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(51) Int.Cl.⁶ C07D 333/66, C07F 7/10, C07D 409/12, A61K 31/445,
A61K 31/40, A61K 31/535, A61K 31/55, A61K 31/38
(30) 1996/09/24 (60/026,556) US
(54) **COMPOSES DE BENZOTHIOPHENE, INTERMEDIAIRES,
PROCEDES, COMPOSITIONS ET METHODES**
(54) **BENZOTHIOPHENE COMPOUNDS, INTERMEDIATES,
PROCESSES, COMPOSITIONS, AND METHODS**

(57) L'invention porte sur des composés de benzothiophène, des formulations et des méthodes pour inhiber la perte osseuse ou la résorption osseuse, particulièrement l'ostéoporose, et les états pathologiques apparentés aux maladies cardio-vasculaires, dont l'hyperlipidémie, et d'autres affections cardio-vasculaires.

(57) The invention provides benzothiophene compounds, formulations, and methods of inhibiting bone loss or bone resorption, particularly osteoporosis, and cardiovascular-related pathological conditions, including hyperlipidemia, and other cardiovascular pathologies.

Abstract

The invention provides benzothiophene compounds,
formulations, and methods of inhibiting bone loss or bone
5 resorption, particularly osteoporosis, and cardiovascular-
related pathological conditions, including hyperlipidemia,
and other cardiovascular pathologies.

BENZOTHIOPHENE COMPOUNDS, INTERMEDIATES, PROCESSES,
COMPOSITIONS, AND METHODS

5 Osteoporosis describes a group of diseases which arises
from diverse etiologies, but which are characterized by the
net loss of bone mass per unit volume. The consequence of
this loss of bone mass and resulting bone fracture is the
10 failure of the skeleton to provide adequate support for the
body. One of the most common types of osteoporosis is
associated with menopause. Most women lose from about 20%
to about 60% of the bone mass in the trabecular compartment
of the bone within 3 to 6 years after the cessation of
15 menses. This rapid loss is generally associated with an
increase of bone resorption and formation. However, the
resorptive cycle is more dominant and the result is a net
loss of bone mass. Osteoporosis is a common and serious
disease among postmenopausal women.

 There are an estimated 25 million women in the United
20 States alone who are afflicted with this disease. The
results of osteoporosis are personally harmful, and also
account for a large economic loss due to its chronicity and
the need for extensive and long term support
(hospitalization and nursing home care) from the disease
25 sequelae. This is especially true in more elderly patients.
Additionally, although osteoporosis is generally not thought
of as a life threatening condition, a 20% to 30% mortality
rate is related to hip fractures in elderly women. A large
percentage of this mortality rate can be directly associated
30 with postmenopausal osteoporosis.

 The most vulnerable tissue in the bone to the effects
of postmenopausal osteoporosis is the trabecular bone. This
tissue is often referred to as spongy or cancellous bone and
is particularly concentrated near the ends of the bone (near
35 the joints) and in the vertebrae of the spine. The
trabecular tissue is characterized by small osteoid
structures which interconnect with each other, as well as

the more solid and dense cortical tissue which makes up the outer surface and central shaft of the bone. This interconnected network of trabeculae gives lateral support to the outer cortical structure and is critical to the biomechanical strength of the overall structure. In postmenopausal osteoporosis, it is primarily the net resorption and loss of the trabeculae which leads to the failure and fracture of bone. In light of the loss of the trabeculae in the postmenopausal woman, it is not surprising that the most common fractures are those associated with bones which are highly dependent on trabecular support, for example, the vertebrae, the neck of the weight-bearing bones such as the femur and the forearm. Indeed, hip fracture, collicles fractures, and vertebral crush fractures are hallmarks of postmenopausal osteoporosis.

The most generally accepted method for the treatment of postmenopausal osteoporosis is estrogen replacement therapy. Although therapy is generally successful, patient compliance with the therapy is low, primarily because estrogen treatment frequently produces undesirable side effects. An additional method of treatment would be the administration of a bisphosphonate compound, such as, for example, Fosamax[®] (Merck & Co., Inc.).

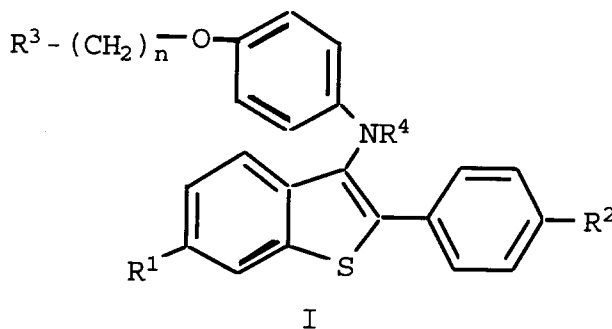
Throughout premenopausal time, most women have less incidence of cardiovascular disease than men of the same age. Following menopause, however, the rate of cardiovascular disease in women slowly increases to match the rate seen in men. This loss of protection has been linked to the loss of estrogen and, in particular, to the loss of estrogen's ability to regulate the levels of serum lipids. The nature of estrogen's ability to regulate serum lipids is not well understood, but evidence to date indicates that estrogen can up regulate the low density lipid (LDL) receptors in the liver to remove excess cholesterol. Additionally, estrogen appears to have some effect on the biosynthesis of cholesterol, and other beneficial effects on cardiovascular health.

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It has been reported in the literature that serum lipid levels in postmenopausal women having estrogen replacement therapy return to concentrations found in the premenopausal state. Thus, estrogen would appear to be a reasonable treatment for this condition. However, the side effects of estrogen replacement therapy are not acceptable to many women, thus limiting the use of this therapy. An ideal therapy for this condition would be an agent which regulates serum lipid levels in a manner analogous to estrogen, but which is devoid of the side effects and risks associated with estrogen therapy.

The instant invention provides benzo[b]thiophene compounds, pharmaceutical formulations thereof, and methods of using such compounds for inhibiting the above-mentioned pathologies.

The present invention relates to compounds of formula I



wherein:

R^1 is -H, -OH, -O(C₁-C₄ alkyl), -OCOAr, -O(CO)OAr, where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₂-C₆ alkyl);

R^2 is -H, -Cl, -F, -OH, -O(C₁-C₄ alkyl), -OCOAr, -O(CO)OAr, where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₂-C₆ alkyl);

R^3 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, or 1-hexamethyleneimino;

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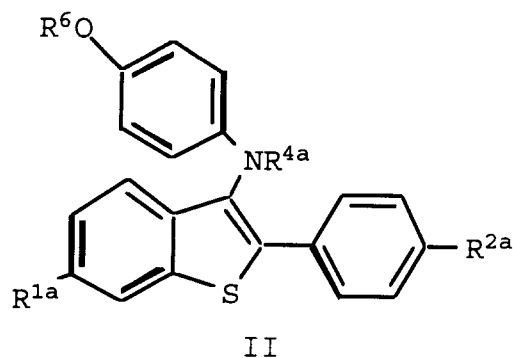
R^4 is -H, C₁-C₅ alkyl, -COAr, -(CO)H, -CO(C₁-C₆ alkyl), -SO₂(C₂-C₆ alkyl), or -SO₂Ar, where Ar is phenyl or substituted phenyl; and

n is 2 or 3;

5 or a pharmaceutically acceptable salt or solvate thereof.

Also provided by the present invention are intermediate compounds of formula II which are useful for preparing the pharmaceutically active compounds of the present invention, and are shown below:

10



wherein:

15 R^{1a} is -H or -OR⁷ in which R⁷ is a hydroxy protecting group;

R^{2a} is -H, -Cl, -F, or -OR⁷ in which R⁷ is a hydroxy protecting group;

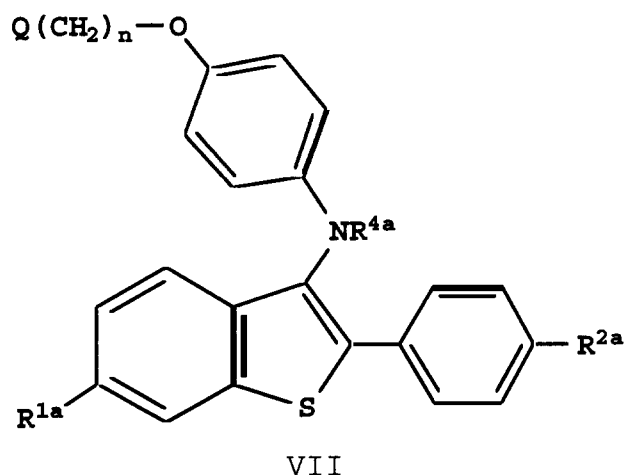
R^{4a} is -CO(C₁-C₄ alkyl) or -(CO)H; and

20 R^6 is -H or R⁸, wherein R⁸ is a hydroxy protecting group which can be selectively removed in the presence of -OR⁷.

Further, the present invention provides compounds of formula VII, which are useful for the synthesis of the compounds of formula I:

25

-5-



wherein: R^{1a}, R^{2a}, R^{4a}, and n have their previous meanings
5 and Q is a leaving group.

The present invention further relates to pharmaceutical
formulations containing compounds of formula I, and the use
of such compounds for alleviating the symptoms of bone loss
or bone resorption, particularly osteoporosis,
10 cardiovascular-related pathological conditions, and the
like.

General terms used in the description of compounds
herein described bear their usual meanings. For example,
"C₁-C₆ alkyl" refers to straight or branched aliphatic
15 chains of 1 to 6 carbon atoms including methyl, ethyl,
propyl, isopropyl, butyl, n-butyl, pentyl, isopentyl, hexyl,
isohexyl, and the like. Similarly, the term "-OC₁-C₄ alkyl"
represents a C₁-C₄ alkyl group attached through an oxygen
such as, for example, methoxy, ethoxy, n-propoxy,
20 isopropoxy, and the like. Of these C₁-C₄ alkoxy groups,
methoxy is highly preferred.

The term "substituted phenyl" refers to a phenyl group
having one or more substituents selected from the group
consisting of C₁-C₄ alkyl, -OC₁-C₄ alkyl, hydroxy, nitro,
25 chloro, fluoro, or tri(chloro or fluoro)methyl.

The term "hydroxy protecting group" contemplates
numerous functionalities used in the literature to protect a
hydroxyl function during a chemical sequence and which can

be removed to yield the phenol. Included within this group would be acyls, mesylates, tosylates, benzyl, alkylsilyloxy, C₁-C₄ alkyls, and the like. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, *Protective Groups in Organic Chemistry*, Plenum Press (London and New York, 1973); Green, T.W., *Protective Groups in Organic Synthesis*, Wiley, (New York, 1981); and *The Peptides*, Vol. I, Schroeder and Lubke, Academic Press (London and New York, 1965). Methods for removing preferred R⁷ hydroxy protecting groups, particularly methyl and alkylsilyloxy, are essentially as described in the Examples, *infra*.

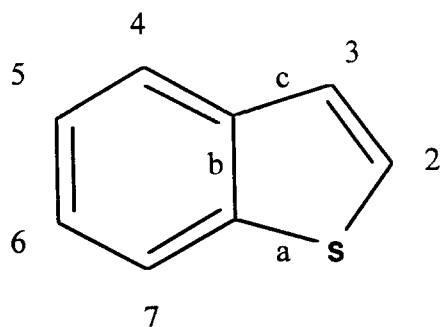
The term "leaving group (Q)" means a chemical entity which is capable of being displaced by an amino function via an SN₂ reaction. Such reactions are well known in the art and such groups would include halogens, mesylates, tosylates, and the like. A preferred leaving group would be bromo.

The term "inhibit" includes its generally accepted meaning which includes prohibiting, preventing, restraining, and slowing, stopping, or reversing progression, severity, or ameliorating a resultant symptom or effect.

The term "solvate" represents an aggregate that comprises one or more molecules of the solute, such as a formula I compound, with one or more molecules of solvent.

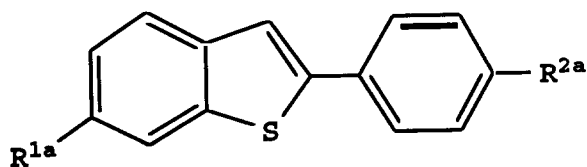
The compounds of this invention are derivatives of centrally located carbon, for example, the "-CO-", "-CHOH-", or "-CH₂-" moiety in formula I are therefore derivatives of methanones, methanols, or methanes. For example, a compound of A-CO-B, would be named [A][B]methanone. Further, the compounds of formula I are derivatives of benzo[b]thiophene which is named and numbered according to the Ring Index, The American Chemical Society, as follows:

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Preferred compounds of the present invention are
 2-(4-hydroxyphenyl)-3-[N-[4-[2-(1-
 5 piperidinyl)ethoxy]phenyl]amino]-6-hydroxybenzo[b]thiophene
 hydrochloride and 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-
 piperidinyl)ethoxy]phenyl]amino]-6-methoxybenzo[b]thiophene
 di-hydrochloride.

Several synthetic pathways are available for preparing
 10 the compounds of the instant invention. The first synthetic
 route is illustrated in Scheme I, below. The starting
 material for one route for preparing compounds of formula I
 of the present invention, compounds of formula III, are
 prepared essentially as described by Jones *et al.* in U.S.
 15 Pat. Nos. 4,418,068, and 4,133,814, the disclosures of which
 are herein incorporated by reference. Formula III has the
 following structure:



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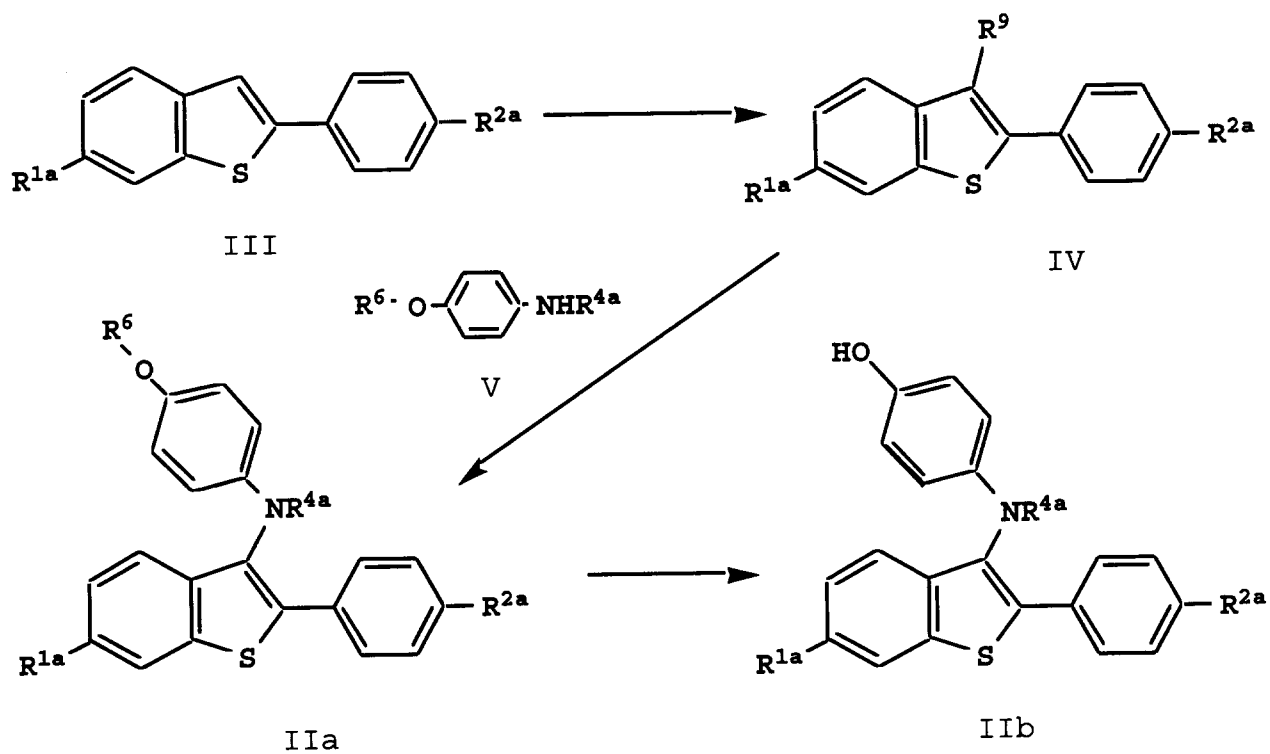
III

wherein R^{1a} and R^{2a} are as defined above.

For compounds of formula III, a preferred R⁷
 substituent is methyl or methoxymethyl. Compounds in which
 25 R^{1a} and R^{2a} each are methoxy, as well as other derivatives,
 are prepared via the procedure described in Jones *et al.*,
supra.

The first steps of the present process for preparing certain compounds of formula I include selectively placing a leaving group at the 3 position of a formula III compound, coupling the reaction product of the first step with a 4-(protected-hydroxy)phenylacylamide (formula V), and removing the hydroxy protecting group to generate a phenol of compound IIb. The process is depicted in Scheme I below.

Scheme I



10

15

20

In the first step of Scheme I, an appropriate leaving group is selectively placed at the 3-position of the formula III starting material via standard procedures. Appropriate R^9 leaving groups include sulfonates such as methanesulfonate, 4-bromobenzenesulfonate, toluenesulfonate, ethanesulfonate, isopropanesulfonate, 4-methoxybenzenesulfonate, 4-nitrobenzenesulfonate, 2-chlorobenzenesulfonate, triflate, and the like, halogens such as bromo, chloro, and iodo, and other related leaving groups. However, to insure proper placement of the leaving

group, the named halogens are preferred, and bromo is especially preferred.

The present reaction is carried out using standard procedures. For example, when the preferred halogenating agents are used, an equivalent of such a halogenating agent, preferably bromine, is reacted with an equivalent of the formula III substrate, in the presence of a suitable solvent such as, chloroform or acetic acid. The reaction is run at a temperature from about 40° C to about 80° C and is usually complete in one to six hours.

The reaction product from the above process step, a compound of formula IV, is then reacted with a 4-(protected-hydroxy)phenylalkylamide (formula V), for example, in which R^{4a} is -(CO)H or -CO(C₁-C₄ alkyl), to form compounds of formula II in which R⁸ is a selectively-removable hydroxy protecting group. Generally, the 4-hydroxy protecting moiety of the phenol may be any known protecting group which can be selectively removed without removing the R⁷, when present, moiety of a formula II compound. A preferred R⁸ protecting group is benzyl. The 4-(protected-hydroxy)phenylalkylamides are known compounds and can be prepared via standard procedures. For example, a preferred reagent, for example, 4-benzyloxyphenyl acetamide, may be synthesized from commercially available 4-benzyloxyaniline and acetic anhydride by methods known in the art.

This coupling reaction of IV and V is known in the art as an Ullman-type reaction, and various standard procedures are listed. [See, for example, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Fourth Edition, 3-16, (J. March, ed., John Wiley & Sons, Inc. 1992); Jones, C.D., *J. Chem. Soc. Perk. Trans. I*, 4 :407 (1992)].

Although several variations of the standard Ullman-type reactions were attempted, for example, reacting an aniline or an anilinosulfamide with aryl bromide in the presence of a copper catalyst, only a variant known as a Goldberg reaction was successful. Details of this reaction are given below.

In general, equivalent amounts of the two aryl substrates, in the presence of up to an equimolar amount of a copper(I) oxide catalyst and an appropriate solvent, are heated to reflux under an inert atmosphere. Examples of a suitable catalytic copper (I) salt would include but not be limited to Cu_2O , CuI , and Cu_2CO_3 . Preferably, an equivalent of a formula IV compound in which R^9 is bromo is reacted with an equivalent amount of 4-benzyloxyphenylacetamide in the presence of an equivalent of cuprous oxide.

Appropriate solvents for this reaction are those solvents or mixture of solvents which remain inert throughout the reaction. Typically, organic bases, particularly a hindered base such as, for example, 2,4,6-collidine, are preferred solvents.

The temperature employed in this step should be sufficient to effect completion of this coupling reaction, and will influence the amount of time required therefor. When the reaction mixture is heated to reflux under an inert atmosphere such as nitrogen. The reaction is usually complete in twenty to one hundred-twenty hours.

Following the coupling reaction, which forms a formula IIa compound, formula IIb compounds are prepared, via well known reduction procedures, by selectively removing the R^6 hydroxy protecting group. It is imperative that the selected procedure will not affect, when present, the R^7 hydroxy protecting group.

When R^8 is the preferred benzyl moiety, and R^7 , when present, is methyl, the present process step is carried out via standard hydrogenolysis procedures. Typically, the formula IIa substrate is added to a suitable solvent or mixture of solvents, followed by the addition of a proton donor to accelerate the reaction and an appropriate hydrogenation catalyst.

Appropriate catalysts include noble metals and oxides such as palladium, platinum, and rhodium oxide on a support such as carbon or calcium carbonate. Of these, palladium-

on-carbon, particularly 10% palladium-on-carbon, is preferred.

5 Solvents for this reaction are those solvents or mixture of solvents which remain inert throughout the reaction. Typically, ethylacetate and C₁-C₄ aliphatic alcohols, particularly ethanol, is preferred.

For the present reaction, hydrochloric acid serves as an adequate and preferred proton donor.

10 When run at ambient temperature and at a hydrogen pressure ranging from about 30 psi to about 50 psi, the present reaction runs quite rapidly. Progress of this reaction may be monitored by standard chromatographic techniques such as thin layer chromatography.

15 Compounds of formula IIa and IIb are encompassed within the genus described herein as formula II compounds, and are useful for preparing the pharmaceutically active compounds of formula I.

Examples of the compounds of formula II include, but are not limited to:

20 2-(4-methoxyphenyl)-3-[N-(4-hydroxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene

2-phenyl-3-[N-(4-hydroxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene

25 2-(4-fluorophenyl)-3-[N-(4-hydroxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene

2-(4-chlorophenyl)-3-[N-(4-hydroxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene

2-(4-methoxyphenyl)-3-[N-(4-benzyloxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene

30 2-phenyl-3-[N-(4-benzyloxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene

2-(4-methoxyphenyl)-3-[N-(4-hydroxyphenyl)propanoylamido]-6-methoxy-benzo[b]thiophene

35 2-(4-methoxyphenyl)-3-[N-(4-benzyloxyphenyl)butanoylamido]-6-methoxy-benzo[b]thiophene

2-(4-chlorophenyl)-3-[N-(4-benzyloxyphenyl)acetamido]benzo[b]thiophene

2-(4-methoxyphenyl)-3-[N-(4-hydroxyphenyl)acetamido]benzo[b]thiophene

2-(4-methoxyphenyl)-3-[N-(4-benzyloxyphenyl)acetamido]benzo[b]thiophene

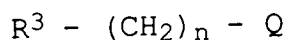
5 2-(4-methoxyphenyl)-3-[N-(4-benzyloxyphenyl)formylamido]benzo[b]thiophene

2-(4-fluorophenyl)-3-[N-(4-benzyloxyphenyl)propanoylamido]benzo[b]thiophene, and the like.

10 The compounds of formula IIb may be converted into the compounds of formula Ia by one of two different synthetic routes, which are illustrated in Scheme II, below.

The first method is the direct conversion of IIb to Ia by using a reagent of formula VI:

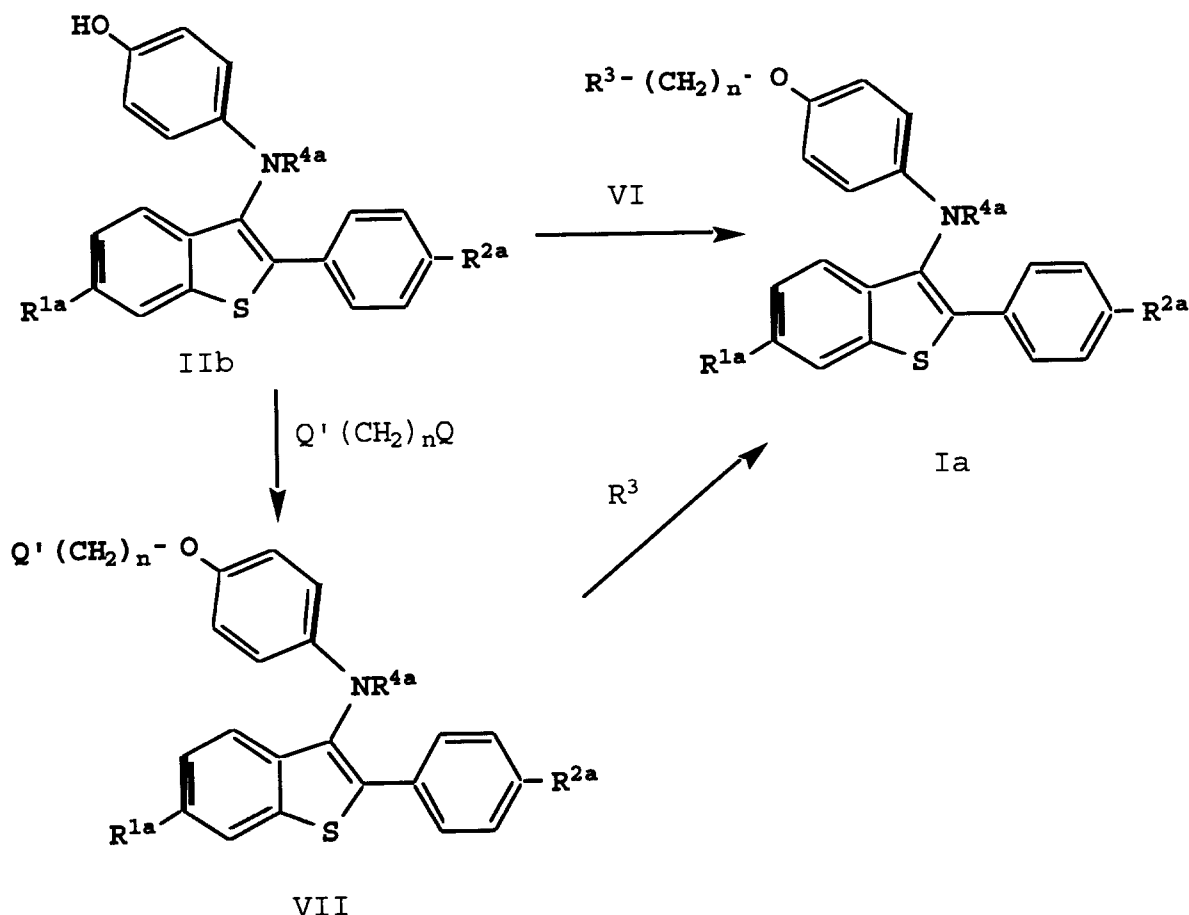
15



VI

20 wherein R^3 and n are as defined above, and Q is a leaving group, such as a bromo or chloro moiety.

Scheme II



5 The direct alkylation process, shown in Scheme II, is carried out via standard procedures. Compounds of formula VI are commercially available or are prepared by means well known to one of ordinary skill in the art. Preferably, the hydrochloride salt of a formula VI compound, particularly

10 preferred is 2-chloroethylpiperidine hydrochloride.

 Generally, at least about 1 equivalent of formula IIb substrate are reacted with 2 equivalents of a formula VI compound in the presence of at least about 4 equivalents of an alkali metal carbonate, preferably cesium carbonate, and

15 an appropriate solvent.

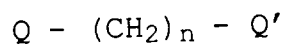
 Solvents for this reaction are those solvents or mixtures of solvents which remain inert throughout the reaction. N,N-dimethylformamide, especially the anhydrous form thereof, is preferred.

The temperature employed in this step should be sufficient to effect completion of this alkylation reaction. Typically, ambient temperature is sufficient and preferred.

The present reaction preferably is run under an inert atmosphere, particularly nitrogen.

Under the preferred reaction conditions, this reaction will run to completion in about 16 to about 20 hours. Of course, the progress of the reaction can be monitored via standard chromatographic techniques.

The second method for preparing compounds of formula Ia from a formula IIb compound is to proceed through an intermediate compound (formula VII) in a two-step sequence (see Scheme II, *supra*). A compound of formula IIb is reacted with an excess of an alkylating agent of the formula



wherein Q and Q' each are the same or different leaving groups, in an alkali solution. Appropriate leaving groups can be, for example, chloro, bromo, mesylates, tosylates and the like. A preferred alkali solution for this alkylation reaction contains potassium carbonate in an inert solvent such as, for example, methylethyl ketone (MEK) or DMF. In this solution, the 4-hydroxy group of the phenyl moiety of a formula IIb compound exists as a phenoxide ion which displaces one of the leaving groups of the alkylating agent.

This reaction proceeds rapidly when the alkali solution containing the reactants and reagents is brought to reflux and allowed to run to completion. When using MEK as the preferred solvent, reaction times run from about 6 hours to about 20 hours.

The compounds of formula VII are useful in the synthesis of the compounds of formula I. Compounds of formula VII would include, but are not limited to:

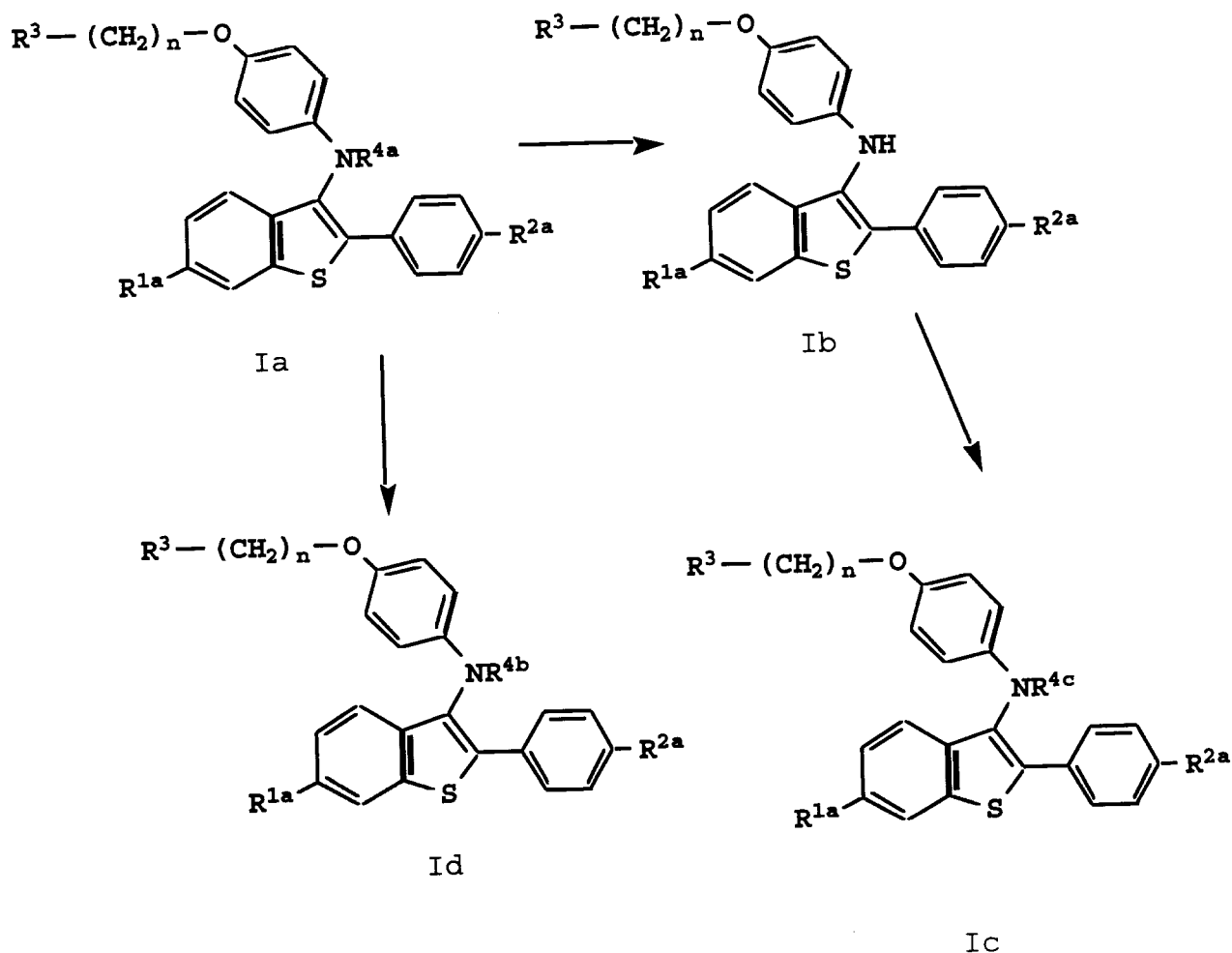
2-(4-methoxyphenyl)-3-[N-[4-(2-bromoethoxy)phenyl]acetylamido]-6-methoxybenzo[b]thiophene

2-phenyl-3-[N-[4-(2-bromoethoxy)phenyl]acetylamido]-6-methoxybenzo[b]thiophene
2-(4-methoxyphenyl)-3-[N-[4-(2-bromoethoxy)phenyl]acetylamido]benzo[b]thiophene
5 2-(4-methoxyphenyl)-3-[N-[4-(3-bromopropoxy)phenyl]acetylamido]-6-methoxybenzo[b]thiophene
2-(4-methoxyphenyl)-3-[N-[4-(2-chloroethoxy)phenyl]acetylamido]-6-methoxybenzo[b]thiophene
2-(4-methoxyphenyl)-3-[N-[4-(2-tosylethoxy)phenyl]acetylamido]-6-methoxybenzo[b]thiophene
10 2-(4-methoxyphenyl)-3-[N-[4-(2-bromoethoxy)phenyl]butanoylamido]-6-methoxybenzo[b]thiophene
2-(4-methoxyphenyl)-3-[N-[4-(2-bromoethoxy)phenyl]formylamido]-6-methoxybenzo[b]thiophene,
15 and the like.

The reaction product (formula VII) from this step is then reacted with an amine (R^3), for example, 1-piperidine, 1-pyrrolidine, methyl-1-pyrrolidine, dimethyl-1-pyrrolidine, 4-morpholine, dimethylamine, diethylamine, diisopropylamine,
20 or 1-hexamethyleneimine, via standard techniques, to form compounds of formula Ia. Preferably, the hydrochloride salt of piperidine is reacted with a compound of formula VII in an inert solvent, such as anhydrous DMF, and heated to a temperature in the range from about 60° C to about 110° C.
25 When the mixture is heated to a preferred temperature of about 90° C, the reaction only takes about 30 minutes to about 1 hour. However, changes in the reaction conditions will influence the amount of time this reaction needs to be run for completion. Of course, the progress of this
30 reaction step may be monitored via standard chromatographic techniques.

Conversion of the compounds of formula Ia to other compounds of formula I is shown in Scheme III and may involve: the removal of the N-acyl group to form the di-
35 aryl amino series (Ib), removal and re-introduction to form another acyl or a sulfonyl series (Ic), or the reduction of the N-acyl to a N-alkyl series (Id).

Scheme III



5

Removal of the N-acyl group from a compound of formula Ia can readily be accomplished by either acid or base hydrolysis to form a compound of Ib, where R^{1a}, R^{2a}, R³, and n have their previous meanings. The preferred method involves heating a formula Ia compound in a solution of alcohol and concentrated alkoxide. Typically, EtOH is used as the organic solvent and 50% NaOH solution is used as the source of base. The substrate is dissolved in an equal mixture of the alcohol and base and heated to the reflux temperature of the combined solvent. The reaction usually requires between 6 and 24 h for completion.

15

Compounds of formula Ib are pharmaceutically active for the methods herein described. Accordingly, such compounds

are encompassed by the definition herein of compounds of formula I.

5 Additionally, compounds of formula Ib may serve as substrates for preparing compounds of formula Ic where R^{1a}, R^{2a}, R³, and n have their previous meanings and R^{4c} is -
CO(C₁-C₆ alkyl), -(CO)H, -C₆H₅, -SO₂C₆H₅, or -SO₂(C₂-C₆alkyl). To form these compounds, the nitrogen is either acylated or sulfonated. This can readily be accomplished by a variety of acylation and alkylation methods that are well
10 known in the art. For further methods on such acylations and sulfonations, the discussion on derivatization of the phenols (see below) is applicable.

The compounds of formula Ia may also be converted to the compounds of formula Id, where R^{1a}, R^{2a}, R³, and n have their previous meanings and R^{4b} is C₁-C₅ alkyl. This
15 transformation may be achieved by the reduction of the amide carbonyl in Ia to its corresponding methylene with a reducing reagent such as LAH. These reductions are known in the art and are usually carried out in inert solvents such as anhydrous THF, ether, and the like. These reactions are
20 run with an excess of the reducing reagent and at temperatures of -50 to 30° C under a nitrogen atmosphere. Reactions are normally complete within two to twenty-four hours, standard techniques such as tlc may be used to
25 monitor the extent of the reaction.

The compounds of formula Ia, Ib, Ic, and Id are pharmacologically active for the methods herein described, and are encompassed in formula I as defined herein. Additionally, compounds of formula Ia-d may serve as
30 substrates for other compounds of formula I, such as, for example, compounds where R^{1a} and R^{2a} are converted to R¹ and R², respectively.

Preferred compounds of formula I are obtained by cleaving the R⁷ hydroxy protecting group, when present, of
35 formulae Ia-d compounds via well known procedures. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works

including, for example, *Protective Groups in Organic Chemistry*, Plenum Press (London and New York, 1973); Green, T.W., *Protective Groups in Organic Synthesis*, Wiley, (New York, 1981); and *The Peptides*, Vol. I, Schrooder and Lubke, Academic Press (London and New York, 1965). Methods for removing the preferred R⁷ hydroxy protecting group, methyl, is essentially as described in the Examples, *infra*

Other preferred compounds of formula I are prepared by converting 6- and/or 4'-position hydroxy moieties, when present, to a moiety of the formula -O-CO-(C₁-C₆ alkyl), -OCOC₆H₅, -O(CO)O(C₁-C₆ alkyl) or -O-SO₂-(C₂-C₆ alkyl) via well known procedures. Such methods are described in US Pat. Nos. 5,393,763 and 5,482,949 the disclosures of which are herein incorporated by reference.

For example, when an -O-CO(C₁-C₆ alkyl) group is desired, a mono- or dihydroxy compound of formula Ia-d is reacted with an agent such as acyl chloride, bromide, cyanide, or azide, or with an appropriate anhydride or mixed anhydride. The reactions are conveniently carried out in a basic solvent such as pyridine, lutidine, quinoline or isoquinoline, or in a tertiary amine solvent such as triethylamine, tributylamine, methylpiperidine, and the like. The reaction also may be carried out in an inert solvent such as ethyl acetate, dimethylformamide, dimethylsulfoxide, dioxane, dimethoxyethane, acetonitrile, acetone, methyl ethyl ketone, and the like, to which at least one equivalent of an acid scavenger (except as noted below), such as a tertiary amine, has been added. If desired, acylation catalysts such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine may be used. See, for example, Haslam, *et al.*, *Tetrahedron*, 36: 2409-2433 (1980).

The present reactions are carried out at moderate temperatures, in the range from about -25° C to about 100° C, frequently under an inert atmosphere such as nitrogen gas. However, ambient temperature is usually adequate for the reaction to run.

Side-reactions of acylating the bis-aryl nitrogen (formula Ib compounds) may be reduced by not using excess amounts of acylating reagent and using lower temperatures. Undesired isomers may be removed by chromatography on silica gel eluted with mixtures of solvents, such as, MeOH-CHCl₃ (1:99) (v/v) or EtOAc-hexane mixtures.

Acylation of a 6-position and/or 4'-position hydroxy group also may be performed by acid-catalyzed reactions of the appropriate carboxylic acids in inert organic solvents. Acid catalysts such as sulfuric acid, polyphosphoric acid, methanesulfonic acid, and the like are used.

The aforementioned R¹ and/or R² groups of formula Ia-d compounds also may be provided by forming an active ester of the appropriate acid, such as the esters formed by such known reagents such as dicyclohexylcarbodiimide, acylimidazoles, nitrophenols, pentachlorophenol, N-hydroxysuccinimide, and 1-hydroxybenzotriazole. See, for example, *Bull. Chem. Soc. Japan*, 38:1979 (1965), and *Chem. Ber.*, 788 and 2024 (1970).

Each of the above techniques which provide -O-CO-(C₁-C₆ alkyl) moieties are carried out in solvents as discussed above. Those techniques which do not produce an acid product in the course of the reaction, of course, do not call for the use of an acid scavenger in the reaction mixture.

When a formula Ia-d compound is desired in which the 6- and/or 4'-position hydroxy group of a formula I compound is converted to a group of the formula -O-SO₂-(C₂-C₆ alkyl), the mono- or dihydroxy compound is reacted with, for example, a sulfonic anhydride or a derivative of the appropriate sulfonic acid such as a sulfonyl chloride, bromide, or sulfonyl ammonium salt, as taught by King and Monoir, *J. Am. Chem. Soc.*, 97 :2566-2567 (1975). The dihydroxy compound also can be reacted with the appropriate sulfonic anhydride or mixed sulfonic anhydrides. Such reactions are carried out under conditions such as were

explained above in the discussion of reaction with acid halides and the like.

The compounds of formula Ia-d, their phenolic hydroxyl compounds, and their corresponding derivatized phenols, combined, constitute the compounds of formula I of the current invention.

Examples of the compounds of formula I include, but are not limited to:

- 10 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-methoxybenzo[b]thiophene
- 2-(4-hydroxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-hydroxybenzo[b]thiophene
- 15 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-hydroxybenzo[b]thiophene
- 2-(4-hydroxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]amino]-6-methoxybenzo[b]thiophene
- 20 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]-N-ethylamino]-6-methoxybenzo[b]thiophene
- 2-(4-Methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]propanoylamido]-6-methoxybenzo[b]thiophene
- 25 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-methoxybenzo[b]thiophene
- 2-(4-methoxyphenyl)-3-[N-[4-[3-(1-piperidinyl)propoxy]phenyl]acetamido]benzo[b]thiophene
- 30 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-methoxybenzo[b]thiophene
- 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]amino]-6-methoxybenzo[b]thiophene
- 35

2-(4-chlorophenyl)-3-[N-[4-[3-(1-hexamethylene)propoxy]phenyl]butanoylimido]-6-methoxybenzo[b]thiophene

2-phenyl-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]-N-methylamino]benzo[b]thiophene

2-(4-chlorophenyl)-3-[N-[4-[3-(1-pyrrolidinyl)propoxy]phenyl]-N-butylamino]-6-hydroxybenzo[b]thiophene

2-(4-acetyloxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-methoxybenzo[b]thiophene

2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-n-butylsulfonyloxybenzo[b]thiophene

2-phenyl-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-benzoyloxybenzo[b]thiophene

2-(4-benzoyloxyphenyl)-3-[N-[4-[3-(1-piperidinyl)propoxy]phenyl]acetamido]-6-methoxybenzo[b]thiophene

2-(4-benzoyloxyphenyl)-3-[N-[4-[3-(1-hexamethyleneimino)propoxy]phenyl]-N-2-butylamino]-6-methoxybenzo[b]thiophene

2-[4-(4-methoxybenzoyloxy)phenyl]-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]-N-methylamino]-6-methoxybenzo[b]thiophene, and the like.

Although the free-base form of formula I compounds can be used in the methods of the instant invention, it is preferred to prepare and use a pharmaceutically acceptable salt form. The term "pharmaceutically acceptable salt" refers to either acid or base addition salts which are known to be non-toxic and are commonly used in the pharmaceutical literature. 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. The compounds used in the methods of this invention primarily form pharmaceutically acceptable acid addition salts with a

wide variety of organic and inorganic acids, and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention.

5 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 alkanolic acids, hydroxyalkanoic
10 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,
15 methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caproate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycolate, heptanoate,
20 hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate,
25 bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, *p*-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, *p*-toluenesulfonate,
30 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
35 equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or ethyl acetate. 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. The instant invention further provides for pharmaceutically acceptable formulations for administering to a mammal, including humans, in need of treatment, which comprises an effective amount of a compound of formula I and a pharmaceutically acceptable diluent or carrier.

As used herein, the term "effective amount" means an amount of compound of the instant invention which is capable of inhibiting, alleviating, ameliorating, treating, or preventing further symptoms in mammals, including humans, suffering from bone loss or bone resorption, particularly osteoporosis, and cardiovascular-related pathological conditions including hyperlipidemia, and other cardiovascular pathologies.

In the case of estrogen-dependent cancers, the term "effective amount" means the amount of compound of the instant invention which is capable of alleviating, ameliorating, inhibiting cancer growth, treating, or preventing the cancer and/or its symptoms in mammals, including humans.

By "pharmaceutically acceptable formulation" it is meant that the carrier, diluent, excipients and salt must be compatible with the active ingredient (a compound of formula I) of the formulation, and not be deleterious to the recipient thereof. Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds of this invention can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, 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 agar agar, 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 polyethylene glycols. Final pharmaceutical forms may be: pills, tablets, powders, lozenges, syrups, aerosols, saches, cachets, elixirs, suspensions, emulsions, ointments, suppositories, sterile injectable solutions, or sterile packaged powders, and the like, depending on the type of excipient used.

Additionally, the compounds of this invention are well suited to formulation as sustained release dosage forms. The formulations can also 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. Such formulations would involve coatings, envelopes, or protective matrices which may be made from polymeric substances or waxes.

The particular dosage of a compound of formula I required to treat, inhibit, or prevent the symptoms and/or disease of a mammal, including humans, suffering from the above maladies according to this invention will depend upon the particular disease, symptoms, and severity. Dosage, routes of administration, and frequency of dosing is best decided by the attending physician. Generally, accepted and effective doses will be from 15mg to 1000mg, and more typically from 15mg to 80mg, from one to three times per day. Such dosages will be administered to a patient in need thereof, for at least one month, and typically for six months, or chronically.

The formulations which follow are given for purposes of illustration and are not intended to be limiting in any way. The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. The term "active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules

	Ingredient	Quantity (mg/capsule)
	Active Ingredient	0.1-1000
5	Starch NF	0-500
	Starch flowable powder	0-500
	Silicone fluid 350 centistokes	0-15

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

Formulation 2: Tablets

	Ingredient	Quantity (mg/tablet)
	Active Ingredient	2.5-1000
15	Starch	10-50
	Cellulose, microcrystalline	10-20
	Polyvinylpyrrolidone (as 10% solution in water)	5
	Sodium carboxymethylcellulose	5
20	Magnesium stearate	1
	Talc	1-5

25 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 thus produced are dried at 50-60 °C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethylcellulose, magnesium stearate, and talc,
30 previously passed through a No. 60 mesh U.S. sieve, are added to the above granules and thoroughly mixed. The resultant material is compressed in a tablet forming machine to yield the tablets.

Formulation 3: Aerosol

Ingredient	Weight %
Active Ingredient	0.25
5 Ethanol	29.75
Propellant 22	70.00
(Chlorodifluoromethane)	
Total	100.00

10 The active ingredient is mixed with ethanol and the
mixture added to a portion of the propellant 22, cooled to -
30 °C and transferred to a filling device. The required
amount is then fed to a stainless steel container and
diluted with the remainder of the propellant. The valve
15 units are then fitted to the container.

Formulation 4: Suppositories

Ingredient	Weight
Active ingredient	150 mg
20 Saturated fatty acid	
	glycerides 3000mg

The active ingredient is passed through a No. 60 mesh
U.S. sieve and suspended in the fatty acid glycerides which
25 had previously heated to their melting point. The mixture
is poured into a suppository mold and allowed to cool.

Formulation 5: Suspension

30 Suspensions each containing 0.1-1000 mg of a compound
of formula I per 5 mL dose.

Ingredient	Weight
Active Ingredient	0.1-1000 mg
35 Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL

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Benzoic acid solution (0.1M)	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to total	Total 5 mL

5

A compound of formula I 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 diluted in water are added and mixture stirred thoroughly. Additional water is added to bring the formulation to final volume.

10

The following Examples and Preparations are provided to better elucidate the practice of the instant invention and should not be interpreted in any way as to limit the scope of same. Those skilled in the art will recognize that various modifications may be made while not departing from the spirit and scope of the invention. All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains.

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NMR data for the following Examples were generated on a GE 300 MHz NMR instrument, and anhydrous CDCl_3 was used as the solvent unless otherwise indicated. Field strength for ^{13}C NMR spectra was 75.5 MHz, unless otherwise indicated.

25

Preparation 1

2-(4-Methoxyphenyl)-3-bromo-6-methoxybenzo[b]thiophene

To a solution of 2-(4-methoxyphenyl)-6-methoxybenzo[b]thiophene (27.0 g, 100 mmol) in 1.10 L of chloroform at 60° C was added bromine (15.98 g, 100 mmol) dropwise dissolved in 200 mL of chloroform. After the addition was complete, the reaction was cooled to room temperature, and the solvent removed *in vacuo* to provide 34.2 g (100%) of 2-(4-methoxyphenyl)-3-bromo-6-methoxybenzo[b]thiophene as a white solid. mp 83-85° C. ^1H NMR ($\text{DMSO}-d_6$) δ 7.70-7.62 (m, 4H), 7.17 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 2H). FD mass spec: 349, 350. Anal.

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Calcd. for C₁₆H₁₃BrO₂S: C, 55.03; H, 3.75. Found: C, 54.79; H, 3.76.

Preparation 2

5 2-(4-Methoxyphenyl)-3-[N-(4-benzyloxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene

To a solution of 2-(4-methoxyphenyl)-3-bromo-6-methoxybenzo[b]thiophene (34.20 g, 0.098 mol) and N-4-benzyloxyphenylacetamide (23.7 g, 0.098 mol) in 100 mL of 2,4,6-collidine under N₂ was added Cu₂O (14.0 g, 0.098 mol).
10 The resulting mixture was heated to reflux for 72 h. Upon cooling, the reaction was diluted with CH₂Cl₂ and the precipitated solids were removed by filtration. The filtrate was concentrated *in vacuo*, and the residue dissolved in EtOAc.
15 The organic was then extracted several times with 5.0 N HCl. The organic was dried (Na₂SO₄) and concentrated *in vacuo* to a solid. Chromatography (SiO₂, CHCl₃) provided 2.43 g (5%) of 2-(4-methoxyphenyl)-3-[N-(4-benzyloxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene as an amber foam. ¹H NMR (DMSO-*d*₆)
20 d (doubling due to amide rotamers) 7.70-6.80 (m, 16H), 4.90 (bs, 2H), 3.78-3.75 (m, 6H), 2.11 and 1.78 (s, 3H). FD mass spec: 509.

Preparation 3

25 2-(4-Methoxyphenyl)-3-[N-(4-hydroxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene

2-(4-Methoxyphenyl)-3-[N-(4-benzyloxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene (2.43 g, 4.77 mmol) was dissolved in 50 mL of 1:1 EtOH/EtOAc containing 5% con. HCl. To this
30 solution was added 1.0 g of 5% Pd/C. The resulting mixture was hydrogenated at 40 psi for 4 h. The mixture was then filtered through Celite to remove the catalyst. The filtrate was concentrated *in vacuo* to a semi-solid. Chromatography (SiO₂, CHCl₃) provided 1.32 g (83%) of 2-(4-methoxyphenyl)-3-
35 [N-(4-hydroxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene as an amber foam. ¹H NMR (DMSO-*d*₆) d (doubling due to amide

rotamers) 9.53 and 9.36 (s, 1H), 7.62-6.51 (m, 11 H), 3.78 and 3.58 (s, 6H), 2.01 and 1.76 (s, 3H). FD mass spec: 419. Anal. Calcd. for C₂₄H₂₁NO₄S•0.19 CHCl₃: C, 65.71; H, 4.83; N, 3.17. Found: C, 65.80; H, 4.70; N, 3.01.

5

Example 1

2-(4-Methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-methoxybenzo[b]thiophene

10

To a solution of 2-(4-methoxyphenyl)-3-[N-(4-hydroxyphenyl)acetamido]-6-methoxy-benzo[b]thiophene (1.31 g, 3.13 mmol) and Cs₂CO₃ (4.10 g, 12.50 mmol) in 15 mL of anhydrous DMF was added 2-chlorethylpiperidine hydrochloride (1.15 g, 6.26 mmol). The resulting mixture was stirred vigorously at room temperature for 5 h. The reaction mixture was diluted with 200 mL of H₂O, and then extracted several times with EtOAc. The combined organic was then washed with H₂O several times and then dried (Na₂SO₄), Concentration in vacuo provided an oil. Chromatography (1% CH₃OH/CHCl₃, SiO₂) provided 1.49 g (90%) of 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-methoxybenzo[b]thiophene as an amber oil. ¹H NMR (DMSO-*d*₆) δ (doubling due to amide rotamers) 7.66-6.70 (m, 11 H), 3.93 (m, 2H) 3.78 and 3.58 (s, 6H), 2.8-2.30 (m, 6H), 2.01 and 1.78 (s, 3H), 1.52-1.11 (m, 6H). FD mass spec: 530. Anal. Calcd. for C₃₁H₃₄N₂O₄S: C, 70.16; H, 6.46; N, 5.28. Found: C, 70.33; H, 6.34; N, 5.35.

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Example 2

2-(4-Methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]amino]-6-methoxybenzo[b]thiophene
Di-Hydrochloride

To a solution of 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]acetamido]-6-methoxybenzo[b]thiophene 1.49 g, 2.80 mmol) in 10 mL of absolute EtOH was added 10 mL of 50% NaOH solution. The

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resulting mixture was heated to reflux for 18 h. Upon cooling, the mixture was diluted with 200 mL of H₂O. The aqueous was then extracted with EtOAc (3 x 100 mL). The organic was combined, washed with brine, then dried (Na₂SO₄).

5 Concentration *in vacuo* provided a foam that was chromatographed (CHCl₃, SiO₂). The isolated oil was converted to the hydrochloride salt by treatment with Et₂O•HCl in EtOAc. Isolation by filtration provided 1.37 g (100%) of 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]amino]-6-methoxybenzo[b]thiophene hydrochloride as a white solid. mp 10 126-130 °C. ¹H NMR (DMSO-*d*₆) δ 7.54 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.91 (dd, J = 8.9, 2.2 Hz, 1H), 6.73 (d, J = 8.9 Hz, 2H), 6.50 (d, J = 8.9 Hz, 2H), 4.21 (t, J = 4.7 Hz, 2H), 15 3.78 (s, 3H), 3.71 (s, 3H), 3.43-3.31 (m, 4H), 2.97-2.90 (m, 2H), 1.80-1.61 (m, 5H), 1.35 (m, 1H). FD mass spec: 488. Anal. Calcd. for C₂₉H₃₄N₂O₃S•2.0 HCl: C, 62.03; H, 6.10; N, 4.99. Found: C, 61.79; H, 6.35; N, 5.27.

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Example 3

2-(4-Hydroxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]amino]-6-hydroxybenzo[b]thiophene Hydrochloride

To a solution of 2-(4-methoxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]amino]-6-methoxybenzo[b]thiophene hydrochloride (0.70 g, 1.25 mmol) in 40 mL of anhydrous CH₂Cl₂ under N₂ 10 °C was added BBr₃ (0.36 mL, 3.80 mmol). The solution was allowed to gradually warm to room temperature and stirred for a total of 6 h. The reaction was quenched by 30 pouring the mixture into an excess of sat. NaHCO₃ solution. The aqueous was then extracted several times with 5% EtOH/EtOAc. The organic was combined and dried (Na₂SO₄) and then concentrated *in vacuo* to a foam. The crude product was chromatographed (1-6% CH₃OH/CHCl₃) to provide 325 mg (49%) of 35 2-(4-hydroxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]amino]-6-hydroxybenzo[b]thiophene as an oil. This material was converted to the hydrochloride salt.

by treatment with Et₂O•HCl in EtOAc, and isolated as a white solid by filtration. Data for 2-(4-Hydroxyphenyl)-3-[N-[4-[2-(1-piperidinyl)ethoxy]phenyl]amino]-6-hydroxybenzo[b]thiophene Hydrochloride: mp 140-150 °C. ¹H NMR (DMSO-*d*₆) δ 9.57 (s, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 10.1 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 6.75 (dd, J = 10.1, 2.0 Hz, 1H), 6.70 (d, J = 8.6 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 6.46 (d, J = 8.8 Hz, 2H), 4.21 (m, 2H), 3.50-3.30 (m, 4H), 3.01-2.95 (m, 2H), 1.81-1.63 (m, 5H), 1.38 (m, 1H). FD mass spec: 461. *Anal.* Calcd. for C₂₇H₂₈N₂O₃S•1.5 HCl: C, 62.94; H, 5.77; N, 5.44. Found: C, 62.99; H, 5.88; N, 5.27.

In the examples illustrating the methods, a postmenopausal model was used in which effects of different treatments upon circulating lipids were determined.

Seventy-five day old female Sprague Dawley rats (weight range of 200 to 225g) were obtained from Charles River Laboratories (Portage, MI). The animals were either bilaterally ovariectomized (OVX) or exposed to a Sham surgical procedure at Charles River Laboratories, and then shipped after one week. Upon arrival, they were housed in metal hanging cages in groups of 3 or 4 per cage and had *ad libitum* access to food (calcium content approximately 0.5%) and water for one week. Room temperature was maintained at 22.2° ± 1.7° C with a minimum relative humidity of 40%. The photoperiod in the room was 12 hours light and 12 hours dark.

Dosing Regimen Tissue Collection. After a one week acclimation period (therefore, two weeks post-OVX) daily dosing with test compound was initiated. 17α-ethynyl estradiol or the test compound were given orally, unless otherwise stated, as a suspension in 1% carboxymethylcellulose or dissolved in 20% cyclodextrin. Animals were dosed daily for 4 days. Following the dosing regimen, animals were weighed and anesthetized with a ketamine: Xylazine (2:1, V:V) mixture and a blood sample was collected by cardiac puncture. The animals were then

sacrificed by asphyxiation with CO₂, the uterus was removed through a midline incision, and a wet uterine weight was determined.

5 Cholesterol Analysis. Blood samples were allowed to clot at room temperature for 2 hours, and serum was obtained following centrifugation for 10 minutes at 3000 rpm. Serum cholesterol was determined using a Boehringer Mannheim Diagnostics high performance cholesterol assay. Briefly the cholesterol was oxidized to cholest-4-en-3-one and hydrogen
10 peroxide. The hydrogen peroxide was then reacted with phenol and 4-aminophenazone in the presence of peroxidase to produce a p-quinone imine dye, which was read spectrophotometrically at 500 nm. Cholesterol concentration was then calculated against a standard curve. The entire
15 assay was automated using a Biomek Automated Workstation. Uterine Eosinophil Peroxidase (EPO) Assay. Uteri were kept at 4° C until time of enzymatic analysis. The uteri were then homogenized in 50 volumes of 50 mM Tris buffer (pH -
20 8.0) containing 0.005% Triton X-100. Upon addition of 0.01% hydrogen peroxide and 10 mM O-phenylenediamine (final concentrations) in Tris buffer, increase in absorbance was monitored for one minute at 450 nm. The presence of
eosonophils in the uterus is an indication of estrogenic activity of a compound. The maximal velocity of a 15 second
25 interval was determined over the initial, linear portion of the reaction curve.

Source of Compound: 17 α -ethynyl estradiol was obtained from Sigma Chemical Co., St. Louis, MO.

30 Influence of Formula I Compounds on Serum Cholesterol and Determination of Agonist/Non-Agonist Activity

Data presented in Table 1 below show comparative results among ovariectomized rats, rats treated with 17 α -ethynyl estradiol (EE₂; an orally available form of
35 estrogen), and rats treated with certain compounds of the instant invention. Although EE₂ caused a decrease in serum

cholesterol when orally administered at 0.1 mg/kg/day, it also exerted a stimulatory action on the uterus so that EE₂ uterine weight was substantially greater than the uterine weight of ovariectomized test animals. This uterine response to estrogen is well recognized in the art.

Not only did the compounds of the instant invention generally reduce serum cholesterol compared to the ovariectomized control animals, but uterine weight was only minimally increased to slightly decreased with the majority of the formula compounds tested. Compared to estrogenic compounds known in the art, the benefit of serum cholesterol reduction without adversely affecting uterine weight is quite rare and desirable.

As is expressed in the data below, estrogenicity also was assessed by evaluating the adverse response of eosinophil infiltration into the uterus. The compounds of the instant invention did not cause any increase in the number of eosinophils observed in the stromal layer of ovariectomized rats, while estradiol cause a substantial, expected increase in eosinophil infiltration.

The data presented in Table 1 below reflects the response of 5 to 6 rats per treatment.

Table 1

Compound No.	Dose mg/kg ^a	Uterine Weight % Inc ^b	Uterine Eosinophil (Vmax) ^c	Serum Cholest. % Dec. ^d
EE2 ^e	0.1	124.4*	85.5*	78.1*
Example 2	0.1	55.4*	10.2	42.8*
	1.0	89.5*	12.9	46.4*
	10.	86.3*	6.6	66.8*
Example 3	0.1	45.2*	1.2	63.0*
	1.0	39.4*	4.5	51.7*
	10.0	35.0*	4.8	64.9*

^a mg/kg PO

- b Uterine Weight % increase versus the ovariectomized controls
 - c Eosinophil peroxidase Vmax
 - d Serum cholesterol decrease versus ovariectomized controls
 - e 17-a-Ethynyl-estradiol
- * p<.05

In addition to the demonstrated benefits of the compounds of the instant invention, the above data clearly demonstrate that compounds of Formula I are not estrogen mimetics. Furthermore, no deleterious toxicological effects (for example, survival numbers) were observed with any treatment.

Osteoporosis Test Procedure

Following the General Preparation Procedure, *infra*, the rats are treated daily for 35 days (6 rats per treatment group) and sacrificed by carbon dioxide asphyxiation on the 36th day. The 35 day time period is sufficient to allow maximal reduction in bone density, measured as described herein. At the time of sacrifice, the uteri are removed, dissected free of extraneous tissue, and the fluid contents were expelled before determination of wet weight in order to confirm estrogen deficiency associated with complete ovariectomy. Uterine weight is routinely reduced about 75% in response to ovariectomy. The uteri are then placed in 10% neutral buffered formalin to allow for subsequent histological analysis.

The right femurs are excised and digitized x-rays generated and analyzed by an image analysis program (NIH image) at the distal metaphysis. The proximal aspect of the tibiae from these animals are also scanned by quantitative computed tomography.

In accordance with the above procedures, compounds of the instant invention and ethynyl estradiol (EE₂) in 20% hydroxypropyl b-cyclodextrin are orally administered to test animals. Distal femur metaphysis and proximal tibiae data

results are reported as percent protection relative to ovariectomy.

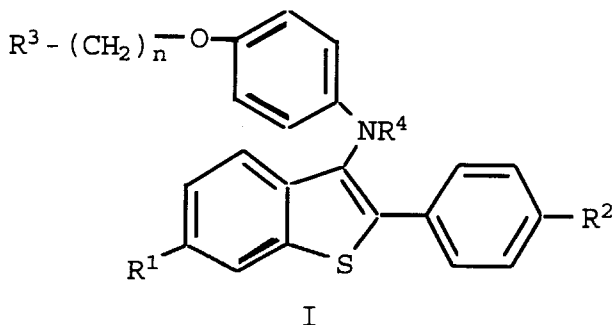
5 In summary, ovariectomy of the test animals caused a significant reduction in femur density compared to intact, vehicle treated controls. Orally administered ethynyl estradiol (EE₂) prevents this loss, but the risk of uterine stimulation with this treatment is ever-present.

10 The compounds of the instant invention also prevent bone loss in a general, dose-dependent manner. Accordingly, the compounds of the instant invention are useful for the treatment of osteoporosis, particularly caused by postmenopausal syndrome.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of formula I

5 formula I



wherein:

10 R^1 is -H, -OH, -O(C₁-C₄ alkyl), -COAr, -O(CO)OAr, where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₂-C₆ alkyl);

15 R^2 is -H, -Cl, -F, -OH, -O(C₁-C₄ alkyl), -COAr, -O(CO)OAr, where Ar is phenyl or substituted phenyl, -OCO(C₁-C₆ alkyl), -O(CO)O(C₁-C₆ alkyl), or -OSO₂(C₂-C₆ alkyl);

20 R^3 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, or 1-hexamethyleneimino;

R^4 is -H, C₁-C₅ alkyl, -COAr, -(CO)H, -CO(C₁-C₆ alkyl), -SO₂(C₂-C₆ alkyl), or -SO₂Ar, where Ar is phenyl or substituted phenyl; and

25 n is 2 or 3;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to Claim 1 wherein n is

2.

3. A compound according to Claim 1 wherein R³ is 1-piperidinyl.

4. A pharmaceutical composition comprising a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, and optionally an effective amount of estrogen or progestin, in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

5. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of post-menopausal syndrome.

6. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of the post-menopausal syndrome pathological condition of osteoporosis.

7. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of the post-menopausal syndrome pathological condition related to a cardiovascular disease.

8. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of a cardiovascular disease related to hyperlipidemia.

9. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of the post-menopausal syndrome pathological condition of estrogen-dependent cancer.

10. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of breast or uterine cancer.

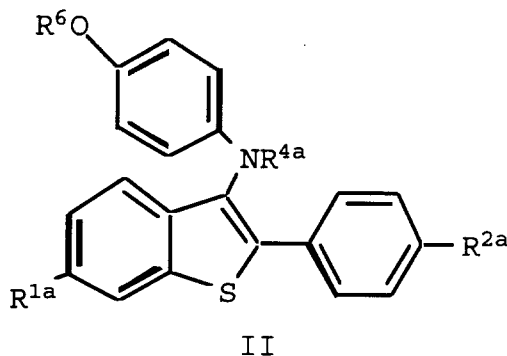
11. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of uterine fibroid disease.

5 12. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of endometriosis.

10 13. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of aortal smooth muscle cell proliferation.

15 14. A compound of formula I as claimed in any of Claims 1-3 for use in alleviating the symptoms of restenosis.

15. A compound of formula II



20 wherein

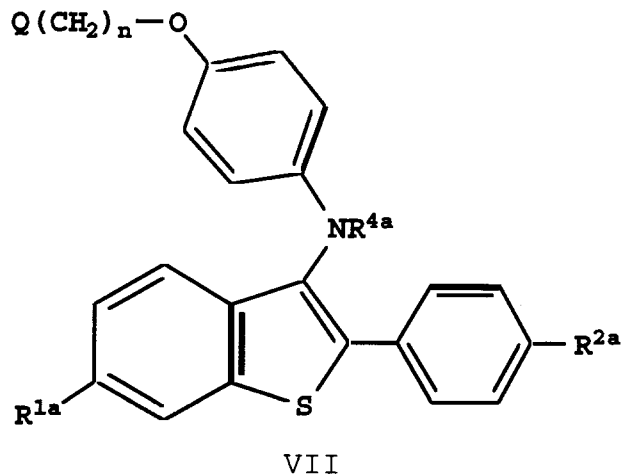
R^{1a} is -H or $-OR^7$ in which R^7 is a hydroxy protecting group;

25 R^{2a} is -H, -Cl, -F, or $-OR^7$ in which R^7 is a hydroxy protecting group;

R^{4a} is $-CO(C_1-C_4 \text{ alkyl})$ or $-(CO)H$; and

R^6 is -H or R^8 , wherein R^8 is a hydroxy protecting group which can be selectively removed if in the presence of $-OR^7$.

16. A compound of formula VII:



5 wherein

R^{1a} is $-H$ or $-OR^7$ in which R^7 is a hydroxy protecting group;

R^{2a} is $-H$, $-Cl$, $-F$, or $-OR^7$ in which R^7 is a hydroxy protecting group;

10 R^{4a} is $-CO(C_1-C_4 \text{ alkyl})$ or $-(CO)H$;

n is 2 or 3; and

Q is a leaving group.

15