Title: PHARMACEUTICAL COMPOUNDS

\[
\begin{aligned}
\text{PO}_3R^1R^2 & \quad (1) \\
\text{A} \longrightarrow \text{L} \longrightarrow \text{C} (\text{B})_t \\
\text{PO}_3R^3R^4
\end{aligned}
\]

Abstract: The invention provides the use of an aryl-substituted 1,1-diphosphonate for the manufacture of a medicament for stimulating bone formation; said aryl-substituted 1,1-diphosphonate being a compound of formula (I) in which A is (a) or (b) or (c) where X³⁺ is H, an alkyl group having from 1 to 4 carbon atoms, X¹ and X² are identical or different and are H, a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms, X² is H, a straight or branched alkyl group having from 1 to 8 carbon atoms, an optionally substituted benzyl group, X³ is H, a straight or branched alkyl group having from 1 to 8 carbon atoms, X²⁺ is H or an alkyl group having from 1 to 4 carbon atoms, q is 0 or 1, R¹, R², R³ and R⁴ are identical or different and are H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms, or R¹, R² and R⁴ may form an alkylidenedioxy ring comprising 2 to 8 carbon atoms, L is -CH=CH₂, -y₂CH₂, -O(CH₂)₂, -S, -SO₂, -SO₂CH₂, or where n is an integer from 1 to 7, or together with B, L is (CH₂)₈-C=CH₂ where \( k \) is 0 or 1 and \( d \) is an integer from 0 to 4, -B is H, an alkyl group having from 1 to 4 carbon atoms, -t is 0 or 1, with the proviso that \( t \) is 0 only when L, together with B, is (CH₂)₈-C=CH₂ where \( k \) and \( d \) are as described above, and with the further proviso that when L is -CH₂, at least one of R¹, R², R³ and R⁴ is other than hydrogen.
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PHARMACEUTICAL COMPOUNDS

The present invention relates to the use of diphosphonate compounds in the treatment or prevention of bone diseases such as osteoporosis, and in particular those bone diseases requiring bone anabolic activity.

Throughout this text, the terms “diphosphonate ester” and “bisphosphonate ester”, respectively “diphosphonic acid” and “bisphosphonic acid” will be used interchangeably; the terms “diphosphonate ester” and “diphosphonic acid” being an older terminology which however is still widely used.

Background of the Invention

Osteoporosis is caused by an imbalance between bone formation and bone resorption, resulting in bone loss and fractures. Osteoporosis represents a major public health problem and it is estimated that one out of two women who have reached the age of 50 will sustain an osteoporotic fracture during her remaining life.

Two approaches toward bone mass manipulation are currently used, namely prevention of bone resorption and stimulation of bone formation (bone anabolism). The bisphosphonic acids (also diphosphonic acids) and their salts are a class of compounds which decrease the activity of the bone resorbing cells (osteoclasts); they are cytotoxic to the osteoclasts and prevent bone destruction by this mechanism. They do not affect the activity of the bone forming cells. Anti-resorptive bisphosphonic acids are currently used for the treatment of various bone diseases such as osteoporosis, hypercalcemia due to malignancies and inhibition of tumor cell metastasis in bone tissue. Despite their proven pharmacological efficacy, the clinical utility of the bisphosphonic acids is limited by their very low oral bioavailability and their gastrointestinal toxicity.

The ideal treatment for the prevention and the treatment of bone diseases would be to increase bone formation by stimulating the bone forming cells (osteoblasts). However, the large majority of therapeutic agents which stimulate bone
formation or inhibit bone turnover are hormones or derivatives of hormones (estrogens, anabolic steroids, calcitonin, parathyroid hormone, vitamin D) with numerous side effects which can be expected from their hormonal activities. Sodium fluoride, the old prophylactic agent for dental caries, is still the most widely used compound for the stimulation of bone formation. There is thus a need for new orally active compounds that act by stimulating bone formation (bone anabolic drugs).

US Patent N° 5,043,330 and US Patent N° 5,204,336 each discloses a class of aryl-substituted diphosphonate esters falling within the general formula (I) set out below. The compounds are stated to be potential lipid lowering agents. US Patent No. 6,127,350 further states that a subgroup of compounds within formula (I) are potential antineoplastic agents.

Further examples and uses of diphosphonates are disclosed in US Patent N° 5,153,183 and JP 06199881.

**Summary of the Invention**

The applicants have now found that diphosphonate compounds of the formula (I) as set out below have bone anabolic activity. Furthermore, contrary to the diphosphonic acids and salts previously used in the treatment of bone diseases, diphosphonate esters of the formula (I) below have a high oral bioavailability.

Accordingly, the invention provides novel uses and methods, and novel compounds *per se* as defined in the claims appended hereto and described and defined below.

The diphosphonate esters of the formula (I) are not competitive inhibitors of HMGCoA reductase but exert a hypocholesterolemic activity by increasing the rate of HMGCoA reductase degradation. The resulting decrease in cholesterol and in isoprenoid synthesis triggers an increase in the activity of the bone forming cells. Thus the bisphosphonate esters of the invention are useful for the treatment of diseases of bone metabolism such as osteoporosis.
The diphosphonate compounds of the formula (I), and in particular diphosphonate esters, have been found to increase bone formation in treated mice. The bone anabolic activity of the compounds of the present invention is clearly demonstrated by the increase in the number of bone forming osteoblasts, increase in bone weight and in calcium and phosphorus concentration, as compared to the respective parameters of the control group. Because of the coordinative nature of the regulation of bone formation and bone resorption, an increase in osteoblastic activity will lead to a decrease in osteoclastic bone resorption.

Without wishing to be bound by any theory, it is believed that the favourable pharmacological property of the diphosphonate esters of the formula (I) is due to their inhibitory activity of the mevalonate/isoprenoid/cholesterol synthetic pathway since these bisphosphonate esters increase the rate of degradation of HMGCoA reductase. This mechanism of action is comparable to the recently demonstrated bone anabolic activity of the inhibitors of HMGCoA reductase, the so called statins, see for instance: Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutierrez G “Stimulation of bone formation in vitro and in rodents by statins” Science 1999, 286:1946-1949.

Furthermore, the diphosphonate esters of the formula (I) display a remarkable systemic bioavailability compared to both the inhibitors of HMGCoA reductase and the classical bisphosphonic acids. Thus, the diphosphonate esters of this invention can be administered orally, intradermally and locally; which represents an advantage over bisphosphonic acids from the prior art which need to be given by injection due to their poor cell penetration that results from their ionic chemical structures.

The compounds of the formula (I) are thus useful for the treatment (or prevention) of diseases involving bone tissue such as:

- osteoporosis,
- prevention and accelerated repair of bone fracture,
- prevention and treatment of metastasis of cancer cells in bone,
- prevention and treatment of osteolytic bone lesions,
- prevention and treatment of osteoblastic bone metastasis.
- prevention and treatment of increased bone remodeling, bone hypertrophy and abnormal bone structure (i.e. Paget's disease),
- prevention and treatment of bone loss associated with cancer therapies (e.g., bone loss associated with the treatment of gonadotropin-releasing hormone agonists for prostate cancer and bone loss associated with chemotherapy for breast cancer, wherein such chemotherapy includes, but is not limited to, cyclophosphamide, methotrexate, fluorouracil, paclitaxel, doxorubicin, tamoxifen and combinations thereof),
- prevention and treatment of bone loss in HIV patients associated with lipodystrophy and treatment with antiviral drugs,
- prevention of the calcification of soft tissues (i.e. kidneys and and other organs),
- prevention of the calcification of surgical implants (i.e. natural and artificial organs such as cardiac valves),
- treatment of patients suffering from calcified soft tissues and calcified surgical implants,
- prevention and treatment of calcification and calcified arteries (atherosclerosis),
- hypercalcemia secondary to an increase in bone resorption,
- hypercalcemia secondary to malignancies,
- tumoral osteolysis
- drug and hormonal (e.g. corticoids, retinoids, vitamin D3) induced bone pathologies,
- bone remodeling (plastic surgery),
- operative repair of cartilage,
- dental surgery and
- orthodontic pathologies.

In one aspect, the invention provides the use of a compound for the manufacture of a medicament for the prevention or treatment of bone diseases and/or for increasing bone formation, said compound having the formula (I):
in which A is

where:
- $X^0$ is $H$, or an alkyl group having from 1 to 4 carbon atoms;
- $X^1$, $X^2$ and $X^3$ are identical or different and are $H$, a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms,
- $X^4$ is $H$, a straight or branched alkyl group having from 1 to 8 carbon atoms, or an optionally substituted benzyl group,
- $X^5$ is $H$, or a straight or branched alkyl group having from 1 to 8 carbon atoms,
- $X^6$ is $H$ or an alkyl group having from 1 to 4 carbon atoms,
- $q$ is 0 or 1,
- $R^1$, $R^2$, $R^3$ and $R^4$ are identical or different and are $H$, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms, or $R^1$, $R^2$ and $R^3$ and $R^4$ may form an alkyldenedioxy ring comprising from 2 to 8 carbon atoms,
- $L$ is $-\text{CH=CH-CH}_2-\text{-CH}_2-\text{-O(CH}_2\text{)}_n-\text{-S-}\text{-SO}_2-\text{-S(CH}_2\text{)}_n-\text{-SO}_2\text{(CH}_2\text{)}_n$,
  where $n$ is an integer from 1 to 7,
  or together with B, L is $\text{(CH=CH)}_k\text{-CH}_2\text{-CH=CH}_2\text{-CH-CH=}$ where $k$ is 0 or 1 and $d$ is an integer from 0 to 4,
- B is $H$, or an alkyl group having from 1 to 4 carbon atoms,
- $t$ is 0 or 1, with the proviso that $t$ is 0 only when L, together with B, is $\text{(CH=CH)}_k\text{-CH}_2\text{-CH=CH}_2\text{-CH=}$ where $k$ and $d$ are as described above, and with the further proviso that when L is $\text{-(CH}_2\text{)}_n$ or $\text{-S-}$, at least one of $R^1$, $R^2$, $R^3$ and $R^4$ is other than hydrogen.
In one preferred embodiment of the invention, there is provided the use of a compound of the formula (I) as hereinbefore defined provided that when L is other than \((\text{CH} = \text{CH})_k - (\text{CH}_2)_d - \text{CH} =\) where \(k\) is 0 or 1 and \(d\) is an integer from 0 to 4, at least one of \(R^1, R^2, R^3\) and \(R^4\) is other than hydrogen.

In the compounds of the formula (I) generally, at least one of \(R^1, R^2, R^3\) and \(R^4\) can be a straight, branched or cyclic alkyl group having from 1 to 8 carbon atoms. Preferably, at least two, more preferably at least three, and most preferably all four of the groups \(R^1, R^2, R^3\) and \(R^4\) are straight, branched or cyclic alkyl groups having from 1 to 8 carbon atoms.

In another aspect, the invention provides the use of a compound of formula (I) as hereinbefore defined for the manufacture of a medicament for the prevention and treatment of osteoporosis and Paget’s disease, e.g. by increasing bone formation.

In a further aspect, the invention provides the use of a compound of the formula (I) as hereinbefore defined for the manufacture of a medicament for the prevention and treatment of bone diseases due to cancer metastasis, for example osteolytic and osteoplastic bone metastasis or tumoral osteolysis, e.g. by increasing bone formation.

In a further aspect, the invention provides the use of a compound of the formula (I) as hereinbefore defined for the manufacture of a medicament for the prevention and treatment of conditions due to hypercalcemia, for example calcification of soft tissues (e.g. kidneys and other organs), or calcification of surgical implants, calcification of arteries due to late stage atherosclerosis.

In a still further aspect, the invention provides a method of prevention and/or treatment of a bone disease, which method comprises administering to a patient at risk of or suffering from said disease, an effective (preferably non-toxic) preventive or
therapeutic amount of a compound of the formula (I) as hereinbefore defined. In some embodiments, the aforementioned method of treatment of a bone disease further comprises administering, in combination with an effective amount of a compound of the formula (I), an effective amount of a bone resorption inhibitor. Such bone resorption inhibitors comprise the following classes of compounds: bisphosphonic acids, such as alendronate, cinamadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, midronic acid, icandronic acid, and S-12911; selective estrogen receptor modulators (SERMs), such as: raloxifene; HMG CoA reductase inhibitors, such as simvastatin, atorvastatin and cerivastatin; steroid hormones, such as Vitamin D; and polypeptide hormones, such as calcitonin.

In another aspect, the invention provides pharmaceutical compositions comprising an amount of a compound of formula (I) as hereinbefore defined effective to stimulate bone formation in a patient in need of such treatment and a pharmaceutically acceptable carrier. In a preferred embodiment, the pharmaceutical composition is an oral pharmaceutical compositions comprising an amount of a compound of formula (I) as hereinbefore defined effective to stimulate bone formation in a patient in need of such treatment and a pharmaceutically acceptable carrier.

In the compounds of formula (I), examples of A include:

The currently preferred definition of A is:
Examples of groups $X^0$ include hydrogen, C$_{1-4}$ alkyl; the preferred definition of $X^0$ being hydrogen.

Examples of groups $X^1$, $X^2$ and $X^3$ include hydrogen, straight or branched alkyl groups and alkoxy groups having from 1 to 5 carbon atoms, more particularly from 1 to 4 carbon atoms. Preferred groups $X^1$ and $X^2$ are methyl, ethyl, n-propyl, isopropyl, sec-butyl, tert-butyl, methoxy and ethoxy groups, a particularly preferred group being tert-butyl. The preferred definition of $X^3$ is hydrogen and the preferred definitions of both $X^1$ and $X^2$ are tert-butyl.

Examples of $X^4$ are H and alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, heptyl and nonyl. Examples of optionally substituted phenylalkyl groups $X^4$ include optionally substituted benzyl, phenethyl and phenylpropyl groups. Examples of optional substituents for the phenylalkyl groups include alkyl groups, alkoxy and alkylthio groups, halogens such as fluoro, chloro, bromo and iodo, hydroxy, thio, amino and mono- and di-alkylamino groups and their amide (in the case of unsubstituted and monoalkylamino groups) derivatives, nitro, alkylsulphonyl, trifluoromethyl and alkoxy carbonyl groups.

Examples of groups $R^1$, $R^2$, $R^3$ and $R^4$ include hydrogen, methyl, ethyl, n-propyl, isopropyl, sec-butyl and tert-butyl. The preferred definitions of $R^1$, $R^2$, $R^3$ and $R^4$ are ethyl and isopropyl.

Thus, in accordance with the invention, the applicants have found that compounds of formula (I) are surprisingly effective for increasing bone formation and thus are useful in diseases of bone metabolism.
The compounds of formula (I) include the alkylidene-diphosphonates (Ia) and the alkenylidene-diphosphonates (Ib).

\[
P_\text{O}_3 R^1 R^2
\| \\
A \longrightarrow L \longrightarrow C \longrightarrow B
\mid \\
P_\text{O}_3 R^3 R^4
\]

(Ia)

\[
P_\text{O}_3 R^1 R^2
\| \\
A \longrightarrow (\text{CH}=\text{CH})_k \longrightarrow (\text{CH}_2)_{d-CH \equiv C} \longrightarrow \\
P_\text{O}_3 R^3 R^4
\]

(Ib)

where A, L, B, k, d, R\text{I}, R\text{II}, R\text{III} and R\text{IV} are as described above.

Compounds of structure (Ia) include, for example, those in which:

- \(X^0\) is H, an alkyl group having from 1 to 4 carbon atoms;
- \(X^1, X^2\) and \(X^3\) are identical or different and are H, a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms,
- \(X^4\) is H, a straight or branched alkyl group having from 1 to 8 carbon atoms, an optionally substituted benzyl group,
- \(X^5\) is H, a straight or branched alkyl group having from 1 to 8 carbon atoms,
- \(X^6\) is H or an alkyl group having from 1 to 4 carbon atoms,
- q is 0 or 1,
- \(R^1, R^2, R^3\) and \(R^4\) are identical or different and are H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms, \(R^1, R^2\) and \(R^3\) and \(R^4\) may form an alkylidenedioxy ring comprising from 2 to 8 carbon atoms,
- L is \(\text{CH}=\text{CH-CH}_2, -\text{(CH}_2)_n\text{-, -O(CH}_2)_n\text{-, -S, -SO}_2\text{-, -S(CH}_2)_n\text{-, -SO}_2\text{(CH}_2)_n\text{, where } n \text{ is an integer from 1 to 7,}
- B is H, an alkyl group having from 1 to 4 carbon atoms.

Compounds of structure (Ib) include, for example, those in which:

- \(X^0\) is H, an alkyl group having from 1 to 4 carbon atoms;
- \(X^1, X^2\) and \(X^3\) are identical or different and are H, a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms,
- $X^4$ is H, a straight or branched alkyl group having from 1 to 8 carbon atoms, an optionally substituted benzyl group,
- $X^5$ is H, a straight or branched alkyl group having from 1 to 8 carbon atoms,
- $X^6$ is H or an alkyl group having from 1 to 4 carbon atoms,
- q is 0 or 1,
- $R^1$, $R^2$, $R^3$ and $R^4$ are identical or different and are H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms, $R^1$, $R^2$ and $R^3$ and $R^4$ may form an alkylidenedioxy ring comprising from 2 to 8 carbon atoms,
- k is zero or 1 and d is zero to 4.

Particular compounds of the formula (I) are as defined in the examples 1-4 and the claims appended hereto.

Compounds of the formula (I) can be prepared by methods disclosed in US Patents N° 5,043,330 and N° 5,204,336 or as described in the examples below.

For example, compounds of formula (I) where A is

![Chemical Structure](image)

where:
- $X^0$ is H, an alkyl group having from 1 to 4 carbon atoms;
- $X^1$, $X^2$ and $X^3$ are identical or different and are H, a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms,

may be prepared in accordance with the procedures described in the US Patent N° 5°043°330, the disclosure of which is incorporated herein by reference.
Compounds of formula (I) where A is

\[ \text{X}^0 \text{-- O --} \text{X}^4 \quad \text{or} \quad \text{X}^0 \text{-- O --} \text{X}^5 \text{-- C(H}_2_\text{)}_q \text{--} \text{X}^6 \]

where:
- \( \text{X}^0 \) is H, an alkyl group having from 1 to 4 carbon atoms;
- \( \text{X}^4 \) is H, a straight or branched alkyl group having from 1 to 8 carbon atoms,
- \( \text{X}^5 \) is H, a straight or branched alkyl group from 1 to 8 carbon atoms,
- \( \text{X}^6 \) is H or an alkyl group from 1 to 4 carbon atoms,
- \( q \) is 0 or 1,

may be prepared in accordance with the procedures described in US Patent No. 5,204,336, the disclosure of which is incorporated herein by reference.

Compounds of the formula (I) wherein \( \text{X}^4 \) is an optionally substituted aralkyl group (e.g. benzyl group) can be prepared by the methods set out in the examples or methods analogous thereto.

The compounds of formula (I) can be administered by any of a variety of routes. Thus, for example, they can be administered orally, or by delivery across another mucosal surface (for example across the nasal, buccal, bronchial or rectal mucosa), transdermally, or by injection (for example intradermal, intraperitoneal, intravenous or intramuscular injection).

When the compounds are intended for oral administration, they can be formulated, for example, as tablets, capsules, ovules, granules, pills, lozenges, powders, solutions, emulsions, syrups, elixirs, suspensions, or any other pharmaceutical form suitable for oral administration. Oral dosage forms can, if desired, be coated with one or more release delaying coatings to allow the release of the active compound to be controlled or targeted at a particular part of the enteric tract.
Tablets and other solid or liquid oral dosage forms can be prepared (e.g. in standard fashion) from the compounds of formula (I) and a pharmaceutically acceptable solubilizer, diluent or carrier. Examples of solubilizers, diluents or carriers include sugars such as lactose, starches, cellulose and its derivatives, powdered tracanghanth, malt, gelatin, talc, stearic acid, magnesium stearate, calcium sulfate, vegetable oils, polyols such as glycerol, propylene glycol and polyethylene glycols, alginic acids and alginites, agar, pyrogen free water, isotonic saline, phosphate buffered solutions, and optionally other pharmaceutical excipients such as disintegrants, lubricants, wetting agents such as sodium lauryl sulfate, coloring agents, flavoring agents and preservatives, etc..

Capsules can be of the hard or soft variety and can contain the active compound in solid, liquid or semisolid form. Typically such capsules are formed from gelatine or an equivalent substance and can be coated or uncoated. If it is desired to delay the release of the active compound until the capsule has passed through the stomach and into the intestine, the capsule can be provided with a pH sensitive coating adapted to dissolve at the pH found in the duodenum or ileum. Examples of such coatings include the Eudragits, the uses of which are well known.

Formulations for injection will usually be made up of the appropriate solubilizers such as detergents which may also include compounds and excipients such as buffering agents to provide an isotonic solution having the correct physiological pH. The injectable solutions are typically pyrogen-free and can be provided in sealed vials or ampoules containing a unit dose of compound. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavoring or coloring agents.
A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

The choice of form for administration as well as effective dosages will vary depending, inter alia, on the condition being treated. The choice of mode of administration and dosage is within the ability of the person skilled in the art.

A unit dosage form of the compounds of the invention typically will contain from 0.1% to 99% by weight of the active substance, more usually from 5% to 75% of the active substance. By way of example, a unit dosage form can contain from 1mg to 1g of the compound, more usually from 10mg to 500mg, for example between 50mg and 400mg, and typically in doses of 100mg to 200mg.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a
compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The compounds of the invention will be administered in amounts that are effective to provide the desired therapeutic effect. The concentrations necessary to provide the desired therapeutic effect will vary according to among other things the precise nature of the disease, the size, weight and age of the patient and the severity of the disease.

The doses administered will preferably be non-toxic to the patient, although in certain circumstances the severity of the disease under treatment may necessitate administering an amount of compound that causes some signs of toxicity.

Typically, the compounds of the invention will be administered in amounts in the range 0.01 mg/kg to 100 mg/kg body weight, more preferably 0.1 mg/kg to 10 mg/kg body weight and particularly 1 mg/kg to 5 mg/kg body weight.

The pharmaceutically acceptable compounds of the invention will normally be administered to a subject in a daily dosage regimen. For an adult patient this may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Thus, for an average human of 70 kg weight, a typical daily dosage of the compounds of the invention would be in the range of 70 mg to 700 mg. Such a dosage can be administered, for example from two to four times daily.

Ultimately however, the size of the doses administered and the frequency of administration will be at the discretion and judgement of the physician treating the patient.
The compounds of the invention may also be administered in combination with an effective amount of a bone resorption inhibitor. Bone resorption inhibitors are those agents known in the art to inhibit the absorption of bone and include, but are not limited to the following classes of compounds: bisphosphonic acids, such as alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, midronic acid, icandronic acid, and S-12911; selective estrogen receptor modulators (SERMs), such as: raloxifene; HMG CoA reductase inhibitors, such as simvastatin, atorvastatin and cerivastatin; steroid hormones, such as Vitamin D; and polypeptide hormones, such as calcitonin. Dosage ranges and regimens for bone resorption inhibitors are those which are known in the art. In particular, when a bisphosphonic acid is employed, a daily dosage of 2.5 to 100 mg may be used. In accordance with the method of the present invention, the components of a combination of the compounds of the present invention and bone resorption inhibitors can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. According to the instant invention, the term administering is to be understood as embracing all such regimes of simultaneous or alternating treatment and the scope of combinations of the compounds of this invention and bone resorption inhibitors includes in principle, any combination useful for inhibiting bone loss and building new bone.

Disease states which could benefit from increasing bone formation include, but are not limited to:

- osteoporosis,
- prevention and accelerated repair of bone fracture,
- prevention and treatment of metastasis of cancer cells in bone
- prevention and treatment of osteolytic bone lesions,
- prevention and treatment of osteoblastic bone metastasis,
- prevention and treatment of increased bone remodeling, bone hypertrophy and abnormal bone structure (i.e. Paget’s disease),
- prevention and treatment of bone loss associated with cancer therapies (e.g., bone loss associated with the treatment of gonadotropin-releasing hormone agonists for prostate cancer and bone loss associated with chemotherapy for breast cancer, wherein such cl
- not limited to, cyclophosphamide, methotrexate, fluorouracil, paclitaxel, doxorubicin, tamoxifen and combinations thereof,
- prevention and treatment of bone loss in HIV patients associated with lipodystrophy and treatment with antiviral drugs,
- prevention of the calcification of soft tissues (i.e. kidneys and and other organs),
- prevention of the calcification of surgical implants (i.e. natural and artificial organs such as cardiac valves),
- treatment of patients suffering from calcified soft tissues and calcified surgical implants,
- prevention and treatment of calcification and calcified arteries (arteriosclerosis),
- hypercalcemia secondary to an increase in bone resorption,
- hypercalcemia secondary to malignancies,
- tumoral osteolysis
- drug and hormonal (e.g. corticoids, retinoid, vitamin D3) induced bone pathologies,
- bone remodeling (plastic surgery),
- operative repair of cartilage,
- dental surgery and
- orthodontic pathologies.

The compounds of this invention increase bone formation and are therefore of value in the treatment of any of these conditions.

**Brief Description of the Drawings**

FIG. 1 represents the plasma concentration at Day 21 of Compound 1 and Compound 2 given orally to cynomologus monkeys (n=4, 25 mg/kg for 3 weeks).

**Detailed Description of the Preferred Embodiments**

The invention will now be illustrated, but not limited in any way, by the following examples.
Examples 1-4 of this application describe the synthesis of compounds:

\[
\begin{align*}
\text{where:} \\
\text{- } X^0 \text{ is H, an alkyl group having from 1 to 4 carbon atoms;} \\
\text{- } X^4 \text{ is an optionally substituted benzyl (Bn) group.}
\end{align*}
\]

Examples 5-9 describe the bone anabolic activity of the compounds of formula (I).

**Example 1: Tetraethyl 2-(3-benzyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate**

\[
\begin{align*}
\text{HO} & \quad \text{CH} = C & \quad \text{PO}_3\text{Et}_2 \\
\text{Bn} & & \text{PO}_3\text{Et}_2
\end{align*}
\]

a) 3-Benzyl-4-hydroxynaphthaldehyde

Potassium tert-butoxide (36.0 g, 0.32 mol) was added cautiously to a solution of 1-tetralone (23.4 g, 0.16 mol) and benzaldehyde (16.96 g, 0.16 mol) in tert-butanol (1600 ml) and the resulting mixture was refluxed overnight under nitrogen. The mixture was cooled, acidified with dilute HCl solution and concentrated under vacuum to remove tert-butanol. The concentrated aqueous phase was extracted with ethyl acetate and the residue obtained after evaporation of the organic phase was purified by column chromatography, yielding 34 g of 2-benzyl-1-naphthol.
To a 0°C solution of 2-benzyl-1-naphthol (10.67 g, 45.6 mmol) dissolved in 60 ml dichloromethane was added dry stannic chloride (21.38 g, 82.1 mmol), then 1,1-dichloromethyl methyl ether (7.92 g, 68.86 mmol) was added dropwise. The resulting mixture was stirred at 0°C for 30 min, then was poured into ice water. The resulting aqueous phase was extracted with diethyl ether, the ether phase was washed with water until the wash was no longer acidic. The dried (MgSO₄) ether phase was evaporated to give an oil which became solid after trituration in an ether-pentane solution. Ca 10 g (85%) of the title compound was obtained, mp = 157-159°C.

b) Tetraethyl 2-(3-benzyl-4-hydroxynaphthyl)ethylenedien-1,1-diphosphonate

Titanium tetrachloride (10.89 g, 57.3 mmol) was added dropwise while stirring to 60 ml of dry tetrahydrofuran. The following compounds were then added sequentially at 5 min intervals while stirring at 0-5°C: 3-benzyl-4-hydroxynaphthaldehyde (5.0 g, 19.1 mmol), then tetraethyl methylenediphosphonate (6.6 g, 22.9 mmol) and finally N-methylmorpholine (11.58 g, 114.6 mmol). After the addition was completed, the reaction was stirred for 3 h at room temperature then ice water was added. The quenched reaction mixture was extracted with diethyl ether, the ether extracts back extracted with brine until neutral pH then concentrated in vacuo to give a residue which was purified by column chromatography (SiO₂, 95/5 CHCl₃/MeOH) to give 4.2g (42% yield) of the title compound, mp = 152-155°C

MS (m/e) = 532: M⁺, 395 (100%): M⁺ - PO₃Et₂

NMR (CDCl₃):

δ = 8.8 (dxd; J=28 and 48 Hz, 1H): CH=CP₂
8.18, 7.8, 7.74, 7.45, 7.18: (5m, 5H total): naphthyl H
7.24 (m, 5H total): benzyl H
4.25 and 3.90 (2m, 8H): P-O-CH₂-CH₃
4.12 (s, 2H): CH₂ -Ph
1.41 and 0.12: (2t; J=7Hz, 12H): P-O-CH₂-CH₃
Example 2: Tetraisopropyl 2-(3-benzyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate

Titanium tetrachloride (10.89 g, 57.3 mmol) was added dropwise while stirring to 60 ml of dry tetrahydrofuran. The following compounds were then added sequentially at 5 min intervals while stirring at 0-5°C: 3-benzyl-4-hydroxynaphthaldehyde (5.0 g, 19.1 mmol), then tetraisopropyl methylenediphosphonate (7.9 g, 22.9 mmol) and finally N-methylmorpholine (11.58 g, 114.6 mmol). After the addition was completed, the reaction was stirred for 3 h at room temperature then ice water was added. The quenched reaction mixture was extracted with diethyl ether, the ether extracts back extracted with brine until neutral pH then concentrated in vacuo to give a residue which was purified by trituration in a mixture of petroleum ether and diethyl ether then recrystallisation in tert-butyl methyl ether to give 4.1 g (37% yield) of the title compound, mp = 112-115°C

MS (m/e) = 588: M⁺, 546: M⁺ - iPr, 420: M⁺ - 4iPr, 339 (100%): M⁺ - 2iPr - PO₃iPr₂

NMR (CDCl₃):
δ = 8.7 (dxd; J=28 and 48 Hz, 1H): CH=CP₂
8.18, 7.82, 7.68, 7.4: (4m, 5H total): naphthyl H
7.24 (m, 5H total): benzyl H
4.87 and 4.55 (2m, 4H): P-O-CH-(CH₃)₂
4.14 (s, 2H): CH₂ –Ph
1.42, 1.09 and 1.0: (3d; J=7Hz, 12H): P-O-CH-(CH₃)₂
Example 3: Tetra-n-propyl 2-(3-benzyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate

\[
\begin{array}{c}
\text{Bn} \\
\text{HO} \\
\text{CH} = C \\
\text{PO}_3n\text{Pr}_2 \\
\text{PO}_3n\text{Pr}_2
\end{array}
\]

The procedure described in example 1 was repeated at the same scale while using tetra-n-propyl methylenediphosphonate (7.88 g, 22.9 mmol) as the phosphonate reagent. Column chromatography (SiO₂, 95/5 CHCl₃/MeOH) gave 6.1 g (54% yield) of the title compound.

MS (m/e) = 588: M⁺, 423 (100%): M⁺ - PO₃nPr₂

NMR (CDCl₃):
\[\delta = 8.8 \text{ (dxd; J=28 and 48 Hz, 1H): CH=CP₂}\]
\[8.16, 7.74, 7.45, 7.1: (4m, 5H total): \text{naphthyl H}\]
\[7.24 \text{ (m, 5H total): benzyl H}\]
\[4.15 \text{ and 3.8 (2m, 8H): P-CH₂-CH₂-CH₃}\]
\[4.14 \text{ (s, 2H): CH₂-Ph}\]
\[1.8 \text{ and 1.38 (2 sextuplets, J=7Hz, 8H): P-CH₂-CH₂-CH₃}\]
\[1.12 \text{ and 0.7: (2t; J=7Hz, 12H): P-CH₂-CH₂-CH₃}\]

Example 4: Tetrabutyl 2-(3-benzyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate

\[
\begin{array}{c}
\text{Bn} \\
\text{HO} \\
\text{CH} = C \\
\text{PO}_3n\text{Bu}_2 \\
\text{PO}_3n\text{Bu}_2
\end{array}
\]

The procedure described in example 1 was repeated at the same scale while using tetrabutyl methylenediphosphonate (9.16 g, 22.9 mmol) as the phosphonate reagent.
reagent. Column chromatography (SiO₂, 95/5 CHCl₃/MeOH) gave 9.3 g (76% yield) of the title compound.

MS (m/e) = 650: M⁺ + 4, 457 (100%): M⁺ - PO₃nBu₂

NMR (CDCl₃):
δ = 8.78 (dxd; J=28 and 48 Hz, 1H): CH=CP₂
8.18, 7.8, 7.7, 7.4 and 7.14: (5m, 5H total): naphthyl H
7.24 (m, 5H total): benzyl H
4.18 and 3.84 (2m, 8H): P-O-CH₂-CH₂-CH₂.CH₃
4.0 (s, 2H): CH₂-Ph
1.75 and 1.35 (2 quintuplets, J=7Hz, 8H): P-O-CH₂-CH₂-CH₂.CH₃
1.45 and 1.12 (2 sextuplets, J=7Hz, 2H): P-O-CH₂-CH₂-CH₂.CH₃
0.94 and 0.27: (2t; J=7Hz, 12H): P-O-CH₂-CH₂-CH₂.CH₃

Chemical Structures of Compounds of formula (I) tested for bone anabolic activity

Compound 1: Tetraisopropyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethyldene-1,1-diphosphonate

Compound 2: Tetraethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethyldene-1,1-diphosphonate
Compound 3: 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethyldiene-1,1-diphosphonic acid

\[
\begin{align*}
\text{HO} & \quad \text{PO}_2\text{H}_2 \\
\text{t-Bu} & \quad \text{PO}_2\text{H}_2
\end{align*}
\]

Compound 4: Tetraethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylenediene-1,1-diphosphonate

\[
\begin{align*}
\text{HO} & \quad \text{PO}_2\text{Et}_2 \\
\text{t-Bu} & \quad \text{PO}_2\text{Et}_2
\end{align*}
\]

Compound 5: 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylenediene-1,1-diphosphonic acid

\[
\begin{align*}
\text{HO} & \quad \text{PO}_2\text{H}_2 \\
\text{t-Bu} & \quad \text{PO}_2\text{H}_2
\end{align*}
\]

Example 5: Bone anabolism activity of Compounds of Formula (I): subcutaneous administration

Method

The anabolic activity of selected compounds of formula (I) was investigated in OFI mice and Simvastatin and Dexamethasone were used as reference compounds in this model for the following reasons:

- The present mice model has previously been characterized with cholesterol synthesis inhibitors such as Simvastatin, see for instance: Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutierrez G “Stimulation of bone formation in vitro and in rodents by statins” Science 1999, 286:1946-1949.
- Dexamethasone has been widely used as a potent anabolic drug in vitro in osteoblast cells, see for instance: Scutt A, Bertram P, Brautigam M “The role of glucocorticoids
and prostaglandin E(2) in the recruitment of bone marrow mesenchymal cells to the osteoblastic lineage - positive and negative effects" *Calcified Tissue International* 1996, 59:154-162 and in vivo.

**Protocol:**

Four week old male OF1 mice (Iffa-Credo, Les Oncins, France) were divided into four groups of 5 animals. Test compounds of formula (I) were given at the dose 20 mg/kg by subcutaneous administration (s.c.) in comparison to Dexamethasone (10 mg/kg s.c.) and Simvastatin (10 mg/kg s.c.) and the control group received vehicle alone (propylene glycol, 50 ul). All drugs were given s.c. in the central part of the calvaria on a basis of five administrations per week for 3 weeks. At the end of the study, animals were sacrificed under pentobarbital anesthesia, blood was collected and serum was obtained. The femur and calvaria (a flat bone on the cranium) were dissected and frozen. Dry bone weight, ash weight and bone calcium were measured after drying and calcination of the calvaria. Bone phosphorus was quantified by a colorimetric molybdate method.

**Results:**

The results of the study are presented in Table 1. The markers for anabolic activity are:

- the increase in calvaria weight as compared to femur weight,
- the increase of calcium and phosphorus, which are the major ions of bone (mineral content).

The anabolic activity of the reference compounds Simvastatin and Dexamethasone was confirmed, thus validating this model. Thus, Simvastatin and Dexamethasone increased calvaria weight by +27% and +17% respectively whereas femur weight decreased or remained constant; the calcium and phosphorus ions were similarly increased.

The Diphosphonate Ester compounds 1, 2 and 4 and the vinylic diphosphonic acid compound 5 showed a clear profile of anabolic activity judging from the increase in calvaria weight as compared to femur weight, measured as a control. Both relevant
ions, calcium and phosphorus are increased. More specifically, The Diphosphonate Ester compound 1 increased calvaria weight by +19%, calvaria calcium by +12% and calvaria phosphorus by +20%. In contrast, the non-vinlyc Diphosphonic Acid Compound 3 was inactive.

Table 1: Effect of selected compounds of formula (I) on calvaria ash weight and mineral content (calcium and phosphorus) in treated mice, expressed as % change from the control group

<table>
<thead>
<tr>
<th>Test Compound</th>
<th>Femur ash weight (mg) % Change</th>
<th>Calvaria ash weight (mg) % Change</th>
<th>Calcium (mg/calvaria) % Change</th>
<th>Phosphorus (mg/calvaria) % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>-27</td>
<td>+18</td>
<td>+14</td>
<td>+8</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-2</td>
<td>+27</td>
<td>+19</td>
<td>+16</td>
</tr>
<tr>
<td>Compound 1</td>
<td>-8</td>
<td>+19</td>
<td>+12</td>
<td>+20</td>
</tr>
<tr>
<td>Compound 2</td>
<td>0</td>
<td>+28</td>
<td>+22</td>
<td>+22</td>
</tr>
<tr>
<td>Compound 3</td>
<td>-7</td>
<td>+3</td>
<td>-4</td>
<td>0</td>
</tr>
<tr>
<td>Compound 4</td>
<td>-11</td>
<td>+26</td>
<td>+20</td>
<td>+20</td>
</tr>
<tr>
<td>Compound 5</td>
<td>-14</td>
<td>+27</td>
<td>+26</td>
<td>+24</td>
</tr>
</tbody>
</table>

Example 6: Bone anabolism activity of Compound 1; oral administration

Groups of six mice were administered Compound 1 orally at doses of 50 and 100mg/kg for 18 days. At sacrifice the metaphysis containing trabecular bone was separated and weighed. The content of mineral ions, calcium and phosphorus of trabecular bone were measured by chemical methods, the density of trabecular bone was determined by peripheral Quantitative Computerized Tomography (pQCT) using a Stratec apparatus. The results presented in Table 2 show that Compound 1 increased trabecular bone ash weight and mineral (calcium and phosphorus) content.
Table 2: Effect of Compound 1 on femur trabecular ash weight and mineral content in mice

<table>
<thead>
<tr>
<th>Dose of Compound 1</th>
<th>Ash weight (mg/bone) % control</th>
<th>Calcium (mg/bone) % control</th>
<th>Phosphorus (mg/bone) % control</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/kg/day</td>
<td>+15</td>
<td>+27</td>
<td>+10</td>
</tr>
<tr>
<td>100 mg/kg/day</td>
<td>+37 (p&lt;0.002)</td>
<td>+66 (p&lt;0.02)</td>
<td>+32 (p&lt;0.05)</td>
</tr>
</tbody>
</table>

It was further confirmed by peripheral quantitative computer tomography (pQCT) that Compound 1 at the higher dose (100mg/kg/day) increased significantly (p<0.005) bone trabecular mineral density by 27.5% as compared to the control group; see Table 3.

Table 3: Effect of Compound 1 in bone density as determined by pQCT

<table>
<thead>
<tr>
<th></th>
<th>Trabecular Density (g/cm²)</th>
<th>Trabecular Density (% control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>212.7 ± 12.4</td>
<td>0</td>
</tr>
<tr>
<td>Compound 1 (50mg/kg)</td>
<td>224.2 ± 25.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Compound 1 (100mg/kg)</td>
<td>271.2 ± 10.1</td>
<td>27.5 (p=0.004)</td>
</tr>
</tbody>
</table>

Example 7: Effect of Compound 1, one representative compound of the formula (I), on osteoblast numbers

In order to confirm the activity observed with the compounds 1-4 given by subcutaneous administration, one selected compound of formula (I) was further tested in another model by oral administration.

Groups of 12 mice were treated orally with 200 mg/kg of Compound 1 for 3 weeks. Bone tissue was fixed, processed and stained for the histomorphometric measurement of the number of osteoblasts.
Compound 1 increased significantly the number of osteoblasts by 31% (p<0.05) in the tibia of treated mice.

It will be appreciated that the test method described above can also be used to determine the activities of other compounds of the formula (I).

**Example 8: Bone anabolic activity of Compound 1 in the monkey**

The foregoing data provided evidence that the anabolic activity of the diphosphonate esters occurs via an increase in the activity and number of bone forming osteoblasts. Subsequently the prototype Compound 1 was given orally to monkeys in order to verify that this anabolic activity can be also manifested in primates. Bone specific Alkaline Phosphatase was used as a surrogate plasma marker reflecting an increase in osteoblastic activity in monkeys.

In this study protocol male Cynomolgus monkeys weighing between 3 and 7 kg were divided into groups of 4 animals each. Test compounds were given orally by gavage at the dose of 25 mg/kg/day for 3 weeks and plasma bone specific alkaline phosphatase was measured twice before (pre-dose) and at days 8, 15 and 21 during the dosing period using a specific quantitative immunological method (ELISA). Results (mean of 4 values of each group) were expressed as % of pre-dose (day -1).

<table>
<thead>
<tr>
<th>Cpd</th>
<th>Plasma % change from pre-dose at Day 8</th>
<th>Bone % change from pre-dose at Day 15</th>
<th>Specific % change from pre-dose at Day 21</th>
<th>Alkaline Phosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>+16</td>
<td>+25</td>
<td>+24</td>
<td></td>
</tr>
</tbody>
</table>
Bone specific alkaline phosphatase was selected for measurement as it is the most important marker which has been correlated with bone formation. The results from Table 4 show that Compound 1 given orally induces bone alkaline phosphatase. This increase in bone alkaline phosphatase occurred without a simultaneous increase in total plasma alkaline phosphatase produced by non-bone tissues, eg liver (data not shown). These data clearly demonstrate that the compounds of formula (I) have a specific activity on osteoblast differentiation leading to bone growth.

Example 9: Bone anabolic activity of Compound 1 in humans

The preliminary results from a clinical study confirm the foregoing results measured in animals, see Table 5.

Briefly, a patient was treated with Compound 1 for 21 days with a dose of 50mg twice daily. Total alkaline phosphatase and bone specific alkaline phosphatase in plasma were measured at days 8, 15 and 21. Results are expressed in Table 5 as % of pre-dose (Day -1). Bone specific alkaline phosphatase increased up to 52% during treatment (Day 21) and returned to normal levels a month after the treatment was interrupted. Total alkaline phosphatase was unchanged during the treatment period. Taken together, these data indicate that in humans Compound 1 acts specifically on bone alkaline phosphatase, the enzyme associated with osteoblast differentiation leading to bone growth.

<table>
<thead>
<tr>
<th>Table 5: Changes in Plasma Bone Specific Alkaline Phosphatase (BAP) in a patient orally treated with Compound 1 at the 50 mg/kg/day dose bid for 3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Compound 1</td>
</tr>
</tbody>
</table>
Favorable pharmacokinetic profile

The diphosphonate esters being high lipophilic are very efficiently absorbed when given orally in rodents, primates and in man. For example, as shown in FIG. 1, plasma levels greater than 1000ng/ml were reached and maintained for several hours in Cynomolgus monkeys receiving Compounds 1 and 2 administered orally (25mg/kg) for three weeks. Pharmacokinetic samples were obtained on the last day of compound administration.

In conclusion, the diphosphonates of formula (I) are active for increasing bone cells, as demonstrated by their activity in the following models:
- increase activity and in number of osteoblasts, the bone forming cells in rodents,
- enhance bone mineral content and increase trabecular bone density in mice and
- increase bone specific alkaline phosphatase, the specific enzyme for osteoblastic activity in monkeys and in man.

This favorable activity in animals is believed to be translatable to humans. Compound 1, a typical prototype of compounds of formula (I), was demonstrated to have a good toxicity profile in animals and in addition has high oral bioavailability (greater than 30%) and sufficient systemic exposure in man.

This is to be contrasted with the very limited bioavailability of the bisphosphonic acids (typically less than 1% for alendronate and risedronate) which necessitate their administration under the i.v. form. Similarly, the anabolic compounds in development such as PTH (parathyroid hormone) or calcitonin all need to be given as continuous infusions or daily subcutaneous injections. The other class of compounds which has potential utility for bone formation, the statins, are very poorly bioavailable as they were designed to target the liver, the target organ for cholesterol synthesis. For example the C\textsubscript{max} of active lovastatin is 0.033 \textmu g equiv/ml after a 40mg oral dose in man. Furthermore, high systemic exposure of this class of compound has been shown to result in marked toxicity both in animals and in man.
Thus the diphosphonates of formula (I) are a new class of bone anabolic agents with potential utility for treating conditions associated with loss of bone mass due to aging or diseases, such as the following:
- osteoporosis,
- prevention and accelerated repair of bone fracture,
- prevention and treatment of metastasis of cancer cells in bone,
- prevention and treatment of osteolytic bone lesions,
- prevention and treatment of osteoblastic bone metastasis,
- prevention and treatment of increased bone remodeling, bone hypertrophy and abnormal bone structure (i.e. Paget's disease),
- prevention and treatment of bone loss associated with cancer therapies (e.g., bone loss associated with the treatment of gonadotropin-releasing hormone agonists for prostate cancer and bone loss associated with chemotherapy for breast cancer, wherein such chemotherpay includes, but is not limited to, cyclophosphamide, methotrexate, fluorouracil, paclitaxel, doxorubicin, tamoxifen and combinations thereof),
- prevention and treatment of bone loss in HIV patients associated with lipodystrophy and treatment with antiviral drugs,
- prevention of the calcification of soft tissues (i.e. kidneys and and other organs),
- prevention of the calcification of surgical implants (i.e. natural and artificial organs such as cardiac valves),
- treatment of patients suffering from calcified soft tissues and calcified surgical implants,
- prevention and treatment of calcification and calcified arteries (arteriosclerosis),
- hypercalcemia secondary to an increase in bone resorption,
- hypercalcemia secondary to malignancies,
- tumoral osteolysis
- drug and hormonal (e.g. corticoids, retinoid, vitamin D3) induced bone pathologies,
- bone remodeling (plastic surgery),
- operative repair of cartilage,
- dental surgery and
- orthodontic pathologies.
Claims:

1. The use of an aryl-substituted 1,1-diphosphonate for the manufacture of a medicament for stimulating bone formation; said aryl-substituted 1,1-diphosphonate being a compound of formula (I):

\[
\begin{align*}
&\text{PO}_2R^1R^2 \\
&\text{A} - \text{L} - \text{C} - (\text{B})_t \\
&\text{PO}_2R^3R^4
\end{align*}
\]  

(I)

in which A is

\[
\begin{align*}
&x^0 - o - \text{aromatic ring} \\
&x^1 \quad x^2 \quad x^3 \\
&\text{or} \\
&x^4 - o - \text{aromatic ring} \\
&x^5 \quad x^6 \\
&\text{or} \\
&x^0 - o - \text{aromatic ring} \\
&x^6 \quad \text{CH}_2_\text{a}
\end{align*}
\]

where:
- \(x^0\) is H, an alkyl group having from 1 to 4 carbon atoms;
- \(x^1, x^2, x^3\) are identical or different and are H, a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms,
- \(x^4\) is H, a straight or branched alkyl group having from 1 to 8 carbon atoms, an optionally substituted benzyl group,
- \(x^5\) is H, a straight or branched alkyl group having from 1 to 8 carbon atoms,
- \(x^6\) is H or an alkyl group having from 1 to 4 carbon atoms,
- \(q\) is 0 or 1,
- \(R^1, R^2, R^3\) and \(R^4\) are identical or different and are H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms, or \(R^1, R^2\) and \(R^3\) and \(R^4\) may form an alkylidenedioxy ring comprising from 2 to 8 carbon atoms;

- \(L\) is -CH=CH-CH2-, -(CH2)n-, O(CH2)n-, S-, SO2-, S(CH2)n-, SO2(CH2)n,

where \(n\) is an integer from 1 to 7,

or together with \(B\), \(L\) is (CH=CH)k-(CH2)d-CH= where \(k\) is 0 or 1 and \(d\) is an integer from 0 to 4,
- B is H, an alkyl group having from 1 to 4 carbon atoms,
- t is 0 or 1, with the proviso that t is 0 only when L, together with B, is \((CH=CH)_k-(CH_2)_d-CH=\) where k and d are as described above, and with the further proviso that when L is \(-(CH_2)_n\) or \(-S-\), at least one of \(R^1\), \(R^2\), \(R^3\) and \(R^4\) is other than hydrogen.

2. The use according to claim 1, wherein said diphosphonate is an aryl substituted alkylidene diphosphonate selected from compounds of formula (Ia)

\[
\begin{array}{c}
\text{PO}_3R^1R^2 \\
\text{A} \quad -L \quad \text{C} \quad -B \\
\text{PO}_3R^3R^4
\end{array}
\]

(IIa)

wherein A, L, B, \(R^1\), \(R^2\), \(R^3\) and \(R^4\) are as defined in claim 1.

3. The use according to claim 1, wherein the diphosphonate is an aryl substituted alkenylidene diphosphonate selected from compounds of formula (Ib)

\[
\begin{array}{c}
\text{A} \quad -(CH=CH)_k-(CH_2)_d-\text{CH}=\text{C} \\
\text{PO}_3R^1R^2 \\
\text{PO}_3R^3R^4
\end{array}
\]

(IIb)

wherein A, \(k\), \(d\), \(R^1\), \(R^2\), \(R^3\) and \(R^4\) are as described above.

4. The use according to any one of claims 1 to 3 wherein A is:

\[
\begin{array}{c}
X^0 \\
\text{O} \\
X^1 \\
X^2 \\
X^3
\end{array}
\]
5. The use according to any one of the preceding claims wherein \( X^0 \) is H.

6. The use according to any one of the preceding claims wherein \( X^1 \) and \( X^2 \) are the same and are both tert-Bu.

7. The use according to any one of the preceding claims wherein \( X^3 \) is H.

8. The use according to any one of claims 1, 4, 5, 6 and 7 wherein L is \( \text{CH}_2- \) and \( t \) is 1 or L is \( \text{CH}= \) and \( t \) is 0.

9. The use according to any one of claims 1, 2 and 5 to 8 wherein B is H.

10. The use according to any one of the preceding claims wherein \( R^1, R^2, R^3 \) and \( R^4 \) are the same or different and are selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl and tert-butyl.

11. The use according to any one of the preceding claims wherein \( R^1, R^2, R^3 \) and \( R^4 \) are identical but are not H.

12. The use according to claim 11 wherein \( R^1, R^2, R^3 \) and \( R^4 \) are isopropyl.

13. The use according to claim 1 wherein the diphosphonate is tetraisopropyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1- diphosphonate.

14. The use according to claim 1, wherein the diphosphonate is selected from: tetramethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
   tetraethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
   tetra-n-propyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
   tetra-n-butyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(3,5-di-sec-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
tetraethyl 2-(3,5-diisopropyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(3,5-diisopropyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxy-5-methylphenyl)-ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-5-methylphenyl)-ethylidene-1,1-diphosphonate,
tetraethyl 3,5-di-tert-butyl-4-hydroxyphenyl thiomethylene-diphosphonate,
tetraisopropyl 3,5-di-tert-butyl-4-hydroxyphenyl thiomethylene-diphosphonate,
tetraisopropyl 2-(3,4,5-trimethoxyphenyl)-ethylidene-1,1-diphosphonate,
dIBUTYL DIETHYL 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
diethyl diisopropyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
tetraethyl 1-(3,5-di-tert-butyl-4-hydroxyphenyl)-butylidene-2,2-diphosphonate,
2-(3,5-di-tert-butyl-4-hydroxyphenyl)ethylidene-1,1-bis(2-oxo-1,3,2-dioxaphosphorinan),
2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonic acid,
tetramethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3,5-di-sec-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(3,5-di-sec-butyl-4-hydroxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraisopropyl 2-(3,5-diisopropyl-4-hydroxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxy-5-methylphenyl)-ethenyldene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-5-methylphenyl)-ethenyldene-1,1-diphosphonate,
tetraethyl 2-(3,5-dimethoxy-4-hydroxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraisopropyl 2-(3,5-dimethoxy-4-hydroxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraisopropyl 2-(3,4,5-trimethoxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraisopropyl 2-(3-ethoxy-4-hydroxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3-butadienylidene-1,1-diphosphonate,
tetraisopropyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3-butadienylidene-1,1-diphosphonate,
dibutyl diethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenyldene-1,1-diphosphonate,
diethyl diisopropyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraethyl 2-(3,5-di-tert-butyl-4-methoxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraethyl 2-(3,4-methylene dioxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraethyl 2-(3,4-ethylenedioxyphenyl)-ethenyldene-1,1-diphosphonate,
tetraethyl 2-(3-benzyl-4-hydroxynaphthyl)ethenyldene-1,1-diphosphonate,
tetraisopropyl 2-(3-benzyl-4-hydroxynaphthyl)ethenyldene-1,1-diphosphonate,
tetra-n-propyl 2-(3-benzyl-4-hydroxynaphthyl)ethenyldene-1,1-diphosphonate,
tetra-n-butyl 2-(3-benzyl-4-hydroxynaphthyl)ethenyldene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxynaphthyl)ethenyldene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetramethyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenyldiene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenyldiene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenyldiene-1,1-diphosphonate,
tetra-n-propyl 2-(6-tert-butyl-7-hydroxy-4-indanyl)ethenyldiene-1,1-diphosphonate,
tetra-n-butyl 2-(6-tert-butyl-7-hydroxy-4-indanyl)ethenyldiene-1,1-diphosphonate,
tetramethyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethyldiene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethyldiene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-3-methyl-1-naphthyl)ethyldiene-1,1-diphosphonate,
tetraethyl 2-(4-hydroxy-1-naphthyl)ethyldiene-1,1-diphosphonate,
tetraisopropyl 2-(4-hydroxy-1-naphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-1-naphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-butyl 2-(4-hydroxy-1-naphthyl)ethyldiene-1,1-diphosphonate,
tetraethyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethyldiene-1,1-diphosphonate,
tetraisopropyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-butyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethyldiene-1,1-diphosphonate,
tetramethyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-
naphthyl)ethyldiene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-
naphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-
naphthyl)ethyldiene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-
naphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-
naphthyl)ethyldiene-1,1-diphosphonate,
tetra-n-propyl 2-(6-tert-butyl-7-hydroxy-4-indanyl)ethyldiene-1,1-
diphosphonate and
tetra-n-butyl 2-(6-tert-butyl-7-hydroxy-4-indanyl)ethyldiene-1,1-
diphosphonate.

15. The use according to any one of the preceding claims wherein the medicament is for stimulating bone formation in a subject characterised by a condition selected from the group consisting of osteoporosis, Paget’s disease, bone fracture or deficiency, drug and hormone-induced bone pathologies, hyperparathyroidism, periodontal disease or defect, post-plastic surgery, post-prosthetic joint surgery and post-dental implantation.

16. The use according to claim 15, wherein said drug and hormone induced pathology is selected from the group consisting of corticoids, retinoids and vitamin D3 induced bone pathologies.

17. The use according to any one of claims 1 to 14 wherein the medicament is for stimulating bone formation in a subject characterised by a condition selected from metastasis of cancer cells in bones, tumoral osteolysis, and hypercalcemia, wherein said hypercalcemia is secondary to malignancies.
18. The use according to claim 17 wherein said metastasis of cancer cells in bone is osteolytic or osteoplastic bone metastasis.

19. The use according to any one of claims 1 to 14 wherein the medicament is for stimulating bone formation in a subject characterised by a condition selected from periodontal disease or defect, post-plastic surgery, post-prosthetic joint surgery and post-dental implantation.

20. The use according to any one of claims 1 to 14 wherein the medicament is for stimulating bone formation in a subject, characterised by a condition arising from hypercalcemia, the said condition being selected from the group consisting of: calcification of soft tissues, calcification of surgical implants and calcification of arteries due to late stage atherosclerosis.

21. The use according to claim 20, wherein said soft tissue is selected from the group comprising kidney, blood vessels and heart valves.

22. The use according to any one of the claims 1 to 14, wherein the medicament is for stimulating bone formation in a subject, characterized by a condition arising from bone loss associated with therapy for cancer.

23. The use according to claim 22, wherein said therapy for cancer comprises treatment with gonadotropin-releasing hormone agonists.

24. The use according to claim 23, wherein said treatment with gonadotropin-releasing hormone agonists is for prostate cancer.

25. The use according to any one of the claims 1 to 14, wherein the medicament is for stimulating bone formation in a subject, characterized by a condition arising from bone loss associated with cancer chemotherapy.
26. The use according to claim 25, wherein said cancer chemotherapy comprises administration of cyclophosphamide, methotrexate, fluorouracil, paclitaxel, doxorubicin, tamoxifen or combinations thereof.

27. The use according to claim 25, wherein said cancer chemotherapy is for the treatment of breast cancer.

28. The use according to any one of the claims 1 to 14, wherein the medicament is for stimulating bone formation in a subject, characterized by a condition arising from bone loss associated with treatment with antiviral agents.

29. The use according to claim 28, wherein said subject has HIV.

30. The use according to claim 29, wherein said subject with HIV has lipodystrophy.

31. The use according to any one of the preceding claims wherein the medicament is for co-administration with or contains a bone resorption inhibitor.

32. The use according to claim 31, wherein said bone resorption inhibitor is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, midronic acid, icandronic acid, S-12911, raloxifene, simvastatin, atorvastatin, cerivastatin, vitamin D and calcitonin.

33. The use of a compound for the manufacture of a medicament for treating or preventing a bone disease or pathology, the compound being an aryl-substituted 1,1-diphosphonate compound of formula (I):

\[
\begin{align*}
\text{PO}_3R^1R^2 \\
\text{A} - \text{L} - \text{C} - (\text{B})_t \\
\text{PO}_3R^3R^4
\end{align*}
\]
in which A is

\[ x^0 \rightarrow O \rightarrow x^1 \] or \[ x^0 \rightarrow O \rightarrow x^4 \] or \[ x^2 \rightarrow O \rightarrow x^5 \]

where:
- \( x^0 \) is \( H \), an alkyl group having from 1 to 4 carbon atoms;
- \( x^1, x^2 \) and \( x^3 \) are identical or different and are \( H \), a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms,
- \( x^4 \) is \( H \), a straight or branched alkyl group having from 1 to 8 carbon atoms, an optionally substituted benzyl group,
- \( x^5 \) is \( H \), a straight or branched alkyl group having from 1 to 8 carbon atoms,
- \( x^6 \) is \( H \) or an alkyl group having from 1 to 4 carbon atoms,
- \( q \) is 0 or 1,
- \( R^1, R^2, R^3 \) and \( R^4 \) are identical or different and are \( H \), a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms, or \( R^1, R^2 \) and \( R^3 \) and \( R^4 \) may form an alkylidenedioxy ring comprising from 2 to 8 carbon atoms;
- \( L \) is \(-CH=CH-CH_2-\) or \(-C(H)CH=CH-\) or \(-C,H_2)n, \(-O(CH_2)n, \(-S, \(-SO_2, \(-S(OH)_2, \(-SO_2(CH_2)n, \(-SO_2(CO_2)n, \)

where \( n \) is an integer from 1 to 7,

or together with \( B \), \( L \) is \((CH=CH)k-(CH_2)d-CH=\) where \( k \) is 0 or 1 and \( d \) is an integer from 0 to 4,
- \( B \) is \( H \), an alkyl group having from 1 to 4 carbon atoms,
- \( t \) is 0 or 1, with the proviso that \( t \) is 0 only when \( L \), together with \( B \), is \((CH=CH)k-(CH_2)d-CH=\) where \( k \) and \( d \) are as described above, and with the further proviso that when \( L \) is \(-CH_2)n \) or \(-S, \) at least one of \( R^1, R^2, R^3 \) and \( R^4 \) is other than hydrogen, effective to stimulate bone formation.
34. The use according to claim 33, wherein said diphosphonate is an aryl substituted alkylidene diphosphonate selected from compounds of formula (Ia)

\[
\begin{align*}
A & \xrightarrow{L} C \xrightarrow{B} \text{PO}_3R^1R^2 \\
\text{PO}_3R^3R^4
\end{align*}
\]

wherein A, L, B, R^1, R^2, R^3 and R^4 are as defined in claim 1.

35. The use according to claim 33, wherein the diphosphonate is an aryl substituted alkenylidene diphosphonate selected from compounds of formula (Ib)

\[
\begin{align*}
A & \xrightarrow{(\text{CH}=\text{CH})_k} (\text{CH}_2)_d \xrightarrow{\text{CH}=\text{C}} \text{PO}_3R^1R^2 \\
\text{PO}_3R^3R^4
\end{align*}
\]

wherein A, k, d, R^1, R^2, R^3 and R^4 are as described above.

36. The use according to any one of claims 33 to 35, wherein A is:

\[
\begin{align*}
 x^0 & \xrightarrow{o} x^1 \\
 x^2 & \xrightarrow{x^3}
\end{align*}
\]

37. The use according to any one of claims 33 to 36 wherein X^0 is H.

38. The use according to claim 37 wherein X^1 and X^2 are the same and are both tert-butyl.

39. The use according to claim 38 wherein X^3 is H.

40. The use according to any one of claims 33, 34 and 37 to 39, wherein L is CH_2- and t is 1 or L is CH= and t is 0.
41. The use according to any one of claims 33, 34 and 37 to 40, wherein B is H.

42. The use according to any one of claims 33 to 41, wherein \( R^1, R^2, R^3 \) and \( R^4 \)
are the same or different and are selected from hydrogen, methyl, ethyl, n-propyl,
isopropyl, n-butyl, s-butyl and tert-butyl.

43. The use according to any one of claims 33 to 42, wherein \( R^1, R^2, R^3 \) and \( R^4 \)
are identical but are not H.

44. The use according to claim 43, wherein \( R^1, R^2, R^3 \) and \( R^4 \) are isopropyl.

45. The use according to claim 33, wherein the diphosphonate is tetraisopropyl 2-
(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1- diphosphonate.

46. The use according to claim 33, wherein the diphosphonate is selected from:
tetramethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-
diphosphonate,
tetraethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-
diphosphonate,
tetra-n-butyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-
diphosphonate,
tetraisopropyl 2-(3,5-di-sec-butyl-4-hydroxyphenyl)-ethylidene-1,1-
diphosphonate,
tetraethyl 2-(3,5-diisopropyl-4-hydroxyphenyl)-ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(3,5-diisopropyl-4-hydroxyphenyl)-ethylidene-1,1-
diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxy-5-methylphenyl)-ethylidene-1,1-
diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-5-methylphenyl)-ethylidene-1,1-
diphosphonate,
tetraethyl 3,5-di-tert-butyl-4-hydroxyphenyl thiome
tetraisopropyl 3,5-di-tert-butyl-4-hydroxyphenyl thiomethylene-diphosphonate,
tetraisopropyl 2-(3,4,5-trimethoxyphenyl)-ethylidene-1,1-diphosphonate,
dibutyl diethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-
diphosphonate,
5
diethyl diisopropyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethylidene-1,1-
diphosphonate,
tetraethyl 1-(3,5-di-tert-butyl-4-hydroxyphenyl)-butylidene-2,2-diphosphonate,
2-(3,5-di-tert-butyl-4-hydroxyphenyl)ethylidene-1,1-bis(2-oxo-1,3,2-
dioxaphosphorinan),
10
2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonic acid,
tetramethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
tetraethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
15
tetraisopropyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
tetra-n-propyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
tetra-n-butyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
20
tetraethyl 2-(3,5-di-sec-butyl-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
tetraisopropyl 2-(3,5-di-sec-butyl-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
25
tetraisopropyl 2-(3,5-diisopropyl-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxy-5-methylphenyl)-ethenylidene-1,1-
diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-5-methylphenyl)-ethenylidene-1,1-
diphosphonate,
30
tetraethyl 2-(3,5-dimethoxy-4-hydroxyphenyl)-ethenylidene-1,1-
diphosphonate,
tetraisopropyl 2-(3,5-dimethoxy-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(3,4,5-trimethoxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-ethoxy-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3-butadienylidene-1,1-diphosphonate,
tetraisopropyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3-butadienylidene-1,1-diphosphonate,
dibutyl diethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
diethyl diisopropyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3,5-di-tert-butyl-4-methoxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3,4-methylenedioxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3,4-ethylenedioxyphenyl)-ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3-benzyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-benzyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-benzyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3-benzyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-4-hydroxynaphthyl)ethenylidene-1,1-diphosphonate,
tetramethyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl) ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl) ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl) ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-3-methyl-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(4-hydroxy-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethenylidene-1,1-diphosphonate,
tetra-n-propyl 2-(6-tert-butyl-7-hydroxy-4-indanyl)ethenylidene-1,1-diphosphonate,
tetra-n-butyl 2-(6-tert-butyl-7-hydroxy-4-indanyl)ethenylidene-1,1-diphosphonate,
tetramethyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydroanaphthyl)ethylidene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydroanaphthyl)ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydroanaphthyl)ethylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydroanaphthyl)ethylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydroanaphthyl)ethylidene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-3-methyl-1-naphthyl)ethylidene-1,1-diphosphonate,
tetraethyl 2-(4-hydroxy-1-naphthyl)ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(4-hydroxy-1-naphthyl)ethylidene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-1-naphthyl)ethylidene-1,1-diphosphonate,
tetra-n-butyl 2-(4-hydroxy-1-naphthyl)ethylidene-1,1-diphosphonate,
tetraethyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetra-n-propyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetra-n-butyl 2-(4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetramethyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetraethyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetra-n-propyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetraisopropyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetra-n-butyl 2-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)ethylidene-1,1-diphosphonate,
tetra-n-propyl 2-(6-tert-butyl-7-hydroxy-4-indanyl)ethylidene-1,1-diphosphonate and
tetra-n-butyl 2-(6-tert-butyl-7-hydroxy-4-indanyl)ethylidene-1,1-diphosphonate.

47. The use according to any one of claims 33 to 46 wherein the medicament is for stimulating bone formation in a subject characterised by a condition selected from the group consisting of osteoporosis, Paget's disease, bone fracture or deficiency, drug and hormone-induced bone pathologies, hyperparathyroidism, periodontal disease or defect, post-plastic surgery, post-prosthetic joint surgery and post-dental implantation.

48. The use according to claim 47, wherein said drug and hormone induced pathology is selected from the group consisting of corticoids, retinoids and vitamin D3 induced bone pathologies.

49. The use according to any one of claims 33 to 46, wherein the medicament is for stimulating bone formation in a subject characterised by a condition selected from metastasis of cancer cells in bones, tumoral osteolysis and hypercalcemia, wherein said hypercalcemia is secondary to malignancies.

50. The use according to claim 49, wherein said metastasis of cancer cells in bone is osteolytic or osteoplastic bone metastasis.

51. The use according to any one of claims 33 to 46, wherein the medicament is for stimulating bone formation in a subject characterized by a condition selected from periodontal disease or defect, post-plastic surgery, post-prosthetic joint surgery and post-dental implantation.

52. The use according to any one of claims 33 to 46, wherein the medicament is for stimulating bone formation in a subject characterized by a condition arising from hypercalcemia, the said condition being selected from the group consisting of:
calcification of soft tissues, calcification of surgical implants and calcification of arteries due to late stage atherosclerosis.

53. The use according to claim 52, wherein said soft tissue is selected from the group comprising kidney, blood vessels and heart valves.

54. The use according to any one of the claims 33 to 46, wherein the medicament is for stimulating bone formation in a subject, characterized by a condition arising from bone loss associated with therapy for cancer.

55. The use according to claim 54, wherein said therapy for cancer comprises treatment with gonadotropin-releasing hormone agonists.

56. The use according to claim 55, wherein said treatment with gonadotropin-releasing hormone agonists is for prostate cancer.

57. The use according to any one of the claims 33 to 46, wherein the medicament is for stimulating bone formation in a subject, characterized by a condition arising from bone loss associated with cancer chemotherapy.

58. The use according to claim 57, wherein said cancer chemotherapy comprises administration of cyclophosphamide, methotrexate, fluorouracil, paclitaxel, doxorubicin, tamoxifen or combinations thereof.

59. The use according to claim 57, wherein said cancer chemotherapy is for the treatment of breast cancer.

60. The use according to any one of the claims 33 to 46, wherein the medicament is for stimulating bone formation in a subject, characterized by a condition arising from bone loss associated with treatment with antiviral agents.

61. The use according to claim 60, wherein said subject has HIV.
62. The use according to claim 61, wherein said subject with HIV has lipodystrophy.

63. The use according to any one of claims 33 to 46 wherein the medicament is for co-administration with or contains a bone resorption inhibitor.

64. The use according to claim 63, wherein said bone resorption inhibitor is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, midronic acid, icandronic acid, S-12911, raloxifene, simvastatin, atorvastatin, cerivastatin, vitamin D and calcitonin.

65. The use according to any one of the preceding claims provided that when L is other than \((\text{CH=CH})_k-(\text{CH}_2)_d\text{-CH} =\) where \(k\) is 0 or 1 and \(d\) is an integer from 0 to 4, at least one of \(R^1, R^2, R^3\) and \(R^4\) is other than hydrogen.

66. The use according to claim 65 wherein \(L\) is a group \((\text{CH=CH})_k-(\text{CH}_2)_d\text{-CH}=\) wherein \(k\) and \(d\) are both 0.

67. The use according to claim 66 wherein \(R^1, R^2, R^3\) and \(R^4\) are all hydrogen.

68. The use according to claim 66 wherein \(R^1, R^2, R^3\) and \(R^4\) are all straight or branched alkyl of 1 to 8 carbon atoms.

69. The use according to claim 68 wherein \(R^1, R^2, R^3\) and \(R^4\) are all ethyl or isopropyl groups, preferably ethyl groups.
70. A compound of formula (I):

\[
A \quad \underline{L} \quad C \quad \underline{(B)}_t \quad (I)
\]

in which A is

\[
\begin{array}{c}
\hat{x}^0 \\
\hat{x}^4
\end{array}
\]

where:
- \( x^0 \) is H, an alkyl group having from 1 to 4 carbon atoms and \( x^4 \) is an optionally substituted arylalkyl group,
- \( R^1, R^2, R^3 \) and \( R^4 \) are identical or different and are H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms, or \( R^1, R^2 \) and \( R^3 \) and \( R^4 \) may form an alkylidenedioxy ring comprising from 2 to 8 carbon atoms
- \( L \) is \(-\text{CH} = \text{CH}-\text{CH}_2-, -\text{(CH}_2\text{)}_n-, -\text{O(}	ext{CH}_2\text{)}_n-, -\text{S-, -SO}_2-, -\text{S(}	ext{CH}_2\text{)}_n-, -\text{SO}_2(\text{CH}_2\text{)}_n\), where \( n \) is an integer from 1 to 7,
- or together with \( B \), \( L \) is \((\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}= \) where \( k \) is 0 or 1 and \( d \) is an integer from 0 to 4,
- \( B \) is H, an alkyl group having from 1 to 4 carbon atoms,
- \( t \) is 0 or 1, with the proviso that \( t \) is 0 only when \( L \), together with \( B \), is \((\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}= \) where \( k \) and \( d \) are as described above.

71. A pharmaceutical composition comprising a compound as according to claim 70 and a pharmaceutically acceptable carrier.

72. A compound according to claim 70 for use in medicine.
73. A pharmaceutical composition comprising an amount of an aryl-substituted 1,1-diphosphonate compound of formula (I):

\[
\begin{array}{c}
\text{PO}_3R^1R^2 \\
\text{A} \quad \text{L} \quad \text{C} \quad \text{(B)}_t \quad \text{PO}_3R^3R^4
\end{array}
\]

in which A is

\[
\begin{array}{c}
\text{x}^0 \quad \text{x}^1 \\
\text{x}^2 \quad \text{x}^3 \\
\text{x}^4 \\
\text{x}^5 \\
\text{x}^6
\end{array}
\]

where:
- \(X^0\) is H, an alkyl group having from 1 to 4 carbon atoms,
- \(X^1, X^2\) and \(X^3\) are identical or different and are H, a straight or branched alkyl or alkoxy group having from 1 to 8 carbon atoms,
- \(X^4\) is H, a straight or branched alkyl group having from 1 to 8 carbon atoms, an optionally substituted benzyl group,
- \(X^5\) is H, a straight or branched alkyl group having from 1 to 8 carbon atoms,
- \(X^6\) is H or an alkyl group having from 1 to 4 carbon atoms,
- \(q\) is 0 or 1,
- \(R^1, R^2, R^3\) and \(R^4\) are identical or different and are H, a straight, branched or cyclic alkyl group comprising from 1 to 8 carbon atoms, or \(R^1, R^2\) and \(R^3\) and \(R^4\) may form an alkylidenedioxy ring comprising from 2 to 8 carbon atoms,
- \(L\) is \(-\text{CH}=\text{CH}-\text{CH}_2,-(\text{CH}_2)_n,-\text{O}(\text{CH}_2)_n,-\text{S},-\text{SO}_2,-\text{S}(\text{CH}_2)_n,-\text{SO}_2(\text{CH}_2)_n\)
where \(n\) is an integer from 1 to 7,
- or together with B, \(L\) is \((\text{CH}=\text{CH})_k-(\text{CH}_2)_d-\text{CH}=\) where \(k\) is 0 or 1 and \(d\) is an integer from 0 to 4,
- \(B\) is H, an alkyl group having from 1 to 4 carbon atoms,
t is 0 or 1, with the proviso that t is 0 only when L, together with B, is \((\text{CH} = \text{CH})_k-(\text{CH}_2)_d-\text{CH} =\) where k and d are as described above, and with the further proviso that when L is \(-\text{(CH}_2)_n\) or \(-\text{S}-\), at least one of \(R^1, R^2, R^3\) and \(R^4\) is other than hydrogen, effective to stimulate bone formation in a subject in need of such treatment, and a pharmaceutically acceptable carrier.

74. The composition of claim 73, wherein said pharmaceutical composition is an oral pharmaceutical composition.

75. A method of stimulating bone formation in a subject in need of such treatment comprising administering to said subject an effective amount of an aryl-substituted 1,1-diphosphonate compound of the formula (I) as defined in any one of claims 1 to 14 and 65 to 69.

76. A method according to claim 75 wherein the subject is as defined in any one of claims 15 to 30.

77. A method of treating or preventing a bone disease or pathology, comprising administering to a subject in need of such treatment in an amount effective to stimulate bone formation an aryl-substituted 1,1-diphosphonate compound of the formula (I) as defined in any of claims 33 to 46 and 65 to 69.

78. A method according to claim 77 wherein the subject is as defined in any one of claims 47 to 62.

79. A method according to any one of claims 75 to 78 further comprising administering to said subject an effective amount of bone resorption inhibitor.

80. A method according to claim 79 wherein the bone resorption inhibitor is as defined in claim 32 or claim 64.