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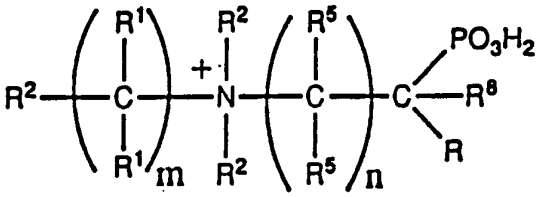

(I)

(57) Abstract

The present invention relates to quaternary nitrogen-containing phosphonate compounds, and the pharmaceutically-acceptable salts and esters thereof having general formula (I). The present invention further relates to pharmaceutical compositions containing a safe and effective amount of a compound of the present invention, and pharmaceutically-acceptable excipients. Finally, the present invention relates to methods for treating or preventing pathological conditions characterized by abnormal calcium and phosphate metabolism such as osteoporosis and arthritis, especially rheumatoid arthritis, and osteoarthritis, in humans or other mammals. This method comprises administering to a human or other mammal in need of such treatment a safe and effective amount of a compound or composition of the present invention.

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QUATERNARY NITROGEN-CONTAINING PHOSPHONATE COMPOUNDS, FOR TREATING ABNORMAL CALCIUM AND PHOSPHATE METABOLISM.

BACKGROUND OF INVENTION

This invention relates to novel quaternary, nitrogen-containing phosphonate compounds, including bisphosphonates, phosphonoalkylphosphinates, phosphonocarboxylates, and phosphonosulfonates. This invention also relates to pharmaceutical compositions containing these novel compounds as well as to a method of treating or preventing certain metabolic bone disorders characterized by abnormal calcium and phosphate metabolism by utilizing a compound or pharmaceutical composition of the present invention. Specifically, this invention relates to a method of treating or preventing osteoporosis and arthritis, especially rheumatoid arthritis and osteoarthritis by utilizing a compound or pharmaceutical composition of the present invention.

A number of pathological conditions which can afflict warm-blooded animals involves abnormal calcium and phosphate metabolism. Such conditions may be divided into two broad categories.

1. Conditions which are characterized by anomalous mobilization of calcium and phosphate leading to general or specific bone loss, such as osteoporosis and Paget's disease, or excessively high calcium and phosphate levels in the fluids of the body, such as hypercalcemia of tumor origin. Such conditions are sometimes referred to herein as pathological hard tissue demineralizations.

2. Conditions which cause or result from deposition of calcium and phosphate anomalously in the body, such as arthritis, particularly rheumatoid arthritis and osteoarthritis. These conditions are sometimes referred to herein as pathological calcifications.

The first category includes the most common metabolic bone disorder, osteoporosis; osteoporosis is a condition in which bone hard tissue is lost disproportionately to the development of new hard tissue. Osteoporosis can be generally defined as the reduction in the quantity of bone, or the atrophy of skeletal tissue. Marrow and bone spaces become larger, fibrous binding decreases, and compact bone becomes fragile. Osteoporosis can be subclassified as menopausal, senile, drug-induced (e.g. adrenocorticoid, as can occur in steroid therapy); disease-induced (arthritic and tumor), etc.; however, the manifestations are essentially the same.

In general, there are two types of osteoporosis: primary and secondary. "Secondary osteoporosis" is the result of a separate disease process or agent. However, approximately 90% of all osteoporosis cases are "primary osteoporosis". Such primary osteoporosis includes postmenopausal osteoporosis, age-associated osteoporosis, disuse osteoporosis (affecting a majority of individuals over the age of 70 to 80), and idiopathic osteoporosis affecting middle-aged and younger men and women.

For some osteoporotic individuals, the loss of bone tissue is sufficiently great so as to cause mechanical failure of the bone structure. Bone fractures often occur, for example, in the hip and spine of women suffering from postmenopausal osteoporosis. Kyphosis (abnormally increased curvature of the thoracic spine) may also result.

The mechanism of bone loss in osteoporotics is believed to involve an imbalance in the process of "bone remodeling". Bone remodeling occurs throughout life, renewing the skeleton and maintaining the strength of bone. This remodeling involves the erosion and filling of discrete sites on the surface of bones, by an organized group of cells called "basic multicellular units" or

"BMUs". BMUs primarily consist of "osteoclasts", "osteoblasts", and their cellular precursors. In the remodeling cycle, bone is resorbed at the site of an "activated" BMU by an osteoclast, forming a resorption cavity. This cavity is then filled with bone by an osteoblast.

Normally, in adults, the remodeling cycle results in a small deficit in bone, due to incomplete filling of the resorption cavity. Thus, even in healthy adults, age-related bone loss occurs. However, in osteoporotics, there may be an increase in the number of BMUs that are activated. This increased activation accelerates bone remodeling, resulting in abnormally high bone loss.

Although its etiology is not fully understood, there are many risk factors thought to be associated with osteoporosis. These include low body weight, low calcium intake, physical inactivity, and estrogen deficiency.

Current osteoporosis treatment consists primarily of calcium and estrogen administration.

The second category, involving conditions manifested by anomalous calcium and phosphate deposition, includes myositis ossificans progressiva, calcinosis universalis, and such afflictions as arthritis (including, for example, rheumatoid arthritis and osteoarthritis), neuritis, bursitis, tendonitis, and conditions which predispose involved tissue to deposition of calcium.

In addition to osteoporosis, bone loss can result from rheumatoid arthritis and osteoarthritis. Rheumatoid arthritis is a chronic, systemic and articular inflammatory disorder characterized by weakening of the joint capsules and ligaments, followed by destruction of cartilage, ligaments, tendon and bone, and a decrease in viscosity and other alterations in the synovial fluid. Rheumatoid arthritis symptoms include systemic weakness, fatigue, localized pain, stiffness and weakness and swelling and deformation of the joints of the body. Rheumatoid arthritis is most common in women in the fourth to sixth decade of life.

The pathogenesis of rheumatoid arthritis, leading to the destruction of the joints, is characterized by two phases: 1) an exudative phase involving the microcirculation and the synovial cells that allow an influx of plasma proteins and cellular elements into the joint and 2) a chronic inflammatory phase occurring in the sub-synovium and sub-chondral bone, characterized by pannus (granulation tissue) formation in the joint space, bone erosion, and cartilage destruction. The pannus may form adhesions and scar tissue which causes the joint deformities characteristic of rheumatoid arthritis.

The etiology of rheumatoid arthritis remains obscure. Infectious agents such as bacteria and viruses have been implicated. A current hypothesis is that the Epstein-Barr (EBV) virus is a causative agent for rheumatoid arthritis.

Current rheumatoid arthritis treatment consists predominantly of symptomatic relief by administration of non-steroidal anti-inflammatory drugs. Non-steroidal anti-inflammatory drug treatment is mainly effective in the early stages of rheumatoid arthritis; it is unlikely it will produce suppression of joint inflammation if the disease is present for more than one year. Gold, methotrexate, immunosuppressants and corticosteroids have been tried with limited success.

On the other hand, osteoarthritis, is an inherently non-inflammatory disorder of the movable joints characterized by deterioration and abrasion of articular cartilage, as well as by formation of new bone at the joint surface. As osteoarthritis progresses, the surface of the articular cartilage is disrupted and wear particles gain access to the synovial fluid which in turn stimulates phagocytosis by macrophage cells. Thus, an inflammatory response is eventually induced in osteoarthritis. Common clinical symptoms of osteoarthritis include cartilaginous and bony enlargements of the finger joints and stiffness on awakening and painful movement.

Common symptomatic treatments for osteoarthritis include analgesics, anti-inflammatories, steroids, and physical therapy.

A variety of phosphonic acid derivatives have been proposed for use in the treatment and prophylaxis of diseases involving abnormal calcium and phosphate metabolism. For example, numerous references, all incorporated by reference herein, disclose compositions containing polyphosphonates, in particular diphosphonates such as ethane-1-hydroxy-1,1-diphosphonic acid ("EHDP"), and their use in inhibiting anomalous deposition and mobilization of calcium and phosphate in animal tissue: U.S. Patent 3,683,080, issued August 8, 1972 and U.S. Patent 4,230,700, issued October 28, 1980, both to Francis, and U.S. Patent 4,868,164 to Ebetino, issued September 19, 1989. Numerous other references describe heterocyclic substituted diphosphonic acids useful for the treatment of osteoporosis and/or arthritis, and are hereby incorporated by reference herein: U.S. Patent 5,071,840, to Ebetino, et al., issued December 10, 1991; U.S. Patent 4,868,164, to Ebetino, et al., issued September 19, 1989; U.S. Patent 5,104,863, to Benedict, et al., issued April 14, 1992; U.S. Patent 4,267,108, to Blum et al., issued May 12, 1981; U.S. Patent 4,746,654 to Breliere et al., issued May 24, 1988; U.S. Patent 4,876,247 to Barbier, et al., issued October 24, 1989, and European Patent Application Publication No. 100,718, of Breliere, published February 15, 1984; European Patent Application Publication No. 170,228, of Boehringer Mannhein GmbH, published February 5, 1986; European Patent Application Publication No. 186,405, of Benedict and Perkins, published July 2, 1986; European Patent Application No. 298,553, of Ebetino, published January 11, 1989; U.S. 4,754,993, to Bosies, et al., issued November 15, 1988; U.S. 4,939,130, to Jaeggi, et al., issued July 3, 1990; U.S. 4,971,958 to Bosies, et al., issued November 20, 1990; WO 90/12017, Dunn, et al. published October 18, 1990; WO 91/10646, Youssefyeh, R., et al. published July 25, 1991; AU-A-26738/88, Jaeggi, publication date June 15, 1989; AU-A-45467/89 of Ciba-Geigy, publication date May 31, 1990.

Finally, U.S. 4,208,401 to Bauman, issued June 17, 1980, discloses non-heterocyclic ring substituted quaternary ammonium bisphosphonates useful as anti-calculus agents.

DE 40 11 777 to Jaeggi, K., disclosed October 18, 1990; (DE '777) discloses a heterocyclic ring substituted diphosphonate wherein said heterocyclic ring can be lower alkyl substituted. Said heterocyclic ring is bridged to the phosphonic acid group via a quaternary non-ring nitrogen atom. DE '777 also discloses that the compounds produce pronounced inhibition of bone resorption and thus are useful in treating osteoporosis, inflammatory and degenerative joint diseases, peridontitis, and hyperparathyroidism. The disclosures of these references are incorporated by reference herein.

The compounds of the present invention have osteoprotective activity at the site of joint destruction in arthritis conditions and have that activity as an additional benefit in the treatment of arthritis over the above merely relieving the symptoms of inflammation. The term "osteoprotecive activity" as used herein means disease-modifying activity on bone and surrounding soft tissue at the site of joint destruction.

It has been surprisingly discovered that the compounds of the present invention, wherein the nitrogen is quaternized, have more potent bone antiresorptive activity and therapeutic utility in treating osteoporosis and rheumatoid arthritis and osteoarthritis than nitrogen-containing compounds where the nitrogen atom is <u>not</u> quaternized. Moreover, the compounds of the present invention exhibit unusual solubility properties. Thus, the compounds of the present invention may be more readily orally absorbed compounds. The more readily absorbed a compound, the more effective it may be at lower doses. Lower doses are generally preferable because undesirable side effects are decreased.

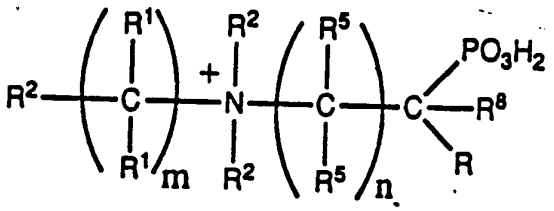
It is therefore an object of the present invention to provide new, more potent compounds which are useful in osteoporosis therapy and anti-arthritic agents especially useful in the treatment of osteoarthritis and rheumatoid arthritis.

It is a further object of the present invention to provide pharmaceutical compositions useful for the treatment and prophylaxis of osteoporosis and arthritis, especially rheumatoid arthritis and osteoarthritis. In addition, it is an object of the present invention to provide methods for treating or preventing osteoporosis and arthritis, especially rheumatoid arthritis and osteoarthritis.

These and other objects of the present invention will become apparent from the detailed disclosure of the present invention provided hereinafter.

SUMMARY OF THE INVENTION

The present invention relates to quaternary nitrogen-containing phosphonate compounds, and the pharmaceutically-acceptable salts and esters thereof having the following general formula:



wherein m is an integer from 0-10; and n is an integer from 1-10; m + n is from 1-10;

(a) R^1 is selected from the group consisting of nil; $-SR^6$; $-R^9SR^6$; hydrogen; substituted or unsubstituted C_1-C_8 alkyl; $-OR^3$; $-CO_2R^3$; $-O_2CR^3$; $-NR^3_2$; $-N(R^3)C(O)R^3$; $-C(O)N(R^3)_2$; halogen; $-C(O)R^3$; nitro; hydroxy; substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic rings; substituted or unsubstituted saturated monocyclic or polycyclic carbocyclic rings;

(b) R^5 is selected from the group consisting of $-SR^6$; $-R^9SR^6$; hydrogen; substituted or unsubstituted C_1-C_8 alkyl;

$-OR^3$; $-CO_2R^3$; $-O_2CR^3$; $-NR^3{}_2$; $-N(R^3)C(O)R^3$; $-C(O)N(R^3)_2$; halogen; $-C(O)R^3$; nitro; hydroxy; substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic rings; substituted or unsubstituted saturated monocyclic or polycyclic carbocyclic rings; substituted or unsubstituted unsaturated monocyclic or polycyclic heterocyclic rings; substituted or unsubstituted unsaturated monocyclic or polycyclic carbocyclic rings and combinations thereof;

(c) each R^2 is selected from the group consisting of substituted or unsubstituted C_1-C_{35} alkyl; unsubstituted or substituted phenyl; benzyl; or R^9SR^6;

(d) R^3 is selected from the group consisting of H; unsubstituted or substituted C_1-C_8 alkyl; R^9SR^6;

(e) R^6 is selected from the group consisting of -H; $-C(O)R^7$; $-C(S)R^7$; $-C(O)N(R^7)_2$; $-C(O)OR^7$; $-C(S)N(R^7)_2$; $-C(S)OR^7$; where R^7 is hydrogen or unsubstituted or substituted C_1-C_8 alkyl;

(f) R is selected from the group consisting of -COOH; $-SO_3H$; $-PO_3H_2$; and $-P(O)(OH)R^4$, where R^4 is an alkyl group having 1-3 carbons.

(g) R^9 is substituted or unsubstituted C_1-C_8 alkyl;

(h) R^8 is selected from the group consisting of hydrogen, halogen; SR^6; R^9SR^6; amino; hydroxy; substituted and unsubstituted C_1-C_8 alkyl;

In this general structure, the quaternary nitrogen atom must be linked to the phosphonic acid containing carbon atom via a linking chain. It cannot be bonded directly to the phosphonic acid containing carbon atom.

The present invention further relates to pharmaceutical compositions containing a safe and effective amount of a compound of the present invention, and pharmaceutically-acceptable excipients. Finally, the present invention relates to methods for treating or preventing pathological conditions characterized by abnormal calcium and phosphate metabolism such as osteoporosis and arthritis, especially rheumatoid arthritis, and

osteoarthritis, in humans or other mammals. This method comprises administering to a human or other mammal in need of such treatment a safe and effective amount of a compound or composition of the present invention.

Definitions and Usage of Terms

The following is a list of definitions for terms used herein.

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing one or more heteroatoms may contain different heteroatoms.

"Alkyl" is an unsubstituted or substituted, straight-chain or branched, saturated or unsaturated hydrocarbon chain, said hydrocarbon chain may be saturated having 1 to 8 carbon atoms, and preferably, unless otherwise stated, from 1 to 4 carbon atoms; said hydrocarbon chain may be unsaturated, having 2 to 8 carbon atoms, and preferably, unless otherwise stated, 2 to 4 carbon atoms. Accordingly, the term "alkyl", as used herein, encompasses alkenyl hydrocarbon unsaturated chains having at least one olefinic double bond and alkynyl hydrocarbon unsaturated chains having at least one triple bond. Preferred alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, and butyl.

"Carbocyclic ring" or "Carbocycle" as used herein is an unsubstituted or substituted, saturated, unsaturated or aromatic, hydrocarbon ring; Carbocyclic rings may be monocyclic or polycyclic: Monocyclic ring generally contain from 3 to 8 atoms, preferably 5 to 7 atoms. Polycyclic rings containing two rings contain 6 to 16, preferably 10 to 12, atoms and those with three rings generally contain 13 to 17, preferably 14 to 15, atoms.

"Heteroalkyl" is an unsubstituted or substituted, saturated chain having from 3 to 8-members and comprising carbon atoms and one or two heteroatoms.

"Heterocyclic ring" or "Heterocycle" as used herein is an unsubstituted or substituted, saturated, unsaturated or aromatic

ring comprised of carbon atoms and one or more heteroatoms in the ring. Heterocyclic rings may be monocyclic or polycyclic rings.

Monocyclic rings generally contain from 3 to 8 atoms, preferably 5 to 7 atoms. Polycyclic ring systems consisting of two rings generally contain 6 to 16, preferably from 10 to 12 atoms. Polycyclic ring systems consisting of three rings generally contain 13 to 17 atoms, preferably 14 to 15 atoms. A heterocyclic ring moiety may consist of heterocycles or heterocycles and carbocycles. Each heterocyclic ring moiety must have at least one nitrogen atom. Unless otherwise stated any additional heteroatoms may be independently chosen from nitrogen, sulfur, and oxygen.

"Aryl" is an aromatic carbocyclic ring. Preferred aryl groups include, but are not limited to, phenyl, tolyl, xylyl, cumenyl, and naphthyl.

"Heteroaryl" is an aromatic heterocyclic ring. Preferred heteroaryl groups include, but are not limited to, thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, oxazolyl, thiazolyl, quinolinyl, pyrimidinyl, and tetrazolyl.

"Alkoxy" is an oxygen atom having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl or alkenyl (e.g., -O-alkyl or -O-alkenyl). Preferred alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, and alkyloxy.

"Hydroxyalkyl" is a substituted hydrocarbon chain which has a hydroxy substituent (e.g., -OH), and may have other substituents. Preferred hydroxyalkyl groups include, but are not limited to, hydroxyethyl, hydroxypropyl.

"Carboxyalkyl" is a substituted hydrocarbon chain which has a carboxy substituent (e.g. -COOH) and may have other substituents. Preferred carboxyalkyl groups include carboxymethyl, carboxyethyl, and their acids and esters.

"Aminoalkyl" is a hydrocarbon chain (e.g. alkyl) substituted with an amine moiety (e.g., NH-alkyl-) such as aminomethyl.

"Alkylamino" is an amino moiety having one or two alkyl substituents (e.g., -N-alkyl) such as dimethylamino.

"Alkenylamino" is an amino moiety having one or two alkenyl substituents (e.g., -N-alkenyl).

"Alkynalamino" is an amino moiety having one or two alkynyl substituents (e.g., -N-alkynyl).

"Alkylimino" is an imino moiety having one or two alkyl substituents (e.g., -N-alkyl-).

"Arylalkyl" is an alkyl moiety substituted with an aryl group. Preferred arylalkyl groups include benzyl and phenylethyl.

"Arylamino" is an amine moiety substituted with an aryl group (e.g., -NH-aryl).

"Aryloxy" is an oxygen atom having an aryl substituent (e.g., -O-aryl).

"Acyl" or "carbonyl" is a carbon to oxygen double bond, e.g. R-C(=O). Preferred acyl groups include, but are not limited to, acetyl, propionyl, butanoyl, and benzoyl.

"Acyloxy" is an oxygen atom having an acyl substituent (e.g., -O-acyl); for example, -O-C(=O)-alkyl.

"Acylamino" is an amino moiety having an acyl substituent (e.g., -N-acyl); for example, -NH-(C=O)-alkyl.

"Halo", "halogen", or "halide" is a chloro, bromo, fluoro, or iodo atom radical. Chloro, bromo, and fluoro are preferred halides.

As referred to herein, a "lower" hydrocarbon moiety (e.g., "lower" alkyl) is a hydrocarbon chain comprised of from, unless otherwise stated, 1 to 6, preferably from 1 to 4, carbon atoms.

Also, as used herein, the term "thio-substituent" (SR^6 or R^9SR^6) includes thiols [-SH] where R^6=H; thioesters [$-SC(O)R^7$] where R^6=$C(O)R^7$; dithioesters [$-SC(S)R^7$] where R^6=$C(S)R^7$; thiocarbamates [$-SC(O)N(R^7)_2$] where R^6=$C(O)N(R^7)_2$; dithiocarbamates [$-SC(S)N(R^7)_2$] where R^6=$C(S)N(R^7)_2$; thiocarbonates [$=SC(O)OR^7$] where R^6=$C(O)OR^7$; and dithiocarbonates [$-SC(S)OR^7$] where R^6=$C(S)OR^7$. R^7 is generally a hydrogen or C_1-C_8 alkyl. Any of the SR^6 substituents may themselves be substituted with an R^9 moiety, i.e. R^9SR^6, where R^9 is a substituted or unsubstituted C_1-C_8 alkyl. Accordingly,

additional thio-substituents denoted by R^9SR^6 are alkylthiols, alkylthioesters, alkyldithioesters, alkylthiocarbamates, alkyldithiocarbmates, alkylthiocarbonates, and alkyldithiocarbonates.

The terms "bisphosphonate" or "bisphosphonic acid" as used herein relate to those phosphonate or phosphonic acid compounds that have two phosphonate groups attached to the same carbon atom and are used interchangeably with the terms "diphosphonate" and "diphosphonic acids." Using the structures described herein, the moiety R is PO_3H_2.

As used herein, the term "phosphonic acid carbon" refers to the carbon atom to which a phosphonic acid group (PO_3H_2) is attached. When another phosphonic acid group is attached to said carbon atom, the resulting compound is bisphosphonate. When a sulfonate group is attached to said carbon atom, the resulting compound is a phosphonosulfonate. When a carboxylate group is attached to said carbon atom, the resulting compound is a phosphonocarboxylate. When a phosphinic acid group is attached to said carbon atom, the resulting compound is a phosphonoalkylphosphinate.

A "pharmaceutically-acceptable" salt is a catonic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987, hereby incorporated by reference herein. Preferred catonic salts include the alkali-metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium). Preferred anionic salts include the halide (such as chloride), acetate and phosphate salts.

A "biohydrolyzable ester" is an ester of the quaternary nitrogen-containing heterocyclic phosphonate compounds that does not interfere with the therapeutic activity of the compounds, or that is readily metabolized by a human or other mammal. Many such esters are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published

September 11, 1987, and hereby incorporated by reference herein. Such esters include lower alkyl esters, lower acyloxyalkyl esters (such as acetoxymethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl, and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters).

As defined above and as used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include, but are not limited to, those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), hereby incorporated by reference herein. Preferred substituents include, but are not limited to, alkyl, alkenyl, alkoxy, hydroxy, oxo, amino, aminoalkyl (e.g. aminomethyl, etc.), cyano, halo, carboxy, alkoxyacetyl (e.g. carboethoxy, etc.), thio, thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, etc.), imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

DETAILED DESCRIPTION OF THE INVENTION

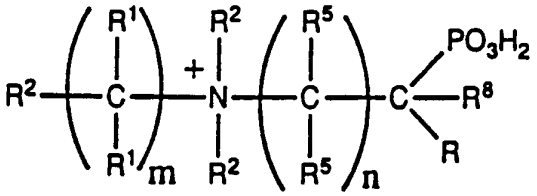
Novel Quaternary Nitrogen-Containing Phosphonate Compounds

The compounds of the present invention are quaternary nitrogen-containing phosphonate compounds, and the pharmaceutically-acceptable salts and esters thereof, having a quaternary nitrogen atom. The quaternary nitrogen atom is bonded to the phosphonic acid containing carbon via a linking chain to the phosphonic acid containing carbon.

The carbon atom which has the phosphonic acid group attached to it may be unsubstituted (i.e., a hydrogen atom) or substituted. The phosphonic acid carbon may contain two phosphonate groups, rendering a bisphosphonate compound; a phosphonate group

and an carboxylate group, rendering a phosphonocarboxylate compound; a phosphonate group and a sulfonate group, rendering a phosphonosulfonate compound, a phosphinate group and a phosphonate group, rendering a phosphonoalkylphosphinate compound.

Thus, the quaternary nitrogen-containing phosphonate compounds of the present invention, and the pharmaceutically-acceptable salts and esters thereof, have the general structure:



In this general structure, R^1 is selected from a variety of non-ring moieties such as nil, $-SR^6$, $-R^9SR^6$, hydrogen, alkyl having 1-8 carbons, $-OR^3$, $-CO_2R^3$, $-O_2CR^3$, $-NR^3_2$, $-N(R^3)C(O)R^3$, $-C(O)N(R^3)_2$; halogen, $-C(O)R^3$, nitro, hydroxy, substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic rings, substituted or unsubstituted saturated monocyclic or polycyclic carbocyclic rings.

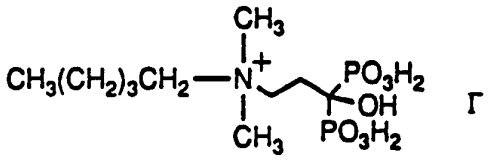
Also, in this general structure, the quaternary nitrogen atom is linked to the phosphonic acid carbon by a linking chain. Further, in this general structure, n, which is an integer from 1-10, represents said linking chain.

Said linking chain members are selected from a variety of R^5 moieties. R^5 can be $-SR^6$, $-R^9SR^6$, hydrogen, C_1-C_8 alkyl, $-OR^3$, $-CO_2R^3$; $-O_2CR^3$; $-NR^3_2$; $-N(R^3)C(O)R^3$, $-C(O)N(R^3_2)$; halogen, $-C(O)R^3$; nitro; hydrogen; unsubstituted or substituted saturated monocyclic or polycyclic heterocyclic ring, unsubstituted or substituted saturated monocyclic or polycyclic carbocyclic rings, unsubstituted or substituted unsaturated monocyclic or polycyclic

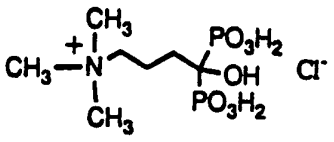
heterocyclic rings, unsubstituted or substituted unsaturated monocyclic or polycyclic carbocyclic rings and combinations thereof.

Finally, in the quaternary nitrogen containing phosphonate compounds of the present invention, R can be -COOH, $-SO_3H$, $-PO_3H_2$ and $-P(O)(OH)R^4$ where R^4 is C_1-C_8 alkyl. Preferred R is PO_3H_2 and $P(O)(OH)R^4$. R^8 is a substituent on the phosphonic acid containing carbon selected from hydrogen, halogen, SR^6, R^9,SR^6, amino, hydroxy, substituted and unsubstituted C_1-C_8 alkyl. Preferred R^8 is hydroxy, halogen and amino. R^2 is substituted or unsubstituted C_1-C_{35} alkyl, substituted or unsubstituted phenyl, benzyl; or R^9SR^6. Preferred R^2 is substituted or unsubstituted C_1-C_8 alkyl and R^9SR^6.

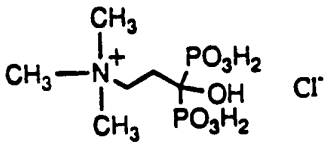
Preferred quaternary nitrogen-containing phosphonates having an R^1 moiety selected from the R^1 moieties described herein before include,



N-(3-hydroxy-3,3-diphosphonopropyl)-N,N-dimethyl-N-pentylammonium chloride



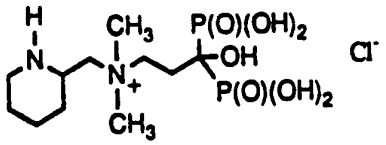
N-(4-hydroxy-4,4-diphosphonobutyl)-N,N,N-trialkylammonium salt



N-(3-hydroxy-3,3-diphosphonopropyl)-N,N,N-trialkylammonium salts

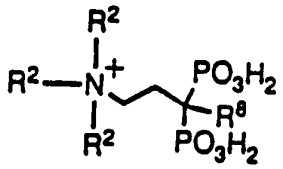
Also, in this general structure, the R^1 moiety can also be saturated monocyclic or polycyclic heterocycle.

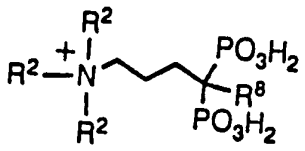
Preferred quaternary nitrogen-containing phosphonates having a saturated monocyclic or polycyclic heterocycle as an R^1 moiety wherein the quaternary nitrogen atom is linked via a linking chain to the phosphonic acid carbon include:



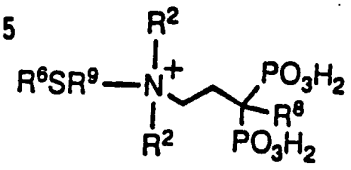
N-(3-hydroxy-3,3-diphosphonopropyl)-N,N-dimethyl-N-(2-piperidine-methyl) ammonium chloride

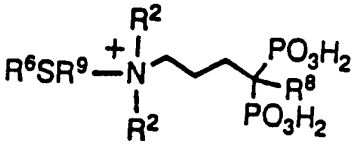
Additionally, preferred compounds of the present invention include those compounds having the following structures:

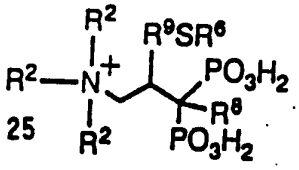


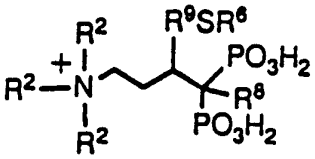


Preferred compounds of the present invention also include the thio-substituted quaternary nitrogen containing phosphonates.









Specific examples of compounds of the present invention include:

N-(4-hydroxy-4,4-diphosphonobutyl)-N,N,N-trimethyl ammonium iodide;

N-(3-hydroxy-3,3-diphosphonopropyl)-N,N-dimethyl-N-pentyl ammonium iodide;

N-(3-hydroxy-3,3-diphosphonopropyl)-N,N,N-trimethyl ammonium iodide;

N-cycloheptyl-N,N-dimethyl-N-(diphosphonomethyl) ammonium iodide;

N-(2-acetylthioethyl)-N-(4-hydroxy-4,4-diphosphonobutyl)-N,N-dimethyl ammonium bromide;

N-(2-acetylthioethyl)-N-(3-hydroxy-3,3-diphosphonopropyl)-N-methyl-N-pentyl ammonium bromide;

N-(4-hydroxy-4,4-diphosphonobutyl)-N-(3-mercaptopropyl)-N,N-dimethyl ammonium chloride;

N-(4-hydroxy-4,4-diphosphonobutyl)-N-(mercaptomethyl)-N,N-dimethyl ammonium chloride;

N-(4-hydroxy-4,4-diphosphonobutyl)-N-(4-methoxybutyl)-N,N-dimethyl ammonium chloride;

N-(4-hydroxy-2-mercapto-4,4-diphosphonobutyl)-N,N,N-trimethyl ammonium chloride;

N-(4-hydroxy-2-acetylthio-4,4-diphosphonobutyl)-N,N,N-trimethyl ammonium chloride;

N-(3-hydroxy-2-mercapto-3,3-diphosphonopropyl)-N,N-dimethyl-N-pentyl ammonium chloride;

N-(3-hydroxy-2-acetylthio-3,3-diphosphonopropyl)-N,N-dimethyl-N-pentyl ammonium chloride;

N-(3-hydroxy-3,3-diphosphonopropyl)-N-methyl-N-pentyl-N-(2-(3-pyridyl)ethyl) ammonium chloride;

N-cycloheptyl-N-(2-mercaptoethyl)-N-methyl-N-(diphosphonomethyl) ammonium chloride;

N-cycloheptyl-N-(mercaptomethyl)-N-methyl-N-(diphosphonomethyl) ammonium chloride;

N,N-dimethyl-N-(4,4-diphosphonobutyl)-N-(2-(3-piperidinyl)ethyl) ammonium chloride;

In order to determine and assess pharmacological activity, testing of the phosphonate compounds in animals is carried out using various assays known to those skilled in the art. Thus, the In vivo bone antiresorptive activity may be conveniently demonstrated using an assay designed to test the ability of these compounds to inhibit the resorption of bone, which bone resorption is characteristic of abnormal calcium and phosphate metabolism. One such test known to the art is the Schenk model. Another useful art-known test is the adjuvant arthritis test. Also useful is the in vitro hydroxyapatite crystal growth

inhibition test. These and other appropriate tests for pharmacological activity are disclosed and/or referred to in Shinoda et al., Calcified Tissue International, 35, pp 87-99 (1983); Schenk et al. , Calcified Tissue Research, 11, pp 196-214 (1973); Russell et al., Calcified Tissue Research, 6, pp 183-196 (1970); Muhlbauer and Fleisch, Mineral Electrolyte Metab. , 5 , pp 296-303 (1981); Nancollas et al., Oral Biol., 15, 731 (1970); U.S. Patent 3,683,080, to Francis, issued August 8, 1972; U. S. Patent 4,134,969, to Schmidt-Dunker, Issued January 16, 1979; and EPO Patent Application Publication No. 189,662, published August 6, 1986; the disclosures of all these articles and patent specifications being incorporated herein by reference in their entirety. Certain of these tests for pharmacological activity are also described in more detail in the Examples provided hereinafter.

In addition to being useful for treating or preventing pathological conditions characterized by abnormal calcium or phosphate metabolism, the compounds of the present invention may have other uses. For example, the compounds of the present invention are believed to be useful as bone scanning agents after labeling with 99m-technetium. In addition, the compounds of the present invention are useful as sequestering agents for polyvalent metal ions, particularly di-(e.g. calcium and magnesium) and trivalent (e.g. indium) metal ions. Thus, the compounds of the present invention are useful as builders in detergents and cleansers, or for treating water. They are also useful as stabilizers for compounds. In addition, they may be useful in preventing the formation of tartar (i.e., calculus) and/or plaque on teeth. Finally, the compounds of the present invention may be useful as herbicides which are non-toxic to animals.

The quaternary nitrogen-containing phosphonates to be included in the pharmaceutical compositions of the present invention can be made according to the following non-limiting Examples 1 to 5.

Compositions Containing Novel Quaternary Nitrogen Containing Phosphonate Compounds

The novel quaternary nitrogen-containing phosphonate compounds of the present invention may be administered to humans or other mammals by a variety of routes, including, but not limited to, oral dosage forms and injections (intravenous, intramuscular, intraperitoneal and subcutaneous). Numerous other dosage forms containing the novel quaternary nitrogen-containing phosphonate compounds of the present invention can be readily formulated by one skilled in the art, utilizing the suitable pharmaceutical excipients as defined below. For considerations of patient compliance, oral dosage forms are generally most preferred.

The term "pharmaceutical composition" as used herein means a combination comprised of a safe and effective amount of the quaternary nitrogen-containing phosphonate compound active ingredient, or mixtures thereof, and pharmaceutically-acceptable excipients.

The phrase "safe and effective amount", as used herein, means an amount of a compound or composition large enough to significantly positively modify the symptoms and/or condition to be treated, but small enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of active ingredient for use in the pharmaceutical compositions to be used in the method of the invention herein will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient being employed, the particular pharmaceutically-acceptable excipients utilized, and like factors within the knowledge and expertise of the attending physician.

The term "pharmaceutically-acceptable excipients" as used herein includes any physiologically inert, pharmacologically inactive material known to one skilled in the art, which is compatible with the physical and chemical characteristics of the

particular quaternary nitrogen-containing phosphonate compound active ingredient selected for use. Pharmaceutically-acceptable excipients include, but are not limited to, polymers, resins, plasticizers, fillers, binders, lubricants, glidants, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes or pigments, and viscosity agents.

The term "oral dosage form" as used herein means any pharmaceutical composition intended to be systemically administered to an individual by delivering said composition to the gastrointestinal tract of an individual, via the mouth of said individual. For purposes of the present invention, the delivered form can be in the form of a tablet, coated or non-coated; solution; suspension; or a capsule, coated or non-coated.

The term "injection" as used herein means any pharmaceutical composition intended to be systemically administered to a human or other mammal, via delivery of a solution or emulsion containing the active ingredient, by puncturing the skin of said individual, in order to deliver said solution or emulsion to the circulatory system of the individual either by intravenous, intramuscular, intraperitoneal or subcutaneous injection.

The rate of systemic delivery can be satisfactorily controlled by one skilled in the art, by manipulating any one or more of the following:

(a) the active ingredient proper;

(b) the pharmaceutically-acceptable excipients; so long as the variants do not interfere in the activity of the particular active ingredient selected;

(c) the type of the excipient, and the concomitant desirable thickness and permeability (swelling properties) of said excipients;

(d) the time-dependent conditions of the excipient itself and/or within the excipients;

(e) the particle size of the granulated active ingredient; and

(f) the pH-dependent conditions of the excipients.

In particular, the solubility, acidity, and susceptibility to hydrolysis of the different quaternary non-ring nitrogen-containing phosphonate active ingredients, such as acid addition salts, salts formed with the carboxylic group, e.g., alkali metal salts, alkaline earth metal salts, etc., and esters, e.g., alkyl, aryl, aralkyl, may be used as guidelines for the proper choice. In addition, suitable pH-conditions might be established within the oral dosage forms by adding a suitable buffer to the active ingredient in accordance with the desired release pattern.

As stated hereinabove, pharmaceutically-acceptable excipients include, but are not limited to, resins, fillers, binders, lubricants, solvents, glidants, disintegrants cosolvents, surfactants, preservatives, sweetener agents, flavoring agents, buffer systems, pharmaceutical-grade dyes or pigments, and viscosity agents.

The preferred solvent is water.

Flavoring agents among those useful herein include those described in Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company, 1990, pp. 1288-1300, incorporated by reference herein. The pharmaceutical compositions suitable for use herein generally contain from 0-2% flavoring agents.

Dyes or pigments among those useful herein include those described in Handbook of Pharmaceutical Excipients, pp. 81-90, 1986 by the American Pharmaceutical Association & the Pharmaceutical Society of Great Britain, incorporated by reference herein. The pharmaceutical compositions herein generally contain from 0-2% dyes or pigments.

Preferred co-solvents include, but are not limited to, ethanol, glycerin, propylene glycol, polyethylene glycols. The pharmaceutical compositions of the present invention include from 0-50% co-solvents.

Preferred buffer systems include, but are not limited to, acetic, boric, carbonic, phosphoric, succinic, malaic, tartaric, citric, acetic, benzoic, lactic, glyceric, gluconic, glutaric and

glutamic acids and their sodium, potassium and ammonium salts. Particularly preferred are phosphoric, tartaric, citric, and acetic acids and salts. The pharmaceutical composition of the present invention generally contain from 0-5% buffer systems.

Preferred surfactants include, but are not limited to, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters and lanolin esters and ethers, alkyl sulfate salts, sodium, potassium, and ammonium salts of fatty acids. The pharmaceutical compositions of the present invention include 0-2% surfactants.

Preferred preservatives include, but are not limited to, phenol, alkyl esters of parahydroxybenzoic acid, o-phenylphenol benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chlorobutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred are the salts of benzoic acid, cetylpyridinium chloride, methyl paraben and propyl paraben. The compositions of the present invention generally include from 0-2% preservatives.

Preferred sweeteners include, but are not limited to, sucrose, glucose, saccharin, sorbitol, mannitol, and aspartame. Particularly preferred are sucrose and saccharin. Pharmaceutical compositions of the present invention include 0-5% sweeteners.

Preferred viscosity agents include, but are not limited to, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl-methylcellulose, hydroxypropylcellulose, sodium alginate, carbomer, povidone, acacia, guar gum, xanthan gum and tragacanth. Particularly preferred are methylcellulose, carbomer, xanthan gum, guar gum, povidone, sodium carboxymethylcellulose, and magnesium aluminum silicate. Compositions of the present invention include 0-5% viscosity agents.

Preferred fillers include, but are not limited to, lactose, mannitol, sorbitol, tribasic calcium phosphate, dibasic calcium phosphate, compressible sugar, starch, calcium sulfate, dextro

and microcrystalline cellulose. The compositions of the present invention contain from 0-75% fillers.

Preferred lubricants include, but are not limited to, magnesium stearate, stearic acid, and talc. The pharmaceutical compositions of the present invention include 0.5-2% lubricants.

Preferred glidants include, but are not limited to, talc and colloidal silicon dioxide. The compositions of the present invention include from 1-5% glidants.

Preferred disintegrants include, but are not limited to, starch, sodium starch glycolate, crospovidone, croscarmelose sodium, and microcrystalline cellulose. The pharmaceutical compositions of the present invention include from 4-15% disintegrants.

Preferred binders include, but are not limited to, acacia, tragacanth, hydroxypropylcellulose, pregelatinized starch, gelatin, povidone, hydroxypropylcellulose, hydroxypropyl-methylcellulose, methylcellulose, sugar solutions, such as sucrose and sorbitol, and ethylcellulose. The compositions of the present invention include 1-10% binders.

Compounds of the present invention may comprise from about 0.1% to about 99.9% by weight of the pharmaceutical compositions of the present invention.

Preferably the compounds of the present Invention comprise from about 20% to about 80% by weight of the pharmaceutical compositions of the present invention.

Accordingly, the pharmaceutical compositions of the present invention include from 15-95% of a quaternary nitrogen-containing phosphonate compound active ingredient, or mixture, thereof; 0-2% flavoring agents; 0-50% co-solvents; 0-5% buffer system; 0-2% surfactants; 0-2% preservatives; 0-5% sweeteners; 0-5% viscosity agents; 0-75% fillers; 0.5-2% lubricants; 1-5% glidants; 4-15% disintegrants; and 1-10% binders.

Suitable pharmaceutical compositions are described herein in Examples 9 to 11. It is well within the capabilities of one skilled in the art to vary the non-limiting examples described herein to achieve a broad range of pharmaceutical compositions.

The choice of a pharmaceutical excipient to be used in conjunction with the quaternary nitrogen-containing phosphonate compounds of the present compositions is basically determined by the way the phosphonate is to be administered. If the compound is to be injected, the preferred pharmaceutical carrier is sterile, physiological saline, the pH of which has been adjusted to about 7.4. However, the preferred mode of administering the phosphonates of the present invention is orally, and the preferred unit dosage form is therefore tablets, capsules and the like, comprising from about 0.1 mg P to about 600 mg P of the phosphonic acid compounds described herein. Pharmaceutical carriers suitable for the preparation of unit dosage forms for oral administration are well known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the present Invention, and can be made without difficulty by a person skilled in the art.

The term "mg P", as used herein, means the weight of the phosphorus atoms present in an amount of a phosphonic acid compound of the present invention. This unit is used to standardize the amount of the phosphonic acid compounds of the present invention to be used in the pharmaceutical compositions and methods of the present inventions. For example, N-(4-hydroxy-4,4-diphosphonobutyl)-N,N-dimethyl-N-(2-mercaptoethyl)-ammonium chloride has a molecular weight of 373.5 g/mole, of which 17% (62 g/mole) is due to the two phosphorus atoms present in this molecule. One milligram of this compound is therefore calculated to have 0.17 mg P. Thus, to prepare a pharmaceutical composition containing 0.17 mg P of this compound, the composition should contain 1 mg of the compound; and to dose 0.17 mg P/kg of this compound to a 50 kg patient, the patient would be dosed with 50 mg of this compound.

The pharmaceutically-acceptable excipient employed in conjunction with the diphosphonates of the present invention is used at a concentration sufficient to provide a practical size to

dosage relationship. Preferably, the pharmaceutically-acceptable carriers, in total, may comprise from about 0.1% to about 99.9% by weight of the total composition and more preferably from about 20% to about 80%.

Method for Treating or Preventing Diseases Characterized by Abnormal Calcium and Phosphate Metabolism

Another aspect of the present invention is methods for treating or preventing diseases characterized by abnormal calcium and phosphate metabolism. Such methods comprise administering to a human or lower animal in need of such treatment a safe and effective amount of phosphonate compound of the present invention.

The preferred mode of administration is oral, but other known methods of administration are contemplated as well, e.g., dermatomucosally (for example, dermally, rectally and the like) and parenterally (for example, by subcutaneous injection, intramuscular injection, intra-articular injection, intravenous injection and the like). Inhalation is also included. Thus, specific modes of administration include, without limitation, oral, transdermal, mucosal, sublingual, intramuscular, intravenous, intraperitoneal, and subcutaneous administration, as well as topical application.

The term "abnormal calcium and phosphate metabolism", as used herein, means (1) conditions which are characterized by anomalous mobilization of calcium and phosphate leading to general or specific bone loss, or excessively high calcium and phosphate levels in the fluids of the body; and (2) conditions which cause or result from deposition of calcium and phosphate anomalously in the body. The first category includes, but is not limited to, osteoporosis, Paget's disease, hyperparathyroidism, hypercalcemia of malignancy, heterotopic ossification, and osteolytic bone metastases. The second category includes, but is not limited to, myositis ossificans progressiva, calcinosis universalis, and such afflictions as arthritis, osteoarthritis,

neuritis, bursitis, tendonitis and other inflammatory conditions which predispose involved tissue to deposition of calcium and phosphate.

The term "rheumatoid arthritis" as used herein, means a chronic systemic and articular inflammatory disorder of unknown etiology. It is characterized by destruction of articular cartilage, ligaments, tendons, and bone.

The term "osteoarthritis" as used herein, means a non-inflammatory disorder of the movable joints. It is characterized by deterioration and abrasion of the articular cartilage; and new bone formation at the joint surface.

The terms "person at risk" and "person in need of such treatment", as used herein, mean any human or lower animal which suffers a significant risk of abnormal calcium and phosphate metabolism if left untreated, and any human or lower animal diagnosed as being afflicted with abnormal calcium and phosphate metabolism. For example, postmenopausal women; persons undergoing certain steroid therapy; persons on certain anti-convulsant drugs; persons diagnosed as having Paget's disease, hyperparathyroidism, hypercalcemia of malignancy, or osteolytic bone metastases; persons diagnosed as suffering from one or more of the various forms of osteoporosis; persons belonging to a population group known to have a significantly higher than average chance of developing osteoporosis, e.g., postmenopausal women, men over age 65, and persons being treated with drugs known to cause osteoporosis as a side effect; persons diagnosed as suffering from myositis ossificans progressiva or calcinosis universalis; and persons afflicted with arthritis, osteoarthritis, neuritis, bursitis, tendonitis and other inflammatory conditions which predispose involved tissue to deposition of calcium and phosphate.

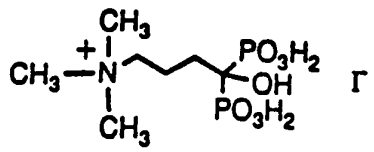
The phrase "safe and effective amount", as used herein, means an amount of a compound or composition of the present invention high enough to significantly positively modify the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of

sound medical judgment. The safe and effective amount of phosphonate compounds of the present invention will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific phosphonate employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician. However, single dosages can range from 0.01 mg P to 3500 mg P, or from 0.0002 to 70 mg P/kg of body weight (based on a body weight of 50 kg). Preferred single dosages are from 1 mg P to 600 mg P, or from 0.02 to 12 g P/kg of body weight (based on a body weight of 50 kg). Up to four single dosages per day may be administered. Daily dosages greater than 500 mg P/kg are not required to produce the desired effect and may produce undesirable side effects. The higher dosages within this range are, of course, required in the case of oral administration because of limited absorption.

The following Examples further describe and demonstrate the preferred embodiments within the scope of the present invention. The Examples are given solely for the purpose of illustration, and are not to be construed as limitations of the present invention since many variations thereof are possible without departing from its spirit and scope.

Example 1

Synthesis of N-(4-hydroxy-4,4-diphosphonobutyl)-N,N,N-trimethyl ammonium iodide



I. Synthesis of [4-(N,N-dimethylamino)-1-hydroxy butylidene]bis[phosphonic acid]

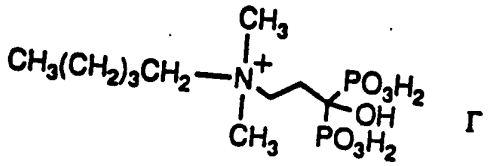
A solution containing 4-(N,N-dimethylamino) butanoic acid (2.9 mmol), phosphorus trichloride (2.0 mmol) and diethylphosphite (12 mmol) is stirred 30 minutes at room temperature and then heated at 60°C for 24 hours. The reaction mixture is then cooled to room temperature and concentrated hydrochloric acid (50 ml) is added. The reaction mixture is then heated an additional 24 hours at reflux; then cooled to room temperature and filtered through celite and the filtrate is concentrated under vacuum. The crude product is triturated in ethanol, collected by filtration and then dried under vacuum.

II. Synthesis of N-(4-hydroxy-4,4-diphosphonobutyl)-N,N,N-trimethyl ammonium iodide

The bisphosphonic acid (0.30 mmol) is dissolved in water (10 ml) and ethanol (15 ml) and the pH is adjusted to 7.0 by the addition of 1N NaOH. To this is added methyl iodide (1.50 mmol) and the reaction is heated at reflux for 24 hours. The mixture is then cooled and concentrated under reduced pressure. The solid residue is dissolved in a minimum amount of water and the quaternized product is precipitated by the addition of isopropanol. The product is collected by filtration, rinsed with acetone and then further dried under vacuum.

Example 2

Synthesis of N-(3-hydroxy-3,3-diphosphonopropyl)--N,N-dimethyl-N-pentyl ammonium iodide



I. Synthesis of [3-(N,N-dimethylamino)propylidene]bis[phosphonic acid]

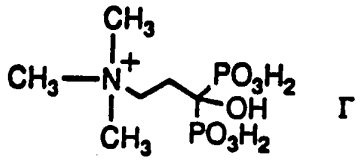
Using essentially the same procedure as described in Example 1, part I, hereinbefore, 3-(N,N-dimethylamino) propanoic acid is converted to [3,-(N,N-dimethylamino)propylidene]bis-[phosphonic acid].

II. Synthesis of N-(3-hydroxy-3,3-diphosphonopropyl)-N,N-dimethyl-N-pentyl ammonium iodide

The bisphosphonic acid (0.50 mmol) is dissolved in water (15 ml) and acetonitrile (20 ml) and the pH is adjusted to 7.0 by the addition of 1N NaOH. To this is added pentyliodide (2.50 mmol) and the reaction mixture is heated at reflux for 22 hours. The mixture is then concentrated under reduced pressure and the solid residue is triturated in acetone. The product can then be recrystallized from water and ethanol.

Example 3

Synthesis of N-(3-hydroxy-3,3-diphosphonopropyl)-N,N,N-trimethylammonium iodide

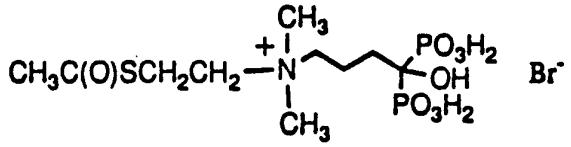


Using essentially the same procedure as described in Example 1, part II, hereinbefore, [3-(N,N-dimethylamino)propylidene]bis[phosphonic acid], prepared as described in Example 2, part I, hereinbefore, is converted to

N-(3-hydroxy-3,3-diphosphonopropyl)-N,N,N-trimethylammonium iodide.

Example 4

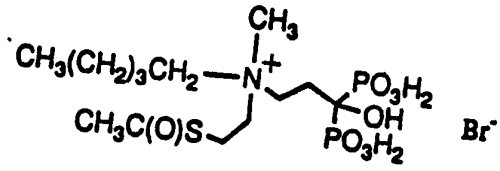
Synthesis of N-(2-acetylthioethyl)-N-(4-hydroxy-4,4-diphosphonobutyl)-N,N-dimethyl ammonium bromide



[4-(N,N-dimethylamino)-1-hydroxybutylidene]bis[phosphonic acid] (0.75 mmol), prepared as described in Example 1, part I, hereinbefore, is dissolved in water (50 ml) and acetonitrile (35 ml). To this is added S-acetyl-2-bromoethanethiol (3.75 mmol) and the reaction mixture is heated at reflux for 12 hours. The mixture is then concentrated under reduced pressure and the solid residue is triturated in acetone. The quaternized product can be recrystallized from water and ethanol.

Example 5

Synthesis of N-(2-acetylthioethyl)-N-(3-hydroxy-3,3-diphosphonopropyl)-N-methyl-N-pentyl ammonium bromide



I. Synthesis of [3-(N-methyl-N-pentylamino)propylidene]bis-[phosphonic acid]

Using essentially the same procedure as described in Example 1, part I, hereinbefore, 3-(N-methyl-N-pentylamino)propanoic acid is converted to [3-(N-methyl-N-pentylamino)propylidene]bis[phosphonic acid].

II. Synthesis of N-(2-acetylthioethyl)-N-(3-hydroxy-3,3-diphosphonopropyl)-N-methyl-N-pentyl ammonium bromide

Using essentially the same procedure as described in Example 4, hereinbefore, [3-(N-methyl-N-pentylamino)propylidene]-bis[phosphonic acid] is converted to N-(2-acetylthioethyl)-N-(3-hydroxy-3,3-diphosphonopropyl)-N-methyl-N-pentyl ammonium bromide.

Example 6

Schenk Model

The compounds are evaluated for in vivo bone resorption inhibition and mineralization inhibition in an animal model system known in the field of bone metabolism as the Schenk Model. The general principles of this model system are disclosed in Shinoda et al., Calcif. Tissue Int., 35, 87-99 (1983); and in Schenk et al., Calcif. Tissue Res. 11 , 196-214 (1973), the disclosures of which are incorporated herein by reference.

Materials and Methods:

Animals

Preweaning 17-day-old (30 gms) male Sprague Dawley rats (Charles River Breeding Laboratories) are shipped with their mothers and placed in plastic cages with their mothers upon arrival. At 19 days of age, pups receiving Rat Chow and water ad libitum are randomly allocated into treatment or control groups comprising seven animals per group. On day 1 and again on day 7 all animals are given an intraperitoneal ("IP") injection of Calcein (1% solution in 0.9% saline solution; dosed at 0.2 ml/100 g body weight). On day 4 all animals are given an IP injection of tetracycline hydrochloride (1% solution in 0.9% saline

solution; dosed at 0.2 ml/100 g body weight). These compounds label actively mineralizing bone and cartilage.

Dose Solutions and Dosing Procedure

All solutions are prepared for subcutaneous injection in 0.9% normal saline and adjusted to pH 7.4 using NaOH and/or HCI. Dose solution calculation is made by considering the mass of powder (based on molecular weight, hydration) of the active material in mg/kg (body weight) that corresponds to mgp/kg. Concentrations are based on dosing 0.2 ml/100 g body weight. Typically, all compounds are administered at 0.01, 0.1, 1.0 and 10.0 mg P/kg/day for 7 days. Compounds showing activity at 0.1 mg P/kg/day are then tested at logarithmic decrements down to 0.001 mg P/kg/day. Adjustments in dosage based on changes in body weight are made on a daily basis.

Necropsy, Tissue Processing and Histomorphometry

On day 8 after the start of dosing, all animals are sacrificed by IP overdose of pentabarbitol. Tibias are dissected free and placed in 70% ethyl alcohol. One tibia is dehydrated in graded ethanol solutions and embedded in methyl methacrylate as described in Schenk, Methods of Calcified Tissue Preparation (G.R. Dickson, Editor; Elsevier Science Publ., The Netherlands; 1984), the disclosures of which are incorporated herein by reference in their entirety. The tibia is sectioned longitudinally through the metaphyseal area. Specimens are stained on one surface with silver nitrate and mounted on microscope slides for evaluation with a Quantimet Image Analyzer (Cambridge Instruments, Inc.) using both incandescent and ultraviolet illumination. Metaphyseal trabecular bone content is measured in the region between the fluorescent label and the growth plate: expressed as percent of total area (bone + marrow). Epiphyseal growth plate width is obtained as the mean value of 10 equally-spaced measurements across the section.

Statistical evaluation of data is made using parametric and non-parametric analysis of variance and Wilcoxons rank sum test to determine a statistically significant effect compared to

control animals. The Schenk model provides data for in vivo bone resorption inhibition by the compounds.

Example 7

Adjuvant Arthritis Model

There are numerous animal models of arthritis, among these is adjuvant-induced arthritis using *Mycobacterium butyricum*. This model in a number of ways mimics rheumatoid arthritis in the human (joint swelling associated with cellular and pannus invasion of the joint space, bone resorption, and release of chemotaxic factors and lysosomal constituents into the joint space) (1,2). A number of prophylactic and therapeutic studies have indicated the potential use of anti-inflammatory drugs (3,4) and diphosphonates in arthritis (5,6).

REFERENCES

1. Pearson, C., Wood F. (1959), Studies of Polyarthritis and Other Lesions Induced by Injection of Mycobacterial Adjuvant. 1. General Clinical and Pathological Characteristics and Some Modifying Factors, Arth. Rheum., 2:440-459.

2. Blackman, A., Burns, J.W., Framer, J.B., Radziwonik, H., Westwick, J. (1977), An X-ray Analysis of Adjuvant Arthritis in the Rat. The Effect of Prednisolone and Indomethacin, Agents and Actions, 7:145-151.

3. Winter, C.A., Nuss, G.W. (1966), Treatment of Adjuvant Arthritis in Rats with Anti-inflammatory Drugs, Arth. Rheum., 9:394-404.

4. Winder, C.V., Lembke, L.A., Stephens, M.D. (1969), Comparative Bioassay of Drugs in Adjuvant-Induced Arthritis in Rats: Flufenamic Acid, Mefenamic Acid, and Phenylbutazone, Arth. Rheum., 12:472-482.

5. Francis, M.D., Flora, L. King, W.R. (1972), The Effects of Disodium Ethane-1-Hydroxy-1-Diphosphonate on Adjuvant Induced Arthritis in Rats, Calcif. Tiss. Res., 9:109-121.

6. Flora, L. (1979), Comparative Antiinflammatory and Bone Protective Effects of Two Diphosphonates in Adjuvant Arthritis, Arth. Rheum, 22:340-346.

Adjuvant arthritis is a severe cellulitis and synovitis induced in male rats (either Sprague Dawley or Lewis strain) by a single subcutaneous (SC) injection of *Mycobacterium butyricum* (8 mg/ml) in mineral oil on day 0. The compounds are dosed once daily either orally (PO) or parenterally (SC) and can be tested in either prophylactic (from day 0) or therapeutic (from day 9 or 10 or 14) protocols. Antiarthritic efficacy can be measured as a reduction in paw volume, body weight loss, bone loss or reactive new bone formation compared to the saline-treated arthritic controls. Treatment can be stopped and the "flare" response (rapid increase in inflammation) examined, which indicates a compound's ability to maintain efficacy.

Materials and Methods

A. Animals

Animals used are male Lewis rats (LEW). On arrival, the rats are randomized by computer generated random numbers and placed in individual wire suspended cages. Food and water are administered *ad libitum*, throughout the entire study. Routine care and maintenance of the animals are performed according to State and Federal regulations. Each rat is identified with a number placed in front of the cage and on the tail of the rat.

B. Experimental Design

On day 1 body weights (BW) and hind paw volume [(PV) recorded by a mercury displacement method using a pressure transducer linked into a computer] measurements are taken on all rats. On day 0, the induction of arthritis using MFA [*Mycobacterium butyricum* (Mb) 4.4 mg/kg in oil] is as follows: rats are anesthetized and receive a single SC injection of MFA at the base of the tail under aseptic conditions.

Paw volumes and body weights are measured thereafter on various days, usually twice a week. For the prophylactic

protocol, rats are randomly allocated into groups of 8-10 rats and treatment begins on day 0 and continues daily until termination. For the therapeutic protocol, the rats are randomized into treatment groups of 8-10 rats according to their PV on day 10. Dosing begins on day 10 and continues daily until termination. For both protocols, animals are placed in shoe box cages with deep bedding on or before day 10.

Dosing Solutions

For Compounds Unlikely to Oxidize

Drugs are weighed out on a calibrated balance and then mixed with distilled water in a volumetric flask. The solution is adjusted to pH 7.4 with 0.1N NaOH. Then the solution is filtered through a 0.45 μm sterile filter into a sterile storage container. When not in use, the solution is stored in the refrigerator.

For Compounds Likely to Oxidize

Drugs are weighed out on a calibrated balance and then mixed with deoxygenated water in a volumetric flask. The stock solution is filtered through a 0.45 μm sterile filter into a sterile storage container. When not in use, the stock solution is kept refrigerated.

On a daily basis, a specific amount of solution is removed from the stock solution, put into small dosing beaker and then adjusted to pH 7.4 according to a predetermined calculation. Further dilutions of the adjusted solution can be made if necessary (with deoxygenated water).

Drug calculations are made based on the molecular weight, the purity of the compound, the amount based on mg/kg (body weight) and the desired final concentration in mgP/kg. The volume dosed per rat is 0.1 ml/100 gm of body weight subcutaneously, given as an injection in the inguinal fold of the animal, alternating sides each day or 1 ml/200 gm BW given orally using a curved stainless steel dosing tube. Adjustments based on changes in body weight are made weekly.

Radiographs, Necropsy and Tissue Collection

At termination, each rat is sacrificed with 1 ml Socomb® intraperitoneally (IP). Immediately a whole body radiograph is taken by a Torrox 120D x-ray unit at MA=5, ISUP=50 and time=60 second on Kodak non-screen medical film. Hind legs are removed from each rat and fixed in 10% buffered formalin along with a piece of liver, kidney, spleen, and thimus. The tibiotarsal joints are decalcified in 4% EDTA, pH 7.4 and processed routinely in paraffin blocks and H+E stain. The organ parts also processed in paraffin and stained H+E.

The histology sections are evaluated qualitatively for bone and soft tissue lesions using light microscopy. Radiographs are graded for bone resorption (BR) in 6 anatomical trabecular bone sites in each hind leg and 4 sites in each front leg on a scale of 0-3 giving an arbitrary score of 0-60 for all 4 legs. For reactive new bone formation (RNB), radiographs are graded on a severity scale of 0-3 for the lateral and medical surfaces of the tibia and then 0-2 for all other areas mentioned above, giving an arbitrary score of 0-44.

D. Statistical Analysis:

Data analysis on paw volume, bone resorption and reactive new bone formation is performed by student's t-test and one-way analysis of variance with Tukeys (SAS) (12). Differences are considered significant at p=0.05 or less.

This model provides in vivo data for the efficacy of antiarthritic compounds in terms of reducing paw swelling bone loss and reactive new bone formation compared to the saline treated arthritic animals.

Example 8

Capsules are prepared having the following composition:

Active Ingredient	Mg Per Capsule
N-(3-hydroxy-3,3-diphosphonopropyl)-N,N,N-trimethyl ammonium chloride	350.0

Excipients	
Lactose	90.0
Microcrystalline Cellulose	60.0
Magnesium Stearate	1.0

The capsules having the above composition are prepared using conventional methods as described below,

The active ingredient is mixed with the microcrystalline cellulose in a turn shell blender for approximately ten (10) minutes.

The resulting mixture is passed through a hammer mill with an 80 mesh screen.

The mixture is put back into the twin shell blender along with the lactose and is then mixed for approximately fifteen (15) minutes.

The magnesium stearate is next added and blended for an additional five (5) minutes. The resulting blend is then compressed on a piston-activated capsule filler.

Any of the compounds prepared according to Examples 1 to 5 may be substituted for the active ingredient in the capsule prepared hereinabove.

Example 9

Tablets are prepared having the following composition:

Active Ingredient	Mg Per Tablet
N-(4-hydroxy-4,4-diphosphonobutyl)-N,N-dimethyl-N-(2-mercaptoethyl) ammonium chloride	700.00
Excipients	
Lactose (spray-dried)	200.0
Starch (1500)	100.0
Magnesium Stearate	25.0

Tablets are prepared having the above composition using conventional methods as described below:

The active ingredient is ground in a ball mill for approximately thirty (30) minutes. The milled active ingredient is then blended in a twinblade mixer with the spray-dried lactose for approximately twenty (20) minutes.

The starch is added to the mixture and is then mixed for an additional fifteen (15) minutes. The blend is compressed into tablets on a standard tablet press.

Any of the compounds prepared according to Examples 1 to 5 may be substituted for the active ingredient in the tablet prepared hereinabove.

Example 10

Injectable solutions are prepared by conventional methods using 10.0 ml of physiological saline solution and N-(4-hydroxy-4,4-diphosphonobutyl)-N, N, N-trimethyl ammonium chloride, adjusted to pH = 7.4.

One injection, one time daily for 4 days, results in appreciable alleviation of rheumatoid arthritis in patients weighing approximately 70 kilograms.

Any of the compounds prepared according to Examples 1 to 5 may be substituted for the active ingredient in the injectable solution prepared hereinabove.

Example 11

A Caucasian male, weighing approximately 92 kilograms, seventy-two years of age, suffering from moderate to severe pain, and occasional swelling, of the right knee. After approximately one year of steadily increasing discomfort, he visits a physician who renders a clinical diagnosis of osteoarthritis of the right knee, which was subsequently verified by X-ray diagnosis.

After a period of ameliorative therapy of various NSAIDs, including aspirin, naprosen, and ketoprofen, his symptoms continue to worsen and his condition appears to degenerate. He returns to his physician who then prescribes the tablets prepared as described in Example 9 twice daily two hours before or after meals for a period of three months. His clinical symptoms of

pain and swelling, particularly with extended walking, improved significantly after his 3 months of therapy. At the conclusion of three months at a dosage of 2 tablets per day, the therapy is continued at one-half the dosage originally prescribed (i.e. 1 capsule, prepared as described in Example 8, per day) indefinitely.

Example 12

A black female, weighing approximately 65 kilograms, fifty-five years of age, presents with swelling and deformation of the finger joints of both hands, with partial loss of strength and/or dexterity of her fingers and hands. Upon visual and X-ray examination and various appropriate clinical tests approved by the American Rheumatological Association (ARA) she is diagnosed with rheumatoid arthritis.

After an unsuccessful analgesic and anti-inflammatory therapy, her physician prescribes the tablets prepared as described in Example 9, two times daily two hours before or after meals for a period of four months. After a month of therapy, her symptoms of knuckle swelling noticeably improves and her range of finger motion increases significantly; she continues therapy for the remainder of the four months, after which her physician continues the prescribed dose for an additional two months.

Example 13

A female of Hispanic origin, twelve years of age, weighing approximately 37 kilograms, presents to the physician with idiopathic juvenile rheumatoid arthritis. Her symptoms include marked inflammation of multiple joints, complicated by heat and tenderness and indicating rapid and pathological degeneration of joint function.

Her physician refers her to a rheumatologist who immediately prescribes aggressive therapy by IV administration of the solution prepared as described in Example 10 over a period of three days, at the rate of 1 injection per day, administered over two hours. At the conclusion of the IV regimen, the physician

prescribes the tablets prepared as described in Example 9, for a period of two months, during which she exhibits marked improvement with increased mobility and decreased pain. For the succeeding two months, the physician reduces her dose to 3/4 of the original oral dose by prescribing 3 tablets over a period of two days, i.e. one 2-tablet day alternating with one 1-tablet day. At the conclusion of this regimen the dosage is again reduced to 1/4 of the original dose by giving her the tablets prepared as described in Example 9, 1 tablet every day for an additional four months.

Example 14

A 60-year-old Caucasian female weighing 62 kg, experiences severe back pain. Her physician, with the aid of a radiologist, diagnoses her as having a crush fracture of the L1 vertebrae presumably due to osteoporotic bone loss. The patient is prescribed a three month, once-daily dosage regimen of a 700 mg tablet prepared described in Example 9. The 700 mg tablet is taken either two hours before or two hours after any given meal. After three months, the dosage is reduced to a 350 mg capsule, prepared according to the procedure described in Example 8, taken every other day for a period of three months. Her physician then puts her on a maintenance dosing regimen wherein she takes a 100 mg capsule, prepared according to the procedures described in Example 8, every day for six months. After six months on the maintenance dosing regimen the patient is not experiencing any further back pain. Follow-up x-rays reveal no additional fractures.

Example 15

A 75-year-old Oriental female weighing 53 kg suffers a fractured hip after a fall. She is hospitalized and diagnosed as having osteoporosis. A treatment regimen of calcitonin injections is prescribed. The calcitonin injections are painful to the patient and she is unable to comply with said calcitonin treatment. Her physician then switches her therapy to an oral

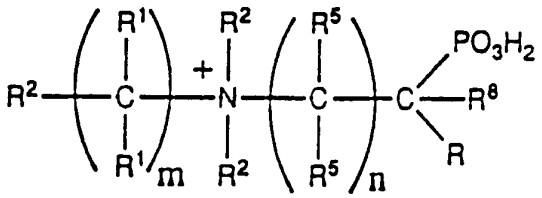
phosphonate regimen. She is administered a 700 mg tablet prepared according to the procedure described in Example 9, twice daily for one month. At the end of this one month of therapy, she is given a 700 mg tablet once daily for two months. At the end of this two month period, she is given a 100 mg capsule daily, prepared according to the procedure described in Example 8, for three months. A follow-up visit to her physician reveals no apparent decrease in mineral density of the forearm as determined by photonabsorptimetry.

Example 16

A 85-year-old Native American male weighing 65 kg presents to his physician with severe back pain. X-rays reveal multiple minor vertebral body collapse resulting from significant bone loss due to osteoporosis. The patient is prescribed a two month regimen of a 700 mg tablet and a 350 mg capsule to be taken on the same day, eight hours apart, prepared according to the procedures described in Examples 9 and 8, respectively. After two months on this regimen, his dosage is reduced to a 350 mg capsule once a day for two months. X-rays are then taken and an additional crush fracture is noted. He is then put on a maintenance regimen of a 100 mg capsule, prepared according to the procedure described in Example 8, once a day for six months. At the end of this six months, no significant apparent decrease in bone density is observed.

What is claimed is:

1. Quaternary nitrogen-containing compounds which are useful in treating or preventing disorders of abnormal calcium and phosphate metabolism and the pharmaceutically-acceptable salts and esters thereof characterized in that they have the general structure:



wherein m is an integer from 0-10; and n is an integer from 1-10; m + n is from 1-10;

(a) R^1 is selected from the group consisting of nil; $-SR^6$; $-R^9SR^6$; hydrogen; substituted or unsubstituted C_1-C_8 alkyl; $-OR^3$; $-CO_2R^3$; $-O_2CR^3$; $-NR^3_2$; $-N(R^3)C(O)R^3$; $-C(O)N(R^3)_2$; halogen; $-C(O)R^3$; nitro; hydroxy; substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic rings; substituted or unsubstituted saturated monocyclic or polycyclic carbocyclic rings, preferably substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic rings; substituted or unsubstituted saturated monocyclic or polycyclic carbocyclic rings and nil, H, SR^6; R^9SR^6;

(b) R^5 is selected from the group consisting of $-SR^6$; $-R^9SR^6$; hydrogen; substituted or unsubstituted C_1-C_8 alkyl; $-OR^3$; $-CO_2R^3$; $-O_2CR^3$; $-NR^3_2$; $-N(R^3)C(O)R^3$; $-C(O)N(R^3)_2$; halogen; $-C(O)R^3$; nitro; hydroxy; substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic rings; substituted or unsubstituted saturated monocyclic or polycyclic carbocyclic rings; substituted or unsubstituted unsaturated monocyclic or

polycyclic heterocyclic rings; substituted or unsubstituted unsaturated monocyclic or polycyclic carbocyclic rings and combinations thereof, preferably $-SR^6$; $-R^9SR^6$; hydrogen; substituted or unsubstituted C_1-C_8 alkyl or substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic rings or substituted or unsubstituted saturated monocyclic or polycyclic carbocyclic rings.

(c) each R^2 is selected from the group consisting of substituted or unsubstituted C_1-C_{35} alkyl; unsubstituted or substituted phenyl; benzyl; or R^9SR^6, preferably substituted or unsubstituted C_1-C_{35} alkyl or R^9SR^6;

(d) R^3 is selected from the group consisting of H; unsubstituted or substituted C_1-C_8 alkyl; R^9SR^6, preferably H;

(e) R^6 is selected from the group consisting of -H; $-C(O)R^7$; $-C(S)R^7$; $-C(O)N(R^7)_2$; $-C(O)OR^7$; $-C(S)N(R^7)_2$; $-C(S)OR^7$; where R^7 is hydrogen or unsubstituted or substituted C_1-C_8 alkyl, preferably H or $-C(O)R^7$ or $C(S)R^7$;

(f) R is selected from the group consisting of $-PO_3H_2$; and $-P(O)(OH)R^4$, where R^4 is an alkyl group having 1-3 carbons, preferably PO_3H_2 or $P(O)(OH)R^4$;

(g) R^9 is substituted or unsubstituted C_1-C_8 alkyl;

(h) R^8 is selected from the group consisting of hydrogen, halogen; SR^6; R^9SR^6; amino; hydroxy; substituted and unsubstituted C_1-C_8 alkyl, preferably H or SR^6.

2. A compound according to Claim 1, wherein R^1 is a substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic ring or a substituted or unsubstituted saturated monocyclic or polycyclic carbocyclic ring.

3. A compound according to Claim 1, where R^5 is selected from hydrogen; $-SR^6$; $-R^9SR^6$, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted saturated monocyclic or polycyclic heterocyclic rings.

4. A compound according to Claim 1, wherein R^1 is selected from nil; $-SR^6$, $-R^9SR^6$ and hydrogen.

5. A compound according to Claim 1, wherein R^5 is selected from $-SR^6$; $-R^{9SR6}$; hydrogen; substituted or unsubstituted C_1-C_8 alkyl.

6. A compound according to Claim 1, wherein R^5 is a substituted or unsubstituted C_1-C_8 alkyl.

7. A compound according to Claim 1, wherein R^5 is R^9SR^6.

8. A compound according to Claim 1, wherein R^5 is a substituted or unsubstituted, saturated or unsaturated heterocyclic ring.

9. A pharmaceutical composition useful for the treatment of conditions associated with abnormal calcium and phosphate metabolism characterized in that it is comprised of:

(a) a safe and effective amount of phosphonate compound of Claim 1 and

(b) a pharmaceutically-acceptable excipient.

10. The use of a compound of Claim 1 in the manufacture of a medicament to be used for treating or preventing pathological conditions associated with abnormal calcium and phosphate metabolism in humans or other mammals in need of such treatment, characterized in that it is comprised of administering to said humans or other mammals a safe and effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/04469

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07F9/38; A61K31/66; C07F9/59

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07F ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	DE,A,4 011 777 (CIBA-GEIGY AG) 18 October 1990 cited in the application see the whole document	1-10
X	PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS vol. 54, nr.1-4, 1990 pages 197-202 K.A. JAEGGI ' A novel rearrangement in the series of gem-bisphosphonic acids' see page 202	1
A	FR,A,2 319 646 (HENKEL & CIE GMBH) 25 February 1977 see the whole document	1,9,10

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19 AUGUST 1993	06.09.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BESLIER L.M.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9304469 SA 74283

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-A-4011777	18-10-90	None		
FR-A-2319646	25-02-77	DE-A-	2534391	17-02-77
		AT-B-	350161	10-05-79
		AT-B-	349642	10-04-79
		BE-A-	844649	31-01-77
		CH-A-	599234	31-05-78
		CH-A-	620359	28-11-80
		GB-A-	1540238	07-02-79
		JP-C-	1248823	25-01-85
		JP-A-	52019628	15-02-77
		JP-B-	59025798	21-06-84
		NL-A-	7607703	03-02-77
		US-A-	4054598	18-10-77