[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.

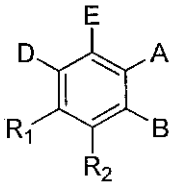
[0013] Additional features of the invention will be apparent from a review of the discussion, figures and description of the invention herein.

BRIEF SUMMARY OF THE DISCLOSURE

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

[0015] Particular aspects of the disclosure relate to the use of compounds and compositions for the prevention and/or treatment of osteoporosis. Certain aspects concerns 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.

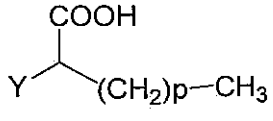
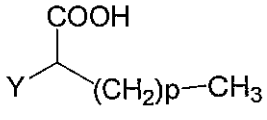
[0015a] In one aspect, the disclosure relates to the use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof in the manufacture of a medicament for preventing and/or treating of osteoporosis, wherein Formula I is:



Formula I

wherein:

R_1 and R_2 are independently equal to H, F or OH;

A is $(CH_2)_mCOOH$, $W(CH_2)_mCOOH$ or  when B is H; or B is $(CH_2)_mCOOH$, $W(CH_2)_mCOOH$ or  when A is H; or

A and B are covalently bonded to form a five (5), six (6) or seven (7)-membered cycloalkyl substituted with COOH;

where:

Y is O, S, NH, or CH_2;

W is O, S, or NH;

m is 0-2; and

p is 3-7;

D is $CO(CH2)_nCH3$ or $CHOH(CH2)_nCH3$ or $O(CH2)_nCH3$ where n is 2-6; and

E is H or F.

[0015b] In another aspect, the disclosure relates to the use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, in the manufacture of a medicament for preventing and/or reducing bone loss in a subject in need thereof.

[0015c] In another aspect, the disclosure relates to the use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, in the manufacture of a medicament for inhibiting osteoclastogenesis, wherein said compound inhibits differentiation of the osteoclast precursor cell into an osteoclast cell.

[0015d] In another aspect, the disclosure relates to the use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, in the manufacture of a medicament for stimulating interleukin-12 (IL-12) production by a stimulated osteoclast precursor cell, wherein an increased IL 12 production is measured in the stimulated osteoclast precursor cell.

[0015e] In another aspect, the disclosure relates to the use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, in the manufacture of a medicament for reducing acid phosphatase activity in bone cells, wherein a reduced phosphatase activity is measurable in bone cells.

[0015f] In another aspect, the disclosure relates to the use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, in the manufacture of a medicament, for reducing expression and/or activity of receptor activator of NF-κB ligand/Osteoprotegerin ratio (RANKL /OPG ratio) in bone cells.

[0015g] In another aspect, the disclosure relates to the use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, in the manufacture of a medicament for increasing collagen content in bone in a subject in need thereof.

[0015h] In another aspect, the disclosure relates to the use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof as defined herein, in the manufacture of a medicament 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 in a subject in need thereof.

[0016] According to particular embodiments, the compounds and compositions of the disclosure 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 embodiment of the disclosure 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 disclosure also relates to treatment methods wherein the compounds of the disclosure 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-κB ligand (RANKL) over Osteoprotegerin (OPG) ratio (RANKL/ PG ratio) in bone, which indicates a reduction in osteoclastogenesis; and increase of collagen content in bone.

[0019] According to another embodiment, the disclosure 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 woman.

[0020] According to another embodiment, the disclosure 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 embodiment, the disclosure 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 embodiment, the disclosure 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 embodiment, the disclosure relates to a method for reducing expression and/or activity of receptor activator of NF-κB 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 embodiment, the disclosure 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 embodiment, the disclosure 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] Additional embodiments of the disclosure relate 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.

[0027] Another related embodiment of the disclosure to pharmaceutical compositions comprising compounds of Formula I for the manufacture of medicaments, 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 preventing or treating osteoporosis, comprising a compound as defined in **Table 1**, and more particularly, a pharmaceutical composition comprising Compound I. Related embodiment 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.

[0028] According to another embodiment, the disclosure 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.

[0029] Further embodiments of the disclosure will be apparent to a person skilled in the art from the following description, claims, and generalizations herein.

BRIEF DESCRIPTION OF THE FIGURES

[0030] Figure 1 is a line graph demonstrating the effect of Compound I on body weight of ovariectomized (OVX) rats, according to Example 3.

[0031] Figure 2 is a panel with bar graphs demonstrating the effect of Compound I on calcium in urine of ovariectomized (OVX) rats, according to Example 4.

[0032] Figure 3 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.

[0033] Figure 4 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.

[0034] Figure 5 is a bar graph demonstrating the effect of Compound I on collagen content in metaphyse of rat's femur, according to Example 4.

[0035] Figure 6 is a panel with pictures illustrating the effect of Compound I on collagen content in metaphyse of rat's femur, according to Example 4.

[0036] Figure 7 is a panel with enlarged pictures corresponding to the pictures of Figure 6.

DETAILED DESCRIPTION OF THE INVENTION

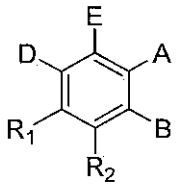
The present discloses compounds of Formula I, pharmaceutically acceptable salts thereof, compositions comprising same and uses thereof. Various embodiments of the present invention include:

A) Compounds of the invention

[0037] According to one aspect, the invention concerns the pharmaceutical uses of compounds represented by **Formula I**, or pharmaceutically acceptable salts thereof:

CLAIMS:

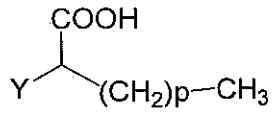
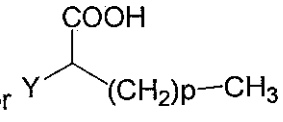
1. Use of a compound represented by Formula I or a pharmaceutical acceptable salt thereof in the manufacture of a medicament for preventing and/or treating of osteoporosis, wherein Formula I is:



Formula I

wherein:

R_1 and R_2 are independently equal to H, F or OH;

A is $(CH_2)_mCOOH$, $W(CH_2)_mCOOH$ or  when B is H; or B is $(CH_2)_mCOOH$, $W(CH_2)_mCOOH$ or  when A is H; or

A and B are covalently bonded to form a five (5), six (6) or seven (7)-membered cycloalkyl substituted with COOH;

where:

Y is O, S, NH, or CH_2;

W is O, S, or NH;

m is 0-2; and

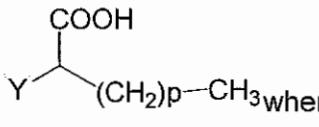
p is 3-7;

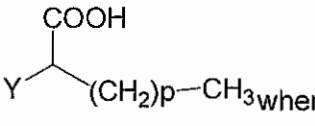
D is $CO(CH2)_nCH3$ or $CHOH(CH2)_nCH3$ or $O(CH2)_nCH3$ where n is 2-6; and

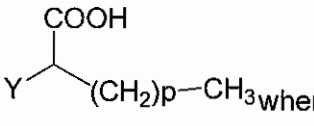
E is H or F.

2. The use of claim 1, wherein R_1 is H and R_2 is H.

3. The use of claim 1 or 2, wherein m is 1 or 2.

4. The use of claim 1 to 3, wherein A is H and B is  wherein Y is O, and p is 5-7.

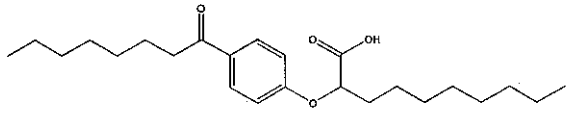
5. The use of claim 1, wherein R_1 and R_2 are H; B is H; A is  wherein p is 5-7; Y is O; and E is H

6. The use of claim 1, wherein R_1 and R_2 are H; A is H; B is  wherein p is 5-7; Y is O; and E is H.

7. The use of any one of claims 1 to 6, wherein D is $CO(CH_2)_nCH_3$.

8. The use of any one of claims 1 to 7, wherein n is 4-6.

9. The use of claim 1, wherein said compound is selected from the group consisting of the compounds represented by the following structures:



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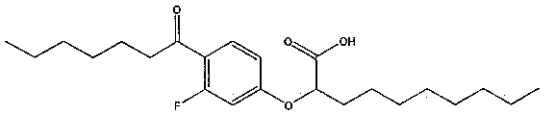

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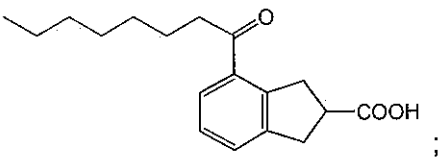

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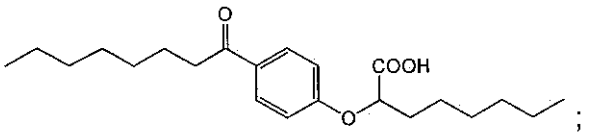

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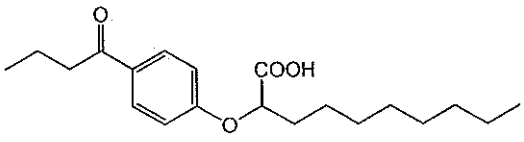

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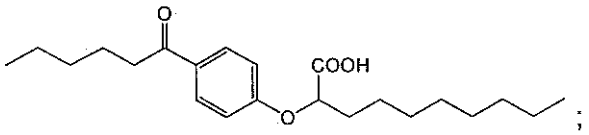

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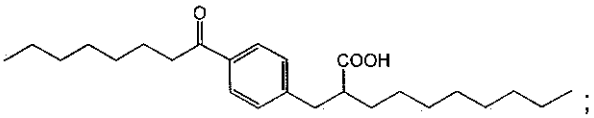
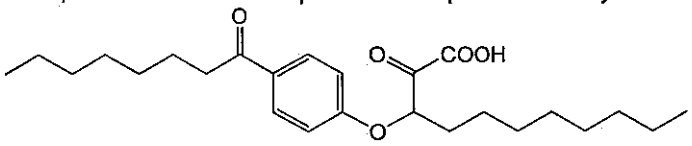


;

and pharmaceutical acceptable salts thereof.

10. The use of claim 9, wherein said compound is represented by the following structure:



or pharmaceutical acceptable salt thereof.

11. The use of any one of claims 1-10, 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 use of any one of claims 1-10, wherein the pharmaceutically acceptable salt is sodium.

13. The use of claim 1, wherein the osteoporosis is selected from the group consisting of primary type 1 osteoporosis, 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 use of claim 13, wherein osteoporosis is post-menopausal osteoporosis (primary type 1), primary type 2 osteoporosis or secondary osteoporosis.

15. The use of claim 13, wherein osteoporosis is post-menopausal osteoporosis (primary type 1).

16. The use of any one of claims 1 to 15, wherein the compound has one or more of the following activities in the subject:

- inhibition of osteoclastogenesis;
- stimulating interleukin-12 (IL-12) production in bone;
- reduction of acid phosphatase activity in bone;
- reduction of Receptor activator of NF-κB ligand/ Osteoprotegerin ratio (RANKL/OPG ratio) in bone;
- increase of collagen content in bone.

17. 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 the manufacture of a medicament for preventing and/or reducing bone loss in a subject in need thereof.

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

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

20. The use of any one of claims 17 to 19, wherein the subject is a postmenopausal women.

21. 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 the manufacture of a medicament for inhibiting osteoclastogenesis, wherein said compound inhibits differentiation of the osteoclast precursor cell into an osteoclast cell.

22. 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 the manufacture of a medicament for stimulating interleukin-12 (IL-12) production by a stimulated osteoclast precursor cell, wherein an increased IL 12 production is measured in the stimulated osteoclast precursor cell.

23. 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 the manufacture of a medicament for reducing acid phosphatase activity in bone cells, wherein a reduced phosphatase activity is measurable in bone cells.

24. 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 the manufacture of a medicament, for reducing expression and/or activity of receptor activator of NF-κB ligand/Osteoprotegerin ratio (RANKL /OPG ratio) in bone cells.

25. 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 the manufacture of a medicament for increasing collagen content in bone in a subject in need thereof.

26. 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 the manufacture of a medicament 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 in a subject in need thereof.

27. The use of any one of claims 1 to 26, wherein the compound is to be administered in combination with a drug selected from the group consisting of: bisphosphonates, Odanacatib, Alendronate, Risedronate, Etidronate, Zoledronate, Pamidronate, Teriparatide, Tamoxifen, Raloxifene, and Denosumab.