. Examples of alkynyl groups include ethynyl, 1- and 3-propynyl, 3-butynyl and higher homologs and isomers thereof.

[0035] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from alkyl, as exemplified by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. Typically, an alkyl (or alkylene) 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 alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0036] 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.

[0037] 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 may be 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, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[0038] The terms "cycloalkyl", "heterocyclyl" 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, piperadinyl, tetrahydropyridinyl, piperazinyl, piperazin-1-oxide, morpholinyl, thiomorpholinyl, azepanyl, azepinyl, oxazepane, thiazepane,

azocanyl, azocinyl, indolyl, azaindole, tetrahydroquinoliny, decahydroquinoliny, tetrahydrobenzooxazepinyl dihydrodibenzooxepin, and the like.

[0039] 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 $(2m'+1)$, where m' is the total number of carbon atoms in the alkyl group. For example, the term "haloC₁₋₆alkyl" 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 $(2m'+1)$ halogen atoms). The term "perhaloalkyl" means, unless otherwise stated, alkyl substituted with $(2m'+1)$ halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example, the term "perhaloC₁₋₆alkyl", is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like.

[0040] 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-pyrimidyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1H-indazole, carbazole, α -carboline, β -carboline, γ -carboline, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl and 8-quinolyl.

[0041] 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, quinoxalyl or quinolyl group which is unsubstituted or substituted.

[0042] 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., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0043] 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.

[0044] 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'' R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR''R''', -NR'-SO₂NR''R''', -NR'CO₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -SO₂R', -SO₂NR'R'', -NR'SO₂R, -CN and -NO₂, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R', R'' and R''' each independently refer to hydrogen, unsubstituted C₁₋₆alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-C₁₋₆alkyl 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-morpholinyl. 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).

[0045] In some embodiments, substituents for the alkyl and heteroalkyl radicals are selected from: -OR', =O, -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'-SO₂NR''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', =O, -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.

[0046] 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''C(O)₂R', -NR'-C(O)NR''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, perfluoroC₁₋₆alkoxy, and perfluoroC₁₋₆alkyl, 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, C₁₋₆alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-C₁₋₆alkyl, and (unsubstituted aryl)oxy-C₁₋₆alkyl.

[0047] 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)_q-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)_r-B-, wherein A and B are independently -CH₂-, -O-, -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)_s-X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted C₁₋₆alkyl. Otherwise, R' is as defined above.

[0048] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0049] 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, monohydrogencarbonic, 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)). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention.

[0050] 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.

[0051] 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
5 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.

10 **[0052]** 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
15 intended to be within the scope of the invention.

[0053] 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
20 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 auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group,
25 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 diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0054] The compounds of the invention may also contain unnatural proportions of atomic
30 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 (^{125}I) or carbon-14 (^{14}C). 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.

5 **[0055]** 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.

10 **[0056]** 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.

[0057] “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.

15 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
20 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
25 relative to the control is 110%, optionally 150%, optionally 200-500%, or 1000-3000% higher.

[0058] 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,
30 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.

[0059] 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.

[0060] 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.

[0061] 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 biologics. 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.

[0062] 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.

[0063] 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 PGD₂ *in vitro* or *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.

[0064] As used herein, the terms "other PGD₂ receptor", "another PGD₂ 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 PGD₂ in vitro or in vivo. Another PGD₂ receptor may be selective for PGD₂, e.g., DP-1 (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 PGD₂ 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 PGD₂ receptor). The amino acid sequence of other PGD₂ receptor variants preferably is at least about 80% identical to the corresponding native other PGD₂ receptors, more preferably at least about 90% identical, and most preferably at least about 95% identical. Preferably, another PGD₂ receptor is DP-1.

[0065] As used herein, the term "DP-1" refers to a DP-1 receptor protein (RefSeq Accession No. NP-000944) or a variant thereof that is capable of mediating a cellular response to PGD₂ in vitro or in vivo. DP-1 variants include proteins substantially homologous to native DP-1, i.e., proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (e.g., DP-1 derivatives, homologs and fragments). The amino acid sequence of DP-1 variant preferably is at least about 80% identical to a native DP-1, more preferably at least about 90% identical, and most preferably at least about 95% identical.

[0066] As used herein, the term "TP" refers to a TP protein (RefSeq Accession No. NP-963998) or variant thereof that is capable of mediating a cellular response to PGD₂ *in vitro* or *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.

[0067] 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 PGD₂ receptors, e.g., DP-1, where such function may include transcription regulatory activity and/or protein-binding. Modulation may occur in vitro or in vivo. Modulation, as described
5 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 PGD₂ receptors, either directly or indirectly, and/or the upregulation or downregulation of the expression of DP-2 and/or one or more other PGD₂ receptors, either directly or indirectly. In a preferred embodiment, the modulation is direct. Inhibitors or antagonists are compounds
10 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 PGD₂ receptors can be demonstrated in
15 a biochemical assay, e.g., binding assay, or a cell-based assay, e.g., a transient transfection assay.

[0068] As used herein, the term "condition or disorder responsive to modulation of PGD₂ or a PGD₂ 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 PGD₂ receptor and at
20 least partially responsive to or affected by modulation of a PGD₂ receptor (e.g., a PGD₂ receptor antagonist or agonist results in some improvement in patient well-being in at least some patients). Inappropriate functional activity of a PGD₂ receptor might arise as the result of expression of a PGD₂ receptor in cells which normally do not express the receptor, greater than normal production of PGD₂, or slower than normal metabolic inactivation or elimination
25 of PGD₂ or its active metabolites, increased expression of a PGD₂ receptor or degree of intracellular activation (leading to, e.g., inflammatory and immune-related disorders and conditions) or decreased expression of a PGD₂ receptor. A condition or disorder associated with a PGD₂ receptor may include a "DP-2-mediated condition or disorder".

[0069] As used herein, the phrases "condition or disorder responsive to the antagonizing a
30 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

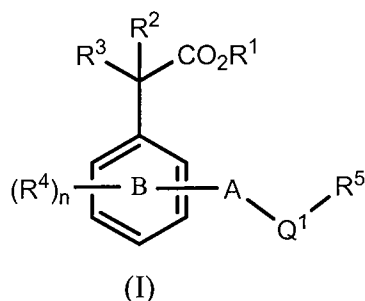
[0070] A class of compounds that antagonize DP-2 has been discovered. Depending on the biological environment (e.g., cell type, pathological condition of the host, etc.), these compounds can antagonize DP-2 and/or one or more other PGD₂ receptors (e.g., ligand binding). By antagonizing DP-2 and/or one 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.

[0071] 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.

[0072] Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein.

Compounds of the Invention

[0073] In one embodiment, the present invention provides compounds of the general structure (I):



[0074] A is a 5-14-membered heterocyclic ring fused or bonded to phenyl ring B 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.

[0075] Q¹ is selected from the group consisting of: a bond, -C₁-C₄alkylene-, -C₁-C₄heteroalkylene-, -CO-, -NH-, -O-, -SO_q-, -C(O)O-, -OC(O)-, -CONH-, -NHCO-, -NHCONH-, -NHSO_q-, -SO_qNH- and -COCH₂HNSO_q.

[0076] Each R¹, R² and R³ is independently selected from the group consisting of H, C₁₋₆alkyl, C₀₋₆alkylaryl and C₀₋₆alkylheteroaryl; wherein the aryl or heteroaryl portions are optionally substituted with C₁₋₆alkyl, CN, OR, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO_qR, SO_qNR₂, OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R and NRC(O)OR.

[0077] Each R⁸ is independently selected from the group consisting of C₁₋₆alkyl, C₀₋₆alkylC₃₋₆cycloalkyl, C₀₋₆alkylaryl, C₀₋₆alkylheteroaryl, oxo, C₁₋₆alkyl, CN, OR, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO_qR, SO_qNR₂, OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R and NRC(O)OR.

[0078] Each R⁴ is independently selected from the group consisting of C₁₋₆alkyl, C₀₋₄alkylC₃₋₁₀cycloalkyl, C₀₋₄alkylaryl, C₀₋₄alkylheteroaryl, C₂₋₄alkenylaryl, C₂₋₄alkynylaryl, C₀₋₄alkylheterocyclyl, CN, amino, NHCOR¹, hydroxy, C₁₋₆alkoxy, OC(O)R¹, -OC₀₋₄alkylaryl, OC₀₋₄alkylheteroaryl, -OC₀₋₄alkylC₃₋₁₀cycloalkyl, OC₀₋₄alkylC₃₋₁₀heterocyclyl, OC₀₋₄alkylNR⁸, nitro, halo and haloC₁₋₆alkyl; or are combined together to form an aryl or heterocyclyl ring 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 C₁₋₆alkyl, CN, CONHR¹, CO₂R¹, amino, C₁₋₆alkoxy, halo, haloC₁₋₆alkyl and SO_qR¹.

[0079] 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 C_{0-4} alkylheteroaryl, each of which is optionally substituted with 1-3 R^9 substituents.

[0080] 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_qR , SO_qNR_2 , $OC(O)OR$, $OC(O)R$, $OC(O)NR_2$, $NRC(O)NR_2$, $NRC(O)R$ and $NRC(O)OR$.

[0081] Each R is independently selected from the group consisting of H, C_{1-6} alkyl, C_{0-4} alkylheteroaryl, C_{0-4} heterocyclyl, C_{3-8} cycloalkyl and C_{0-4} 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.

[0082] The subscript n is independently 0, 1, 2, 3 or 4;

[0083] The subscript o is independently 0 or 1;

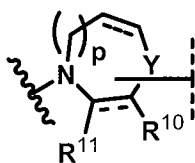
[0084] Each subscript q is independently 0, 1 or 2.

[0085] In another embodiment, the present invention provides pharmaceutically acceptable derivatives thereof.

[0086] In another embodiment, A is fused to phenyl ring B. In another embodiment, A is bonded to phenyl ring B.

[0087] In another embodiment, R^1 , R^2 and R^3 are each independently selected from the group consisting of H, C_{1-6} alkyl and C_{0-6} alkylaryl. In one embodiment, R^1 , R^2 and R^3 are each independently selected from the group consisting of H, CH_3 and phenyl. In one embodiment, R^1 is H. In another embodiment, R^2 and R^3 are H.

[0088] In another embodiment, A has the structure (II):



(II)

wherein

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

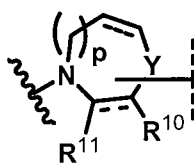
R¹⁰ and R¹¹ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;

the subscript p is independently 0, 1 or 2;

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

the wavy line indicates the point of attachment to Q¹ and the dashed line indicates the point
of attachment to phenyl ring B.

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



(II)

wherein

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

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

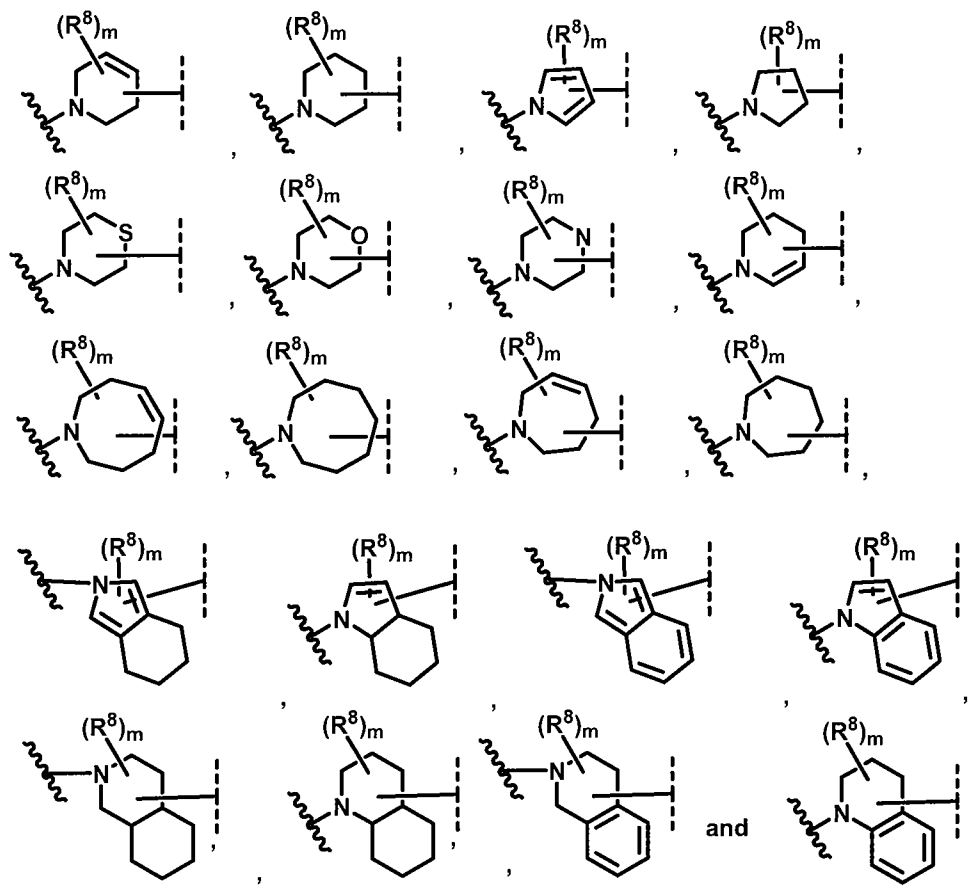
the subscript p is independently 0, 1 or 2;

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

the dashed line indicates the point of attachment to Q¹ and the wavy line indicates the point
of attachment to phenyl ring B.

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

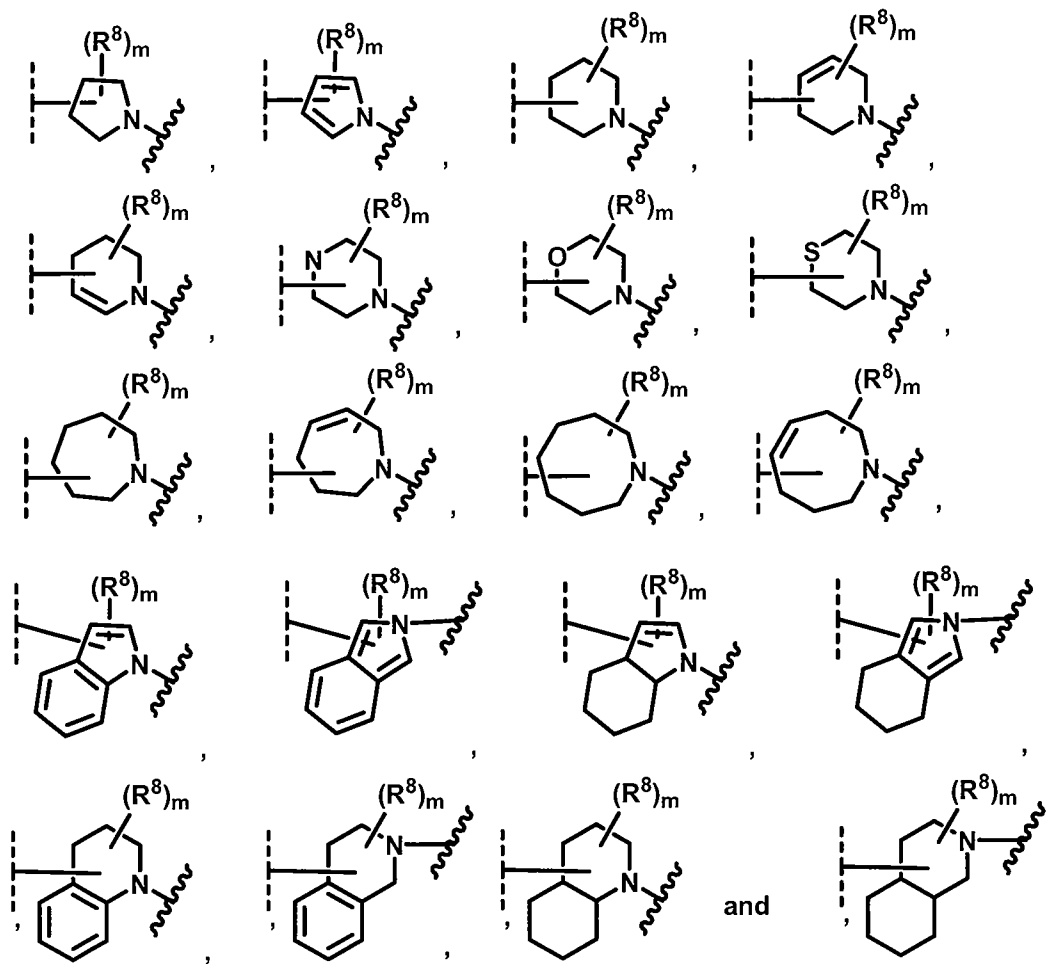
[0091] In another embodiment, A has a formula selected from the group consisting of:



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 phenyl ring B.

- 5 [0092] In another embodiment, A has a formula selected from the group consisting of:

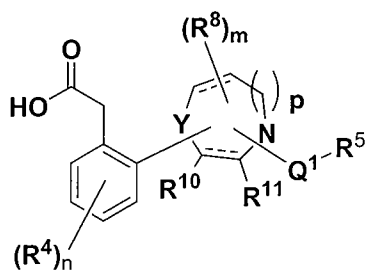


m is an integer from 0 to 3; and

the wavy line indicates the point of attachment to Q¹ and the dashed line indicates the point of attachment to phenyl ring B.

- 5 [0093] In another embodiment, Q¹ is selected from a bond, -C₁-C₄alkylene-, -C₁-C₄heteroalkylene-, -CO-, -NH-, -O-, -SO_q-, -C(O)O-, -OC(O)-, -CONH-, -NHCO-, -NHCONH-, -NHSO_q-, -SO_qNH- and -COCH₂HNSO_q. In another embodiment, Q¹ is a bond. In another embodiment, Q¹ is -C₁-C₄alkylene-. In another embodiment, Q¹ is -C₁-C₄heteroalkylene-. In another embodiment, Q¹ is -CO-. In another embodiment, Q¹ is a -NH-. In another embodiment, Q¹ is a -O-. In another embodiment, Q¹ is -SO_q-. In another embodiment, Q¹ is -C(O)O-. In another embodiment, Q¹ is -OC(O)-. In another embodiment, Q¹ is -CONH-. In another embodiment, Q¹ is -NHCO-. In another embodiment, Q¹ is -NHCONH-. In another embodiment, Q¹ is -NHSO_q-. In another embodiment, Q¹ is -SO_qNH-. In another embodiment, Q¹ is -COCH₂HNSO_q.

- 15 [0094] In another embodiment, the compound has a structure (III):



(III)

wherein

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

5 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

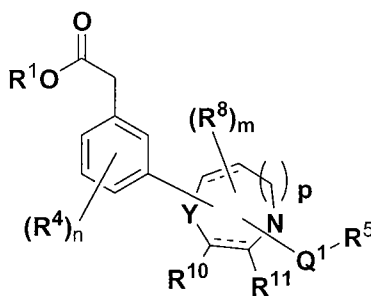
each dashed ring bond independently indicates the presence of a single, double or normalized bond.

10 [0095] In another embodiment, A is fused to phenyl ring B. In another embodiment, A is bonded to phenyl ring B.

[0096] In another embodiment, Y is CH₂ and p is 0.

[0097] In another embodiment, the compound is 2-(2-(1-tosylpiperidin-3-yl)phenyl)acetic acid or 2-(2-(1-tosylpiperidin-4-yl)phenyl)acetic acid.

15 [0098] In another embodiment, the compound has a structure (IV):



(IV)

wherein

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

R^{10} and R^{11} are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;

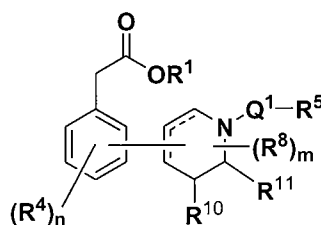
the subscript m is independently 0, 1, 2 or 3;

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

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

[0099] In another embodiment, Y is CH_2 and p is 0.

[0100] In another embodiment, the compound has the general structure (IVa):



(IVa).

10 [0101] In another embodiment, Q^1 is $-CO-$.

[0102] In another embodiment, the compound is
{3-[1-(4-fluoro-benzoyl)-piperidin-3-yl]-phenyl}-acetic acid.

[0103] In another embodiment, Q^1 is $-SO_q-$.

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

- 15 {3-[1-(4-fluoro-benzenesulfonyl)-piperidin-2-yl]-phenyl}-acetic acid;
2-(3-(1-(methylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(4-(4-chlorobenzoyloxy)-3-(1-(methylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(thiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(thiophen-3-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
20 2-(3-(1-(5-chlorothiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(5-bromothiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(benzofuran-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(pyridin-3-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(benzylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
25 (E)-2-(3-(1-(styrylsulfonyl)piperidin-3-yl)phenyl)acetic
acid; {3-[1-(Toluene-4-sulfonyl)-decahydro-quinolin-3-yl]-phenyl}-acetic acid;

- {3-[1-(4-Fluoro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-3-yl]-phenyl}-acetic acid;
2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid; 2-(3-(1-tosylpiperidin-3-yl)phenyl)
acetic acid; 2-(4-(4-chlorobenzyloxy)-3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(3,5-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
5 (2-(3-(1-(2,3-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(4-nitrophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(naphthalen-1-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
{3-[1-(4-Fluoro-benzenesulfonyl)-6-methyl-piperidin-3-yl]-phenyl}-acetic acid methyl
2-(3-(1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetate;
10 2-(3-(1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid;
2-(3-(1-(4-fluorophenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid;
{3-[1-(4-Fluoro-benzenesulfonyl)-4-methyl-piperidin-3-yl]-phenyl}-acetic acid methyl ester;
{3-[1-(4-Fluoro-benzenesulfonyl)-4-methyl-piperidin-3-yl]-phenyl}-acetic acid;
{3-[1-(4-Fluoro-benzenesulfonyl)-2-methyl-piperidin-3-yl]-phenyl}-acetic acid;
15 {3-[1-(4-Fluoro-benzenesulfonyl)-6-methyl-piperidin-3-yl]-phenyl}-acetic acid;
2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(4-(4-chlorobenzyloxy)-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(4-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid; methyl
2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate;
20 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-chloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(2-chloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-2-methylphenyl)acetic acid;
{3-[1-(4-Fluoro-benzenesulfonyl)-piperidin-3-yl]-5-hydroxy-phenyl}-acetic acid;
25 {3-Benzyloxy-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
{3-(4-Chloro-benzyloxy)-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic
acid; {3,4-Dichloro-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
{3-Amino-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
{3-[4-Cyclohexyl-1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
30 {3-[1-(4-Fluoro-benzenesulfonyl)-4-phenyl-piperidin-3-yl]-phenyl}-acetic acid;
{3-[1-(4-Fluoro-benzenesulfonyl)-4-phenyl-piperidin-3-yl]-phenyl}-acetic acid;
{3-Acetylamino-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
{3-[1-(4-Fluoro-benzenesulfonyl)-piperidin-3-yl]-5-phenoxy-phenyl}-acetic acid;
2-(3-(1-(4-fluorophenylsulfonyl) piperidin-3-yl)-4-methylphenyl) acetic acid;

- 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-methoxyphenyl)acetic acid;
 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-hydroxyphenyl)acetic acid;
 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-methylphenyl)acetic acid;
 2-(5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-2-methylphenyl)acetic acid;
 5 2-(3-(1-(4-cyanophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(4-*tert*-butylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(2,4-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(4-methoxyphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(*o*-tolylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 10 2-(3-(1-(2-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(4-ethylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(phenethylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(2-chloro-4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(butylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 15 2-(3-(1-(4-(methylsulfonyl)phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(3,4-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(4-fluoro-2-methylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(3-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
 2-(3-(1-(*m*-tolylsulfonyl)piperidin-3-yl)phenyl)acetic acid; Methyl
 20 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)phenyl)acetate; and
 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)phenyl)acetic acid.

[0105] In another embodiment, Y is a bond and p is 0.

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

- 2-(3-(1-(4-fluorophenylsulfonyl)pyrrolidin-3-yl)phenyl)acetic acid;
 25 2-(3-(1-(4-fluorophenylsulfonyl)-1H-pyrrol-3-yl)phenyl)acetic acid;
 {3-[1-(4-Fluoro-benzenesulfonyl)-4-phenyl-1H-pyrrol-3-yl]-phenyl}-acetic acid;
 [3-(1-Benzenesulfonyl-1H-indol-3-yl)-phenyl]-acetic acid;
 [3-(1-Methanesulfonyl-1H-indol-3-yl)-phenyl]-acetic acid;
 {3-[1-(4-Methoxy-benzenesulfonyl)-1H-indol-3-yl]-phenyl}-acetic acid;
 30 {3-[1-(4-Fluoro-benzenesulfonyl)-1H-indol-3-yl]-phenyl}-acetic acid;
 {3-[1-(Toluene-4-sulfonyl)-1H-indol-3-yl]-phenyl}-acetic acid; and
 {3-[1-(4-Fluoro-benzenesulfonyl)-2-methyl-1H-indol-3-yl]-phenyl}-acetic acid.

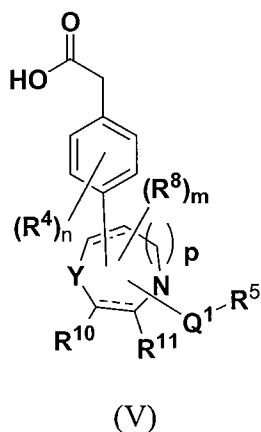
[0107] In another embodiment, Y is selected from the group consisting of N, O, NO and SO_q ;

[0108] In another embodiment, Q^1 is $-\text{CONH}-$.

[0109] In another embodiment, the compound is

5 {3-[1-(4-Fluoro-phenylcarbamoyl)-piperidin-3-yl]-phenyl}-acetic acid.

[0110] In another embodiment, the compound has a structure (V):



wherein

10 Y is selected from the group consisting of a bond, CH_2 , N, O, NO and SO_q ;

R^{10} and R^{11} are H or are combined together to form an aryl, heteroaryl, or cycloalkyl ring;

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

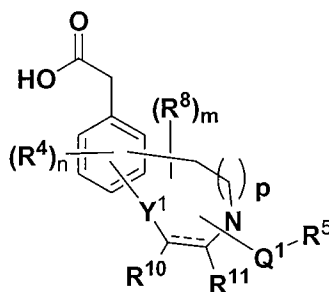
the subscript p is independently 0, 1 or 2; and

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

[0111] 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 $-\text{C}_1-\text{C}_4\text{heteroalkylene}-$. In another embodiment, Q^1 is $-\text{CO}-$. In another embodiment, Q^1 is $-\text{NH}-$. In another embodiment, Q^1 is $-\text{O}-$. 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 $-\text{NH}\text{SO}_q-$. In another embodiment, Q^1 is $-\text{SO}_q\text{NH}-$. In another embodiment, Q^1 is $-\text{COCH}_2\text{HNSO}_q$.

[0112] In another embodiment, the compound is
 {4-[1-(Toluene-4-sulfonyl)-piperidin-3-yl]-phenyl}-acetic acid.

[0113] In another embodiment, the compound has the structure (VI):



(VI)

wherein

Y^1 is selected from the group consisting of a bond, CH_2 , N, O, NO and SO_q ;

R^{10} and R^{11} are H or are combined together to form an aryl, heteroaryl, or cycloalkyl ring;

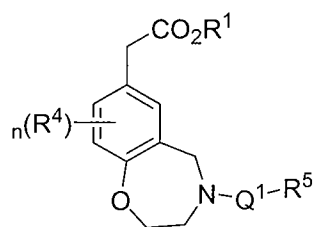
the subscript m is independently 0, 1, 2 or 3;

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.

[0114] In another embodiment, Q^1 is a bond. In another embodiment, Q^1 is $-C_1-C_4$ alkylene-. In another embodiment, Q^1 is $-C_1-C_4$ heteroalkylene-. In another embodiment, Q^1 is $-CO-$. In another embodiment, Q^1 is $-NH-$. In another embodiment, Q^1 is $-O-$. 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 $-NHCO-$. In another embodiment, Q^1 is $-NHCONH-$. In another embodiment, Q^1 is $-NHSO_q-$. In another embodiment, Q^1 is $-SO_qNH-$. In another embodiment, Q^1 is $-COCH_2HNSO_q-$.

[0115] In another embodiment, the compound has the general structure (VII):



(VII)

wherein R^1 is H or C_{1-6} alkyl;

each R^2 is independently selected from the group consisting of C_{1-4} alkyl, halo,
 5 aryl C_{1-4} alkoxy, optionally substituted with 1-3 R^7 substituents;

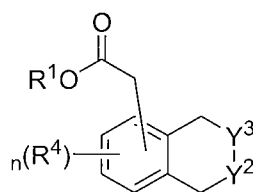
R^5 is aryl optionally substituted with 1-3 R^9 substituents; and

each R^9 is independently selected from the group consisting of halo and C_{1-6} alkyl.

[0116] In another embodiment, the compound is

2-(4-(2-(4-methylphenylsulfonamido)acetyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)ac
 10 etic acid.

[0117] In another embodiment, the compound has the general structure (VIII):



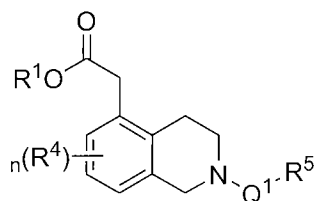
(VIII)

wherein:

15 each Y^2 or Y^3 is independently CH_2 or NQ^1R^5 ;

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

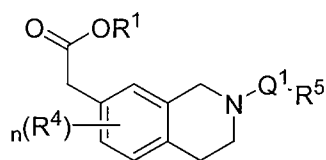
[0118] In another embodiment, the compound has the general structure (IX):



(IX).

[0119] In another embodiment, the compound is selected from the group consisting of: methyl 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetate; 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid; methyl 2-(2-(2-(4-fluorophenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetate; and 2-(2-(2-(4-fluorophenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid.

[0120] In another embodiment, the compound has the general structure (X):



(X)

wherein R¹ is H or C₁₋₆alkyl;

each R² is independently selected from the group consisting of C₁₋₄alkyl, halo, arylC₁₋₄alkoxy, optionally substituted with 1-3 R⁷;

R⁵ is aryl optionally substituted with 1-3 R⁹ substituents;

each R⁹ is independently selected from the group consisting of halo and C₁₋₆alkyl; and

the subscript n is independently 0 or 1.

[0121] In another embodiment, the compound is selected from the group consisting of: methyl 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetate; 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid; and 2-(2-(2-(4-methylphenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid.

[0122] Other embodiments, are disclosed in U.S. Patent Application., Dudler *et al.* and filed 9 June 2006, entitled "Substituted Phenyl Acetic Acids as DP-2 Antagonists" Attorney Docket No. 014233-003300US (which is incorporated herein by reference in its entirety).

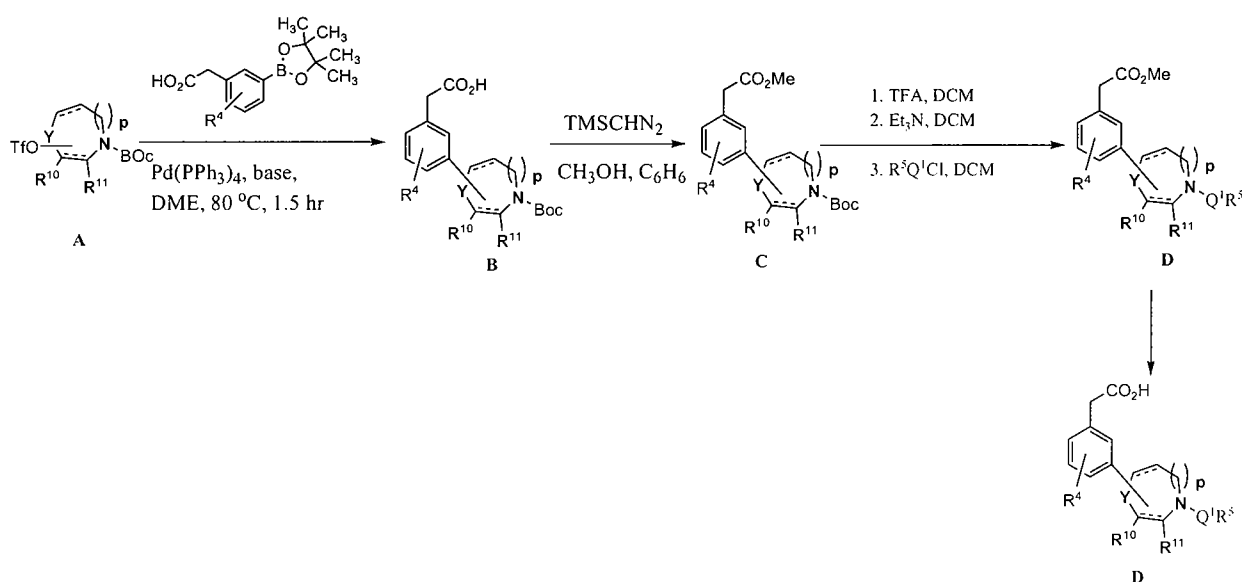
[0123] The invention encompasses novel compounds, novel pharmaceutical compositions and/or novel methods of use. While some compounds disclosed herein are available from commercial sources, the pharmaceutical compositions or methods of using these compounds are novel. Unless otherwise indicated, it is 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 PGD₂ receptors), and the like which include both the novel compounds of the invention and compounds that are commercially available.

Preparation of the Compounds

- 5 [0124] Synthetic routes to the compounds provided herein are also described in Schemes A-D 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
- 10 conditions compatible with a selected protecting group. Accordingly, the methods and reagents described herein are all expressed as non-limiting embodiments.

Scheme A



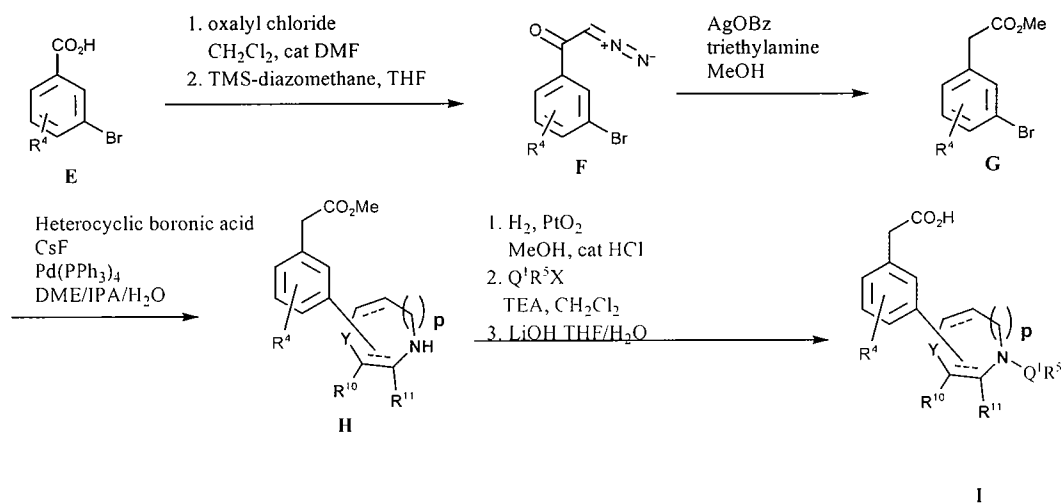
15

- [0125] In some embodiments, as shown in Scheme A, a triflate A can be obtained by treating a oxosubstituted heterocycle with triflic anhydride or N-phenyl triflimide in an anhydrous solvent such as THF, in the presence of a base such as LDA or nBuLi, at temperatures ranging from -78 °C to RT. The triflate can then be cross coupled with an
- 20 available aryl boronate ester in the presence of a palladium (0) source, and a base such as Na₂CO₃, in a solvent system such as DME/water or alternatively under anhydrous conditions

such as DME or DMF, and a base such as sodium carbonate Na_2CO_3 , or K_2PO_4 , optionally in the presence of CsF at temperatures varying from 40-100 °C, for 1-6 hours. The carboxylic acid **B** is then esterified using trimethyl silyl diazomethane in a solvent such as hexanes.

Removal of the protecting group occurs under standard conditions using for example TFA in a solvent such as DCM, at room temperature for 1-6 hours. Alkylation or acylation with a compound such as halide $\text{Q}^1\text{R}^5\text{X}$ under basic conditions such as Et_3N or DIEA in a solvent such as DCM, or alternatively using pyridine both as a solvent and a base, for a period of 5-12 hours, at room temperature leads to substituted heterocycle **C**. Saponification with a base such as KOH or NaOH in a solvent system such as methanol: water, for a period of 1-6 hours at temperatures between 35-65 °C, followed by a mild hydrogenation with a catalyst such as for example Pearlman's catalyst, or 10% palladium on carbon or platinum oxide, at room temperature under atmospheric pressure to 50 psi, in a solvent such as methanol, leads to a carboxylic acid of formula **D**.

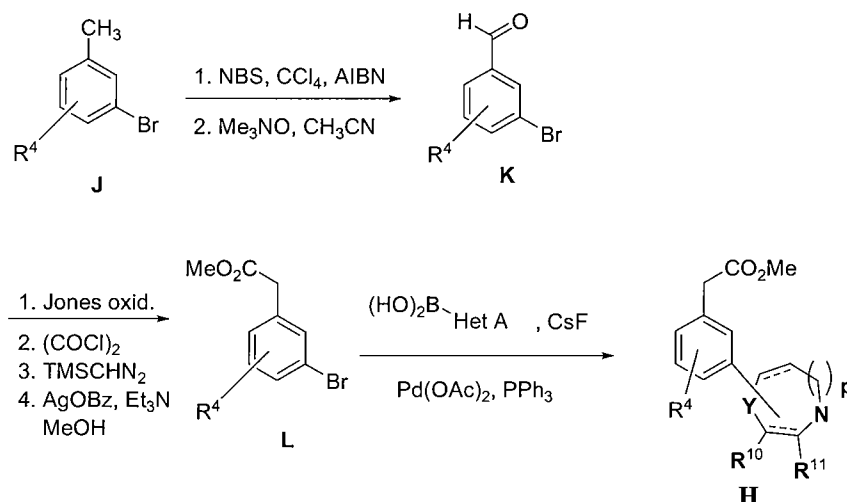
Scheme B



[0126] In some embodiments, as shown in Scheme B, an aryl benzoic acid **E** can be converted to a phenyl acetate **G** using an Arndt-Eistert reaction. Cross coupling of the aryl halide with a heterocyclic boronic acid or stannane in the presence of a palladium (0) source such as palladium tetrakis triphenyl phosphine, in a mixed solvent system such as DME/water, and a base such as cesium fluoride from 1 to 6 hours, at temperatures ranging from 25 to 80 °C. The heterocyclic methyl ester **H** may optionally be reduced using hydrogenation conditions such as platinum oxide, in a solvent like methanol, at room temperature, under pressure ranging from 10-50 psi for 1 to 9 hours and converted to

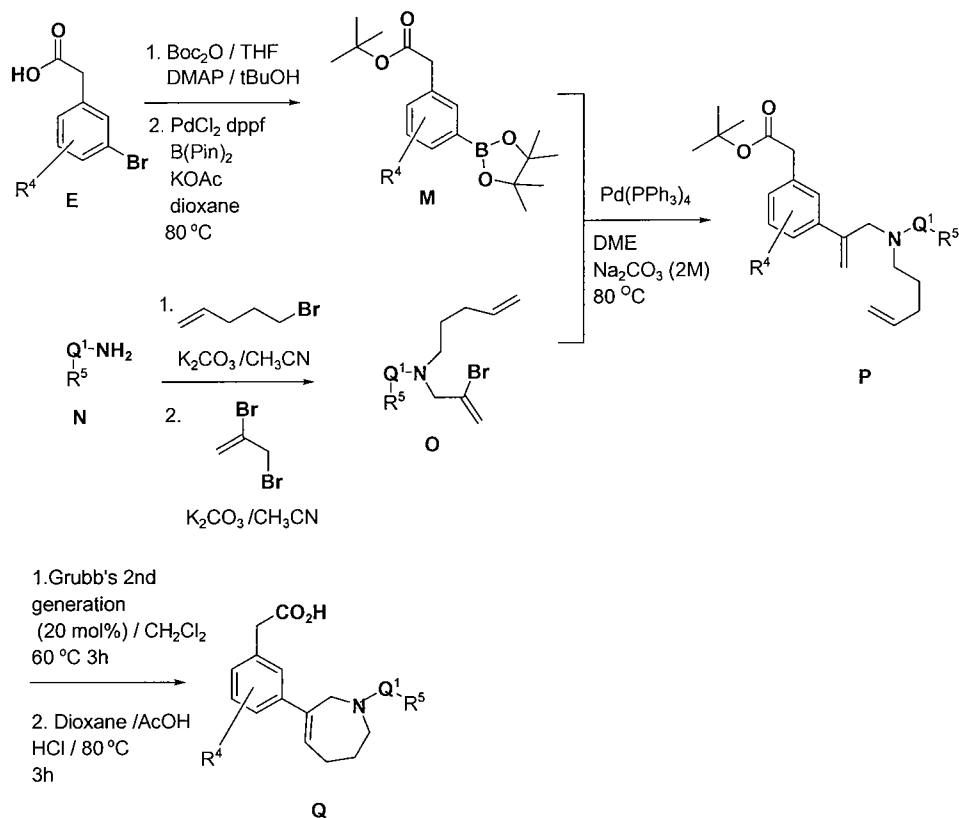
substituted heterocycle **I** upon treatment with acylating or alkylating agent such as halide Q^1R^5X , under conditions described in Scheme A, followed by a saponification described in Scheme A as well.

5 Scheme C



[0127] In some embodiments, as shown in Scheme C, aldehyde **J** was obtained by treatment with NBS and AIBN in a solvent such as carbon tetrachloride, followed by addition of trimethylamine N-oxide in a solvent such as CH_3CN , at temperatures ranging from room temperature to 80°C , over 15 hours. Oxidation of **K** with Jones's reagent in a solvent such as acetone, followed by the Arndt-Eistert reaction leads to **H**. Compound **H** is then converted to other products using chemistry described in Schemes A- B.

Scheme D



[0128] In some embodiments, as shown in Scheme D, esterification of aryl bromide **E** with di-tert-butyl dicarbonate in a mixed solvent system such as THF/tert-butyl alcohol ($tBuOH$), followed by treatment with bis-pinacolato diboron in the presence of a palladium (0) source and a mild base such as potassium acetate for example in dioxane at temperatures ranging from room temperature to $80^\circ C$ leads to boronate ester **M**. Tri-alkylated amine **O** was obtained by successive treatment of an amine **N** with alkyl halides in a solvent system such as AcCN at room temperature or acetone under reflux conditions for a period of time ranging from 3-12 hours, in the presence of a mild base such as K_2CO_3 or Cs_2CO_3 . A standard cross coupling between boronate ester **M** and alkenyl bromide **O** leads to amine **P** in the presence of a palladium (0) source such as palladium tetrakis triphenylphosphine in a solvent system such as DME, an aqueous base such as sodium carbonate at temperatures ranging from 25 to $90^\circ C$, for 2-13 hours. A ring cyclization, facilitated by Grubb's second generation catalyst, for example benzylidene [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]di(chloro(tricyclohexylphosphine) ruthenium in a solvent such as DCM at temperatures varying from 25 to $60^\circ C$, for a period of 1 to 6 hours leads to a seven-membered heterocycle. Saponification under acidic conditions, using hydrochloric acid in dioxane for a period of 2 to 10 hours at temperatures close to reflux leads to heterocycle **Q**.

Analysis of the Compounds

[0129] 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.

[0130] 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.

[0131] 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 **[0132]** 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 PGD₂, to pharmaceutical compositions containing these derivatives and to processes for their preparation.

10 **[0133]** 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 PGD₂ and its metabolites. Non-limiting example of such conditions and disorders include:

15 **[0134]** 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;
20 sarcoidosis; farmers 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;

30 **[0135]** 2) Skin and Eyes conditions or disorders such as dermatitis, e.g., allergic contact dermatitis, atopic dermatitis (eczema), contact (and irritant contact) dermatitis, excematous dermatitis, neurodermatitis, perioral dermatitis, seborrheic dermatitis, stasis 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;

[0136] 3) Gastrointestinal System conditions or disorders such as food-induced allergies (e.g., those that have effects remote from the gut such as migraine, rhinitis and eczema); eosinophilic gastroenteritis; mastocytosis; ulcerative colitis; Crohn's disease; irritable bowel syndrome; celiac disease;

[0137] 4) Central nervous system conditions or disorders such as inflammatory pain, neuropathic pain;

[0138] 5) Conditions or disorders relating to other systems: e.g., eosinophilic fascitis; hyper IgE syndrome; systemic mast cell disorder; Idiopathic 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;

[0139] 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 nodosa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), psoriatic arthritis, Raynaud's phenomenon, and Still's disease;

[0140] 7) Autoimmune conditions or disorders, e.g., systemic lupus erythematosus, 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 leukocytoclastic angiitis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, autoimmune neutropenia, Diabetes mellitus, Hashimoto's disease, Grave's disease, autoimmune polyglandular syndromes, multiple sclerosis, myasthenia gravis, Behcet's

syndrome, pernicious anemia, primary biliary sclerosis, autoimmune hepatitis, autoimmune myocarditis, Goodpasture's syndrome, glomerular nephritis, and tubulointerstitial nephritis; and

[0141] 8) Other conditions or disorders associated with raised levels of PGD₂ or its metabolites.

[0142] 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 PGD₂ 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 PGD₂ 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 parasital 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), Sjögren'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.

10 [0143] 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 a condition or disorder a therapeutically effective amount of one or more of the subject compounds or compositions.

15 [0144] 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- $\Delta^{12,14}$ PGJ₂, 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.

20 [0145] 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.

25 [0146] 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.

30 [0147] 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.

[0148] 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, intracisternal 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.

[0149] 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.

[0150] 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

[0151] 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.

[0152] 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).

[0153] 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.

[0154] 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.

- 5 [0155] 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.

- 10 [0156] 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
15 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
20 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.

- 25 [0157] 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.

- 30 [0158] 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.

[0159] 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.

[0160] 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.

[0161] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous 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.

[0162] 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.

[0163] 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

[0164] In some embodiments, the agents are administered directly to the lung by inhalation.

5 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).

[0165] For aerosol delivery in humans or other primates and mammals, the aerosol is
10 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
15 not be too irritating at the required dosage.

[0166] 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
20 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
25 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.

[0167] The total amount of compound delivered to a mammalian host will depend upon
30 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.

[0168] 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

[0169] 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 TG134a, 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.

[0170] 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 [0171] 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
10 most preferably up to 30 percent by volume. The remainder of the volume is made up of water.

Combination Therapy

- 15 [0172] 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.
- 20 [0173] 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,
25 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.
- [0174] Such other agents, or drugs, may be administered, by a route and in an amount
30 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.

[0175] 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, Prograf[®]), rapamycin (sirolimus, Rapamune[®]) and other FK-506 type immunosuppressants, and mycophenolate, e.g., mycophenolate mofetil (CellCept[®]); (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine, pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β 2-agonists (e.g., terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, salmeterol, bitolterol and pirbuterol) and β 2-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, iralukast, 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, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid and tioxaprofen), acetic acid derivatives (e.g., indomethacin, acemetacin, alclofenac, clidanac, 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 flufenisal),

oxicams (e.g., isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (e.g., acetyl salicylic acid and sulfasalazine) and the pyrazolones (e.g., apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone and phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex[®]) and rofecoxib (Vioxx[®]); (h) inhibitors of

5 phosphodiesterase type IV (PDE-IV); (i) other PGD₂ receptor antagonists, especially DP-1 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,

10 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 benzaifibrate), probucol, nitroglycerin, and inhibitors of cholesterol absorption (e.g., beta-sitosterol and acylCoA-cholesterol acyltransferase (ACAT) inhibitors such as

15 melinamide), HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthetase inhibitors; (l) 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

20 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 (Rezulin[®]), 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

25 aurothioglucose, (p) TNF inhibitors, e.g., etanercept (Enbrel[®]), antibody therapies such as orthoclone (OKT3), 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)

30 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 (ST1571, Gleevec[®]) and rituximab (Rituxan[®]), 5-lipoxygenase activating protein (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

[0176] 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.

[0177] 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.

[0178] 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.

5 [0179] 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.

[0180] 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
10 challenge with a symptom-producing substance or activity, the spirometry test is readministered. If the spirometry measurements fall significantly, asthma is indicated.

[0181] 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.

15

EXAMPLES

General methods:

[0182] 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
20 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 MgSO_4 or Na_2SO_4 . Evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids such as
25 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
30 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 (TLC), 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:

[0183] 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

Time	% organic	Organic Solvent
0.0	10	AcCN
0.2	10	AcCN
3.8	95	AcCN
4.1	95	AcCN
4.4	10	AcCN
6.0	10	AcCN

Method B:

[0184] 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

Time	% organic	Organic Solvent
0.0	10	AcCN
0.2	10	AcCN
3.8	95	AcCN
4.1	95	AcCN
4.4	10	AcCN
6.0	10	AcCN

Method C:

[0185] 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.

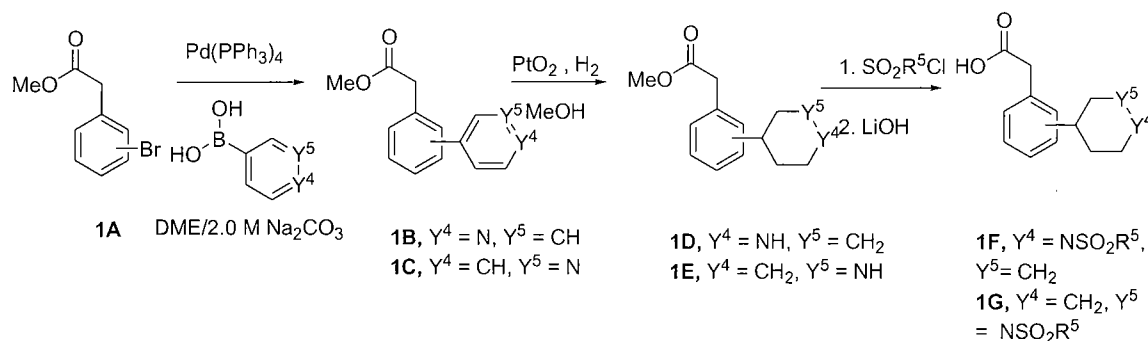
10 **Gradient**

Time	% organic	Organic Solvent
0.0	35	methanol
0.2	35	methanol
3.6	98	methanol
4.1	98	methanol
4.4	35	methanol
6.0	35	methanol

Examples 1-3

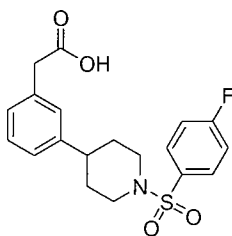
[0186] A general procedure for the synthesis of phenyl piperidine series are shown below (Scheme 1).

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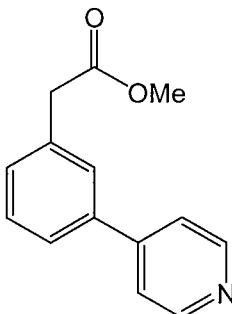
Scheme 1

Example 1

2-(3-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)phenyl)acetic acid (**Compound 1G**)

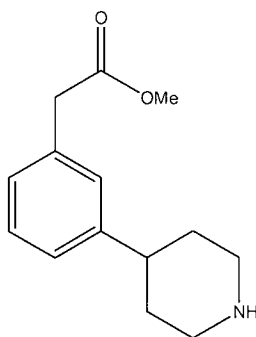


Methyl 2-(3-(pyridin-4-yl)phenyl)acetate (**Compound 1B**)



- [0187] 4-Pyridine boronic acid (325 mg, 2.64 mmol) and palladium tetrakis (140 mg, 0.12 mmol) were added to a stirring solution of methyl 2-(3-bromophenyl)acetate (550 mg, 2.4 mmol) in dimethoxy ethane and 2 M Na₂CO₃ (2:1 mixture, 12 mL). The resulting suspension was refluxed for 3 h, cooled, and then diluted with ethyl acetate (EtOAc) (10 mL). The mixture was washed with H₂O (20 mL) and the organic layers were dried over Na₂SO₄ (s) and concentrated to give a yellow oil (630 mg). Flash chromatography (3:1 hexanes/EtOAc) afforded pure acetate **2** (221 mg, 41 %) as a clear oil: ES/MS, calcd for C₁₄H₁₄NO₂ 228.1, found 228.1 (M+H).

Methyl 2-(3-(piperidin-4-yl)phenyl)acetate (**Compound 1D**)

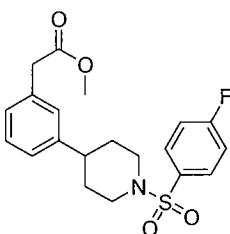


- [0188] PtO₂ (12 mg, 0.053 mmol) and conc. HCl (2 drops) were added to a solution of **2** (120 mg, 0.53 mmol) in MeOH (5 mL). The resulting mixture was attached to Parr shaker and pressurized to 40 psi (H₂) and shook for 1 h. Once the reaction is completed the

suspension was filtered through CELITE and filter cake was washed with MeOH. The combined organic layer was concentrated to give crude piperidine **1D** (76 mg) as a clear oil. The crude mixture was carried to the next step with no further purification: ES/MS, calcd for $C_{14}H_{20}NO_2$ 234.1, found 234.1 (M+H).

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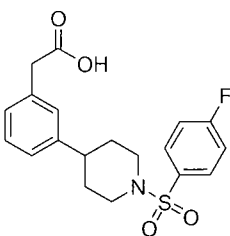
Methyl 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)phenyl)acetate (**Compound 1E**).



[0189] Hünig's base (0.515 mL, 2.96 mmol) and 4-fluorobenzenesulfonyl chloride (210 mg, 1.08 mmol) were added to a stirring solution of **4** (230 mg, 0.986 mmol) in CH_2Cl_2 (5 mL) at RT. The resulting suspension was quenched with satd. $NaHCO_3$ (20 mL) after 15 h and the aqueous layer was extracted with EtOAc (3 X 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated to give brown oil (337 mg). The chromatography (1:1 hexanes/EtOAc) afforded **6a** as a clear oil (155 mg): ES/MS, calcd for $C_{20}H_{22}FNO_4S$ 391.1, found 391.1 (M+H).

15

2-(3-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)phenyl)acetic acid (**Compound 1G**)

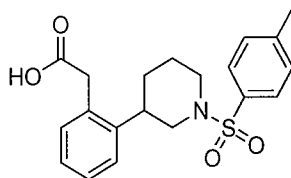


[0190] Lithium hydroxide (160 mg, 3.83 mmol) was added to a stirring solution of **1E** (150 mg, 0.383 mmol) in THF/MeOH/ H_2O (3:1:1, 5 mL) at RT. The resulting suspension was concentrated after 16 h then diluted back with H_2O (10 mL). The aqueous was washed with ether then acidified with conc. HCl (pH >1). The white precipitate was filtered (143 mg) and purified with HPLC to give **1G** (29 mg); ^1H NMR (400 MHz, $DMSO-d_6$) δ 12.28 (1H, bs) 7.86 (2H, m) 7.52 (2H, t, $J = 8.4$ Hz) 7.22 (1H, t, $J = 8.4$ Hz) 7.08 (3H, m) 3.77 (2H, d, $J =$

9.9 Hz) 3.15 (2H, s) 2.5 2.33 (2H, t, $J = 9.9$ Hz) 1.81 (2H, d, $J = 11.0$ Hz) 1.65 (2H, m); ES/MS, calcd for $C_{19}H_{21}FNO_4S$ 378.1, found 378.1 (M+H).

Example 2

- 5 Methyl 2-(2-(1-tosylpiperidin-3-yl)phenyl)acetic acid (**Compound 2A**) and 2-(2-(1-tosylpiperidin-3-yl)phenyl)acetic acid (**Compound 2B**):

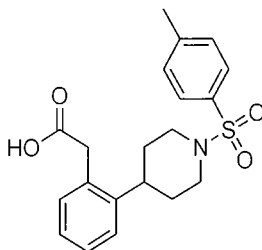


[0191] The compound(s) were prepared by the same procedure as

- 10 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)phenyl)acetic acid, **Compound IG**, using p-methyl phenylsulfonyl chloride; **Compound 2B** ^1H NMR (400 MHz, CD_3CN) δ 7.63 (2H, d, $J = 8.2$ Hz) 7.40 (2H, d, $J = 9.3$ Hz) 7.18 (4H, m) 3.80-5.65 (4H, m) 2.94 (1H, m) 2.43 (3H, s) 2.30 (3H, m) 1.78 (2H, m) 1.65 (1H, m) 1.42 (1H, m); ES/MS, m/z 374.1 (M+H).

15 Example 3

Methyl 2-(2-(1-tosylpiperidin-4-yl)phenyl)acetate (**Compound 3A**) and 2-(2-(1-tosylpiperidin-4-yl)phenyl)acetic acid (**Compound 3B**)

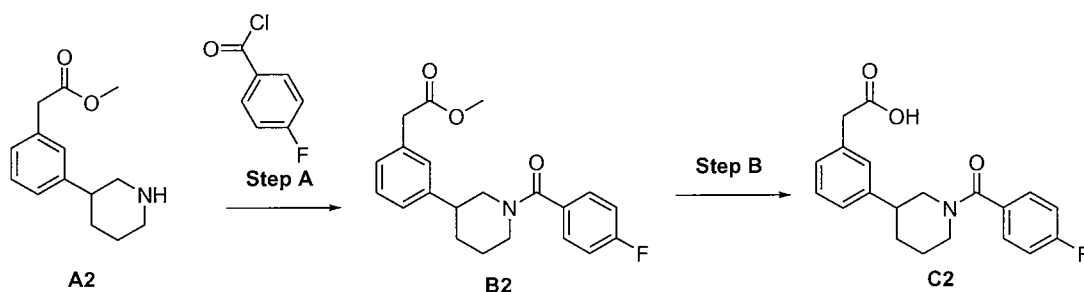


- 20 [0192] The compound(s) were by the same procedure as 2-(2-(1-tosylpiperidin-3-yl)phenyl)acetic acid, **Compound I**, using methyl 2-(2-bromophenyl)acetate; **Compound 3B** ^1H NMR (400 MHz, CD_3CN) δ 7.68 (2H, d, $J = 8.2$ Hz) 7.44 (2H, dd, $J = 0.7, 8.6$ Hz) 7.25 (2H, m) 7.15 (2H, m) 3.83 (2H, m) 3.61 (2H, s) 2.61 (1H, m) 2.45 (3H, s) 2.30 (2H, m) 2.16 (1H, brs) 1.74 (4H, m); ES/MS, calcd for $C_{20}H_{23}NO_4S$ 374.1, found 374.0 (M+H).
- 25

Example 4

Methyl 2-(3-(1-(4-fluorobenzoyl)piperidin-3-yl)phenyl)acetate (**Compound 4A**) and

2-(3-(1-(4-fluorobenzoyl)piperidin-3-yl)phenyl)acetic acid (**Compound 4B**):

5 **Scheme 2**10 **Step A:**

Methyl 2-(3-(1-(4-fluorobenzoyl)piperidin-3-yl)phenyl)acetate (**Compound 4A**)

[0193] To a solution of 100 mg (0.429 mmol, 1.0 equivalent) of methyl 2-(3-(piperidin-3-yl)phenyl)acetate (**A2**) in AcCN (5 ml) was added 1.1 equivalents of 4-fluorobenzoyl chloride (0.47 mmol, .0565 ml) and 3.0 equivalents (177.7 mg) K_2CO_3 .

15 Reaction was heated in the microwave to 150°C at 300 W power for 5 min. Reaction mixture was washed with water 3 times. Combined aqueous phase was extracted with EtOAc. Combined organic phase was washed with brine, dried over sodium sulfate, and concentrated to dryness on the RotorVap to yield crude methyl 2-(3-(1-(4-fluorobenzoyl)piperidin-3-yl)phenyl)acetate. MS (m/z) 356 (M+H)

20

Step B:

2-(3-(1-(4-fluorobenzoyl)piperidin-3-yl)phenyl)acetic acid (**Compound 4B**)

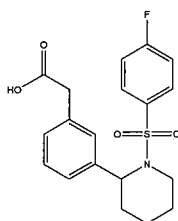
[0194] Crude methyl 2-(3-(1-(4-fluorobenzoyl)piperidin-3-yl)phenyl)acetate from step A was dissolved in THF (3 ml) and aqueous KOH (1.0 N, 3 ml) was added. Reaction was stirred for 4 hours. Reaction was acidified to pH 2-4 with 1.0 N aqueous HCl and extracted with EtOAc. Organic extracts were washed with brine, dried over sodium sulfate, and concentrated to dryness. Crude yield = 150 mg (0.439 mmol, >100%). Final product was

25

purified by HPLC using 0.05% formic acid modifier. Final yield = 70.37 mg (0.206 mmol).
LC/MS (Method A) Rt = 3.204 min. MS (m/z) 342 (M+H)

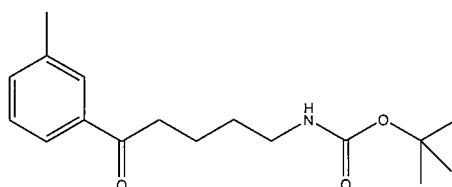
Example 5

5 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-2-yl)phenyl)acetic acid (**Compound 5G**)



Step A:

tert-butyl 5-oxo-5-m-tolylpentyl carbamate (**Compound 5A**)

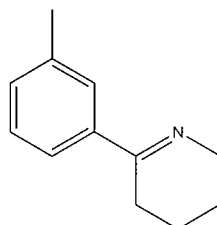


10

[0195] To N-Boc valerolactam (0.250g, 1.25mmol) in 3mL THF at -78 °C is added 3-tolyl
magnesium bromide (1.0M, 1.5mmol). The reaction stirs about 2 hours slowly warming to
room temperature. The reaction is quenched with sat. NH₄Cl (5mL) and extracted into DCM
3X. The combined extracts are dried over Na₂SO₄. The reaction is filtered, dried and passed
15 over silica eluting with 20% EtOAc in hexanes yielding the title compound. LC/MS (Method
A) Rt = 4.70 min. MS: 292 m/z (M+H).

Step B:

6-m-tolyl-2,3,4,5-tetrahydropyridine (**Compound 5B**)



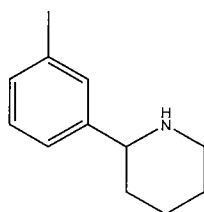
20

[0196] To *tert*-butyl 5-oxo-5-m-tolylpentyl carbamate, **Compound 5A**, (0.30g, 1.03mmol) in DCM (2mL) is added TFA (0.5mL). The reaction is judged complete by LC/MS after 4 hours. The mixture is dried and used without further purification. LC/MS (Method A) R_t = 0.99 min. MS: 174 m/z (M+H).

5

Step C:

2-m-tolylpiperidine (**Compound 5C**)

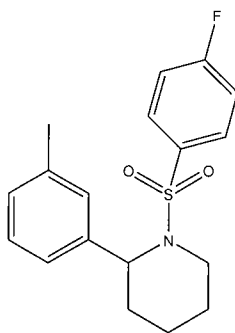


10 [0197] To compound 8 (0.050g, 0.29mmol) in methanol, **Compound 5B**, (1mL) is added sodium borohydride (0.0055g, 0.145mmol). The reaction is judged complete after 90 min. by LC/MS and quenched with water. The mixture is extracted into DCM 3X, the organic layers combined and dried. The material is used without further purification. LC/MS (Method A) R_t = 1.37 min. MS: 176 m/z (M+H).

15

Step D:

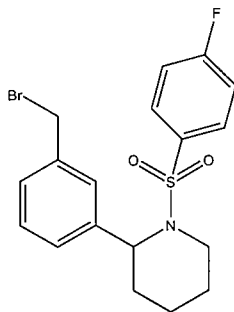
1-(4-fluorophenylsulfonyl)-2-m-tolylpiperidine (**Compound 5D**)



20 [0198] To 2-m-tolylpiperidine, **Compound 5C**, (0.017g, 0.097mmol) in 0.5mL DCM with DIEA (0.014g, 0.10mmol) is added 4-fluoro phenyl sulfonyl chloride (0.019g, 0.10mmol). The reaction is judged complete after 1 hour and dried. The resulting oil is purified over silica eluting with 25% EtOAc in hexanes. LC/MS (Method A) R_t = 4.30 min. MS: 334 m/z (M+H).

Step E:

2-(3-(bromomethyl)phenyl)-1-(4-fluorophenylsulfonyl)piperidine (**Compound 5E**)



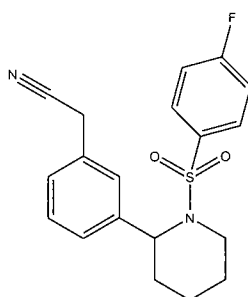
5

[0199] To 1-(4-fluorophenylsulfonyl)-2-m-tolylpiperidine, **Compound 5C**, (0.090g, 0.27mmol) in 2mL CCl₄ is added AIBN (0.004g, 0.027mmol) and NBS (0.058g, 0.32mmol). The mixture is stirred in a sealed tube at 80 °C. Two more equal portions of NBS are added over the next 48 hours. At the end of this time the reaction is worked up by passing over silica eluting with 50% EtOAc in hexanes. The material is used as a mixture of the alpha-bromo and tolyl phenyl piperidines. LC/MS (Method A) Rt = 4.28 min. MS: 410 m/z (M+H).

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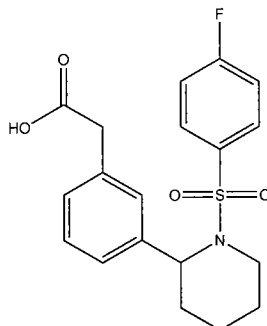
Step F:

2-(3-(1-(4-fluorophenylsulfonyl)piperidin-2-yl)phenyl)AcCN (**Compound 5F**)



[0200] To 2-(3-(bromomethyl)phenyl)-1-(4-fluorophenylsulfonyl)piperidine (0.035g, 0.084mmol) in 2mL AcCN is added K₂CO₃ (0.023g, 0.168mmol) and NaCN (0.005g, 0.10mmol). The mixture is stirred 16 hours at 80 °C, then cooled to RT. The title compound is purified by HPLC eluting with AcCN and water both modified with 0.05% formic acid. LC/MS (Method A) Rt = 3.86 min. MS: 359 m/z (M+H).

20

Step G:2-(3-(1-(4-fluorophenylsulfonyl)piperidin-2-yl)phenyl)acetic acid (**Compound 5G**)

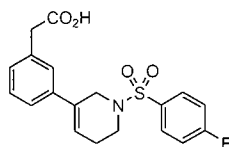
5

[0201] To 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-2-yl)phenyl)AcCN, **Compound 5F**, (0.005g, 0.014mmol) in 0.25mL methanol is added 0.5mL 3N NaOH. The reaction is stirred at 40 °C for 48hours, then concentrated *in vacuo*. The basic solution is acidified to pH 1 with 1N HCl. The aqueous is extracted into DCM 3X. The dried material is used without further purification. LC/MS (Method A) Rt = 3.56 min. MS: 378 m/z (376 m/z M-H).

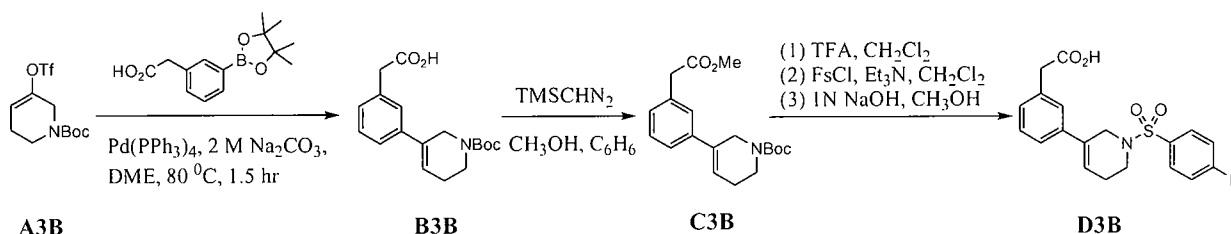
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Example 6

2-(3-(1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid (**Compound 6**)

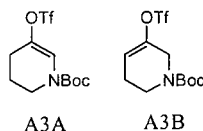


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Scheme 3

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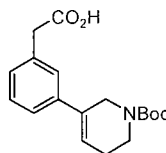
Step A: *tert*-butyl 5-(trifluoromethylsulfonyloxy)-3,4-dihydropyridine-1-(2H)-carboxylate (**Compound A3A**) and *tert*-butyl 3-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1-(2H)-carboxylate (**Compound A3B**)



- 5 **[0202]** The synthesis of the triflates **A3A** and **A3B** was based on the procedure reported (Vicart, N. et al. *Tetrahedron* 1996, **52**(27): 9101-10) with some modifications: To a solution of LDA (2M solution from Aldrich, 14.3 ml) in THF (50ml) at -78 °C was added a solution of N-Boc-3-piperidone (4 g, 20 mmol) in THF (10 ml) dropwise. After 15 min, N-phenyltriflimide (8.6 g, 24 mmol) in THF (20 ml) was added. The reaction mixture was slowly warmed up to RT, and stirred at RT overnight. After addition of saturated NH₄Cl (15 ml) at 0°C, the mixture was diluted with water (100 ml), and extracted with CH₂Cl₂ (3 x 100 ml). The extracts were dried (Na₂SO₄), evaporated and flash chromatographed on silica-gel with 20% EtOAc/Hexane. Further purification on silica-gel (5%, 10% and 20% EtOAc/Hexane) gave the triflate **A3A** (2.6 g, 44 %) and **A3B** (2.1 g, 35.6 %) as yellow oils.
- 10 The triflate **A3A**: ¹H NMR (300 MHz, DMSO-d₆) δ: 7.15 (1H, bs), 3.45 (2H, m), 2.40 (2H, t, J=5 Hz), 1.86 (2H, m), 1.44 (9H, s). The triflate **A3B**: ¹H NMR (300 MHz, DMSO-d₆) δ: 6.12 (1H, m), 4.0 (2H, b), 3.39 (2H, t, J=5.5 Hz), 2.26 (2H, m), 1.41 (9H, s).

Step A:

- 20 2-(3-(1-(*tert*-butoxycarbonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid (**Compound B3**)



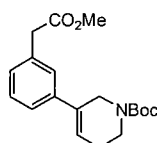
- [0203]** To a degassed mixture of the triflate **A3B** (100 mg, 0.34 mmol), 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetic acid (135 mg, 0.51 mmol) in 2M Na₂CO₃ (aq. 1.1 ml) and DME (1.7 ml) was added Pd(PPh₃)₄ (20 mg). The reaction mixture was stirred at 80°C under N₂ for 1.5 h, and diluted with H₂O (10 ml) and acidified with 10% KHSO₄ at 0°C, followed by extraction with EtOAc (3 x 10 ml). The combined

organic layers were dried (Na_2SO_4), evaporated and chromatographed on silica-gel with 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ to yield the desired product (60 mg, 56%) as a black residue. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 12.3 (1H, bs), 7.28 (3H, m), 7.17 (1H, m), 6.25 (1H, m), 4.19 (2H, b), 3.57 (2H, s), 3.46 (2H, t, $J=5.5$ Hz), 2.25 (2H, m), 1.42 (9H, s).

5

Step B:

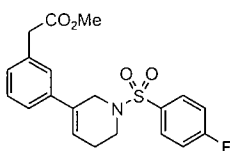
tert-butyl 3-(3-(2-methoxy-2-oxoethyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate
(Compound C3B)



- 10 [0204] To a solution of
2-(3-(1-(*tert*-butoxycarbonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid (60 mg, 0.19 mmol) in MeOH (0.42 ml) and C_6H_6 (1.5 ml) was added TMSCHN_2 (2 M solution in hexane, 0.12 ml, 0.24 mmol). The reaction mixture was stirred at rt for 0.5 hr. The volatiles were removed *in vacuo*, and the resulting residues were co-evaporated with MeOH to yield the
15 desired product (60 mg, 100%), which was used in the next step without further purification.
 ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 7.30 (3H, m), 7.18 (1H, m), 6.26 (1H, m), 4.19 (2H, b), 3.70 (2H, s), 3.62 (3H, s), 3.46 (2H, t, $J=6$ Hz), 2.25 (2H, m), 1.43 (9H, s).

Step C: Methyl

- 20 2-(3-(1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetate (Compound D3A)

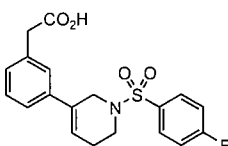


- [0205] To a solution of *tert*-butyl 3-(3-(2-methoxy-2-oxoethyl)phenyl)-5,6-dihydropyridine
25 -1(2H)-carboxylate (60 mg, 0.19 mmol) in CH_2Cl_2 (1.5 ml) was added TFA (1.5 ml). The reaction mixture was stirred at rt for 0.5 hr. The volatiles were removed *in vacuo*, and the resulting residues were co-evaporated with CHCl_3 twice. To a solution of this amine as a TFA salt in CH_2Cl_2 (2.5 ml) was added Et_3N (0.066 ml, 0.47 mmol), followed by

p-fluorobenzenesulfonyl chloride (0.044 g, 0.23 mmol). After stirred at rt overnight, the reaction mixture was quenched by addition of saturated NaHCO_3 (15 ml). After stirring at rt for 1 h with cat. amount of DMAP, the mixture was extracted with EtOAc (3 x 15 ml). The combined organic layers were washed with 1N HCl (15 ml), saturated NaHCO_3 (15 ml) and saturated NaCl (15 ml), then dried (MgSO_4) and evaporated to dryness to yield the desired product (63 mg, 85%) as an orange residue. MS (m/z) 390.1 ($\text{M}+\text{H}$)/Rt = 3.91 min.

Step D: Methyl

2-(3-(1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetate (**Compound D3B**)

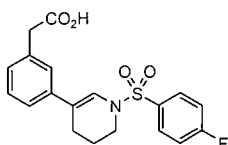


[0206] To a solution of methyl

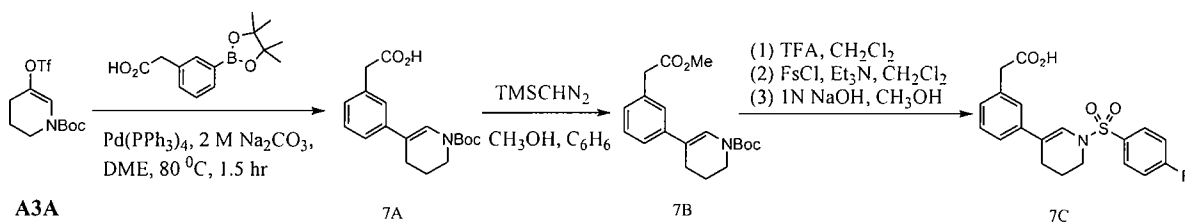
2-(3-(1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetate (0.063 g, 0.16 mmol) in MeOH (2 ml) was added 1N NaOH (1ml). The reaction mixture was stirred at rt for 4 hr, acidified with 1N HCl at 0°C and evaporated to dryness. The resulting residues were purified by HPLC (Column: Phenomenex, 250 X 10 mm, 10 micro, Luna 10 μ ; Gradient: 90%:10%:0.05% $\text{H}_2\text{O}/\text{CH}_3\text{CN}/\text{TFA}$ to 5%/95%/0.05% $\text{H}_2\text{O}/\text{CH}_3\text{CN}/\text{TFA}$ over 16 min) to afford the title product, 36.7 mg (61%), as a white solid: MS (m/z) 376.1 (M^{H})/Rt = 3.43 min.

Example 7

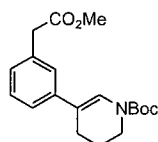
2-(3-(1-(4-fluorophenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid (**Compound 7**)



Scheme 4

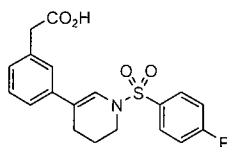


5 **Steps A and B:** *tert*-butyl 5-(3-(2-methoxy-2-oxoethyl)phenyl)-3,4-dihydropyridine-1-(2H)-carboxylate (**Compound 7B**)



[0207] To a degassed mixture of the triflate **A3A** (100 mg, 0.34 mmol), the boronic acid
 10 (135 mg, 0.51 mmol) in 2 M Na₂CO₃ (1.1 ml) and DME (1.7 ml) was added Pd(PPh₃)₄ (20 mg). The reaction mixture was stirred at 80°C under N₂ for 1.5 h, and diluted with H₂O (10 ml) and acidified with 10% KHSO₄ at 0°C, followed by extraction with EtOAc (3 x 10 ml). The combined organic layers were dried (Na₂SO₄), evaporated to yield a black residue (100 mg). To a solution of the resulting residues in MeOH (0.75 ml) and C₆H₆ (2.6 ml) was added
 15 TMSCHN₂ (2 M solution in hexane, 0.88 ml). The reaction mixture was stirred at rt for 0.5 hr. The volatiles were removed *in vacuo*. The resulting residues were co-evaporated with MeOH, and chromatographed on silica-gel with 15% EtOAc/hexane to yield the desired product (44 mg, 39%) as a colorless residue. MS (m/z) 232.1 (M⁺-Boc+H)/Rt = 4.25 min.

20 **Step C:** 2-(3-(1-(4-fluorophenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid (**Compound 7C**)

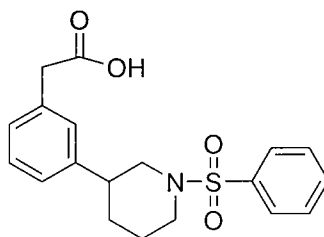


[0208] To a solution of *tert*-butyl 3-(3-(2-methoxy-2-oxoethyl)phenyl)-5,6-dihydropyridine-1-(2H)-carboxylate (44 mg, 0.133 mmol) in CH₂Cl₂ (1.5 ml) was added TFA
 25 (0.75 ml). The reaction mixture was stirred at RT for 0.5 hr. The volatiles were removed *in vacuo*, and the resulting residues were co-evaporated with CHCl₃ twice. To a solution of this amine as a TFA salt in CH₂Cl₂ (2.0 ml) was added Et₃N (0.047 ml, 0.34 mmol), followed by

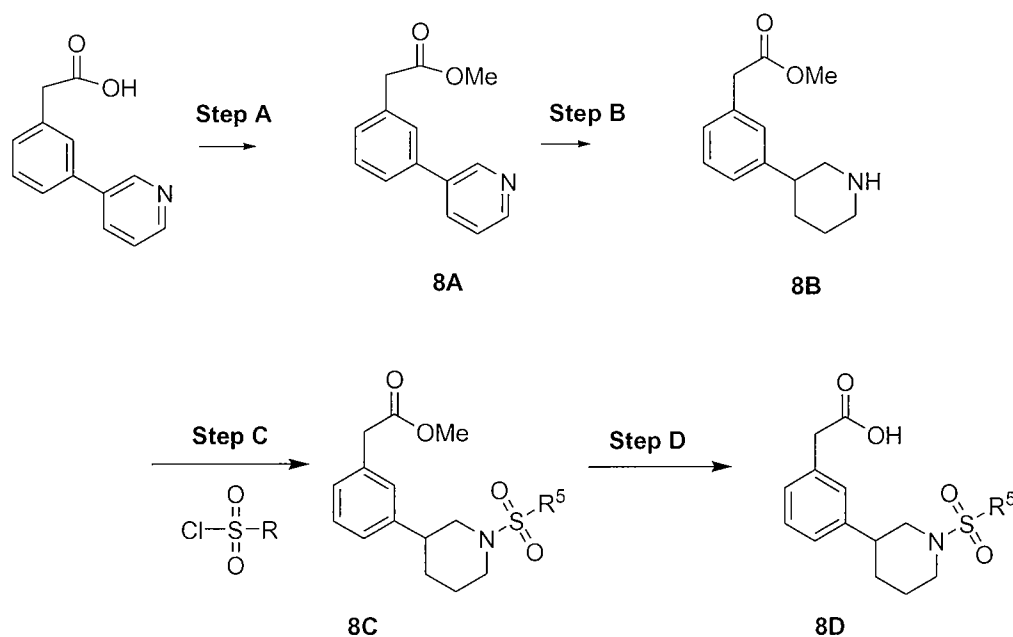
p-fluorobenzenesulfonyl chloride (0.031 g, 0.16 mmol). After stirred at RT overnight, the reaction mixture was quenched by addition of saturated NaHCO_3 (10 ml). After stirring at RT for 1 h with cat. amount of DMAP, the mixture was extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with 1N HCl (10 ml), saturated NaHCO_3 (10 ml) and saturated NaCl (10 ml), then dried (MgSO_4) and evaporated to dryness to yield a residue (44 mg). To a solution of the resulting residue in MeOH (1 ml) was added 1N NaOH (0.25 ml), The reaction mixture was stirred at RT overnight, acidified with 1N HCl at 0°C and evaporated to dryness. The resulting residues were purified by HPLC (Column: Phenomenex, 250 X 10 mm, 10 micro, Luna 10 μ ; Gradient: 90%:10%:0.05% $\text{H}_2\text{O}/\text{CH}_3\text{CN}/\text{TFA}$ to 5%/95%/0.05% $\text{H}_2\text{O}/\text{CH}_3\text{CN}/\text{TFA}$ over 16 min) to afford the title product, 12.9 mg (25.9%), as a white solid: MS (m/z) 376.1 ($\text{M}^+ + \text{H}$)/ R_t = 3.53 min.

Example 8

2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 8**)



Scheme 5



Step A: Methyl 2-(3-(pyridine-3-yl)phenyl)acetate (Compound 8A)

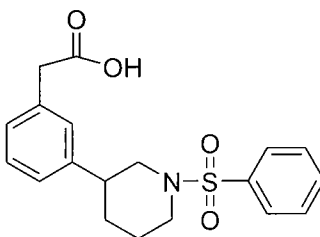
[0209] To 2-(3-(pyridine-3-yl)phenyl) acetic acid (400mg, 1.878mmol) in MeOH (5ml) was added thionyl chloride (0.205ml, 2.817mmol), the solution was brought to reflux for 5h.

5 The product (0.426mg, 100%) was afforded after concentration. LC/MS Rt = 2.126 min. (Method A); MS (m/z) 228 (M + H).

Step B: Methyl 2-(3-(piperidin-3-yl)phenyl)acetate (Compound 8B)

10 [0210] To the methyl ester (280mg, 1.234mmol) in MeOH (5ml) was added the catalytic amount of PtO₂. The suspension was purged 3 times, and was stirred at 1atm under H₂ overnight. The catalyst was filtered off through CELITE. The mixture was concentrated to remove solvent, the product methyl 2-(3-(piperidin-3-yl)phenyl) acetate (Intermediate 1, 287mg, 100%) was obtained. Rt = 1.624 min. (Method A); MS (m/z) 234 (M + H).

15

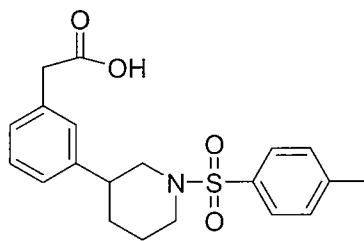
Steps C and D: 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (Compound 8D)

20 [0211] To intermediate 1 (84.8mg, 0.364mmol) in DCM (2ml) was added DIEA (0.095ml, 0.546mmol), followed by the addition of phenylsulfonyl chloride (0.056ml, 0.437mmol). The mixture was stirred at RT overnight. The methyl ester (63.6mg, 47%) was afforded after flash column chromatography with EtOAc/hexanes. The product was then dissolved in THF (1ml), 1ml of aqueous 1N NaOH was added. The mixture was stirred overnight. Diluted with EtAc (15ml), washed with 1N HCl (3 X 2ml), dried over Na₂SO₄, the desired material

25 (55.4mg, 93%) was obtained. LC/MS Rt = 3.486 min. (Method A); MS (m/z) 360 (M + H).

Example 9

Methyl 2-(3-(1-tosylpiperidin-3-yl)phenyl) acetate (**Compound 9A**) and
2-(3-(1-tosylpiperidin-3-yl)phenyl) acetic acid (**Compound 9B**)



[0212] The title compounds were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using

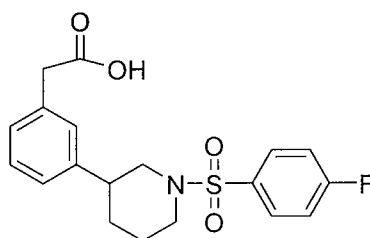
5 4-methyl-phenyl sulfonyl chloride. **Compound 9B** Rt = 3.639 min. (Method A); MS (m/z) 374 (M + H)

Example 10

Methyl 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 10A**)

10 and

2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 10B**)



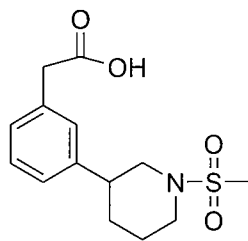
[0213] The title compounds were obtained using the same experimental procedure

15 described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 4-fluorophenyl sulfonyl chloride. **Compound 10B** Rt = 3.562 min. (Method A); MS (m/z) 378 (M + H).

Example 11

Methyl 2-(3-(1-(methylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 11A**) and

20 2-(3-(1-(methylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 11B**)



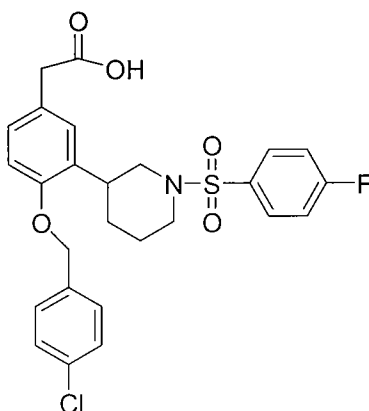
[0214] The title compounds were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using methyl sulfonyl chloride. Rt = 2.895 min. (Method A); MS (m/z) 298 (M + H).

5

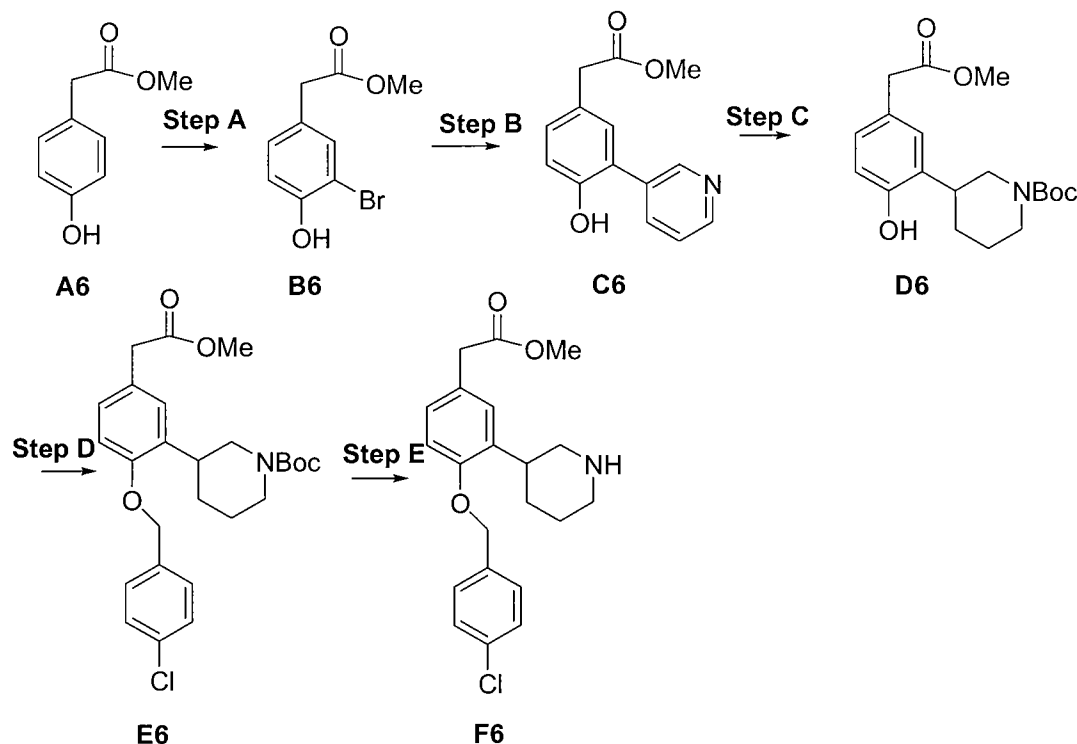
Example 12

Methyl 2-(4-(4-chlorobenzyloxy)-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate
(**Compound 12A**) and

2-(4-(4-chlorobenzyloxy)-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid

10 (**Compound 12B**)

Scheme 6



5 **Methyl 2-(4-(4-chlorobenzoyloxy)-3-(piperidin-3-yl)phenyl)acetate (F6)**

Step A:

[0215] To 4-hydroxyphenyl methyl acetate (6.0g, 36mmol) in DCM (30ml) was added Br₂ (2.22ml, 43.2mmol) at 0 °C. After 30min, the mixture was allowed to warm up to RT, and
 10 stirred at the temperature for 2h. The mixture was diluted with 80ml of DCM, and was washed with H₂O (3 X 20ml), dried over Na₂SO₄, 3-bromo-4-hydroxyphenyl methyl acetate (8.86g, 100%) was yielded.

Step B:

[0216] To the mixture of 3-bromo-4-hydroxyphenyl methyl acetate (1.56g, 6.341mmol) and pyridin-3-ylboronic acid in DME (15ml) was added palladium tetrakis (366mg, 0.317mmol), followed by the addition of CsF (2.89g, 19.0mmol) in water (5ml). The mixture
 15 was heated at 85 °C overnight. The reaction mixture was diluted with EtAc (100ml), washed with sat Na₂CO₃ (3 X 20ml), dried over Na₂SO₄. The product (0.818g, 55%) was afforded after column chromatography on silica gel.

Step C:

[0217] To 4-hydroxy-3-(pyridin-3-yl)phenyl methyl acetate (300mg, 1.234mmol) in MeOH (2ml) was added 1ml of 1N HCl in Et₂O, after stirred for 5min, the solvents were pumped off. The residue was dissolved in MeOH (5ml), and was added the catalytic amount of PtO₂. The suspension was purged 3 times, and was stirred at 1atm under H₂ for 3h. The catalyst was filtered off through CELITE. Concentrated to remove solvent, the product amine was obtained and dissolved in DCM (4ml). DIEA (0.644ml, 3.70mmol) and Boc anhydride (404mg, 1.852mmol) were added into the solution. The mixture was stirred at RT overnight. The product (223mg, 50%) was obtained after flash column chromatography on silica gel.

Step D:

[0218] To the previous product (223mg, 0.640mmol) in CH₃CN (3ml) were added K₂CO₃ and chlorobenzyl chloride (124mg, 0.768mmol). The reaction mixture was heated at 80 °C overnight. The desired product (217mg, 72%) was yielded after flash column chromatography, and was treated with TFA (0.35ml) in 4ml DCM. After 1h stirring at RT, the SM had disappeared, intermediate **2** was used without further purification. Rt = 2.553 min. (Method A); MS (m/z) 374 (M⁺ + H).

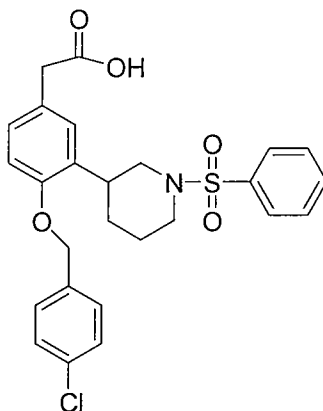
Step E:

[0219] To intermediate **F6** (56.9mg, 0.152mmol) in DCM (2ml) was added DIEA (0.133ml, 0.763mmol), followed by the addition of the 4-fluorophenylsulfonyl chloride (35.6mg, 0.183mmol). The mixture was stirred at RT for 3h. The product (80mg, 99%) was afforded after flash column chromatography on silica gel. The product was then dissolved in THF (1ml), 1ml of aqueous 1N NaOH was added. The mixture was stirred overnight. Diluted with EtOAc (15ml), washed with 1N HCl (3 X 2ml), dried over Na₂SO₄, the final product (73.5 mg, 95%) was obtained. Rt = 4.209 min. (Method A); MS (m/z) 518 (M + H).

Example 13

Methyl 2-(4-(4-chlorobenzyloxy)-3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 13A**) and

2-(4-(4-chlorobenzoyloxy)-3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid
(**Compound 13B**)

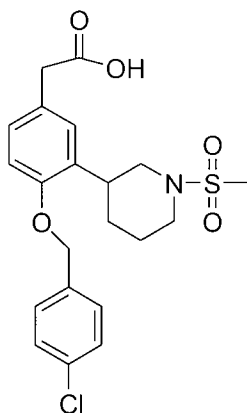


[0220] The desired material using the procedure described for

- 5 2-(4-(4-chlorobenzoyloxy)-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using phenyl sulfonyl chloride. **Compound 13B** LC/MS Rt = 4.156 min. (Method A); MS (m/z) 501 (M + H)

Example 14

- 10 Methyl 2-(4-(4-chlorobenzoyloxy)-3-(1-(methylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 14A**) and
2-(4-(4-chlorobenzoyloxy)-3-(1-(methylsulfonyl)piperidin-3-yl)phenyl)acetic acid
(**Compound 14B**)



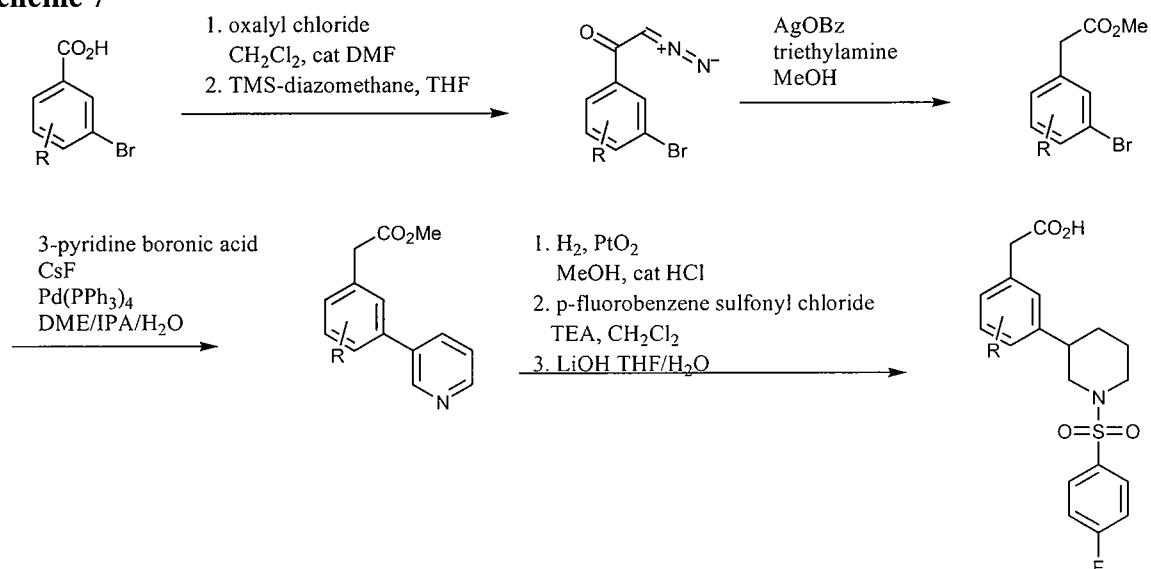
- 15 [0221] The desired material using the procedure described for
2-(4-(4-chlorobenzoyloxy)-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using methyl sulfonyl chloride. **Compound 14B** LC/MS Rt = 3.699 min. (Method A); MS (m/z) 438 (M+ H)

Examples 15-20

2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 15**) and analogs

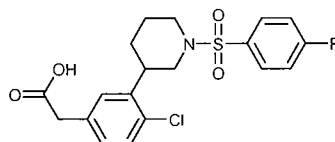
- 5 **[0222]** Substituted analogues of were prepared according to Scheme 7. The benzoic acids were homologated using an Arndt-Eistert protocol. The esters were then coupled to a boronic acid, which was reduced and sulfonylated. Finally, the ester was saponified to produce the free acid.

10 **Scheme 7**



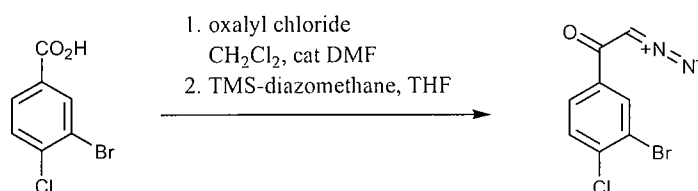
Example 15

2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 15F**)



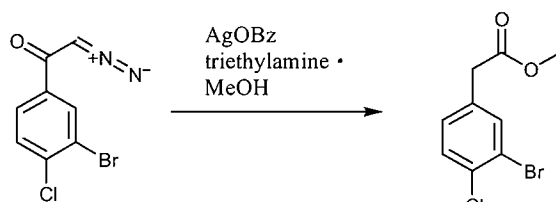
15

Step A: 1-(3-bromo-4-chlorophenyl)-2-diazoethanone (**Compound 15A**)



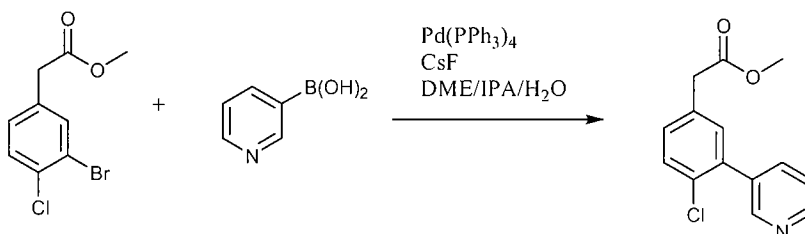
[0223] 1.5 g of 3-bromo-4-chlorobenzoic acid (6.4 mmol, 1.0 Eq) was dissolved in 25 mL anhydrous CH_2Cl_2 and cooled to -5°C (ice/brine). 831 μL oxalyl chloride (9.6 mmol, 1.5 eq) was then added dropwise, along with 4 drops anhydrous DMF. The reaction was warmed to 25°C overnight and concentrated to dryness. The resulting oil was then dissolved in 50 mL anhydrous THF, and cooled to -5°C (ice/brine), and 7.2 mL TMS-diazomethane (2.0 M in hexanes, 2.25 eq) was added via syringe. The reaction was allowed to warm to 25° overnight, and concentrated to dryness. The resulting yellow oil was then subjected to silica flash chromatography (90:10 hexanes:EtOAc) to provide 930 mg of bright yellow solid. (58% yield over two steps). ^1H NMR (400 MHz, CDCl_3) δ 5.95 (s, 1H), 7.35 (m, 1H), 7.60 (m, 1H), 8.05 (m, 1H).

Step B: Methyl 2-(3-bromo-4-chlorophenyl)acetate (Compound 15B)



[0224] 930 mg of the diazoketone (3.58 mmol, 1.0 eq) was dissolved in 35 mL dry methanol; in a separate round bottom, 492 mg of silver benzoate (2.15 mmol, 0.6 eq) was dissolved in 8 mL anhydrous triethylamine. This solution was then added dropwise at room temperature, to the diazoketone solution via syringe. The resulting black solution was stirred at room temperature overnight. The solvent was evaporated, and the residue dissolved in EtOAc, washed with saturated aqueous NH_4Cl (x3) and brine (x2), dried over MgSO_4 , and concentrated to give 790 mg of yellow oil. (83% yield). ^1H NMR (400 MHz, CDCl_3) δ 3.45 (s, 2H), 3.70 (s, 3H), 7.17 (app d, 1H), 7.4 (m, 1H), 7.55 (m, 1H).

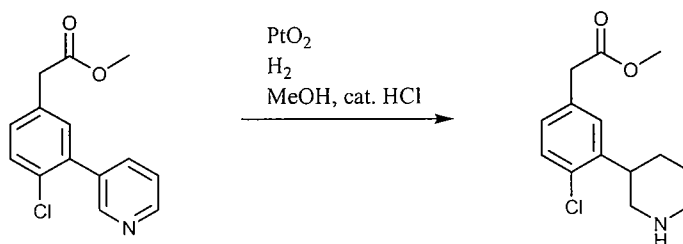
Step C: Methyl 2-(4-chloro-3-(pyridin-3-yl)phenyl)acetate (Compound 15C)



[0225] Into a 100 mL sealed reaction flask was placed 390 mg of methyl 2-(3-bromo-4-chlorophenyl)acetate (1.48 mmol, 1.0 eq), 279 mg of 3-pyridine boronic acid (1.9 mmol, 1.3 eq), 790 mg of CsF (5.2 mmol, 3.5 eq), 119 mg Pd(PPh₃)₄ (0.12 mmol, 0.07 eq), and 4 mL dimethoxyethane, 2 mL isopropyl alcohol, and 2 mL distilled water. The reaction was sealed and heated to 115°C (oil bath) overnight. The reaction was cooled, partitioned between EtOAc and brine, and washed brine (x2). After drying with MgSO₄ and concentrating, the resulting oil was then subjected to silica flash chromatography (1:1 hexanes:EtOAc) to give 278 mg of yellow oil. (72% yield). ¹H NMR (400 MHz, CDCl₃) δ 3.65 (s, 2H), 3.75 (s, 3H), 7.27 (m, 2 H), 7.4-7.55 (m, 2H), 7.85 (m, 1H), 8.65 (m, 1H), 8.78 (m, 1H).

Step D:

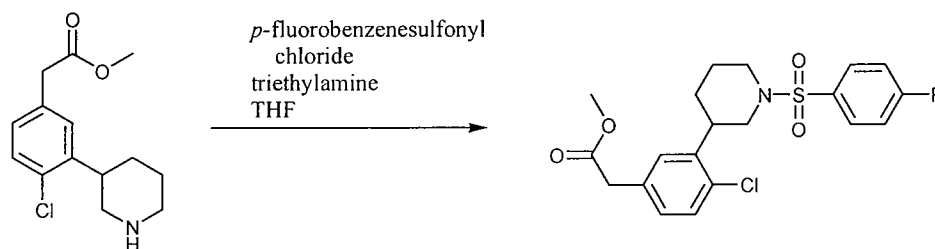
Methyl 2-(4-chloro-3-(piperidin-3-yl)phenyl)acetate (**Compound 15D**)



[0226] 278 mg of methyl 2-(4-chloro-3-(pyridin-3-yl)phenyl)acetate (1.06 mmol, 1.0 eq) was dissolved in 7 mL anhydrous methanol. About 10 mg of PtO₂ was added, along with 4 drops concentrated HCl. A hydrogen balloon was attached, the round bottom was evacuated and backflushed with H₂ (x3), and stirred at room temperature for 7 hrs. The methanol was evaporated, the residue diluted with EtOAc, washed with sat. aqueous NaHCO₃ (x2) and brine (x2), dried over MgSO₄, and concentrated to give 265 mg of clear oil. (93% yield). LC/MS (Standard Method B). Rt = 1.42 min. MS 269.1 (M +H).

Step E:

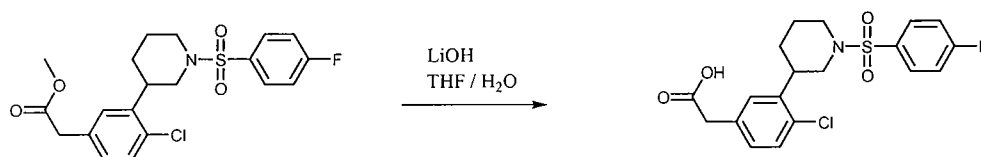
Methyl 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 15E**)



[0227] 100 mg of 2-(4-chloro-3-(piperidin-3-yl)phenyl)acetate (0.37 mmol, 1.0 eq) was dissolved in 7 mL anhydrous CH₂Cl₂. 77 μ L triethylamine (0.56 mmol, 1.5 eq) was added, and the reaction cooled to 0°C, and 92 mg *p*-fluorobenzenesulfonyl chloride (0.47 mmol, 1.25 eq) was added, and the reaction allowed to warm to 25°C overnight. The reaction was concentrated and purified via silica flash chromatography (90:10 hexanes: EtOAc) to give 112 mg clear oil. (71% yield). LC/MS (Method A). Rt = 3.99 min. MS= 426.1 (M +H).

Step F:

10 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 15F**)



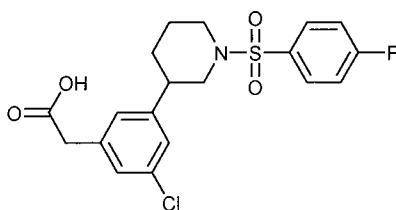
[0228] 100 mg of the methyl ester (0.24 mmol, 1.0 eq) was suspended in 5 mL 1:1

THF/H₂O, and 17 mg LiOH (0.72 mmol, 3.0 eq) was added, and the reaction stirred at 25°C overnight. The THF was then evaporated, the reaction acidified (0°C, conc. HCl), and extracted with EtOAc (x3). The organic were combined, washed with brine, dried over MgSO₄, and purified via reverse phase HPLC, and lyophilized to give 17 mg of white amorphous powder. LC/MS (Method B). Rt = 3.59 min. MS= 412.1 (M+H). ¹H NMR (400

MHz, d₆-DMSO) δ 1.56-1.85 (m, 4H), 2.07 (s, 1H), 2.23-2.40 (m, 2H), 3.54 (s, 2H), 3.73 (m, 2H), 7.16 (d of d, 1H), 7.23 (d, 1H), 7.39 (d, 1H), 7.44-7.48 (m, 2H), 7.81-7.85 (m, 2H).

Example 16

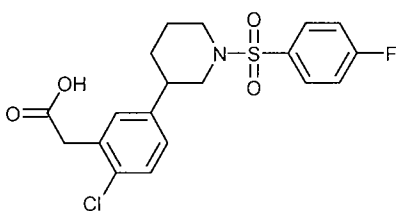
Methyl 2-(3-Chloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 16A**) and 2-(3-chloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 16B**):



[0229] The title materials were obtained using the same procedure described for 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, starting with 5-chloro-3-bromo benzoic acid. **Compound 16B** LC/MS (Method B). Rt = 3.52 min. MS 412.1 m/z (M + H). ¹H NMR (400 MHz, d₆-DMSO) δ 1.55 (m, 2H), 1.79 (m, 2H), 2.82 (m, 1H), 3.56 (s, 2H), 3.65 (m, 2H), 7.13 (s, 1H), 7.21 (s, 1H), 7.25 (s, 1H), 7.47 (app t, 2H), 7.83 (app d of d, 2H).

10 Example 17

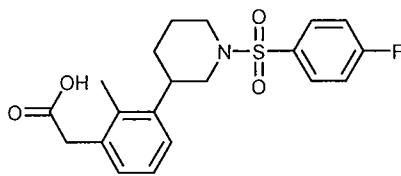
Methyl 2-(2-chloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 17A**) and 2-(2-chloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 17B**)



[0230] The title material was obtained using the same procedure described for 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, starting with 6-chloro-3-bromo benzoic acid. LC/MS (Method B). **Compound 17B** Rt = 3.47 min. MS 412.1 m/z (M + H). ¹H NMR (400 MHz, d₆-DMSO) δ 1.57 (m, 2H), 1.79 (m, 2H), 2.28 (m, 2H), 2.80 (m, 1H), 3.62 (m, 2H), 3.66 (s, 2H), 7.20 (app d of d, 1H), 7.31 (m, 1H), 7.36 (d, 1H), 7.48 (app t, 2H), 7.82 (m, 2H).

Example 18

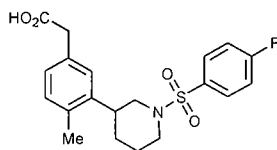
Methyl 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-2-methylphenyl)acetate (**Compound 18A**) and 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-2-methylphenyl)acetic acid (**Compound 18B**)



[0231] The title material was obtained using the same procedure described for 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 2-methyl-3-bromo benzoic acid. LC/MS (Method B). **Compound 18B** Rt = 3.54 min. MS 392.3 m/z (M + H). ¹H NMR (400 MHz, d₆-DMSO) δ 1.57 (m, 1H), 1.72 (m, 2H), 1.85 (1H), 2.22 (s, 3H), 2.30 (m, 1H), 2.35 (t, 1H), 3.05 (t, 1H), 3.62 (m, 1H), 3.64 (s, 2H), 3.75 (m, 1H), 7.06 (app s, 3H), 7.46 (m, 2H), 7.83 (m, 2H).

10 Example 19

Methyl 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-4-methylphenyl)acetate (**Compound 19A**) and 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-4-methylphenyl)acetic acid (**Compound 19B**)



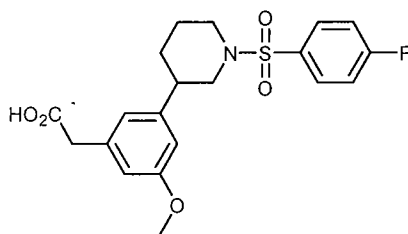
[0232] The title material was obtained using the same procedure described for 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, using 4-methyl-3-bromo benzoic acid. LC/MS (Method B). **Compound 19B** Rt = 33.40 min. MS 392.3 m/z (M + H). ¹H NMR (400 MHz, d₆-DMSO) δ 1.48-1.1.88 (m, 4H), 2.25 (s, 3H), 2.35 (m, 1H), 2.97 (m, 1H), 3.48 (s, 2H), 3.62 (m, 1H), 3.66 (m, 1H), 7.02 (m, 2H), 7.15 (m, 1H), 7.47 (app t, 1H), 7.83 (m, 1H).

Example 20

Methyl 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-methoxyphenyl)acetate

(**Compound 20A**) and

2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-methoxyphenyl)acetic acid (**Compound 20B**)

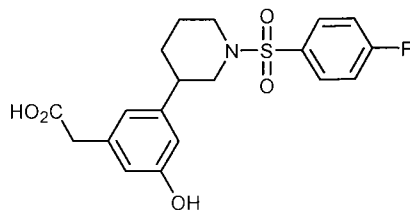


[0233] The title material was obtained using the same procedure described for 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, using 5-methoxy-3-bromo benzoic acid. LC/MS (Method B). **Compound 20B** Rt = 3.51 min. MS 408.1 m/z (M + H). ¹H NMR (400 MHz, CDCl₃) δ 1.55 (br m, 2H), 1.76 (m, 2H), 2.30 (app t, 2H), 2.75 (m, 1 H), 3.49 (s, 2H), 3.68 (br m, 2 H), 3.73 (s, 3H), 6.70 (m, 3 H), 7.45 (m, 2H), 7.82 (m, 2H).

10 Example 21

Methyl 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-hydroxyphenyl)acetate (**Compound 21A**) and

2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-hydroxyphenyl)acetic acid (**Compound 21B**)

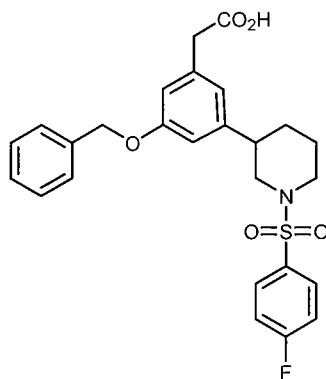


[0234] The methyl ester of 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-methoxyphenyl)acetic acid was treated with 3.0 eq of BBr₃ at 0°C in CH₂Cl₂. Following an aqueous workup, the free phenol was obtained as a white foam in 92% yield. This was then saponified as described in Step F of 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid to give the title compound. **Compound 21B** LC/MS (Method B). Rt = 3.20 min. MS 394.1 m/z (M+H). ¹H NMR (400 MHz, d₆-DMSO) δ 1.57 (br m, 2H), 1.79 (m, 2H), 2.22 (m, 2 H), 2.65 (m, 1 H), 3.30 (v broad s, Ar-OH), 3.40 (s, 2H), 3.62 (m, 1 H), 6.50 (m, 3H), 7.46 (m 2H), 7.82 (m, 2H).

Example 22

Methyl 2-(3-(benzyloxy)-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate
(**Compound 22A**) and

2-(3-(benzyloxy)-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid

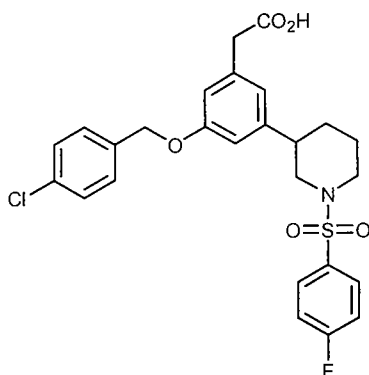
5 (**Compound 22B**):

[0235] Methyl- 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-hydroxyphenyl)acetate
10 was treated with benzyl bromide in presence of K_2CO_3 (2.0 eq) in DMF at RT, overnight.
EtOAc was added, and the organic layer washed with brine (x3), dried over $MgSO_4$. Upon
filtration and evaporation of the solvent under reduced pressure, the crude material was
submitted to hydrolysis with NaOH (1.0 eq) in THF:water. The reaction was stirred at RT for
four hours, and submitted to an acid/base work-up. Upon extraction with EtOAc, the desired
15 material was obtained as a foam. **Compound 22B** LC/MS (Standard Method B). R_t = 3.91
min. MS 484.2 m/z (M+H). ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (m, 1H), 1.85 (m, 2H), 1.88
(m, 2H), 2.26 (m, 2H), 2.88 (m, 1H), 3.61 (s, 2H), 3.78 (m, 1H), 5.15 (s, 2H), 6.41 (m, 1H),
6.82 (m, 1H), 7.20 (m, 1H), 7.31-7.85 (m, 8H), 7.76 (m, 1H).

20 Example 23

Methyl 2-(3-(4-chlorobenzyloxy)-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate
(**Compound 23A**) and

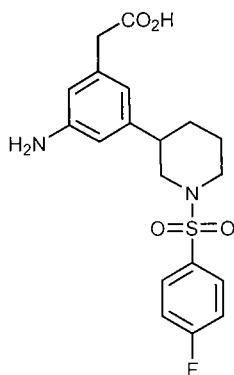
2-(3-(4-chlorobenzyloxy)-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid
(**Compound 23B**)



[0236] The desired material was obtained using the procedure described for the synthesis of 2-(3-(benzyloxy)-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 4-chloro benzyl bromide. **Compound 23B** LC/MS (Standard Method B). Rt = 4.2 min. MS 516.0 m/z (M⁻H). ¹H NMR (400 MHz, CDCl₃) δ 1.51 (m, 1H), 1.82 (m, 2H), 1.88 (m, 2H), 2.26 (m, 2H), 2.78 (m, 1H), 3.61 (s, 2H), 3.78 (m, 1H), 5.05 (s, 2H), 6.77 (m, 3H), 7.43 (m, 6H), 7.81 (m, 2H).

10 Example 24

Methyl 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 24A**) and 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 24B**)



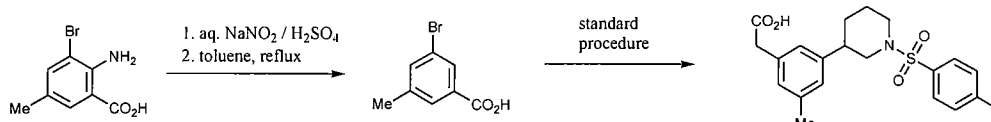
[0237] These compound(s) were synthesized starting with 3-bromo-5-nitrobenzoic acid, using the procedure described for

2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, followed by a hydrogenation in MeOH using a catalytic amount of PtO₂, under reduced pressure. Upon filtration over CELITE, the material was isolated. LC/MS (Standard Method B). **Compound 24B** Rt = 3.43 min. MS 393.10 m/z (M⁻H). ¹H NMR (400 MHz, d₆-DMSO) δ 1.55 (m, 2H),

1.79 (m, 2H), 2.22 (m, 2 H), 2.65 (m, 1 H), 3.52 (s, 2H), 3.62 (m, 2H), 6.92 (app t, 3H), 7.43 (app t, 2H), 7.77 (m, 2H).

Example 25

- 5 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-methylphenyl)acetic acid (**Compound 25B**)



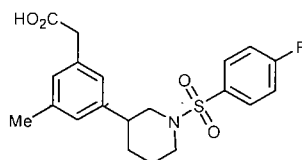
Step A:

- 10 3-bromo-5-methylbenzoic acid (**Compound 25A**)

[0238] 2.0 g of 2-amino-3-bromo-5-methylbenzoic acid (8.7 mmol, 1.0 eq) was dissolved in 45 mL toluene and 15 mL reagent grade ethanol. The reaction was cooled to 0 °C, and 1.5 mL concentrated H₂SO₄ was added dropwise. 1.32 g NaNO₂ was added portionwise, and then stirred at the same temperature for 35 min., and finally refluxed for 1.5 hours. The mixture was cooled to room temperature, diluted with EtOAc and brine, and extracted (x3) with EtOAc. After combining the organics, these were washed with 1 M HCl (x3), brine (x3) and dried over MgSO₄. After filtering and concentrating, 910 mg of yellow solid was obtained. (49% yield). LC/MS (Method B). Rt = 3.24 min. MS 215.2 m/z (M + H).

20 Step B:

- 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-methylphenyl)acetic acid (**Compound 25B**)

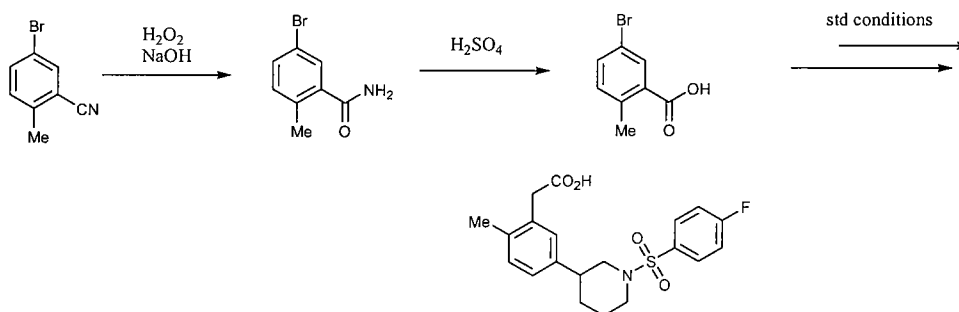


- [0239] The title material was obtained from 3-bromo-5-methylbenzoic acid using the procedure described for -(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid. LC/MS (Method B). Rt = 3.82 min. MS 392.1 m/z (M + H). ¹H NMR (400 MHz,

d_6 -DMSO) δ 1.42-1.68 (m, 2H), 1.8 (m, 2H), 2.24 (s, 3H), 2.32 (m, 2H), 2.73 (m, 1H), 3.49 (s, 2H), 3.66 (m, 2H), 6.85 (m, 3H), 7.47 (app t, 2H), 7.85 (m, 2H).

Example 26

5 2-(5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-2-methylphenyl)acetic acid (**Compound 26B**)



10

Step A: 5-bromo-2-methylbenzoic acid

[0240] 3.75 g of 5-bromo-2-methylbenzonitrile (19.0 mmol, 1.0 eq) was dissolved in 175 mL ethanol, and heated to 40 °C. 70 mL of 1N aqueous NaOH was then added, followed by 70 mL 10% H_2O_2 , and heating continued for 35 min. After cooling, half the ethanol was
 15 evaporated, and the reaction was partitioned between EtOAc and brine. After standard workup and drying, 3.4 g yellow orange solid was obtained. This material was then heated to 110 °C in 30 mL conc. H_2SO_4 and 60 mL H_2O overnight. After cooling, this was diluted with water and extracted with EtOAc. After washing with brine and drying over $MgSO_4$, 2.02 g of beige crystals were obtained. (49% over two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 7.33 (m, 1H), 7.51 (m, 1H), 7.8 (m, 1H). ^{13}C NMR ((100 MHz, $CDCl_3$) δ 20.57, 129.54, 130.25, 131.41, 132.25, 133.46, 138.00, 167.41.
 20

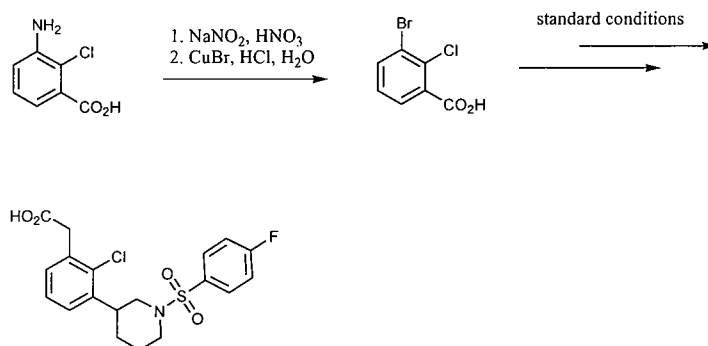
Step B: 2-(5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-2-methylphenyl)acetic acid (**Compound 26B**)

25 [0241] The title material was obtained from 5-bromo-2-methylbenzoic acid using the procedure described for 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid. LC/MS (Method B) R_t = 3.46 min. MS 392.2 m/z (M + H). ^1H NMR (400 MHz, d_6 -DMSO) δ 1.52 (m, 1H),

1.61 (m, 1H), 1.80 (m, 2H), 2.17 (s, 3H), 2.34 (m, 2H), 3.55 (s, 2H), 3.66 (m, 2H), 7.05 (m, 3H), 7.46 (m, 2H), 7.81 (m, 2H).

Example 27

5 2-(2-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 27B**)



10 **Step A:** 3-amino-2-chlorobenzoic acid (**Compound 27A**)

[0242] 2.0 g of 3-amino-2-chlorobenzoic acid (11.7 mmol, 1.0 eq) was dissolved in 35 mL H₂O and 9 mL conc HCl at 0 °C. To this was added a solution of 849 mg NaNO₂ (12.3 mmol, 1.05 eq) dissolved in 3 mL H₂O, dropwise; this solution was stirred at 0 °C for 20 min. 1.8 g CuBr (12.9 mmol, 1.1 eq) was slurried in 10 mL H₂O, and heated to 95 °C in a separate round bottom. The solution of the diazonium salt was then added via pipette to the CuBr slurry dropwise. After the addition was complete, heating continued for 30 min., when the reaction was cooled to RT Extraction into EtOAc, washing with brine, drying a concentration give 2.25 g of a thick brown gum. LC/MS (Method B, negative mode). Rt = 2.96 min. MS 234.3 m/z (M - H).

20 **Step B:** 2-(2-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 27B**)

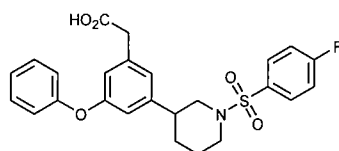
[0243] The title material was obtained from 3-amino-2-chlorobenzoic acid using the procedure described for

25 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid. LC/MS (Method B). Rt = 3.56 min. MS 412.0 m/z (M + H). ¹H NMR (400 MHz, d₆-DMSO) δ 1.56-1.85 (m,

4H), 2.07 (s, 1H), 2.23-2.40 (m, 2H), 3.54 (s, 2H), 3.73 (m, 2H), 7.24 (m, 3H), 7.42 (app t, 2H), 7.83 (m, 2H).

Example 28

- 5 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-phenoxyphenyl)acetic acid (**Compound 28A**) and 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-phenoxyphenyl)acetic acid (**Compound 28B**)

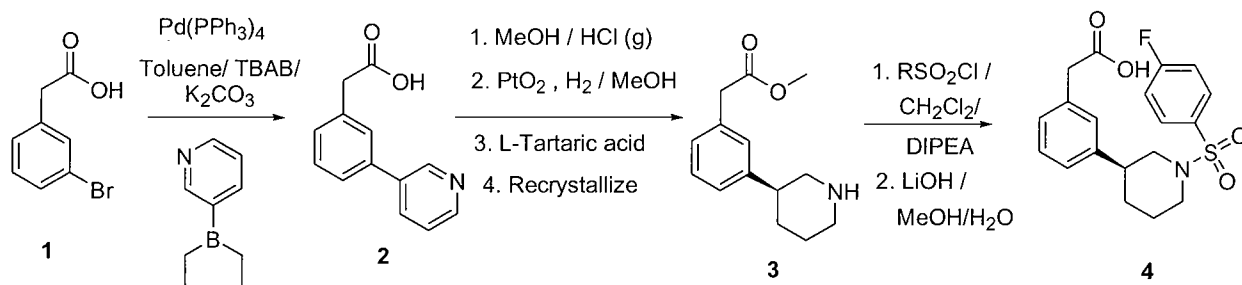


- [0244] Methyl 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-hydroxyphenyl)acetate
10 (400 mg, 0.97 mmol, 1.0 eq) was dissolved in 10 mL anhydrous CH_2Cl_2 . To this was added 236 mg $\text{PhB}(\text{OH})_2$ (1.94 mmol, 2.0 eq), 176 mg anhydrous $\text{Cu}(\text{OAc})_2$ (0.97 mmol, 1.0 eq), 338 μL diisopropylamine (1.94 mmol, 2.0 eq), and a spatula tip of 4Å molecular sieves. The reaction was then stirred under Ar at RT for 48 hrs. After filtering, washing with brine, drying and concentrating, the resulting dark residue was subjected to the general
15 saponification conditions to give the title **compound 28B**. LC/MS (Method B). $R_t = 3.99$ min. MS 470.10 m/z ($M + H$). ^1H NMR (400 MHz, d_6 -DMSO) δ 1.52 (br s, 2H), 1.79 (m, 2H), 2.31 (m, 2H), 2.77 (s, 1H), 3.52 (s, 2H), 3.65 (m, 2H), 6.75 (m, 1H), 6.83 (m, 1H), 6.93 (m, 1H), 6.99 (m, 1H), 7.13 (m, 1H), 7.38 (m, 2H), 7.47 (m, 2H), 7.82 (m, 2H).

20 Example 29

(S)-2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 29C**) and (R)-2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 29D**)

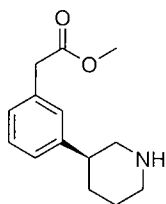
Scheme 8



5

Step A: 2-(3-(pyridin-4-yl)phenyl)acetic acid (Compound 29A)

[0245] To a dry 3-neck reaction flask was added 3-bromophenyl acetic acid (1, 10g, 46.6mmol), tetrabutyl ammonium bromide (TBAB, 1.3g, 4.01mmol), diethyl-(3-pyridyl)borane (6.83g, 46.4mmol) and toluene (60mL). The resulting suspension was stirred for 15 min., then a solution of K₂CO₃ (19.12g, 138.4mmol) in H₂O (60mL) was added. Finally a slurry of tetrakis(triphenylphosphine) palladium (0) (0.36g, 0.31mmol) in toluene (5mL) was added and the suspension heated on oil bath to 84 °C and let reflux 16h. The reaction mixture was cooled and transferred to a separatory funnel. The organic layer (20mL) was separated, the aqueous layer was washed with CH₂Cl₂ (2 x100mL), acidified and washed with CH₂Cl₂ (2 x100mL) and concentrated *in vacuo* to give a paste of salts. This was completely dried and extracted with methanol to give 9.83 g of product upon concentration. MS 214.1m/z (M+H).

Step B: (S)-methyl 2-(3-(piperidin-3-yl)phenyl)acetate (Compound 29B)

20

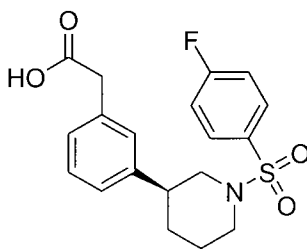
[0246] The crude product 2-(3-(pyridin-4-yl)phenyl)acetic acid was taken up in MeOH (80mL) and hydrogen chloride gas bubbled through it until gas absorption ceased - light yellow solution turns brown. MS 228.09 m/z(M+H). The ester product was filtered to remove residual salts. The solution was transferred to a PARR hydrogenation bottle, Platinum (IV) oxide catalyst (300mg) added and Parr shaken at 10 psi (H₂) for 12 h. The suspension was filtered through a pad of CELITE and concentrated to give crude oily product (8.04g).

25

This was taken up in CH₂Cl₂ (300mL) and 1.0M NaOH (150mL) added to achieve a basic pH. Separation of organic layer, drying with anhydrous Na₂SO₄ followed by concentration *in vacuo* afforded 5.7g of an amber oily product.

[0247] A solution of L-tartaric acid (1.2g, 8.02mmol) in MeOH (7mL) was added to a solution of product above (1.7g, 7.29mmol) in MeOH (3 mL) and heated to 70 °C. Let stir for 20 min. and forced into clear solution by addition of H₂O (4.5mL). Let cool slowly with stirring. After 14 h, the crystals were filtered into a white powder (1.2g). This was recrystallized from 18mL of MeOH-H₂O to give pure product (411mg). 500mg of this product was free-basified to give 222mg of product 3 (analyzed on chiral LC column to give a purity of 98.6%ee). The mother liquor was free-based and treated analogously with D-tartaric acid to give the corresponding enantiomer of 99.6% ee purity.

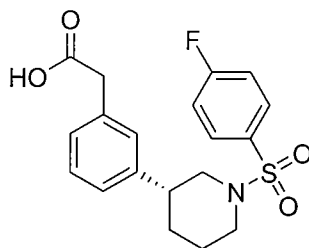
Step C: (S)-2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (Compound 29C)



[0248] (S)-methyl 2-(3-(piperidin-3-yl)phenyl)acetate (3, 222mg, 0.95mmol) and N,N-diisopropylethylamine (0.5mL, 2.85mmol) were taken up in CH₂Cl₂ (3mL) and cooled to 0 °C on ice-bath. To this was added a solution of 4-fluorophenylsulfonylchloride (203.7mg, 1.05mmol) in CH₂Cl₂ (1mL). Let warm to room temperature. After 2 h, the reaction was diluted with EtOAc (60mL) and washed with brine (30mL), dried (Na₂SO₄) and concentrated into oily product (366mg). Recrystallized from hot MeOH into needles (Melting point 100.57 °C). LC/MS (Method A) MS 393.2 m/z (M+H), (Rt = 4.023 min).

[0249] The crystalline ester (160mg, 0.409mmol) and lithium hydroxide (50mg, excess) were suspended in THF-H₂O mixture (1:2) and stirred for 4 hours. The mixture was then diluted with EtOAc (60mL), neutralized with 1.0M HCl to pH <7 and washed with brine. The solution was then dried and concentrated to give crystalline product (109.7mg). LC/MS (Method A) MS m/z 378.1 (M+H), Rt = 3.47 min)..

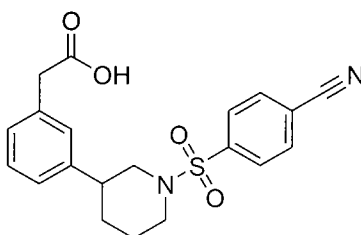
(R)-2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 29D**)



- 5 [0250] (R)-2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (5) was prepared following the procedure described for the S-enantiomer (4) but substituting D-tartaric acid for the S-tartaric acid in the chiral salt formation step). LC/MS (Method A) MS m/z 378.1 (M+H), (Rt = 3.426 min).

10 Example 30

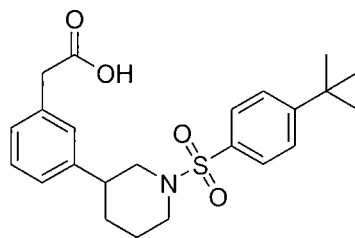
Methyl 2-(3-(1-(4-cyanophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 30A**) and 2-(3-(1-(4-cyanophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 30B**)



- 15 [0251] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 4-cyano phenylsulfonyl chloride. **Compound 30B** LC/MS (Method A) Rt = 3.467 min. MS (m/z) 385 (M + H).

20 Example 31

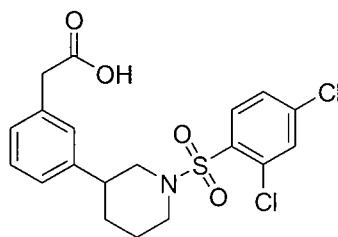
Methyl 2-(3-(1-(4-*tert*-butylphenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 31A**) and 2-(3-(1-(4-*tert*-butylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 31B**)



[0252] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 4-*tert*-butyl phenyl sulfonyl chloride. LC/MS (Method A) Rt = 4.110 min. MS (m/z) 416 (M+H).

Example 32

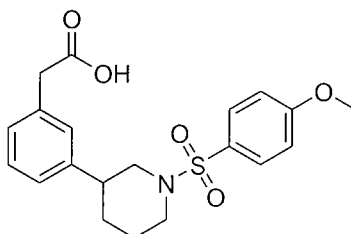
Methyl 2-(3-(1-(2,4-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 32A**) and 2-(3-(1-(2,4-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 32B**)



[0253] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 2,4-dichloro phenyl sulfonyl chloride. **Compound 32B** LC/MS (Method A) Rt = 3.921 min. MS (m/z) 428 (M+H).

Example 33

Methyl 2-(3-(1-(4-methoxyphenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 33A**) and 2-(3-(1-(4-methoxyphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 33B**)

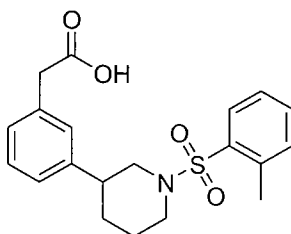


[0254] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 4-methoxy phenylsulfonyl chloride. **Compound 33B** LC/MS (Method A) $R_t = 3.518$ min. MS (m/z) 390 ($M+H$).

5

Example 34

Methyl 2-(3-(1-(*o*-tolylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 34A**) and 2-(3-(1-(*o*-tolylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 34B**)



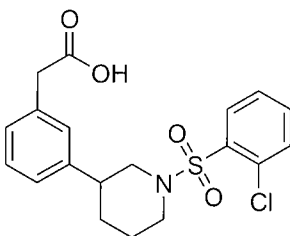
10

[0255] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 2-methyl phenylsulfonyl chloride. LC/MS (Method A) **Compound 34B** $R_t = 3.614$ min. MS (m/z) 374 ($M+H$)

15

Example 35

Methyl 2-(3-(1-(2-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 35A**) and 2-(3-(1-(2-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 35B**)



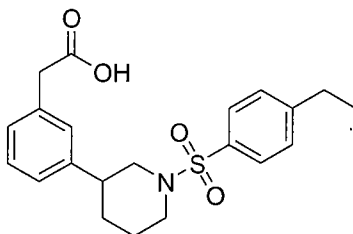
20

[0256] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 2-chloro phenylsulfonyl chloride. **Compound 35B** LC/MS (Method A) $R_t = 3.659$ min. MS (m/z) 394 ($M+H$)

Example 36

Methyl 2-(3-(1-(4-ethylphenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 36A**) and 2-(3-(1-(4-ethylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 36B**)

5



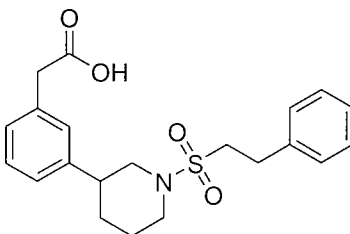
[0257] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 4-ethyl phenyl sulfonyl chloride. **Compound 36B** LC/MS (Method A) Rt = 3.849 min. MS (m/z) 388 (M+H).

10

Example 37

Methyl 2-(3-(1-(phenethylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 37A**) and 2-(3-(1-(phenethylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 37B**)

15

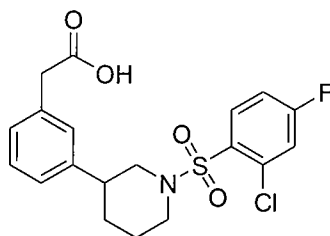


[0258] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using phenethyl sulfonyl chloride. **Compound 37B** LC/MS (Method A) Rt = 3.628 min. MS (m/z) 388 (M+H).

20

Example 38

Methyl 2-(3-(1-(2-chloro-4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 38A**) and 2-(3-(1-(2-chloro-4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 38B**)



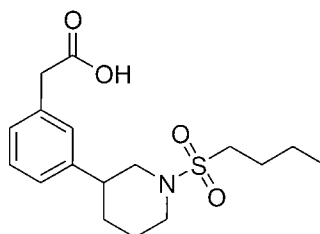
5

[0259] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 2-chloro-4-fluoro phenylsulfonyl chloride. **Compound 38B** LC/MS (Method A) Rt = 3.696 min. MS (m/z) 412 (M+H).

10

Example 39

Methyl 2-(3-(1-(butylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 39A**) and 2-(3-(1-(butylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 39B**)

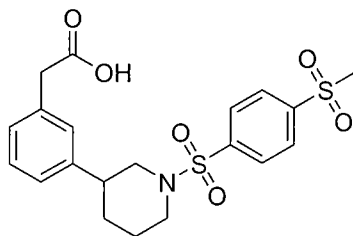


15

[0260] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 4-butylsulfonyl chloride. **Compound 39B** LC/MS (Method A) Rt = 3.454 min. MS (m/z) 340 (M+H).

20 Example 40

Methyl 2-(3-(1-(4-(methylsulfonyl)phenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 40A**) and 2-(3-(1-(4-(methylsulfonyl)phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 40B**)



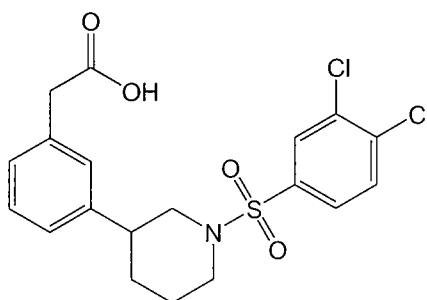
[0261] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using

5 (methanesulfonyl)phenylsulfonyl chloride. **Compound 40B** LC/MS (Method A) Rt = 3.293 min. MS (m/z) 438 (M+H).

Example 41

Methyl 2-(3-(1-(3,4-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 41A**)

10 and 2-(3-(1-(3,4-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 41B**)

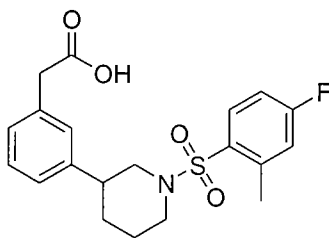


[0262] The title compound(s) were obtained using the same experimental procedure

15 described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 3,4-dichlorophenyl sulfonyl chloride. **Compound 41B** LC/MS (Method A) Rt = 3.928 min. MS (m/z) 428 (M+H).

Example 42

20 Methyl 2-(3-(1-(4-fluoro-2-methylphenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 42A**) and 2-(3-(1-(4-fluoro-2-methylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 42B**)



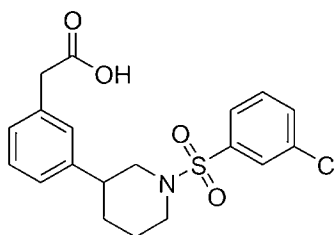
[0263] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using

- 5 2-methyl-4-fluoro phenylsulfonyl chloride. **Compound 42B** LC/MS (Method A) Rt = 3.686 min. MS (m/z) 392 (M+H).

Example 43

Methyl 2-(3-(1-(3-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 43A**) and

- 10 2-(3-(1-(3-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 43B**)



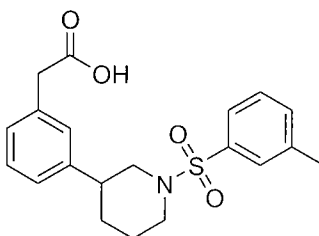
[0264] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 3-chloro

- 15 phenylsulfonyl chloride. **Compound 43B** LC/MS (Method A) Rt = 3.706 min. MS (m/z) 394 (M+H).

Example 44

Methyl 2-(3-(1-(m-tolylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 44A**) and

- 20 2-(3-(1-(m-tolylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 44B**)

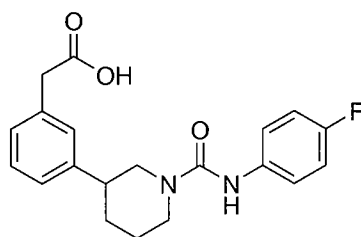


[0265] The title compound(s) were obtained using the same experimental procedure described for 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid using 3-methyl phenylsulfonyl chloride. **Compound 44B** LC/MS (Method A) $R_t = 3.654$ min. MS (m/z) 374 ($M+H$).

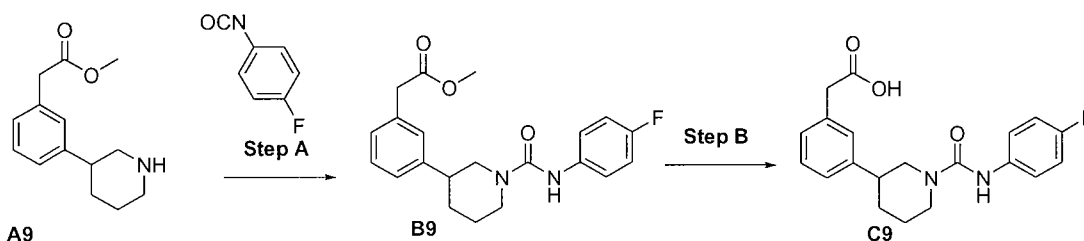
5

Example 45

2-(3-(1-(4-fluorophenylcarbamoyl)piperidin-3-yl)phenyl)acetic acid (**Compound 45B**)



10 Scheme 9



Step A: Methyl 2-(3-(1-(4-fluorophenylcarbamoyl)piperidin-3-yl)phenyl)acetate (**Compound 45A**)

[0266] To a solution of 100 mg (0.429 mmol, 1.0 equivalent) of methyl 2-(3-(piperidin-3-yl)phenyl)acetate (**A9**) in EtOAc (5 ml) was added 1.2 equivalents of 1-fluoro-4-isocyanatobenzene (0.514 mmol, 70.5 mg) and 2.0 equivalents (0.120 ml) of triethylamine. Reaction was heated in the microwave to 150°C at 300 W power for 10 min. Reaction mixture was washed with water 3 times. Combined aqueous phase was extracted with EtOAc. Combined organic phase was washed with brine, dried over sodium sulfate, and concentrated to dryness on the RotorVap. Yield = 160 mg of crude methyl 2-(3-(1-(4-fluorophenylcarbamoyl)piperidin-3-yl)phenyl)acetate as an orange oil. MS (m/z) 371 ($M+H$)

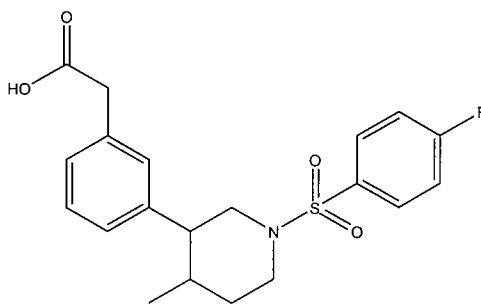
Step B: Methyl 2-(3-(1-(4-fluorophenylcarbamoyl)piperidin-3-yl)phenyl)acetate (**Compound 45B**)

25

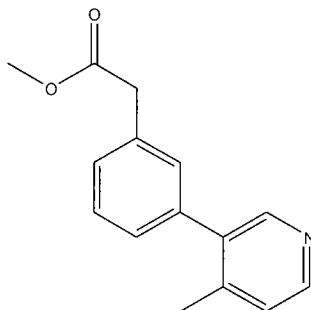
[0267] Crude methyl 2-(3-(1-(4-fluorophenylcarbamoyl)piperidin-3-yl)phenyl)acetate from step A was dissolved in THF (3 ml) and aqueous KOH (1.0 N, 3 ml) was added. Reaction was stirred for 4 hours. Reaction was acidified to pH 2-4 with 1.0 N aqueous HCl and extracted with EtOAc. Organic extracts were washed with brine, dried over sodium sulfate, and concentrated to dryness. Crude yield = 185 mg (0.52 mmol, >100%). Final product was purified by HPLC using 0.05% formic acid modifier. Final yield = 29.35 mg (0.08 mmol). LC/MS (Method A) Rt = 3.274 min. MS (m/z) 357 (M+H)

Example 46

2-(3-(1-(4-fluorophenylsulfonyl)-4-methylpiperidin-3-yl)phenyl)acetic acid (**Compound 46D**)



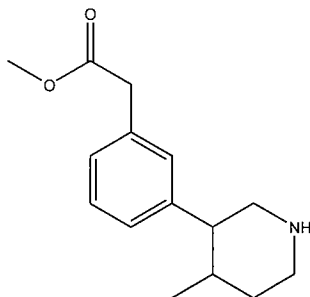
Step A: Methyl 2-(3-(4-methylpyridin-3-yl)phenyl)acetate (**Compound 46A**)



[0268] To 3 phenyl acetic acid boronic ester (0.15g, 0.57 mmol) in 0.5mL DME and 0.25mL water is added 4-methyl 3-bromo pyridine (0.119g, 0.69mmol) sodium carbonate (0.121g, 1.14mmol) and palladium tetrakis (0.032g, 0.028mmol) and stirred at 90 °C for 3 hours. The base is filtered away, and the solvents removed *in vacuo*. The resulting material is resuspended in MeOH (5mL) and HCl (g) is bubbled through. The solvent is evaporated away, and the material taken up in water and extracted 2X with DCM. The pH is increased to 14 and the aqueous is extracted 3X with DCM. The combined basic extracts are dried and

the resulting material used without further purification. LC/MS (Method A) $R_t = 1.97$ min.
MS: 242 m/z. (M+H)

Step B: Methyl 2-(3-(4-methylpiperidin-3-yl)phenyl)acetate (**Compound 46B**)



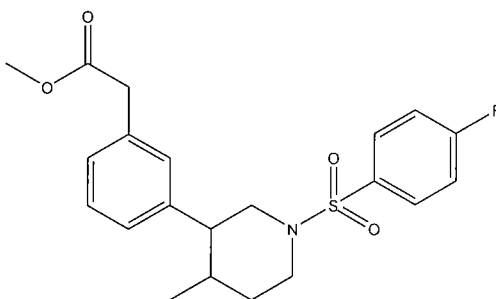
5

[0269] To methyl 2-(3-(4-methylpyridin-3-yl)phenyl)acetate (0.060g, 0.25mmol) in MeOH (3mL) is added catalytic PtO_2 . The mixture is evacuated 3X and flushed with H_2 . The mixture is stirred under balloon pressure for 16 hours at which time the reaction is judged complete by LC/MS (small amount of over-reduction observed as well). The catalyst is filtered away and the solvents removed *in vacuo*. The title compound is achieved without further purification. LC/MS (Method A) R_t 2.01 min. MS: 248 m/z. (M+H).

10

Step C: Methyl 2-(3-(1-(4-fluorophenylsulfonyl)-4-methylpiperidin-3-yl)phenyl)acetate (**Compound 46C**)

15

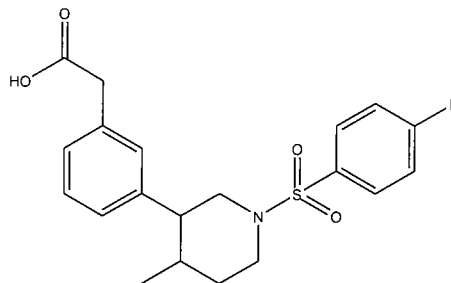


[0270] To methyl 2-(3-(4-methylpiperidin-3-yl)phenyl)acetate (0.036g, 0.14mmol) in 1mL DCM is added DIEA (0.036g, 0.28mmol) and 4-fluoro phenyl sulfonyl chloride (0.029g, 0.15mmol). The reaction stirs 16 hours and is then worked up by drying and purifying by HPLC eluting with AcCN/water both modified with 0.05% formic acid. LC/MS (Method A) R_t 4.11 min. MS: 406 m/z (M+H).

20

Step D:

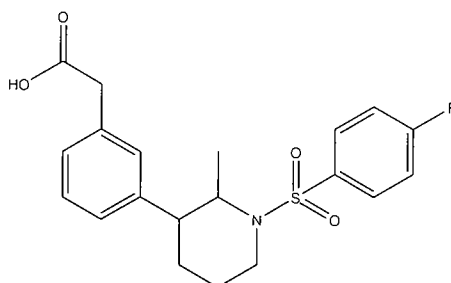
2-(3-(1-(4-fluorophenylsulfonyl)-4-methylpiperidin-3-yl)phenyl)acetic acid (**Compound 46D**)



[0271] To methyl 2-(3-(1-(4-fluorophenylsulfonyl)-4-methylpiperidin-3-yl)phenyl)acetate (0.008g, 0.02mmol) in 2mL MeOH is added 1mL 3N NaOH. The reaction stirs 16 hours. Acidify with 1N HCl to pH 1, and then dry. The title compound is extracted into DCM and used without further purification. LC/MS (Method A) Rt 3.69 min. MS: 391 m/z (390 m/z negative ion). ¹H NMR (300MHz, CDCl₃) 7.8-7.85 (2H, m); 7.1-7.3 (6H, m); 3.65 (3H, s); 3.2-3.35 (2H, m); 3.1-3.18 (2H, m); 2.95-3.05 (1H, m); 1.95-2.05 (1H, m); 2.8-2.9 (1H, m); 2.6-2.7 (1H, m); 0.7 (0.3H, d J=15Hz); 0.6 (2.7H, d J=15Hz).

Example 47

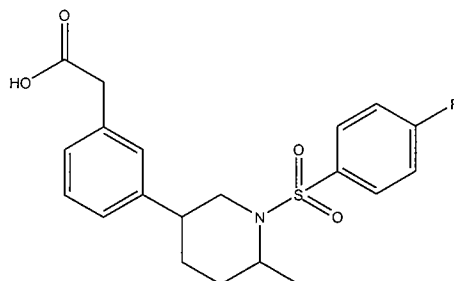
Methyl 2-(3-(1-(4-fluorophenylsulfonyl)-2-methylpiperidin-3-yl)phenyl)acetate (**Compound 47A**) and 2-(3-(1-(4-fluorophenylsulfonyl)-2-methylpiperidin-3-yl)phenyl)acetic acid (**Compound 47B**)



[0272] 2-(3-(1-(4-fluorophenylsulfonyl)-2-methylpiperidin-3-yl)phenyl)acetic acid is prepared using the same methodology as was used to prepare using 2-methyl-3-bromopyridine (steps A-D). LC/MS (Method A) Rt 3.64min; MS: 391 m/z (390 m/z negative ion).

Example 48

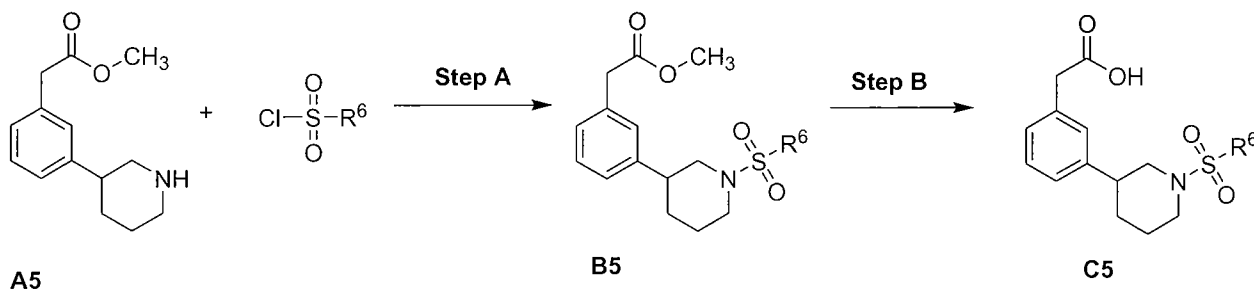
Methyl 2-(3-(1-(4-fluorophenylsulfonyl)-6-methylpiperidin-3-yl)phenyl)acetate (**Compound 48A**) and 2-(3-(1-(4-fluorophenylsulfonyl)-6-methylpiperidin-3-yl)phenyl)acetic acid (**Compound 48B**)



- 5 [0273] 2-(3-(1-(4-fluorophenylsulfonyl)-6-methylpiperidin-3-yl)phenyl)acetic acid is prepared using the same methodology as was used to prepare **46D** using 6-methyl-3-bromo pyridine (steps A-D). LC/MS (Method A) Rt 3.64 min; MS: 391 m/z (390 m/z negative ion).

Example 49

10 Scheme 5



General procedure for Step A:

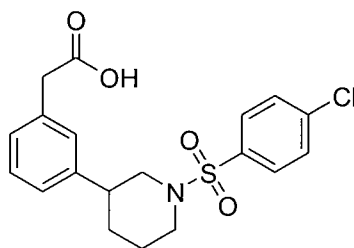
- 15 [0274] To a solution of 100 mg (0.429 mmol, 1.0 equivalent) of methyl 2-(3-(piperidin-3-yl)phenyl)acetate (**A5**) in DCM (4 ml) was added 1.2 equivalents of the sulfonyl chloride and 2.5-10 equivalents (150- of triethyl amine. Reaction was stirred at room temperature for 12-18 hours. Reaction mixture was concentrated to dryness on RotorVap. The residue was brought up in EtOAc, washed with water and brine, dried over sodium sulfate and concentrated to dryness. The crude product was taken to next step as is.

General procedure for Step B:

[0275] The intermediate from step A was dissolved in THF (2-3 ml) and aqueous KOH (1.0 N, 3 ml) was added. Reaction was stirred for 30 min. to 12 hours until hydrolysis was complete. Reaction was acidified to pH 2-4 with 1.0 N aqueous HCl and extracted with EtOAc. Organic extracts were washed with brine, dried over sodium sulfate, and concentrated to dryness. Final products were purified by HPLC.

Example 49

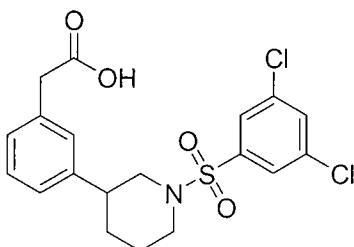
Methyl 2-(3-(1-(4-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 49A**) and 2-(3-(1-(4-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 49B**):



[0276] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except 4-chloro phenyl sulfonyl chloride was used. Crude yield = 81 mg (0.206 mmol, 48% over 2 steps). Crude product **Compound 49B** was purified by HPLC using 0.05% TFA modifier. Final yield = 26.1 mg (0.066 mmol). LC/MS (Method A) Rt = 3.792 min. MS (m/z) 394 (M+H).

Example 50

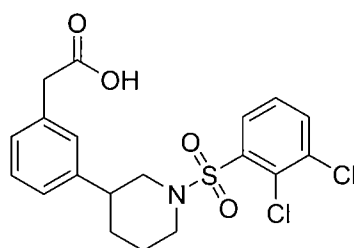
Methyl 2-(3-(1-(3,5-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 50A**) and 2-(3-(1-(3,5-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 50B**):



[0277] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except 3,5-dichlorophenylsulfonyl chloride was used. **Compound 50B**: Crude yield = 150 mg (0.35 mmol, 81.6% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = 15 mg (0.035 mmol). LC/MS (Method A) Rt = 3.993 min. MS (m/z) 428 (M + H).

Example 51

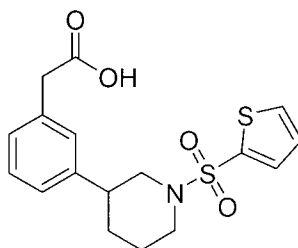
Methyl 2-(3-(1-(2,3-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 51A**) and 2-(3-(1-(2,3-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 51B**)



[0278] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except 3,5-dichlorophenylsulfonyl chloride was used. **Compound 51B**: Crude yield = 180 mg (0.42 mmol, 97% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = 75 mg (0.175 mmol). LC/MS (Method A) Rt = 3.870 min. MS (m/z) 429 (M+H)

Example 52

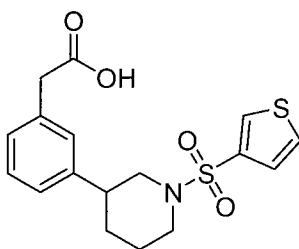
Methyl 2-(3-(1-(thiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 52A**) and 2-(3-(1-(thiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 52B**)



[0279] This compound(s) were using General procedures for **step A** and **step B** except thiophen-2-ylsulfonyl chloride was used. **Compound 52B**: Crude yield = 101 mg (0.276 mmol, 64.4% over 2 steps). Crude product was purified by HPLC using 0.05% Formic Acid modifier. Final yield = 49 mg (0.134 mmol). LC/MS (Method A) Rt = 3.426 min. MS (m/z) 366 (M + H).

Example 53

Methyl 2-(3-(1-(thiophen-3-ylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 53A**) and 2-(3-(1-(thiophen-3-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 53B**)

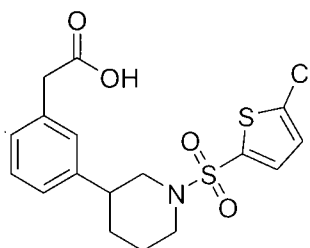


[0280] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making

2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except starting with 133 mg of intermediate **A5** (0.57 mmol) and thiophen-3-ylsulfonyl chloride. All other reagents were scaled up accordingly. **Compounds 53B**: Crude yield = 185.6 mg (0.35 mmol, 61.4% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = 80.5 mg (0.22 mmol). LC/MS (Method A) Rt = 3.374 min. MS (m/z) 366 (M + H)

Example 54

Methyl 2-(3-(1-(5-chlorothiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 54A**) and 2-(3-(1-(5-chlorothiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 54B**)



[0281] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making

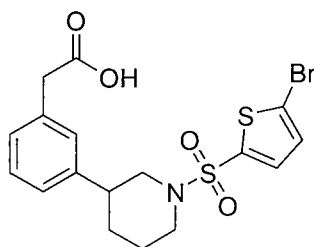
2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except

5-chlorothiophen-2-ylsulfonyl chloride was used. **Compound 54B**: Crude yield = 111 mg

5 (0.277 mmol, 65% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = 32 mg (0.08 mmol). LC/MS (Method A) Rt = 3.798 min. MS (m/z) 400 (M+H).

Example 55

- 10 Methyl 2-(3-(1-(5-bromothiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 55A**) and 2-(3-(1-(5-bromothiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 55B**)



[0282] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making

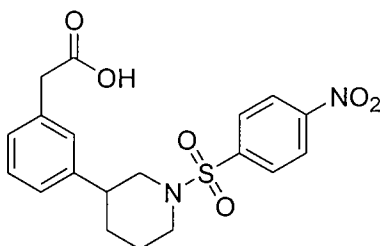
2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except

5-bromothiophen-2-ylsulfonyl chloride was used. **Compound 55B**: Crude yield = 124 mg

(0.279 mmol, 65% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = 50 mg (0.113 mmol). MS (m/z) 446 (M + 2).

Example 56

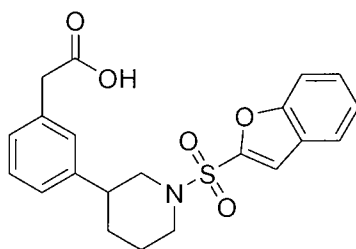
Methyl 2-(3-(1-(4-nitrophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 56A**) and 2-(3-(1-(4-nitrophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 56B**):



- 5 [0283] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except 4-nitrophenylsulfonyl chloride was used. **Compound 56B**: Crude yield = 160 mg (0.396 mmol, 92% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = 7 mg (0.017 mmol). LC/MS (Method A) Rt = 3.591 min. MS (m/z) 405 (M + H)
- 10

Example 57

Methyl 2-(3-(1-(benzofuran-2-ylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 57A**) and 2-(3-(1-(benzofuran-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 57B**):

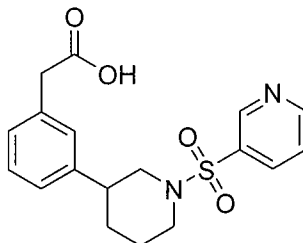


15

- [0284] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except benzofuran-2-ylsulfonyl chloride was used. **Compound 57B**: Crude yield = 66 mg (0.165 mmol, 38.5% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = 25 mg (0.0625 mmol). LC/MS (Method A) Rt = 3.759 min. MS (m/z) 400 (M + H)
- 20

Example 58

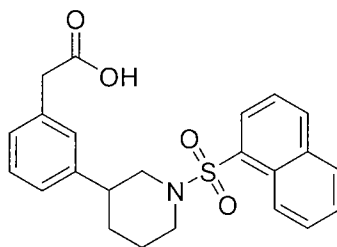
Methyl 2-(3-(1-(pyridin-3-ylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 58A**) and 2-(3-(1-(pyridin-3-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 58B**)



- 5 [0285] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except pyridin-3-ylsulfonyl chloride was used. **Compound 58B**: Crude yield = 108.5 mg (0.30 mmol, 70.2% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = 23
- 10 mg (0.064 mmol). LC/MS (Method A) Rt = 3.080 min. MS (m/z) 361 (M+H).

Example 59

Methyl 2-(3-(1-(naphthalen-1-ylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 59A**) and 2-(3-(1-(naphthalen-1-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 59B**)



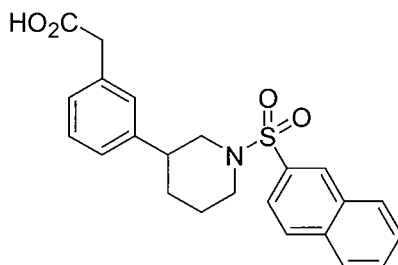
15

- [0286] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except naphthalen-1-ylsulfonyl chloride was used. Crude yield = 105 mg (0.257 mmol, 59.8% over 2 steps). Crude product
- 20 was purified by HPLC using 0.05% Formic Acid modifier. Final yield = 60 mg (0.147 mmol). MS data is not available. ¹H NMR (300 MHz, CDCl₃) δ ; 8.76 (d, 1H, aromatic); 8.22 (dd, 1H, aromatic); 8.07 (d, 1H, aromatic); 7.95 (d, 1H, aromatic); 7.7-7.51 (m, 3H, aromatic); 7.32-7.23 (m, 1H); 7.16 (d, 1H, aromatic); 7.07 (d, 2H, aromatic); 3.97 (m, 2H);

3.62 (s, 2H); 2.87-2.72 (tt, 1H); 2.68-2.53 (m, 2H); 1.95 (d, 1H); 1.88-1.59 (m, 2H); 1.56-1.38 (qd, 1H).

Example 60

- 5 Methyl {3-[1-(Naphthalene-2-sulfonyl)-piperidin-3-yl]-phenyl}-acetate (**Compound 60A**) and {3-[1-(Naphthalene-2-sulfonyl)-piperidin-3-yl]-phenyl}-acetic acid (**Compound 60B**)



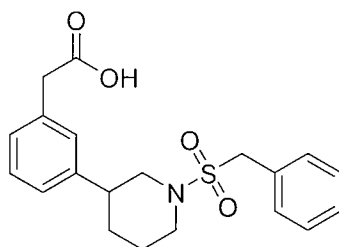
[0287] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making

- 10 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except naphthalen-1-ylsulfonyl chloride was used. MS m/z 410 (M+H).

Example 61

Methyl 2-(3-(1-(benzylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 61A**) and

- 15 2-(3-(1-(benzylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 61B**):

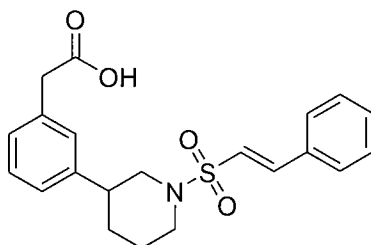


[0288] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making

- 20 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid. Crude yield = 200 mg (0.42 mmol, >100% over 2 steps). Crude product was purified by HPLC using 0.05% TFA modifier. Final yield = mg (0.175 mmol). LC/MS (Method A) Rt = 3.423 min. MS (m/z) 374 (M +H)

Example 62

Methyl (E)-2-(3-(1-(styrylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 62A**) and (E)-2-(3-(1-(styrylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 62B**):



5

[0289] The title compound(s) were obtained using the same general experimental procedure described for **step A** and **step B** for making

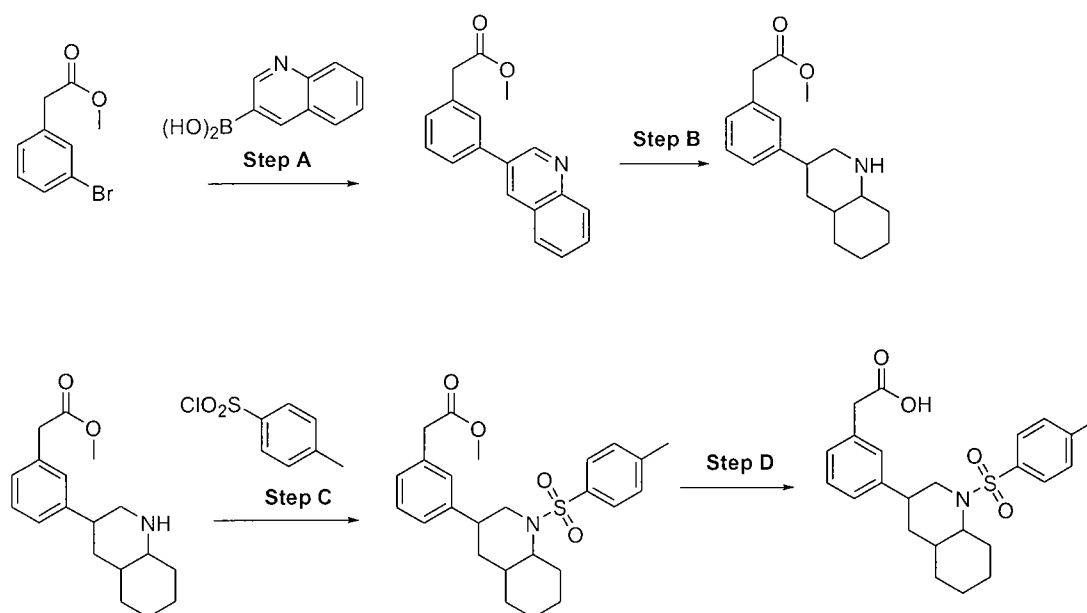
2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid, except styryl sulfonyl chloride was used. The product after step A was purified by HPLC using 0.05% TFA modifier. Final product was also purified by HPLC using 0.05% TFA modifier. Final yield = 42 mg (0.109 mmol). LC/MS (Method A) Rt = 3.663 min. MS (m/z) 386 (M + H).

10

Example 63

Methyl 2-(3-(1-tosyldecahydroquinolin-3-yl)phenyl)acetate (**Compound 63C**) and 2-(3-(1-tosyldecahydroquinolin-3-yl)phenyl)acetic acid (**Compound 63D**):

15

Scheme 10

Step A: Methyl 2-(3-(quinolin-3-yl)phenyl)acetate (Compound 63A)

[0290] Dissolved in 2 ml of DME in a microwave reactor were 200 mg (1.0 eq, 0.87 mmol) of methyl 2-(3-bromophenyl)acetate, 180 mg (1.2 eq, 1.04 mmol) of quinolin-3-ylboronic acid, 2 ml (4.5 eq) of 2M aq. sodium carbonate, and 48 mg (5 mol%, 0.043 mmol) of palladium tetrakis, with the catalyst added last. Reaction was heated in the microwave to 180°C at 300 W power for 7 min. Reaction was quenched with water, extracted with EtOAc, and concentrated to dryness on RotorVap. Yield = 413 mg (1.49 mmol, >100%) of crude methyl 2-(3-(quinolin-3-yl)phenyl)acetate as a thin yellow oil. MS (m/z) 278 (M+H).

10

Step B: Methyl 2-(3-(decahydroquinolin-3-yl)phenyl)acetate (Compound 63B)

[0291] Crude methyl 2-(3-(quinolin-3-yl)phenyl)acetate from step A was dissolved in 10 ml methanol. To this solution were added catalytic amounts of concentrated HCl and platinum (IV) oxide hydrate. The vessel was charged to 10 psi on the Parr hydrogenator and agitated for 5 hours. Reaction was filtered through a pad of CELITE and the filtrate was concentrated to dryness. Yield = 145 mg (0.5 mmol) crude methyl 2-(3-(decahydroquinolin-3-yl)phenyl)acetate as a yellow oil. MS (m/z) 288 (M+H).

15

Step C: Methyl 2-(3-(1-tosyldecahydroquinolin-3-yl)phenyl)acetate (Compound 63C)

[0292] Crude methyl 2-(3-(decahydroquinolin-3-yl)phenyl)acetate (145 mg, 1.0 eq, 0.5 mmol) from step B was dissolved in 10 ml of DCM. To this solution was added 105.8 mg (0.55 mmol, 1.1 eq) of 4-methylbenzene-1-sulfonyl chloride, and 0.176 ml (1.26 mmol, 2.5 eq) of triethylamine. Reaction was stirred for 18 hours at room temperature. Reaction was quenched with water and extracted with EtOAc 3 times. Combined organic phase was dried over sodium sulfate and concentrated to dryness. Yield = 171 mg (0.38 mmol) of crude methyl 2-(3-(1-tosyldecahydroquinolin-3-yl)phenyl)acetate as a yellow oil. MS (m/z) 442 (M+H).

20

25

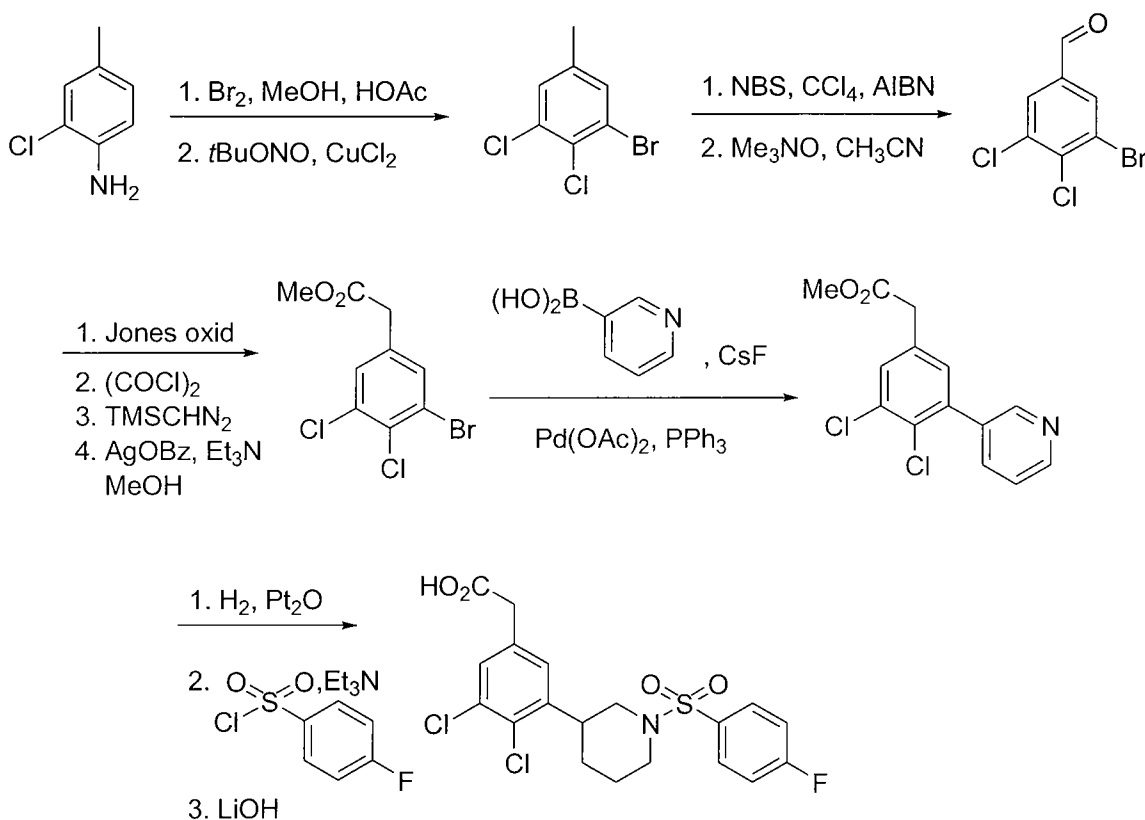
Step D: 2-(3-(1-tosyldecahydroquinolin-3-yl)phenyl)acetic acid (Compound 63D)

[0293] Crude methyl 2-(3-(1-tosyldecahydroquinolin-3-yl)phenyl)acetate from step 3 (171 mg) was dissolved in 3 ml of THF and 3 ml of 1N aq. KOH was added. Reaction was stirred for 18 hours at room temperature. Reaction was acidified to pH 2-4 with 1.0 N aqueous HCl and extracted with EtOAc. Organic extracts were washed with brine, dried over sodium sulfate, and concentrated to dryness. Final product was purified by HPLC using 0.05% formic Acid modifier. Final yield = 9.27 mg (0.021 mmol). LC/MS (Method A) RT = 4.048 min. MS (m/z) 428 (M+H).

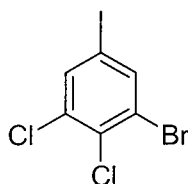
Example 64

- 10 Methyl 2-(3,4-dichloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate (**Compound 6C**) and 2-(3,4-dichloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 64D**)

Scheme 11:

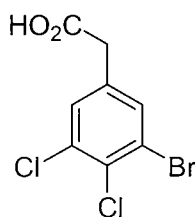


Step A: 1-bromo-2,3-dichloro-5-methylbenzene (**Compound 64A**)



[0294] To a solution of commercially available 2-chloro-4-methylaniline (25.2 g, 177.8 mmol) in MeOH (80 mL)-HOAc (26 mL) at 0°C was added dropwise bromine (9.1 mL, 177.8 mmol) in HOAc (80 mL). The mixture was stirred for 3 hours before NaOH (10%, 100 mL) and water were added. The mixture (pH 5) was extracted with EtOAc, and dried over Na₂SO₄. Solvent was removed to give a dark brown solid. A solution of the above solid (7.81 g, 35.4 mmol) in CH₃CN (50 mL) was added dropwise in 25 min. to a solution of CuCl₂ (5.71 g, 42.5 mmol) and *t*-butyl nitrite (*t*-BuONO) (6.32 mL, 53.1 mmol) at 65°C. Gas evolution was observed. Upon completion of addition, gas evolution ceased and the mixture was cooled to room temperature and stirred for 15 h. Solvent was removed and the residue purified on silica gel to give a white needle (6.35 g, 75%). MS (Method B) Rt=4.47 min.

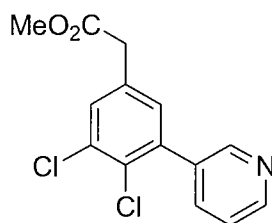
Step B: 2-(3-bromo-4,5-dichlorophenyl)acetic acid (Compound 64B)



[0295] To 1-bromo-2,3-dichloro-5-methylbenzene (2.81 g, 11.7 mmol) was added NBS (2.29 g, 12.8 mmol), AIBN (192 mg, 1.17 mmol), and CCl₄ (50 mL). The mixture was stirred at rt for 30 min. and then at 80°C for another 17 h. Solvent was removed and the residue purified on silica gel to give 3.32 g (89%) of a white solid. To a solution of the above solid (674 mg, 2.1 mmol) in CH₃CN (5 mL) at 0°C was added trimethyl amine N-oxide (317 mg, 4.2 mmol). The mixture was warmed up to rt and stirred for 30 min. and then purified using silica gel chromatography to give 3-bromo-4,5-dichlorobenzaldehyde as a white solid (219 mg). To thus obtained aldehyde (219 mg, 0.86 mmol) was added acetone (6 mL) and Jones's reagent (1.35 mL, ~0.7 M) and stirred for 40 min. before MeOH (6 mL) was added and the mixture stirred for another 5 min. CH₂Cl₂ and water were added and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄.

Removal of solvent gave a white solid (226 mg, 0.837 mmol) in 97% yield. MS (Method B) $R_t=3.86$ min, (m/z) 268.9 (M^+).

Step C: Methyl 2-(3,4-dichloro-5-(pyridin-3-yl)phenyl)acetate (Compound 64C)

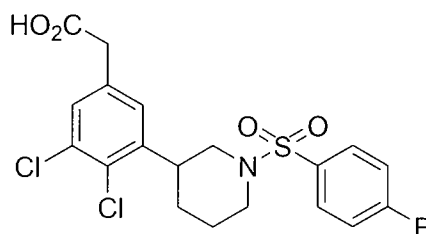


5

[0296] The above acid was dissolved in CH_2Cl_2 (8 mL) and oxalyl chloride (95 μL , 1.09 mmol) was added, followed by a drop of DMF. After 16 h, solvent was removed and the residue was subjected to vacuum for 20 min. and dissolved in THF (8 mL) and cooled to 0°C . DIEA (291 μL , 1.67 mmol) was then added, followed by TMSCHN_2 (1 mL, 2.09 mmol).

- 10 After 2 h, solvent was removed and residue purified on silica gel to give 97 mg (39% for 2 steps) of an off-white solid. To a solution of this solid (97 mg, 0.33 mmol) in MeOH (4.6 mL) was added dropwise a solution of AgOBz (45 mg, 0.198 mmol) in Et_3N (0.9 mL). After 3 d, solvent was removed and the residue purified on silica gel to give methyl
- 15 2-(3-bromo-4,5-dichlorophenyl)acetate as a colorless oil (34.5 mg). To thus obtained methyl ester methyl (34.5 mg, 0.13 mmol) was added pyridin-3-ylboronic acid (32 mg, 0.26 mmol), $\text{Pd}(\text{OAc})_2$ (2 mg, 0.0091 mmol), PPh_3 (7 mg, 0.027 mmol), CsF (69 mg, 0.455 mmol), DME (1 mL), isopropyl alcohol (0.5 mL), and water (0.5 mL). The reaction vial was heated at 95°C for 20 h. The mixture was purified directly on silica gel to give methyl
- 20 2-(3,4-dichloro-5-(pyridin-3-yl)phenyl)acetate as a colorless oil (11.5 mg, 30% for 2 steps). MS (Method B) $R_t=3.27$ min, (m/z) 296 (M^+).

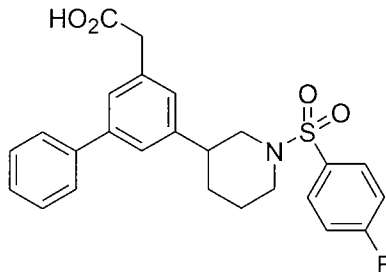
Step D: 2-(3,4-dichloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (Compound 64D)



[0297] To a solution of methyl 2-(3,4-dichloro-5-(pyridin-3-yl)phenyl)acetate (11.5 mg, 0.0388 mmol) in MeOH (2 mL) was added concentrated HCl (200 μ L) and Pt₂O (cat.). The mixture was stirred under H₂ (1 atm) for 1 h before filtered through a plug of CELITE[®] with EtOAc-MeOH. Solvent was removed to give a colorless oil (18.5 mg). The crude product was dissolved in CH₂Cl₂ (3 mL), and Et₃N (43 μ L, 0.31 mmol) was added, followed by 4-fluorobenzene-1-sulfonyl chloride (15 mg, 0.0776 mmol). The mixture was stirred for 17 h before it was diluted with CH₂Cl₂ and water and extracted with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄. Solvent was removed and the crude product was dissolved in THF-water (2 mL-0.5 mL). LiOH·H₂O (13 mg, 0.31 mmol) was added. After 16 h, the mixture was acidified with 1N HCl and extracted with EtOAc. Purification on reverse phase HPLC yielded the title compound as a white solid. MS (Method B), Rt=3.87 min, (m/z) 445 (M⁺H). ¹H NMR (DMSO-d₆): ppm 12.4 (s, 1H), 7.83 (m, 2H), 7.5 (m, 3H), 7.2 (s, 1H), 3.7 (m, 2H), 3.56 (s, 2H), 3.2 (m, 1H), 2.3 (m, 2H), 1.8 (m, 2H), 1.6 (m, 2H).

Example 65

{5-[1-(4-Fluoro-benzenesulfonyl)-piperidin-3-yl]-biphenyl-3-yl}-acetic acid (**Compound 65**)



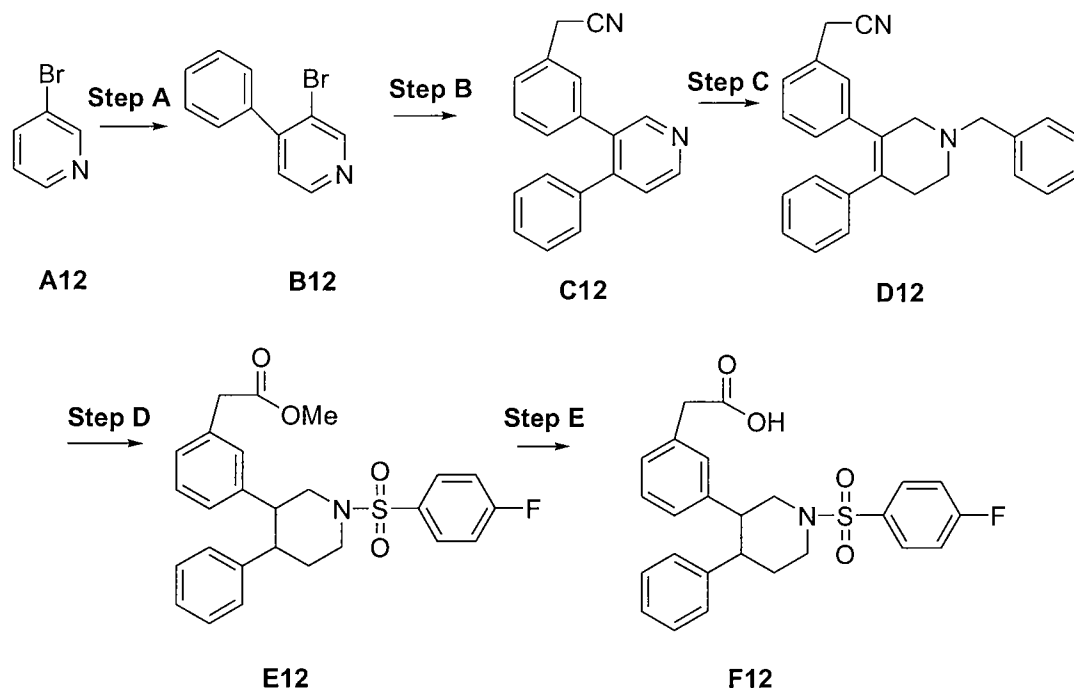
[0298] Purification on reverse phase HPLC yielded the title compound as a white solid. MS m/z 454 (M+H).

20

Example 66

2-(3-(1-(4-fluorophenylsulfonyl)-4-phenylpiperidin-3-yl)phenyl)acetic acid (**Compound 66**):

Scheme 12:

5 **Step A: 3-bromo-4-phenylpyridine (B12)**

[0299] To 3-bromopyridine (2ml, 20mmol) in THF (25ml) was slowly injected LDA in THF (12ml, 24mmol) at -95 °C. The resulting solution was stirred at -95 °C for 30 min. At this time, anhydrous ZnCl₂ (24ml, 24mmol) in Et₂O was added dropwise at the temperature, and the solution was allowed to warm to RT to provide 3-bromo-4-pyridyl zinc chloride. To this solution, was added iodobenzene (2.2ml, 20mmol) followed by a solution of Pd(PPh₃)₄ (500mg, 0.43mmol) in dry THF (5ml) solution was then heated to reflux for 4h. After aqueous work up, the product was afforded after flash chromatography on silica gel. LC/MS Rt = 3.578 min. LC/MS (Method A); MS (m/z) 234.00 (M⁺ +H).

15 **Step B: 2-(3-(4-phenylpyridin-3-yl)phenyl)acetonitrile (C12)**

[0300] To a mixture of 3-bromo-4-phenyl pyridine (610mg, 2.62mmol) and 3-(cyanomethyl)phenylboronic acid (533mg, 3.31mmol) in DME (10ml) was added Pd(PPh₃)₄ (150mg, 0.131mmol), followed by addition of Na₂CO₃ (555mg, 5.24mmol) in water (3ml). The mixture was heated at 85 °C overnight. The reaction mixture was diluted with EtOAc (100ml), washed with sat Na₂CO₃ (3 X 20ml), dried over Na₂SO₄. The product

was afforded after flash chromatography on silica gel. RT = 2.969 min. LC/MS (Method A); MS (m/z) 271.1(M⁺ + H).

Step C:

5 2-(3-(1-benzyl-4-phenyl-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetonitrile (**D12**)

[0301] To **intermediate C12** (245.8mg, 0.91mmol) in CH₃CN (5ml) was added benzyl bromide (0.13ml, 1.09mmol), and the solution was refluxed for 2h. The solvent was removed under the reduced pressure.

10 [0302] The salt (150mg, 0.418mmol) was then dissolved in THF (2ml), NaBH₄ (32mg, 0.836mmol) was added at 0 °C. After 1h, the reaction was quenched with H₂O (0.5ml). Diluted with EtOAc (15ml), washed with H₂O (3 X 3ml), dried over Na₂SO₄, the desired product was obtained after the solvent was removed. Rt = 2.564 min. LC/MS (Method A); MS (m/z) 365.2(M⁺ + H).

15 **Step D: Methyl 2-(3-(1-benzyl-4-phenyl-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetate (E12**

[0303] To **intermediate D12** (152mg, 0.418mmol) in MeOH (5ml) was bubbled HCl gas. The solution was refluxed overnight. The desired material was obtained after the solvent was removed. Rt = 2.564 min. LC/MS (Method A); MS (m/z) 398.2(M⁺ + H).

20 [0304] To this product in MeOH (5ml) was added a catalytic amount of 10% Pd(OH)₂/C. After purging 3 times with H₂, the reaction was run under a H₂ balloon for 12h. The solution was concentrated under reduced pressure, the residue was then dissolved in DCM (5ml). DIEA (0.29ml, 1.67mmol) was added, followed by the addition of 4-fluorobenzene-1-sulfonyl chloride (122mg, 0.627mmol). The mixture was stirred at RT overnight. The product (73mg) was afforded after flash column chromatography on silica gel.
25 Rt = 4.297 min. LC/MS (Method A); MS (m/z) 468.1(M⁺ + H).

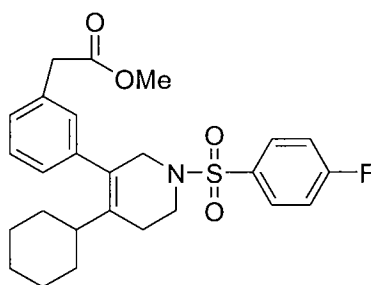
[0305] **Step E: 2-(3-(1-(4-fluorophenylsulfonyl)-4-phenylpiperidin-3-yl)phenyl)acetic acid (Compound 66)**

[0306] To intermediate **4** (73mg, 0.156mmol) dissolved in THF (1ml), 1ml of aqueous 1N NaOH was added. The mixture was stirred overnight. Diluted with EtOAc (15ml), washed with 1N HCl (3 X 2ml), dried over Na₂SO₄, the final product (72.2mg) was obtained. Rt = 3.886 min. LC/MS (Method A); MS (m/z) 454.1(M⁺ + H).

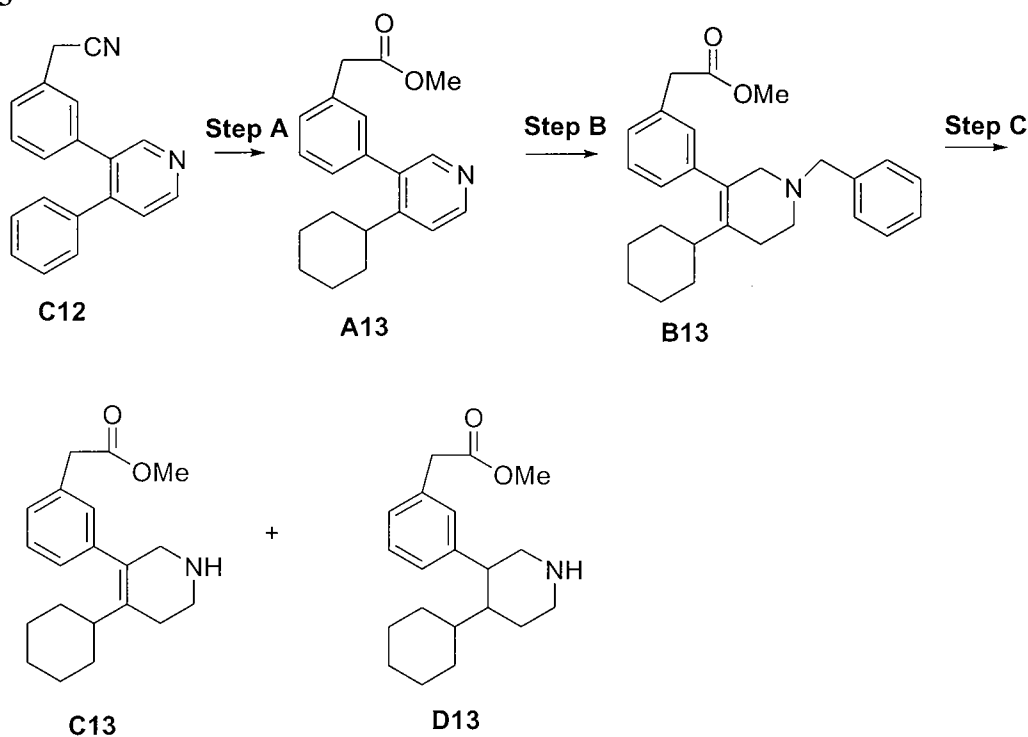
5

Example 67

2-(3-(4-cyclohexyl-1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid (**Compound 67D**)



10 Scheme 13



Step A: Methyl 2-(3-(4-cyclohexylpyridin-3-yl)phenyl)acetate (**A13**)

[0307] To intermediate **2** (135mg, 0.50mmol) in MeOH (5ml) was bubbled HCl gas. The solution was refluxed overnight. LC/MS was used to monitor the reaction. A catalytic

15

amount of PtO₂ was added to the solution. After purging 3 times with H₂, the reaction was run under H₂ balloon for 12h. The catalyst was filtered through CELITE, the product was obtained after removal of the solvent. Rt = 2.898 min. LC/MS (Method A); MS (m/z) 310.2(M⁺ + H).

5

Step B: Methyl 2-(3-(1-benzyl-4-cyclohexyl-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetate (**B13**)

[0308] Same experimental procedure as for

2-(3-(1-benzyl-4-phenyl-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetonitrile. LC/MS Rt = 2.849 min. (Method A); MS (m/z) 404.2(M⁺ + H).

10

[0309] **Step C:** Methyl 2-(3-(4-cyclohexyl-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetate (**C13**) & Methyl 2-(3-(4-cyclohexylpiperidin-3-yl)phenyl)acetate (**D13**)

[0310] To the intermediate **B13** (157mg, 0.388mmol) in MeOH (5ml) was added a catalytic amount of 10% Pd(OH)₂/C. After purging 3 times with H₂, the reaction was run under a H₂ balloon for 12h. The solution was concentrated under reduced pressure, giving both intermediate **C13**. LC/MS (Method A) Rt = 2.522 min.; MS (m/z) 314.2(M⁺ + H) and intermediate **D13**. LC/MS (Method A) Rt = 2.688 min.; MS (m/z) 316.2(M⁺ + H).

15

20 [0311] **Step D:**

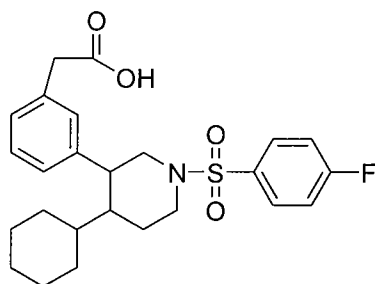
2-(3-(4-cyclohexyl-1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid (**Compound 67D**)

[0312] Intermediate **C13** was dissolved in DCM (5ml). Hunig base (0.20ml, 1.165mmol) was added, followed by the addition of the 4-fluorobenzene-1-sulfonyl chloride (91mg, 0.466mmol). The mixture was stirred at RT overnight. The product was afforded after flash column chromatography. To the product in THF (1ml), was added aqueous 1N NaOH (1ml). The mixture was stirred overnight. Diluted with EtAc (15ml), washed with 1N HCl (3 X 2ml), dried over Na₂SO₄, the final product (40mg) was obtained. Rt = 4.283 min. LC/MS (Method A); MS (m/z) 458.2(M⁺ + H). ¹H NMR (300 MHz, CDCl₃) δ 7.80 (m, 2H), 7.31

25

(m, 1H), 7.22 (m, 3H), 7.02 (m, 2H), 3.67 (s, 4H), 3.27 (t, 2H), 2.30(t, 2H), 2.11 (m, 1H), 1.68-1.52 (m, 3H), 1.38 (m, 2H), 1.25 (m, 2H), 1.06 (m, 3H).

- 5 2-(3-(4-cyclohexyl-1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid (**Compound 67E**)



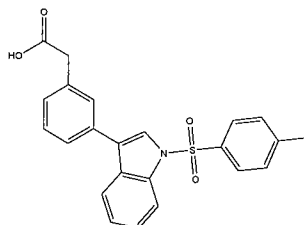
[0313] The same experimental procedure described for

- 10 2-(3-(4-cyclohexyl-1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid was followed starting with methyl 2-(3-(4-cyclohexylpiperidin-3-yl)phenyl)acetate. Rt = 4.378 min. LC/MS (Method A); MS (m/z) 460.2 ($M^+ + H$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.58 (d, 1H), 7.40 (s, 1H), 7.31 (m, 2H), 7.22 (m, 2H), 4.02(d, 1H), 3.92 (d, 1H), 3.67 (s, 2H), 3.09 (s, 1H), 2.58 (dd, 1H), 2.25 (m, 1H), 1.90 (m, 1H), 1.68-0.20 (m, 13H).

15

Example 68

2-(3-(1-(tosyl)-1H-indol-3-yl)phenyl)acetic acid (**Compound 68**)

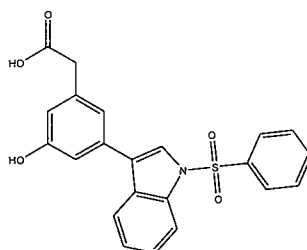


- 20 [0314] To 3-bromo phenyl acetic acid (0.215g, 1.0mmol) in 2mL dimethoxyethane and 1mL water was added N-tosyl indole 3-boronic acid (0.315g, 1.0mmol), palladium tetrakis (0.058g, 0.05mmol) and sodium carbonate (0.211g, 2.0mmol). The mixture was heated to 65 °C and stirred for 18 hours at which time the reaction was deemed complete by LC/MS. The reaction mixture was diluted with water and extracted into EtOAc 2X. The aqueous acidified

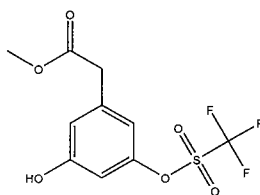
to pH 1 and was extracted 3X with EtOAc. The dried material was purified over HPLC to yield the title compound. MS m/z 406 (M+H); LC/MS (Method A) R_t = 4.01 min.

Example 69

5 2-(3-hydroxy-5(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl acetic acid (**Compound 69C**)



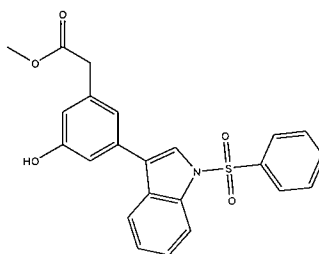
Step A: Methyl 3-hydroxy-5-trifluoromethane sulfonyloxy-phenyl acetate (**Compound 69A**)



10 **[0315]** To 3,5 dihydroxy phenyl acetic acid methyl ester (5.0g, 27.0mmol) in 100mL DCM at 0 °C was added DIEA (4.71mL, 27.0mmol) and triflic anhydride (11.4mL, 67.5mmol) dropwise. The reaction was allowed to slowly warm to room temperature and stir 3 days at RT at which time it was deemed complete by LC/MS. It was used without further purification. MS m/z 315.0 (M+H); LC/MS(Method A) R_t = 3.50min

15

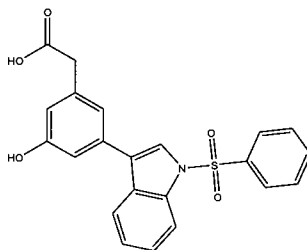
Step B: Methyl 2-(3-hydroxy-5(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl)acetate (**Compound 69B**)



[0316] The title compound(s) were synthesized using the procedure described for 2-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid, starting with methyl 3-hydroxy-5-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl acetate. MS m/z 422.0 (M+H); LC/MS (Method A) R_t = 3.94min

5

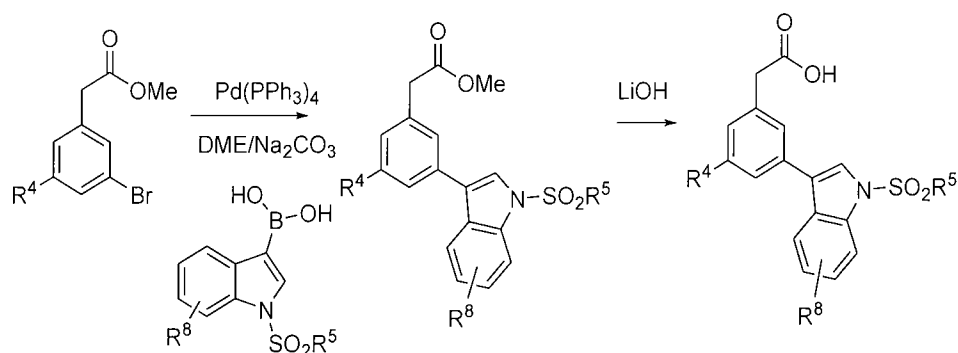
Step C: 2-(3-hydroxy-5(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl acetic acid (**Compound 69C**)



[0317] To the previous ester (0.016g, 0.038mmol) in 1mL methanol was added 0.5mL 3N NaOH. The reaction stirred at room temperature for 18 hours. The completed reaction was acidified to pH 1 and extracted into DCM 3X. The combined organic layers were dried to yield the title compound requiring no further purification. MS m/z 408.0 (M+H), LC/MS(Method A) R_t = 3.54 min.

15 Examples 70-74

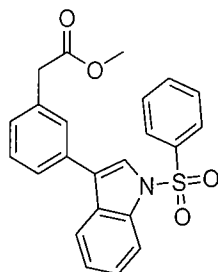
Scheme 14



Example 70

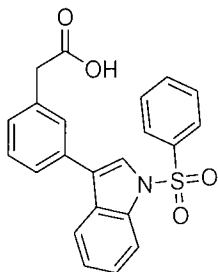
Methyl 2-(3-(1-(phenylsulfonyl)-1*H*-indol-3-yl)phenyl)acetate (**Compound 70A**) and 2-(3-(1-(phenylsulfonyl)-1*H*-indol-3-yl)phenyl)acetic acid (**Compound 70B**).

Step A: Methyl 2-(3-(1-(phenylsulfonyl)-1*H*-indol-3-yl)phenyl)acetate (**Compound 70A**).



- 5 [0318] 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid (620 mg, 2.07 mmol) and Pd(PPh₃)₄ (109 mg, 0.0939 mmol) were added to a stirring solution of methyl 2-(3-bromophenyl)acetate (430 mg, 1.88 mmol) in dimethoxy ethane/ 2 M Na₂CO₃ (2:1, 12 mL). The resulting solution was refluxed for 3 h, cooled to RT, then diluted EtOAc (10 mL). The organic layer was washed with H₂O (10 mL), dried over Na₂SO₄, and concentrated to give the crude
- 10 material(1.13 g) as a green oil. A column chromatography on silica gel (3:1, hexanes/EtOAc) afforded pure material (760 mg, 99 %) as a light turquoise oil.

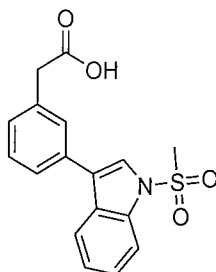
Step B: 2-(3-(1-(phenylsulfonyl)-1*H*-indol-3-yl)phenyl)acetic acid (**Compound 70B**).



- 15 [0319] Solid LiOH (227 mg, 5.43 mmol) was added to a stirring solution of methyl 2-(3-(1-(phenylsulfonyl)-1*H*-indol-3-yl)phenyl)acetate (220 mg, 0.543 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 layer was extracted with EtOAc (3 X 20 mL), dried over Na₂SO₄, and concentrated to give crude acid (260 mg) as a light brown oil. HPLC
- 20 purification afforded pure compound: ES/MS 392.1 (M+H); LC/MS (Method B) Rt = 3.849 min.

Example 71

Methyl 2-(3-(1-(methylsulfonyl)-1H-indol-3-yl)phenyl)acetate, (**Compound 71A**) and 2-(3-(1-(methylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid, (**Compound 71B**)

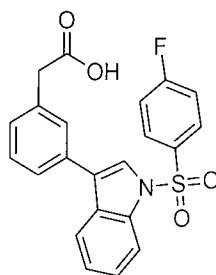


- 5 **[0320]** The title material was obtained using the procedure described for 2-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid, starting from 1-(methylsulfonyl)-1H-indol-3-ylboronic acid. **Compound 71B**: ES/MS, m/z found 330.1 (M+H); LC/MS (Method B) Rt = 3.285 min.

10 Example 72

Methyl 2-(3-(1-(4-fluorophenylsulfonyl)-1H-indol-3-yl)phenyl)acetate (**Compound 72A**) and

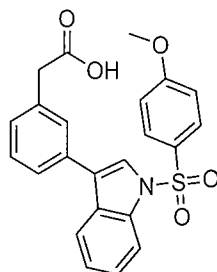
2-(3-(1-(4-fluorophenylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid (**Compound 72B**)



- 15 **[0321]** The title material was obtained using the procedure described for 2-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid, starting from 1-(4-fluorophenylsulfonyl)-1H-indol-3-ylboronic acid, which was synthesized using the procedure described in Garg., N.K., et al., *J. Am. Chem. Soc.*, 2002, **124**:1317984. ¹H NMR (400 MHz, DMSO-d₆) δ 12.36 (1H, brs) 8.18 (2H, m) 8.10 (1H, s) 8.04 (1H, m) 7.86 (1H, m) 7.65~7.60 (2H, m)
- 20 7.48~7.42 (4H, m) 7.36 (1H, m) 7.29 (1H, m) 3.68 (2H, s); ES/MS, m/z 419.1 (M+H); LC/MS (Method A) Rt = 3.909 min.

Example 73

Methyl 2-(3-(1-(4-methoxyphenylsulfonyl)-1H-indol-3-yl)phenyl)acetate (**Compound 73A**) and 2-(3-(1-(4-methoxyphenylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid (**Compound 73B**)



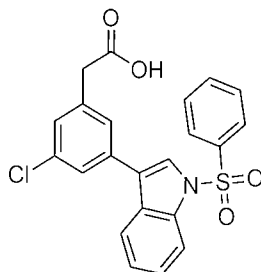
5

[0322] The title material was obtained using the procedure described for 2-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid, starting from 1-(4-methoxyphenylsulfonyl)-1H-indol-3-ylboronic acid, which was synthesized using the procedure described in Garg., N.K., et al., *J. Am. Chem. Soc.*, 2002, **124**:1317984. **Compound 73B**: ES/MS, m/z 422.1 (M+H); LC/MS (Method A) Rt = 3.878 min.

10

Example 74

Methyl 2-(3-chloro-5-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl)acetate (**Compound 74A**) and 2-(3-chloro-5-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid (**Compound 74B**)



15

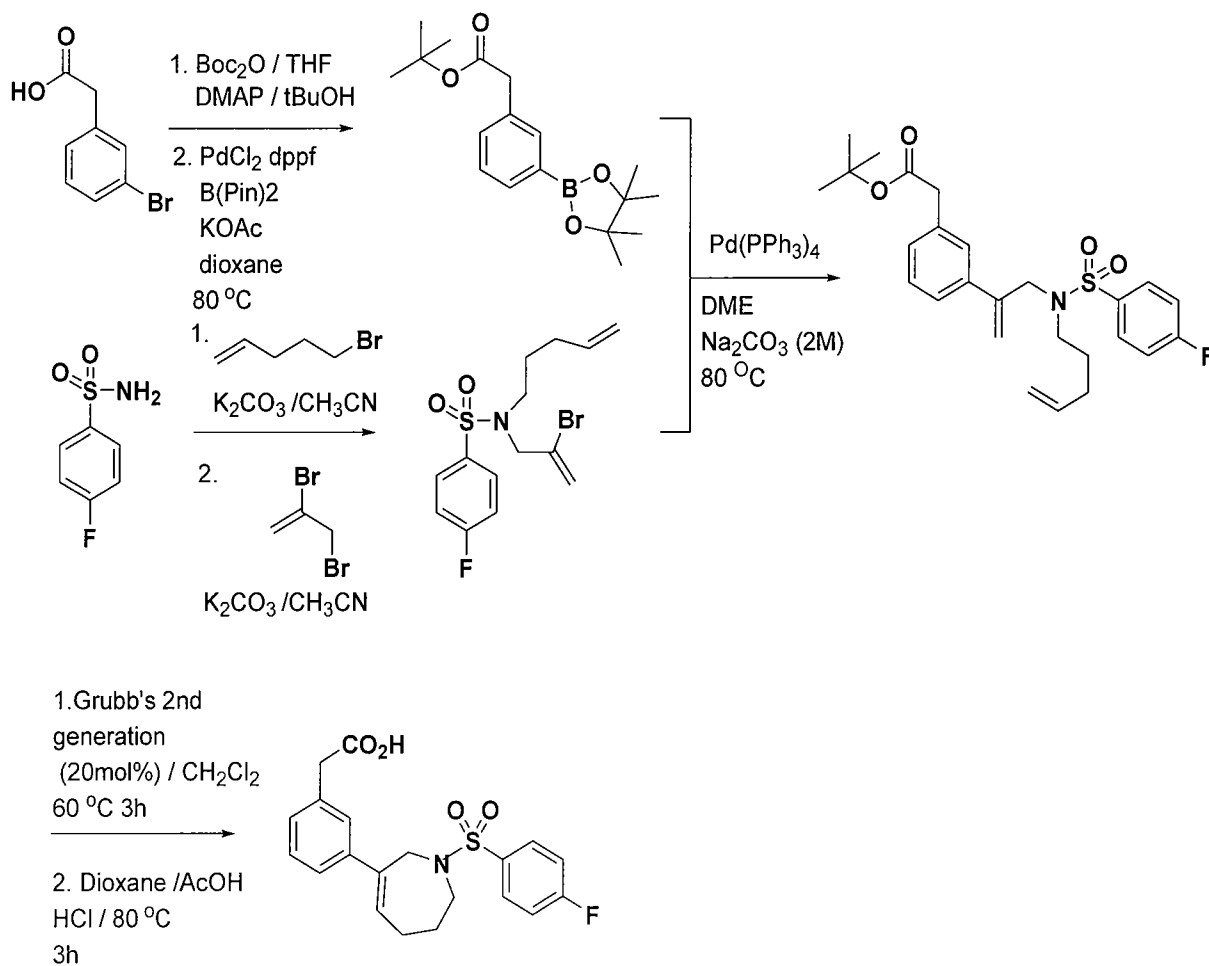
[0323] The title material was obtained using the procedure described for 2-(3-(1-(phenylsulfonyl)-1H-indol-3-yl)phenyl)acetic acid, starting from 1-(4-phenylsulfonyl)-1H-indol-3-ylboronic acid and methyl 2-(3-bromo-5-chlorophenyl)acetate. **Compound 74B**: ES/MS, m/z 426.1 (M+H); LC/MS (Method A) Rt = 3.97 min.

20

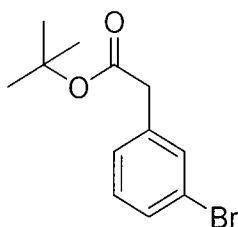
Example 75

(Z)-2-(3-(1-(4-fluorophenylsulfonyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl)phenyl)acetic acid
(Compound 75G)

Scheme 15:



Step A: *tert*-butyl 2-(3-bromophenyl)acetate (Compound 75A)

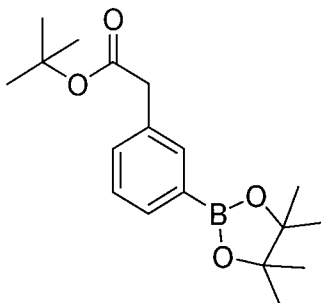


- 10 [0324] To a mixture of 2-(3-bromophenyl)acetic acid (10.0g, 0.046mol), *t*BuOH (34.0 g, 0.46mol), di-*tert*-butyl dicarbonate (20.4g 0.094mol) in THF (50mL) was added DMAP (1.7g, 0.014mol) portion wise, slowly due to effervescence. The reaction was stirred for 24h then concentrated *in vacuo*. The residue was passed through a silica plug (9:1 hexane/EtOAc) and the fractions concentrated and the residue subjected to vacuum
- 15 distillation to give *tert*-butyl 2-(3-bromophenyl)acetate as a colorless oil (9.9g, 0.036, 78%):

b.p 122 °C at 0.05mmHg; ^1H NMR (300MHz, CDCl_3) 7.45-7.37 (m, 2H), 7.22-7.17 (m., 2H), 3.49 (s, 2H), 1.4 (s, 9H).

Step B: *tert*-Butyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate

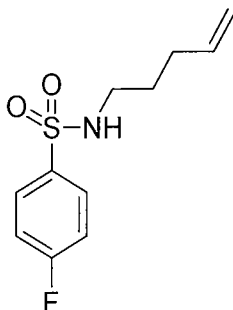
5 **(Compound 75B)**



[0325] A mixture of *tert*-butyl 2-(3-bromophenyl)acetate (9.5g, 0.035 mol), bis(pinacolato)diboroane (10.6g, 0.042mol) and potassium acetate (10.6g, 0.11 mol) in dioxane (270mL) was purged with argon for 30 min. To the mixture was added
 10 dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) DCM adduct (1.2g, 1.7mmol) and 1,1'-bis(diphenylphosphino)ferrocene (0.94g, 1.7mmol) and then vigorously stirred at 80 °C for 4h. The solution was cooled, concentrated *in vacuo* to which was added 5g of activated charcoal and 150mL of hexanes. The mixture was passed through a plug of CELITE and the filtrate concentrated *in vacuo*. The volatile impurities were removed with kugelrohr distillation
 15 (135 °C at 0.02mmHg) and the resulting residue was passed through a silica plug (9:1 EtOAc/hexane) to give *tert*-butyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate as a colorless solid (9.1g, 0.028mol, 82%); ^1H NMR (300MHz, CDCl_3) 7.75-7.65 (m, 2H), 7.41-7.30 (m., 2H), 3.51 (s, 2H), 1.42 (s, 9H), 1.35 (s, 12H).

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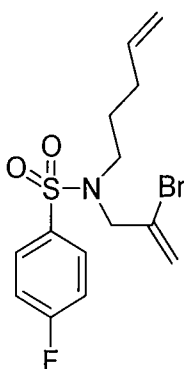
Step C: 4-fluoro-N-(pent-4-enyl)benzenesulfonamide (**Compound 75C**)



[0326] A mixture of 4-fluorobenzenesulfonamide (5g, 0.03mol), 5-bromopentene (3.5mL, 0.03mol) and K_2CO_3 (4.27g, 0.031mol) in acetone (75mL) was heated to reflux for 14h. The resulting suspension was cooled and passed through a plug of CELITE and the concentrated *in vacuo*. Column chromatography (silica gel, 0→60% hexane / EtOAc), furnished

5 4-fluoro-N-(pent-4-enyl)benzenesulfonamide as a colorless oil (1.7g, 6.95mmol, 23%); ^1H NMR (300MHz, $CDCl_3$) 7.9-7.8 (m, 2H), 7.25-7.1 (m, 2H), 5.8-5.6 (m, 1H), 5.0-4.9 (m, 2H), 4.6-4.5 (m, 1H), 2.95 (q, 2H), 2.05 (m, 2H), 1.6-1.5 (m, 2H).

Step D: N-(2-bromoallyl)-4-fluoro-N-(pent-4-enyl)benzenesulfonamide (**Compound 75D**)

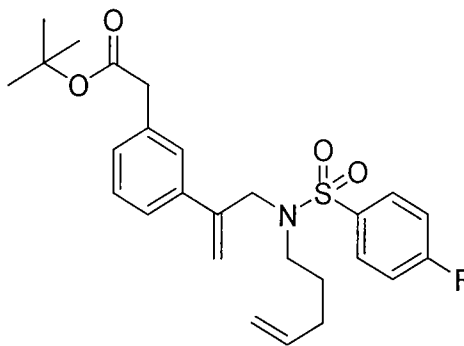


10 [0327] A mixture of 4-fluoro-N-(pent-4-enyl)benzenesulfonamide (1.7g, 0.0069 mol), 2,3-dibromoprop-1-ene (1.99g, 0.01mol) and Cs_2CO_3 (4.55g, 0.014 mol) in CH_3CN (20mL) was stirred at RT for 12h. The mixture was filtered through a plug of CELITE and concentrated *in vacuo*. Column chromatography (silica gel, 0→30% hexane/EtOAc) gave

15 N-(2-bromoallyl)-4-fluoro-N-(pent-4-enyl)benzenesulfonamide (2.1g, 0.0058mol, 84%) as a colorless oil; ^1H NMR (300MHz, $CDCl_3$) 7.9-7.8 (m, 2H), 7.20-7.1 (m., 2H), 5.9 (s, 1H), 5.8-5.6 (m, 1H), 5.6 (d, 1H), 5.0 (m, 2H), 4.05 (s, 2H), 3.2-3.1 (m, 2H), 2.05 (m, 2H), 1.7-1.5 (m, 2H).

20 **Step E:** *tert*-Butyl

2-(3-(3-(4-fluoro-N-(pent-4-enyl)phenylsulfonamido)prop-1-en-2-yl)phenyl)acetate (**Compound 75E**)



[0328] To a mixture of N-(2-bromoallyl)-4-fluoro-N-(pent-4-enyl)benzenesulfonamide (1.6g, 4.4mmol) and *tert*-butyl

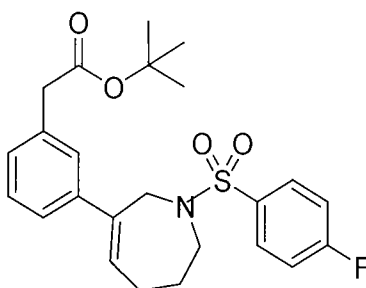
2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (2.1g, 6.6mmol) was added degassed Na₂CO₃ (15mL, 2M), degassed DME (30 mL) and tetrakis(triphenylphosphine)palladium (0) (254mg, 0.22mmol). The solution was vigorously stirred at 90 °C for 4h. The mixture was cooled, diluted with EtOAc (30mL) and the organic layers separated, washed with brine (10mL), dried (Na₂SO₄) and concentrated *in vacuo*.

Column chromatography (silica gel, 0→60% hexane / EtOAc), furnished *tert*-butyl

2-(3-(3-(4-fluoro-N-(pent-4-enyl)phenylsulfonylamido)prop-1-en-2-yl)phenyl)acetate as a colorless oil (1.63g, 3.4mmol, 78%); ¹H NMR (300MHz, CDCl₃) 7.8-7.7 (m, 2H), 7.30-7.1 (m., 6H), 5.7-5.6 (m, 1H), 5.49 (s, 1H), 5.2 (s, 1H), 5.0-4.9 (m, 2H), 4.2 (s, 2H), 3.5 (s, 2H), 3.05 (m, 2H), 2.0-1.85 (m, 2H), 1.6-1.4 (m, 11H), 1.4-1.3 (m, 2H).

Step F: (Z)-*tert*-butyl

2-(3-(1-(4-fluorophenylsulfonyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl)phenyl)acetate (Compound 75F)



[0329] To a solution of *tert*-butyl

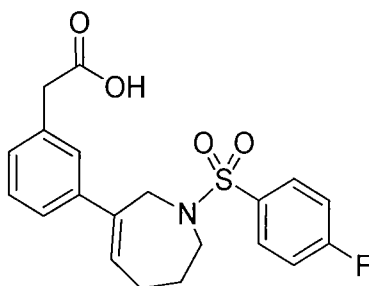
2-(3-(3-(4-fluoro-N-(pent-4-enyl)phenylsulfonylamido)prop-1-en-2-yl)phenyl)acetate (1.5g, 0.032mol) in CH₂Cl₂ (330mL) was added

benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]

dichloro(tricyclohexylphosphine) ruthenium (537mg, 0.63mmol). The solution was heated at reflux 4h, then cooled and concentrated *in vacuo*. Column chromatography (silica gel, 0→50% hexane / EtOAc), furnished (Z)-*tert*-butyl 2-(3-(1-(4-fluorophenylsulfonyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl)phenyl)acetate as a colorless oil (1.25g, 0.028 mol, 88%); ¹H NMR (300MHz, CDCl₃) 7.9-7.7 (m, 2H), 7.40-7.1 (m, 6H), 5.9 (t, 1H), 4.4(s, 2H), 3.55-3.34 (m, 4H), 2.3-2.2 (m, 2H), 1.9-1.8 (m, 2H), 1.45 (s, 9H)

Step G:

- 10 (Z)-2-(3-(1-(4-fluorophenylsulfonyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl)phenyl)acetic acid
(**Compound 75G**)

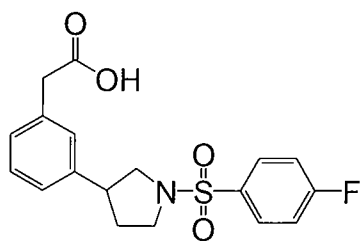


[0330] A mixture of (Z)-*tert*-butyl

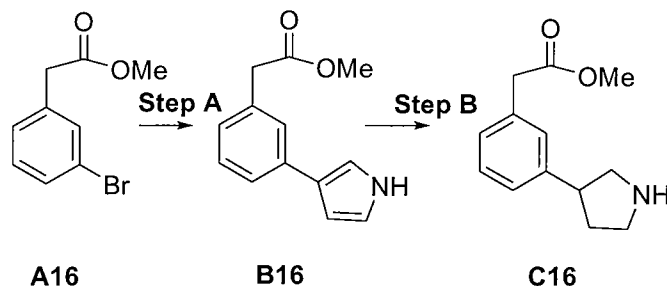
- 2-(3-(1-(4-fluorophenylsulfonyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl)phenyl)acetate (1.25g, 0.028mol), AcOH (4mL), dioxane (40mL) and HCl(15mL, 2M) was heated to 80 °C for 4h, cooled, then concentrated *in vacuo*. Column chromatography (silica gel, 0→10% CH₂Cl₂ / methanol), (Z)-2-(3-(1-(4-fluorophenylsulfonyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl)phenyl)acetic acid as a colorless solid (0.9g, 0.023mol, 82%); LC/MS (Method A) Rt = 3.681 min., MS m/z 390 (M+ H).

Example 76

2-(3-(1-(4-fluorophenylsulfonyl)pyrrolidin-3-yl)phenyl)acetic acid (**Compound 76A**) and 2-(3-(1-(4-fluorophenylsulfonyl)-1H-pyrrol-3-yl)phenyl)acetic acid (**Compound 76B**)



Scheme 16



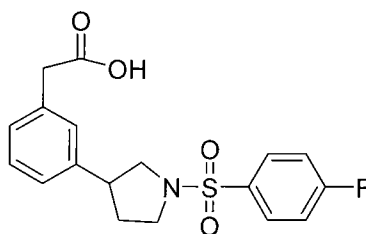
Step A: Methyl 2-(3-(1H-pyrrol-3-yl)phenyl)acetate (**B16**)

- 5 **[0331]** To the mixture of methyl 2-(3-bromophenyl)acetate (400mg, 1.747mmol) and 1-(triisopropylsilyl)-1H-pyrrol-3-ylboronic acid (467mg, 1.747mmol) in DME (4ml) was added palladium tetrakis (100mg, 0.087mmol), followed by the addition of CsF (796mg, 5.24mmol) in water (1ml). The mixture was heated at 90 °C for 4ht. The reaction mixture was diluted with EtAc (30ml), washed with sat H₂O (3 X 10ml), dried over Na₂SO₄. The product, 10 intermediate **3** (0.232g, 64%) was afforded after column chromatography on silica gel.

Step B: Methyl 2-(3-(1H-pyrrolidin-3-yl)phenyl)acetate (**C16**)

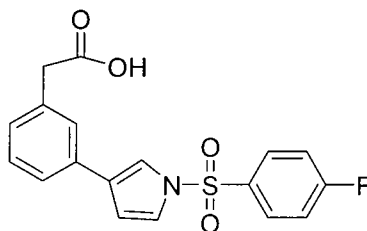
- [0332]** To intermediate **B16** (92.7mg, 0.431mmol) in MeOH (2ml) was added 1ml of 1N HCl in Et₂O, after stirred for 5min, the solvents were pumped off. The residue was dissolved 15 in MeOH (5ml), and was added the catalytic amount of PtO₂. The suspension was purged 3 times, and was stirred at 1atm under H₂ for 3h. The catalyst was filtered off through CELITE[®]. Concentrated to remove solvent, intermediate **4** (94.2mg, 100%) was obtained. Rt = 0.545 min. (Method A); MS (m/z) 220 (M + H).

- 20 2-(3-(1-(4-fluorophenylsulfonyl)pyrrolidin-3-yl)phenyl)acetic acid (**Compound 76A**)



[0333] To intermediate **C16** (66.4mg, 0.302mmol) in DCM (2ml) was added Hunig's base (0.21ml, 1.207mmol), followed by the addition of the 4-fluorophenylsulfonyl chloride (117mg, 0.604mmol). The mixture was stirred at RT overnight. The product was afforded after flash column chromatography on silica gel. The product was then dissolved in THF (1ml), 1ml of aqueous 1N NaOH was added. The mixture was stirred overnight. Diluted with EtAc (15ml), washed with 1N HCl (3 X 2ml), dried over Na₂SO₄, the final product (18.5mg) was obtained after HPLC. Rt = 3.358 min. (Method A); MS (m/z) 364 (M + H)

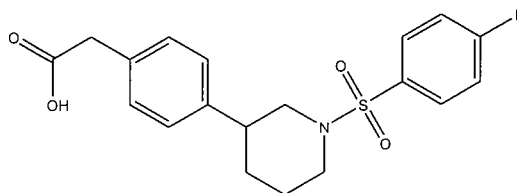
10 2-(3-(1-(4-fluorophenylsulfonyl)-1H-pyrrol-3-yl)phenyl)acetic acid (**Compound 76B**)



[0334] To intermediate **B16** (42.5mg, 0.198mmol) in DCM (2ml) was added NaOH (40mg, 0.989mmol), followed by the addition of the 4-fluorophenylsulfonyl chloride (46mg, 0.604mmol). The mixture was stirred at RT for 2 days. 0.5ml of H₂O was added to the mixture, the product was obtained after HPLC (3.2mg). MS (m/z) 360 (M + H); ¹H NMR (300 MHz, CDCl₃) δ 7.93 (m, 2H), 7.42 (m, 3H), 7.35 (m, 1H), 7.20 (m, 4H), 6.63 (s, 1H), 3.68 (s, 2H).

20 Example 77

2-(4-(1-(4-fluorophenylsulfonyl) piperidin-3-yl)phenyl)acetic acid (**Compound 77**)



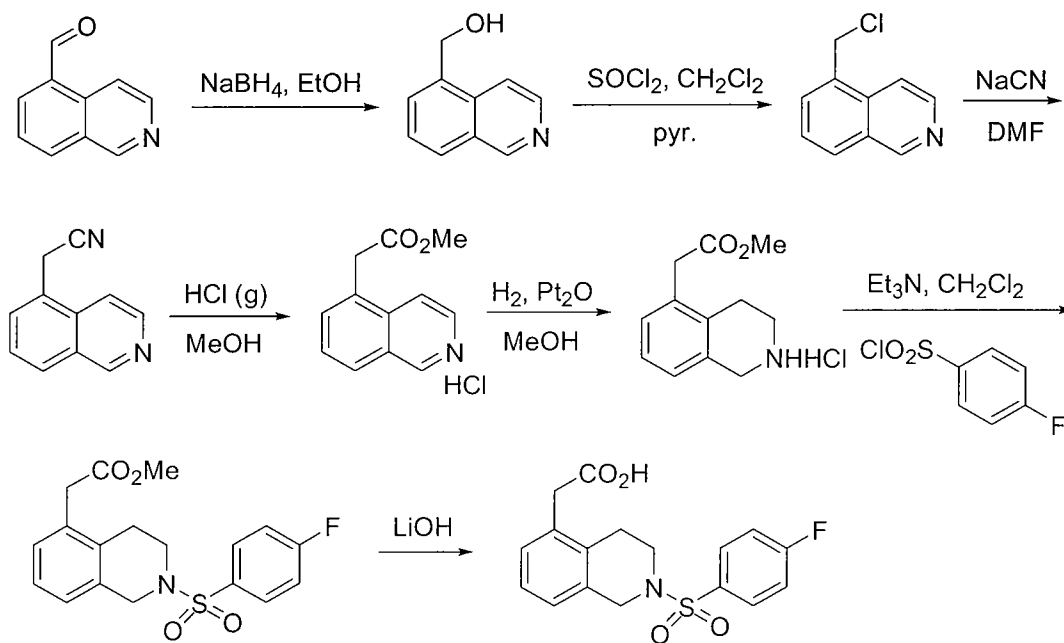
[0335] 2-(4-(1-(4-fluorophenylsulfonyl) piperidin-3-yl)phenyl)acetic acid is prepared using the same methodology as was used to prepare 2-(3-(1-(4-fluorophenylsulfonyl) piperidin-3-yl)phenyl)acetic acid using methyl-4-bromo phenyl acetic acid ester (steps A-D).

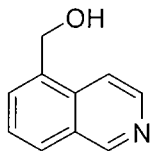
5 LC/MS (Method A) Rt = 3.54 min; MS: 378 m/z (376 m/z negative ion).

Example 78

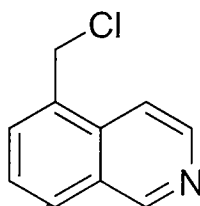
2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid (**Compound 78**)

Scheme 17

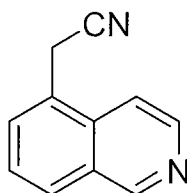


Step A. Preparation of isoquinolin-5-ylmethanol (**Compound 78A**)

[0336] To a solution of commercially available isoquinoline-5-carbaldehyde (808 mg, 5.1 mmol) in EtOH (10 mL) at 0°C was added NaBH₄ (194 mg, 5.1 mmol). The mixture was stirred at 0°C for 2.5 hours before 10% NaOH solution was added. It was stirred for additional 18 hours. Solvent was removed under reduced pressure and the mixture extracted with CH₂Cl₂. The crude mixture was purified using silica gel chromatography to give a pale yellowish oil (690 mg, 4.3 mmol). MS (m/z) 160.1 (M⁺+H).

10 Step B. Preparation of 5-(chloromethyl)isoquinoline (**Compound 78B**)

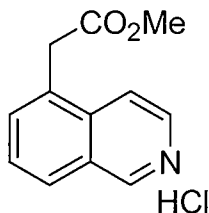
[0337] To isoquinolin-5-ylmethanol was added the thus obtained oil was added CH₂Cl₂ (10 mL), SOCl₂ (2.52 mL, 34.6 mmol), and pyridine (1.4 mL, 17.3 mmol). The mixture was stirred for 20 hours before being cooled to 0°C and quenched with H₂O. The mixture was basified with 10% NaOH and extracted with CH₂Cl₂, and dried over Na₂SO₄. The crude chloride was purified using silica gel chromatography to give an off-white solid (464 mg, 2.61 mmol). MS (m/z) 178.6 (M⁺+H).

Step C: Preparation of 2-(isoquinolin-5-yl)acetonitrile (**Compound 78C**)

[0338] To 5-(chloromethyl)isoquinoline (174 mg, 0.98 mmol) was added thus obtained chloride (174 mg, 0.98 mmol) was added NaCN (98 mg, 2 mmol) and DMF (6 mL). The

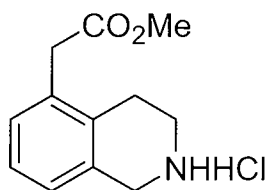
mixture was heated at 70°C for 1.5 hours and purified directly using silica gel chromatography to give an off-white solid (194 mg, 1.15 mmol). MS (m/z) 169.2 ($M^+ + H$).

Step D. Preparation of methyl 2-(isoquinolin-5-yl)acetate hydrochloride (**Compound 78D**)



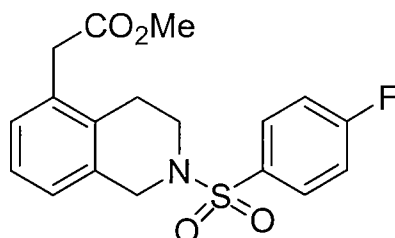
[0339] 2-(isoquinolin-5-yl)acetonitrile was dissolved in MeOH (5 mL) and HCl(g) was bubbled for 5 min. (exothermic). The resulting clear solution was stirred for 3 hours. Solvent was removed and the crude hydrochloride salt was used in the next step as is. MS (m/z) 202.2 ($M^+ + H$).

Step E.. Preparation of methyl 2-(1,2,3,4-tetrahydroisoquinolin-5-yl)acetate hydrochloride (**Compound 78E**)



[0340] To methyl 2-(isoquinolin-5-yl)acetate hydrochloride (125 mg, 0.618 mmol) was added Pt₂O (cat.) and MeOH (4 mL), and it was hydrogenated under H₂ balloon for 19 hours. The mixture was filtered through a plug of CELITE and flushed with MeOH. Removal of solvent gave methyl 2-(1,2,3,4-tetrahydroisoquinolin-5-yl)acetate hydrochloride as an off-white solid (125 mg, 0.51 mmol). MS (m/z) 206.2 ($M^+ + H$).

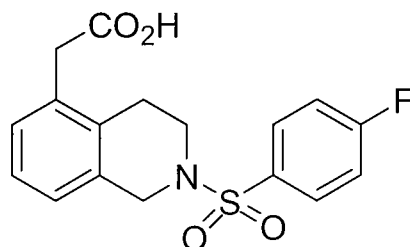
Step F..Preparation of methyl

2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetate_(**Compound 78F**)

[0341] Methyl 2-(1,2,3,4-tetrahydroisoquinolin-5-yl) acetate hydrochloride (59 mg, 0.24 mmol) was dissolved in CH₂Cl₂ (4 mL). TEA (134 μ L, 0.96 mmol) was then added followed by 4-fluorobenzene-1-sulfonyl chloride (71 mg, 0.36 mmol). The mixture was stirred for 19 hours before it was diluted with CH₂Cl₂ and H₂O. The aqueous layer was extracted with CH₂Cl₂ and the crude mixture was purified using silica gel chromatography to give a white solid (48 mg, 0.13 mmol). MS (m/z) 364.4 (M⁺+H).

10

Step G. Preparation of

2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid (**Compound 78G**)

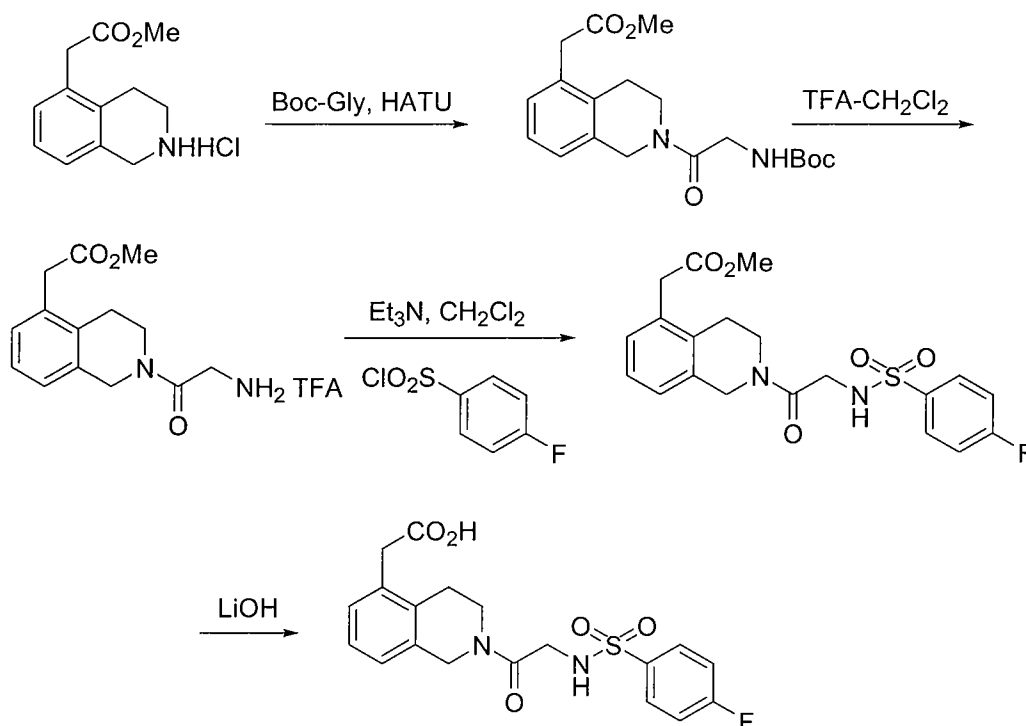
[0342] To methyl 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl) acetate was added THF-H₂O (2 mL-0.5 mL) and LiOH·H₂O (45 mg, 1.06 mmol). It was stirred for 16 hours before THF was removed and mixture acidified with 1N HCl. It was extracted with EtOAc, dried over Na₂SO₄. Removal of solvent gave 46 mg (100%) of the title compound 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid as a white solid.

LC/MS (m/z) 350.00 (M⁺+H); Rt = 3.13 min.

Example 79

2-(2-(2-(4-fluorophenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid
(Compound 79G)

Scheme 18

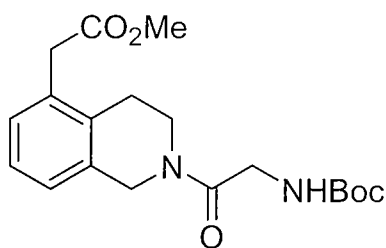


5

Step A. Preparation of methyl

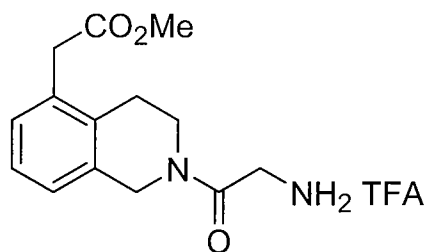
2-(2-(2-(*tert*-butoxycarbonylamino)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetate

(Compound 79A)



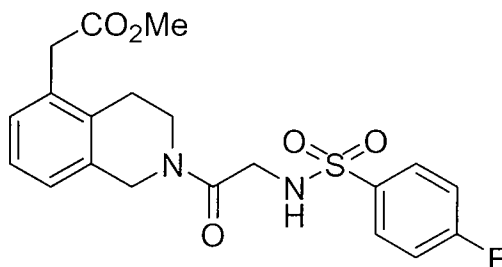
- 10 [0343] To the previously obtained methyl 2-(1,2,3,4-tetrahydroisoquinolin-5-yl)acetate hydrochloride (66 mg, 0.272 mmol) was added Boc-glycine (95 mg, 0.544 mmol), CH₃CN (4 mL), DIEA (237 μ L, 1.36 mmol) and HATU (207 mg, 0.544 mmol). The mixture was stirred for 18 hours before the solvent was removed and the mixture diluted with EtOAc and washed with NaHCO₃ (sat.) and brine. The combined organic layer was dried over Na₂SO₄. Solvent was removed to give an oil. It was used as is in the next step. MS (m/z) 363.4 (M⁺+H).
- 15

Step B. Preparation of methyl

2-(2-(2-aminoacetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetate TFA salt (**Compound 79B**)

- 5 [0344] To the above crude methyl 2-(2-(2-(tert-butoxycarbonylamino)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl) acetate was added CH_2Cl_2 (2 mL) and TFA (1 mL) and stirred for 2.5 hours. Solvent was removed to give the TFA amine salt as an oil. It was used as is in the next step. MS (m/z) 263.3 ($\text{M}^+ + \text{H}$).

10 Step C. Preparation of methyl

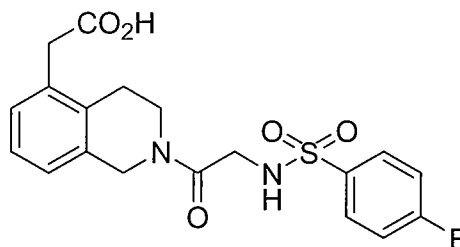
2-(2-(2-(4-fluorophenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetate (**Compound 79C**)

[0345] To this crude methyl

- 15 2-(2-(2-aminoacetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetate TFA salt was added CH_2Cl_2 (4 mL). TEA (335 μL , 2.4 mmol) was then added followed by 4-fluorobenzene-1-sulfonyl chloride (84 mg, 0.43 mmol). The mixture was stirred for 16 hours before it was diluted with CH_2Cl_2 and H_2O . The organic layer was dried over Na_2SO_4 . Removal of solvent gave the sulfonamide as a brown oil. It was used in the next step without further purification. MS
- 20 (m/z) 421.4 ($\text{M}^+ + \text{H}$).

Step D. Preparation of

2-(2-(2-(4-fluorophenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid
(**Compound 79D**)



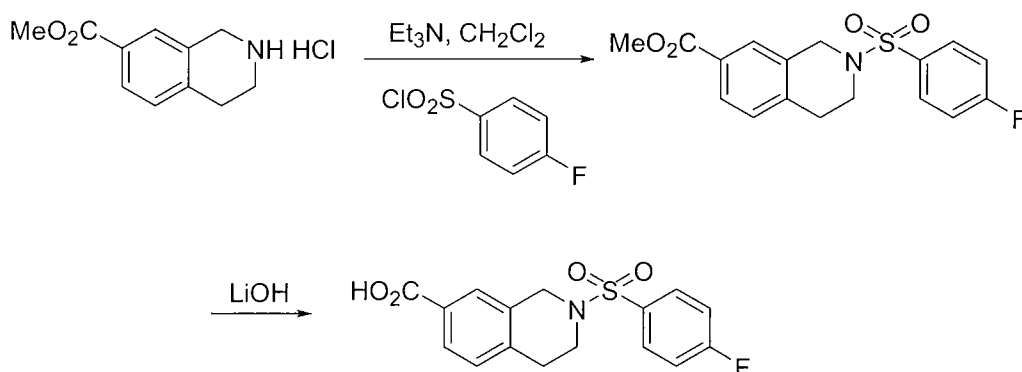
- 5 [0346] The subsequent hydrolysis was conducted in THF-H₂O (2 mL-0.5 mL) and LiOH·H₂O (114 mg, 2.72 mmol). It was stirred for 3 days before being quenched with 1N HCl and extracted with EtOAc. Reverse phase HPLC purification yielded the title compound 2-(2-(2-(4-fluorophenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid as a white solid. MS (m/z) 407.20 (M⁺+H); Rt = 2.73 min.

10

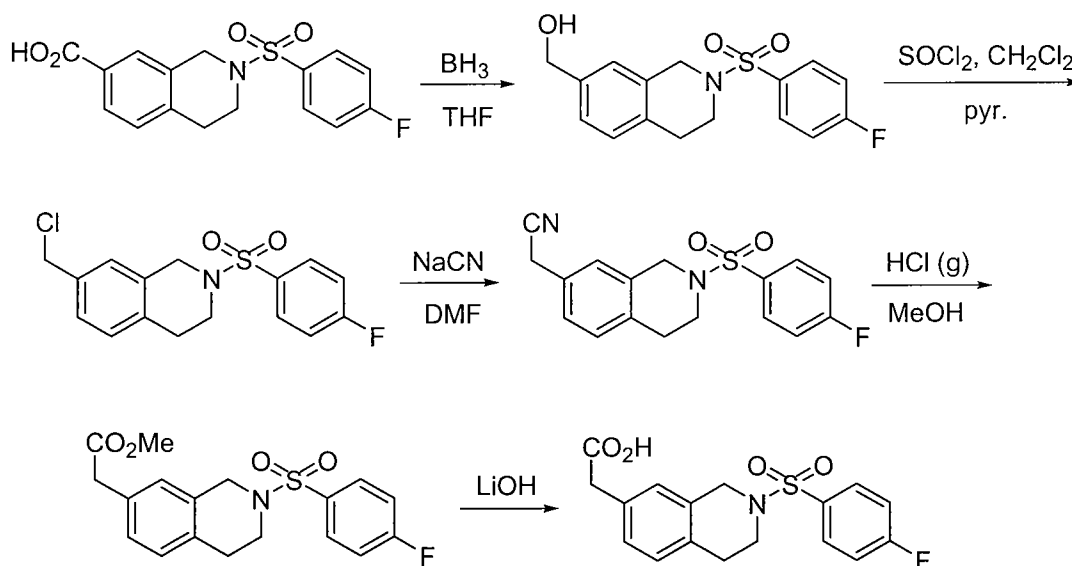
Example 80

Preparation of 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid
(**Compound 80**)

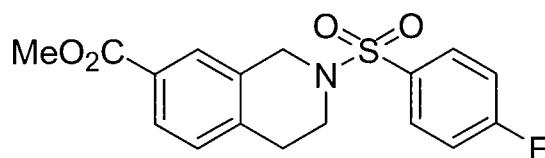
Scheme 19



15



Step A. 2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate
(Compound 80A)

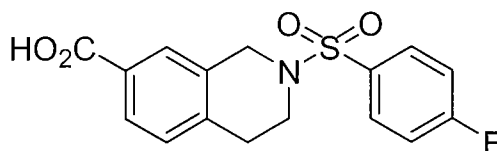


5

[0347] To 560 mg (2.45 mmol) of commercially available methyl 1,2,3,4-tetrahydroisoquinoline-7-carboxylate hydrochloride was added CH_2Cl_2 (20 mL). TEA (1.36 mL, 9.8 mmol) was then added followed by 4-fluorobenzene-1-sulfonyl chloride (718 mg, 3.7 mmol). The mixture was stirred for 17 hours before it was purified directly with silica gel chromatography to give 798 mg (93%) of the sulfonamide as a white solid. MS (m/z) 350.3 ($\text{M}^+ + \text{H}$).

10

Step B. 2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid
(Compound 80B)



15

[0348] To the methyl 2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate was added

THF-H₂O (8 mL-2 mL) and LiOH·H₂O (765 mg, 18.2 mmol). It was stirred for 1 day at ambient temperature and then heated at 60°C for 4 h before THF was removed carefully by blowing a stream of N₂. The mixture was acidified with 1N HCl and extracted with EtOAc. The combined organic layer was dried over Na₂SO₄. Removal of solvent yielded 760 mg

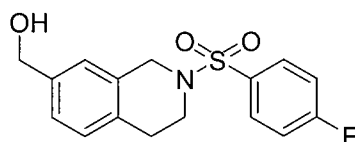
(99%) of the title compound

2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid as a white solid.

MS (m/z) 334.10 (M⁻H); Rt = 3.07 min.

Step C. (2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)methanol

(**Compound 80C**)



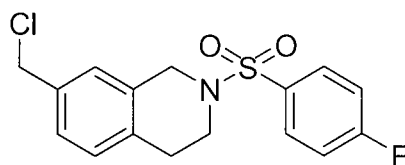
[0349] To the previously obtained

2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (463 mg, 1.38 mmol) in THF at 0°C was added BH₃·THF (4.14 mL, 4.14 mmol). The mixture was stirred at 0°C for 2.5 hours then at ambient temperature for 4 hours before being quenched with MeOH. Solvent was removed and 1N HCl and EtOAc were added and the slurry stirred for overnight. The aqueous layer was basified with 10% NaOH to pH=9 and extracted with CH₂Cl₂ and dried over Na₂SO₄. Removal of solvent gave 320 mg of a white solid (72%).

MS (m/z) 322.3 (M⁺+H).

Step D. 7-(chloromethyl)-2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline

(**Compound 80D**)



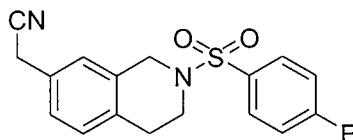
[0350] To (2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl) methanol was

added CH₂Cl₂ (4 mL), SOCl₂ (1 mL), and pyridine (2 mL). The mixture was stirred for 18 hours before solvent was removed. The mixture was basified with 10% NaOH and extracted

with CH_2Cl_2 , and purified using silica gel chromatography to give 60 mg of a white solid (18%). MS (m/z) 340.8 ($\text{M}^+\text{+H}$).

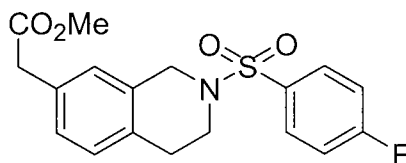
Step E. 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetonitrile

5 (Compound 80E)



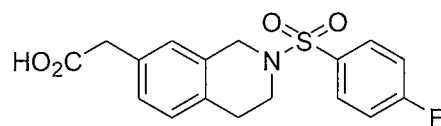
[0351] To 7-(chloromethyl)-2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline was added NaCN (18 mg, 0.36 mmol) and DMF (2 mL). The mixture was heated at 70 °C for 2 hours and purified directly using silica gel chromatography to give 37 mg of a white solid
10 (65%). MS (m/z) 331.3 ($\text{M}^+\text{+H}$).

Step F. 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetate (Compound 80F)



15 [0352] 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetonitrile dissolved in MeOH (4 mL) and EtOAc (3 mL). HCl(g) was bubbled for 1 min. (exothermic). The resulting clear solution was stirred for 35 min. Solvent was removed and the crude product was used as is. MS (m/z) 364.4 ($\text{M}^+\text{+H}$).

Step G. 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid
(Compound 80G)

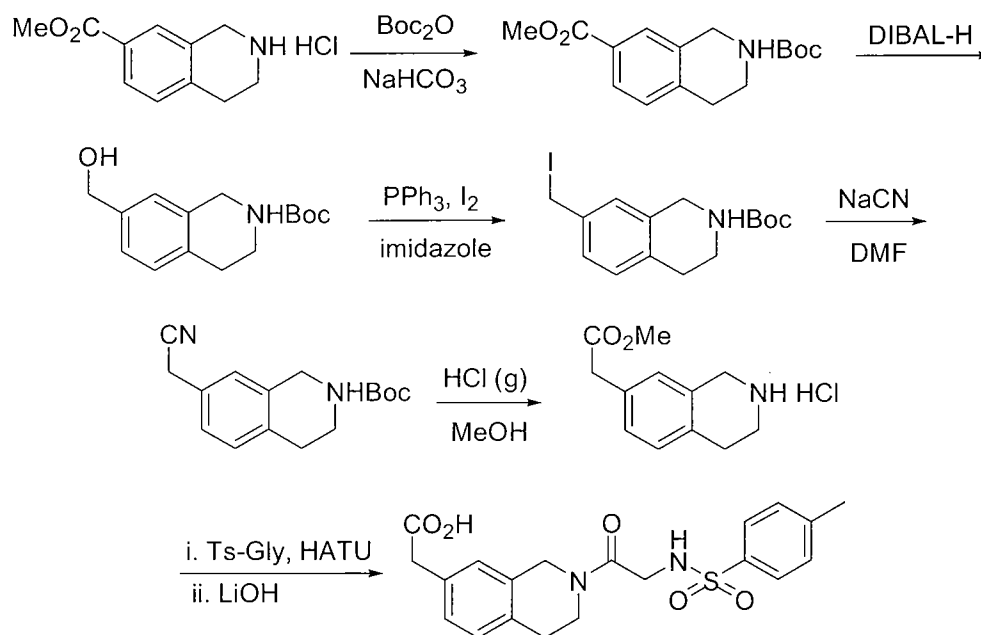


[0353] To methyl 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetate was added THF-H₂O (2.5 mL-0.5 mL) and LiOH·H₂O (149 mg, 3.56 mmol). It was stirred for 18 hours before being acidified with 1N HCl. It was extracted with EtOAc. Reverse phase HPLC purification yielded the title compound 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid as a white solid. MS (m/z) 350.05 (M⁺+H); Rt = 3.08 min.

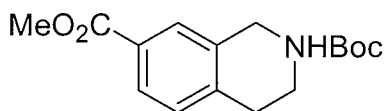
Example 81

2-(2-(2-(4-methylphenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid
(Compound 81)

Scheme 20



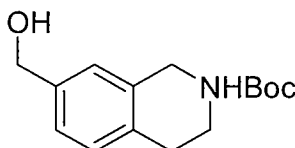
Step A. 2-*tert*-butyl 7-methyl 3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate (**Compound 81A**)



[0354] To 616 mg (2.7 mmol) of commercially available methyl

- 5 1,2,3,4-tetrahydroisoquinoline-7-carboxylate hydrochloride was added THF-H₂O (16 mL-4 mL), NaHCO₃ (1.36 g) and Boc₂O (1.18 g). The mixture was stirred for 17 hours and extracted with EtOAc. Silica gel chromatography gave a colorless oil (100%). MS (m/z) 293.3 (M⁺+H).

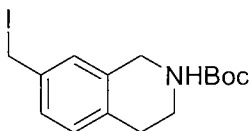
- 10 Step B. *tert*-butyl 7-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**Compound 81B**)



[0355] 2-*tert*-butyl 7-methyl-3,4-dihydroisoquinoline-2, 7-(1H)-dicarboxylate was

- dissolved in THF (30 mL) and cooled to 0°C. DIBAL-H (8.1 mL, 8.1 mmol, 1 M in THF)
15 was added. The mixture was stirred at ambient temperature for 16 hours before a solution of Na-K tartrate was added and the mixture stirred for 5 hours. The mixture was extracted with EtOAc and purification by silica gel chromatography gave 294 mg the desired alcohol (41%) as well as recovered starting ester (320 mg, 41%). MS (m/z) 265.3 (M⁺+H).

- 20 Step C. *tert*-butyl 7-(iodomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**Compound 81C**)

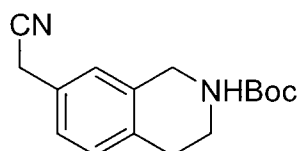


[0356] To *tert*-butyl 7-(hydroxymethyl)-3,4-dihydroisoquinoline-2 (1H)-carboxylate in

- THF (10 mL) at 0°C was added PPh₃ (441 mg, 1.68 mmol), imidazole (190 mg, 2.8 mmol)
25 and I₂ (426 mg, 1.68 mmol). The mixture was stirred at 0°C for 30 min. and then at ambient

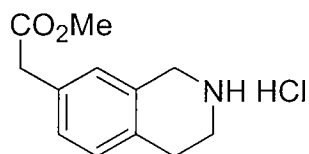
temperature for 3 more hours. Solvent was removed and the residue purified by silica gel chromatography to give 65 mg of the desired iodide (16%) as well as the recovered starting alcohol (116 mg, 40%). MS (m/z) 375.2 ($M^+ + H$).

5 Step D. 7-(cyanomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**Compound 81D**)



[0357] To *tert*-butyl 7-(iodomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate was added NaCN (17 mg, 0.34 mmol) and DMF (2 mL). The mixture was heated at ambient temperature for 30 min. and then purified directly using silica gel chromatography to give 41
10 mg of a colorless oil (89%). MS (m/z) 274.3 ($M^+ + H$).

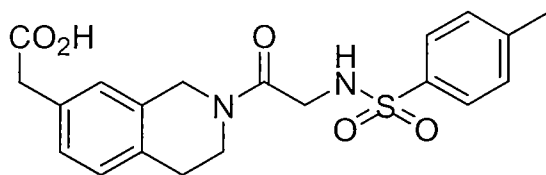
Step E. Methyl 2-(1,2,3,4-tetrahydroisoquinolin-7-yl)acetate hydrochloride (**Compound 80E**)



15 [0358] *tert*-butyl 7-(cyanomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate was dissolved in MeOH (3 mL) and HCl(g) was bubbled for 20 seconds (exothermic). The resulting clear solution was stirred for 16 hours. Solvent was removed and the crude product was used as is. MS (m/z) 206.2 ($M^+ + H$).

Step F.

2-(2-(2-(4-methylphenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid
(**Compound 81F**)

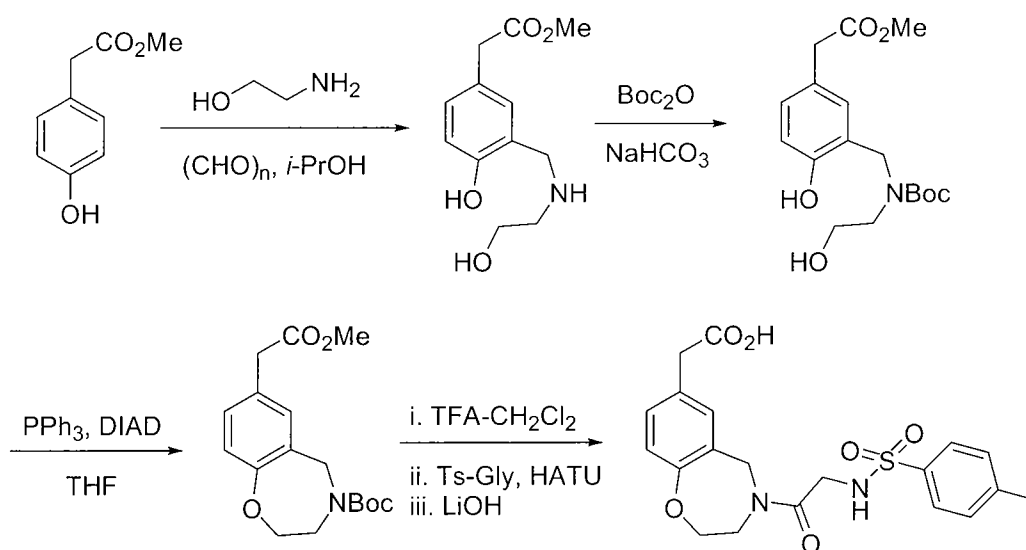


- 5 [0359] To methyl 2-(1,2,3,4-tetrahydroisoquinolin-7-yl) acetate hydrochloride was added added Ts-glycine (15 mg, 0.065 mmol), CH₃CN (2 mL), DIEA (45 μ L, 0.26 mmol) and HATU (33 mg, 0.0868 mmol). The mixture was stirred for 3 days before THF-H₂O (2 mL-0.5 mL) was added, followed by LiOH·H₂O (40 mg, 0.95 mmol). It was stirred for 3 days before being acidified with 1N HCl and extracted with EtOAc. Reverse phase HPLC
- 10 purification yielded the title compound 2-(2-(2-(4-methylphenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid as a white solid. MS (m/z) 403.10 (M⁺+H); Rt = 2.80 min.

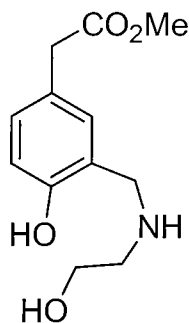
Example 82

- 15 2-(4-(2-(2-(4-methylphenylsulfonamido)acetyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)acetic acid (**Compound 82**)

Scheme 21



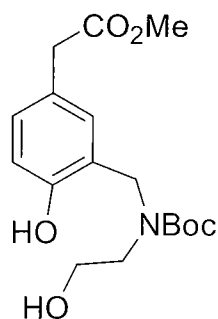
Step A. Methyl 2-(4-hydroxy-3-((2-hydroxyethylamino)methyl)phenyl)acetate (**Compound 82A**)



[0360] To 7.82 g (47 mmol) of commercially available methyl 2-(4-hydroxyphenyl)acetate
5 was added ethanol amine (2.8 mL, 47 mmol), paraformaldehyde (1.55 g, 52 mmol) and isopropyl alcohol (100 mL). The slurry was refluxed at 95°C for 19 hours. Solvent was removed and silica gel chromatography purification gave 1.4 g of a colorless oil (12%). MS (m/z) 240.2 ($M^+ + H$).

10 Step B. Methyl

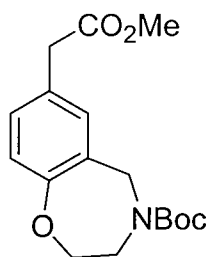
2-(3-((*tert*-butoxycarbonyl(2-hydroxyethyl)amino)methyl)-4-hydroxyphenyl)acetate
(**Compound 82B**)



[0361] To 252 mg of methyl 2-(4-hydroxy-3-((2-hydroxyethylamino) methyl) phenyl)
15 acetate was added THF-H₂O (8 mL-2 mL), NaHCO₃ (441 mg) and Boc₂O (345 mg). The mixture was stirred for 18 hours and extracted with EtOAc. Silica gel chromatography gave 214 mg of N-Boc derivative as a white solid (60%). MS (m/z) 340.3 ($M^+ + H$).

Step C. *tert*-butyl

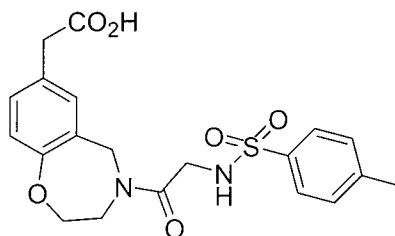
7-(2-methoxy-2-oxoethyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate
(**Compound 82C**)



- 5 **[0362]** To 115 mg of methyl 2-(3-((*tert*-butoxycarbonyl(2-hydroxyethyl) amino) methyl)-4-hydroxyphenyl) acetate in THF (3.5 mL) was added PPh₃ (267 mg, 1.02 mmol) and DIAD (197 μ L, 1.02 mmol, slow addition in 14 min.). The mixture was stirred for 30 min. and quenched with NaHCO₃ (sat.) and extracted with EtOAc. Silica gel chromatography gave 44 mg of the cyclized product as a colorless oil (40%). MS (m/z)
- 10 322.3 (M⁺+H).

Step D.

2-(4-(2-(4-methylphenylsulfonamido)acetyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)acetic acid (**Compound 82D**)



15

- [0363]** To the above oil was added added CH₂Cl₂ (2 mL) and TFA (1 mL). The mixture was stirred for 2 hours and solvent was removed. To this hydrochloride salt was added added Ts-glycine (47 mg, 0.2 mmol), CH₃CN (4 mL), DIEA (120 μ L, 0.685 mmol) and HATU (104 mg, 0.27 mmol). The mixture was stirred for 6 hours before solvent was removed and
- 20 THF-H₂O (4 mL-0.8 mL) was added, followed by LiOH·H₂O (86 mg, 2.06 mmol). It was stirred for 20 hours before THF was carefully blown off by a stream of N₂. The mixture was acidified with 1N HCl and extracted with EtOAc and dried over Na₂SO₄. Removal of solvent gave 37 mg of the title compound

2-(4-(2-(4-methylphenylsulfonamido)acetyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)acetic acid as a white solid (64%). MS (m/z) 419.10 ($M^+ + H$); $R_t = 2.69$ min.

Pharmacological Data:

5 Receptor Interaction Assay

Cell culture:

[0364] Human Jurkat cells transfected with DP-2, DP-1 or TP receptors were maintained in culture in a humidified atmosphere at 37 °C (5% CO₂) 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.

15 Preparation of cell membranes:

[0365] Frozen Jurkat cell pellets expressing either DP-2 , DP-1 or TP were thawed on ice. Each pellet was suspended in membrane buffer (25mM Hepes[®] pH7.2, 6mM MgCl₂, 1mM EDTA) plus Complete[®] protease inhibitor cocktail tablets (Roche Mannheim Germany). The pellets were dounce homogenized and centrifuged at 1900 RPM for 10 min. in a table top centrifuge (Beckman Coulter Allegra[®] 6R). The supernatants were collected and pellets resuspended in 10mls of membrane buffer, dounce homogenized again and centrifuged as above. The 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 membrane pellets suspended in membrane buffer and pooled. Protein concentration was determined and membranes adjusted to approximately 1.5mgs/ml.

DP-2 Binding Assay:

[0366] 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] PGD₂ (166Ci/mmol) as a radioactive tracer. Assays were performed in a final volume of 150μl of assay buffer (10mM Hepes[®], 10mM MnCl₂, 1mM

EDTA and 1% DMSO). Test article serially diluted in assay buffer was incubated with 1nM radioactive tracer and 10ug/well of the membranes prepared from DP-2 expressing cells in a 96 well polypropylene plate for one hour at room temperature. The reaction mixture was then transferred to a Millipore(Bedford, MA) MultiScreen[®], 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 TM(Wallac Oy Turku, Finland) 1450 micro beta liquid scintillation counter

DP-2 Chemotaxis Assay

[0367] 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 1nM PGD₂ as a chemoattractant, and 600ul of this mixture were transferred into the bottom wells of a Costar Transwell[®] plate (8 µm pore size). DP-2 transfected Jurkat cells were harvested, re-suspended at 7.5x10⁶/ml complete media, and 100 µL of this cell suspension was added into the pore filter inserts. After equilibration of all the components to 37 °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 °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-1 binding assay

[0368] DP-1 binding assays were performed in a manner substantially identical to the DP-2 binding assay, except that DP-1 transfected cell membranes were used.

Human TP binding assay

[0369] TP receptor interaction was assessed in competition binding assays using membranes from TP receptor transfected cells (prepared as above) and ³[H] SQ29,548

(48.2uCi/mmol) as a TP-selective tracer. Assays were performed in a final volume of 150ul of binding buffer (10mM Hepes, 10mM MnCl₂, 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

5 temperature the reaction mixture was transferred to a Millipore® (Bedford, MA) MultiScreen®, FC MAFCNOB 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
10 Turku, Finland) 1450 micro beta liquid scintillation counter.

[0370] All of the acid compounds of the Examples that were tested in the assay exhibited IC₅₀ values less than 10 µM, for example the acid compounds of examples 2, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60,
15 61, 62, 63, 64, 65, 69, 70, 71, 72, 73, 76. In some embodiments, the compounds of the invention exhibited IC₅₀ values less than 1 µM. In some embodiments, the compounds of the invention exhibited IC₅₀ values less than 0.1 µM.

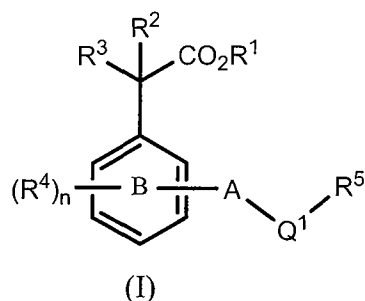
[0371] All of the acid compounds of the Examples that were tested in the above-described ligand binding assays exhibited an average IC₅₀ value which was least 2-fold lower for DP-2
20 over DP-1 or TP, for example the acid compounds of examples 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 21, 22, 29, 33, 34, 44, 46, 47, 49, 50, 52, 53, 54, 55, 57, 58, 59, 61, 63, 64, 69 and 76. In some embodiments, the acid compounds of the invention exhibited an average IC₅₀ value which was least 10-fold lower for DP-2 over DP-1 or TP, for example the acid compounds of examples 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 21, 22, 29, 33, 34, 44, 46, 47, 49, 52, 53, 54, 55,
25 57, 59, 63, 64, 69 and 76. In some embodiments, the acid compounds of the invention exhibited an average IC₅₀ value which was least 50-fold lower for DP-2 over DP-1 or TP, for example the compounds of examples 8, 9, 10, 11, 12, 13, 14, 16, 17, 21, 22, 29, 33, 34, 44, 46, 47, 49, 59, 64, 69 and 76.

[0372] All publications and patent applications cited in this specification are herein
30 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 IS CLAIMED IS:

1. A compound having the structure (I):



wherein:

A is a 5-14-membered heterocyclic ring fused or bonded to phenyl ring B 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 R^8 substituents;

Q^1 is selected from the group consisting of: a bond, $-C_1-C_4$ alkylene-, $-C_1-C_4$ heteroalkylene-, $-CO-$, $-NH-$, $-O-$, $-SO_q-$, $-C(O)O-$, $-OC(O)-$, $-CONH-$, $-NHCO-$, $-NHCONH-$, $-NHSO_q-$, $-SO_qNH-$ and $-COCH_2HNSO_q-$;

each R^1 , R^2 and R^3 is independently selected from the group consisting of H, C_{1-6} alkyl, C_{0-6} alkylaryl and C_{0-6} alkylheteroaryl; wherein the aryl or heteroaryl portions are optionally substituted with 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_qR , SO_qNR_2 , $OC(O)OR$, $OC(O)R$, $OC(O)NR_2$, $NRC(O)NR_2$, $NRC(O)R$ and $NRC(O)OR$;

each R^8 is independently selected from the group consisting of C_{1-6} alkyl, C_{0-6} alkyl C_{3-6} cycloalkyl, C_{0-6} alkylaryl, C_{0-6} 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_qR , SO_qNR_2 , $OC(O)OR$, $OC(O)R$, $OC(O)NR_2$, $NRC(O)NR_2$, $NRC(O)R$ and $NRC(O)OR$;

each R^4 is independently selected from the group consisting of C_{1-6} alkyl, C_{0-4} alkyl C_{3-10} cycloalkyl, C_{0-4} alkylaryl, C_{0-4} alkylheteroaryl, C_{2-4} alkenylaryl, C_{2-4} alkynylaryl, C_{0-4} alkylheterocyclyl, CN, amino, $NHCOR^1$, hydroxy, C_{1-6} alkoxy, $OC(O)R^1$, $-OC_{0-4}$ alkylaryl, OC_{0-4} alkylheteroaryl, $-OC_{0-4}$ alkyl C_{3-10} cycloalkyl, OC_{0-4} alkyl C_{3-10} heterocyclyl, OC_{0-4} alkyl NR^8 , nitro, halo and halo C_{1-6} alkyl; or are combined together to form an aryl or

heterocyclyl ring 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 C₁₋₆alkyl, CN, CONHR¹, CO₂R¹, amino, C₁₋₆alkoxy, halo, haloC₁₋₆alkyl and SO_qR¹;

R⁵ is selected from the group consisting of C₁₋₆alkyl, C₀₋₄alkylaryl, C₂₋₄alkenylaryl, C₂₋₄alkynylaryl and C₀₋₄alkylheteroaryl, each of which is optionally substituted with 1-3 R⁹ substituents;

each R⁹ is independently selected from the group consisting of C₁₋₆alkyl, CN, OR, oxo, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, NR₂, NO₂, halo, C(O)R, CO₂R, CONR₂, SO_qR, SO_qNR₂, OC(O)OR, OC(O)R, OC(O)NR₂, NRC(O)NR₂, NRC(O)R and NRC(O)OR;

each R is independently selected from the group consisting of H, C₁₋₆alkyl, C₀₋₄alkylheteroaryl, C₀₋₄heterocyclyl, C₃₋₈cycloalkyl and C₀₋₄alkylaryl 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;

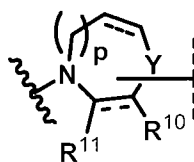
the subscript n is independently 0, 1, 2, 3 or 4;

the subscript o is independently 0 or 1;

each subscript q is independently 0, 1 or 2; and

pharmaceutically acceptable derivatives thereof.

2. The compound of claim 1, wherein A has the structure (II):



(II)

wherein

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

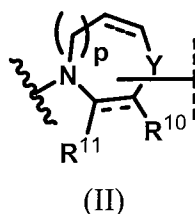
R¹⁰ and R¹¹ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;

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 wavy line indicates the point of attachment to Q¹ and the dashed line indicates the point of attachment to phenyl ring B.

3. The compound of claim 1, wherein A has the structure (II):



wherein

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

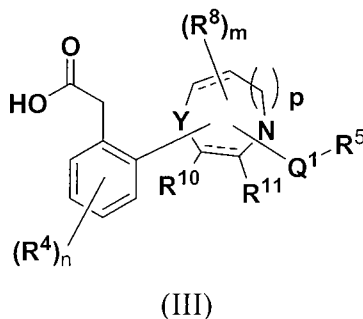
R¹⁰ and R¹¹ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;

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 wavy line indicates the point of attachment to phenyl ring B and the dashed line indicates the point of attachment to Q¹.

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



wherein

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

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

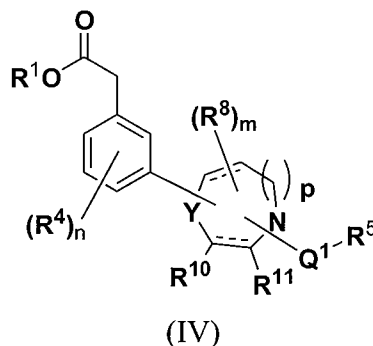
the subscript m is independently 0, 1, 2 or 3;

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.

5. A compound of claim 4 selected from the group consisting of:
2-(2-(1-tosylpiperidin-3-yl)phenyl)acetic acid; and 2-(2-(1-tosylpiperidin-4-yl)phenyl)acetic acid.

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



wherein

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

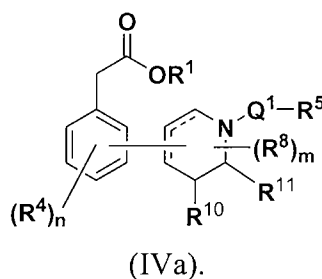
R¹⁰ and R¹¹ are H or are combined together to form an aryl, heteroaryl or cycloalkyl ring;

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.

7. A compound of claim 6 having the general structure (IVa):



8. A compound of claim 7 selected from the group consisting of: {3-[1-(4-Fluoro-benzoyl)-piperidin-3-yl]-phenyl}-acetic acid;
2-(3-(1-(4-Fluoro-benzenesulfonyl)-piperidin-2-yl)-phenyl)-acetic acid; {3-[1-(4-Fluoro-benzenesulfonyl)-piperidin-2-yl]-phenyl}-acetic acid
2-(3-(1-(methylsulfonyl)piperidin-3-yl)phenyl)acetic acid;

- 6 2-(4-(4-chlorobenzoyloxy)-3-(1-(methylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
7 2-(3-(1-(thiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
8 2-(3-(1-(thiophen-3-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
9 2-(3-(1-(5-chlorothiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
10 2-(3-(1-(5-bromothiophen-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
11 2-(3-(1-(benzofuran-2-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
12 2-(3-(1-(pyridin-3-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
13 2-(3-(1-(benzylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
14 (E)-2-(3-(1-(styrylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
15 {3-[1-(Toluene-4-sulfonyl)-decahydro-quinolin-3-yl]-phenyl}-acetic acid;
16 {3-[1-(4-Fluoro-benzenesulfonyl)-1,2,3,4-tetrahydro-quinolin-3-yl]-phenyl}-acetic acid;
17 2-(3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid; 2-(3-(1-tosylpiperidin-3-yl)phenyl)
18 acetic acid; 2-(4-(4-chlorobenzoyloxy)-3-(1-(phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
19 2-(3-(1-(3,5-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
20 (2-(3-(1-(2,3-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
21 2-(3-(1-(4-nitrophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
22 2-(3-(1-(naphthalen-1-ylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
23 2-{3-[1-(4-Fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid; methyl
24 2-(3-(1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetate;
25 2-(3-(1-(4-fluorophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid;
26 2-(3-(1-(4-fluorophenylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)phenyl)acetic acid;
27 {3-[1-(4-Fluoro-benzenesulfonyl)-4-methyl-piperidin-3-yl]-phenyl}-acetic acid methyl ester;
28 {3-[1-(4-Fluoro-benzenesulfonyl)-4-methyl-piperidin-3-yl]-phenyl}-acetic acid;
29 {3-[1-(4-Fluoro-benzenesulfonyl)-2-methyl-piperidin-3-yl]-phenyl}-acetic acid;
30 {3-[1-(4-Fluoro-benzenesulfonyl)-6-methyl-piperidin-3-yl]-phenyl}-acetic acid;
31 2-(4-(4-chlorobenzoyloxy)-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
32 2-(3-(1-(4-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid; methyl
33 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetate;
34 2-(4-chloro-3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
35 2-(3-chloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
36 2-(2-chloro-5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid; and
37 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-2-methylphenyl)acetic acid;
38 {3-[1-(4-Fluoro-benzenesulfonyl)-piperidin-3-yl]-5-hydroxy-phenyl}-acetic acid;
39 {3-Benzoyloxy-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;

40 {3-(4-Chloro-benzyloxy)-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic
41 acid; {3,4-Dichloro-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
42 {3-Amino-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
43 {3-[4-Cyclohexyl-1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
44 {3-[1-(4-Fluoro-benzenesulfonyl)-4-phenyl-piperidin-3-yl]-phenyl}-acetic acid; {3-[4-
45 Benzyl-1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
46 {3-Acetylamino-5-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-phenyl}-acetic acid;
47 {3-[1-(4-fluoro-benzenesulfonyl)-piperidin-3-yl]-5-phenoxy-phenyl}-acetic acid;
48 2-(3-(1-(4-fluorophenylsulfonyl) piperidin-3-yl)-4-methylphenyl) acetic acid;
49 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-methoxyphenyl)acetic acid;
50 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-5-hydroxyphenyl)acetic acid;
51 2-(3-(1-(4-fluorophenylsulfonyl) piperidin-3-yl)-5-methylphenyl) acetic acid;
52 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-4-methylphenyl)acetic acid;
53 2-(5-(1-(4-fluorophenylsulfonyl)piperidin-3-yl)-2-methylphenyl)acetic acid;
54 2-(3-(1-(4-cyanophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
55 2-(3-(1-(4-*tert*-butylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
56 2-(3-(1-(2,4-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
57 2-(3-(1-(4-methoxyphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
58 2-(3-(1-(*o*-tolylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
59 2-(3-(1-(2-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
60 2-(3-(1-(4-ethylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
61 2-(3-(1-(phenethylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
62 2-(3-(1-(2-chloro-4-fluorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
63 2-(3-(1-(butylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
64 2-(3-(1-(4-(methylsulfonyl)phenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
65 2-(3-(1-(3,4-dichlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
66 2-(3-(1-(4-fluoro-2-methylphenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
67 2-(3-(1-(3-chlorophenylsulfonyl)piperidin-3-yl)phenyl)acetic acid;
68 2-(3-(1-(*m*-tolylsulfonyl)piperidin-3-yl)phenyl)acetic acid; Methyl
69 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)phenyl)acetate;
70 2-(3-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)phenyl)acetic acid;
71 2-(3-(1-(4-fluorophenylsulfonyl)pyrrolidin-3-yl)phenyl)acetic acid;
72 2-(3-(1-(4-fluorophenylsulfonyl)-1H-pyrrol-3-yl)phenyl)acetic acid;
73 {3-[1-(4-Fluoro-benzenesulfonyl)-4-phenyl-1H-pyrrol-3-yl]-phenyl}-acetic acid;

1 9. A compound of claim 1 having a structure (V):



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(VI)

wherein

Y^1 is selected from the group consisting of a bond, CH_2 , N, O, NO and SO_q ;

R^{10} and R^{11} 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.

12. A compound of claim 11 having the following structure:

2-(4-(2-(4-methylphenylsulfonamido)acetyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)acetic acid; methyl 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetate; 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid; methyl 2-(2-(2-(4-fluorophenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)-acetate; 2-(2-(2-(4-fluorophenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid; methyl 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetate; 2-(2-(4-fluorophenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid; and 2-(2-(2-(4-methylphenylsulfonamido)acetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)acetic acid.

13. A pharmaceutical composition comprising a compound of any one of claims 1 to 11 and a pharmaceutically acceptable carrier, excipient, diluent or delivery system.

14. A method of antagonizing a DP-2 receptor comprising contacting a DP-2 receptor with a compound of any one of claims 1 to 11.

15. A use of a compound of any one of claims 1 to 11 for treating or preventing a disorder or condition responsive to modulation of PGD_2 or a PGD_2 receptor.

16. A use of a compound of any one of claims 1 to 11 for treating or preventing a disorder or condition responsive to the antagonizing a DP-2 receptor.

17. A use of a compound of any one of claims 1 to 11 for treating or preventing a disorder or condition associated with elevated levels of PGD_2 or a metabolite thereof.

1 18. The use of any one of claims 15 to 17 wherein the disorder or
2 condition is selected from the group consisting of: Obstructive airway diseases; bronchitis,
3 chronic obstructive pulmonary disease; rhinitis; fibroid lung; cystic fibrosis; idiopathic
4 interstitial fibrosis; chronic cough associated with inflammation; and sinusitis; dermatitis;
5 conjunctivitis; psoriasis; urticaria; erythemas; cutaneous eosinophilia; chronic skin ulcers;
6 food-induced allergies; eosinophilic gastroenteritis; mastocytosis; ulcerative colitis; Crohn's
7 disease; irritable bowel syndrome; celiac disease; inflammatory pain, neuropathic pain;
8 eosinophilic fascitis; hyper IgE syndrome; systemic mast cell disorder; Idiopathic
9 thrombocytopenia purpura; atherosclerosis; lupus erythematosus; systemic lupus
10 erythematosus; sepsis; reperfusion injury; glomerulonephritis; allergic nephritis; nephritic
11 syndrome; eosinophil related disorders such as Churg-Strauss syndrome; basophilic
12 leukocytosis and basophilic leukemia; acquired immunodeficiency syndrome; arthritis and
13 conditions associated therewith and other conditions or disorders associated with raised levels
14 of PGD₂ or its metabolites.

1 19. The use of any one of claims 15 to 17 wherein said compound is
2 administered in combination with a second therapeutic agent.

1 20. The use of claim 19 wherein said second therapeutic agent is useful for
2 preventing or treating a disorder or condition selected from the group consisting of: asthma,
3 rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive
4 pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer's lung, fibroid lung, chronic
5 cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis,
6 AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body
7 dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating
8 polyradiculoneuropathy, multifocal motor neuropathy, plexopathy, multiple sclerosis,
9 encephalomyelitis, panencephalitis, cerebellar degeneration, CNS trauma, migraine, stroke,
10 rheumatoid arthritis, ankylosing spondylitis, Behcet's disease, bursitis, carpal tunnel
11 syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, dermatomyositis,
12 Ehlers-Danlos Syndrome (EDS), fibromyalgia, pain, osteoarthritis (OA), osteonecrosis,
13 psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's
14 Syndrome, soft tissue disease, Still's Disease, tendonitis, polyarteritis Nodosa, Wegener's
15 Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus
16 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 infection, thrombosis, fibrosis, flushing, inflammation, nasal congestion, urticaria, contact hypersensitivity (including contact dermatitis), food allergies, eosinophilic gastroenteritis, mastocytosis, acne, colitis ulcerosa, pruritis, angioedema, excematous dermatides, erytherma, cutaneous eosinophilia, chronic skin ulcers, celiac disease, systemic mast cell disorder; idiopathic thrombocytopenia purpura, Churg-Stauss syndrome, basophilic leukocytosis, basophilic leukemia and acquired immunodeficiency syndrome (AIDS).

21. The use of claim 19 wherein said second therapeutic agent is selected from the group consisting of: a corticosteroid, a corticosteroid analog, an antihistamine, a β_2 -agonist, a cromolyn, a leukotriene antagonist, an anti-IgE antibody therapy, an anti-infective, an anti-fungal, an immunosuppressant, a PGD_2 or DP antagonist, a PDE4 inhibitor, a cytokine modulator, a PPAR- γ agonist, a 5-lipoxygenase inhibitor, a FLAP inhibitor, and a PLA₂ inhibitor.