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(54) **GLYCOPROTEIN IIb/IIIa ANTAGONISTS**

GLYCOPROTEIN IIB/IIIA-ANTAGONISTEN

ANTAGONISTES DE LA GLYCOPROTEINE IIb/IIIa

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(73) Proprietor: **ELI LILLY AND COMPANY**
Indianapolis, Indiana 46285 (US)

(72) Inventors:
- **FISHER, Matthew, Joseph**
  Carmel, IN 46033 (US)
- **JAKUBOWSKI, Joseph, Anthony**
  Indianapolis, IN 46208 (US)
- **MARTINELLI, Michael, John**
  Indianapolis, IN 46254 (US)
- **MORIN, John, Michael, Jr.**
  Brownsburg, IN 46112 (US)
- **PAAL, Michael**
  D-22335 Hamburg (DE)
- **RUHTER, Gerd**
  D-21129 Hamburg (DE)
- **RUTERBORIES, Kenneth, James**
  Indianapolis, IN 46278 (US)
- **SCHOTTEN, Theo**
  D-21444 Vierhoefen (DE)
- **STENZEL, Wolfgang**
  D-21465 Reinbek (DE)
- **VASILEFF, Robert, Theodore**
  Indianapolis, IN 46208 (US)

(74) Representative: **Van Malderen, Joelle et al**
Office Van Malderen,
Place Reine Fabiola 6/1
1083 Bruxelles (BE)

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EP-A- 0 655 439
WO-A-93/12074
US-A- 4 026 907
US-A- 4 752 646
US-A- 4 789 750
US-A- 4 806 661
US-A- 4 853 472

- **ELLIS ET AL: 'Benzopyrones, 14 synthesis and antiallergic properties of some n-tetrazolyl carboxamides and related compounds' JOURNAL OF MEDICINAL CHEMISTRY vol. 21, no. 11, 1978, pages 1120 - 1126**

EP 0 804 431 B9

Description

Field of the Invention

[0001] This invention relates to bicyclic compounds useful as glycoprotein IIb/IIIa antagonists for the prevention of thrombosis.

Background of the Invention

[0002] The most prevalent vascular disease states are related to platelet dependent narrowing of the blood supply such as atherosclerosis and arteriosclerosis, acute myocardial infarction, chronic stable angina, unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis or abrupt closure following angioplasty, carotid endarterectomy, anastomosis of vascular grafts, and etc. These conditions represent a variety of disorders thought to be initiated by platelet activation on vessel walls. Platelet adhesion and aggregation is believed to be an important part of thrombus formation. This activity is mediated by a number of platelet adhesive glycoproteins. The binding sites for fibrinogen, fibronectin and other clotting factors have been located on the platelet membrane glycoprotein complex IIb/IIIa. When a platelet is activated by an agonist such as thrombin the GPIIb/IIIa binding site becomes available to fibrinogen, eventually resulting in platelet aggregation and clot formation.

[0003] Heretofore it has been proposed to block these thrombus formation sites by the use of various therapeutic agents.

[0004] U.S. Patent No. 5,064,814 teaches N-amidinopiperidine carboxyl cyclic amino acid derivatives as antithrombotic agents.

[0005] U.S. Patent 5,039,805 teaches various benzoic acid and phenylacetic acid derivatives for the inhibition of the binding of fibrinogen to the fibrinogen receptor, glycoprotein IIb/IIIa.

[0006] Seven membered ring containing bicyclic compounds are taught to be fibrinogen antagonists in PCT International patent application WO 93/00095.

[0007] EP 456835 describes bicyclic compounds having fused six membered rings (quinazoline-3-alkanoic acid derivates) which are reported to have an inhibitory effect on platelet aggregation.

[0008] PCT International patent application WO 93/08174 describes nonpeptidyl integrin inhibitors which are bicyclic 6 and 7 membered fused ring systems which have therapeutic applications in diseases for which blocking platelet aggregation is indicated.

[0009] Patent Application WO94/12478 describes the preparation of 6,5-bicyclic compounds stated to be effective for inhibiting platelet aggregation.

[0010] Patent Application WO94/08962 describes the preparation of 6,5-bicyclic compounds stated to be effective for inhibiting platelet aggregation.

[0011] British Patent application GB 2276384 describes novel oxoquinazolin derivatives stated to have fibrinogen receptor antagonistic activity.

[0012] The article, "From Peptide to Non-Peptide. 1. The Elucidation of a Bioactive Conformation of the arginine-glycine-aspartic Acid Recognition Sequence", by Robert S. McDowell, et. al., J. Am. Chem. Soc. 1994, 116, pp. 5069-5076, describes design of non-peptidal inhibitors of fibrinogen-glycoprotein IIb/IIIa binding.

[0013] The publication, "Chapter 9. Glycoprotein IIbIIIa Antagonists" by Brent K. Blackburn and Thomas R. Gadek, Annual Reports in Medicinal Chemistry -28, Section II - Cardiovascular, and Pulmonary Agents, pp 79-88, 1993, publ. by Academic Pres, Inc., describes non-peptides as antagonists of GPIIbIIIa/fibrinogen interaction.

[0014] The article, "From Peptide to Non-Peptide. 2. The de Novo Design of Potent, Non-Peptidal Inhibitors of Platelet Aggregation Based on a Benzodiazepinedione Scaffold", by Robert S. MoDowell, et. al., J. Am. Chem. Soc. 1994, 116, pp 5077-5083, describes benzodiazepinedione which are inhibitors of platelet aggregation.

[0015] Quinoline compounds have been recited in the patent literature for a variety of medicinal uses. For example, European Patent Application 0 315 399; U.S. Patent No. 5,041,453; PCT Patent Application WO 89/04303, and PCT Patent Application WO 89/04304 describe quinoline derivatives useful as lipoxygenase inhibitors and/or leukotriene antagonists possessing anti-inflammatory and anti-allergic properties. These compounds must contain three aromatic rings, each interrupted with oxygen, or sulfur, and possibly other groups

[0016] The document EP-A-0635492 describes bicyclic compounds based on isoquinoline, isoquinolone, tetrahydronaphtalene, dihydronaphtalene and tetralone, which are useful in the inhibition of platelet aggregation.

[0017] The document EP-A-0655439 discloses 5,6 fused ring bicyclic compounds based on indoles, benzofurans and benzothiophenes, which are useful in inhibition of platelet aggregation.

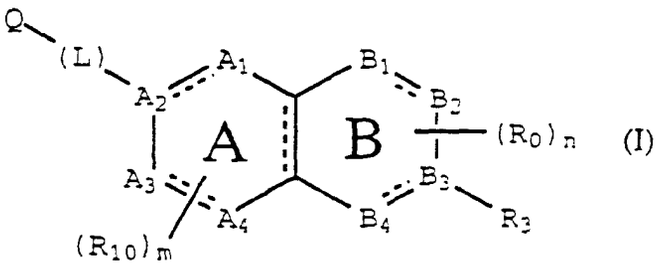
[0018] The document WO-A-93/12074 discloses peptide mimetic compounds, which are useful in inhibiting platelet aggregation.

[0019] There is a need in the area of cardiovascular and cerebrovascular therapeutics for alternative agents which can be used in the prevention and treatment of thrombi.

[0020] It is a discovery of this invention that certain novel bicyclic compounds block the GPIIb/IIIa fibrinogen receptor, thereby inhibiting platelet aggregation and subsequent thrombus formation. Pharmaceutical formulations containing the bicyclic compounds of this invention inhibit aggregation and are useful for the prophylaxis and treatment of thrombogenic diseases, such as myocardial infarction, angina, stroke, peripheral arterial disease, disseminated intravascular coagulation and venous thrombosis.

Summary of the Invention

[0021] The present invention is a novel bicyclic compound having a nucleus formed from two fused six membered rings, A and B, represented by the formula (I), as hereinafter defined, and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof:



(I)

[0022] Another aspect of the invention is a pharmaceutical formulation containing the novel bicyclic compounds of the invention.

[0023] Another aspect of the invention is a method of inhibiting platelet aggregation, inhibiting fibrinogen binding, or preventing thrombosis by administering to a mammal the bicyclic compounds of the invention.

[0024] Another aspect of this invention is a method of treating a human to alleviate the pathological effects of atherosclerosis and arteriosclerosis, acute myocardial infarction, chronic stable angina, unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis following angioplasty, carotid endarterectomy, and anastomosis of vascular grafts; wherein the method comprises administering to said human the novel bicyclic compound of this invention.

Detailed Description of the Invention

[0025] The term "alkyl" used herein refers to a monovalent straight or branched chain radical of from one to ten carbon atoms, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-hexyl, and the like.

[0026] The term, "halosubstituted alkyl" as used herein refers to an alkyl group as just defined, substituted by one, two or three halogen atoms selected from fluorine, chlorine, bromine, and iodine. Examples of such groups include chloromethyl, bromoethyl, trifluoromethyl, and the like.

[0027] The term, "aryl", when used alone means a homocyclic aromatic radical whether or not fused. Preferred aryl groups include phenyl, napthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like.

[0028] The term, "substituted aryl", denotes an aryl group substituted with one, two, or three substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, trifluoromethyl, amino, aminomethyl, and the like. Examples of such groups are 4-chlorophenyl, 2-methylphenyl, 3-methyl-4-hydroxyphenyl, and 3-ethoxyphenyl.

[0029] The term, "arylalkyl", means one, two or three aryl groups having the number of carbon atoms designated, appended to an alkyl radical having the number of carbon atoms designated. A typical arylalkyl group is the benzyl group.

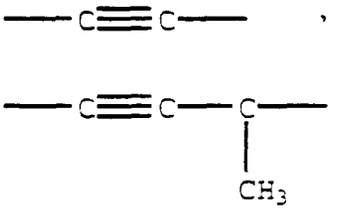
[0030] The term "alkenyl" as used herein refers to a monovalent straight or branched chain radical of from two to six carbon atoms containing a carbon double bond including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

[0031] The term, "alkylene" as used herein refers to a divalent straight or branched chain group of from one to ten carbon atoms, including but not limited to, -CH_2-, -$(CH_2)_2$-. -$(CH_2)_3$-, -$CH(CH_3)$-, -$CH(C_2H_5)$-, -$CH(CH_3)CH_2$-, and the

like.

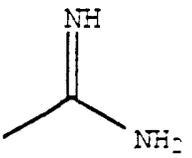
[0032] The term "alkenylene" as used herein refers to a divalent straight or branched chain group of from two to ten carbon atoms containing a carbon-carbon double bond, including but not limited to, -CH=CH-, -$C(CH_3)$=CH-, CH=CH-CH_2-, -CH=$C(CH_3)$-CH_2-, -$CH_2CH(CH=CH_2)CH_2$, and the like.

[0033] The term, "alkynylene" as used herein refers to a divalent straight or branched chain group of from two to ten carbon atoms containing a carbon-carbon triple bond, including but not limited to,



and the like.

[0034] The term, "amidino" refers to the radical having the structural formula;

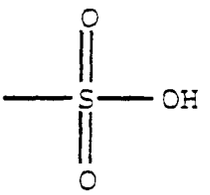


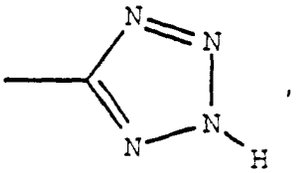
[0035] The term, "basic radical" refers to an organic radical which is a proton acceptor. Illustrative basic radicals are amidino, piperidyl, guanidino, and amino.

[0036] The term, "basic group" refers to an organic group containing one or more basic radicals. A basic group may comprise only an basic radical.

[0037] The term, "non-interfering organc radical" is any organic substituent present on the bicyclic compound of formula (I) which is not deleterious to its efficacy as a Glycoprotein IIb/IIIa antagonist.

[0038] The term, "acid radical" refers to an organic radical which is a proton donor. Illustrative acid radicals include;





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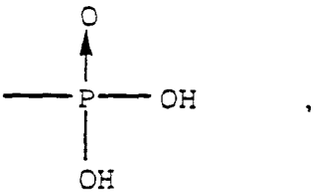

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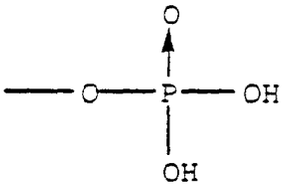

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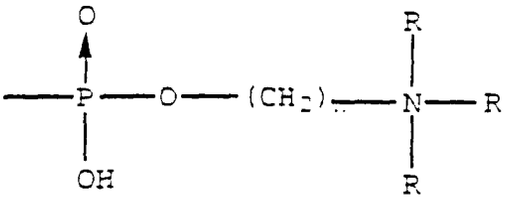

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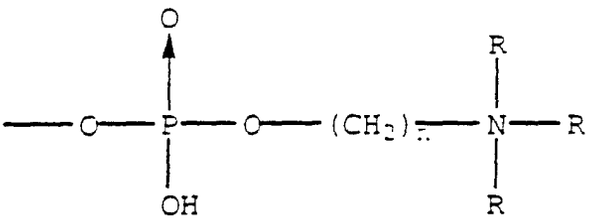

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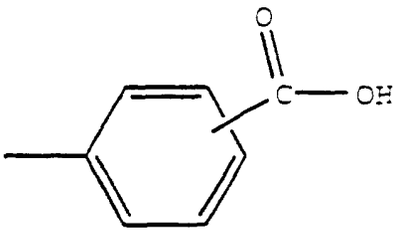

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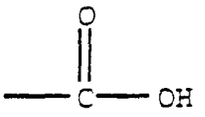
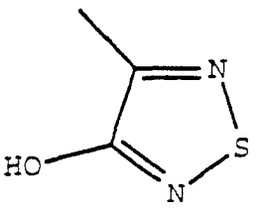


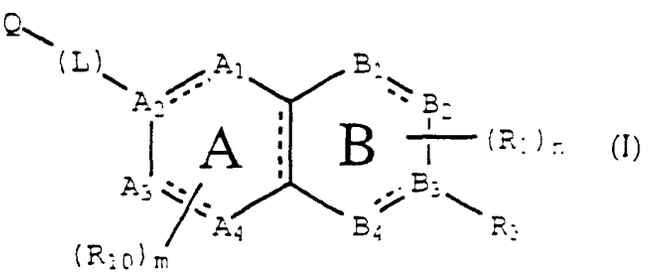
and



[0039] The term, "acidic group" is an organic group containing one or more acid radicals. An acidic group may comprise only an acid radical.

Compounds of the Invention:

[0040] Compounds of this invention have the general formula (I) shown below:

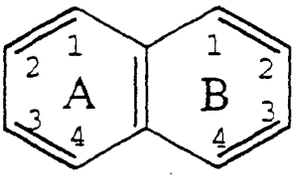


(I)

and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof.

[0041] The bicyclic nucleus of (I) is formed from the fusion of two six membered rings "A" and "B" having carbon bridging atoms. The dashed lines in the structural formula (I) signify the optional presence of an additional bond, that is, unsaturation that will lend aromatic character to the ring structure. It will be understood that the bridging carbon atoms will either be unsubstituted or substituted (with hydrogen) depending on the degree of unsaturation in the bicyclic ring system. The A ring atoms A_1, A_2, A_3, and A_4 and the B ring atoms B_1, B_2, B_3, B_4 of formula (I) are independently selected from carbon, oxygen, sulfur, and nitrogen, with the proviso that at least two of B_1, B_2, B_3, B_4 are carbon. More precisely, A_1, A_3, and A_4 are independently selected from carbon, oxygen, sulfur, and nitrogen and A_2 is independently selected from carbon or nitrogen, provided that A_2 have an unsatisfied bond if A_2 is N and provided that at least two of A_1, A_2, A_3, and A_4 are carbon. Correspondingly, B_1, B_2, and B_4 are independently selected from carbon, oxygen, sulfur, and nitrogen and B_3 is independently selected from carbon or nitrogen and provided that B_3 have an unsatisfied bond if B_3 is N and provided that at least two of B_1, B_2, B_3 and B_4 are carbon.

[0042] The bicyclic nuclei of the compounds of the invention may be formed from ring systems inclusive of, but not limited to, any of the nuclei (1 through 16) depicted below:



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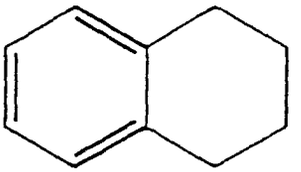
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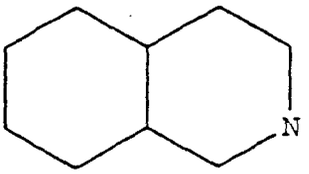

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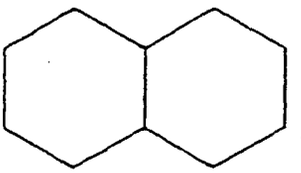
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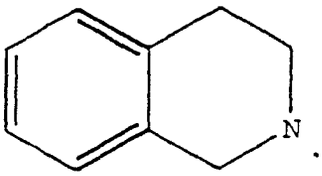

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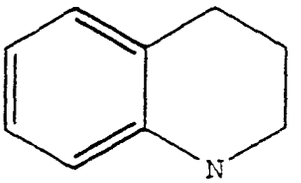

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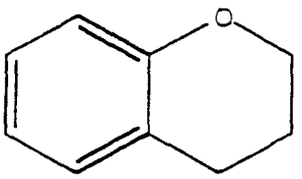

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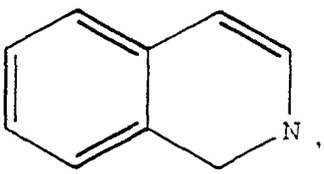

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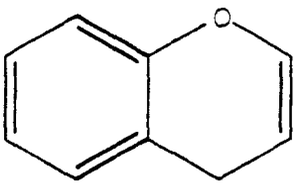

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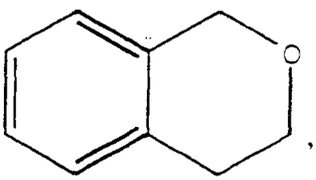

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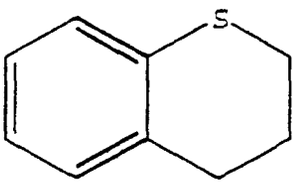

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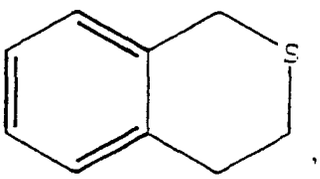

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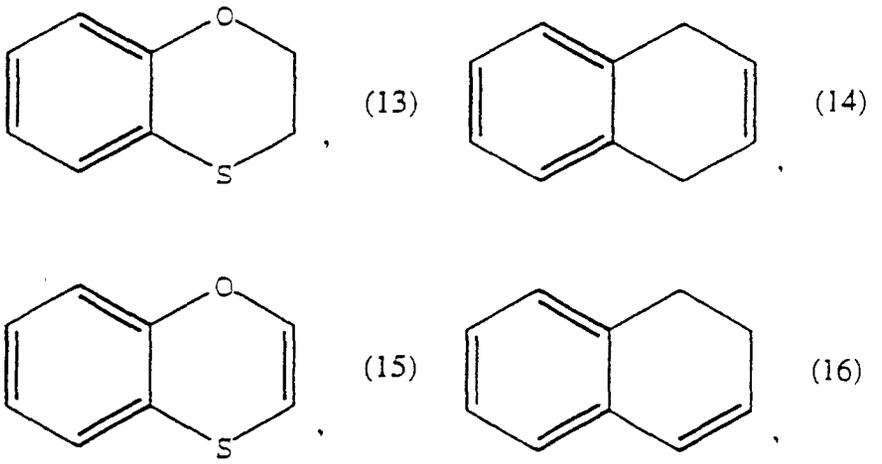
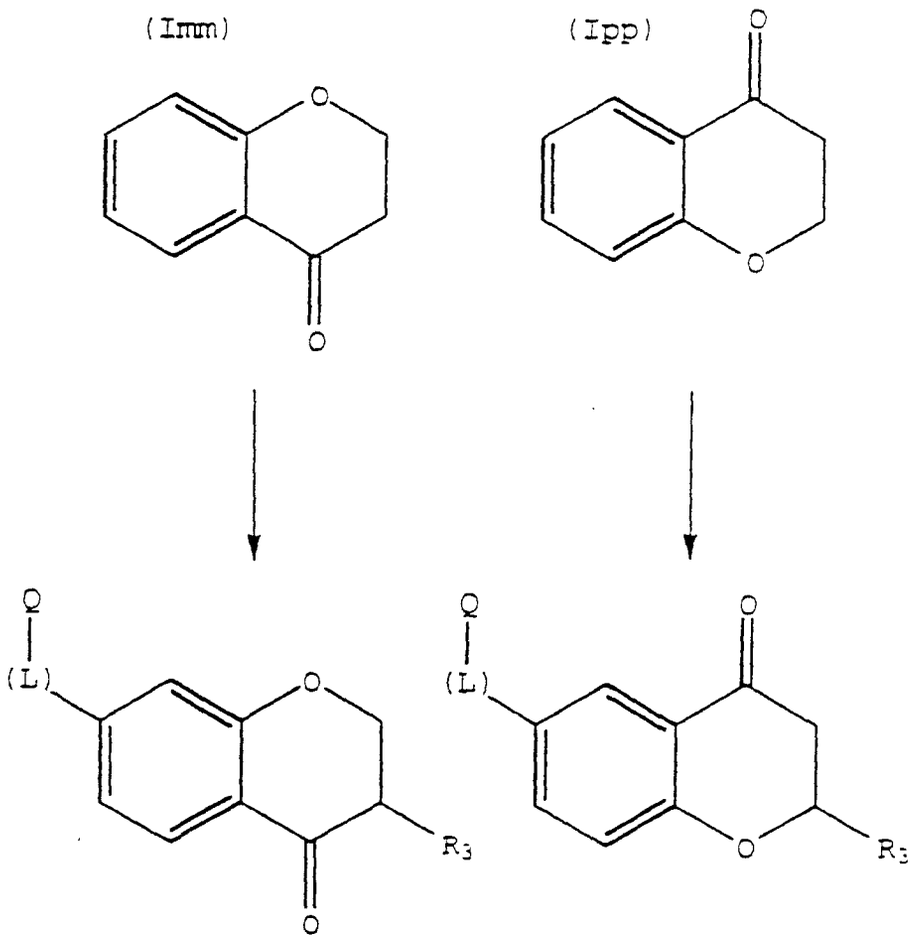
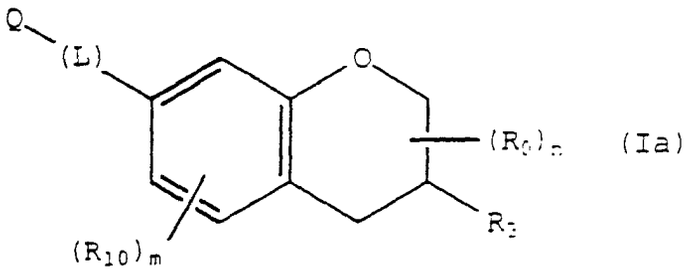


[0043] The nuclei depicted by formulae (1) to (16) supra., and (17) to (30) infra., have the A and B ring atom numberings and corresponding substituent placements as shown in (1) above. For example, the nuclei (Imm) and (Ipp).



would yield different products within the scope of formula (I).

[0044] Compounds of the invention corresponding to formula (I) with nuclei (1) to (19) are represented by the formulae (Ia) to (Ie) below: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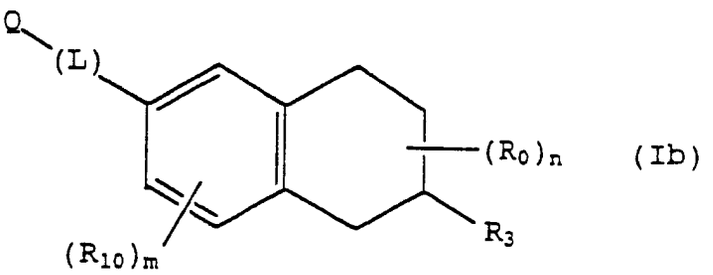
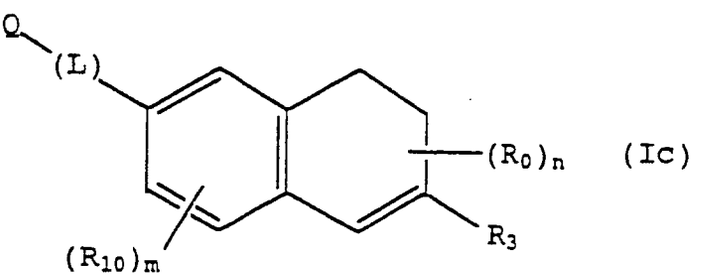
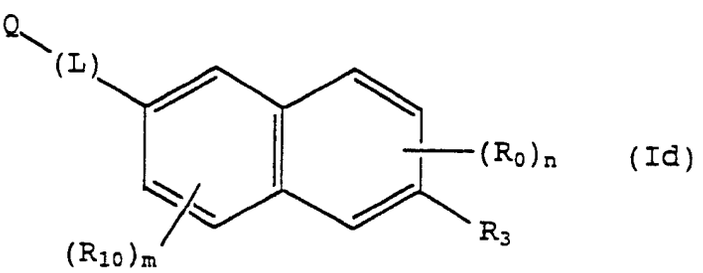
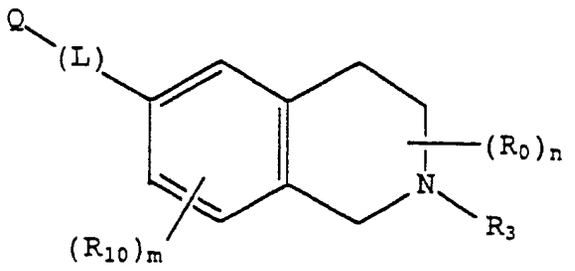

(Ib)

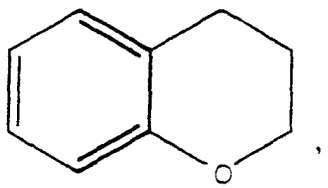

(Ic)


(Id)

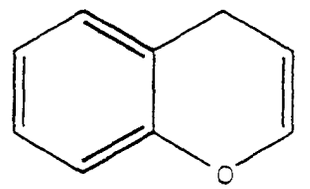


(Ie)

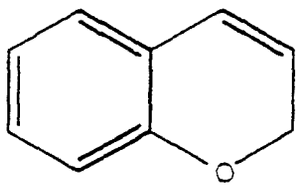
[0045] Other bicyclic nuclei suitable for forming the compounds of formula (I) are represented by the formulae (17) through (21a) below:



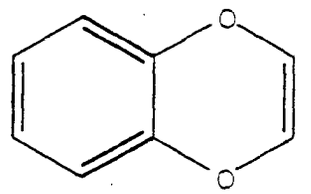
(17),



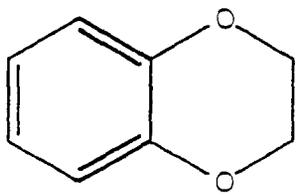
(18),



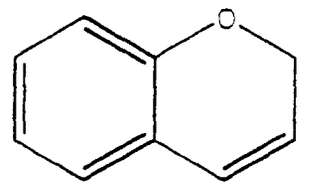
(19),



(20),

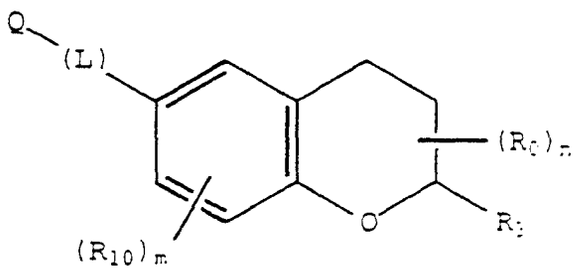


(21),

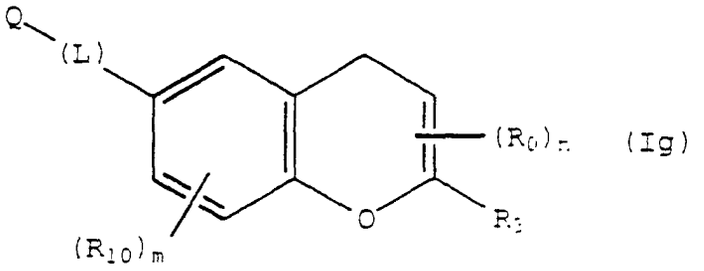


(21a).

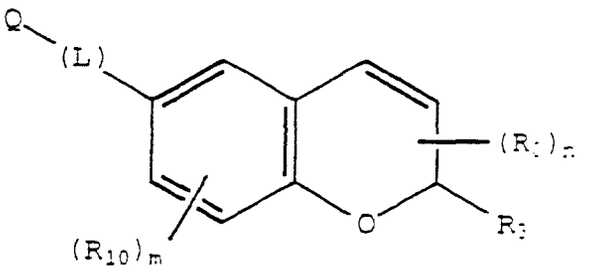
[0046] Compounds of the invention corresponding to formula (I) with nuclei (17) to (21a) are represented by the formulae (If) through (Ijj) below:



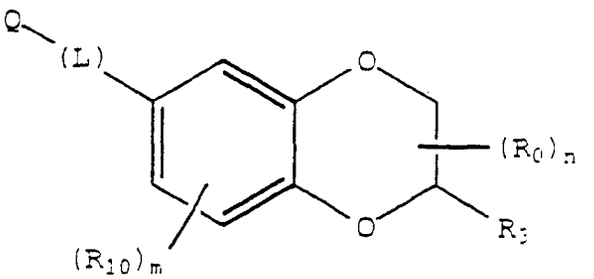
(If)


Q
(L)
$(R_0)_n$
O
R_3
$(R_{10})_m$

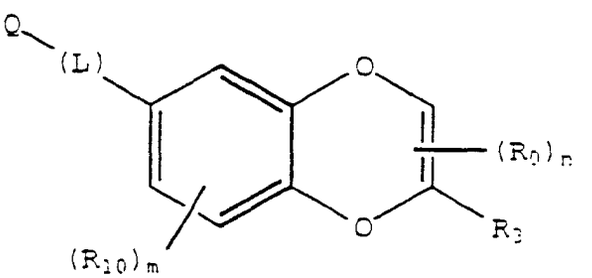
(Ig)


Q
(L)
$(R_0)_n$
O
R_3
$(R_{10})_m$

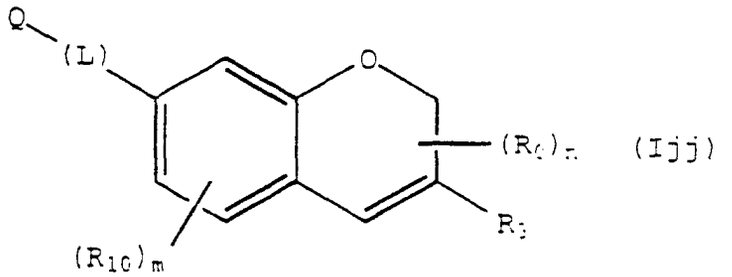
(Ih)


Q
(L)
O
$(R_0)_n$
O
R_3
$(R_{10})_m$

(Ii)

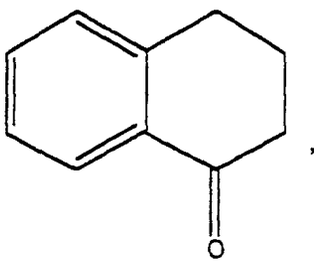

Q
(L)
O
$(R_0)_n$
O
R_3
$(R_{10})_m$

(Ij)

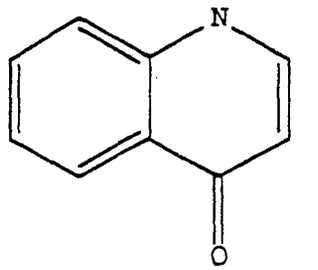


(Ijj)

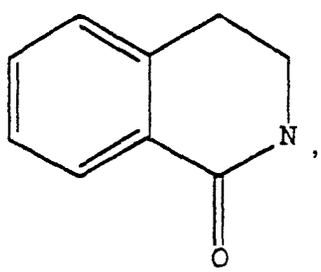
[0047] Bicyclic nuclei ring substituted with =O suitable for forming the compounds of formula (I) are represented by the formulae (22) through (27) below:



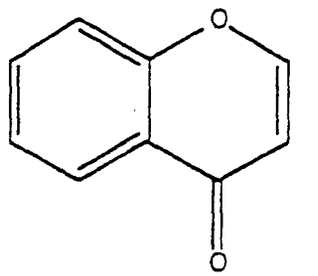
(22),



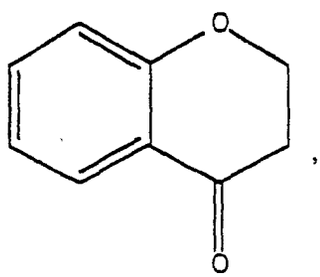
(23),



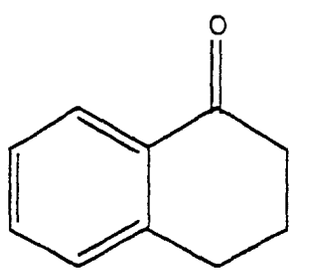
(24),



(25),

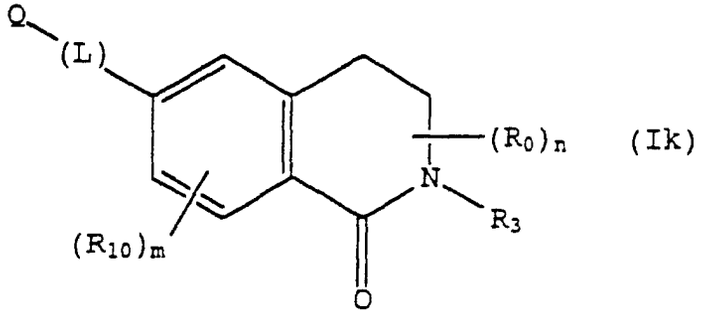


(26),

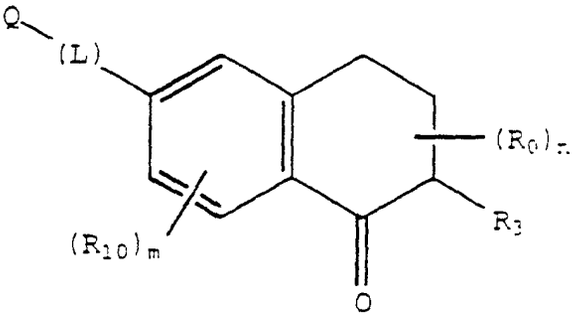


(27).

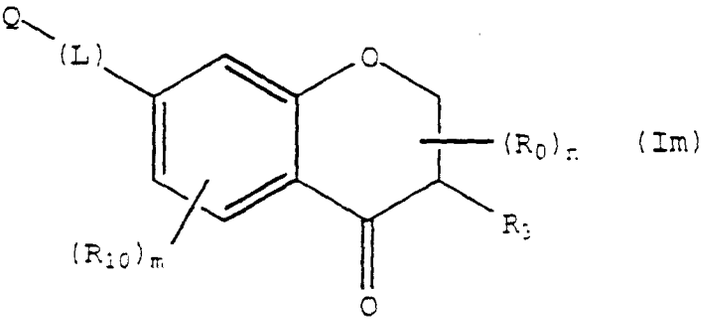
[0048] Compounds of the invention corresponding to formula (I) with oxo substituted nuclei (22) to (27) are represented by the formulae (Ik) to (Im) below:



(Ik)

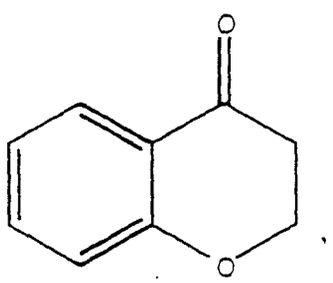


(Il)

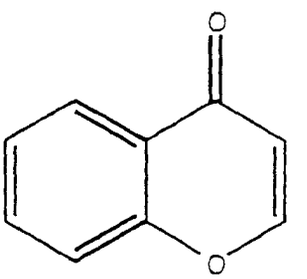


(Im)

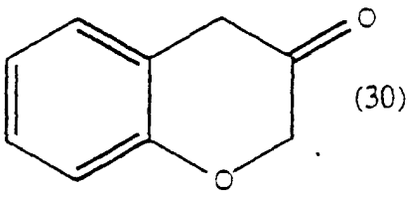
[0049] Other bicyclic nuclei ring substituted with =O suitable for forming the compounds of formula (I) are represented by the formulae (28) through (30) below:



(28)

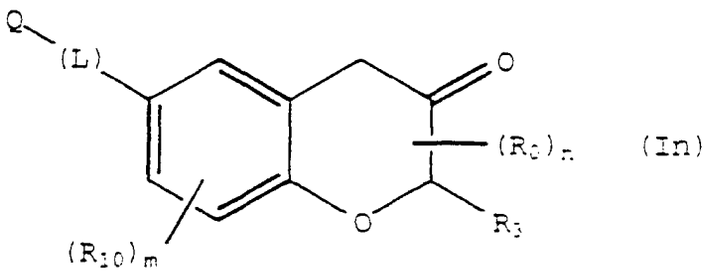


(29)

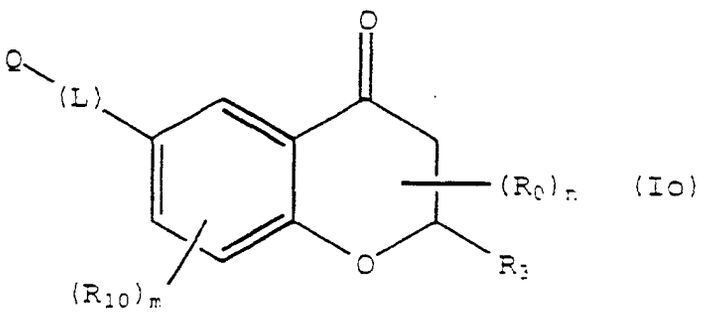


(30)

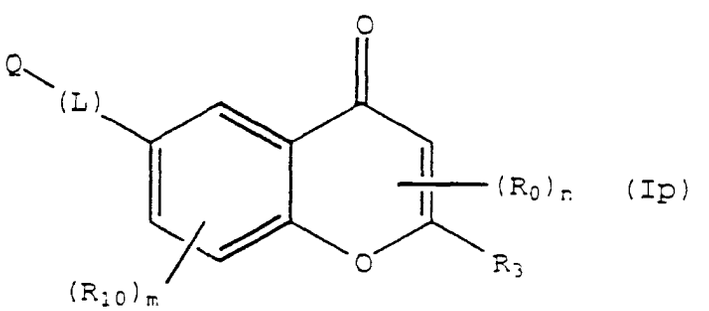
[0050] Compounds of the invention corresponding to formula (I) with nuclei (28) to (30) are represented by the formulae (In) to (Ip) below:



(In)



(Io)



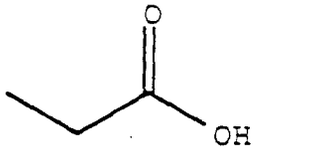
(Ip)

[0051] The most preferred nuclei for the compounds of this invention are isoquinoline, isoquinolone, naphthalene, tetrahydronapthalene, tetralone, dihydronaphthalene, and benzopyran.

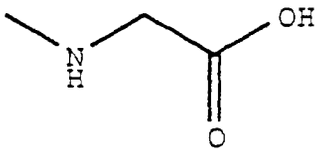
[0052] The substituent R_3 is an acidic group or a pharmaceutically acceptable salt or solvate thereof, (or a prodrug derivative of said acidic group) and preferably is an acidic group containing carboxyl functionality. The R_3 group may be the sole substituent of ring atom B_3. Alternatively, when the B_3 atom can accept two bonds, these bonds may be satisfied by a double bond on the R_3 group (with the R_3 double bond attached directly to the B ring of formula I), or a second R_3 group, or a second group selected from hydrogen, C_1-C_{10} alkyl, C_1-C_{10} halosubstituted alkyl, C_2-C_{10} alkenyl,

C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, aryl, C_7-C_{12} aralkyl, hydroxy, C_1-C_{10} alkoxy, C_1-C_{10} aralkoxy, carboxy, acyl, cyano, halo, nitro, and sulfo.

[0053] R_3, the acidic group, is preferably selected from the group having members represented by the following formulae:



,



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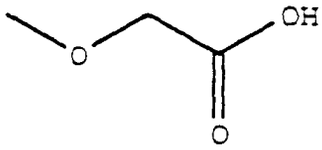

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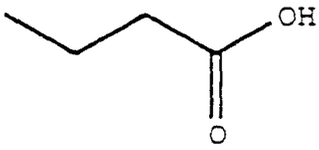

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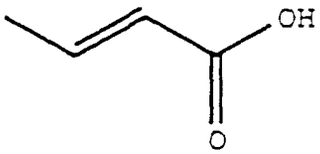

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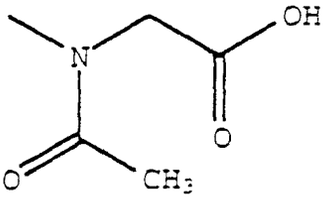

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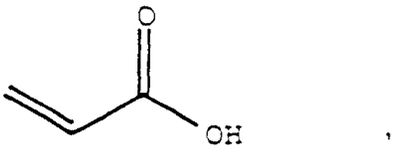
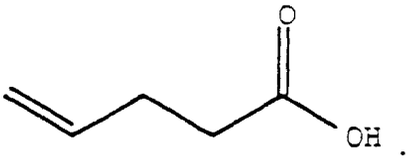
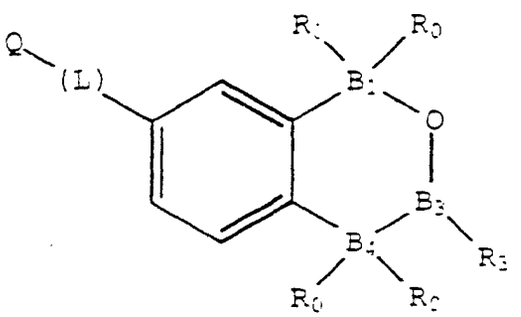




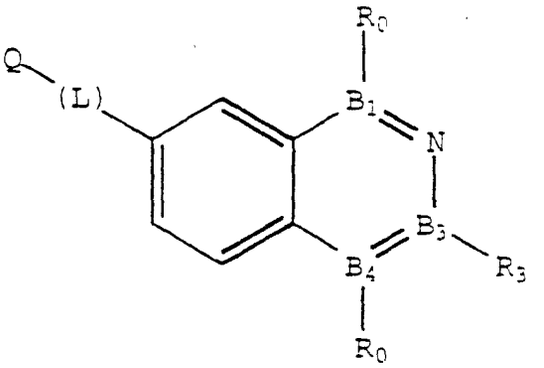
[0054] The substituents R_0 are non-interfering organic radicals and are the same or different on each atom B_1, B_2, and B_4 and the same or different between atoms B_1, B_2, and B_4 and are independently selected from hydrogen, C_1-C_{10} alkyl, C_1-C_{10} halosubstituted alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, aryl, C_6-C_{12} arylalkyl, hydroxy, C_1-C_{10} alkoxy, C_6-C_{12} arylalkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, sulfo; with the proviso that only one of B_1, B_2, and B_4 may also be substituted with =O or =S.

[0055] The number, n, of R_0 substituents attached to the atoms B_1, B_2, and B_4 of the B ring is an integer from 0 to 6 and depends on the sum of the number of unsatisfied bonds present in the individual atoms B_1, B_2, and B_4. Typically, n will be from 2 to 6 for most of the compounds of the invention. Thus, for example, where the B ring is saturated, B_2 is oxygen, and B_1 and B_4 are carbon, then no R_0 substituent will be present on atom B_2 as shown in structural formula (Iq) below:



(Iq)

For B rings having unsaturation, the number of unsatisfied bonds present in the individual atoms B_1, B_2, and B_4 is decreased and the number of R_0 substituents required is correspondingly less. Thus, for example, where the 3 ring is unsaturated, B_2 is nitrogen, and B_1 and B_4 are carbon, then no R_0 substituent will be present on B_2 as shown in structural formula (Ir) below:

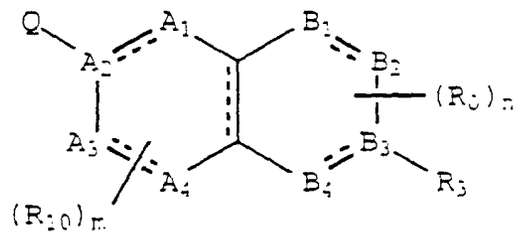


(Ir)

[0056] The A ring atoms A_1, A_2, A_3, and A_4 are independently selected from carbon, oxygen, sulfur, and nitrogen, with the proviso that at least two of A_1, A_2, A_3, and A_4 are carbon. The substituents R_{10} are the same or different on each atom A_1, A_3, and A_4 and the same or different between atoms A_1, A_3 and A_4, and are independently selected from hydrogen, C_1-C_{10} alkyl, C_1-C_{10} halosubstituted alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, aryl, C_6-C_{12} arylalkyl, hydroxy, alkoxy, C_6-C_{12} arylalkoxy, carboxy, acyl, cyano, halo, nitro, and sulfo; with the proviso that only one of A_1, A_3, and A_4 may also be substituted with =O or =S when two sites are available for substitution on a single atom (viz., when one or more of the dashed lines in the A ring of Formula I are absent and an A atom is carbon).

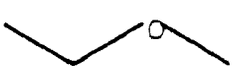
[0057] The number, m, of R_{10} substituents attached to the atoms A_1, A_3, and A_4 of the A ring is an integer from 0 to 6 and depends on the sum of the number of unsatisfied bonds present in the individual atoms A_1, A_3, and A_4 in a manner analogous to the substitution of R_0 groups on the B ring as described above. Typically, n will be from 2 to 6 for most of the compounds of the invention. The atom, A_2, of the A ring is substituted by linking group -(L)- alone when A_2 has only one unsatisfied bond, however, when A_2 has two unsatisfied bonds the second bond may be satisfied by a group selected from hydrogen, alkyl, halosubstituted C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, aryl, C_7-C_{12} arylalkyl, hydroxy, C_1-C_{10} alkoxy, C_7-C_{12} arylalkoxy, acyl, cyano, halo, nitro, sulfo, and a basic group.

[0058] The linking group -(L)- attached to the A_2 atom of the A ring and is (i) a bond, or (ii) a divalent substituted or unsubstituted chain of from 1 to 10 atoms (viz., there are 1 to 10 atoms in the chain between the linking divalent bonds, with all other atoms pendent from these chain atoms). For example, when -(L)- is a bond the compound of the invention may have the structural formula Is as follows:

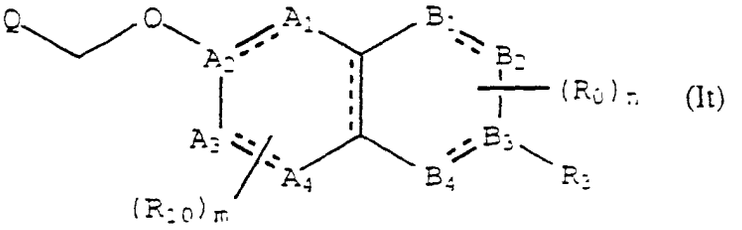


(Is)

Alternatively, when -(L)- is the linking group

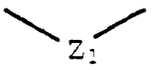


the compound of the invention may have the structural formula (It) as follows:

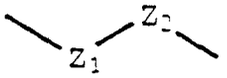


(It)

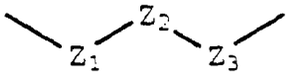
Alkylene, alkenylene and alkynylene groups are suitable as linking groups. Preferred linking groups have 1 to 4 chain atoms and correspond to the general formulae:



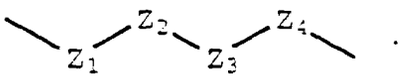
or



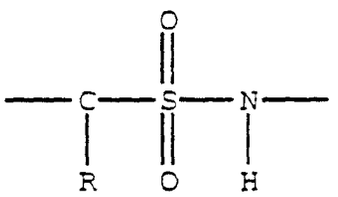
or

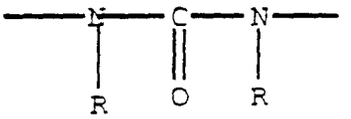


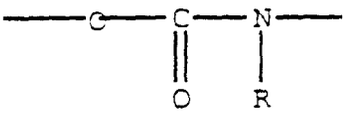
or

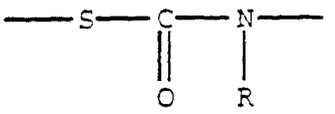


where Z_1, Z_2, Z_3, and Z_4 are atoms selected from the group consisting of carbon, nitrogen, sulfur, and oxygen. Linking groups containing three chain atoms such as,



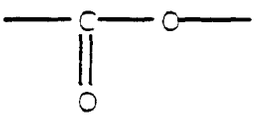


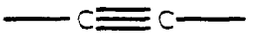


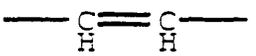


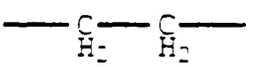
where R is hydrogen or alkyl, may be used.

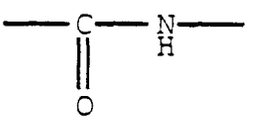
[0059] Particularly preferred are linking groups containing two chain atoms such as;

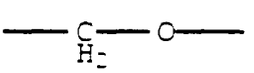




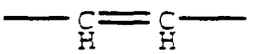






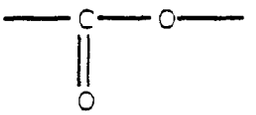


The linking group;

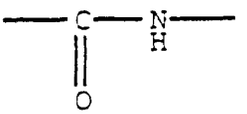


has cis and trans forms and both such forms and their mixtures in all proportions are within this invention.

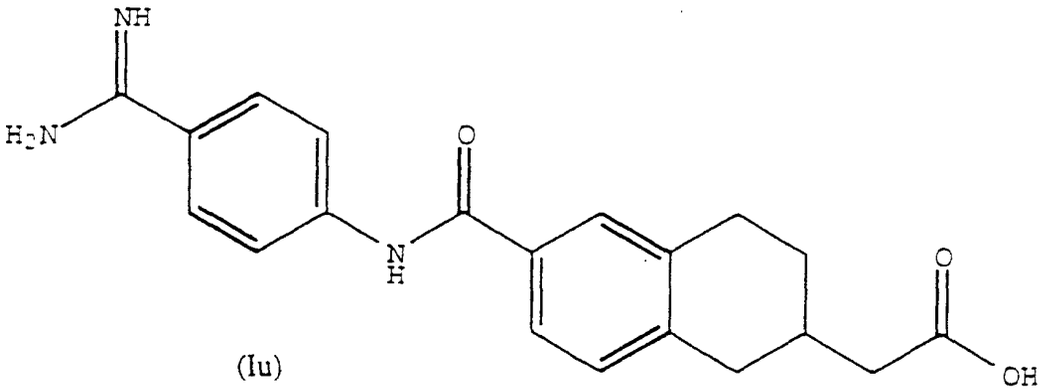
[0060] Asymmetric linkers, for example, the linkers



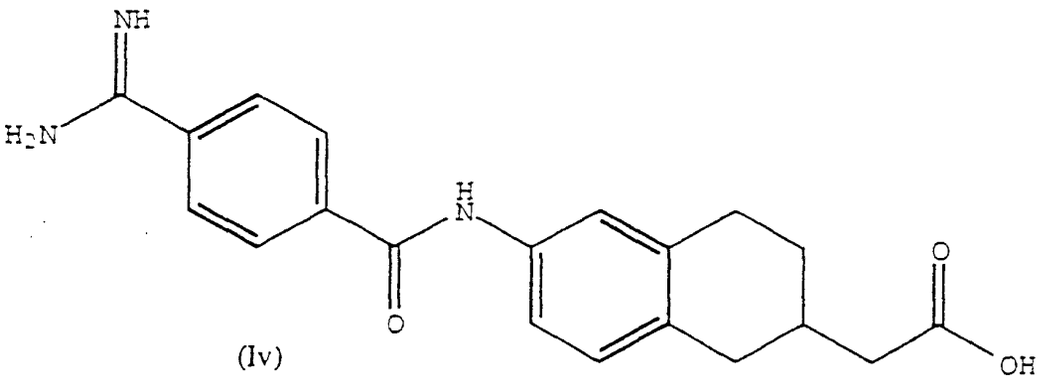
or



may be reversed in their point of attachment between the nucleus A ring and the basic group Q, as depicted in formulae (Iu) and (Iv) below:



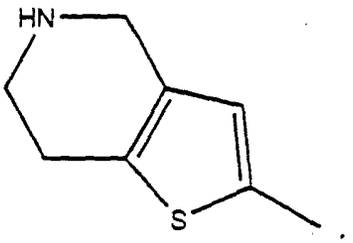
(Iu)



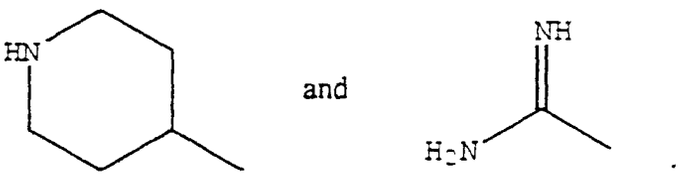
(Iv)

[0061] The substituent Q of formula (I) is a basic group. A basic group contains one or more basic radicals, Q_1.

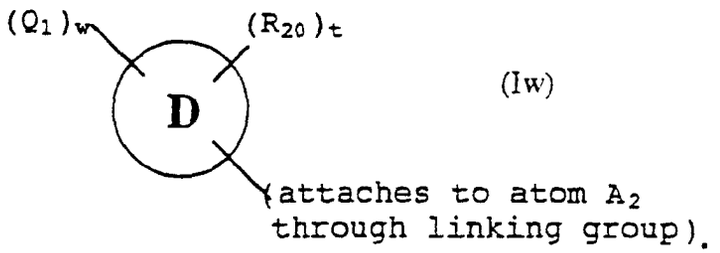
[0062] Suitable basic radicals contain one or more nitrogen atoms and include amino, imino, amidino, N-alkylamidines, N,N'-dialkyamidines, N-arylamidines, aminomethyleneamino, iminomethylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylideneamino, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, amide, thioamide, benzamidino, pteridinyl, 4aH-carbozolyl, carbozolyl, beta-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, or any of the preceding substituted with amino, imino, amidino, aminomethyleneamino, iminomethylamino, guanidino, alkylamino, dialkylamino, trialkylamino, tetrahydroisoquinoline, dihydrosioindole, alkylideneamino groups or a group represented by the formula;



Preferred basic radicals are selected from amino, piperidyl, guanidino, and amidino. The most preferred basic radicals are amidino and piperidyl represented by the formulae;



[0063] The basic group Q may have the form of a basic radical (such as Q_1 on formula Iw, infra.) pendant on a cyclic ring. Thus, Q, the basic group, may comprise two parts, namely, (i) one or more basic radicals, Q_1 and (ii) a cyclic group, "D", having from 5 to 8 ring atoms. The D ring attached to the A_2 atom of the A ring of the bicyclic nucleus throuth the linking group -(L)- as shown in formula (I), supra. The D ring may also have substituents R_{20} which are selected from chlorine, fluorine or non-interfering organic radicals. The R_{20} substituents may be t in number, where t is an integer from zero to the number of unsatisfied bonds in the D ring. The basic radical Q_1 attaches to the D ring in the manner shown in formula (Iw) below:

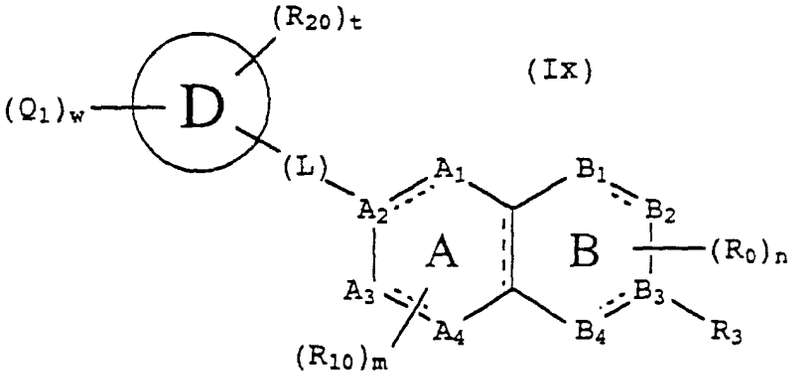


(Iw)

[0064] Suitable D rings are formed from a nucleus selected from the group consisting of; benzene, cycloheptadiene, cycloheptatriene, cycloheptane, cyclohexane, cyclohexene, cyclohexadiene, cycloheptene, cyclooctadiene, cyclooctane, cyclooctatetraene, cyclooctene, cyclopentane, cyclopentene, imidazole, isooxazole, morpholine, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, tetrahydropyridine, tetrahydropyrimidine, 1H-tetrazole, thiazolidine, thiazole, thiopyran, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, dihydrofuran,

dihydropyran, dioxane, dioxepin, dioxolane, furan, oxocane, tetrahydrofuran, tetrahydropyran, thiophene, and tetrahydrothiophene.

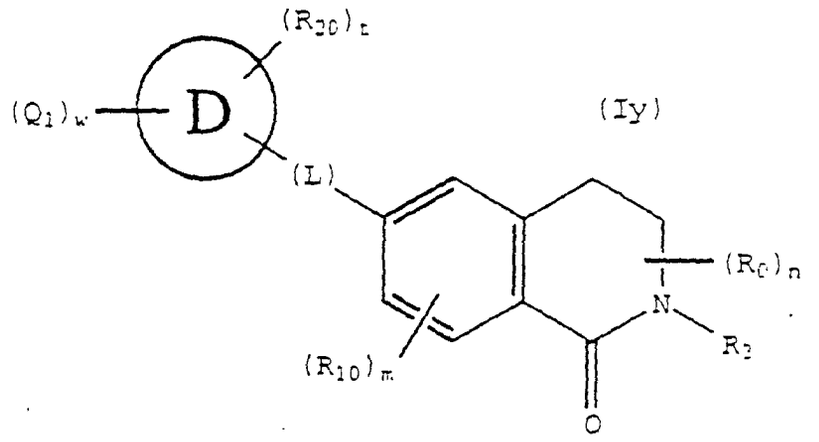
[0065] General formula (Ix) for the preferred compounds of the invention having a basic radical attached to a cyclic ring of 5 to 8 atoms is shown below:



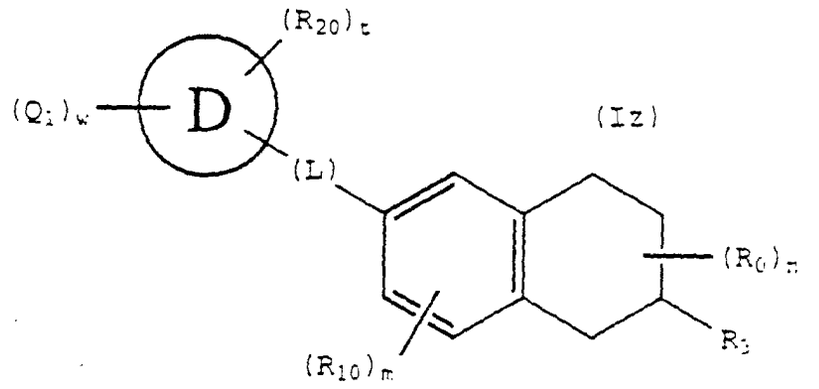
wherein;

A_1, A_3, A_4 are independently selected from carbon, oxygen, sulfur, and nitrogen;
A_2 is independently selected from carbon or nitrogen, provided that A_2 have an unsatisfied bond if A_2 is N and provided that at least two of A_1, A_2, A_3, and A_4 are carbon;
B_1, B_2, B_4 are independently selected from carbon, oxygen, sulfur, and nitrogen;
B_3 is independently selected from carbon or nitrogen, provided that B_3 have an unsatisfied bond if B_3 is N and provided that at least two of B_1, B_2, B_3, B_4 are carbon;
R_3 is an acidic group containing one or more acid radicals;
n is a number from 0 to 6;
R_0 is the same or different and is independently selected from hydrogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, sulfo, =O, or =S; with the proviso that if R_0 is =0 or =S, then only one of B_1, B_2, B_3, and B_4 may be nitrogen;
m is a number from 0 to 6;
R_{10} is the same or different and is independently selected from hydrogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, carboxy, acyl, cyano, halo, nitro, sulfo, =O, and =S; with the proviso that only one R_{10} may be =0 or =S;
t is a number from 0 to 3;
R_{20} is the same or different and is independently selected from hydrogen, halogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, carboxy, acyl, cyano, halo, nitro, sulfo;
linking group -(L)- is a bond or a divalent substituted or unsubstituted chain of from 1 to 10 atoms selected from the group consisting of carbon, nitrogen, sulfur, and oxygen; and;
D is a ring formed from 5 to 8 ring atoms and said ring atoms are independently selected from carbon, nitrogen, oxygen, or sulfur, with the proviso that at least two D ring atoms are carbon;
w is an integer from 1 to 3;
Q_1 is a basic radical.

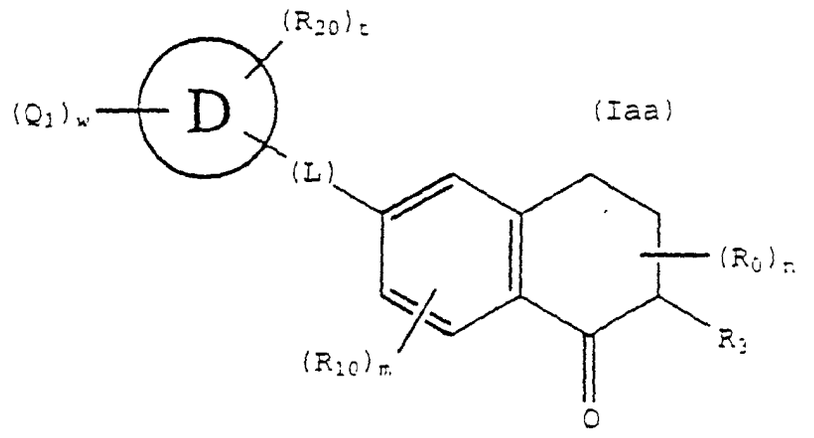
[0066] Compounds of the invention having A, B, and D rings are represented by the following formulae (Iy) to (Iah) below:



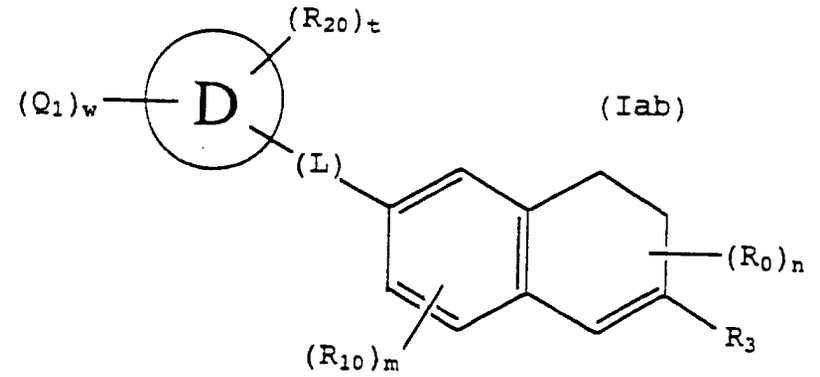
(Iy)

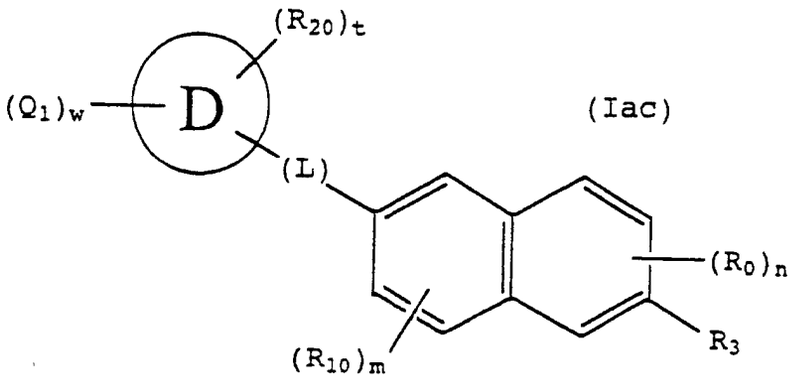


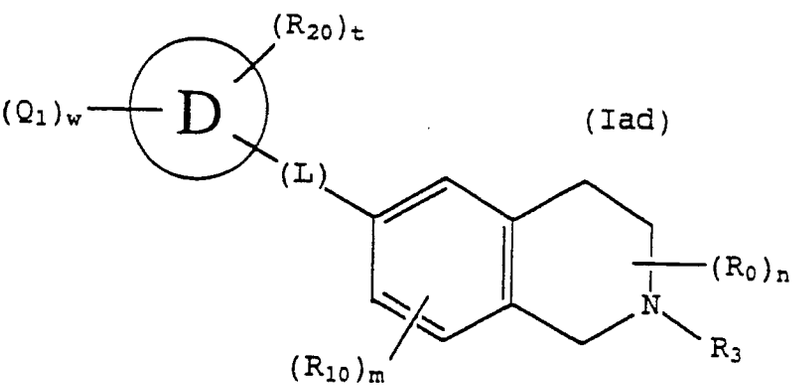
(Iz)

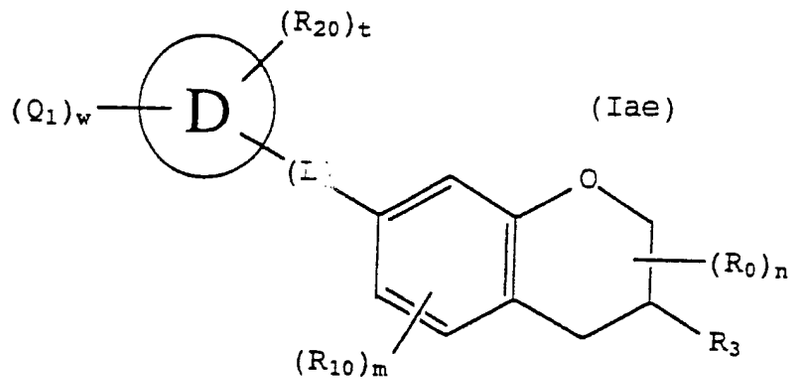


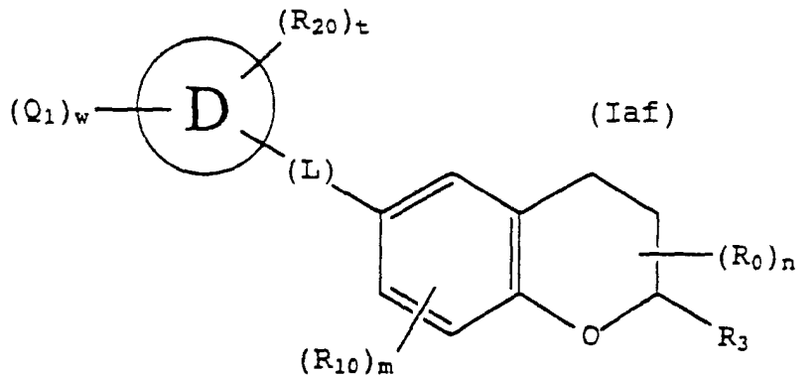
(Iaa)

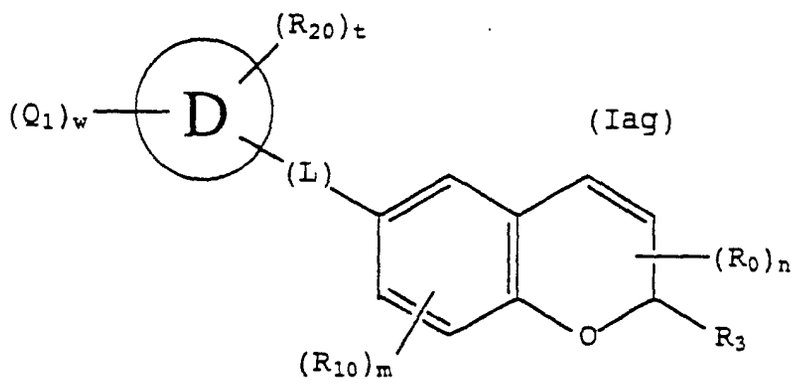

(R20)t
(Q1)w
D
(L)
(Iab)
(R0)n
R3
(R10)m

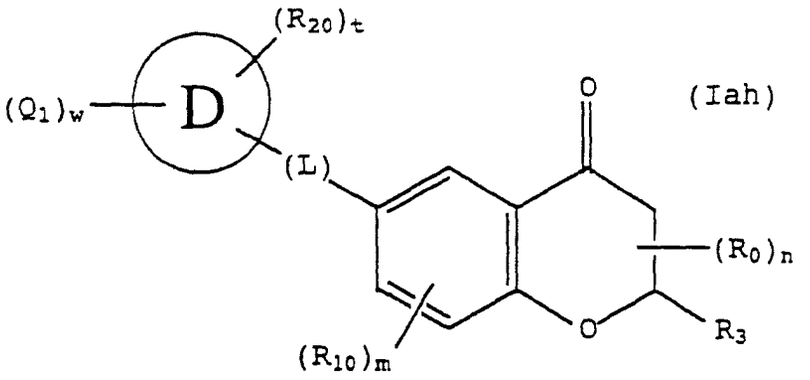

(R20)t
(Q1)w
D
(L)
(Iac)
(R0)n
R3
(R10)m


(R20)t
(Q1)w
D
(L)
(Iad)
(R0)n
N
R3
(R10)m

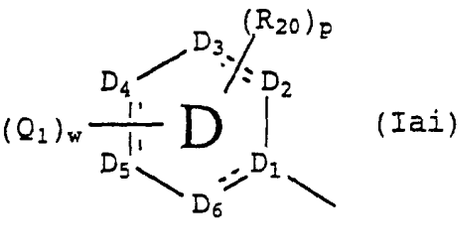

(R20)t
(Q1)w
D
(Iae)
(L)
O
(R0)n
R3
(R10)m


(R20)t
(Q1)w
D
(Iaf)
(L)
(R0)n
O
R3
(R10)m

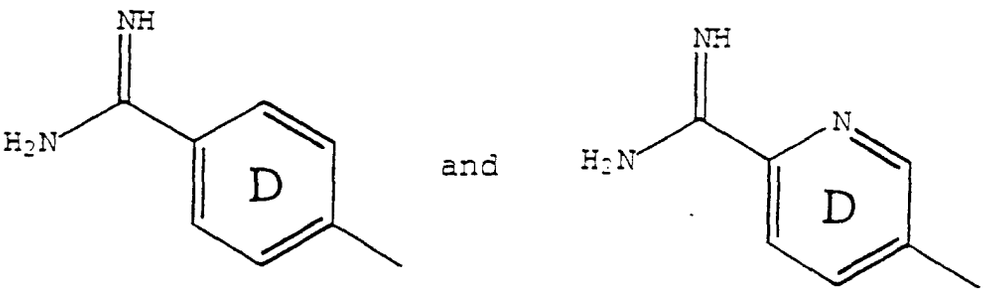

(R20)t
(Q1)w
D
(Iag)
(L)
(R0)n
O
R3
(R10)m



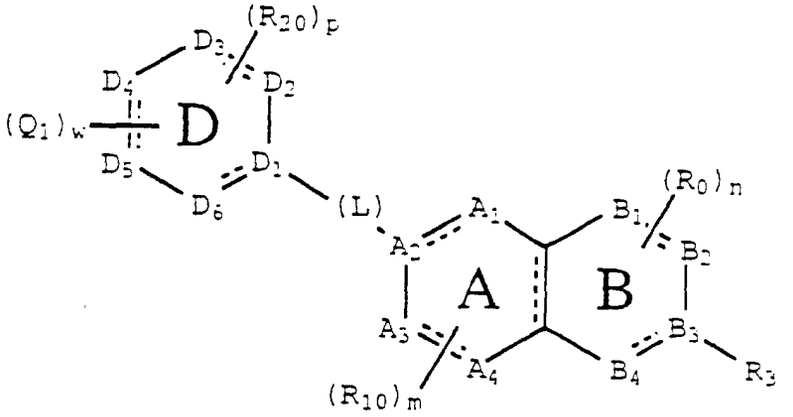
[0067] A preferred basic group Q has a six membered D ring as represented by formula (Iai) below;



where p is an integer from 0 to 8, as for example, the specific Q groups:



[0068] A preferred embodiment of the compound of the invention is represented by formula II, below:



(II)

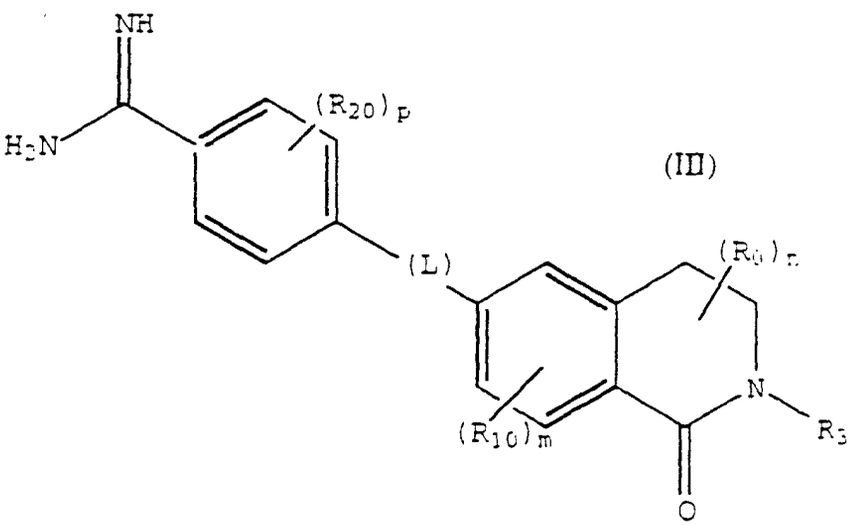
In formula II the basic group on atom A_2 of the nucleus has two parts, namely, (i) a six membered ring, D, which attaches to linking group -(L)-, and (ii) basic radical(s), Q_1, (where w is an integer from 1 to 3) attached to the D ring. The basic radicals are as previously defined.

[0069] Atoms D_2, D_3, D_4, D_5 and D_6 are independently selected from carbon, nitrogen, oxygen, or sulfur and atom D_1 is selected from carbon or nitrogen; with the proviso that at least two of D_1, D_2, D_3, D_4, D_5 and D_6 are carbon. Q_1 is a basic radical as previously defined. Preferred ring structures having pendant Q_1 are those where atoms D_1, D_2, D_3, D_4, D_5 and D_6 form a cyclic ring selected from the group consisting of benzene, pyridine, piperidine, 1,2-piperazine, 1,3-piperazine, 1,4-piperazine, pyran, thiopyran, thiabenzene, cyclohexene, and cyclohexane, with benzene being the most preferred.

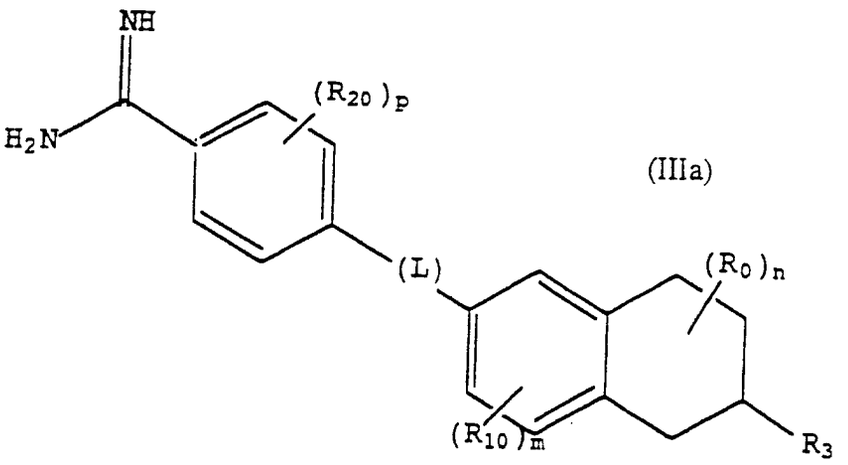
[0070] A preferred basic radical Q_1 is an amidino radical.

[0071] The substituents R_{20} are the same or different on each atom D_2, D_3, D_5, and D_6 and the same or different between atoms D_2, D_3, D_5, and D_6 and are non-interfering organic radicals independently selected from hydrogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, and sulfo. The number, p, of substituents R_{20} is an integer from 0 to 8 depending on the sum of the number of unsatisfied bonds present in the individual atoms D_2, D_3, D_5, and D_6.

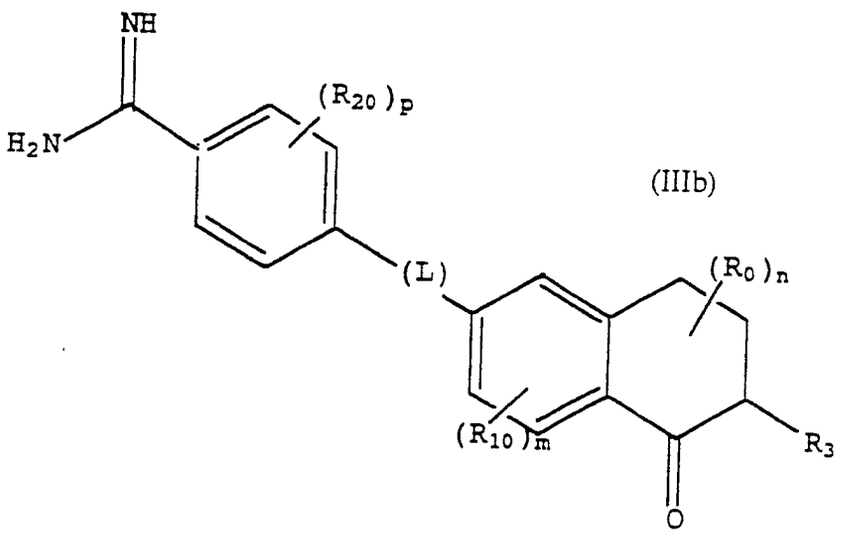
[0072] Preferred compounds of this invention are based on benzamidine substituted isoquinoline, isoquinolone, naphthalene, tetrahydronaphthalene, dihydronaphthalene, benzopyran, and tetralone nuclei, as partially illustrated in formulae (III) through (IIIe) below:



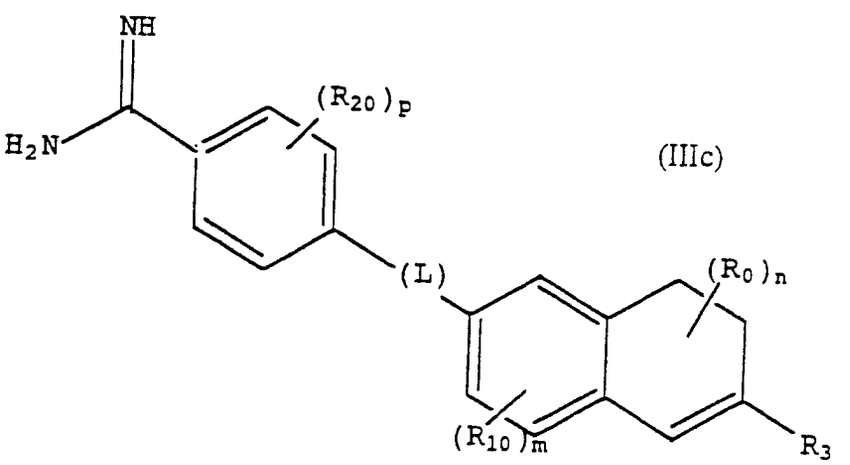
(III)



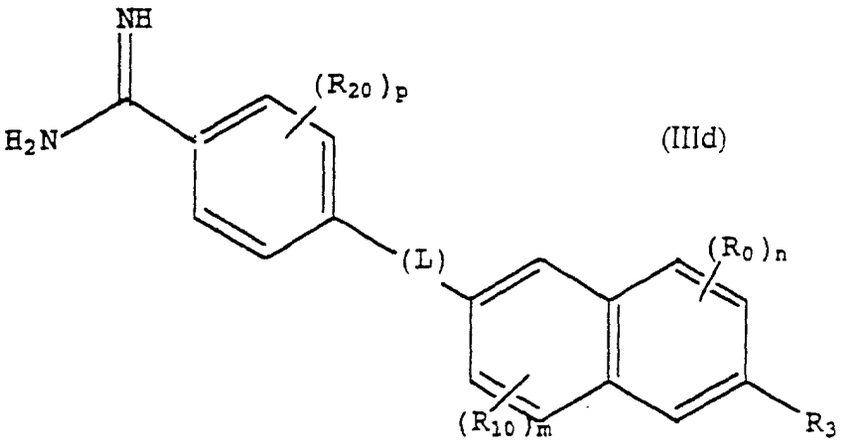
(IIIa)



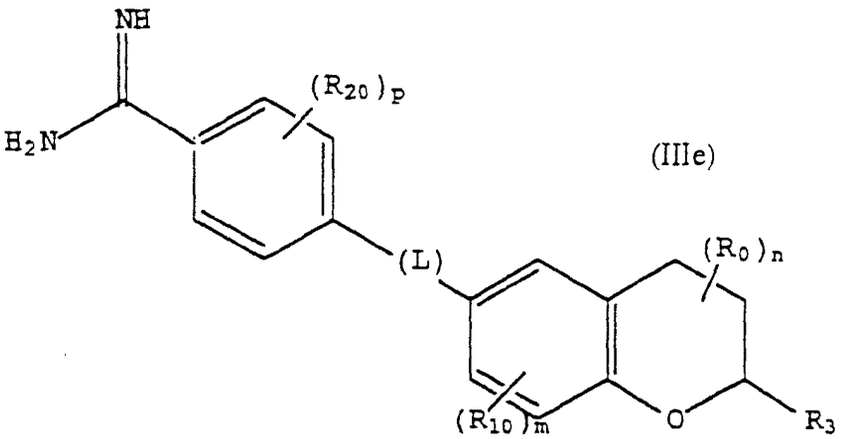
(IIIb)



(IIIc)



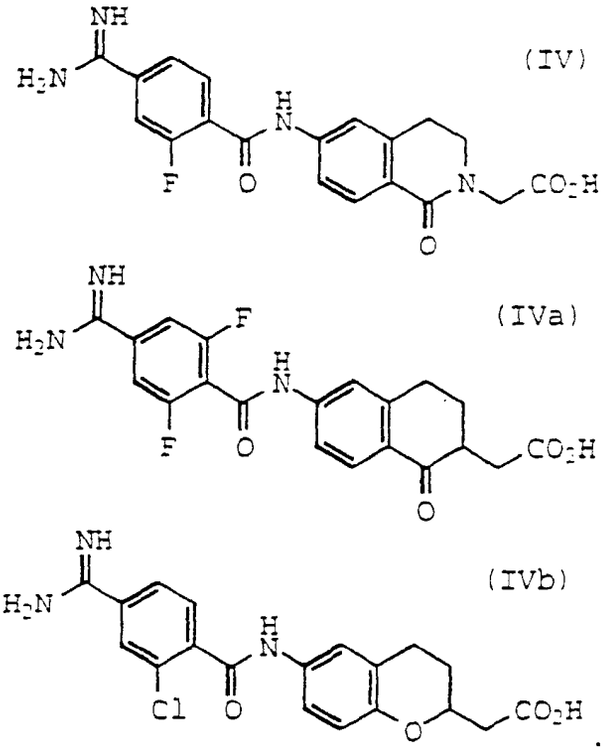
(IIId)



(IIIe)

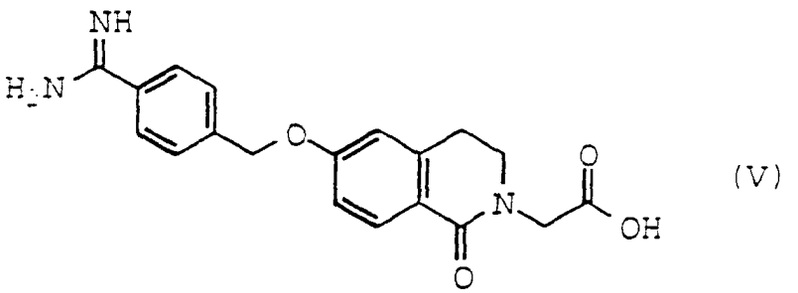
where -(L)-, n, m, p, R_0, R_3, R_{10} and R_{20} are as previously defined. Most preferred are compounds where R_{10} and R_{20} are hydrogen and -(L)- has 2 carbon atoms.

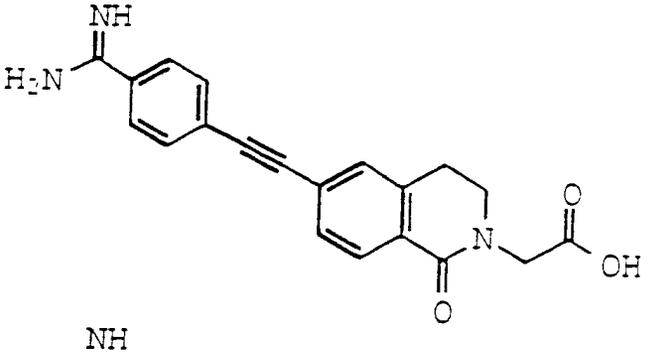
[0073] Another preferred aspect of the invention is where the D ring is contains one or more (preferably 1 or 2) substituents independently selected from chlorine or fluorine. The chlorine and fluorine substituents may be added to any 5 to 8 membered D ring described above. Illustrative compounds of the invention with substitution of six membered D rings are shown in formulae (IV) to (IVb) below:



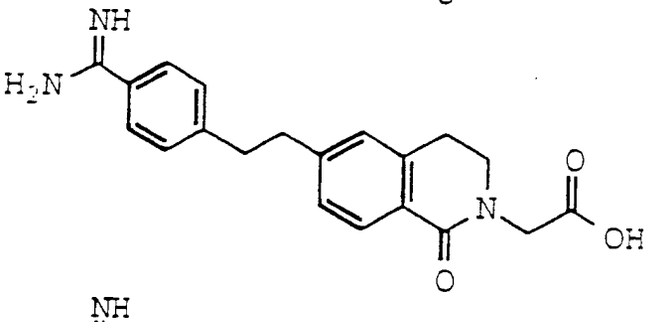
[0074] Without being bound by any theory of operation it is believed that the electron withdrawing groups such as fluorine reduce the basicity of the basic group and enhance the oral bioavailability of the compounds of the invention.

[0075] Specific compounds of the invention of the isoquinoline type which are highly preferred are represented by the following structural formulas (V) to (Vv) or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof:

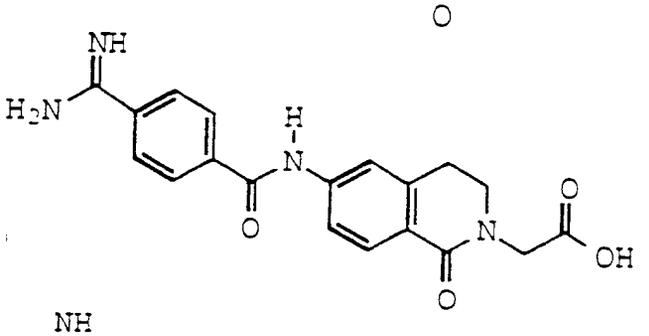




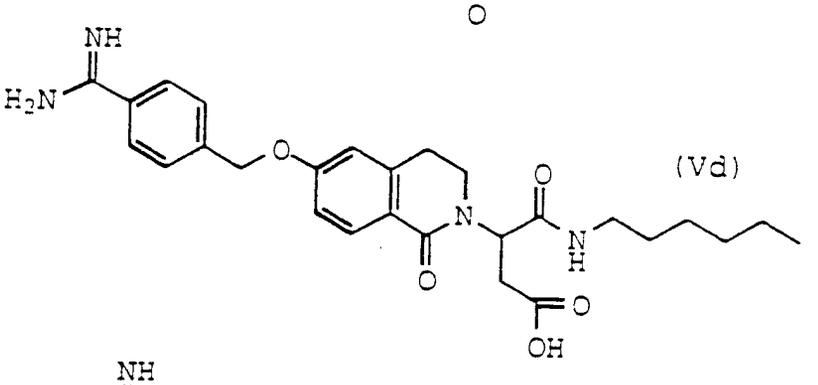
(Va)



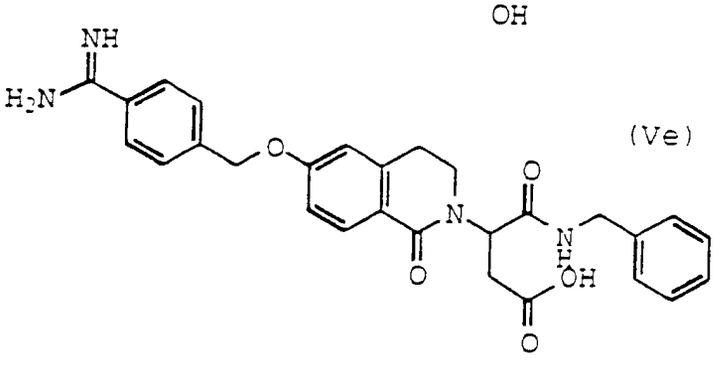
(Vb)



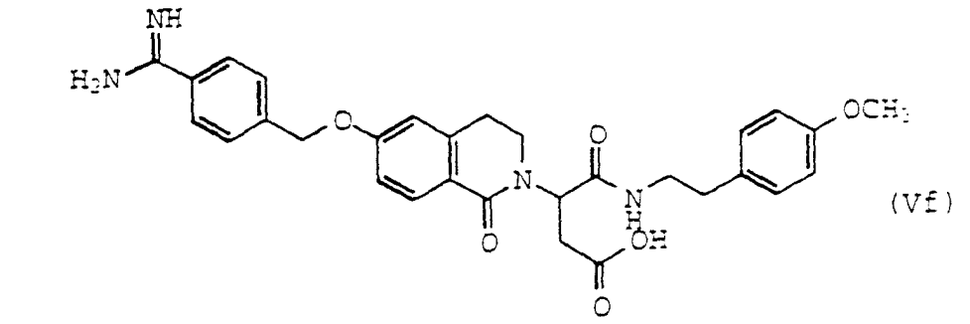
(Vc)



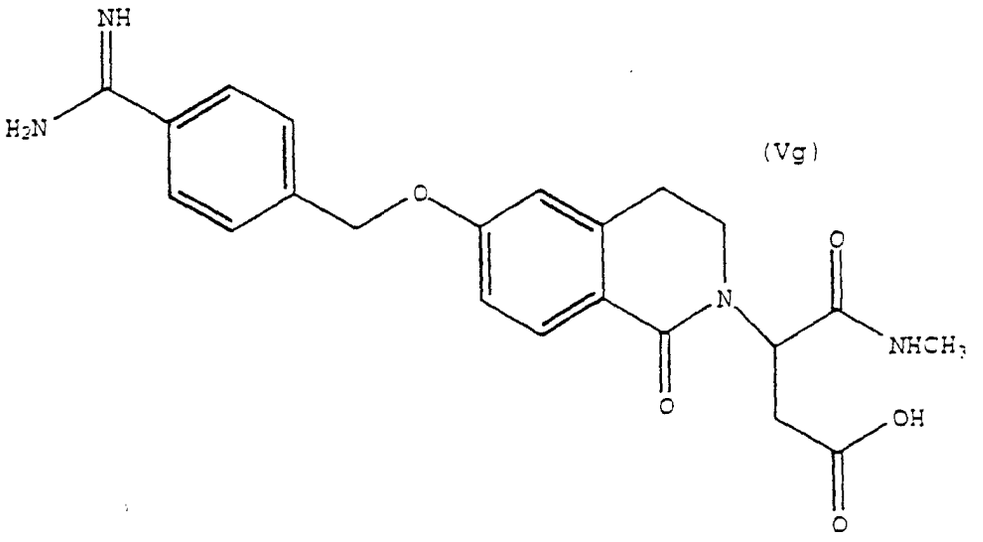
(Vd)



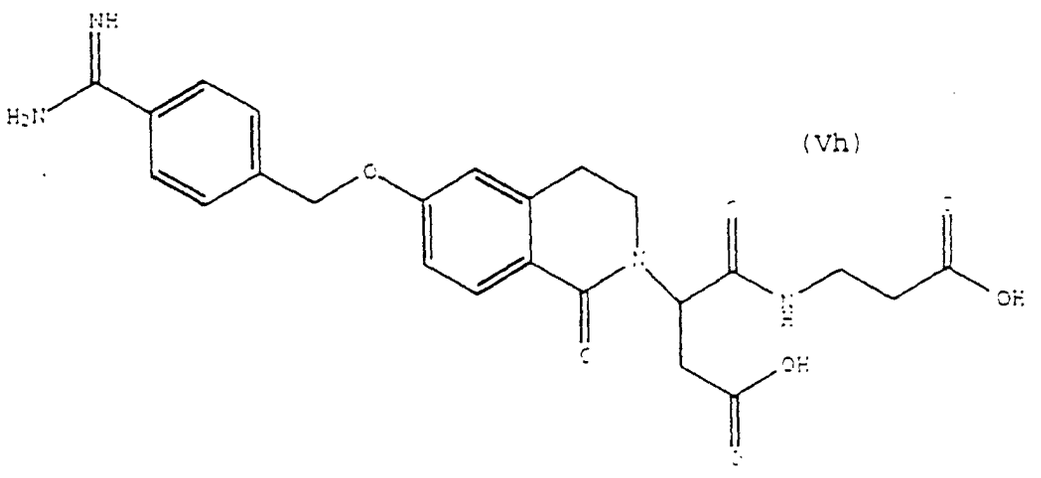
(Ve)



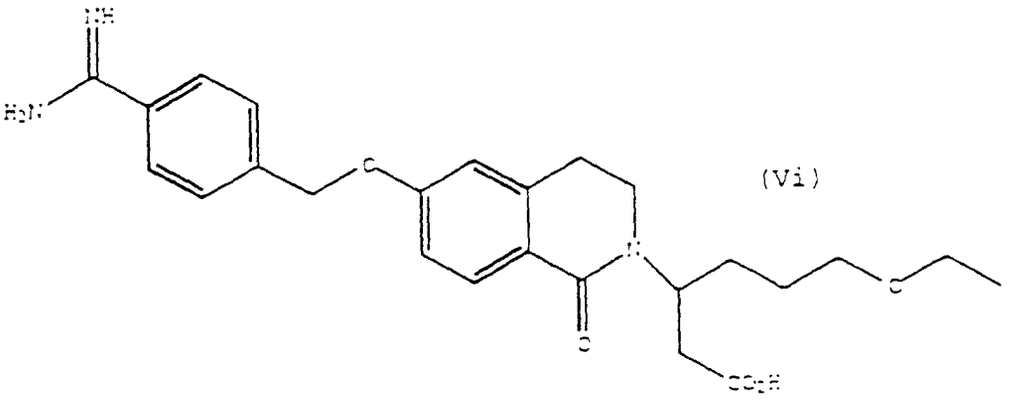
(Vf)



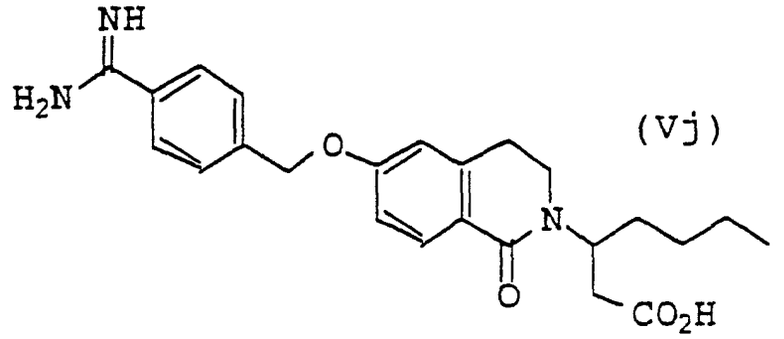
(Vg)



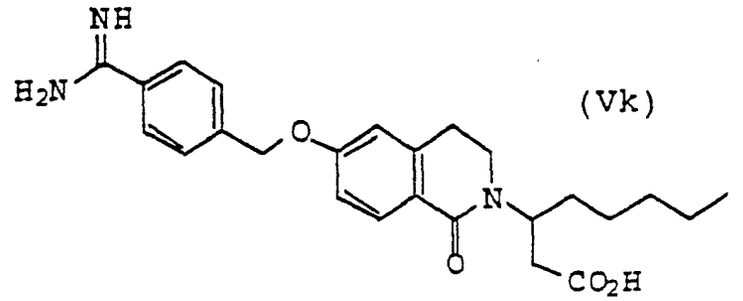
(Vh)



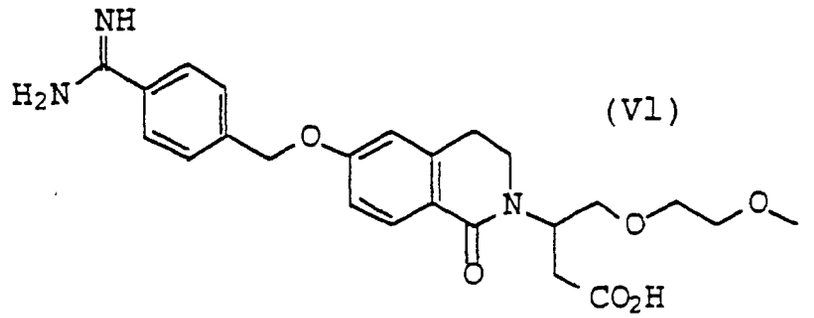
(Vi)



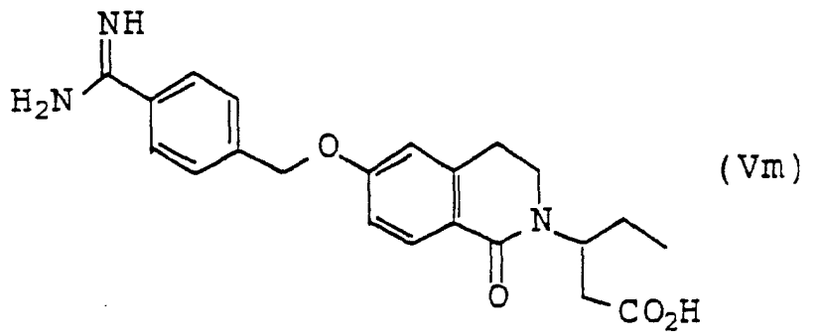
(Vj)



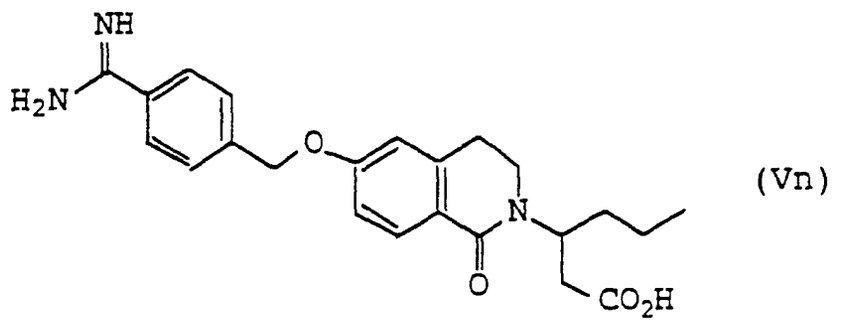
(Vk)



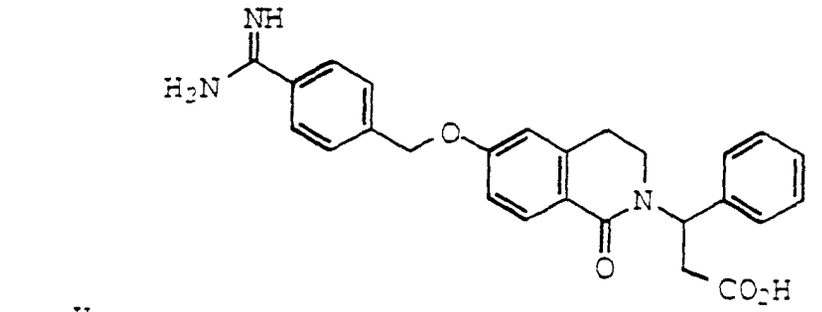
(Vl)



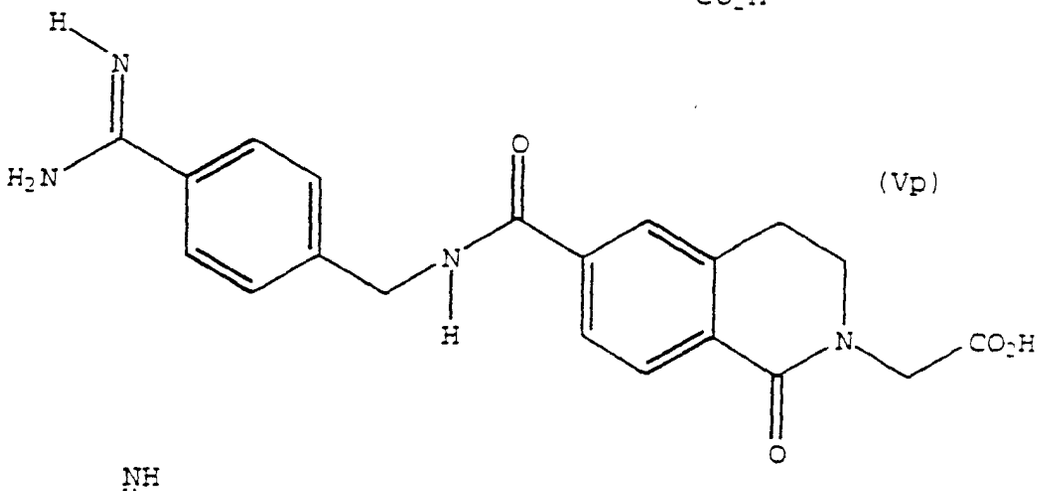
(Vm)



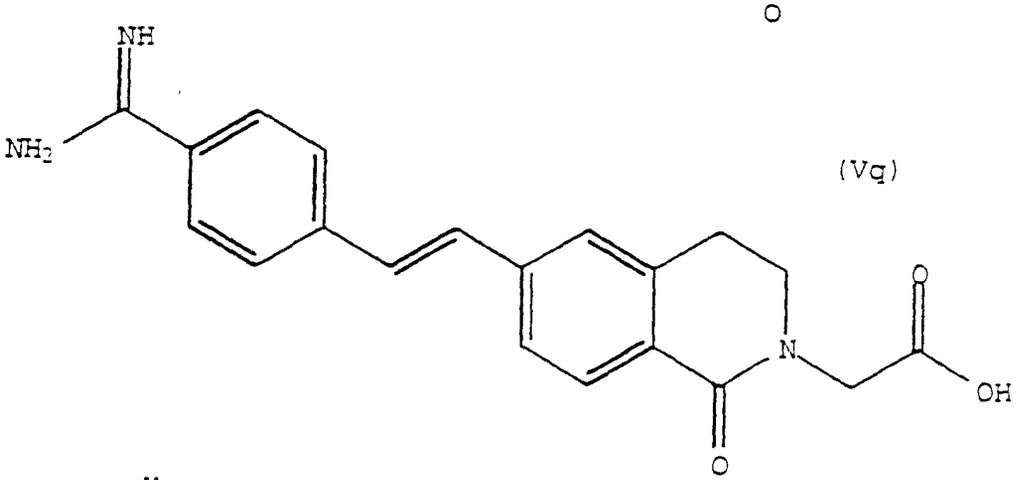
(Vn)



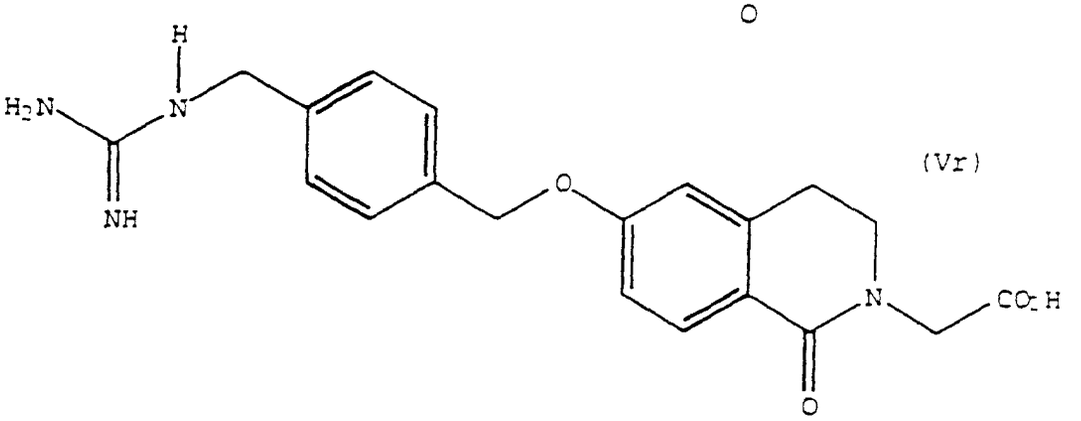
(Vo)



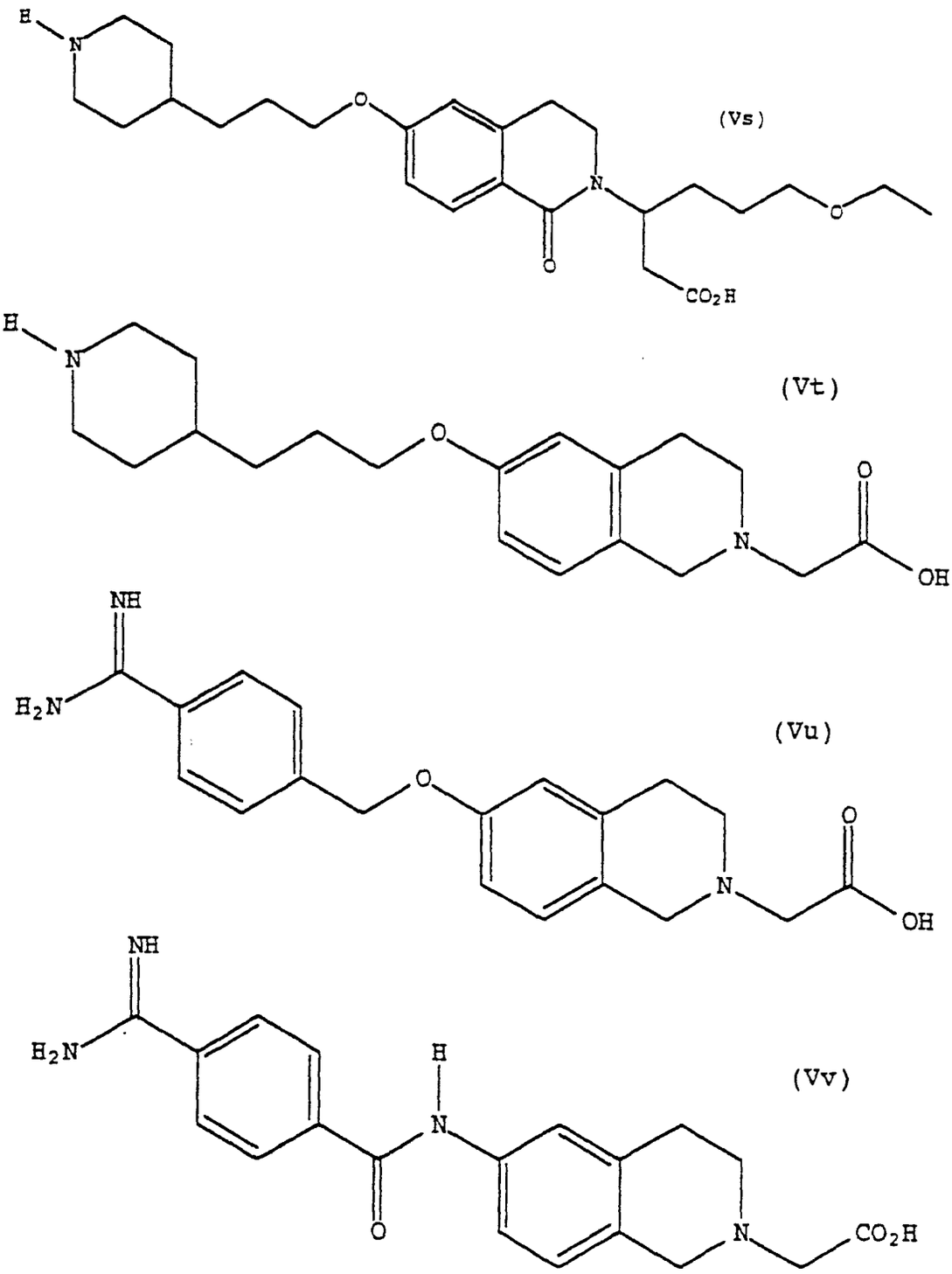
(Vp)



(Vq)

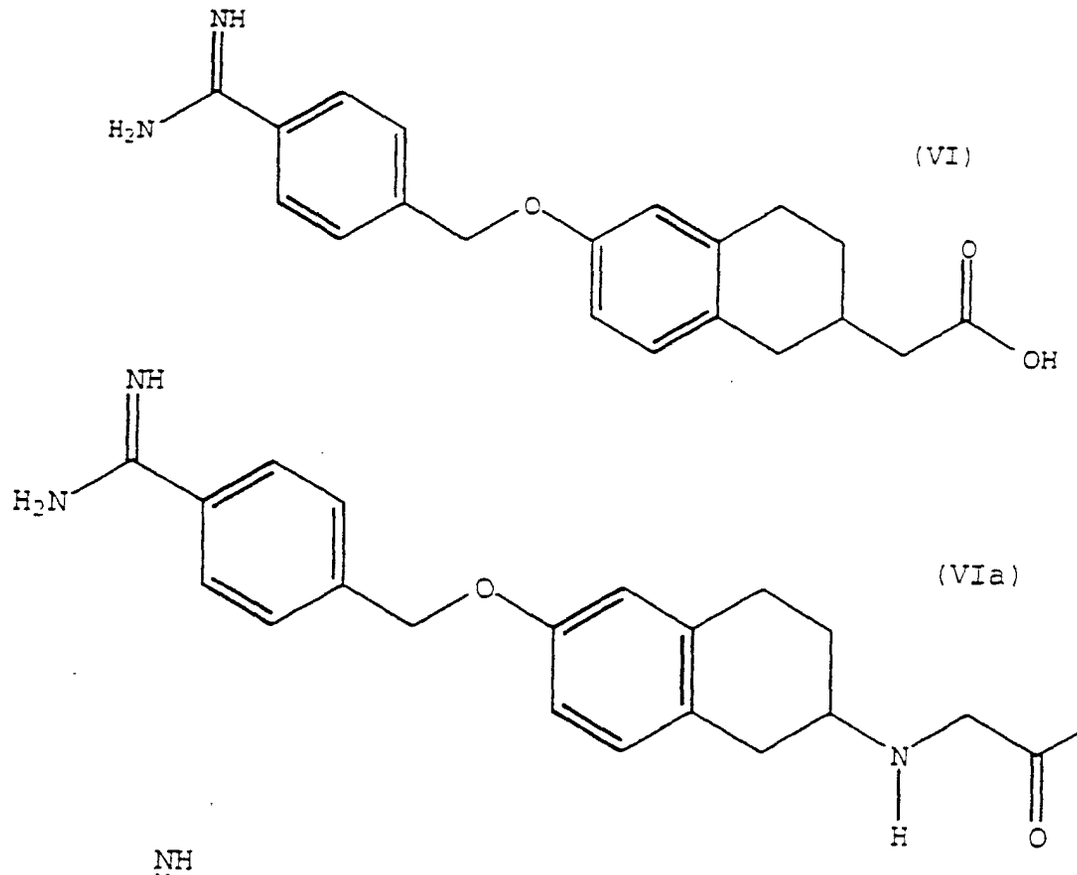


(Vr)



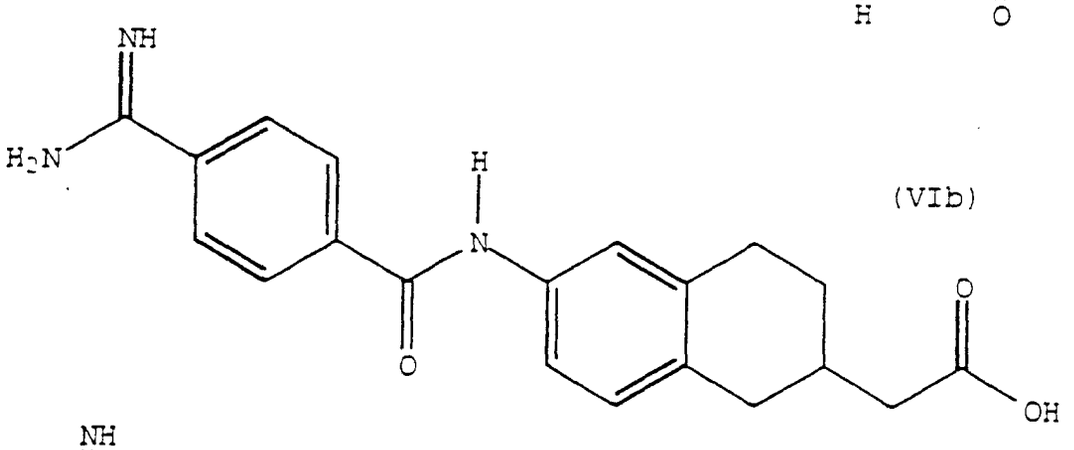
and mixtures of compounds (V) to (Vv).

[0076] Other specific compounds of the invention of the naphthalene/tetralin-type which are highly preferred are represented by the following structural formulae (VI) to (VIp) or pharmaceutically acceptable salts, solvates or prodrug derivatives thereof:

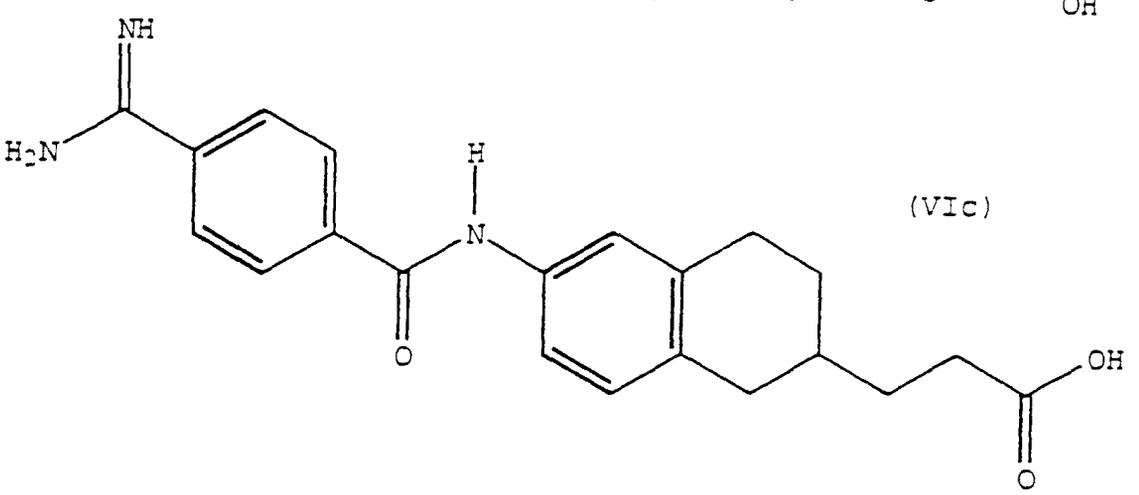


(VI)

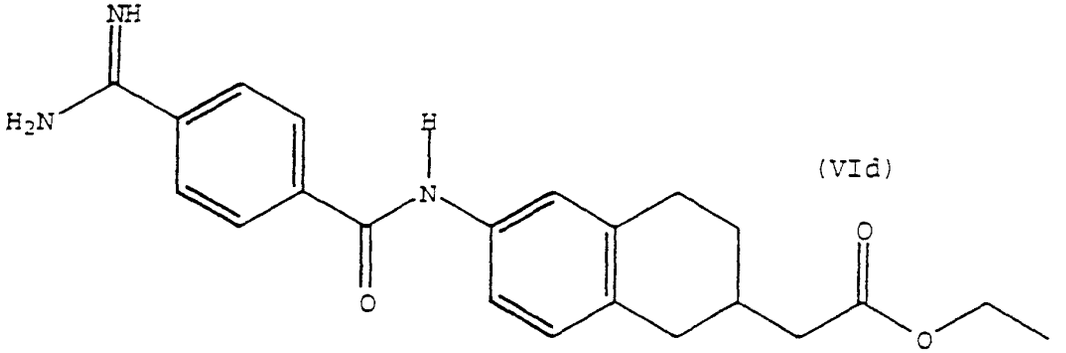
(VIa)



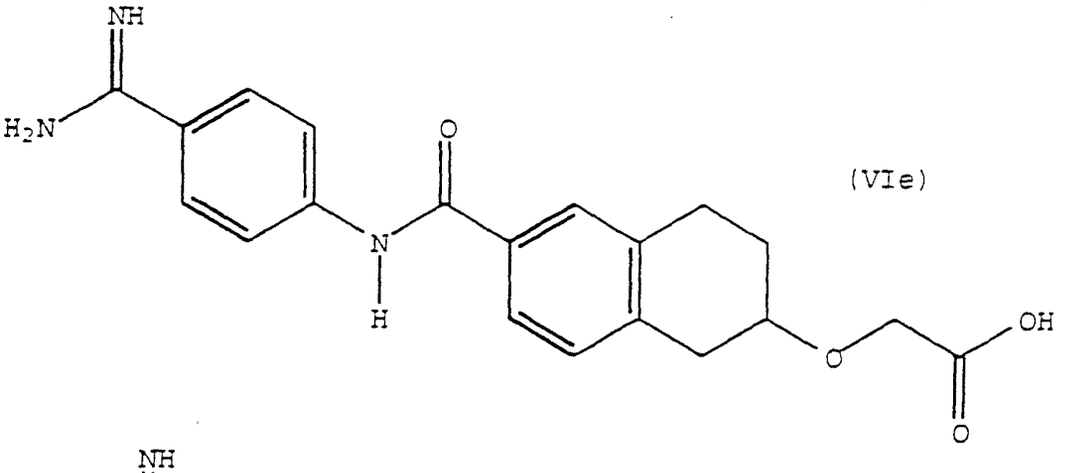
(VIb)



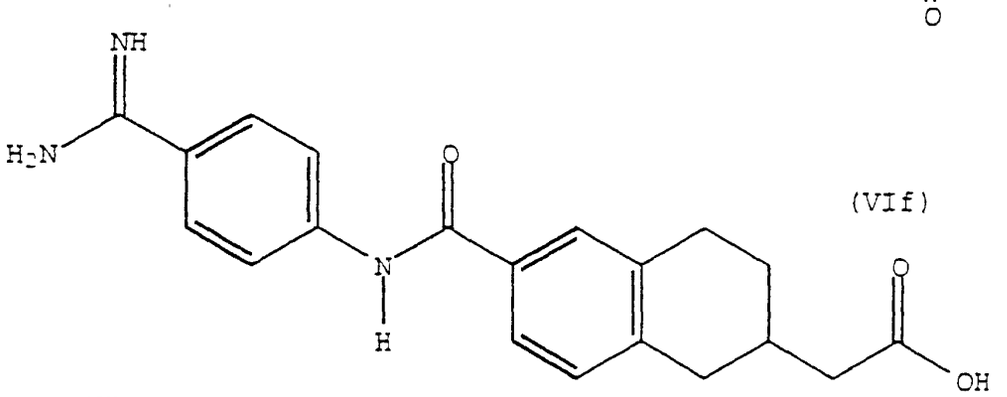
(VIc)



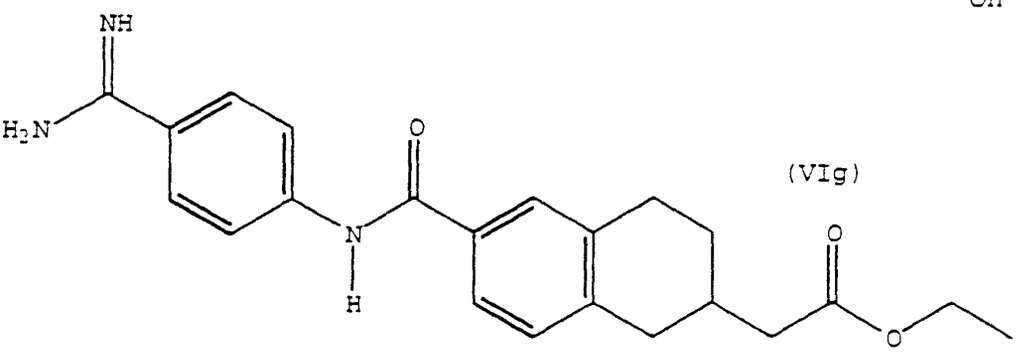
(VId)



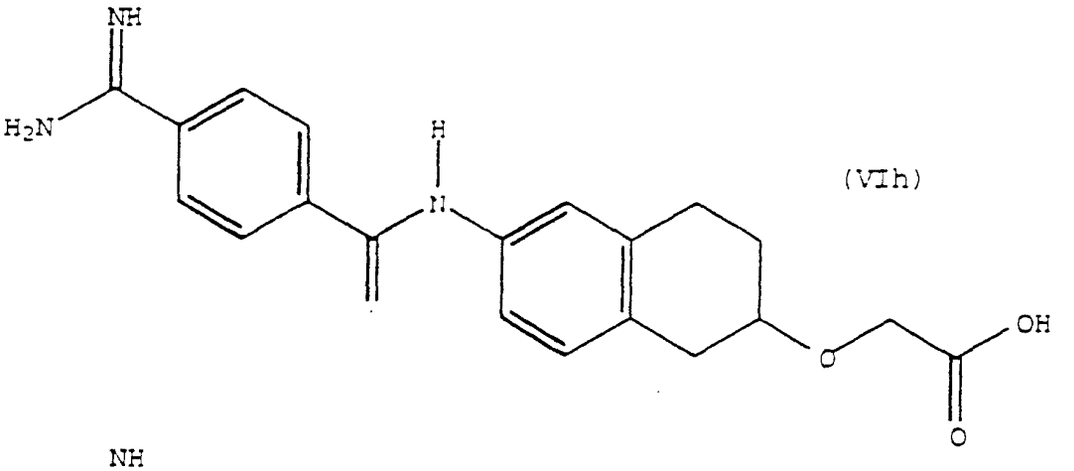
(VIe)



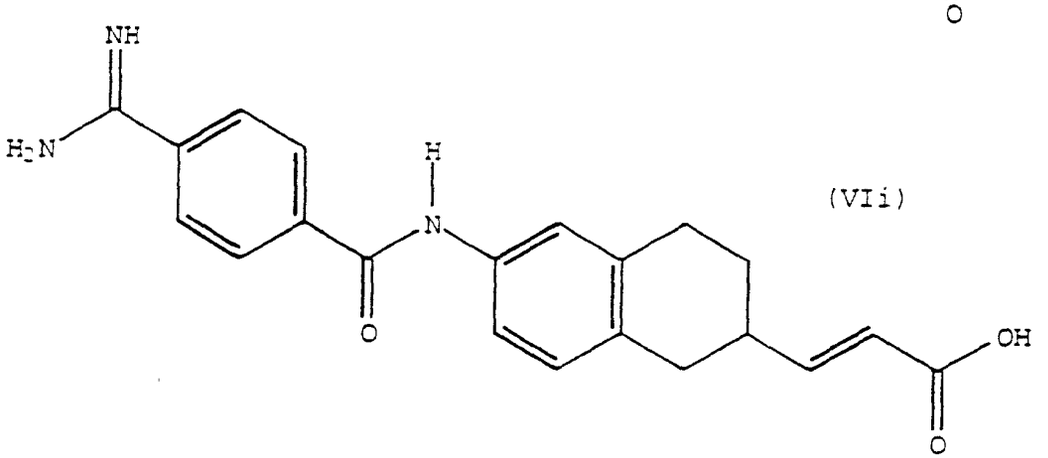
(VIf)



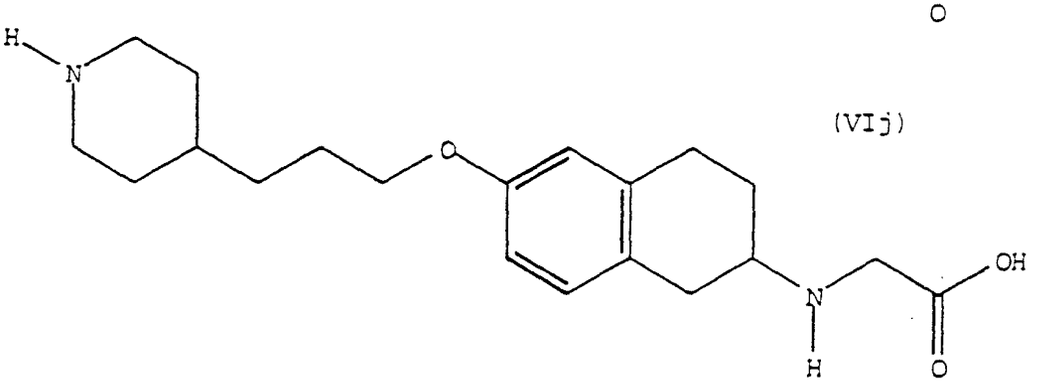
(VIg)



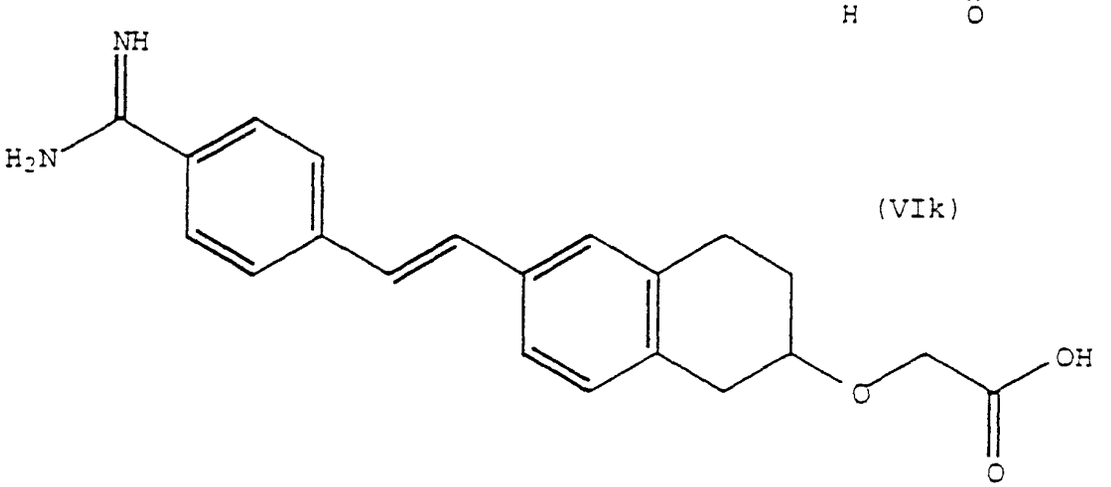
(VIh)



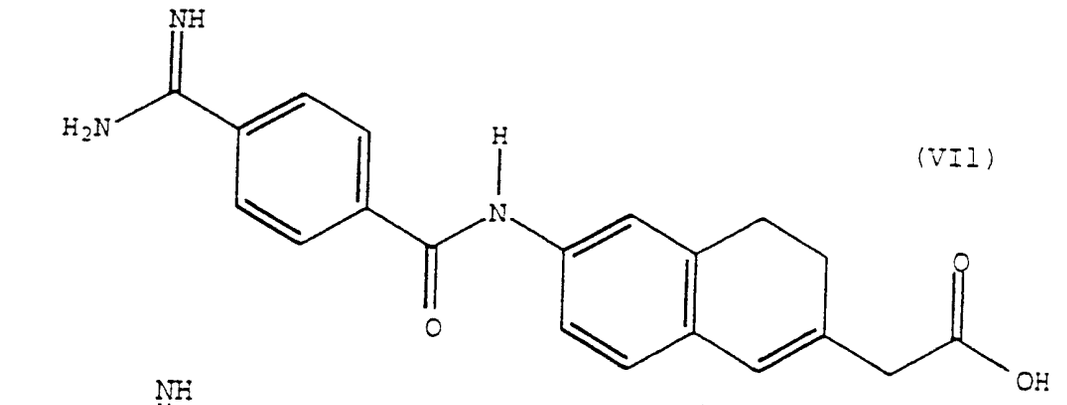
(VIi)



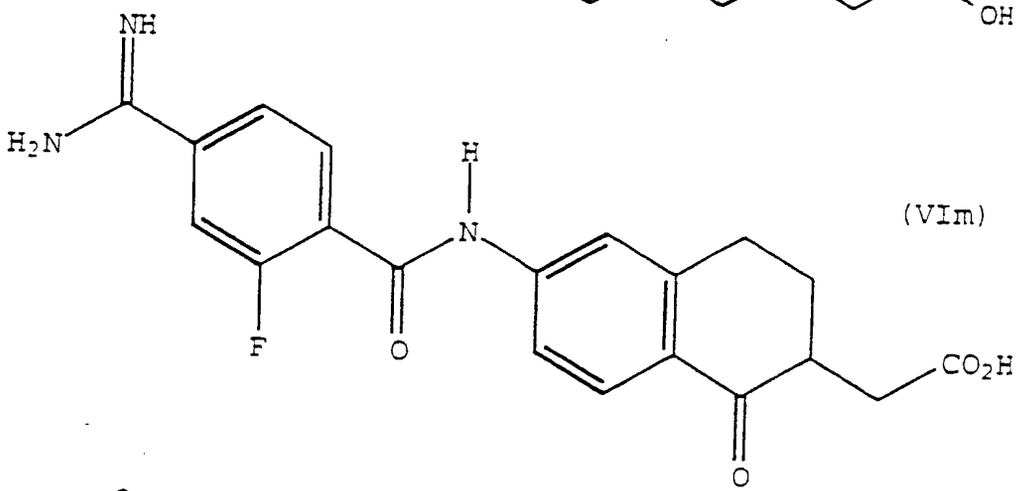
(VIj)



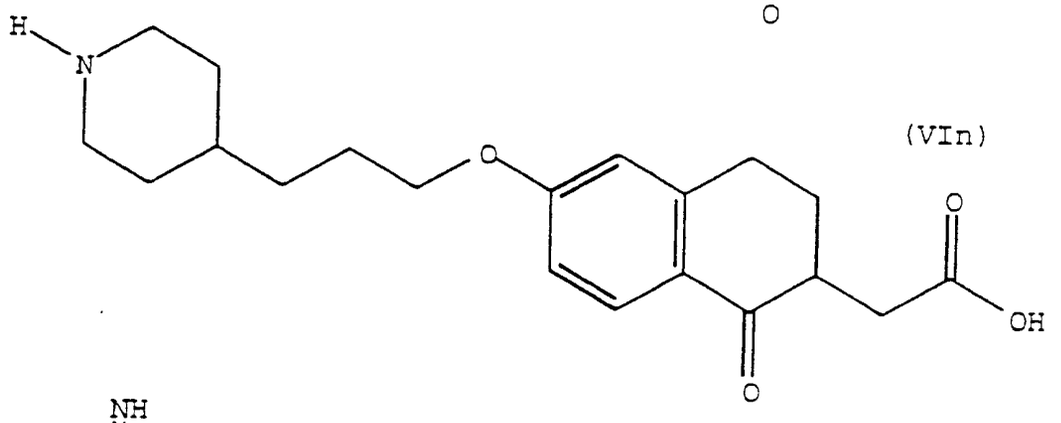
(VIk)



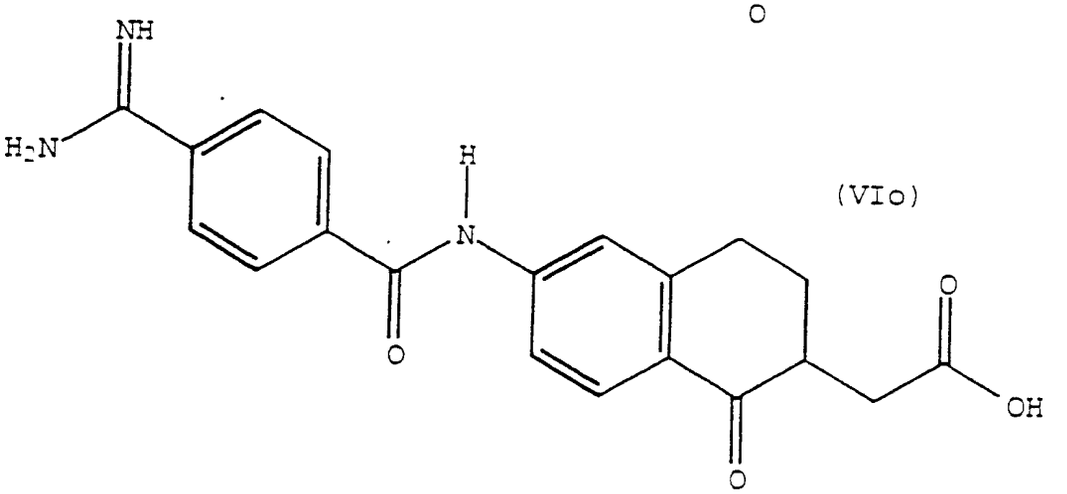
(VIl)



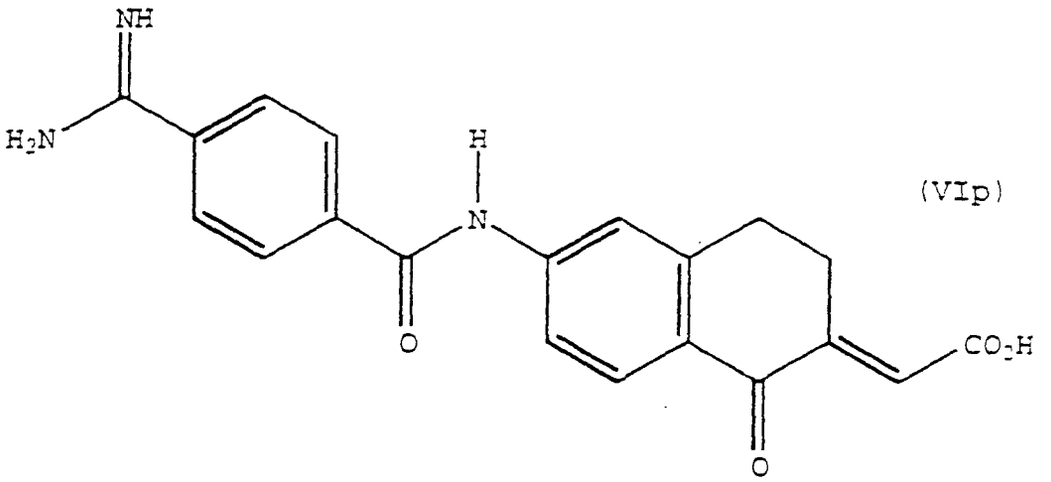
(VIm)



(VIn)



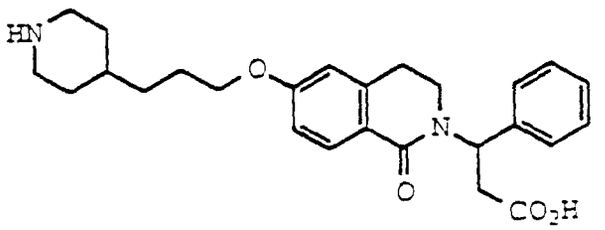
(VIo)



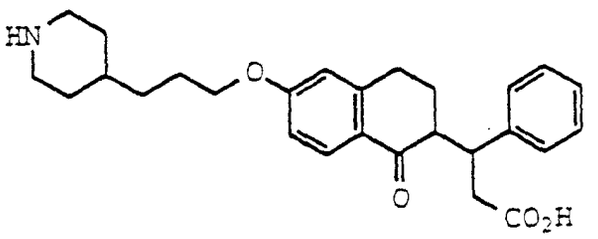
(VIp)

and mixtures of compounds (VI) through (VIp).

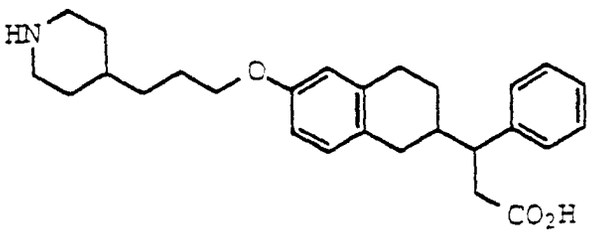
[0077] Other preferred specific compounds of the invention are represented by the following structural formulae (L) to LXIII) and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof:



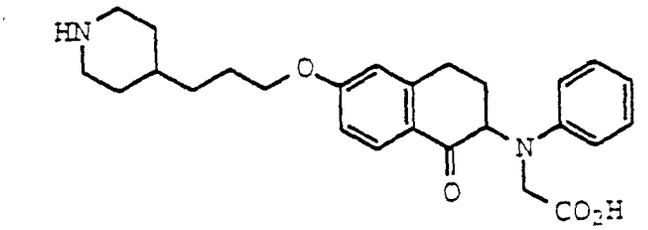
(L)



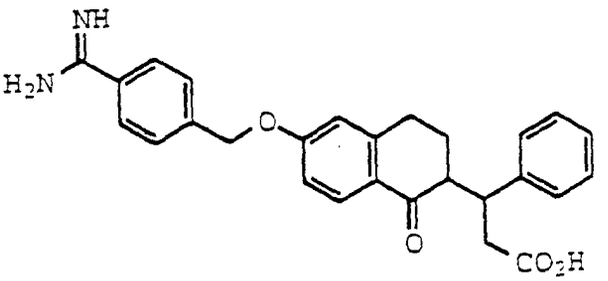
(LI)



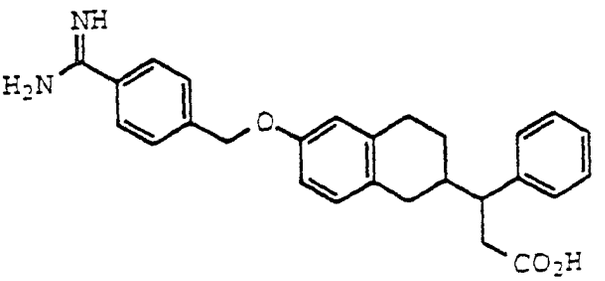
(LII)



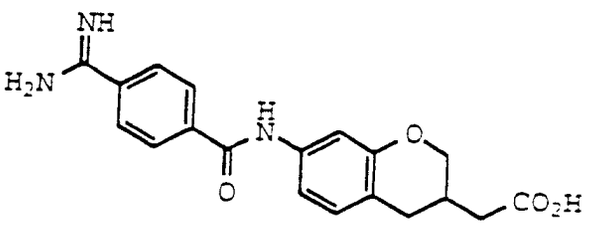
(LIII)



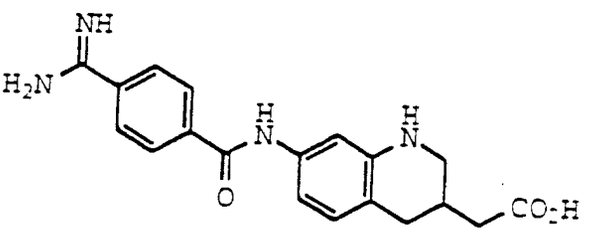
(LIV)



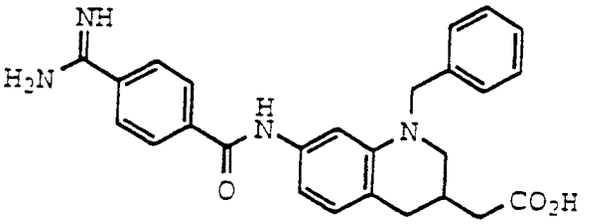
(LV)



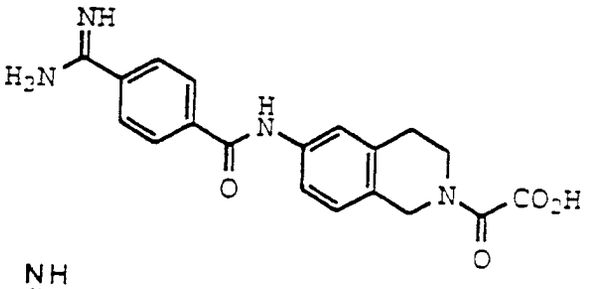
(LVI)



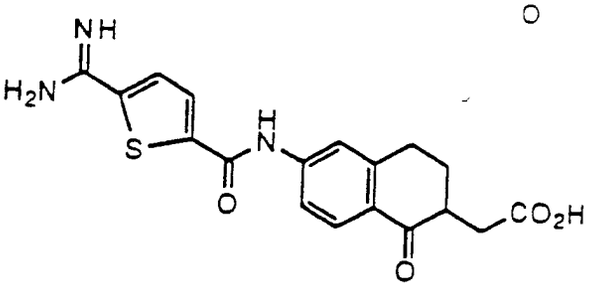
(LVII)



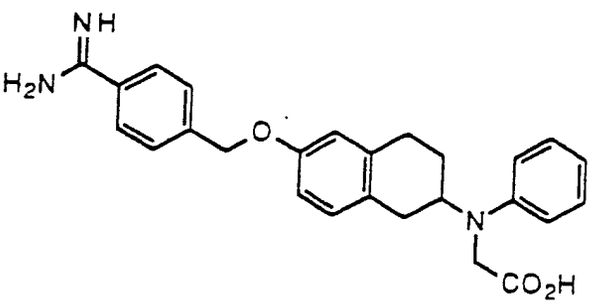
(LVIII)



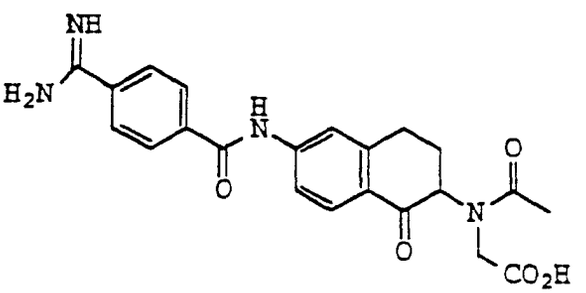
(LIX)



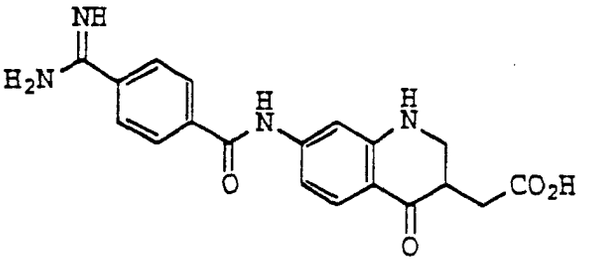
(LX)



(LXI)



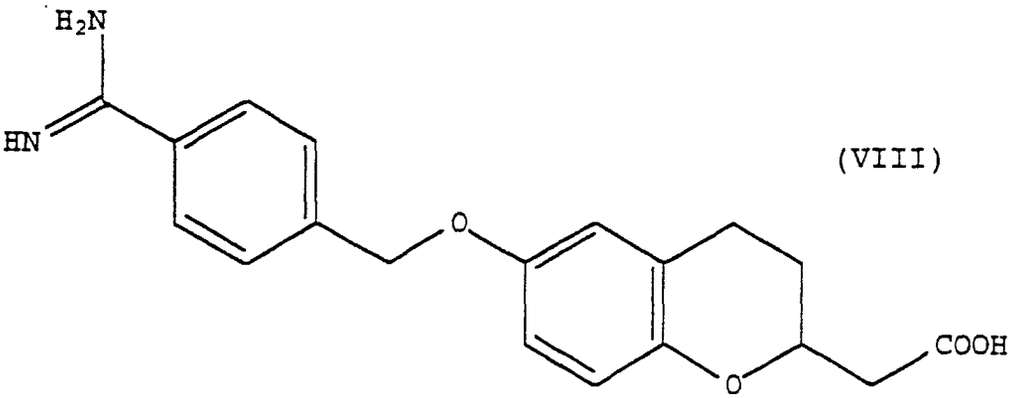
(LXII)



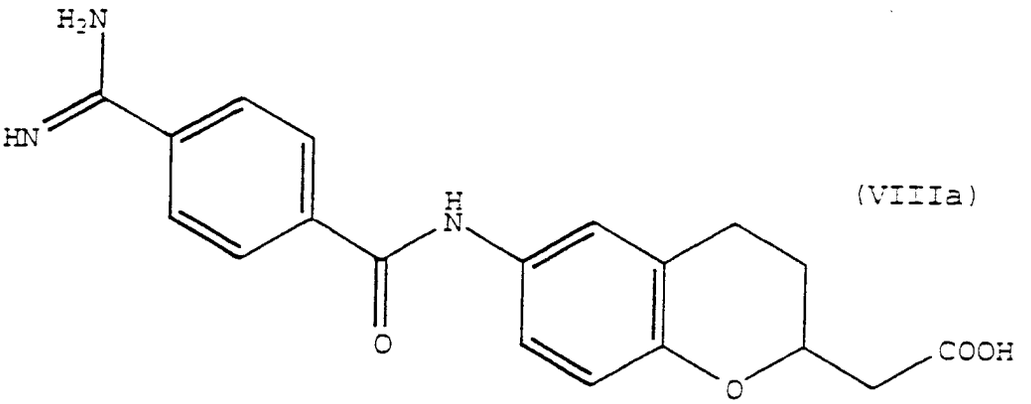
(LXIII)

and mixtures of any of (L) to (LXIII)

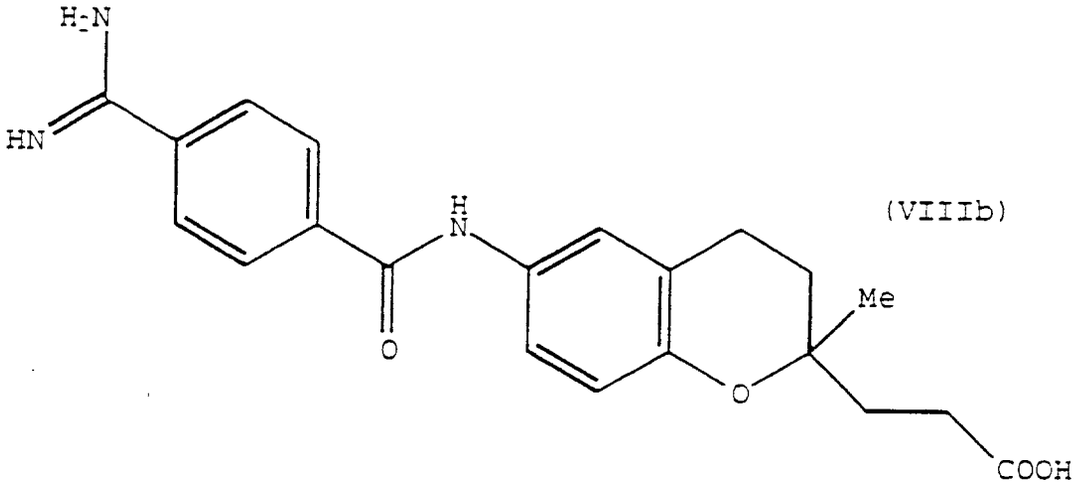
[0078] Other specific compounds of the invention of the benzopyran-type which are highly preferred are represented by the following structural formulae (VIII) to (VIIIi) or a pharmaceutically acceptable salt, solvate or prodrug derivatives thereof:



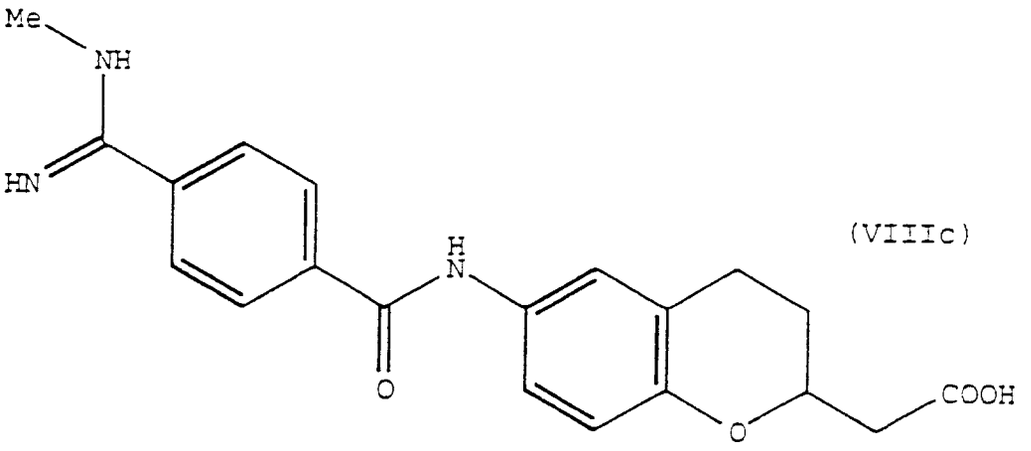
(VIII)



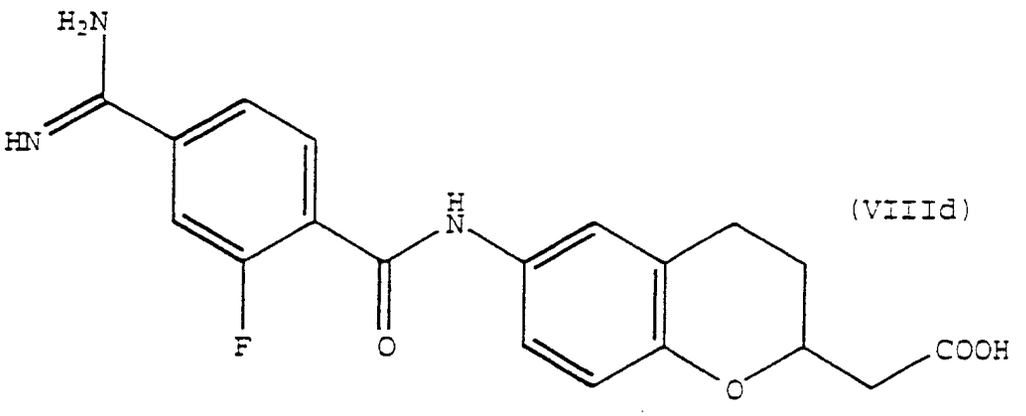
(VIIIa)



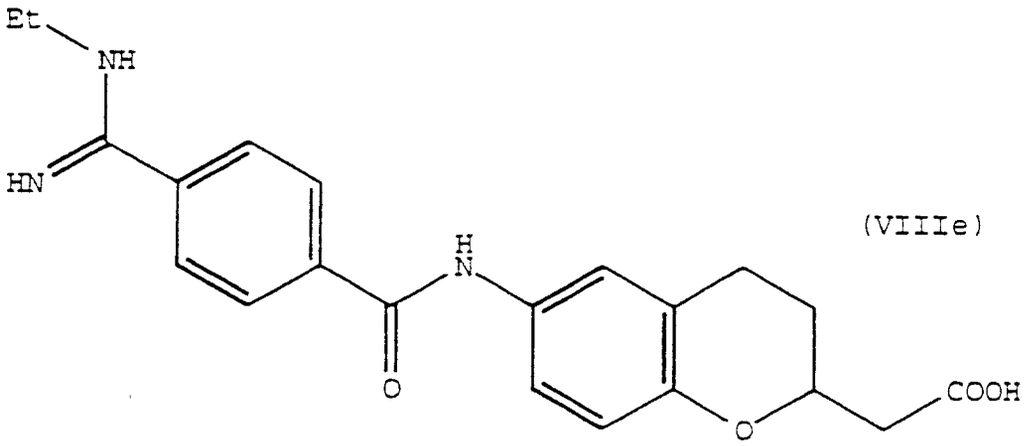
(VIIIb)



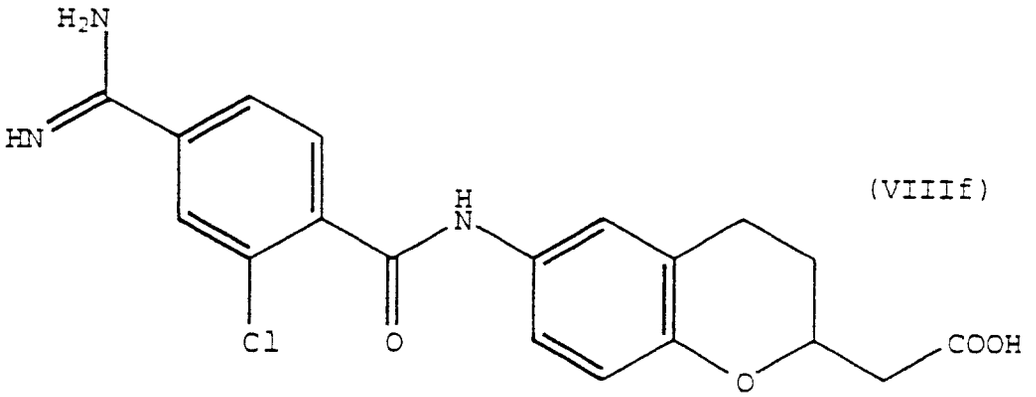
(VIIIc)



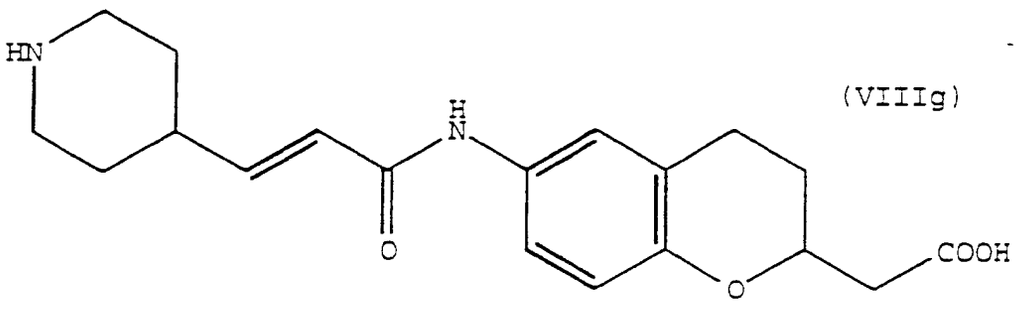
(VIIId)



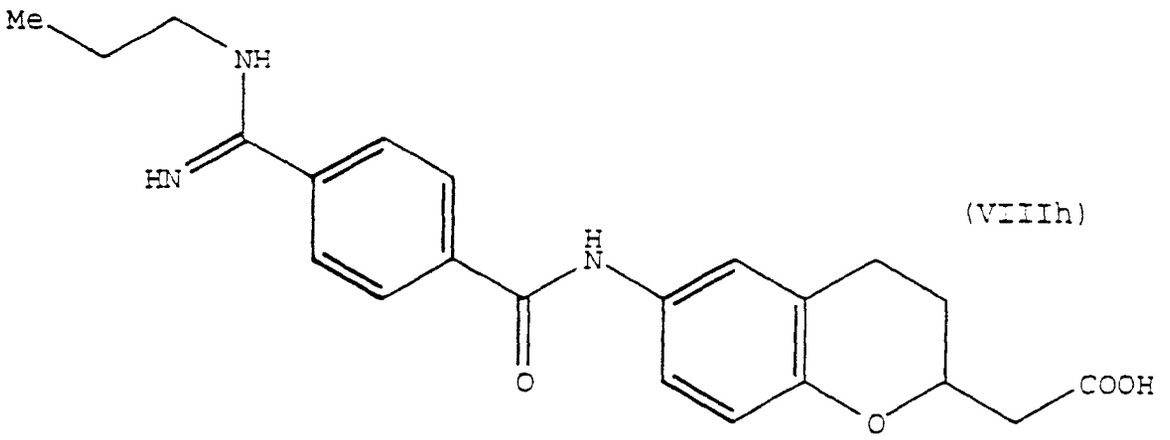
(VIIIe)



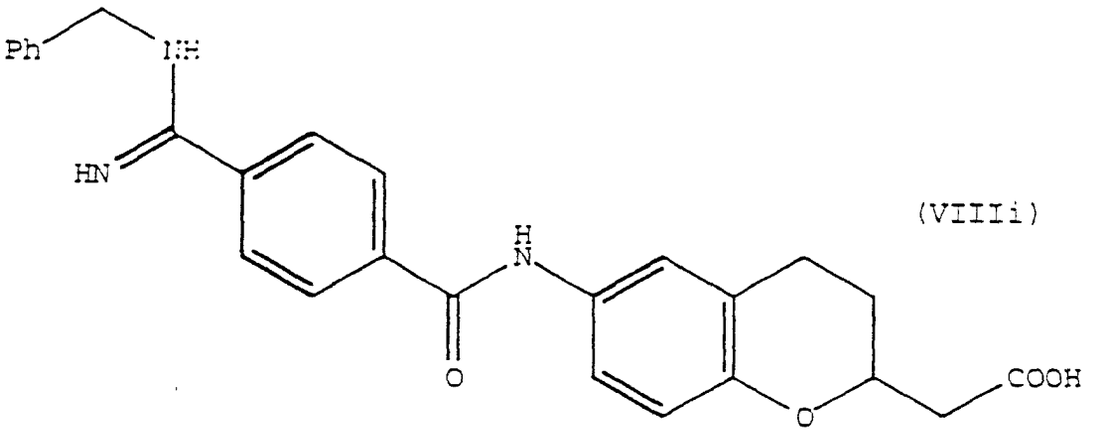
(VIIIf)



(VIIIg)

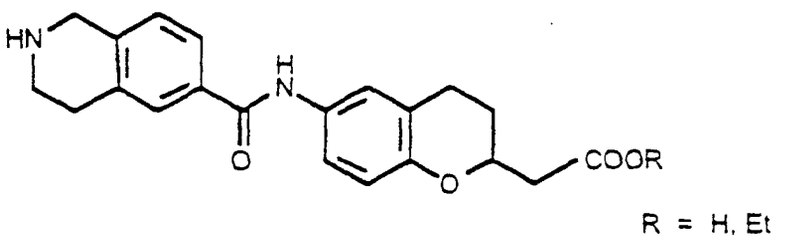


(VIIIh)



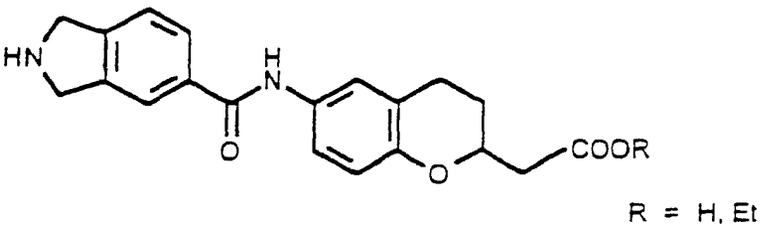
(VIIIi)

Other compounds of the invention having a bicyclic nucleus with an A ring oxygen atom are represented for the following formulae (IX) to (IXl) below:



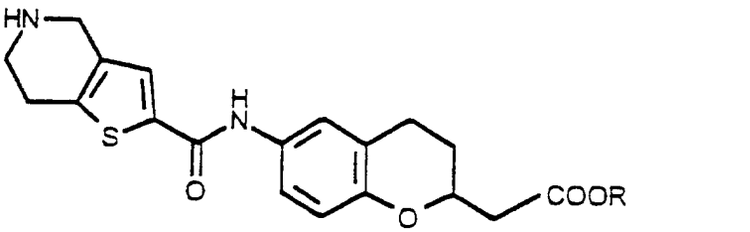
R = H, Et

(IX)



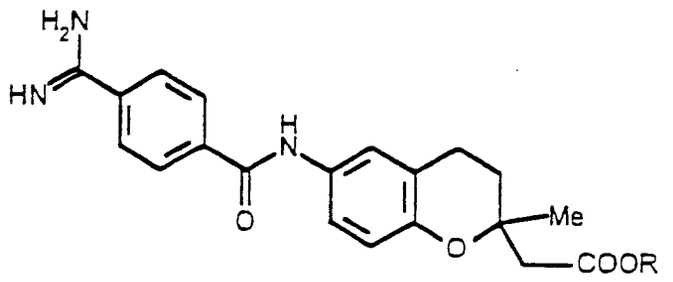
R = H, Et

(IXa)



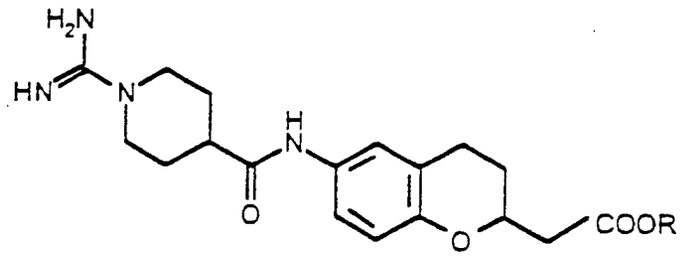
R = H, Et

(IXb)



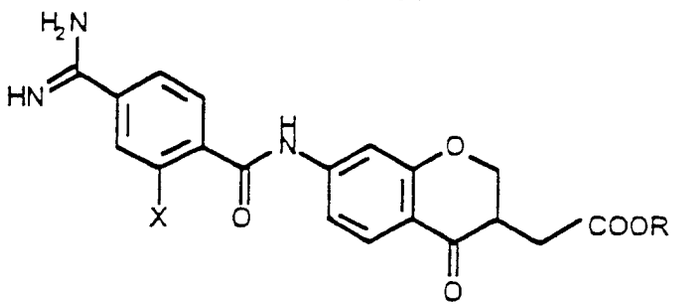
R = H, Et

(IXc)



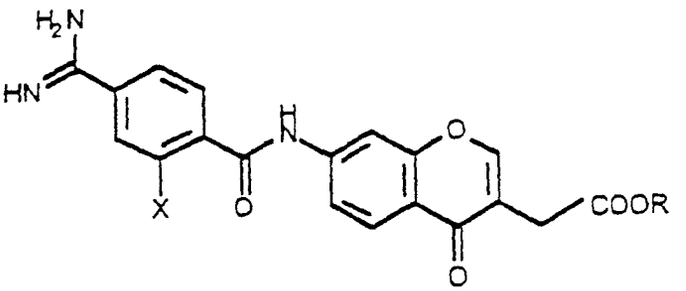
R = H, Et

(IXd)



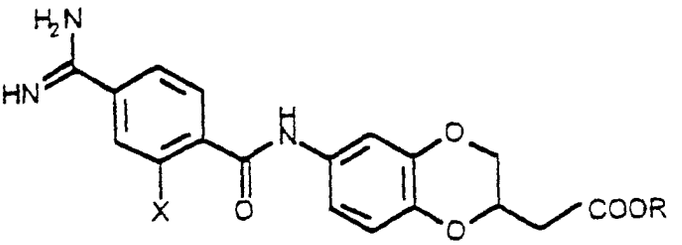
R = H, Et; X = H, F

(IXe)



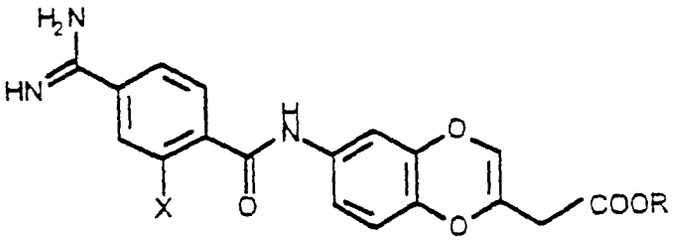
R = H, Et; X = H, F

(IXf)



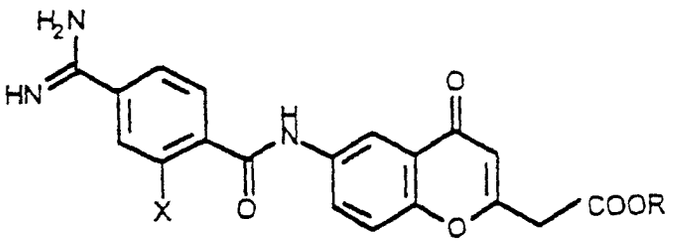
R = H, Et; X = H, F

(IXg)



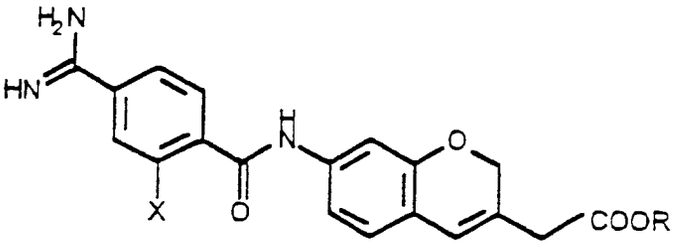
R = H, Et; X = H, F

(IXh)



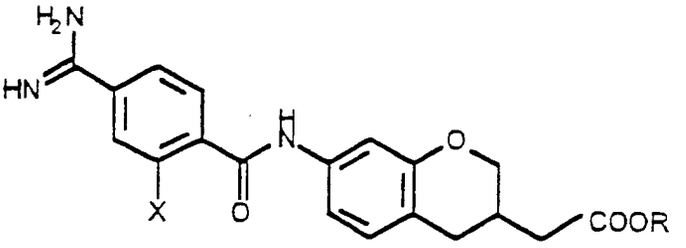
R = H, Et; X = H, F

(IXi)



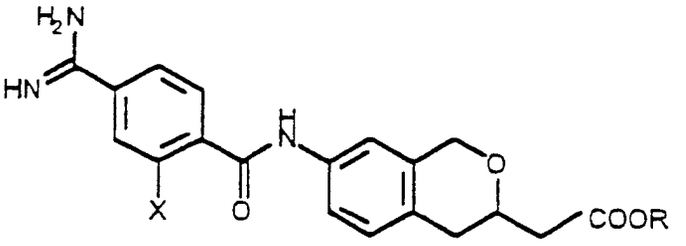
R = H, Et; X = H, F

(IXj)



R = H, Et; X = H, F

(IXk)



R = H, Et; X = H, F

(IXl)

[0079] The compounds of the invention possess at least one acidic functional substituent (viz., R_3 of Formula I) and, as such, are capable of forming salts. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an anion exchange resin on the salt cycle.

[0080] Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine actions, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Serge, et. al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)).

[0081] The basic portion of the compounds of the invention (viz., group Q of formula I and group Q_1 of formula II) may be reacted with suitable organic or inorganic acids to form salts of the invention. Representative salts include those selected from the group comprising; acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, camsylate, carbonate, chloride, clavulanate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanllate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hy-

droxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, malseate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

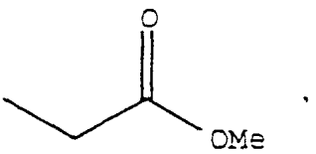
[0082] The compounds of the formula (I) can also be in the form of zwitterions, since they contain both acidic and basic functionality and are capable of self-protonation.

[0083] Certain compounds of the invention possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of *cis*- and trans- isomeric forms of the compounds. The *R*- and *S*-isomers and mixtures thereof, including racemic mixtures as well as mixtures of *cis*- and *trans*- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods.

Prodrug Derivatives of Compounds of the Invention:

[0084] Prodrugs are derivatives of the compounds of the invention which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active *in vivo*. For example, ester derivatives of compounds of this invention are often active in vivo, but not in vitro. Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine. Simple aliphatic or aromatic esters derived from acidic groups pendant on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl) oxy)alkyl esters.

[0085] Preferred are the C_1-C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl esters of the compounds of the invention (per formula I) Particularly preferred are the C_1-C_4 alkyl esters, for example, where the R_3 acidic group has been esterified to form a group represented by one of the following formulae:



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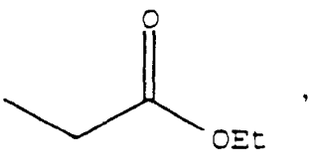

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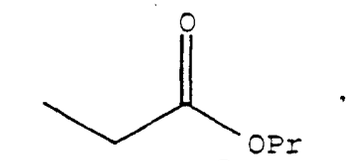
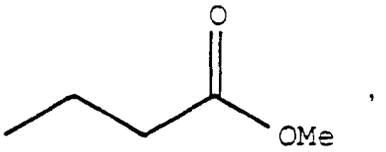
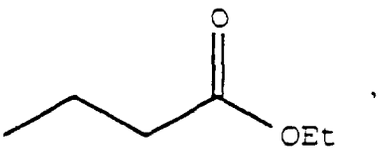
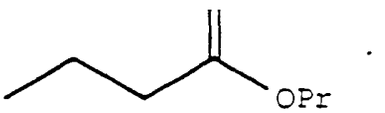


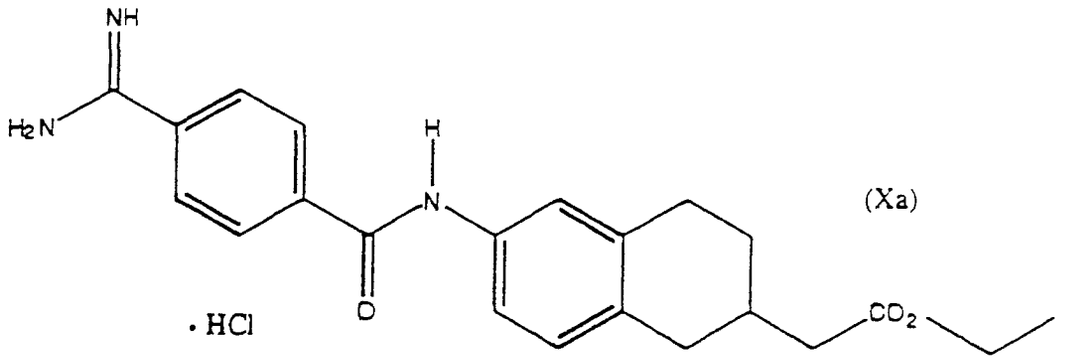




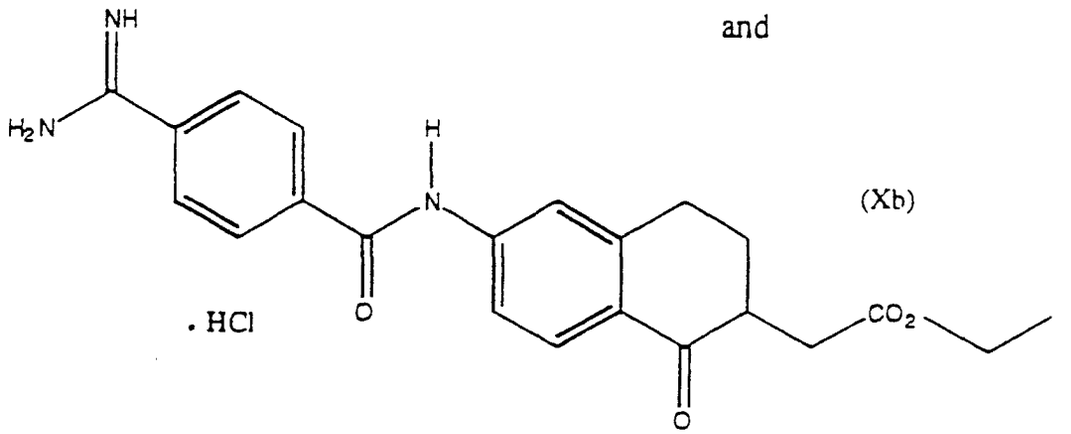
and



[0086] Other specific prodrug derivatives which are compounds of the invention are represented by the formulae (Xa) and (Xb) shown below:

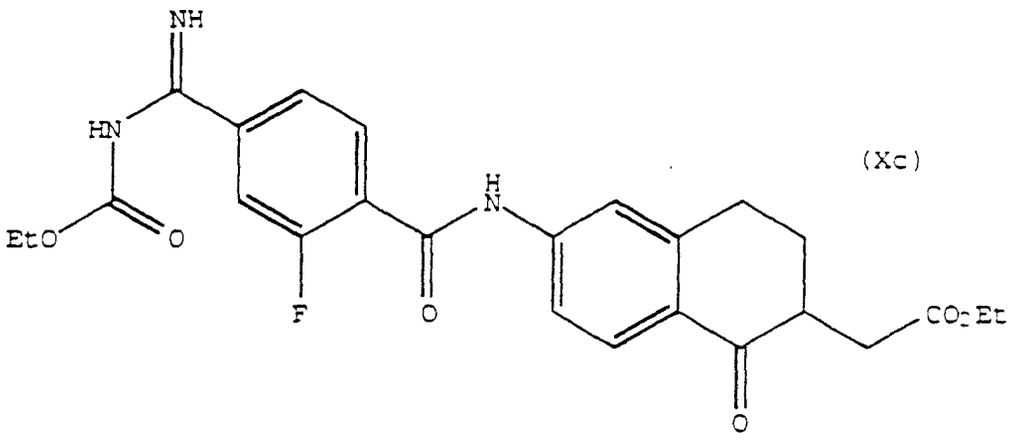


and

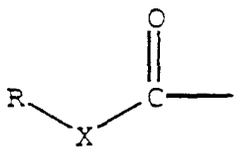


[0087] Acylated basic radicals which are part of basic group on the compounds of the invention have been found to significantly enhance bioavailability. Without being bound by any theory of operation, it is believed that lowering the basicity of basic group (Q) makes the compounds of this invention less subject to "food effect", that is, they have good availability in therapeutic administration to an animal without fasting.

[0088] Compounds of this invention may beneficially be dual prodrug derivatives. For example, the acidic group (R_3) may be reacted to form an ester and the basic group Q (or basic radical Q_1) may additionally be reacted to form an acylated basic derivative. Moreover, the prodrug derivatives of the compounds of this invention may be combined with other features herein taught to enhance bioavailability, for example, substitution of fluorine atoms on the D ring of the compounds of formula (II). These combined features result in a compound such as represented by the formula (Xc) :

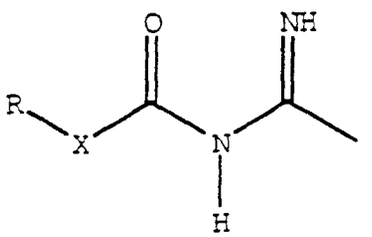


[0089] Another highly preferred class of prodrugs of the invention are those formed by acylating the basic radicals (e.g., Q_1) present on the compounds of the invention. The acyl portion of the acylated basic radical has the general formula:

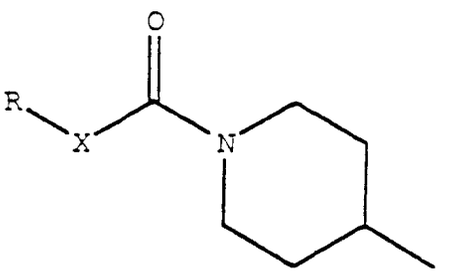


where R is C_1-C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl; and X is a bond, C, O, S, or N. Preferably R is C_1-C_4 alkyl and X is oxygen. For example, acylated basic radical prodrugs of the invention are prepared and illustrated in A, B, C, and D below:

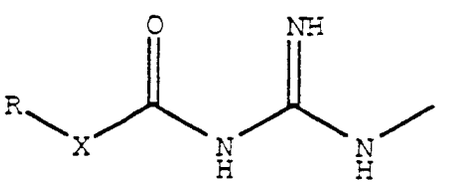
A) acylation of amidine results in a prodrug derivative group:



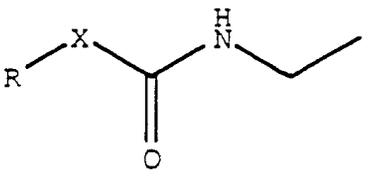
B) acylation of a cyclic amine such as piperidine results in a prodrug derivative group:



C) acylation of guanidine results in a prodrug derivative group:

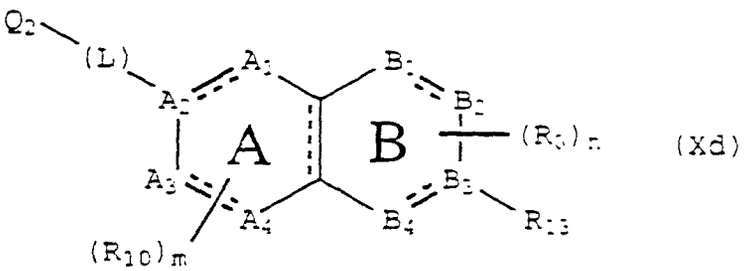


D) acylation of a primary amine results in a prodrug derivative group:



where, for A, B, C, and D above, R is as defined above for the acylated portion of the basic group.

[0090] The therapeutic compounds of this invention include prodrug derivatives of bicyclic compounds having a nucleus formed from two fused six membered rings, A and B, represented by the formula (Xd):



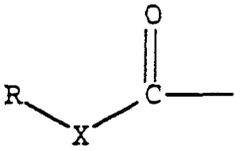
(Xd)

wherein;

A_1, A_3, A_4 are independently selected from carbon, oxygen, sulfur, and nitrogen;
A_2 is independently selected from carbon or nitrogen, provided that A_2 have an unsatisfied bond if A_2 is N and provided that at least two of A_1, A_2, A_3, and A_4 are carbon;
B_1, B_2, B_4 are independently selected from carbon, oxygen, sulfur, and nitrogen;
B_3 is independently selected from carbon or nitrogen, provided that B_3 have an unsatisfied bond if B_3 is N and provided that at least two of B_1, B_2, B_3, B_4 are carbon;
n is a number from 2 to 6;
R_0 is the same or different and is independently selected from hydrogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, sulfo, =O, or =S; with the proviso that if R_0 is =O or =S, then only one of B_1, B_2, B_3, and B_4 may be nitrogen;
m is a number from 2 to 6;
R_{10} is the same or different and is independently selected from hydrogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, carboxy, acyl, cyano, halo, nitro, sulfo, =O, and =S; with the proviso that only one R_{10} may be =O or =S;
linking group -(L)- is a bond or a divalent substituted or unsubstituted chain of from 1 to 10 atoms selected from the group consisting of carbon, nitrogen, sulfur, and oxygen; and;
Q_2 is selected from (i) a basic group, or (ii) a basic group containing an acylated basic radical;
R_{13} is selected from (i) an acidic group containing an acid radical, or (ii) an acidic group containing an ester derivative of an acid radical;
provided that at Q_2 is a basic group containing an acylated basic radical or R_{13} is an acidic group containing an ester derivative of an acid radical.

[0091] A preferred form of prodrug derivative is a compound of formula (Xd) having dual prodrug functionality, that is, where Q_2 is a basic group containing an acylated basic radical and R_{13} is an acidic group containing an ester derivative of an acid radical.

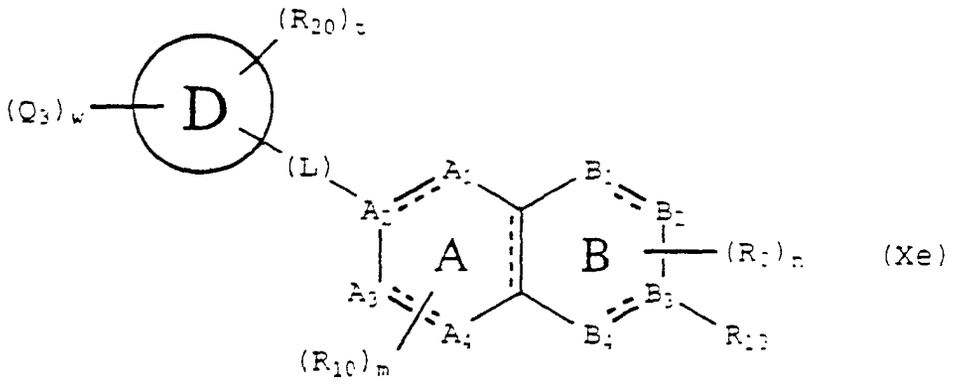
[0092] Another preferred form of prodrug is a compound of formula (Xd) wherein the acylated portion of the acylated basic radical has the general formula:



where R is C_1-C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl; and X is a bond, C, O, S, or N. Preferably R is C_1-C_4 alkyl and X is oxygen.

[0093] The group Q_2 may comprise two parts, namely, (i) one or more radicals selected from basic radicals or acylated basic radicals each designated, "Q_3", and (ii) a cyclic group D (as previously defined form formula Iw). zzz

[0094] A general formula for the prodrug derivatives of this invention is a bicyclic compound having a nucleus formed from two fused six membered rings, A and B, represented by the formula (Xe), or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof:



(Xe)

wherein;

A_1, A_3, A_4 are independently selected from carbon, oxygen, sulfur, and nitrogen;

A_2 is independently selected from carbon or nitrogen, provided that A_2 have an unsatisfied bond if A_2 is N and provided that at least two of A_1, A_2, A_3, and A_4 are carbon;

B_1, B_2, B_4 are independently selected from carbon, oxygen, sulfur, and nitrogen;

B_3 is independently selected from carbon or nitrogen, provided that B_3 have an unsatisfied bond if B_3 is N and provided that at least two of B_1, B_2, B_3, B_4 are carbon;

n is a number from 0 to 6;

R_0 is the same or different and is independently selected from hydrogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, sulfo, =O, or =S; with the proviso that if R_0 is =O or =S, then only one of B_1, B_2, B_3, and B_4 may be nitrogen;

m is a number from 0 to 6;

R_{10} is the same or different and is independently selected from hydrogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, carboxy, acyl, cyano, halo, nitro, sulfo, =O, and =S; with the proviso that only one R_{10} may be =O or =S;

t is a number from 0 to 3;

R_{20} is the same or different and is independently selected from hydrogen, halogen, alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, carboxy, acyl, cyano, halo, nitro, sulfo;

linking group -(L)- is a bond or a divalent substituted or unsubstituted chain of from 1 to 10 atoms selected from the group consisting of carbon, nitrogen, sulfur, and oxygen; and;

D is a ring formed from 5 to 8 ring atoms and said ring atoms are independently selected from carbon, nitrogen, oxygen, or sulfur, with the proviso that at least two D ring atoms are carbon;

w is an integer from 1 to 3;

Q_3 is selected from (i) a basic radical, or (ii) an acylated basic radical;

R_{13} is selected from (i) an acidic group containing an acid radical, or (ii) an acidic group containing an ester derivative of an acid radical;
provided that Q_3 is an acylated basic radical or R_{13} is an acidic group containing an ester derivative of an acid radical;

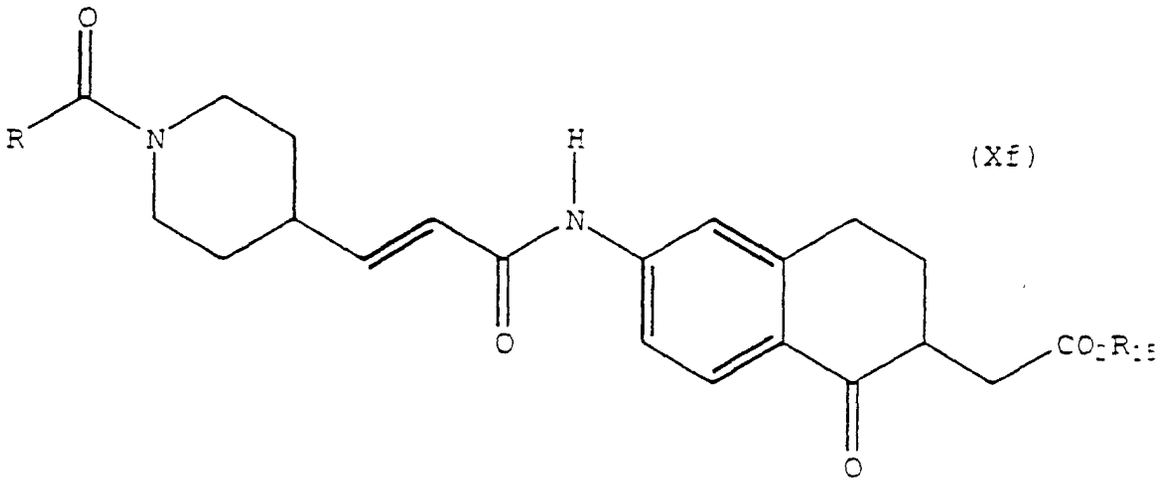
[0095] The integer w is preferably 1.

[0096] It is preferred in formula (Xe) that R_{20} be chlorine and/or fluorine and t equal 1 or 2. Also preferred are compounds of formula (Xe) wherein Q_3 is an acylated basic radical and R_{13} is an acidic group containing an ester derivative of an acid radical.

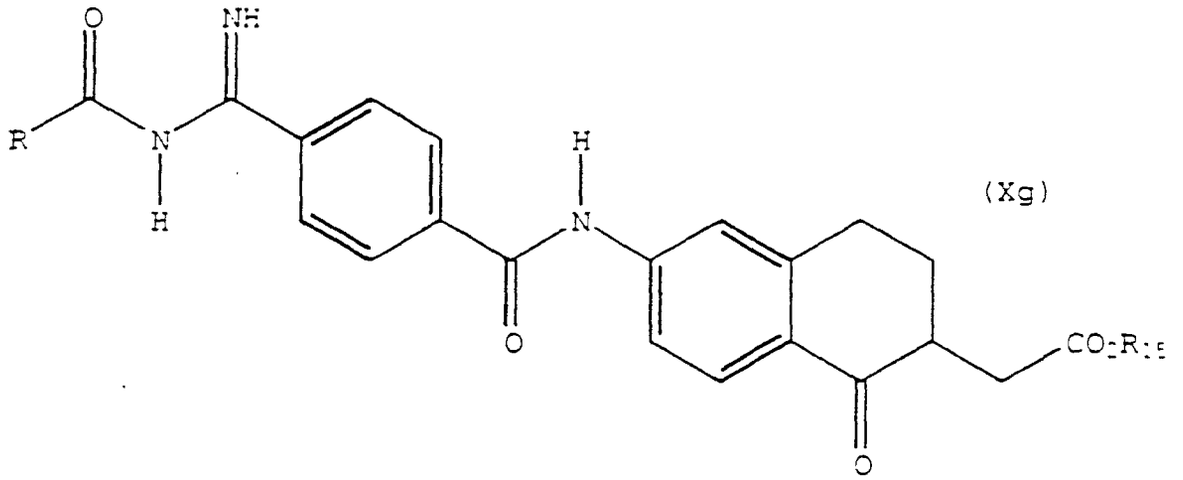
[0097] The most preferred acylated basic groups are carbamic acid esters of amidine, piperidine, or guanidine basic radicals. Carbamate acid C_1 to C_4 alkyl esters of amidine radicals are most highly preferred.

[0098] Carbamate ester prodrug derivatives of the invention may be prepared by a method such as shown in Scheme 27.

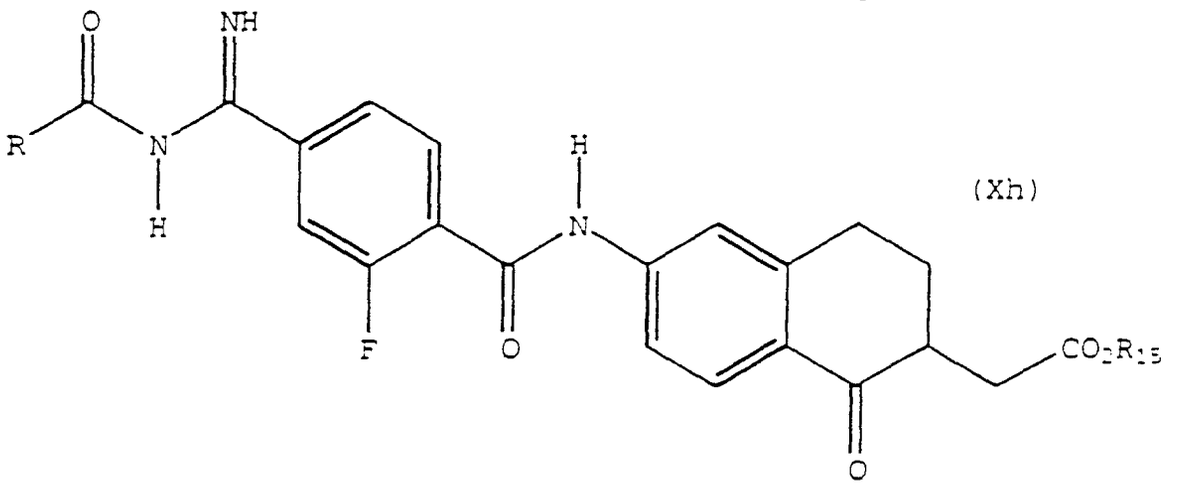
[0099] Preferred prodrug derivatives of the compounds of the invention having various features discused in this section are represented by the formulae (Xf) to (Xr) below:



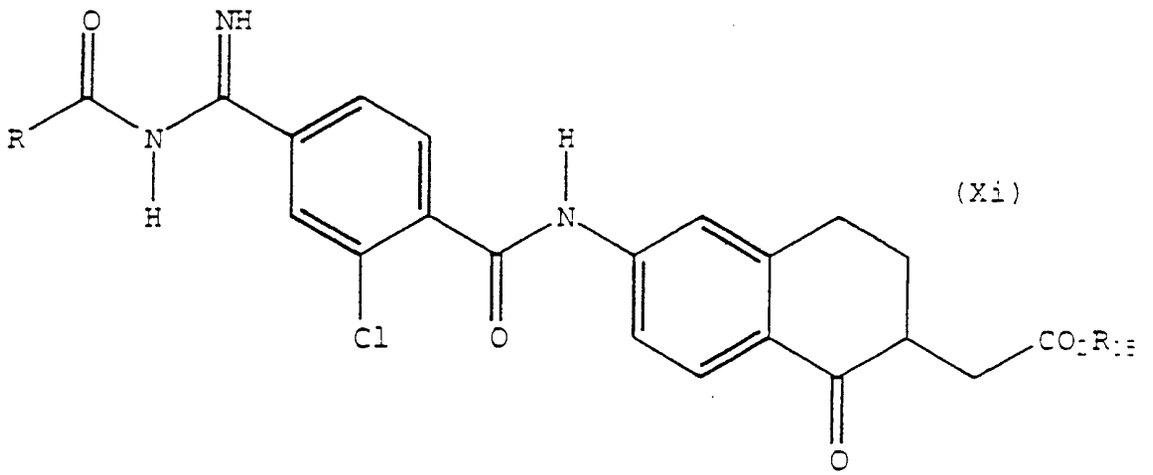
(Xf)



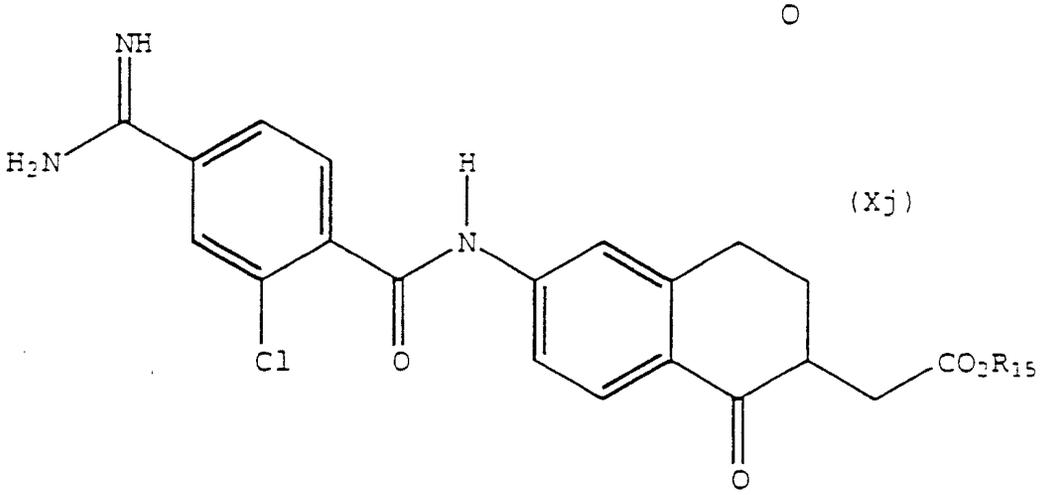
(Xg)



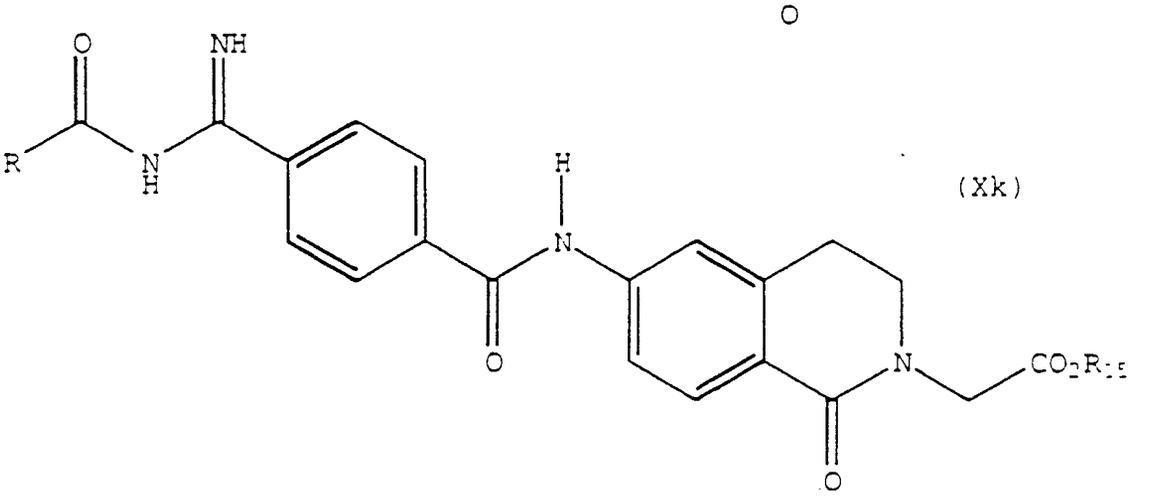
(Xh)



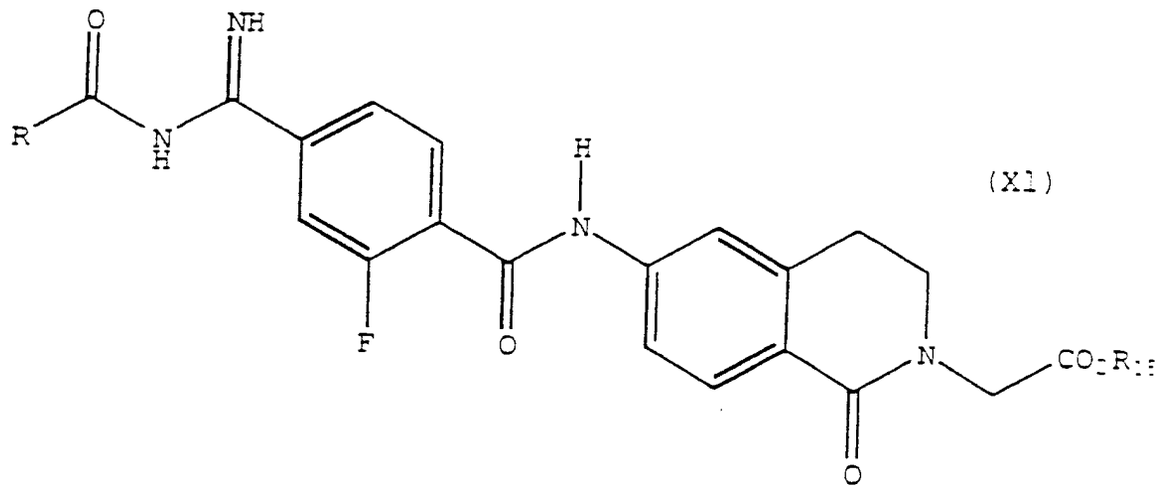
(Xi)



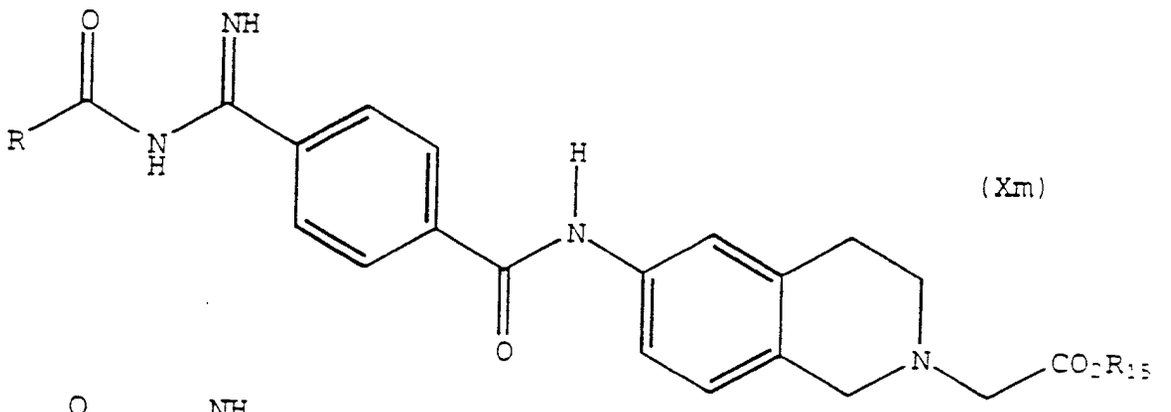
(Xj)



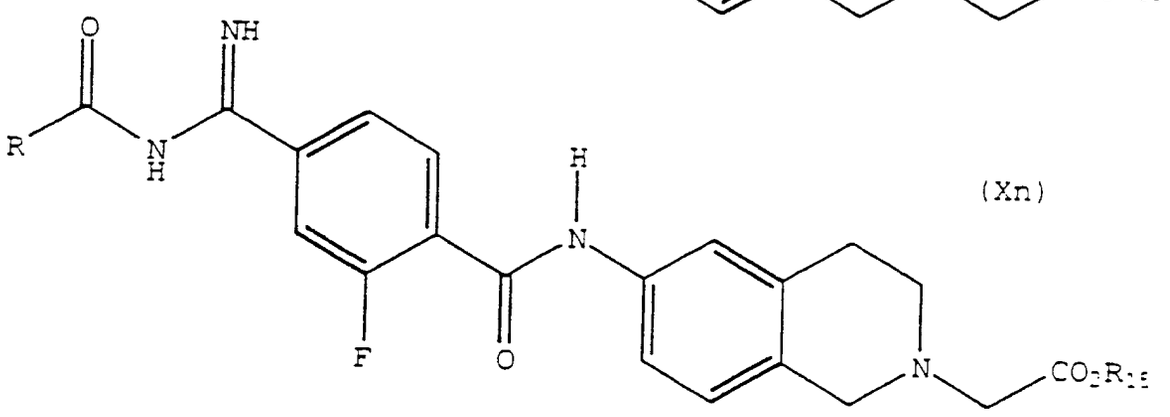
(Xk)



(XI)

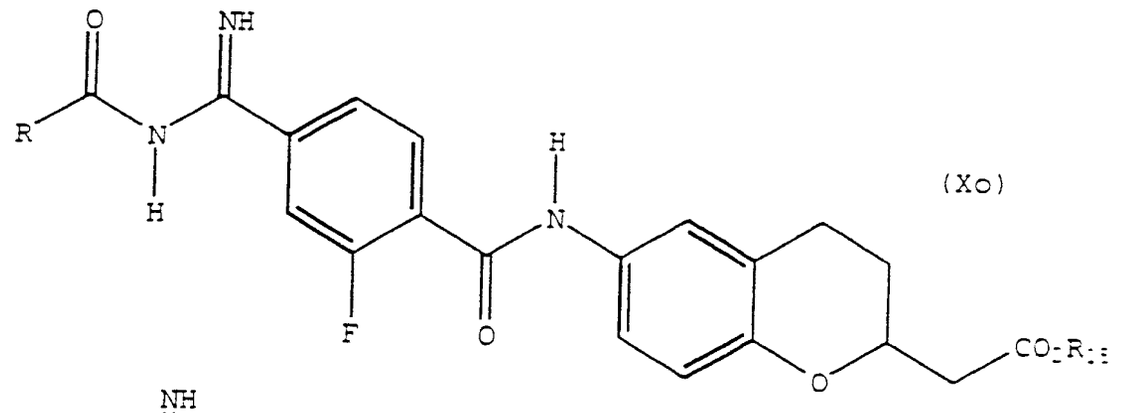


(Xm)

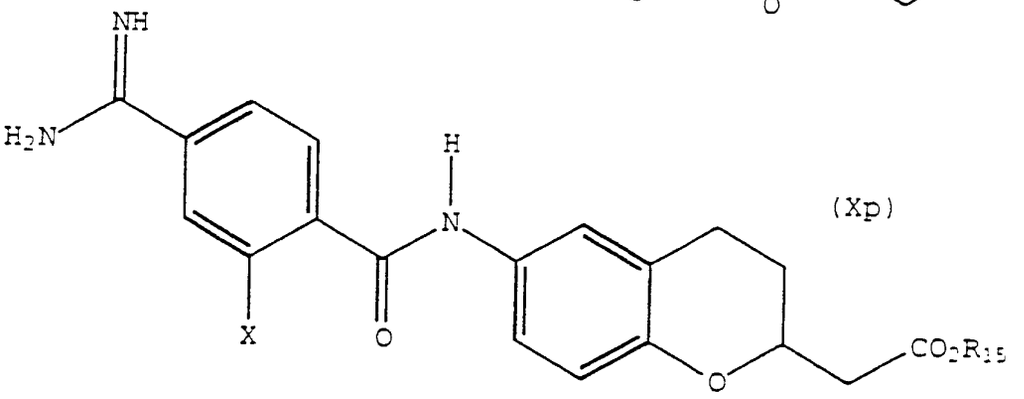


(Xn)

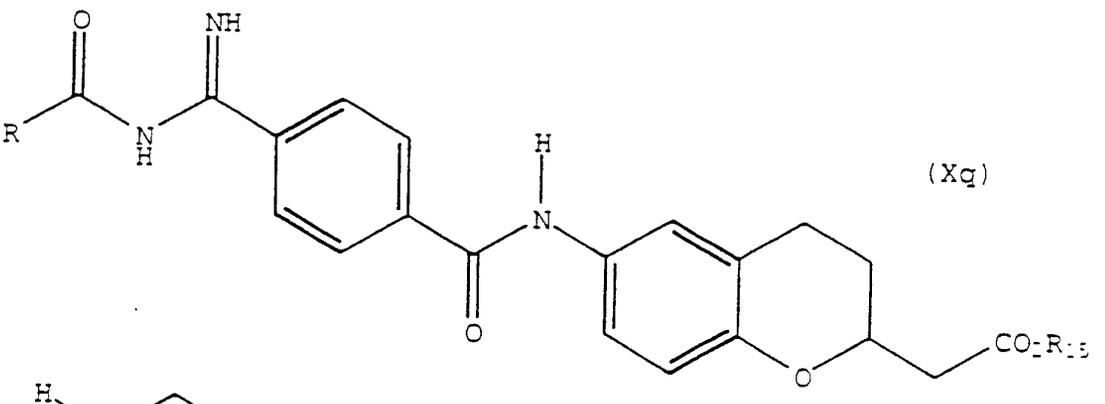
where, R = -H, -OMe, -OEt, -OPr, C1-C4 alkyl; R15 = Me, Et, Pr; and



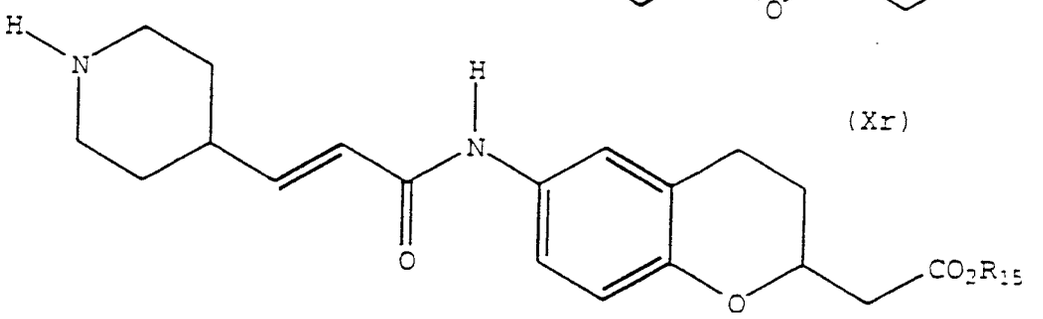
(Xo)



(Xp)



(Xq)



(Xr)

where,

R = -H, -OMe, -OEt, -OPr,
X = -Cl, -F, -H,
R_{15} = Me, Et, Pr.

Method of Making Compounds of the Invention

[0100] General synthesis schemes 1 through 33, infra., are used to prepare the compounds of the invention.

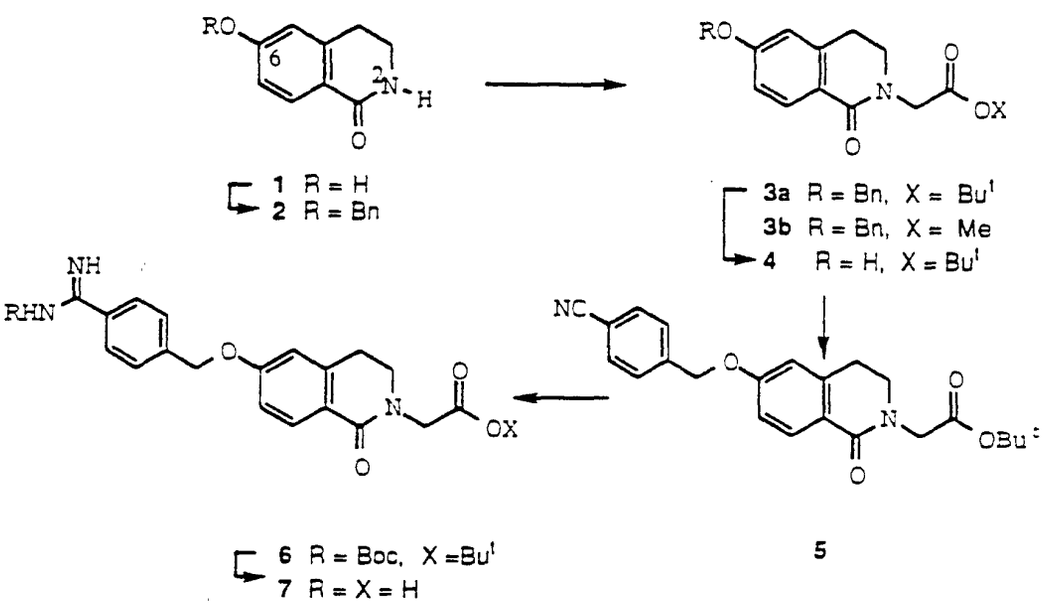
[0101] The following abbreviations are used throughout the synthesis Schemes and Examples:

TBAF	tetra-butyl ammonium fluoride
Tf	(triflate) - trifluoromethane sulfonate
Boc	tertiary-butoxy carbonyl
Bn	benzyl
Bu^t	tertiary butyl
DMF	dimethyl formamide
TFA	trifluoroacetic acid
Cbz	benzyloxycarbonyl
EDCI	1-(3-dimethylaminopropyl)-3-ethyl carbodiimide
DMAP	dimethylaminopyridine
LHMDS	lithium hexamethyl disilazane
THF	tetrahydrofuran
DIBAH	diisobutyl aluminum hydride
Boc_2O	di-tert-butyl dicarbonate
HMDS	hexamethyl disilazane
TSOH	p-toluene sulfonic acid
MCPBA	meca-chloro-peroxy benzoic acid
NMO	4-methylmorpholine-N-oxide
TFAA	Trifluoroacetic anhydride
TBSCL	tert-butyl dimethyl silyl chloride
TMEDA	N,N,N',N'-tetramethylethylenediamine
LDA	lithium diisopropylamide

General Comments :

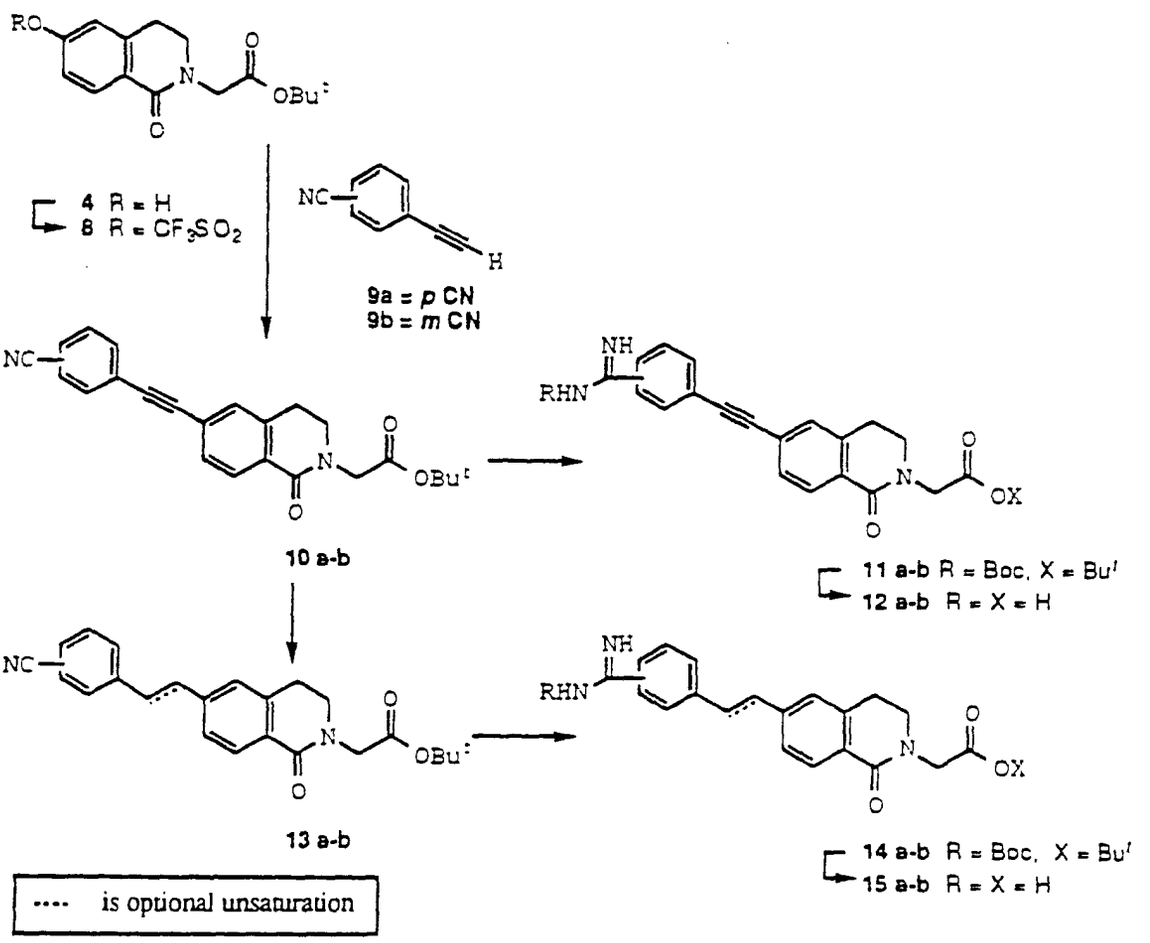
[0102] The reactions described in the reaction schemes are carried out using standard chemical methodologies described and referenced in standard textbooks. Starting materials are commercially available reagents and reactions are carried out in standard laboratory glassware under reaction conditions of standard temperature and pressure, except where otherwise indicated.

Scheme 1



[0103] Scheme 1 teaches a method of preparing 2,6-disubstituted isoquinolones having an ether linked arginine isostere at C_6 and an acetic acid residue at position 2. In the first step of Scheme 1, isoquinolone (1) reacts with benzyl bromide in the presence of potassium carbonate in refluxing acetone to give a benzyl protected phenol (2). This compound reacts with sodium hydride and is then alkylated on nitrogen with either alpha-bromo tert-butyl acetate or alpha-bromo methyl acetate to give a 2-substituted isoquinolone (3a) (6-benzyloxy-3,4-dihydro-1-oxo-2(1H)isoquinolone acetic acid -1,- dimethylethyl ester) or (3b). The C_6 benzyl group is subsequently removed with hydrogen and palladium and subsequent alkylation of the 6-hydroxy group is accomplished with K_2CO_3 and alkyl bromide to give the di-substituted isoquinolone (5). Compound (5) is then transformed into the Boc protected amidine (6) using a series of reactions, namely; (i) reacting the nitrile with H_2S, (ii) alkylating the intermediate thioamide with methyl iodide, (iii) reacting the intermediate thioimidate with ammonium acetate, and (iv) thereafter Boc protecting the formed amidine to give compound (6). Compound (6) is deprotected with neat TFA giving (7) as the TFA salt.

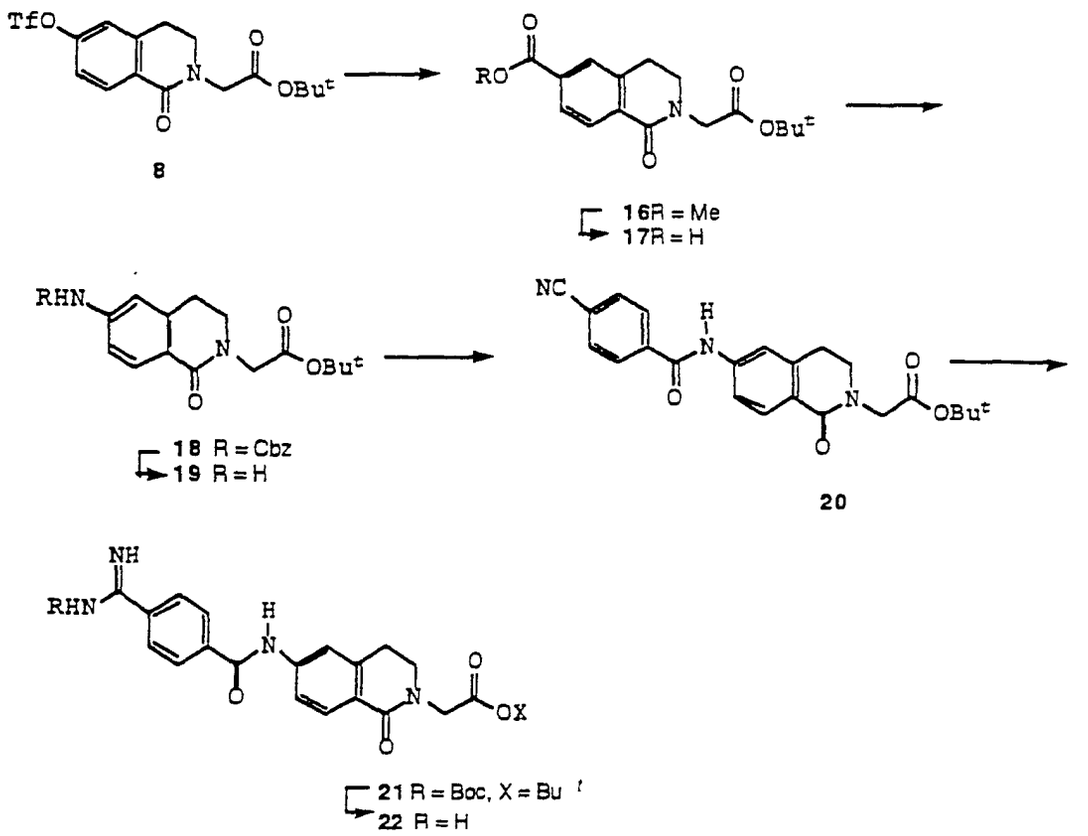
Scheme 2



[0104] Scheme 2 describes a synthesis method suitable to give carbon substitution at position C_6 of the bicyclic nucleus. In this scheme compound (4) (6-hydroxy-3,4-dihydro-1-oxo-2(1H) isoquinolone acetic acid -1,1- dimethylethyl ester) from Scheme 1 is transformed into the triflate (8) using triflic anhydride and pyridine. The compound is thereafter reacted with the acetylenic compound (9a) or (9b) in the presence of palladium to give acetylene linked benzonitrile (10a) or (10b). Compound (10a) or (10b) is transformed again with the same set of procedures used to transform compound (5) (6-[(4 cyanophenyl) methoxy]-3,4-dihydro-1-oxo-2(1H) isoquinolone acetic acid, -1,1-dimethyl ethyl ester) to compound (6) (6-[[4-(1,1 dimethyl ethoxy carbonyl aminoiminomethyl)phenyl] methoxy]-3,4-dihydro-1-oxo-2(1H) isoquinolone acetic acid -1,1-dimethyl ethyl ester) to yield the amidine product (11a) or (11b). Compounds (11a) or (11b) may also be deprotected again with TFA to give compound (12a) or (12b). Alternatively, intermediate (10a) or (10b) can be either partially or fully hydrogenated as shown in the scheme giving the alkylene or alkenylene linked

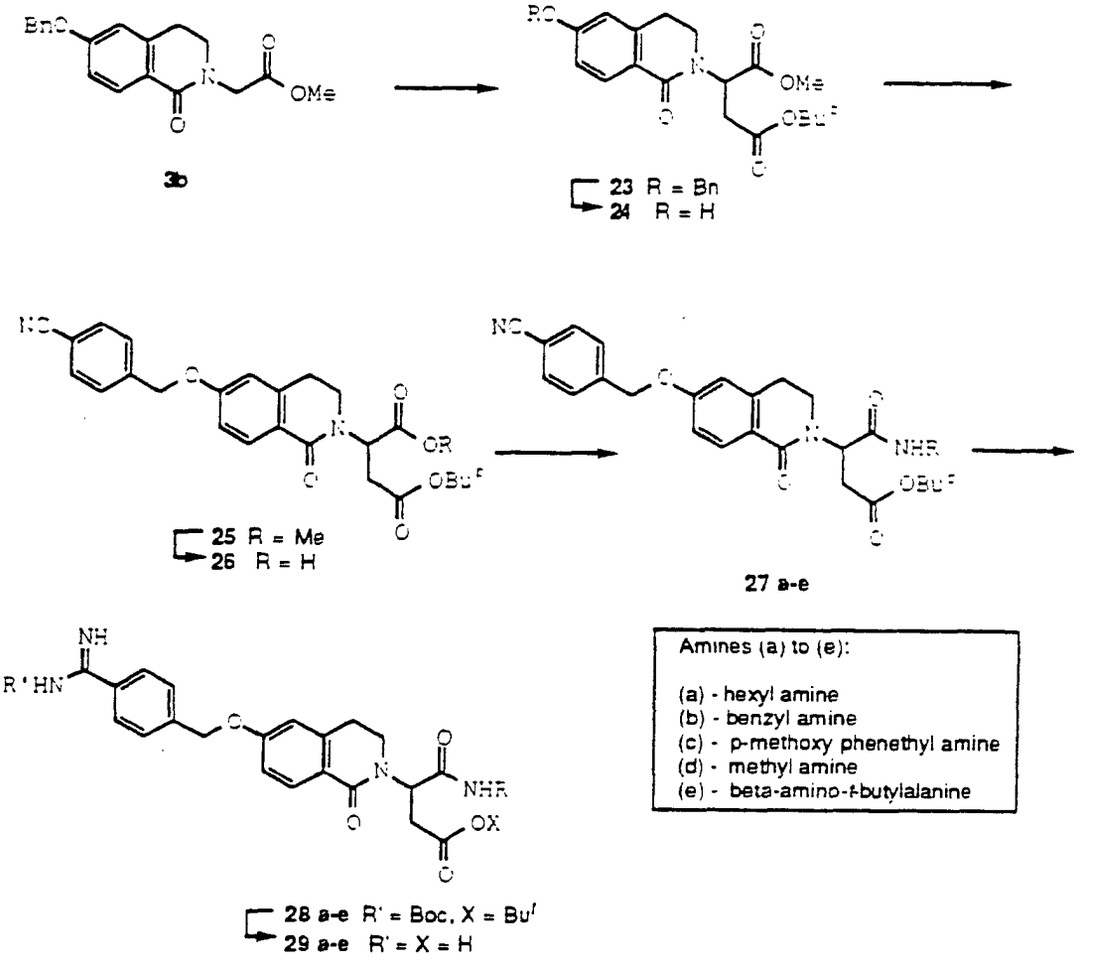
compound (13a) or (13b). Compound (13a) or (13b) is again transformed using the nitrile to amidine conversion previously described (Scheme 1, steps 5>6), giving compound (14a) or (14b) which is subsequently deprotected with TFA to give compound (15a) or (15b).

Scheme 3



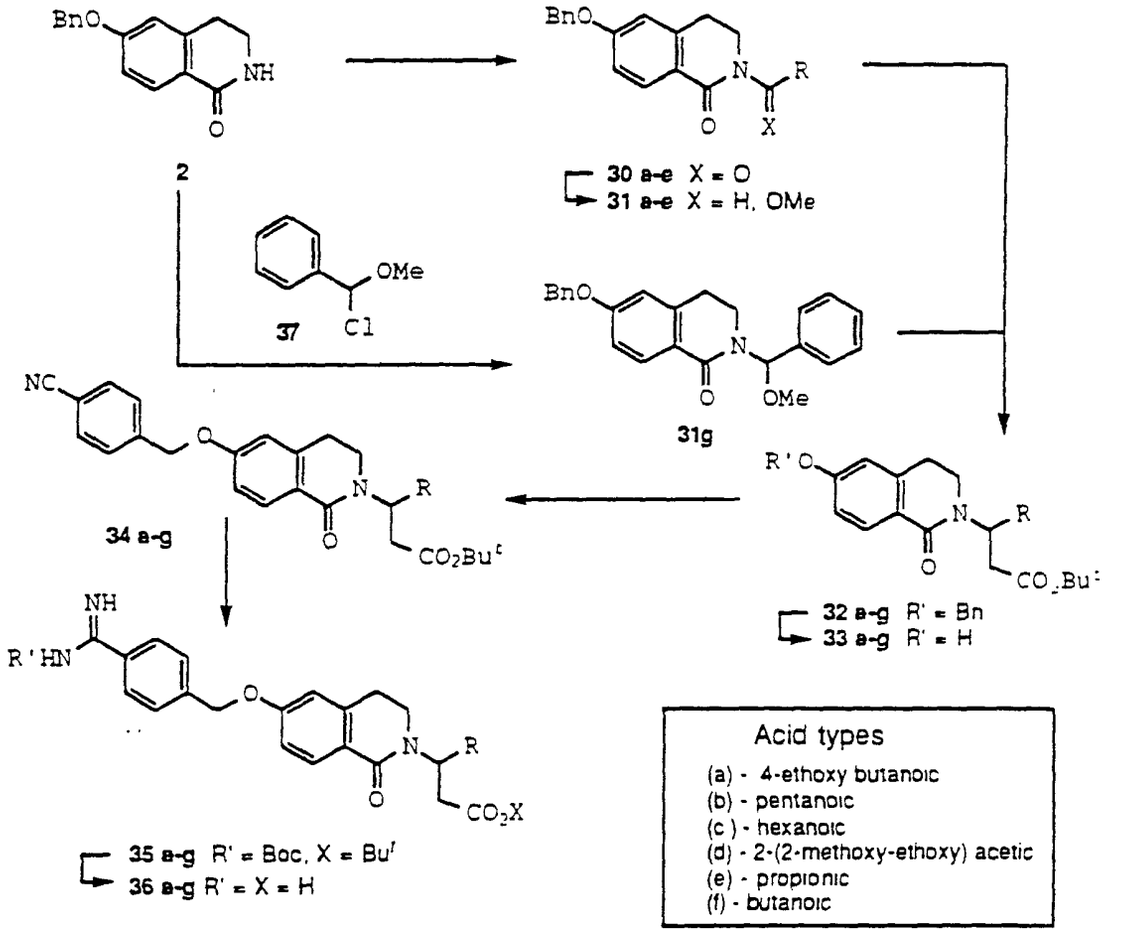
[0105] Scheme 3 describes the preparation of isoquinolones containing nitrogen substitution at C_6. This scheme starts with triflate (8) whose preparation was previously described in Scheme 2. The triflate is transformed to aryl ester (16) via the use of palladium, carbon monoxide and methanol. The ester (16) is then saponified with lithium hydroxide in aqueous THF. The free acid (7) is then subjected to a Curtius rearrangement (viz., formation of an isocyanate by thermal decomposition of acyl azides). The required acyl azide is formed with a triphenyl phosphoryl azide and then pyrolized *in situ* to give an isocyanate which is then trapped with benzyl alcohol giving Cbz protected aniline (18). CBz-Aniline (18) is then transformed into free amine (19) with catalytic hydrogenation. Amine (19) is then acylated with paracyanobenzoic acid in the presence of EDCI and DMAP giving the amide-linked compound (20). Compound (20) is then transformed into the Boc protected amidine (21) again using the conditions of Scheme 1 and that compound is then deprotected with TFA to give compound (22).

Scheme 4



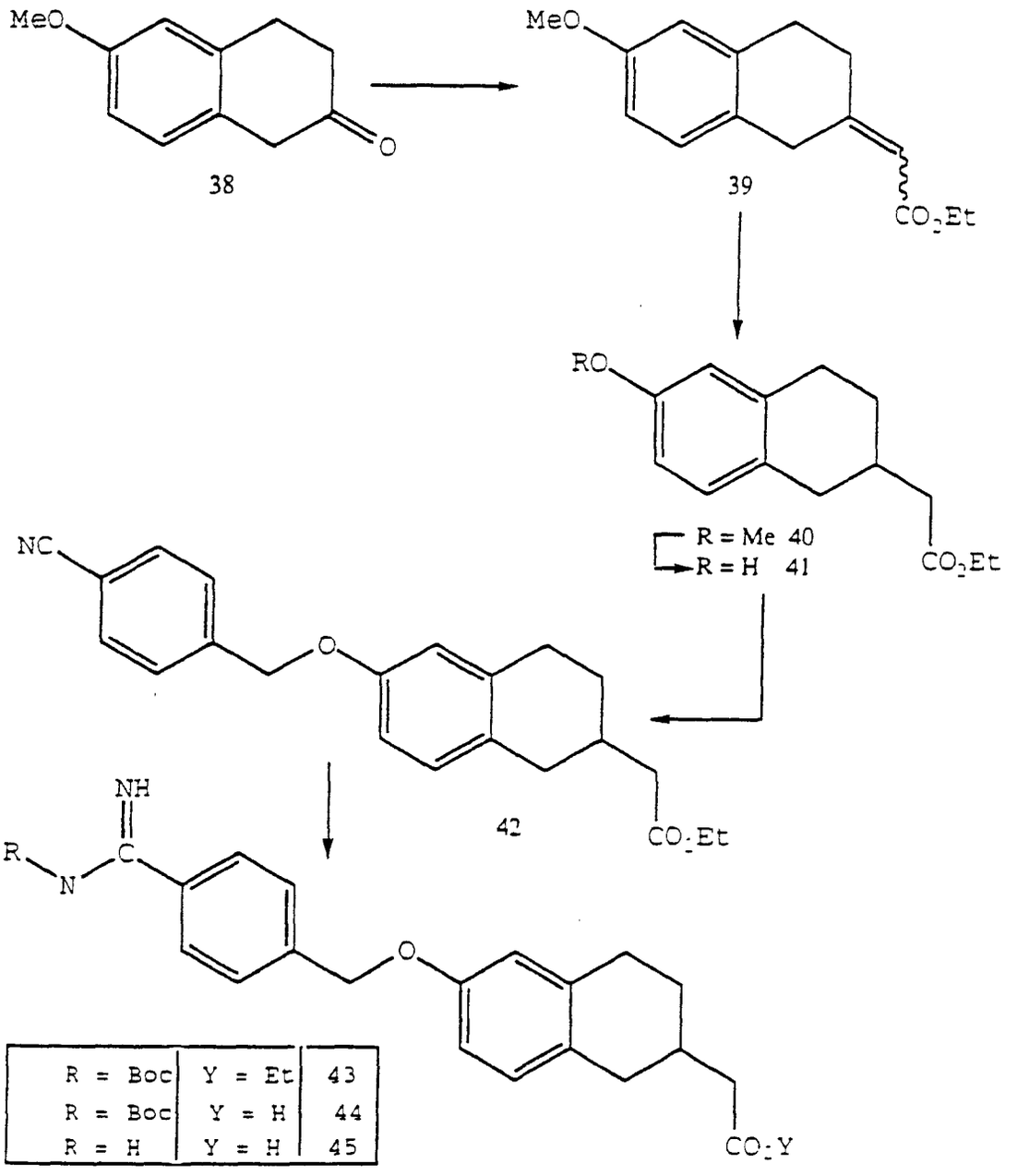
[0106] Scheme 4 describes how to make 2,6-disubstituted isoquinilones in which the 2-position is substituted with an aspartic acid moiety. Scheme 4 starts with compound (3b) whose preparation is described in Scheme 1. Compound (3b) is deprotonated with LHMDS and the resulting anion is quenched with alpha-bromo-*t*-butyl acetate to give compound (23). The 6-benzyl group of compound (23) is removed with palladium and hydrogen to give the free phenol (24). Compound (24) is then alkylated as described for the preparation of compound (5) in Scheme 1. The methyl ester (25) is then saponified with lithium hydroxide in THF to give the free carboxylate (26). The free carboxylate is then coupled with a variety of amines in the presence of EDCI and DMAP to give the half amide esters (27a) thru (27e). The half amide esters (27a) thru (27e) are then transformed again using the same protocol as previously described in Scheme 1 (steps 5-6)to give the Boc protected amidines (28a) thru (28e). The Boc protected amidine is then deprotected with TFA to give compounds (29a) thru (29e).

Scheme 5



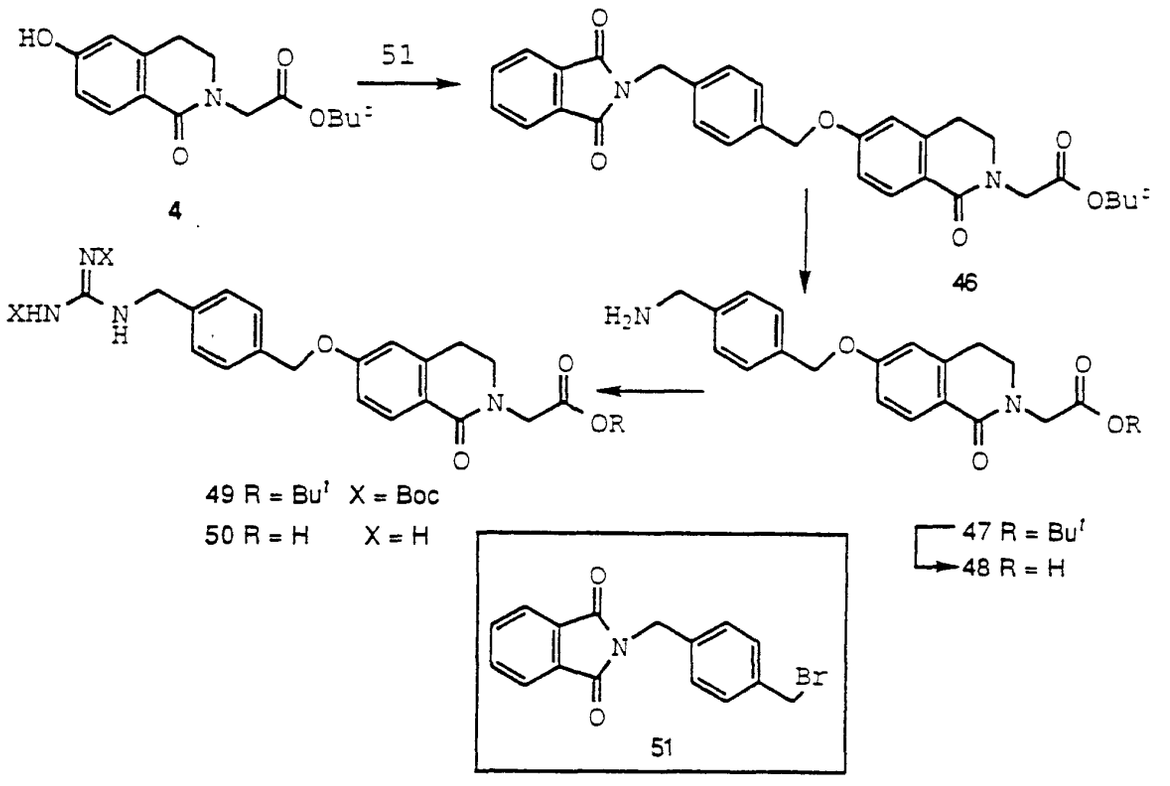
[0107] Scheme 5 describes the preparation of 2,6-disubstituted isoquinilones in which the 2-position is substituted by an aspartate isostere. Scheme 5 compounds differ from the compounds prepared in Scheme 4 in that the R group of the Scheme 5 compound (36) does not contain an amide linkage like the Scheme 4 compounds (29a) thru (29e). Compound (2), the starting material, is prepared by the method of Scheme 1, then acylated with a variety of activated acids (acid halides or anhydrides) to give the corresponding imides (30a) thru (30e). Thereafter the imide is selectively reduced at its exocyclic carbonyl with DIBAH and then entrapped with acidic methanol to give alpha-methoxy amides (31a) thru (31e). Alternatively, alpha-methoxy amides (31) can be prepared by reacting the sodium salt of (2) with an appropriate alpha chloro ether (37). All of the alpha-methoxy amides (31a) thru (31g) are reacted with boron trifluoride etherate in the presence of a ketene acetal to give the beta,beta-di-substituted propionates (32a) through (32g). Thereafter, the benzyl group is removed from the 6 position by catalytic hydrogenation and phenols can be alkylated again in the same manner as shown in Scheme 1 (steps 4>5) to give the ether linked nitriles (34a) to (34g). That nitrile can then be converted to the Boc protected amidine (35a) to (35g) as shown in Scheme 1 (steps 5>6), Thereafter, deprotection gives the final compounds (36a) to (36g).

Scheme 6



[0108] Scheme 6 describes the preparation of compounds of the invention having a tetralin nucleus. 6-methoxy-2-tetralone (38) is reacted with tert-butyl diethylphosphono acetate to give unsaturated ester (39). Subsequent hydrogenation removes the unsaturation to give compound (40). Compound (40) is treated with boron tribromide and the crude product is reesterified with HCl and ethanol to give (41). The phenol (41) is then alkylated in the same manner as shown in Scheme 1 (step 4-5) giving (42). The nitrile can then be converted to the Boc protected amidine (43) as shown in Scheme 1 (step 5-6). The amidino ester (43) is then saponified with sodium hydroxide to give compound (44), which then is later deprotected with TFA and anisole to give the final product (45).

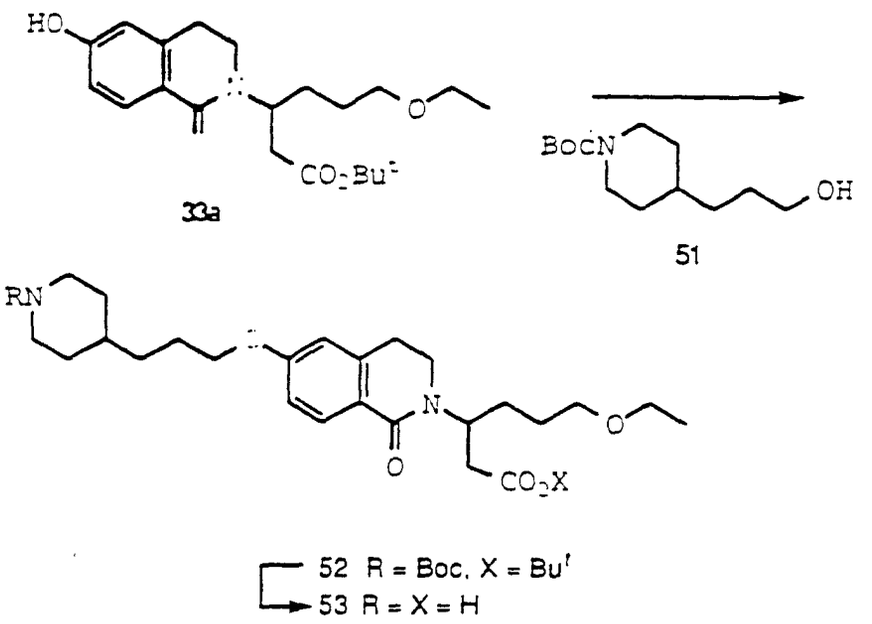
Scheme 7



[0109] Scheme 7 describes the preparation of compounds of the invention having a guanidine group as the basic functionality. Phenol (4), prepared in scheme 1, is alkylated with bromide (51) (prepared from the dibromide and potassium pthalimide) giving adduct (46). This compound is deprotected with aqueous hydrazine giving amine (47). Compound (47) is transformed into protected guanidine (49) with N,N'-bis(tert-butoxy carbonyl)-S-methyl-isothiourea.

[0110] Compound (49) is deprotected with TFA giving product (50) as the trifluoroacetate salt.

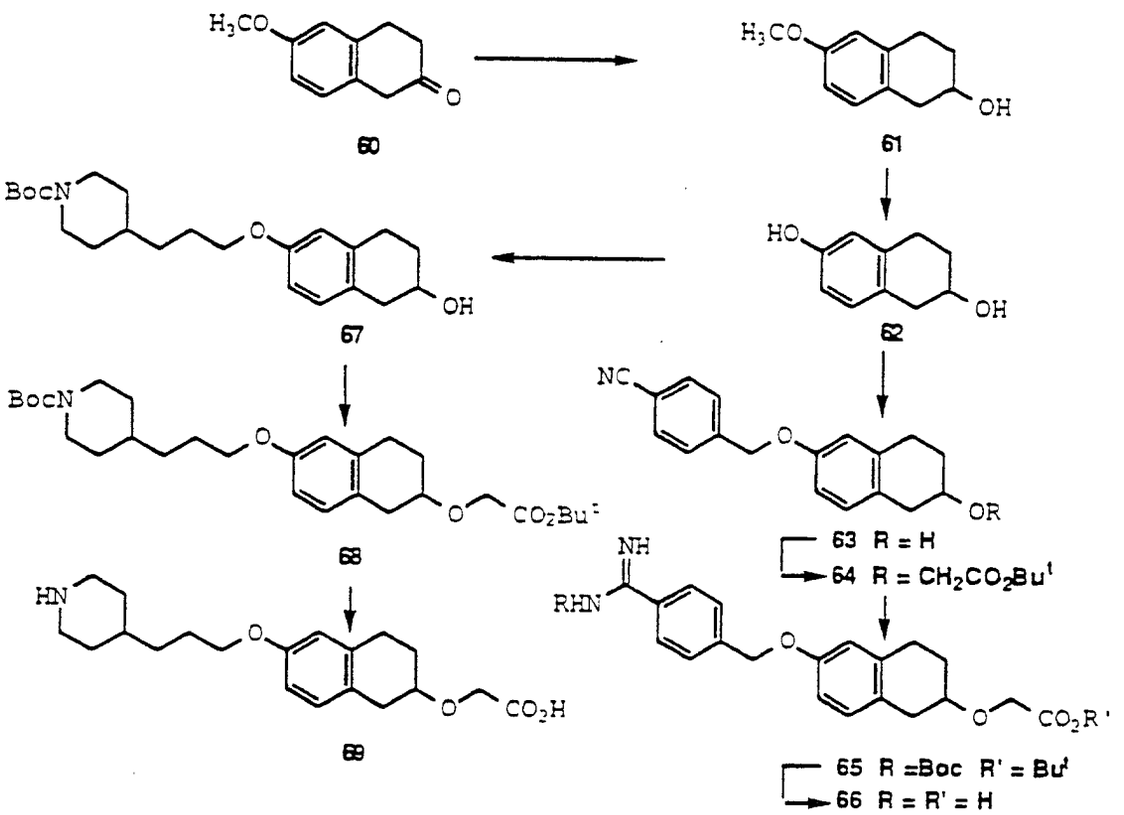
Scheme 8



[0111] Scheme 8 describes the preparation of compounds of the invention having an amine group as the basic functionality.

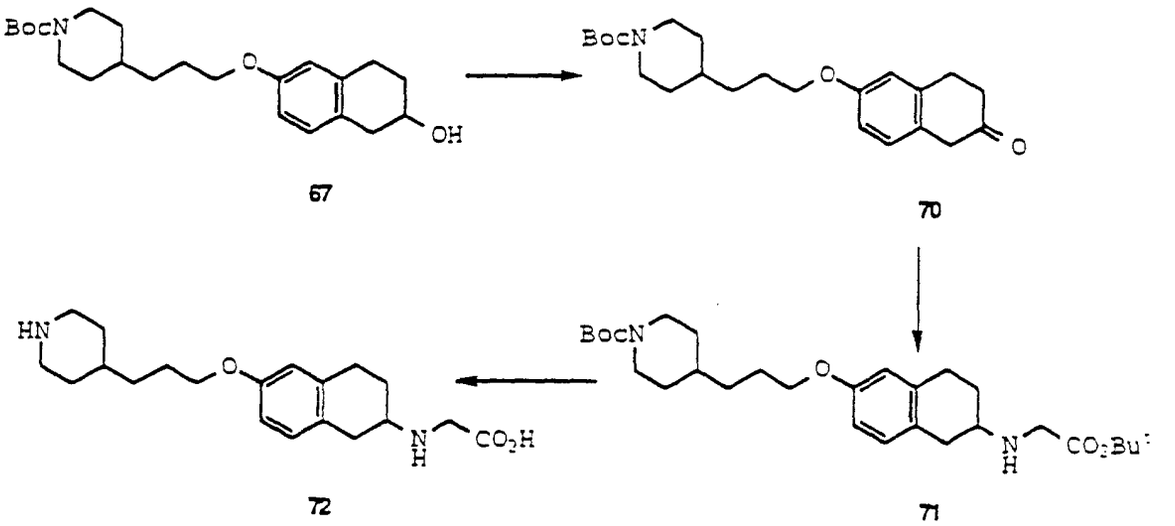
[0112] Compound (33a), prepared in scheme 5, is coupled with alcohol (51) (prepared from 3-(4-pyridyl)-propanol using standard protocols) using triphenyl phosphene and diethyl azodicarboxylate giving compound (52). Compound (52) is deprotected with neat TFA giving product (53) as the TFA salt.

Scheme 9



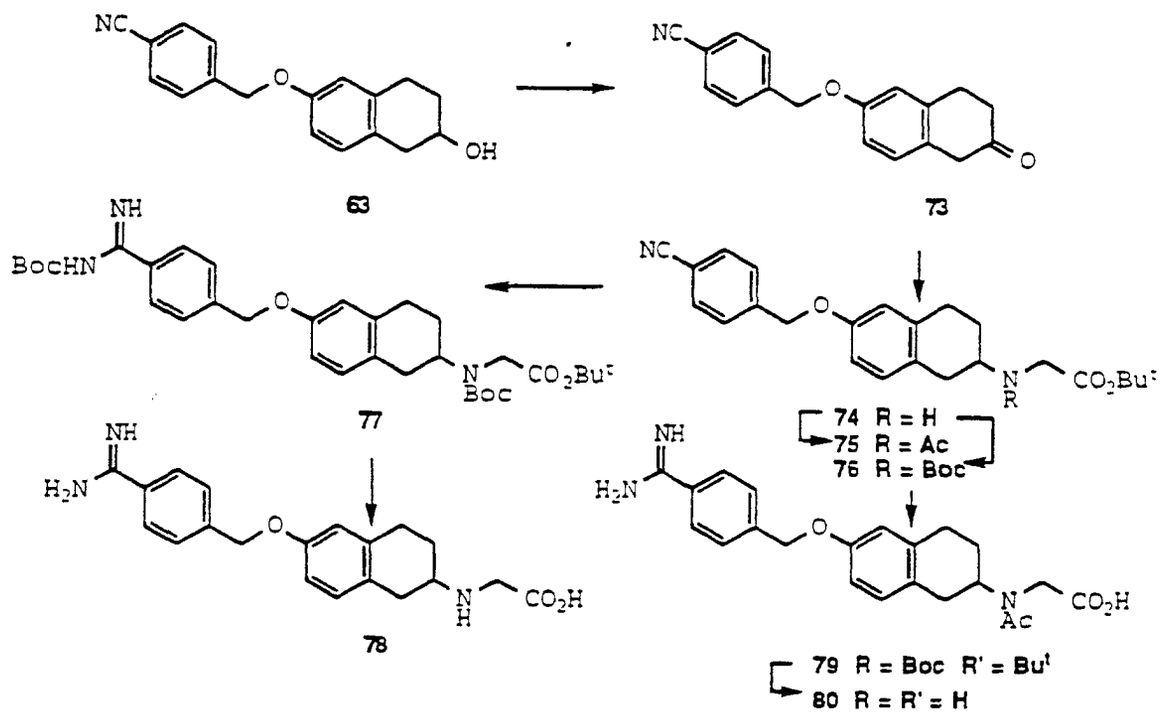
[0113] Scheme 9 describes the preparation of 2-6 disubstituted tetralins in which the 2 position is occupied by an a-alkoxyacetic acid residue and the 6 position retains either an ether linked benzamidine or an ether linked 4-alkylpiperidine moiety. The scheme begins with 6-methoxy-2-tetralone (60) which is sequentially treated with $NaBH_4$ and then with DIBAH giving dihydoxy compound 62. The phenolic hydroxyl can be selectively alkylated with either α-bromo-p-tolunitrile or the appropriate 4-alkylpiperidine giving compounds 63 and 67 respectively. Both compounds are then alkylated with tert-butyl bromoacetate under phase transfer conditions providing 64 and 68. Nitrile 64 is converted to the Boc protected amidine 65 and then to product 66 using the same sequence of reactions described in Scheme 1. Compound 68 is converted to the fully deprotected 69 by treatment with TFA.

Scheme 10



[0114] Scheme 10 outlines the preparation of 2,6-disubstituted tetralins in which an α-aminoacetic acid moiety resides at position 2 and an ether linked 4-alkylpiperidiene emanates from position 6. Alcohol 67, prepared in Scheme 9, is oxidized with DMSO and TFAA using the conditions of Swern giving ketone 70 which is reductively aminated with glycine tert-butyl ester giving 71. This material is then deprotected with TFA giving 72.

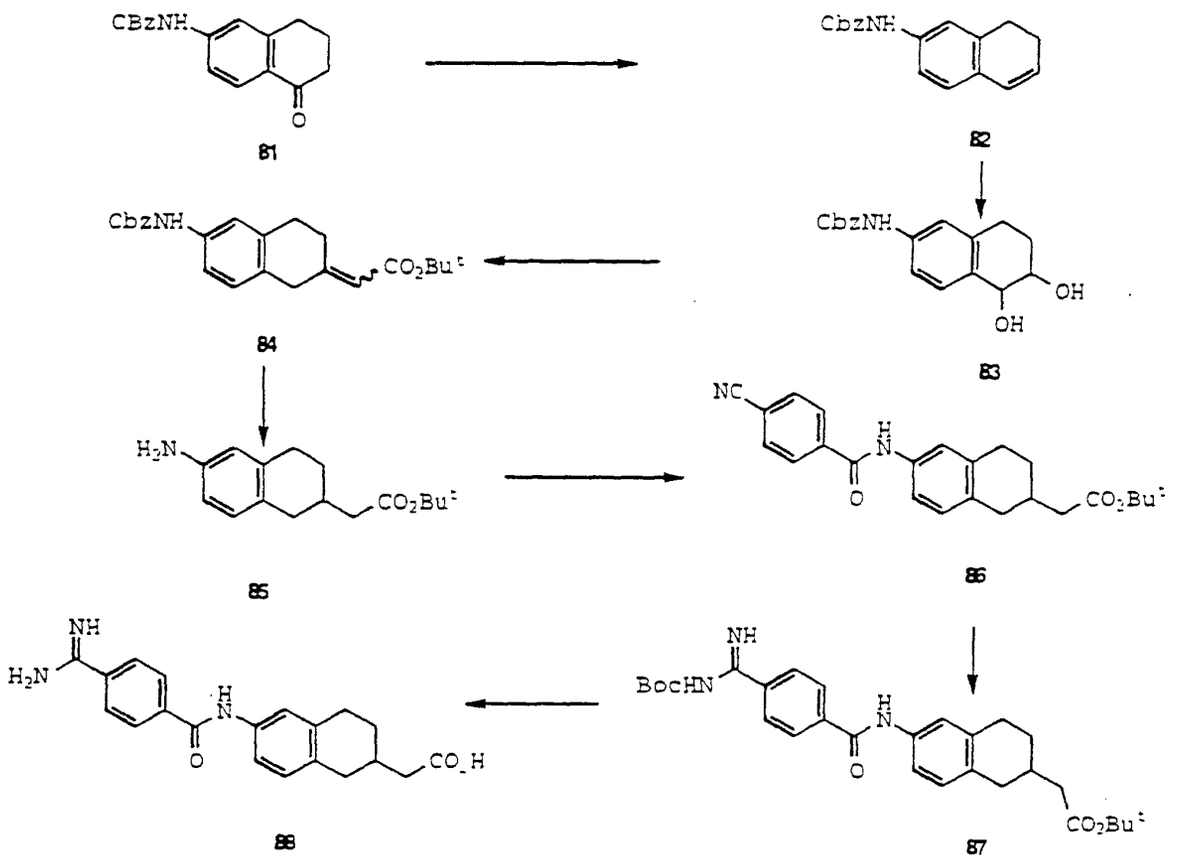
Scheme 11



[0115] Scheme 11 outlines the preparation of 2,6-disubstituted tetralins in which the 2 position retains an α-ami-

noacetic acid residue and the 6 position is occupied by an ether linked benzamidine. The synthesis starts with alcohol 63 (Scheme 9) which is oxidized with TFAA and DMSO (method of Swern) giving ketone 73. This material is then reductively aminated with glycine tert-butyl ester giving 74. The secondary nitrogen is then either Boc protected (76) or acylated (75). The Boc derivative is then transformed into protected amidine 77 using the same sequence of reactions outlined in Scheme 1. The material is then fully deprotected with TFA giving 78. In a like manner, the acetyl derivative 75 is transformed into 80.

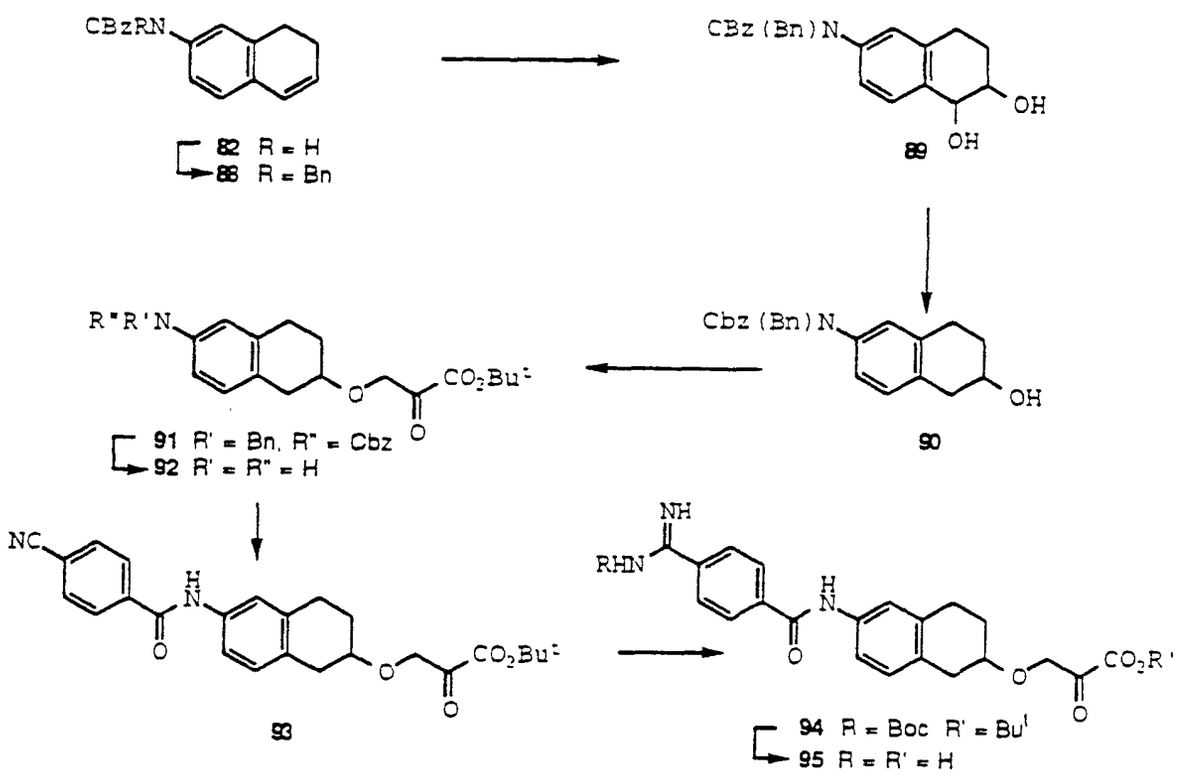
Scheme 12



[0116] Scheme 12 outlines the preparation of tetralins having an acetic acid residue at C_2 and an amide linked benzamidine at C_6. In the first step, tetralone 81 is reduced with $NaBH_4$ and the resultant unstable alcohol is dehydrated with TsOH in benzene giving dihydronapchalene 82. Osymylation of 82 affords diol 83 which is then subjected to the action of TsOH in refluxing benzene. The unstable 2-tetralone thus formed is not isolated but rather allowed to react with the sodium salt of tert-butyl diethylphosphonoacetate giving unsaturated ester 84 as a mixture of olefin isomers. This material is subjected to hydrogenation over palladium which effects saturation of the olefin and removal of the CBz group providing aniline 85.

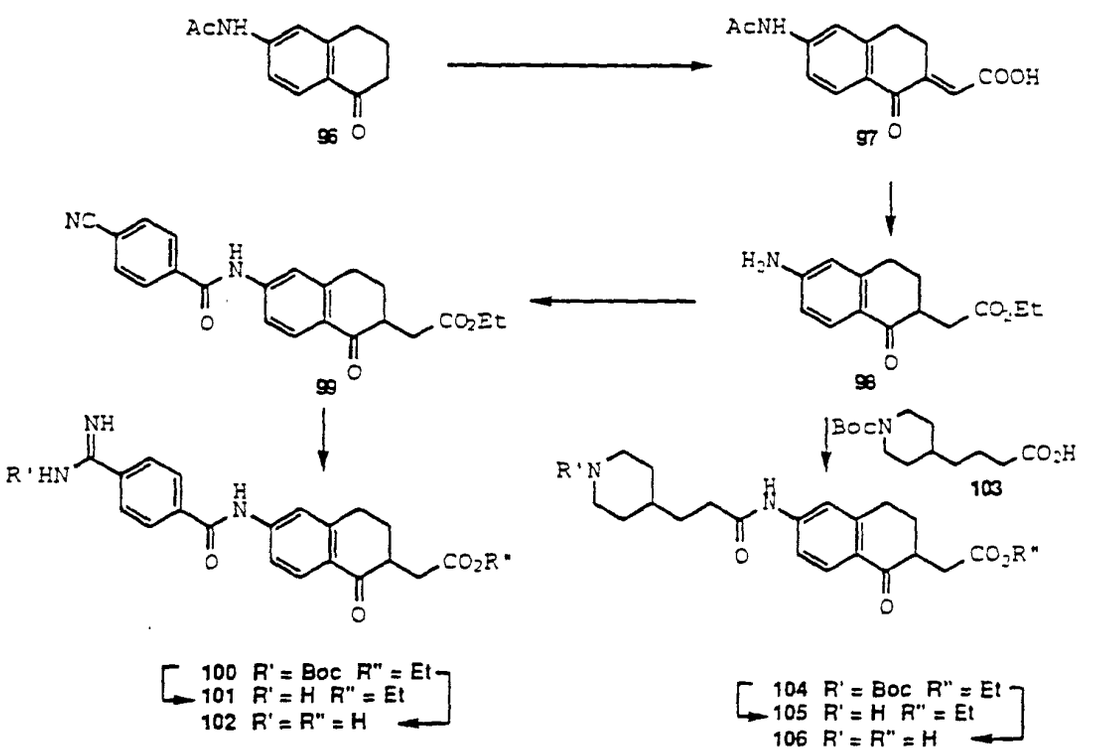
[0117] Acylation of 85 with 4-cyanobenzoic acid is accomplished with the aid of EDCI and the resulting amide 86 is transformed into the Boc protected amidine 87 using conditions previously described in Scheme 1. Removal of the Boc moiety and cleavage of the tert-butyl ester is accomplished with TFA giving 88.

Scheme 13



[0118] Scheme 13 describes the preparation of tetralin derivatives in which position 2 is substituted with an a-alkoxy-acetic acid moiety and position 6 is substituted by an amide linked benzamidine. In this scheme, compound 82 from Scheme 12 is allowed to react with NaH and benzylbromide giving tertiary carbamate 88. This material is then subjected to oshylation and dehydration in the same manner as described for compound 83 in Scheme 12. The formed unstable 2-tetralone is immediately reduced to alcohol 90 with $NaBH_4$. This material is alkylated with tert-butyl bromoacetate under phase transfer conditions resulting in ether 91. Catalytic hydrogenation liberates the 6-amino moiety (92) which is acylated with 4-cyanobenzoic acid in the presence of EDCI giving 93. Nitrite 93 is transformed into Boc protected amidine 94 using the series of transformations described in Scheme 1. Simultaneous deprotection of the amidine and acid moieties is accomplished with TFA giving final product 95,

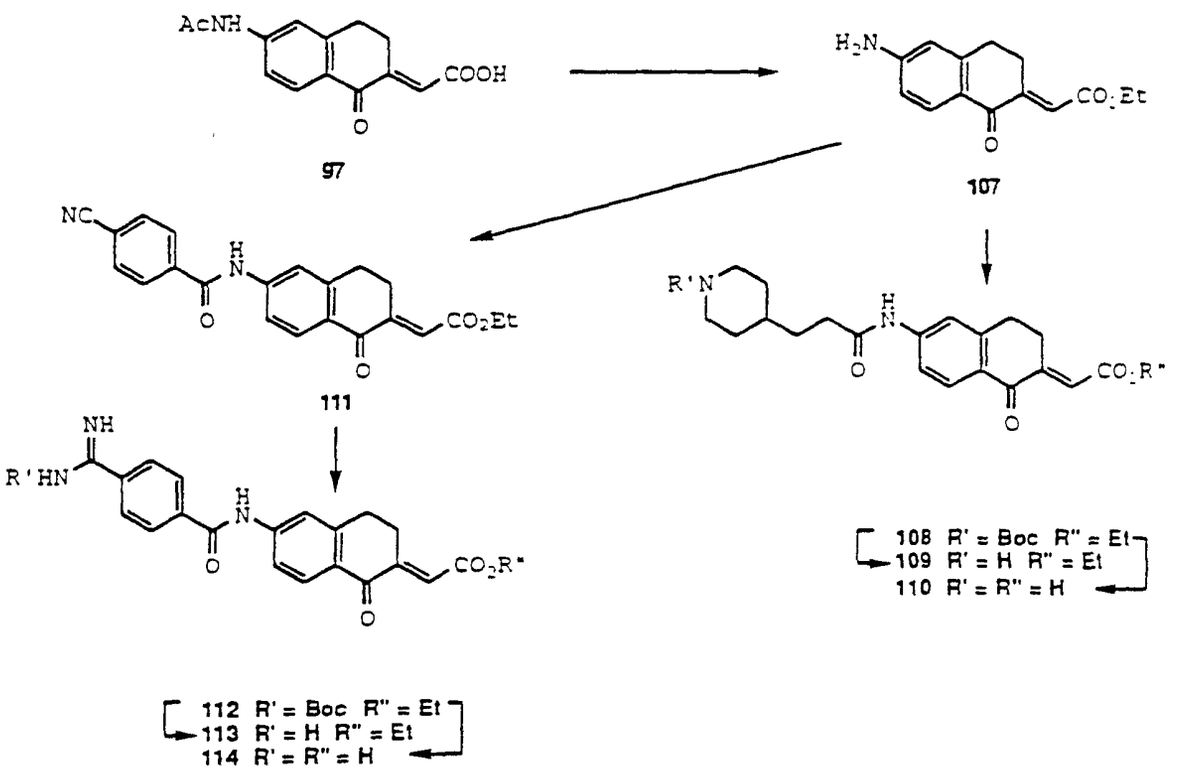
Scheme 14



[0119] Scheme 14 outlines the synthesis of tetralones bearing an acetic acid moiety at position 2 and either an amide linked benzamidine or amide linked 4-alkylpiperidine at position 6. The scheme starts with tetralone 96 which is allowed to react with glyoxylic acid in the presence of NaOH yielding condensation product 97. The unsaturated ester 97 is reduced with Zn in HOAc and the resulting compound is transformed into aniline 98 by first removing the acetate with 6N HCl and then esterifying the acid moiety with ethanolic HCl. This material is then acylated with 4-cyanobenzoic acid via the agency of EDCI giving 99. The nitrile moiety of 99 is converted to Boc protected amidine 100 using the series of reactions described in Scheme 1. Saponification of the ester moiety with NaOH followed by treatment with TFA gives 102.

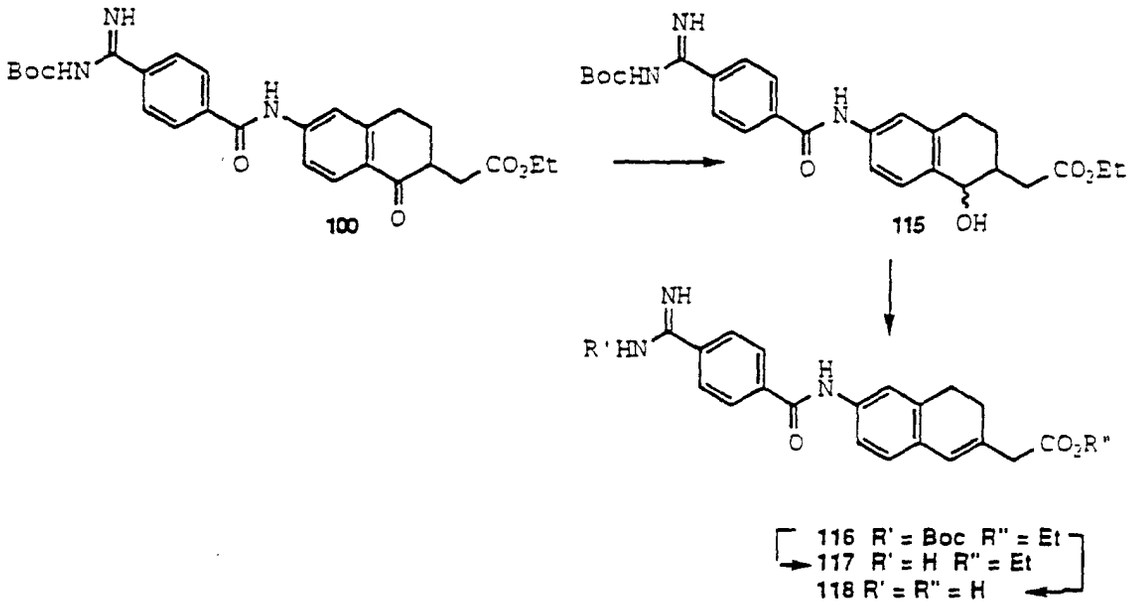
[0120] Compounds containing an amide linked 4-alkylpiperdine can be prepared by acylating aniline 98 with 103 giving analog 104. Saponification of ester 104 followed by TFA deprotection of the piperidine gives 106.

Scheme 15



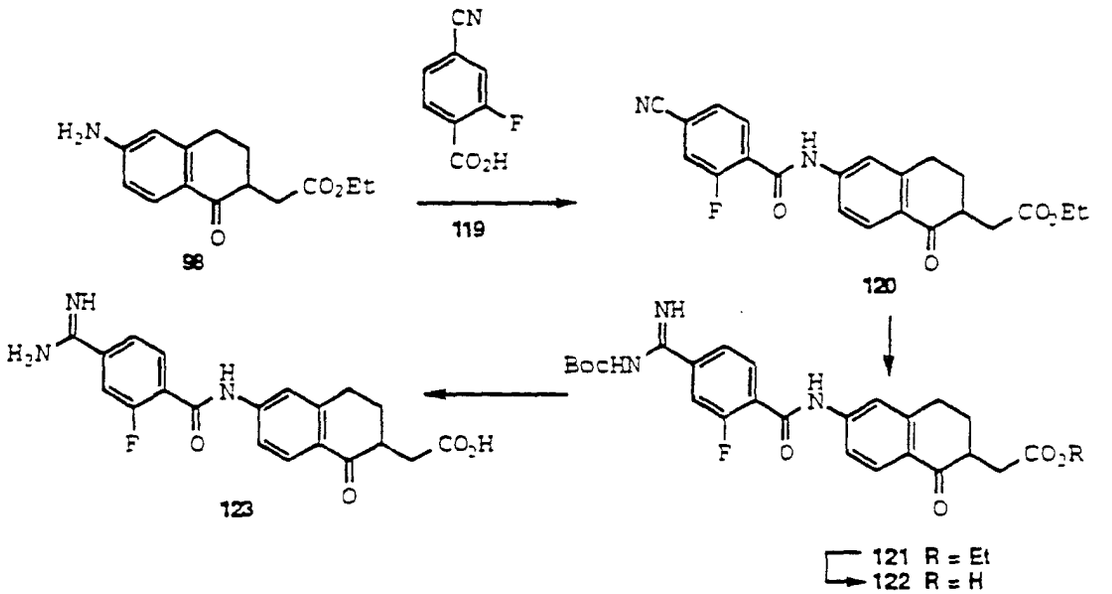
[0121] Scheme 15 teaches a method of preparing tetralone derivatives in which position 2 is occupied by an unsaturated acid and position 6 is substituted by either an amide linked benzamidine or a 4-akylpiperidine. In the first step, compound 97 (scheme 14) can be converted to aniline 107 by removing the acetate with 6N HCl and subsequent esterification with ethanolic HCl. This material can then be acylated with either 4-cyanobenzoic acid or the appropriate 4-alkylpiperidine (103). In the former case, the nitrile 111 can be transformed into amidine 112 using the same sequence of reactions described in Scheme 1. Saponification of 112 followed by treatment with TFA should yield 114. Piperidine adduct 108 can be subjected to saponification and TFA deprotection providing 110 in a similar manner.

Scheme 16



Scheme 16 describes the preparation of dihydronapthalene derivatives containing an acetic acid moiety at position 2 and an amide linked benzamidine at position 6. Tetralone 100 (Scheme 14) is allowed to react with $NaBH_4$ in ethanol giving unstable alcohol 115. This material is treated with TsOH in THF giving dehydrated product 116. Ester saponification followed by deblocking the amidine with TFA gives the desired product 118.

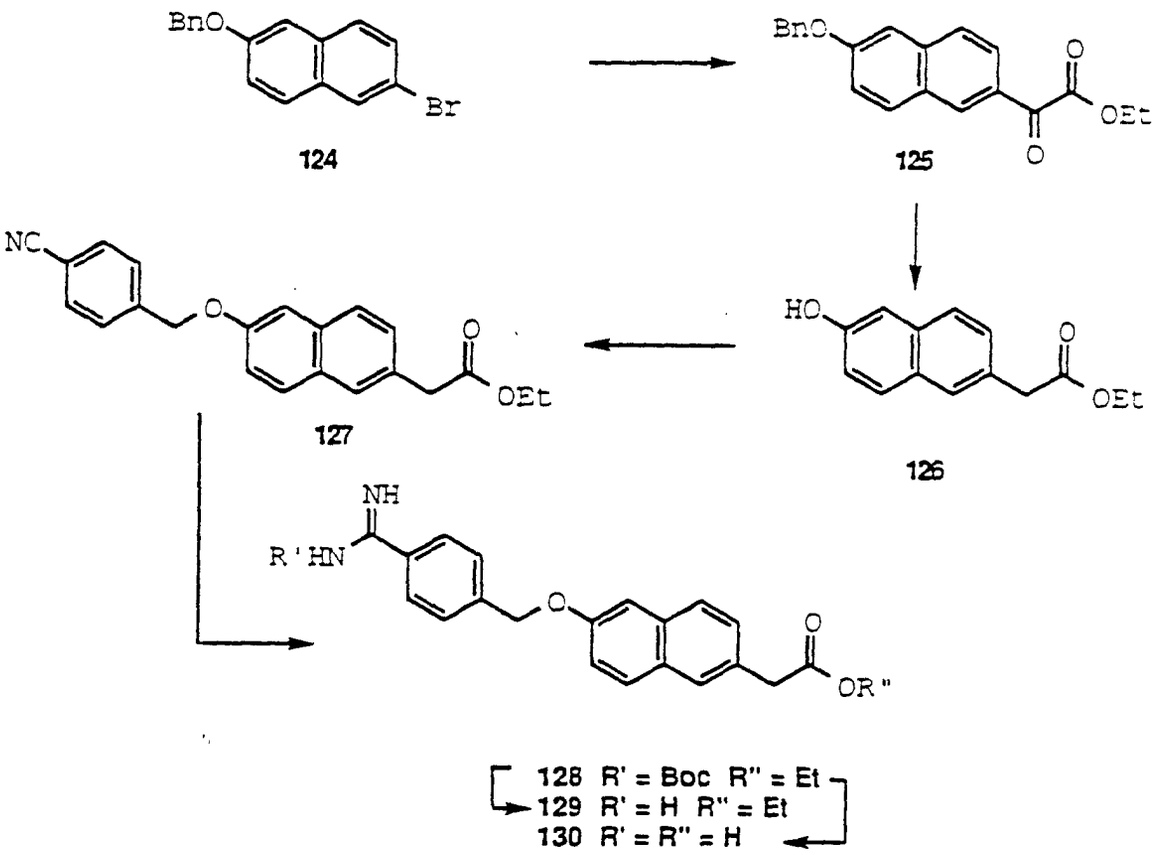
Scheme 17



[0122] Scheme 17 outlines the general preparation of 2,6-disubstituted tetralones in which the 2 position is substituted with an acetic acid residue and the 6 position contains an amide-linked halogen-substituted benzamidine. Aniline 98 (prepared in Scheme 14) is allowed to react with benzoic acid 119 (prepared from 4-amino-2-fluoro-toluene using

standard methods) in the presence of EDCI and DMAP. The resulting amide (120) is transformed into Boc protected amidine 121 using the same procedures outlined in Scheme 1. The ester moiety is then hydrolyzed giving acid 122 and then treatment with TFA provides compound 123.

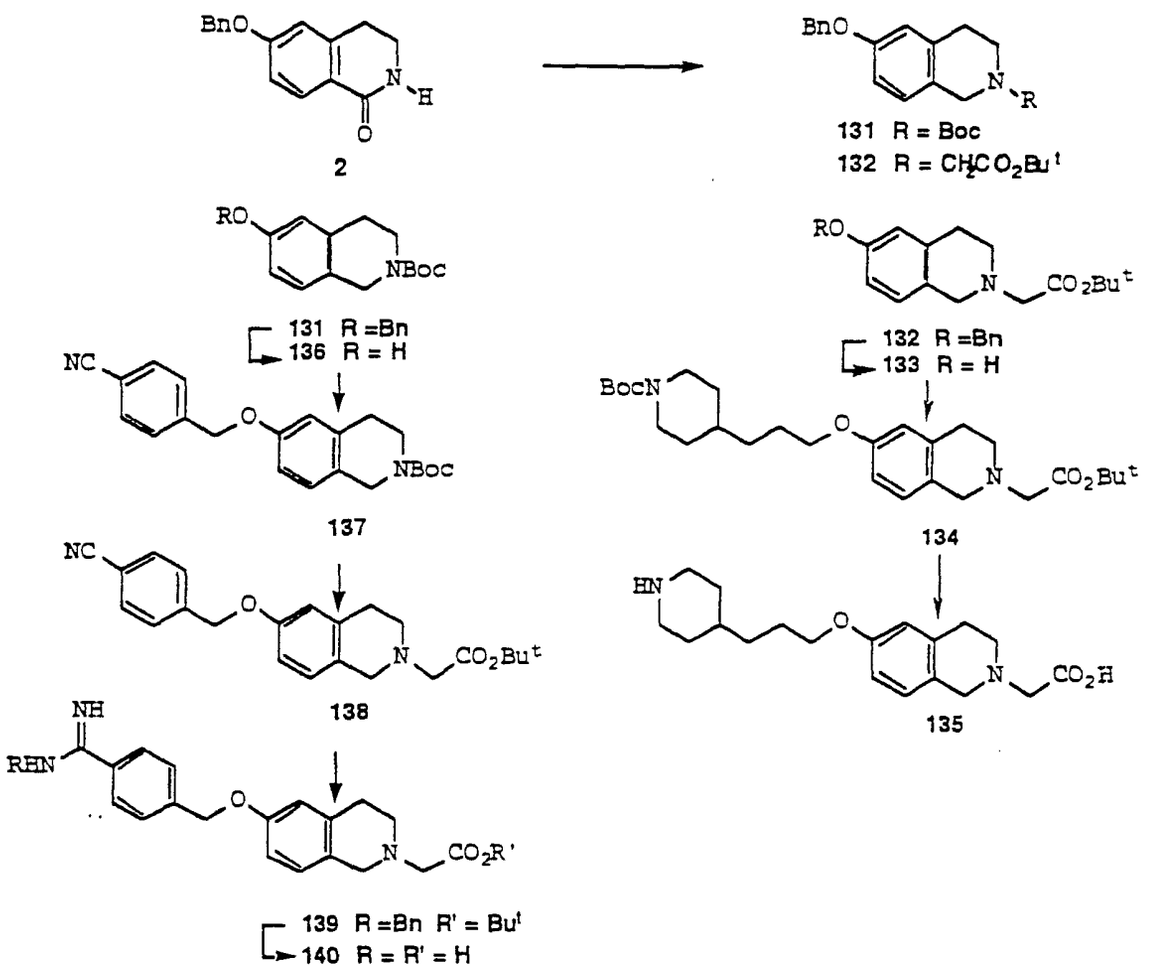
Scheme 18



[0123] Scheme 18 teaches a method of preparing 2,6-disubstituted napthalenes having an acetic acid residue at position 2 and an ether linked arginine isostere at position 6. In the first step of Scheme 18, bromonapthalene 124 is subjected to transmetalation with t-BuLi and the resulting anion is quenched with ethyl oxalate. The resulting adduct 125 is then reduced with $NaBH_4$ and the formed alcohol is acylated with acetic anhydride. Catalytic hydrogenation removes the benzilic acetate and liberates the 6-hydroxy moiety giving compound 126. The free phenol is then alkylated with α-bromo-p-tolunitrile in the presence of K_2CO_3 giving disubstituted naphthalene 127. The nitrile moiety is then transformed into the Boc protected amidine 128 using the same sequence of reactions previously described in Scheme 1.

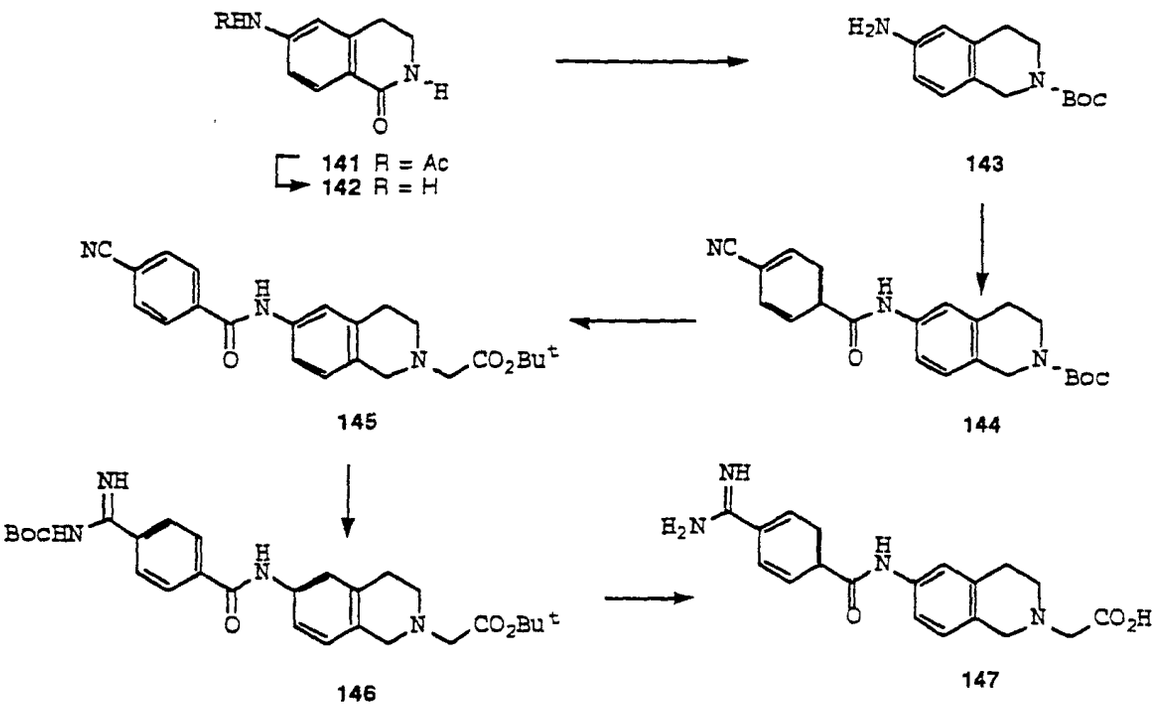
[0124] Saponification of the ester in 128 followed by removal of the Boc group with TFA gives final compound 130.

Scheme 19



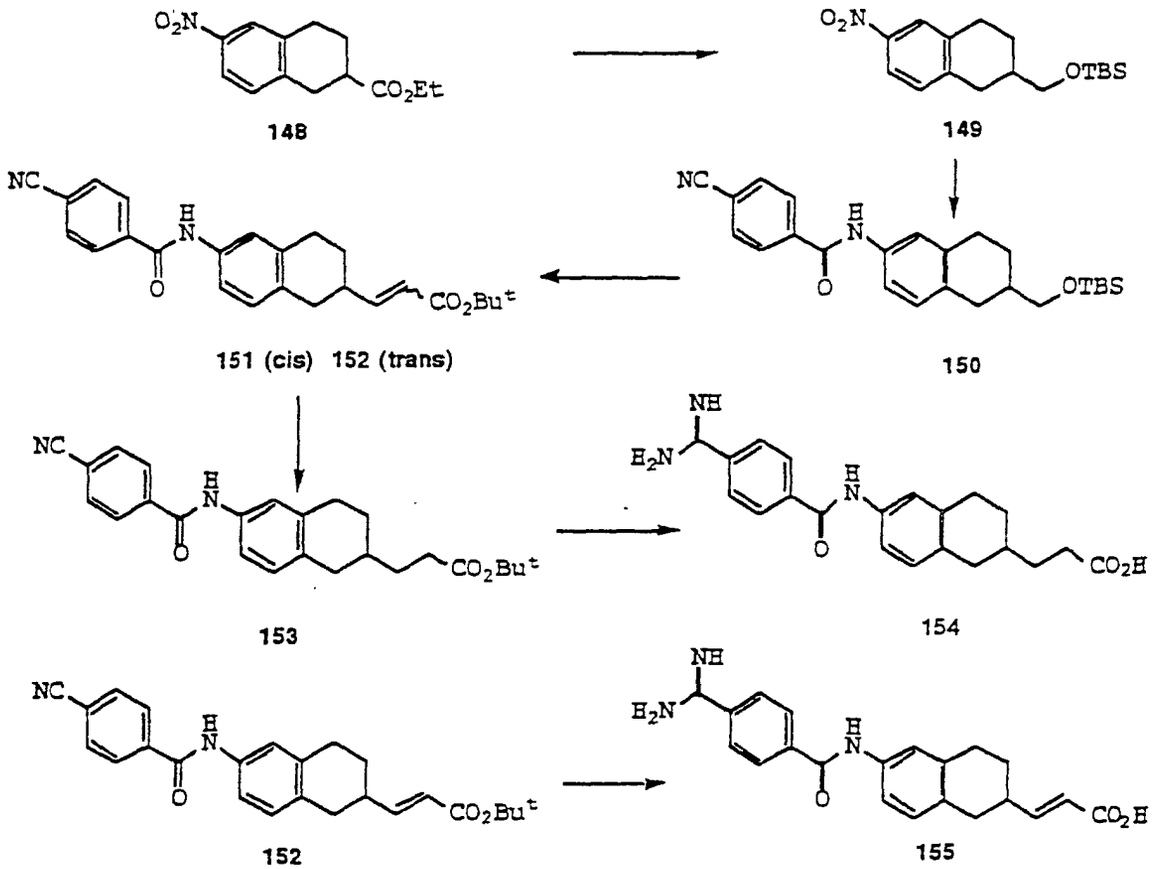
[0125] Scheme 19 describes the preparation of disubstituted tetrahydroisoquinoline derivatives bearing an acetic acid moiety at position 2 and either an ether linked benzamidine or 4-alkyl piperidine moiety at position 6. The initial isoquinoline nucleus is prepared by $LiAlH_4$ reduction of benzyl protected isoquinolone 2 (Scheme 1). This material was processed by either Boc protection giving compound 131 or alkylated with tert-butyl bromoacetate resulting in the formation of 132. The Boc protected material was subjected to hydrogenation which liberated the C_6 phenol which was then alkylated with α-bromotolunitrile giving adduct 137. The Boc group of this compound was cleaved with TFA and the resulting amine was then alkylated with tert-butyl bromoacetate giving compound 138. This compound was transformed into the Boc protected amidine 139 and then to the deprotected variant 140 using the procedures outlined in Scheme 1. The *N*-alkylated compound 132 was similarly subjected to hydrogenation and the resulting phenol was alkylated with the appropriate 4-alkylpiperidine giving 134. This material was deprotected with TFA giving 135.

Scheme 20



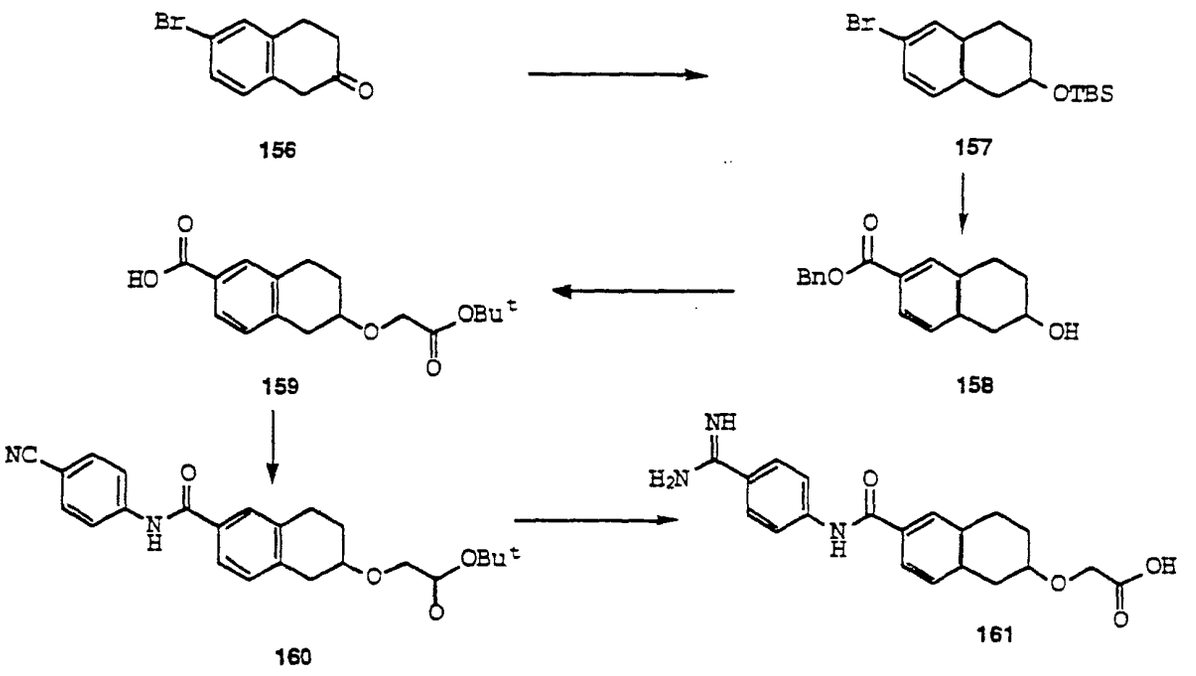
[0126] Scheme 20 teaches how to prepare 2,6-disubstituted tetrahydroisoquinoline derivatives bearing an acetic acid residue at position 2 and an amide linked benzamidine at position 6. The synthesis begins with acidic hydrolysis of the 6-acetamido group of isoquinolone 141 giving aniline 142. The crude material is then subjected to the action of benzyl bromide and K_2CO_3 in CH_3CN giving a mixture of mono and di-benzyl protected isoquinolones. This mixture is subjected to $LiAlH_4$ reduction forming the tetrahydroisoquinoline which is immediately treated with di-tert-butyl dicarbonate. The formed Boc protected material is then hydrogenated over palladium providing aniline 143. This material is acylated with p-cyanobenzoic acid giving 144. Treatment of this material with TFA gives the secondary amine which is alkylated with tert-butyl bromoacetate providing 145. Conversion of 145 to the Boc protected amidine 146 and then to its deprotected congener 147 is accomplished using the same procedures as outlined in Scheme 1.

Scheme 21



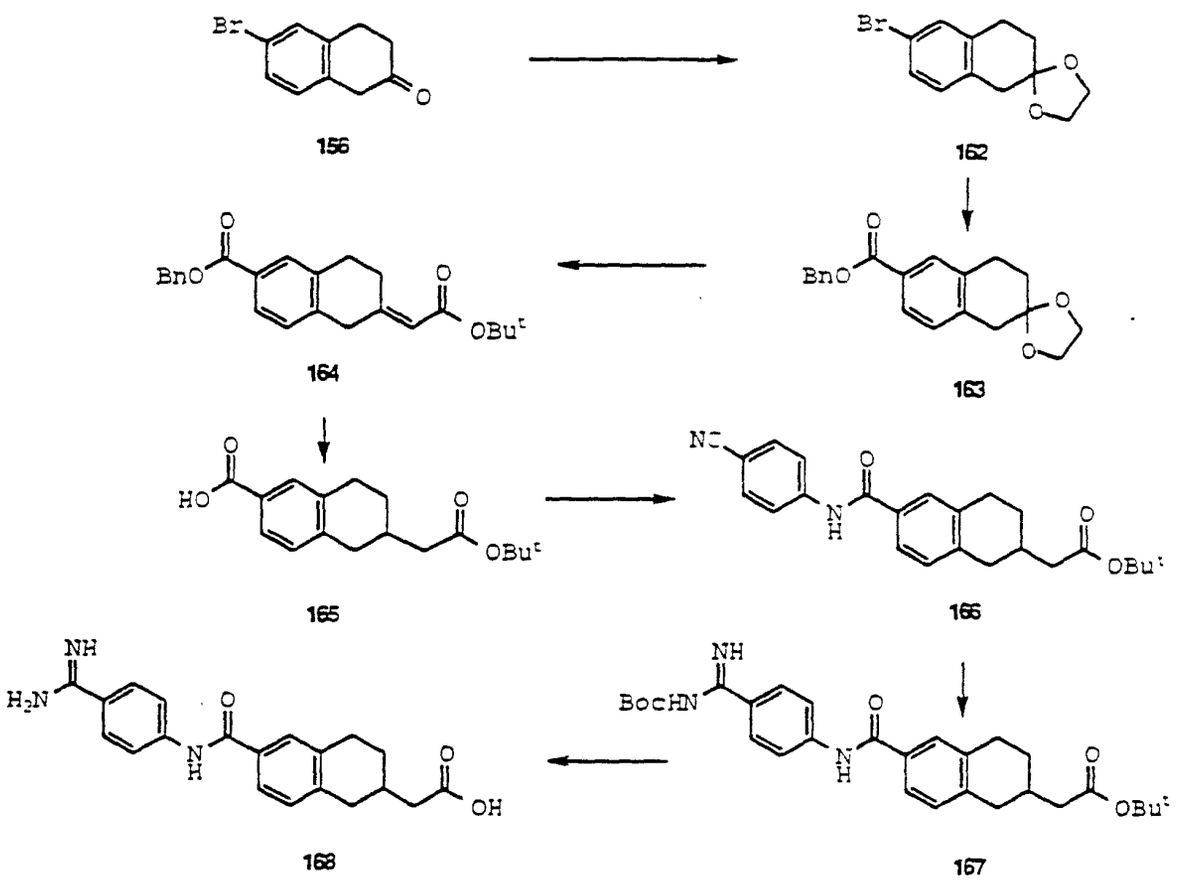
[0127] Scheme 21 describes a synthesis method suitable for the formation of 2,6-disubstituted tetralins containing a propionate or propenoate moiety at position 2 and an amide linked benzamidine at position 6. In the first step, nitro ester 148 is reduced with $LiBH_4$ and the resultant alcohol is protected as its TBS ether. Compound 149 is then subjected to hydrogenation and the formed aniline is immediately treated with EDCI and p-cyanobenzoic acid giving amide 150. The silyl group of 150 is removed and the derived alcohol is subjected to oxidation with DMSO and oxalyl chloride (method of Swern). The aldehyde thus formed is not purified, rather it is allowed to react with the sodium salt of t-butyl diethylphosphonoacetate which yields a separable mixture of 151(cis) and 152 (trans) olefin isomers. The trans isomer 152 is converted to the Boc protected amidine and then to deprotected compound 155 using the sequence described in Scheme 1. The cis isomer is subjected to hydrogenation over palladium to give saturated analog 153. This material is also converted to the Boc protected amidine and then to its deprotected congener 154 as described in Scheme 1.

Scheme 22



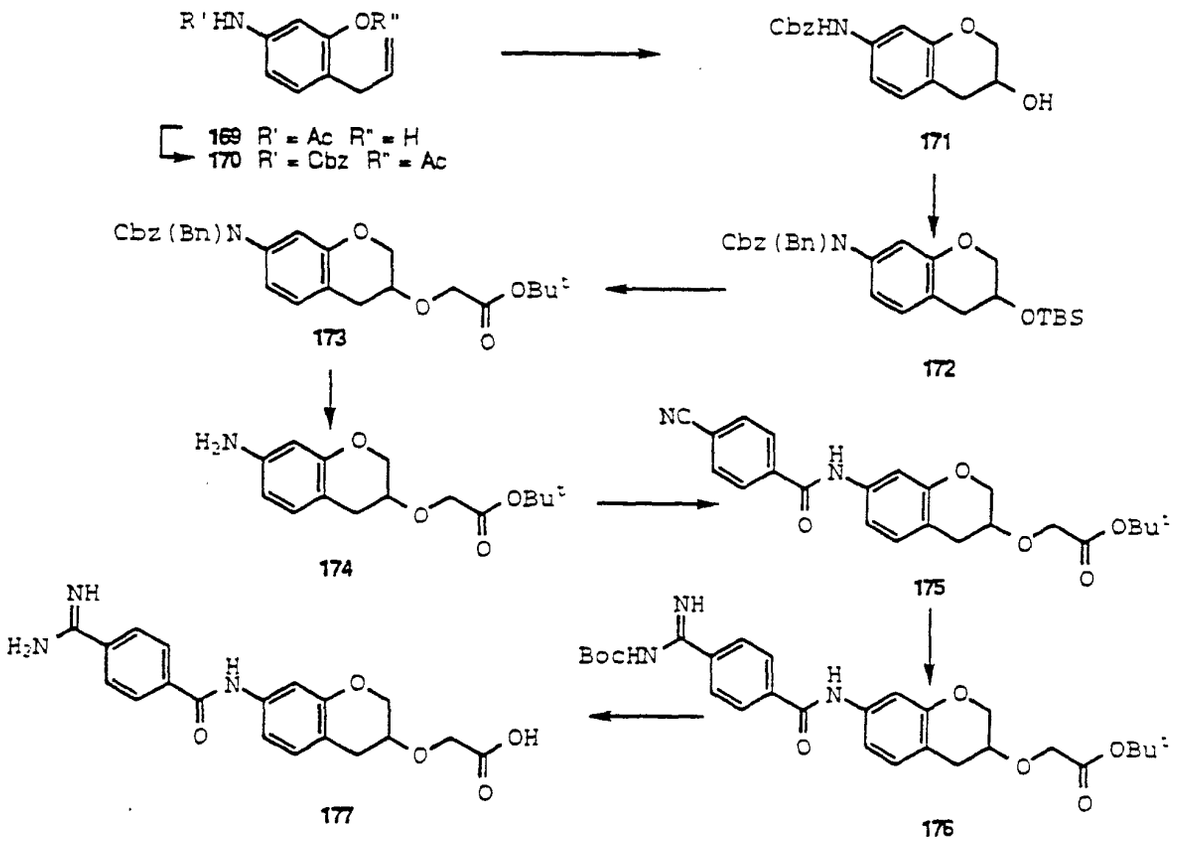
[0128] Scheme 22 describes a synthesis method for disubstituted tetralins bearing an α-alkoxyacetic acid residue at C_2 and a C_6 carboxyl linked benzamidine. This scheme begins with 6-bromo-2-tetralone (156) which is reduced with $NaBH_4$ and the resultant alcohol protected as its tert-butyldimethylsilyl (TBS) ether giving 157. Treatment of this compound with t-BuLi effects halogen metal exchange and the formed anion is quenched with CO_2. The resulting carboxylate is immediately transformed into the benzyl ester with benzyl alcohol and EDCI. The TBS group is removed during workup with TBAF affording alcohol 158. The free secondary hydroxyl is alkylated with tert-butyl bromoacetate using phase transfer conditions and the 6-carboxylate is liberated via catalytic hydrogenation affording 159. Amide 160 is the result of allowing 159 to react with 4-cyanoaniline in the presence of EDCI and DMAP. Nitrile 160 is converted to the BOC protected amidine and thereafter to the fully deprotected 161 using conditions outlined in Scheme 1.

Scheme 23



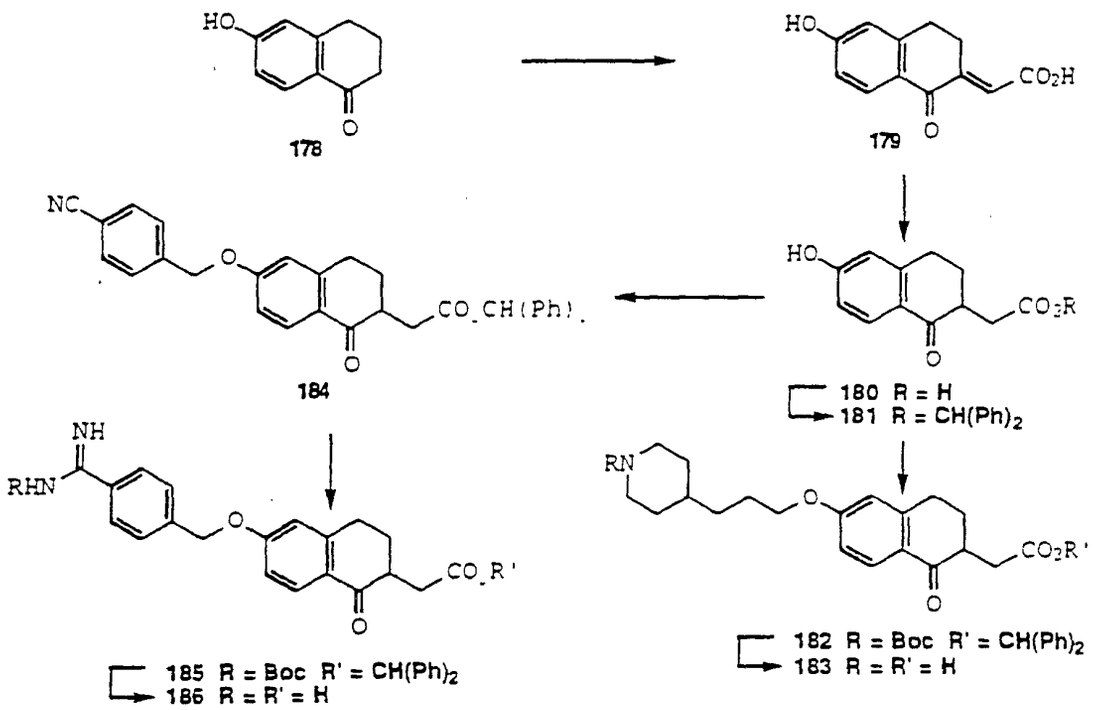
[0129] Scheme 23 outlines the preparation of tetralins having an acetic acid residue at C_2 and a C_6 carboxyl linked benzamidine. In the first step, bromotetralone 156 is treated with ethylene glycol and TsOH under dehydrating conditions giving ketal 162. This material is treated with tBuLi and the resulting anion is quenched with CO_2. The formed acid is immediately esterified with benzyl alcohol and EDCI giving 163. The spiro ketal contained in 163 is cleaved with aqueous HCl in acetone and the formed ketone is allowed to react with the sodium salt of tert butyl diethylphosphonoacetate giving 164 as a mixture of olefin isomers. Catalytic hydrogenation over Pd removes the unsaturation and liberates the C_6 carboxylate giving acid 165. Condensation of this compound with 4-aminobenzonitrile gives amide 166. Conversion of 166 to Boc protected amidine 167 and then to final compound 168 is accomplished using the same sequence outlined in Scheme 1.

Scheme 24



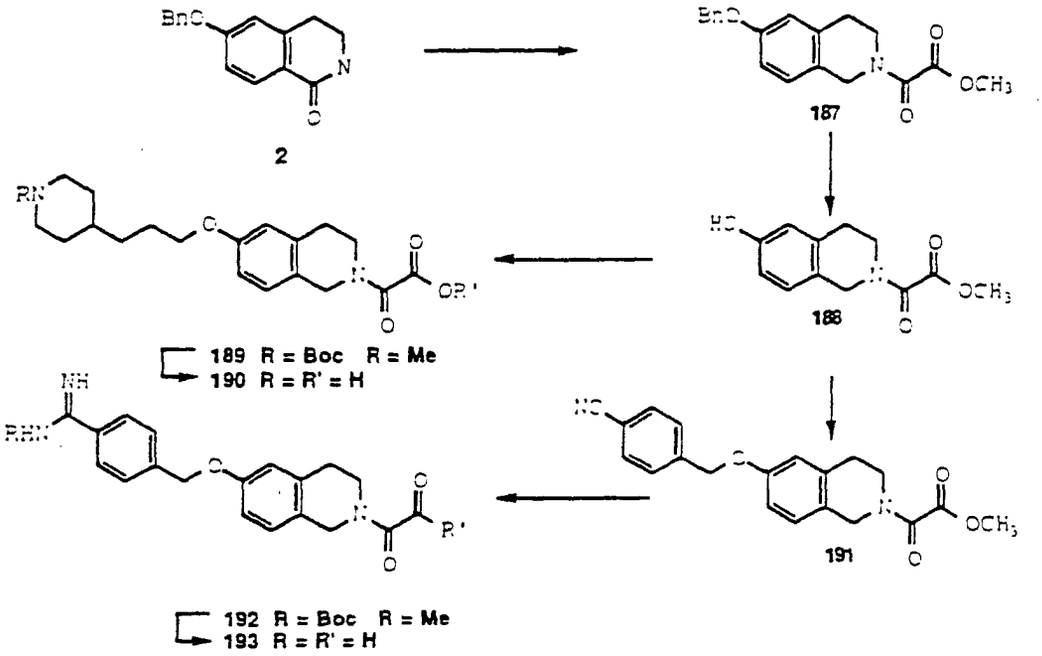
[0130] Scheme 24 describes the preparation of 3,7-disubstituted benzopyrans in which the 3-position is substituted with an α-alkoxyacetic acid moiety and the 7 position is substituted with an amide linked benzamidine. The synthesis begins with the allyl substituted aromatic 169. Acetamide hydrolysis is effected with NaOH in EtOH (Claisens alkali) and the resulting aniline is re-protected as its CBz counterpart. The free phenol is then acylated with acetic anhydride giving 170. The olefin is reacted with MCPBA giving the corresponding epoxide which is rearranged in the presence of NaI giving a mixture of 3-hydroxy and 3-acetoxy benzopyrans. This mixture is treated with LiOH giving alcohol 171. The alcohol moiety of 171 is then converted to its TBS ether and the resulting compound is alkylated on nitrogen to give fully protected 172. Liberation of the C_3 hydroxy with TBAF followed by alkylation with tert-butyl bromoacetate under phase transfer condition gives 173. Catalytic hydrogenation provides aniline 174 which is acylated with 4-cyanobenzoic acid, providing amide 175. This material is first converted to the corresponding protected benzamidine 176 and then to its deblocked congener 177 using the same sequence of events outlined in Scheme 1.

Scheme 25



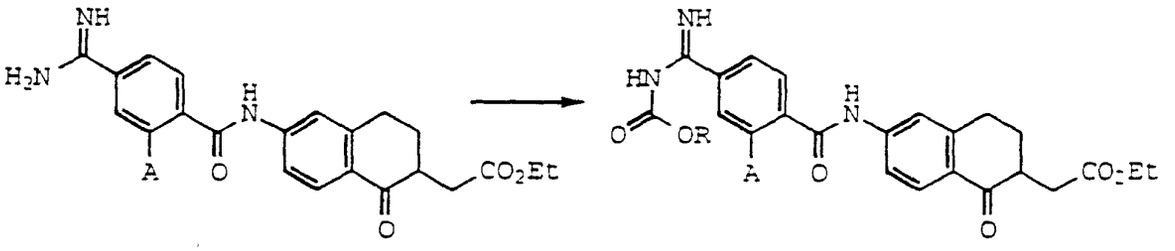
[0131] Scheme 25 outlines the preparation of 2,6-disubstituted tetralones in which the 2 position is substituted by an acetic acid moiety and the 6 position is substituted by either an alkoxy-linked benzamidine or alkoxy-linked 4-alkylpiperidine. In the first step, tetralone 178 is treated with NaOH and glyoxylic acid giving adduct 179. This material is reduced with Zn in acetic acid and the resulting acid (180) is reacted with diphenyldiazomethane giving benzhydryl ester 181. The free phenol can then be alkylated with α-bromo-p-tolunitrile to give 184 or with the appropriate 4-alkylpiperdine giving 182. Nitrile 184 is then converted to the corresponding Boc protected amidine 185 and then to the fully deprotected compound 186 using the same sequence of reaction outlined in Scheme 1. Compound 182 is deprotected with TFA giving compound 183.

Scheme 26



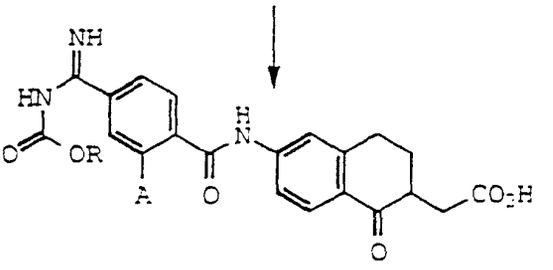
[0132] Scheme 26 teaches a method to prepare tetrahydroisoquinolins in which the 2-position is substituted by an oxamic acid residue and the 6-position contains an ether linked benzamidine. In the first step, isoquinolone 2 is treated with $LiAlH_4$ and the resulting product of reduction is acylated with methyl oxalylchloride giving compound 187. This material is subjected to hydrogenation and the resulting phenol is alkylated with either α-bromotolunitrile or the appropriate 4-alkylpiperidine giving compounds 191 and 189 respectively. The nitrile moiety of 191 is transformed into Boc protected amidine 192 using the same procedures described in scheme 1. This material is then saponified with NaOH and the resulting acid is treated with TFA giving 193. Compound 190 is prepared using a similar saponification deprotection sequence.

Scheme 27



COMPOUND	A
365	H
366	F

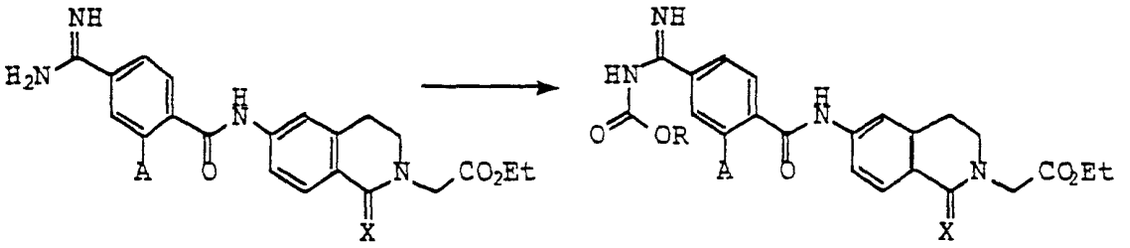
COMPOUND	A	R
367	H	Ethyl
368	H	Propyl
369	F	Ethyl
370	F	Propyl



COMPOUND	A	R
371	H	Propyl

[0133] Scheme 27 describes the acylation of the amidine moiety contained in 2,6-disubstituted tetralones 365 and 366 which are prepared from compounds 102 and 123 (Scheme 14 and 17 respectively) by esterification with ethanol. The acylation is accomplished by reacting the benzamidine containing compound with an alkyl chloroformate in the presence of aqueous base, thus forming the derivatives 367 to 370. These materials can then be subjected to saponification with ethanolic NaOH yielding the free acid (see 371 in Scheme 27).

Scheme 28

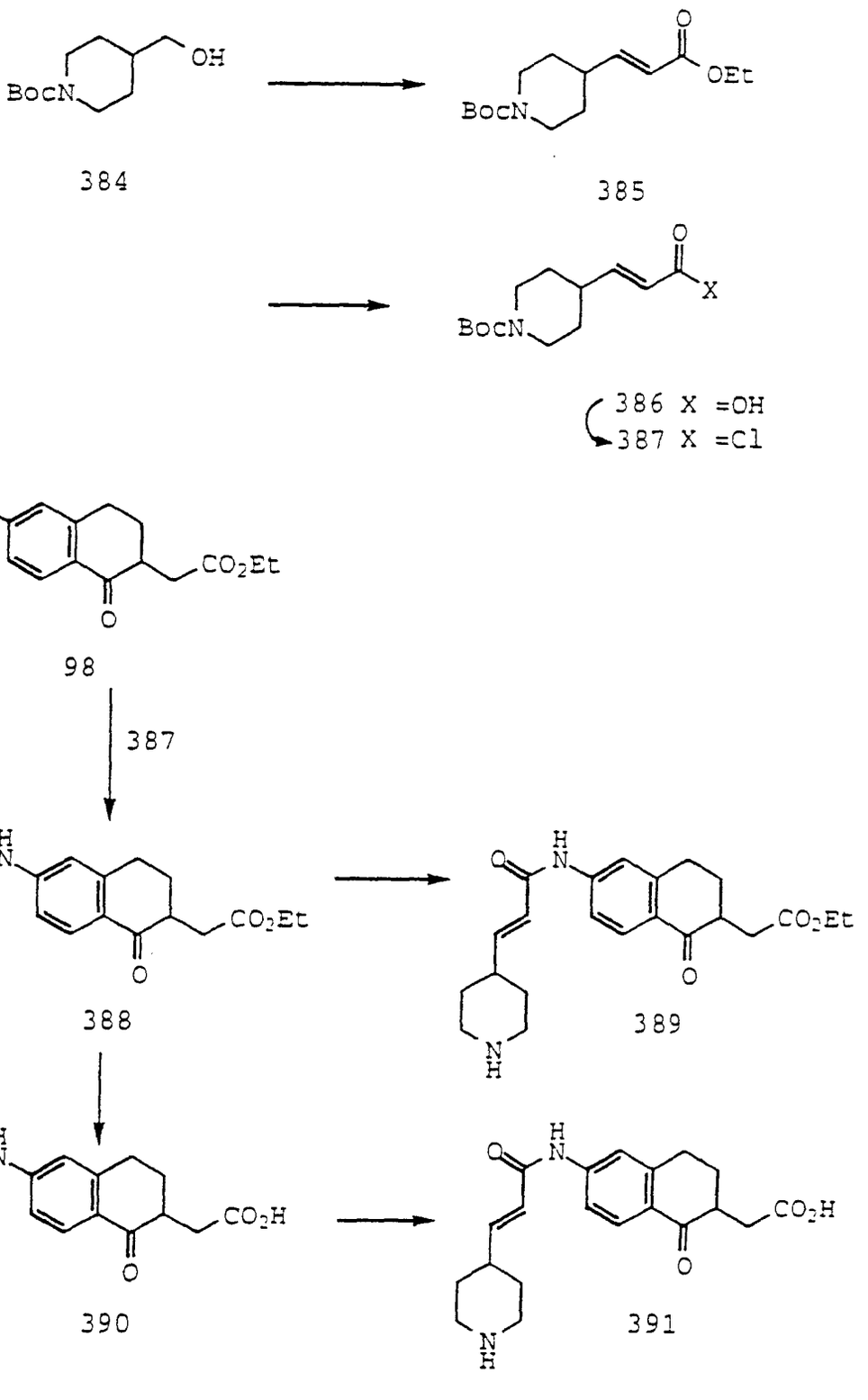


COMPOUND	A	X
372	H	H,H
373	F	H,H
374	H	O
375	F	O

COMPOUND	A	X	R
376	H	H,H	Ethyl
377	H	H,H	Propyl
378	F	H,H	Ethyl
379	F	H,H	Propy
380	H	O	Ethyl
381	H	O	Propyl
382	F	O	Ethyl
383	F	O	Propyl

[0134] The procedure of Scheme 27 is general and has also been applied to compounds containing an isoquinolone nucleus as shown in Scheme 28. In a like manner, one can also prepare N-acylated derivatives of benzamidine containing tetrahydroisoquinolins or benzopyrans.

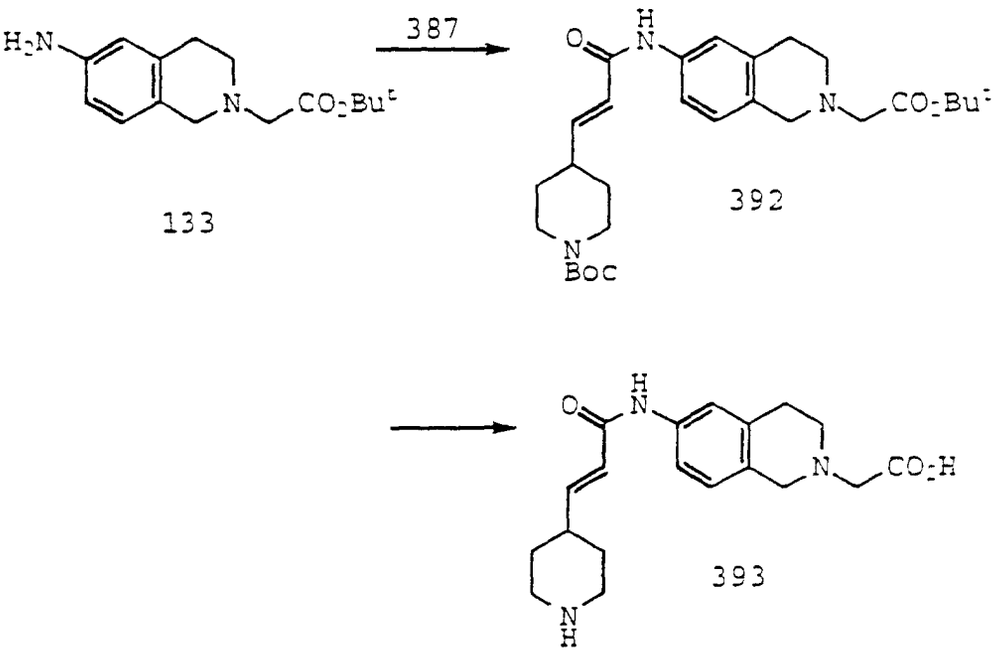
Scheme 29



[0135] Scheme 29 describes the preparation of 2,6-disubstituted tetralones in which the 2-position is occupied by an acetic acid residue and the 6-position maintains an amide linked 4-propenoyl piperidine moiety. In the first step,

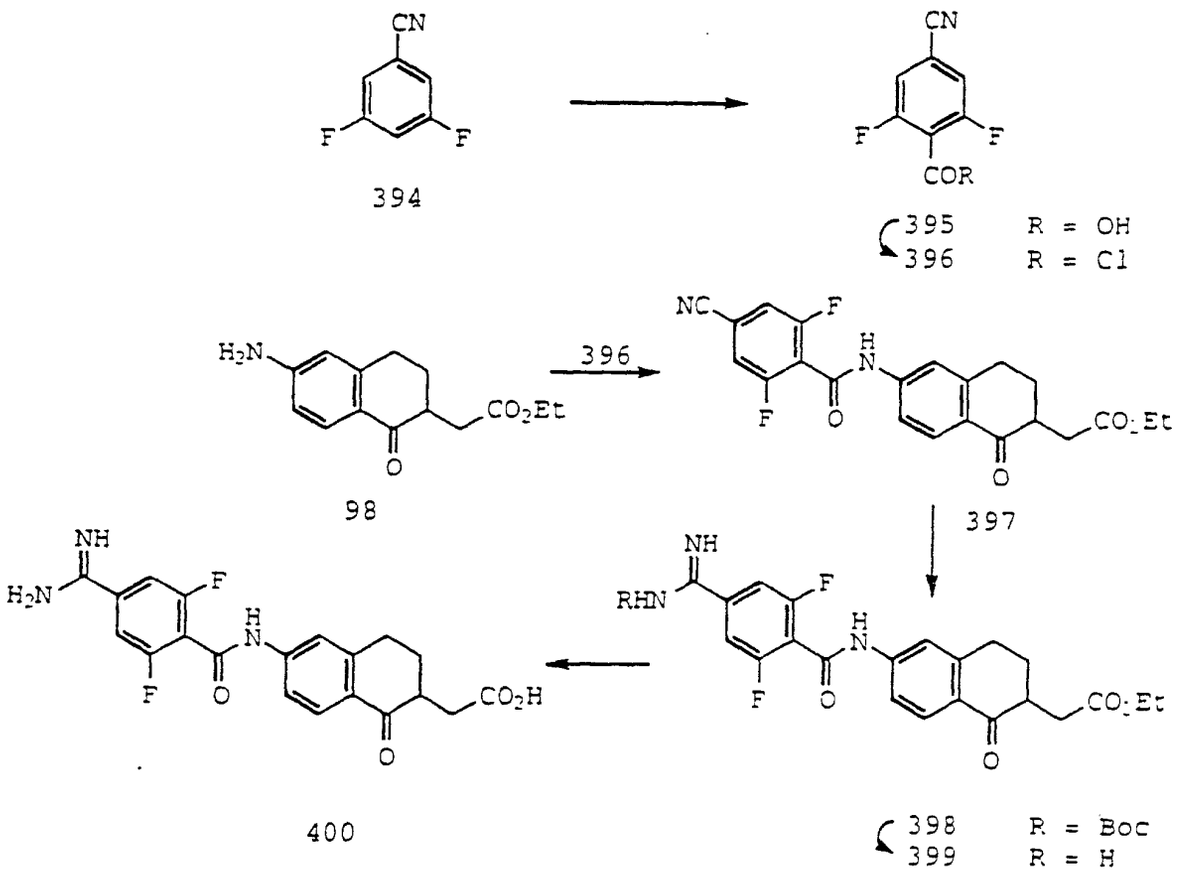
alcohol 384 (prepared form 4-pyridylcarbinol by hydrogenation and protection) is oxidized with oxalyl chloride and DMSO giving the corresponding aldehyde. This material is not characterized but rather, reacted crude with the sodium salt of triethyl phosphonoacetate which gives the desired unsaturated ester 385. This material is saponified with LiOH and the resulting acid 386 is activated with oxalyl chloride giving 387. Aniline 98 reacts with acid chloride 387 giving adduct 388. This compound is N-deprotected with TFA giving ester 389 after salt exchange with HCl. Alternatively, saponification with LiOH first gives the free acid 390 which can then be N-deprotected with TEA providing 391.

Scheme 30



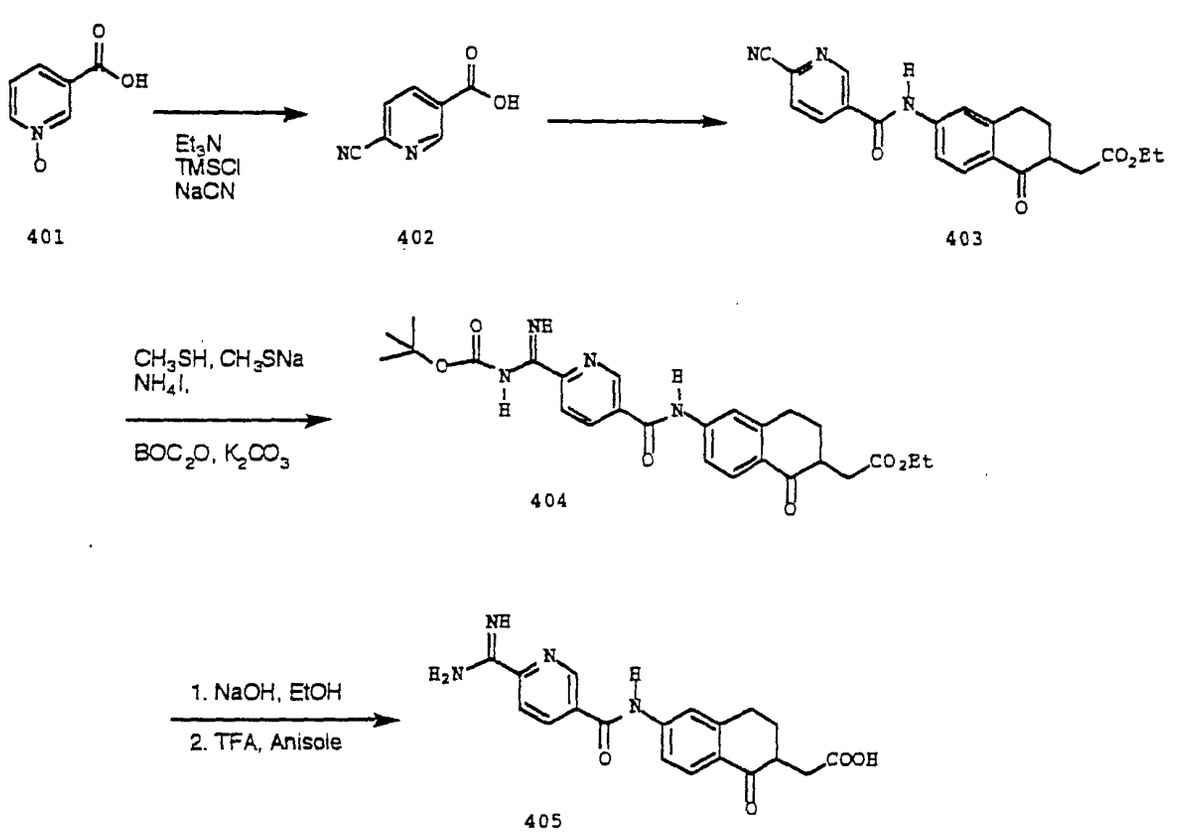
[0136] Scheme 30 teaches the preparation of 2,6 disubstituted tetrahydroisoquinolines bearing an acetic acid residue at position 2 and an amide linked 4-propenoyl piperidine at position 6. In the first step, the 6-amino moiety of 133 is acylated with acid chloride 387 (Scheme 29) giving adduct 392. This material can be fully deprotected with TFA providing 393.

Scheme 31



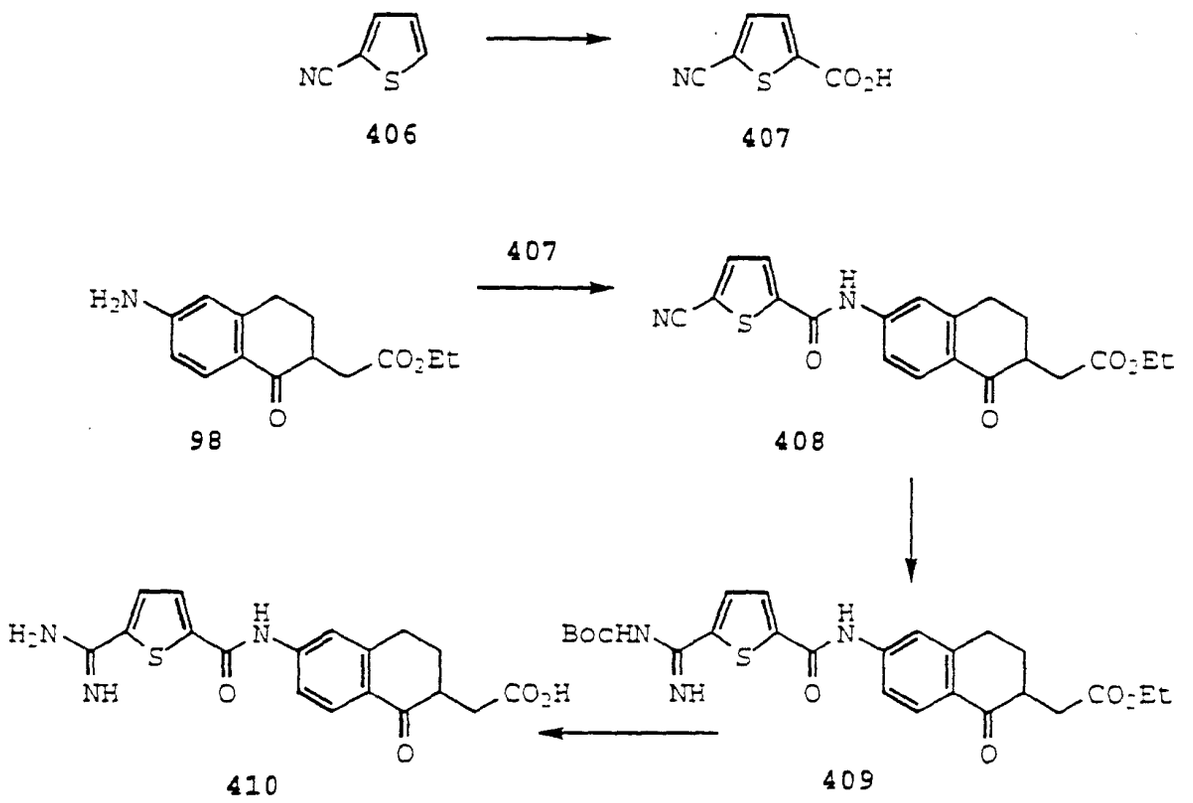
[0137] Scheme 31 outlines the preparation of 2,6-disubstituted tetralones in which the 2 position is occupied by an acetic acid moiety and the 6 position supports an amide-linked difluoro benzamidine. In the first step, difluoro benzonitrile 394 is lithiated with n-butyl lithium and the resulting anion is quenched with CO_2 giving acid 395. This compound is then treated with oxalyl chloride and the resulting acid chloride 396 is reacted with aniline 98 giving adduct 397. The nitrile moiety in 397 is transformed into Boc protected amidine 398 using the same sequence of reactions employed for conversion of 5 to 6 as described in Scheme 1. Compound 398 can be deprotected with TFA providing 399. Alternatively, 398 can be fully deprotected by first cleaving the ester moiety with NaOH and then deprotecting the amidine with TFA yielding 400.

Scheme 32



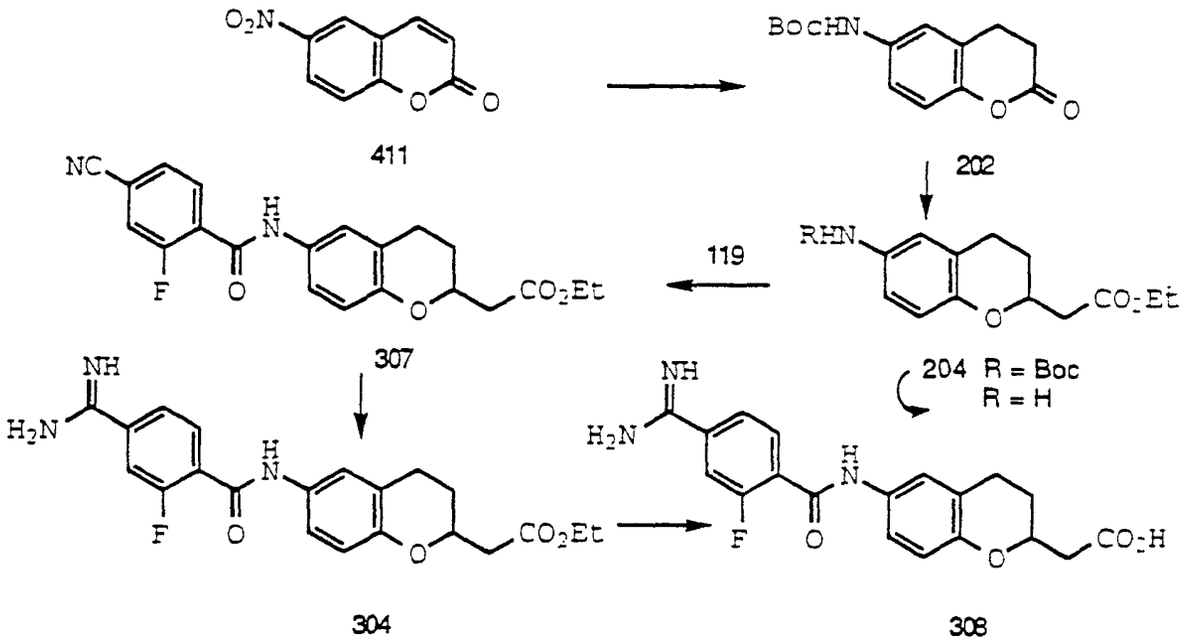
[0138] Scheme 32 describes the preparation of 2,6-disubstituted tetralones bearing an acetic acid moiety at position 2 and an amide-linked amidino pyridine at position 6. In the first step, pyridine 401 is reacted with Et_3N, TMSCl, and NaCN giving acid 402. This material is coupled with aniline 98 giving adduct 403. The nitrile in 403 is then reacted with the sodium salt of methane thiol giving the methylthioimidate. This intermediate is reacted with ammonium iodide providing an amidine which is BOC protected giving 404. Compound 404 is first reacted with ethanolic NaOH to cleave the ester and then with TFA to deprotect the amidine providing the fully deprotected congener 405.

Scheme 33



[0139] Scheme 33 describes the preparation of 2,6-disubstituted tetralones in which the amide-linked amidine contains a thiophene nucleus. In the first step, thiophene 406 is metalated with LDA and the resulting anion is quenched with CO_2 giving acid 407. This acid is reacted with compound 98 in the presence of EDCI giving amide 408. The nitrile moiety in 408 is converted to a Boc protected amidine 409 using the same sequence of reactions used for the formation of compound 6 in Scheme 1. The resulting compound is first saponified with ethanolic NaOH and then N-deprotected with TFA giving compound 410 as the TFA salt.

Scheme 34



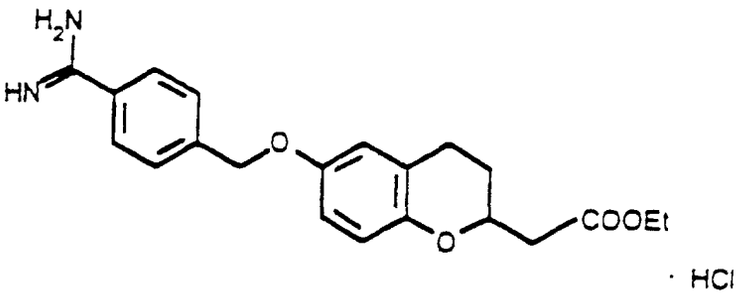
[0140] Scheme 34 teaches the preparation of 2,6 disubstituted benzopyrans in which the 2 position retains an acetic acid moiety and the 6 position contains an amide-linked fluoro-substituted benzamidine. In the first transformation, the nitro group is reduced with ammonium formate and palladium and the resulting aniline is Boc protected. The B ring unsaturation is then removed with Pd/C giving lactone 202. This material is reduced with DIBAH giving an intermediate lactol which is reacted with ethoxycarbonylmethylene triphenylphosphorane giving benzopyran 204. This material is then N-deprotected with TFA and the resulting aniline reacted with the acid chloride derived from fluoro-acid 119 giving adduct 307. This material was then subjected to the action of HCl in ethanol giving the intermediate imino-ether which was not characterized but instead reacted with ammonia resulting in the formation of 304. This material was then hydrolyzed with NaOH in ethanol giving the desired free acid 308 after neutralization.

Examples

[0141] The following examples are provided to enable one skilled in the art to practice the present invention. These examples, however, are not to be read as limiting the scope of the invention as it is defined by the appended claims.
[0142] The reference numbers used in the following Examples refer to the corresponding compound shown in the preceding reaction Schemes 1 through 26:

Example 1

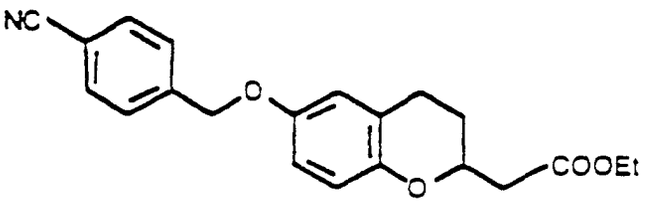
[0143] Preparation of Ethyl rac-(6-(4-(Aminoiminomethyl)phenylmethoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate hydrochloride, a compound represented by the formula (194):



(194)

Step A: Preparation of ethyl rac-(6-(4-cyanophenyl)methoxy-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (195)

[0144]

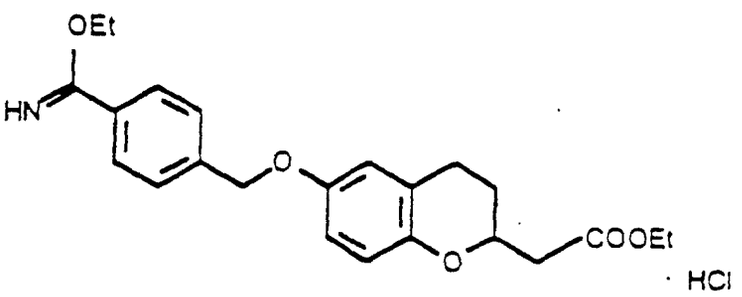


(195)

[0145] 6.0 g (25.4 mmol) ethyl rac-(3,4-dihydro-6-hydroxy-2H-1-benzopyran-2-yl)acetate (prepared according to Eur. Pat. Appl. EP 129 906, the disclosure of which is incorporated herein by reference) and 4.9 g (25.0 mmol) 4-cyanobenzyl bromide were dissolved 36 ml in dry acetone, and 3.5 g (25.3 mmol) potassium carbonate were added. After stirring overnight at 50 °C another 0.3 g (1.3 mmol) of the benzopyran were added, and the reaction was continued for the same time. The inorganic solid was removed by filtration, the filtrate concentrated in vacuo, and the pure nitrite obtained from the residue by chromatography on silica gel with hexane/acetone 40:5.
Yield: 6.7 g (76 %) of pale yellow solid, m.p. 75-76 °C

Step B: Preparation of ethyl rac-(3,4-dihydro-6-(4-(ethoxycarbonimidoyl)phenylmethoxy)-2H-1-benzopyran-2-yl) acetate hydrochloride, an intermediate represented by the formula (196):

[0146]



(196)

7.45 g (21.2 mmol) of the nitrile from Step (A) were suspended in 340 ml dry ethanol. The suspension was cooled with an ice bath and saturated with gaseous hydrogen chloride (approximately 5 hours). After standing overnight a clear solution had been formed. The solution was evaporated to dryness in vacuo, and the compound (196) was stirred with hexane, filtered with suction, and dried in vacuo.

Yield: 6.43 g (70 %) of a pale yellow powder,
m.p. 118-119 °C

Step C: Preparation of compound (194), ethyl rac-(6-(4-(aminoiminomethyl)phenylmethoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate hydrochloride:

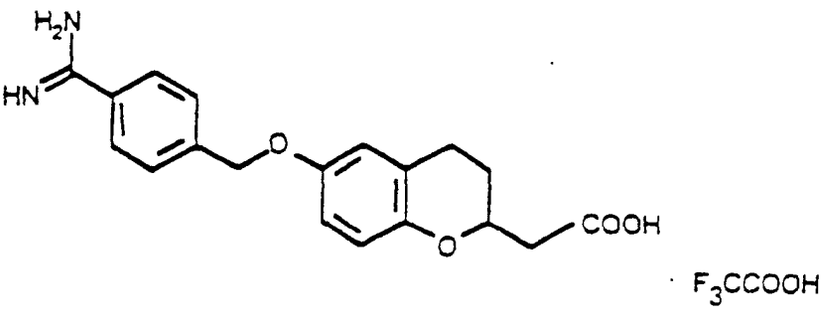
[0147] 385 ml of a saturated solution of ammonia in ethanol were cooled with ice, and 6.43 g (14.8 mmol) of the intermediate from Step B were added. The Step B intermediate was stirred overnight at room temperature, and the solvent was removed in vacuo. The remaining solid title compound was stirred with hexane, filtered with suction, and dried in vacuo at 40 °C.

Yield: 5.32 g (89 %) of white powder, m.p. 123-125 °C

Example 2

Preparation of rac-(6-(4-(Aminoiminomethyl)phenylmethoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid trifluoroacetate, a compound represented by the formula (197)

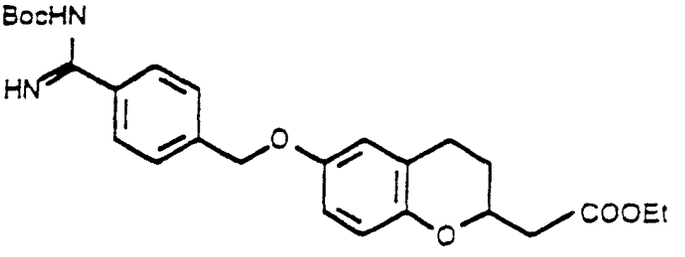
[0148]



(197)

Step A: Preparation of ethyl rac-(6-(4-(N-tert.-butoxycarbonyl(aminoiminomethyl))phenylmethoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (198):

[0149]



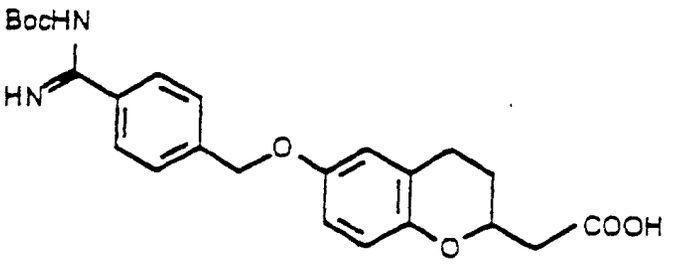
(198)

3.7 g (9.1 mmol) of the amidine of Example 1 was dissolved in 55 ml of a mixture of THF / H_2O 1:1. After addition of 1.65 g (11.9 mmol) potassium carbonate, 1.99 g (9.1 mmol) Boc_2O was added dropwise, and the mixture was stirred overnight at room temperature. The mixture was then diluted with 100 ml ethyl acetate. The organic layer was separated,

washed with water, dried over sodium sulfate, and concentrated in vacuo to give the pure protected amidine.
Yield: 4.3 g (100 %) of an oil.

Step B: Preparation of rac-(6-(4-(N-tert.-butoxycarbonyl(aminoiminomethyl))phenylmethoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid, an intermediate represented by the formula (199):

[0150]



(199)

5.2 g (11.1 mmol) of the ester from Step A was dissolved in 75 ml of ethanol. After addition of 36 ml 2N aqueous sodium hydroxide the mixture was heated at 60 °C for some minutes. The mixture was then adjusted to pH 6 with acetic acid. The ethanol was removed in vacuo, and ethyl acetate was added. The organic layer was separated, dried over sodium sulfate, concentrated in vacuo, and the title carboxylic acid was obtained from the residue by chromatography on silica gel with dichloromethane / ethanol 40:5.
Yield: 2.0 g (41 %) of a white powder, m.p. 220-222 °C (dec.)

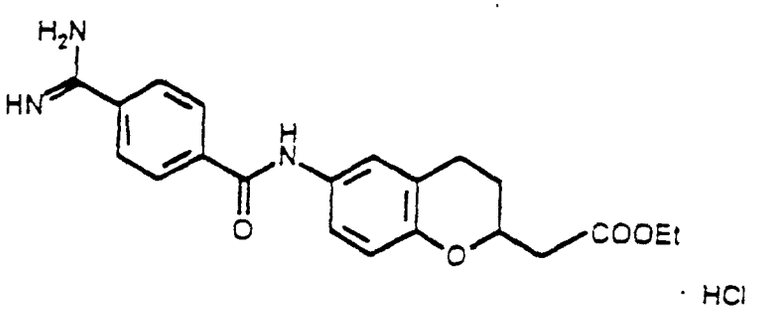
Step C: Preparation of rac-(6-(4-(aminoiminomethyl)phenylmethoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid trifluoroacetate

[0151] 0.15 g (0.34 mmol) of the protected amidine from Step B and 2.8 ml trifluoroacetic acid were mixed and stirred at room temperature for 1.5 hours. The solvent was removed in vacuo, and the title amidine precipitated after addition of 10 ml water. The product was filtered with suction, stirred again with 10 ml water, filtered, and dried in vacuo.
Yield: 0.09 g (58 %) of a white powder, m.p. 210-212°C

Example 3

Preparation of Ethyl rac-(6-(N-(4-(Aminoiminomethyl)benzoyl)amino)-3,4-dihydro-2H-l-benzopyran-2-yl)acetate hydrochloride, a compound represented by the formula (200):

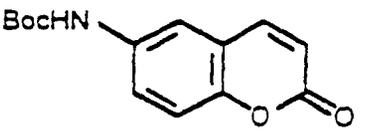
[0152]



(200)

Step A: Preparation of tert.-butyl (2-oxo-2H-1-benzopyran-6-yl)carbamate, an intermediate represented by the formula (201):

[0153]

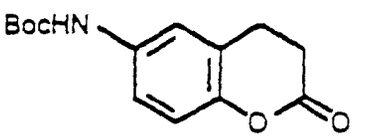


(201)

100 g (523 mmol) 6-Nitrocoumarin was dissolved in 600 ml dry ethanol, and the solution was kept under an atmosphere of argon. 86 g (1.364 mol) ammonium formate and 6 g 10 % Pd-C were added with stirring, while the temperature rose to 45 °C and a gas evolution was observed. The reaction mixture was heated with reflux for 3 hours and diluted with another 200 ml ethanol. The hot mixture was filtered through Celite followed by washing with 200 ml hot ethanol. The unprotected amine precipitated upon cooling, filtered with suction, washed with hexane, and dried in vacuo. Another crop of the amine was obtained by concentration of the filtrate.
Total yield of the intermediate amine was 74 g.
The crude amine was dissolved in 300 ml of a mixture of THF/H_2O 1:1 and kept under an atmosphere of argon. 110 g (504 mmol) Boc_2O and 95 g (687 mmol) dried potassium carbonate were added. The reaction mixture was stirred overnight at room temperature, diluted with 750 ml water, and extracted with ethyl acetate (3 x 1 l). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in 2 L dichloromethane and stirred in the presence of 1 kg silica gel, which was filtered with suction and washed with dichloromethane. The filtrate was concentrated in vacuo to give the title compound. An analytical sample was purified by chromatography on silica gel with dichloromethane.
Yield: 112 g (82 %) of pale yellow crystals,
m.p. 142-143 °C

Step B: Preparation of tert.-butyl (3,4-dihydro-2-oxo-2H-1-benzopyran-6-yl)carbamate, an intermediate represented by the formula (202):

[0154]

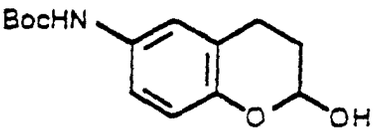


(202)

85 g (325 mmol) of the coumarin from Step A were dissolved in a mixture of 1150 ml ethanol and 115 ml acetic acid, and the solution was filled into a hydrogenation autoclave.
6 g 10 % Pd-C were added, and it was hydrogenated at room temperature and a pressure of 20 atm hydrogen. After two days another 3 g Pd-C were added, and the reaction was continued for two days. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was dissolved in 1 L ethyl acetate, washed with 500 ml saturated aqueous sodium bicarbonate, dried over sodium sulfate, and the solvent was removed in vacuo. The title lactone was purified by chromatography on silica gel with dichloromethane containing 1 % ethanol.
Yield: 21 g (25 %) of colorless crystals,
m.p. 158-159 °C

Step C: Preparation of tert.-butyl rac-(3,4-dihydro-2-hydroxy-2H-1-benzopyran-6-yl)carbamate, an intermediate represented by the formula (203):

[0155]

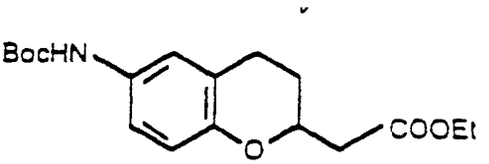


(203)

21 g (79.8 mmol) of the lactone from the previous Step was dissolved in 340 ml dry dichloromethane and kept under an atmosphere of argon. The solution was cooled to -70 °C and maintained at this temperature, while 67 ml of a 25 % solution of diisobutylaluminum hydride (DIBAL-H) in toluene was added dropwise within 45 minutes. After an additional hour stirring at this temperature 20 ml methanol were added slowly, and the mixture was poured into 1 L saturated aqueous ammonium chloride solution. Solids were removed by filtration through Celite and washed with dichloromethane. The filtrate was dried over sodium sulfate, concentrated in vacuo to give the pure title compound as detected by its ^{1}H-NMR.
Yield: 16.5 g (78 %) of a yellow oil.

Step D: Preparation of ethyl rac-(6-(N-tert.-butoxycarbonylamino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (204):

[0156]

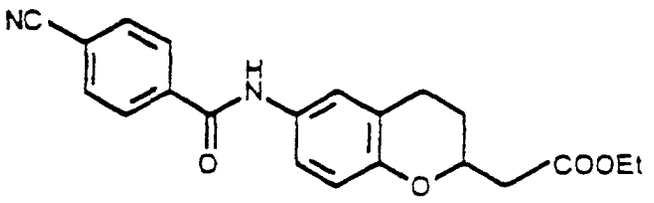


(204)

11.2 g (42.2 mmol) of the compound from Step C and 14.7 g (42.2 mmol) ethoxycarbonylmethylene triphenylphosphorane were dissolved in 130 ml dry toluene and heated with reflux for 22 hours. The reaction mixture was cooled to room temperature, and 300 mg sodium hydride were added. After additional 5 hours heating the mixture was poured into 1 L ice-cold water. It was extracted three times with ethyl acetate, and the combined organic layers were washed with 300 ml water, dried over sodium sulfate, and concentrated in vacuo. The benzopyran (204) was obtained from the residue by chromatography on silica gel with dichloromethane.
Yield: 5.5 g (39 %) of a colorless amorphous solid, m.p. 67-69°C

Step E: Preparation of ethyl rac-(6-(N-(4-cyanobenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (205) :

[0157]



(205)

2.0 g (6.0 mmol) of the protected amine from the previous step was treated with 6 ml trifluoroacetic acid and stirred for 2 hours at room temperature. The mixture was neutralized with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to leave a dark oil of unprotected ethyl rac-(6-amino-3,4- dihydro-2H-1-benzopyran-2-yl)acetate. It was dissolved in 40 ml dry THF, treated with 4 ml dry pyridine and 1.0 g (6.0 mmol) 4-cyanobenzoyl chloride, and stirred overnight at room temperature. The mixture was poured into ice-cold aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed successively with aqueous copper(II) sulfate solution and with brine, dried over sodium sulfate, and concentrated in vacuo. The nitrite (205) was obtained from the residue by chromatography on silica gel with dichloromethane/ethanol 96:4.
Yield: 1.4 g (64 %) of pale yellow crystals,
m.p.146-148 °C

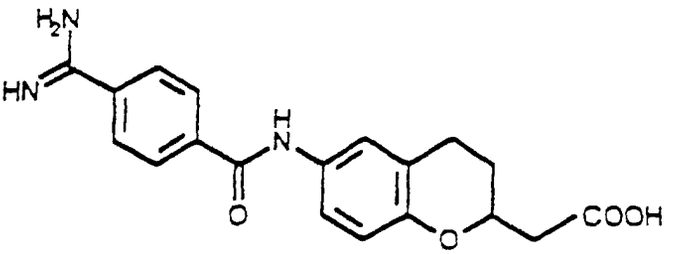
Step F: Preparation of ethyl rac-(6-(N-(4-(aminoiminomethyl)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl) acetate hydrochloride

[0158] 1.4 g (3.8 mmol) of the nitrile from the previous Step was dissolved in 50 ml dry ethanol. The solution was cooled with ice and saturated with gaseous hydrogen chloride. After stirring overnight at room temperature the solvent was removed under reduced pressure, and the residue was treated with a saturated solution of ammonia in ethanol. The reaction mixture was stirred for three days, evaporated in vacuo, and the title compound was obtained as a yellow oil by chromatography on silica gel with dichloromethane/ethanol 65:35 containing 5% ammonia in ethanol. A crystalline sample for analytical and biological tests was obtained by stirring with a mixture of ethanol/etheral hydrogen chloride/ether.
Yield: 0.9 g (56 %) of yellow crystals, m.p. 253 °C (dec.)

Example 4

Preparation of rac-(6-(N-(4-(Aminoiminomethyl)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (206):

[0159]



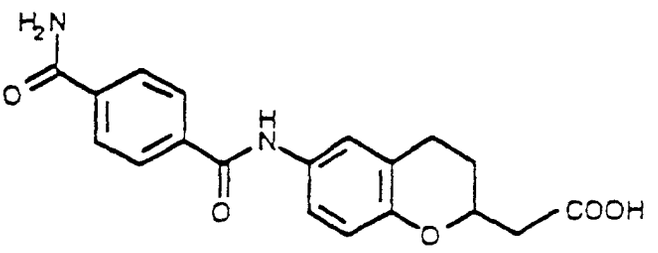
(206)

0.2 g (0.48 mmol) of the ester from Example 47 were added to a mixture of 4 ml ethanol and 0.5 ml 2 N aqueous sodium hydroxide. The mixture was diluted with water until it became a clear solution. After slight warming it was stirred at room temperature for 3 hours and acidified with 2 N acetic acid, while a precipitate was formed, which was filtered, washed with water, and dried in vacuo. The very unsoluble compound (206) was characterized by elemental analysis and mass spectrum.
Yield: 0.16 g (95 %) of a colorless amorphous solid,
m.p. 291-292°C (dec.).

Example 5

Preparation of rac-(6-(N-(4-Carbamoylbenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (207):

[0160]



(207)

Method A:

[0161] 0.47 g (1.12 mmol) of the ester from Example 3 were added to a mixture of 5 ml ethanol and 5 ml 2 N aqueous sodium hydroxide. The mixture was heated on a steam bath for 15 minutes, cooled to room temperature, and brought to pH 4 with 2 N aqueous hydrochloric acid, while a precipitate was formed. The precipitate was filtered with suction, and the amide (207) was purified by suspension in a small amount of hot ethanol.
Yield: 60 mg (15 %) of a beige amorphous solid,
m.p. 273-274°C

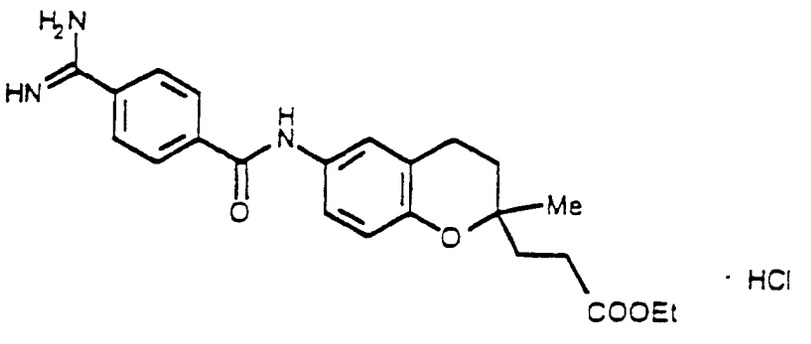
Method B:

[0162] 0.7 g (1.92 mmol) of the nitrile from Example 3, Step E were dissolved in 15 ml 98 % formic acid, and a stream of gaseous hydrogen chloride was passed through the mixture for 4 hours. The reaction mixture was stirred overnight at room temperature, and the solvent was removed in vacuo. The remaining solids were stirred with water, filtered with suction, and washed with ethanol and ether, successively. The amide was suspended in hot ethanol, filtered, and dried in vacuo.
Yield: 0.45 g (66 %) of grey crystals,
m.p. 264-265°C.

Example 6

Preparation of Ethyl rac-3-(6-(N-(4-(Aminoiminomethyl)benzoyl)amino)-3,4-dihydro-2-methyl-2H-1-benzopyran-2-yl) propanoate hydrochloride, a compound represented by formula (208):

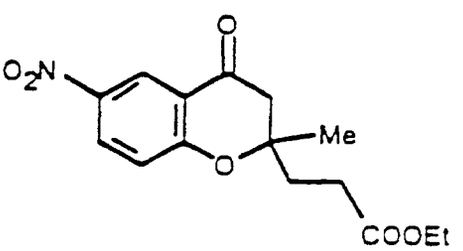
[0163]



(208)

Step A: Preparation of ethyl rac-3-(3,4-dihydro-2-methyl-6-nitro-4-oxo-2H-1-benzopyran-2-yl)propanoate, an intermediate represented by the formula (209):

[0164]



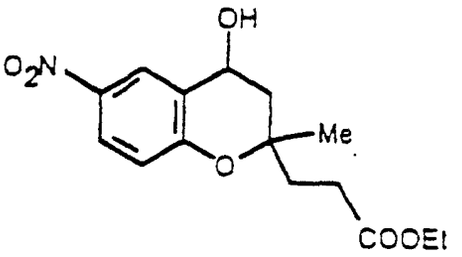
(209)

5.4 g (29.8 mmol) 2-hydroxy-5-nitroacetophenone (prepared by methods from J. Am. Chem. Soc. 1954, 76, 4993, the disclosure of which is incorporated herein by reference), 5.8 g (40.2 mmol) ethyl 4-oxopentanoate, and 1.7 ml pyrrolidine were dissolved in 50 ml toluene, and the mixture was heated for 6 hours with azeotropic removal of water. The mixture was concentrated in vacuo, and the remaining oil was dissolved in ethyl acetate. The solution was washed with 1 N aqueous hydrochloric acid and with brine, successively, dried over sodium sulfate, and the solvent was removed under reduced pressure. The chromanone (209) crystallized from the residue.
Yield: 5.3 g (58 %) of a pale yellow amorphous solid, m.p.

88-90°C.

Step B: Preparation of ethyl 3-(3,4-dihydro-4-hydroxy-2-methyl-6-nitro-2H-1-benzopyran-2-yl)propanoate, an intermediate represented by the formula (210):

[0165]

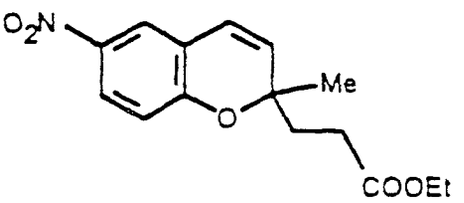


(210)

3.2 g (10.4 mmol) of the chromanone from Step A were dissolved in 100 ml ethanol. 0.76 g (20.0 mmol) sodium borohydride were added in small portions, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated in vacuo, acidified with 1 N aqueous hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and the solvent removed under reduced pressure. The benzopyran (210) was obtained by chromatography on silica gel with dichloromethane containing 4 % ethanol.
Yield: 2.0 g (62 %) of an oil.

Step C: Preparation of ethyl rac-3-(2-methyl-6-nitro-2H-1-benzopyran-2-yl)propanoate, an intermediate represented by the formula (211) :

[0166]

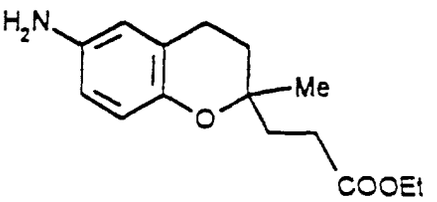


(211)

2.0 g (6.5 mmol) of the alcohol from the previous step were dissolved in 75 ml toluene, and a catalytic amount of 4-toluenesulfonic acid was added. The mixture was heated with reflux for 7 hours, while water was removed azeotropically. The reaction mixture was washed with aqueous sodium bicarbonate solution, the organic layer dried over sodium sulfate, and concentrated in vacuo. The title chromene was obtained from the residue by chromatography on silica gel with ethyl acetate/hexane 1:3.
Yield: 0.85 g (45 %) of an oil

Step D: Preparation of ethyl rac-3-(6-amino-3,4-dihydro-2-methyl-2H-1-benzopyran-2-yl)propanoate, an intermediate represented by the formula (212):

[0167]

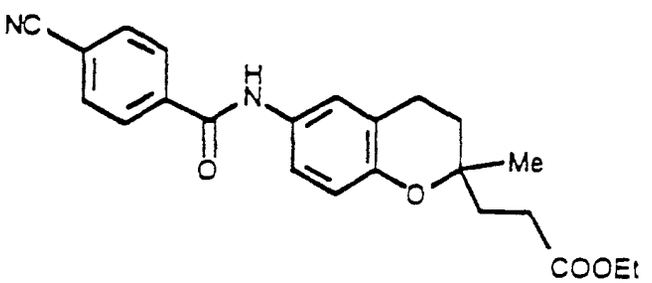


(212)

1.6 g (5.5 mmol) of the 6-nitrochromene from the previous Step was dissolved in a mixture of 20 ml ethanol and 10 ml acetic acid. 400 mg Pd-C were added and the mixture was filled into an autoclave. It was stirred overnight at room temperature under an atmosphere of 20 bar hydrogen until the reduction was complete. The catalyst was removed by filtration, and ethanol was distilled in vacuo. The reaction mixture was diluted with ethyl acetate, washed with concentrated aqueous sodium bicarbonate solution, dried over sodium sulfate, and concentrated under reduced pressure to give the crude title amine, which was pure as detected by ^{1}H-NMR.
Yield: 1.6 g of an oil, which darkened upon standing.

Step E: Preparation of ethyl rac-3-(6-(N-(4-cyanobenzoyl)amino)-3,4-dihydro-2-methyl-2H-1-benzopyran-2-yl) propanoate, a compound represented by the formula (213):

[0168]



(213)

1.6 g (6.1 mmol) of the crude amine from Step D were dissolved in 40 ml dry THF. 5ml dry pyridine and 1.0 g (6.0 mmol) 4-cyanobenzoyl chloride were added successively. The mixture was stirred overnight at room temperature and poured into an ice-cold solution of aqueous sodium bicarbonate. It was extracted with ethyl acetate, and the organic layer was washed with aqueous copper(II) sulfate and wich brine, dried over sodium sulfate, and concentrated in vacuo. The pure nitrile was obtained by chromatography on silica gel with dichloromethane/ethanol 97:3.
Yield: 1.5 g (63 %) of a dark viscous oil.

Step F: Preparation of ethyl rac-3-(6-(N-(4-(aminoiminomethyl)benzoyl)amino)-3,4-dihydro-2-methyl-2H-1-benzopyran-2-yl)propanoate hydrochloride

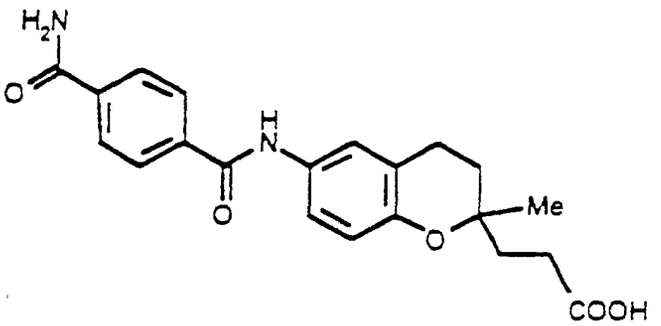
[0169] 1.5 g (3.8 mmol) of the nitrite from Step E were dissolved in 50 ml dry ethanol. The solution was cooled with an ice bath, saturated with gaseous hydrogen chloride, and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was treated with a saturated solution of ammonia in ethanol. It was stirred for additional 24 hours at room temperature, concentrated in vacuo, and chromatographed on silica gel with dichloromethane/ethanol 65:35 containing 5 % saturated ammonia in ethanol to give the title amidine as an oil. A

crystalline sample for analytical and biological tests was obtained by stirring in a mixture of ethanol/etheral hydrogen chloride/ether.
Yield: 0.94 g (55 %) of yellow crystals,
m.p. 118-120°C

Example 7

Preparation of rac-3-(6-(N-(4-Carbamoylbenzoyl)amino)-3,4-dihydro-2-methyl-2H-1-benzopyran-2-yl)propanoic Acid, a compound represented by the formula (214):

[0170]



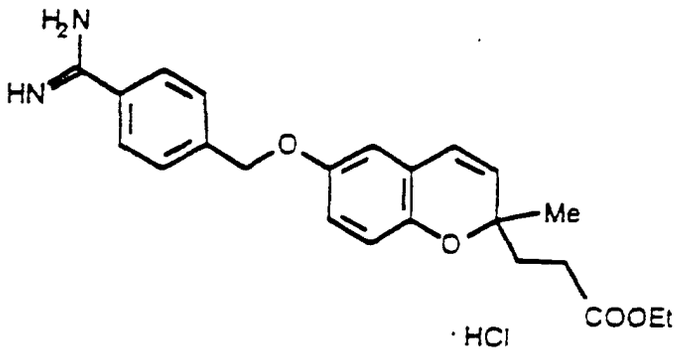
(214)

0.5 g (1.12 mmol) of the ester from Example 6 was added to a mixture of 5 ml 2N aqueous sodium hydroxide and 5 ml ethanol. The reaction mixture was stirred with heating on a steam bath for 20 minutes, while the mixture became a clear solution, and was then brought to pH 4 with 2N aqueous hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated in vacuo. The reaction mixture was purified by chromatography on silica gel with chloroform/ethanol 1:1. The remaining oil obtained from the pure fractions was treated with 2 ml trifluoroacetic acid and stirred for 2 hours at room temperature. The solvent was removed under reduced pressure, and the title amide crystallized from the residue by treating with ethanol.
Yield: 70 mg (16 %) of a beige amorphous solid,
m.p. 237-238°C.

Example 8

Preparation of Ethyl rac-3-(6-(4-(Aminoiminomethyl)phenylmethoxy)-2-methyl-2H-1-benzopyran-2-yl)propanoate hydrochloride, a compound represented by the formula (215):

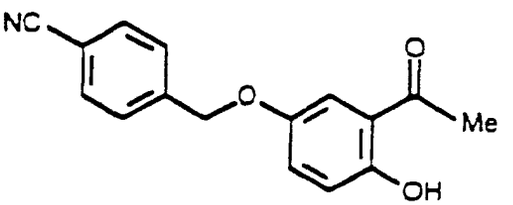
[0171]



(215)

Step A: Preparation of 4-((3-acetyl-4-hydroxyphenoxy)methyl)benzonitrile, an intermediate represented by the formula (216):

[0172]

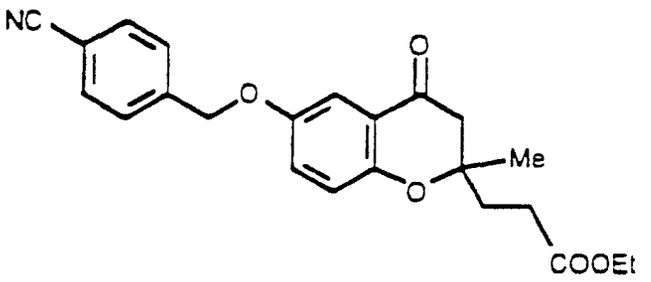


(216)

45 g (296 mmol) 2,5-dihydroxyacetophenone and 58.4 g (298 mmol) 4-cyanobenzyl bromide were dissolved in 650 ml dry acetone, and 45 g (326 mmol) potassium carbonate and 4.5 g potassium iodide were added. After heating with reflux for 6.5 hours the inorganic solids were removed by filtration and washed with acetone. The combined filtrates were concentrated in vacuo, and the residue was stirred with 600 ml hot methanol. The methanol solution was cooled to room temperature, and the compound (216) was filtered with suction, washed successively with methanol and hexane, and dried in vacuo at 40 °C.
Yield: 69.5 g (88 %) of beige crystals,
m.p. 123-127°C

Step B: Preparation of ethyl rac-3-(6-(4-cyanophenylmethoxy)-3,4-dihydro-2-methyl-4-oxo-2H-1-benzopyran-2-yl)propanoate, an intermediate represented by the formula (217):

[0173]

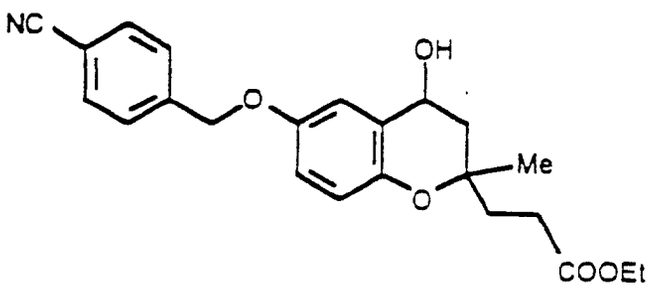


(217)

30 g (112.2 mmol) of the acetophenone from the previous Step, 20.4 g (141.5 mmol) ethyl 4-oxopentanoate, and 9.6 ml pyrrolidine were dissolved in 500 ml dry toluene. The mixture was stirred 20 hours at room temperature followed by 5.5 hours heating with azeotropic removal of water. The mixture was concentrated under reduced pressure, and the remaining oil was stirred for 30 minutes in 200 ml aqueous 2N hydrochloric acid. It was extracted with dichloromethane, and the organic layer was washed successively with 2N hydrochloric acid, water, and with brine. It was then dried over 0.4 nm mole sieve and concentrated in vacuo to leave a brown oil, which was chromatographed on silica gel with dichloromethane. The oily benzopyran (217) solidified by stirring with aqueous 2N hydrochloric acid. It was filtered with suction, washed successively with water and hexane, and dried in vacuo.
Yield: 12.27 g (28 %) of yellow crystals,
m.p. 88-92°C

Step C: Preparation of ethyl 3 - (6-(4-cyanophenylmethoxy)-3,4-dihydro-4-hydroxy-2-methyl-2H-1-benzopyran-2-yl)propanoate, an intermediate represented by the formula (218):

[0174]

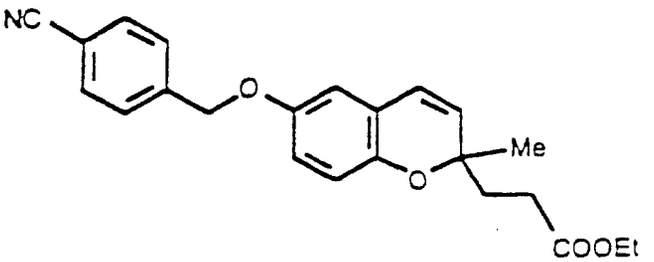


(218)

0.8 g (2.0 mmol) of the chromanone from Step B were dissolved in 10 ml dry ethanol, and 40 mg (1.06 mmol) sodium borohydride were added. After stirring overnight at room temperature another 40 mg of the hydride were added, and stirring was continued for 4 hours until the reduction was complete. The solvent was removed in vacuo, and the residue was treated with a mixture of water and dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over 0.4 nm mole sieve. After concentration under reduced pressure the benzopyran was obtained by chromatography on silica gel with dichloromethane containing up to 2 % ethanol.
Yield: 0.46 g (57 %) of an oil.

Step D: Preparation of ethyl rac-3-(6-(4-cyanophenylmethoxy)-2-methyl-2H-1-benzopyran-2-yl)propanoate, an intermediate represented by the formula (219):

[0175]



(219)

380 mg (0.96 mmol) of the compound from the previous step were dissolved in 25 ml toluene. After addition of a catalytic amount of 4-toluenesulfonic acid the mixture was heated for 1 hour with azeotropic removal of water until the reaction was complete. It was washed two times with saturated aqueous sodium bicarbonate, dried over 0.4 nm mole sieve, and concentrated in vacuo. The crude chromene was purified by chromatography on silica gel with dichloromethane.
Yield: 230 mg (63 %) of an oil.

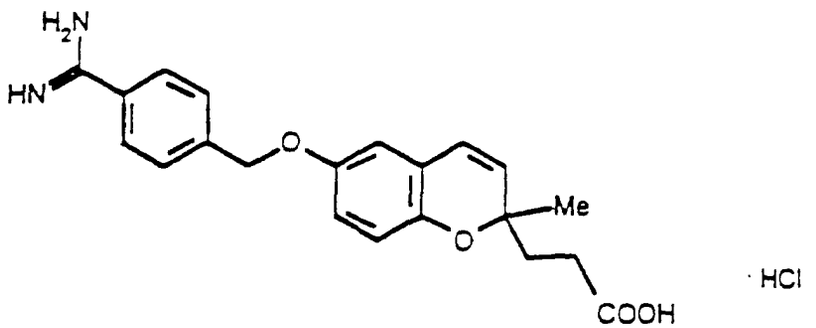
Step E: Preparation of ethyl rac-3-(6-(4-(aminoiminomethyl)phenylmethoxy)-2-methyl-2H-1-benzopyran-2-yl) propanoate hydrochloride

[0176] 1.5 g (4.0 mmol) of the nitrile from the previous Step were dissolved in 100 ml dry ethanol. The solution was cooled to 5-10 °C, saturated with hydrogen chloride, stirred at room temperature overnight, and concentrated in vacuo. The remaining brown oil was treated with 100 ml saturated ethanolic solution of ammonia and stirred for two days. The solvent was removed in vacuo, and the title amidine was obtained from the residue by chromatography on silica gel with dichloromethane/ethanol 95:5 and ascending polarity up to 80:20.
Yield: 1.19 g (69 %) of a yellow, amorphous solid;
m.p. < 50 °C

Example 9

Preparation of rac-3-(6-(4-(Aminoiminomethyl)phenylmethoxy)-2-methyl-2H-1-benzopyran-2-yl)propanoic acid hydrochloride, a compound represented by the formula (220):

[0177]



(220)

200 mg (0.464 mmol) of the ester from Example 52 were dissolved in 5 ml ethanol. Two drops of water and 0.64 ml of

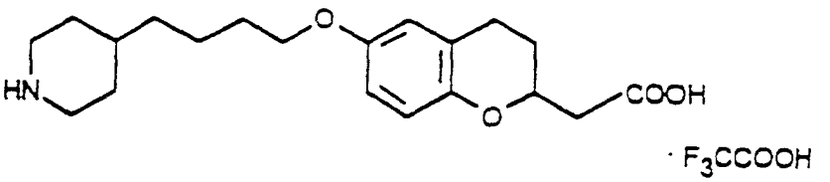
a 0.9 N ethanolic sodium ethoxide solution were added, and the mixture was stirred for 3 hours at 50 °C. After addition of the same amount of sodium ethoxide, the reaction was continued for 2 hours at 50 °C and for three days at room temperature. A precipitate had been formed, which was filtered with suction, washed successively with ethanol and hexane. The crude solid was heated in a mixture of 4 ml water and 1 ml aqueous 2N hydrochloric acid for some minutes and stirred for 2 hours at room temperature. The mixture was evaporated to dryness, and the title hydrochloride was suspended three times in 3 ml hot isopropanol. The hot solutions were decanted, combined, and concentrated to dryness. It was washed two times with ether, and dried in vacuo.

Yield: 68 mg (36 %) of a beige, amorphous solid,
m.p. 56°C.

Example 10

Preparation of rac-(3,4-Dihydro-6-(4-(piperidin-4-yl)butoxy)-2H-1-benzopyran-2-yl)acetic acid trifluoroacetate, a compound represented by the formula a (225) :

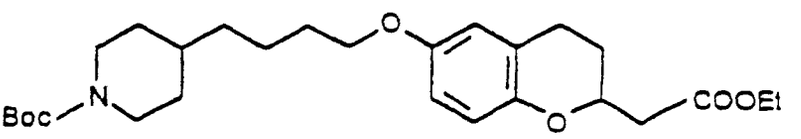
[0178]



(225)

Step A: Preparation of ethyl rac-(6-(4-(1-(tert.-butoxycarbonyl)piperidin-4-yl)butoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (226):

[0179]



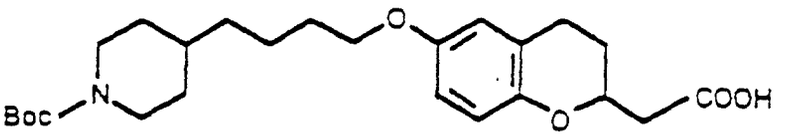
(226)

0.92 g (3.9 mmol) ethyl rac-(3,4-dihydro-6-hydroxy-2H-1-benzopyran-2-yl)acetate (prepared according to Eur. Pat. Appl. EP 129 906, the disclosure of which is incorporated herein by reference) were dissolved in 25 ml dry DHF. The solution was cooled to -5 °C, and 1.8 ml 40 % benzyltrimethylammonium hydroxide (Triton B) in methanol were added dropwise. After 40 minutes at this temperature 1.25 g (3.9 mmol) 4-(4-bromobutyl)-1-(tert.-butoxycarbonyl)piperidine (prepared according to Eur. Pat. Appl. EP 478 328, the disclosure of which is incorporated herein by reference) were added. The mixture was stirred at -5 °C for additional 3 hours, warmed to room temperature, stirred overnight, and poured into 150 ml ethyl acetate. It was then washed with water, 1 N aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate, water, and with brine, successively. The organic layer was dried over sodium sulfate and concentrated in vacuo. The title compound was obtained by chromatography on silica gel with hexane/ethyl acetate 4:1.

Yield: 0.64 g (35 %) of a colorless oil.

Step B: Preparation of rac-(6-(4-(1-(tert.-butoxycarbonyl)piperidin-4-yl)butoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid, an intermediate represented by the formula (227):

[0180]



(227)

0.64 g (1.35 mmol) of the ester from Step A were dissolved in 10 ml ethanol, and 5.6 ml of a 1 N ethanolic solution of sodium ethoxide were added. The reaction mixture was stirred at room temperature for seven days and concentrated to dryness under reduced pressure. The residue was treated with water and neutralized with 10 % aqueous $KHSO_4$ solution. It was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and the solvent was removed in vacuo to give the pure carboxylic acid.
Yield: 0.58 g (96 %) of a pale yellow oil, which slowly solidified upon standing

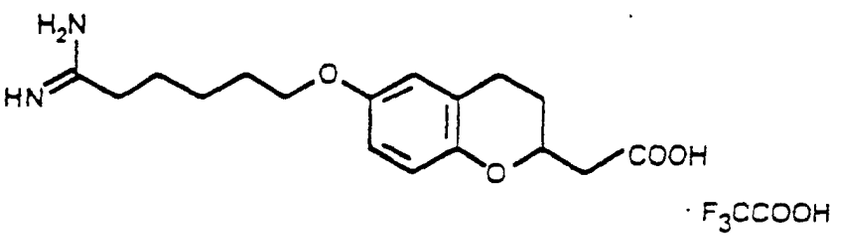
Step C: Preparation of rac-(3,4-dihydro-6-(4-(piperidin-4-yl)butoxy)-2H-1-benzopyran-2-yl)acetic acid trifluoroacetate

[0181] 0.4 g (0.9 mmol) of the protected piperidine from the previous Step were treated with 6 ml trifluoroacetic acid. The mixture was stirred for 2 hours at room temperature and evaporated in vacuo. After addition of water it was extracted with ether, and the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The title compound was purified by chromatography on silica gel with dichloromethane/ethanol 96:4.
Yield: 120 mg (29 %) of a beige oil, which solidified in part upon standing.

Example 11

Preparation of rac-(6-(5-(Aminoiminomethyl)pentoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid trifluoroacetate, a compound represented by the formula (253):

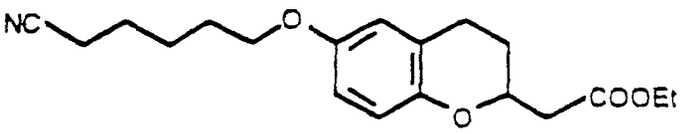
[0182]



(253)

Step A: Preparation of ethyl rac-(6-(5-cyanopentoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (254):

[0183]

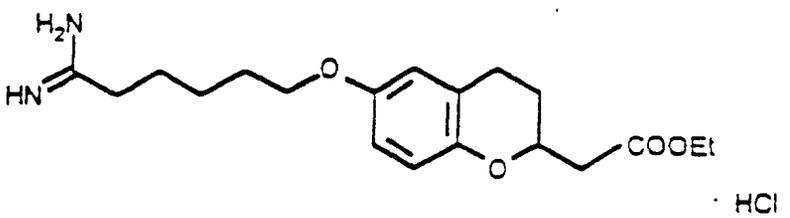


(254)

2.19 g (9.27 mmol) ethyl rac-(3,4-dihydro-6-hydroxy-2H-1-benzopyran-2-yl)acetate (prepared according to Eur. Pat. Appl. EP 129 906, the disclosure of which is incorporated herein by reference) and 2.0 g (11.4 mmol) 6-bromocapronitrile were dissolved in 30 ml dry acetone. 2.0 g (14.5 mmol) potassium carbonate, 250 mg potassium iodide, and 100 mg triethylbenzylammonium chloride were added, and the mixture was heated with reflux for 10 hours followed by stirring at room temperature for two days. The inorganic solid was removed by filtration and washed with acetone, and the combined filtrates were concentrated in vacuo. The nitrile (254) was obtained from the residue by chromatography on silica gel with dichloromethane containing up to 4 % ethanol.
Yield: 1.32 g (43 %) of an oil.

Step B: Preparation of ethyl rac-(6-(5-(aminoiminomethyl)pentoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate hydrochloride, an intermediate represented by the formula (255):

[0184]

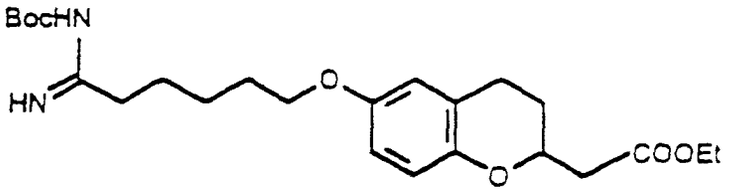


(255)

1.25 g (3.77 mmol) of the nitrile from Step A were dissolved in 50 ml dry ethanol. The solution was cooled to 0 °C and saturated with hydrogen chloride. After stirring overnight it was concentrated in vacuo. The residue was treated with a mixture of 10 ml liquid ammonia and 50 ml dry ethanol and stirred overnight at room temperature. The solvent was removed under reduced pressure, and the remaining material was stirred with ethanol and dichloromethane, successively. Solids were removed by filtration after each procedure, and the filtrates were concentrated under reduced pressure. The crude title compound from the last filtrate was purified by chromatography on silica gel with dichloromethane/ethanol 9:1 followed by 8:2.
Yield: 0.97 g (67 %) of a white powder,
m.p. 82-84°C.

Step C: Preparation of ethyl rac-(6-(5-(N-tert.-butoxycarbonylaminoiminomethyl)pentoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (256):

[0185]

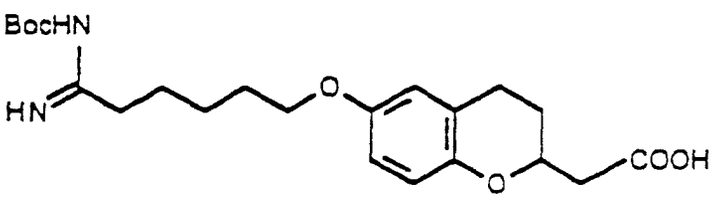


(256)

0.7 g (1.82 mmol) of the amidine from Step B were dissolved in 11 ml THF/H_2O 1:1. After addition of 335 mg (2.42 mmol) potassium carbonate and 0.4 g (1.83 mmol) Boc_2O the mixture was stirred overnight at room temperature. It was diluted with 25 ml ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated to dryness in vacuo to give the crude protected amidine, which was used for the next Step.
Yield: 0.87 g of a yellow oil.

Step D: Preparation of rac-(6-(5-(N-tert.-butoxycarbonylaminoiminomethyl)pentoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid, an intermediate represented by the formula (257)

[0186]



(257)

A mixture of 13 ml ethanol and 6 ml 2 N aqueous sodium hydroxide was added to 0.81 g (1.81 mmol) of the ester from the previous Step. The mixture was stirred at room temperature for 4 hours and neutralized with diluted acetic acid. After evaporation in vacuo the residue was stirred with a mixture of dichloromethane/methanol 1:1. Solids were removed by filtration and washed, and the combined filtrates were concentrated under reduced pressure. The carboxylic acid (257) was obtained by chromatography on silica gel with dichloromethane and enhancing the polarity by addition of 3 % ethanol.
Yield: 215 mg (28 %) of an oil.

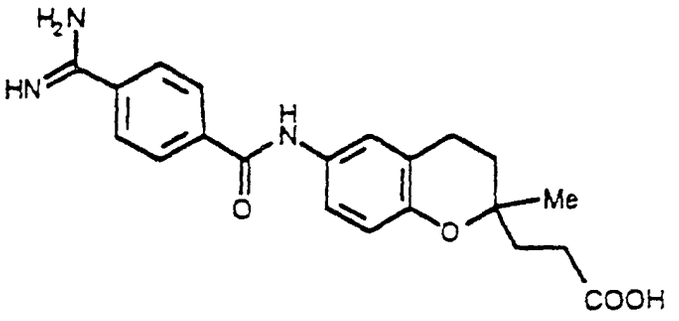
Step E: Preparation of rac-(6-(5-(aminoiminomethyl)pentoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid trifluoroacetate

[0187] 112 mg (0.266 mmol) of the protected amidine from Step D were treated with 2.2 ml trifluoroacetic acid, and the mixture was stirred at room temperature for 1 hour. The solvent was removed in vacuo, and the residue was stirred with 10 ml water, while the title compound precipitated. The product was filtered with suction, washed with water and with ether, successively, and dried in vacuo. Another crop was obtained from the combined filtrates, which were washed two times with ether and concentrated under reduced pressure.
Total yield: 91 mg (79 %) of a beige powder,
m.p. 132-134°C.

Example 12

Preparation of rac-3-(6-(N-(4-(Aminoiminomethyl)benzoyl)amino)-3,4-dihydro-2-methyl-2H-1-benzopyran-2-yl) propanoic Acid, a compound represented by the formula (258)

[0188]



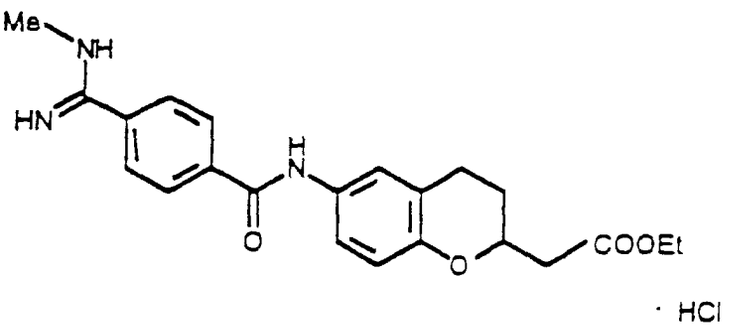
(258)

0.4 g (0.9 mmol) of the ester from Example 50 were added to a mixture of 8 ml ethanol and 0.5 ml 2 N aqueous sodium hydroxide. It was stirred overnight at room temperature, diluted with 10 ml water, and brought to pH 4 with acetic acid. The title compound precipitated from the solution. It was filtered, washed with water, and dried in vacuo.
Yield: 280 mg (82 %) of a colorless amorphous powder,
m.p. 278-280 °C (dec.).

Example 13

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(4-((methylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl) acetate hydrochloride, a compound represented by the formula (260):

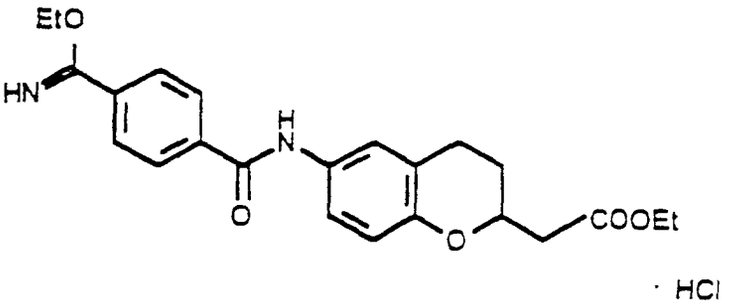
[0189]



(260)

Step A: Preparation of ethyl rac-(3,4-dihydro-6-(N-(4-(ethoxycarbonimidoyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetate hydrochloride, an intermediate represented by the formula (261):

[0190]



(261)

2.0 g (5.5 mmol) of the nitrile from Example 3, Step E were dissolved in 65 ml dry ethanol. The solution was cooled with ice and saturated with gaseous hydrogen chloride. It was stirred overnight at room temperature and concentrated under reduced pressure to give the intermediate as a crystalline solid, which was used for the next step.
Yield: 2.4 g (98 %)

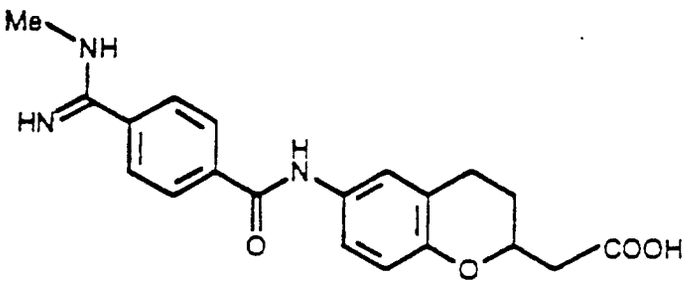
Step B: Preparation of ethyl rac-(3,4-dihydro-6-(N-(4-((methylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetate hydrochloride

[0191] 1.35 g (3.0 mmol) of the crude intermediate from the previous Step in 50 ml dry ethanol were cooled with ice. It was neutralized with a 30 % ethanolic solution of methylamine followed by 2 hours stirring. Another 5 ml of the methylamine solution were added, and stirring was continued for 6 hours, while the temperature was maintained below 5 °C. A clear solution was obtained, which was concentrated under reduced pressure. The title compound crystallized upon treating of the residue with ethanol, and was purified by heating of an ethanolic suspension.
Yield: 0.9 g (69 %) of a yellow amorphous solid,
m.p. 278-279°C.

Example 14

Preparation of rac-(3,4-Dihydro-6-(N-(4-((methylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (262) :

[0192]



(262)

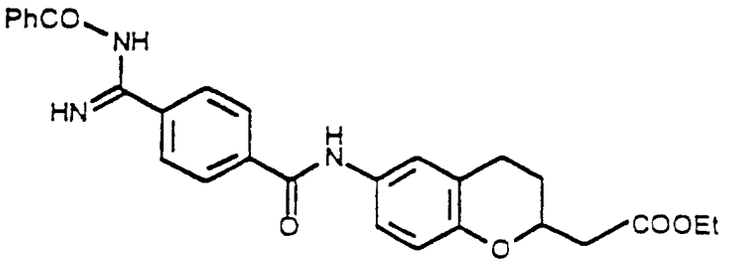
To 207 mg (0.48 mmol) of the ester from Example 13 were given 4 ml ethanol, 0.5 ml 2 N aqueous sodium hydroxide, and three drops of water, and the mixture was stirred overnight at room temperature. A precipitate was formed. It was

brought to pH 5 with 2 N acetic acid, and the title compound was filtered with suction, washed with water and with ethanol, successively, and dried in vacuo.
Yield: 0.12 g (68 %) of a pale yellow powder,
m.p. 275-276°C (dec.).

Example 15

Preparation of Ethyl rac-(6-(N-(4-((Benzoylamino)iminomethyl)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl) acetate, a compound represented by the formula (263):

[0193]



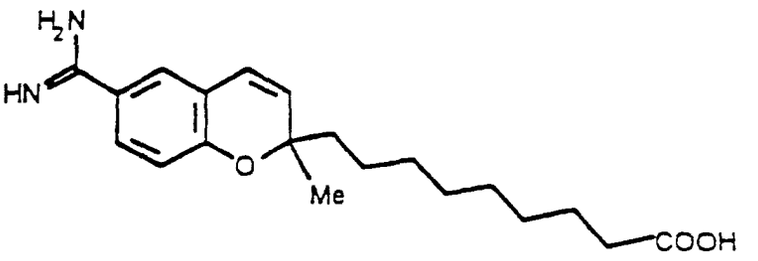
(263)

A solution of 0.42 g (1.0 mmol) of the ester from Example 47, 0.22 g triethylamine, and 20 mg 4-dimethylaminopyridine in 20 ml dry dichloromethane was cooled to -20 °C, and a solution of 0.15 g (1.1 mmol) benzoyl chloride in 2 ml dichloromethane was added dropwise at this temperature. The mixture became clear by slow warming to room temperature, and stirring was continued for 3 hours. After addition of water it was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The title benzoate was obtained by chromatography on silica gel with dichloromethane/ethanol 96:4 as an oil. A crystalline sample for analytical and biological tests was obtained by stirring with ether.
Yield: 0.21 g (43 %) of a beige powder,
m.p. 149-150°C (dec.).

Example 16

Preparation of rac-9-(6-Aminoiminomethyl-2-methyl-2H-1-benzopyran-2-yl)nonanoic acid, a compound represented by the formula (264)

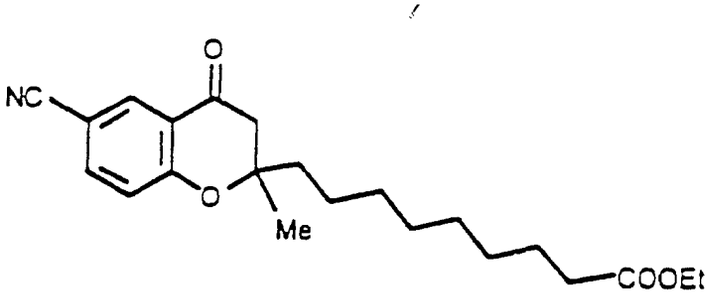
[0194]



(264)

Step A: Preparation of ethyl rac-9-(6-cyano-3,4-dihydro-2-methyl-4-oxo-2H-1-benzopyran-2-yl)nonanoate, an intermediate represented by the formula (265) :

[0195]

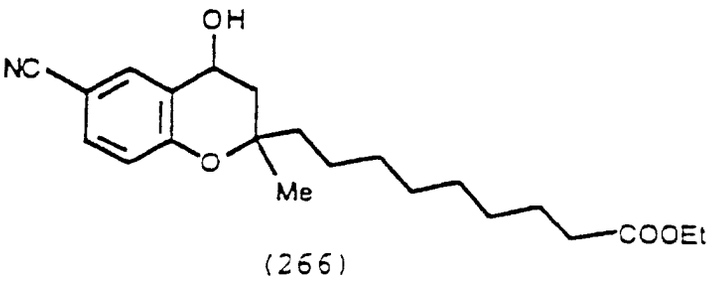


(265)

5-Cyano-2-hydroxyacetophenone was prepared by rearrangement of 4-acetoxybenzonitrile (Arch. Pharm. 1977, 310, 119, the disclosure of which is incorporated herein by reference) and ethyl 10-oxoundecanoate by $PdCl_2$-catalyzed oxidation of ethyl 10-undecenoate (J. Organomet. Chem. 1987, 334, C 5, the disclosure of which is incorporated herein by reference). 32.4 g (201 mmol) of the acetophenone, 35.0 g (153.3 mmol) of the ester, and 7 ml pyrrolidine were dissolved in 160 ml toluene. After standing at room temperature for 1 hour it was heated with azeotropic removal of water for 8 hours. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane. It was washed with water, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The title chromanone was obtained by chromatography on silica gel with dichloromethane.
Yield: 12.6 g (22 %) of an oil.

Step B: Preparation of ethyl 9-(6-cyano-3,4-dihydro-4-hydroxy-2-methyl-2H-1-benzopyran-2-yl)nonanoate, an intermediate represented by the formula (266):

[0196]

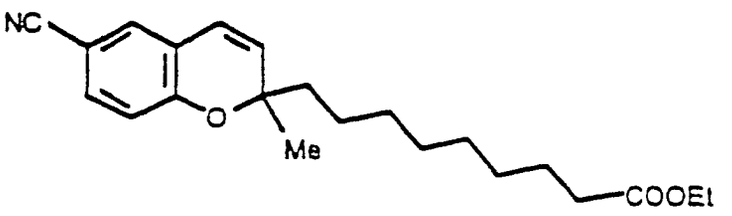


(266)

12.6 g (33.9 mmol) of the chromanone from Step A were dissolved in 300 ml dry ethanol. 2.6 g (68.7 mmol) sodium borohydride were added in small portions, while the temperature was kept below 25 °C. It was stirred overnight, concentrated in vacuo, hydrolyzed with a mixture of ice and aqueous hydrogen chloride, and extracted with dichloromethane for three times. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The title benzopyran was obtained by chromatography on silica gel with dichloromethane.
Yield: 11.2 g (88 %) of an oil.

Step C: Preparation of ethyl rac-9-(6-cyano-2-methyl-2H-1-benzopyran-2-yl)nonanoate, an intermediate represented by the formula (267)

[0197]

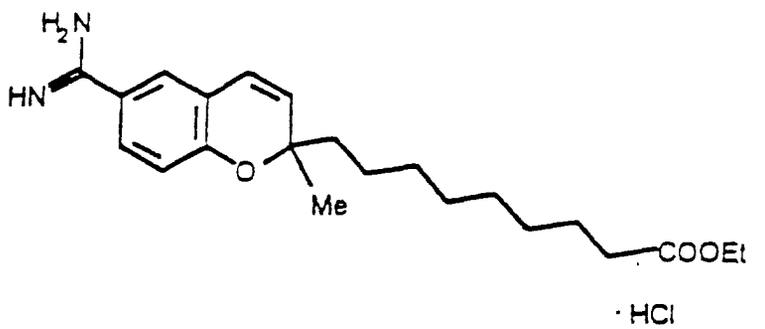


(267)

11.2 g (30.0 mmol) of the compound from Step B were dissolved in 200 ml toluene. A catalytic amount of p-toluenesulfonic acid was added, and it was heated with azeotropic removal of water for 7 hours. The mixture was washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, and concentrated under reduced pressure. The title benzopyran was purified by chromatography on silica gel with dichloromethane.
Yield: 3.0 g (28 %) of an oil.

Step D: Preparation of ethyl rac-9-(6-aminoiminomethyl-2-methyl-2H-1-benzopyran-2-yl) nonanoate hydrochloride, an intermediate represented by the formula (268) :

[0198]



(268)

1.5 g (4.2 mmol) of the chromene from the previous Step were dissolved in 50 ml dry ethanol. The solution was saturated with hydrogen chloride and stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was treated with a saturated solution of ammonia in ethanol. It was stirred overnight and concentrated to dryness under reduced pressure to give the pure title amidine.
Yield: 1.4 g (81 %) of an oil.

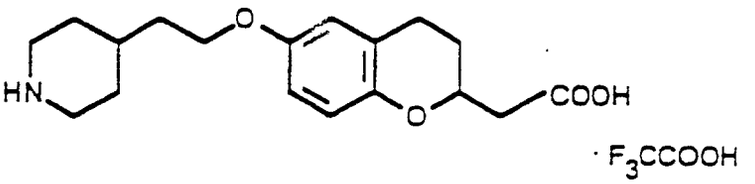
Step E: Preparation of rac-9-(6-aminoiminomethyl-2-methyl-2H-1-benzopyran-2-yl)nonanoic acid

[0199] 7 ml 2 N aqueous sodium hydroxide and 5 ml acetonitrile were added to 0.6 g (1.47 mmol) of the ester from the previous Step, and the mixture was heated for 30 minutes on a steam bath. It was brought to pH 7 with 2 N acetic acid, while a precipitate formed. It was filtered with suction, washed successively with ice-water and acetone, and dried in vacuo. Yield: 0.4 g (79 %) of a white powder,
m.p. 223-225 °C (dec.).

Example 17

Preparation of rac-(3,4-Dihydro-6-(2-(piperidin-4-yl)ethoxy)-2H-1-benzopyran-2-yl)acetic Acid Trifluoroacetate, a compound represented by the formula (269):

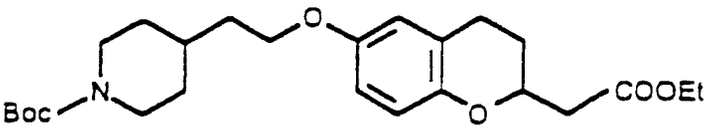
[0200]



(269)

Step A: Preparation of ethyl rac-(6-(2-(1-(tert.-butoxycarbonyl)piperidin-4-yl)ethoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (270) :

[0201]

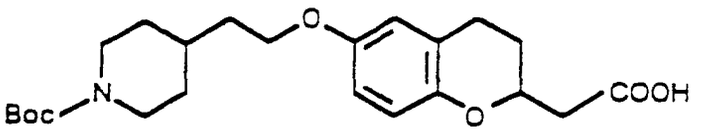


(270)

To a solution of 2.2 g (7.5 mmol) 4-(2-bromoethyl)-1-(tert.-butoxycarbonyl)piperidine (prepared by bromination of 2-(1-(tert.-butoxycarbonyl)piperidin-4-yl)ethanol according to Eur. Pat. Appl. EP 478 328) in 50 ml dry acetonitrile were added 2.84 g (8.72 mmol) dry cesium carbonate. After dropwise addition of a solution of 3.05 g (12.9 mmol) ethyl rac-(3,4-dihydro-6-hydroxy-2H-1-benzopyran-2-yl)acetate (prepared according to Eur. Pat. Appl. EP 129 906) in 20 ml dry acetonitrile it was stirred over night at room temperature. Another 1 g cesium carbonate was added and stirring was continued for 2 hours at 70 °C and overnight at room temperature. The mixture was filtered through Celite, which was washed with acetonitrile and acetone. The filtrate was concentrated under reduced pressure, and the residue was stirred with hexane/ethyl acetate 4:1 and two times with ethyl acetate, successively. The combined solutions, which had been separated from insoluble material, were concentrated in vacuo, and the compound (270) was obtained by chromatography on silica gel with hexane followed by hexane/ethyl acetate 4:1.
Yield: 2.9 g (86 %) of a yellow oil, which solidified upon standing

Step B: Preparation of rac-(6-(2-(1-(tert.-butoxycarbonyl)piperidin-4-yl)ethoxy)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid, an intermediate represented by the formula (271)

[0202]



(271)

To a solution of 1.5 g (3.35 mmol) of the ester from the previous step in 100 ml ethanol were added 6.8 ml 2 N aqueous sodium hydroxide, and the mixture was stirred overnight at room temperature. It was adjusted to pH 5 with diluted acetic acid and concentrated under reduced pressure. The title acid was obtained by chromatography on silica gel with dichloromethane followed by addition of up to 3 % ethanol. Yield: 0.54 g (38 %) of a beige oil.

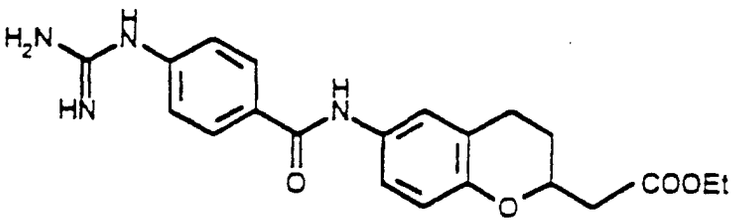
Step C: Preparation of rac-(3,4-dihydro-6-(2-(piperidin-4-yl)ethoxy)-2H-1-benzopyran-2-yl)acetic acid trifluoroacetate

[0203] 117 mg (0.28 mmol) of the protected piperidine from Step B were stirred in 2.3 ml trifluoroacetic acid at room temperature for 30 minutes, and it was concentrated to dryness in vacuo to leave the pure title compound.
Yield: 115 mg (95 %) of a brown resin.

Example 18

Preparation of Ethyl rac-(6-(N-(4-((Aminoiminomethyl)amino)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl) acetate, an compound represented by the formula (283):

[0204]



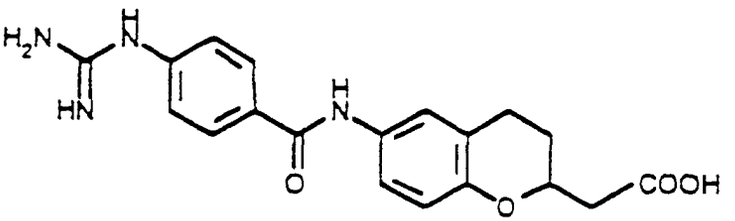
(283)

4-Guanidinobenzoic acid hydrochloride was prepared from 4-aminobenzoic acid according to a literature procedure (Recl. Trav. Chim. Pays-Bas 1953, 72, 643, the disclosure of which is incorporated herein by reference). It was heated in thionyl chloride for one hour followed by concentration to dryness to give the crude benzoyl chloride hydrochloride. 0.62 g (1.85 mmol) of the compound from Example 3, Step D were stirred for 1 hour at room temperature in 2 ml triflucroacetic acid, and the mixture was concentrated to dryness in vacuo. The mixture was treated with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure, and the oily residue was dissolved in 20 ml dry pyridine followed by addition of 0.44 g (1.88 mmol) crude 4-guanidinobenzoyl chloride hydrochloride. After stirring overnight at room temperature the mixture was poured into 100 ml water, while a precipitate was formed, which was collected by filtration, washed with water, and dried in vacuo. The title compound was purified by chromatography on silica gel with ethanol/concentrated aqueous ammonia 85:15.
Yield: 0.15 g (20 %) of a brown amorphous solid

Example 19

Preparation of rac- (6- (N-(4-((Aminoiminomethyl)amino)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (284):

[0205]



(284)

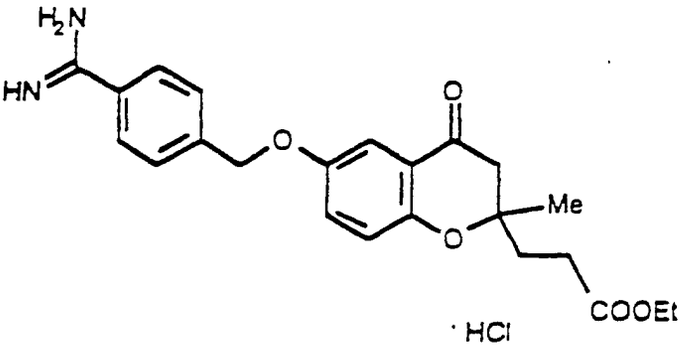
0.08 g (0.2 mmol) of the ester from Example 18 were dissolved in 30 ml ethanol followed by addition of 0.4 ml aqueous 2 N sodium hydroxide solution. The mixture was stirred at room temperature for two days, and the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in water, and the solution was neutralized with acetic acid, while the title acid precipitated. It was filtered with suction, washed with water, and dried in vacuo.
Yield: 0.045 g (61 %) of a beige crystalline solid, m.p. 258-260°C.

Example 20

[BL-43]

Ethyl rac-3-(6-(4-(Aminoiminomethyl)phenylmethoxy)-3,4-dihydro-2-methyl-4-oxo-2H-1-benzopyran-2-yl)propanoate hydrochloride, a compound represented by the formula (299):

[0206]

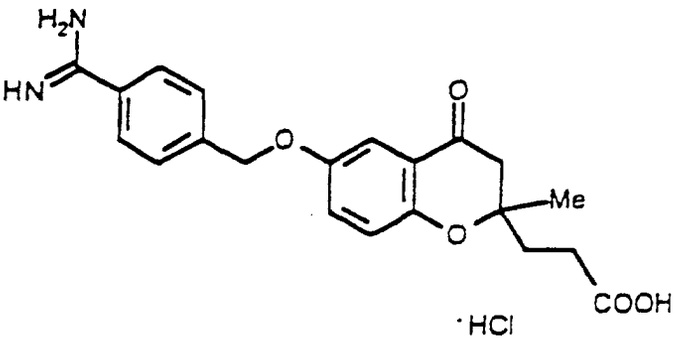


(299)

Example 21

rac-3-(6-(4-(Aminoiminomethyl)phenylmethoxy)-3,4-dihydro-2-methyl-4-oxo-2H-1-benzopyran-2-yl)propanoic Acid hydrochloride, a compound represented by the formula (300):

[0207]

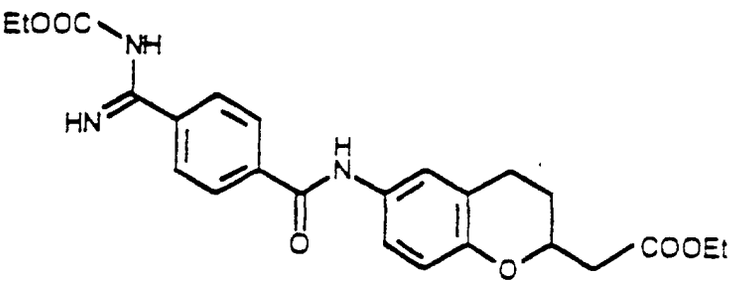


(300)

Example 22

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(4-((ethoxycarbonylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetate, a compound represented by the formula (303) :

[0208]



(303)

418 mg (1 mmol) of the benzopyran from Example 3, 0.3 ml triethylamine, and 20 mg 4-dimethylaminopyridine were dissolved in 20 ml dry dichloromethane, and the solution was cooled to -20 °C. 119 mg (1.1 mmol). Ethyl chloroformate in 2 ml dry dichloromethane was added dropwise at this temperature, and after 30 min it was warmed to room temperature and stirred for additional 2 hours. The mixture was poured into ice-cold water, and the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The remaining crystalline title compound was stirred with ether, filtered, and dried in vacuo.

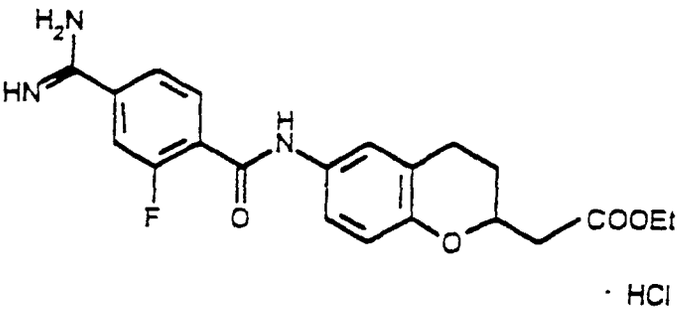
Yield: 360 mg (79 %) of a pale yellow solid,

m.p. 163-165°C.

Example 23

Preparation of Ethyl rac-(6-(N-(4-(Aminoiminomethyl)-2-fluorobenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl) acetate hydrochloride, a compound represented by the formula (304):

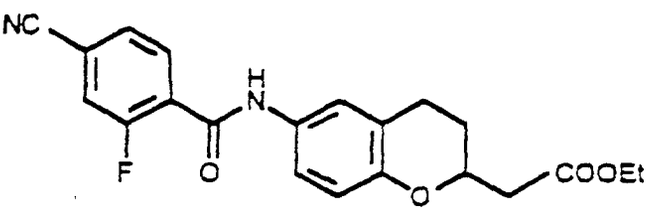
[0209]



(304)

Step A: Preparation of ethyl rac-(6-(N-(4-cyanc-2-fluorobenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl) acetate, an intermediate represented by the formula (307):

[0210]



(307)

5.0 g (30.3 mmol) of the acid 119 were heated for 1 hour with reflux in 50 ml thionyl chloride containing one drop of DMF. The reaction mixture was concentrated under reduced pressure, and the crude acid chloride was dissolved in 130 ml dry THF. This solution was added dropwise at 0 °C to crude ethyl (6-amino-3,4-dihydro-2H-1-benzopyran-2-yl) acetate in 200 ml dry THF and 20 ml dry pyridine, which had been obtained according to Example 3, Step E from 10.0 g (29.8 mmol) of the protected derivative with 20 ml trifluoroacetic acid. After stirring overnight at room temperature the mixture was poured into ice-cold water containing sodium bicarbonate. The precipitate of the title nitrile was filtered with suction, heated for some minutes in ethanol, filtered again after cooling, and the crystals were washed with hexane and dried in vacuo.
Yield: 8.6 g (75 %) of a beige amorphous solid,
m.p. 154-155°C.

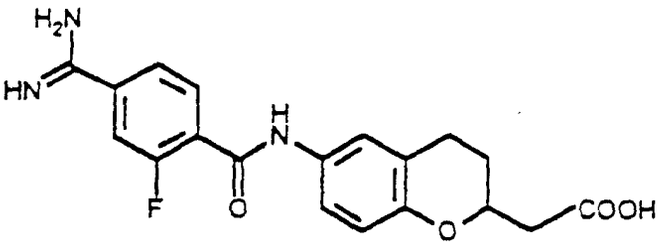
Step B: Preparation of ethyl rac-(6-(N-(4-(aminoiminomethyl)-2-fluorobenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate hydrochloride

[0211] 4.5 g (11.8 mmol) of the nitrile from the previous Step in 150 ml dry ethanol were cooled to 0 °C and saturated with gaseous hydrogen chloride. After stirring overnight at room temperature it was concentrated under reduced pressure. The crystalline residue was treated with 150 ml of a saturated ethanolic solution of ammonia and stirred again overnight. The crude title compound was obtained after concentration in vacuo, recrystallized from ethanol followed by crystallization from a mixture of ethanol/water/ether. Yield: 3.0 g (58 %) of a pale yellow powder,
m.p. 198-200°C.

Example 24

Preparation of rac-(6-(N-(4-(Aminoiminomethyl)-2-fluorobenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (308):

[0212]



(308)

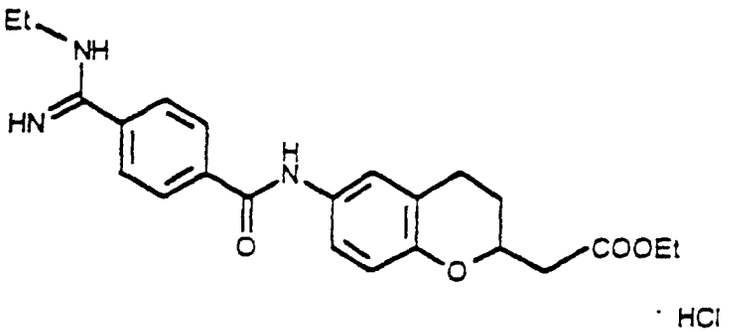
1.2 g (2.75 mmol) of the ester from Example 23 were stirred overnight at room temperature in a mixture of 20 ml ethanol and 5 ml 2 N aqueous sodium hydroxide solution. It was brought to pH 4 with 2 N acetic acid, and the precipitate of the title compound was filtered with suction, washed successively with water and with acetone, and dried in vacuo at 50 °C.

Yield: 0.84 g (82 %) of a pale yellow powder,
m.p. 250°C.

Example 25

Preparation of Ethyl rac- (3,4-Dihydro-6- (N-(4-((ethylamino)iminomethyl)benzoyl)amino)-2H-1-benzozpyran-2-yl) acetate hydrochloride, a compound represented by the formula (309):

[0213]



(309)

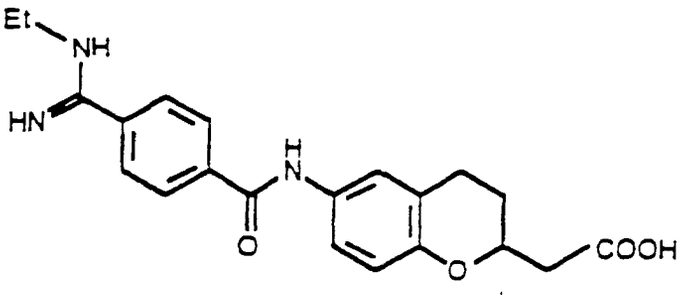
1.8 g (4.0 mmol) of the crude intermediate of Example 13, Step A were dissolved in 50 ml ethanol. The solution was cooled with ice, and 2 ml of a 50 % ethanolic solution of ethylamine were added. It was stirred overnight at room temperature, and the solvent was removed under reduced pressure. The residue was stirred with a small amount of ethanol to give the pure crystalline title compound, which was filtered and dried in vacuo.

Yield: 1.6 g (89 %) of a pale yellow powder,
m.p. 290-291°C.

Example 26

Preparation of rac-(3,4-Dihydro-6-(N-(4-((ethylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetic acid, a compound represented by the formula (310) :

[0214]



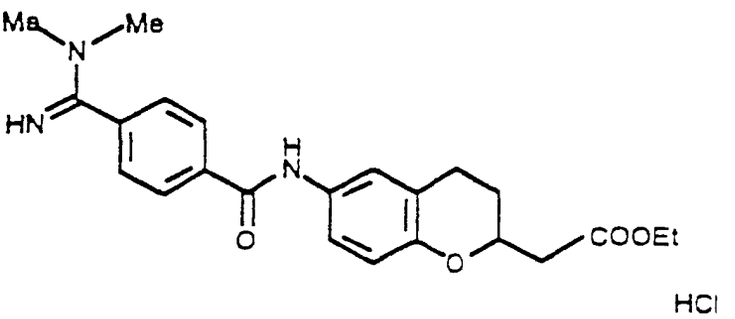
(310)

0.8 g (1.8 mmol) of the ester from Example 25 were suspended in a mixture of 16 ml ethanol, 2 ml 2 N aqueous sodium hydroxide, and some drops of water. It was stirred overnight at room temperature, while the suspension became a solution, which was brought to pH 5 with 2 N acetic acid. The precipitate of the pure title compound was collected by filtration, washed successively with water and acetone, and dried in vacuo.
Yield: 0.65 g (95 %) of a yellow powder,
m.p. 260-262 °C(dec.).

Example 27

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(4-((dimethylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl) acetate hydrochloride, a compound represented by the formula (311):

[0215]



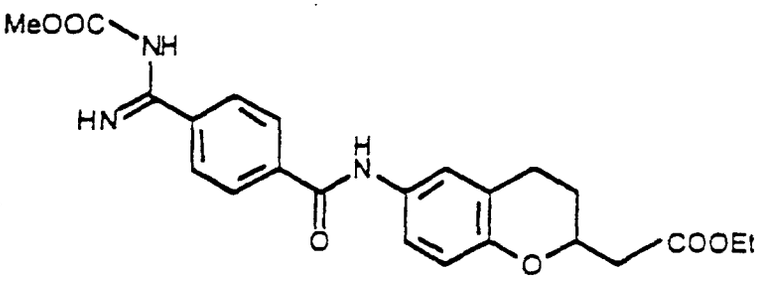
(311)

1.8 g (4.0 mmol) of the crude intermediate of Example 13, Step A were dissolved in 50 ml ethanol. The solution was cooled with ice, and 2 ml of a 50 % ethanolic solution of dimethylamine were added. It was stirred overnight at room temperature, and the solvent was removed under reduced pressure. The residue was stirred with a small amount of ethanol to give the pure crystalline title compound, which was filtered and dried in vacuo.
Yield: 1.35 g (75 %) of a white powder,
m.p. 248°C.

Example 28

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(4-((methoxycarbonylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetate, a compound represented by the formula (312):

[0216]



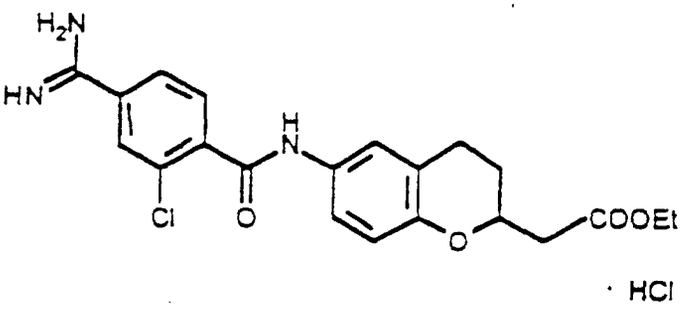
(312)

To 417 mg (1.0 mmol) of the amidine from Example 3, 0.3 ml triethylamine, and 20 mg 4-dimethylaminopyridine in 40 ml dichloromethane were added at 0°C 104 mg (1.1 mmol) methyl chloroformate, and the mixture was stirred overnight at room temperature. A white precipitate was formed, which was collected by filtration and chromatographed on silica gel with dichloromethane/ethanol 9:1 to give the pure title carbamate.
Yield: 0.21 g (48%) of a white powder,
m.p. 204-206 °C

Example 29

Preparation of Ethyl rac-(6-(N-(4-(Aminoiminomethyl)-2-chlorobenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl) acetate Hydrochloride, a compound represented by the formula (313):

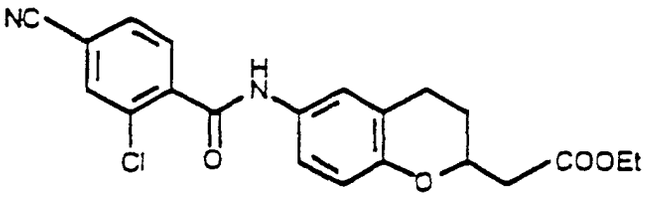
[0217]



(313)

Step A: Preparation of ethyl rac-(6-(N-(2-chloro-4-cyanobenzoyl) amino)-3,4-dihydro-2H-1-benzopyran-2-yl) acetate, an intermediate represented by the formula (314):

[0218]



(314)

3.0 g (8.94 mmol) of the benzopyran from Example 3, Step D were stirred with 6 ml trifluoroacetic acid for 2 hours at room temperature. The mixture was treated with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and the solvent was removed in vacuo to give the crude unprotected aminobenzopyran, which was dissolved in a mixture of 50 ml dry THF and 8 ml dry pyridine. 50 ml of a solution of crude 2-chloro-4-cyanobenzoyl chloride in dry THF, which had been prepared from 1.1 g (6.1 mmol) 2-chloro-4-cyanobenzoic acid (Chem. Ber. 1936, 69, 537, the disclosure of which is incorporated herein by reference) according to Example 62, Step A, was added dropwise at 0 °C. After stirring overnight at room temperature the mixture was poured into ice-cold water containing sodium bicarbonate. It was extracted with ethyl acetate, and the organic layer was washed successively with aqueous Cu(II) sulfate solution and with brine, dried over sodium sulfate, and concentrated under reduced pressure. The nitrile (314) was obtained from the residue by chromatography on silica gel with chloroform/methanol 96:4. It crystallized from the pure fractions after stirring with a small amount of ethanol.
Yield: 1.1 g (46 %) of beige crystals,
m.p. 152-154°C.

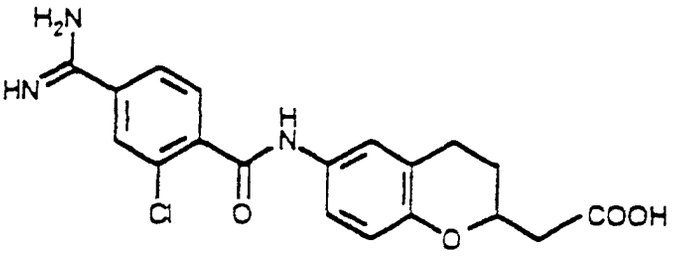
Step B: Preparation of ethyl rac-(6-(N-(4-(aminoiminomethyl)-2-chlorobenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate hydrochloride:

[0219] 1.1 g (2.76 mmol) of the nitrile from the previous Step were dissolved in 25 ml ethanol, and the solution was cooled to 0 °C and saturated with gaseous hydrogen chloride. It was stirred overnight at room temperature followed by concentration under reduced pressure. The residue was treated with 20 ml of a saturated solution of ammonia in ethanol, and again it was stirred overnight. After removal of the solvent in vacuo the remaining title compound was recrystallized from ethanol/water/ether.
Yield: 0.9 g (72 %) of a pale yellow powder,
m.p. 225-226°C.

Example 30

Preparation of rac-(6-(N-(4-(Aminoiminomethyl)-2-chlorobenzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic acid, a compound represented by the formula (314) :

[0220]



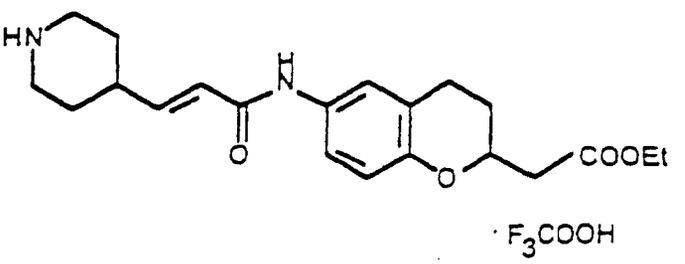
(314)

0.3 g (0.66 mmol) of the ester from Example 29 were stirred overnight at room temperature with a mixture of 5 ml ethanol and 0.5 ml 2 N aqueous sodium hydroxide solution. It was brought to pH 5 with 2 N acetic acid. The precipitate of the title compound was filtered with suction, washed successively with water and with acetone, and dried in vacuo.
Yield: 0.19 g (74 %) of a white powder,
m.p. 269-270°C(dec.).

Example 31

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(3-(piperidine-4-yl)propenoyl)amino)-2H-1-benzopyran-2-yl)acetate Trifluoroacetate, a compound represented by the formula (327):

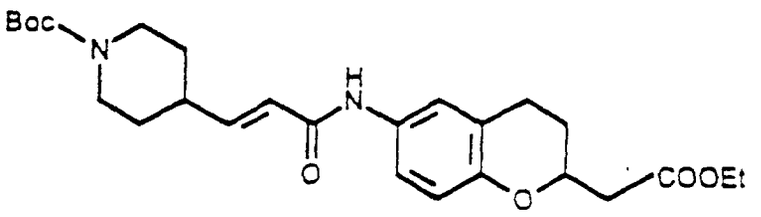
[0221]



(327)

Step A: Preparation of ethyl rac-(6-(N-(3-(1-(tert.-butoxycarbonyl)piperidine-4-yl)propenoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (329):

[0222]



(329)

0.85 g (3.33 mmol) of the acid 386 were dissolved in a mixture of 23 ml dry dichloromethane and 0.25 ml dry DMF. The solution was kept at a temperature between -10 °C and 0 °C, while 0.46 g (3.6 mmol) oxalyl chloride were added slowly. After stirring for 40 minutes at this temperature the mixture was added dropwise to a solution of 0.5 ml triethylamine and crude ethyl (6-amino-3,4-dihydro-2H-1-benzopyran-2-yl)acetate (prepared with trifluoroacetic acid from 1.5 g (4.5 mmol) of the Boc-protected amine as described in Example 3) in 35 ml dry dichloromethane. After stirring for 90 minutes at this temperature the mixture was poured into ice-cold water, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The title compound was purified by chromatography on silica gel with dichloromethane/ethanol 80:1.
Yield: 0.81 g (51 %) of an oil.

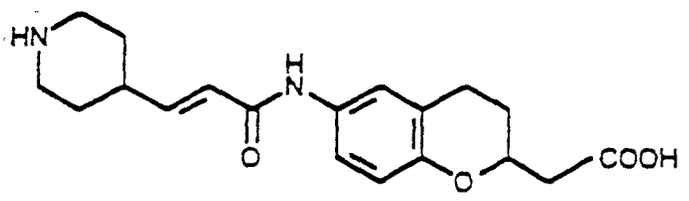
Step B: Preparation of ethyl rac-(3,4-dihydro-6-(N-(3-(piperidine-4-yl)propenoyl)amino)-2H-1-benzopyran-2-yl) acetate trifluoroacetate

[0223] 0.81 g (1.71 mmol) of the protected piperidine from the previous Step were stirred for 2 hours at room temperature in 6 ml trifluoroacetic acid. It was poured into ice-cold water, adjusted to pH 7 with sodium bicarbonate, and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure, and the residue was stirred with a mixture of hexane and ether to give the crystalline title compound, which was collected by filtration, and dried at 50 °C in vacuo.
Yield: 0.18 g (22 %) of reddish crystals,
m.p. 72-73°C.

Example 32

Preparation of rac-(3,4-Dihydro-6-(N-(3-(piperidine-4-yl)propenoyl)amino)-2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (330) :

[0224]



(330)

0.1 g (0.2 mmol) of the ester from Example 31 were stirred overnight at room temperature in a mixture 2.5 ml ethanol

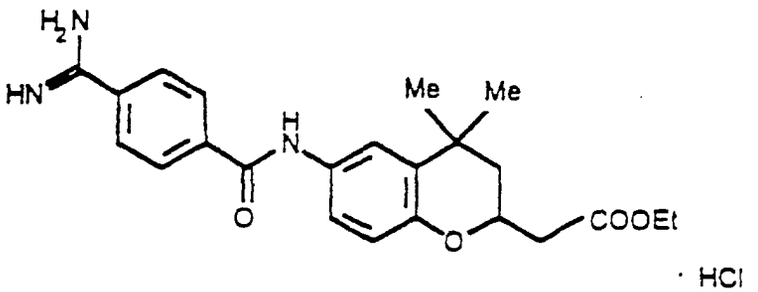
and 0.35 ml 2 N aqueous sodium hydroxide solution. The reaction mixture was cooled with ice and brought to pH 5.5 with 2 N acetic acid. The precipitate of the title acid was filtered with suction, washed with a small amount of cold water, and dried at 50 °C in vacuo.

Yield: 42 mg (59 %) of beige crystals,
m.p. 175-178°C.

Example 33

Preparation of Ethyl rac-(6-(N-(4-(Aminoiminomethyl)benzoyl)amino)-3,4-dihydro-4,4-dimethyl-2H-1-benzopyran-2-yl)acetate Hydrochloride, a compound represented by the formula (331) :

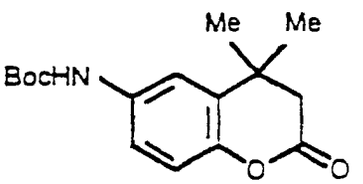
[0225]



(331)

Step A: Preparation of tert.-butyl (3,4-dihydro-4,4-dimethyl-2-oxo-2H-1-benzopyran-6-yl)carbamate, an intermediate represented by the formula (332):

[0226]



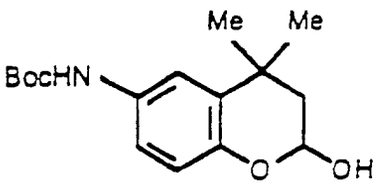
(332)

To a suspension of 1.5 g 10 % Pd-C in 300 ml ethanol were added under an atmosphere of argon 29.2 g (132.0 mmol) 3,4-dihydro-4,4-dimethyl-6-nitro-2-oxo-2H-1-benzopyran (prepared by nitration of 3,4-dihydro-4,4-dimethyl-2-oxo-2H-l-benzopyran according to J. Am. Chem. Soc. 1970, 92, 4377, the disclosure of which is incorporated herein by reference) and 21.4 g (339.4 mmol) ammonium formate. The temperature raised for approximately 1 hour to 50 °C accompanied by a gas evolution, and it was heated for additional 3 hours at 80 °C. The catalyst was filtered through Celite, which was washed with 500 ml hot ethanol. The combined filtrates were concentrated under reduced pressure to a volume of 100 ml, and the formed precipitate was filtered with suction. A second crop of the crude 6-amino-3,4-dihydro-4,4-dimethyl-2-oxo-2H-1-benzopyran was obtained after further concentration. Both crops were combined and dissolved in 80 ml THF followed by addition of 80 ml water, 25.3 g (183 mmol) potassium carbonate, and 29.2 g (133.8 mmol) Boc_2O. After 8 hours stirring at room temperature another 2.9 g Boc_2O and 2.5 g potassium carbonate were added, and stirring was continued overnight. The mixture was poured into 300 ml water and extracted with ethyl acetate, and the organic layer was dried over sodium sulfate and concentrated under reduced pressure. A first crop of the title compound crystallized from the oily residue with diisopropylether. An additional amount was obtained from the concentrated mother liquid by chromatography on silica gel with toluene crystallizing from the oily pure fractions with diisopropylether.

Total yield: 31.6 g (82 %) of colorless crystals,
m.p. 106-108°C.

Step B: Preparation of tert.-butyl rac-(3,4-dihydro-4,4-dimethyl-2-hydroxy-2H-1-benzopyran-6-yl)carbamate, an intermediate represented by the formula (333):

[0227]

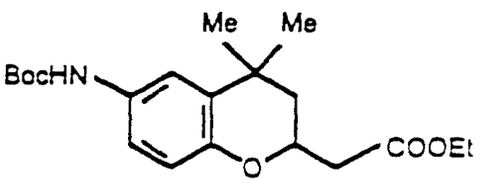


(333)

31.6 g (108.5 mmol) of the benzopyran from the previous Step were dissolved in 450 ml dry THF and cooled to -70 °C under an atmosphere of argon. At this temperature 133 ml of a 25 % solution of DIBAH in toluene was added dropwise within 1 hour, and the mixture was stirred for additional 2 hours. It was quenched carefully with 35 ml methanol and warmed to room temperature, and the mixture was poured into 1000 ml saturated aqueous ammonium chloride solution. After vigorous stirring the upper organic layer solidified to a gel, which was separated and stirred with 1000 ml ethyl acetate. It was then filtered through Celite and washed with 500 ml ethyl acetate. The combined filtrates were dried over sodium sulfate and concentrated in vacuo to give a brown resin, from which the pure title acetal was obtained by chromatography on silica gel with toluene/acetone 95:5.
Yield: 25.9 g (81 %) of a yellow resin

Step C: Preparation of ethyl rac-(6-(N-tert.-butoxycarbonylamino)-3,4-dihydro-4,4-dimethyl-2H-1-benzopyran-2-yl)acetate, an intermediate represented by the formula (334):

[0228]

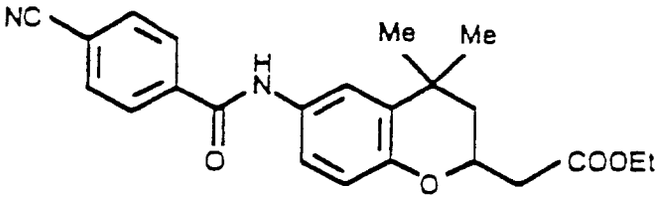


(334)

To a solution of 25.9 g (88.3 mmol) of the compound from Step B in 150 ml toluene were added 32.4 g (93.0 mmol) of ethoxycarbonylmethylene triphenylphosphorane followed by 0.6 g (15 mmol) 60 % sodium hydride in small portions. The mixture was heated at 120 °C for 3 hours, cooled to room temperature, and solids were removed by filtration. The filtrate was concentrated under reduced pressure, and the compound (334) was obtained by chromatography on silica gel with hexane / ethyl acetate 4:1 to 1:1.
Yield: 6.9 g (22 %) of colorless crystals,
m.p. 116-119°C.

Step D: Preparation of ethyl rac-(6-(N-(4-cyanobenzoyl)amino)-3,4-dihydro-4,4-dimethyl-2H-1-benzopyran-2-yl) acetate, an intermediate represented by the formula (335) :

[0229]



(335)

2.18 g (6.0 mmol) of the compound from the previous Step were deprotected by stirring in 10 ml trifluoroacetic acid as described in Example 3, Step E, and the brown oil of the crude 6-aminobenzopyran was dissolved in 40 ml dry pyridine. After addition of 0.99 g (6.0 mmol) 4-cyanobenzoyl chloride the mixture was stirred at room temperature overnight. It was concentrated to dryness in vacuo and dissolved three times in toluene followed by concentration under reduced pressure, in order to remove remaining pyridine. The title nitrile crystallized from the brown residue upon stirring with a small amount of ethanol. It was filtered with suction, washed with cold ethanol, and dried in vacuo.
Yield: 1.7 g (72 %) of a white powder,
m.p. 163-165°C.

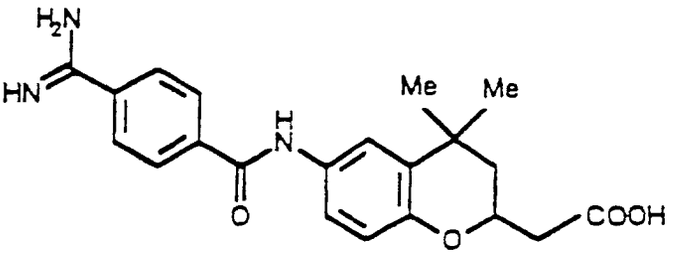
Step E: Preparation of ethyl rac-(5-(N-(4-(aminoiminomethyl)benzoyl)amino)-3,4-dihydro-4,4-dimethyl-2H-1-benzopyran-2-yl)acetate hydrochloride

[0230] A suspension of 1.7 g (4.33 mmol) of the nitrile from Step D in 100 ml dry ethanol was cooled with ice and saturated with gaseous hydrogen chloride. After standing overnight at room temperature it was concentrated to dryness under reduced pressure, and the residue was dissolved in 50 ml 10 % ethanolic solution of ammonia. The mixture was stirred at room temperature for three days until the reaction was complete. The solvent was removed in vacuo, and the resinous residue was dissolved in toluene/acetone 7:3. A first crop of the title amidine crystallized from the solution, and another crop was obtained by chromatography on silica gel using the same mixture of solvents.
Total yield: 1.6 g (83 %) of a yellow crystalline solid, m.p. 122-124°C.

Example 34

Preparation of rac-(6-(N-(4-(Aminoiminomethyl)benzoyl)amino)-3,4-dihydro-4,4-dimethyl-2H-1-benzopyran-2-yl) acetic Acid, a compound represented by the formula (336):

[0231]



(336)

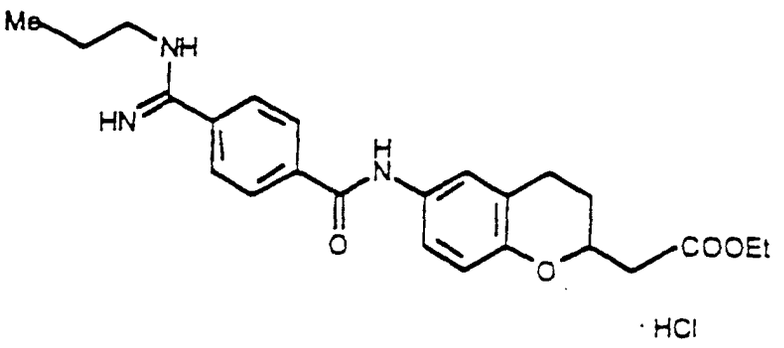
0.3 g (0.67 mmol) of the ester from Example 33 were suspended in 10 ml ethanol followed by addition of 1 ml aqueous 2 N sodium hydroxide. It was stirred at room temperature for 4 hours. The mixture was filtered, the filtrate concentrated

to dryness under reduced pressure, and the residue was dissolved in water. It was then neutralized with diluted acetic acid, and the precipitate of the compound (336) was filtered with suction, washed thoroughly with water, and dried in vacuo at 50 °C.
Yield: 0.2 g (78 %) of a yellow crystalline solid,
m.p. 248-250°C.

Example 35

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(4-((propylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl) acetate hydrochloride, a compound represented by the formula (337):

[0232]



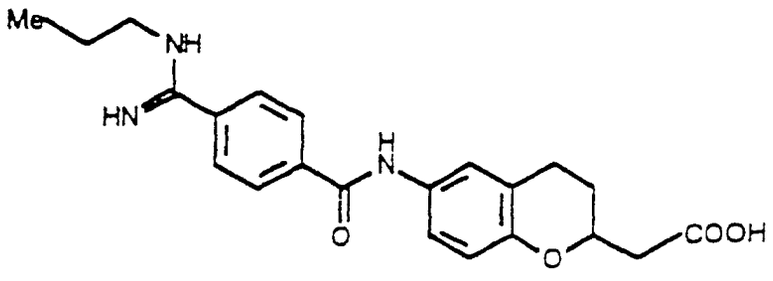
(337)

To a solution of 0.8 g (1.8 mmol) of the crude intermediate of Example 13, Step A in 20 ml ethanol were added at 0 °C 0.3 ml n-propylamine. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was treated with ethanol and ether to give the pure crystalline title compound, which was collected by filtration and dried in vacuo.
Yield: 0.63 g (76 %) of a white powder,
m.p. 271-273°C.

Example 36

Preparation of rac-(3,4-Dihydro-6-(N-(4-((propylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (338):

[0233]



(338)

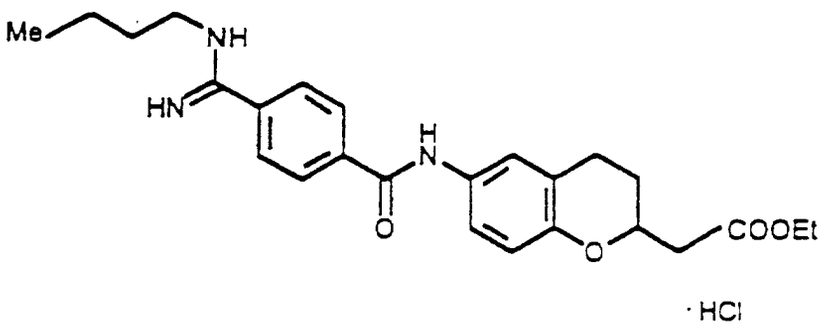
0.25 g (0.54 mmol) of the ester from Example 35 were stirred at room temperature overnight with 5 ml ethanol and 0.7 ml 2 N aqueous sodium hydroxide. The mixture was brought to pH 4 with 2 N acetic acid, and the precipitate of the

acid (338) was filtered with suction, washed successively with water and with acetone, and dried in vacuo.
Yield: 0.16 g (74 %) of a pale yellow powder,
m.p. 241-242°C (dec.).

Example 37

Preparation of Ethyl rac-(6-(N-(4-((Butylamino)iminomethyl)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl) acetate hydrochloride, a compound represented by the formula (339):

[0234]



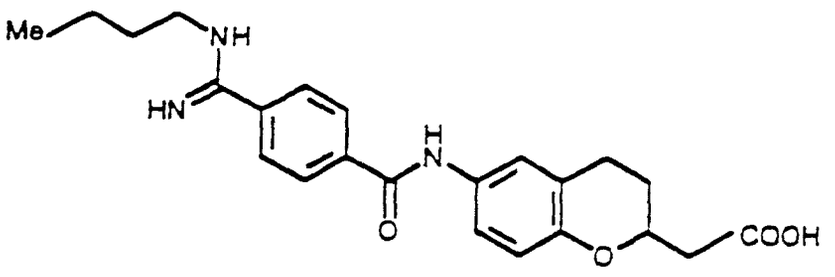
(339)

The compound was prepared from 0.8 g (1.8 mmol) of the crude intermediate of Example 13, Step A and 0.3 ml n-butylamine as described in Example 35.
Yield: 0.6 g (71 %) of a pale yellow powder,
m.p. 265-267°C.

Example 38

Preparation of rac-(6-(N-(4-((Butylamino)iminomethyl)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (340):

[0235]



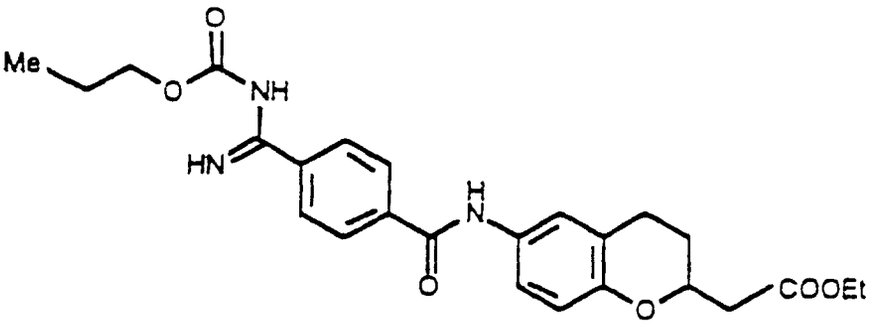
(340)

0.25 g (0.53 mmol) of the ester from Example 37 were hydrolyzed to the title acid as described in Example 36.
Yield: 0.13 g (60 %) of a white powder,
m.p. 240-241°C (dec.).

Example 39

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(4-((propoxycarbonylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetate, a compound represented by the formula (341):

[0236]



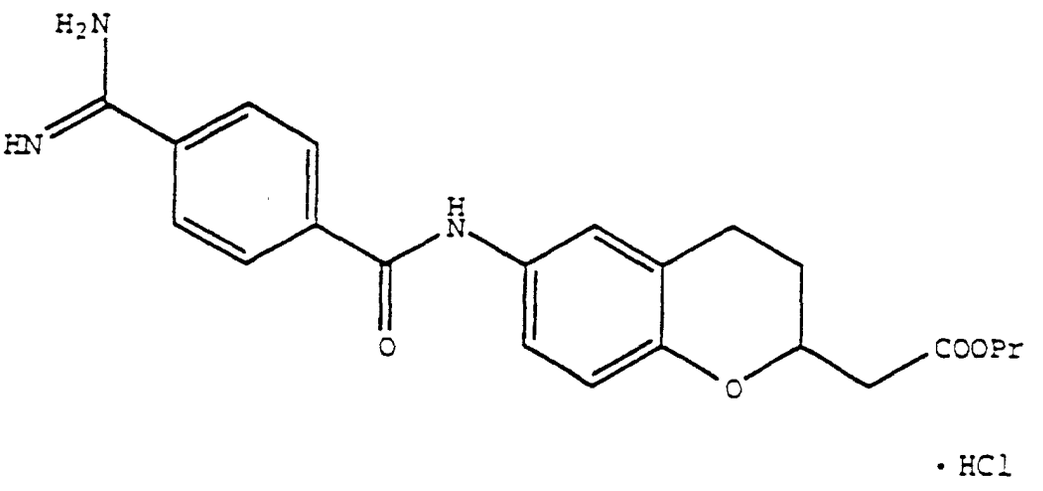
(341)

[0237] 417 mg (1.0 mmol) of the compound from Example 3, 0.3 ml triethylamine, 20 mg 4-dimethylaminopyridine, and 135 mg (1.1 mmol) propyl chloroformate were dissolved in 20 ml dichloromethane at 0 °C followed by stirring overnight at room temperature. After addition of the same volume of water it was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give the crude title compound, which was recrystallized from dichloromethane/hexane.
Yield: 0.27 g (58 %) of a pale yellow amorphous solid, m.p. 183-184°C.

Example 40

Preparation of Propyl rac-(6-(N-(4-(Aminoiminomethyl)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate hydrochloride, a compound represented by the formula (342) :

[0238]



(342)

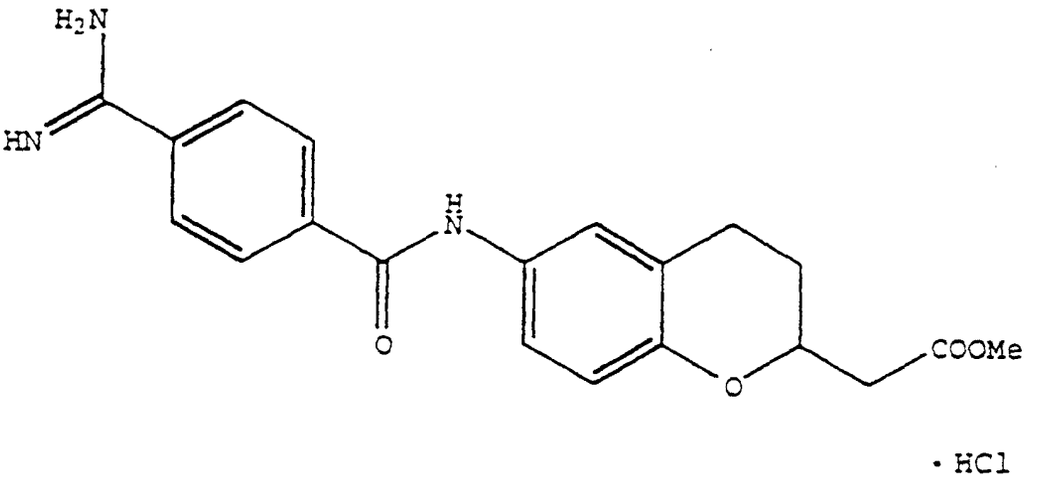
A solution of 0.5 g (1.37 mmol) of the nitrile from Example 3, Step E in 50 ml n-propanol was cooled with ice and saturated with gaseous hydrogen chloride. After stirring overnight at room temperature the mixture was concentrated

under reduced pressure, and the residue was treated with 50 ml of a saturated solution of ammonia in n-propanol. Again the mixture was stirred overnight at room temperature, the solvent removed in vacuo, and the remaining title amidine was recrystallized from n-propanol.
Yield: 0.36 g (61 %) of a yellow powder,
m.p. 238-240°C (dec.).

Example 41

Preparation of Methyl rac-(6-(N-(4-(Aminoiminomethyl)benzoyl)amino)-3,4-dihydro-2H-1-benzopyran-2-yl)acetate hydrochloride, a compound represented by the formula (343):

[0239]



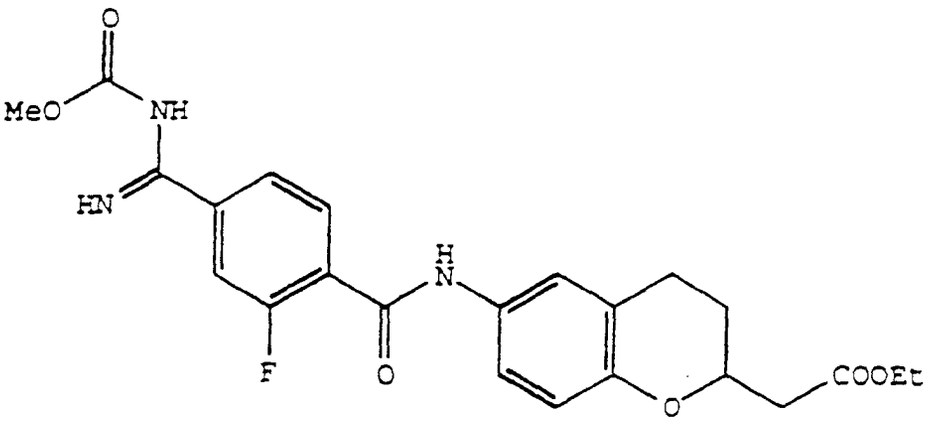
(343)

A suspension of 0.35 g (1.0 mmol) of the acid from Example 4 in 20 ml methanol was cooled to 0°C and saturated with gaseous hydrogen chloride. After 2 hours stirring it was concentrated under reduced pressure, and the remaining compound (343) was recrystallized from methanol/ether.
Yield: 0.29 g (72 %) of yellow crystals,
m.p. 235-237°C.

Example 42

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(2-fluoro-4-((methoxycarbonylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetate, a compound represented by the formula (349)

[0240]



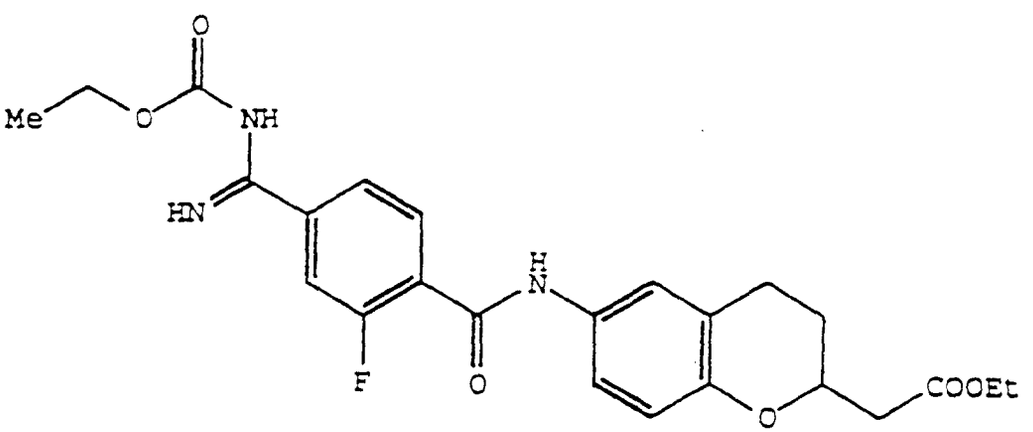
(349)

436 mg (1.0 mmol) of the amidine from Example 23, 0.3 ml triethylamine, and 20 mg 4-dimethylaminopyridine were dissolved in 29 ml dichloromethane followed by addition of 104 mg (1.1 mmol) methyl chloroformate at 0 °C. After stirring overnight at room temperature a white precipitate of the title compound had been formed. It was filtered with suction and washed successively with water and with ether.
Yield: 0.35 g (77%) of a pale yellow powder,
m.p. 202-204 °C

Example 43

Preparation of Ethyl rac- (3,4-Dihydro-6-(N-(4-((ethoxycarbonylamino)iminomethyl)-2-fluorobenzoyl)amino)-2H-1-benzopyran-2-yl)acetate, a compound represented by the formula (350):

[0241]



(350)

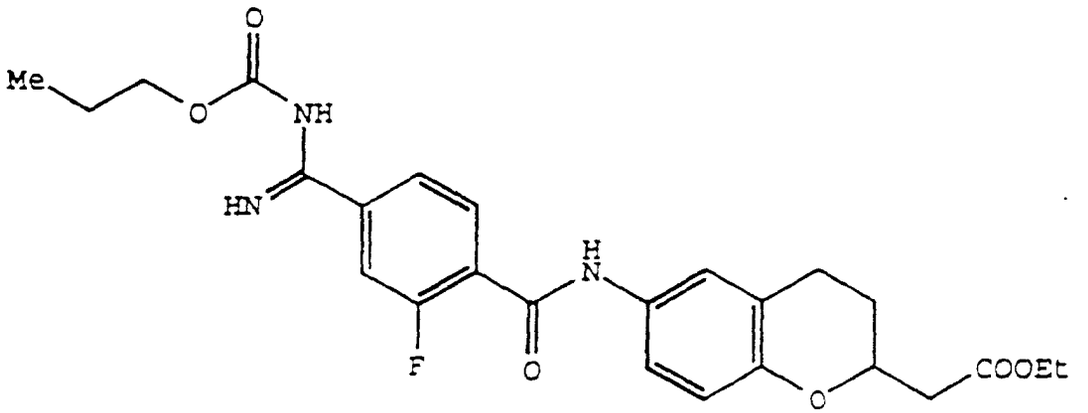
The title carbamate was prepared as described in Example 42 from 436 mg (1.0 mmol) of the amidine from Example 23 and 119 mg (1.1 mmol) ethyl chloroformate. It was recrystallized from dichloromethane/hexane.

Yield: 0.35 g (74%) of a white powder,
m.p. 168-169 °C

Example 44

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(2-fluoro-4-((propoxycarbonylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetate, a compound represented by the formula (351):

[0242]



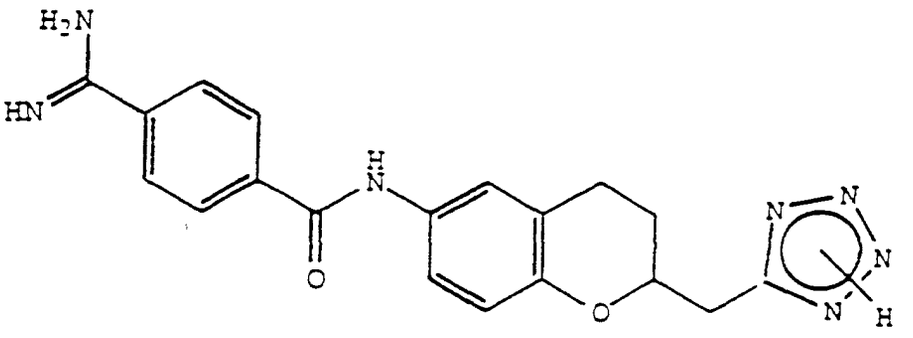
(351)

The title compound was prepared as described in Example 39 from 436 mg (1.0 mmol) of the amidine from Example 23 and 135 mg (1.1 mmol) propyl chloroformate.
Yield: 0.29 g (60%) of a white crystalline solid,
m.p. 157-159 °C

Example 45

Proposed Method for Preparation of rac-4-Aminoiminomechyl-N-(3,4-dihydro-2-(1H-cetrazol-5-yl)methyl-2H-1-benzopyran-6-yl)benzamide, a compound represented by the formula (352)

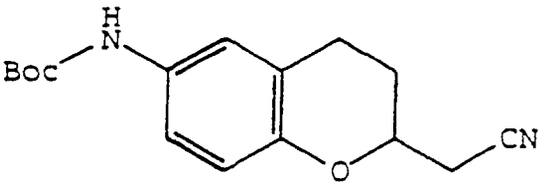
[0243]



(352)

Step A: Preparation of tert.-butyl rac-(2-cyanomethyl-3,4-dihydro-2H-1-benzopyran-6-yl)carbamate, an intermediate represented by the formula (353):

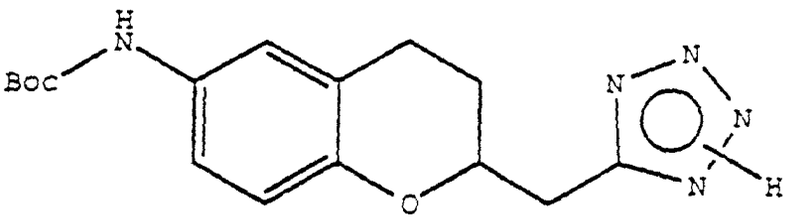
[0244]



(353)

Step B: Preparation of tert.-butyl rac-(3,4-dihydro-2-(1H-tetrazol-5-yl)methyl-2H-1-benzopyran-6-yl)carbamate, an intermediate represented by the formula (354) :

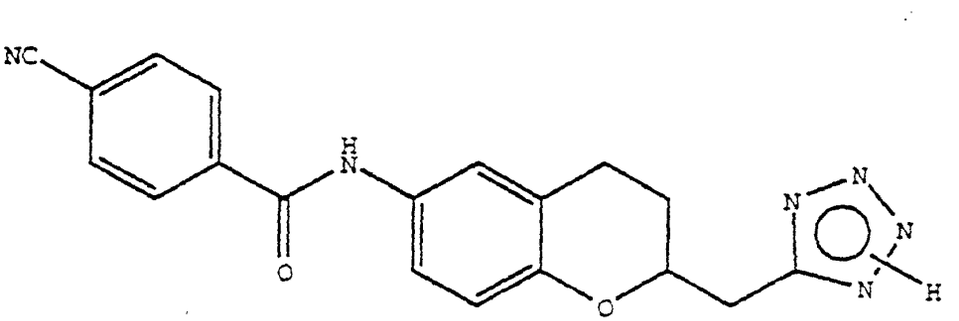
[0245]



(354)

Step C: Preparation of rac-4-cyano-N-(3,4-dihydro-2-(1H-tetrazol-5-yl)methyl-2H-1-benzopyran-6-yl)benzamide, a compound represented by the formula (355):

[0246]

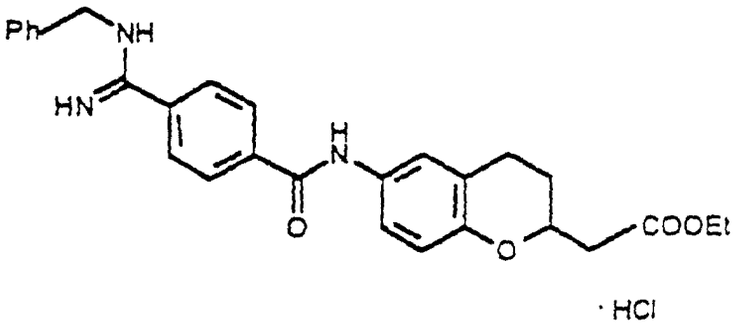


(355)

Example 46

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(4-(N'-(phenylmethylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl)acetate hydrochloride, a compound represented by the formula (356)

[0247]



(356)

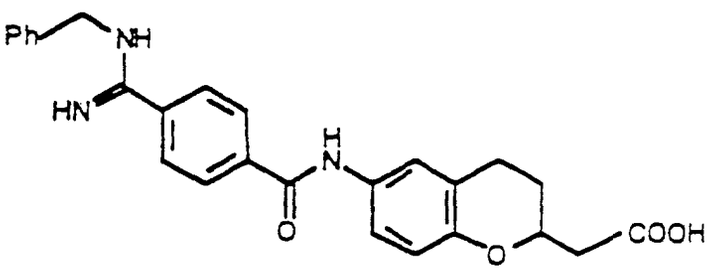
A mixture of 0.49 g (1.1 mmol) of the intermediate from Example 13 Step A and 0.5 ml benzylamine in 15 ml dry ethanol was stirred for 5 hours at room temperature. The solvent was removed under reduced pressure, and the remaining title compound crystallized from ethanol/ether. The crystals were collected by filtration, washed with ether, and dried in vacuo.

Yield: 0.49 g (88%) of pale yellow crystals,
m.p. 254-256 °C

Example 47

Preparation of rac-(3,4-Dihydro-6-(N-(4-(N'-(phenylmethylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl) acetic Acid, a compound represented by the formula (357)

[0248]



(357)

0.2 g (0.39 mmol) of the ester from Example 46 were added to a mixture of 10 ml ethanol and 0.5 ml 2 N aqueous sodium hydroxide solution. After gentle warming it was stirred overnight at room temperature. The mixture was brought to pH 4 with 2 N acetic acid, and the precipitate of the title acid was filtered with suction, washed successively with water and with acetone, and dried in vacuo.

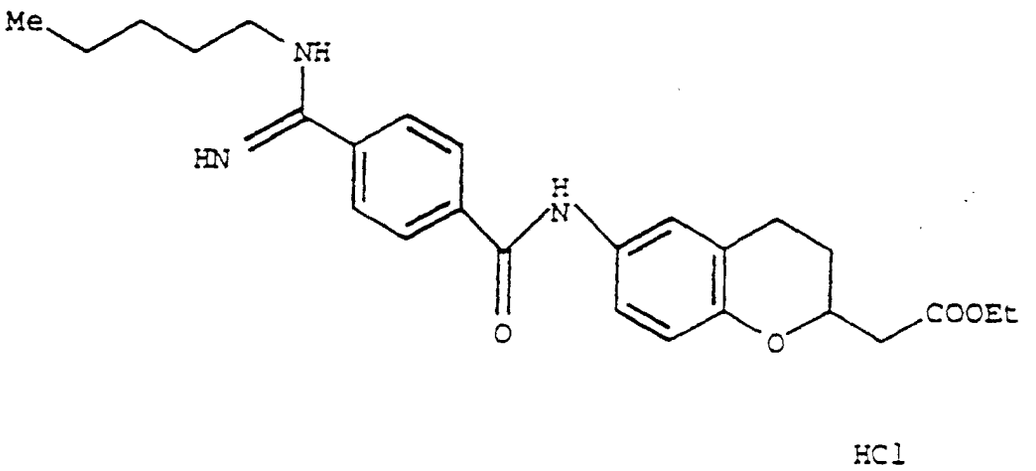
Yield: 0.12 g (69%) of a pale yellow powder,

m.p. 220 °C (dec.)

Example 48

Preparation of Ethyl rac-(3,4-Dihydro-6-(N-(4-((pentylamino)iminomethyl)benzoyl)amino)-2H-1-benzopyran-2-yl) acetate hydrochloride, a compound represented by the formula (363) :

[0249]



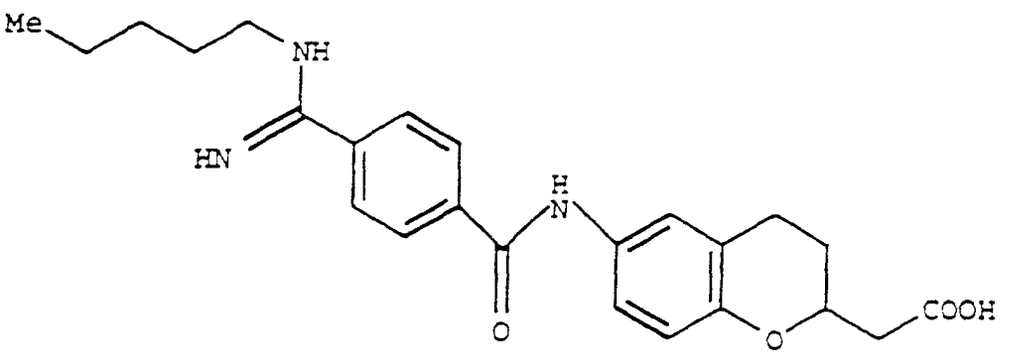
(363)

To a suspension of 447 mg (1.0 mmol) of the intermediate from Example 13, Step A in 15 ml dry ethanol were added at 0 °C 0.5 ml n-pentylamine. The mixture became a clear solution upon stirring overnight at room temperature. It was concentrated under reduced pressure, and the crystalline residue of the title compound was recrystallized from ethanol/ ether.
Yield: 0.33 g (68%) of pale yellow crystals,
m.p. 267-269°C.

Example 49

Preparation of rac-(3,4-Dihydro-6-(N-(4-((pentylamino)iminomethyl)benzoyl)amino) -2H-1-benzopyran-2-yl)acetic Acid, a compound represented by the formula (364):

[0250]



(364)

0.15 g (0.31 mmol) of the ester from Example 48 were stirred overnight at room temperature in a mixture of 10 ml ethanol and 0.7 ml 2 N aqueous sodium hydroxide solution. It was brought to pH 4 with 2 N acetic acid, and the precipitate of the title acid was filtered, washed successively with water and with acetone, and dried in vacuo.
Yield: 98 mg (75%) of colorless crystals,
m.p. 223-225 °C (dec.).

[0251] Reference numbers in the following Examples are found in Reaction Schemes 27 to 33, supra.

Assay Methods:

[0252] The identification of compounds which are active platelet aggregation inhibitors (PAI) is made possible by the observation that compounds which block the binding of fibrinogen to the GPIIb-IIIa complex in vitro also are capable of inhibiting thrombin or ADP-induced aggregation of human platelets and the formation of platelet-thrombi in vivo. This observation provides the basis for obtaining potent PAI's by evaluating the ability of test materials to disrupt fibrinogen-GPIIb-IIIa interactions.

[0253] The following assay methods were used to evaluate the compounds of the invention, inclusive of the compounds represented by formulae (I), (II), (Ix), (Xd) and (Xe) as previously described.

No. 1 - The ELISA IIb-IIIa Assay:

[0254] In the following assay, GPIIb-IIIa is prepared in purified form, by a method such as described by Fitzgerald, L.A., et al., Anal Biochem (1985) 151:169-177, (the disclosure of which is incorporated herein by reference). GPIIb-IIIa is coated onto microtiter plates. The coated support is then contacted with fibrinogen and with the test material (e.g., compounds of Formula I) and incubated for a sufficient time to permit maximal binding of fibrinogen to the immobilized GPIIb-IIIa. Fibrinogen is typically provided at a concentration of about 5-50 nM and the test material can, if desired, be added at a series of dilution. Typical incubations are 2 to 4 hours at 25 °C, the time and temperature being interdependent.

[0255] After incubation, the solution containing the fibrinogen and test material is removed and the level of binding of fibrinogen measured by quantitating bound fibrinogen to GPIIb-IIIa. Any suitable means of detection may be used, but it is convenient to employ labeled fibrinogen, for example using biotinylated labels. Such methods are well known in the art.

A. Description of Assays--Plate Assays

[0256] Purified platelet GPIIb-IIIa receptor was prepared as described by Fitzgerald, L.A., et al., Anal Biochem (1985) 151:169-177 (1985). Vitronectin receptor was prepared as described by Smith, J.W., J. Biol Chem (1988) 263: 18726-18731. After purification, the receptors were stored in 0.1% Triton X-100 at 0.1-1.0 mg/ml.

[0257] The receptors were coated to the wells of 96-well flat-bottom ELISA plates (Linbro EIA-Plus microtiter plate, Flow Laboratories) after diluting 1:200 with a solution of 20 mM Tris-HCl, 150 mM NaCl, 1 mM $CaCl_2$, pH 7.4, to reduce the Triton X-100 concentration to below its critical micellar concentration and adding an aliquot of 100 ul to each well. The wells were all allowed to incubate overnight at 4 °C, and then aspirated to dryness. Additional sites were blocked by the addition of bovine serum albumin (BSA) at 35 mg/ml in the above buffer for 2 hours at 30 °C to prevent nonspecific binding. The wells were then washed once with binding buffer (50 nM Tris-HCl, 100 mM NaCl 2 mM $CaCl_2$, 1 mg/ml BSA).

[0258] The corresponding ligands (fibrinogen, von Willebrand Factor, or vitronectin) were conjugated to biotin using commercially available reagents and standard protocols. The labeled ligands were added to the receptor-coated wells at final concentration of 10 nM (100 ul/well) and incubated for 3 hours at 25 °C in the presence or absence of the test samples. After incubation, the wells are aspirated to dryness and bound ligand is quantitated.

[0259] The bound protein is detected by the addition of antibiotin antibody conjugated to alkaline phosphatase followed by addition of substrate (p-nitrophenyl phosphate), and determination of the optical density of each well at 405 nM. Decreased color development is observed in wells incubated with test samples which inhibit binding of ligand to receptor.

No. 2 - The Platelet Aggregation Assay

[0260] In addition to the ELISA IIb-IIIa assay previously described the Aggregation-Human PRP/ADP Assay is useful for evaluating therapeutic compounds.

[0261] Platelet-rich plasma was prepared from healthy human volunteers for use in determining inhibition of platelet aggregation by the compounds. Blood was collected via a 21 gauge butterfly cannula, using a two-syringe technique

into 1/10 volume of 3.8% trisodium citrate.

[0262] Platelet-rich plasma was prepared at room temperature by centrifugation of the citrated whole blood at 100 x g for 12 minutes. The platelet rich plasma contained approximately 200-400,000 platelets/μl.

[0263] Platelet-poor plasma was prepared by centrifugation of citrated whole blood at 12,000 x g for 2 minutes.

[0264] Platelet aggregation was assayed in a 4-channel platelet aggregation profiler (PAP-4, Biodata, Hatboro, PA) according to the manufacturers directions. Inhibition of platelet aggregation was studied by adding varying amounts of adenosine diphosphate (ADP) to stirred human platelet-rich plasma. Specifically, the human platelet-rich plasma was incubated with the compound being tested for 1 minute at 37 °C prior to the addition of a variety of aggregating agents most often ADP 5 μM, but also 1 μg/ml collagen, 1 μM U46619 and 0.3 μM platelet activating factor.

Table of Assay Test Results

Example No.	ELISA IIB/IIIa	Agg: Human PRP/ADP
	IC_{50} μM	IC_{50}μm
1	NT	11
2	0.0033	2.5
3	0.77	0.24
4	0.004	0.066
5	NT	100
6	3.93	100
7	1.16	40
8	NT	100
9	0.72	21
10	NT	12
11	3.46	>100
12	0.14	0.9
13	>10	0.66
14	0.0334	0.28
15	>10	21
16	1.8	>10
17	>1	100
18	0.80	11
19	0.18	4.8
20	NT	>100
21	NT	29
22	>1	NT
23	0.009	0.16
24	0.0013	0.082
25	>10	1.5
26	0.0185	0.28
27	>10	1.2
28	NT	NT
29	NT	1.8
30	0.014	0.56
31	NT	1.3
32	0.02	0.18
33	NT	>100
34	1	>100
35	NT	0.39
36	0.019	0.12
37	NT	0.14
38	0.0055	0.084
39	NT	>100

(continued)

Table of Assay Test Results		
Example No.	ELISA IIB/IIIa	Agg: Human PRP/ADP
	IC_{50} μM	IC_{50}μm
40	NT	0.078
41	NT	0.084
42	0.099	0.084
43	NT	NT
44	NT	NT
45	NT	NT
46	NT	0.24
47	0.0094	0.086
48	NT	NT
49	NT	NT
Note: NT = not tested		

Pharmaceutical Compositions

[0265] Pharmaceutical formulations containing compounds of the invention can be administered orally in the form of tablets, capsules, solutions, emulsions or suspensions, inhaled liquid or solid particles, as a spray, through the skin by an appliance such a transdermal patch (such as described in US Patents No. 5,296,222 and 5,271,940, the disclosures of which are incorporated herein by reference) or rectally, for example, in the form of suppositories. The. lipophilic prodrug derivatives of the invention (e.g., formula Xd, Xe) are particularly well suited for transdermal absorption administration and delivery systems. Administration can also take place parenterally, for example in the form of injectable solutions.

[0266] Tablets are prepared by mixing the Active

[0267] Ingredient ("Active Ingredient" is one or more compounds of the invention inclusive of those corresponding to formulae I, II, Xd, or Xe) with pharmaceutically inert, inorganic or organic carriers, diluents, and/or excipients. Examples of such excipients which can be used for tablets, are lactose, maize starch or derivatives thereof, talc, stearic acid or salts thereof. Examples of suitable excipients for soft gelatin capsules are vegetable oils, waxes, fats, semisolid and liquid polyols.

[0268] Suitable excipients for the preparation of solutions and syrups are water, polyols, sucrose, invert sugar and glucose.

[0269] Suitable excipients for injectable solutions are water, alcohols, polyols, glycerol and vegetable oils.

[0270] These pharmaceutical products can additionally contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorings, buffers, coating agents and antioxidants.

[0271] Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use.

[0272] The Active Ingredient can also be made in micro-encapsulated form.

[0273] Exemplary formulations using the Active Ingredient are described below:

Formulation 1

[0274] Hard gelatin capsules are prepared using the following ingredients:

	(mg/capsule)
Active Ingredient	250.0
Starch	305.0
Magnesium stearate	5.0

[0275] The above ingredients are mixed and filled into hard gelatin capsules in 560 mg quantities.

Formulation 2

[0276] A tablet formula is prepared using the ingredients below:

	(mg/tablet)
Active Ingredient	250.0
Cellulose, microcrystalline	400.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

[0277] The components are blended and compressed to form tablets, each weighing 665 mg.

Formulation 3

[0278] A dry powder inhaler formulation is prepared containing the following components:

	Weight %
Active ingredient	5
Lactose	95

[0279] The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation 4

[0280] Tablets, each containing 60 mg of active ingredient, are prepared as follows:

	(milligrams)
Active ingredient	60.0
Starch	45.0
Microcrystalline cellulose	35.0
Polyvinylpyrrolidone (as 10% solution in water)	4.0
Sodium carboxymethyl starch	4.5
Magnesium stearate	0.5
Talc	1.0
Total	150.0

[0281] The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U. S. sieve. The granules as produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150mg.

Formulation 5

[0282] Capsules, each containing 80 mg of medicament are made as follows:

	(milligrams)
Active ingredient	80.0
Starch	109.0
Magnesium stearate	1.0
Total	190.0

[0283] The active ingredient, cellulose, starch, and magnesium stearate are blended passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 190 mg quantities.

Formulation 6

[0284] Suppositories, each containing 225 mg of active ingredient are made as follows:

Active Ingredient	225 mg
Saturated fatty acid glycerides to	2000 mg

[0285] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation 7

[0286] Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

Active ingredient		50.0 mg
Xanthan gum		4.0 mg
Sodium carboxymethyl cellulose		(11%)
Microcrystalline cellulose	(89%)	50.0 mg
Sucrose		1.75 g
Sodium benzoate		10.0 mg
Flavor		q.v.
Color		q.v.
Purified water to		5.0mL

[0287] The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

[0288] Capsules, each containing 150 mg of medicament, are made as follows:

	(milligrams)
Active ingredient	150.0
Starch	407.0
Magnesium stearate	3.0
Total	560.0

[0289] The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

Method of Treatment

[0290] This invention provides a method of preventing or treating thrombosis in mammals, especially humans, which method comprises administering to the human or mammal a therapeutically effective amount of the compounds of this invention. The platelet aggregation inhibitors of the invention are useful therapeutically to prevent thrombus formation. Indications appropriate to such treatment include, without limitation, atherosclerosis and arteriosclerosis, acute myocardial infarction, chronic unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis and/or thrombosis following angioplasty, carotid endarterectomy, anastomosis of vascular grafts, and chronic cardiovascular devices (e.g., in-dwelling catheters or shunts "extracorpor-

eal circulating devices"). These syndromes represent a variety of stenotic and occlusive vascular disorders thought to be initiated by platelet activation on vessel walls.

[0291] The PAIs may be used for prevention or abortion of arterial thrombus formation, in unstable angina and arterial emboli or thrombosis, as well as treatment or prevention of myocardial infarction (MI) and mural thrombus formation post MI. For brain-related disorders, treatment or prevention of transient ischemic attack and treatment of thrombotic stroke or stroke-in-evolution are included.

[0292] The PAIs may also be used for prevention of platelet aggregation, embolization, or consumption in extracorporeal circulations, including improving renal dialysis, cardiopulmonary bypasses, hemoperfusions, and plasmapheresis.

[0293] PAIs prevent platelet aggregation, embolization, or consumption associated with intravascular devices, and administration results in improved utility of intraaortic balloon pumps, ventricular assist devices, and arterial catheters.

[0294] The PAIs will also be useful in treatment or prevention of venous thrombosis as in deep venous thrombosis, IVC, renal vein or portal vein thrombosis, and pulmonary venous thrombosis.

[0295] Various disorders involving platelet consumption, such as thrombotic thrombocytopenic purpura are also treatable.

[0296] In addition, the PAIs of the present invention may be used in numerous nontherapeutic applications where inhibiting platelet aggregation is desired. For example, improved platelet and whole blood storage can be obtained by adding sufficient quantities of the compounds, the amount of which will vary depending upon the length of proposed storage time, the conditions of storage, the ultimate use of the stored material, etc.

[0297] Preferably, the compounds of this invention are administered in the form of a pharmaceutical formulation. Thus, the compounds of this invention may be administered orally, parenterally, topically, rectally and etc., in, appropriate dosage units, as desired.

[0298] The term parenteral as used herein includes subcutaneous, intravenous, intraarterial, injection or infusion techniques, without limitation. The term, "topically" encompasses administration rectally and by inhalation spray, as well as the more common routes of the skin and the mucous membranes of the mouth and nose.

[0299] Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to administer an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient.

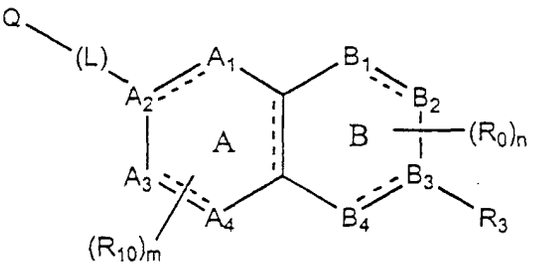
[0300] The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g., two to four separate doses per day. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the body weight, general health, diet, time and route of administration, combination with other drugs and the severity of the particular disease being treated.

[0301] The range of therapeutic dosages is from about 0.01 to about 10,000 milligrams per day, with from 1 to 300 milligrams being preferred.

[0302] Many modifications and variations of this invention may be made without departing from its scope, as is apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims.

Claims

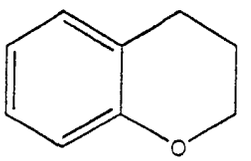
1. A bicyclic compound having a nucleus formed from two fused six membered rings, A and B, represented by the formula (I), or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof:



(I)

wherein;

the bicyclic nucleus of rings A and B is selected from the group consisting of formulae (17) through (21) below:



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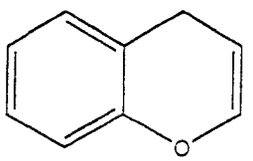

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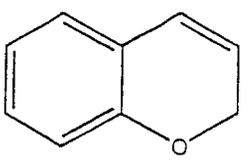

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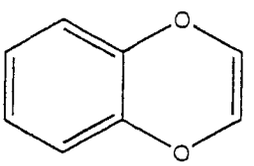

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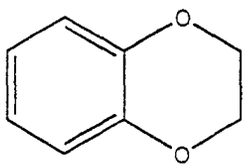

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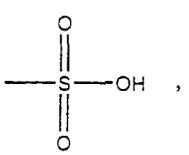
R_3 is an organic group comprising an acid radical selected from the group consisting of the following formulae:



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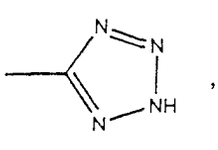

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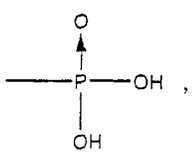

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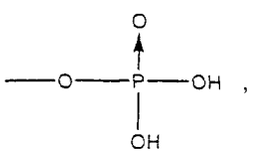

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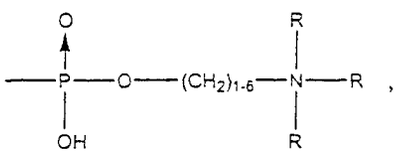

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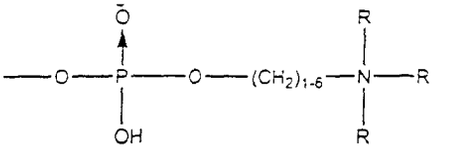
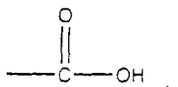
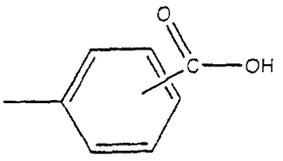
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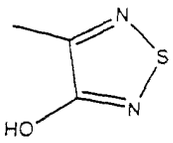
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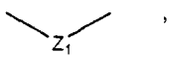
n is a number from 1 to 5;

R_0 are independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} halosubstituted alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{6-18} aryl, C_{6-12} arylalkyl, hydroxy, $C_{1-10,}$ alkoxy, C_{6-12} aralkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, sulfo, =O, and =S;

m is 3;

R_{10} are independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} halosubstituted alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{6-18} aryl, C_{6-12} arylalkyl, hydroxy, alkoxy, C_{6-12} aralkoxy, carboxy, acyl, cyano, halo, nitro, and sulfo;

linking group -(L)- is a bond or a divalent substituted or unsubstituted chain of from 1 to 4 atoms selected from the group consisting of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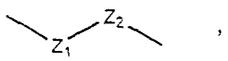
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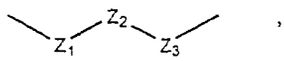
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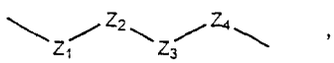
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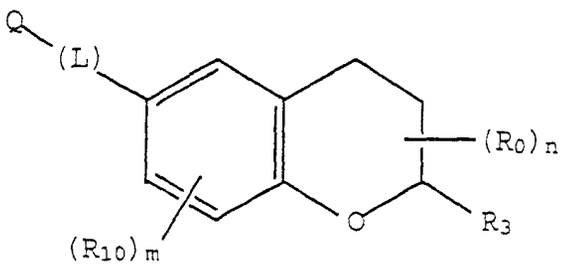
wherein Z_1, Z_2, Z_3, and Z_4 atoms are independently selected from the group consisting of: carbon, nitrogen, sulfur, and oxygen; and

Q is a basic group containing one or more basic radicals selected from the group consisting of amino, imino, amidino, N-alkylamidines, N,N'-dialkyamidines, N-arylamidines, aminomethyleneamino, iminomethylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylideneamino, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, amide, thioamide, benzamidino, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbozolyl, carbozolyl, beta-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, and any of

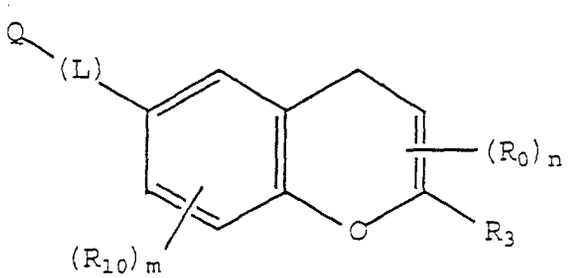
the preceding groups substituted with amino, imino, amidino, aminomethyleneamino, iminomethylamino, guanidino, alkylamino, dialkylamino, trialkylamino, or alkylideneamino groups.

2. A compound of claim 1 represented by formula (If):



(If

3. A compound of claim 1 represented by formula (Ig):



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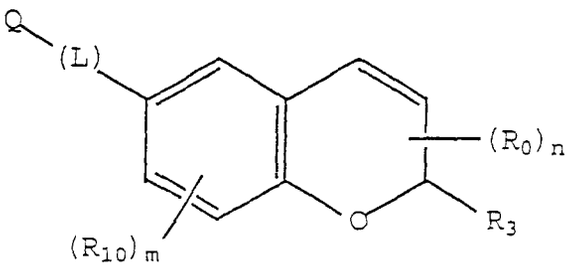
4. A compound of claim 1 represented by formula (Ih):



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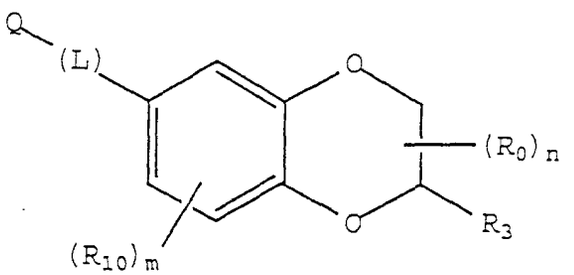
5. A compound of claim 1 represented by formula (Ii):



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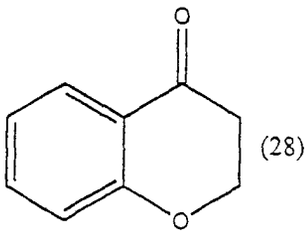
6. A compound of claim 1 where the oxo substituted bicyclic nucleus of rings A and B is selected from the group consisting of formulae (28) through (30) below: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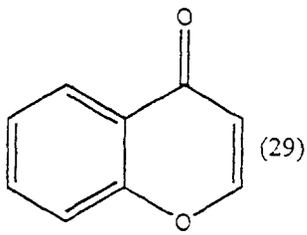
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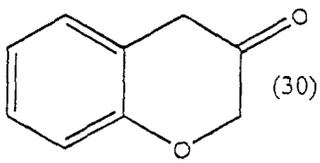
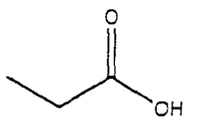

(30)

7. The compound of claim 1 where the acid radicals in R_3 are selected from the group: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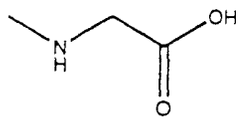
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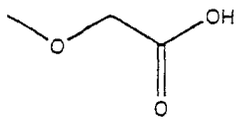
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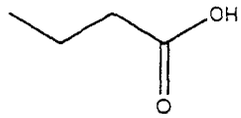
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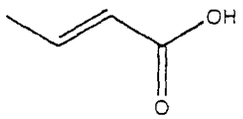
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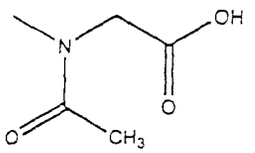
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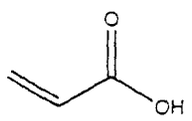
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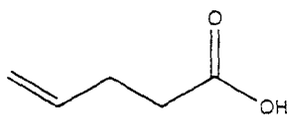
;

8. The compound of claim 1 wherein the linking group is selected from the formulae:


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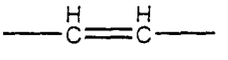
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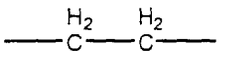
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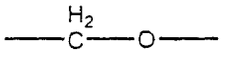
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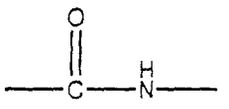
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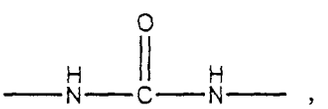
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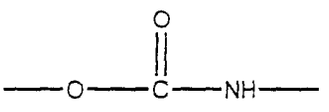
and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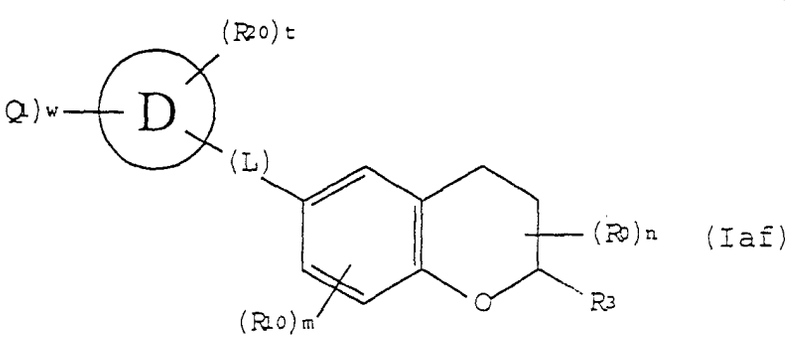
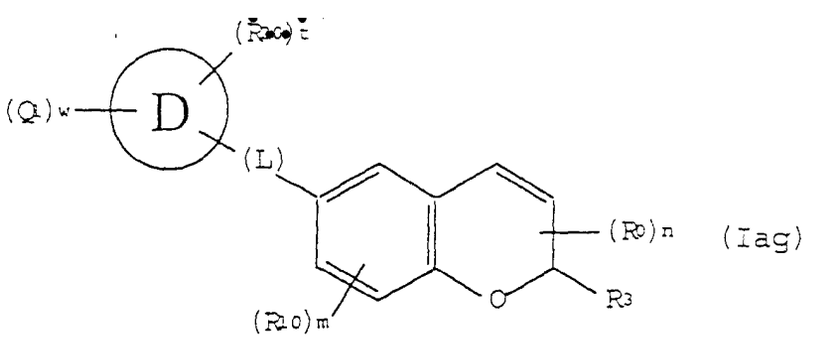
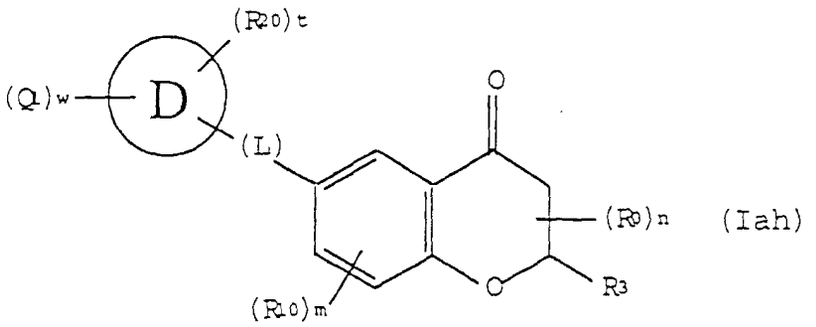
9. A bicyclic compound or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof, having a nucleus formed from two fused six membered rings, selected from formulae (Iaf), (Iag), and (Iah) below


(Iaf)

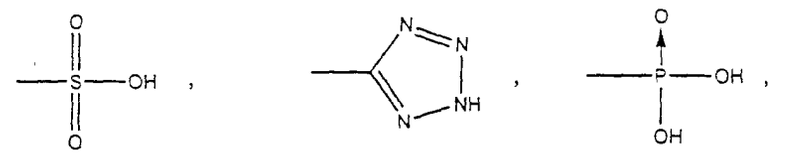

(Iag)

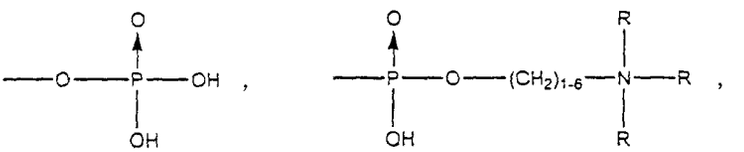


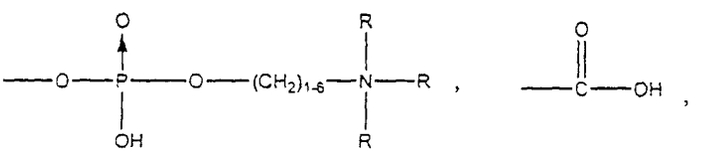
(Iah)

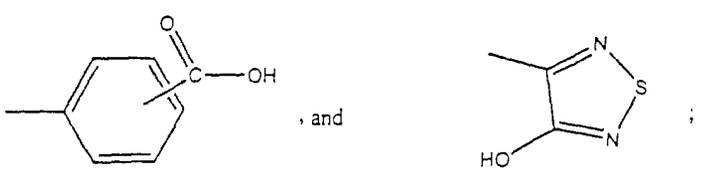
wherein;

R_3 is an organic group comprising an acid radical selected from the group consisting of the following formulae:









n is a number from 1 to 5;

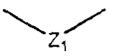
R_0 are independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} halosubstituted alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{6-18} aryl, C_{6-12} arylalkyl, hydroxy, C_{1-10}, alkoxy, C_{6-12} aralkoxy, amino, substituted amino, carbamoyl, carboxy, C_{1-10} acyl, cyano, halo, nitro, sulfo, =O and =S;

m is 3;

R_{10} are independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} halosubstituted alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{6-18} aryl, C_{6-12} arylalkyl, hydroxy, alkoxy, C_{6-12} aralkoxy, carboxy, acyl, cyano, halo, nitro, and sulfo;

t is a number from 0 to 3;

R_{20} are independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} halosubstituted alkyl, C_{2-6} alkenyl, alkynyl, cycloalkyl, C_{6-18} aryl, arylalkyl, hydroxy, alkoxy, aralkoxy, carboxy, acyl, cyano, halo, nitro, and sulfo;
linking group -(L)- is a bond or a divalent substituted or unsubstituted chain of from 1 to 4 atoms selected from the group consisting of



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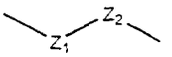

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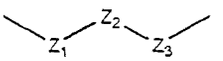

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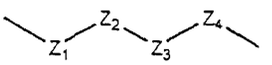
and



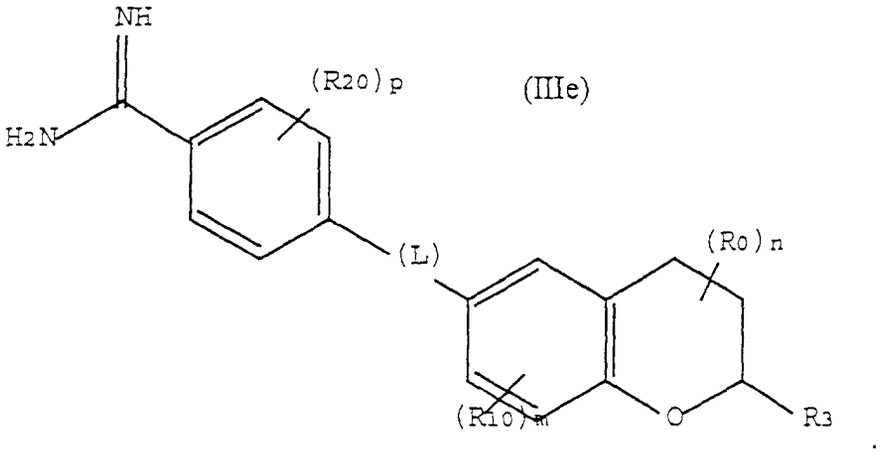
,

wherein Z_1, Z_2, Z_3, and Z_4 atoms are independently selected from the group consisting of: carbon, nitrogen, sulfur, and oxygen; with the proviso that the linking groups are not CH_2CH_2 CH_2O, CH_2 CH_2 CONH and CH_2NHCO and
D is a ring formed from 5 to 8 ring atoms and said ring atoms are independently selected from carbon, nitrogen, oxygen, or sulfur, with the proviso that at least two D ring atoms are carbon;
w is an integer from 1 to 3; and
Q_1 is a basic radical selected from the group consisting of amino, imino, amidino, aminomethyleneamino, iminomethylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylideneamino, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbozolyl, carbozolyl, beta-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, and any of the preceding groups substituted with amino, imino, amidino, aminomethyleneamino, iminomethylamino, guanidino, alkylamino, dialkylamino, trialkylamino, or alkylideneamino groups.

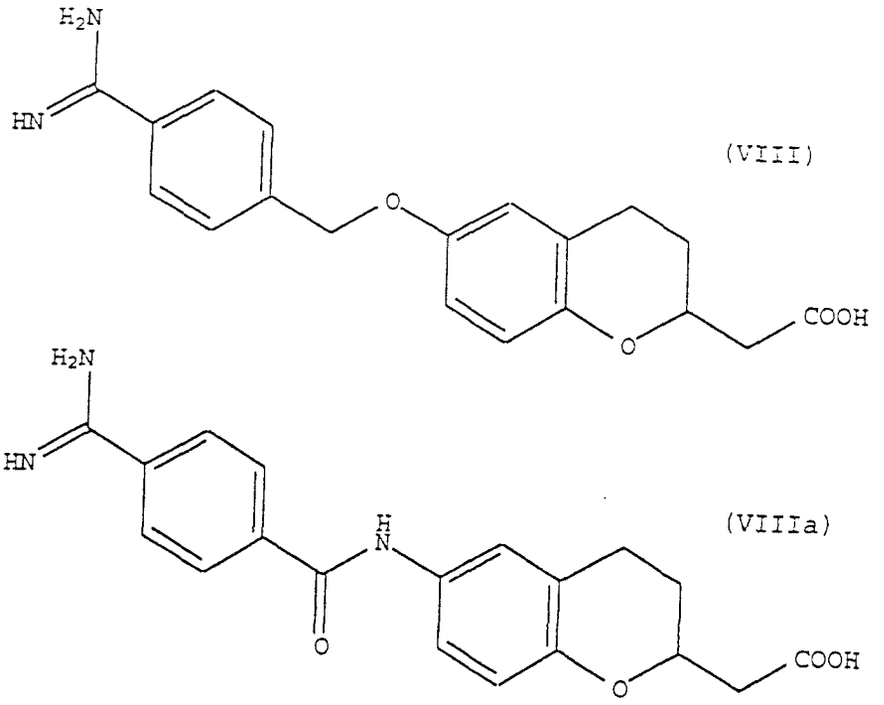
10. A compound of Claim 9 wherein the D ring is formed from a nucleus selected from the group consisting of; benzene, cycloheptadiene, cycloheptatriene, cycloheptane, cyclohexane, cyclohexene, cyclohexadiene, cycloheptene, cyclooctadiene, cyclooctane, cyclooctatetraene, cyclooctene, cyclopentane, cyclopentene, imidazole, isooxazole, morpholine, oxazole, piperazine, piperidine, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, tetrahydropyridine, tetrahydropyrimidine, 1H-tetrazole, thiazolidine, thiazole, thiopyran, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, dihydrofuran,dihydropyran, dioxane, dioxepin, dioxolane, furan, oxocane, tetrahydrofuran, tetrahydropyran, thiophene, and tetrahydrothiophene.

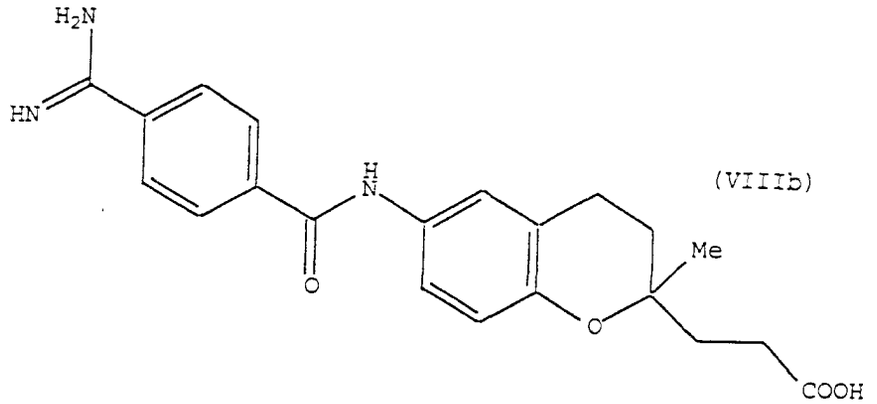
11. A compound of claim 9 wherein R_{20} is chlorine or fluorine and t is equal 1 or 2.

12. A compound of claim 1 having a nucleus based on benzopyran as represented by the structural formula (IIIe):

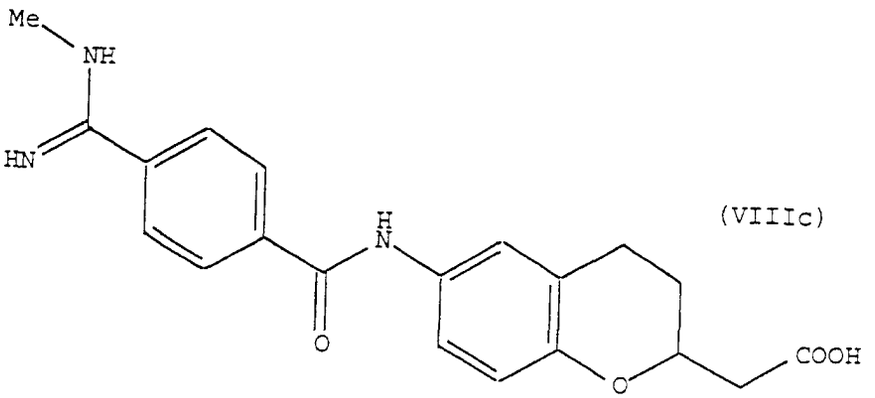


13. A compound selected from the group consisting of compounds represented by the following formulae (VIII) to (VIIIi) or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof:

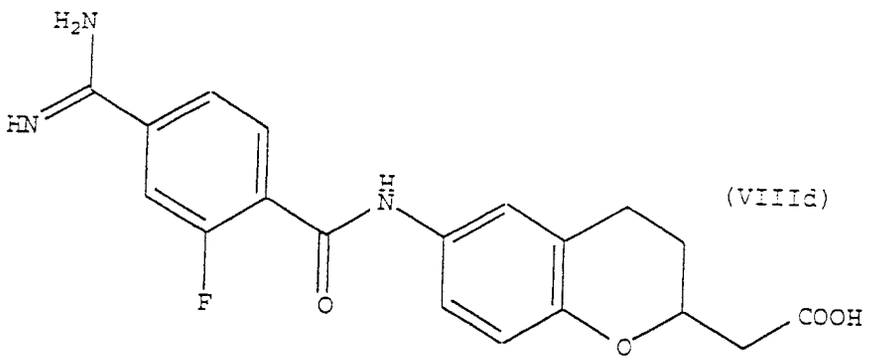




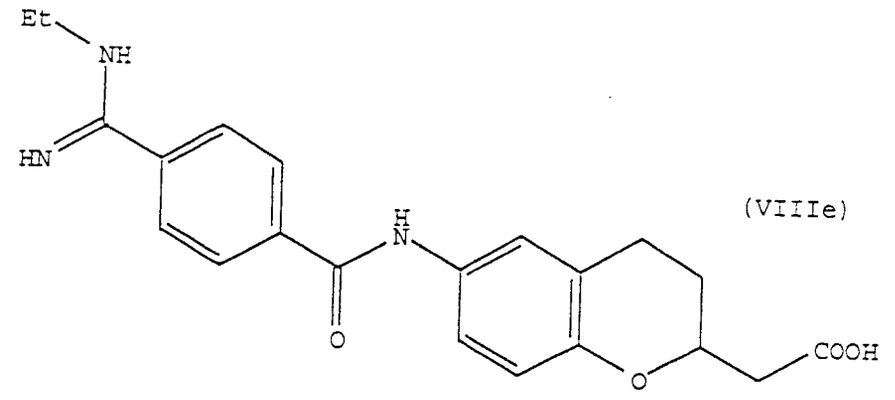
(VIIIb)



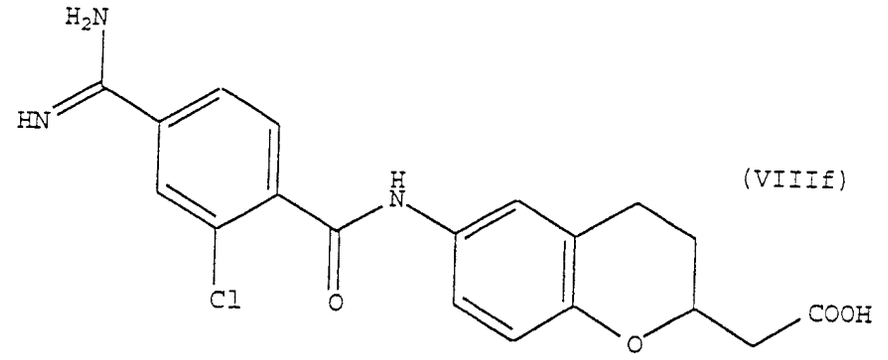
(VIIIc)



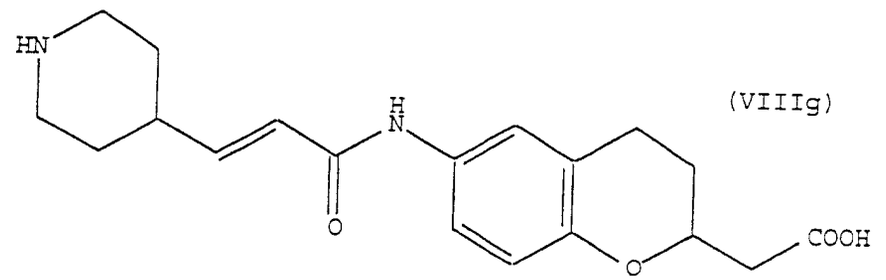
(VIIId)



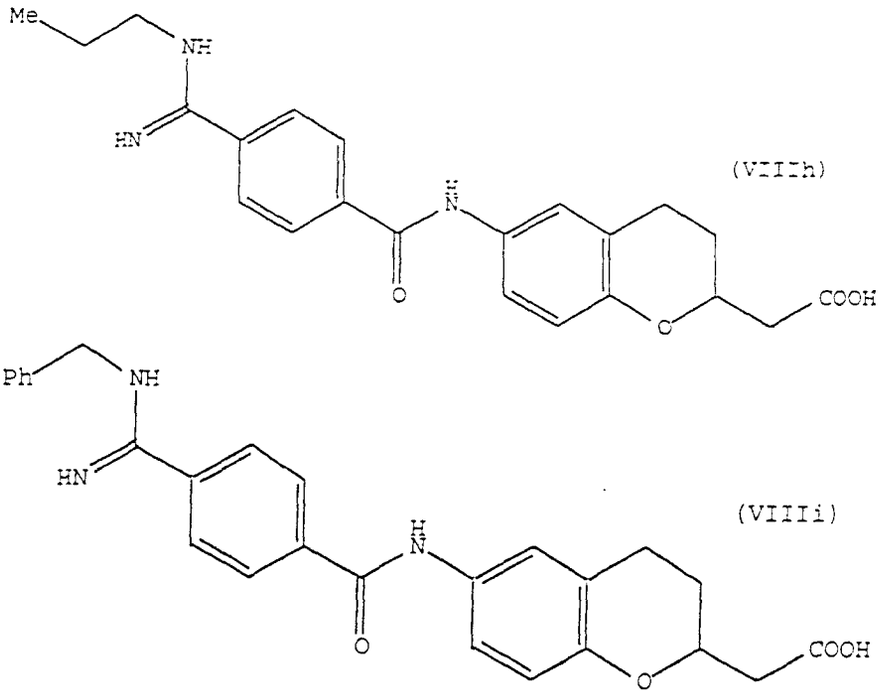
(VIIIe)



(VIIIf)



(VIIIg)



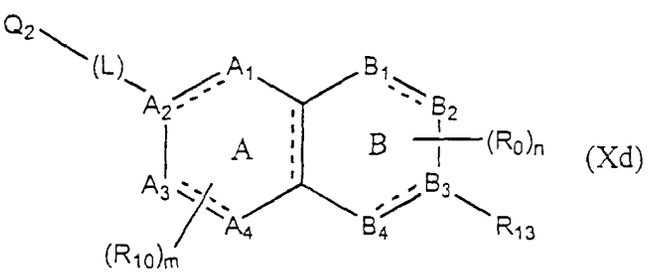
or mixtures of any of (VIII) to (VIIIi).

14. A platelet aggregation inhibiting pharmaceutical formulation comprising:

(i) a therapeutically effective platelet aggregation inhibiting amount of a bicyclic compound of Claim 1; and
(ii) a pharmaceutically acceptable carrier or diluent therefor.

15. A bicyclic compound as claimed in Claim 1, or a pharmaceutically acceptable salt thereof, for use in alleviating the pathological effects of atherosclerosis and arteriosclerosis, acute myocardial infarction, chronic stable angina, unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis following angioplasty, carotid endarterectomy, and anastomosis of vascular grafts.

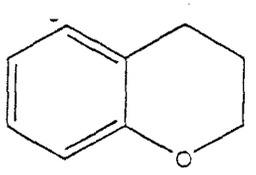
16. A prodrug derivative of a bicyclic compound having a nucleus formed from two fused six membered rings, A and B, represented by the formula (Xd):

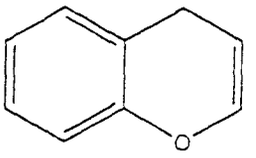


(Xd)

wherein;

the bicyclic nucleus of rings A and B is selected from the group consisting of formulae (17) through (21) below:


(17)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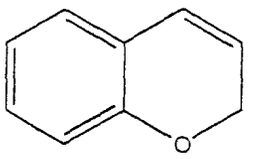
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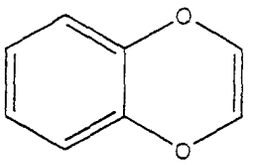
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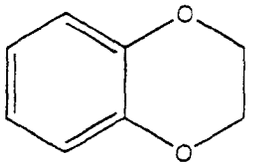

(21)

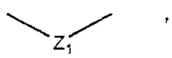
n is a number from 1 to 5;

R_0 are independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} halosubstituted alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{6-18} aryl, C_{6-12} arylalkyl, hydroxy, C_{1-10} alkoxy, C_{6-12} aralkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, sulfo, =O, and =S;

m is 3;

R_{10} are independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} halosubstituted alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{6-18} aryl, C_{6-12} arylalkyl, hydroxy, alkoxy, C_{6-12} aralkoxy, carboxy, acyl, cyano, halo, nitro, and sulfo;

linking group -(L)- is a bond or a divalent substituted or unsubstituted chain of from 1 to 4 atoms selected from the group consisting of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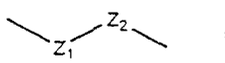
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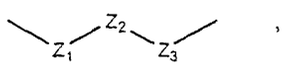
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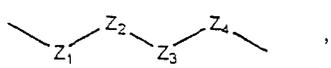

,

wherein Z_1, Z_2, Z_3, and Z_4 atoms are independently selected from the group consisting of: carbon, nitrogen, sulfur, and oxygen; and

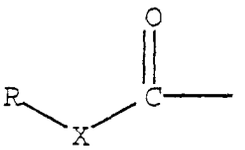
Q_2 is selected from (i) a basic group comprising a basic radical, or (ii) a basic group comprising an acylated

basic radical; wherein the basic radical is selected from the group of amino, imino, amidino, N-alkylamidines, N,N'-dialkyamidines, N-arylamidines, aminomethyleneamino, iminomethylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylideneamino, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, amide, thioamide, benzamidino, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbozolyl, carbozolyl, beta-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, and any of the preceding groups substituted with amino, imino, amidino, aminomethyleneamino, iminomethylamino, guanidino, alkylamino, dialkylamino, trialkylamino, and alkylideneamino groups; and

R_{13} is selected from (i) an acidic group comprising an acid radical, or (ii) an acidic group comprising an ester derivative of an acid radical;

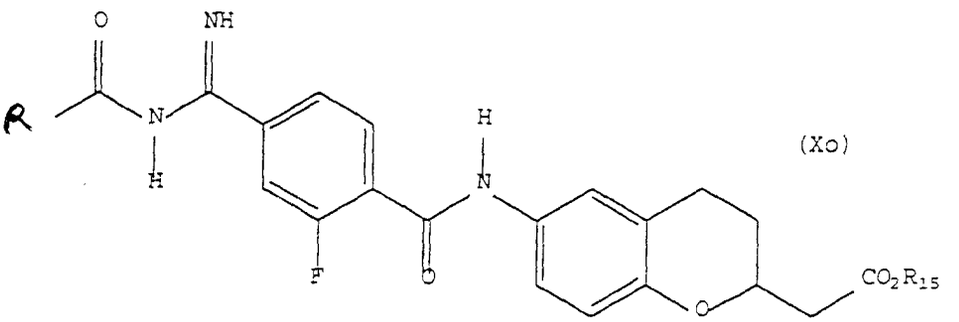
provided that Q_2 is a basic group containing an acylated basic radical or R_{13} is an acidic group containing an ester derivative of an acid radical.

17. The compound of claim 16 wherein the acylated portion of the acylated basic radical has the formula:

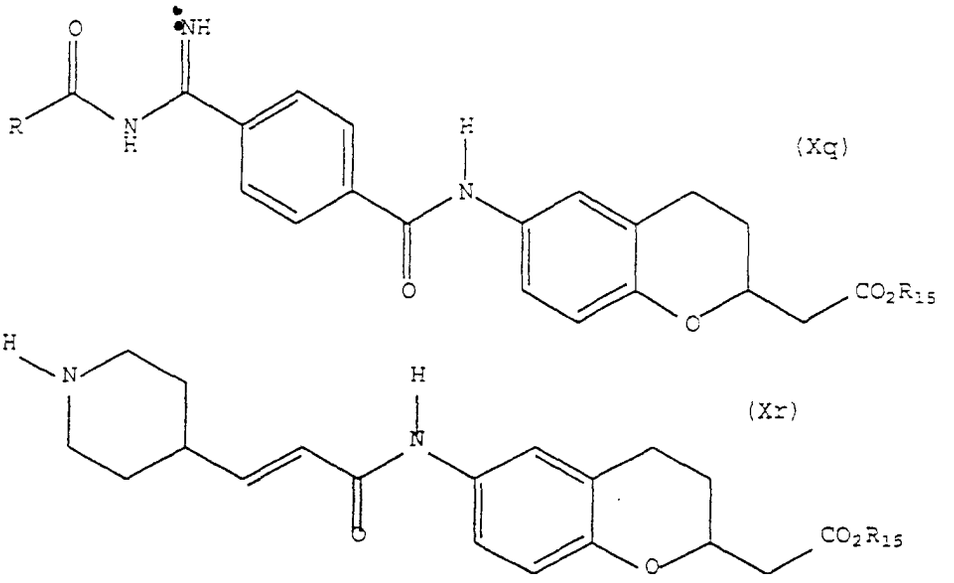


where R is C_1-C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl; and X is a bond, C, O, S, or N.

18. A prodrug derivative compound selected from the group consisting of compounds represented by formulae (Xo), (Xq) and (Xr) below:



(Xo)



(Xq)

(Xr)

where,

R = -H, -OMe, -OEt, -OPr,
X = -Cl, -F, -H,
R_{15} = Me, Et, Pr.

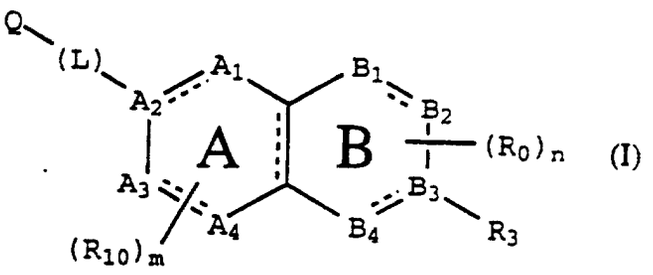
19. A platelet aggregation inhibiting pharmaceutical formulation comprising:

(i) a therapeutically effective platelet aggregation inhibiting amount of a bicyclic compound of Claim 16; and
(ii) a pharmaceutically acceptable carrier or diluent therefor.

20. A prodrug derivative as in Claim 16, for use in alleviating the pathological effects of atherosclerosis and arteriosclerosis, acute myocardial infarction, chronic stable angina, unstable angina, transient ischemic attacks and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis following angioplasty, carotid endarterectomy, and anastomosis of vascular grafts.

Patentansprüche

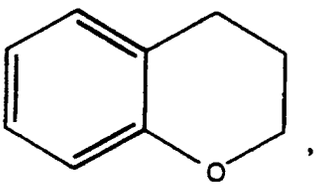
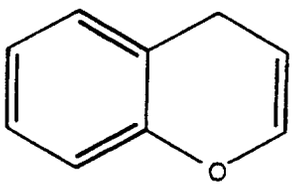
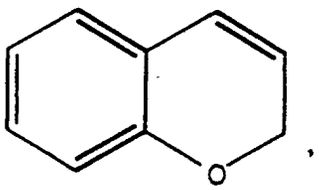
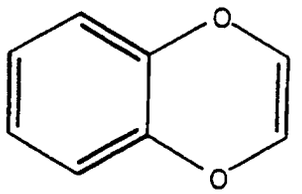
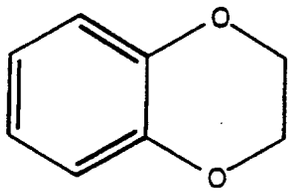
1. Bicyclische Verbindung mit einem Kern, der von zwei kondensierten aus sechs Gliedern bestehenden Ringen A und B gebildet wird, wobei die bicyclische Verbindung durch die Formel (I), oder durch ein pharmazeutisch zulässiges Salz, Solvat oder Prodrugderivat derselben dargestellt wird:



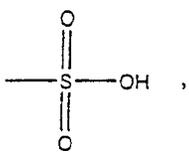
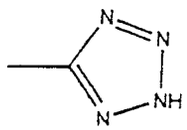
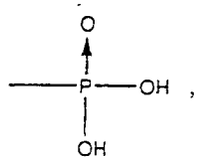
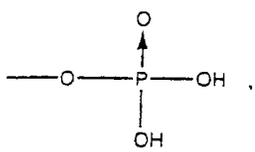
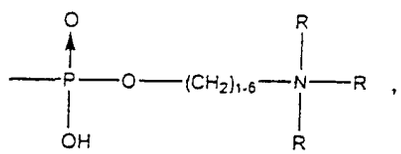
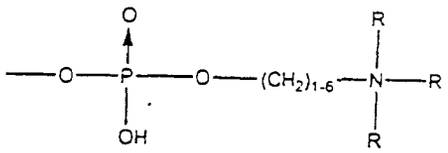
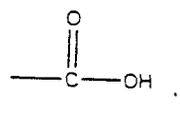
(I)

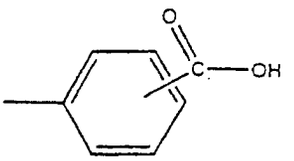
in welcher Formel:

der bicyclische Kern der Ringe A und B aus der Gruppe bestehend aus den nachstehenden Formeln (17) bis (21) ausgewählt wird:

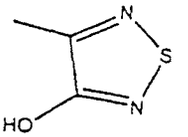

(17),

(18),

(19),

(20),

(21);

R_3 ist eine organische Gruppe und enthält ein saures Radikal, welches aus der Gruppe ausgewählt wird, die von den nachfolgenden Formeln gebildet wird:

 ,
 ,
 ,
 ,
 ,
 .
 .



, und



;

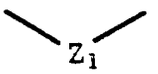
n ist eine Zahl von 1 bis 5;

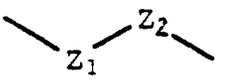
R_0 werden unter Wasserstoff, Alkyl C_{1-10}, halogensubstituiertem Alkyl C_{1-10}, Alkenyl C_{2-10}, Alkynyl C_{2-10}, Cycloalkyl C_{3-10}, Aryl C_{6-18}, Arylalkyl C_{6-12}, Hydroxy, Alkoxy C_{1-10}, Aralkoxy C_{6-12}, Amino, substituiertem Amino, Carbamoyl, Carboxy, Acyl, Cyano, Halo, Nitro, Sulfo, =O und =S unabhängig ausgewählt;

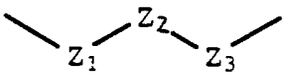
m ist 3;

R_{10} werden unter Wasserstoff, Alkyl C_{1-10}, halogensubstituiertem Alkyl C_{1-10}, Alkenyl C_{2-10}, Alkynyl C_{2-10}, Cycloalkyl C_{3-10}, Aryl C_{6-18}, Arylalkyl C_{6-12}, Hydroxy, Alkoxy, Aralkoxy C_{6-12}, Carboxy, Acyl, Cyano, Halo, Nitro und Sulfo unabhängig ausgewählt;

die Verbindungsgruppe -(L)- ist eine Bindung oder eine divalente Kette, substituiert oder nicht substituiert, mit von 1 bis 4 Atomen, ausgewählt aus der Gruppe bestehend aus:







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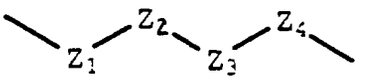
und



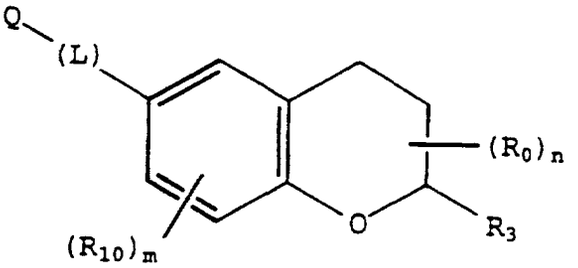
.

in welcher die Atome Z_1, Z_2, Z_3 und Z_4 aus der Gruppe bestehend aus Kohlenstoff, Stickstoff, Schwefel und Sauerstoff unabhängig ausgewählt werden; und

Q ist eine basische Gruppe mit einem oder mit mehreren basischen Radikalen, die aus der Gruppe bestehend aus Amino, Imino, Amidino, N-Alkylamidinen, N,N'-Dialkylamidinen, N-Arylamidinen, Aminomethylenamino, Iminomethylamino, Guanidino, Aminoguanidino, Alkylamino, Dialkylamino, Trialkylamino, Alkylidenamino,

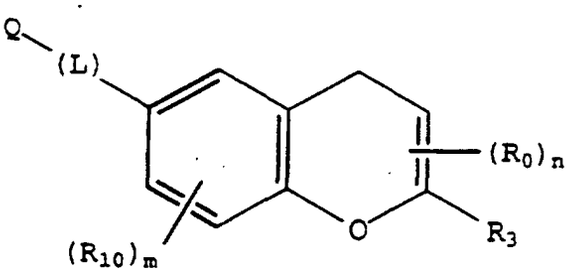
Pyrrolyl, Imidazolyl, Pyrazolyl, Pyridyl, Pyrazinyl, Pyrimidinyl, Indolizinyl, Isoindolyl, 3H-Indolyl, Indolyl, 1H-Indazolyl, Purinyl, 4H-Quinolizinyl, Isoquinolyl, Quinolyl, Phthalazinyl, Naphthyridinyl, Quinoxalinyl, Amid, Thioamid, Benzamidino, Quinazolinyl, Cinnolinyl, Pteridinyl, 4aH-Carbozolyl, Carbozolyl, beta-Carbolinyl, Phenanthridinyl, Acridinyl, Pyrimidinyl, Phenanthrolinyl, Phenazinyl, Phenarsazinyl, Phenothiazinyl, Pyrrolinyl, Imidazolidinyl, Imidazolinyl, Pyrazolidinyl, Pyrazolinyl, Piperidyl, Piperazinyl, Indolinyl, Isoindolinyl, Quinuclidinyl, Morpholinyl und gleich welche der vorhergehenden Gruppen substituiert mit den Gruppen Amino, Imino, Amidino, Aminomethylenamino, Iminomethylamino, Guanidino, Alkylamino, Dialkylamino, Trialkylamino oder Alkylidenamino ausgewählt werden.

2. Verbindung gemäß Patentanspruch 1, dargestellt durch die Formel (If):



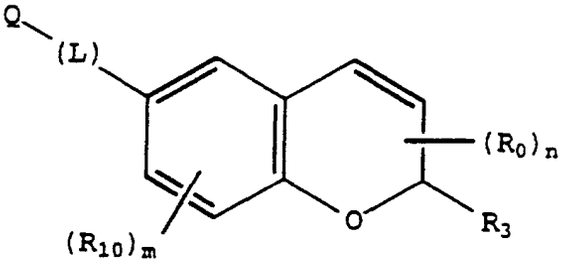
(If)

3. Verbindung gemäß Patentanspruch 1, dargestellt durch die Formel (Ig):



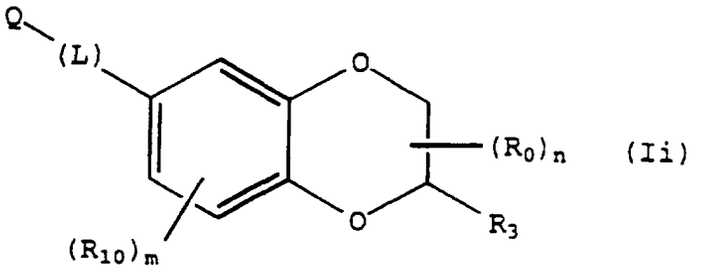
(Ig)

4. Verbindung gemäß Patentanspruch 1, dargestellt durch die Formel (Ih) :



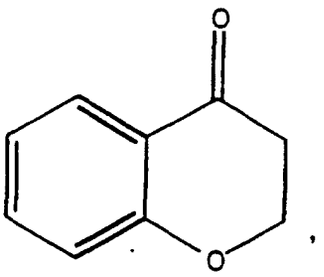
(Ih)

5. Verbindung gemäß Patentanspruch 1, dargestellt durch die Formel (Ii) :

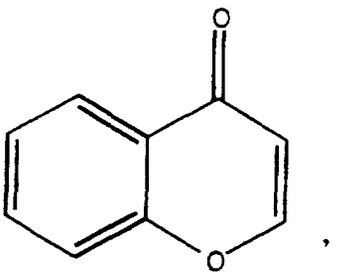


(Ii)

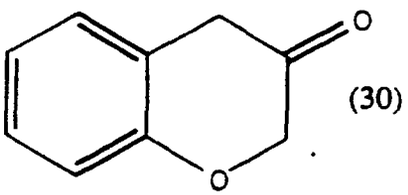
6. Verbindung gemäß Patentanspruch 1, bei welcher der durch eine Gruppe Oxo substituierte bicyclische Kern der Ringe A und B aus der Gruppe bestehend aus den nachstehenden Formeln (28) bis (30) ausgewählt wird:



(28),

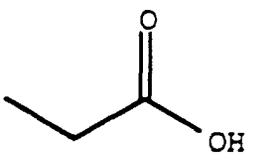


(29),

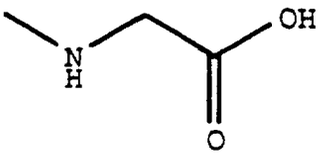


(30).

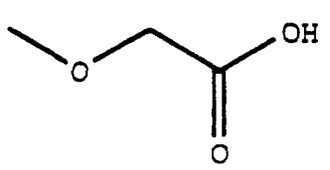
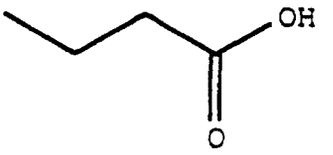
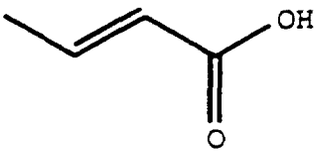
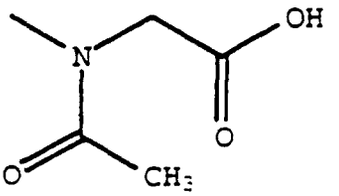
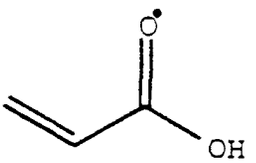
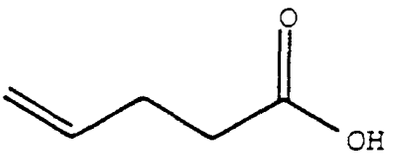
7. Verbindung gemäß Patentanspruch 1, bei welcher die sauren Radikale in R_3 aus der nachstehenden Gruppe ausgewählt werden:



,

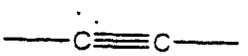
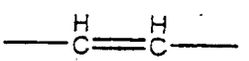
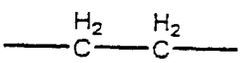
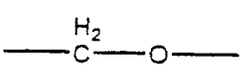
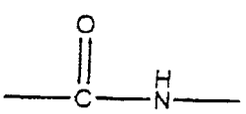
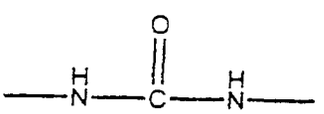


,

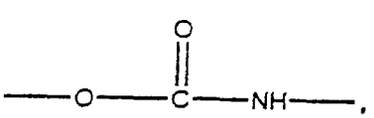







und

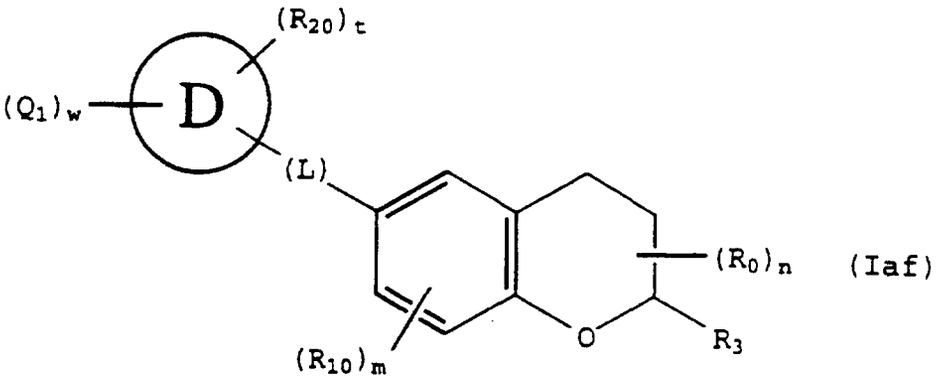
8. Verbindung gemäß Patentanspruch 1, bei welcher die Verbindungsgruppe unter den nachstehenden Formeln ausgewählt wird:

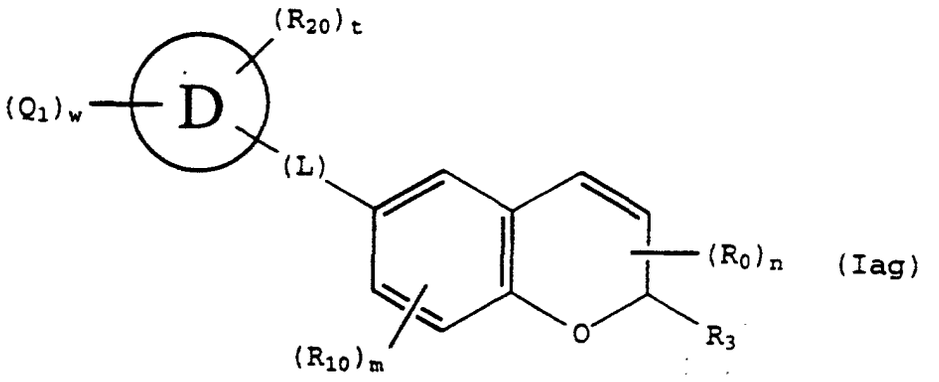







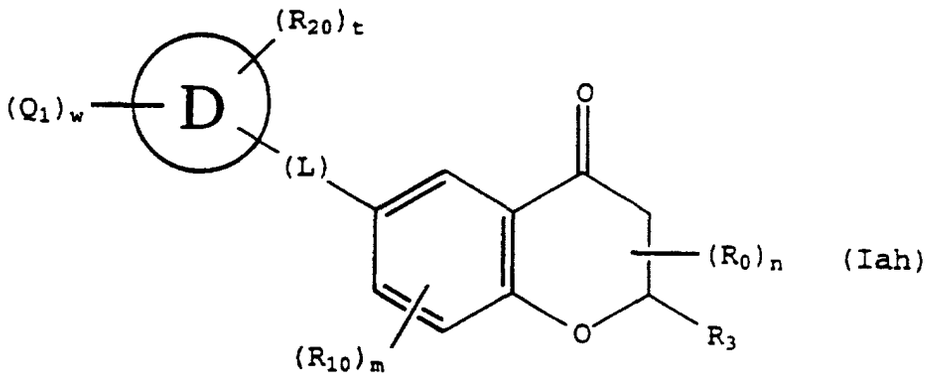
und



9. Bicyclische Verbindung oder pharmazeutisch zulässiges Salz, Solvat oder Prodrugderivat derselben, welche einen Kern enthält, der von zwei kondensierten aus sechs Gliedern bestehenden Ringen gebildet wird, die unter den nachstehenden Formeln (Iaf), (Iag) und (Iah) ausgewählt werden:

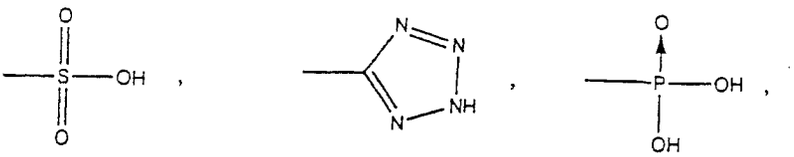


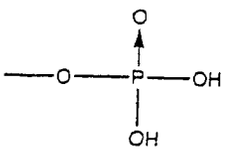
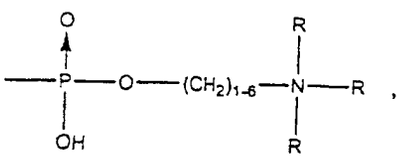
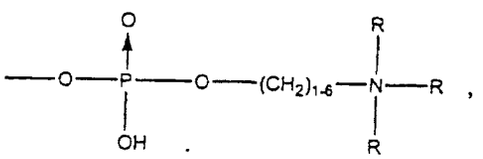
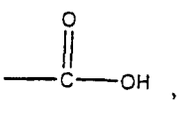
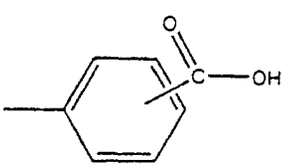
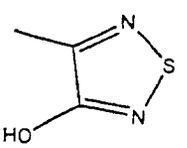




in welchen

R_3 eine organische Gruppe ist und ein saures Radikal enthält, welches aus der Gruppe ausgewählt wird, die aus den nachfolgenden Formeln besteht:








, und

;

n ist eine Zahl von 1 bis 5;

R_0 werden unter Wasserstoff, Alkyl C_{1-10}, halogensubstituiertem Alkyl C_{1-10}, Alkenyl C_{2-10}, Alkynyl C_{2-10}, Cycloalkyl C_{3-10}, Aryl C_{6-18}, Arylalkyl C_{6-12}, Hydroxy, Alkoxy C_{1-10}, Aralkoxy C_{6-12}, Amino, substituiertem Amino, Carbamoyl, Carboxy, Acyl C_{1-10}, Cyano, Halo, Nitro, Sulfo, =O und =S unabhängig ausgewählt;

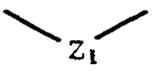
m ist 3;

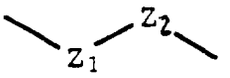
R_{10} werden unter Wasserstoff, Alkyl C_{1-10}, halogensubstituiertem Alkyl C_{1-10}, Alkenyl C_{2-10}, Alkynyl C_{2-10}, Cycloalkyl C_{3-10}, Aryl C_{6-18}, Arylalkyl C_{6-12}, Hydroxy, Alkoxy, Aralkoxy C_{6-12}, Carboxy, Acyl, Cyano, Halo, Nitro und Sulfo unabhängig ausgewählt;

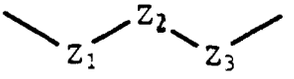
t ist eine Zahl von 0 bis 3;

R_{20} werden unter Wasserstoff, einer Gruppe Alkyl C_{1-10}, halogensubstituiertem Alkyl C_{1-10}, Alkenyl C_{2-6}, Alkynyl, Cycloalkyl, Aryl C_{6-18}, Arylalkyl, Hydroxy, Alkoxy, Aralkoxy, Carboxy, Acyl, Cyano, Halo, Nitro und Sulfo unabhängig ausgewählt;

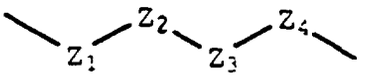
die Verbindungsgruppe -(L)- ist eine Bindung oder eine divalente Kette, substituiert oder nicht substituiert, mit von 1 bis 4 Atomen, ausgewählt aus der Gruppe bestehend aus:







und



in welcher die Atome Z_1, Z_2, Z_3 und Z_4 aus der Gruppe bestehend aus Kohlenstoff, Stickstoff, Schwefel und Sauerstoff unabhängig ausgewählt werden und unter der zusätzlichen Bedingung, daß die Verbindungsgruppe nicht CH_2 CH_2 CH_2O, CH_2 CH_2 CONH und CH_2 NHCO ist; und

D ist ein aus 5 bis 8 Ringatomen gebildeter Ring, und die genannten Ringatome werden unter Kohlenstoff, Stickstoff, Sauerstoff oder Schwefel unabhängig ausgewählt, unter der Bedingung, daß wenigstens zwei Ringatome D Kohlenstoff sind;

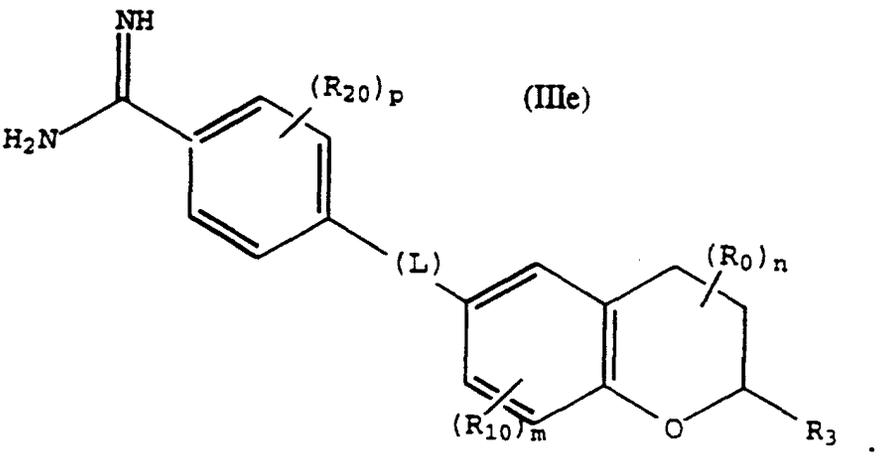
w ist eine ganze Zahl von 1 bis 3; und

Q_1 ist ein basisches Radikal, das aus der Gruppe bestehend aus den Gruppen von Amino, Imino, Amidino, Aminomethylenamino, Iminomethylamino, Guanidino, Aminoguanidino, Alkylamino, Dialkylamino, Trialkylamino, Alkylidenamino, Pyrrolyl, Imidazolyl, Pyrazolyl, Pyridyl, Pyrazinyl, Pyrimidinyl, Indolizinyl, Isoindolyl, 3H-Indolyl, Indolyl, 1H-Indazolyl, Purinyl, 4H-Quinolizinyl, Isoquinolyl, Quinolyl, Phthalazinyl, Naphthyridinyl, Quinoxalinyl, Quinazolinyl, Cinnolinyl, Pteridinyl, 4aH-Carbozolyl, Carbozolyl, beta-Carbolinyl, Phenanthridinyl, Acridinyl, Pyrimidinyl, Phenanthrolinyl, Phenazinyl, Phenarsazinyl, Phenothiazinyl, Pyrrolinyl, Imidazolidinyl, Imidazolinyl, Pyrazolidinyl, Pyrazolinyl, Piperidyl, Piperazinyl, Indolinyl, Isoindolinyl, Quinuclidinyl, Morpholinyl und gleich welche der vorgehenden Gruppen substituiert mit den Gruppen Amino, Imino, Amidino, Aminomethylenamino, Iminomethylamino, Guanidino, Alkylamino, Dialkylamino, Trialkylamino oder Alkylidenamino ausgewählt wird.

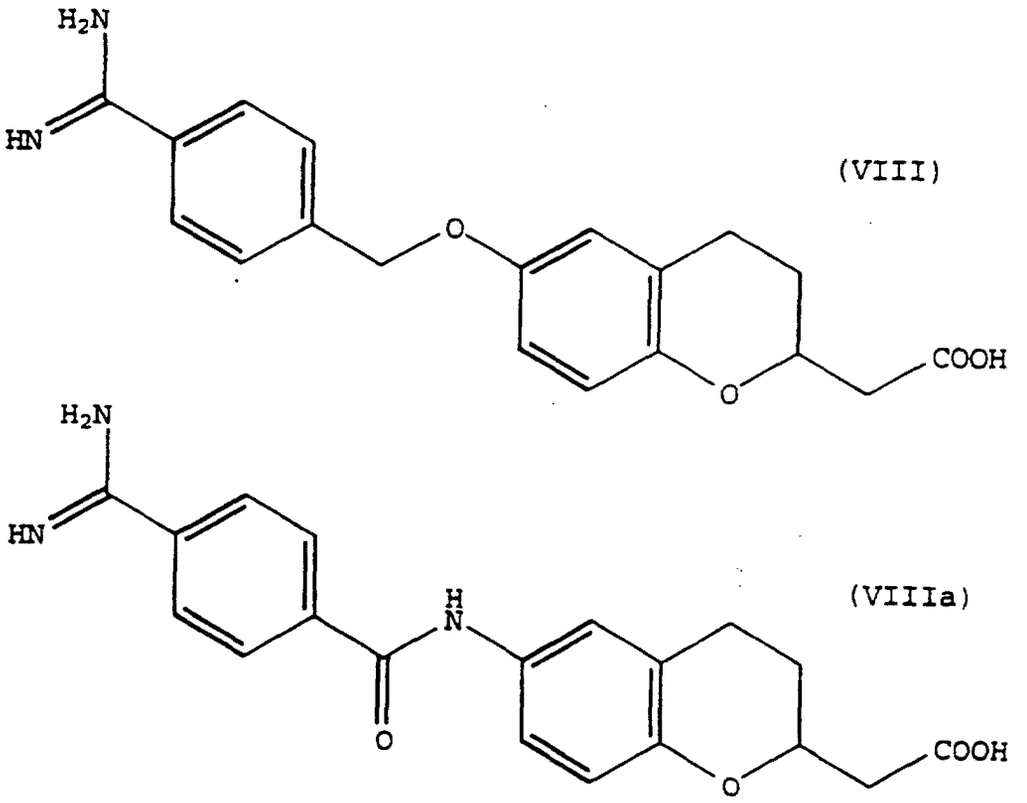
10. Verbindung gemäß Patentanspruch 9, bei welcher der Ring D ausgehend von einem Kern gebildet wird, der aus der Gruppe bestehend aus Benzol, Cycloheptadien, Cycloheptatrien, Cycloheptan, Cyclohexan, Cyclohexen, Cyclohexadien, Cyclohepten, Cyclooctadien, Cyclooctan, Cyclooctatetraen, Cycloocten, Cyclopentan, Cyclopenten, Imidazol, Isooxazol, Morpholin, Oxazol, Piperazin, Piperidin, Pyrazin, Pyrazol, Pyridin, Pyrimidin, Pyrrolyl, Pyrrolidin, Pyrrolin, Tetrahydropyridin, Tetrahydropyrimidin, 1H-Tetrazol, Thiazolidin, Thiazol, Thiopyran, 1,3,5-Triazin, 1,2,3-Triazol, 1,2,4-Triazol, Dihydrofuran, Dihydropyran, Dioxan, Dioxepin, Dioxolan, Furan, Oxocan, Tetrahydrofuran, Tetrahydropyran, Thiophen und Tetrahydrothiophen ausgewählt wird.

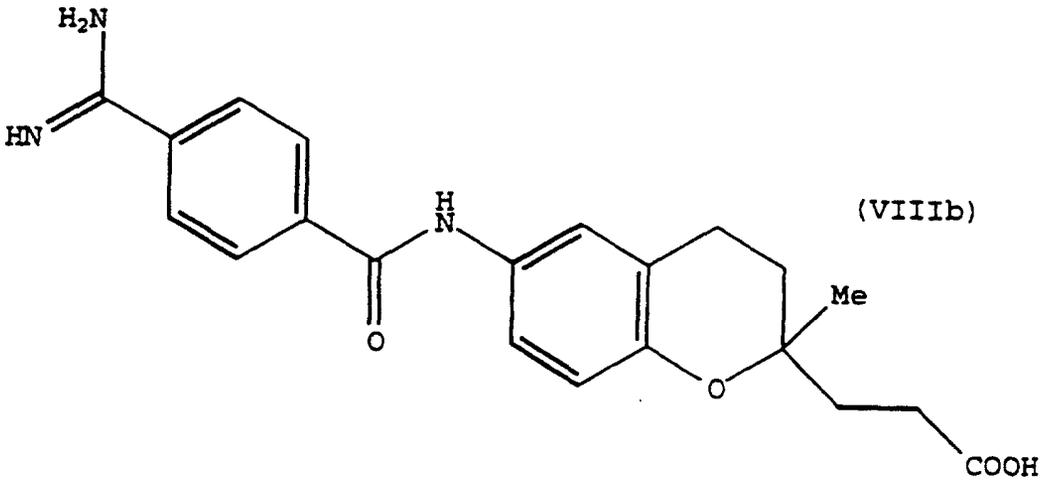
11. Verbindung gemäß Patentanspruch 9, bei welcher R_{20} ein Chlor oder ein Fluor ist und t gleich 1 oder 2 ist.

12. Verbindung gemäß Patentanspruch 1, welche einen Kern enthält, der auf einem Benzopyran beruht, wie es durch die Strukturformel (IIIe) dargestellt ist:

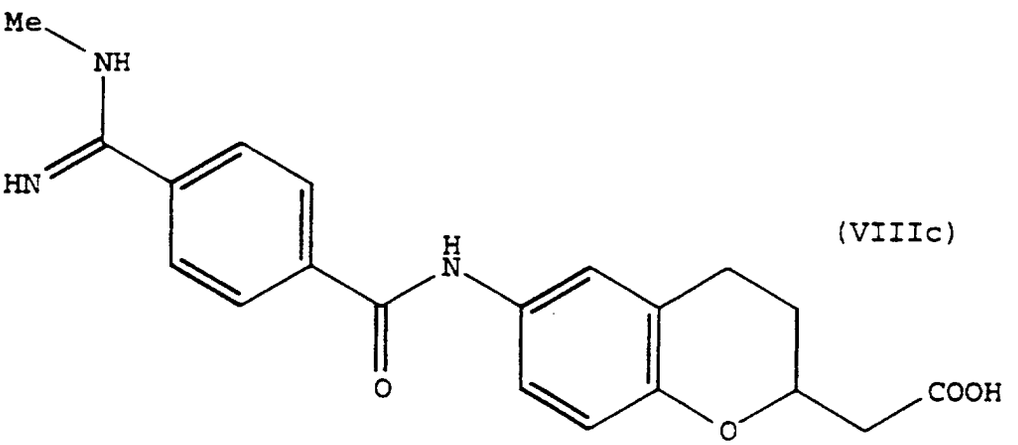


13. Verbindung, die aus der Gruppe bestehend aus Verbindungen ausgewählt wird, welche durch die nachfolgenden Formeln (VIII) bis (VIIIi) oder durch ein pharmazeutisch zulässiges Salz, Solvat oder Prodrugderivat derselben dargestellt sind:

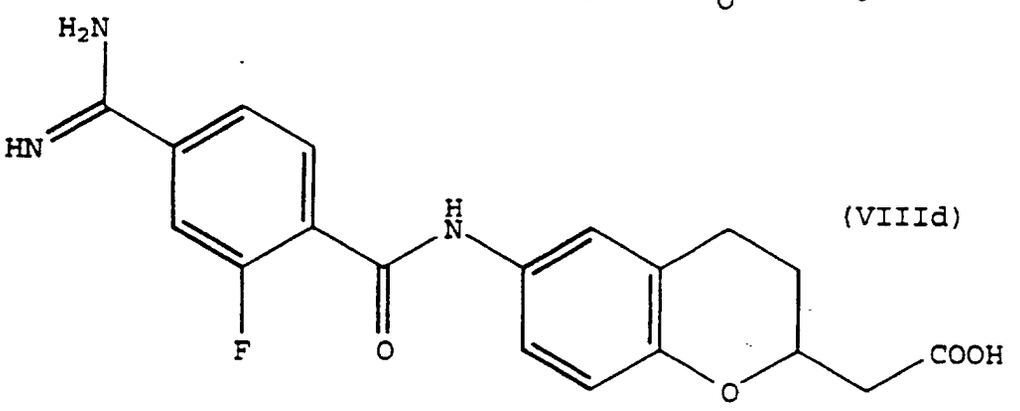




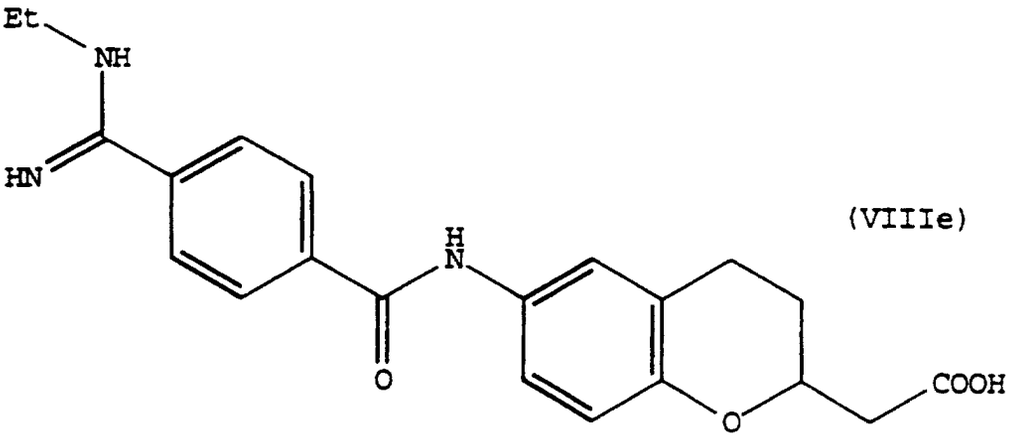
(VIIIb)



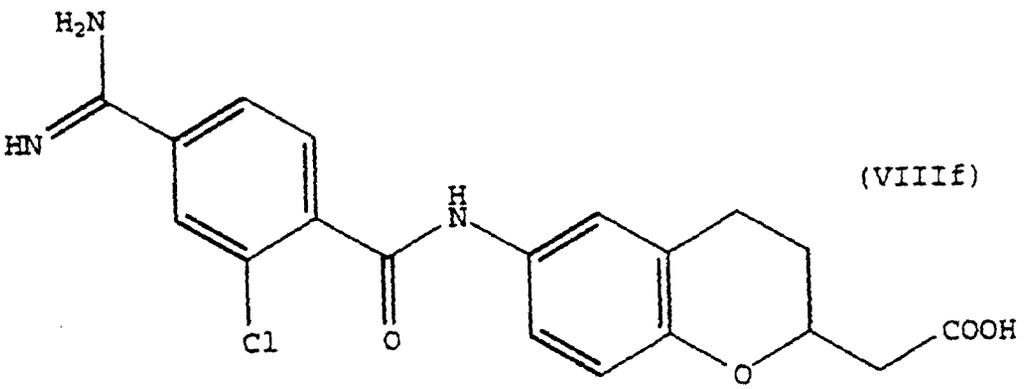
(VIIIc)



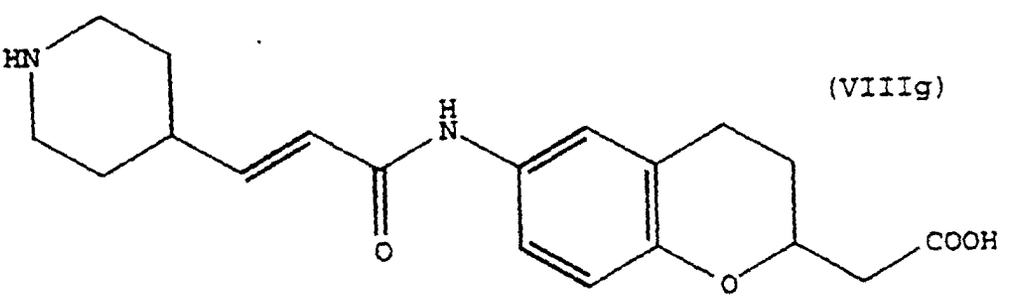
(VIIId)



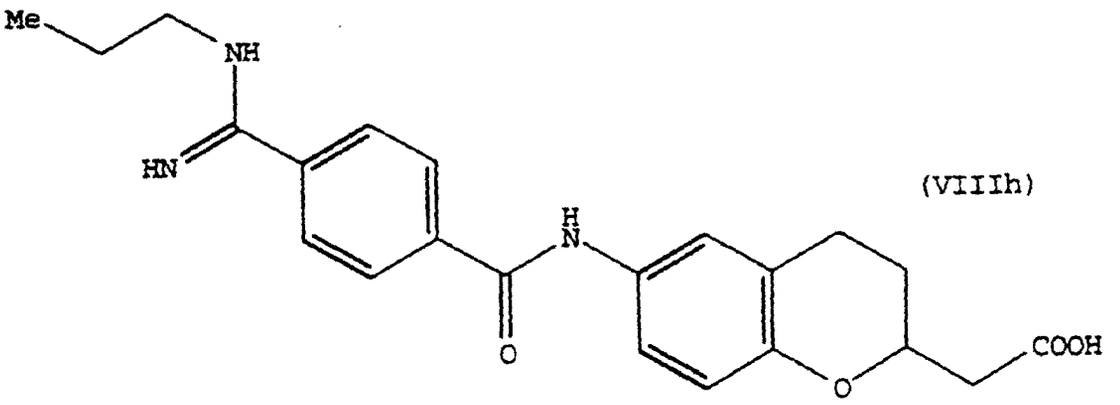
(VIIIe)



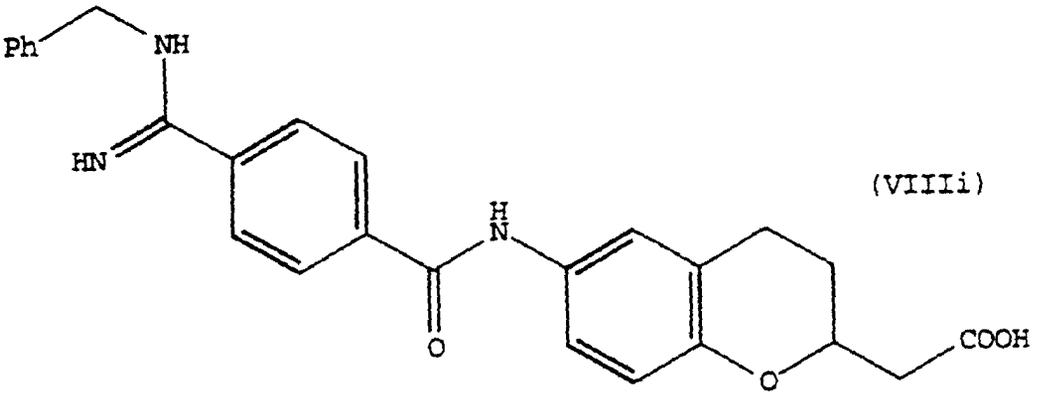
(VIIIf)



(VIIIg)



(VIIIh)



(VIIIi)

oder durch Mischungen aus irgendeiner der Formeln von (VIII) bis (VIIIi).

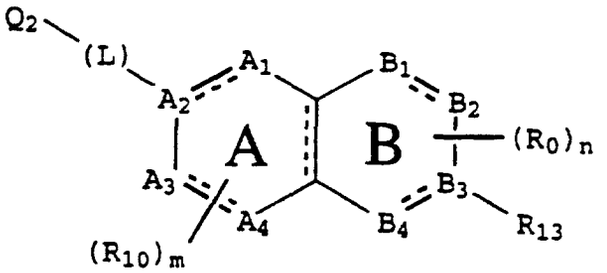
14. Eine Plättchenaggregation verhindernde pharmazeutische Formulierung mit:

(i) einer therapeutisch wirksamen Plättchenaggregation verhindernden Menge einer bicyclischen Verbindung gemäß Patentanspruch 1; und

(ii) einem pharmazeutisch zulässigen Träger oder einem Verdünnungsmittel für diesen Träger.

15. Bicyclische Verbindung gemäß Patentanspruch 1, oder pharmazeutisch zulässiges Salz derselben für eine Anwendung, die es erlaubt, die pathologischen Auswirkungen bei einer Atherosklerose und einer Arteriosklerose, einem akuten Myokardinfarkt, einer stabilen chronischen Angina, einer instabilen Angina, transitorischen ischämischen Attacken und Schlaganfällen, einer peripheren Verschlusskrankheit, einem arteriellen Thrombus, einer Präeklampsie, einer Embolie, einer auf eine Angioplastie folgende Restenose, eine Endarteriektomie der Halsschlagader und einer Anastomose von Gefäßtransplantaten zu erleichtern.

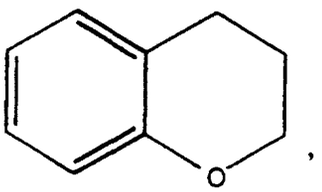
16. Prodrugderivat einer bicyclischen Verbindung, die einen Kern besitzt, welcher von zwei kondensierten aus sechs Gliedern bestehenden Ringen A und B gebildet wird, welche durch die Formel (Xd) dargestellt sind:



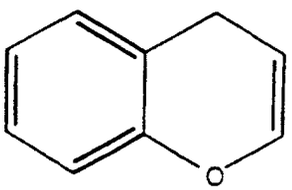
(Xd)

in welcher

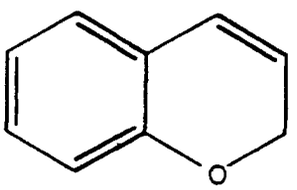
der bicyclische Kern der Ringe A und B aus der Gruppe bestehend aus den nachstehenden Formeln (17) bis (21) ausgewählt wird:



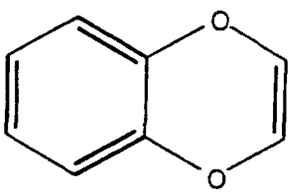
(17),



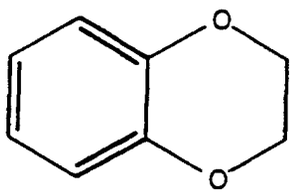
(18).



(19),



(20).



(21);

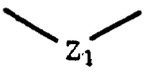
n ist eine Zahl von 1 bis 5;

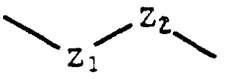
R_0 werden unter Wasserstoff, Alkyl C_{1-10}, halogensubstituiertem Alkyl C_{1-10}, Alkenyl C_{2-10}, Alkynyl C_{2-10}, Cycloalkyl C_{3-10}, Aryl C_{6-18}, Arylalkyl C_{6-12}, Hydroxy, Alkoxy C_{1-10}, Aralkoxy C_{6-12}, Amino, substituiertem Amino, Carbamoyl, Carboxy, Acyl, Cyano, Halo, Nitro, Sulfo, =O und =S unabhängig ausgewählt;

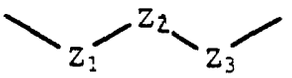
m ist 3;

R_{10} werden unter Wasserstoff, Alkyl C_{1-10}, halogensubstituiertem Alkyl C_{1-10}, Alkenyl C_{2-10}, Alkynyl C_{2-10}, Cycloalkyl C_{3-10}, Aryl C_{6-18}, Arylalkyl C_{6-12}, Hydroxy, Alkoxy, Aralkoxy C_{6-12}, Carboxy, Acyl, Cyano, Halo, Nitro und Sulfo unabhängig ausgewählt;

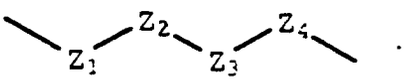
die Verbindungsgruppe -(L)- ist eine Bindung oder eine divalente Kette, substituiert oder nicht substituiert, mit von 1 bis 4 Atomen, ausgewählt aus der Gruppe bestehend aus:







und



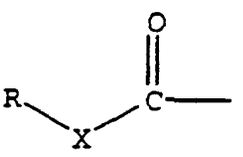
in welcher die Atome Z_1, Z_2, Z_3 und Z_4 aus der Gruppe bestehend aus Kohlenstoff, Stickstoff, Schwefel und Sauerstoff unabhängig ausgewählt werden; und

Q_2 wird ausgewählt (i) aus einer basischen Gruppe, die ein basisches Radikal enthält, oder (ii) aus einer basischen Gruppe, die ein acyliertes basisches Radikal aufweist; in welcher das basische Radikale aus der Gruppe bestehend aus den Gruppen von Amino, Imino, Amidino, N-Alkylamidinen, N,N'-Dialkylamidinen, N-Arylamidinen, Aminomethylenamino, Iminomethylamino, Guanidino, Aminoguanidino, Alkylamino, Dialkylamino, Trialkylamino, Alkylidenamino, Pyrrolyl, Imidazolyl, Pyrazolyl, Pyridyl, Pyrazin, Pyrimidin, Indolizinyl, Isoindolyl, 3H-Indolyl, Indolyl, 1H-Indazolyl, Purinyl, 4H-Quinolizinyl, Isoquinolyl, Quinolyl, Phthalazinyl, Naphthyridinyl, Quinoxalinyl, Amid, Thioamid, Benzamidino, Quinazolinyl, Cinnolinyl, Pteridinyl, 4aH-Carbozolyl, Carbozolyl, beta-Carbolinyl, Phenanthridinyl, Acridinyl, Pyrimidin, Phenanthrolinyl, Phenazinyl, Phenarsazinyl, Phenothiazinyl, Pyrrolinyl, Imidazolidinyl, Imidazolinyl, Pyrazolidinyl, Pyrazolinyl, Piperidin, Piperazin, Indolinyl, Isoindolinyl, Quinuclidinyl, Morpholinyl und gleich welche der vorhergehenden Gruppen substituiert mit den Gruppen Amino, Imino, Amidino, Aminomethylenamino, Iminomethylamino, Guanidino, Alkylamino, Alkylamino, Trialkylamino oder Alkylidenamino ausgewählt wird; und

R_{13} wird (i) aus einer sauren Gruppe, die ein saures Radikal enthält, oder (ii) aus einer sauren Gruppe, die ein Esterderivat eines sauren Radikals enthält, ausgewählt ;

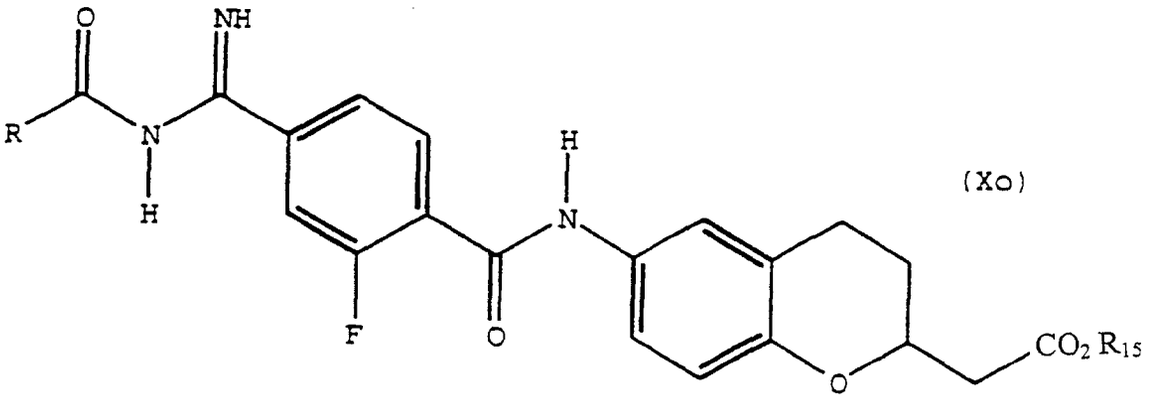
unter der Voraussetzung, daß Q_2 eine basische Gruppe ist, welche ein acyliertes basisches Radikal enthält oder, daß R_{13} eine saure Gruppe ist, welche ein Esterderivat eines sauren Radikals enthält.

17. Verbindung gemäß Patentanspruch 16, bei welcher der acylierte Anteil des basischen Radikals die folgende Formel aufweist:

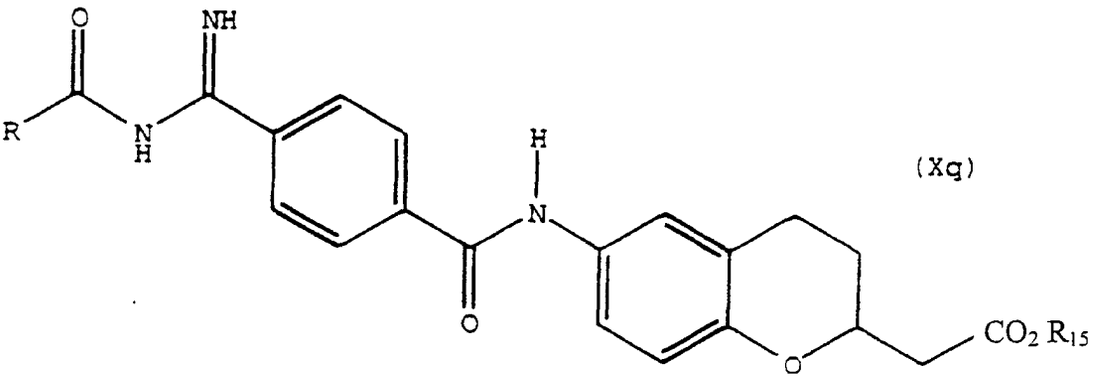


in welcher R für Alkyl C_1-C_8, Alkenyl C_2-C_8, Aryl, substituiertes Aryl C_7-C_{12} und Arylalkyl C_7-C_{12} steht; und X eine Bindung, C, O, S oder N ist.

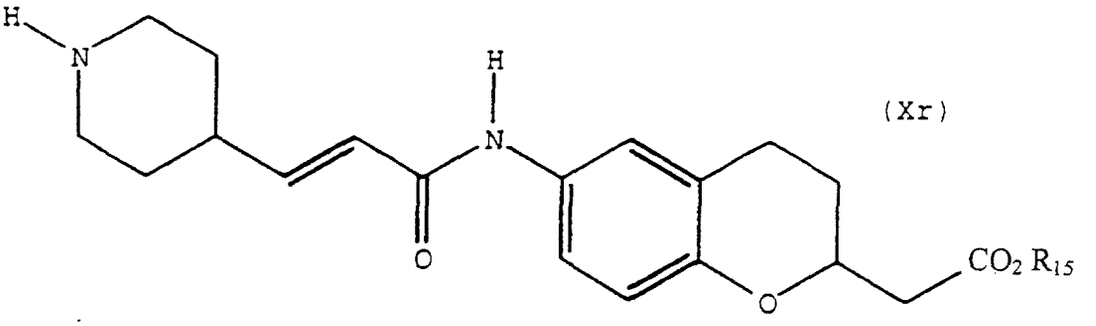
18. Verbindung eines Prodrugderivats, welche aus der Gruppe bestehend aus den Verbindung ausgewählt wird, welche durch die nachstehenden Formeln (Xo), (Xq) und (Xr) dargestellt sind:



(Xo)



(Xq)



(Xr)

in welchen,

R = -H, -OMe, -OEt, -OPr,
X = -Cl, -F, -H,
R_{15} = Me, Et, Pr.

19. Plättchenaggregation verhindernde pharmazeutische Formulierung mit:

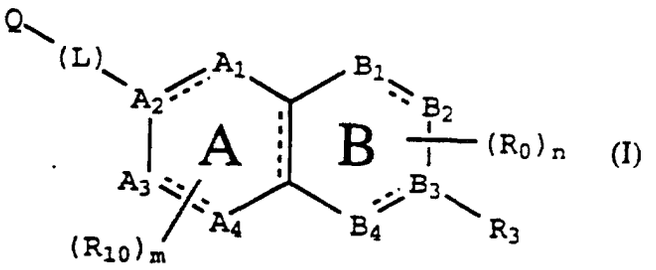
(i) einer therapeutisch wirksamen Plättchenaggregation verhindernden Menge einer bicyclischen Verbindung gemäß Patentanspruch 16; und

(ii) einem pharmazeutisch zulässigen Träger oder einem Verdünnungsmittel für diesen Träger.

20. Prodrugderivat gemäß Patentanspruch 16, für eine Anwendung die es erlaubt, die pathologischen Auswirkungen bei einer Atherosklerose und einer Arteriosklerose, einem akuten Myokardinfarkt, einer stabilen chronischen Angina, einer instabilen Angina, transitorischen ischämischen Attacken und Schlaganfällen, einer peripheren Verschlusskrankheit, einem arteriellen Thrombus, einer Präeklampsie, einer Embolie, einer auf eine Angioplastie folgende Restenose, eine Endarteriektomie der Halsschlagader und einer Anastomose von Gefäßtransplantaten zu erleichtern.

Revendications

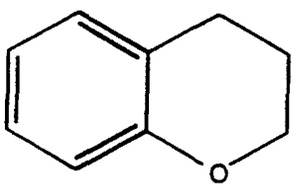
1. Composé bicyclique comprenant un noyau formé à partir de deux cycles condensés à six membres, A et B, représenté par la formule (I) ou un sel, un solvate ou un dérivé de promédicament pharmaceutiquement acceptables de celui-ci:



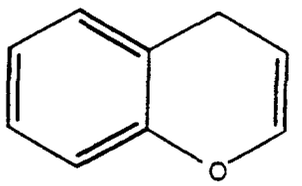
(I)

dans laquelle:

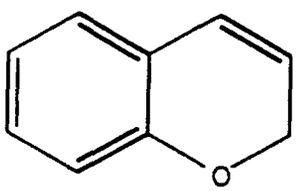
le noyau bicyclique des cycles A et B est choisi dans le groupe constitué des formules (17) à (21) ci-dessous:



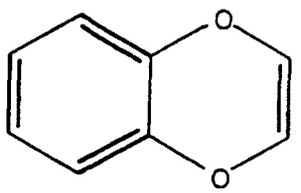
(17),



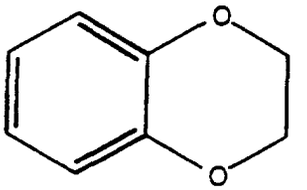
(18).



(19),



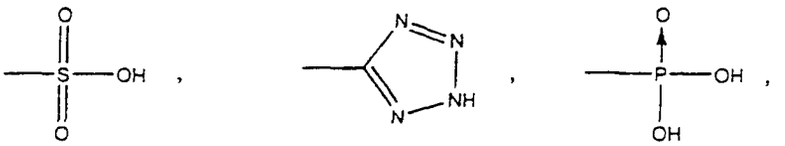
(20).

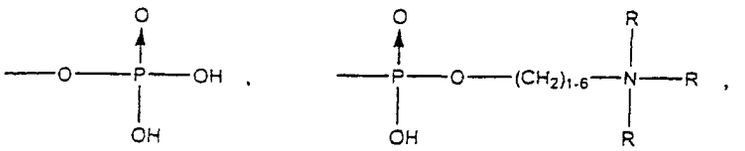


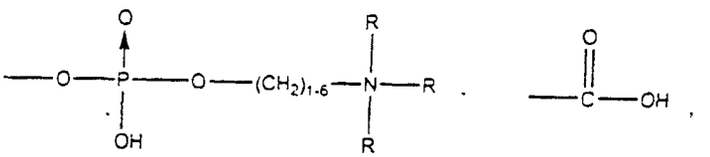
(21)

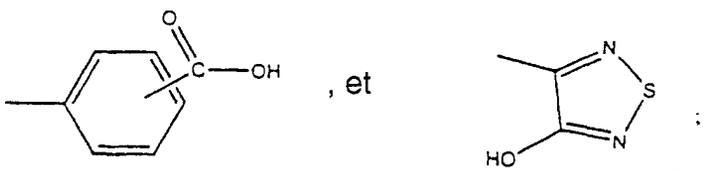
;

R_3 est un groupe organique comprenant un radical acide choisi dans le groupe constitué des formules suivantes:









, et

;

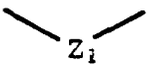
n est un nombre de 1 à 5;

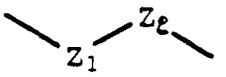
R_0 sont indépendamment choisis parmi un hydrogène, un groupe alkyle C_{1-10}, alkyle C_{1-10} halosubstitué, alcényle C_{2-10}, alcynyle C_{2-10}, cycloalkyle C_{3-10}, aryle C_{6-18}, arylalkyle C_{6-12}, hydroxy, alkoxy C_{1-10}, aralkoxy C_{6-12}, amino, amino substitué, carbamoyle, carboxy, acyle, cyano, halo, nitro, sulfo, =O et =S;

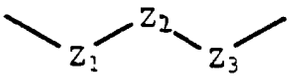
m est 3;

R_{10} sont indépendamment choisis parmi un hydrogène, un groupe alkyle C_{1-10}, alkyle C_{1-10} halosubstitué, alcényle C_{2-10}, alcynyle C_{2-10}, cycloalkyle C_{3-10}, aryle C_{6-18}, arylalkyle C_{6-12}, hydroxy, alkoxy, aralkoxy C_{6-12}, carboxy, acyle, cyano, halo, nitro et sulfo;

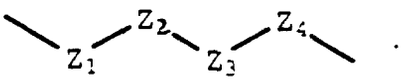
le groupe de liaison -(L)- est une liaison ou une chaîne divalente substituée ou non substituée de 1 à 4 atomes choisie dans le groupe constitué de:







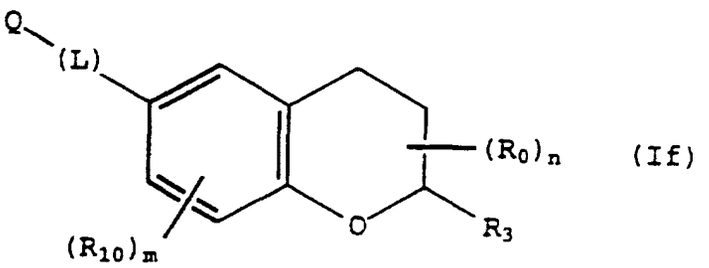
et



dans laquelle les atomes Z_1, Z_2, Z_3 et Z_4 sont indépendamment choisis dans le groupe constitué de carbone, azote, soufre et oxygène; et

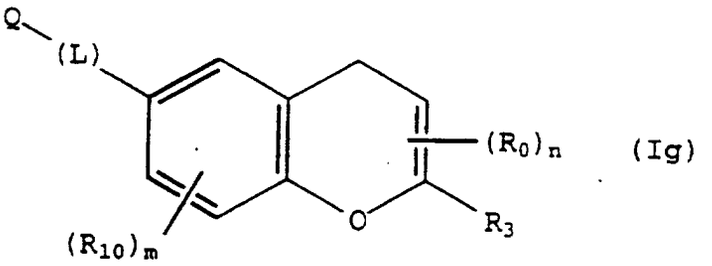
Q est un groupe basique contenant un ou plusieurs radicaux basiques choisis dans le groupe constitué de groupes amino, imino, amidino, N-alkylamidines, N,N'-dialkylamidines, N-arylamidines, aminométhylèneamino, iminométhylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylidèneamino, pyrrolyle, imidazolyle, pyrazolyle, pyridyle, pyrazinyle, pyrimidinyle, indolizinyle, isoindolyle, 3H-indolyle, indolyle, 1H-indazolyle, purinyle, 4H-quinolizinyle, isoquinolyle, quinolyle, phtalazinyle, naphtyridinyle, quinoxalinyle, amide, thioamide, benzamidino, quinazolinyle, cinnolinyle, ptéridinyle, 4aH-carbozolyle, carbozolyle, bêta-carbolinyle, phénanthridinyle, acridinyle, pyrimidinyle, phénanthrolinyle, phénazinyle, phénarsazinyle, phénothiazinyle, pyrrolinyle, imidazolidinyle, imidazolinyle, pyrazolidinyle, pyrazolinyle, pipéridyle, pipérazinyle, indolinyle, isoindolinyle, quinuclidinyle, morpholinyle et n'importe lequel des groupes précédents substitués avec des groupes amino, imino, amidino, aminométhylèneamino, iminométhylamino, guanidino, alkylamino, dialkylamino, trialkylamino ou alkylidèneamino.

2. Composé suivant la revendication 1, représenté par la formule (If):



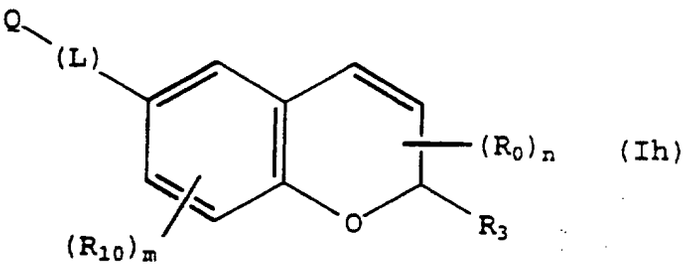
(If)

3. Composé suivant la revendication 1, représenté par la formule (Ig):



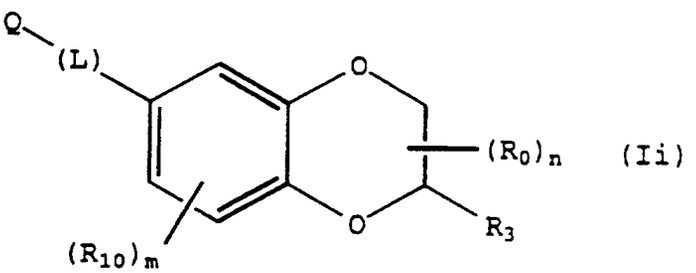
(Ig)

4. Composé suivant la revendication 1, représenté par la formule (Ih):



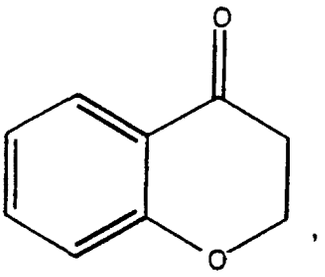
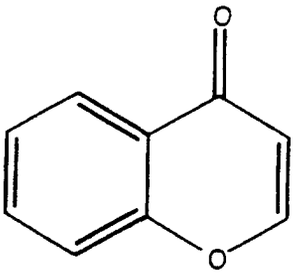
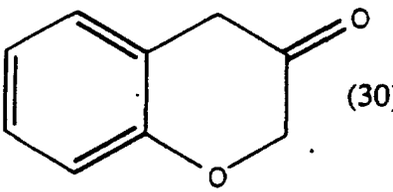
(Ih)

5. Composé suivant la revendication 1, représenté par la formule (Ii):

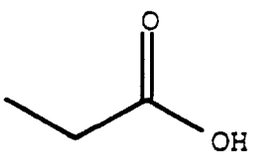
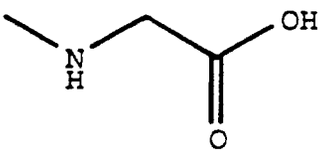
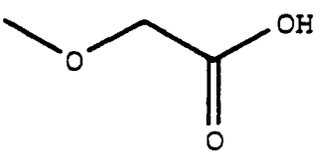
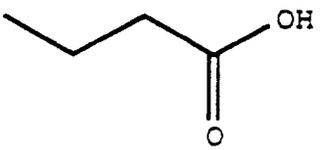
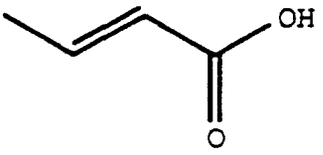
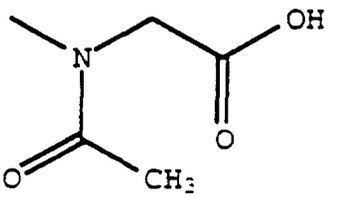
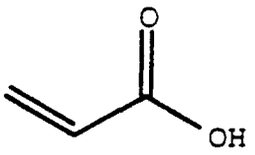
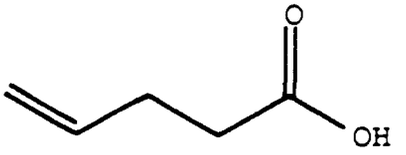


(Ii)

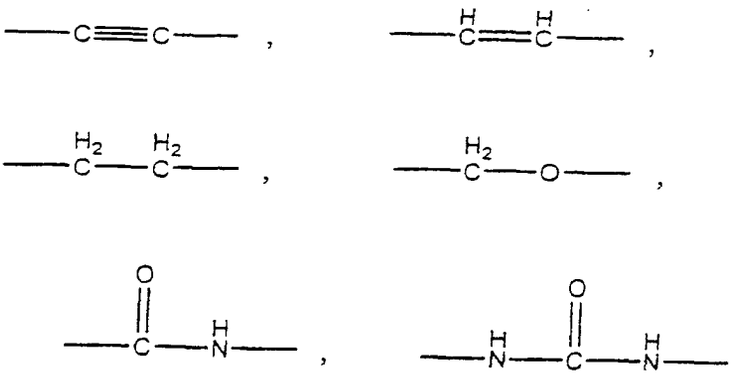
6. Composé suivant la revendication 1, dans lequel le noyau bicyclique substitué par un groupe oxo de cycles A et B est choisi dans le groupe constitué des formules (28) à (30) ci-dessous:


(28),

(29),

(30).

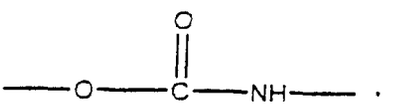
7. Composé suivant la revendication 1, dans lequel les radicaux acides dans R_3 sont choisis dans le groupe:


,

,

,

,

,

,

,

et
.

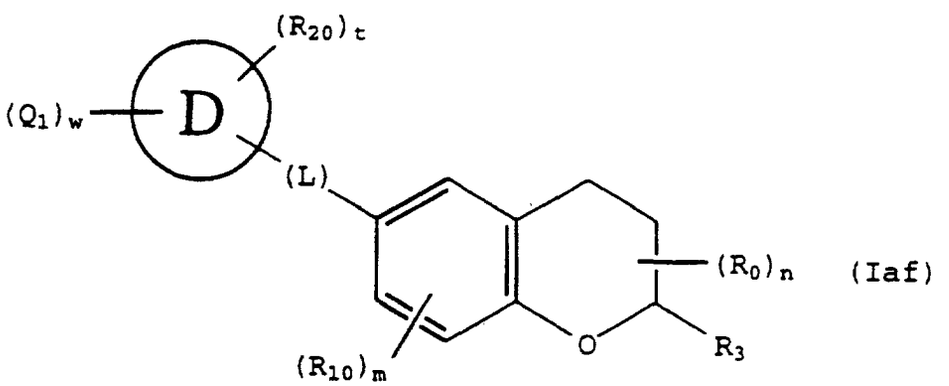
8. Composé suivant la revendication 1, dans lequel le groupe de liaison est choisi parmi les formules:



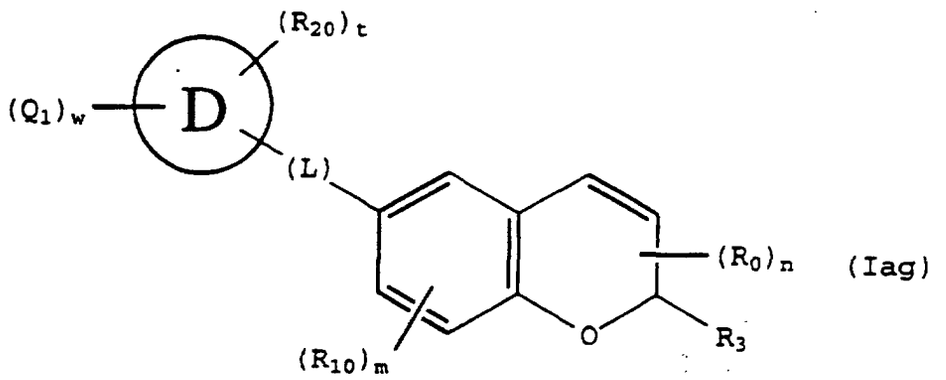
et

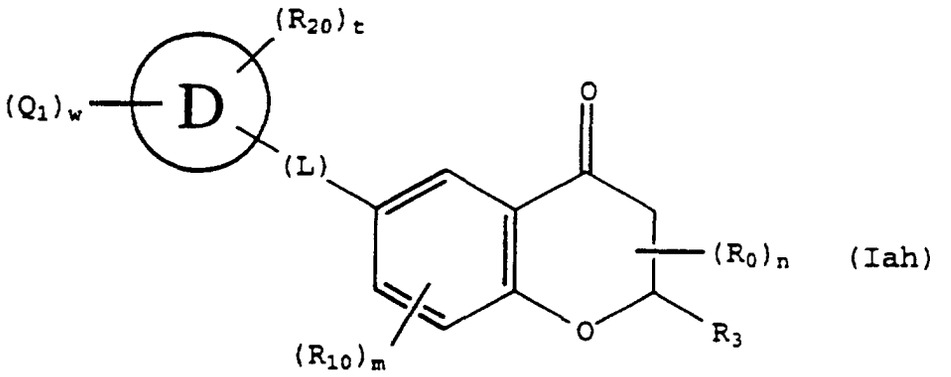


9. Composé bicyclique ou un sel, un solvate ou un dérivé de promédicament pharmaceutiquement acceptables de celui-ci, comprenant un noyau formé à partir de deux cycles condensés à six membres, choisi parmi les formules (Iaf), (Iag) et (Iah) ci-dessous:



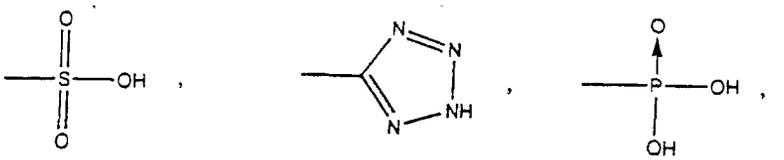
(Iaf)

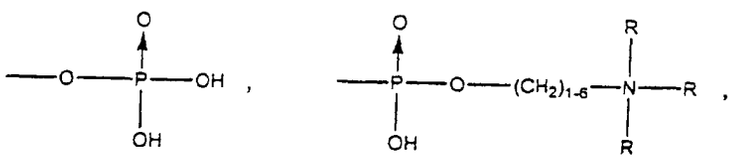


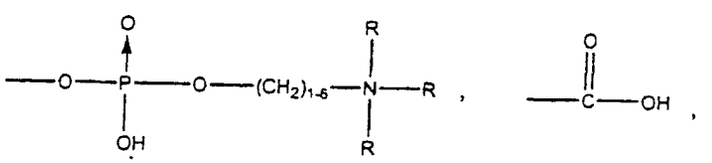


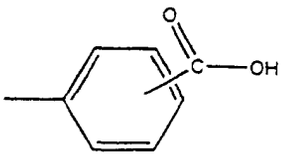
dans lesquelles:

R_3 est un groupe organique comprenant un radical acide choisi dans le groupe constitué des formules suivantes:

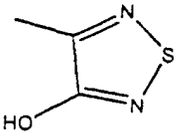








, et



;

n est un nombre de 1 à 5;

R_0 sont indépendamment choisis parmi un hydrogène, un groupe alkyle C_{1-10}, alkyle C_{1-10} halosubstitué, alcényle C_{2-10}, alcynyle C_{2-10}, cycloalkyle C_{3-10}, aryle C_{6-18}, arylalkyle C_{6-12}, hydroxy, alkoxy C_{1-10}, aralkoxy C_{6-12}, amino, amino substitué, carbamoyle, carboxy, acyle C_{1-10}, cyano, halo, nitro, sulfo, =O et =S;

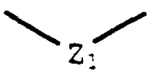
m est 3;

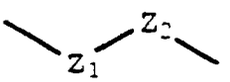
R_{10} sont indépendamment choisis parmi un hydrogène, un groupe alkyle C_{1-10}, alkyle C_{1-10} halosubstitué, alcényle C_{2-10}, alcynyle C_{2-10}, cycloalkyle C_{3-10}, aryle C_{6-18}, arylalkyle C_{6-12}, hydroxy, alkoxy, aralkoxy C_{6-12}, carboxy, acyle, cyano, halo, nitro et sulfo;

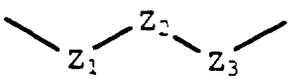
t est un nombre de 0 à 3;

R_{20} sont indépendamment choisis parmi un hydrogène, un groupe alkyle C_{1-10}, alkyle C_{1-10} halosubstitué, alcényle C_{2-6}, alcynyle, cycloalkyle, aryle C_{6-18}, arylalkyle, hydroxy, alkoxy, aralkoxy, carboxy, acyle, cyano, halo, nitro et sulfo;

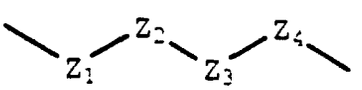
le groupe de liaison -(L)- est une liaison ou une chaîne divalente substituée ou non substituée de 1 à 4 atomes choisie dans le groupe constitué de:







et



.

dans laquelle les atomes Z_1, Z_2, Z_3 et Z_4 sont indépendamment choisis dans le groupe constitué de carbone, azote, soufre et oxygène et avec la condition supplémentaire que le groupe de liaison n'est pas CH_2 CH_2 CH_2O, CH_2 CH_2 CONH et CH_2 NHCO ; et

D est un cycle formé de 5 à 8 atomes de cycle et lesdits atomes de cycle sont indépendamment choisis parmi le carbone, l'azote, l'oxygène ou le soufre, sous réserve qu'au moins deux atomes du cycle D soient du carbone;

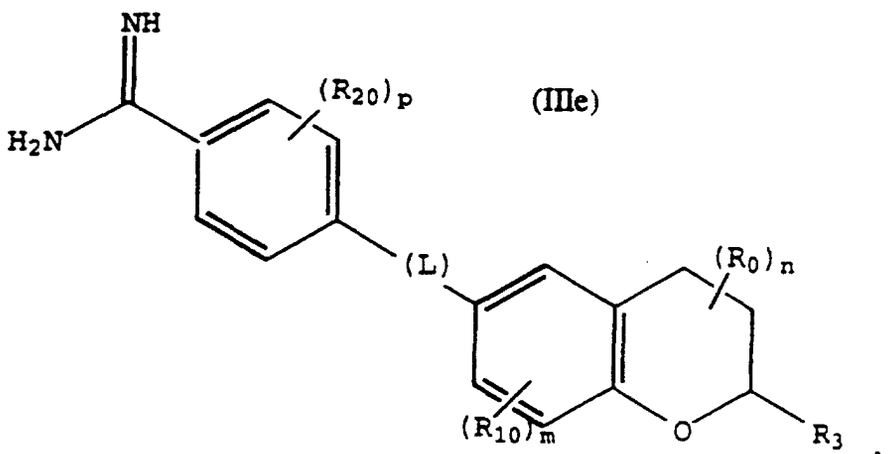
w est un nombre entier de 1 à 3; et

Q_1 est un radical basique choisi dans le groupe constitué de groupes amino, imino, amidino, aminométhylèneamino, iminométhylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylidèneamino, pyrrolyle, imidazolyle, pyrazolyle, pyridyle, pyrazinyle, pyrimidinyle, indolizinyle, isoindolyle, 3H-indolyle, indolyle, 1H-indazolyle, purinyle, 4H-quinolizinyle, isoquinolyle, quinolyle, phtalazinyle, naphtyridinyle, quinoxalinyle, quinazolinyle, cinnolinyle, ptéridinyle, 4aH-carbozolyle, carbozolyle, bêta-carbolinyle, phénanthridinyle, acridinyle, pyrimidinyle, phénanthrolinyle, phénazinyle, phénarsazinyle, phénothiazinyle, pyrrolinyle, imidazolidinyle, imidazolinyle, pyrazolidinyle, pyrazolinyle, pipéridyle, pipérazinyle, indolinyle, isoindolinyle, quinuclidinyle, morpholinyle et n'importe lequel des groupes précédents substitués avec des groupes amino, imino, amidino, aminométhylèneamino, iminométhylamino, guanidino, alkylamino, dialkylamino, trialkylamino ou alkylidèneamino.

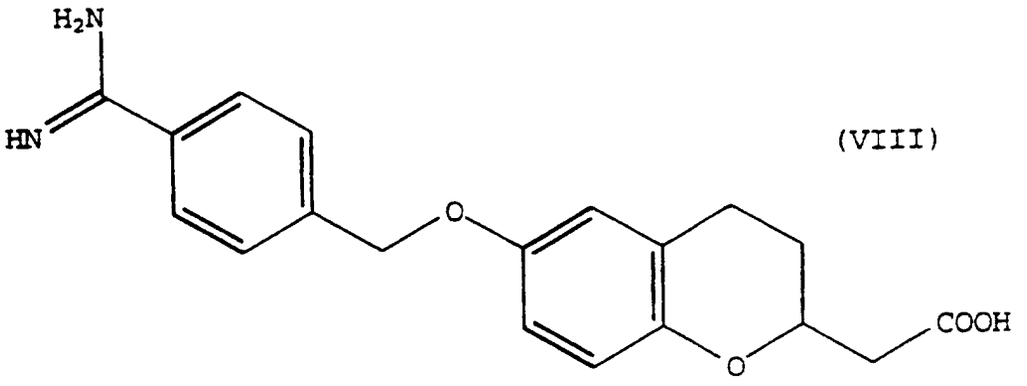
10. Composé suivant la revendication 9, dans lequel le cycle D est formé à partir d'un noyau choisi dans le groupe constitué de: benzène, cycloheptadiène, cycloheptatriène, cycloheptane, cyclohexane, cyclohexène, cyclohexadiène, cycloheptène, cyclooctadiène, cyclooctane, cyclooctatétraène, cyclooctène, cyclopentane, cyclopentène, imidazole, isooxazole, morpholine, oxazole, pipérazine, pipéridine, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, tétrahydropyridine, tétrahydropyrimidine, 1H-tétrazole, thiazolidine, thiazole, thiopyranne, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, dihydrofuranne, dihydropyranne, dioxanne, dioxépine, dioxolanne, furanne, oxocane, tétrahydrofuranne, tétrahydropyranne, thiophène et tétrahydrothiophène.

11. Composé suivant la revendication 9, dans lequel R_{20} est un chlore ou un fluor et t est égal à 1 ou 2.

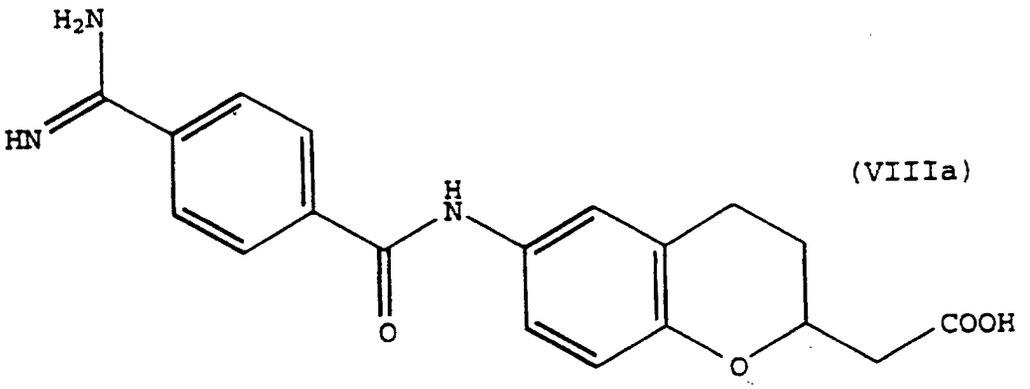
12. Composé suivant la revendication 1, contenant un noyau basé sur un benzopyranne comme représenté par la formule développée (IIIe):



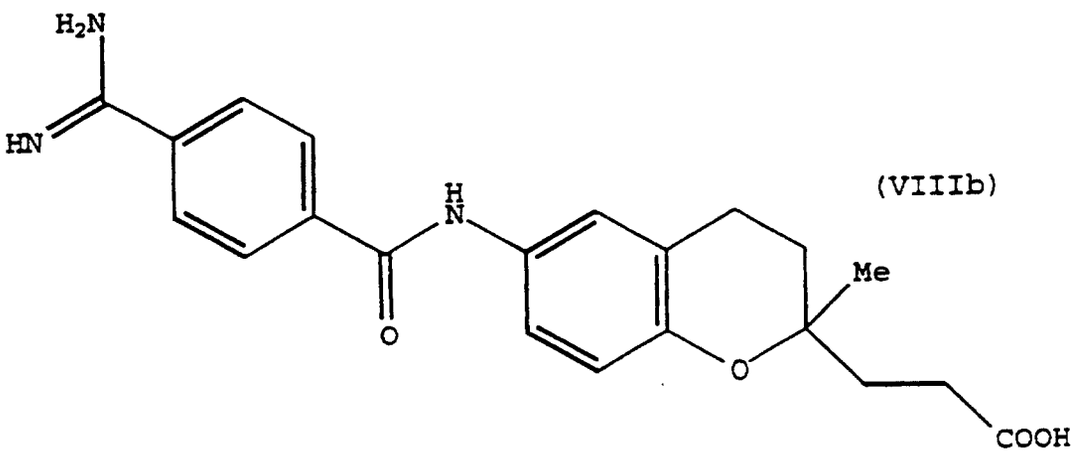
13. Composé choisi dans le groupe constitué de composés représentés par les formules (VIII) à (VIIIi) suivantes ou un sel, un solvate ou un dérivé de promédicament pharmaceutiquement acceptables de celui-ci:



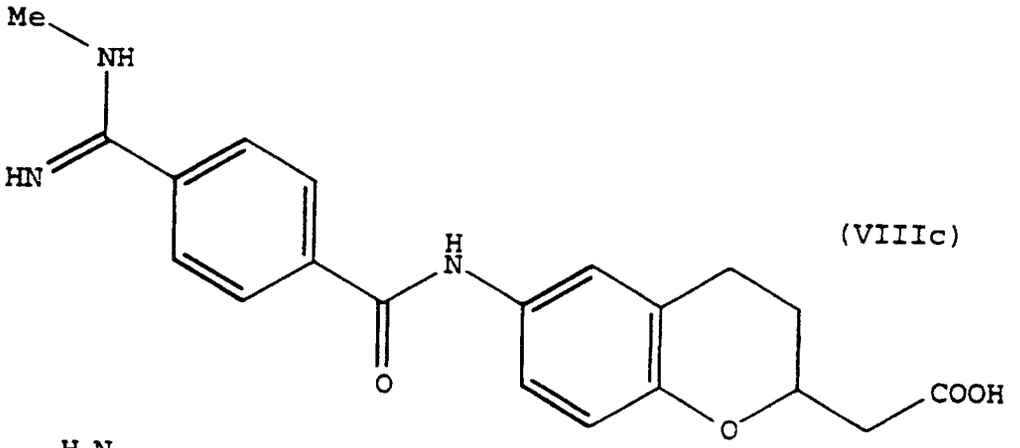
(VIII)



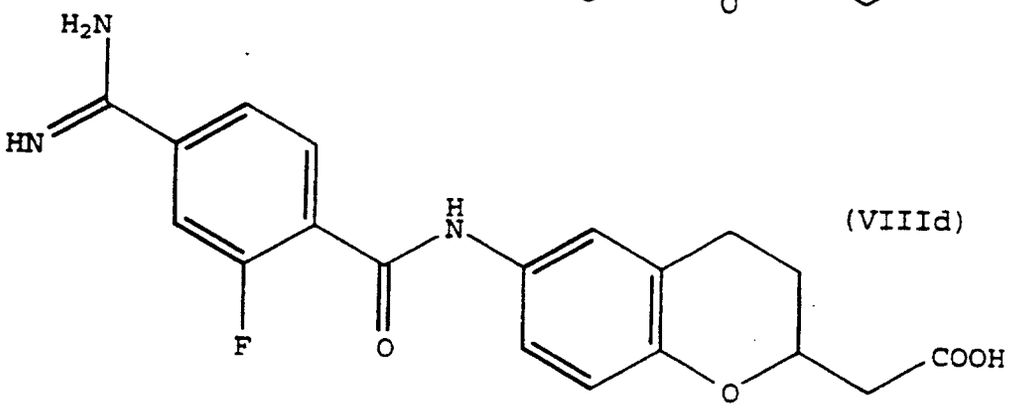
(VIIIa)



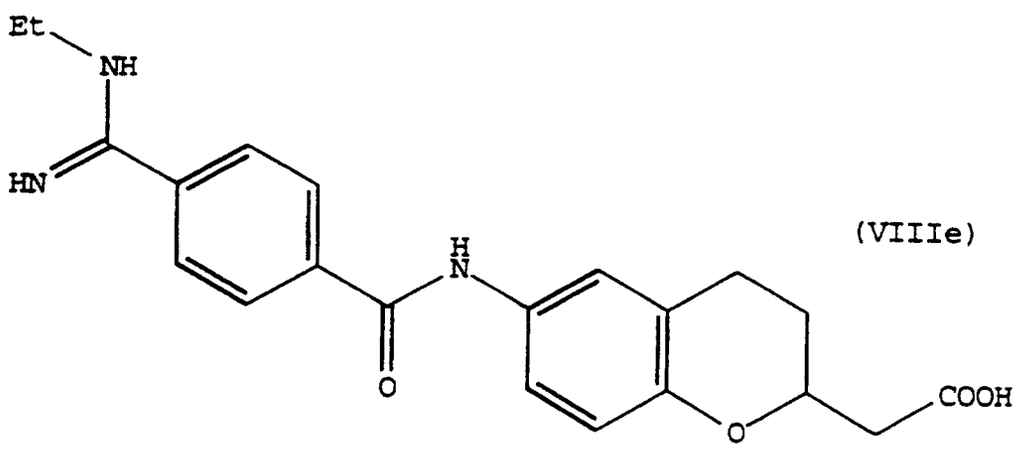
(VIIIb)



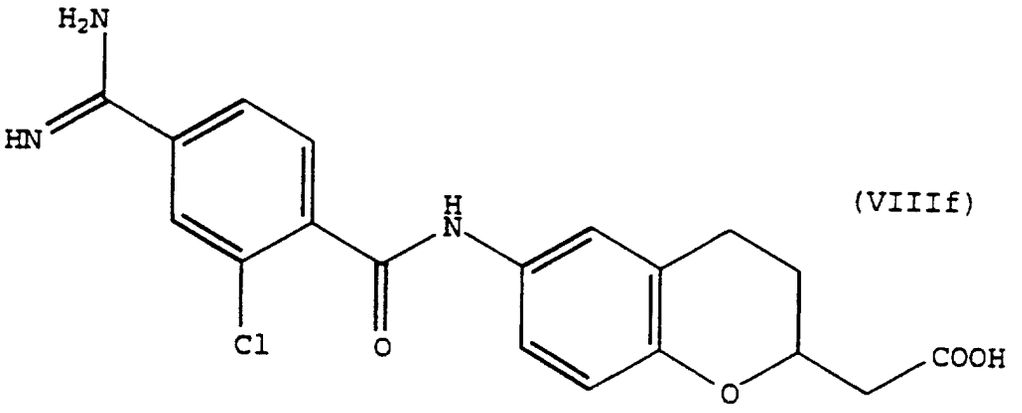
(VIIIc)



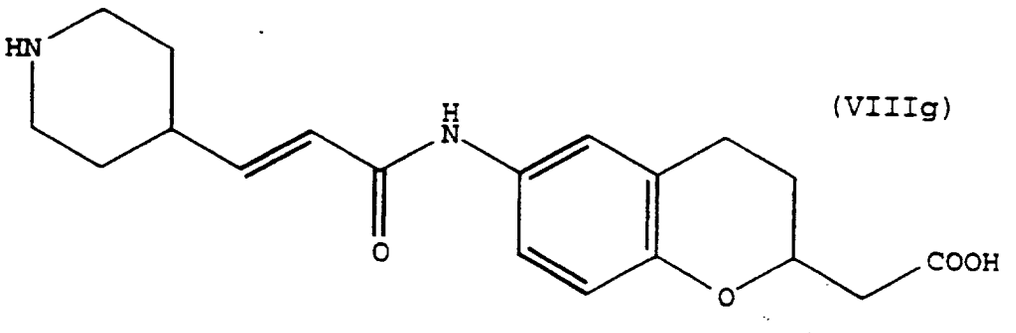
(VIIId)



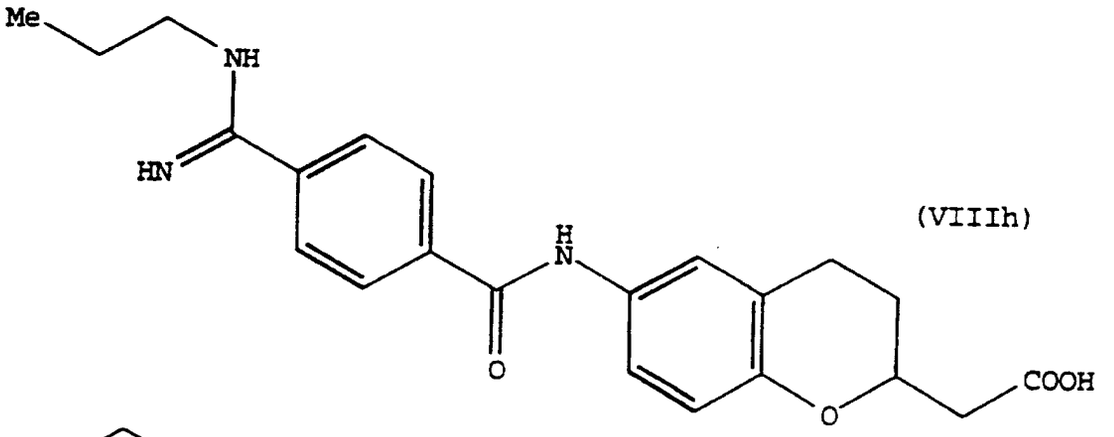
(VIIIe)



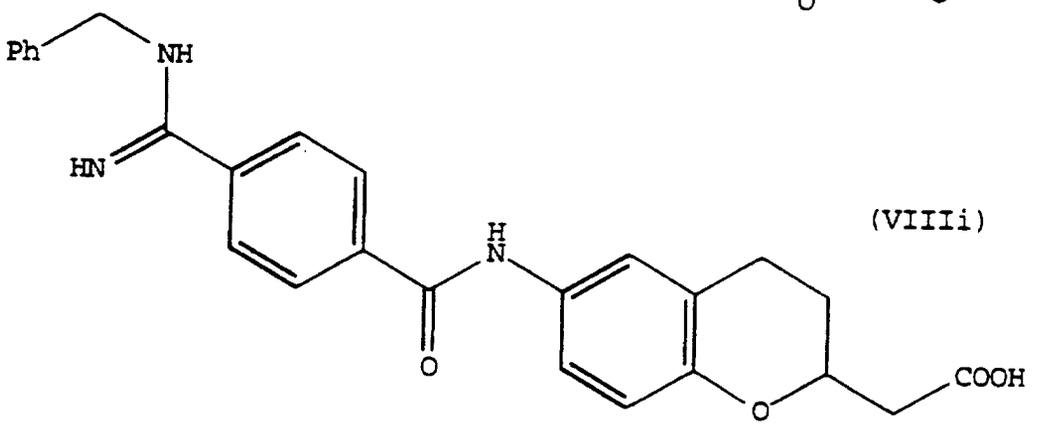
(VIIIf)



(VIIIg)



(VIIIh)



(VIIIi)

ou des mélanges de n'importe lesquels de (VIII) à (VIIIi).

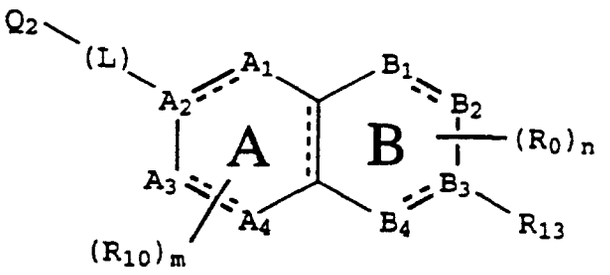
14. Formulation pharmaceutique inhibant l'agrégation plaquettaire comprenant:

(i) une quantité thérapeutiquement efficace inhibant l'agrégation plaquettaire d'un composé bicyclique suivant la revendication 1; et

(ii) un excipient pharmaceutiquement acceptable ou un diluant pour celui-ci.

15. Composé bicyclique selon la revendication 1, ou sel pharmaceutiquement acceptable de celui-ci, pour une utilisation permettant d'alléger les effets pathologiques d'une athérosclérose et d'une artériosclérose, d'un infarctus aigu du myocarde, d'une angine stable chronique, d'une angine instable, d'accidents et d'attaques ischémiques transitoires, d'un acrosyndrome, d'une thrombose artérielle, d'une pré-éclampsie, d'embolies, d'une resténose à la suite d'une angioplastie, d'une endartériectomie de la carotide et d'une anastomose de prothèses vasculaires.

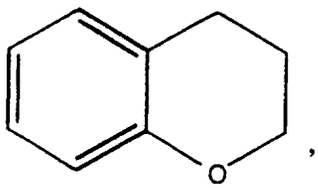
16. Dérivé de promédicament d'un composé bicyclique comprenant un noyau formé à partir de deux cycles condensés à six membres, A et B, représenté par la formule (Xd) :



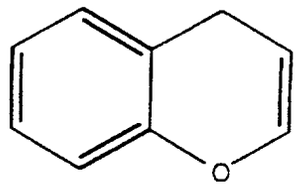
(Xd)

dans laquelle:

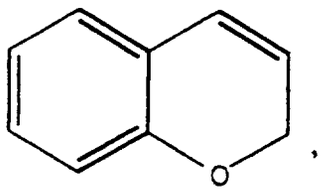
le noyau bicyclique des cycles A et B est choisi dans le groupe constitué des formules (17) à (21) ci-dessous:



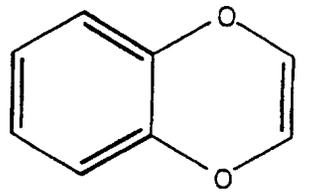
(17),



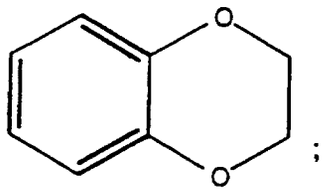
(18).



(19),



(20).



(21);

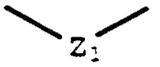
n est un nombre de 1 à 5;

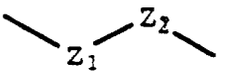
R_0 sont indépendamment choisis parmi un hydrogène, un groupe alkyle C_{1-10}, alkyle C_{1-10} halosubstitué, alcényle C_{2-10}, alcynyle C_{2-10}, cycloalkyle C_{3-10}, aryle C_{6-18}, arylalkyle C_{6-12}, hydroxy, alkoxy C_{1-10}, aralkoxy C_{6-12}, amino, amino substitué, carbamoyle, carboxy, acyle, cyano, halo, nitro, sulfo, =O et =S;

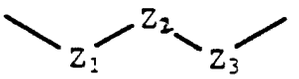
m est 3;

R_{10} sont indépendamment choisis parmi un hydrogène, un groupe alkyle C_{1-10}, alkyle C_{1-10} halosubstitué, alcényle C_{2-10}, alcynyle C_{2-10}, cycloalkyle C_{3-10}, aryle C_{6-18}, arylalkyle C_{6-12}, hydroxy, alkoxy, aralkoxy C_{6-12}, carboxy, acyle, cyano, halo, nitro et sulfo;

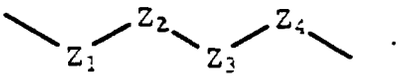
le groupe de liaison -(L)- est une liaison ou une chaîne divalente substituée ou non substituée de 1 à 4 atomes choisie dans le groupe constitué de:







et



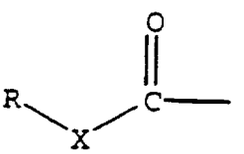
dans laquelle les atomes Z_1, Z_2, Z_3 et Z_4 sont indépendamment choisis dans le groupe constitué de carbone, azote, soufre et oxygène; et

Q_2 est choisi parmi (i) un groupe basique comprenant un radical basique; ou (ii) un groupe basique comprenant un radical basique acylé; dans lequel le radical basique est choisi dans le groupe d'amino, imino, amidino, N-alkylamidines, N,N'-dialkylamidines, N-arylamidines, aminométhylèneamino, iminométhylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylidèneamino, pyrrolyle, imidazolyle, pyrazolyle, pyridyle, pyrazinyle, pyrimidinyle, indolizinyle, isoindolyle, 3H-indolyle, indolyle, 1H-indazolyle, purinyle, 4H-quinolizinyle, isoquinolyle, quinolyle, phtalazinyle, naphtyridinyle, quinoxalinyle, amide, thioamide, benzamidino, quinazolinyle, cinnolinyle, ptéridinyle, 4aH-carbozolyle, carbozolyle, bêta-carbolinyle, phénanthridinyle, acridinyle, pyrimidinyle, phénanthrolinyle, phénazinyle, phénarsazinyle, phénothiazinyle, pyrrolinyle, imidazolidinyle, imidazolinyle, pyrazolidinyle, pyrazolinyle, pipéridyle, pipérazinyle, indolinyle, isoindolinyle, quinuclidinyle, morpholinyle et n'importe lequel des groupes précédents substitués avec des groupes amino, imino, amidino, aminométhylèneamino, iminométhylamino, guanidino, alkylamino, dialkylamino, trialkylamino et alkylidèneamino; et

R_{13} est choisi parmi (i) un groupe acide comprenant un radical acide, ou (ii) un groupe acide comprenant un dérivé d'ester d'un radical acide;

sous réserve que Q_2 soit un groupe basique contenant un radical basique acylé ou que R_{13} soit un groupe acide contenant un dérivé d'ester d'un radical acide.

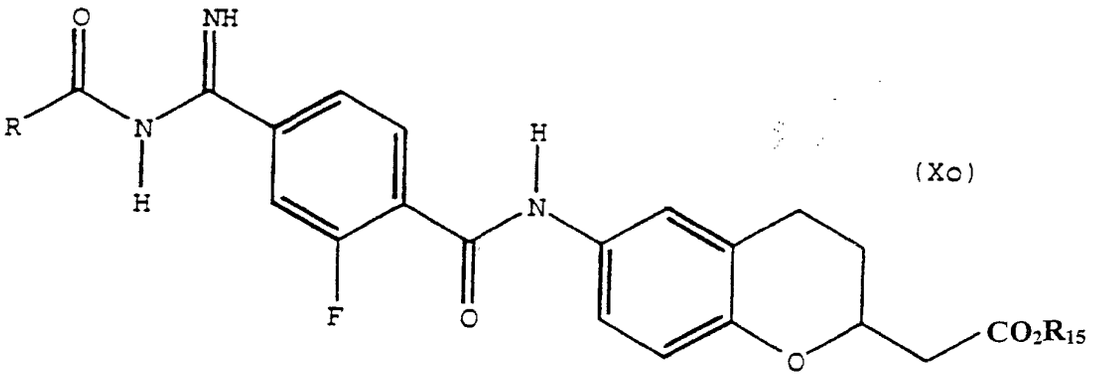
17. Composé suivant la revendication 16, dans lequel la portion acylée du radical basique acylé présente la formule:



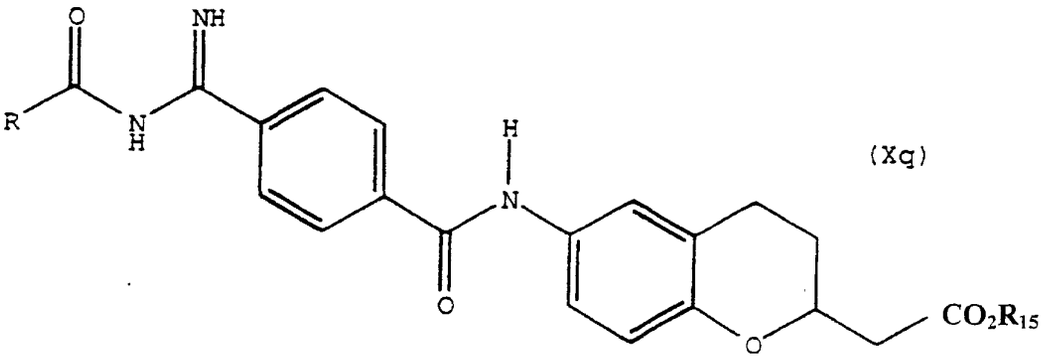
dans laquelle R est un groupe alkyle C_1-C_8, alcényle C_2-C_8, aryle, aryle C_7-C_{12} substitué et arylalkyle C_7-C_{12}; et

X est une liaison, C, O, S ou N.

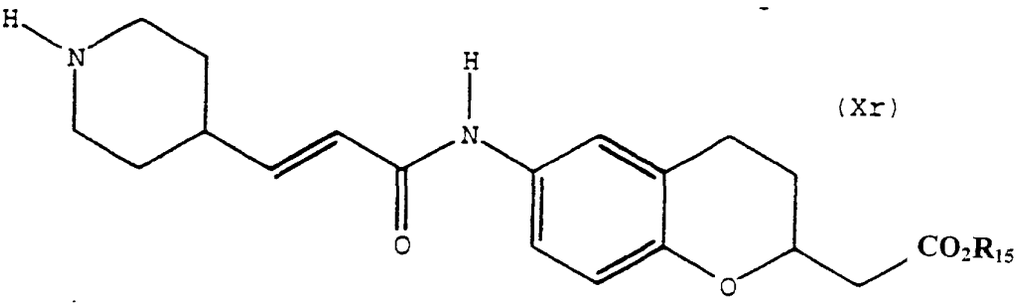
18. Composé dérivé de promédicament choisi dans le groupe constitué de composés représentés par les formules (Xo), (Xq) et (Xr) ci-dessous:



(Xo)



(Xq)



(Xr)

dans lesquelles, R = -H, -OMe, -OEt, -OPr,

X = -Cl, -F, -H,

R_{15} = Me, Et, Pr.

19. Formulation pharmaceutique inhibant l'agrégation plaquettaire comprenant:

(i) une quantité thérapeutiquement efficace inhibant l'agrégation plaquettaire d'un composé bicyclique selon la revendication 16; et

(ii) un excipient pharmaceutiquement acceptable ou un diluant pour celui-ci.

20. Dérivé de promédicament selon la revendication 16, pour une utilisation permettant d'alléger les effets pathologiques d'une athérosclérose et d'une artériosclérose, d'un infarctus aigu du myocarde, d'une angine stable chronique, d'une angine instable, d'accidents et d'attaques ischémiques transitoires, d'un acrosyndrome, d'une thrombose artérielle, d'une pré-éclampsie, d'embolies, d'une resténose à la suite d'une angioplastie, d'une endartériectomie de la carotide et d'une anastomose de prothèses vasculaires.