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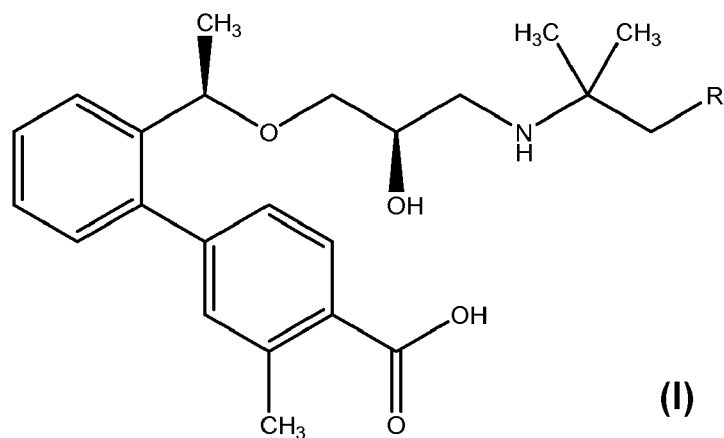
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(54) Title: 1,1-(Dimethyl-Ethylamino)-2-Hydroxy-Propoxy]-Ethyl}-3-Methyl-Biphenyl-4- Carboxylic Acid Derivatives As Calcium Receptor Antagonists



(57) Abstract: The present invention is directed to novel 1,1 -(dimethyl-ethylamino)-2- hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid derivatives and pharmaceutically acceptable salts thereof of structural formula I wherein the variable R¹ is as described herein. Also provided are pharmaceutical compositions comprising the compounds of formula I as well as methods of treatment employing compounds of formula I to treat a disease or disorder characterized by abnormal bone or mineral homeostasis such as hypoparathyroidism, osteoporosis, osteopenia, periodontal disease, Paget's disease, bone fracture, osteoarthritis, rheumatoid arthritis, and humoral hypercalcemia of malignancy.



WO 2010/103429 A1

1,1-(Dimethyl-Ethylamino)-2-Hydroxy-Propoxy]-Ethyl}-3-Methyl-Biphenyl-4-Carboxylic Acid Derivatives As Calcium Receptor Antagonists

FIELD OF INVENTION

5 The present invention is directed toward novel 1,1-(dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid derivatives, pharmaceutical compositions containing these compounds, methods for their use and processes for their production. These novel 1,1-(dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid derivatives inhibit calcium receptor activity and thus are calcium receptor antagonists.

BACKGROUND OF THE INVENTION

15 In mammals, extracellular Ca^{2+} is under rigid homeostatic control with the serum calcium concentration strictly maintained at a concentration of approximately 1.1 to 1.3 mM in a healthy mammal. The extracellular Ca^{2+} homeostasis depends on integrated regulation of Ca^{2+} fluxes with respect to the intestine, kidneys and bone. The extracellular Ca^{2+} regulates various processes such as blood coagulation, nerve and muscle excitability, and normal bone homeostasis. When the Ca^{2+} serum concentration decreases by 50% tetania occurs, and when the Ca^{2+} serum concentration increases by 50% consciousness is clouded, in both instances a potentially life threatening circumstance. Extracellular Ca^{2+} also inhibits the secretion of parathyroid hormone (PTH) from parathyroid cells, inhibits bone resorption by osteoclasts, stimulates secretion of calcitonin from C-cells and is involved in re-absorption and excretion in the kidney.

25 The extracellular calcium-sensing receptor (CaSR) is a hormone-like receptor, more particularly a plasma membrane-bound G protein-coupled receptor (GPCR) that belongs to family 3 of the GPCR superfamily. Family 3 of the GPCR superfamily includes metabotropic glutamate receptors (mGluRs), γ -aminobutyric acid B-type receptors (GABA_B Rs) as well as putative pheromone and taste receptors. The CaSR has a large extracellular domain exhibiting "Venus flytrap" topology, a seven-transmembrane domain

and a relatively large cytoplasmic domain. Human CaSR consists of 1078 amino acids and shares 93% amino acid homology with bovine CaSR. The CaSR senses and is activated by changes in extracellular Ca^{2+} levels. The presence of CaSR on certain specialized cells enables those Ca^{2+} -sensing
5 cells to respond to changes in extracellular Ca^{2+} concentration. Examples of Ca^{2+} -sensing cells include the parathyroid-secreting cells of the parathyroid gland, the calcitonin-secreting C cells of the thyroid gland and certain cells in the kidney. In addition, the CaSR has been found in a wide variety of other tissues including intestine, bone, bone marrow, brain, skin, pancreas, lung
10 and heart.

The CaSR on the surface of parathyroid chief cells is the primary entity that regulates secretion of PTH from parathyroid cells. Activation of the CaSR on parathyroid chief cells by extracellular Ca^{2+} suppresses PTH production and secretion, inhibits parathyroid cellular proliferation and likely inhibits PTH
15 gene expression. The CaSR on the surface of the calcitonin-secreting C cells of the thyroid gland mediate the stimulatory action of high extracellular Ca^{2+} concentration on calcitonin secretion, thereby increasing the circulating level of the Ca^{2+} -lowering hormone calcitonin. The CaSR is also present in the kidney, along much of the nephrons and at the basolateral surface in the
20 cortical thick ascending limb. In the basolateral surface in the cortical thick ascending limb the CaSR is thought to mediate high Ca^{2+} -induced inhibition of the tubular re-absorption of Ca^{2+} and magnesium. A reduction of renal cortical synthesis of $1,25(\text{OH})_2$ vitamin D and polyuria with dilute urine are partially the result of hypercalcaemic activation of the CaSR in the nephron.

PTH is the primary endocrine hormone regulating Ca^{2+} homeostasis in the blood and extracellular fluids. PTH, by acting on bone and kidney cells, increases the level of Ca^{2+} in the plasma. This increase in plasma Ca^{2+} concentration then acts as a negative feedback signal, thereby depressing PTH secretion. The reciprocal relationship between extracellular Ca^{2+} and
30 PTH secretion forms an important mechanism for maintaining bodily Ca^{2+} homeostasis. PTH has been found to increase bone turnover, but the overall

effect on bone is dependent on temporal changes in circulating levels of PTH.

Sustained elevations in circulating plasma PTH levels, as occurs in hyperparathyroidism, have been found to result in a net catabolic effect on bone. By contrast, transient increases in plasma PTH levels, achieved by
5 daily or near daily injection of exogenous hormone, have been found to exhibit a net anabolic effect on bone. The effect of PTH on bone is due to PTH being able to stimulate the differentiation and proliferation of osteoblast, the bone forming cells, thereby increasing bone formation and bone mass. PTH affects cellular metabolic activity, ion transport, cell shape, gene transcriptional
10 activity and secretion of proteases in osteoblasts. Also, PTH stimulates the production of RANKL, a protein that plays a crucial role in osteoclast differentiation and activity.

Various compounds are known to modulate the effects of extracellular Ca^{2+} on the CaSR. Calcimimetics are agents that act as allosteric modulators
15 of the CaSR that increase the sensitivity of the CaSR to activation by extracellular Ca^{2+} . Calcilytics, or calcium receptor antagonists, are agents that act as modulators of the CaSR that inhibit CaSR activity. This inhibition of the CaSR activity results in a decrease of one or more CaSR activities that are evoked by extracellular Ca^{2+} .

20 Certain urea derivatives, such as those disclosed in PCT International Publication WO 02/059102, are described as having calcimimetic activity. In addition, certain phenylalkylamine derivatives have been identified as calcimimetics. Phenylalkylamine calcimimetic compounds include (*R*)-N-(1-(3-methoxyphenyl)ethyl)-3-phenylpropan-1-amine hydrochloride (NPS-467);
25 (*R*)-3-(2-chlorophenyl)-N-(1-(3-methoxyphenyl)ethyl)propan-1-amine hydrochloride (NPS R-568, tecalcet hydrochloride) and (*R*)-(-)-N-(1-(naphthalen-1-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)propan-1-amine hydrochloride (NPS-1493, cinacalcet hydrochloride). Cinacalcet hydrochloride and uses thereof are disclosed in U.S. Patent Nos. 6,011,068; 6,031,003;
30 6,211,244 and 6,313,146. Cinacalcet hydrochloride is marketed as Sensipar® and Minpara® in the U.S. and Europe, respectively, and is

indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis and for hypercalcemia in patients with parathyroid carcinoma.

Calcilytics, or calcium receptor antagonists, have been described in various publications such as PCT International Publication Nos. WO 93/04373; WO 94/18959; WO 95/11211; WO 97/37967; WO 98/44925; WO 98/45255; WO 99/51241; WO 99/51569; WO 00/45816; WO 02/14259; WO 02/38106; WO 2004/041755; and WO 2005/030746; Nemeth, E.F.; *Journal of Molecular Endocrinology* (2002) 29, 15-21; Kessler, A. et al.; *ChemBioChem* (2004) 5, 1131; Steddon, S.J. et al.; *Lancet* (2005) 365, 2237-2239; and Shcherbakova, I.; et al.; *Bioorganic & Medicinal Chemistry Letters* (2005) 15, 1557-1560.

Calcium receptor antagonists are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides such as hormones, enzymes or growth factors, the expression and/or secretion of which is regulated or affected by activity at one or more CaSR. Target diseases or disorders for calcium receptor antagonists include diseases involving abnormal bone and mineral homeostasis. Abnormal calcium homeostasis is characterized by one or more of the following activities: an abnormal increase or decrease in serum calcium; an abnormal increase or decrease in urinary excretion of calcium; an abnormal increase or decrease in bone calcium levels (for example, as assessed by bone mineral density measurements); an abnormal absorption of dietary calcium; an abnormal increase or decrease in the production and/or release of messengers which affect serum calcium levels such as PTH and calcitonin; and an abnormal change in the response elicited by messengers which affect serum calcium levels.

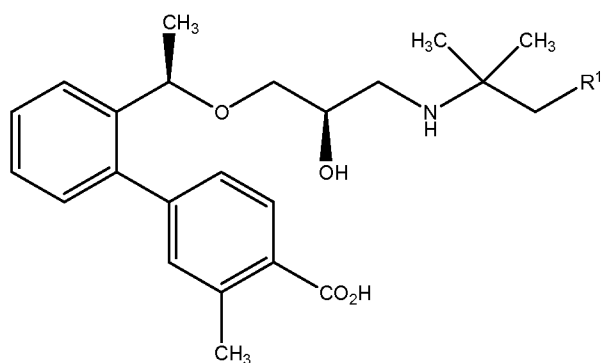
The novel calcium receptor antagonists of this invention are useful in the treatment of diseases associated with abnormal bone or mineral homeostasis. Thus, these calcium receptor antagonists are useful in the treatment of hypoparathyroidism, osteoporosis, osteopenia, periodontal

disease, bone fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy.

SUMMARY OF THE INVENTION

5 The present invention is directed towards calcium receptor antagonist compounds, pharmaceutical compositions comprising the calcium receptor antagonist compounds and methods of treatment employing the calcium receptor antagonist compounds.

10 More specifically, the present invention is directed to calcium receptor antagonist derivatives of structural formula I



wherein

R^1 is methylsulfanyl-phenyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl, wherein said methylsulfanyl-phenyl is optionally substituted on phenyl with a methyl or fluoro and said cyclohexyl is optionally substituted with two fluoro; or a pharmaceutically acceptable salt thereof.

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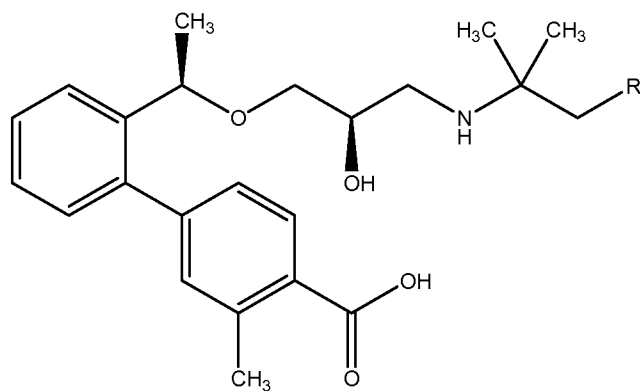
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a chart depicting plasma PTH levels from the time of intravenous injection to 480 minutes following intravenous injection of 1 mg/kg of the compound of Example 1, in normal rats.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel 1,1-(dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid derivatives and pharmaceutically acceptable salts thereof of structural formula I



wherein the variable R¹ is described hereinabove. The pharmaceutically acceptable salts of the compounds of formula I include the acid addition and
5 base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate,
10 hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate,
15 tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. For a review on suitable
20 salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of formula I may be readily prepared by mixing together solutions of the compound of formula I and the desired acid or base, as appropriate. The salt may precipitate from
25 solution and be collected by filtration or may be recovered by evaporation of

the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The compounds of the invention include compounds of formula I as hereinbefore defined, polymorphs, and isomers thereof (including optical,
5 geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula I.

The compounds of the present invention may be administered as prodrugs. Thus certain derivatives of compounds of formula I which may have little or no pharmacological activity themselves can, when administered into or
10 onto the body, be converted into compounds of formula I having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon
15 Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs can, for example, be produced by replacing appropriate functionalities present in the compounds of formula I with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

20 Some examples of such prodrugs include:

- (i) where the compound of formula I contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (C₁-C₈)alkyl;
- (ii) where the compound of formula I contains an alcohol functionality (-OH),
25 an ether thereof, for example, replacement of the hydrogen with (C₁-C₆)alkanoyloxymethyl; and
- (iii) where the compound of formula I contains a secondary amino functionality (-NHR where R is not H), an amide thereof, for example, replacement of one hydrogen with (C₁-C₁₀)alkanoyl. Further examples of replacement groups in
30 accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Compounds of formula I contain two asymmetric carbon atoms with the stereochemistry as depicted in formula I. It is to be understood that the other three diastereomers corresponding to the compounds of formula I can be prepared by analogous methods.

5 Included within the scope of the claimed compounds of formula I are pharmaceutically acceptable acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine. *Cis/trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example,
10 chromatography and fractional crystallisation. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

15 Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or
20 fractional crystallization and the diastereoisomers converted to the corresponding pure diastereomers by means well known to a skilled person. The chiral compounds of the invention (and chiral precursors thereof) may be obtained in diastereomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a
25 hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Mixtures of diastereoisomers may be separated by conventional techniques known to those skilled in the art. [see, for example,
30 "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).]

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S . Certain isotopically-labelled compounds of formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

A preferred embodiment of the present invention are compounds of Formula I as described above wherein R^1 is methylsulfanyl-phenyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl, wherein said methylsulfanyl-phenyl is optionally substituted on phenyl with a methyl or fluoro and said cyclohexyl is optionally substituted with two fluoro; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment of the present invention is a compound of Formula I, wherein R¹ is methylsulfanyl-phenyl, 3-fluoro-4-methylsulfanyl-phenyl, 3-methyl-4-methylsulfanyl-phenyl, cyclohexyl, difluorocyclohexyl, cycloheptyl or bicyclo[2.2.1]hept-2-yl; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment of the present invention is a compound of Formula I, wherein R¹ is 3-methylsulfanyl-phenyl or 4-methylsulfanyl-phenyl; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment of the present invention is a compound selected from the group consisting of:

- 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-[2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-(2-Cyclohexyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-[2-(4,4-Difluoro-cyclohexyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid; and
2'-((R)-1-((R)-3-(2-Cycloheptyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a pharmaceutical composition comprising a compound according to Formula I as described in any of the preceding embodiments hereinabove and a pharmaceutically acceptable carrier, adjuvant or diluent.

Another embodiment of the present invention is a method of treating a disease or disorder characterized by abnormal bone or mineral homeostasis which comprises the administration to a patient in need of treatment thereof a therapeutically effective amount of a compound according to Formula I as described in any of the preceding embodiments hereinabove. A preferred embodiment of the present invention is the method according to the preceding embodiment wherein the disease or disorder characterized by abnormal bone or mineral homeostasis is selected from the group consisting of osteoporosis, osteopenia, periodontal disease, Paget's disease, bone fracture, osteoarthritis, rheumatoid arthritis, and humoral hypercalcemia of malignancy. Yet another preferred embodiment is the method according to the preceding embodiment wherein the disease or disorder characterized by abnormal bone or mineral homeostasis is osteoporosis.

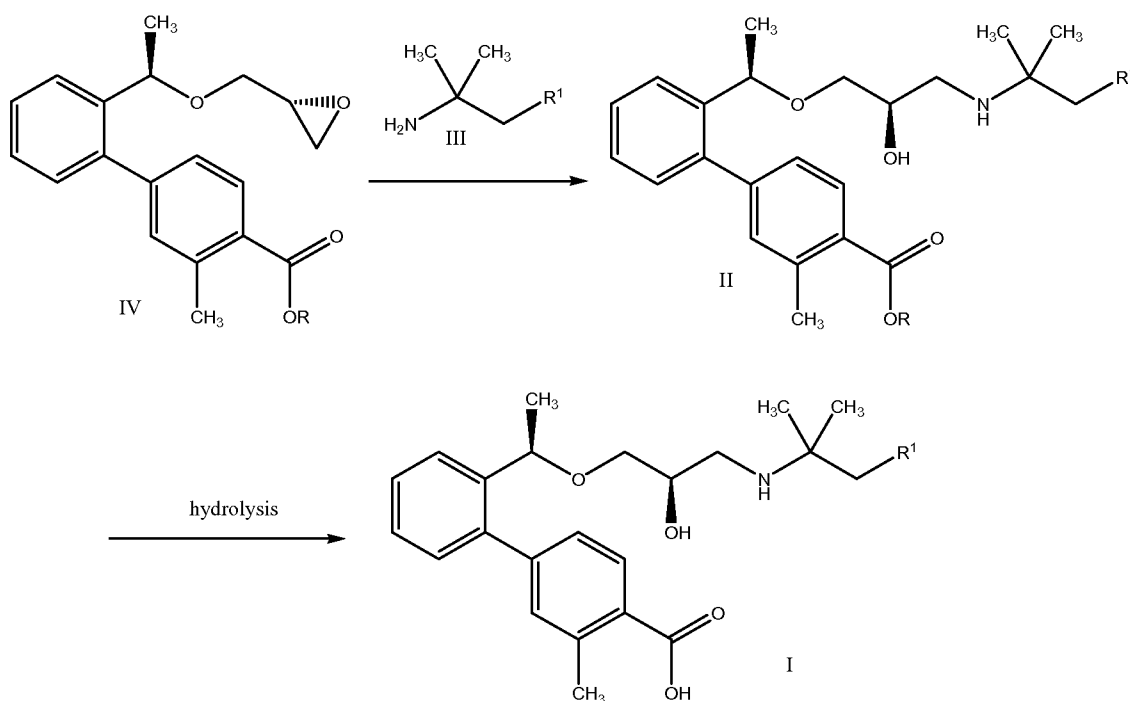
The following reaction scheme, Reaction Scheme I, depicts methods of synthesis for compounds of formula I. In the following general methods for preparation of the compounds of formula I the variable R^1 is as previously defined for a compound of the formula I unless otherwise stated. The Reaction Scheme herein described is intended to provide a general description of the methodology employed in the preparation of many of the Examples given. However, it will be evident from the detailed descriptions given in the Experimental section that the modes of preparation employed extend further than the general procedures described herein. In particular, it is noted that the compounds prepared according to the Scheme may be modified further to provide new Examples within the scope of this invention. The reagents and intermediates used in the following examples are either commercially available or can be prepared according to standard literature procedures by those skilled in the art of organic synthesis.

Reaction Scheme I, below, depicts the synthesis of compounds of formula I. Treatment of an appropriately substituted oxirane derivative of formula IV with an appropriate amine of formula III, in an appropriate solvent, such as toluene, trifluoroethanol or acetonitrile, within a temperature range of

approximately room temperature to 150 °C for a period of approximately 30 minutes to 24 hours provides the corresponding ester compound of formula II.

In Reaction Scheme I, the group C(O)OR in compounds of formula IV and II represents an appropriate ester moiety wherein R is preferably a lower alkyl group such as methyl or ethyl. Preferred conditions for reacting the oxirane compound of formula IV with the amine of formula III to provide compounds of formula II include carrying out the reaction in toluene at room temperature in the presence of lithium perchlorate for 12 to 24 hours followed by an extractive workup. Alternatively, the oxirane compound of formula IV can be reacted with the amine of formula III in an appropriate solvent such as acetonitrile or trifluoroethanol under microwave irradiation to provide the compound of formula II. Treatment of the compound of formula II with an appropriate base, such as lithium hydroxide, sodium hydroxide or potassium hydroxide, in an appropriate solvent, such as ethanol or methanol, followed by acidification, with an appropriate acid such as citric acid or hydrochloric acid, provides the compound of formula I.

Reaction Scheme I



In the reaction scheme described herein it is to be understood that hydroxy groups in intermediates useful for preparing compounds of Formula I may be protected by conventional protecting groups known to those skilled in the art, as required. For example, intermediates containing a hydroxy group may be protected as the corresponding benzyloxy ether and subsequently deprotected by hydrogenation to provide the free hydroxy derivative. Suitable protecting groups and methods for their removal are illustrated in Protective Groups in Organic Synthesis, 3rd Ed., Theodora W. Greene, and Peter G.M. Wuts (John Wiley & Sons, 1999).

The term "patient in need of treatment thereof" means humans and other animals who have or are at risk of having a disease or disorder characterized by abnormal bone or mineral homeostasis. The "patient in need of treatment thereof" may have or be at risk of having a disease or disorder characterized by abnormal bone or mineral homeostasis selected from the group consisting of osteoporosis, osteopenia, periodontal disease, Paget's disease, bone fracture, osteoarthritis, rheumatoid arthritis, and humoral hypercalcemia of malignancy. As certain of the conditions being treated have a higher incidence in females a preferred patient is a female, and particularly a postmenopausal female human.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic), palliative, adjuvant and curative treatment. For example, the treatment of osteoporosis, as used herein means that a patient having osteoporosis or at risk of having osteoporosis can be treated according to the methods described herein. For patients undergoing preventative treatment, a resulting reduction in the incidence of the disease state being preventively treated is the measurable outcome of the preventative treatment.

The present invention provides methods of treating osteopenia and osteoporosis by administering to a patient in need thereof a therapeutically effective amount of a compound of formula I. Osteopenia is a thinning of the bones, but less than is seen with osteoporosis and is the stage before true

osteoporosis. The World Health Organization has developed diagnostic categories based on bone mass density (BMD) to indicate if a person has normal bones, has osteopenia or has osteoporosis. Normal bone density is within one standard deviation (+1 or -1) of the young adult mean bone density.

- 5 Osteopenia (low bone mass) is defined as bone density of 1 to 2.5 standard deviations below the young adult mean (-1 to -2.5), and osteoporosis is defined as a bone density that is 2.5 standard deviations or more below the young adult mean (>-2.5).

The present invention provides methods of treating bone fractures by
10 administering to a patient in need thereof a therapeutically effective amount of a compound of formula I. Bone fractures can be a fracture to any bone in the body, and hip fracture being of particular concern. Hip fracture has a significant impact on medical resources and patient morbidity and mortality. Few patients admitted with a hip fracture are considered for prophylactic
15 measures aimed at the reduction of further fracture risk. Currently, 10-13% of patients will later sustain a second hip fracture. Of patients who suffered a second hip fracture, fewer patients maintained their ability to walk independently after the second fracture than did so after the first (53 and 91% respectively, $P < 0.0005$). Pearse E.O. et al., *Injury*, 2003, 34(7), 518-521.
20 Following second hip fracture, patients' level of mobility determined their future social independence. Older patients and those with a history of multiple falls had a shorter time interval between fractures. Second hip fracture has a significant further impact on patients' mobility and social independence. It is therefore desirable to have new methods for the treatment of bone fractures
25 including hip fracture.

The compounds of Formula I can be administered together with additional agents which are useful for treating a disease or disorder characterized by abnormal bone or mineral homeostasis. Particularly contemplated additional agents include calcium receptor antagonists other
30 than those of Formula I, selective estrogen receptor modulators (SERMs), bisphosphonates, parathyroid hormone (PTH) and fragments and analogues

thereof, estrogens, calcitonins, synthetic steroids, synthetic isoflavones, vitamin D analogues, vitamin K analogues, strontium salts, cathepsin K inhibitors, $\alpha_v\beta_3$ integrin (vitronectin) antagonists, prostaglandin (PGE2) receptor agonists and receptor activator of nuclear factor κ B ligand (RANKL) inhibitors.

Additional calcium receptor antagonists that can be used together with compounds of Formula I in the methods and compositions of this invention include those described in PCT International Publication Nos. WO 93/04373; WO 94/18959; WO 95/11211; WO 97/37967; WO 98/44925; WO 98/45255; WO 99/51241; WO 99/51569; WO 00/45816; WO 02/14259; WO 02/38106; WO 2004/041755; and WO 2005/030746; Nemeth, E.F.; *Journal of Molecular Endocrinology* (2002) 29, 15-21; Kessler, A. et al.; *ChemBioChem* (2004) 5, 1131; Steddon, S.J. et al.; *Lancet* (2005) 365, 2237-2239; and Shcherbakova, I.; et al.; *Bioorganic & Medicinal Chemistry Letters* (2005) 15, 1557-1560.

Specific calcilytic compounds that can be used together with compounds of Formula I in the methods and compositions of this invention include NPS-2143 and 423562.

SERMs that can be used together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, lasofoxifene (Fablyn®), raloxifene (Evista®), arzoxifene, bazedoxifene, ospemifene, Chiesi's CHF-4227 and Prostrakan's PSK-3471. Bisphosphonates that can be used together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, tiludronate (Skelid®), clondronate (Bonefos®), etidronate (Didronel®), alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), zoledronate (Zometa®), minodronate (Onobis®), neridronate and pamidronate.

In humans, PTH is an 84 amino acid polypeptide produced by the parathyroid gland that controls serum calcium levels through its action on various cells. Several N-terminal amino acids fragments of PTH, including the 1-31, 1-34 and 1-38 fragments (PTH-related proteins; "PTHrP") are

considered biologically equivalent to the full length hormone. Parathyroid hormone (PTH) and fragments and analogues thereof that can be used together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, the full length PTH (such as PTH 1-84, Preos®/Preotact®, Unigene's 768974, Bone Medical's BN-003), the 1-31 (such as Zelos Therapeutics' Ostabolin-C), 1-34 (such as teriparatide, Forteo®, or Ipsen's BIM-44058) or 1-38 fragments.

Estrogens that can be used together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, estradiol, conjugated equine estrogens (Wyeth's Premarin®) or other estrogens.

Calcitonin is a 32 amino-acid peptide hormone produced by the thyroid gland which inhibits osteoclast activity by binding to calcitonin receptors on the surface of those cells. Calcitonins that can be used together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, human calcitonin or salmon or eel calcitonins. The calcitonins may be used as injectable or intranasal formulations such as Miacalcin®, Miacalcic®, Calcitonin®, Fortical® or Elcitonin® or as oral formulations such as Novartis' SMC-021, Bone Medical's BN-002 (Capsitonin®) or Nobex's NCT-025 (Oratonin®).

Synthetic steroids that can be used together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, mixed estrogen and progesterone agonists such as tibolone which is marketed as Livial®. Synthetic isoflavones are chemically synthesized derivatives of plant isoflavones, such as phytoestrogens extracted from soy products. A synthetic isoflavone that can be used together with compounds of Formula I in the methods and compositions of this invention includes, but is not limited to, ipraflavone which is marketed by Takeda as Iprosten® and Osten®.

Vitamin D analogues are compounds that act by binding to the nuclear vitamin D receptor in osteoblasts. Vitamin D analogues that can be used

together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, Chugai's ED-71 and Deltanoid's 2MD.

A strontium salt that can be used together with compounds of Formula I in the methods and compositions of this invention includes, but is not limited to, strontium ranelate (Servier's Protelos®). Cathepsin K inhibitors that can be used together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, Novartis's AAE-581, balicatib, GlaxoSmithKline's SB-462795 and Merck's c-3578. An $\alpha_v\beta_3$ integrin (vitronectin) antagonist that can be used together with compounds of Formula I in the methods and compositions of this invention includes, but is not limited to, Merck's MRL-123.

Prostaglandin E2 (PGE2) receptor agonists that can be used together with compounds of Formula I in the methods and compositions of this invention include, but are not limited to, PGE2 subtype 2 (EP2) receptor agonists, such as (3-[[4-Tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino]-methyl]-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof or PGE2 subtype 4 (EP4) receptor agonists, such as ONO-4819. A receptor activator of nuclear factor κ B ligand (RANKL) inhibitor that can be used together with compounds of Formula I in the methods and compositions of this invention includes, but is not limited to, Amgen's RANKL antibody AMG-162.

Specific combinations of particular interest include compounds of Formula I and lasofoxifene or compounds of Formula I and (3-[[4-Tert-butyl-benzyl)-(pyridine-3-sulfonyl)-amino]-methyl]-phenoxy)-acetic acid, or a pharmaceutically acceptable salt thereof.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. The compounds may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

For the above-mentioned therapeutic uses, the dosage administered will, of course, vary with the compound employed, the mode of administration,

the treatment desired and the disorder indicated. The total daily dosage of the compound of formula I/salt/solvate (active ingredient) will, generally, be in the range from 1 mg to 1 gram, preferably 1 mg to 250 mg, more preferably 10 mg to 100 mg. The total daily dose may be administered in single or divided
5 doses. The present invention also encompasses sustained release compositions.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension; for parenteral injection as a sterile
10 solution, suspension or emulsion; for topical administration as an ointment or cream; or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the
15 invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc. The dissolution rate of poorly water-soluble compounds may be enhanced by the use of a spray-dried dispersion, such as those described by Takeuchi, H., et al. in "Enhancement of the dissolution rate of a poorly water-soluble drug
20 (tolbutamide) by a spray-drying solvent deposition method and disintegrants" J. Pharm. Pharmacol., 39, 769-773 (1987).

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be
25 suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various
30 excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and

with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefor, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof. Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 17th Edition (1985).

Dosage regimens may be adjusted to provide the optimum desired response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form, as used herein, refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the chemotherapeutic agent and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. Thus, the skilled artisan would appreciate, based upon the disclosure provided herein, that the dose and dosing regimen is adjusted in accordance with methods

well-known in the therapeutic arts. That is, the maximum tolerable dose can be readily established, and the effective amount providing a detectable therapeutic benefit to a patient may also be determined, as can the temporal requirements for administering each agent to provide a detectable therapeutic benefit to the patient. Accordingly, while certain dose and administration regimens are exemplified herein, these examples in no way limit the dose and administration regimen that may be provided to a patient in practicing the present invention.

It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated, and may include single or multiple doses. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. For example, doses may be adjusted based on pharmacokinetic or pharmacodynamic parameters, which may include clinical effects such as toxic effects and/or laboratory values. Thus, the present invention encompasses intra-patient dose-escalation as determined by the skilled artisan. Determining appropriate dosages and regimens for administration of the chemotherapeutic agent are well-known in the relevant art and would be understood to be encompassed by the skilled artisan once provided the teachings disclosed herein.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in bulk, as a single unit dose, or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

The relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and condition of the subject treated and further depending upon the route by which
5 the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

In addition to the active ingredient, a pharmaceutical composition of the invention may further comprise one or more additional pharmaceutically active agents. Particularly contemplated additional agents include selective
10 estrogen receptor modulators (SERMs), bisphosphonates, parathyroid hormone (PTH) and fragments and analogues thereof, estrogens, calcitonins, synthetic steroids, synthetic isoflavones, vitamin D analogues, vitamin K analogues, strontium salts, cathepsin K inhibitors, $\alpha_v\beta_3$ integrin (vitronectin) antagonists, prostaglandin (PGE2) receptor agonists and receptor activator of
15 nuclear factor κ B ligand (RANKL) inhibitors, such as those described hereinabove.

Controlled- or sustained-release formulations of a pharmaceutical composition of the invention may be made using conventional technology.

As used herein, "parenteral administration" of a pharmaceutical
20 composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue. Parenteral administration thus includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a
25 surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to, subcutaneous, intraperitoneal, intramuscular, intrasternal injection, and kidney dialytic infusion techniques.

30 Formulations of a pharmaceutical composition suitable for parenteral administration comprise the active ingredient combined with a

pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as
5 in ampules or in multi-dose containers containing a preservative. Formulations for parenteral administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations as discussed below. Such formulations may further comprise one or more additional
10 ingredients including, but not limited to, suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (i.e. powder or granular) form for reconstitution with a suitable vehicle (e.g. sterile pyrogen-free water) prior to parenteral administration of the reconstituted composition.

15 A composition of the present invention can be administered by a variety of methods known in the art. The route and/or mode of administration vary depending upon the desired results. The active compounds can be prepared with carriers that protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches,
20 and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are described by e.g., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, (1978). Pharmaceutical compositions are
25 preferably manufactured under GMP conditions.

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and
30 may comprise, in addition to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents described

herein. Such sterile injectable formulations may be prepared using a non-toxic parenterally-acceptable diluent or solvent, such as water or 1,3-butane diol, for example. Other acceptable diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and
5 fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form, in a liposomal preparation, or as a component of a biodegradable polymer systems. Compositions for sustained release or implantation may comprise pharmaceutically acceptable polymeric
10 or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

While the precise dosage administered of each active ingredient will vary depending upon any number of factors, including but not limited to, the type of animal and type of disease state being treated, the age of the animal
15 and the route(s) of administration. The amounts of various CaR antagonist compounds of formula I to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50} , EC_{50} , the biological half-life of the compound, the age, size and weight of the patient, and the type of condition or symptom associated with the patient. The
20 importance of these and other factors to be considered are known to those of ordinary skill in the art.

PTH secretion can be measured using techniques known in the art (see, *e.g.*, U.S. 6,031,003, hereby incorporated by reference). For example, PTH secretion can be measured by first suspending cells in parathyroid cell
25 buffer containing 0.5 mM $CaCl_2$ and 0.1% bovine serum albumin. Incubations can be performed in plastic tubes (Falcon 2058) containing 0.3 mL of the cell suspension with or without small volumes of $CaCl_2$ and/or organic polycations. After incubation at 37 °C, typically 30 minutes, the tubes can then be placed on ice and the cells pelleted at 2 °C. Samples of the
30 supernatant should then be brought to pH 4.5 with acetic acid and, if needed, stored at - 70 °C. The amount of PTH in bovine cell supernatants

can be determined by a homologous radioimmunoassay using GW-1 antibody or its equivalent at a final dilution of 1/45,000. 125I-PTH (65-84; INCSTAR, Stillwater, Minn.) can be used as tracer and fractions separated by dextran-activated charcoal. Counting of samples and data reduction can
5 be performed on a Packard Cobra 5005 gamma counter. For testing PTH levels in human cell supernatants, a commercially available radioimmunoassay kit (INS-PTH; Nichols Institute, Los Angeles, Calif.) which recognizes intact and N-terminal human PTH is preferable because GW-1 antibody recognizes human PTH poorly.

10 In addition, specific assays useful for evaluating the compounds of Formula I include the FLIPR Assay for Evaluating the Potency and Selectivity of Test Compounds; Assay for Evaluating the Effects of Test Compounds on Endogenous PTH Secretion; Evaluation of Effects of Test Compounds on PTH Secretion In Vivo; Effect of Calcium Receptor
15 Antagonist Compound of Formula I on Body Weight, Body Composition and Bone Density in the Aged Intact and Ovariectomized Female Rat; and Fracture Healing Assays as described below.

FLIPR Assay for Evaluating the Potency and Selectivity of Test Compounds

20 Human kidney cell (HEK 293) expressing the calcium receptor (CasR) are used to detect antagonists of the receptor using Fluorometric imaging plate reader (FLIPR, Molecular Devices, Sunnyvale CA). Receptor activation by extracellular calcium results in the release of calcium from intracellular stores into the cytosol. A fluorescent indicator (Fluo-4) is internalized by the
25 cells from growth media and interacts with calcium released into the cytosol to provide a means of quantifying intracellular Ca^{2+} levels and receptor agonism/antagonism. Fluorescence intensity is detected by the FLIPR CCD camera and traced as a function of time. Potential antagonists are identified by their ability to decrease this fluorescent response.

30

To determine the IC_{50} values cells are loaded with Fluo4 (2.05 mM

Fluo-4, 0.04% pluronic acid, 2.6 mM probenecid in 90% DMEM high glucose, 10% dialyzed Fetal Bovine Serum , 1X Pen Strep, 1X L-Glutamine, 3ug/ml Puromycin, 27.5nM Methotrexate) for 1 hour at 37°C. Prior to the addition of test compound cells are washed with a 10 mM HEPES buffer solution. The test compound, for example the compound of Example 1, is added at various doses (from 1 μ M to 3 nM) and pre-incubated with cells for 30 minutes followed by stimulation of the CasR by the addition of 1.7 mM Ca^{2+} . IC₅₀ values are based on the ability of the cells to inhibit the Ca^{2+} induced increase in intracellular Ca^{2+} . Fluorescence signal is read 42 seconds after the stimulation of the CasR by the addition of 1.7 mM Ca^{2+} .

Assay for Evaluating the Effects of Test Compounds on Endogenous PTH Secretion

Adult male or female Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) with jugular vein catheter are used in this assay. The test compounds at various doses are given to the animals by various routes of administration including subcutaneous injection, or intravenous injection. Serum or plasma PTH concentrations are examined before and after dosing at various times using a commercially available rat intact PTH ELISA kit (Immutopics, Inc. San Clemente, CA. Cat.#60-2500).

Evaluation of Effects of Test Compounds on PTH Secretion In Vivo

Overnight fasted male Sprague-Dawley rats (250 g) with jugular vein catheter are used in this study. Whole blood sample is collected from each animal prior to compound treatment for measuring baseline PTH concentrations. The test animals are then given a single dose of the tested compound at 1 mg/kg in glycerol formal: 2% DMSO by intravenous administration via jugular vein. Whole blood samples are collected at 0, 2, 5, 15, 30 and 60 minutes after dosing. Plasma samples are obtained by centrifugation and PTH concentrations are determined using a commercially available rat intact PTH ELISA kit (Immutopics, Inc. San Clemente, CA. Cat.#60-2500). A significant burst of PTH was seen following the treatment

with the tested compound. The elevated PTH secretion induced by the tested compound was peak at 2 minutes and returned to baseline level at 30 minutes after dosing (Figure 1).

5 Effect of Calcium Receptor Antagonist Compound of Formula I on Body Weight, Body Composition and Bone Density in the Aged Intact and Ovariectomized Female Rat

10 The purpose of this study is to test the effects of test compositions comprising compounds of Formula I in aged intact or ovariectomized (OVX) female rat model. In the following protocol the compound of Formula I can be administered as a pharmaceutically acceptable salt or prodrug thereof.

Study Protocol

15 Sprague-Dawley female rats are sham-operated or OVX at 18 months of age, while a group of rats is necropsied at day 0 to serve as baseline controls. One day post-surgery, the rats are treated with either vehicle or test compound of Formula I, or a combination of test compound of Formula I and other active agent test compound for 59 days. The vehicle or test compound of Formula I is administered either orally, by oral gavage, or by
20 subcutaneous injection (s.c.), with the test compound being administered at a therapeutically effective dose.

25 All rats are given s.c. injection of 10 mg/kg of calcein (Sigma, St.Louis, MO) for fluorescent bone label 2 and 12 days before necropsy. On the day of necropsy, all rats under ketamine/xylazine anesthesia are weighed and undergoe dual-energy X-ray absorptiometry (DXA, QDR-4500/W, Hologic Inc., Waltham, MA) equipped with Rat Whole Body Scan software for lean
30 and fat body mass determination. The rats are necropsied, then autopsied and blood is obtained by cardiac puncture. The distal femoral metaphysis and femoral shafts from each rat are analyzed by peripheral quantitative computerized tomography (pQCT), and volumetric total, trabecular and cortical bone mineral content and density are determined.

Peripheral Quantitative Computerized Tomography (pQCT) Analysis: Excised femurs are scanned by a pQCT X-ray machine (Stratec XCT Research M, Norland Medical Systems, Fort Atkinson, WI.) with software version 5.40. A 1 millimeter (mm) thick cross section of the femur metaphysis is taken at 5.0 mm (proximal femoral metaphysis, a primary cancellous bone site) and 13 mm (femoral shafts, a cortical bone site) proximal from the distal end with a voxel size of 0.10 mm. Cortical bone is defined and analyzed using contour mode 2 and cortical mode 4. An outer threshold setting of 340 mg/cm³ is used to distinguish the cortical shell from soft tissue and an inner threshold of 529 mg/cm³ to distinguish cortical bone along the endocortical surface. Trabecular bone is determined using peel mode 4 with a threshold of 655 mg/cm³ to distinguish (sub)cortical from cancellous bone. An additional concentric peel of 1% of the defined cancellous bone is used to ensure that (sub)cortical bone was eliminated from the analysis. Volumetric content, density, and area are determined for both trabecular and cortical bone (Jamsa T. et al., Bone 23:155-161, 1998; Ke, H.Z. et al., Journal of Bone and Mineral Research, 16:765-773, 2001).

The experimental groups for the protocol are as follows:

- Group I: Baseline controls
- Group II: Sham + Vehicle
- Group III: OVX + Vehicle
- Group IV: OVX + Test Compound of Formula I (in Vehicle)
- Group V: OVX + Test Compound of Formula I and Additional Active Agent

Note: Group V only employed when it is desired to test a combination of a compound of Formula I and an additional active agent.

Fracture Healing Assays

Assay For Effects On Fracture Healing After Systemic Administration

Fracture Technique: Sprague-Dawley rats at 3 months of age are anesthetized with Ketamine. A 1 cm incision is made on the anteromedial

aspect of the proximal part of the right tibia or femur. The following describes the tibial surgical technique. The incision is carried through to the bone, and a 1 mm hole is drilled 4 mm proximal to the distal aspect of the tibial tuberosity 2 mm medial to the anterior ridge. Intramedullary nailing is performed with a 0.8 mm stainless steel tube (maximum load 36.3 N, maximum stiffness 61.8 N/mm, tested under the same conditions as the bones). No reaming of the medullary canal is performed. A standardized closed fracture is produced 2 mm above the tibiofibular junction by three-point bending using specially designed adjustable forceps with blunt jaws. To minimize soft tissue damage, care is taken not to displace the fracture. The skin is closed with monofilament nylon sutures. The operation is performed under sterile conditions. Radiographs of all fractures are taken immediately after nailing, and rats with fractures outside the specified diaphyseal area or with displaced nails are excluded. The remaining animals are divided randomly into the following groups with 10 - 12 animals per each subgroup per time point for testing the fracture healing. The first group receives daily gavage of vehicle (water : 100% Ethanol = 95 : 5) at 1 ml/rat, while the others receive daily gavage from 0.01 to 100 mg/kg/day of the compound of Formula I to be tested (1 ml/rat) for 10, 20, 40 and 80 days.

At 10, 20, 40 and 80 days, 10 - 12 rats from each group are anesthetized with Ketamine and sacrificed by exsanguination. Both tibiofibular bones are removed by dissection and all soft tissue is stripped. Bones from 5 - 6 rats for each group are stored in 70% ethanol for histological analysis, and bones from another 5 - 6 rats for each group are stored in a buffered Ringer's solution (+4°C, pH 7.4) for radiographs and biomechanical testing which is performed.

Histological Analysis: The methods for histologic analysis of fractured bone have been previously published by Mosekilde and Bak (The Effects of Growth Hormone on Fracture Healing in Rats: A Histological Description. Bone, 14:19-27, 1993). Briefly, the fracture site is sawed 8 mm to each side of the fracture line, embedded undecalcified in methymethacrylate, and cut

frontals sections on a Reichert-Jung Polycut microtome in 8 μ m thick. Masson-Trichrome stained mid-frontal sections (including both tibia and fibula) are used for visualization of the cellular and tissue response to fracture healing with and without treatment. Sirius red stained sections are used to demonstrate the characteristics of the callus structure and to differentiate between woven bone and lamellar bone at the fracture site. The following measurements are performed: (1) fracture gap - measured as the shortest distance between the cortical bone ends in the fracture, (2) callus length and callus diameter, (3) total bone volume area of callus, (4) bony tissue per tissue area inside the callus area, (5) fibrous tissue in the callus, and (6) cartilage area in the callus.

Biomechanical Analysis: The methods for biomechanical analysis have been previously published by Bak and Andreassen (The Effects of Aging on Fracture Healing in Rats. Calcif Tissue Int 45:292-297, 1989). Briefly, radiographs of all fractures are taken prior to the biomechanical test. The mechanical properties of the healing fractures are analyzed by a destructive three- or four-point bending procedure. Maximum load, stiffness, energy at maximum load, deflection at maximum load, and maximum stress are determined.

A calcium receptor antagonist may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of osteoporosis. For example, a calcium receptor antagonist, particularly a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from: selective estrogen receptor modulators (SERMs), bisphosphonates, parathyroid hormone (PTH) and fragments and analogues thereof, estrogens, calcitonins, synthetic steroids, synthetic isoflavones, vitamin D analogues, vitamin K analogues, strontium salts, cathepsin K inhibitors, $\alpha_v\beta_3$ integrin (vitronectin) antagonists, prostaglandin (PGE2) receptor agonists and receptor activator of

nuclear factor κ B ligand (RANKL) inhibitors as described hereinabove.

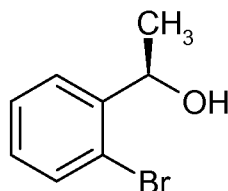
The following non-limiting Preparations and Examples illustrate the preparation of compounds of the present invention.

5 ^1H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra (m/z) were
10 recorded using either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). The following abbreviations have been used for common solvents and various reagents: AcOH, acetic acid; CDCl_3 , deuteriochloroform; CD_3OD , deuteromethanol; CH_2Cl_2 , dichloromethane; DMF, dimethylformamide; DMSO, dimethylsulfoxide; Et_2O , diethyl ether;
15 EtOH, ethanol; EtOAc, ethyl acetate; HCl, hydrochloric acid; H_2SO_4 , sulfuric acid; KOH, potassium hydroxide; LiOH, lithium hydroxide; MeOH, methanol; MgSO_4 , magnesium sulfate; NaH, sodium hydride; NaOH, sodium hydroxide; Na_2SO_4 , sodium sulfate; NH_4Cl , ammonium chloride; RT, room temperature; THF, tetrahydrofuran. 'Ammonia' refers to a concentrated
20 solution of ammonia in water possessing a specific gravity of 0.88. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F₂₅₄ plates, R_f is the distance traveled by a compound divided by the distance travelled by the solvent front on a TLC plate. HPLC refers to high performance liquid chromatography.

25 The following specific examples are included for illustrative purposes and are not to be construed as a limitation to this disclosure.

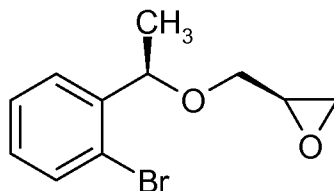
Preparation of Intermediates

Preparation 1: (R)-2-Bromo-phenyl)-ethanol



(+)-DIP-ChlorideTM ((+)-DIP-ChlorideTM is Ipc_2BCl (derived from (–)- α -pinene), DIP-Chloride is a trademark of Sigma-Aldrich Corporation, 50.0 g) was dissolved in dry THF (200 mL) under argon and cooled to $-25\text{ }^\circ\text{C}$. Bromoacetophenone (20.7 g) was then added and the resulting reaction mixture stirred at $<-25\text{ }^\circ\text{C}$ for 5 hours. Solvent was removed under reduced pressure and the residue redissolved in diethyl ether (500 mL). Diethanolamine (24 g) was then added and the reaction mixture stirred at ambient temperature overnight. The reaction mixture was then diluted with hexane, dried over MgSO_4 , filtered and the solvent removed under reduced pressure. Purification via silica gel chromatography (4:1 hexane/EtOAc) afforded the product as a colorless oil (29 g). Chiral GC: t_R 2.99 min (98 % ee). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.47 - 1.51 (m, 3H), 1.94 - 1.98 (m, 1H), 5.21 - 5.28 (m, 1H), 7.09 - 7.16 (m, 1H), 7.32 - 7.38 (m, 1H), 7.49 - 7.54 (m, 1H), 7.58 - 7.62 (m, 1H).

Preparation 2: (R)-2-[(R)-1-(2-Bromo-phenyl)-ethoxymethyl]-oxirane



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(R)-(2-Bromo-phenyl)-ethanol (Preparation 1, 21.0 g) was dissolved in dry DMF (250 mL) under argon. Toluene-4-sulfonic acid (R)-1-oxiranylmethyl ester (28.5 g) was added. The reaction mixture was then cooled to $0\text{ }^\circ\text{C}$ and NaH (5.00 g, 60% dispersion in mineral oil) was added portion-wise. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was cooled to $0\text{ }^\circ\text{C}$

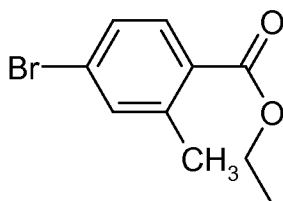
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once more and the excess NaH was quenched with the addition of citric acid (aq.). The product was then extracted with EtOAc (2 x 200 mL), washed with brine (4 x 200 mL), then dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by silica gel chromatography (5:1

5 hexane/EtOAc) to afford the desired product as a very pale yellow oil (21 g).

¹H NMR (400 MHz, CDCl₃) δ ppm 1.43 (d, 3H), 2.53 - 2.58 (m, 1H), 2.73 - 2.78 (m, 1H), 3.10 - 3.17 (m, 1H), 3.27 - 3.34 (m, 1H), 3.56 - 3.61 (m, 1H), 4.89 (q, 1H), 7.08 - 7.16 (m, 1H), 7.30 - 7.37 (m, 1H), 7.47 - 7.53 (m, 2H).

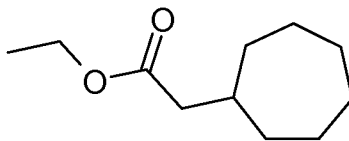
10 Preparation 3: 4-Bromo-2-methyl-benzoic acid ethyl ester



4-Bromo-2-methyl-benzoic acid (24.75 g) was suspended in EtOH (200 mL, 200 proof) and cooled to 0 °C. Thionyl chloride (10 mL) was added dropwise. The mixture was allowed to warm to RT, then heated to reflux for

15 3 h. Upon cooling, the reaction mixture was concentrated *in vacuo* and the residue redissolved in EtOAc, washed with water and brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide an oil (27 g, 96%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.32 (t, 3H), 2.56 (s, 3H), 4.34 (q, 2H), 7.30 - 7.50 (m, 2H), 7.68 - 7.88 (m, 1H). HPLC t_R 10.03 min.

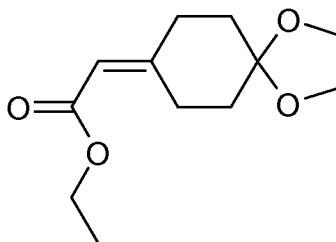
20 Preparation 4: Cycloheptyl-acetic acid ethyl ester



In a similar manner used for Preparation 3, Cycloheptyl-acetic acid ethyl ester (18 g) was obtained from Cycloheptyl-acetic acid (15 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.14 - 1.30 (m, 5H), 1.37 - 1.79 (m, 10H), 1.89 - 2.07 (m, 1H), 2.21 (d, J=7.42 Hz, 2H), 4.06 - 4.18 (m, 2 H).

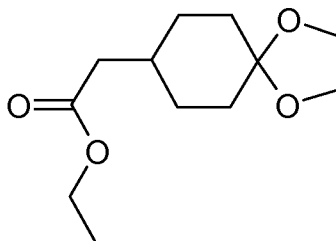
25 (m, 1H), 2.21 (d, J=7.42 Hz, 2H), 4.06 - 4.18 (m, 2 H).

Preparation 5: (1,4-Dioxo-spiro[4.5]dec-8-ylidene)-acetic acid ethyl ester



(Diethoxy-phosphoryl)-acetic acid ethyl ester (7.05 mL) was added dropwise to a suspension of NaH (1540 mg, 60% dispersion in mineral oil) in THF (50 mL) at 0 °C. The resulting solution was stirred for 30 minutes at room temperature under inert atmosphere. A solution of 1,4-Dioxo-spiro[4.5]decan-8-one (5.0 g) in THF (25 mL) was then added dropwise and the resulting mixture was stirred at room temperature under inert atmosphere for 4 h. The solvent was evaporated to a minimum volume, water was added and the resulting residue was extracted with 50% Heptane/EtOAc. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude product (7.2 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.25 (t, *J*=7.22 Hz, 3H), 1.66 - 1.82 (m, 4H), 2.28 - 2.48 (m, 2H), 2.90 - 3.07 (m, 2H), 3.96 (s, 4H), 4.13 (q, *J*=7.03 Hz, 2H), 5.64 (s, 1H). MS (ESI, *m/z*) 227.2 (*M*+*H*).

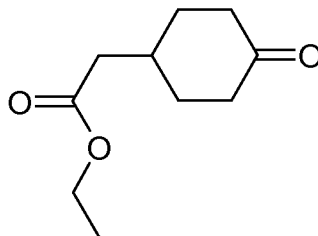
Preparation 6: (1,4-Dioxo-spiro[4.5]dec-8-yl)-acetic acid ethyl ester



Ammonium formate (2.8 g) was added to a suspension of (1,4-Dioxo-spiro[4.5]dec-8-ylidene)-acetic acid ethyl ester (Preparation 5, 2 g) and 10% Palladium on carbon (200 mg) in EtOH (250 mL). The resulting solution was stirred at reflux under N₂ for 1.5 h. The reaction mixture was cooled to room

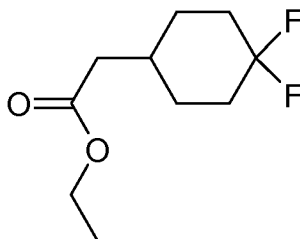
temperature then filtered. The filtrate was evaporated to afford the crude product (2 g). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.79 - 1.01 (m, 5H), 1.16 - 1.28 (m, 5H), 1.42 - 1.54 (m, 3H), 1.54 - 1.75 (m, 3H), 2.14 (d, $J=6.83$ Hz, 1H), 2.25 (d, $J=7.42$ Hz, 1H), 4.04 - 4.18 (m, 2H). MS (ESI, m/z) 229.3 ($M+H$).

5 Preparation 7: (4-Oxo-cyclohexyl)-acetic acid ethyl ester



(1,4-Dioxo-spiro[4.5]dec-8-yl)-acetic acid ethyl ester (Preparation 6, 2 g), acetone (125 mL), phosphoric acid (5.0 mL) and water (25.0 mL) were refluxed overnight (approximately 16 h). The reaction mixture was cooled to room temperature and concentrated to a minimal volume *in vacuo*. The residue was taken up in 50% Heptane/ Et_2O (100 mL) and washed with water (2x50 mL), and brine. The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo* to afford the desired product (1.4 g). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.25 (t, $J=7.12$ Hz, 3H), 1.36 - 1.54 (m, 2H), 2.01 - 2.13 (m, 2H), 2.22 - 2.31 (m, 3H), 2.32 - 2.41 (m, 4H), 4.13 (q, $J=7.22$ Hz, 2H).

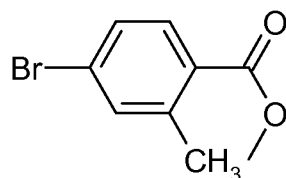
Preparation 8: (4,4-Difluoro-cyclohexyl)-acetic acid ethyl ester



A mixture of [bis(2-methoxyethyl)amino]sulfur trifluoride (2.7 g) and boron trifluoride diethyl etherate (0.1 mL) in toluene (15 mL) at 0 °C was allowed to stand for 1.3 h with occasional stirring. A solution of (4-Oxo-

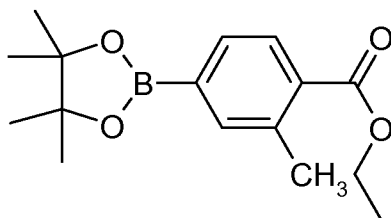
cyclohexyl)-acetic acid ethyl ester (Preparation 7, 1.38 g) in toluene (10 mL) was added. The reaction mixture was stirred at 50 °C for 1 day. The mixture was then cooled to 0 °C and the mixture was added to 50 mL of 5 N NaOH and 100 mL of Et₂O/Heptane (1:1) at 0 °C. After stirring for 30 min,
5 the phases were separated. The organic layer was washed with 100 mL of water, 1 N HCl, and brine. The organic layer was dried over MgSO₄ and concentrated *in vacuo* to afford the desired product. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.18 - 1.40 (m, 6H), 1.62 - 1.93 (m, 4H), 1.98 - 2.14 (m, 2H), 2.19 - 2.30 (m, 2H), 4.12 (q, *J*=7.03 Hz, 2 H).

10 Preparation 9: 4-Bromo-2-methyl-benzoic acid methyl ester



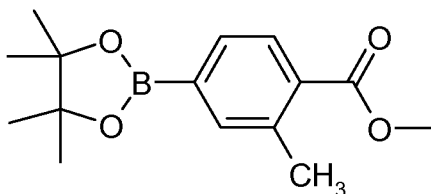
4-Bromo-2-methyl-benzoic acid (100 g) was suspended in MeOH (400 mL) and H₂SO₄ (catalytic) was added dropwise. The reaction mixture
15 was heated at reflux 20 h. The mixture was cooled to room temperature and 300 mL of the MeOH was evaporated. Residue partitioned between EtOAc (500 mL) and water (500 mL). The layers were separated, and the aqueous phase re-extracted with EtOAc (500 mL). The organic phases were combined, dried over MgSO₄, filtered and evaporated to give the desired
20 product as a red oil (109 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.5 (s, 3H), 3.85 (s, 3H), 7.35 (d, 1H), 7.4 (s, 1H), 7.75 (d, 1H).

Preparation 10: 2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid ethyl ester



- 4-Bromo-2-methyl-benzoic acid ethyl ester (Preparation 3, 29 g) was dissolved in DMSO (300 mL) and [1,1'-bis(diphenylphosphine)ferrocene]dichloropalladium (II) (4.5 g), potassium acetate (36 g) and bis(pinacolato)diboron (34 g) were added. The mixture was degassed for 10 min and the solution was warmed up to 80 °C and stirred for 3 h, then cooled to room temperature over approximately 16 h. The reaction mixture was then diluted with EtOAc (500 mL) and water (800 mL). The resulting mixture was filtered through Celite. The organic phase was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were washed with water (2 x 600 mL) and brine (400 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification via flash chromatography (gradient EtOAc/heptane) afforded the desired product as a green liquid (31 g, 91%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.34 (s, 12H), 1.39 (t, 3H), 2.59 (s, 3H), 4.36 (q, 2H), 7.59 - 7.76 (m, 2H), 7.78 - 7.97 (m, 1H).

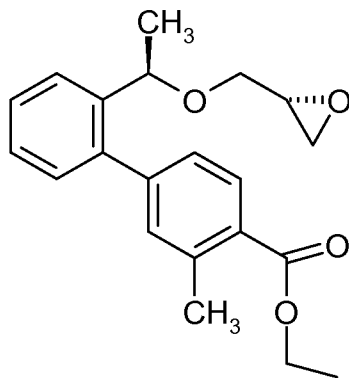
- Preparation 11: 2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester



- In a similar manner used for Preparation 10, 2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester (71 g) was obtained from 4-Bromo-2-methyl-benzoic acid methyl ester (Preparation 9, 109 g). ¹H NMR (400 MHz, CDCl₃) ppm 1.35 (s, 12H), 2.60 (s, 3H), 3.90 (s,

3H), 7.60 (d, 1H), 7.65 (s, 1H), 7.90 (d, 1H).

Preparation 12: of 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-carboxylic acid ethyl ester



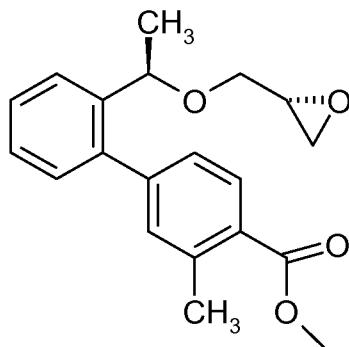
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To (R)-2-[(R)-1-(2-Bromo-phenyl)-ethoxymethyl]-oxirane (Preparation 2, 10 g, 33 mmol) in EtOH and toluene (60 mL) was added 2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid ethyl ester (Preparation 10) in EtOH (120 mL total used), 1,1'-

- 10 Bis(diphenylphosphino)ferrocene palladium dichloride (1.2 g, 1.6 mmol) and sodium carbonate (66 mL, 132 mmol of 2M aq solution). The reaction mixture was degassed for ~10 min and then heated at reflux for 3h. The mixture was cooled to room temperature and stirred 60 h then was concentrated *in vacuo*. Water and EtOAc were added to the mixture and the
- 15 mixture was extracted three times with EtOAc. The organic layer was washed with water, brine, dried and concentrated to give the crude product which was purified by flash chromatography (EtOAc/heptane gradient) to afford the desired product as a yellow viscous liquid (7.66 g, 68%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.37 (d, 3H), 1.42 (t, 3H), 2.44 - 2.49 (m, 1H), 2.64
- 20 (s, 3H), 2.69 - 2.74 (m, 1H), 3.01 - 3.08 (m, 1H), 3.11 - 3.18 (m, 1H), 3.39 - 3.44 (m, 1H), 4.39 (q, 2H), 4.56 (q, 1H), 7.12 - 7.19 (m, 3H), 7.28 - 7.34 (m, 1H), 7.39 - 7.45 (m, 1H), 7.58 - 7.63 (m, 1H), 7.94 - 7.98 (m, 1H).

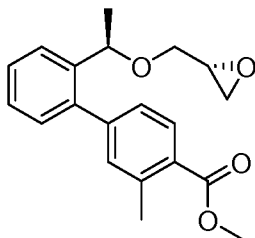
Preparation 13: 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-

carboxylic acid methyl ester



In a similar manner used for Preparation 12, 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-carboxylic acid methyl ester (1.6 g) was
 5 obtained from (R)-2-[(R)-1-(2-Bromo-phenyl)-ethoxymethyl]-oxirane (Preparation 2) and 2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester (Preparation 11, 2.3 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.35 (d, 2H), 2.40 - 2.47 (m, 1H), 2.63 (s, 3H), 2.67 - 2.74 (m, 1H), 2.98 - 3.07 (m, 1H), 3.09 - 3.17 (m, 1H), 3.40 (dd, J=11.13, 3.51 Hz, 1H), 3.90 (s,
 10 3H), 4.53 (q, J=6.31 Hz, 1H), 7.07 - 7.19 (m, 3H), 7.26 - 7.34 (m, 1H), 7.37 - 7.44 (m, 1H), 7.53 - 7.62 (m, 1H), 7.94 (d, J=8.39 Hz, 1H).

Alternate Procedure For Preparation 13: 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-carboxylic acid methyl ester



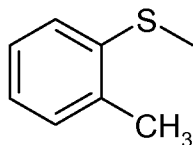
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4-Bromo-2-methyl-benzoic acid methyl ester (preparation 9, 451 g) was dissolved in tetrahydrofuran (4.6 L) and bis(pinacolato)diboron (568 g), potassium acetate (528 g), and [1,1'-bis(diphenylphosphine)ferrocene] dichloropalladium (II) (36.5 g) were added. The mixture was stirred at 70 °C
 20 for 5.5 h, and then cooled to room temperature. (R)-2-[(R)-1-(2-Bromo-phenyl)-ethoxymethyl]-oxirane (Preparation 2, 460 g) dissolved in ethanol (900 mL) was added followed by saturated aqueous sodium bicarbonate (5.5

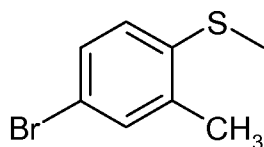
L). The mixture was vigorously stirred at 70 °C for 12 h. The reaction was cooled to room temperature the layers were separated. To the organic layer was added ethyl acetate (1L). and the organic layer was washed with brine (2.3 L). To the organic layer was added Darco™ activated charcoal (115 g)
5 (EM Science, Cherry Hill, NJ 08034) and the slurry was stirred for 15 minutes. The mixture was filtered through a 1 in. bed of celite (~2.2 kg celite). The filter cake was washed with ethyl acetate (2x 900 mL). The filtrate was concentrated under reduced pressure to a brown oil. Purification via flash column chromatography (gradient ethyl acetate / heptane 2-15%) afforded the
10 desired product as a pale yellow oil (346 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.37 (d, 3 H) 2.40-2.47 (m, 1 H) 2.64 (s, 3 H) 2.70 - 2.75 (m, 1 H) 3.01-3.08 (m, 1 H) 3.09-3.17 (m, 1 H) 3.42 (dd, *J*=10.99, 3.53 Hz, 1 H) 3.92 (s, 3 H) 4.55 (q, *J*=6.36 Hz, 1 H) 7.12 - 7.19 (m, 3 H) 7.28 -7.35 (m, 1 H) 7.39 - 7.47 (m, 1 H) 7.58 - 7.63 (m, 1 H) 7.93 - 7.99 (m, 1 H)

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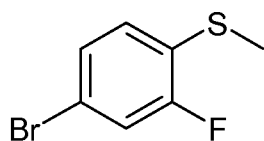
Preparation 14: 1-Methyl-2-methylsulfanyl-benzene



EtOH (20 mL) was added to KOH (1.47 g) and stirred until the KOH dissolved. A solution of 2-Methyl-benzenethiol (3.11 g) in EtOH (20 mL) was
20 then added and the resulting solution was stirred 40 min at room temperature. Methyl iodide (1.6 mL) was added via syringe and a white precipitate formed immediately. The mixture was stirred at room temp 3h. The white solid was filtered off and washed with EtOH. The filtrate was concentrated *in vacuo* to give a white gummy solid, which was dissolved in EtOAc and water. The
25 layers were separated and the aqueous layer was washed with EtOAc. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to afford the desired product (3.06 g) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.34 (s, 3H), 2.46 (s, 3H), 6.98 - 7.11 (m, 1H), 7.11 - 7.23 (m, 3H).

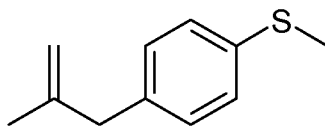
Preparation 15: 4-Bromo-2-methyl-1-methylsulfanyl-benzene

- 5 To 1-Methyl-2-methylsulfanyl-benzene (Preparation 14, 4 g) in CH₂Cl₂ (29 mL) was added bromine (1.5 mL) dropwise at 0 °C. The resulting orange solution was stirred 1 h at room temperature. The reaction mixture was concentrated *in vacuo* and the resulting orange colored crude reaction mixture was purified by silica gel chromatography (0-5% EtOAc/Heptane) to afford the
- 10 desired product (5.98 g) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.30 (s, 3H), 2.44 (s, 3H), 7.00 (d, *J*=8.20 Hz, 1H), 7.27-7.32 (m, 2H).

Preparation 16: 4-Bromo-2-fluoro-1-methylsulfanyl-benzene

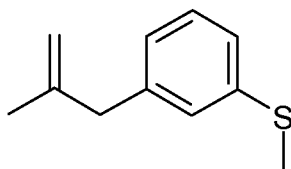
- 15 Bromine (9.9 mL) was added dropwise to a solution of 2-fluorothioanisole (27.5 g) in CH₂Cl₂ (190 mL) at 0 °C. The resulting solution was stirred at room temperature overnight. Half-saturated sodium thiosulfate was added to quench the reaction and the reaction mixture was stirred vigorously for 10 min. The layers were separated and the aqueous layer
- 20 was washed three more times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to afford the desired product as a light yellow oil (41 g, 9:1 mix of product to starting material). The crude material was carried forward without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.45 (s, 3H), 7.13 (t, *J*=8.10 Hz, 1H), 7.22 - 7.24
- 25 (m, 1H), 7.25 - 7.26 (m, 1H).

Preparation 17: 1-(2-Methyl-allyl)-4-methylsulfanyl-benzene



To magnesium turnings (4.9 g) in THF (100 mL) iodine (1.94 g) was added. 4-Bromothioanisole (32 g) was then added dropwise as a solution in THF (200 mL). The mixture was heated to reflux and then heating was discontinued and the mixture was stirred for 1 h at room temperature, then cooled to 0 °C. Copper iodide (2.97 g) and 3-chloro-2-methyl-1-propene (22.4 mL) were then added and the mixture was stirred 90 min at 0 °C then at room temperature for 30 min. The mixture was then recooled to 0 °C and saturated aqueous NH₄Cl solution (4 mL) was added. The mixture was stirred at room temperature for 20 min and MgSO₄ (16 g) was added. The reaction mixture was filtered, the filter cake was washed with heptane and the resulting filtrate was concentrated *in vacuo*. Heptane was added to the obtained residue and the resulting mixture filtered through a silica plug. The resulting solution was concentrated *in vacuo* to provide the product as a colorless liquid (10.4 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.67 (s, 3H), 2.47 (s, 3H), 3.27 (s, 2H), 4.69 - 4.75 (m, 1H), 4.77 - 4.82 (m, 1H), 7.08 - 7.14 (m, 2H), 7.17 - 7.23 (m, 2H).

Preparation 18: 1-(2-Methyl-allyl)-3-methylsulfanylbenzene

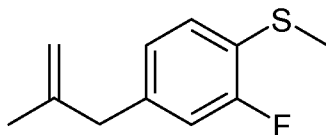


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In a similar manner used for Preparation 17, 1-(2-Methyl-allyl)-3-methylsulfanylbenzene (2.1 g) was obtained from 3-bromoanisole (4 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.66 (s, 3H), 2.46 (s, 3H), 3.27 (s, 2H), 4.70 - 4.74 (m, 1H), 4.78 - 4.82 (m, 1H), 6.92 - 6.98 (m, 1H), 7.06 - 7.11 (m, 2H), 7.16 - 7.22 (m, 1H).

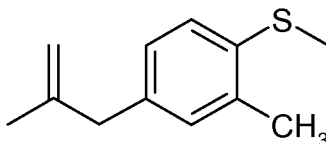
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Preparation 19: 2-Fluoro-4-(2-methyl-allyl)-1-methylsulfanyl-benzene



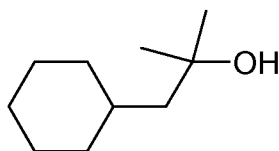
To a solution of isopropylmagnesium chloride (81.4 mL, 2M in THF) was added butyllithium (125 mL, 2.5 M in hexanes) at 0 °C. The resulting solution was stirred for 15 min., then cooled to -78 °C, and a solution of 4-Bromo-2-fluoro-1-methylsulfanyl-benzene (30 g) in THF (540 mL) was added dropwise. After stirring 1.5 h at -78 °C, 3-Bromo-2-methyl-propene (41 mL) was added, followed by CuI (2.6 g). The reaction mixture was stirred 30 min at -78 °C. Saturated NH₄Cl was added to quench the reaction, which was then further diluted with EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to afford the desired product as a light brown oil (28 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.66 (s, 3H), 2.45 (s, 3H), 3.27 (s, 2H), 4.72 - 4.75 (m, 1H), 4.83 (br s, 1H), 6.85 - 6.96 (m, 2H), 7.17 - 7.23 (m, 1H).

Preparation 20: 2-Methyl-4-(2-methyl-allyl)-1-methylsulfanyl-benzene



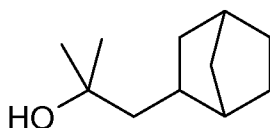
In a similar manner used for Preparation 19, 2-Methyl-4-(2-methyl-allyl)-1-methylsulfanyl-benzene (2.6 g) was obtained from 4-Bromo-2-methyl-1-methylsulfanyl-benzene (2.9 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.67 (s, 3H), 2.32 (s, 3H), 2.45 (s, 3H), 3.24 (s, 2H), 4.70 - 4.75 (m, 1H), 4.77 - 4.83 (m, 1H), 6.95 - 7.04 (m, 2H), 7.08 - 7.12 (m, 1H).

Preparation 21: 1-Cyclohexyl-2-methyl-propan-2-ol



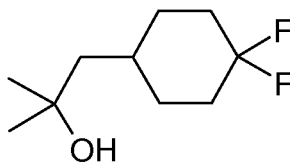
Methylmagnesium bromide (100 mL, 3.0 M in Et₂O) was added dropwise to cyclohexyl-acetic acid methyl ester (16.4 mL, 100 mmol) in THF (200 mL) at 0 °C and the mixture was stirred overnight and allowed to warm to room temperature. The reaction mixture was cooled to 0 °C, quenched with sat. aq. NH₄Cl (200 mL), diluted with water, and extracted with EtOAc (3x 400 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to provide the desired product as a clear oil (15.8 g, 101%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.90 - 1.05 (m, 2H), 1.05 - 1.19 (m, 2H), 1.20 - 1.34 (m, 8H), 1.34 - 1.52 (m, 3H), 1.55 - 1.72 (m, 3H), 1.72 - 1.81 (m, 2H).

Preparation 22: 1-Bicyclo[2.2.1]hept-2-yl-2-methyl-propan-2-ol



In a similar manner used for Preparation 21, 1-bicyclo[2.2.1]hept-2-yl-2-methyl-propan-2-ol (7.6 g) was obtained from bicyclo[2.2.1]hept-2-yl-acetic acid methyl ester (7.3 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.04 - 1.16 (m, 3H), 1.17 - 1.25 (m, 8H), 1.26 - 1.39 (m, 2H), 1.40 - 1.51 (m, 2H), 1.51 - 1.63 (m, 3H), 1.96 - 2.02 (m, 1H), 2.16 - 2.23 (m, 1 H).

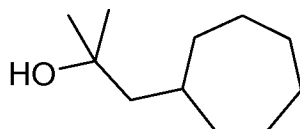
Preparation 23: of 1-(4,4-Difluoro-cyclohexyl)-2-methyl-propan-2-ol



In a similar manner used for Preparation 21, 1-(4,4-Difluoro-

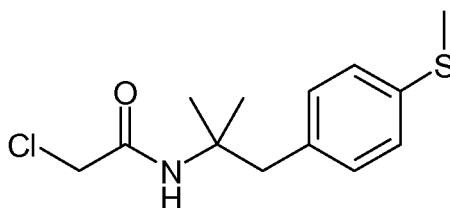
cyclohexyl)-2-methyl-propan-2-ol (864 mg) was obtained from (4,4-Difluoro-cyclohexyl)-acetic acid ethyl ester (1.3 g). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.68 - 0.95 (m, 1H), 0.99 - 1.94 (m, 15H), 1.95 - 2.31 (m, 2H).

5 Preparation 24: 1-Cycloheptyl-2-methyl-propan-2-ol



In a similar manner as Preparation 21, 1-Cycloheptyl-2-methyl-propan-2-ol (17 g) was obtained from cycloheptyl-acetic acid ethyl ester (18 g). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.20 - 1.35 (m, 8H), 1.36 - 1.53 (m, 6H), 1.54 - 1.69 (m, 6H), 1.70 - 1.81 (m, 2 H).

Preparation 25: 2-Chloro-N-[1,1-dimethyl-2-(4-methylsulfanyl-phenyl)-ethyl]-acetamide

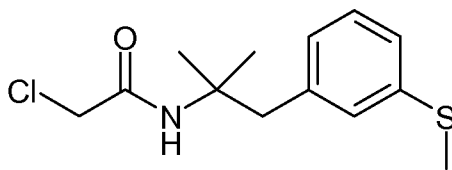


15 1-(2-Methyl-allyl)-4-methylsulfanyl-benzene (Preparation 17, 10.4 g) was dissolved in chloroacetonitrile (15 mL) and cooled to 0 °C. AcOH (13 mL, 404 mmol) was added, then H_2SO_4 (3.9 mL) was added dropwise. The reaction mixture was then stirred at RT for 16 h. The resulting mixture was recooled to 0 °C and NaOH (3M) was added dropwise until the pH was 7.

20 The mixture was then extracted with EtOAc (x2) and the combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to provide a pale yellow solid (12 g). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.34 (s, 6H), 2.46 (s, 3H), 2.98 (s, 2H), 3.93 (s, 2H), 6.18 (br s, 1H), 7.01 - 7.06 (m, 2H), 7.15 - 7.20 (m, 2H). MS (ESI, m/z) 272.2 (M+H).

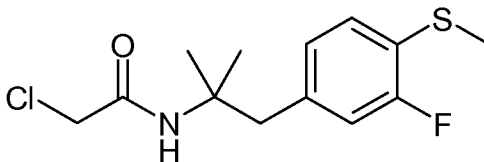
25

Preparation 26: 2-Chloro-N-[1,1-dimethyl-2-(3-methylsulfanyl-phenyl)-ethyl]-acetamide



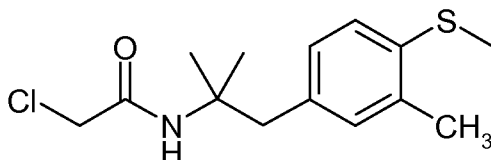
5 In a similar manner used for Preparation 25, 2-Chloro-N-[1,1-dimethyl-2-(3-methylsulfanyl-phenyl)-ethyl]-acetamide (2.6 g) was obtained from 1-(2-Methyl-allyl)-3-methylsulfanyl-benzene (Preparation 18, 2.1 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.37 (s, 6H), 2.48 (s, 3H), 3.01 (s, 2H), 3.95 (s, 2H), 6.22 (br s, 1H), 6.88 - 6.93 (m, 1H), 6.99 - 7.04 (m, 1H), 7.10 - 7.17 (m, 1H), 7.22 (t, 10 J=7.71 Hz, 1H). MS (ESI, m/z) 272.2 (M+H).

Preparation 27: 2-Chloro-N-[2-(3-fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethyl]-acetamide



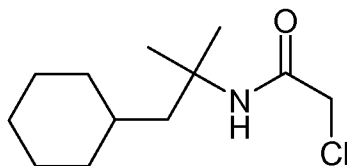
15 In a similar manner used for Preparation 25, 2-Chloro-N-[2-(3-fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethyl]-acetamide (37 g) was obtained from 2-Fluoro-4-(2-methyl-allyl)-1-methylsulfanyl-benzene (Preparation 19, 28 g). ¹H NMR (CDCl₃, 400 MHz) δ ppm 1.37 (s, 6H), 2.47 (s, 3H), 3.04 (s, 2H), 3.97 (s, 2H), 6.19 (br s, 1H), 6.83 (dd, 1H), 6.68 (dd, 1H), 7.19 (t, 1H). 20 MS(ESI, m/z) 290.3 (M+H). HPLC t_R 8.83 min.

Preparation 28: 2-Chloro-N-[1,1-dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethyl]-acetamide



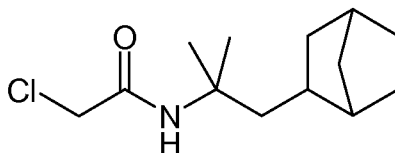
In a similar manner used for Preparation 25, 2-Chloro-N-[1,1-dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethyl]-acetamide (1.5 g) was obtained from 2-Methyl-4-(2-methyl-allyl)-1-methylsulfanyl-benzene (Preparation 20, 2.6 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.36 (s, 6H), 2.30 (s, 3H), 2.44 (s, 3H), 2.94 (s, 2H), 3.93 (s, 2H), 6.22 (br s, 1H), 6.89 - 6.99 (m, 2H), 7.08 (d, *J*=8.00 Hz, 1H).

Preparation 29: 2-Chloro-N-(2-cyclohexyl-1,1-dimethyl-ethyl)-acetamide



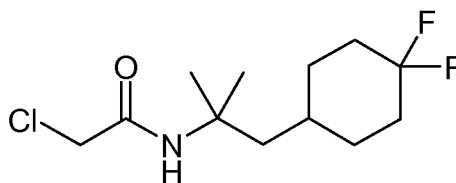
1-Cyclohexyl-2-methyl-propan-2-ol (Preparation 21, 15.8 g, 101 mmol) was dissolved in chloroacetonitrile (32 mL, 510 mmol) and cooled to 0 °C in an ice bath. AcOH (23.2 mL, 404 mmol) was added, then H₂SO₄ (5.56 mL, 101 mmol) was added dropwise. The solution, which turned from yellowish to reddish brown, was removed from the ice bath and stirred at RT overnight. The reaction mixture was then recooled to 0 °C and NaOH (3M) was added dropwise until the pH was 7. The reaction mixture was extracted with EtOAc (x2) and the combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide a tan oil (23.6 g, 100%). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.91 - 1.31 (m, 5H), 1.37 (s, 6H), 1.49 - 1.74 (m, 8H), 3.91 (s, 2H), 6.32 (br s, 1H).

Preparation 30: N-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethyl)-2-chloro-acetamide



In a similar manner used for Preparation 29, N-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethyl)-2-chloro-acetamide (12 g) was prepared from 1-Bicyclo[2.2.1]hept-2-yl-2-methyl-propan-2-ol (Preparation 22, 7.6 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.06 - 1.22 (m, 4H), 1.23 - 1.34 (m, 2H), 1.37 (s, 6H), 1.39 - 1.59 (m, 4H), 1.79 (dd, *J*=14.15, 4.98 Hz, 1H), 1.92 - 1.98 (m, 1H), 2.17 - 2.23 (m, 1H), 3.95 (s, 2H), 6.35 (br. s., 1H).

Preparation 31: 2-Chloro-N-[2-(4,4-difluoro-cyclohexyl)-1,1-dimethyl-ethyl]-acetamide

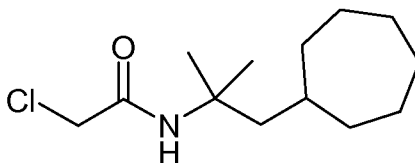


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In a similar manner used for Preparation 29, 2-Chloro-N-[2-(4,4-difluoro-cyclohexyl)-1,1-dimethyl-ethyl]-acetamide (707 mg) was obtained from 1-(4,4-Difluoro-cyclohexyl)-2-methyl-propan-2-ol (Preparation 23, 850mg). Purification via reverse phase HPLC afforded the desired product. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.31 - 1.53 (m, 9 H), 1.59 - 1.82 (m, 6 H), 1.98 - 2.11 (m, 2 H), 3.99 (s, 2 H), 6.02 (br. s., 1 H). MS (ESI, *m/z*) 268.3 (M+H).

15

Preparation 32: 2-Chloro-N-(2-cycloheptyl-1,1-dimethyl-ethyl)-acetamide

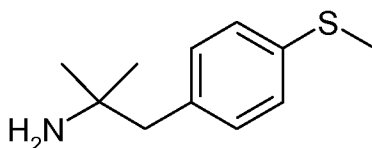


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In a similar manner used for Preparation 29, 2-Chloro-N-(2-

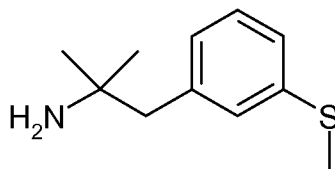
cycloheptyl-1,1-dimethyl-ethyl)-acetamide (32 g, >100%) was obtained from 1-Cycloheptyl-2-methyl-propan-2-ol (Preparation 24, 17 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.23 - 1.36 (m, 2H), 1.38 (s, 6H), 1.40 - 1.54 (m, 4H), 1.54 - 1.67 (m, 8H), 1.67 - 1.78 (m, 2H), 3.95 (s, 2H).

5 Preparation 33: 1,1-Dimethyl-2-(4-methylsulfanyl-phenyl)-ethylamine



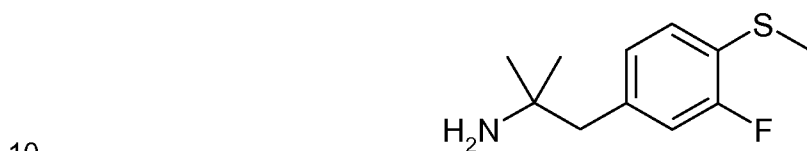
To a solution of 2-Chloro-N-[1,1-dimethyl-2-(4-methylsulfanyl-phenyl)-ethyl]-acetamide (Preparation 25, 12 g) in acetic acid (20 mL) and ethanol (147 mL) was added thiourea (4 g) and the reaction mixture was heated to 100 °C. The reaction mixture was allowed to stir at 100 °C for approximately 16 h. The reaction mixture was cooled to room temperature and the precipitate was filtered off. The filtrate was concentrated to afford a yellow solid, which was diluted with EtOAc and 1N sodium hydroxide. The aqueous layer was washed with EtOAc twice and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to afford the desired product (7.2 g) as a reddish oil. The oil was redissolved in EtOAc, cooled in an ice bath and HCl (67 mL, 1M in Et₂O) was added. The resulting mixture was allowed to warm to room temperature over 16 h then was concentrated *in vacuo*. The residue was suspended in hexane/EtOAc (220 mL, 10:1 mixture) and was stirred 36 h. The precipitate was collected by filtration and dried under reduced pressure to afford the desired product (7 g). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.30 (s, 6H), 2.45 (s, 3H), 2.84 (s, 2H), 7.15 (d, *J*=8.39 Hz, 2H), 7.21 - 7.30 (m, 2 H).

25 Preparation 34: 1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamine



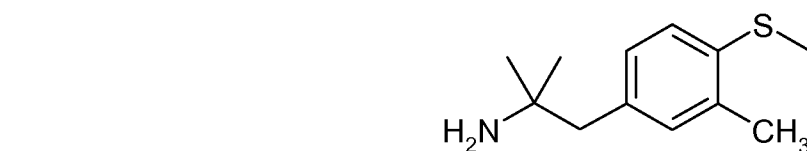
In a similar manner used for Preparation 33, 1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamine (840 mg) was obtained from 2-Chloro-N-[1,1-dimethyl-2-(3-methylsulfanyl-phenyl)-ethyl]-acetamide (Preparation 26, 2.6 g). The product was isolated as the free base (i.e. the hydrochloride salt formation was not carried out). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.10 (s, 6H), 2.46 (s, 3H), 2.61 (s, 2H), 6.92 - 6.97 (m, 1H), 7.05 - 7.08 (m, 1H), 7.09 - 7.15 (m, 1H), 7.20 (t, *J*=7.71 Hz, 1H). MS (ESI, *m/z*) 196.3 (M+H).

Preparation 35: 2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamine



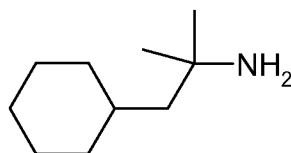
In a similar manner used for Preparation 33, 2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamine (10.7 g) was obtained from 2-Chloro-N-[2-(3-fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethyl]-acetamide (Preparation 27, 28 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.12 (s, 6H), 2.46 (s, 3H), 2.62 (s, 2H), 6.86 - 6.96 (m, 2H), 7.18 - 7.24 (m, 1H).

Preparation 36: 1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamine



In a similar manner used for Preparation 33, 1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamine (0.97 g) was obtained from 2-Chloro-N-[1,1-dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethyl]-acetamide (Preparation 28, 1.5 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.11 (s, 6H), 2.33 (s, 3H), 2.45 (s, 3H), 2.59 (s, 2H), 6.94 - 7.04 (m, 2H), 7.08 - 7.12 (m, 1H).

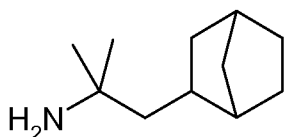
25 Preparation 37: 2-Cyclohexyl-1,1-dimethyl-ethylamine



To a solution of 2-Chloro-N-(2-cyclohexyl-1,1-dimethyl-ethyl)-acetamide (Preparation 29, 23.6 g) in AcOH (47 mL) and EtOH (200 mL) was added thiourea (9.3 g) and the reaction mixture was heated to 100 °C.

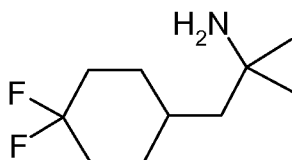
- 5 The reaction mixture was allowed to stir at 100 °C for approximately 16 h. The reaction was cooled to room temperature and the precipitate was filtered off. The filtrate was concentrated to afford a yellow solid, which was diluted with EtOAc and 1N NaOH. The aqueous layer was washed with EtOAc twice and the combined organic layers were washed with brine, dried over Na₂SO₄
- 10 and concentrated under reduced pressure to afford the desired product as a brown oil (13.7 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.91 - 1.05 (m, 2H), 1.06 - 1.50 (m, 14H), 1.55 - 1.77 (m, 5H).

Preparation 38: 2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamine



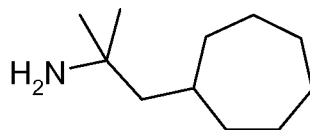
- 15 In a similar manner used for Preparation 37, 2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamine (6.6 g) was obtained from N-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethyl)-2-chloro-acetamide (Preparation 30, 11 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.00 - 1.34 (m, 13H), 1.37 - 1.60 (m, 6H), 1.89 - 1.99 (m, 1H),
- 20 2.13 - 2.22 (m, 1H).

Preparation 39: 2-(4,4-Difluoro-cyclohexyl)-1,1-dimethyl-ethylamine



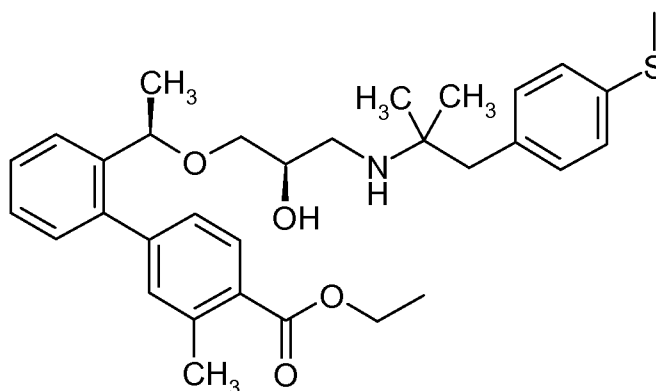
In a similar manner used for Preparation 37, 2-(4,4-Difluoro-cyclohexyl)-1,1-dimethyl-ethylamine (401 mg) was obtained from 2-Chloro-N-[2-(4,4-difluoro-cyclohexyl)-1,1-dimethyl-ethyl]-acetamide (Preparation 31, 707 mg). ¹H NMR (500 MHz, CDCl₃) δ ppm 1.07 - 1.18 (m, 6H), 1.29 - 1.42 (m, 4H), 1.44 - 1.58 (m, 1H), 1.64 - 1.87 (m, 4H), 1.88 - 2.11 (m, 4H).

Preparation 40: 2-Cycloheptyl-1,1-dimethyl-ethylamine



In a similar manner used for Preparation 37, 2-Cycloheptyl-1,1-dimethyl-ethylamine (14.2 g) was obtained from 2-Chloro-N-(2-cycloheptyl-1,1-dimethyl-ethyl)-acetamide (Preparation 32, 32 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.16 (s, 6H), 1.21 - 1.64 (m, 15H), 1.66 - 1.77 (m, 2H).

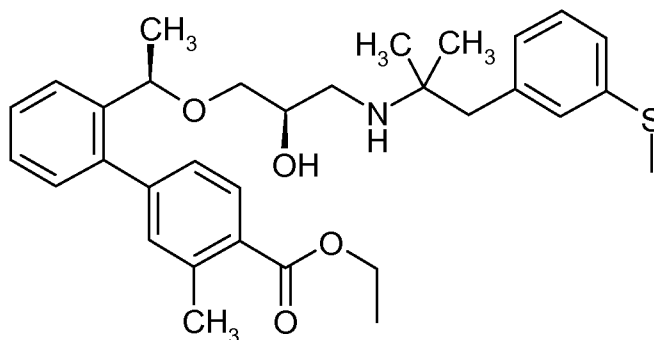
Preparation 41: 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(4-methylsulfonyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester



1,1-Dimethyl-2-(4-methylsulfonyl-phenyl)-ethylamine-hydrochloride salt (Preparation 33, 6.7 g) was dissolved in CH₂Cl₂ and NaHCO₃ (sat. aqueous solution) was added. The mixture was stirred for 15 min then the layers were separated and the aqueous layer was washed (x4) with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered

and concentrated *in vacuo* to afford the free base amine.(5.6 g). The free base amine was added to 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-carboxylic acid ethyl ester (Preparation 12, 7 g) and dissolved in toluene (220 mL). Lithium perchlorate (2.53 g) was then added and the
 5 reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and EtOAc. The organic phase was separated and was washed with sat NaHCO₃, brine, then dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluted with heptane / 2-propanol with 1% NH₄OH) to afford the desired
 10 product (8.5 g). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.01 - 1.09 (m, 6H), 1.16 - 1.23 (m, 4H), 1.28 - 1.34 (m, 2H), 1.39 (t, *J*=7.12 Hz, 3H), 2.60 - 2.67 (m, 6H), 2.79 (dd, *J*=11.91, 4.10 Hz, 1H), 3.09 - 3.23 (m, 2H), 3.66 - 3.78 (m, 1H), 3.95 - 4.05 (m, 1H), 4.37 (q, *J*=7.22 Hz, 2H), 4.46 (q, *J*=6.44 Hz, 1H), 7.01 - 7.08 (m, 2H), 7.09 - 7.19 (m, 5H), 7.25 - 7.33 (m, 1H), 7.35 - 7.43 (m, 1H), 7.52 (dd,
 15 *J*=7.81, 1.17 Hz, 1H), 7.89 - 7.98 (m, 1H). MS(ESI, *m/z*) 536.5 (M+H).

Preparation 42: 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester

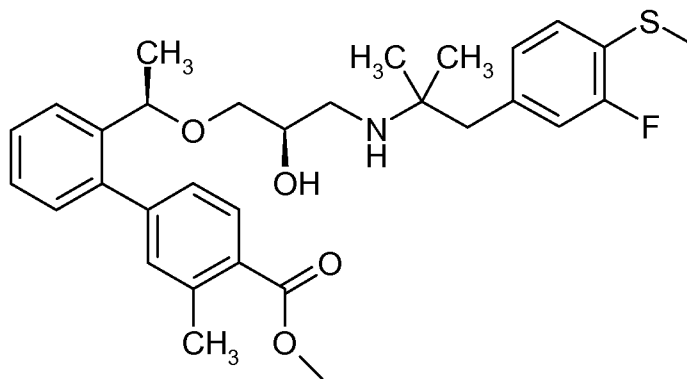


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In a similar manner used for Preparation 41, excluding the free base step, 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester (378 mg) was obtained from 1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamine
 25 (Preparation 34, 214 mg) and 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-

ethyl]-biphenyl-4-carboxylic acid ethyl ester (Preparation 12). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.01 (d, $J=7.42$ Hz, 6H), 1.19 - 1.36 (m, 5H), 1.40 (t, $J=7.12$ Hz, 3H), 2.44 (s, 3H), 2.50 - 2.65 (m, 6H), 2.70 (dd, $J=11.71$, 3.90 Hz, 1H), 3.09 - 3.23 (m, 2H), 3.59 - 3.68 (m, 1H), 4.37 (q, $J=7.22$ Hz, 2H), 4.47 (q, $J=6.38$ Hz, 1H), 6.85 - 6.93 (m, 1H), 7.00 - 7.05 (m, 1H), 7.05 - 7.19 (m, 5H), 7.25 - 7.32 (m, 1H), 7.34 - 7.43 (m, 1H), 7.53 (dd, $J=7.81$, 1.17 Hz, 1H), 7.94 (d, $J=8.39$ Hz, 1H). MS(ESI, m/z) 536.5 ($M+H$).

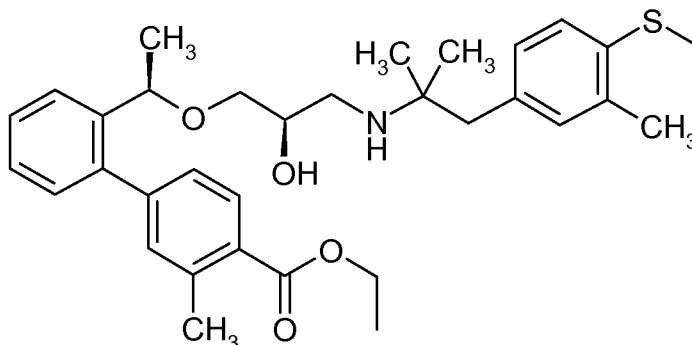
Preparation 43: 2'-((R)-1-((R)-3-[2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid methyl ester



In a similar manner used for Preparation 41, 2'-((R)-1-((R)-3-[2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid methyl ester (7.8 g) was obtained from 2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamine (Preparation 35, 9.7 g) and 3-Methyl-2'-((R)-1-((R)-1-oxiranylmethoxy)-ethyl)-biphenyl-4-carboxylic acid methyl ester (Preparation 13, 6.3 g). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.00 - 1.07 (m, 6H), 1.21 (d, $J=6.05$ Hz, 1H), 1.31 - 1.38 (m, 3H), 2.44 (s, 3H), 2.54 - 2.67 (m, 6H), 2.73 (dd, $J=11.71$, 3.90 Hz, 1H), 3.12 - 3.25 (m, 2H), 3.63 - 3.74 (m, 1H), 3.92 (s, 3H), 4.48 (q, $J=6.31$ Hz, 1H), 6.81 - 6.93 (m, 2H), 7.10 - 7.21 (m, 4H), 7.28 - 7.35 (m, 1H), 7.36 - 7.44 (m, 1H), 7.55 (dd, $J=7.81$, 1.17 Hz, 1H), 7.92 - 7.99 (m, 1H).

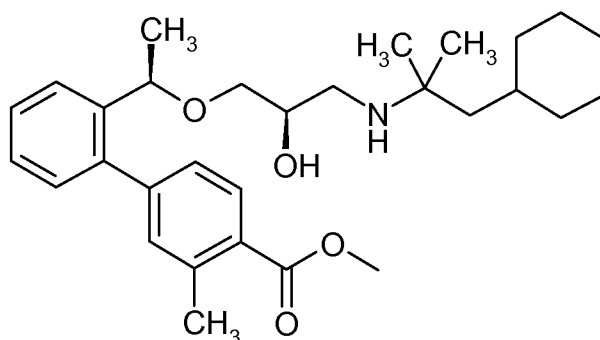
Preparation 44: 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-

phenyl)-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester



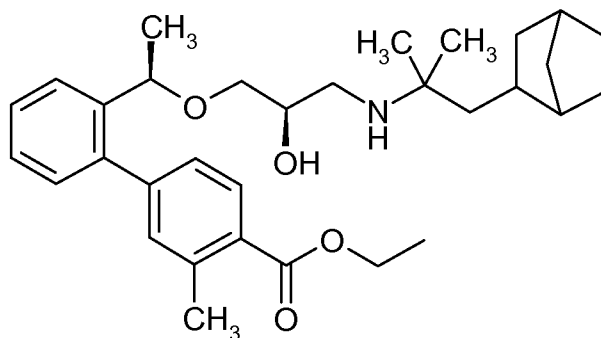
- In a similar manner used for Preparation 41, 2'-((R)-1-((R)-3-[1,1-
- 5 Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester (194 mg) was obtained from 1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamine (Preparation 36, 102 mg) and 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-carboxylic acid ethyl ester (Preparation 12, 152 mg). ¹H
- 10 NMR (400 MHz, CDCl₃) δ ppm 1.01 (d, *J*=8.59 Hz, 6H), 1.31 - 1.37 (m, 3H), 1.41 (t, *J*=7.13 Hz, 3H), 2.30 (s, 3H), 2.44 (s, 3H), 2.50 - 2.60 (m, 3H), 2.64 (s, 3H), 2.71 (dd, *J*=11.71, 4.10 Hz, 1H), 3.11 - 3.25 (m, 2H), 3.59 - 3.73 (m, 1H), 4.39 (q, *J*=7.22 Hz, 2H), 4.49 (q, *J*=6.25 Hz, 1H), 6.89 - 6.99 (m, 2H), 7.06 (d, *J*=8.00 Hz, 1H), 7.11 - 7.20 (m, 3H), 7.27 - 7.33 (m, 1H), 7.36 - 7.43 (m, 1H),
- 15 7.55 (dd, *J*=7.81, 1.37 Hz, 1H), 7.92 - 8.00 (m, 1H).

Preparation 45: 2'-((R)-1-((R)-3-(2-Cyclohexyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid methyl ester



2-Cyclohexyl-1,1-dimethyl-ethylamine (Preparation 37, 7.6 g) and 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-carboxylic acid methyl ester (Preparation 13, 12.3 g) were dissolved in toluene (200 mL) and lithium perchlorate (4.64 g) was added portion wise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and EtOAc. The organic phase was separated, washed with sat NaHCO₃ and brine, then dried over MgSO₄ and concentrated *in vacuo*. Purification by silica gel chromatography (eluted with heptane / 2-propanol with 1% Et₃N) to afforded the crude product (12.5 g). The crude product was redissolved in a hot solution of 10% 2-propanol / heptane (100 mL). The resulting solution was cooled to room temperature and placed in the freezer for 16 h. The resulting precipitate was collected by filtration and washed with heptane to afford the desired product (9 g) as an off-white / tan solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 0.79 - 1.02 (m, 7H), 1.03 - 1.36 (m, 9H), 1.37 - 1.75 (m, 11H), 2.38 - 2.50 (m, 1H), 2.55 - 2.67 (m, 3H), 3.09 - 3.22 (m, 2H), 3.55 - 3.68 (m, 1H), 3.90 (s, 2H), 4.46 (q, 1H), 7.08 - 7.19 (m, 1H), 7.26 - 7.33 (m, 1H), 7.37 - 7.45 (m, 1H), 7.52 - 7.60 (m, 1H), 7.90 - 7.97 (m, 1H). MS(ESI, m/z) 482 (M+H).

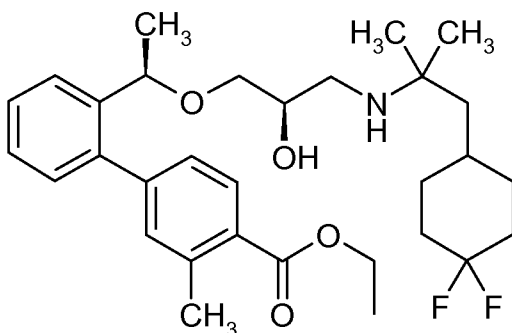
Preparation 46: 2'-{(R)-1-[(R)-3-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid ethyl ester



In a similar manner used for Preparation 45, 2'-{(R)-1-[(R)-3-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-

methyl-biphenyl-4-carboxylic acid ethyl ester (891 mg) was obtained from 3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-carboxylic acid ethyl ester (Preparation 12, 578 mg) and 2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamine (Preparation 38, 369 mg). Purification by silica gel chromatography (heptane / dioxane) afforded the desired product. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.01 (s, 5H), 1.27 (s, 1H), 1.37 (d, *J*=6.44 Hz, 3H), 1.43 (t, *J*=7.22 Hz, 5H), 1.44 (s, 5H), 1.90 (br. s., 1H), 2.17 (br. s., 1H), 2.45 (s, 1H), 2.65 (s, 4H), 3.19 (s, 1H), 3.18 (d, *J*=5.66 Hz, 1H), 3.71 (s, 10H), 4.40 (d, *J*=7.22 Hz, 1H), 4.50 (d, *J*=6.25 Hz, 1H), 7.14 - 7.19 (m, 1H), 7.16 (dd, *J*=2.93, 1.56 Hz, 2H), 7.43 (d, *J*=1.37 Hz, 1H), 7.59 (dd, *J*=7.81, 1.17 Hz, 1H). MS(ESI, *m/z*) 508.5 (M+H).

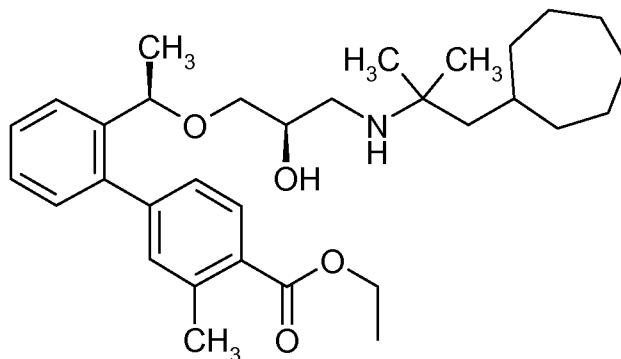
Preparation 47: 2'-((R)-1-((R)-3-[2-(4,4-Difluoro-cyclohexyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester



3-Methyl-2'-[(R)-1-((R)-1-oxiranylmethoxy)-ethyl]-biphenyl-4-carboxylic acid ethyl ester (Preparation 12, 200 mg) and 2-(4,4-Difluorocyclohexyl)-1,1-dimethyl-ethylamine (Preparation 39, 225 mg) in acetonitrile (0.5 mL) was added to a solution of 4 M potassium carbonate buffer (2 mL) and was heated for 45 minutes at 125 °C under microwave energy. The crude reaction mixture was purified by reverse phase HPLC to afford the desired product (192 mg). ¹H NMR (500 MHz, CDCl₃) δ ppm 0.99 - 1.07 (m, 6H), 1.19 - 1.51 (m, 12H), 1.59 - 1.83 (m, 4H), 1.93 - 2.07 (m, 2H), 2.46 (dd, *J*=11.59, 7.20 Hz, 1H), 2.60 (dd, *J*=11.59, 4.03 Hz, 1H), 2.65 (s, 3H), 3.09 - 3.25 (m, 2H), 3.60 - 3.68 (m, 1H), 4.40 (q, *J*=7.08 Hz, 2H), 4.49 (q, *J*=6.35

Hz, 1H), 7.10 - 7.21 (m, 3H), 7.29 - 7.36 (m, 1H), 7.39 - 7.46 (m, 1H), 7.57 (dd, $J=7.93, 1.10$ Hz, 1H), 7.94 - 8.00 (m, 1H). MS(ESI, m/z) 532.6 (M+H).

Preparation 48: 2'-{(R)-1-[(R)-3-(2-Cycloheptyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid ethyl ester



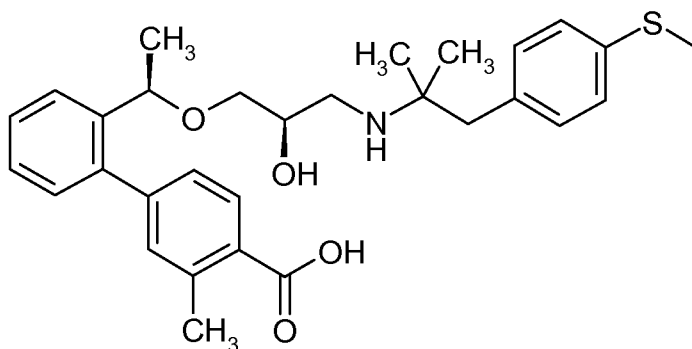
2-Cycloheptyl-1,1-dimethyl-ethylamine (Preparation 40, 309 mg) and 3-Methyl-2'-[(R)-1-[(R)-1-oxiranylmethoxy]-ethyl]-biphenyl-4-carboxylic acid ethyl ester (Preparation 12, 345 mg) were dissolved in trifluoroethanol (5 mL).
 10 The reaction mixture was stirred and heated in the microwave for 50 min at 100 °C. The reaction mixture was concentrated to dryness and purified by silica gel chromatography (5-10% MeOH/CH₂Cl₂) to afford the desired product as a brown oil (487 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.03 (s, 6H), 1.16 - 1.73 (m, 23H), 2.41 - 2.51 (m, 1H), 2.59 - 2.65 (m, 4H), 3.09 - 3.22 (m, 2H),
 15 3.61 - 3.72 (m, 1H), 4.37 (q, $J=7.29$ Hz, 2H), 4.42 - 4.52 (m, 1H), 7.08 - 7.18 (m, 3H), 7.29 (t, $J=7.22$ Hz, 1H), 7.40 (t, $J=7.22$ Hz, 1H), 7.55 (d, $J=8.00$ Hz, 1H), 7.94 (d, $J=8.39$ Hz, 1H).

Preparation of Compounds of Formula I

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Example 1

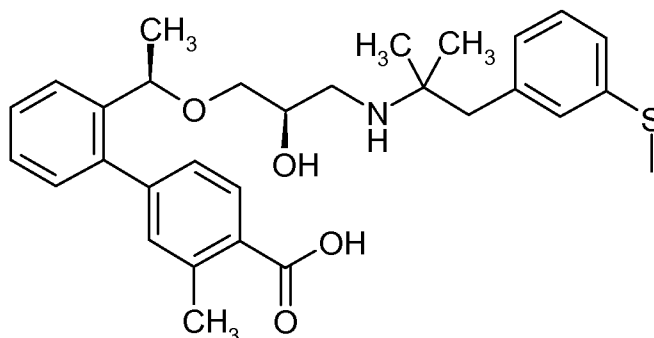
Preparation of 2'-{(R)-1-[(R)-3-[1,1-Dimethyl-2-(4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid



To a solution of 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester (Preparation 41, 8.5 g) in EtOH (160 mL) was added LiOH (48 mL, 2M aqueous solution) and the reaction was heated at 50 °C for 16 h. The solvent was removed *in vacuo*, water was added and the pH was adjusted to 6 by addition of citric acid (10% aq. solution). The mixture was extracted with EtOAc and the organic layer was washed with water (x2) and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. A solution of HCl (31 mL, 1M in Et₂O) was added and stirred to a gummy solid. Decanted the Et₂O away and the resulting solid was dried under reduced pressure to afford the desired product (6.5 g) as the HCl salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.26 (s, 6H), 1.33 (d, *J*=6.44 Hz, 3H), 2.44 (s, 3H), 2.61 (s, 3H), 2.84 - 3.00 (m, 3H), 3.14 - 3.26 (m, 3H), 3.81 - 3.96 (m, 1H), 4.52 (q, *J*=6.38 Hz, 1H), 7.12 - 7.26 (m, 7H), 7.29 - 7.36 (m, 1H), 7.39 - 7.47 (m, 1H), 7.56 (dd, *J*=7.81, 1.37 Hz, 1H), 7.93 - 7.99 (m, 1H). MS(ESI, *m/z*) 508.4 (M+H).

Example 2

Preparation of 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid

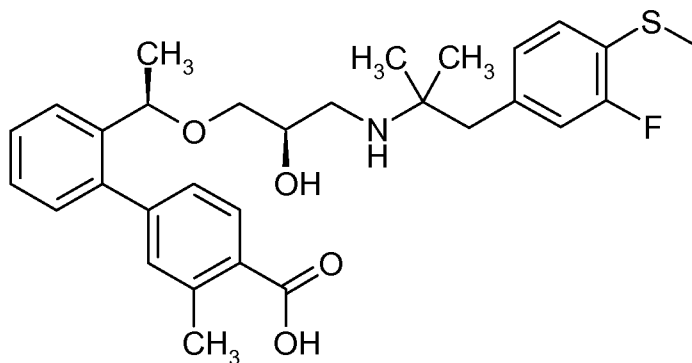


To a solution of 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester (Preparation 42, 375 mg) in EtOH (7 mL) was added LiOH (2.1 mL, 2M aqueous solution) and the reaction mixture was heated at reflux over 60 h. Solvent was removed *in vacuo* then water was added to the residue and the pH was adjusted to approximately 7 by addition of citric acid (10% aq. solution). The resulting precipitate was collected by filtration and dried under reduced pressure to afford the desired product (140 mg). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.25 (s, 6H), 1.31 (d, *J*=6.25 Hz, 3H), 2.44 - 2.51 (m, 5H), 2.84 - 2.94 (m, 3H), 3.08 - 3.25 (m, 4H), 3.74 - 3.84 (m, 1H), 4.51 - 4.60 (m, 1H), 6.96 - 7.05 (m, 3H), 7.10 - 7.21 (m, 3H), 7.23 - 7.32 (m, 2H), 7.34 - 7.42 (m, 1H), 7.47 - 7.55 (m, 2H). MS(ESI, *m/z*) 508.4 (M+H).

15

Example 3

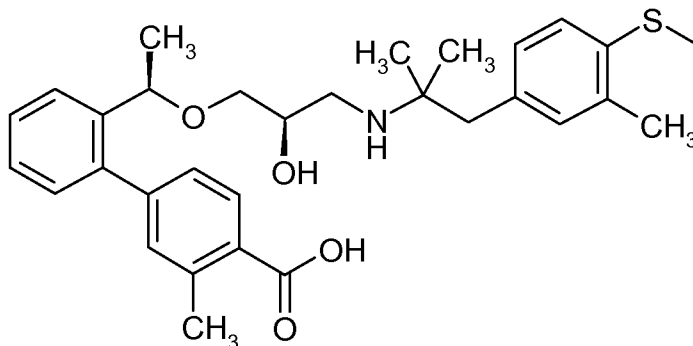
Preparation of 2'-((R)-1-((R)-3-[2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid



In a similar manner used for Example 1 excluding the HCl salt formation step, 2'-((R)-1-((R)-3-[2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid (7 g) was obtained from 2'-((R)-1-((R)-3-[2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid methyl ester (Preparation 43, 7.8 g). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.28 (s, 6H), 1.33 - 1.42 (m, 3H), 1.84 - 1.90 (m, 1H), 2.42 - 2.48 (m, 3H), 2.59 (s, 3H), 2.91 - 2.95 (m, 3H), 3.15 - 3.27 (m, 3H), 3.69 - 3.75 (m, 1H), 3.82 - 3.90 (m, 1H), 4.55 (q, *J*=6.25 Hz, 1H), 6.99 - 7.09 (m, 2H), 7.12 - 7.23 (m, 3H), 7.27 - 7.38 (m, 2H), 7.39 - 7.48 (m, 1H), 7.57 (dd, *J*=7.81, 1.17 Hz, 1H), 7.85 (d, *J*=8.59 Hz, 1 H).

Example 4

Preparation of 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid



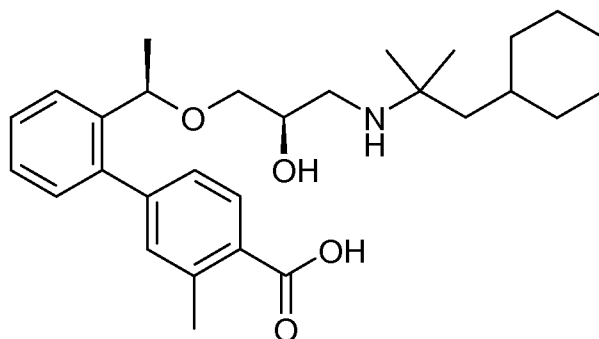
In a similar manner used for Example 1 excluding the HCl salt formation step, 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid (174 mg) was obtained from 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester (Preparation 44, 190 mg). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.28 (s, 6H), 1.32 (d, *J*=6.44 Hz, 3H), 2.28 (s, 3H), 2.44 (s, 3H), 2.62 (s, 3H), 2.86 - 3.04 (m, 3H), 3.15 - 3.27 (m, 3H), 3.81 - 3.96 (m,

1H), 4.52 (q, $J=6.96$ Hz, 1H), 6.99 - 7.14 (m, 2H), 7.14 - 7.27 (m, 4H), 7.29 - 7.40 (m, 1H), 7.40 - 7.50 (m, 1H), 7.56 (d, $J=7.61$ Hz, 1H), 7.96 (d, $J=8.40$ Hz, 1 H).

5

Example 5

Preparation of 2'-{(R)-1-[(R)-3-(2-Cyclohexyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid

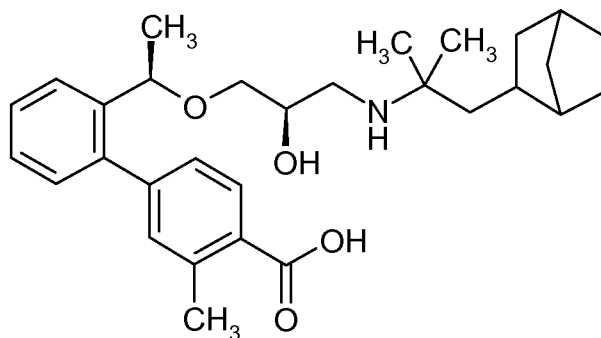


2'-{(R)-1-[(R)-3-(2-Cyclohexyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid methyl ester
(Preparation 45, 9 g, 18.8 mmol) was dissolved in EtOH (100 mL) and LiOH (56 mL, 100 mmol) was added. The solution was heated at reflux for 20 h then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with EtOAc and sat. aq. NH_4Cl until the pH was 7. The layers were separated and the aqueous was washed again with EtOAc. The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo* to afford a white residue. The white residue was slurried in 2-propanol / water and concentrated to dryness *in vacuo* to afford the desired product as a white solid (6.7 g). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.89 - 1.41 (m, 18H), 1.46 - 1.73 (m, 7H), 2.52 (s, 3H), 2.72 - 2.85 (m, 1H), 3.04 - 3.14 (m, 1H), 3.20 - 3.37 (m, 2H), 4.16 (br. s., 1H), 4.51 - 4.61 (m, 1H), 6.99 - 7.07 (m, 2 H), 7.13 (dd, $J=7.51, 1.27$ Hz, 1 H), 7.21 - 7.29 (m, 1 H), 7.31 - 7.40 (m, 1 H), 7.47 - 7.55 (m, 1 H), 7.73 (d, $J=7.03$ Hz, 1 H). HPLC : t_R 7.32 min.

25

Example 6

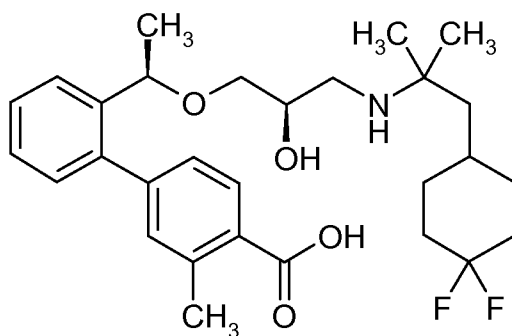
Preparation of 2'-{(R)-1-[(R)-3-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid



- 5 In a similar manner used for Example 5, 2'-{(R)-1-[(R)-3-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid (756 mg) was obtained from 2'-{(R)-1-[(R)-3-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid ethyl ester (Preparation 46, 891
- 10 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.06 - 1.33 (m, 9H), 1.35 - 1.60 (m, 12H), 1.73 - 1.84 (m, 1H), 1.89 - 1.95 (m, 1H), 2.18 (br. s., 1H), 2.53 (s, 3H), 2.73 - 2.84 (m, 1H), 3.13 - 3.21 (m, 1H), 3.20 - 3.28 (m, 1H), 3.29 - 3.38 (m, 1H), 4.24 (br. s., 1H), 4.53 - 4.62 (m, 1H), 7.02 - 7.10 (m, 2H), 7.11 - 7.21 (m, 2H), 7.21 - 7.31 (m, 1H), 7.38 (t, *J*=6.83 Hz, 1H), 7.52 (dd, *J*=7.91, 1.27 Hz, 1H), 7.82 (d, *J*=7.42 Hz, 1H). MS(ESI, *m/z*) 480.4 (M+H).
- 15

Example 7

Preparation of 2'-{(R)-1-[(R)-3-[2-(4,4-Difluoro-cyclohexyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid

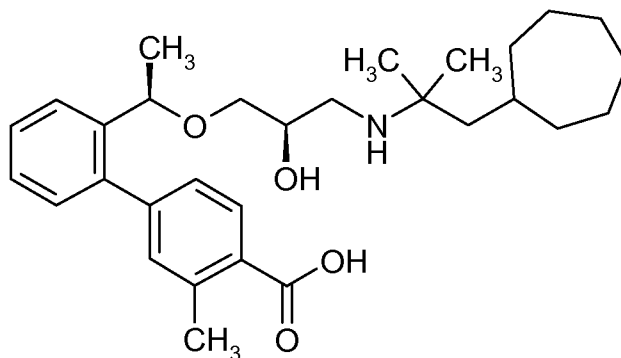


- 20 2'-{(R)-1-[(R)-3-[2-(4,4-Difluoro-cyclohexyl)-1,1-dimethyl-ethylamino]-2-

hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid ethyl ester (Preparation 47, 192 mg) in MeOH (1 mL) and LiOH (1.0 mL, 2N in water) was heated at 115 °C for 10 minutes in a microwave oven. The reaction mixture was neutralized with 1 N HCl solution (5.0 mL), evaporated to a minimum volume (1.5 mL), and the residue purified by reverse phase HPLC to afford the desired product (150 mg). ¹H NMR (500 MHz, CD₃OD) δ ppm 1.28 - 1.45 (m, 11H), 1.58 (br. s., 3H), 1.69 - 1.90 (m, 4H), 1.95 - 2.07 (m, 2H), 2.51 (s, 3H), 2.79 (dd, *J*=12.32, 9.64 Hz, 1H), 3.05 (dd, *J*=12.32, 2.56 Hz, 1H), 3.13 - 3.27 (m, 2H), 3.75 - 3.85 (m, 1H), 4.59 (q, *J*=6.18 Hz, 1H), 6.97 - 7.10 (m, 2H), 7.18 (d, *J*=7.57 Hz, 1H), 7.32 (t, *J*=7.32 Hz, 1H), 7.40 (t, *J*=7.32 Hz, 1H), 7.53 (dd, *J*=21.35, 7.69 Hz, 2H). MS(ESI, *m/z*) 504.6 (M+H).

Example 8

Preparation of 2'-{(R)-1-[(R)-3-(2-Cycloheptyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid



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In a similar manner used for Example 5, 2'-{(R)-1-[(R)-3-(2-Cycloheptyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid (268 mg) was obtained from 2'-{(R)-1-[(R)-3-(2-Cycloheptyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy]-ethyl}-3-methyl-biphenyl-4-carboxylic acid ethyl ester (Preparation 48, 487 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.20 - 1.75 (m, 26H), 2.55 (s, 3H), 2.76 - 2.88 (m, 1H), 3.14 (d, *J*=12.50 Hz, 1H), 3.24 - 3.39 (m, 2H), 4.22 (br. s., 1H), 4.53 - 4.63 (m, 1H), 7.00 - 7.08 (m, 1H), 7.13 - 7.19 (m, 1H), 7.23 - 7.31 (m, 2H), 7.38 (t, *J*=7.32 Hz, 1H), 7.53 (d, *J*=8.00 Hz, 1H), 7.78 (d, *J*=6.83 Hz, 1H).

25

The following table provides FLIPR IC₅₀ data for the specified Examples. The IC₅₀s are reported as micromolar concentration with n being the number of times the particular compound was assayed.

5

Table of FLIPR assay data

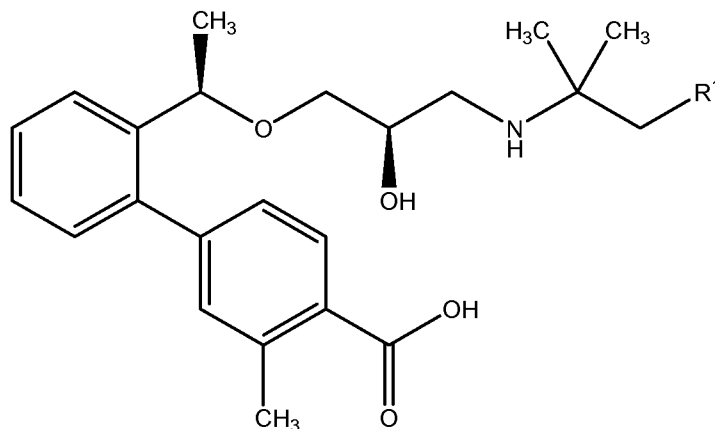
Example	n =	FLIPR IC ₅₀ (uM)
1	3	0.0258
2	11	0.0417
3	10	0.0223
4	2	0.0264
5	8	0.0298
6	2	0.0439
7	4	0.0689
8		0.0237

All documents cited in this application, including scientific publications, patents and patent applications, are hereby incorporated by reference in their entirety.

CLAIMS

What is claimed is:

- 5 1. A compound of formula I



wherein

- 10 R¹ is methylsulfanyl-phenyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl, wherein said methylsulfanyl-phenyl is optionally substituted on phenyl with methyl or fluoro and said cyclohexyl is optionally substituted with two fluoro;
or a pharmaceutically acceptable salt thereof.

15

2. The compound according to claim 1, wherein R¹ is methylsulfanyl-phenyl, 3-fluoro-4-methylsulfanyl-phenyl, 3-methyl-4-methylsulfanyl-phenyl, cyclohexyl, difluorocyclohexyl, cycloheptyl or bicyclo[2.2.1]hept-2-yl; or a pharmaceutically acceptable salt thereof.

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3. The compound according to claim 2, wherein R¹ is 4-methylsulfanyl-phenyl, 3-methylsulfanyl-phenyl, 3-fluoro-4-methylsulfanyl-phenyl or 3-methyl-4-methylsulfanyl-phenyl; or a pharmaceutically acceptable salt thereof.

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4. The compound according to claim 2, wherein R¹ is cyclohexyl or 4,4-difluorocyclohexyl; or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 2, wherein R¹ is cycloheptyl or bicyclo[2.2.1]hept-2-yl; or a pharmaceutically acceptable salt thereof.

5 6. A compound selected from
2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
10 2'-((R)-1-((R)-3-[2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
15 2'-((R)-1-((R)-3-(2-Cyclohexyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-[2-(4,4-Difluoro-cyclohexyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or
20 2'-((R)-1-((R)-3-(2-Cycloheptyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 6 which is 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 6 which is 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy)-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or a pharmaceutically acceptable

salt thereof.

9. The compound according to claim 6 which is 2'-((R)-1-((R)-3-[2-(3-Fluoro-4-methylsulfanyl-phenyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or
5 2'-((R)-1-((R)-3-[1,1-Dimethyl-2-(3-methyl-4-methylsulfanyl-phenyl)-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 6 which is 2'-((R)-1-((R)-3-(2-Cyclohexyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
10 2'-((R)-1-((R)-3-(2-Bicyclo[2.2.1]hept-2-yl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid;
2'-((R)-1-((R)-3-[2-(4,4-Difluoro-cyclohexyl)-1,1-dimethyl-ethylamino]-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or
15 2'-((R)-1-((R)-3-(2-Cycloheptyl-1,1-dimethyl-ethylamino)-2-hydroxy-propoxy}-ethyl)-3-methyl-biphenyl-4-carboxylic acid; or a pharmaceutically acceptable salt thereof.

20 11. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, adjuvant or diluent.

12. A method of treating a disease or disorder in a patient, the
25 method comprising administering to said patient in need thereof a therapeutically effective amount of a compound according to claim 1, wherein said disease or disorder is selected from the group consisting of hypoparathyroidism, osteoporosis, osteopenia, periodontal disease, Paget's disease, bone fracture, osteoarthritis, rheumatoid arthritis and humoral
30 hypercalcemia of malignancy.

13. The method according to claim 12 wherein the disease or disorder is osteoporosis.

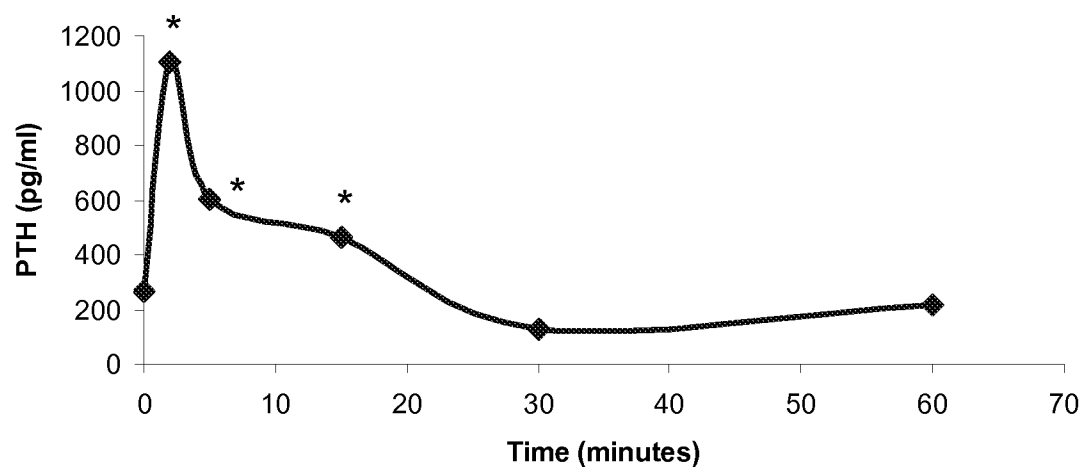
14. A method of treating a disease or disorder in a patient, the
5 method comprising administering to said patient in need thereof a
therapeutically effective amount of a pharmaceutical composition according
to claim 11, wherein said disease or disorder is selected from the group
consisting of hypoparathyroidism, osteoporosis, osteopenia, periodontal
disease, Paget's disease, bone fracture, osteoarthritis, rheumatoid arthritis
10 and humoral hypercalcemia of malignancy.

15. The method according to claim 14 wherein the disease or disorder is osteoporosis.

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FIG. 1

PTH vs. time following 1 mg/kg iv bolus of the tested compound



INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2010/050911

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C217/28 C07C323/32 A61K31/192 A61P19/00 A61P29/00
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 619 180 A1 (JAPAN TOBACCO INC [JP]) 25 January 2006 (2006-01-25) claims 1,19,23 paragraph [0001] page 64, table 8, compound 1-20	1-15
A	WO 00/45816 A1 (SMITHKLINE BEECHAM CORP [GB]; LAGO AMPARO M [US]) 10 August 2000 (2000-08-10) cited in the application page 2, line 18 - page 4, line 12	1,6,11, 12,14



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

12 April 2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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