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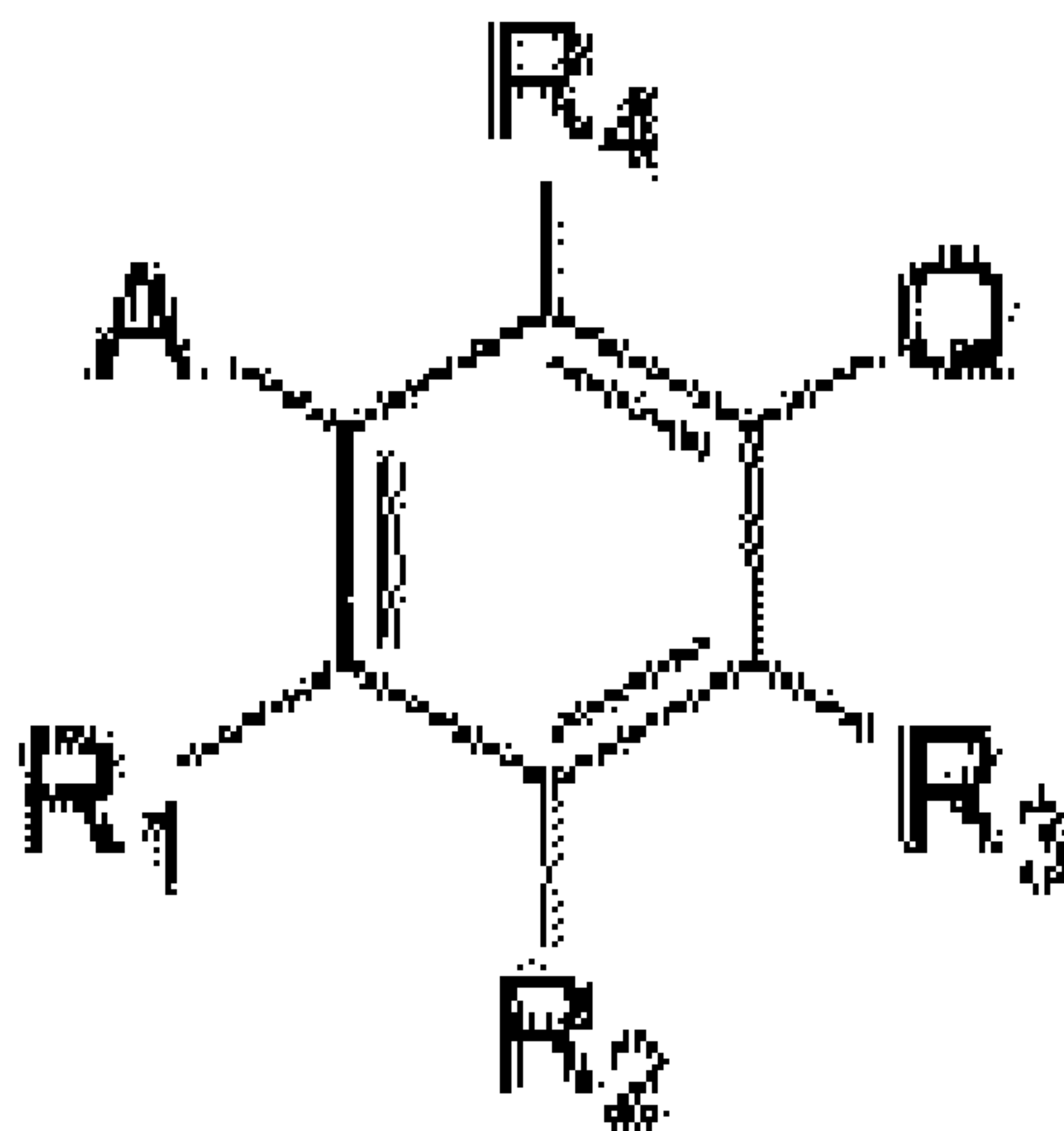
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(54) Titre : COMPOSES AROMATIQUES SUBSTITUES ET COMPOSITIONS PHARMACEUTIQUES POUR LA
PREVENTION ET LE TRAITEMENT DE L'OSTEOPOROSE

(54) Title: SUBSTITUTED AROMATIC COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS FOR THE
PREVENTION AND TREATMENT OF OSTEOPOROSIS



Formula I

(57) Abrégé/Abstract:

The present invention concerns the use of compounds for preventing and/or treating osteoporosis, for stimulating bone formation, for stimulating bone remodeling, for stimulating the differentiation and mineralization of osteoblasts, for inhibiting bone resorption



(57) Abrégé(suite)/Abstract(continued):

and for modulating serum level of adiponectin in a subject. These uses have been found for compounds represented by Formula I and pharmaceutically acceptable salts thereof. wherein A is C₅ alkyl, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4; R₁ is H, F or OH; R₂ is H, F, OH, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4; R₃ is H, F, OH or CH₂Ph; R₄ is H, F, or OH; Q is 1) (CH₂)_mC(O)OH wherein m is 1 or 2, 2) CH(F)-C(O)OH, 3) CF₂-C(O)OH or 4) C(O)-C(O)OH.

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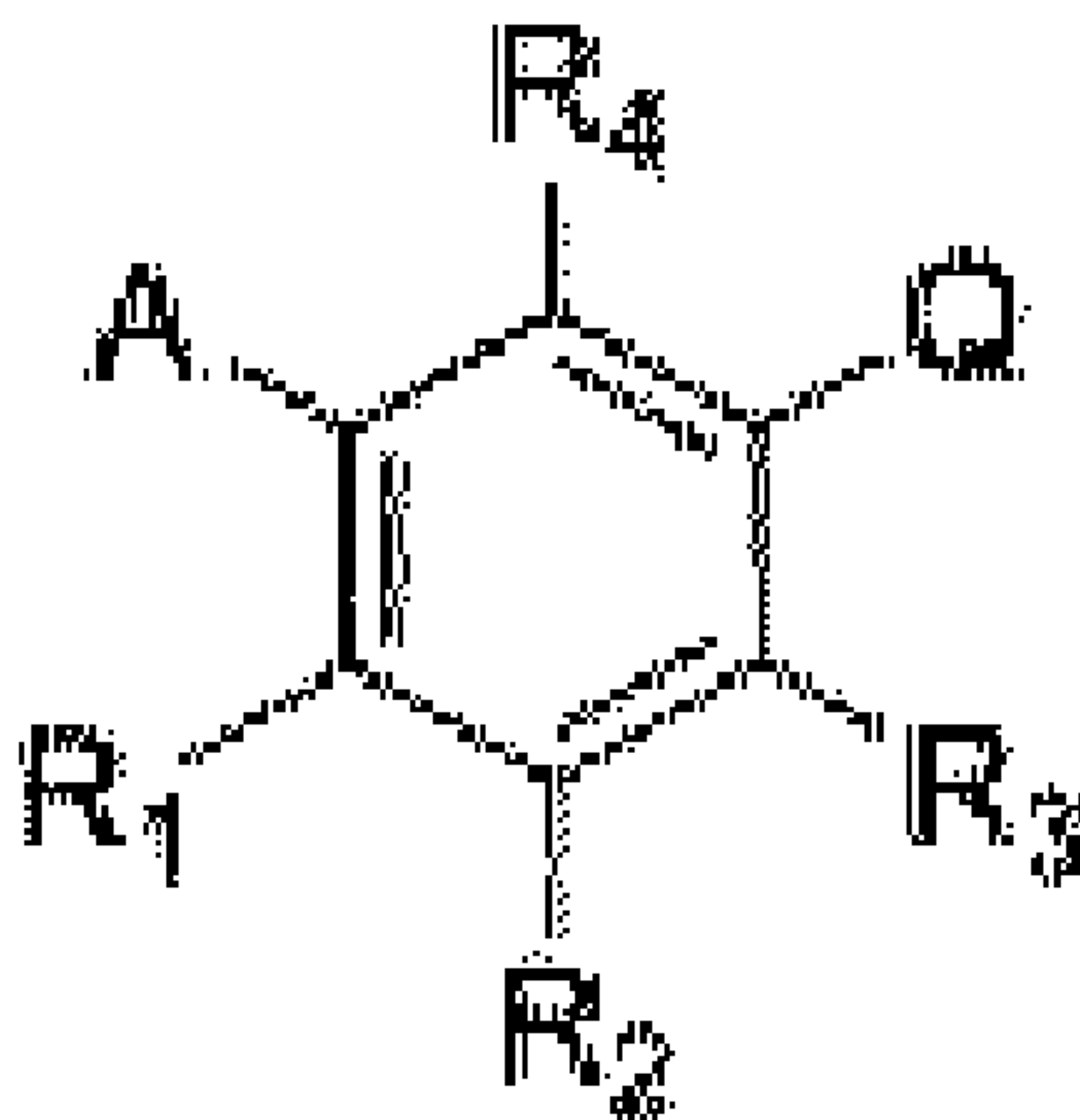
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(54) Title: SUBSTITUTED AROMATIC COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS FOR THE PREVEN-
 TION AND TREATMENT OF OSTEOPOROSIS

**Formula I**

(57) Abstract: The present invention concerns the use of compounds for preventing and/or treating osteoporosis, for stimulating bone formation, for stimulating bone remodeling, for stimulating the differentiation and mineralization of osteoblasts, for inhibiting bone resorption and for modulating serum level of adiponectin in a subject. These uses have been found for compounds represented by Formula I and pharmaceutically acceptable salts thereof. wherein A is C₅ alkyl, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4; R₁ is H, F or OH; R₂ is H, F, OH, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4; R₃ is H, F, OH or CH₂Ph; R₄ is H, F, or OH; Q is 1) (CH₂)_mC(O)OH wherein m is 1 or 2, 2) CH(F)-C(O)OH, 3) CF₂-C(O)OH or 4) C(O)-C(O)OH.

SUBSTITUTED AROMATIC COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS FOR THE PREVENTION AND TREATMENT OF OSTEOPOROSIS

FIELD OF INVENTION

[001] The present invention relates to the field of medicine. Particular aspects of the invention relates to compounds, pharmaceutical compositions and uses thereof for the prevention or treatment of osteoporosis.

BACKGROUND OF INVENTION

[002] Bone is a highly dynamic tissue which is constantly turned over and replaced by a process which is known as bone remodeling. The ability to remodel bone ensures that old bone or damaged tissue is renewed and that the architecture of the skeleton can most efficiently adapt to mechanical demands. Bone remodeling commences with the removal of old bone by osteoclast cells in a resorption phase lasting several weeks. Osteoblasts then migrate to the erosion cavity and deposit new bone over three or four months. In the normal skeleton, bone remodeling couples the activities of the osteoclast and osteoblast cells such that the amount of new bone laid down is equal to the bone that was removed, thereby maintaining a healthy bone mass. However, if bone resorption exceeds bone formation, there is a net loss of bone. The resultant condition, osteoporosis, is characterized by excessive bone resorption and subsequent low bone mass with increased bone fragility.

[003] Osteoporosis is the general term used for diseases of the bone of diverse etiology that are characterized by a reduction in the mass of bone per unit volume to a level below that required for adequate mechanical support (Krane, S.M. *et al.*, "Metabolic Bone Disease" in Harrison's Principles of Internal Medicine, page 1889, Edition 11 (1987)). One form of osteoporosis is senile osteoporosis which is responsible for a large portion of the health dollars spent on the geriatric population (Resnick, N.M. *et al.* "Senile Osteoporosis Reconsidered", JAMA 261, 1025–1029 (1989)). The two other most common forms of osteoporosis are pre- or postmenopausal osteoporosis and corticosteroid induced osteoporosis. Patients with chronic kidney disease (CKD) may develop bone diseases which can include osteoporosis as a result of changes in mineral metabolism and subsequent alterations in bone structure. Most often these changes worsen with progressive loss of kidney function. Indeed, and as summarized in the paragraph below, a number of pathological conditions can occur which increase the probability of the development of osteoporosis. Osteomalacia-like osteoporosis shares many of the symptoms of

osteoporosis such as loss of calcium. Osteopenia refers to a lower than normal bone density but not as low as that observed in osteoporosis. It is considered to be a precursor to osteoporosis. Osteogenesis imperfecta is a congenital bone disorder characterized by brittle bones prone to bone fracture. Osteopetrosis is a rare inherited disease whereby the bones harden but are more brittle than normal. Osteonecrosis is a disease that causes bone death and collapse due to loss of blood supply to the bone. Paget's disease of bone is caused by excessive degradation and formation of bone followed by disorganized bone remodeling.

[004] As is known, various diseases and conditions may cause osteoporosis: autoimmune diseases which include rheumatoid arthritis, lupus and multiple sclerosis; gastrointestinal disorders which include celiac disease, inflammatory bowel disease, gastrectomy and gastrointestinal by-pass procedures; endocrine/hormonal disorders which include diabetes, hyperparathyroidism, thyrotoxicosis and Cushing's syndrome; hematological disorders which include leukemia, lymphoma, multiple myeloma, sickle cell disease anemia (bone marrow disorders) and thalassemia; cancer which includes breast and prostate cancer; neurological disorders which include depression, Parkinson's disease and spinal cord injury; organ diseases which include lung (COPD, emphysema), liver and chronic kidney diseases; ankylosing spondylitis; AIDS/HIV; bone fracture; poor diet which includes eating disorders and malnutrition; and menopause (Pre-Menopause and Post-Menopause).

[005] Historically, the osteoblast has been considered the master cell in the control of osteoclast development and, therefore, bone resorption. Now the interactions between cells of the immune system and bone cells have redefined the thinking on the regulation of bone resorption. The identification of the osteoclast and its role in bone destruction permits targeted therapy to reduce its resorptive capacity. Such therapies include the use of agents that can interfere with receptor activator of NF κ B ligand (RANKL), one of the key cytokines promoting osteoclast differentiation. This may be achieved through the use of recombinant Fc osteoprotegerin (Fc-OPG) or a humanised anti-RANKL antibody (Denosumab) that is being developed by Amgen. Both products have demonstrated efficacy in preclinical models of bone loss, with Denosumab progressing through clinical trials; Fc-OPG was withdrawn from clinical trials due to immune side effects. Other inhibitors of osteoclast activity include the bisphosphonates, c-src inhibitors, cathepsin K inhibitors and inhibitors of the chloride channel CLC7 (Gillespie, M.T. (2007) Arthritis Research & Therapy, Volume 9, No. 2, pp. 103-105). Notably, bisphosphonates have been successful in limiting bone loss in rodent models of arthritis, although it should be noted that the nitrogen-containing bisphosphonates (which include alendronate, ibandronate, pamidronate and zoledronate) enhance

proliferation of γ/δ T lymphocytes, while non nitrogen-containing bisphosphonates (for example, clondronate) do not (Gillespie, M.T. (2007) Arthritis Research & Therapy, Volume 9, No. 2, pp. 103-105).

[006] Most current treatment strategies attempt to reduce the bone loss of calcium in order to retard the onset of osteoporosis (Dawson-Hughes, B. *et al.*, "A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women" NEJM 323, 878–883 (1990)). As such, the most commonly used compounds for treatment of osteoporosis belong to the bisphosphonate drug class. They avidly bind to bone and are internalized by osteoclasts to inhibit bone resorption. Bisphosphonates may be administered by oral or intravenous routes. Alendronate (Fosmax™, oral) is the most commonly prescribed drug for the treatment of postmenopausal osteoporosis. Other US FDA approved bisphosphonates are Risedronate (Actonel™, oral), Etidronate (Didronel™, oral), Zoledronate (Aclasta™, infusion) and Pamidronate (Aredial™, infusion). Oral bisphosphonates are associated with gastrointestinal side effects. Side effects associated with bisphosphonates in general include unusual fractures in the femur (thigh bone) rather than at the head of the bone, which is the most common site of fracture. However, these fractures which are associated with long-term use of bisphosphonates are rare when compared to the frequency of common hip fractures associated with osteoporosis. Nonetheless, there are concerns that long-term bisphosphonate use can result in over-suppression of bone turnover with subsequent difficulty in the healing of micro-cracks in the bone, propagation of these cracks and ultimately atypical fractures. Additionally, an increased risk of oesophageal cancer is associated with long-term use of oral bisphosphonates. Also, bisphosphonate use, specifically Zoledronate and Alendronate, have been reported as a risk factor for atrial fibrillation. Finally, intravenous administered bisphosphonates for the treatment of cancer have been associated with osteonecrosis of the jaw.

[007] Parathyroid hormone (1-84 PTH) plays a central role in calcium homeostasis and, upon intermittent administration, an anabolic effect on bone remodeling. Teriparatide, approved by the US FDA (Forteo), is a recombinant form of a portion (amino acids 1-34) of PTH used for the treatment of osteoporosis in men and postmenopausal women who are at a high risk of a bone fracture. It may find some use off-label to speed healing of a bone fracture. Teriparatide enhances osteoblast formation and prevents osteoblast apoptosis. However, in spite of the anabolic effect of Teriparatide on bone, use for the treatment of osteoporosis has been guarded due to the associated high incidence of osteosarcoma in animal models. Therefore, Teriparatide is not recommended for use in patients with increased risk of bone tumors.

[008] As a result of the potential adverse effects of long-term hormone replacement therapy (cardiovascular disorders, uterine and cancers, etc.), it is no longer recommended for the prevention of osteoporosis. As such, this has been somewhat replaced by the introduction of the Selective Estrogen Receptor Modulators (SERM) class of drugs, as exemplified by Tamoxifen and Raloxifene. Raloxifene hydrochloride was approved by the US FDA (Evista) for prevention of osteoporosis in postmenopausal women. In fact, a direct comparison with daily oral Alendronate (bisphosphonate) demonstrated that daily oral Raloxifene was equally effective at reducing the risk of bone fracture. However, side effects of Raloxifene include an increased risk of fatal stroke and venous thromboembolism. Other adverse effects include leg swelling, difficulty breathing and vision changes.

[009] Denosumab is a fully human monoclonal antibody for the treatment of osteoporosis, treatment-induced bone loss, bone metastases, multiple myeloma and giant cell tumor of bone. Denosumab was approved by the US FDA (Prolia) for prevention of osteoporosis in postmenopausal women and (Xgeva) for the prevention of skeleton-related events in patients with bone metastases from solid tumors. This antibody binds to and inhibits RANKL (RANK ligand), a protein that acts as the primary signal for bone removal in many bone loss conditions. Osteoclast cell precursors (pre-osteoclasts) express RANK receptors. Subsequent binding of RANKL induces activation of the receptor and maturation of the pre-osteoclasts into osteoclasts. However, side effects of Denosumab include infections of the urinary and respiratory tracts, cataracts, constipation, rash and joint pain.

[0010] As may be seen from the above, multiple options are available for the prevention and/or treatment of osteoporosis but implicit with this choice is the fact that there is no universal drug available for the prevention and/or treatment of osteoporosis. As is also evident from the above, each of the cited treatment options is accompanied by multiple side effects. Indeed, the above drugs approved for human use and side effects are well documented in the scientific literature. For example, a relatively recent review article on the subject of osteoporosis and current therapies and their side effects is, "Osteoporosis – a current view of pharmacological prevention and treatment" Das, S. Crockett, J.C. Drug Design, Development and Therapy 7, 435–448 (2013). As such, a need exists for a more universal, safer (especially in view of increased longevity and hence increased duration of drug administration) drug for the prevention and/or treatment of osteoporosis. Therefore there is a need for new treatment methods.

[0011] US patent No. 6,372,728 (2002) assigned to AstraZeneca AB describes an improved oral formulation of bisphosphonates, e.g. Alendronate. According to this patent, the oral bioavailability of many bisphosphonates is 1%-10% between meals. The improved formulation employs a medium-chain glyceride absorption enhancer. US patent No. 5,070,108 (1991) assigned to the University of Pennsylvania claims treatment of osteoporosis with a retinoid such as etretinate. Although initially approved by the FDA for the treatment of psoriasis, etretinate has been removed from the North American market due to the high risk of birth defects. Odanacatib is a novel drug, an inhibitor of the enzyme cathepsin K, which is under clinical development for the treatment of osteoporosis and bone metastasis.

[0012] The present invention aims to address the need for new treatment methods, compounds and pharmaceutical compositions for patients afflicted by, or susceptible to, osteoporosis.

[0013] Additional features of the invention will be apparent from a review of the discussion, figures and description of the invention herein.

BRIEF SUMMARY OF THE INVENTION

[0014] General aspects of the invention relate to the pharmaceutical use of compounds according to Formula I as defined herein and pharmaceutically acceptable salts thereof.

[0015] Particular aspects of the invention relates to the use of compounds and compositions for the prevention and/or treatment of osteoporosis. Certain aspects concern compounds according to Formula I as defined herein and pharmaceutically acceptable salts thereof, as prophylactically effective and/or therapeutically effective agents against various forms of osteoporosis in subjects. According to particular embodiments, the subject is afflicted by, or susceptible to be afflicted by, bone loss, bone fracture and the like.

[0016] According to particular embodiments, the compounds and compositions of the invention are useful for stimulating bone formation and/or for stimulating bone remodeling and/or for stimulating the differentiation and mineralization of osteoblasts and/or for inhibiting bone resorption.

[0017] A particular aspect of the invention relates to a method for the prevention and/or treatment of osteoporosis, comprising the step of administering to a subject in need thereof a compound represented by Formula I, or a pharmaceutical acceptable salt thereof, as defined herein. In some embodiments, the osteoporosis is selected from the group consisting of post-menopausal

osteoporosis (primary type 1), primary type 2 osteoporosis, secondary osteoporosis abnormally high osteoclastogenesis, osteomalacia-like osteoporosis, osteopenia, osteogenesis imperfecta, osteopetrosis, osteonecrosis, Paget's disease of bone, hypophosphatemia and combinations thereof. In particular embodiment the osteoporosis is post-menopausal osteoporosis (primary type 1), primary type 2 osteoporosis or secondary osteoporosis. In more specific embodiments, the osteoporosis is post-menopausal osteoporosis (primary type 1).

[0018] The invention also relates to treatment methods wherein the compounds of the invention exhibit one or more of the following biological activities in a subject: inhibition of osteoclastogenesis; stimulation of interleukin-12 (IL-12) production by a stimulated osteoclast precursor cell; reduction of acid phosphatase activity in bone cells (demonstrates a reduction in osteoclastogenesis); reduction of the Receptor activator of NF- κ B ligand (RANKL) over Osteoprotegerin (OPG) ratio (RANKL/ OPG ratio) in bone, which indicates a reduction in osteoclastogenesis; increase of collagen content in bone; and modulation (e.g. increase) of the serum level of adiponectin.

[0019] According to another aspect, aspect of the invention relates to a method for preventing and/or reducing bone loss, comprising the step of administering to a subject in need thereof a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein. In one embodiment, the administration of the compound reduces loss of calcium. In one embodiment, the subject is afflicted by or susceptible of osteoporosis. In one embodiment, the subject is a postmenopausal women.

[0020] According to another aspect, the invention relates to a method for inhibiting osteoclastogenesis, comprising contacting an osteoclast precursor cell with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, wherein the compound inhibits differentiation of the precursor cell into an osteoclast cell.

[0021] According to another aspect, the invention relates to a method for stimulating interleukin-12 (IL-12) production by a stimulated osteoclast precursor cell, comprising contacting said stimulated osteoclast precursor cell with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, wherein an increased IL-12 production is measurable in presence of the compound.

[0022] According to another aspect, the invention relates to a method for reducing acid phosphatase activity in bone cells, comprising contacting the bone cells with a compound

represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, wherein a reduced phosphatase activity is measurable in presence of the compound.

[0023] According to another aspect, the invention relates to a method for reducing expression and/or activity of receptor activator of NF- κ B ligand/Osteoprotegerin ratio (RANKL /OPG ratio) in bone cells, comprising contacting the bone cells with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein.

[0024] According to another aspect, the invention relates to a method for increasing collagen content in bone, comprising contacting the bone with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein.

[0025] According to another aspect, the invention relates to a method for stimulating bone formation and/or for stimulating bone remodeling and/or for stimulating the differentiation and mineralization of osteoblasts and/or for inhibiting bone resorption, comprising contacting osteoblasts in said bone with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein.

[0026] According to another aspect, the invention relates to a method for modulating serum level of adiponectin in a subject, comprising the step of administering to a subject in need thereof a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein. In one embodiment, the subject is obese and/or diabetic.

[0027] Additional aspects of the invention relates to the methods mentioned hereinabove, further comprising the step of administering concomitantly a drug selected from the group consisting of: bisphosphonates, Odanacatib, Alendronate, Risedronate, Etidronate, Zoledronate, Pamidronate, Teriparatide, Tamoxifen, Raloxifene, and Denosumab.

[0028] Another related aspect of the invention relates to pharmaceutical compositions comprising compounds of Formula I for the manufacture of a medicament, e.g. a medicament for the prevention and/or treatment of osteoporosis. One particular example is a pharmaceutical composition for preventing or treating osteoporosis, comprising a compound represented by Formula I as defined herein, and a pharmaceutically acceptable carrier. Another particular example is a pharmaceutical composition for use in preventing or treating osteoporosis, comprising a compound as defined in Table 1, and more particularly, a pharmaceutical composition comprising Compound I and/or Compound XXXI. Related aspect concerns methods

for the prevention and/or treatment of osteoporosis, comprising administering to a patient a therapeutically effective amount of a pharmaceutical composition as defined herein.

[0029] According to another aspect, the invention relates to a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein or to a composition comprising the same, for use in the prevention and/or treatment of osteoporosis.

[0030] Further aspects of the invention will be apparent to a person skilled in the art from the following description, claims, and generalizations herein.

BRIEF DESCRIPTION OF THE FIGURES

[0031] **Figure 1** is a panel with pictures illustrating the effect of Compound I on LPS-induced osteoclastogenesis in RAW264.7 cells, according to Example 2.

[0032] **Figure 2** is a bar graph demonstrating that Compound I induces the production of IL-12 in LPS-stimulated RAW264.7 cells, according to Example 2.

[0033] **Figure 3** is a line graph demonstrating the effect of Compound I on body weight of ovariectomized (OVX) rats, according to Example 3.

[0034] **Figure 4** a panel with bar graphs demonstrating the effect of Compound I on calcium in urine of ovariectomized (OVX) rats, according to Example 4.

[0035] **Figure 5** a panel with bar graphs demonstrating the effect of Compound I on acid phosphatase activity in serum of ovariectomized (OVX) rats, according to Example 4.

[0036] **Figure 6** is a bar graph demonstrating the effect of Compound I on RANKL/OPG mRNA expression of osteoclast marker in ovariectomized (OVX) rat tibia, according to Example 4.

[0037] **Figure 7** is a bar graph demonstrating the effect of Compound I on collagen content in metaphyse of rat's femur, according to Example 4.

[0038] **Figure 8** is a panel with pictures illustrating the effect of Compound I on collagen content in metaphyse of rat's femur, according to Example 4.

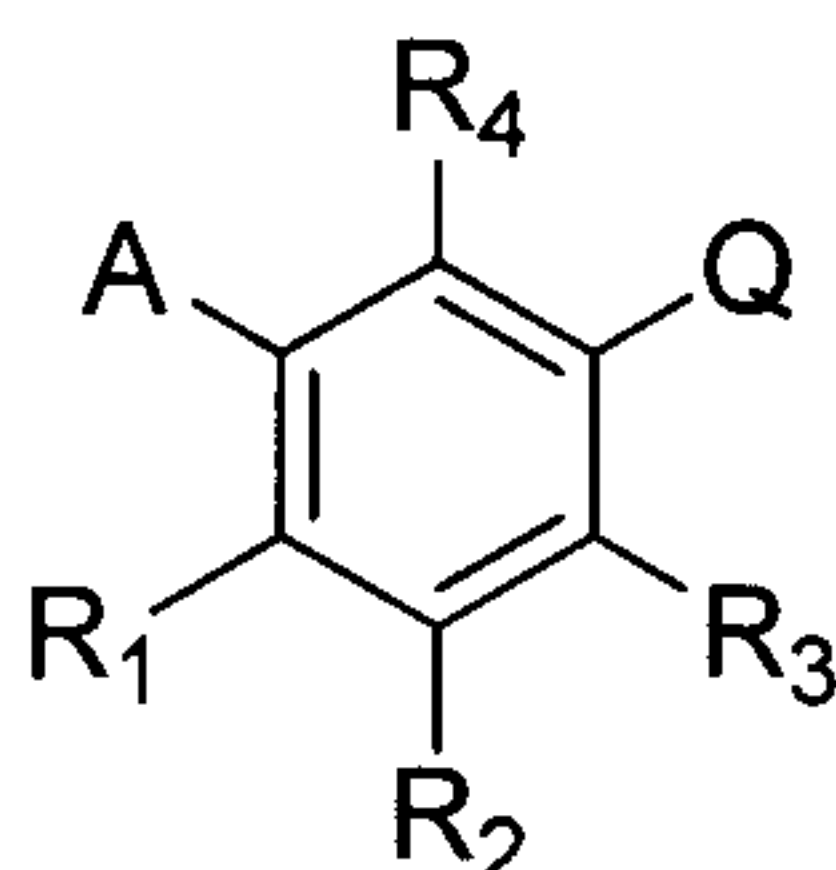
[0039] **Figure 9** is a dot graph demonstrating that Compound XIV increases serum adiponectin level, a marker of modulation of bone formation and remodeling, according to Example 5.

DETAILED DESCRIPTION OF THE INVENTION

The present discloses compounds of Formula I, pharmaceutically acceptable salts thereof, compositions comprising same and uses thereof. Various embodiments of the present invention include:

A) Compounds of the invention

[0040] According to one aspect, the invention concerns the pharmaceutical uses of a compound represented by **Formula I**, or a pharmaceutically acceptable salt thereof:



Formula I

wherein

A is C₅ alkyl, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4; or is preferably C₅ alkyl, C₅ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3; or is preferably C₆ alkyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 4; or is preferably straight chain C₅ alkyl, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4; or is preferably straight chain C₅ alkyl, C₅ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3;

R₁ is H, F or OH; or is preferably H or OH;

R₂ is H, F, OH, C₅ alkyl, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4; or is preferably H, F, OH, C₅ alkyl, C₅ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3; or is preferably H, F, OH, C₆ alkyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 4; or is preferably H, F, OH, straight chain C₅ alkyl, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4; or is preferably H, F, OH, straight chain C₅ alkyl, C₅ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3; or is preferably H, OH, F or C₅ alkyl; or is preferably H, OH, F or straight chain C₅ alkyl;

R₃ is H, F, OH or CH₂Ph; or is preferably H, F or OH; or is preferably H or OH;

R₄ is H, F or OH; or is preferably H or OH;

Q is

- 1) (CH₂)_mC(O)OH wherein m is 1 or 2,
- 2) CH(F)-C(O)OH,
- 3) CF₂-C(O)OH, or
- 4) C(O)-C(O)OH.

[0041] According to a particular embodiment, A is C₅ alkyl or C₆ alkyl.

[0042] According to a particular embodiment, R₁ is H or OH.

[0043] According to a particular embodiment, R₂ is H, F, OH, C₅ alkyl or C₆ alkyl.

[0044] According to a particular embodiment, R₃ is H or OH.

[0045] According to a particular embodiment, R₄ is H or OH.

[0046] According to a particular embodiment, Q is:

- 1) (CH₂)_mC(O)OH wherein m is 1 or 2,
- 2) CH(F)-C(O)OH, or
- 3) CF₂-C(O)OH.

[0047] According to a particular embodiment, Q is:

- 1) (CH₂)_mC(O)OH wherein m is 1,
- 2) CH(F)-C(O)OH,
- 3) CF₂-C(O)OH, or
- 4) C(O)-C(O)OH.

[0048] According to a particular embodiment, Q is:

- 1) (CH₂)_mC(O)OH wherein m is 1,
- 2) CH(F)-C(O)OH, or
- 3) CF₂-C(O)OH.

[0049] According to a particular embodiment, Q is (CH₂)_mC(O)OH where m is 1 or 2.

[0050] According to another embodiment, the compound is of Formula I, wherein A is C₅ alkyl or C₆ alkyl; R₁ is H, F or OH; R₂ is H, F, OH, C₅ alkyl or C₆ alkyl; R₃ is H, OH or CH₂Ph; R₄ is H, F or OH; and Q is (CH₂)_mC(O)OH where m is 1 or 2.

[0051] According to another embodiment, the compound is of Formula I; wherein A is C₅ alkyl; R₁ is H; R₂ is H or C₅ alkyl; R₃ is H; R₄ is H; and Q is (CH₂)_mC(O)OH where m is 1.

[0052] Compounds of Formula I corresponding to any combinations of A, Q, R₁, R₂, R₃ and R₄ or a particular or preferred embodiment thereof are expressly aimed by the present invention.

[0053] As used herein, the term “alkyl” is intended to include a straight chain saturated aliphatic hydrocarbon group having the specified number of carbon atoms in a linear arrangement.

[0054] As used herein, the term, “alkenyl” is intended to mean unsaturated straight chain hydrocarbon groups having the specified number of carbon atoms therein, and in which at least two of the carbon atoms are bonded to each other by a double bond, and having either E or Z regiochemistry and combinations thereof.

[0055] Examples of compounds of Formula I include, but are not limited to, Compounds I to XXIV listed in **Table 1** hereinbelow. In a preferred embodiment, the compound is represented by the acid form or a pharmaceutically acceptable salt of any one of Compounds I to XXIV.

Table 1: Representative compounds of Formula I

Compound	Structure
I	
II	
III	
IV	
V	
VI	
VII	

Compound	Structure
VIII	
IX	
X	
XI	
XII	
XIII	
XIV	
XV	
XVI	
XVII	
XVIII	
XIX	
XX	

Compound	Structure
XXI	
XXII	
XXIII	
XXIV	

[0056] The Applicants have described elsewhere compounds whose structure is related to the structure of some of the compounds of the present invention. Reference is made for instance to the compounds disclosed international PCT patent publications Nos WO 2010/127448, WO 2010/127440 and WO 2014/138906 which are incorporated herein by reference in their entirety. Accordingly, in particular embodiments any one or all the Compounds disclosed these PCT applications is(are) excluded from the scope of the present invention.

Salts

[0057] As used herein, the term “pharmaceutically acceptable salt” is intended to mean base addition salts. Example of pharmaceutically acceptable salts are also described, for example, in Berge *et al.*, “Pharmaceutical Salts”, *J. Pharm. Sci.* 66, 1-19 (1977). Pharmaceutically acceptable salts may be synthesized from the parent agent that contains an acidic moiety, by conventional chemical methods. Generally, such salts are prepared by reacting the free acid forms of these agents with a stoichiometric amount of the appropriate base in water or in an organic solvent, or in a mixture of the two. Salts may be prepared *in situ*, during the final isolation or purification of the agent or by separately reacting a purified compound of the invention in its free acid form with the desired corresponding base, and isolating the salt thus formed.

[0058] The pharmaceutically acceptable salt of the compounds of Formula I may be selected from the group consisting of base addition salts of sodium, potassium, calcium, magnesium, lithium, ammonium, manganese, zinc, iron, or copper. In preferred embodiments, the pharmaceutically acceptable salt of the compounds according to the invention may be the sodium, potassium, calcium, magnesium or lithium salt. More preferably the pharmaceutically acceptable salt is sodium.

[0059] All acid, salt and other ionic and non-ionic forms of the compounds described are included as compounds of the invention. For example, if a compound is shown as an acid herein, the salt forms of the compound are also included. Likewise, if a compound is shown as a salt and the acid forms are also included.

Prodrugs

[0060] In certain embodiments, the compounds of the present invention as represented by generalized Formula I, wherein said compounds are present in the free carboxylic acid form, may also include all pharmaceutically acceptable salts, isosteric equivalents such as tetrazole and prodrug forms thereof. Examples of the latter include the pharmaceutically acceptable esters or amides obtained upon reaction of alcohols or amines, including amino acids, with the free acids defined by Formula I.

Chirality

[0061] The compounds of the present invention, their pharmaceutically acceptable salts, or prodrugs thereof, may contain one or more asymmetric centers, chiral axes and chiral planes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms and may be defined in terms of absolute stereochemistry, such as (R)- or (S)-. The present invention is intended to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. The racemic mixtures may be prepared and thereafter separated into individual optical isomers or these optical isomers may be prepared by chiral synthesis. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may then be separated by crystallization, gas-liquid or liquid chromatography, selective reaction of one enantiomer with an enantiomer specific reagent. It will also be appreciated by those skilled in the art that where the desired enantiomer is converted into another chemical entity by a separation

technique, an additional step is then required to form the desired enantiomeric form. Alternatively specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts, or solvents or by converting one enantiomer to another by asymmetric transformation.

[0062] Certain compounds of the present invention may exist in Zwitterionic form and the present invention includes Zwitterionic forms of these compounds and mixtures thereof.

Hydrates

[0063] In addition, the compounds of the invention also may exist in hydrated and anhydrous forms. Hydrates of any of the formulas described herein are included as compounds of the invention which may exist as a monohydrate or in the form of a polyhydrate.

B) Methods of preparation

[0064] In general, all compounds of the present invention may be prepared by any conventional methods, using readily available and/or conventionally preparable starting materials, reagents and conventional synthesis procedures. Of particular interest is the work of Hundertmark, T.; Littke, A.F.; Buchwald, S.L.; Fu, G.C. *Org. Lett.* 12, 1729-1731 (2000).

[0065] The exemplification section hereinafter provides general schemes and specific, but non limitative, examples for the synthesis of Compounds I-XXIV.

C) Pharmaceutical applications

[0066] As indicated and exemplified herein, the compounds of the present invention have beneficial pharmaceutical properties and these compounds may have useful pharmaceutical applications in subjects. Medical and pharmaceutical applications contemplated by the inventors include, but are not limited to, prevention and/or treatment of various forms of osteoporosis. As used herein, the term "osteoporosis" refers to a progressive bone disease that is characterized by a decrease in bone mass and density which can lead to an increased risk of bone fracture. The term "osteoporosis" encompasses primary type 1 osteoporosis or postmenopausal osteoporosis (most common in women after menopause), primary type 2 osteoporosis (occurs in both females and males generally after age 75), and secondary osteoporosis (which may arise at any age, a form that results from chronic predisposing medical problems or disease, or prolonged use of medications such as glucocorticoids (the disease may then be called steroid- or

glucocorticoid-induced osteoporosis)). As used herein, "osteoporosis" also includes bone disorders involving a loss in bone mass and/or density such as abnormally high osteoclastogenesis, osteomalacia-like osteoporosis, osteopenia, osteogenesis imperfecta, osteopetrosis, osteonecrosis, Paget's disease of bone, hypophosphatemia and combinations thereof.

[0067] As is known, various diseases and conditions may cause osteoporosis, and the present invention may be useful in preventing and/or treating osteoporosis related, directly or indirectly to one or more of these causes:

- Autoimmune diseases which include rheumatoid arthritis, lupus and multiple sclerosis;
- Gastrointestinal disorders which include celiac disease, inflammatory bowel disease, gastrectomy and gastrointestinal by-pass procedures;
- Endocrine/Hormonal disorders which include diabetes, hyperparathyroidism, thyrotoxicosis and Cushing's syndrome;
- Hematological disorders which include leukemia, lymphoma, multiple myeloma, sickle cell disease anemia (bone marrow disorders) and thalassemia;
- Cancer which includes breast and prostate cancer;
- Neurological disorders which include depression, Parkinson's disease and spinal cord injury;
- Organ diseases which include lung (COPD, emphysema), liver and chronic kidney diseases (CKD);
- Ankylosing spondylitis;
- AIDS/HIV;
- Bone fracture;
- Poor diet which includes eating disorders and malnutrition; and
- Pre- and post-menopausal osteoporosis and corticosteroid induced osteoporosis.

[0068] In one embodiment the osteoporosis is primary type 1 osteoporosis or postmenopausal osteoporosis. In another embodiment the osteoporosis is primary type 2 osteoporosis.

[0069] The term "subject" includes living organisms in which osteoporosis can occur, or which are susceptible to such disease. The term "subject" includes animals such as mammals or birds. Preferably, the subject is a mammal, including but not limited to human, horse, dog and cat. In some embodiments mouse is excluded from the scope of a mammal. More preferably, the subject is a human. Most preferably, the subject is a human patient in need of treatment. In preferred

embodiments, the subject is a person having or suffering from any of the following conditions: primary type 1 osteoporosis, postmenopausal osteoporosis, menopause (pre-menopause and post-menopause), primary type 2 osteoporosis, more than 75 years old, bone fracture, osteoporosis, chronic predisposing medical problems or disease, prolonged use of medications such as glucocorticoids, abnormally high osteoclastogenesis, osteomalacia-like osteoporosis, osteopenia, osteogenesis imperfecta, osteopetrosis, osteonecrosis, Paget's disease of bone, hypophosphatemia and combinations thereof. In a preferred embodiment, the subject is a postmenopausal woman.

[0070] As used herein, "preventing" or "prevention" is intended to refer to at least the reduction of likelihood of the risk of (or susceptibility to) acquiring a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease). Biological and physiological parameters for identifying such patients are provided herein and are also well known by physicians. In preferred embodiments, "preventing" or "prevention" refers to preventing decrease in bone mass and/or bone density, and/or to reducing risk of bone fracture.

[0071] The terms "treatment" or "treating" of a subject includes the application or administration of a compound of the invention to a subject (or application or administration of a compound of the invention to a cell or tissue from a subject) with the purpose of delaying, stabilizing, curing, healing, alleviating, relieving, altering, remedying, less worsening, ameliorating, improving, or affecting the disease or condition, the symptom of the disease or condition, or the risk of (or susceptibility to) the disease or condition. The term "treating" refers to any indication of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; lessening of the rate of worsening; lessening severity of the disease; stabilization, diminishing of symptoms or making the injury, pathology or condition more tolerable to the subject; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; or improving a subject's physical or mental well-being. In some embodiments, the term "treating" can include increasing a subject's life expectancy and/or delay before additional treatments are required. In preferred embodiments, "treatment" or "treating" refers to increasing bone mass and/or bone density, and/or increasing healing of bone fracture.

[0072] Furthermore, in some embodiments the compounds of the invention are for used monotherapy for the treatment prevention and/or treatment of osteoporosis. In other

embodiments, the compounds of the invention are used in combination with already approved drugs, including but not limited to drugs used for the treatment of osteoporosis. Examples of known osteoporosis-related agents which may be used in combination with the compounds of the present invention include, but are not limited to bisphosphonates, Odanacatib, Alendronate, Risedronate, Etidronate, Zoledronate, Pamidronate, Teriparatide, Tamoxifen, Raloxifene, and Denosumab.

[0073] Accordingly, methods of treatment according to the present invention may also include co-administration of the at least one compound according to the invention, or a pharmaceutically acceptable salt thereof, together with the administration of another therapeutically effective agent. Therefore, an additional aspect of the invention relates to methods of concomitant therapeutic treatment of a subject, comprising administering to a subject in need thereof an effective amount of a first agent and a second agent, wherein the first agent is as defined in Formula I, and the second agent is for the prevention or treatment of any one of disorder or disease as defined hereinbefore. As used herein, the term “concomitant” or “concomitantly” as in the phrases “concomitant therapeutic treatment” or “concomitantly with” includes administering a first agent in the presence of a second agent. A concomitant therapeutic treatment method includes methods in which the first, second, third or additional agents are co-administered. A concomitant therapeutic treatment method also includes methods in which the first or additional agents are administered in the presence of a second or additional agents, wherein the second or additional agents, for example, may have been previously administered. A concomitant therapeutic treatment method may be executed step-wise by different actors. For example, one actor may administer to a subject a first agent and as a second actor may administer to the subject a second agent and the administering steps may be executed at the same time, or nearly the same time, or at distant times, so long as the first agent (and/or additional agents) are after administration in the presence of the second agent (and/or additional agents). The actor and the subject may be the same entity (e.g., a human).

[0074] Accordingly, the invention also relates to a method for preventing, reducing or eliminating a symptom or complication of any one of the above mentioned diseases or conditions. The method comprises administering, to a subject in need thereof, a first pharmaceutical composition comprising at least one compound of the invention and a second pharmaceutical composition comprising one or more additional active ingredients, wherein all active ingredients are administered in an amount sufficient to inhibit, reduce, or eliminate one or more symptoms or complications of the disease or condition to be treated. In one aspect, the administration of the

first and second pharmaceutical composition is temporally spaced apart by at least about two minutes. Preferably the first agent is a compound of Formula I as defined herein, or a pharmaceutically acceptable salt thereof, e.g., sodium salt. The second agent may be selected from the list of compounds given hereinbefore (e.g. agents or drugs used for the prevention and/or treatment of osteoporosis).

Inhibition of osteoclastogenesis

[0075] Osteoclasts are a type of bone cell that resorbs bone tissue. The osteoclast disassembles the bone at a molecular level by secreting acid and a collagenase. This process is known as bone resorption. Osteoclastogenesis refers to the differentiation of precursor of osteoclasts into osteoclasts. In the prevention and/or treatment of osteoporosis, it is desirable to reduce osteoclastogenesis.

[0076] Osteoblast is a type of cells that synthesizes bone. Osteoblasts arise from mesenchymal stem cells. In the prevention and/or treatment of osteoporosis, it is desirable is to stimulate osteoblastic differentiation.

[0077] As shown hereinafter in the examples, the compounds of the invention are capable of inhibiting and/or reducing osteoclastogenesis. This is demonstrated for example by: the absence of TRAP cells (Example 2; Figure 1); a strong induction of IL-12 production in LPS-stimulated RAW264.7 cells (Examples 2 and 3); a reduction of calcium loss *in vivo* (Example 4, Figure 4); a reduction of acid phosphatase activity *in vivo* (Example 4, Figure 5); a decrease of mRNA expression of RANKL/OPG *in vivo* (Example 4, Figure 6); an increase in collagen content *in vivo* (Example 4, Figures 7 and 8); and an increase of the serum level of adiponectin (Example 5, Figure 9).

[0078] These results suggest an ability of the compounds of the present invention to prevent/treat osteoporosis, via the inhibition and/or reduction of activity of osteoclasts.

[0079] The results also demonstrate an ability of the compounds of the present invention to prevent and/or reduce bone loss, including but not limited to, calcium loss. Accordingly, these results further suggest an ability of the compounds of the present invention to prevent/treat osteoporosis, via the stimulation of osteoblastic differentiation.

Stimulation of interleukin-12 (IL-12) production

[0080] As shown hereinafter in the examples, the compounds of the invention induce the production of IL-12 in the presence of LPS. These results suggest an ability of these compounds

to prevent and/or treat osteoporosis, as a result of the induction of IL-12. This is supported by the scientific literature that teaches that IL-12 has a direct inhibitory effect on osteoclastogenesis.

[0081] Accordingly, in some embodiments, the compounds and compositions of the invention are useful for the stimulation of interleukin-12 (IL-12) production including, but not limited to, production by a stimulated osteoclast precursor cell.

Reduction of acid phosphatase activity

[0082] As shown hereinafter in the examples, the compounds of the invention reduce enzymatic acid phosphatase activity, as measured in the serum of ovariectomized rats. These results suggest an ability of these compounds to prevent and/or treat osteoporosis as a result of reduction of enzymatic acid phosphatase activity.

[0083] Accordingly, in some embodiments, the compounds and compositions of the invention are useful for reducing acid phosphatase activity in bone cells.

Reducing expression of Receptor activator of NF- κ B ligand (RANKL)

[0084] As shown hereinafter in the examples, the compounds of the invention reduce mRNA expression of RANKL, as measured in the tibia of ovariectomized rats. These results suggest an ability of these compounds to prevent and/or treat osteoporosis as a result of reduction of RANKL's expression and/or biological activity.

[0085] Accordingly, in some embodiments, the compounds and compositions of the invention are useful for reducing expression and/or activity of RANKL in bone cells.

Increasing collagen content

[0086] As shown hereinafter in the examples, the compounds of the invention increase the content of collagen in bone, as measured in the metaphyse of the femur of ovariectomized rats. These results suggest an ability of these compounds to prevent and/or treat osteoporosis as demonstrated by the increase of the collagen content in the bone.

[0087] Accordingly, in some embodiments, the compounds and compositions of the invention are useful for increasing collagen content in living bone.

Increasing of the level of adiponectin

[0088] As shown hereinafter in the examples, the compounds of the invention increase the level of adiponectin, as measured in the serum of obese diabetic mice. These results suggest an ability of these compounds to prevent and/or treat osteoporosis by stimulating bone formation, remodeling and mineralization and/or by inhibiting bone resorption.

[0089] Accordingly, in some embodiments, the compounds and compositions of the invention are useful for stimulating bone formation and/or for stimulating bone remodeling and/or for stimulating the differentiation and mineralization of osteoblasts and/or for inhibiting bone resorption.

D) Pharmaceutical compositions and formulations

[0090] A related aspect of the invention concerns pharmaceutical compositions comprising a therapeutically effective amount one or more of the compounds of the invention described herein (e.g., a compound of Formula I). As indicated hereinbefore, the pharmaceutical compositions of the invention may be useful: in the prevention and/or treatment of osteoporosis; in the inhibition of osteoclastogenesis; in stimulating interleukin-12 (IL-12) production by a stimulated osteoclast precursor cell; in the reduction of acid phosphatase activity in bone cells; in the reduction of expression of Receptor activator of NF- κ B ligand (RANKL) in bone cells; in increasing collagen content in bone, in stimulating bone formation; in stimulating bone remodeling; in stimulating bone mineralization; and/or in inhibiting bone resorption.

[0091] As used herein, the term “therapeutically effective amount” means the amount of compound that, when administered to a subject for treating or preventing a particular disorder, disease or condition, is sufficient to effect such treatment or prevention of that disorder, disease or condition. Dosages and therapeutically effective amounts may vary for example, depending upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, and any drug combination, if applicable, the effect which the practitioner desires the compound to have upon the subject (e.g., total or partial response as evidenced by factors which include increasing bone mass and/or bone density (or reduction of a decrease thereof), reducing a risk of bone fracture, etc.), the properties of the compounds (e.g., bioavailability, stability, potency, toxicity, etc.), and the particular disorder(s) the subject is suffering from. In addition, the therapeutically effective amount may depend on the subject’s blood parameters (e.g., calcium levels, lipid profile, insulin levels, glycemia), the severity of the disease

state, organ function, or underlying disease or complications. Such appropriate doses may be determined using any available assays including the assays described herein. When one or more of the compounds of the invention is to be administered to humans, a physician may for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. The dose to be administered will ultimately be at the discretion of the oncologist. In general, however, it is envisioned that the dose for the present compounds may be in the range of about 1 to about 50 mg/kg per day in human. In selected embodiments, the range may be between 1 to 30 mg/kg per day in human. In selected embodiments, the range may be between 1 to 20 mg/kg per day in human. In selected embodiments, the range may be between 5 to 18 mg/kg per day in human. In selected embodiments, the range may be between 1 to 18 mg/kg per day in human.

[0092] As used herein, the term “pharmaceutical composition” refers to the presence of at least one compound of the invention according to Formula I as defined herein and at least one pharmaceutically acceptable carrier, diluent, vehicle or excipient. As used herein, the term “pharmaceutically acceptable carrier”, “pharmaceutically acceptable diluent” or “pharmaceutically acceptable excipient” is intended to mean, without limitation, any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, emulsifier, or encapsulating agent, such as a liposome, cyclodextrins, encapsulating polymeric delivery systems or polyethyleneglycol matrix, which is acceptable for use in subjects, preferably humans. It preferably refers to a compound or composition that is approved or approvable by a regulatory agency of the Federal or State government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals and more particularly in humans. The pharmaceutically acceptable vehicle can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Additional examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate. Prevention of the action of microorganisms can be achieved by addition of antibacterial and antifungal agents, for example, parabens,

chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, isotonic agents are included, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

[0093] The composition of the present invention may include one or more compounds of Formula I as defined herein or pharmaceutically acceptable derivatives, salts prodrugs, analogues and isomers or enantiomers thereof. Formulations of the active compound may be prepared so as to provide a pharmaceutical composition in a form suitable for enteral, mucosal (including sublingual, pulmonary and rectal), parenteral (including intramuscular, intradermal, subcutaneous and intravenous) or topical (including ointments, creams or lotions) administration. The formulation may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well-known in the art of pharmaceutical formulation. All methods include the step of bringing together the active pharmaceutical ingredient with liquid carriers or finely divided solid carriers or both as the need dictates. When appropriate, the above-described formulations may be adapted so as to provide sustained release of the active pharmaceutical ingredient. Sustained release formulations well-known to the art include the use of a bolus injection, continuous infusion, biocompatible polymers or liposomes.

E) Kits

[0094] The compound(s) of the invention may be packaged as part of a kit, optionally including a container (e.g., packaging, a box, a vial, etc.). The kit may be commercially used according to the methods described herein and may include instructions for use in a method of the invention. Additional kit components may include acids, bases, buffering agents, inorganic salts, solvents, antioxidants, preservatives, or metal chelators. The additional kit components are present as pure compositions, or as aqueous or organic solutions that incorporate one or more additional kit components. Any or all of the kit components optionally further comprise buffers.

[0095] The compound(s) of the invention may or may not be administered to a patient at the same time or by the same route of administration. Therefore, the methods of the invention encompass kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of two or more active ingredients to a patient.

[0096] A typical kit of the invention comprises a unit dosage form of at least one compound according to the invention as defined by Formula I as defined herein, or a pharmaceutically acceptable salt thereof, and a unit dosage form of at least one additional active ingredient. Examples of additional active ingredients that may be used in conjunction with the compounds of the invention include, but are not limited to, any of the drugs indicated hereinbefore (e.g. drugs used for the treatment of osteoporosis) that could be used in combination with the compound(s) of the invention.

[0097] Kits of the invention can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container or a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles are provided hereinbefore.

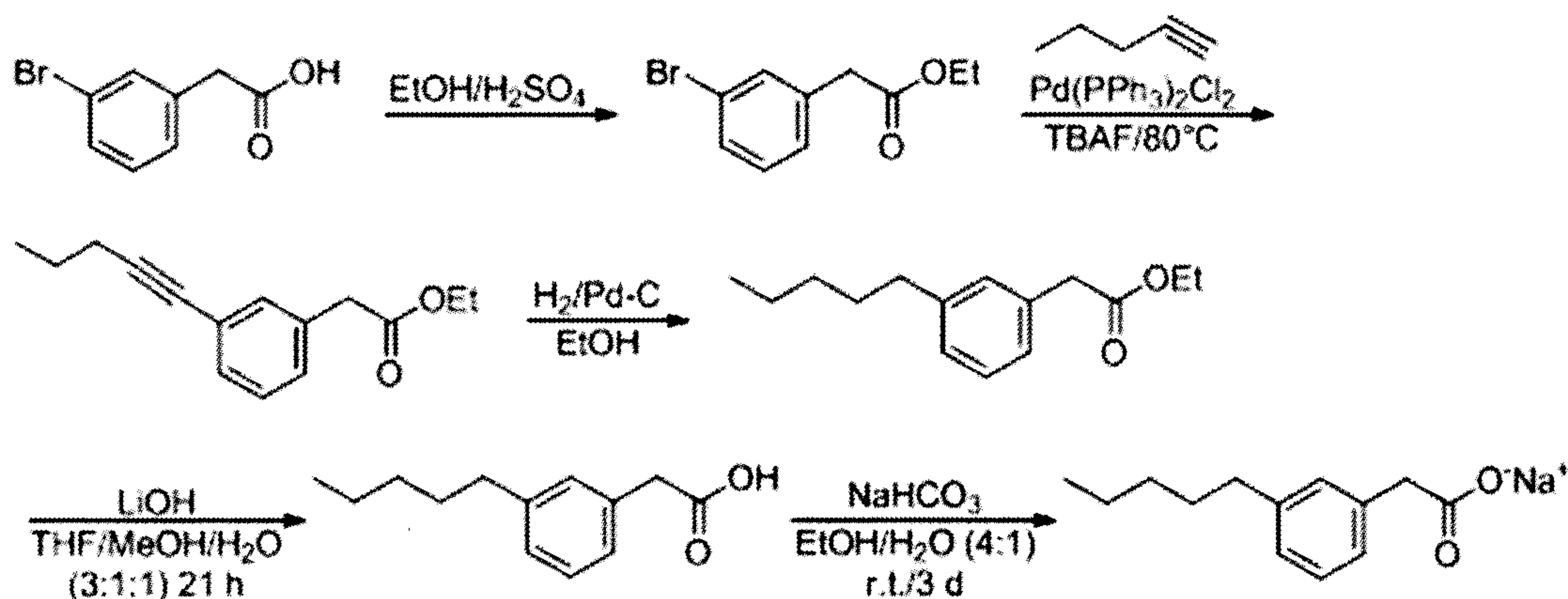
EXAMPLES

[0098] The following examples further illustrate the practice of this invention but are not intended to be limiting thereof.

Example 1: Experimental procedures for the preparation certain representative compounds

[0099] All HPLC chromatograms and mass spectra were recorded on an HP 1100 LC-MS Agilent™ instrument using an analytical C18 column (250 × 4.6 mm, 5 microns) with a gradient over 5 min of 15-99% CH₃CN-H₂O with 0.01% TFA as the eluent and a flow of 2 mL/min.

Compound I: Synthesis of sodium salt of (3-pentylphenyl)acetic acid using a modified Sonogashira procedure



Step 1

[00100] To a solution/suspension of 3-bromophenylacetic acid (5.02 g, 23.33 mmol) in ethanol (100 mL) at room temperature was added concentrated sulfuric acid (1 mL). The colorless solid was then stirred overnight at 80°C. The solution was concentrated under reduced pressure. The residue was diluted with ethyl acetate (25 mL), water (25 mL) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 25 mL) and brine (20 mL). The combined organic layers were washed with saturated solution of NaHCO₃ (2 × 25 mL), brine (25 mL) and dried over sodium sulfate. After filtration the solution it was evaporated to dryness. This gave a light yellow oil (5.4 g, 95%). ¹H-NMR (400 MHz, CDCl₃): δ 1.26 (t, *J* = 4.7 Hz, 3H), 3.57 (s, 2H), 4.15 (q, *J* = 7.0 and 14.3 Hz, 2H), 7.17-7.26 (m, 2H), 7.38-7.44 (m, 1H), 7.44 (d, *J* = 1.56 Hz, 1H).

Step 2

[00101] A mixture of ethyl (3-bromophenyl)acetate (0.3 g, 1.24 mmol) and tetrabutylammonium fluoride hydrate (0.97 g, 3.72 mmol), was treated with PdCl₂(PPh₃)₂ (26 mg, 0.037 mmol; 3 mole %) and 1-pentyne (367 μL, 3.72 mmol) in a sealed tube. The tube was heated at 80°C for 2 h. The mixture was treated with water, and was extracted with diethyl ether. The organic extract was dried over sodium sulfate, filtered and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ 25 M column (silica), eluting with ethyl acetate/hexane 0:1 to 2:98, gave ethyl (3-(pentyne-1-yl)phenyl)acetate as a pale yellow oil (0.23 g, 79%).

Step 3

[00102] To ethyl[3-[pentyne-1-yl]phenyl]-acetate (0.23 g, 0.98 mmol) in ethanol (5 mL) under nitrogen atmosphere was added Pd on carbon (10%, 25 mg, 10% w/w). The mixture was vigorously stirred under hydrogen atmosphere at room temperature overnight. The solution was filtered and the palladium/carbon was washed with ethanol (20 mL). The filtrate was concentrated with silica gel. The crude product was purified by flash chromatography using a mixture of 10% hexanes/ ethyl acetate. A clear oil was obtained (0.21 g, 90%).

Step 4

[00103] To a solution of the ester (0.2 g, 0.9 mmol) in tetrahydrofuran (5 mL), methanol (1.5 mL) and water (1.5 mL) was added lithium hydroxide (0.09 g, 3.6 mmol) at 0°C. The reaction mixture was stirred overnight at room temperature. Insolubles were filtered and the filtrate was concentrated under reduced pressure. The residue was then treated with 2 M HCl and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude material was purified on a 40 L Biotage column (silica) using ethyl acetate/hexanes (0:10 to 4:6) as eluant. This gave pure (3-pentylphenyl)acetic acid (0.19 g, 99%) as a white gummy solid. ¹H NMR (400 MHz, CD₃OD): δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.28-1.38 (m, 4H), 1.61 (qt, *J* = 7.6 Hz, 15.0 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 3.56 (s, 2H), 7.07 (m, 3H), 7.20 (m, 1H); LRMS (ESI): *m/z* 207 (MH⁺); HPLC: 4 min.

Step 5

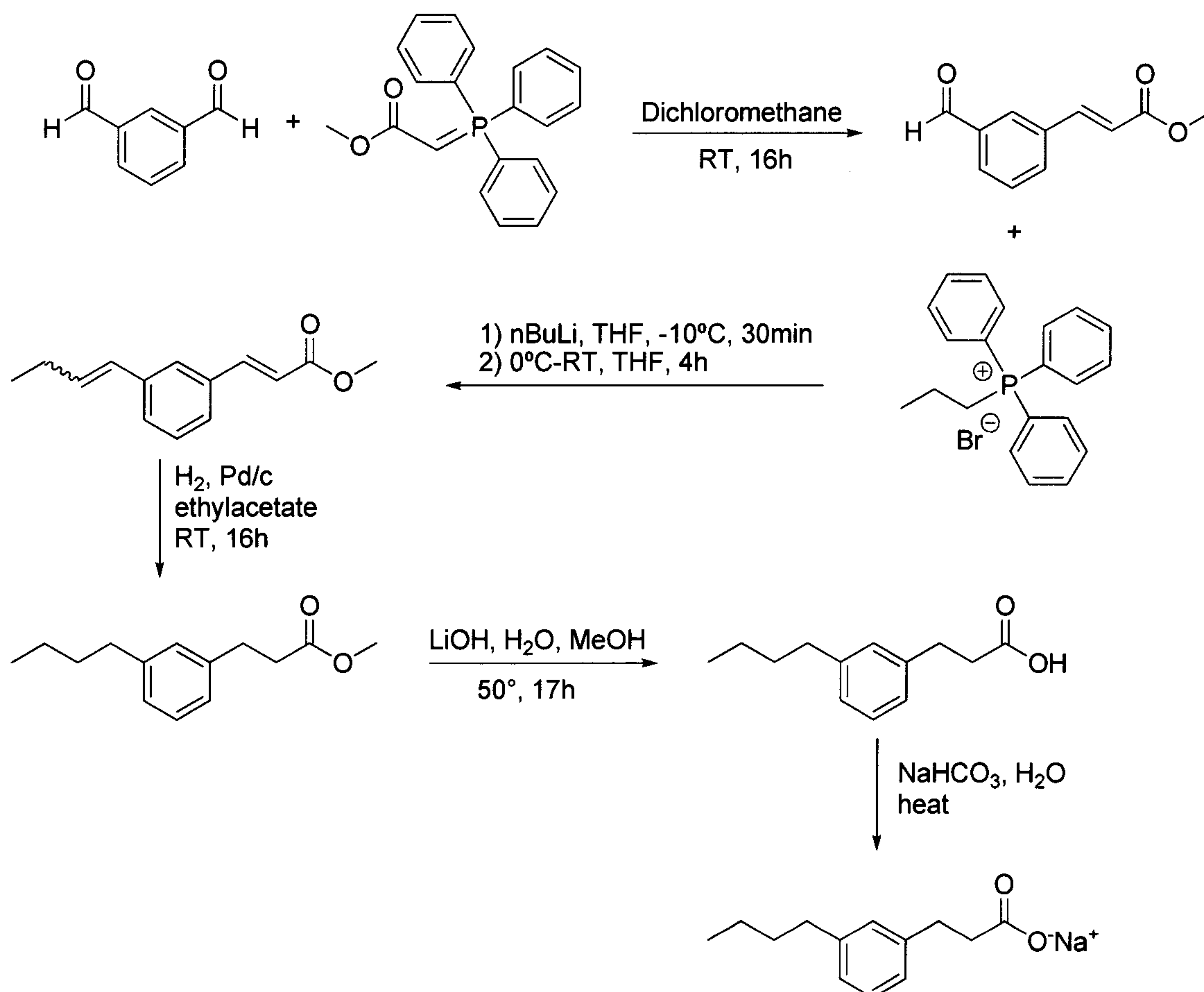
[00104] To a stirred solution of the acid (0.19 g, 0.82 mmol) in ethanol (4 mL) and water (1 mL) was added sodium bicarbonate (0.07 g, 0.82 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the white gummy solid was dissolved in water and the solution was lyophilized. This gave pure sodium salt of (3-pentylphenyl)acetic acid (0.17 g, 92%) as a white solid. mp 110-112°C; ¹H NMR (400 MHz, CD₃OD): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.28-1.37 (m, 4H), 1.60 (qt, *J* = 7.4 Hz, 15.0 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 3.43 (s, 2H), 6.96 (m, 1H), 7.12 (m, 3H); LRMS (ESI): *m/z* 207 ((MH⁺); HPLC: 4 min.

Compound II: Sodium salt of 3-(3-pentylphenyl)propionic acid

[00105] The above compound was prepared as for Compound I starting with 3-Oxo-3-bromophenylpropionic acid ethyl ester. The ketone group and the double bond were

simultaneously reduced using palladium/carbon in ethanol under hydrogen pressure. White solid; ^1H NMR (400 MHz, CDCl_3): δ 7.14-7.10 (m, 1H), 7.04-7.00 (m, 2H), 6.95-6.93 (m, 1H), 2.88-2.84 (m, 2H), 2.55 (t, $J = 7.4$ Hz, 2H), 2.44-2.40 (m, 2H), 1.63-1.55 (m, 2H), 1.35-1.28 (m, 4H), 0.90 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 179.3, 141.2, 140.8, 126.7, 126.4, 124.0, 123.8, 38.6, 34.2, 31.2, 29.9, 29.8, 20.9, 11.7; LRMS (ESI): m/z 203 ($\text{MH}^+ - \text{CO} - \text{NaOH}$); HPLC: 4.5 min.

Compound III: Sodium salt of 3-(3-butylphenyl)propionic acid



Step 1

[00106] In a round bottom flask (250 mL) was weight isophthalaldehyde (1.0 g, 7.5 mmol), followed by dichloromethane (100 mL). Via a separatory funnel with pressure equilibrium was added the Methyl (triphenyl-phosphoranylidene) acetate (2.7 g, 8.2 mmol) in dichloromethane (25 mL) at room temperature. The reaction was stirred at room temperature overnight. The mixture was filtered over a small pad of silica gel, and washed with dichloromethane (150 mL). The solvent

was then evaporated under reduced pressure and the crude product was used in the next step without further purification.

Step 2

[00107] The Propyl triphenylphosphonium Bromide (3.2 g, 8.2 mmol) was placed in a round bottom flask, under nitrogen, and dry THF (5 mL) was added. The flask is cooled in an ice/acetone (-10°C) bath, and nButyllithium (2.5 M in Hexanes, 3.28 mL, 8.2 mmol) was added slowly. The mixture turn dark colored with stirring for 30 minutes. In an ice/acetone (-10°C) bath was placed the crude reaction mixture from the previous step in dry THF (5 mL) under nitrogen. The phosphonium solution was added slowly to the aldehyde solution at -10°C, and the reaction mixture was warmed slowly to room temperature and stirred for 4h. Saturated ammonium chloride solution (10 mL) was added and the organic layer was extracted with ethyl acetate (3x). The organic layer was dried over anhydrous sodium sulfate, filtered and silica gel is added to obtain a drypack. Compound was purified with the SP1 (ethyl acetate/hexanes). This gave the expected product (8.8 g, 54%). ¹H NMR (400 MHz, CDCl₃): δ 7.70-7.65 (m, 1H), 7.45-7.24 (m, 4.5H), 6.45-6.28 (m, 2.5H), 5.70-5.67 (m, 0.5H), 3.78 (m, 3H), 2.34-2.20 (m, 2H), 1.10-1.03 (m, 3H).

Step 3

[00108] In a round bottom flask (25 mL) is placed the unsaturated ester (140 mg, 0.65 mmol), dissolved in ethyl acetate (10 mL). To this solution was added 10% palladium on activated charcoal Pd/C (10 mg). The flask was capped with a septa, and a hydrogen balloon was placed on top. The flask was purged three times with hydrogen, and the reaction was stirred at room temperature overnight. The solid was then filtered over Celite™. Silica gel was added and a drypack is prepared. Purification by flash chromatography using 0-20% ethyl acetate/hexanes gave the desired product (124 mg, 87%). LRMS (ESI): *m/z* 221 (MH⁺); HPLC: 5.0 min.

Step 4

[00109] In a round bottle flask was placed the ester (124 mg, 0.56 mmol) followed by methanol (4 mL) and lithium hydroxide (118 mg, 2.8 mmol). Water (1 mL) was added and the reaction was heated at 50°C with agitation for 17h. The reaction is transferred into a separatory funnel, acidified to pH lower than 4 with HCl (1M), and extracted with ethyl acetate (3x). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated. The crude material was purified by HPLC/Waters. This gave a white solid (80 mg, 70%). ¹H NMR (400 MHz, CD₃OD): δ 7.16-7.12

(m, 1H), 7.01-6.96 (m, 3H), 2.88-2.84 (m, 2H), 2.57-2.53 (m, 4H), 1.60-1.52 (m, 2H), 1.37-1.28 (m, 2H), 0.91(t, 3H, $J = 7.3\text{Hz}$); LRMS (ESI): m/z 205 (M-H); HPLC: 4.2 min.

Step 5

[00110] In a flask (20 mL) was placed the acid (80 mg, 0.39 mmol) followed by NaHCO_3 (33 mg, 0.39 mmol) and water (8 mL). To the mixtures was added acetonitrile (3 mL) and the reaction was sonicated, heated and agitated until almost all the solids were in solution. The solution was filtered over a nylon filter. The water is solidified by plunging the vial in a dry ice/acetone bath, and lyophilized overnight. This gave the desired product as a white solid. ^1H NMR (400 MHz, CD_3OD): δ 7.14-7.10 (m, 1H), 7.04-6.93 (m, 3H), 2.88-2.84 (m, 2H), 2.57-2.54 (m, 2H), 2.44-2.40 (m, 4H), 1.61-1.53 (m, 2H), 1.39-1.30 (m, 2H), 0.93(t, 3H, $J = 7.3\text{Hz}$); ^{13}C NMR (101 MHz, CD_3OD): δ 142.7, 142.4, 128.2, 128.0, 125.6, 125.4, 125.3, 40.1, 35.5, 33.9, 32.7, 22.2, 13.1; LRMS (ESI): m/z 251.0 (m, MNa^+), 229.0 (w, MH^+), 189.2 (100%, acylium ion $[\text{M} - \text{Na}^+ + 2\text{H}^+ - \text{H}_2\text{O}]$); HPLC: 4.1 min.

Compound IV: Sodium salt of *E*-(3-pent-1-enyl-phenyl)acetic acid.

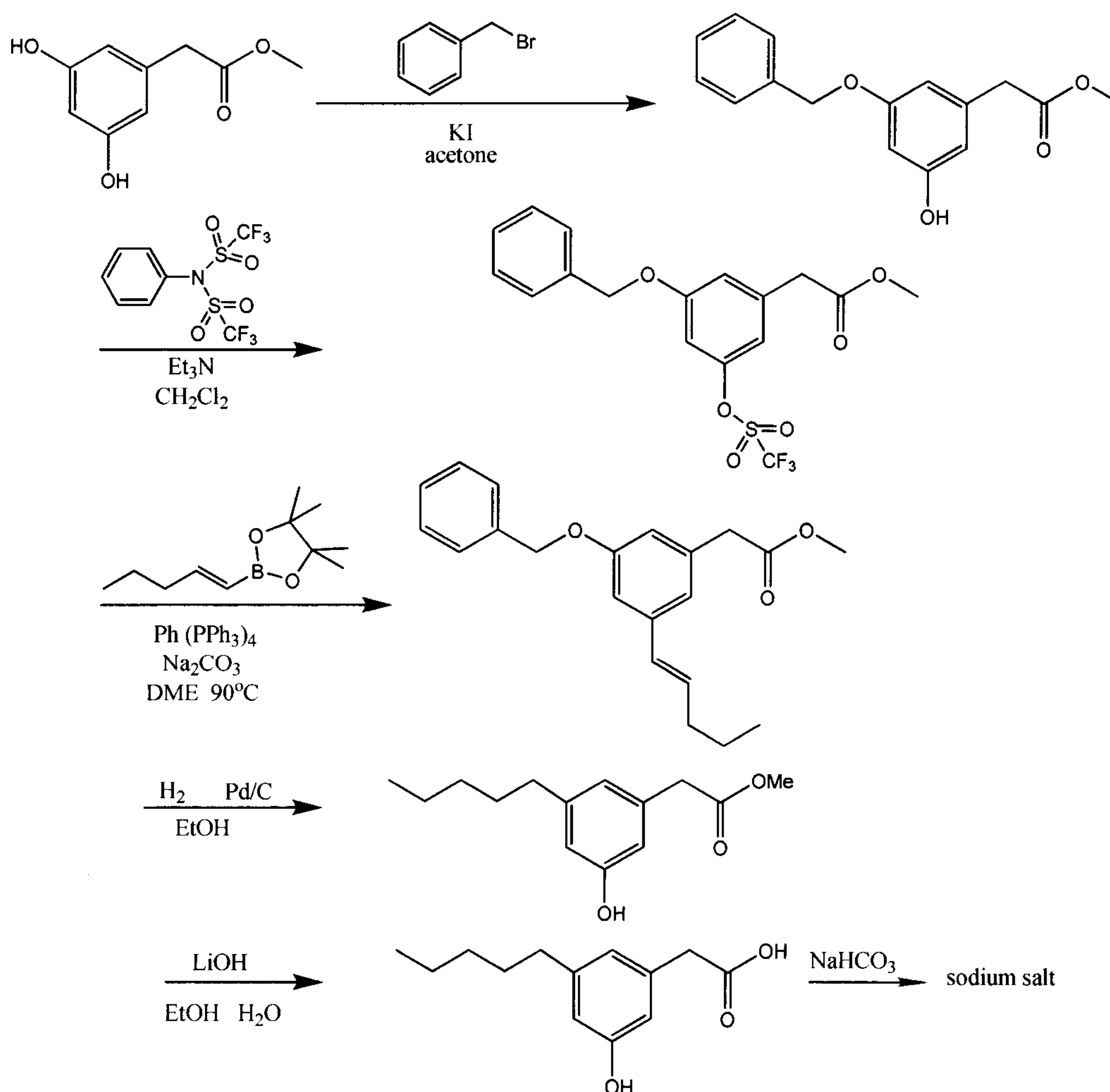
[00111] The above compound was prepared as for Compound I starting with *E*-(3-pent-1-enyl-phenyl)acetic acid methyl ester. The latter was prepared by reacting 3-bromophenyl acetic acid methyl ester with trans-1-pentenylboronic acid pinacol ester under Suzuki conditions. White solid; ^1H NMR (400 MHz, CD_3OD): δ = 7.32 (s, 1H), 7.11-7.18 (m, 3H), 6.35 (d, $J = 15.7\text{ Hz}$, 1H), 6.20-6.27 (m, 1H), 3.44 (s, 2H), 2.19 (m, 2H), 1.45-1.54 (m, 2H), 0.96 (t, $J = 7.4$, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ = 179.26, 138.25, 137.92, 130.32, 130.04, 128.06, 127.59, 126.60, 123.52, 45.21, 35.06, 22.52, 12.89; LRMS (ESI): m/z 205 (MH^+); HPLC: 4.1 min.

Compound V: Sodium salt of 2-(3-(Hex-1-enyl]phenyl)acetic acid.

[00112] The above compound was prepared by Suzuki coupling of methyl 2-(3-bromophenyl)acetate and (*E*)-hex-1-enylboronic acid pinacol ester as for Compound VII; followed by ester hydrolysis and sodium salt formation as for Compound I. White solid: ^1H NMR (400 MHz, CD_3OD): δ 7.33 (s, 1H), 7.12-7.19 (m, 3H), 6.35 (d, $J = 15.8\text{ Hz}$, 1H), 6.20 (dt, $J = 15.8, 6.8\text{ Hz}$, 1H), 3.46 (s, 2H), 2.17-2.22 (m, 2H), 1.33-1.49 (m, 4H), 0.93 (t, $J = 7.2\text{ Hz}$, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 179.35, 138.27, 137.95, 130.27, 130.16, 128.10, 127.61, 126.64, 123.56, 45.24, 32.66, 31.67, 22.16, 13.22; LRMS (ESI): m/z 263.1 (100%, $\text{M} + \text{Na}^+$); HPLC : 4.4 min.

Compound VI: Sodium salt of 2-(3-Hexylphenyl)acetic acid

[00113] The above compound was prepared by Suzuki coupling of methyl 2-(3-bromophenyl)acetate and (*E*)-hex-1-enylboronic acid pinacol ester as for Compound VII; followed by hydrogenation, ester hydrolysis and sodium salt formation as for Compound I. White solid; ^1H NMR (400 MHz, D_2O): δ 7.14 (dd, $J = 7.8, 7.6$ Hz, 1H), 7.01 (s, 1H), 7.00 (d, $J = 7.8$ Hz, 1H), 6.96 (d, $J = 7.6$ Hz, 1H), 3.34 (s, 2H), 2.46 (d, $J = 7.5$ Hz, 2H), 1.41-1.48 (m, 2H), 1.10-1.18 (m, 6H), 0.70 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, D_2O): δ 181.23, 143.98, 137.46, 129.47, 128.73, 126.63, 126.48, 44.58, 35.14, 31.12, 30.94, 28.23, 22.13, 13.53; LRMS (ESI): m/z 265 (100%, $\text{M} + \text{Na}^+$); HPLC: 4.6 min.

Compound VII: Sodium salt of 3-hydroxy-5-pentylphenylacetic acid

Step 1

[00114] A solution of methyl [3,5-dihydroxyphenyl]acetate (2.1 g, 11.5 mmol) in acetone (100 mL) was treated with potassium carbonate (2.4 g, 17.4 mmol), potassium iodide (383 mg, 2.31 mmol) and benzyl bromide (1.5 mL, 12.7 mmol), and the mixture was stirred at room temperature overnight. The reaction was diluted with water and extracted with dichloromethane (x3). Combined organic extracts were dried over sodium sulfate and evaporated *in vacuo*. The crude material was purified on a Biotage™ 40M column (silica), eluting with 40% ethyl acetate/hexane, to give methyl [3-benzyloxy-5-hydroxyphenyl]acetate (1.0 g, 33%). ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.42 (m, 5H), 6.48 (d, *J* = 1.4 Hz, 1H), 6.38-6.39 (m, 2H), 4.99 (s, 2H), 3.69 (s, 3H), 3.53 (s, 2H).

Step 2

[00115] A solution of the benzyl ether (1.04 g, 3.8 mmol) in dichloromethane (15 mL) at 0°C, was treated with *N*-phenyl-bis(trifluorosulfonyl)imide (1.40 g, 3.9 mmol), and then triethylamine (0.6 mL, 4.1 mmol) was added slowly. The reaction was stirred at 0°C for 1 h, and then at room temperature for 1 h. The reaction mixture was diluted with water, and then extracted with diethylether (x 2). Combined organic extracts were washed with 1M aqueous sodium hydroxide, water (x 2) and saturated aqueous sodium chloride, then dried over sodium sulfate, filtered and evaporated *in vacuo*, to give the crude product. Purification on a Biotage™ 40M column (silica), eluting with 25% ethyl acetate/hexane, gave methyl [3-benzyloxy-5-trifluoromethanesulfonyloxyphenyl]acetate (1.2 g, 79%). ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.46 (m, 5H), 6.98 (s, 1H), 6.97 (s, 1H), 6.84 (s, 1H), 5.06 (s, 2H), 3.72 (s, 3H), 3.63 (s, 2H).

Step 3

[00116] A solution of *E*-1-penten-1-ylboronic acid pinacol ester (0.8 g, 3.9 mmol) in dimethoxyethane (5 mL) was treated with a solution of the triflate (1.2 g, 3.0 mmol) in dimethoxyethane (5 mL). The solution was treated with palladium zero (0.7 g, 0.6 mmol) and 2M aqueous sodium carbonate (1.3 mL, 2.6 mmol). The mixture was then heated at 90°C for 3 days. The reaction was cooled to room temperature and filtered through Celite™. The filtrate was evaporated *in vacuo*, and the crude material was purified on a Biotage™ 25M column (silica), eluting with 5% ethyl acetate/hexane, to give methyl [3-benzyloxy-5-[pent-1-enyl]phenyl]acetate (0.4 g, 40%). ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.47 (m, 5H), 6.90-6.92 (m, 2H), 6.79 (dd, *J* =

2.0, 2.0 Hz, 1H), 6.35 (d, $J = 15.9$ Hz, 1H), 6.24 (dt, $J = 15.9, 6.8$ Hz, 1H), 5.07 (s, 2H), 3.70 (s, 3H), 3.59 (s, 2H), 2.20 (td, $J = 7.4, 6.8$ Hz, 2H), 1.51 (dt, $J = 7.4$ Hz, 2H), 0.98 (t, $J = 7.4$ Hz, 3H).

Step 4

[00117] A solution of the alkene (0.4 g, 1.2 mmol) in ethanol (13 mL) was treated with 1% palladium on carbon (40 mg). The mixture was stirred under 1 atm. of hydrogen at room temperature overnight. The reaction was filtered, evaporated *in vacuo*, and purified on a Biotage™ 25S column (silica), eluting with 15% ethyl acetate/hexane, to give methyl [3-hydroxy-5-pentylphenyl]acetate (0.3 g, 93%). ^1H NMR (400 MHz, CDCl_3): δ 6.64 (s, 1H), 6.58-6.60 (m, 2H), 3.70 (s, 3H), 3.55 (s, 2H), 2.51 (t, $J = 7.7$ Hz, 2H), 1.55-1.59 (m, 2H), 1.28-1.34 (m, 4H), 0.88 (t, $J = 7.0$ Hz, 3H).

Step 5

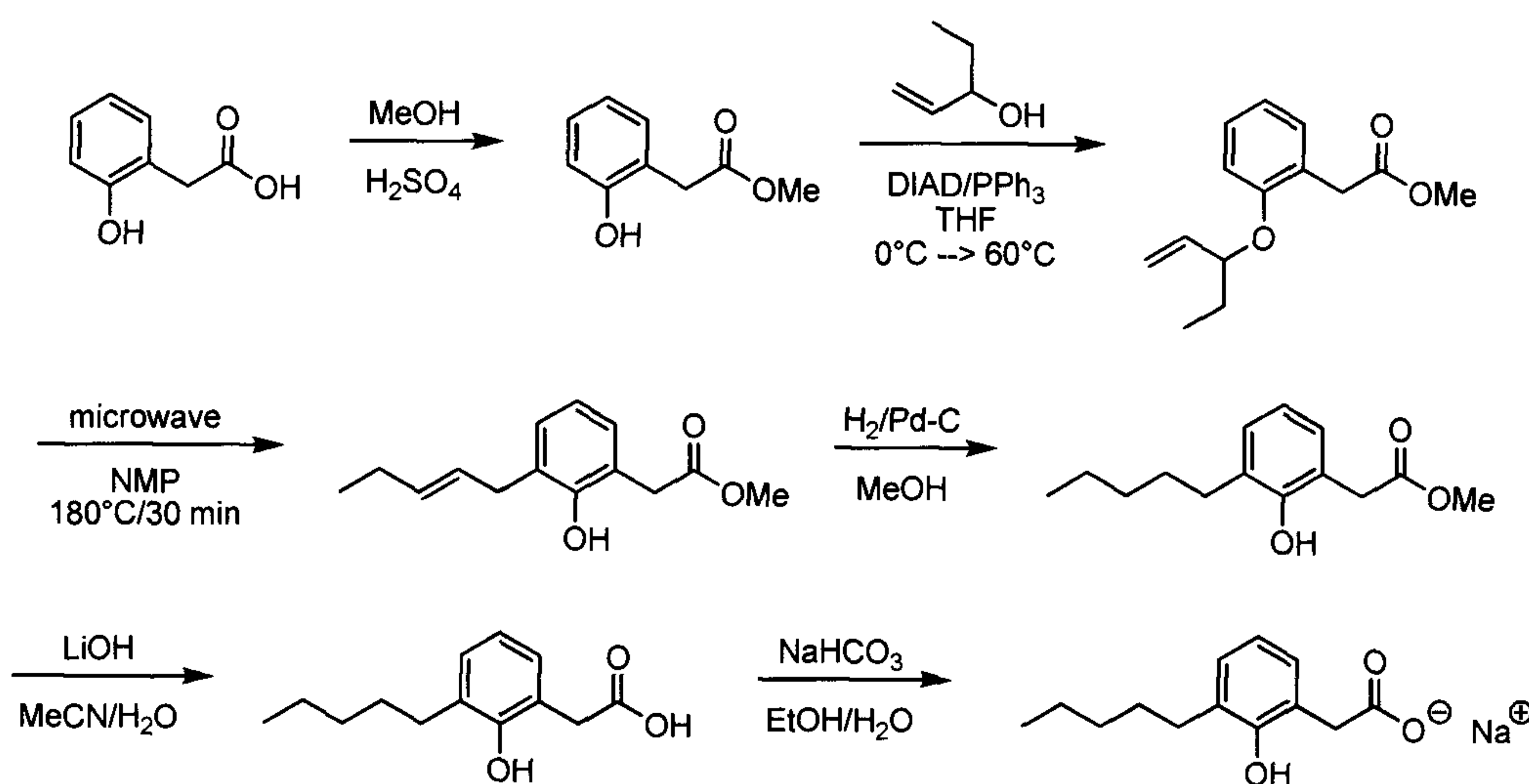
[00118] A solution of the ester (0.3 g, 1.3 mmol) in ethanol (12 mL) was treated with water (3 mL) and lithium hydroxide (155 mg, 6.4 mmol), and the mixture was stirred vigorously at room temperature overnight. The reaction mixture was diluted with water (100 mL); washed with dichloromethane; then acidified to pH 1 with 1M aqueous hydrochloric acid and extracted with dichloromethane (x 3). Combined organic extracts were dried over sodium sulfate (0.3 g, 95%). This material was used without further purification. ^1H NMR (400 MHz, CDCl_3): δ 6.66 (s, 1H), 6.58-6.59 (m, 2H), 3.55 (s, 2H), 2.52 (t, $J = 7.7$ Hz, 2H), 1.55-1.59 (m, 2H).

Step 6

[00119] A solution of the acid (0.27 g, 1.23 mmol) in ethanol (6 mL) and water (6 mL) was treated with a sodium bicarbonate (0.1 g, 1.2 mmol), and the reaction was stirred at room temperature for a few hours. Solvent was concentrated *in vacuo*, and the solution was diluted with water, filtered (0.2 μm), and lyophilized to give sodium [3-hydroxy-5-pentylphenyl]acetate as a white solid (0.3 g, 95%). mp 63-66°C; ^1H NMR (400 MHz, CD_3OD): δ 6.63 (s, 1H), 6.58 (s, 1H), 6.42 (s, 1H), 3.36 (s, 2H), 2.48 (t, $J = 7.6$ Hz, 2H), 1.55-1.62 (m, 2H), 1.26-1.38 (m, 4H), 0.89 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 177.79, 155.31, 142.36, 137.62, 119.08, 111.66, 111.18, 43.70, 34.17, 29.95, 29.56, 20.87, 11.64; LRMS (ESI): m/z 445.2 ($2\text{M} - 2\text{Na}^+ + 3\text{H}^+$), m/z 223 ($\text{M} - \text{Na}^+ + 2\text{H}^+$); HPLC: 3.5 min.

Compound VIII: Sodium salt of 2-(4-Hydroxy-3-pentylphenyl)acetic acid

[00120] The above compound was prepared by Suzuki coupling of benzyl 2-(4-(benzyloxy)-3-bromophenyl)acetate and (*E*)-pent-1-enylboronic acid pinacol ester as for example **VII**; followed by hydrogenation. White solid; melting point 192-195°C; ¹H NMR (400 MHz, CD₃OD): δ 7.01 (d, *J* = 2.3 Hz, 1H), 6.93 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 3.35 (s, 2H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.54-1.61 (m, 2H), 1.30-1.37 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CD₃OD): δ 180.25, 153.20, 130.54, 128.80, 128.76, 127.10, 114.49, 44.45, 31.84, 30.10, 29.73, 22.52, 13.31; LRMS (ESI): *m/z* 245.2 (55%, MH⁺), 177.4 (100%, M – CO₂Na); HPLC: 1.9 min.

Compound IX: Sodium salt of 2-(2-Hydroxy-3-pentylphenyl)acetic acid**Step 1**

[00121] A solution of 2-(2-hydroxyphenyl)acetic acid (3.00 g, 19.7 mmol) in methanol (40 mL) was treated with sulfuric acid (0.95 mL, 17.8 mmol) and the reaction was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (250 mL), and the solution was washed with water (2 x 150 mL) and with saturated aqueous sodium chloride (150 mL); dried over sodium sulfate; filtered and evaporated *in vacuo* to give the crude product. Recrystallization from hot hexanes gave methyl 2-(2-hydroxyphenyl)acetate (2.83 g, 87%). ¹H NMR (400 MHz, CDCl₃): δ 7.20 (ddd, *J* = 7.7, 7.4, 1.8 Hz, 1H), 7.09-7.11 (m, 1H), 6.94 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.88 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 2H).

Step 2

[00122] A solution of methyl 2-(2-hydroxyphenyl)acetate (1.00 g, 6.0 mmol), triphenylphosphine (2.37 g, 9.0 mmol) and pent-1-en-3-ol (0.78 g, 9.0 mmol) in tetrahydrofuran (30 mL) was cooled to 0°C under nitrogen, and diisopropyl azodicarboxylate (1.86 mL; 9.0 mmol) was added dropwise over 10 minutes. The reaction was then heated to 60°C for 21.5 hours. Solvent was evaporated *in vacuo* and the residue was extracted with 5% ethyl acetate in hexanes. The extract was filtered and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ SP1 system (120 g silica cartridge), eluting with 0-3% ethyl acetate in hexanes, gave methyl 2-(2-(pent-1-en-3-yloxy)phenyl)acetate (0.39 g, 28%). ¹H NMR (400 MHz, CDCl₃): δ 7.21-7.26 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 6.91 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.84 (ddd, *J* = 17.4, 10.7, 6.0 Hz, 1H), 5.26 (d, *J* = 17.4 Hz, 1H), 5.22 (d, *J* = 10.7 Hz, 1H), 4.63 (dt, *J* = 6.0, 6.0 Hz, 2H), 3.70 (s, 3H), 3.68 (s, 2H), 1.71-1.87 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 172.58, 156.28, 137.75, 131.19, 128.50, 123.87, 120.52, 116.66, 113.18, 79.76, 52.00, 36.61, 28.71, 9.62.

Step 3

[00123] A solution of methyl 2-(2-(pent-1-en-3-yloxy)phenyl)acetate (0.24 g, 1.0 mmol) in *N*-methyl-2-pyrrolidone (1.0 mL) was irradiated with microwave radiation in a Biotage Initiator at 180°C for 30 minutes, then for 15 minutes. The solution was diluted with ethyl acetate (25 mL), then washed with water (4 x 25 mL) and with saturated aqueous sodium chloride (25 mL); dried over sodium sulfate; filtered and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ SP1 system (40 g silica cartridge), eluting with 0-7% ethyl acetate in hexanes, gave methyl (*E*)-2-(2-hydroxy-3-(pent-2-enyl)phenyl)acetate (0.89 g, 37%). ¹H NMR (400 MHz, CDCl₃): δ 7.09 (s, 1H), 7.08 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.85 (dd, *J* = 7.6, 7.4 Hz, 1H), 5.59-5.70 (m, 2H), 3.75 (s, 3H), 3.69 (s, 2H), 3.41 (d, *J* = 4.7 Hz, 2H), 2.04-2.11 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 174.31, 153.53, 134.44, 129.86, 129.32, 128.62, 127.13, 121.08, 120.82, 52.79, 37.59, 34.17, 25.77, 13.97.

Step 4

[00124] Methyl (*E*)-2-(2-hydroxy-3-(pent-2-enyl)phenyl)acetate (0.14 g, 0.6 mmol) was hydrogenated as for Compound I, step 3, but using methanol as solvent, to give methyl 2-(2-hydroxy-3-pentylphenyl)acetate (0.11 g, 76%). ¹H NMR (400 MHz, CDCl₃): δ 7.57 (s, 1H), 7.11

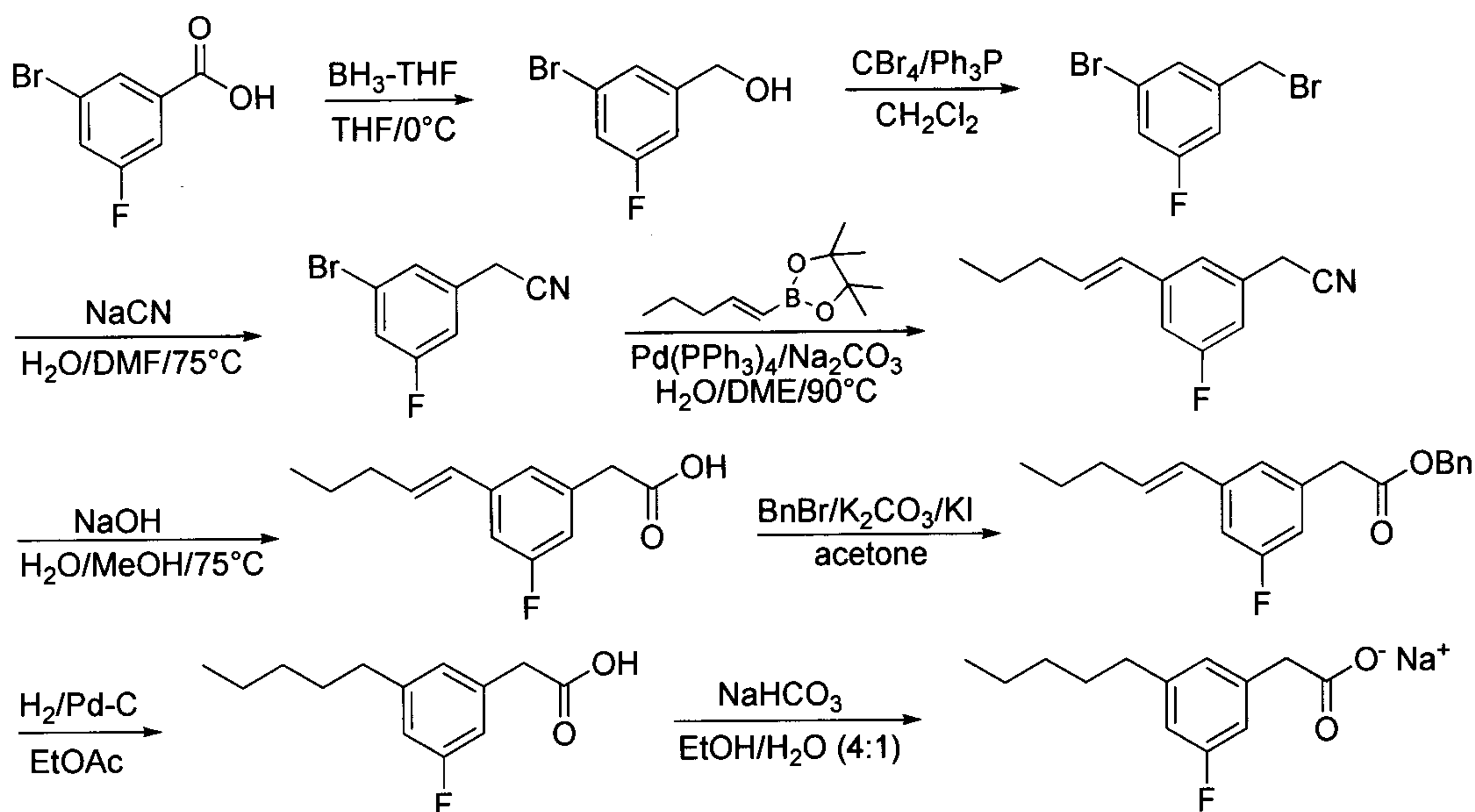
(dd, $J = 7.4, 1.6$ Hz, 1H), 6.96 (dd, $J = 7.4, 1.6$ Hz, 1H), 6.84 (dd, $J = 7.4, 7.4$ Hz, 1H), 3.76 (s, 3H), 3.70 (s, 2H), 2.68 (t, $J = 7.8$ Hz, 2H), 1.61-1.67 (m, 2H), 1.36-1.43 (m, 4H), 0.93 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ 175.01, 153.48, 131.75, 129.98, 128.75, 120.74, 120.60, 53.01, 38.30, 32.10, 30.50, 29.91, 22.87, 14.34.

Step 5

[00125] Methyl 2-(2-hydroxy-3-pentylphenyl)acetate (0.11 g, 0.5 mmol) was hydrolysed as for Compound I, step 4, using acetonitrile/water (4:1) as solvents, to give 2-(2-hydroxy-3-pentylphenyl)acetic acid (0.57 g, 57%). ^1H NMR (400 MHz, CDCl_3): δ 8.70 (br s, 1H), 7.09 (dd, $J = 7.6, 1.6$ Hz, 1H), 6.98 (dd, $J = 7.4, 1.6$ Hz, 1H), 6.84 (dd, $J = 7.6, 7.4$ Hz, 1H), 3.68 (s, 2H), 2.62 (t, $J = 7.8$ Hz, 2H), 1.57-1.65 (m, 2H), 1.31-1.40 (m, 4H), 0.91 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ 179.89, 152.79, 130.92, 130.04, 128.98, 121.08, 120.24, 37.74, 32.02, 30.34, 29.78, 22.80, 14.30.

Step 6

[00126] 2-(2-Hydroxy-3-pentylphenyl)acetic acid (22 mg, 0.098 mmol) was converted to the sodium salt as for Compound I, step 5 to give sodium 2-(2-hydroxy-3-pentylphenyl)acetate (24 mg, 98%). ^1H NMR (400 MHz, CD_3OD): δ 6.91 (dd, $J = 7.5, 1.6$ Hz, 1H), 6.87 (dd, $J = 7.5, 1.6$ Hz, 1H), 6.66 (dd, $J = 7.5, 7.5$ Hz, 1H), 3.49 (s, 2H), 2.59 (t, $J = 7.7$ Hz, 2H), 1.55-1.62 (m, 2H), 1.28-1.38 (m, 4H), 0.90 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 180.26, 154.27, 130.75, 128.21, 127.90, 124.24, 119.23, 42.91, 31.83, 30.21, 29.82, 22.51, 13.29; LRMS (ESI negative): m/z 220.8 (100%, $\text{M} - \text{Na}^+$); UPLC (System A): 5.0 min. UPLC System A: Mobile phase A = 10 mM aqueous ammonium formate; mobile phase B = acetonitrile; solid phase = HSS T3 column; gradient = 5-100% B in A over 10 minutes.

Compound X: Sodium salt of 2-(3-fluoro-5-pentylphenyl)acetic acid**Step 1**

[00127] A solution of 3-bromo-5-fluorobenzoic acid (2.74 g, 12.5 mmol) in tetrahydrofuran (6 mL), at 0°C under nitrogen, was treated with borane-tetrahydrofuran complex (1M, 15 mL, 15 mmol) in small portions over 12 min, and the reaction was then stirred at 0°C for 70 minutes, and at room temperature for 22 h. The reaction was quenched by addition of methanol (10 mL), and the methanolic mixture was stirred at room temperature for 3 h, and then evaporated *in vacuo*, with co-evaporation from methanol, then from ethyl acetate, to give the crude product. The material was dissolved in ethyl acetate (200 mL), and the solution was washed with 0.5M aqueous sodium hydroxide (200 mL), and with saturated aqueous sodium chloride (100 mL); then dried over sodium sulfate; filtered and evaporated *in vacuo* to give 3-bromo-5-fluorobenzyl alcohol (1.79 g, 67%). ¹H NMR (400 MHz, CDCl₃): δ 7.29 (s, 1H), 7.15 (ddd, *J*_{HF} = 8.2 Hz, *J*_{HH} = 2.2, 1.8 Hz, 1H), 7.00-7.02 and 7.02-7.04 (dm, *J*_{HF} = 9.2 Hz, *J*_{HH} = unresolved, 1H), 4.66 (s, 2H), 2.04 (br s, 1H); ¹⁹F NMR (377 MHz, CDCl₃): δ -111.05 (dd, *J*_{HF} = 9.3, 8.0 Hz, 1F); ¹³C NMR (101 MHz, CDCl₃): δ 162.87 (d, *J*_{CF} = 250.6 Hz), 145.42 (d, *J*_{CF} = 6.9 Hz), 125.45 (d, *J*_{CF} = 3.1 Hz), 122.69 (d, *J*_{CF} = 9.2 Hz), 118.01 (d, *J*_{CF} = 24.6 Hz), 112.51 (d, *J*_{CF} = 21.5 Hz), 63.60 (d, *J*_{CF} = 2.3 Hz).

Step 2

[00128] A solution of 3-bromo-5-fluorobenzyl alcohol (1.79 g, 8.39 mmol) and triphenylphosphine (3.65 g, 10.10 mmol) in dichloromethane (45 mL), was treated with carbon tetrabromide (3.34 g,

10.10 mmol) in small portions over 10 min, and the reaction was then stirred at room temperature overnight. Solvent was evaporated *in vacuo*, and the residue was treated with diethylether (50 mL). The resultant white slurry was stirred at room temperature, and then filtered through Celite™. The residue was washed with diethylether (2 x 50 mL), and the combined filtrate and washings were evaporated *in vacuo* to give the crude product. Purification on a silica pad, eluting with 2% ethyl acetate/hexane, gave 3-bromo-5-fluorobenzyl bromide (2.21 g, 98%). ¹H NMR (400 MHz, CDCl₃): δ 7.33 (s, 1H), 7.18 (ddd, *J*_{HF} = 8.2 Hz, *J*_{HH} = 2.0, 2.0 Hz, 1H), 7.05 (ddd, *J*_{HF} = 9.0 Hz, *J*_{HH} = 1.8, 1.6 Hz, 1H), 4.38 (s, 2H); ¹⁹F NMR (377 MHz, CDCl₃): δ -110.19 to -110.14 (m, 1F); ¹³C NMR (101 MHz, CDCl₃): δ 162.67 (d, *J*_{CF} = 252.1 Hz), 141.61 (d, *J*_{CF} = 8.5 Hz), 128.17 (d, *J*_{CF} = 3.1 Hz), 122.94 (d, *J*_{CF} = 10.0 Hz), 119.39 (d, *J*_{CF} = 24.6 Hz), 115.34 (d, *J*_{CF} = 22.3 Hz), 31.31 (d, *J*_{CF} = 2.3 Hz).

Step 3

[00129] A suspension of sodium cyanide (0.38 g, 7.73 mmol) in water (0.35 mL) was treated with a solution of 3-bromo-5-fluorobenzyl bromide (1.38 g, 5.15 mmol) in dimethylformamide (2.6 mL), and the reaction was heated at 75°C in a sealed tube for 3 h. The reaction was cooled to room temperature and was partitioned between ethyl acetate (50 mL) and 2.5% w/v aqueous sodium bicarbonate (100 mL). The aqueous phase was extracted with a further portion of ethyl acetate (50 mL); and the combined extracts were washed with water (2 x 50 mL) and with saturated aqueous sodium chloride (50 mL); dried over sodium sulfate; filtered, and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ 40iM column (silica), eluting with 10% ethyl acetate/hexane, gave 2-[3-bromo-5-fluorophenyl]acetonitrile (0.64 g, 58%). ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.28 (m, 1H), 7.17-7.19 & 7.19-7.21 (dm, *J*_{HF} = 8.0 Hz, *J*_{HH} = unresolved, 1H), 6.98-7.00 & 7.00-7.02 (dm, *J*_{HF} = 8.8 Hz, *J*_{HH} = unresolved, 1H), 3.73 (s, 2H); ¹⁹F NMR (377 MHz, CDCl₃): δ -109.46 (dd, *J*_{HF} = 8.0, 8.0 Hz, 1F); ¹³C NMR (101 MHz, CDCl₃): δ 162.90 (d, *J*_{CF} = 252.1 Hz), 133.95 (d, *J*_{CF} = 8.5 Hz), 127.24 (d, *J*_{CF} = 3.8 Hz), 123.53 (d, *J*_{CF} = 10.0 Hz), 119.22 (d, *J*_{CF} = 23.8 Hz), 117.00, 114.50 (d, *J*_{CF} = 23.1 Hz), 23.30 (d, *J*_{CF} = 1.5 Hz).

Step 4

[00130] A solution of the aryl bromide (0.55 g, 2.58 mmol) and (*E*)-1-penten-1-ylboronic acid pinacol ester (0.61g, 3.13 mmol) in dimethoxyethane (13 mL) was treated with a solution of sodium carbonate (0.55 g, 5.17 mmol) in water (3 mL). The solution was deoxygenated with nitrogen, and was treated with tetrakis(triphenylphosphine)palladium (0.15 g, 0.13 mmol; 5 mole

%). The mixture was then heated at 90°C, in a sealed tube for 17 h. The reaction was cooled to room temperature and was partitioned between ethyl acetate (50 mL) and 1M aqueous hydrochloric acid (50 mL). The organic phase was washed with saturated aqueous sodium chloride (30 mL); dried over sodium sulfate; filtered, and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ 40iM column (silica), eluting with (3%) ethyl acetate/hexane, gave (*E*)-2-[3-fluoro-5-[pent-1-enyl]phenyl]acetonitrile (0.43 g, 82%). ¹H NMR (400 MHz, CDCl₃): δ 7.04 (s, 1H), 6.97 (ddd, *J*_{HF} = 9.8 Hz, *J*_{HH} = 2.0, 1.5 Hz, 1H), 6.82-6.85 (m, 1H), 6.31 (d, *J* = 15.8 Hz, 1H), 6.25 (ddd, *J* = 15.8, 5.9, 0 Hz, 1H), 3.68 (s, 2H), 2.18 (td, *J* = 7.2, 5.4 Hz, 2H), 1.49 (qt, *J* = 7.4, 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ¹⁹F NMR (377 MHz, CDCl₃): δ -112.93 (dd, *J*_{HF} = 10.6, 9.3 Hz, 1F); ¹³C NMR (101 MHz, CDCl₃): δ 163.43 (d, *J*_{CF} = 246.0 Hz), 141.44 (d, *J*_{CF} = 8.5 Hz), 133.99, 132.37 (d, *J*_{CF} = 8.5 Hz), 128.42 (d, *J*_{CF} = 2.3 Hz), 121.60 (d, *J*_{CF} = 3.1 Hz), 117.66, 113.40 (d, *J*_{CF} = 23.1 Hz), 112.21 (d, *J*_{CF} = 22.3 Hz), 35.22, 23.49 (d, *J*_{CF} = 2.3 Hz), 22.51, 13.94.

Step 5

[00131] A solution of the phenylacetonitrile derivative (0.43 g, 2.10 mmol) in methanol (42 mL) was treated with aqueous sodium hydroxide (5M; 21 mL, 105 mmol), and the mixture was heated at 75°C in a sealed tube for 4.5 h. The reaction mixture was cooled to room temperature, and was quenched with 6M aqueous hydrochloric acid (21 mL); stirred at room temperature for 10 min; then extracted with ethyl acetate (2 x 75 mL). The organic extract was washed with saturated aqueous sodium chloride (75 mL); dried over sodium sulfate; filtered, and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ 40iM column (silica), eluting with 70% ethyl acetate/hexane, gave the methyl ester of the desired product (0.09 g, 18%), and ~95% pure (*E*)-2-[3-fluoro-5-[pent-1-enyl]phenyl]acetic acid (0.22 g, 48%). ¹H NMR (400 MHz, CDCl₃): δ 11.17 (br s, 1H), 7.02 (s, 1H), 6.98 (ddd, *J*_{HF} = 9.8 Hz, *J*_{HH} = 2.0, 1.8 Hz, 1H), 6.85 (ddd, *J*_{HF} = 9.0 Hz, *J*_{HH} = 1.8, 1.6 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 6.25 (dt, *J* = 15.8, 6.4 Hz, 1H), 3.62 (s, 2H), 2.17-2.22 (m, 2H), 1.51 (qt, *J* = 7.4, 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ¹⁹F NMR (377 MHz, CDCl₃): δ -114.10 (dd, *J*_{HF} = 9.3, 9.3 Hz, 1F).

Step 6

[00132] A solution of the partially-purified acid (0.28 g, 1.26 mmol) in acetone (5 mL) was treated with potassium carbonate (0.26 g, 1.90 mmol), potassium iodide (0.04 g, 0.25 mmol) and benzyl bromide (0.18 mL, 1.5 mmol), and the reaction was stirred at room temperature for 18 h. The reaction mixture was partitioned between ethyl acetate (25 mL) and 1M aqueous hydrochloric

acid (25 mL). The organic phase was then washed with saturated aqueous sodium chloride (25 mL); dried over sodium sulfate; filtered, and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ 40iM column (silica), eluting with 5% ethyl acetate/hexane gave benzyl (*E*)-2-[3-fluoro-5-[pent-1-enyl]phenyl]acetate (0.3 g, 75%). ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.40 (m, 5H), 7.03 (s, 1H), 6.97 (ddd, *J*_{HF} = 10.0 Hz, *J*_{HH} = 2.3, 1.5 Hz, 1H), 6.86 (ddd, *J*_{HF} = 9.0 Hz, *J*_{HH} = 2.0, 1.7 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.5 Hz, 1H), 5.16 (s, 2H), 3.64 (s, 2H), 2.17-2.23 (m, 2H), 1.52 (qt, *J* = 7.4, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ¹⁹F NMR (377 MHz, CDCl₃): δ -114.34 (dd, *J*_{HF} = 9.3, 9.3 Hz, 1F); ¹³C NMR (101 MHz, CDCl₃): δ 171.08, 163.32 (d, *J*_{CF} = 244.4 Hz), 140.65 (d, *J*_{CF} = 7.7 Hz), 136.17 (d, *J*_{CF} = 8.5 Hz), 135.93, 133.05, 128.95 (d, *J*_{CF} = 3.1 Hz), 128.84, 128.52 (d, *J*_{CF} = 9.2 Hz), 128.48, 123.09 (d, *J*_{CF} = 2.3 Hz), 114.78 (d, *J*_{CF} = 22.3 Hz), 111.46 (d, *J*_{CF} = 22.3 Hz), 67.04, 41.26 (d, *J*_{CF} = 1.5 Hz), 35.27, 22.63, 14.00.

Step 7

[00133] A solution of the benzyl ester (0.16 g, 0.50 mmol) in ethyl acetate (2 mL) was treated with palladium on carbon (1% w/w Pd; 15 mg). The mixture was degassed with hydrogen, and was stirred under 1 atmosphere of hydrogen at room temperature overnight. The reaction was filtered, and evaporated *in vacuo* to give 2-[3-fluoro-5-pentylphenyl]-acetic acid (0.11 g, 97%). ¹H NMR (400 MHz, CDCl₃): δ 11.47 (br s, 1H), 6.89 (s, 1H), 6.81-6.86 (m, 2H), 3.62 (s, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.58-1.66 (m, 2H), 1.28-1.41 (m, 4H), 0.92 (t, *J* = 6.8 Hz, 3H); ¹⁹F NMR (377 MHz, CDCl₃): δ -114.34 (dd, *J*_{HF} = 9.3, 9.3 Hz, 1F); ¹³C NMR (101 MHz, CDCl₃): δ 178.15, 163.08 (d, *J*_{CF} = 246.0 Hz), 145.02 (d, *J*_{CF} = 7.7 Hz), 135.04 (d, *J*_{CF} = 8.5 Hz), 125.49 (d, *J*_{CF} = 2.3 Hz), 114.49 (d, *J*_{CF} = 20.8 Hz), 113.83 (d, *J*_{CF} = 22.3 Hz), 41.01 (d, *J*_{CF} = 1.5 Hz), 35.87 (d, *J*_{CF} = 1.5 Hz), 31.67, 31.03, 22.74, 14.24.

Step 8

[00134] A solution of the acid (0.11 g, 0.49 mmol) in ethanol (3 mL) was treated with a solution of sodium bicarbonate (0.041 g, 0.49 mmol) in water (0.75 mL), and the reaction was stirred at room temperature for 17 h. Ethanol was evaporated *in vacuo*, and the residual aqueous syrup was diluted with water (10 mL), filtered (0.2 μm), and lyophilised to give sodium 2-[3-fluoro-5-pentylphenyl]acetate as a white solid (0.12 g, 99%). mp 120-123°C; ¹H NMR (400 MHz, CD₃OD): δ 6.94 (s, 1H), 6.87 (ddd, *J*_{HF} = 9.8 Hz, *J*_{HH} = 2.0, 2.0 Hz, 1H), 6.70 (ddd, *J*_{HF} = 10.0 Hz, *J*_{HH} = 2.0, 2.0 Hz, 1H), 3.45 (s, 2H), 2.56 (t, *J* = 7.7 Hz, 2H), 1.58-1.63 (m, 2H), 1.26-1.39 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ¹⁹F NMR (377 MHz, CD₃OD): δ -117.54 (dd, *J*_{HF} = 10.0, 10.0 Hz, 1F); ¹³C NMR

(101 MHz, CD₃OD): δ 178.66, 163.04 (d, J_{CF} = 242.9 Hz), 145.07 (d, J_{CF} = 7.7 Hz), 140.42 (d, J_{CF} = 8.5 Hz), 125.03 (d, J_{CF} = 2.3 Hz), 112.99 (d, J_{CF} = 22.3 Hz), 112.30 (d, J_{CF} = 20.8 Hz), 44.96, 35.53 (d, J_{CF} = 1.5 Hz), 31.46, 31.00, 22.45, 13.30; HPLC: 1.2 min.

Compound XI: Sodium salt of 2-(2-Fluoro-3-pentylphenyl)acetic acid

[00135] The above compound was prepared as for Compound X, starting with 3-bromo-2-fluorobenzoic acid. White solid; ¹H NMR (400 MHz, CD₃OD): δ 7.13 (ddd, J_{HF} = 7.0 Hz, J_{HH} = 7.4, 1.9 Hz, 2H), 7.03 (ddd, J_{HF} = 7.0 Hz, J_{HH} = 7.4, 1.9 Hz, 1H), 6.97 (dd, J_{HH} = 7.4, 7.4 Hz, 1H), 3.51 (d, J_{HF} = 1.4 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.56-1.63 (m, 2H), 1.28-1.40 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CD₃OD): δ 178.21, 159.70 (d, J_{CF} = 242.9 Hz), 129.07 (d, J_{CF} = 4.6 Hz), 128.88, 128.43 (d, J_{CF} = 5.4 Hz), 125.02 (d, J_{CF} = 17.7 Hz), 123.31 (d, J_{CF} = 4.6 Hz), 37.89 (d, J_{CF} = 3.8 Hz), 31.55, 29.98, 28.91 (d, J_{CF} = 3.1 Hz), 22.41, 13.26; ¹⁹F NMR (377 MHz, CD₃OD): δ -126.09 to -126.05 (m, 1F); LRMS (ESI): m/z 220.0 (M – CO₂Na + acetonitrile), 179.4 (M – CO₂Na); HPLC: 1.2 min.

Compound XII: Sodium salt of 2-(4-Fluoro-3-pentylphenyl)acetic acid

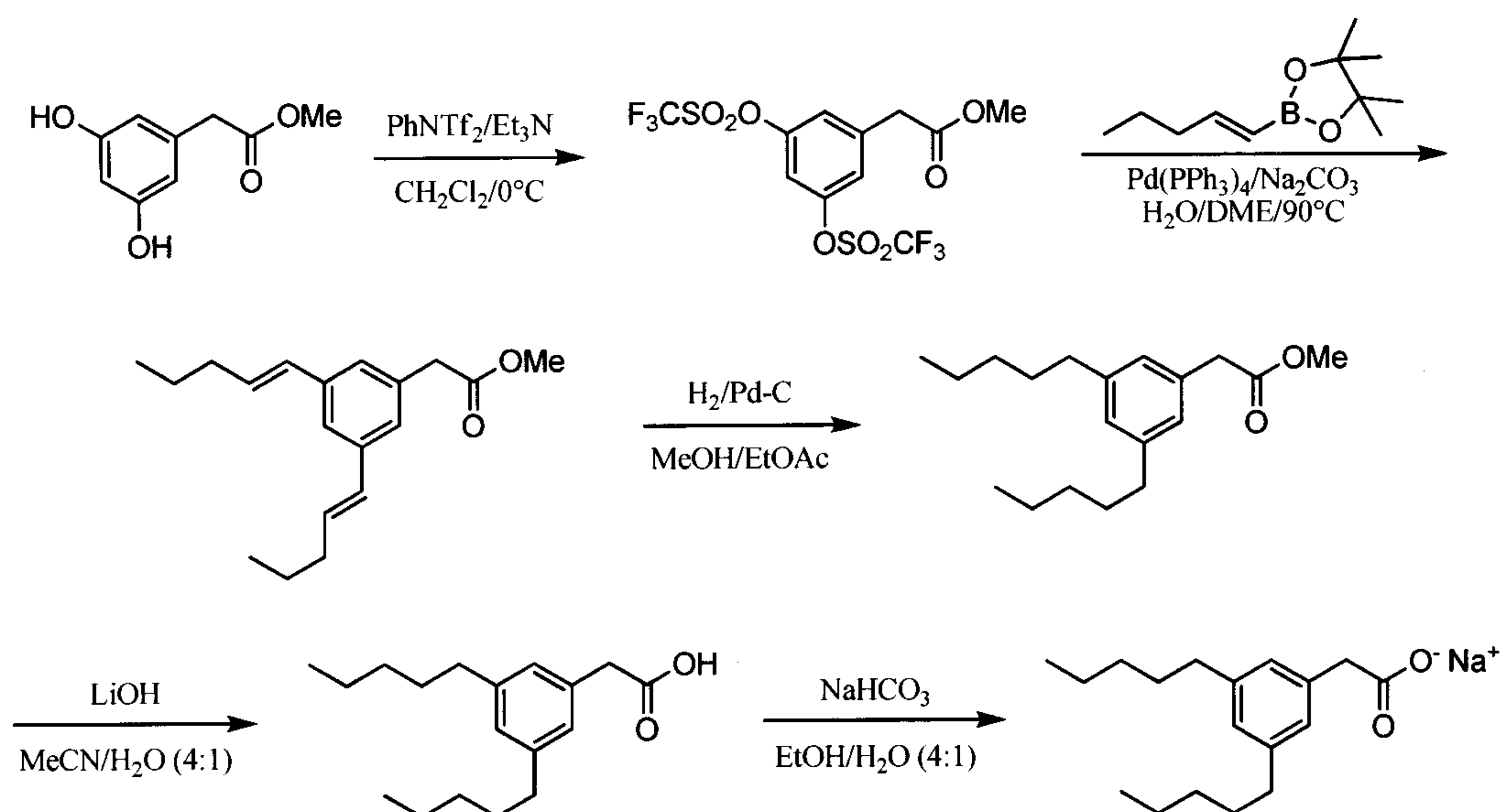
[00136] The above compound was prepared from methyl 2-(3-bromo-4-fluorophenyl)acetate by Suzuki coupling as for Compound VII; followed by hydrogenation, ester hydrolysis and salt formation as for Compound I. The starting ester was prepared by reaction of 2-(3-bromo-4-fluorophenyl)acetic acid with methanol in the presence of sulfuric acid. White solid; ¹H NMR (400 MHz, CD₃OD): δ 7.16 (dd, J_{HF} = 7.4 Hz, J_{HH} = 2.3 Hz, 2H), 7.08 (ddd, J_{HF} = 5.0 Hz, J_{HH} = 8.3, 2.3 Hz, 1H), 6.88 (dd, J_{HF} = 10.1 Hz, J_{HH} = 8.3 Hz, 1H), 3.40 (s, 2H), 2.59 (t, J = 7.7 Hz, 2H), 1.55-1.63 (m, 2H), 1.28-1.40 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CD₃OD): δ 179.12, 159.88 (d, J_{CF} = 240.6 Hz), 133.88 (d, J_{CF} = 3.8 Hz), 131.26 (d, J_{CF} = 4.6 Hz), 128.78 (d, J_{CF} = 16.1 Hz), 127.96 (d, J_{CF} = 8.5 Hz), 114.26 (d, J_{CF} = 23.1 Hz), 44.38, 31.51, 30.00, 28.76 (d, J_{CF} = 1.5 Hz), 22.36, 13.18; ¹⁹F NMR (377 MHz, CD₃OD): δ -126.45 to -126.40 (m, 1F); LRMS (ESI): m/z 225.2 (M – Na⁺ + 2H⁺); HPLC: 1.9 min.

Compound XIII: Sodium salt of (RS)-2-Fluoro-2-(3-pentylphenyl)acetic acid

[00137] The above compound was prepared from ethyl 2-fluoro-2-(3-pentylphenyl)acetate as for Compound I. The ester was prepared by reaction of ethyl 2-(3-pentylphenyl)acetate with lithium diisopropylamide and *N*-fluorobenzenesulfonimide at -78°C in Tetrahydrofuran. White solid; ¹H NMR (400 MHz, CD₃OD): δ 7.34 (s, 1H), 7.30 (dd, J = 7.6, 1.4 Hz, 1H), 7.24 (dd, J = 7.6, 7.6 Hz,

1H), 7.13 (dd, $J = 7.4, 1.0$ Hz, 1H), 5.53 (d, $J_{\text{HF}} = 51.3$ Hz, 1H), 2.60 (t, $J = 7.7$ Hz, 2H), 1.59-1.65 (m, 2H), 1.27-1.39 (m, 4H), 0.76 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 173.73 (d, $J_{\text{CF}} = 23.9$ Hz), 141.34, 136.37 (d, $J_{\text{CF}} = 20.0$ Hz), 126.79 (d, $J_{\text{CF}} = 2.3$ Hz), 126.40, 125.41 (d, $J_{\text{CF}} = 5.4$ Hz), 122.84 (d, $J_{\text{CF}} = 5.4$ Hz), 90.34 (d, $J_{\text{CF}} = 183.4$ Hz), 34.13, 29.91, 29.65, 20.85, 11.64; ^{19}F NMR (377 MHz, CD_3OD): δ -168.83 (d, $J_{\text{HF}} = 51.7$ Hz, 1F); LRMS (ESI negative): m/z 223.0 (100%, $\text{M} - \text{Na}^+$); HPLC: 4.1 min.

Compound XIV: Sodium 2-[3,5-Dipentylphenyl] acetate



Step 1

[00138] A suspension of methyl 2-[3,5-dihydroxyphenyl]acetate (1.00 g, 5.49 mmol) and N-phenyl-bis(trifluoromethylsulfonyl)imide (4.31 g, 12.1 mmol) in dichloromethane (20 mL), at 0°C under nitrogen, was treated with triethylamine (1.68 mL, 12.1 mmol). A clear solution formed. The reaction was then stirred under nitrogen at 0°C for 2 h, and at room temperature for 21 h. The reaction was diluted with ethyl acetate (100 mL), and the solution was washed with 0.5M aqueous sodium hydroxide (2 x 100 mL), and with saturated aqueous sodium chloride (75 mL); then dried over sodium sulphate; filtered and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ 40iM column (silica), eluting with ethyl acetate/hexane 0:1 to 1:9, gave methyl 2-[3,5-bis(trifluoromethylsulfonyloxy)phenyl]acetate (2.23 g, 91%) as pale oil. ^1H NMR (400 MHz, CDCl_3): δ 7.32 (d, $J = 2.2$ Hz, 2H), 7.18 (dd, $J = 2.2, 2.2$ Hz, 1H), 3.72 (s, 5H); ^{19}F NMR (377 MHz, CDCl_3): δ -73.20 (s, 3F); ^{13}C NMR (101 MHz, CDCl_3): δ 170.05, 149.48, 139.01, 122.95, 118.87 (q, $J_{\text{CF}} = 320.5$ Hz), 114.42, 52.62, 40.29.

Step 2

[00139] A solution of the aryl bis(triflate) (2.23 g, 4.99 mmol) and (E)-1-penten-1-ylboronic acid pinacol ester (2.45 g, 12.5 mmol) in 1,2-dimethoxyethane (25 mL) was treated with a solution of sodium carbonate (1.59 g, 15.0 mmol) in water (8 mL). The solution was deoxygenated with nitrogen, and was then treated with Tetrakis(triphenylphosphine) palladium (0.58 g, 0.50 mmol). The mixture was heated at 90°C, in a sealed tube for 17 h. The reaction was cooled to room temperature and was partitioned between ethyl acetate (200 mL) and 1M aqueous hydrochloric acid (150 mL). The organic phase was washed with 5% aqueous sodium bicarbonate (150 mL), and with saturated aqueous sodium chloride (150 mL); then dried over sodium sulphate; filtered, and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ 40iL column (silica), eluting with ethyl acetate/hexane 0:1 to 3:97, gave methyl 2-[3,5-di[(E)-1-pent-1-enyl]phenyl] acetate as an inseparable 10:4 mixture with excess (E)-1-penten-1-ylboronic acid pinacol ester (1.12g, 61%). ¹H NMR (400 MHz, CDCl₃): δ 7.21 (s, 1H), 7.10 (d, *J* = 1.3 Hz, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.22 (dd, *J* = 15.8, 6.7 Hz, 1H), 3.65 (s, 3H), 3.55 (s, 2H), 2.18 (tdd, *J* = 6.8, 6.8, 1.0 Hz, 2H), 1.49 (qt, *J* = 7.4, 7.2 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 172.04, 138.59, 134.47, 131.34, 129.97, 125.57, 122.75, 52.07, 41.32, 35.39, 22.77, 13.97.

Step 3

[00140] A solution of the unsaturated compound (1.12 g, 78.5% w/w, 3.07 mmol) in ethyl acetate (1 mL) and methanol (1 mL) was treated with palladium on carbon (10% w/w Pd; 0.12 g). The mixture was degassed with hydrogen, and was stirred under 1 atm. of hydrogen at room temperature for 22 h. The reaction was filtered, and evaporated *in vacuo* to give methyl 2-[3,5-dipentylphenyl] acetate as an inseparable 10:4 mixture with pentylboronic acid pinacol ester (0.86 g, 76%). ¹H NMR (400 MHz, CDCl₃): δ 6.93 (s, 3H), 3.70 (s, 3H), 3.59 (s, 2H), 2.58 (t, *J* = 7.9 Hz, 2H), 1.58-1.66 (m, 2H), 1.32-1.38 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H).

Step 4

[00141] A solution of the methyl ester (0.86 g, 79% w/w, 2.34 mmol) in acetonitrile (24 mL) was treated with a solution of lithium hydroxide (0.28 g, 11.7 mmol) in water (6 mL), and the reaction was stirred at room temperature for 22 h. The reaction was quenched with 1M aqueous hydrochloric acid (55 mL), and then extracted with ethyl acetate (100 mL). The organic extract was washed with saturated aqueous sodium chloride (50 mL); then dried over sodium sulphate;

filtered, and evaporated *in vacuo* to give the crude product. Purification on a SiliaSep silicon oxide column, eluting with ethyl acetate/hexane 0:1 to 1:4, gave 2-[3,5-dipentyl]phenyl] acetic acid as a colorless oil (0.55 g, 84%). ¹H NMR (400 MHz, CDCl₃): δ 6.99 (s, 3H), 3.65 (s, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.64-1.71 (m, 2H), 1.36-1.44 (m, 4H), 0.97 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 178.96, 143.55, 133.21, 127.93, 127.06, 41.47, 36.13, 31.94, 31.47, 22.86, 14.34.

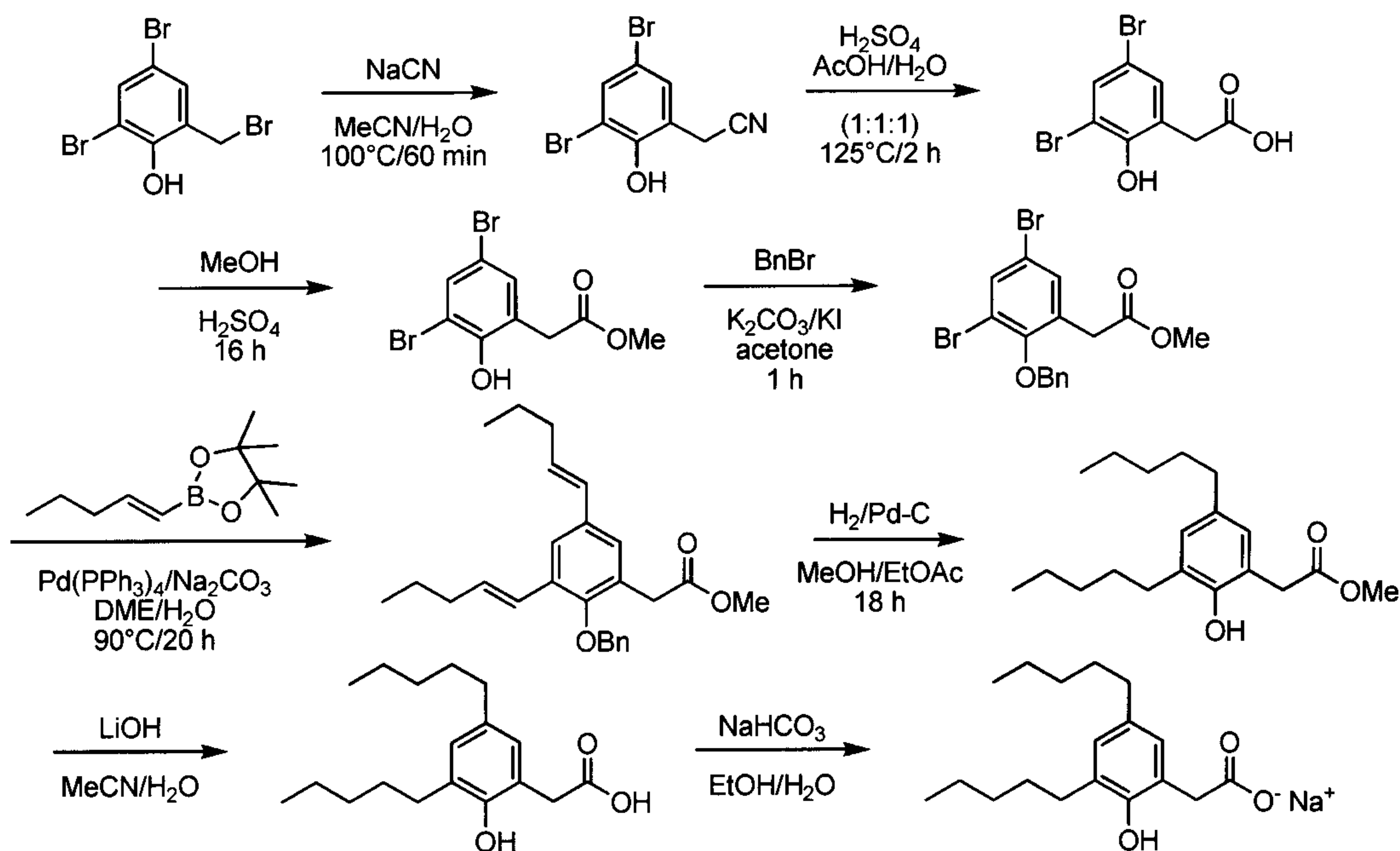
Step 5

[00142] A solution of the acid (0.48 g, 1.75 mmol) in ethanol (12 mL) was treated with a solution of sodium bicarbonate (0.15 g, 1.75 mmol) in water (3 mL), and the reaction was stirred at room temperature for 3 d. Ethanol was evaporated *in vacuo*, and the residual aqueous syrup was diluted with water (50 mL), filtered (PES, 0.2 μm), and lyophilised to give sodium 2-[3,5-dipentylphenyl] acetate as a white solid (0.52 g, quantitative). mp 225-230°C; ¹H NMR (400 MHz, CD₃OD + D₂O): δ 6.92 (s, 2H), 6.76 (s, 1H), 3.41 (s, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 1.52-1.59 (m, 2H), 1.23-1.33 (m, 4H), 0.85 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CD₃OD + D₂O): δ 179.99, 142.66, 137.63, 126.66, 126.16, 45.11, 35.61, 31.36, 31.19, 22.41, 13.47; LRMS (ESI): *m/z* 277.5 (w, [M – Na⁺ + 2H⁺]), 231.1 (100%, tropylium ion from loss of carboxy group); HPLC: 3.0 min.

Compound XV: Sodium salt of 2-(3,5-Dihexylphenyl)acetic acid

[00143] The above compound was prepared from (E)-hex-1-enylboronic acid pinacol ester as for Compound **XIV**. White solid; ¹H NMR (400 MHz, CD₃OD): δ 6.96 (s, 2H), 6.79 (s, 1H), 3.43 (s, 2H), 2.54 (d, *J* = 7.7 Hz, 4H), 1.55-1.63 (m, 4H), 1.28-1.36 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 6H); ¹³C NMR (101 MHz, CD₃OD): δ 179.68, 142.38, 137.82, 126.55, 126.07, 45.30, 35.87, 31.83, 31.67, 29.02, 22.61, 13.42; LRMS (ESI): *m/z* 322.0 (100%, M – Na⁺ + H⁺ + NH₄⁺) and 259.0 (35%, M – CO₂Na); UPLC (System A): 8.9 min. UPLC System A: Mobile phase A = 10 mM aqueous ammonium bicarbonate; mobile phase B = acetonitrile; solid phase = HSS T3 column; gradient = 5-100% B in A over 10 minutes.

Compound XVI: Sodium salt of 2-(2-Hydroxy-3,5-dipentylphenyl)acetic acid



Step 1

[00144] A solution of 2,4-dibromo-6-(bromomethyl)phenol (3.5 g, 10.0 mmol) in acetonitrile (17 mL) was treated with a solution of sodium cyanide (2.5 g, 50.0 mmol) and the reaction was heated at 100°C under reflux for 1 h. The reaction mixture cooled to room temperature and was poured into water (100 mL). The pH was adjusted from 10 to 8 with 1M aqueous hydrochloric acid, and the mixture was extracted with ethyl acetate (3 x 250 mL). Combined extracts were washed with 1M aqueous hydrochloric acid (250 mL) and with saturated aqueous sodium chloride (250 mL); dried over sodium sulfate; filtered and evaporated *in vacuo* to give the crude product. Extraction with acetone; filtration; and evaporation *in vacuo* gave 2-(3,5-dibromo-2-hydroxyphenyl)acetonitrile (2.6 g, 90%). ¹H NMR (400 MHz, d₆-acetone): δ 8.75 (br s, 1H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 3.92 (s, 2H); ¹³C NMR (101MHz, d₆-acetone): δ 151.31, 134.51, 131.92, 122.80, 117.43, 111.89, 111.53, 18.70.

Step 2

[00145] 2-(3,5-Dibromo-2-hydroxyphenyl)acetonitrile (2.6 g, 9.0 mmol) was treated with a mixture of sulfuric acid (2.5 mL), acetic acid (2.5 mL) and water (2.5 mL), and the reaction was heated at 125°C under reflux for 2 h. The reaction mixture was cooled to room temperature and was poured into a mixture of ice (50 mL) and water (50 mL), and was then stirred until the ice had melted. The mixture was extracted with ethyl acetate (250 mL); and the extract was then washed

with water (100 mL) and with saturated aqueous sodium chloride (100 mL); dried over sodium sulfate; filtered and evaporated *in vacuo* to give the crude 2-(3,5-dibromo-2-hydroxyphenyl)acetic acid (3.1 g). This material was used directly in the next step without further purification or characterization.

Step 3

[00146] A solution of crude 2-(3,5-dibromo-2-hydroxyphenyl)acetic acid (3.1 g, 9.0 mmol) in methanol (17 mL) was treated with sulfuric acid (0.43 mL, 8.1 mmol) and the reaction was stirred at ambient temperature for 16 h. Methanol was evaporated *in vacuo*, and the residue was dissolved in ethyl acetate (270 mL). The solution was washed with water (2 x 200 mL) and with saturated aqueous sodium chloride (130 mL); dried over sodium sulfate; filtered and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ SP1 system (120 g silica cartridge), eluting with 0-20% ethyl acetate in hexanes, gave methyl 2-(3,5-dibromo-2-hydroxyphenyl)acetate (1.4 g, 49%). ¹H NMR (400 MHz, CDCl₃): δ 7.52 (d, *J* = 2.2 Hz, 1H), 7.23 (d, *J* = 2.2 Hz, 1H), 6.42 (br s, 1H), 3.72 (s, 3H), 3.65 (s, 2H); ¹³C NMR (101 MHz, CDCl₃): δ 172.06, 150.60, 133.74, 133.50, 123.94, 112.62, 111.77, 52.78, 36.61.

Step 4

[00147] A solution of methyl 2-(3,5-dibromo-2-hydroxyphenyl)acetate (0.5 g, 1.54 mmol) in acetone (5 mL) was treated with potassium carbonate (0.26 g, 1.86 mmol), potassium iodide (0.05 g, 0.32 mmol) and benzyl bromide (0.20 mL, 1.7 mmol), and the reaction was stirred at room temperature for 1 h. Acetone was evaporated *in vacuo*, and the residue was partitioned between ethyl acetate (50 mL) and 1M aqueous hydrochloric acid (50 mL). The organic phase was washed with saturated aqueous sodium chloride (50 mL); dried over sodium sulfate; filtered and evaporated *in vacuo* to give the crude product. Purification on a Biotage™ SP1 system (40 g silica cartridge), eluting with 0-10% ethyl acetate in hexanes, gave methyl 2-(2-(benzyloxy)-3,5-dibromophenyl)acetate (0.6 g, 95%). ¹H NMR (400 MHz, CDCl₃): δ 7.67 (d, *J* = 2.4 Hz, 1H), 7.48-7.51 (m, 2H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.34-7.43 (m, 3H), 4.99 (s, 2H), 3.66 (s, 3H), 3.60 (s, 2H); ¹³C NMR (101 MHz, CDCl₃): δ 171.26, 153.79, 136.56, 135.38, 133.57, 132.04, 128.82, 128.64, 128.52, 118.69, 117.56, 75.53, 52.50, 35.86.

Step 5

[00148] Methyl 2-(2-(benzyloxy)-3,5-dibromophenyl)acetate (0.3 g, 0.73 mmol) and (E)-pent-1-enylboronic acid pinacol ester (0.4 g, 1.79 mmol) were coupled as for Compound I, step 2, to give methyl 2-(2-(benzyloxy)-3,5-di((E)-pent-1-enyl)phenyl)acetate (0.21 mg, 72%). ¹H NMR (400 MHz, CDCl₃): δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.44 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.38 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.32 (dt, *J* = 15.8, 7.0 Hz, 1H), 6.22 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.87 (s, 2H), 3.69 (s, 3H), 3.67 (s, 2H), 2.20-2.29 (m, 4H), 1.50-1.60 (m, 4H), 1.01 (t, *J* = 7.3 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 172.49, 153.59, 137.58, 134.35, 132.91, 131.91, 130.84, 129.53, 128.78, 128.32, 128.30, 128.24, 127.26, 125.21, 123.89, 75.89, 52.21, 35.94, 35.74, 35.42, 22.87, 22.77, 14.07, 14.06.

Step 6

[00149] Methyl 2-(2-(benzyloxy)-3,5-di((E)-pent-1-enyl)phenyl)acetate (0.2 g, 0.53 mmol) was hydrogenated as for Compound I, step 3, to give methyl 2-(2-hydroxy-3,5-dipentylphenyl)acetate (0.12 g, 73%). ¹H NMR (400 MHz, CDCl₃): δ 7.37 (s, 1H), 6.92 (d, *J* = 2.1 Hz, 2H), 6.77 (d, *J* = 2.1 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 1.58-1.66 (m, 4H), 1.31-1.41 (m, 8H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 175.01, 151.27, 135.14, 131.48, 129.92, 128.52, 120.30, 52.95, 38.35, 35.34, 32.15, 31.86, 31.74, 30.61, 30.03, 22.87, 22.83, 14.34, 14.31.

Step 7

[00150] Methyl 2-(2-hydroxy-3,5-dipentylphenyl)acetate (0.2 g, 0.53 mmol) was hydrolysed as for Compound I, step 4, to give the crude product mixed with lactonised material. A small portion was purified on a Biotage™ SP1 system (120 g silica cartridge), eluting with 0-100% ethyl acetate in hexanes, to give 2-(2-hydroxy-3,5-dipentylphenyl)acetic acid (13.5 mg). ¹H NMR (400 MHz, CDCl₃): δ 10.5 (br s, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 6.32 (br s, 1H), 3.66 (s, 2H), 2.58 (t, *J* = 7.9 Hz, 2H), 2.48 (t, *J* = 7.8 Hz, 2H), 1.52-1.63 (m, 4H), 1.26-1.37 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H).

Step 8

[00151] 2-(2-Hydroxy-3,5-dipentylphenyl)acetic acid (13.5 mg, 0.046 mmol) was converted to the sodium salt as for Compound I, step 5 to give sodium 2-(2-hydroxy-3,5-dipentylphenyl)acetate (11 mg, 77%). ¹H NMR (400 MHz, CD₃OD): δ 6.72 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H),

3.46 (s, 2H), 2.56 (t, $J = 7.6$ Hz, 2H), 2.44 (t, $J = 7.6$ Hz, 2H), 1.50-1.61 (m, 4H), 1.25-1.37 (m, 8H), 0.90 (t, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 180.33, 151.94, 133.47, 130.37, 128.21, 127.81, 123.99, 42.90, 34.97, 31.81, 31.60, 31.40, 30.25, 29.88, 22.51, 22.45, 13.29, 13.24; LRMS (ESI negative): m/z 291.2 (100%, $\text{M} - \text{Na}^+$); UPLC (System B): 7.7 min. UPLC System B: Mobile phase A = 0.1% aqueous formic acid; mobile phase B = 0.1% formic acid in acetonitrile; solid phase = HSS T3 column; gradient = 5-100% B in A over 10 minutes.

Compound XVII: Sodium salt of 2-(3,5-Dihexyl-2-hydroxyphenyl)acetic acid

[00152] The above compound was prepared as for Compound XVI, using (E)-hex-1-enylboronic acid pinacol ester. ^1H NMR (400 MHz, CD_3OD): δ 6.72 (d, $J = 2.0$ Hz, 1H), 6.69 (d, $J = 2.0$ Hz, 1H), 3.46 (s, 2H), 2.56 (t, $J = 7.6$ Hz, 2H), 2.44 (t, $J = 7.5$ Hz, 2H), 1.50-1.60 (m, 4H), 1.27-1.37 (m, 12H), 0.89 (t, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 6.80$ Hz, 3H); LRMS (ESI negative): m/z 319 (100%, $\text{M} - \text{Na}^+$); UPLC (System B): 8.7 min. ULC System B: Mobile phase A = 0.1% aqueous formic acid; mobile phase B = 0.1% formic acid in acetonitrile; solid phase = HSS T3 column; gradient = 5-100% B in A over 10 minutes.

Compound XVIII: Sodium salt of 2-(4-Hydroxy-3,5-dipentylphenyl)acetic acid

[00153] The above compound was prepared as for Compound XVI, from 2-(3,5-dibromo-4-hydroxyphenyl)acetic acid. ^1H NMR (400 MHz, CD_3OD): δ 6.87 (s, 2H), 3.33 (s, 2H), 2.55 (t, $J = 7.7$ Hz, 4H), 1.53-1.61 (m, 4H), 1.31-1.37 (m, 8H), 0.90 (t, $J = 7.0$ Hz, 6H); LRMS (ESI negative): m/z 291.1 (100%, $\text{M} - \text{Na}^+$); UPLC (System B): 6.8 min. UPLC System B: Mobile phase A = 0.1% aqueous formic acid; mobile phase B = 0.1% formic acid in acetonitrile; solid phase = HSS T3 column; gradient = 5-100% B in A over 10 minutes.

Compound XIX: Sodium salt of 2-(3,5-Dihexyl-4-hydroxyphenyl)acetic acid

[00154] The above compound was prepared as for Compound XVI, from 2-(3,5-dibromo-4-hydroxyphenyl)acetic acid, and (E)-hex-1-enylboronic acid pinacol ester. ^1H NMR (400 MHz, CD_3OD): δ 6.72 (d, $J = 2.0$ Hz, 1H), 6.69 (d, $J = 2.0$ Hz, 1H), 3.46 (s, 2H), 2.56 (t, $J = 7.6$ Hz, 2H), 2.44 (t, $J = 7.5$ Hz, 2H), 1.50-1.60 (m, 4H), 1.27-1.37 (m, 12H), 0.89 (t, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz, 3H); LRMS (ESI negative): m/z 319.1 (100%, $\text{M} - \text{Na}^+$); UPLC (System B): 7.6 min. UPLC System B: Mobile phase A = 0.1% aqueous formic acid; mobile phase B = 0.1% formic acid in acetonitrile; solid phase = HSS T3 column; gradient = 5-100% B in A over 10 minutes.

Compound XX: Sodium salt of 2-(4-Fluoro-3,5-dihexylphenyl)acetic acid

[00155] The above compound was prepared as for Compound **XVI**, starting from 3,5-dibromo-4-fluorobenzyl bromide and (E)-hex-1-enylboronic acid pinacol ester. 3,5-Dibromo-4-fluorobenzyl bromide was prepared by bromination of 3,5-dibromo-4-fluorotoluene with N-bromosuccinimide and azobisisobutyronitrile in acetonitrile at 80°C. ¹H NMR (400 MHz, CD₃OD): δ 6.98 (d, JHF = 7.0 Hz, 2H), 3.38 (s, 2H), 2.57 (t, J = 7.7 Hz, 4H), 1.54-1.61 (m, 4H), 1.28-1.37 (m, 12H), 0.89 (t, J = 6.7 Hz, 6H); ¹⁹F NMR (377 MHz, CD₃OD): δ -132.17 (d, JHF = 6.6 Hz, 1F); ¹³C NMR (101 MHz, CD₃OD): δ 179.44, 158.11 (d, JCF = 239.8 Hz), 133.26 (d, JCF = 3.8 Hz), 128.73 (d, JCF = 5.4 Hz), 128.56 (d, JCF = 16.9 Hz), 44.52, 31.69, 30.35 (d, JCF = 1.5 Hz), 28.98, 28.97 (d, JCF = 3.1 Hz), 22.51, 13.29; LRMS (ESI negative): *m/z* 321.0 (100%, M – Na⁺); UPLC (System B): 9.2 min. UPLC System B: Mobile phase A = 0.1% aqueous formic acid; mobile phase B = 0.1% formic acid in acetonitrile; solid phase = HSS T3 column; gradient = 5-100% B in A over 10 minutes.

Compound XXI: Sodium salt of 2-(4-Fluoro-3,5-dipentylphenyl)acetic acid

[00156] The above compound was prepared as for Compound **XVI**, starting from 3,5-dibromo-4-fluorobenzyl bromide. ¹H NMR (400 MHz, CD₃OD): δ 6.98 (d, JHF = 6.8 Hz, 2H), 3.37 (s, 2H), 2.57 (t, J = 7.6 Hz, 4H), 1.54-1.62 (m, 4H), 1.28-1.37 (m, 8H), 0.90 (t, J = 7.0 Hz, 6H); ¹⁹F NMR (377 MHz, CD₃OD): δ -132.34 (d, JHF = 6.6 Hz, 1F); ¹³C NMR (101 MHz, CD₃OD): δ 179.41, 158.10 (d, JCF = 239.8 Hz), 133.26 (d, JCF = 3.8 Hz), 128.72 (d, JCF = 4.6 Hz), 128.56 (d, JCF = 16.9 Hz), 44.51, 31.54, 30.07, 28.92 (d, JCF = 3.1 Hz), 22.38, 13.22; LRMS (ESI negative): *m/z* 293.0 (100%, M – Na⁺); UPLC (System B): 8.4 min. UPLC System B: Mobile phase A = 0.1% aqueous formic acid; mobile phase B = 0.1% formic acid in acetonitrile; solid phase = HSS T3 column; gradient = 5-100% B in A over 10 minutes.

Compound XXII: Sodium salt of 2-(2-Benzyl-3,5-dipentylphenyl)acetic Acid

[00157] The title compound was prepared as for Compound **XIV**, from methyl 2-(2-benzyl-3,5-di((E)-pent-1-enyl)phenyl)acetate. The latter was isolated as a side product (1.1% yield) from the scale-up of Compound **XIV**. ¹H NMR (400 MHz, CD₃OD): δ 7.17 (dd, J = 7.3, 7.3 Hz, 2H), 7.09 (dd, J = 7.3, 7.3 Hz, 1H), 6.97-6.99 (m, 3H), 6.86 (d, J = 1.8 Hz, 1H), 4.13 (s, 2H), 3.40 (s, 2H), 2.55 (t, J = 7.7 Hz, 2H), 2.49 (t, J = 7.8 Hz, 2H), 1.59-1.67 (m, 2H), 1.31-1.45 (m, 6H), 1.21-1.26 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H), 0.82 (t, J = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CD₃OD): δ 179.48,

141.46, 141.24, 140.47, 137.46, 133.70, 128.36, 128.05, 127.86, 127.75, 125.42, 43.25, 35.54, 33.90, 33.61, 31.86, 31.65, 31.25, 30.96, 22.49, 22.40, 13.31, 13.23; LRMS (ESI negative): m/z 365.0 (20%, $M - Na^+$), 321.1 (100%, $M - CO_2Na$); UPLC (System B): 9 min. (UPLC System B: Mobile phase A = 0.1% aqueous formic; mobile phase B = 0.1% formic in acetonitrile; solid phase = HSS T3; gradient = 5-100% B in A over 10 min.)

Compound XXIII: Sodium 2-[3,5-Di[(E)-Pent-1-enyl]phenyl]acetate

[00158] The title compound was prepared using the same procedure as for Compound **XIV**, but with the omission of the hydrogenation step. mp 226-30°C; ^1H NMR (400 MHz, CD_3OD): δ 7.18 (d, $J = 1.2$ Hz, 2H), 7.11 (d, $J = 1.2$ Hz, 1H), 6.34 (d, $J = 15.9$ Hz, 2H), 2.23 (dt, $J = 15.9, 6.7$ Hz, 2H), 3.44 (s, 2H), 2.14-2.19 (m, 4H), 1.49 (tq, $J = 7.4, 7.4$ Hz, 4H), 0.95 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (101MHz, CD_3OD): δ 179.41, 138.34, 138.06, 130.30, 130.16, 125.26, 121.60, 45.24, 35.10, 22.55 & 12.98; LRMS (negative mode): m/z 271 (w, $[M - Na^+]$), 227.2 (100%, $[M - Na^+ - CO_2]$); UPLC: 8 min. (UPLC; Conditions solvent A = 0.1% formic acid in water; Solvent B = 0.1% formic acid in acetonitrile; Gradient: 5-100% B in A over 10 min at 0.7 mL/min.)

Compound XXIV: Sodium 3-[3,5-Dipentylphenyl]propanoate

[00159] The title compound was prepared using the same procedure as for Compound **XIV** starting from 3-[3,5-dibromophenyl]propanoic acid. mp 211-217°C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.73 (s, 1H), 6.68 (s, 2H), 2.73-2.77 (m, 2H), 2.42-2.46 (m, 2H), 2.38 (t, $J = 7.8$ Hz, 4H), 1.43-1.51 (m, 4H), 1.19-1.28 (m, 8H), 0.83 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.55, 142.93, 141.85, 125.96, 125.77, 39.80, 36.13, 32.77, 31.99, 31.47, 22.79 & 14.27; LRMS (negative mode): m/z 289.4 (100%, $[M - Na^+]$); UPLC: 9 min. (UPLC: Conditions solvent A = 0.1% formic acid in water, solvent B = 0.1% formic acid in acetonitrile, Gradient: 5-100% B in A over 10 min at 0.7 mL/min.

Example 2: Effect of compounds on LPS-stimulated RAW264.7 cells; an osteoclast progenitor.

[00160] LPS, a bacteria-derived cell wall product, has long been recognized as a key factor in the development of bone loss. LPS plays an important role in bone resorption, which involves recruitment of inflammatory cells, synthesis of cytokines (such as interleukin-6 (IL-6), IL-12 and tumor necrosis factor- α (TNF- α)), and activation of osteoclast formation and differentiation.

[00161] RAW264.7 cells are precursors of osteoclasts and can be differentiated by several factors including Receptor activator of NF- κ B ligand (RANKL) or Lipopolysaccharide (LPS). Osteoclasts are characterized by high expression of tartrate resistant acid phosphatase (TRACP) and Matrix Metalloproteinase-9 (MMP-9) which can be used as markers for osteoclasts. It has been shown that RAW264.7 cells incubated in presence of capric acid resulted in an increase in IL-12 production and in a reduction of phosphatase (TRAP)-positive cells (TRAP expression, an osteoclast differentiation marker) (Wang et al., J. Biol. Chem. (2006), Vol. 281, No. 45, pp.34457-64). Furthermore, LPS strongly upregulated inducible nitric oxide synthase (iNOS) mRNA levels and nitric oxide (NO) production, whereas capric acid inhibited them. Additionally, capric acid also inhibited monocyte chemoattractant protein-1 (MCP-1) mRNA expression.

[00162] The effect of selected compounds on TRAP (osteoclast marker) and IL-12 was undertaken in RAW264.7 cells, a murine osteoclast precursor cell line, in comparison with capric acid, as a positive control for reduction of osteoclastogenesis (Park et al. (2011) PLOS One Volume 6, Issue 11, 8 pages). RAW264.7 cells were differentiated by the incubation with LPS (1 μ g/ml) in presence or not of capric acid or Compound I. On days 3-5, osteoclast formation was evaluated using tartrate-resistant acid phosphatase (TRAP) staining.

[00163] **Figure 1** represents the osteoclastogenesis effect of LPS in RAW264.7 cells as demonstrated by the high expression of TRAP (dark staining). Incubation with capric acid and Compound I indicates a different phenotype that the control and LPS-induced cells and no TRAP cells are observable indicating that the cells are not differentiated in osteoclasts.

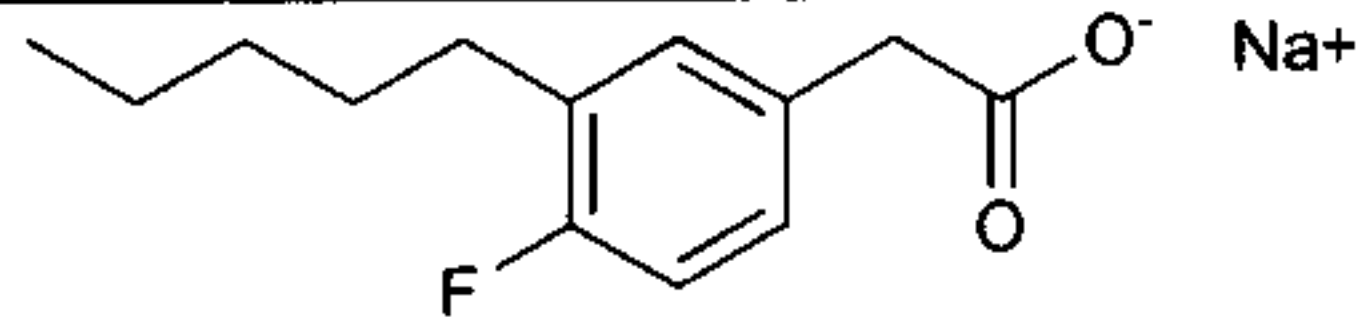
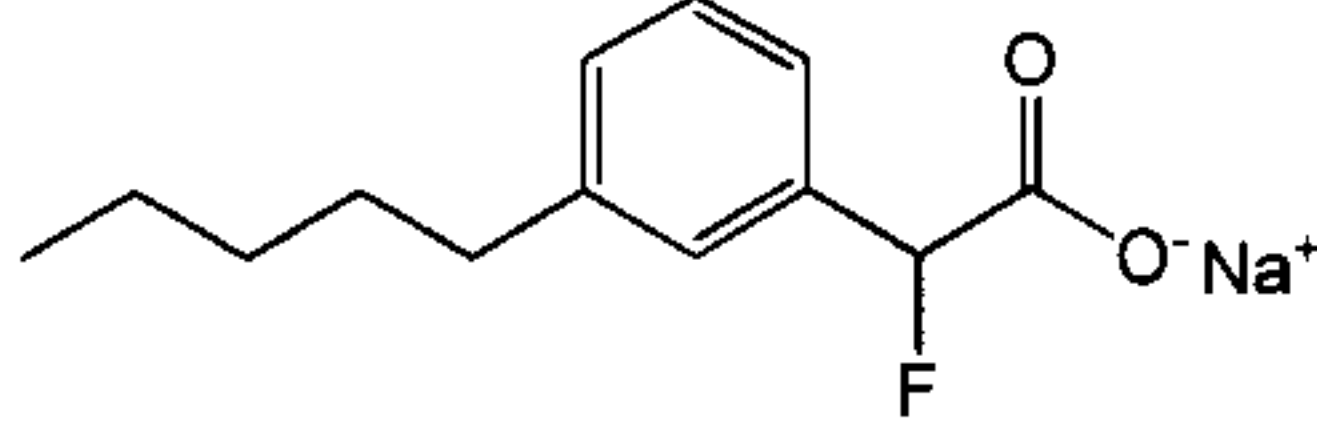
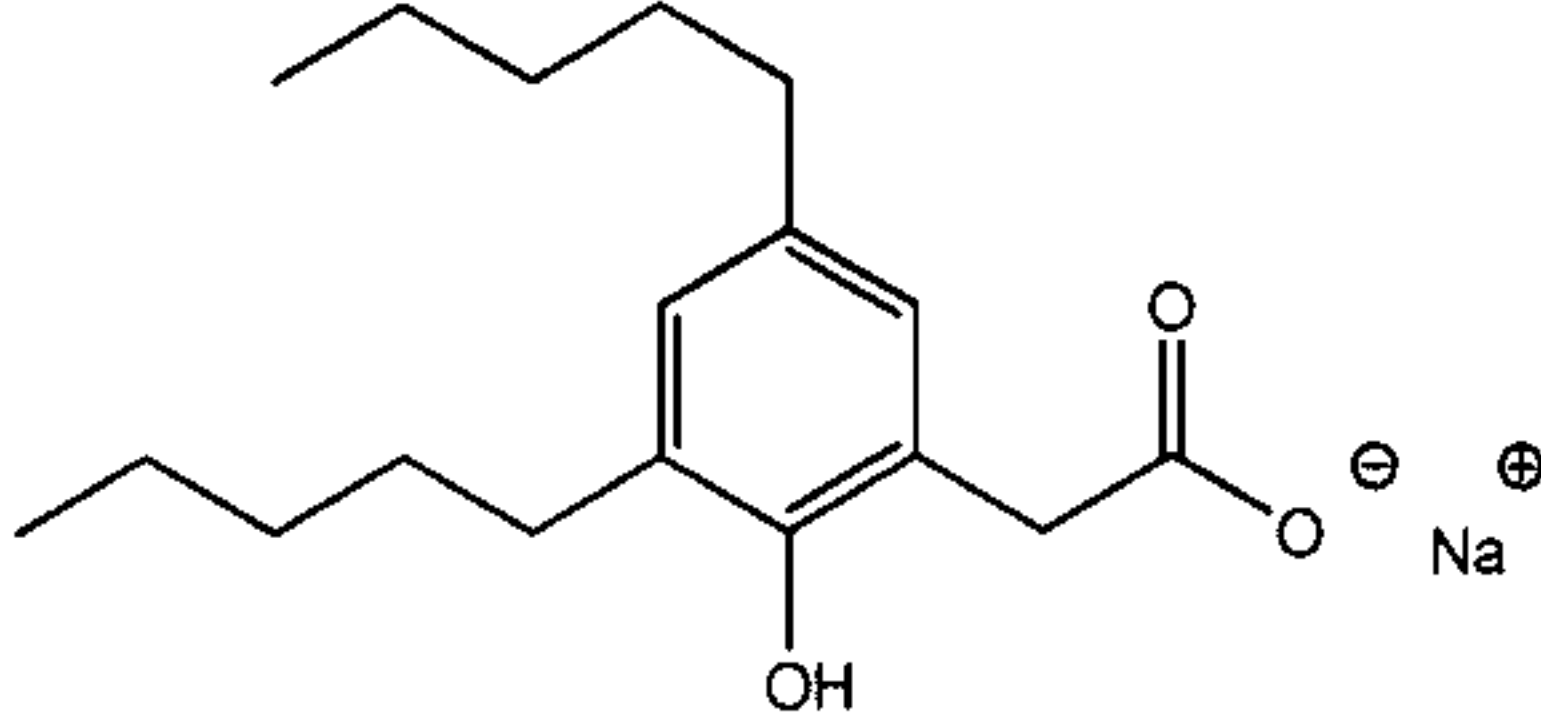
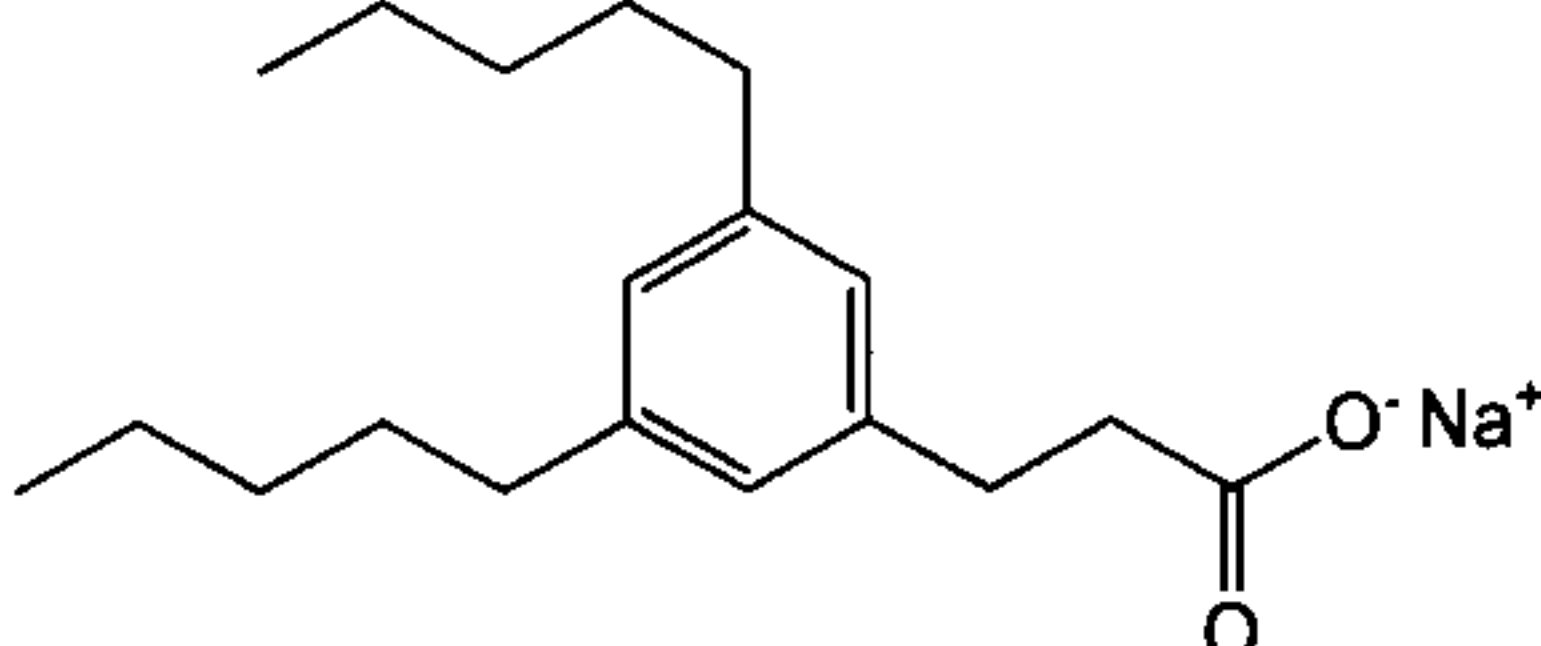
[00164] It has also been reported that capric acid increases the production of IL-12 in LPS-stimulated RAW264.7 (Wang et al., J. Biol. Chem. (2006), Vol. 281, No. 45, pp.34457-64). Since capric acid is also a known osteoclastogenesis inhibitor, an experiment was undertaken to determine if Compound I was capable of promoting an increase in IL-12 production. RAW264.7 cells were cultured with 100 ng/mL of LPS in presence or absence of compounds for 21 hours in a humidified atmosphere of 95% air-5% carbon dioxide at 37°C. IL-12 concentration in the culture medium was measured using the IL-12 ELISA according to the manufacturer (BD Biosciences) recommendations. **Figure 2** illustrates the strong induction of IL-12 production in LPS-stimulated RAW264.7 cells in presence of various concentrations of Compound I.

Example 3: Effect of compounds of Formula I on IL-12 production in LPS-stimulated RAW264.7 cells; an osteoclast progenitor.

[00165] IL-12 is also reported to inhibit osteoclast formation (Horwood and al. (2001) J. of Immunology, Volume 166, No. 8, pp. 4915-4921). As demonstrated in Example 1 that LPS-stimulated RAW264.7 incubated in presence of Compound I increases IL-12 and reduces osteoclastogenesis (TRAP). An *in vitro* IL-12 production assay was used for screening potential inhibitors of osteoclastogenesis. **Table 2** represents the effect of representative compounds of Formula I on IL-12 production. All these compounds induced a significant increase in IL-12 production.

[00166] Table 2: Effect of representative compounds of Formula I on IL-12 production

Compound	Structure	IL12 pg/ml	Compound Concentration
I		54.34	0.50 mM
II		350.65	0.50 mM
III		62.28	0.50 mM
IV		19.31	0.50 mM
V		52.5	0.50 mM
VI		58.87	0.25 mM
VII		16.6	0.50 mM
VIII		20	0.50 mM
IX		12.57	0.1 mM
X		80	0.50 mM
XI		15	0.25 mM

XII		419.6	0.50 mM
XIII		17.6	0.25 mM
XVI		15	0.005 mM
XXIV		79.9	0.0025mM

[00167] These results demonstrate that the tested compounds induce the production of IL-12, in the presence of LPS. The ability to simulate the production of IL-12 means that compounds of Formula I may be useful for preventing and/or treating osteoporosis as a result of the induction of IL-12. This is supported by the above-mentioned references in Examples 1 and 2, which teach that IL-12 has a direct inhibitory effect onto osteoclastogenesis.

Example 4: Effect of Compound I on the reduction of osteoporosis in an ovariectomized-rat model.

[00168] Although in comparison to humans, the skeletal mass of rats remains stable for a protracted period during their lifespan, rats can be ovariectomized to make them sex-hormone deficient, and to stimulate the accelerated loss of bone that occurs in women following menopause. Ovariectomy induces bone loss in the rat and postmenopausal bone loss share many similar characteristics. These include: increased rate of bone turnover with resorption exceeding formation; an initial rapid phase of bone loss followed by a much slower phase; greater loss of cancellous than cortical bone; decreased intestinal absorption of calcium; some protection against bone loss by obesity; and similar skeletal response to therapy with estrogen, tamoxifen, bisphosphonates, parathyroid hormone, calcitonin and exercise. These wide-ranging similarities are strong evidence that the ovariectomized rat bone loss model is suitable for studying problems that are relevant to postmenopausal bone loss.

[00169] Sprague Dawley rats (250g) were ovariectomized (OVX) at day 0. Rats were treated by oral gavage with Compound I (200 mg/kg) from day 14 to day 68. Evaluation of different

parameters (body weight, calcium loss, osteoclast markers (RANKL and TRAP mRNA expression), collagen content and histology) was performed at day 68.

[00170] **Figure 3** illustrates the increase in body weight of the ovariectomized rats (similar to the “postmenopausal obesity”). Compound I reduced ovariectomized-induced obesity.

[00171] **Figure 4** represents the effect of Compound I on calcium loss in ovariectomized rats. Calcium loss is detected in urine from ovariectomized rats from day 28 to day 56. Compound I reduced significantly the calcium loss in ovariectomized rats.

[00172] Furthermore, it is known that acid phosphatase activity in serum is an indication of osteoclastogenesis (Park et al. (2011) PLOS One Volume 6, Issue 11, pp. 1-8). Serum acid phosphatase activity was measured and this activity increases significantly in ovariectomized rats from day 28 to day 56 (**Figure 5**). However, Compound I reduces the acid phosphatase activity in the serum of ovariectomized rats (**Figure 5**), a decrease indicative of a successful reduction in osteoclastogenesis.

[00173] **Figure 6** represents the effect of Compound I on the ratio of mRNA expression of RANKL/OPG at day 68 in rat tibia. As shown, RANKL/OPG mRNA expression increased in rats developing osteoporosis while it decreased with the treatment with Compound I; a decrease is indicative of a successful reduction of osteoclastogenesis.

[00174] As a result of bone loss, collagen content is decreased. This was observed in ovariectomized rats. Compound I increased the collagen content in the metaphyse of the femur of ovariectomized rats, suggesting a reduction of bone loss (**Figure 7**).

[00175] **Figure 8** shows representative pictures of histological bone section of the metaphysis of the femur. Compound I reduced bone loss in the metaphysis portion of the femur.

Example 5: Effect of compounds of Formula I on serum adiponectin level in a model of diabetic obese (db/db) mice.

[00176] It has been documented that adiponectin stimulates bone formation and remodeling as well as inhibits bone resorption, suggesting that adiponectin may be a negative regulator of bone mass (Lubkowska et al. (2014) Disease Markers, Volume 2014, Article ID975178, 14 pages). Also, most *in vitro* studies have demonstrated that adiponectin stimulates the differentiation and mineralization of osteoblasts as well as the expression of osteocalcin,

which acts as a hormone regulating glucose metabolism and fat mass (Lubkowska et al. (2014)). The potential influence of adiponectin on osteoblasts and osteoclasts and consequently on bone remodeling is possibly connected with the interrelationship between the endocrine system and fat metabolism (Lubkowska et al. (2014)).

[00177] To determine if selected compounds of this invention can affect serum adiponectin level, a model of diabetes type II/obesity was used. Briefly, db/db mice (6 weeks-old were uninephrectomized and treated with **Compound XIV** for 113 days (structure is shown in **Table 1** hereinbefore). Serum adiponectin levels were determined with a mouse adiponectin enzyme-linked immunosorbant assay kit (R&D Systems).

[00178] **Figure 9** illustrates the serum adiponectin level as measured in obese db/db diabetic mice. Serum adiponectin level was decreased in non-treated db/db mice while treatment with Compound XIV increased the level of adiponectin to the level of the sham animals, suggesting that this compound may prevent or reduce osteoporosis. Variants of Compound XIV, particularly compounds with a similar chemical structure, may also increase the level of adiponectin and prevent and/or reduce osteoporosis. A non-exhaustive list of chemical variants of Compound XIV include, but is not limited to, Compounds XV to XXIV (and any pharmaceutical acceptable salts thereof) shown in **Table 1** above.

* * *

[00179] Headings are included herein for reference and to aid in locating certain sections. These headings are not intended to limit the scope of the concepts described therein, and these concepts may have applicability in other sections throughout the entire specification. Thus, the present invention is not intended to be limited to the embodiments shown herein but is to be accorded the widest scope consistent with the principles and novel features disclosed herein.

[00180] The singular forms “a”, “an” and “the” include corresponding plural references unless the context clearly dictates otherwise.

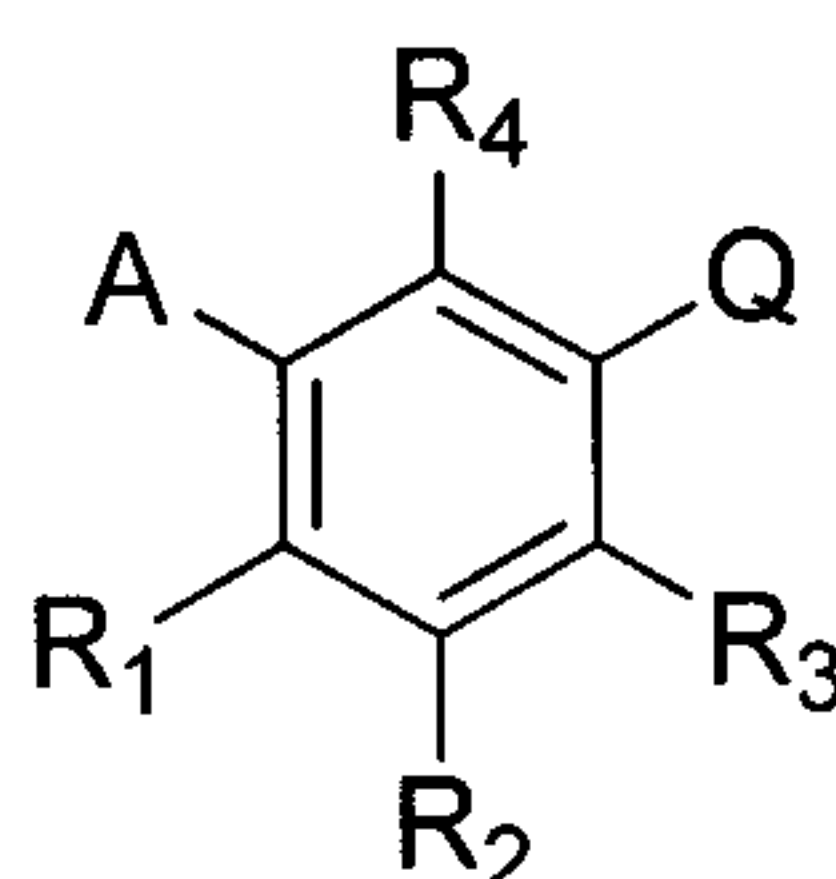
[00181] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, concentrations, properties, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about”. At the very least, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Accordingly, unless indicated to the contrary,

the numerical parameters set forth in the present specification and attached claims are approximations that may vary depending upon the properties sought to be obtained. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the embodiments are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contain certain errors resulting from variations in experiments, testing measurements, statistical analyses and such.

[00182] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the present invention and scope of the appended claims.

CLAIMS:

1. A method for the prevention and/or treatment of osteoporosis, comprising the step of administering to a subject in need thereof a compound represented by Formula I or a pharmaceutical acceptable salt thereof :

**Formula I**

wherein

A is C₅ alkyl, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4;

R₁ is H, F or OH;

R₂ is H, F, OH, C₅ alkyl, C₆ alkyl, C₅ alkenyl, C₆ alkenyl, C(O)-(CH₂)_n-CH₃ or CH(OH)-(CH₂)_n-CH₃ wherein n is 3 or 4;

R₃ is H, F, OH or CH₂Ph;

R₄ is H, F or OH;

Q is

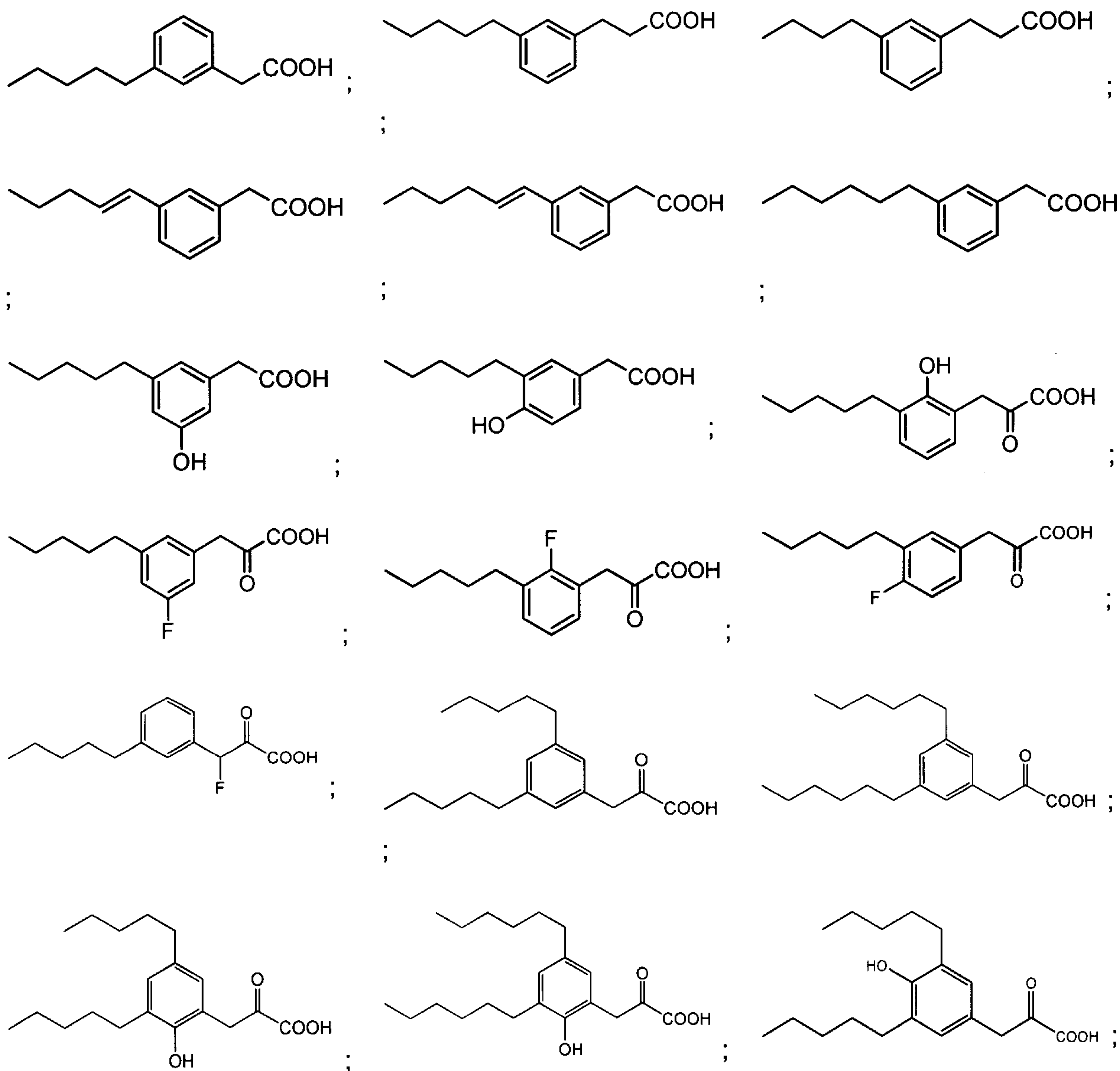
- 1) (CH₂)_mC(O)OH wherein m is 1 or 2,
- 2) CH(F)-C(O)OH,
- 3) CF₂-C(O)OH, or
- 4) C(O)-C(O)OH.

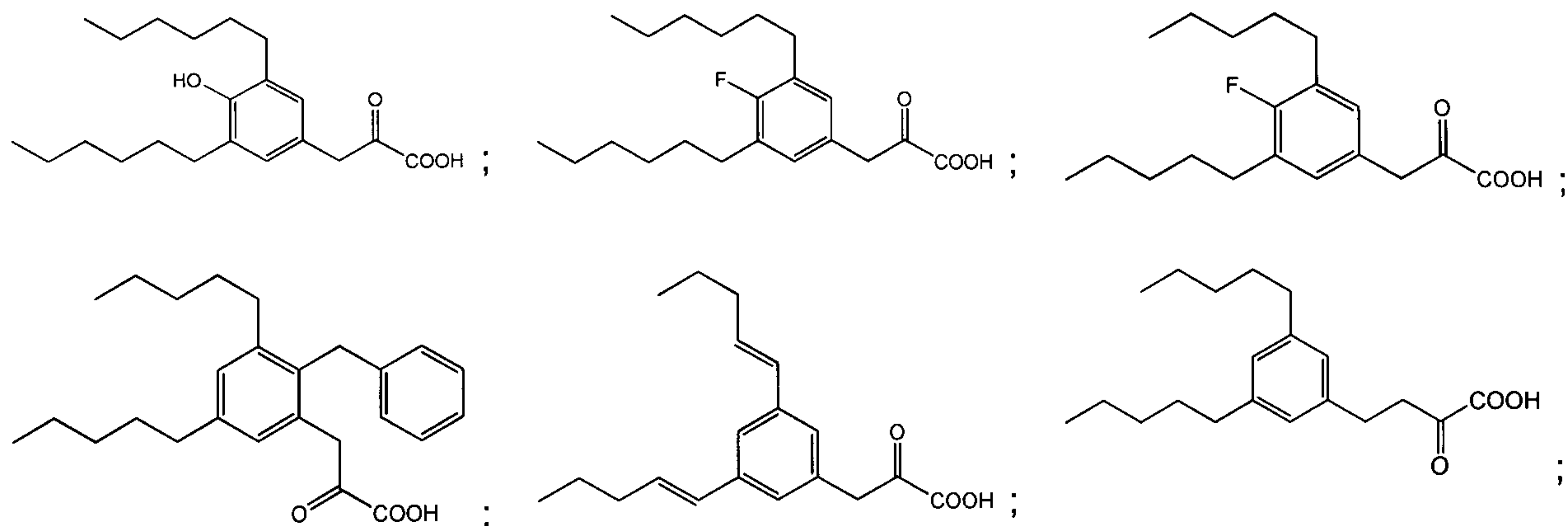
2. The method of claim 1, wherein A is C₅ alkyl or C₆ alkyl.
3. The method of any one of claims 1 or 2, wherein R₂ is H, F, OH, C₅ alkyl or C₆ alkyl.
4. The method of any one of claims 1 to 3, wherein R₃ is H, OH or CH₂Ph.
5. The method of any one of claims 1 to 4, wherein Q is (CH₂)_mC(O)OH where m is 1 or 2.

6. The method of claim 1, wherein A is C₅ alkyl or C₆ alkyl; R₁ is H, F or OH; R₂ is H, F, OH, C₅ alkyl or C₆ alkyl; R₃ is H, OH or CH₂Ph; R₄ is H, F or OH; and Q is (CH₂)_mC(O)OH where m is 1 or 2.

7. The method of claim 1, wherein A is C₅ alkyl; R₁ is H; R₂ is H or C₅ alkyl; R₃ is H; R₄ is H; and Q is (CH₂)_mC(O)OH where m is 1.

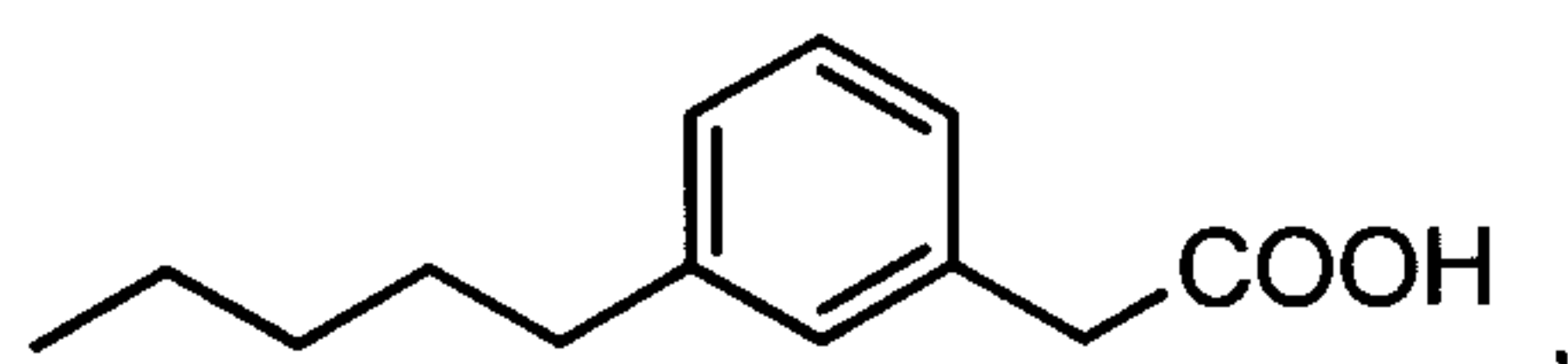
8. The method of any one of claims 1 to 7, wherein said compound is selected from the group consisting of the compounds represented by the following structures:





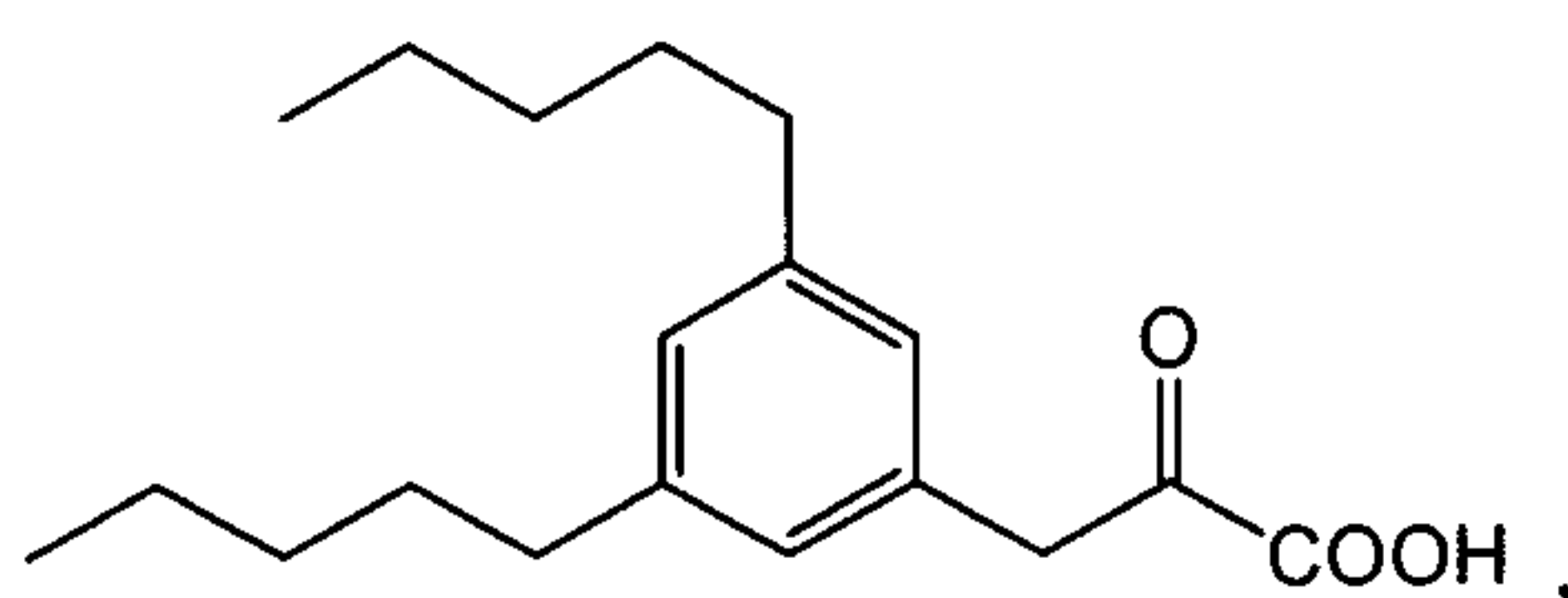
and pharmaceutical acceptable salts thereof.

9. The method of any one of claims 1 to 8, wherein said compound is represented by the following structure:



or a pharmaceutical acceptable salt thereof.

10. The method of any one of claims 1 to 8, wherein said compound is represented by the following structure:



or a pharmaceutical acceptable salt thereof.

11. The method of any one of claims 1 to 10, wherein the pharmaceutically acceptable salt is a base addition salt comprising a metal counterion selected from the group consisting of sodium, potassium, calcium, magnesium lithium, ammonium, manganese, zinc, iron, or copper.

12. The method of any one of claims 1-11, wherein the pharmaceutically acceptable salt is sodium.

13. The method of any one of claims 1 to 12, wherein the osteoporosis is selected from the group consisting of post-menopausal osteoporosis (primary type 1), primary type 2 osteoporosis, secondary osteoporosis abnormally high osteoclastogenesis, osteomalacia-like osteoporosis,

osteopenia, osteogenesis imperfecta, osteopetrosis, osteonecrosis, Paget's disease of bone, hypophosphatemia and combinations thereof.

14. The method of any one of claims 1 to 13, wherein osteoporosis is post-menopausal osteoporosis (primary type 1), primary type 2 osteoporosis or secondary osteoporosis.

15. The method of any one of claims 1 to 13, wherein osteoporosis is post-menopausal osteoporosis (primary type 1).

16. The method of any one of claims 1 to 15, wherein administration of said compound results in one or more of the following biological activities the subject:

- inhibition of osteoclastogenesis;
- reduction of osteoclastogenesis;
- stimulation of interleukin-12 (IL-12) production in bone;
- reduction of acid phosphatase activity in bone;
- reduction of Receptor activator of NF- κ B ligand/ Osteoprotegerin ratio (RANKL/OPG ratio) in bone;
- increase of collagen content in bone; and
- modulation of the serum level of adiponectin.

17. A method for preventing and/or reducing bone loss, comprising the step of administering to a subject in need thereof a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12.

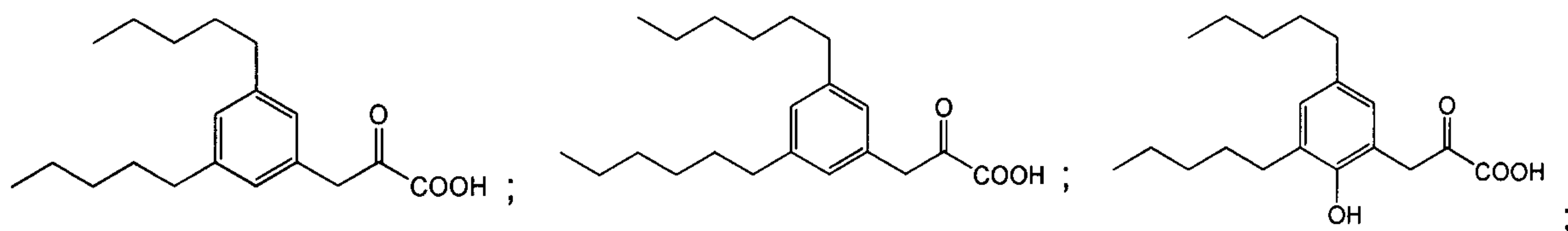
18. The method of claim 17, wherein said compound reduces loss of calcium.

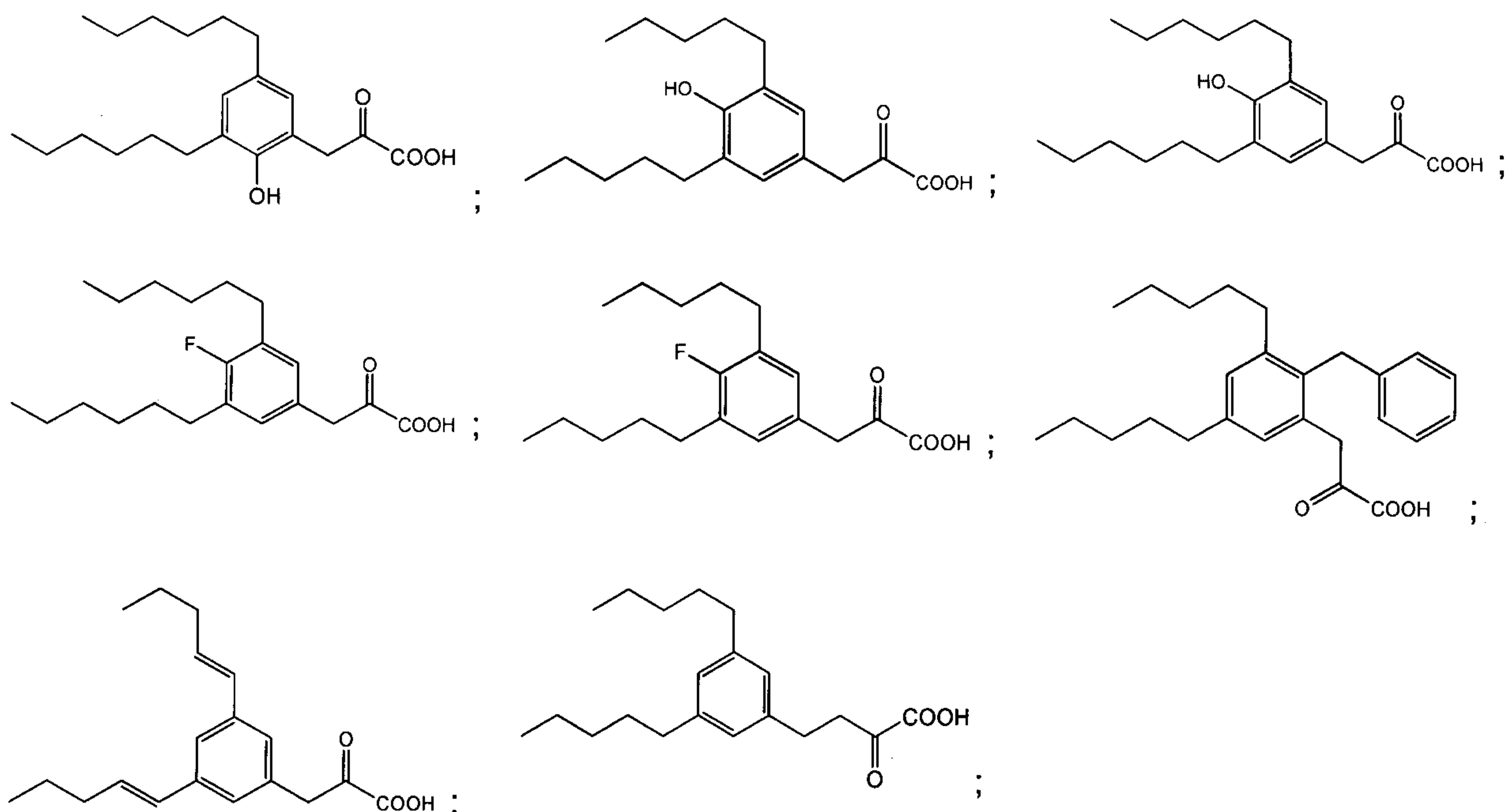
19. The method of claim 17 or 18, wherein the subject is afflicted by or susceptible of osteoporosis.

20. The method of any one of claims 1 to 19, wherein the subject is a postmenopausal women.

21. A method for inhibiting osteoclastogenesis, comprising contacting an osteoclast precursor cell with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12, wherein said compound inhibits differentiation of the precursor cell into an osteoclast cell.

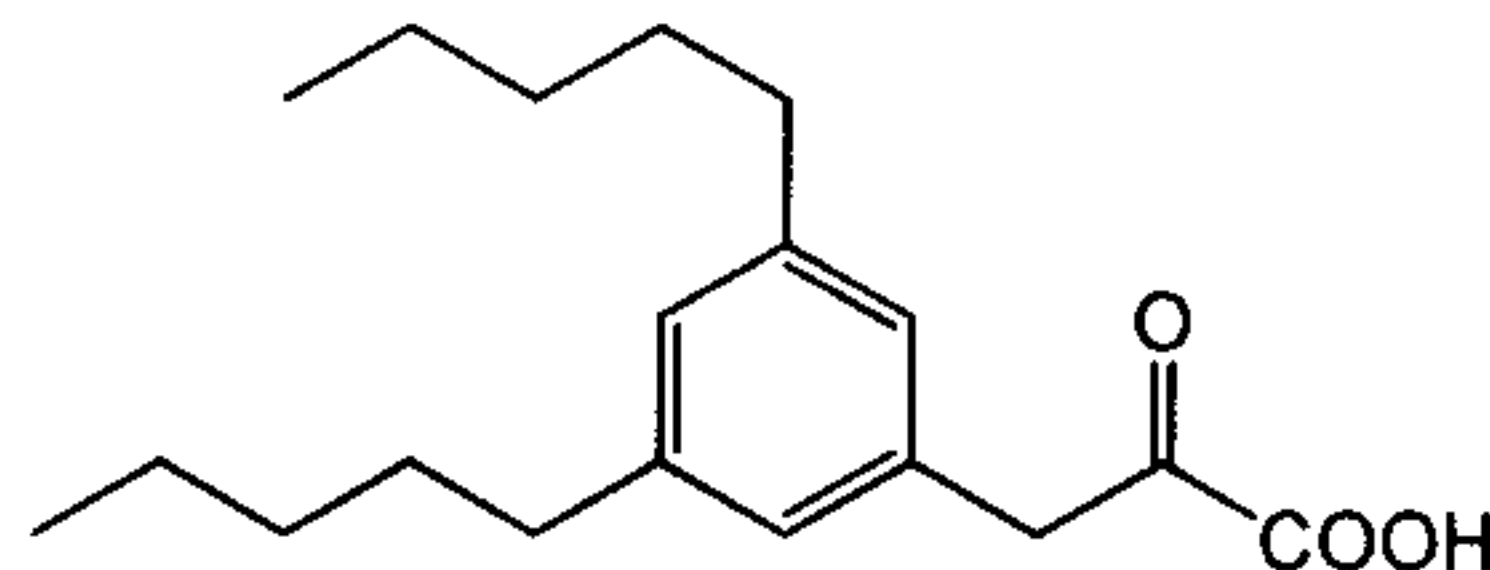
- 22.** A method for stimulating interleukin-12 (IL-12) production by a stimulated osteoclast precursor cell, comprising contacting said stimulated osteoclast precursor cell with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12, wherein an increased IL-12 production is measurable in presence of said compound.
- 23.** A method for reducing acid phosphatase activity in bone cells comprising contacting said bone cells with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12, wherein a reduced phosphatase activity is measurable in presence of said compound.
- 24.** A method for reducing expression and/or activity of receptor activator of NF- κ B ligand/Osteoprotegerin ratio (RANKL /OPG ratio) in bone cells, comprising contacting said bone cells with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12.
- 25.** A method for increasing collagen content in bone, comprising contacting said bone with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12.
- 26.** A method for stimulating bone formation and/or for stimulating bone remodeling and/or for stimulating the differentiation and mineralization of osteoblasts and/or for inhibiting bone resorption, comprising contacting osteoblasts in said bone with a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12.
- 27.** A method for modulating serum level of adiponectin in a subject, comprising the step of administering to a subject in need thereof a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12.
- 28.** The method of claim 27, wherein the compound is selected from the group consisting of the compounds represented by the following structures:





and pharmaceutical acceptable salt thereof.

29. The method of claim 27 or 28, wherein said compound is represented by the following structure:



or pharmaceutical acceptable salt thereof.

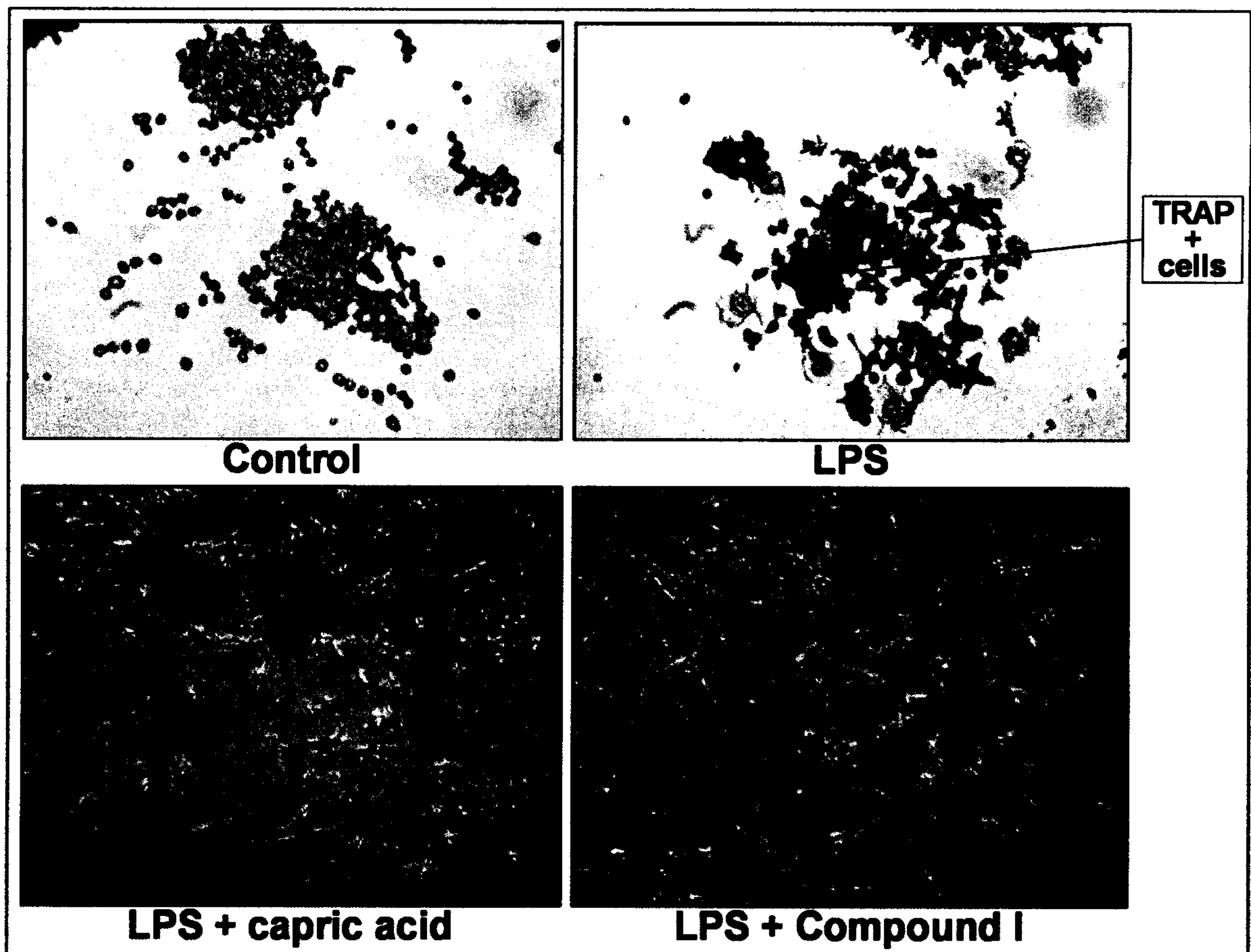
30. The method of any one of claims 27-29, wherein the subject is obese and/or diabetic.

31. The method of any one of claims 1 to 30, further comprising the step of administering concomitantly a drug selected from the group consisting of: bisphosphonates, Odanacatib, Alendronate, Risedronate, Etidronate, Zoledronate, Pamidronate, Teriparatide, Tamoxifen, Raloxifene, and Denosumab.

32. Use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12, in preventing and/or treating osteoporosis.

33. Use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12, for the manufacture of a medicament for the prevention and/or treatment of osteoporosis.

34. A compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined in any one of claims 1 to 12, for use in preventing and/or treating osteoporosis.

**Figure 1**

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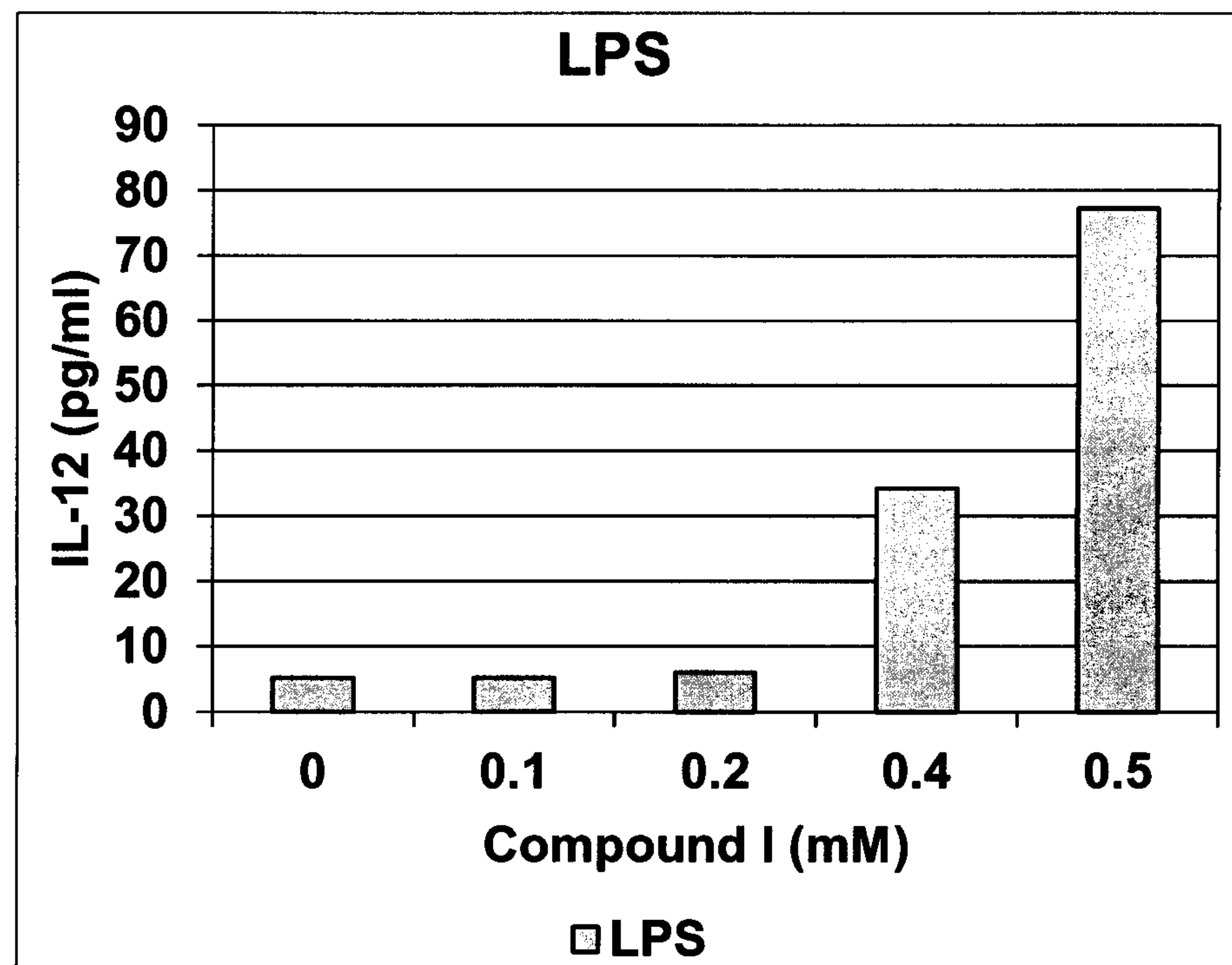


Figure 2

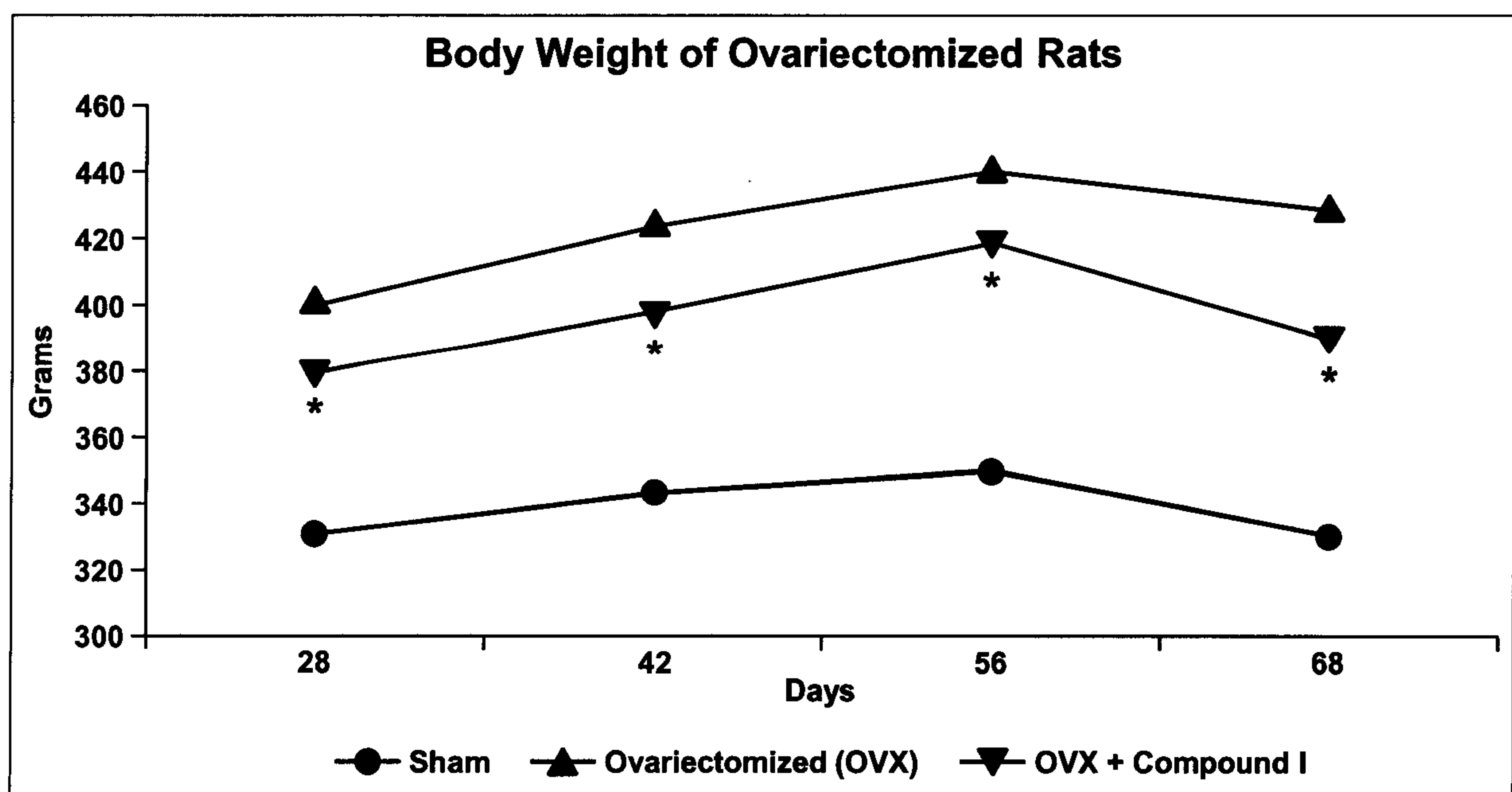


Figure 3

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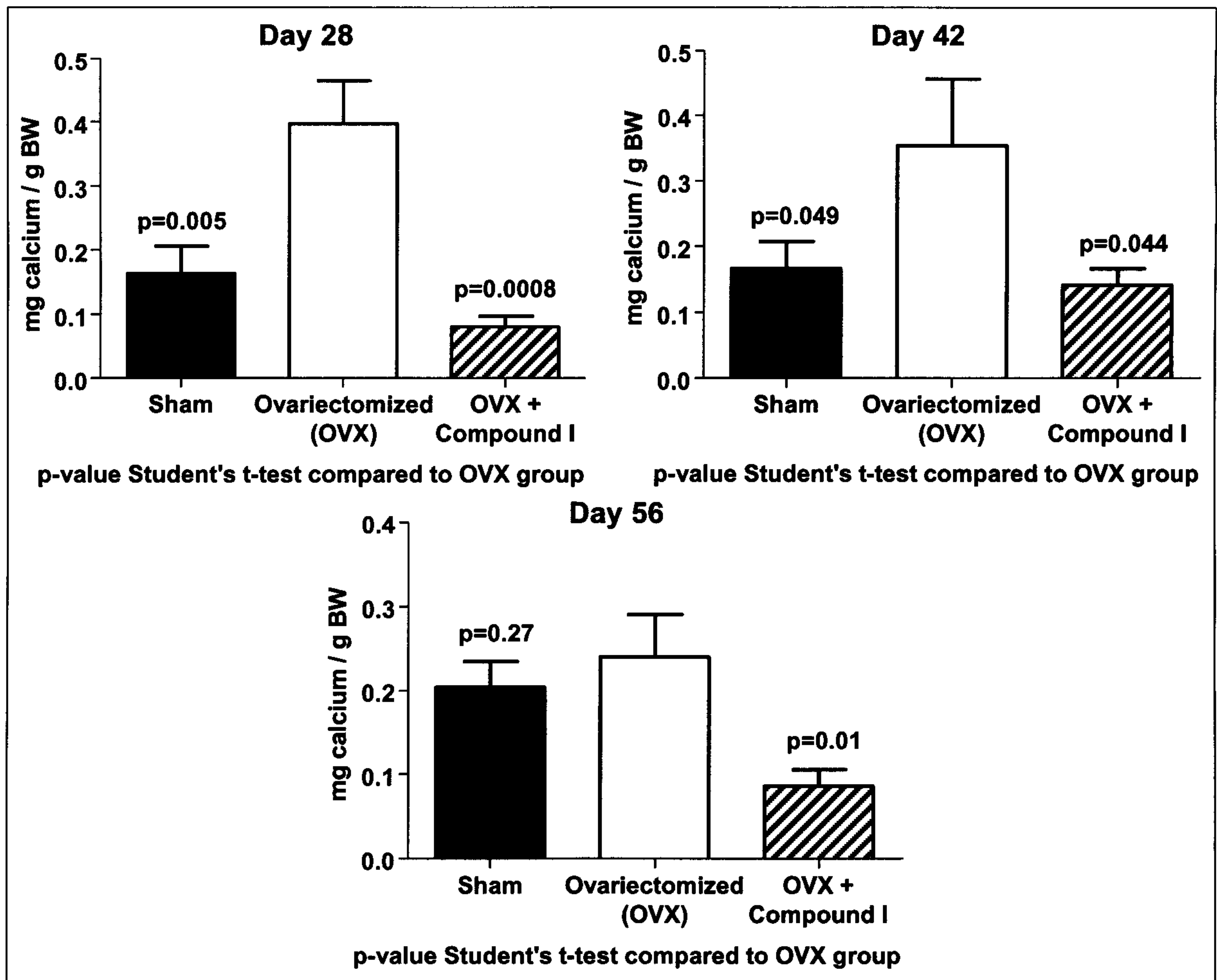


Figure 4

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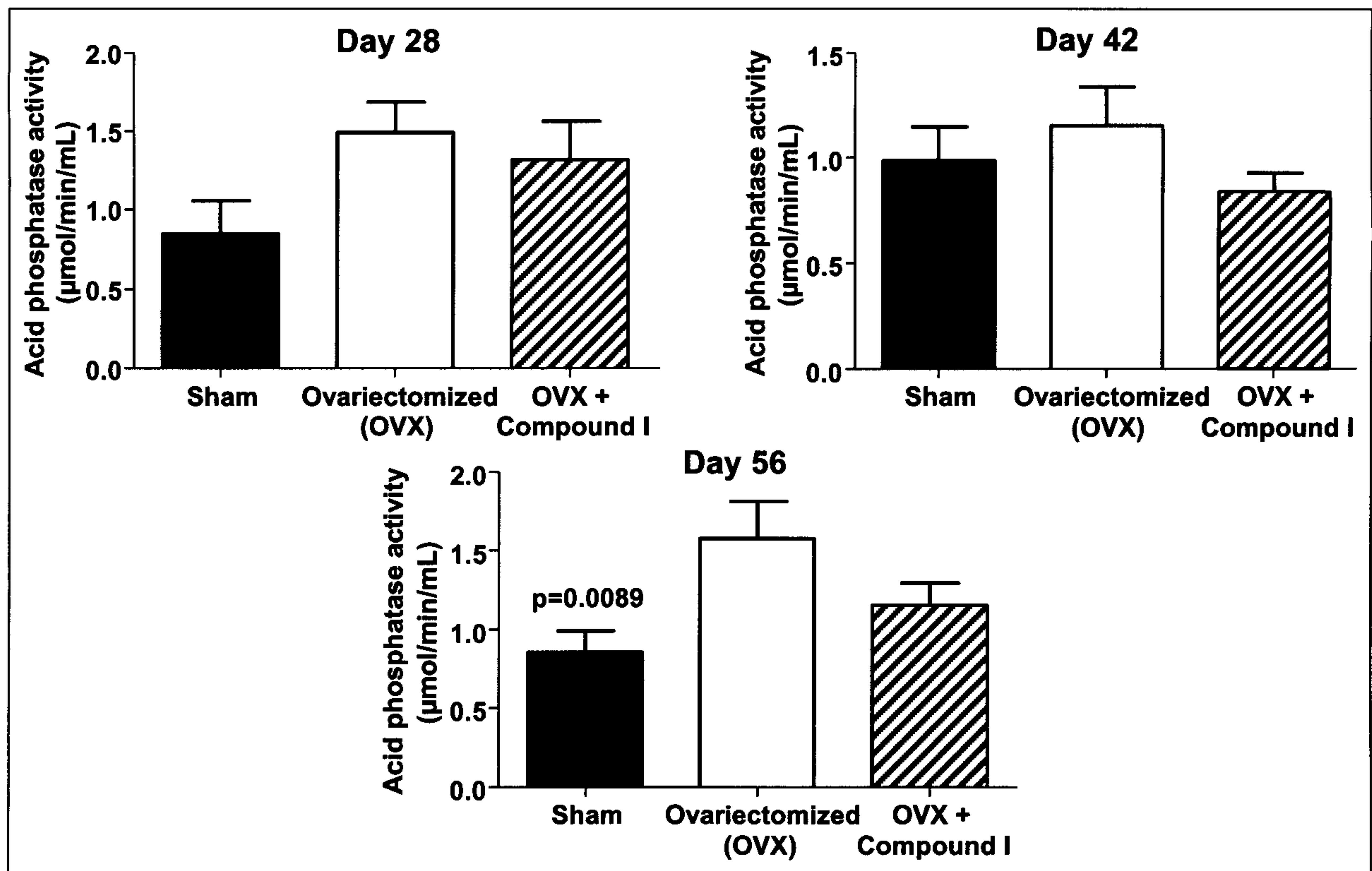


Figure 5

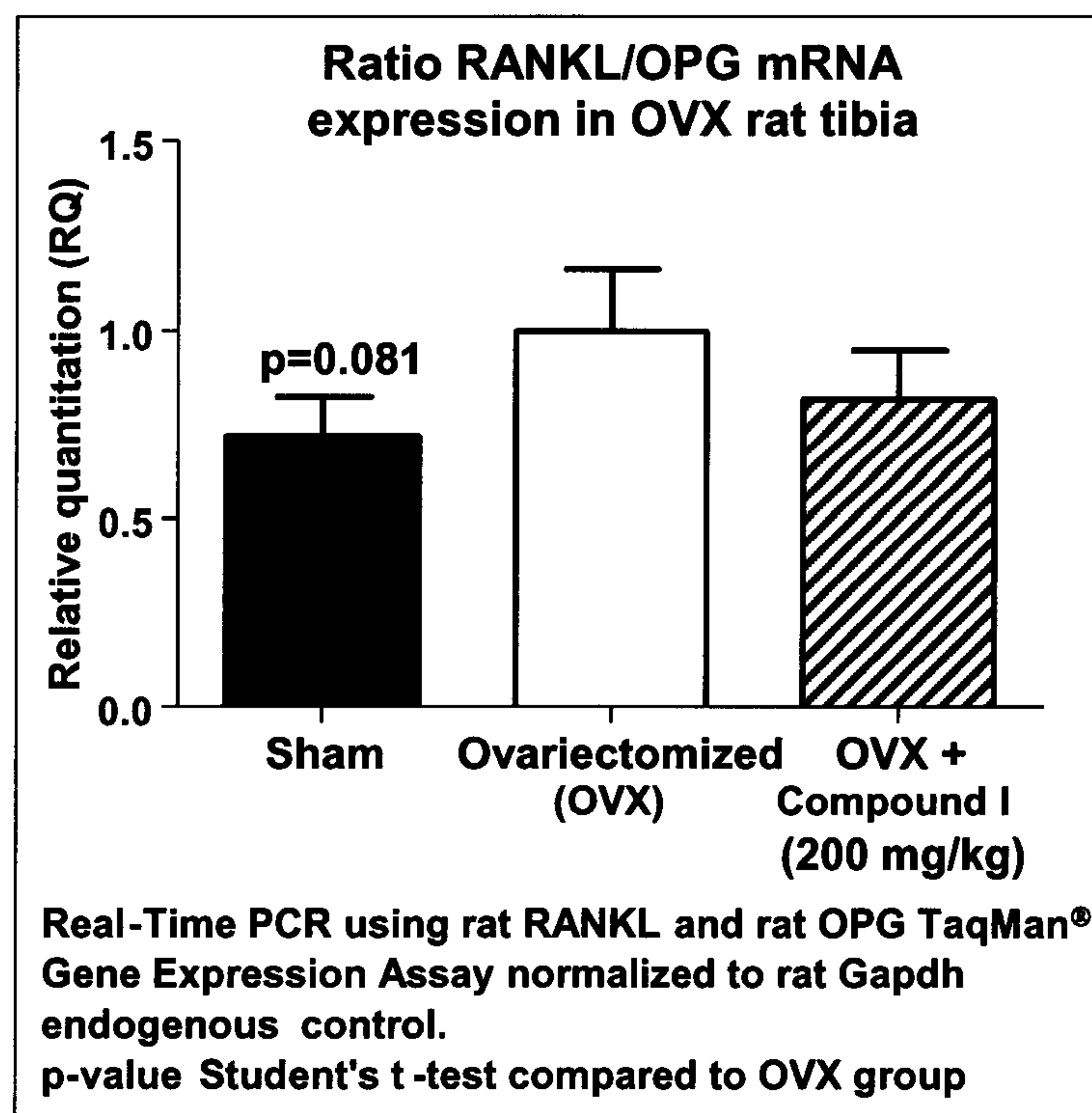


Figure 6

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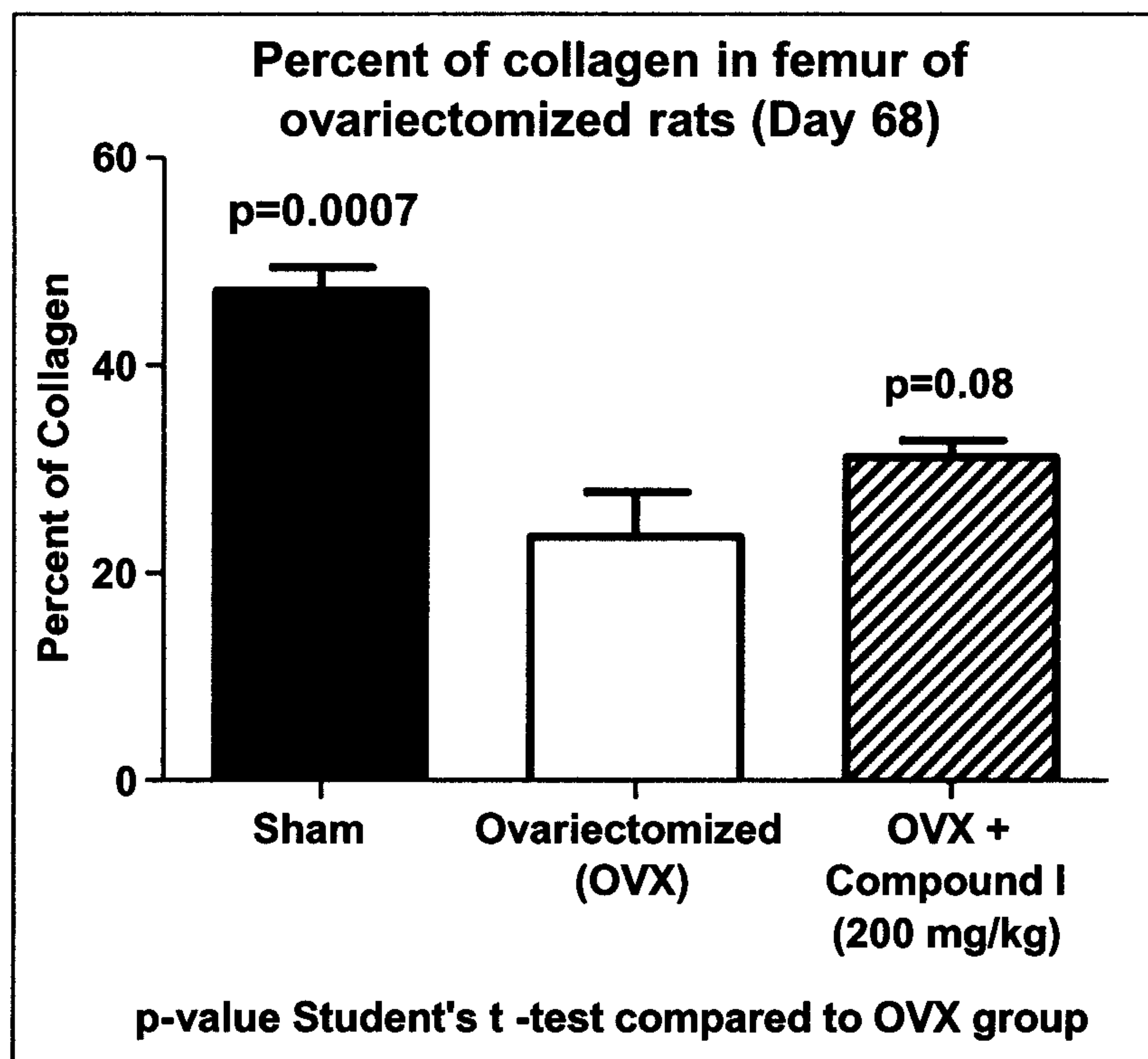


Figure 7

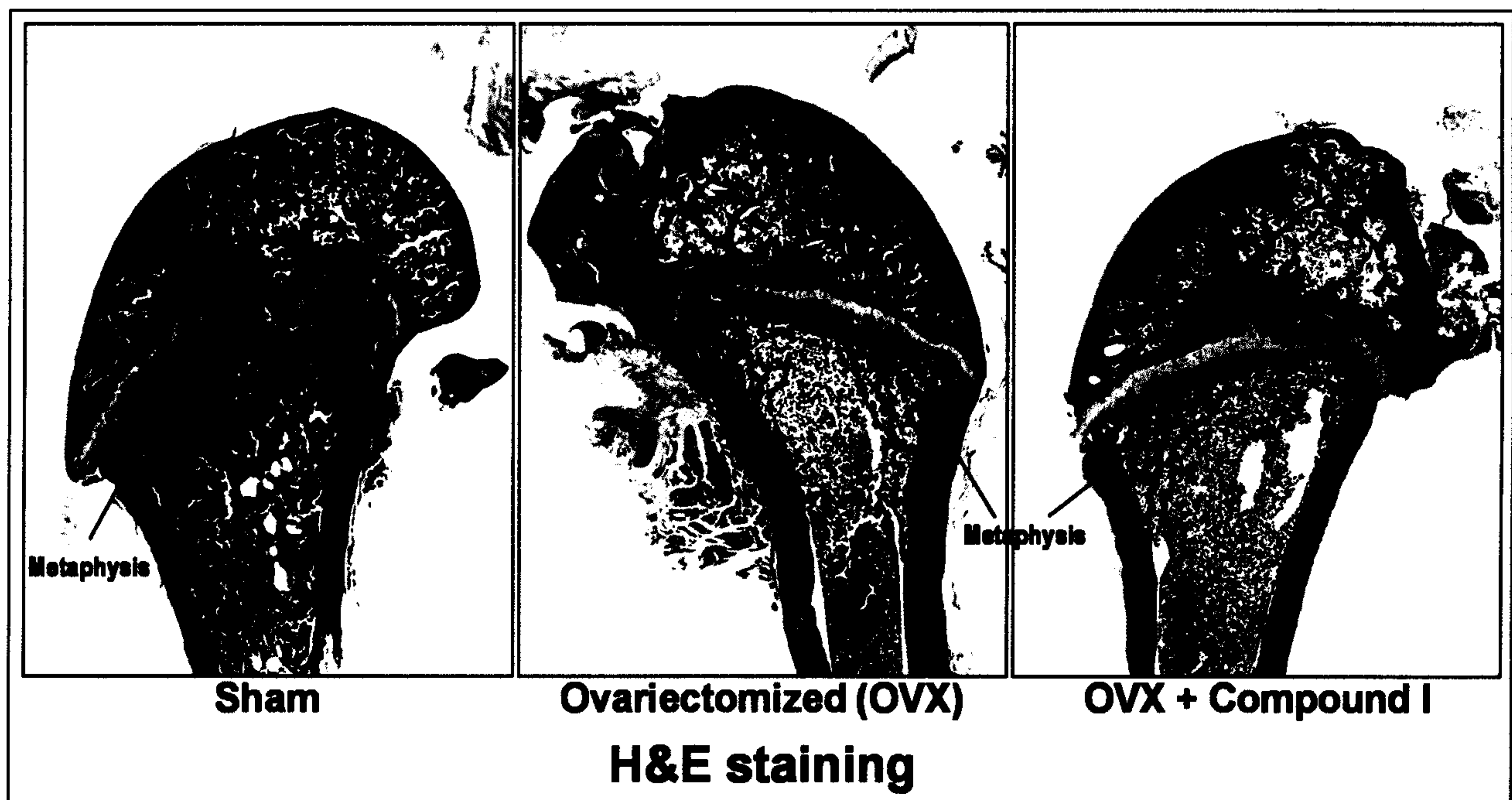
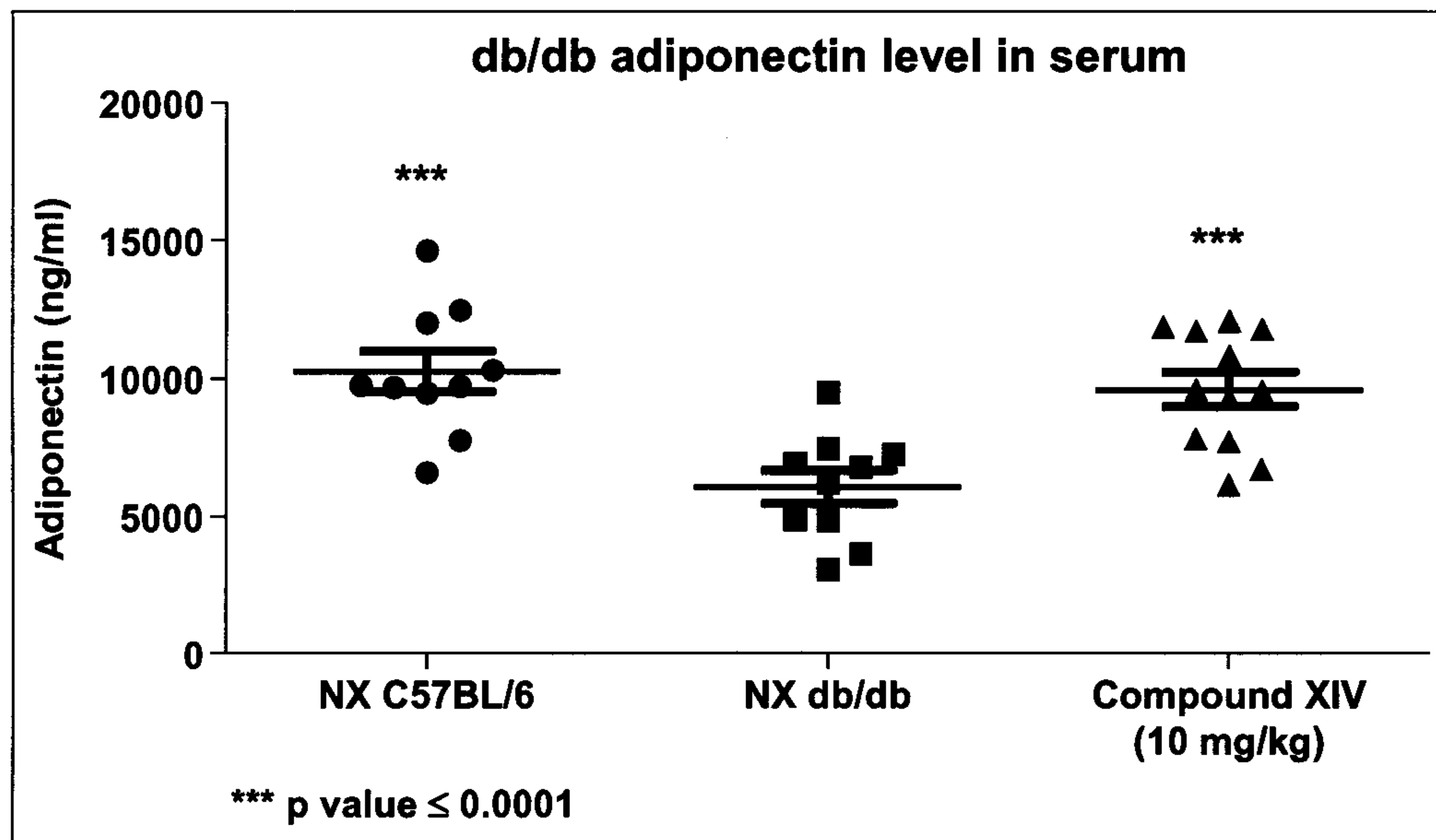
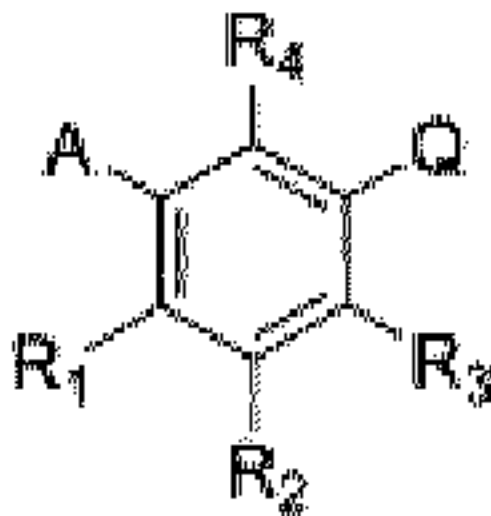


Figure 8

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**Figure 9**



Formula I