METHODS FOR INHIBITING BONE PROSTHESIS DEGENERATION

Currently in modern medical practice there is a growing use of various prosthetic devices which are related to bone. Each year thousands of hip, knee, and other joints, which have been damaged by trauma, osteoarthritis, osteoporosis, etc., are being replaced by prosthetic devices. Additionally, there are thousands of dental procedures being employed which involve prosthesis. All of these prosthetic devices have a common element if they are to be successful in benefiting the patient, *i.e.*, they are all anchored to bones and must remain firmly attached in order to work properly.

Great success has been achieved over the last decade or so, in the use prosthesis to replace damaged joints such knees and hips. Today, it is becoming a very common procedure, benefiting thousand of people who can return to a normal life. The economic impact of these therapies is substantial in that they reduce the need of long term custodial care and allow many people to return to their productive lives. Much of the success of these therapies is due to improved surgical methods and particularly to improvements of materials which are bio-compatible with the bone which they are anchored to. The initial success rate for the implantation of these prosthesis is very high. Most patients achieve a secure bond between the new prosthesis and the existing bone surrounding it. This bond was thought to be sufficient for the life of the individual. However, since the introduction of these therapies, it has now become apparent that in many cases the bone-prosthesis bond has a finite life and that after a period of time, this bond becomes weaker leading to ultimate failure. This problem is only now becoming increasingly important due to the fact that the expected life of the bone-prosthesis bond appears to be about 10-20 years in most individuals. Therefore, it would seem

reasonable that in following years, the medical profession will see increasing numbers of patients presenting with bone prosthesis which beginning to fail, *i.e.*, to become detached from their bone support. Also, a trend which will certainly exacerbate this problem is the use of prosthesis in younger patients. This trend of increasingly younger patients undergoing prosthetic replacement is in large part due to the excellent recovery rate of the technique and to changes in life-style such as increasing sports injuries. It would seem reasonable to expect that a patient of age thirty-five might need to have a knee prosthesis replaced two to four times in their life.

With the increasing numbers of prosthesis failures bound to rise, the orthopedic surgeon faces a daunting task. When bone prosthesis fails, it does not simply mean that the prosthesis becomes totally detached from its bone support. The most likely case is that a relatively small portion loses its structural integrity, causing pain and ultimately a fracture break. Often this fracture destroys part of the surrounding bone which was not involved with the initial bone-prosthesis separation. The orthopedic surgeon must remove the old prosthesis and replace it making sure that the new one will be firmly anchored to the supporting bone. This is where the greatest problem occurs. In the removal of the old device inevitably a portion of the supporting bone around the prosthesis is either damaged or must be removed with the old device, which means there is less good, unaffected, supporting bone left for the attachment of the new one. If there is a prospect that a given prosthesis may have to be replaced more than once, there may be little bone left for such an attachment. This situation may even occur on the first replacement.

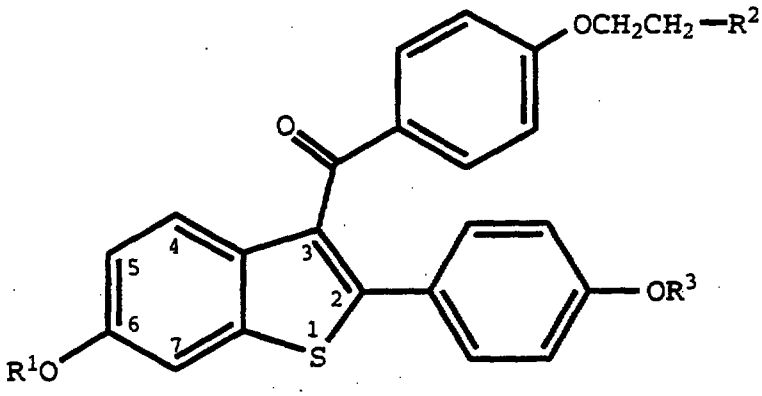
The reason for the failure of the bone-prosthesis bond over time is not well understood. Theories as to its cause have appeared in the literature. One theory suggests that

micro-movement between the supporting bone and the prosthesis induce a focal inflammation leading to bone resorption and failure. Another theory suggests that the prosthesis induces rapid turn-over bone in the proximal bone with an increase both of formation and resorption, but resorption being slightly enhanced thus leading to a net resorption over time. As yet, there is no known way to inhibit this ultimate failure of the prosthesis and the situation will become increasingly critical.

As mentioned earlier, another area of the use of prosthesis which are attached to bone is that of dentistry. Today, thousands of people have dental implants into the jaw to anchor single teeth to entire sets of teeth. The same sequelae as with joint replacement is applicable. The long term results of these implants is often the same.

Clearly, it would of great and increasingly important value to have an agent which prolongs the useful life of bone prosthesis.

This invention provides methods of inhibiting bone prosthesis degeneration 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, $-CH_3$, $-C-(C_1-C_6\ alkyl)$, or $-C-Ar$, 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 inhibiting bone prosthesis degeneration.

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 inhibit bone prosthesis degeneration.

The term "inhibit" includes its generally accepted meaning which includes prohibiting, preventing, restraining, and slowing, stopping or reversing progression, severity or a resultant symptom. As such, the present method includes both medical therapeutic and/or prophylactic administration, as appropriate.

The term "bone prosthesis degeneration" is defined to include the degeneration of the bone-prosthesis bond, and to inhibit such includes prolonging the useful life of the prosthesis.

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 inhibit bone prosthesis degeneration or its symptoms, 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 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, and for a duration sufficiant to effectively inhibit degeneration.

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.

ASSAY

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 have undergone surgery for the placement of a knee or hip joint prosthesis. 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 3-15 years. Accurate records are kept as to the status

of the bone-prosthesis in both groups and at the end of the study these results are compared. The results are compared between members of each group.

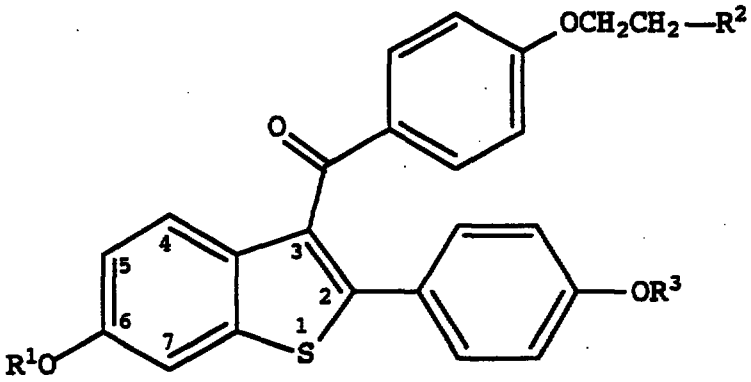
Utility of the compounds of formula I is illustrated by the positive impact they have in the assay described above.

THIS SHEET HAS BEEN REPLACED

* C L M S *

I claim:

1. A method of inhibiting bone prosthesis degeneration 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.

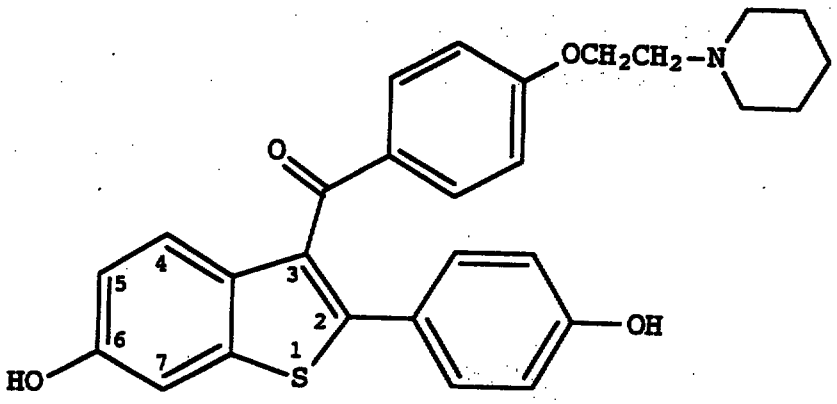
3. The method of Claim 1 wherein said administration is prophylactic.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

* C L M S *

4. The method of Claim 1 wherein said compound is



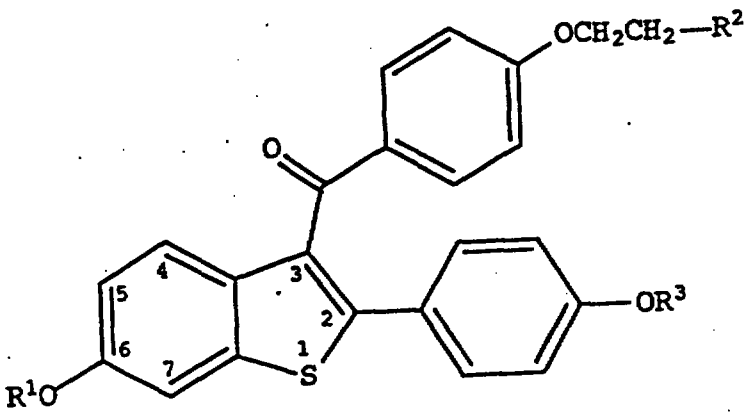
or its hydrochloride salt.

This Sheet Has Been Replaced

REPLACEMENT SHEET
23 FEB 1998
RYMP copy
SG 9700745 5

I CLAIM :

1. A use of an effective amount of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen,

$-CH_3$, $-\overset{O}{\overset{\|}{C}}-(C_1\text{-}C_6$ 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

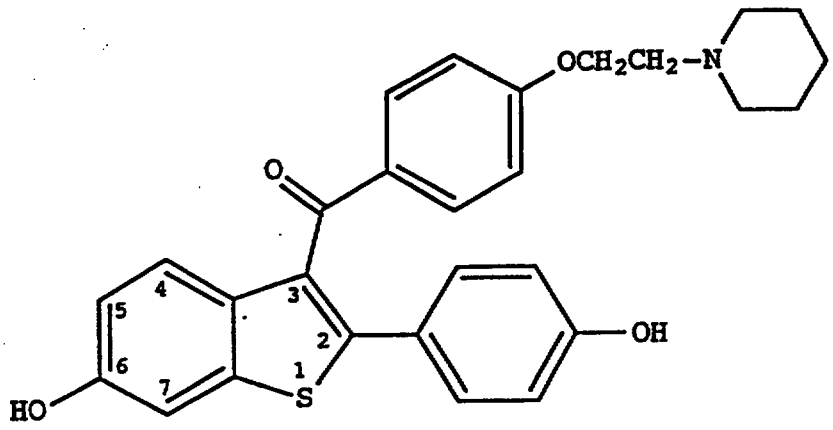
for inhibiting bone prosthesis degeneration in a human in need of such treatment.

2. The use of a compound as claimed in Claim 1 wherein said compound is the hydrochloride salt thereof.

3. The use of a compound as claimed in Claim 1 wherein said treatment is prophylactic.

REPLACEMENT SHEET
23 FEB

4. The use of a compound as claimed in Claim 1 wherein said compound is



or its hydrochloride salt.

SG 9700795-9 R7MP copy

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/38 — A1

(11) International Publication Number: WO 96/05824

(43) International Publication Date: 29 February 1996 (29.02.96)

(21) International Application Number: PCT/US95/10616

(22) International Filing Date: 21 August 1995 (21.08.95)

(30) Priority Data:
08/294,170 22 August 1994 (22.08.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/294,170 (CON)
Filed on 22 August 1994 (22.08.94)

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: CULLINAN, George, Joseph [US/US]; R.R. 1, Box 468, Trafalgar, IN 46181 (US).

(74) Agent: LAMMERT, Steven, R.; Barnes & Thornburg, 1313 Merchants Bank Building, 11 South Meridian Street, Indianapolis, IN 46204 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

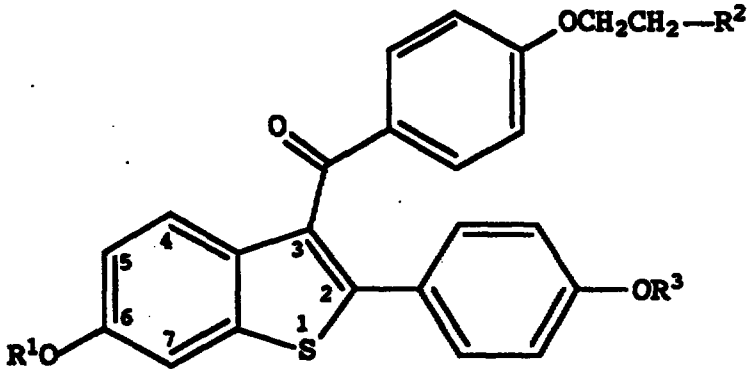
Published
With international search report.

① PCT Pub + SR
② IPER
③ Replacement 23-2-98

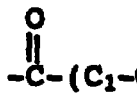
(54) Title: METHODS FOR INHIBITING BONE PROSTHESIS DEGENERATION

(57) Abstract

A method of inhibiting bone prosthesis degeneration comprising administering to a human in need thereof an effective amount of a compound having formula (I), wherein R^1 and R^3 are independently hydrogen, $-CH_3$, (a) or (b), 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.



(I)



(a)



(b)