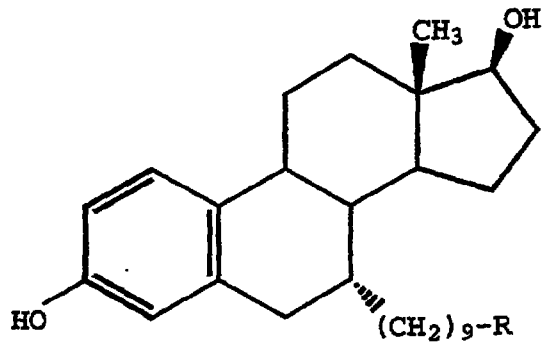
METHODS FOR MINIMIZING BONE LOSS

The present invention relates to the fields of pharmacology and pharmaceutical chemistry, and provides methods for minimizing the bone loss effect induced by the administration of certain pharmaceutical agents, and pharmaceutical compositions therefor.

Compounds of formula I



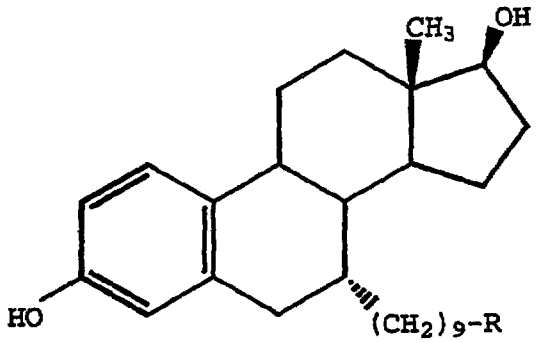
I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof are known in the art as ICI-164384 and ICI-182780, respectively (see, e.g., European Publication 138504; and U.S. Pat. No. 4,659,516). These steroidal compounds have been characterized as Type III antiestrogens by McDonald, D.P., et al., (Steroid Receptor and Anti-Hormones Symposia, New York Acad. Sci., Dallas, TX, Sept. 20-23, 1994), and have further been classified as "pure" antiestrogens which are devoid of agonist activity. As such, compounds of formula I bind to the estrogen receptor (ER) with high affinity, thus blocking the binding of estrogen and its metabolites. These compounds also appear to inhibit ER dimerization and facilitate cytoplasmic accumulation of ER leading to rapid degradation resulting in loss of immunodetectable protein. Accordingly, these compounds are understood to be promising therapeutic agents

for the treatment of inter alia, breast cancer [see, e.g., Howell, A., Lancet, 345:29-30 (1995)] endometriosis, uterine fibroids, and other estrogen-induced maladies.

Unfortunately, compounds of formula I are devoid of estrogen agonist activity and, thus, induce a state similar to that seen in postmenopausal women. More particularly, these compounds are capable of inducing bone loss such as seen with osteoporosis. The induction of a postmenopausal state and, particularly, the induction of bone loss, is one of the most limiting side-effects of these compounds when administered for estrogen-induced maladies in mammals. It, therefore, would be of great value to be able to take advantage of the distinct antiestrogenic activity of formula I compounds while minimizing the negative side effects associated with the use of the compounds via the sequential or concurrent administration of another pharmaceutical agent.

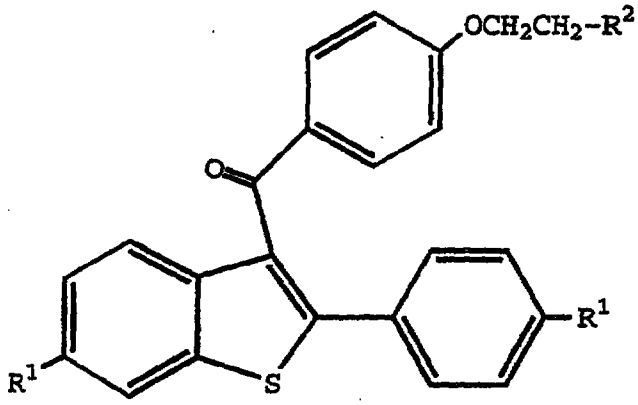
The present invention, therefore, provides a method of minimizing the bone loss effect of a compound of formula I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and wherein said formula I compound is administered to a mammal in need of treatment, comprising concurrently or sequentially

administering to said mammal an effective amount of a compound of formula II



II

wherein

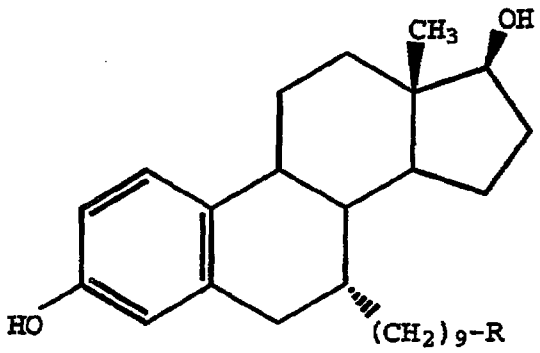
each R^1 is independently -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), or -OSO$_2$(C_4-C_6 alkyl); and

R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof.

Also provided by the present invention are methods for minimizing the bone loss of a compound of formula I via the coadministation (sequential or concurrent) of a bone anabolic agent, particularly parathyroid hormone (PTH) (1-84) or (1-34), with or without the coadministration of a formula II compound.

The present invention further provides pharmaceutical formulations comprising a formula I compound and a formula II compound, with or without a bone anabolic agent, and a formula I compound plus a bone anabolic agent, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

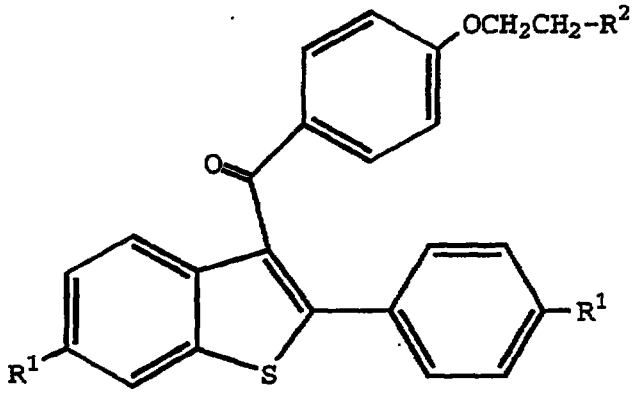
Compounds of formula I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CH_3$, or a pharmaceutically acceptable salt thereof, are well known in the art and are prepared as taught by Bowler, J., in U.S. Pat. No. 4,659,516, which is herein incorporated by reference. A preferred formula I compound is that in which R is $-SO(CH_2)_3CF_2CH_3$ (ICI-182780).

Similarly, compounds of formula II



II

wherein

each R^1 is independently -H, -OH, $-O(C_1-C_4$ alkyl), $-OCOC_6H_5$, $-OCO(C_1-C_6$ alkyl), or $-OSO_2(C_4-C_6$ alkyl); and

R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof, are well known in the art and can be prepared according to

established procedures, such as those detailed in U.S. Pat. Nos. 4,133,814; 4,418,068; and 4,380,635, each of which is incorporated by reference.

Compounds of formula II, particularly raloxifene, in which each R^1 is -OH and R^2 is 1-piperidinyl, has been classified by McDonald, supra, as a type II antiestrogen. Compounds of formula II also are recognized in the art as selective estrogen receptor modulators (SERMs), or tissue selective estrogen receptor agonists/antagonists. As such, the compounds of formula II are recognized as nuclear regulatory molecules. More particularly, raloxifene has been shown to bind to estrogen receptors and originally was demonstrated to have antiestrogenic activity because it blocked the ability of estrogen to activate uterine tissue and estrogen-dependent cancers. Indeed, raloxifene does block the action of estrogen in some cells but, in other cell types, it activates the same genes as estrogen activates and displays the same pharmacology. As a type II antiestrogen, SERM, raloxifene, and its analogs defined above as compounds of formula II, are tissue selective antiestrogens with mixed agonist-antagonist properties.

Although compounds of formulae I and II generally compete for and utilize the same receptors, the pharmacological outcome of administration of these distinct agents is not easily predicted, and is distinct to each.

Bone anabolic agents are those agents which are known in the art to build bone by increasing the production of bone matrix protein. Such anabolic agents include, for example, the various forms of parathyroid hormone (PTH) such as naturally occurring PTH (1-84), PTH (1-34), analogs thereof, and the like, which are prepared via well known procedures.

As used herein, "bone loss" means a reduction of bone mineral density of cancellous bone, which frequently is a side-effect of formula I compound administration to mammals, and the term "minimize", or a derivative thereof,

contemplates partial or complete inhibition and/or repair of a compound of formula I-induced bone loss.

The methods of the present invention can be tailored to counter the bone loss effect induced by the administration of a formula I compound. For example, when administration of a formula I compound is first initiated, particularly as an acute treatment, it is preferred to coadminister a compound of formula II, especially the hydrochloride salt of raloxifene, to counteract the potential bone loss. When administration of a formula I compound will be for the treatment of a chronic malady (e.g., endometriosis; cancer adjuvant following surgery), a formula II compound, preferably raloxifene hydrochloride, and an anabolic bone agent, particularly PTH (1-84) or PTH (1-34), may be coadministered at the time treatment with a formula I compound is initiated, and throughout the course of therapy. However, if a formula I compound is administered for a chronic malady without the coadministration of a formula II compound, a bone anabolic agent may be coadministered with, or following, multiple courses of therapy with a formula I compound. The particular method of the present invention which would optimize the minimization of bone loss induced by the administration of a formula I compound is, therefore, dictated by the duration of a formula I compound's course of therapy, and when administration of a compound of formula II, and/or a bone anabolic agent, is initiated relative to the commencement of therapy of a formula I compound. In essence, the attending physician is best suited to determine whether a formula II compound and/or a bone anabolic agent should be administered, and whether the administration of such agents should be concurrent or sequential to the administration of a formula I compound.

When administered sequentially, pharmaceutical formulations of compound of formulae I and II and bone anabolic agents are prepared by methods known by one of ordinary skill in the art.

When administered concurrently, formulae I and II compounds and bone anabolic agents may be prepared into pharmaceutical formulations via the above-mentioned known methods, and administered as separate entities. Alternatively, they may be combined to form a pharmaceutical composition of the present invention which comprises a compound of formula I, or a pharmaceutically acceptable salt thereof, a compound of formula II, or a pharmaceutically acceptable salt thereof, and, optionally, a bone anabolic agent, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

The present invention also provides pharmaceutical compositions comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a bone anabolic agent, in combination with a pharmaceutically acceptable carrier diluent, or excipient.

Preferred compounds of formulae I and II and bone anabolic agents for pharmaceutical compositions of the present invention are the same as those preferred for the methods of the present invention.

Pharmaceutical compositions of the present invention can be prepared in unit dosage form for parenteral, transdermal, rectal, nasal, intravenous, or oral administration via conventional and well known techniques. Such compositions comprise active ingredient of each desired combinant will be mixed with a carrier, diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semisolid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. Thus, the compositions of the present invention can be in the form of tablets, pills, powders, lozenges, sachets, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders. As used herein, the term "active ingredient" refers to the respective formula I compound, or a pharmaceutically acceptable salt

thereof, a formula II compound, or a pharmaceutically acceptable salt thereof, and a bone anabolic agent, used in a pharmaceutical composition of the present invention.

Additionally, pharmaceutical agents of the present compositions are well suited for formulation as sustained release dosage forms and the like. The compositions can be so constructed that they release active ingredient only or preferably in a particular physiological location, preferably over a long period of time. The coatings envelope and protective matrices may be made, for example from polymeric substances or waxes.

More particularly, pharmaceutical compositions of the present invention which sequentially release, for example, an effective amount of a compound of formula I, followed by the release of an effective amount of a compound of formula II, and/or a bone anabolic agent, may be constructed as an implant device. Such an implant device would consist of an outer, rapidly degradable polymer, such as a low molecular weight wax, impregnated with a compound of formula I. The inner cone of the implant would be made of a slowly degradable polymer, such as a high molecular weight wax, impregnated with a compound of formula II and/or a bone anabolic agent.

Also included within the scope of the present invention are pharmaceutical compositions for transdermal delivery of the pharmaceutical agents used in the methods herein described. The preparation of such compositions are well known to one of ordinary skill in the art.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate alginates, calcium salicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The compositions can additionally include lubricating agents, wetting agents, emulsifying and

suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide quick, sustained, or delayed release of the active ingredient(s) after administration to the patient by employing procedures well known in the art. For oral administration, a compound optionally including a second component compound, can be admixed with carriers and diluents molded into tablets or enclosed in gelatin capsules. The mixtures can alternatively be dissolved in liquids such as 10% aqueous glucose solution, isotonic saline, sterile water, or the like, and administered intravenously or by injection.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg and, more frequently, from about 5 to about 300 mg of the active ingredient(s). The term "unit dosage form" refers to physically discreet units suitable as unitary dosages for human subjects, each unit containing a predetermined quantity of active ingredients calculated to produce the desired therapeutic effect, in association with the required pharmaceutically acceptable carrier. By "pharmaceutically acceptable", it is meant the carrier, diluent, or excipient must be acceptable with the other ingredients of the formulation and not deleterious to the recipient thereof.

The following formulation and composition examples are only illustrative and are not intended to limit the scope of the present invention.

Formulations/Compositions

Formulation 1: Gelatin capsules
Hard gelatin capsules are prepared using the following:

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

Formulation 2: Raloxifene capsule

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

Formulation 3: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene HCl	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 4: Tablet

Ingredient	Quantity (mg/tablet)
Formula I compound	2.5 - 1000
Cellulose, microcrystalline	200 - 650
Silicon dioxide, fumed	10 - 650
Stearate acid	5 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 25 - 1000 mg of a formula I compound are made up as follows:

Formulation 5: Tablet

Ingredient	Quantity (mg/tablet)
Formula I compound	25 - 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 formula I compound, 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 25 - 1000 mg of medicament per 5 ml dose are made as follows:

Formulation 6: Suspension

Ingredient	Quantity (mg/5 ml)
Formula I compound	25 - 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 medicament 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.

Composition 1: Intravenous Solution

Ingredient	Quantity
Formula I compound	50 mg
Formula II compound	50 mg
Isotonic saline	1000 mL

Composition 2: Intravenous Solution

Ingredient	Quantity
Formula I compound	50 mg
PTH (1-84) or (1-34)	0.1-1000 mg
Isotonic saline	1000 mL

Formulation 3: Intravenous Solution

Ingredient	Quantity
Formula I compound	50 mg
Formula II compound	50 mg
PTH (1-84) or (1-34)	0.1-1000 mg
Isotonic saline	1000 mL

The particular dosage of a compound of formula II, particularly raloxifene, with or without the coadministration of a bone anabolic agent, particularly PTH (1-84) or (1-34), required to minimize the bone loss effect of a compound of formula I according to the present invention will depend upon the severity of the condition,

the route of administration, and related factors which will be decided by the attending physician.

Generally, accepted and effective daily doses of a formula II compound will be from about 0.1 mg to about 1000 mg/day, and more typically from about 50 mg to about 250 mg/day. Such dosages will be administered to a mammal in need of treatment from once to about three times each day, or more often as needed to effectively treat the present indication. It, usually, is preferred to administer a formula II compound in the form of an acid addition salt, especially, via the oral route.

Preferred dosages, routes of administration, and frequency of administration of formula I compounds and bone anabolic agents are well established and known to those of ordinary skill in the art.

Test Procedures

Bone Loss I

It is well established in the literature that the ovariectomized rat model is a reasonable model for studying bone loss, particularly osteopenia observed in estrogen-deficient states such as postmenopausal osteoporosis [see, e.g., Wronski, T.J., et al., Cells Mater. Supp, 1:69-74 (1991)]. In this model, compounds of formula I, particularly a formula I compound in which R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$, did not reduce bone loss when administered at a dose from 0.03 mg to 10 mg/kg P.O. Because the bone loss observed in this model is reflective of the bone loss induced by the administration of a formula I compound, administration of a formula II compound, with or without a bone anabolic agent, or coadministration of a bone anabolic agent without a compound of formula II, demonstrates the efficacy of the administered compounds for minimizing the bone loss induced by a formula I compound.

Bone Loss II

Compounds of formula I have been shown to induce bone loss in normal female rats [see, e.g., Gallagher, A., Endocrinology, 133(6):2787-2791 (1993)]. Under the conditions of this experiment, when bone loss is occurring, the coadministration of a formula II compound, with or without a bone anabolic agent, or a bone anabolic agent without a formula II compound, minimizes this bone loss.

Bone Loss III

Using the ovarectomized model described in Bone Loss I, an alternating schedule of administering a compound of formula I, followed by the administration of a compound of formula II, with or without a bone anabolic agent, or followed by the administration of a bone anabolic agent without a compound of formula II, demonstrates the ability of compounds of formula II and bone anabolic agents to minimize the bone loss induced by the administration of formula I compounds. In this model, rats treated only with a compound of formula I is used as a control. The duration of this study may run up to six months or beyond.

Bone Loss IV

In normal female rats, bone loss can be induced by a compound of formula I. A cyclic regimen of therapy of a compound of formula I, alternating with a compound of formula II, minimizes the loss of bone induced by a formula I compound when compared to a control group which has been continuously treated with a compound of formula II. Specifically, three groups of animals are chosen. The first group would be a no treatment control group. The second group would receive a S.C. dose of a formula I compound in an oily suspension every 21 days for six months. The third group would receive an alternating schedule of therapy consisting of a compound of formula I followed after 21 days with a daily dose of a formula II compound for 14 days. This protocol would be repeated for six months. At the end of the experiment, the bone mineral

density is determined by DEXA (Dual Energy X-ray Analysis), demonstrating the bone loss efficacy of the coadministered compound of formula II.

Bone Loss V

Twenty to fifty women with diagnosed estrogen-dependent breast cancer are selected for the study. These women may be pre- or post-menopausal, have a WHO performance status of less than two, and have a life expectancy of greater than one year. Further, these women may or may not have had previous surgical intervention and should not have been treated with tamoxifene or other anti-cancer chemotherapeutic agents.

These patients are initially evaluated for their cancer status by techniques known in the art, (see, e.g., Howell, A., supra, and references cited therein). In addition, the patients are evaluated for bone status by monitoring bone mineral density by DEXA, urinary calcium, creatinine, hydroxyproline, and pyridinoline crosslinks.

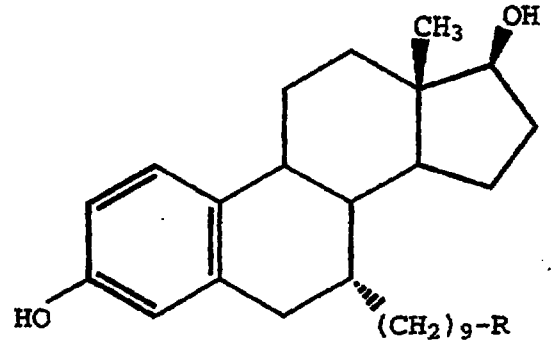
Patients are treated for cancer by monthly injection of an oily suspension of 100-250 mg of a formula I compound. During monthly visits to the attending physician, bone mineral density and the above bone markers are evaluated. Either immediately, or when bone loss reaches about 10% to 20% of the base line measurement, patients additionally receive 50-250 mg of raloxifene, P.O., for the remainder of the trial period. The duration of the present trial is one year.

This trial demonstrates the minimization of bone loss via administration of a formula I compound while not affecting the cancer efficacy of a formula I compound.

Alternatively, a bone anabolic agent, particularly PTH (1-84) or (1-34), can be administered in lieu of, or in addition to, the administration of a formula II compound.

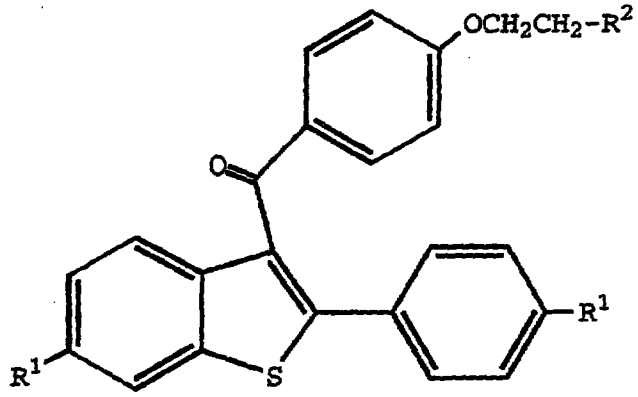
We claim:

1. A method for minimizing the bone loss effect of a compound of formula I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and wherein said formula I compound is administered to a mammal in need of treatment, comprising concurrently or sequentially administering to said mammal an effective amount of a compound of formula II



II

wherein

each R^1 is independently -H, -OH, $-O(C_1-C_4$ alkyl), $-OCOC_6H_5$, $-OCO(C_1-C_6$ alkyl), or $-OSO_2(C_4-C_6$ alkyl); and

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R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof.

2. A method according to Claim 1 wherein R of said formula I compound is $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutical acceptable salt thereof, each R^1 of said formula II compound is -OH, and R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof.

3. A method according to Claim 2 wherein said mammal in need of treatment of a compound of formula I is a human female.

4. A method according to Claim 3 wherein said female is suffering from breast cancer.

5. A method according to Claim 3 wherein said female is suffering from endometriosis or uterine fibroid disease.

6. A method according to Claim 1 wherein R of said formula I compound is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof, each R^1 of a formula II compound is -OH, and R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof.

7. A method according to Claim 6 wherein said mammal in need of treatment of a compound of formula I is a human female.

8. A method according to Claim 7 wherein said female is suffering from breast cancer.

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9. A method according to Claim 7 wherein said female is suffering from endometriosis or uterine fibroid disease.

10. A method for minimizing bone loss comprising the method of Claim 1 and further comprising administering to said mammal an effective amount of a bone anabolic agent.

11. A method according to Claim 10 wherein R of said formula I compound is $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, each R^1 of said formula II compound is -OH, R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

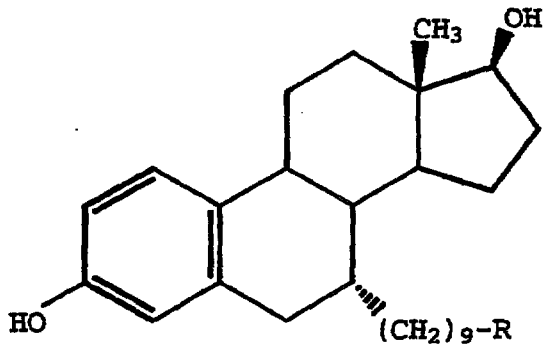
12. A method according to Claim 11 wherein said mammal in need of treatment of a compound of formula I is a human female.

13. A method according to Claim 12 wherein said female is suffering from breast cancer, endometriosis, or uterine fibroid disease.

14. A method according to Claim 10 wherein R of said formula I compound is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof, each R^1 of said formula II compound is -OH, R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

15. A method for minimizing the bone loss effect of a compound of formula I

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I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and wherein said formula I compound is administered to a mammal in need of treatment, comprising concurrently or sequentially administering to said mammal an effective amount of a bone anabolic agent.

16. A method according to Claim 15 wherein R of said formula I compound is $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

17. A method according to Claim 16 wherein said mammal in need of treatment of a compound of formula I is a human female.

18. A method according to Claim 17 wherein said female is suffering from breast cancer, endometriosis, or uterine fibroid disease.

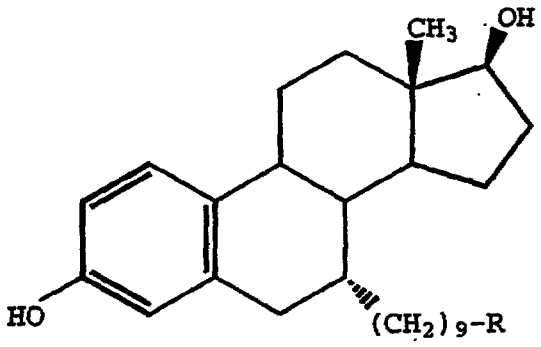
19. A method according to Claim 15 wherein R of said formula I compound is $-CH_2CON(CH_2)_3$-n-$CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

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20. A method according to Claim 19 wherein said mammal in need of treatment of a compound of formula I is a human female.

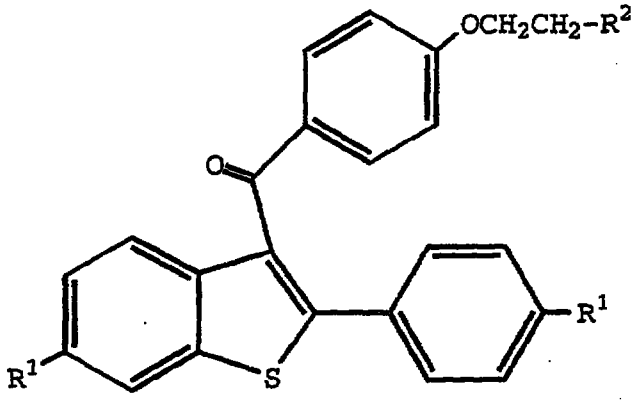
21. A method according to Claim 20 wherein said female is suffering from breast cancer, endometriosis, or uterine fibroid disease.

22. A pharmaceutical composition comprising a compound of formula I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, a compound of formula II



II

wherein

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each R^1 is independently -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), or -OSO$_2$(C_4-C_6 alkyl); and

R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof; and

optionally, a bone anabolic agent, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

23. A pharmaceutical composition according to Claim 22 wherein R of said formula I compound is -SO(CH$_2$)$_3$CF$_2$CF$_3$, or a pharmaceutically acceptable salt thereof, each R^1 of said formula II compound is -OH, and R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition according to Claim 23 wherein said optional bone anabolic agent is parathyroid hormone (1-84) or (1-34).

25. A pharmaceutical composition according to Claim 23 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

26. A pharmaceutical composition according to Claim 24 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

27. A pharmaceutical composition according to Claim 22 wherein R of said formula I compound is -CH$_2$CON(CH$_3$)-n-CH$_2$CH$_2$CH$_2$CH$_3$, or a pharmaceutically acceptable salt thereof, each R^1 of said formula II compound is -OH, and R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof.

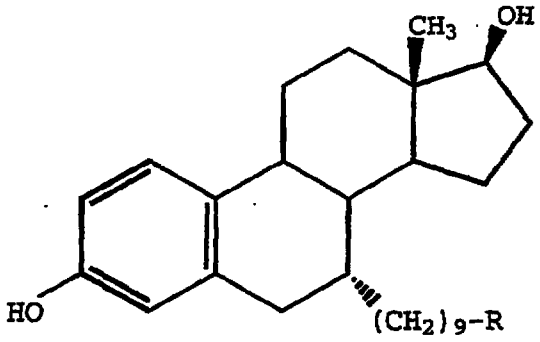
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28. A pharmaceutical composition according to Claim 27 wherein said optional bone anabolic agent is parathyroid hormone (1-84) or (1-34).

29. A pharmaceutical composition according to Claim 27 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

30. A pharmaceutical composition according to Claim 28 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

31. A pharmaceutical composition comprising a compound of formula I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and a bone anabolic agent, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

32. A pharmaceutical composition according to Claim 31 wherein R of said formula I compound is $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

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33. A pharmaceutical composition according to Claim 32 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

34. A pharmaceutical composition according to Claim 31 wherein R of said formula I compound is $-CH_2CON(CH_3)-n-CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

35. A pharmaceutical composition according to Claim 34 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

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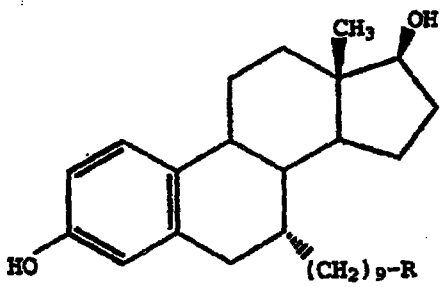
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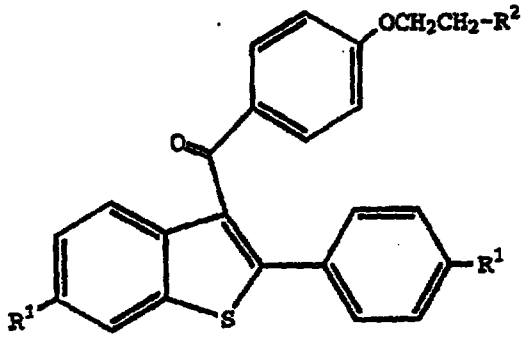
(54) Title: METHODS FOR MINIMIZING BONE LOSS

(57) Abstract

The present invention provides a method for minimizing the bone loss effect of a compound of formula (I) wherein R is $-CH_2CON(CH_3)$ $-n-CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and wherein said formula (I) compound is administered to a mammal in need of treatment, comprising concurrently or sequentially administering to said mammal an effective amount of a compound of formula (II) wherein each R^1 is independently -H, $-OH$, $-O(C_1-C_4$ alkyl), $-OCOC_6H_5$, $-OCO(C_1-C_6$ alkyl), or $-OSO_2(C_4-C_6$ alkyl); and R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof. Also provided is a method for minimizing bone loss induced by the administration of formula (I) compound comprising concurrently or sequentially administering a bone anabolic agent. Pharmaceutical compositions are also provided.



(I)



(II)

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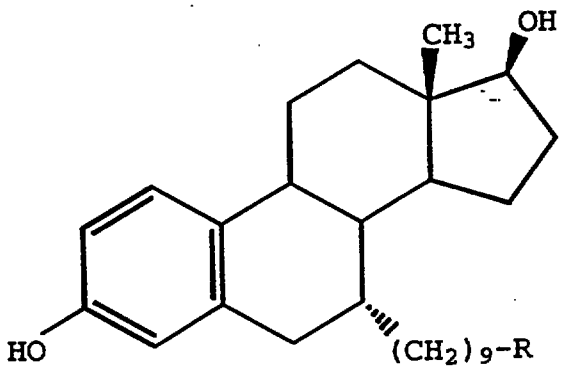
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WE CLAIM :

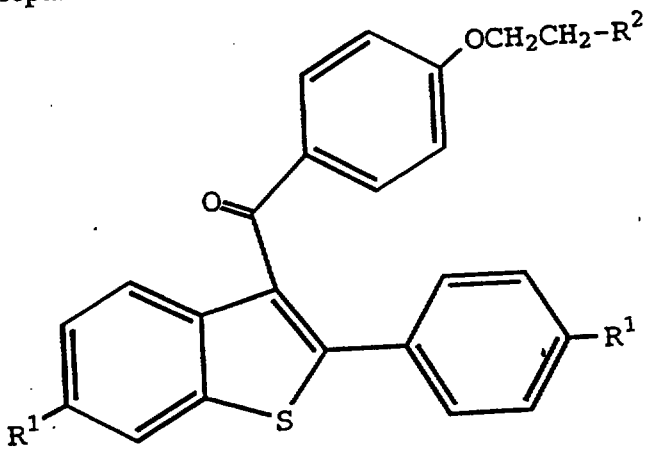
1. A pharmaceutical composition comprising a compound of formula

I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, a compound of formula II



II

wherein

each R^1 is independently -H, -OH, $-O(C_1$-C_4 alkyl), $-OCOC_6H_5$, $-OCO(C_1$-C_6 alkyl), or $-OSO_2(C_4$-C_6 alkyl); and

R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof; and

optionally, a bone anabolic agent, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

2. A pharmaceutical composition according to Claim 1 wherein R of said formula I compound is $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, each R^1 of said formula II compound is -OH, and R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition according to Claim 2 wherein said optional bone anabolic agent is parathyroid hormone (1-84) or (1-34).

4. A pharmaceutical composition according to Claim 2 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

5. A pharmaceutical composition according to Claim 3 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

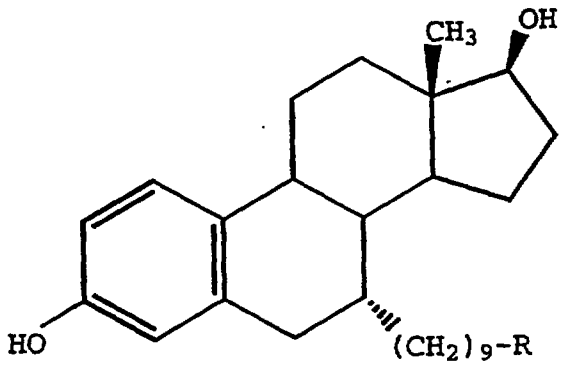
6. A pharmaceutical composition according to Claim 1 wherein R of said formula I compound is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof, each R^1 of said formula II compound is -OH, and R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition according to Claim 6 wherein said optional bone anabolic agent is parathyroid hormone (1-84) or (1-34).

8. A pharmaceutical composition according to Claim 6 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

9. A pharmaceutical composition according to Claim 7 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

10. A pharmaceutical composition comprising a compound of formula I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and a bone anabolic agent, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

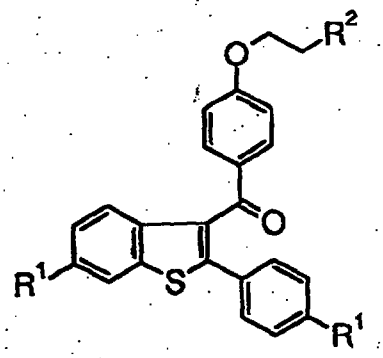
11. A pharmaceutical composition according to Claim 10 wherein R of said formula I compound is $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

12. A pharmaceutical composition according to Claim 11 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

13. A pharmaceutical composition according to Claim 10 wherein R of said formula I compound is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

14. A pharmaceutical composition according to Claim 13 wherein said composition is used for minimizing bone loss from administration of said formula I compound.

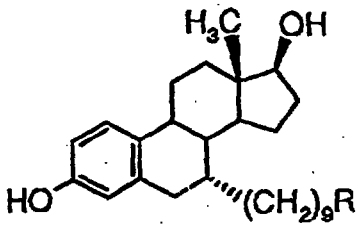
15. The use of a compound of formula II



wherein

R_1 is independently -H, -OH, -O(C_1-C_4 alkyl), $-OCOC_6H_5$, -OCO(C_1-C_6 alkyl), or $-OSO_2$(C_1-C_4 alkyl); and

R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-prrolidinyl, methyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof, for minimizing the bone loss effect of a compound of formula I



wherein

R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, by administering concurrently or sequentially an effective amount of a compound of formula II to a mammal being treated with a compound of formula I.

16. The use of Claim 15 wherein R of said formula I compound is $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, each R^1 of said formula II compound is -OH and R^2 of said formula II compound is 1-piperidinyl, or a pharmaceutically acceptable salt thereof.

17. The use of Claim 16 wherein said mammal in need of such treatment of a compound of formula I is a human female.

18. The use of Claim 17 wherein said female is suffering from breast cancer.

19. The use of Claim 17 wherein said female is suffering from endometriosis or uterine fibroid disease.

20. The use of Claim 15 wherein R of said formula I compound is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof,

* C L M S *

each R^1 of said formula II compound is -OH and R^2 of said formula II compound is 1-piperidinyl or a pharmaceutically acceptable salt thereof.

21. The use of Claim 20 wherein said mammal in need of such treatment is a human female.

22. The use of Claim 21 wherein said female is suffering from breast cancer.

23. The use of Claim 21 wherein said female is suffering from endometriosis or uterine fibroid disease.

24. The use of Claim 15 which further comprises administering to said mammal an effective amount of a bone anabolic agent.

25. The use of Claim 24 wherein R of said formula I compound is -$SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, each R^1 of said formula II compound is -OH, R^2 of said formula II compound is 1-piperidinyl or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

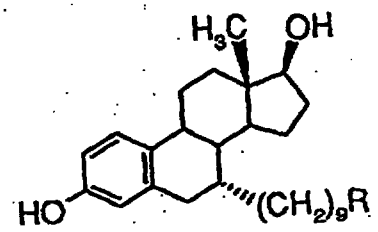
26. The use of Claim 25 wherein said mammal in need of such a treatment of a compound of formula I is a human female.

27. The use of Claim 26 wherein said female is suffering from breast cancer, endometriosis, or uterine fibroid disease.

28. The use of Claim 25 wherein R of said formula I compound is -$CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof,

each R^1 of said formula II compound is -OH, R^2 of said formula II compound is 1-piperidinyl or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

29. The use of a bone anabolic agent for minimizing the bone loss effect of a compound of formula I



wherein

R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$, or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, by administering concurrently or sequentially an effective amount of a bone anabolic agent to a mammal being treated with a compound of formula I.

30. The use of Claim 29 wherein R of said formula I compound is $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

31. The use of Claim 30 wherein said mammal in need of treatment of a compound of formula I is a human female.

32. A method according to Claim 31 wherein said female is suffering from breast cancer, endometriosis, or uterine fibroid disease.

33. A method according to Claim 29 wherein R of said formula I compound is $-CH_2CON(CH_2)_3$-n-$CH_2CH_2CH_2CH_3$, or a pharmaceutically acceptable salt thereof, and said bone anabolic agent is parathyroid hormone (1-84) or (1-34).

34. A method according to Claim 33 wherein said mammal in need of treatment of a compound of formula I is a human female.

35. A method according to Claim 34 wherein said female is suffering from breast cancer, endometriosis, or uterine fibroid disease.