METHODS OF MAINTAINING TEETH AND ORAL BONE

Teeth are constructed of three layers. An outer layer of enamel, very hard and dense, covers the crown of the tooth that extends above the gumline.

The middle layer, dentine, also called dentin, is harder than bone but softer than enamel and consists mainly of apatite crystals of calcium and phosphate. A layer of dentine-producing cells, odontoblasts, line the pulp cavity of the tooth and send projections into the calcified material of the dentine. These projections are enclosed in tubules. Sensitivity to pain, pressure, and temperature is transmitted via the ordontoblastic extensions in the tubules to and from the nerve in the pulp chamber. Secondary dentine, a less well organized form of the tubular dentine, is produced throughout life as a patching material where cavities have begun, where the overlying enamel has been worn away, and within the pulp chamber as part of the aging process. The dentine is nourished by the pulp, which is innermost and consists of cells, tiny blood vessels, and a nerve, enclosed in a pulp chamber.

Below the gumline extends the root of the tooth, covered at least partially by cementation (cementum), less hard than dentine and with characteristics very like those of bone. It is made by a layer of cementum-producing cells - cementoblasts - adjacent to the dentine. The fibres of the periodontal membrane, which holds the tooth in its socket, are embedded in the cementum. Deposition of cementum continues throughout the life of an animal, especially in response to stresses. In humans, for example, as the tooth crown wears down, new cementum is deposited on the roots so that the tooth gradually rises higher in the socket and good occlusion (bite) is maintained.

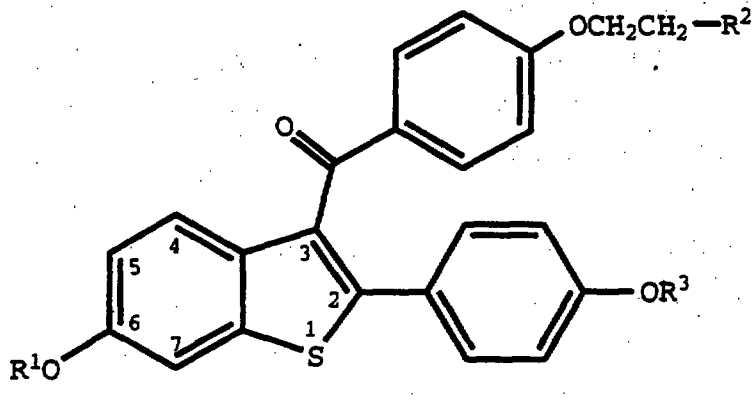
Each tooth has three parts; the root, the neck, and the crown. The root is the part of the tooth that is attached to the tooth-bearing bone - the alveolar processes - of the jaws by a fibrous ligament called the periodontal membrane or ligament. The crown is that portion of the tooth that projects into the mouth. Between the root and the crown is the neck, the portion

of the tooth that is embraced by the fleshy gum tissue, a specialized area of mucous membrane that lines the mouth cavity.

Around each developing tooth, the alveolar bone forms a bony socket to which the tooth becomes attached by the periodontal membrane. During replacement of deciduous teeth by permanent teeth, the overlying bone and the greater part of the root area of each deciduous tooth is resorbed and a fresh socket is produced for the succeeding permanent tooth.

There is a growing understanding of the relationship between systemic osteoporosis and oral bone loss. When alveolar bone is lost, endentilism occurence rises. This seems to be most evident in postmenopausal woman. Loss of teeth, however, is not the only risk of oral bone loss. The person is also at a higher risk for residual ridge resorption, which may result in difficulty wearing dentures. Also, tooth material may be lost through resorption, such as the case with chronic perforating pulp hyperplasia.

This invention provides methods of maintaining teeth and oral bone comprising administering to a human in need thereof an effective amount of a compound of formula I



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$, $-\overset{O}{\overset{\|}{C}}-(C_1-C_6\ \text{alkyl})$, or $-\overset{O}{\overset{\|}{C}}-Ar$, wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidino, hexamethyleneimino, and piperidino; and pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that a select group of 2-phenyl-3-aroylbenzothiophenes (benzothiophenes), those of formula I, are useful for maintaining teeth and oral bone.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a human in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to maintaining teeth and oral bone.

The term "maintain" includes its generally accepted meaning which includes keeping in the existing state; inhibiting failure or decline, or the rate thereof: and retaining. The present method includes both medical therapeutic and/or prophylactic administration, as appropriate.

Maintaining teeth may be accomplished by maintaining the oral bone, or by maintaining tooth material. Oral bone includes alveolar, maxilla and mandible bone.

Raloxifene is a preferred compound of this invention and it is the hydrochloride salt of a compound of formula 1 wherein R^1 and R^3 are hydrogen and R^2 is 1-piperidinyl.

Generally, at least one compound of formula I is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form the

formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. The term "optionally substituted phenyl" includes phenyl and phenyl substituted once or twice with C_1-C_6 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, ß-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an

equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as

sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to maintain teeth and/or oral bone, according to this invention, will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective oral daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need thereof from once to about three times each day, or more often as needed to effectively maintain teeth and/or oral bone. In certain preferred forms of the invention the oral composition may be substantially liquid in character, such as a mouthwash or rinse. In such a preparation the vehicle is typically a water-alcohol mixture desirably including a humectant as described below. Generally, the weight ratio of water to alcohol is in the range of from about 1:1 to about 20:1, preferably about 5:1 to 18:1 and more preferably about 10:1 to about 15:1. The total amount of water-alcohol mixture in this type of preparation is typically in the range of from about 50% to about 99% by weight of the preparation, often combined with about 5 to about 40% of humectant, some or all of which may be xylitol.

The pH of such liquid and other preparations of the invention is generally in the range of from about 4.5 to about 10 and typically from about 5.5 to 9. The pH is preferably in the range of from about 6 to about 8.0. The pH can be controlled with acid (e.g. citric acid or benzoic acid) or base (e.g. sodium hydroxide) or buffered (as with sodium citrate, benzoate, carbonate, or bicarbonate, disodium hydrogen phosphate, sodium dihydrogen phosphate, etc.).

In certain other desirable forms of this invention, a dentifrice composition may be substantially solid or pasty in character, such as toothpowder, a dental tablet, a tooth paste

(cream), or a dental gel. The vehicle of such solid or pasty dentifrice preparations typically contains an orally or dentally acceptable polishing material for use in conjunction with a brushing of teeth. Examples of such polishing materials are water-insoluble sodium metaphosphate, potassium metaphosphate, tricalcium phosphate, dihydrated calcium phosphate, anhydrous dicalcium phosphate, calcium pyrophosphate, magnesium orthophosphate, trimagnesium phosphate, calcium carbonate, aluminum silicate, zirconium silicate, silica, bentonite, and mixtues thereof. Other suitable polishing materials include the particulate thermosetting resins described in U.S. Patent No. 4,070,510 of Dec. 15, 1962 such as melamine-, phenolic, and urea-formaldehydes, and cross-linked polyepoxides and polyesters. Preferred polishing materials include crystalline silica having particle sizes of up to about 5 microns, a mean particule size of up to about 1.1 microns, and a surface area of up to about 50,000 $cm.^2/gm.$, silica gel or colloidal silica, and complex amorphous alkali metal alumino-silicate.

When visually clear gels are desired, a polishing agent of colloidal silica, such as those sold under the trademark SYLOID or SANTOCEL and alkali metal aluminosilicate complexes are particularly useful, since they have refractive indices close to the refractive indices of gelling agent-liquid (including water and/or humectant) systems commonly used in dentifrices.

Many of the so-called "water-insoluble" polishing materials are anionic in character and also include small amounts of soluble material. Thus, insoluble sodium metaphosphate may be formed in any suitable manner as illustrated in Thorpe's Disctionary of Applied Chemistry, Volume 9, 4th Edition, pp. 510-511. The forms of insoluble sodium metaphosphate known as Madrell's salt and Kurrol's salt are further examples of suitable materials. These metaphosphate salts exhibit only a minute solubility in water, and therefore are commonly referred to as insoluble metaphosphates (IMP). There is present therein a minor amount of soluble phosphate material as impurities, usually a few percent up to 4% by weight. The amount of soluble phosphate material, which is

believed to include a soluble sodium trimetaphosphate in the case of insoluble metaphosphate, may be reduced or eliminated by washing with water if desired. The insoluble alkali metal metaphosphate is typically employed in powder form of a particle size such that no more than about 1% of the material is larger than about 37 microns.

The polishing material is generally present in the solid or pasty compositions in weight concentrations of about 10% to about 99%. Perferably, it is present in amounts ranging from about 10% to about 75% in toothpaste or gel and from about 70% to about 99% in toothpowder or tablet.

In a toothpaste, dental cream or gel, the liquid vehicle is typically water in concentrations of about 2% to about 50% and mixed with about 0.2 to about 5 parts of humectant per part by weight of the water. The active xylitol may function as part or all of the humectant. Glycerine, propylene glycol, sorbitol, polypropylene glycol and/or polyethylene glycol (e.g. 400-600) exemplify suitable humectants/carriers. Also advantageous are liquid mixtures of water, glycerine and sorbitol. In clear gels where the refractive index is an important consideration aobut 3-30 wt. % of water, 0 to about 80 wt. % of glycerine, and about 20-80 wt % of sorbitol is preferably employed.

Toothpastes (creams) and gels typically contain a natural or synthetic binder, thickener or gelling agent in proportions of about 0.1 to about 10, preferably about 0.5 to about 5, wt. %. A suitable thickener is synthetic hectorite, a synthetic colloidal magnesium alkali metal silicate complex clay available for example as Laponite (e.g. CP, SP 2002, D) marketed by Laporte Industries Limited. Laponite D analysis shows, approximately by weight 58.00% SiO_2, 25.40% MgO, 3.05% Na_2O, 0.98% Li2O, and some water and trace metals. Its true specific gravity is 2.53 and it has an apparent bulk density (g./ml. at 8% moisture) of 1.0.

Other suitable thickeners include Irish moss, gum tragacanth, starch, polyvinylpyrrolidone, hydroxyethylpropylcellulose, hydroxybutyl methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose (e.g.

available as Natrosol), sodium carboxymethyl cellulose, and colloidal silica such as finely ground Syloid (e.g. 244).

It will be understood that, as is conventional, the oral preparations are to be sold or otherwise distributed in suitable labelled packages. Thus, a toothpaste, cream or gel will usually be in a collapsible tube, typically aluminum, lined lead or plastic, or other squeeze, pump or pressurized dispenser for metering out the contents, having a label describing it, in substance, as a toothpaste, gel or dental cream.

One or more organic surface-active agents are used in the compositions of the present invention to achieve increased wetting, foaming and prophylactice action, assist in achieving thorough and complete dispersion of the composition throughout the oral cavity, and render the instant compositions more cosmetically acceptable. The organic surface-active material is preferably anionic, nonionic or ampholytic in nature, and it is preferred to employ as the surfact-active agent a detersive material which imparts to the composition detersive and foaming properties. Suitable examples of anionic surfactants are water-soluble salts of higher fatty acid monoglyceride monosulfates, such as the sodium salt of the monosulfated monoglyceride of hydrogenated cocomut oil fatty acids, higher alkyl sulfates such as sodium lauryl sulfate, alkyl aryl sulfonates such as sodium dodecyl benzene sulfonate, higher alkul sulfoacettes, higher fatty acid esters of 1,2-dihydroxy propane sulfonate, and the substantially saturated higher aliphatic acyl amides of lower aliphatic amino carboxylic acid compounds such as those having 12 to 16 carbons in the fatty acid, alkyl or acyl radicals, and the like. Examples of the last mentioned amides are N-lauroyl sarcosine, and the sodium, potassium, and ethanolamine salts of N-lauroyl, N-myristoyl, or N-palmitoyl sarcosine which should be substantially free from soap or similar higher fatty acid material. The use of these sarcosinate compounds in the oral compositions of the present invention is particularly advantageous since these materials exhibit a prolonged and markded effect in the inhibition of acid formation in the oral cavity due to carbohydrate breakdown in addition to exerting

some reduction in the solubility of tooth enamel in acid solutions.

Examples of water-soluble nonionic surfactants are condensation products of ethylene oxide with various reactive hydrogen-containing compounds reactive therewith having long hydrophobic chains (e.g. aliphatic chains of about 12 to 20 carbon atoms), which condensation products ("ethoxamers") contain hydrophilic polyoxyethylene moieties, such as condensation products of poly(ethylene oxide) with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols (e.g. sorbitan monostearate) and polypropyleneoxide (e.g. Pluronic materials).

Various other materials may be incorporated in the oral preparations of this invention such as whitening agents, preservatives, silicones, chlorophyll compounds, other anti-calculus agents, and/or ammonizted mateial such as urea, diammonium phosphate, and mixtures thereof. These adjuvants, where present, are incorporated in the preparations in amounts which do not substantially adversely affect the properties and characteristics desired. Significant amounts of zinc and other metal salts and materials, generally soluble, which would complex with the active components of the instant invention are to be avoided.

Any suitable flavoring or sweetening material may also be employed. Examples of suitable flavoring constituents are flavoring oils, e.g. oil, e.g. oil of spearmint, peppermint, wintergren, sassafras, clove, sage, eucalyptus, marjoram, cinnamon, lemon, and orange, and methyl salicylate. Suitable sweetening agents include sucrose, lactose, maltose, dextrose, levulose, sorbitol, d-tryptophan, dihydrochalcones, sodium cyclamate, perillarine, APM (aspartyl phenyl alanine, methyl ester), saccharine and the like. The active zylitol may constitute part of all of the sweetening agent. Suitably, flavor and sweetening agents may together comprise from about 0.1% to 5% or more of the preparation.

It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group,

such as the piperidino ring. For such purposes the following oral dosage forms are available.

Formulations

In the formulations which follow, "Active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of specific capsule formulations of raloxifene that have been made include those shown below:

Formulation 2: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 5: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.

A tablet formulation is prepared using the ingredients below:

Formulation 6: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of Active ingredient are made up as follows:

Formulation 7: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The Active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of Active ingredient per 5 mL dose are made as follows:

Formulation 8: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to

form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 9: Mouthwash

Ingredient	Parts
Deionized water	58.0
Active Ingredient	20.0
Glycerine	7.50
Sorbitol (70% Aqueous Solution)	7.5
Ethanol	4.9
Pluronic F-108	0.9635
Pluronic F-127	0.9635
Sodium Benzoate	0.5
Sodium Fluoride	0.05
FD&C Blue No. 1	0.04
FD&C Yellow No. 5	0.02
Benzoic Acid	0.01
Flavor	0.003
Total	100.0

ASSAYS

ASSAY 1

The baboon model as described by Aufdemorle *et al.*, *Bone, 14*, 581-586 (1993) is employed. The study consists of two groups of between 5 and 15 aged females. Both groups have their oral bone assessed as discussed in Aufdemorle *et al.* One group is the control group, and the other is given a compound of formula I orally in an amount of 15-100 mg per day for a period of 4-12 months, after which time their oral bone are again assessed.

ASSAY 2

Five to fifty women are selected for the clinical study. The women are post-menopausal, *i.e.*, have ceased menstruating for between 6 and 12 months prior to the study's initiation and are in good general health,. The study has a placebo control group, *i.e.*, the women are divided into two groups, one of which receives a compound of formula 1 as the active agent and the other receives a placebo. Women in the test group receive between 50-200 mg of the drug per day by the oral route. They continue this therapy for 1-5 years. Accurate records are kept as status of the patients' teeth and oral bone in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the teeth and oral bone status of each patient before the study began.

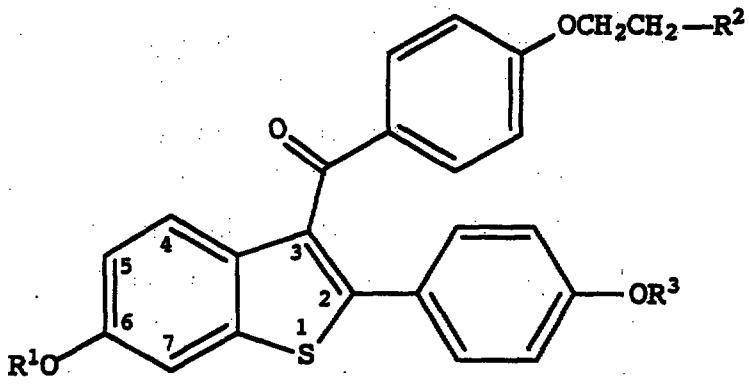
Utility of the compounds of formula I is illustrated by the positive impact they have in at least one of the assays described above.

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I claim:

1. A method of maintaining teeth and oral bone comprising administering to a human in need thereof an effective amount of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$, $-\overset{O}{\overset{\|}{C}}-(C_1-C_6\ \text{alkyl})$, or $-\overset{O}{\overset{\|}{C}}-Ar$, wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidine, hexamethyleneimino, and piperidino; or a pharmaceutically acceptable salt of solvate thereof.

2. The method of Claim 1 wherein said compound is the hydrochloride salt thereof.

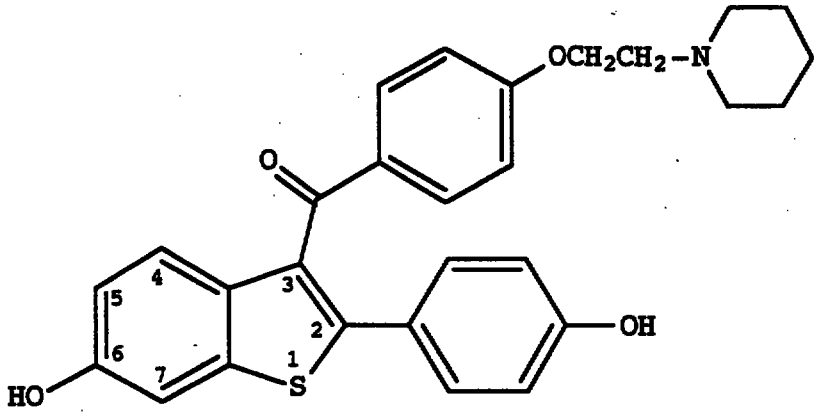
3. The method of Claim 1 wherein said administration is prophylactic.

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4. The method of Claim 1 wherein said compound is



or its hydrochloride salt.

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