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(54) **Sulfonamide derivatives with elastase inhibiting activity**

Sulfonamide mit Elastase inhibierender Wirkung

Dérivés sulfonamide ayant une activité inhibitrice vis-à-vis de l'élastase humaine

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EP-A- 0 484 949

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WO-A-93/11760

- **TRENDS IN PHARMACOLOGICAL SCIENCE**, vol. 8, August 1987, AMSTERDAM, pages 303-307, XP002024127 TRAINOR, D.A.: "Synthetic inhibitors of human neutrophil elastase"
- **ANNU.REP.MED.CHEM.**, vol. 29, 1994, NEW YORK, pages 195-204, XP000650529 HLASTA, D.J. ET AL.: "Human Leukocyte Elastase Inhibitors"

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

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EP 0 769 498 B9

Description

[0001] This invention relates to sulfonamide derivatives useful as pharmaceuticals. More particularly, this invention relates to:

- (1) sulfonamide derivatives of formula (I) as hereinafter defined, and non-toxic salts, acid addition salts and solvates thereof,
- (2) processes for their preparation, and
- (3) pharmaceutical compositions containing them as active ingredient.

[0002] Lysosomal hydrolases of neutrophils have an important role in the defence reaction of organisms against tissue damage caused, for example, by microbes or inflammation.

[0003] Elastase and cathepsin G, which are neutral serine proteinases existing locally in azurophil granules, play a part in the decomposition of connective tissue.

[0004] In particular, elastase degrades elastic connective tissue by cleaving the cross-linking of elastin which directly maintains the elasticity of e.g. lung tissue, by cleaving the hydrophobic part of protein [J. Cell. Biol., 40, 366 (1969)] and selectively degrading the cross-linking of collagen as well as elastin [J. Biochem., 84, 559 (1978)]. It also acts on tissue proteins such as proteoglycans [J. Clin. Invest., 57, 615 (1976)]. It will be seen therefore that elastase plays an important role in the metabolism of connective tissue.

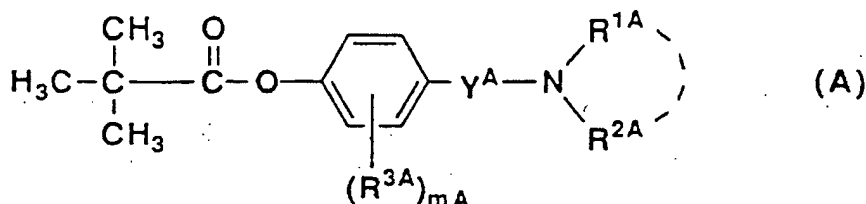
[0005] Elastase is inactivated by α_1 -proteinase inhibitor (α_1 -PI) which is a common inhibitor for serine proteinases *in vivo* and an imbalance of enzyme and inhibitor causes the destruction of tissue [Schweiz. Med. Wshr., 114, 895 (1984)].

[0006] The turnover of elastin in normal tissue is very slow [Endocrinology, 120, 92 (1978)], but pathological acceleration in degradation of elastin is found under various diseased conditions such as pulmonary emphysema [Am. Rev. Respir. Dis., 110, 254 (1974)], atherosclerosis [Lab. Invest., 22, 228 (1970)] and rheumatoid arthritis [in Neutral Proteinases of Human Polymorphonuclear Leukocytes, Urban and Schwarzenberg, Baltimore - Munich (1978), page 390], which suggests a relationship between elastase and diseases [Infection Inflammation Immunity, 13, 13 (1983)].

[0007] In view of this background, many studies on the development of elastase inhibitors have been conducted recently, and various substances inhibiting elastase have been proposed and many patent applications have been filed.

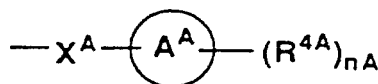
[0008] For example,

- (1) it is disclosed in EP-A-0347168 that the compound of formula (A)



(wherein Y^A is sulfonyl or carbonyl;

- (i) R^{1A} and R^{2A}, which may be the same or different, each represent, inter alia, hydrogen atom, C1-16 alkyl or a group of the formula



(wherein X^A is bond, sulfonyl, C1-4 alkylene, C1-4 alkyl substituted by -COOH or benzyloxycarbonyl;

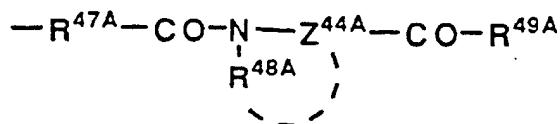


is carbocyclic ring or heterocyclic ring;

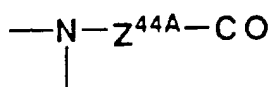
nA is 1-5; and

R^{4A} which may be the same or different, represent,

inter alia, hydrogen atom, C1-8 alkyl, C1-14 alkoxy, C1-6 alkylthio, hydroxy, halogen atom, nitro, trihalomethyl, -Z^{41A}-COOR^{43A}, -CONR^{41A}R^{42A}, a group of the formula



in which the group of formula



is an amino acid residue;

R^{49A} is hydroxy, C1-4 alkoxy, amino, amino or carbamoyl substituted by one or two C1-4 alkyl, etc.) or

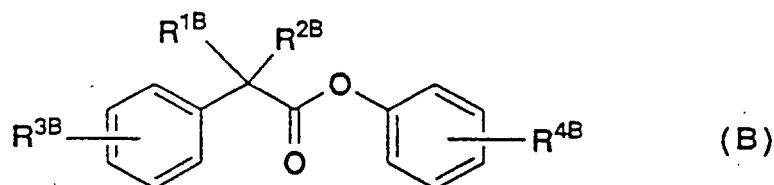
(ii) R^{1A} and R^{2A} and the nitrogen atom bonded to R^{1A} and R^{2A} together represent a heterocyclic ring containing at least one nitrogen atom and substituted by -COOH or an unsubstituted heterocyclic ring containing at least one nitrogen atom;

R^{3A} is hydrogen atom, hydroxy, C1-6 alkyl, etc.; and

mA is 1-4)

and non-toxic salts and acid addition salts thereof have an inhibitory activity on elastase;

(2) it is disclosed in EP-A-0465802 that the compound of formula (B)



(wherein R^{1B} and R^{2B}, which may be the same or different, each represent, hydrogen, C1-6 alkyl or C3-6 cycloalkyl, or R^{1B} and R^{2B} taken together represent -(CH₂)_{nB}- (in which nB is 1-6);

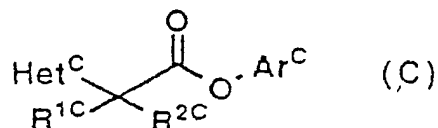
R^{3B} is one to five of hydrogen, halogen, C1-12 haloalkyl, C1-12 alkyl, C1-12 alkoxy, C2-12 alkenyl, C3-12 cycloalkyl, mono or bicyclic aryl, -Z^BR^{5B} (in which Z^B is O, S, S(O) or SO₂; R^{5B} is hydrogen, C1-18 alkyl, C3-12 cycloalkyl, or phenyl), -NR^{6B}R^{7B} (in which R^{6B} and R^{7B}, which may be the same or different, each represent hydrogen, C1-12 alkyl, C3-6 cycloalkyl, phenyl, C1-12 alkoxy or -C(O)-R^{3B}, or R^{6B} and R^{7B} taken together represent -C(O)CH₂CH₂-C(O)-, -C(O)-C₆H₄-C(O)- or -(CH₂)_{xB}- (XB is 2, 3, 4, 5 or 6)), or

morpholino, imidazolyl or piperazino, etc., bonded to phenyl ring on nitro atom; and

R^{4B} is one to five of hydrogen, halogen, nitro, -C(O)CH₃, S(O)_{pB}R^{9B} (pB is 0, 1 or 2; R^{9B} is hydroxy, -ONa, C1-12 alkyl optionally substituted, cycloalkyl optionally substituted))

and non-toxic pharmaceutically acceptable salts thereof have an inhibitory activity on elastase;

(3) it is disclosed in EP-A-0484949 that the compound of formula (C)



(wherein R^{1C} and R^{2C} , which may be the same or different, each represent hydrogen, C1-6 alkyl or C3-6 cycloalkyl, or R^{1C} and R^{2C} taken together represent - $(\text{CH}_2)_{\text{nC}}$ - (in which nC is 1-6); Ar^{C} is optionally substituted phenyl; and Het^{C} is heterocyclic ring containing at least one nitrogen atom, sulfur atom or oxygen atom) have an inhibitory activity on elastase.

[0009] WO-A-93/11760 discloses a class of aromatic esters of phenylenedialkanoates as inhibitors of human neutrophil elastase.

[0010] EP-A-0539223 discloses a glycine derivative monosodium salt tetrahydrate having an inhibitory effect on elastase.

[0011] EP-A-0222608 discloses a class of derivatives of p-guanidinobenzoic acid which have an inhibitory effect on elastase.

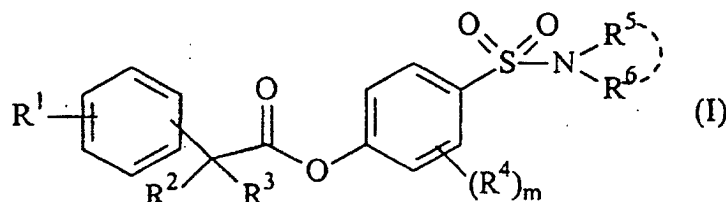
[0012] Synthetic inhibitors of human neutrophil elastase are discussed in Trends in Pharmacological Science, 8, 303-307 (1987).

[0013] Human leukocyte elastase inhibitors are discussed in Annu. Rep. Med. Chem., 29, 195-204 (1994).

[0014] Few of the compounds known to have an inhibitory activity on elastase have been reported to show an inhibitory activity on elastase by oral administration. Most compounds could not be expected to show an effect by oral administration. In order to show activity by oral administration, pharmaceutical agents must be readily absorbed by the digestive organs and must maintain their activity until they are transported to an active site. Therefore, only those compounds having good stability, absorbability and/or solubility in the digestive organs are expected to show sufficient activity by oral administration.

[0015] Energetic investigations have been carried out to find new compounds having good inhibitory activity on elastase and also having high safety. As a result, the present inventors have found that these aims may be accomplished by sulfonamide derivatives of the formula (I). Further, we have found that the new compounds have good stability, absorbability and solubility and are active as elastase inhibitors by oral administration.

[0016] The present invention provides a sulfonamide derivative of formula (I):

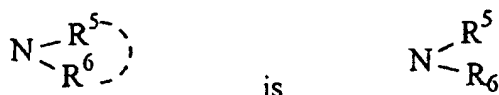


wherein R^{1} is pyrrolidinyl;

R^{2} and R^{3} each, independently, is hydrogen atom or C1-4 alkyl;

R^{4} is C1-4 alkyl;

m is an integer from 0 to 4; and



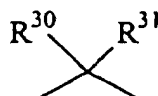
in which R^{5} and R^{6} each, independently, is

1) hydrogen atom,

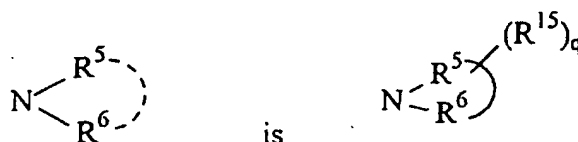
- 2) hydroxy,
- 3) C1-8 alkyl,
- 4) C1-8 alkoxy,
- 5) -M-R¹⁶

(in which M is single bond or C1-8 alkylene), and R¹⁶ is

5-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one to four nitrogen atoms, one or two oxygen atoms or one nitrogen atom and one sulfur atom or oxygen atom, unsubstituted or substituted by 1 to 4 substituents selected from C1-4 alkyl, C1-4 alkoxy, hydroxy, phenyl C1-4 alkyl, -COOR²⁶ (in which R²⁶ is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl), hydroxy C1-4 alkyl or C2-4 alkoxyalkyl), 6) -J-COOR²⁹, in which R²⁹ is hydrogen atom, and J is



(in which R³⁰ and R³¹ each, independently, is hydrogen atom or C1-8 alkyl; or



in which R⁵ and R⁶, taken together with the nitrogen atom to which they are attached represent a 3-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one or two nitrogen atoms or one nitrogen atom and one sulfur atom or oxygen atom, q is an integer from 0 to 4, and R¹⁵ is

- 1) C1-4 alkyl,
- 2) C1-4 alkoxy,
- 3) phenyl C1-4 alkoxy,
- 4) nitro,
- 5) -COOR³⁶ (in which R³⁶ is hydrogen atom, or C1-4 alkyl substituted by -NR³⁹R⁴⁰ (in which R³⁹ and R⁴⁰ each, independently, is hydrogen atom or C1-4 alkyl),
- 6) -NR⁴³R⁴⁴ (in which R⁴³ and R⁴⁴ each, independently, is hydrogen atom, C1-4 alkyl or C2-5 acyl),
- 7) -CONR⁴⁵R⁴⁶ (in which R⁴⁵ and R⁴⁶ each, independently, is hydrogen atom or C1-4 alkyl substituted by hydroxy,
- 8) C1-4 alkyl substituted by -OSO₃H;

or a non-toxic salt, acid addition salt or solvate thereof.

[0017] The sulfonamide derivatives of the present invention are novel compared with compounds disclosed in the prior art.

[0018] To summarize, the compounds of formula (A) described in EP-A-0347168 necessarily contain a pivaloyloxy group. In contrast, the compounds of the present invention have a phenyl ring which may be substituted by various substituents R¹.

[0019] Thus the compounds of the present invention have a chemical structure quite different from that of the compounds of formula (A).

[0020] The compounds of formula (B) described in EP-A-0465802 include compounds in which R^{4B} represents S(O)_{pB}R^{9B}. R^{9B} can represent hydroxy, -ONa, optionally substituted C1-12 alkyl or optionally substituted cycloalkyl, but can not represent amino group. Further, the compounds of formula (C) described in EP-A-0484949 include those in

which a substituent of Ar^C represents $S(O)_{pC}R^{9C}$. R^{9C} can represent hydroxy, -ONa, optionally substituted C1-12 alkyl or optionally substituted cycloalkyl, but can not represent amino group.

[0021] In contrast, the compounds of the present invention have a sulfonamide group which may be substituted by various substituents. Thus the compounds of the present invention have a chemical structure quite different from that of the compounds of formula (B) and (C).

[0022] Furthermore, related compounds show no activity by oral administration, but some compounds in the present invention have good stability, absorbability and solubility, and are, therefore, active as elastase inhibitors by oral administration.

[0023] In the formula (I), C1-4 alkyl means methyl, ethyl, propyl, butyl and isomers thereof.

[0024] In the formula (I), C1-8 alkyl means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomers thereof.

[0025] In the formula (I), C1-8 alkylene represented by M means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene and isomers thereof.

[0026] In the formula (I), phenyl C1-4 alkyl or phenyl C1-4 alkoxy means C 1-4 alkyl or C1-4 alkoxy substituted by a phenyl group.

[0027] In the formula (I), phenyl C1-4 alkyl means methyl, ethyl, propyl, butyl and isomers thereof, which are substituted by a phenyl group.

[0028] In the formula (I), phenyl C1-4 alkoxy means methoxy, ethoxy, propoxy, butoxy and isomers thereof, which are substituted by a phenyl group.

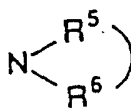
[0029] In the formula (I), C2-5 acyl means acetyl, propionyl, butyryl, valeryl and isomers thereof.

[0030] In the formula (I), C1-8 alkoxy means methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy and isomers thereof.

[0031] In the formula (I), C1-4 alkoxy means methoxy, ethoxy, propoxy, butoxy and isomers thereof.

[0032] In the formula (I), halogen atom means fluorine, chlorine, bromine and iodine.

[0033] In the formula (I), examples of the 3-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one or two nitrogen atoms or one nitrogen atom and one sulfur atom or oxygen atom represented by



that is, R^5 and R^6 , taken together with the nitrogen atom to which they are attached, include

pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, aziridine, azetidine, pyrroline, pyrrolidine; imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyrimidine, hexahydropyrimidine, tetrahydropyridazine, hexahydropyridazine, hexahydroazepine, hexahydrodiazepine, oxazole, isooxazole, thiazole, isothiazole, oxazine, oxazepine, thiazine, thiazepine, indole, isoindole, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzoimidazole, dihydrooxazole, tetrahydrooxazole, dihydroisooxazole, tetrahydroisooxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, indoline, isoindoline, perhydroindole, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole, perhydrobenzoimidazole, 7-azabicyclo[3.2.1]octane, and 3-azabicyclo[3.2.2]nonane rings.

[0034] In formula (I):-

m preferably represents 0, 1 or 2, more preferably 0 or 1.

[0035] R^4 represents C_{1-4} alkyl, for example methyl, ethyl or isopropyl. Methyl is especially preferred. When one or two substituents R^4 are present they preferably occupy one or both positions adjacent to the oxygen atom attached to the phenyl ring.

[0036] Compound in which m is 1 and R^4 represents methyl in the ortho position relative to the oxygen atom attached to the phenyl ring are especially preferred.

[0037] One of R^2 and R^3 preferably represents hydrogen, methyl, or ethyl, and the other represents methyl, ethyl, isopropyl, phenyl or trifluoromethyl. The ethyl group represented by one of R^2 and R^3 is preferably in β -configuration.

[0038] R_1 is preferably on the 4-position of the phenyl ring. Pyrrolidin-1-yl is preferred as R_1 .

[0039] In the grouping NR^5R^6 , when R^5 and R^6 , taken together with the nitrogen atom to which they are attached do not represent a heterocyclic ring, R^5 and R^6 preferably represent hydrogen; methyl; ethyl; propyl; methoxy; hydrogen is especially preferred.

[0040] In the grouping NR^5R^6 , when R^5 and R^6 , taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, the ring preferably represents pyrrolidine; indole; indoline; perhydroindole; benzoimidazole; morpholine; piperidine; piperazine; 7-azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.2]nonane; tetrahydrooxazole; tetrahydrothiazole; Imidazole; hexahydrodiazepine; aziridine; azetidine; piperazine is especially preferred.

[0041] In the grouping NR^5R^6 , when R^5 and R^6 , taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, R^{15} preferably represents amino; methoxy; dimethylamino; acetylamino; nitro; carboxy; ester, e.g. ethoxycarbonyl, t-butoxycarbonyl, 2-aminoethoxycarbonyl, 2-(2-hydroxyethoxy)ethoxycarbonyl, carboxy is especially preferred.

[0042] In the grouping NR^5R^6 , when R^5 and R^6 , taken together with the nitrogen atom to which they are attached represent a heterocyclic ring, q preferably represents 0, 1 or 2, more preferably 0 or 1.

[0043] Throughout the specification including claims, it may be easily understood by those skilled in the art, that all isomers are included in the present invention. For example, the alkyl, alkylene and alkenylene groups include straight-chain and also branched-chain ones. Double bond in alkenylene includes E, Z and EZ mixture. Accordingly, all isomers produced by the existence of asymmetric carbon atoms are included in the present invention when groups such as branched-chain alkyl are present.

[0044] The compounds of the formula (I), of the present invention may be converted into the corresponding non-toxic salts or acid addition salts by methods known *per se*.

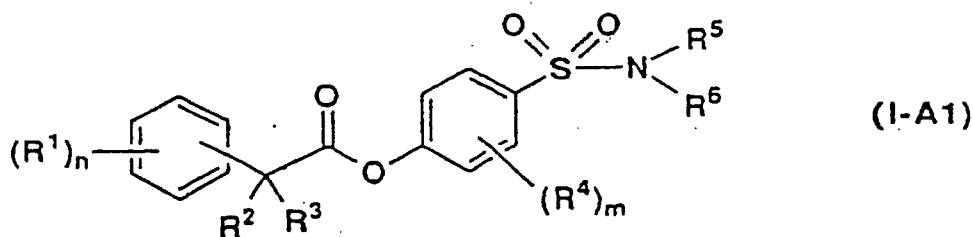
[0045] Water-soluble salts are preferred. Suitable salts, for example, include salts of alkali metals (e.g. potassium or sodium), salts of alkaline earth metals (e.g. calcium or magnesium), ammonium salts, salts of pharmaceutically-acceptable organic amines (e.g. tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine or N-methyl-D-glucamine).

[0046] Water-soluble acid addition salts are also preferred. Suitable acid addition salts, for example, include the salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid, and the salts with organic acids such as acetic acid, trifluoroacetic acid, lactic acid, tartaric acid, oxalic acid, fumaric acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid.

[0047] The compounds of the formula (I) or salts, of the present invention may be converted into the corresponding solvates by methods known *per se*.

[0048] Water-soluble solvates are preferred. Suitable solvates, for example, include the salts with water or with alcohol solvents such as ethanol.

[0049] Preferred compounds of the present invention are of the following formulae (I-A1), (I-A2), (I-B1) and (I-B2).

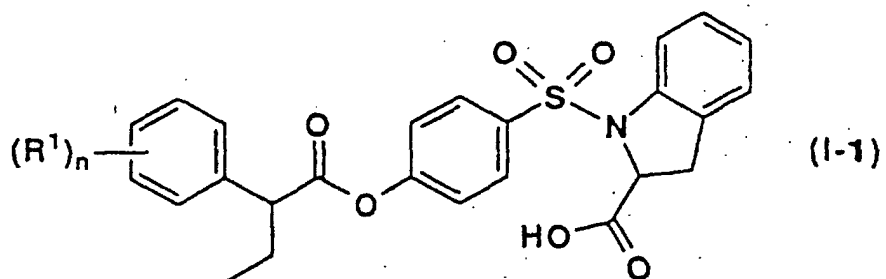


(wherein all symbols are as hereinbefore defined).

[0050] Representative compounds of the present invention are illustrated by the compounds in the following Tables and the non-toxic salts and acid addition salts thereof.

[0051] In the Tables, Me is methyl, Et is ethyl, Pr is propyl, iPr is isopropyl and tBu is tert-butyl.

Table 1



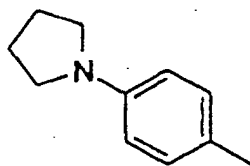
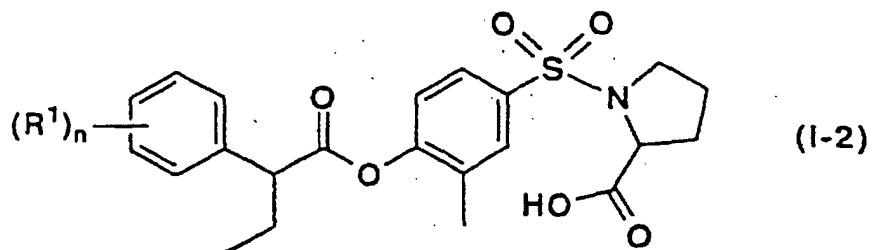
No.	$(R^1)_n$	No.	$(R^1)_n$
4			

Table 2



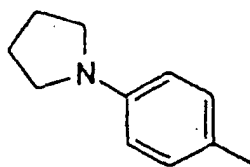
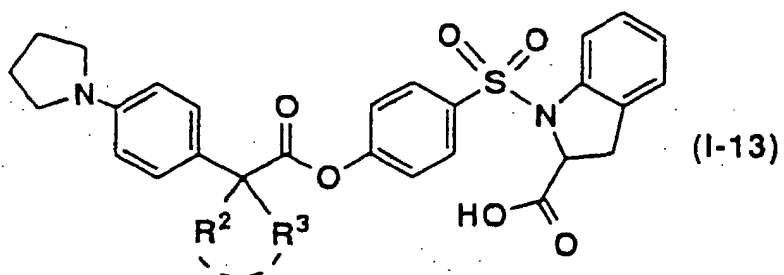
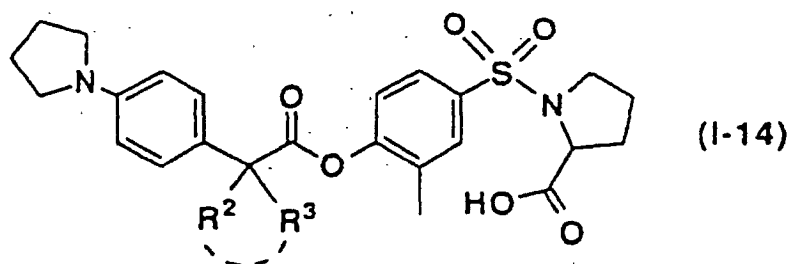
No.	$(R^1)_n$	No.	$(R^1)_n$
4			

Table 13



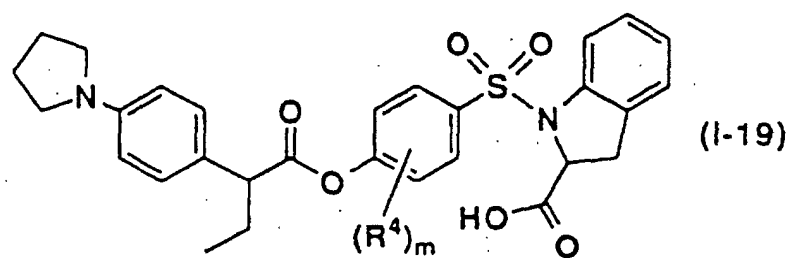
No.		No.	
1			
2			
3			
4			
6			
7			

Table 14



No.	R^2 R^3	No.	R^2 R^3
1	H H		
2	Me H		
3	Me Me		
4	Et Et		
6	Pr H		
7	iPr H		

Table 19



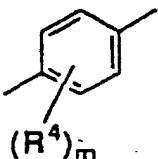
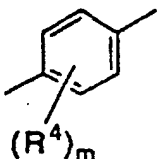
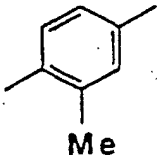
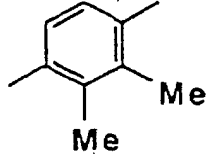
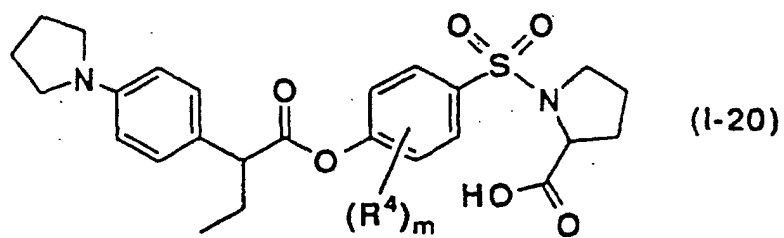
No.		No.	
1			
2			

Table 20

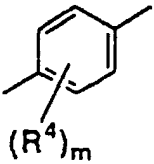
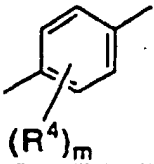
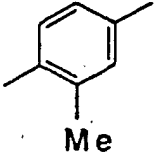
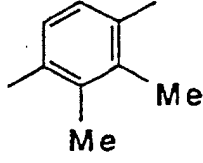
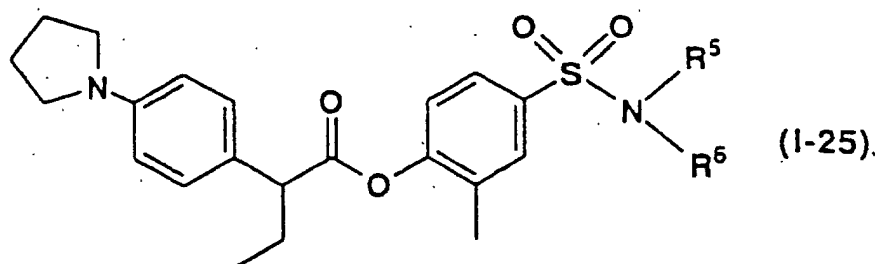
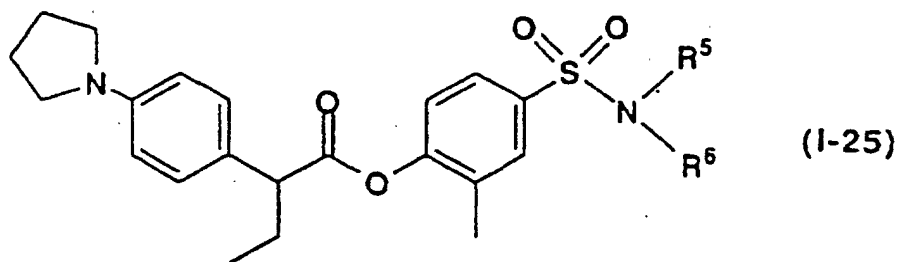
No.		No.	
1			
2			

Table 25



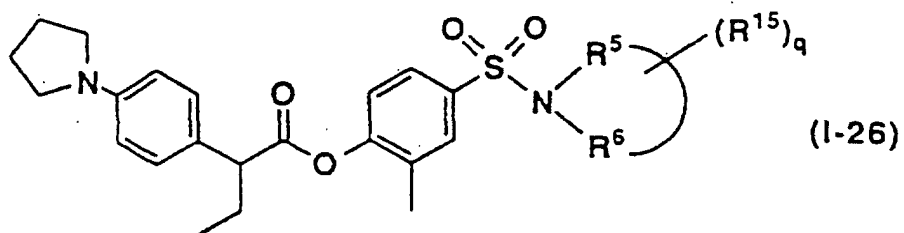
No.	$\text{--N} \begin{matrix} \text{R}^5 \\ \text{R}^6 \end{matrix}$	No.	$\text{--N} \begin{matrix} \text{R}^5 \\ \text{R}^6 \end{matrix}$
1	$\text{--N} \begin{matrix} \text{H} \\ \text{COOH} \end{matrix}$	7	$\text{--N} \begin{matrix} \text{CH}_2\text{CH}_2\text{CH}_3 \\ \text{CH}_2\text{CH}_2\text{CH}_3 \end{matrix}$
		8	$\text{--N} \begin{matrix} \text{Me} \\ \text{CH}_2\text{CH}_2\text{OMe} \end{matrix}$

Table 25 (continued)



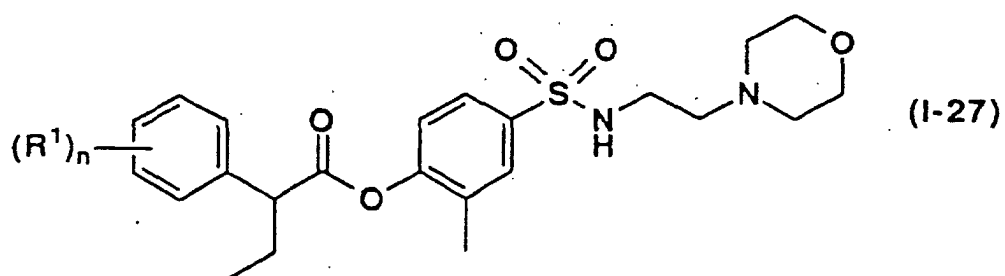
No.	$\text{-N} \begin{matrix} \text{R}^5 \\ \text{R}^6 \end{matrix}$	No.	$\text{-N} \begin{matrix} \text{R}^5 \\ \text{R}^6 \end{matrix}$
13		16	
14		18	
15		19	
		20	

Table 26

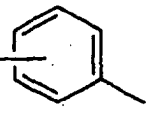
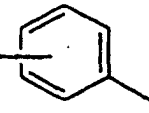
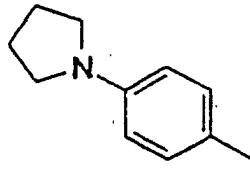


No.		No.	
4		14	
5			
6			
7			

Table 27



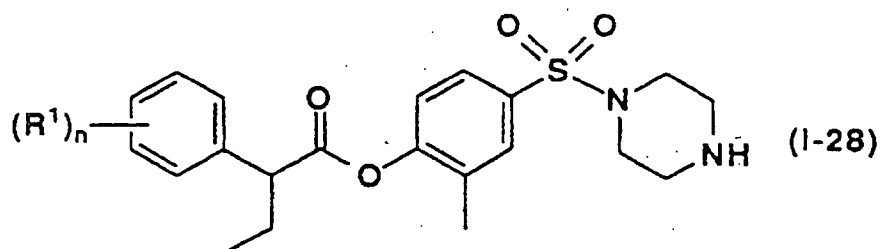
15

No.	(R¹) _n 	No.	(R¹) _n 
4			

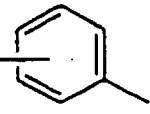
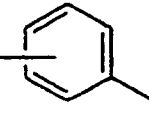
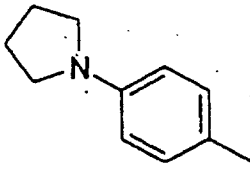
20

25

Table 28



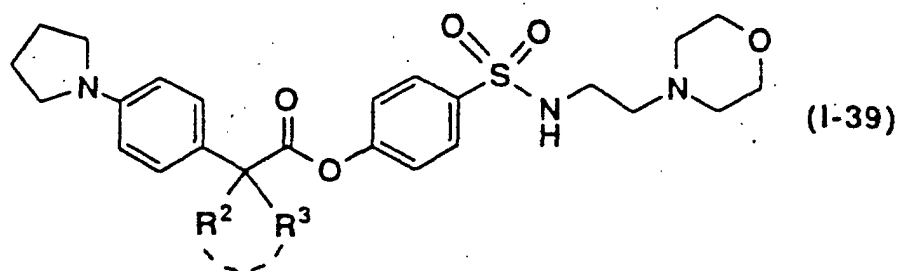
40

No.	(R¹) _n 	No.	(R¹) _n 
4			

45

50

Table 39



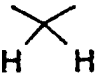
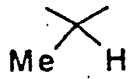


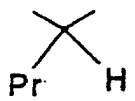
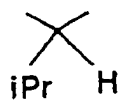
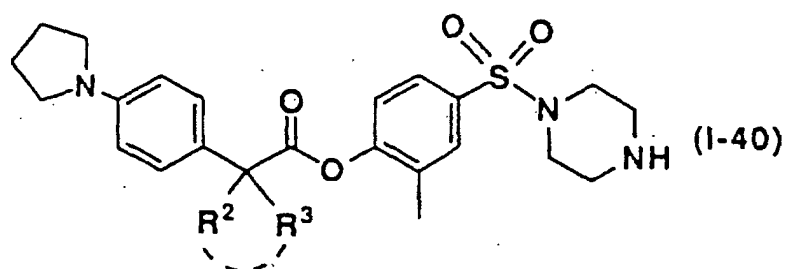
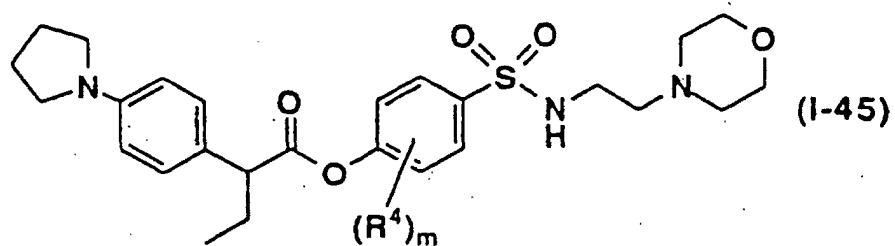
No.	R^2 R^3	No.	R^2 R^3
1			
2			
3			
4			
6			
7			

Table 40



No.		No.	
1			
2			
3			
4			
6			
7			

Table 45



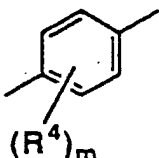
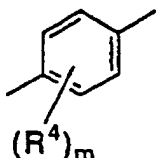
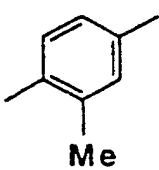
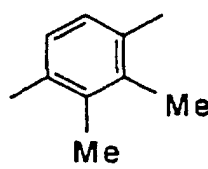
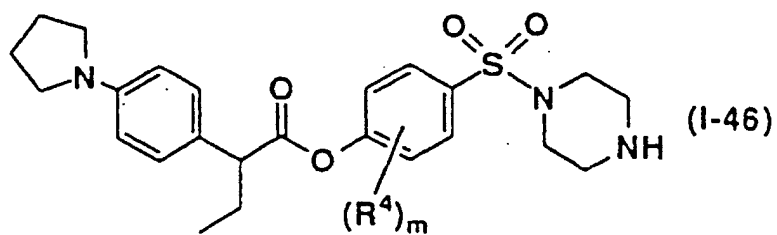
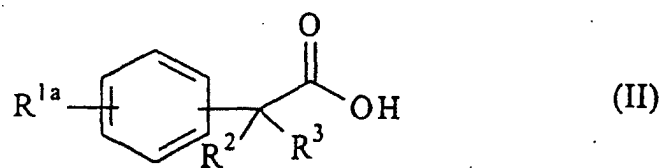
No.		No.	
1			
2			

Table 46

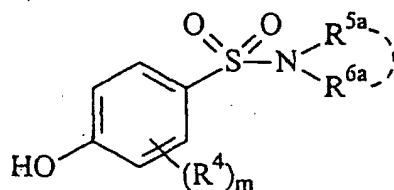


No.		No.	
1			
2			

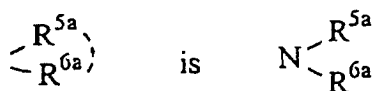
[0052] The compounds of formula (I), of the present invention, may be prepared by esterifying a compound of formula (II)



wherein R^{1a} is pyrrolidinyl;
and R^2 and R^3 are as defined in claim 1,
with a compound of formula (III)



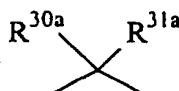
wherein R^4 and m are as defined in claim 1,



(in which R^{5a} and R^{6a} each, independently, is

- 1) hydrogen atom (with the proviso that, R^{5a} and R^{6a} do not represent hydrogen atom at the same time),
- 2) hydroxy,
- 3) hydroxy protected by a protecting group which is removable under acid conditions,
- 4) t-butoxycarbonyl,
- 5) benzyloxycarbonyl,
- 6) C1-8 alkyl,
- 7) C1-8 alkoxy,
- 8) -M- R^{16a} (in which M is as defined in claim 1, and R^{16a} is 5-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one to four nitrogen atoms, one or two oxygen atoms or one nitrogen atom and one sulfur atom or oxygen atom, unsubstituted or substituted by 1 to 4 substituents selected from C1-4 alkyl, C1-4 alkoxy, hydroxy, phenyl C1-4 alkyl, -COOR²⁶ (in which R^{26} is as defined in claim 1), hydroxy C1-4 alkyl in which hydroxy is protected by a protecting group which is removable under acid conditions or C2-4 alkoxyalkyl),
- 9) -J^a-COOR²⁹ (in which R^{29} is as defined in claim 1,

J^a is



(in which

R^{30a} and R^{31a} each, independently, is i) hydrogen atom or, ii) C1-8 alkyl, or



in which R^{5a} and R^{6a} taken together with the nitrogen atom to which they are attached represent a 3-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one or two nitrogen atoms or one nitrogen atom and one sulfur atom or oxygen atom, q is as defined in claim 1,

R^{15a} is

- 1) C1-4 alkyl,
- 2) C1-4 alkoxy,

3) phenyl C1-4 alkoxy,

4) nitro,

5) -COOR^{36a} (in which R^{36a} is hydrogen atom, C1-4 alkyl substituted by -NR^{39a}R^{40a} (in which R^{39a} and R^{40a} each, independently, is hydrogen atom (with the proviso that, R^{39a} and R^{40a} do not represent hydrogen atom at the same time, t-butoxycarbonyl, benzyloxycarbonyl, or C1-4 alkyl),

6) -NR^{43a}R^{44a} (in which R^{43a} and R^{44a} each, independently, is hydrogen atom (with the proviso that, R^{43a} and R^{44a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl, C1-4 alkyl or C2-5 acyl),

7) -CONR^{45a}R^{46a} (in which R^{45a} and R^{46a} each, independently, is hydrogen atom, or C1-4 alkyl substituted by hydroxy or protected hydroxy),

or

may be prepared by esterifying a compound of formula (II) with a compound of formula (III) to obtain a compound having protected group(s) and then eliminating the protecting groups,

or may be prepared by esterifying a compound of formula (II) with a compound of formula (III), if necessary, eliminating the protecting groups to obtain a compound having R¹⁵ represent C1-4 alkyl substituted by hydroxy, and then subjecting to sulfuric acid esterification and optionally converting a compound of formula (I) thus obtained into a non-toxic salt, acid addition salt or solvate thereof.

[0053] Protected hydroxy means, for example, hydroxy protected by a protecting group which is removable under acid conditions (e.g. C2-4 alkoxyalkyl, t-butyldimethylsilyl, tetrahydropyran (THP), triphenylmethyl) or hydroxy protected by a protecting group which is removable by hydrogenation (e.g. benzyl).

[0054] Hydroxy protected by a protecting group which is removable under acid conditions means, for example, hydroxy group protected by C2-4 alkoxyalkyl, t-butyldimethylsilyl, tetrahydropyran (THP) or triphenylmethyl.

[0055] Protected amino acid, α -amino acid or piperazino ring means, for example, amino acid, α -amino acid or piperazino ring protected by t-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz).

[0056] -CHO protected by a protecting group which is removable under acid conditions means, for example, -CHO protected by acetal (e.g. dimethylacetal or diethylacetal or ketal (e.g. ethylenedioxyketal or trimethylenedioxyketal).

[0057] The above esterification is known *per se* and can be carried out by methods for example

(1) using an acid halide,

(2) using a mixed acid anhydride,

(3) using a condensing agent

[0058] Each of these methods can be carried out, for example, as follows

(1) the method using an acid halide may be carried out, for example, by reacting a carboxylic acid with an acid halide (e.g., oxalyl chloride or thionyl chloride) in an inert organic solvent (e.g., chloroform, methylene chloride; diethyl ether or tetrahydrofuran) or without a solvent at from -20°C to the reflux temperature of the solvent, and then by reacting the acid halide obtained with a corresponding alcohol in the presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) in an inert organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran), at a temperature of from 0°C to 40°C.

(2) the method using a mixed acid anhydride may be carried out, for example, by reacting a carboxylic acid and an acid halide (e.g. pivaloyl chloride, tosyl chloride or mesyl chloride) or an acid derivative (e.g. ethyl chloroformate or isobutyl chloroformate) in the presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) in an inert organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran) or without a solvent at a temperature of from 0°C to 40°C, and then by reacting the mixture of acid anhydride obtained with a corresponding alcohol in an inert organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran), at a temperature of from 0°C to 40°C,

(3) the method using a condensing agent (e.g., 1,3-dicyclohexyl carbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino) propyl]carbodiimide (EDC) or 2-chloro-1-methylpyridinium iodide) may be carried out, for example, by reacting a carboxylic acid with a corresponding alcohol using a condensing agent in the presence or absence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) in an inert organic solvent (e.g., chloroform, methylene chloride, dimethyl formamide or diethyl ether) or without a solvent at a temperature of from 0°C to 40°C.

[0059] The reactions (1), (2) and (3) hereinbefore described may be preferably carried out in an atmosphere of inert

gas (e.g. argon or nitrogen) under anhydrous conditions.

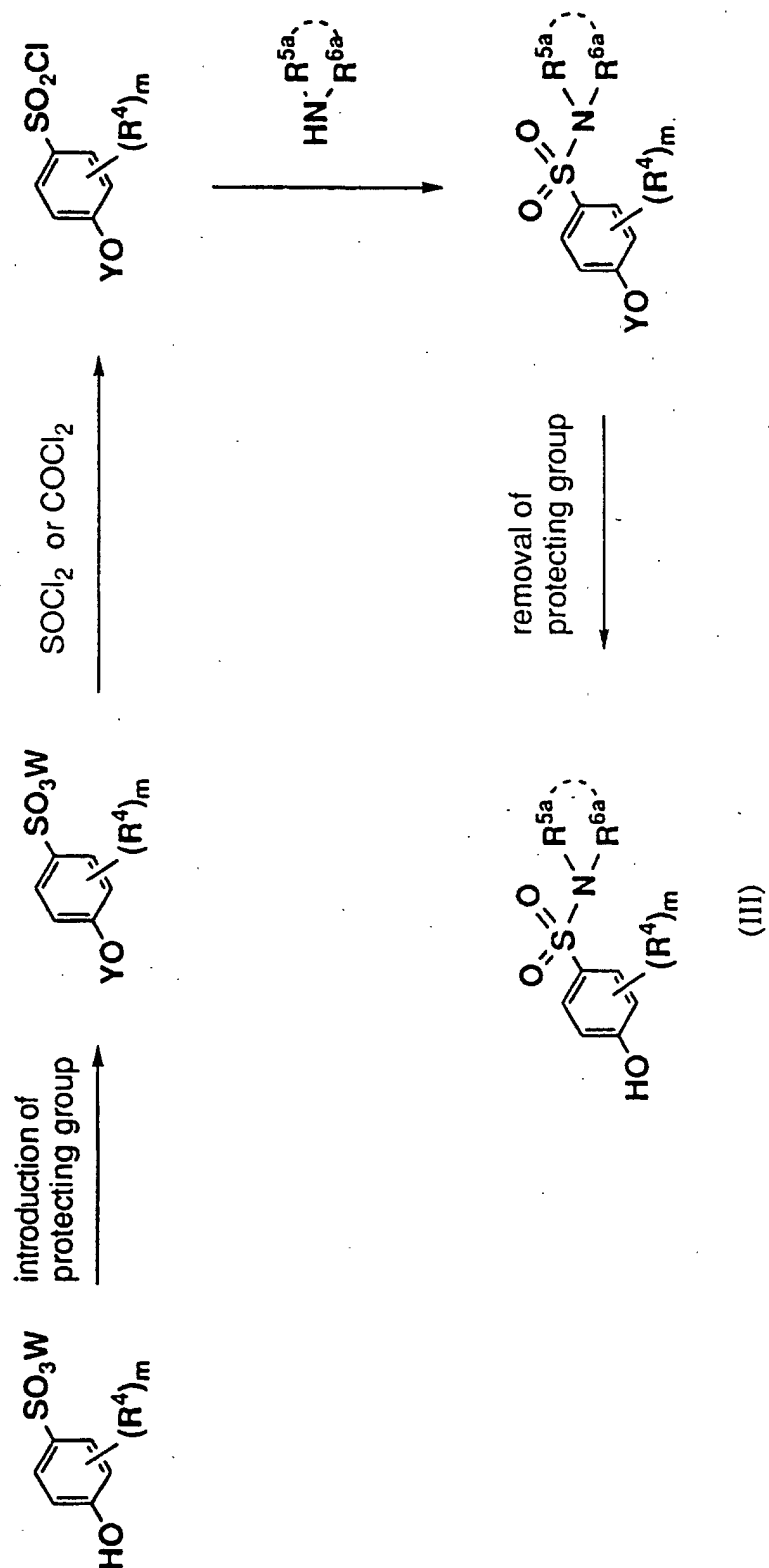
[0060] The hydrolysis of t-butylester group or the reaction resulting from treatment with acid (e.g. elimination of C2-4 alkoxyalkyl, t-butoxycarbonyl or dimethylacetal) is known *per se* and may be carried out, for example, by using an organic acid (e.g. trifluoroacetic acid) or an inorganic acid (e.g. hydrochloric acid), or a mixture thereof, in an inert organic solvent (e.g. methylene chloride, chloroform, methanol, dioxane, ethyl acetate or anisole) at a temperature of from 0°C to 90°C.

[0061] The hydrogenolysis is known *per se*, and may be carried out, for example, in an inert solvent [such as an ether (e.g., tetrahydrofuran, dioxane, diethoxyethane or diethyl ether), an alcohol (e.g., methanol or ethanol), a benzene analogue (e.g. benzene or toluene), a ketone (e.g. acetone or methyl ethyl ketone), a nitrile (e.g. acetonitrile), an amine (e.g., dimethylformamide), water, ethyl acetate, acetic acid or a mixture of two or more of them], in the presence of a hydrogenation catalyst (e.g., palladium on activated carbon, palladium black, palladium, palladium hydroxide on carbon, platinum oxide, nickel or Raney nickel (registered trade mark)), in the presence or absence of an inorganic acid (e.g. hydrochloric acid, sulfuric acid, hypochlorous acid, boric acid or tetrafluoroboric acid) or an organic acid (e.g., acetic acid, p-toluenesulfonic acid, oxalic acid, trifluoroacetic acid or formic acid), at ordinary or elevated pressure under an atmosphere of hydrogen, at a temperature of from 0°C to 200°C. When using an acid, its salt may be used at the same time.

[0062] The sulfuric acid esterification is known *per se*, and may be carried out, for example, by reacting sulfur trioxide pyridine complex in the presence of a tertiary amine (e.g. pyridine) at a temperature of from 0°C to 40°C.

[0063] The compounds of formulae (II) and (III) used as starting materials may be prepared by the methods of the following Scheme 1 or by methods known *per se* or are commercially available compounds. For example, 2-phenylbutanoic acid is commercially available. The compounds may also be prepared by the methods described in the Examples of the present specification.

Scheme 1



[0064] In Scheme 1 hereinbefore described

W is an alkali metal,

Y is benzyl, benzyloxycarbonyl, or a protecting group which may be removed under acid conditions (e.g. C2-4 alkoxyalkyl, t-butylidimethylsilyl, tetrahydropyran (THP) or triphenylmethyl), and

the other symbols are as hereinbefore defined.

[0065] It has been confirmed that the compounds of the formula (I), of the present invention have inhibitory activities on elastase. For example, in laboratory tests the following results were obtained.

(1) Inhibitory effects on human polymorphonuclear elastase

[0066] A mixture with 0.5 ml of 0.2 mM HEPES buffer (pH 8.0), 0.2 ml of 2.5 M NaCl, 0.1 ml of 1 % polyethyleneglycol 6000, 0.13 ml of distilled water, test compound dissolved in 0.01 ml of dimethylsulfoxide (DMSO) and 0.05 ml of 0.8 Unit/ml human polymorphonuclear elastase (HSE) was preincubated at 37 °C for 20 min. 5 mM of Meo-Suc-Ala-Ala-Pro-Val-pNA (DMSO solution, 0.01ml) was then added to the above mixture and was incubated at 37°C for 5 min. The reaction was terminated by 0.1 ml of 50% acetic acid and the p-nitroanilide (pNA) released was measured spectrophotometrically at 405 nM. Percent inhibition of a compound was calculated by the following equation.

$$\text{Inhibition (\%)} = 1 - \{\Delta \text{OD}(\text{test-blank}) / \Delta \text{OD}(\text{control-blank})\} \times 100$$

[0067] Results are shown in Table 47.

[Table 47]

Example No.	IC ₅₀ (μM)	
1(16)	0.017	Inv.
1(40)	0.019	Comp.
1(56)	0.014	Comp.
1(78)	0.0080	Inv.
1(130)	0.022	Inv.
1(139)	0.024	Inv.
2	0.055	Inv.
2(1)	0.012	Inv.
2(42)	0.013	Inv.
2(62)	0.0068	Comp.
2(69)	0.011	Comp.
2(77)	0.018	Inv.
2(111)	0.0097	Comp.
2(120)	0.023	Comp.
2(157)	0.008	Comp.
2(173)	0.014	Comp.
2(179)	0.049	Comp.
2(197)	0.010	Comp.
2(274)	0.012	Inv.
2(276)	0.0093	Inv.
Inv. = inventive example. Comp. = Comparative example.		

(2) Inhibitory effects on human polymorphonuclear elastase induced lung hemorrhage in hamster

[0068] A test compound suspended in 0.5 % Carboxymethylcellulose or 80 % Polyethyleneglycol, 400 or 2 % Tween 80 was administered orally to a group of 5 Syrian hamsters. At 60 min after the administration, 10 U/0.1 ml of HSE was injected intratracheally via surgically exposed trachea under pentobarbital anesthesia (60 mg/kg, i.p.) to induce lung injury. At 60 min after the injection, hamsters were bled to sacrifice and subjected to bronchoalveolar lavage with 2.5 ml of saline and recovered lavage solution (BALF). The recovered BALF (0.5 ml) was diluted by 4 times with 2 % aqueous solution sodium carbonate and sonicated for 10 sec. The lavage fluid was further diluted by 2.5 times with 2% aqueous solution sodium carbonate and the amount of blood in BALF was calculated from absorbance at 414 nM using standard curve.

[0069] Results are shown in Table 48 and 49.

[Table 48]

Example No.	inhibition at 500 mg/kg (%)	
1(68)	51	Comp.
1(90)	65	Inv.
2	81	Inv.
2(42)	67	Inv.
2(69)	83	Comp.

[Table 49]

Example No.	ED ₅₀
1 (139)	192 mg/kg
2(274)	132 mg/kg
2(276)	73 mg/kg

[0070] The above experiments show that compounds of the present invention possess inhibitory activity on elastase, even when administered orally.

[0071] The toxicity of the compounds of the present invention is very low. Therefore, the compounds of the present invention may be considered to be sufficiently safe and suitable for pharmaceutical use.

[0072] The compounds of the formula (I), of the present invention, and non-toxic salts and acid addition salts thereof, possess inhibitory activity on elastase. Accordingly, they are useful for the treatment and/or prevention of diseases induced by an abnormal enhancement of the degradation of elastin, collagen fiber and/or proteoglycan, resulting from the action of elastase on a mammalian animal, especially a human (e.g. chronic obstructive pulmonary disease such as emphysema, rheumatoid arthritis, atherosclerosis, adult respiratory distress syndrome (ARDS), glomerular nephritis, myocardial infarction, idiopathic ulcerative colitis or gingivitis).

[0073] For the purpose above described, the compounds of the formula (I), of the present invention, or non-toxic salts, acid addition salts or solvates thereof may normally be administered systemically or locally usually by oral or parenteral administration.

[0074] The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses per person are generally from 1 mg to 1000 mg, by oral administration, up to several times per day, or from 0.1 mg to 100 mg, by parenteral administration up to several times per day, or by continuous administration for from 1 to 24 hrs. per day from vein.

[0075] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0076] The compounds of the present invention may be administered in the form of, for example, solid compositions, liquid compositions or other compositions for oral administration, injections, liniments or suppositories for parenteral administration.

[0077] Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

[0078] In such compositions, one or more of the active compound(s) may be admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate). The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate), disintegrating agents (such as cellulose calcium glycolate), stabilizing agents (such as lactose), and agents to assist dissolution (such as glutamic acid or asparaginic acid).

[0079] The tablets or pills may, if desired, be coated with a film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate), or be coated with two or more films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

[0080] Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs. In such compositions, one or more of the active compound(s) contained in inert diluent (s) commonly used in the art (e.g. purified water or ethanol). Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents or suspending agents, sweetening agents, flavouring agents, perfuming agents, and preserving agents).

[0081] Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (such as sodium sulfate), isotonic buffers (such as sodium chloride, sodium citrate or citric acid). For preparation of such spray compositions, for example, the method described

[0082] Injections for parenteral administration include sterile aqueous or non aqueous solutions, suspensions and emulsions. In such compositions, one or more active compound(s) may be admixed with at least one inert aqueous diluent(s) (e.g. distilled water for injection or physiological salt solution) or inert non-aqueous diluent(s) (e.g. propylene glycol, polyethylene glycol, olive oil, ethanol or POLYSORBATE80 (registered trade mark)).

[0083] Injections may comprise additional ingredients other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agents (e.g. lactose), assisting agents such as agents to assist dissolution (e.g. glutamic acid or asparaginic acid).

[0084] They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They may also be manufactured in the form of sterile solid compositions, for example, by freeze-drying, which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before used.

[0085] Other compositions for parenteral administration include liquids for external use, and endermic liniments, ointment, suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by methods known *per se*.

Reference examples and Examples

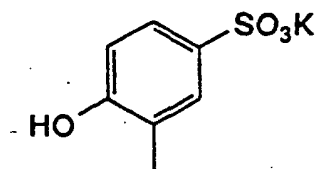
[0086] The following reference examples and examples illustrate, but do not limit, the present invention.

[0087] The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations and TLC.

[0088] The NMR data show the solvents used in the measurements in parentheses.

Reference example 1

[0089] 3-methyl-4-hydroxybenzenesulfonic acid • potassium salt

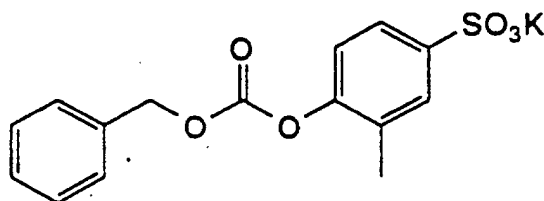


[0090] To stirring conc. sulfuric acid (26 ml) at 100 °C was slowly added o-cresol (50 ml), the mixture was stirred at 100°C for 5 hours. After the reaction mixture was cooled at room temperature, to mixture was neutralized by slowly adding potassium hydroxide (27.5 g) in water (35 ml) solution. After to the mixture was added methanol (100 ml), the precipitate was filtered to give the title compound (56.5 g) having the following physical data.

[0091] TLC : Rf 0.18 (chloroform:methanol:water=6:4:1).

Reference example 2

[0092] 3-methyl-4-(benzyloxycarbonyloxy)benzenesulfonic acid • potassium salt



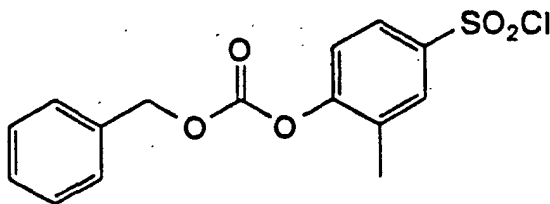
EP 0 769 498 B9 (W1B1)

[0093] To a suspension of the compound prepared in reference example 1 (12.2 g) in tetrahydrofuran (THF) (100 ml) was added 2N aqueous solution of sodium hydroxide (28 ml) at room temperature, following added benzyloxycarbonyl chloride (8 ml) under cooling with ice. The reaction mixture was stirred for 30 min. The reaction mixture was concentrated under reduced pressure, and cooled with ice, and the precipitate was filtered to give the title compound (7.3 g) having the following physical data.

[0094] TLC : Rf 0.51 (chloroform:methanol:water=6:4:1).

Reference example 3

[0095] 3-methyl-4-(benzyloxycarbonyloxy)benzenesulfonyl chloride

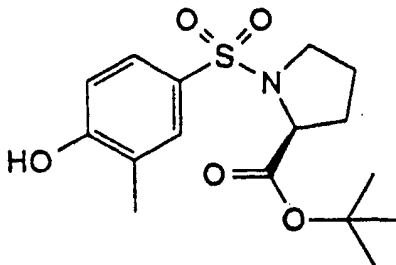


[0096] To a suspension of the compound prepared in reference example 2 (46.1 g) in dimethylformamide (DMF) (100 ml) was slowly added thionyl chloride (15 ml) under cooling with ice. The reaction mixture was stirred for 30 min at 5 °C. To the reaction mixture was added ice water, and the precipitate was filtered to give the title compound (39.4 g) having the following physical data.

[0097] TLC : Rf 0.56 (chloroform:methanol:water=6:4:1).

Reference example 4

[0098] 4-(2S-t-butyloxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenol

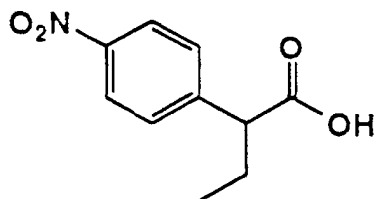


[0099] To a solution of L-proline-t-butylester (1.9 g) in pyridine (10 ml) was added the compound prepared in reference example 3 (3.7 g) under cooling with ice. The reaction mixture was stirred for 30 min. The mixture was quenched by adding 2N aqueous solution hydrochloric acid and extracted with ethyl acetate (200 ml). The organic layer was washed with a saturated aqueous solution of sodium hydrocarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. 10 % Palladium on activated carbon (500 mg) was added to a solution of the residue (4.9 g) in methanol (200 ml) and the mixture was stirred for 2 h at room temperature under an atmosphere of hydrogen. The mixture was filtered through Celite (being on sale). The filtrate was concentrated to give the title compound (3.4 g) having the following physical data.

[0100] TLC : Rf 0.35 (hexane:ethyl acetate=1:1).

Reference example 5

[0101] 2RS-(4-nitrophenyl)butanoic acid

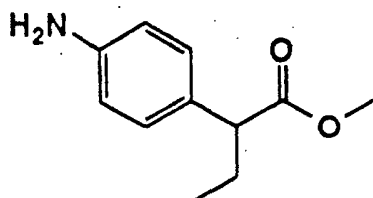


[0102] To a mixture solution of 2-phenylbutanoic acid (200 g) in acetic acid (200 ml) and conc. sulfuric acid (150 ml) was slowly added conc. nitric acid (150 ml) at 15 °C. The reaction mixture was stirred for 10 min at same temperature. The reaction mixture was poured into ice water, and the precipitate was filtered. The residue was recrystallized from the mixture solution of hexane/ethyl acetate to give the title compound (103 g) having the following physical data.

[0103] TLC : R_f 0.50 (ethyl acetate).

Reference example 6

[0104] 2RS-(4-aminophenyl)butanoic acid methylester

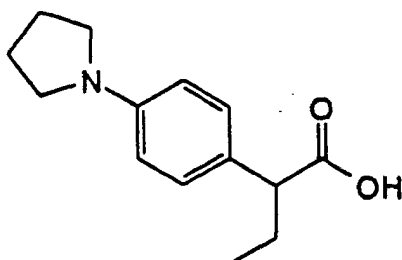


[0105] To a solution of the compound prepared in reference example 5 (15.7 g) in DMF (60 ml) was added potassium carbonate (12 g) under cooling with ice. To the mixture was added methyl iodide (5 ml) at same temperature. The reaction mixture was stirred for 2h at room temperature. The mixture was quenched by adding 1N aqueous solution hydrochloric acid (200 ml) and extracted with the mixture of hexane/ethyl acetate (1:1, 200 ml). The organic layer was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. 5 % Palladium on activated carbon (1.3 g) was added to a solution of the residue in methanol (300 ml) and the mixture was stirred for 2 h at room temperature under an atmosphere of hydrogen. The mixture was filtered through Celite (being on sale). The filtrate was concentrated to give the title compound (14.2 g) having the following physical data.

[0106] TLC : R_f 0.47 (hexane:ethyl acetate=1:1).

Reference example 7

[0107] 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid



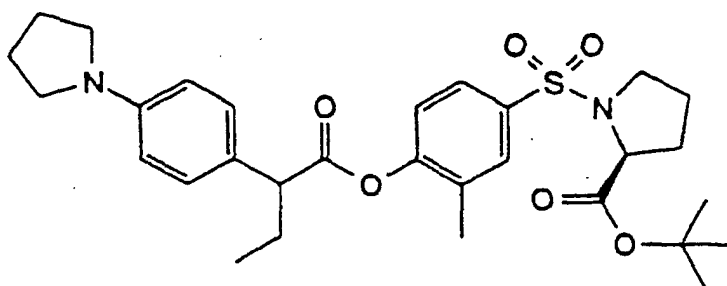
[0108] To a solution of the compound prepared in reference example 6 (14.2 g) in DMSO (75 ml) was added potassium carbonate (11 g) and 1,4-dibromobutane (9 ml). The reaction mixture was stirred for 1h at 40°C. To the mixture was added sodium iodide (11.2 g). the reaction mixture was stirred for 3h at 40 °C and stirred for 2h at 60 °C. The reaction

mixture was quenched by adding water and extracted with the mixture of hexane/ethyl acetate (1:1, 1000 ml). The organic layer was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. To a solution of the residue in methanol (80 ml) was added 5N aqueous solution of sodium hydroxide (20 ml) and the mixture was stirred for 5 h at room temperature. To the mixture was added aqueous solution hydrochloric acid until pH 8, and washed with ethyl acetate. The water layer was neutralized by adding aqueous solution hydrochloric acid, and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from the mixture solution of hexane/ethyl acetate (3:1) to give the title compound (9.83 g) having the following physical data.

[0109] TLC : R_f 0.30 (hexane:ethyl acetate=1:1).

Preparation Example 1

[0110] 4-(2S-t-butyloxycarbonylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



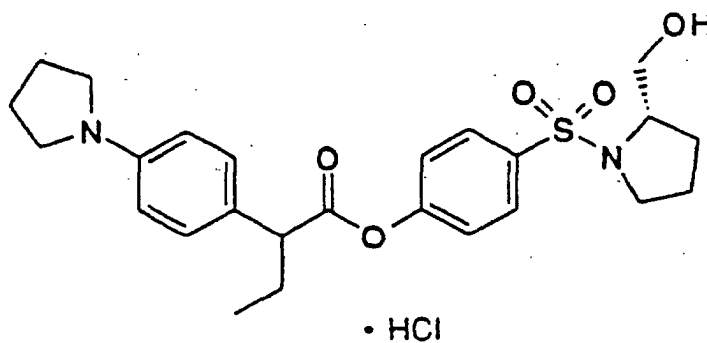
[0111] To a solution of the compound prepared in reference example 4 (748 mg), the compound prepared in reference example 7 (537 mg) and dimethylaminopyridine (64 mg) in dichloromethane (20 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (482 mg) at room temperature. The reaction mixture was stirred for 2h at room temperature. To the reaction mixture was added ethyl acetate, and washed with 1N aqueous solution hydrochloric acid (x2). The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1) to give the title compound (1.04 g) having the following physical data.

[0112] TLC : R_f 0.23 (hexane:ethyl acetate=5:1).

[0113] By the same procedure as Preparation example 1 and by known methods converted to corresponding salts or acid addition salts, the compounds having the following physical data were given by using corresponding phenol derivatives instead of the compound prepared in reference example 4 and by using corresponding carboxylic acid derivatives instead of the compound prepared in reference example 7.

Example 1(1)

[0114] 4-(2S-hydroxymethylpyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

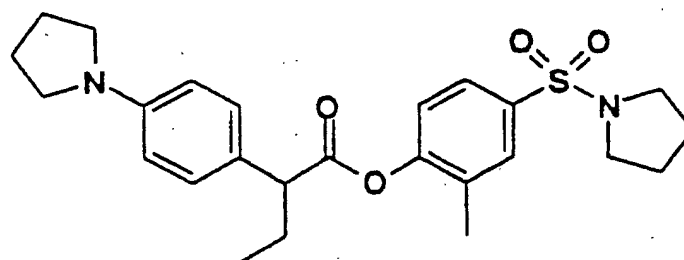


[0115] NMR (DMSO- d_6): δ 7.85 (2H, d, J=9Hz), 7.28 (2H, d, J=9Hz), 7.28 (2H, d, J=9Hz), 6.83 (2H, d, J=9Hz), 3.75 (1H, t, J=7Hz), 3.60-3.44 (2H, m), 3.40-3.20 (6H, m), 3.11-2.95 (1H, m), 2.21-1.90 (5H, m), 1.90-1.65 (3H, m), 1.55-1.30 (2H, m), 0.90 (3H, t, J=7Hz);

[0116] TLC : Rf 0.48 (ethyl acetate:hexane=1:1).

Example 1(3)

[0117] 4-(pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoate ester

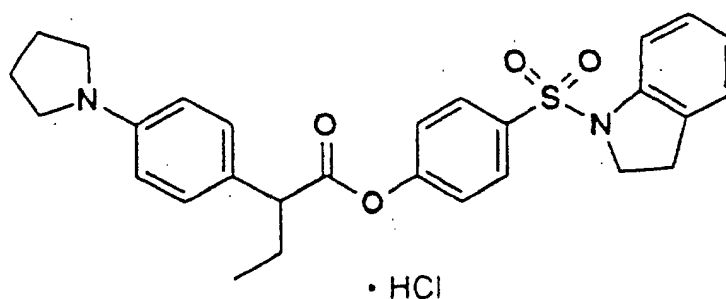


[0118] NMR (CDCl₃): δ 7.68-7.57 (2H, m), 7.23 (2H, d, J=8Hz), 7.06 (1H, d, J=8Hz), 6.55 (2H, d, J=8Hz), 3.61 (1H, t, J=7Hz), 3.35-3.13 (8H, m), 2.30-1.65 (13H, m), 0.98 (3H, t, J=7Hz);

[0119] TLC : Rf 0.49 (ethyl acetate:hexane=3:7).

Example 1(6)

[0120] 4-(indolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoate ester · hydrochloride

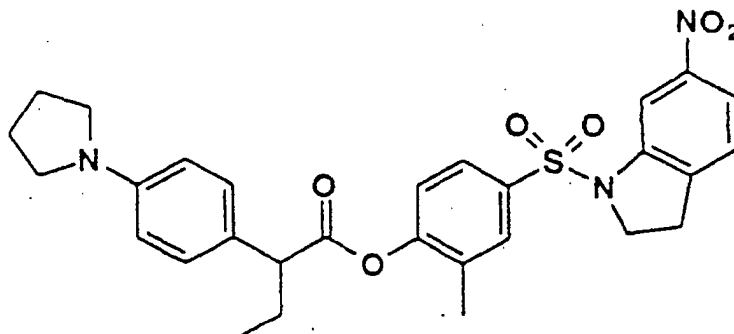


[0121] NMR (CDCl₃): δ 7.78 (2H, d, J=8.8Hz), 7.62 (1H, d, J=8.0Hz), 7.50-7.34 (4H, m), 7.24-7.12 (1H, m), 7.08 (3H, d, J=8.8Hz), 6.97 (1H, dt, J=1.0 and 7.2Hz), 3.90 (2H, d, J=8.4Hz), 3.68 (1H, t, J=7.6Hz), 3.70-3.45 (4H, m), 2.89 (2H, t, J=8.4Hz), 2.40-2.20 (4H, m), 2.30-2.05 and 2.00-1.75 (each 1H, m), 0.96 (3H, t, J=7.2Hz);

[0122] TLC : Rf 0.47 (ethyl acetate:hexane=1:2).

Example 1(11)

[0123] 4-(6-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

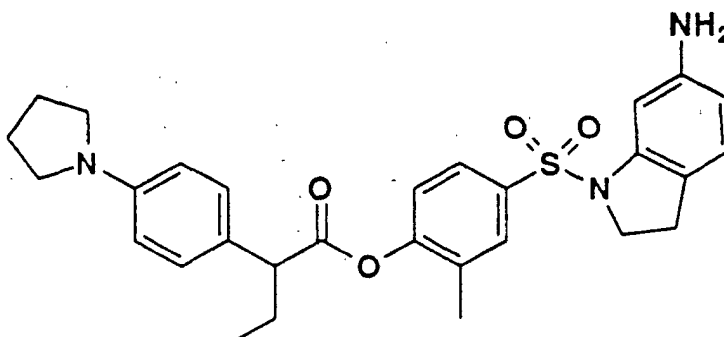


[0124] NMR (CDCl₃): δ 8.10 (dd, J=2.4, 8.8Hz, 1H), 7.96 (s, 1H), 7.7-7.6 (m, 3H), 7.18 (d, J=8.4Hz, 2H), 7.05 (d, J=8.0Hz, 1H), 6.52 (d, J=8.4Hz, 2H), 4.01 (t, J=8.6Hz, 2H), 3.58 (t, J=7.8Hz, 1H), 3.3-3.2 (m, 4H), 3.08 (t, J=8.6Hz, 2H), 2.3-1.8 (m, 2H), 2.00 (s, 3H), 2.1-1.9 (m, 4H), 0.96 (t, J=7.4Hz, 3H);

[0125] TLC : Rf 0.33 (hexane:ethyl acetate=3:1).

Example 1(12)

[0126] 4-(6-aminoindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

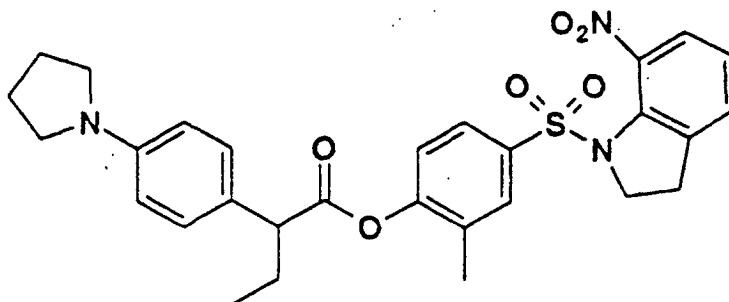


[0127] NMR (CDCl₃): δ 7.6-7.4 (m, 3H), 7.20 (d, J=8.7Hz, 2H), 6.94 (d, J=8.4Hz, 1H), 6.53 (d, J=8.7Hz, 2H), 6.6-6.4 (m, 2H), 3.83 (t, J=8.2Hz, 2H), 3.58 (t, J=7.7Hz, 1H), 3.4-3.2 (m, 4H), 2.64 (t, J=8.2Hz, 2H), 2.3-1.8 (m, 6H), 1.95 (s, 3H), 0.97 (t, J=7.4Hz, 3H);

[0128] TLC : Rf 0.59 (hexane:ethyl acetate=1:1).

Example 1(13)

[0129] 4-(7-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

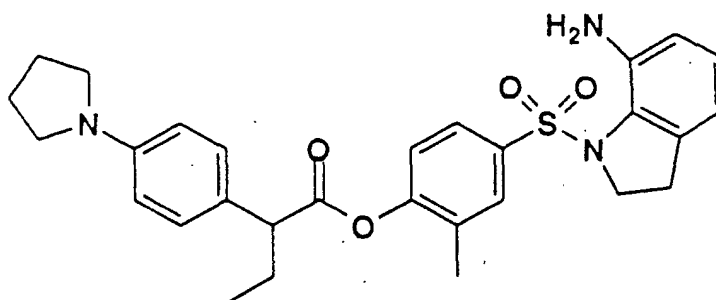


[0130] NMR (CDCl₃): δ 8.38 (d, J=2.2Hz, 1H), 7.85 (dd, J=2.0, 8.4Hz, 1H), 7.8-7.6 (m, 2H), 7.2-7.1 (m, 1H), 7.18 (d, J=8.6Hz, 2H), 7.03 (d, J=8.2Hz, 1H), 6.52 (d, J=8.6Hz, 2H), 3.99 (t, J=8.6Hz, 2H), 3.58 (t, J=7.6Hz, 1H), 3.3-3.2 (m, 4H), 3.05 (t, J=8.6Hz, 2H), 2.3-1.7 (m, 9H), 0.96 (t, J=7.4Hz, 3H);

[0131] TLC : R_f 0.49 (hexane:ethyl acetate=1:1).

Example 1(14)

[0132] 4-(7-aminoindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

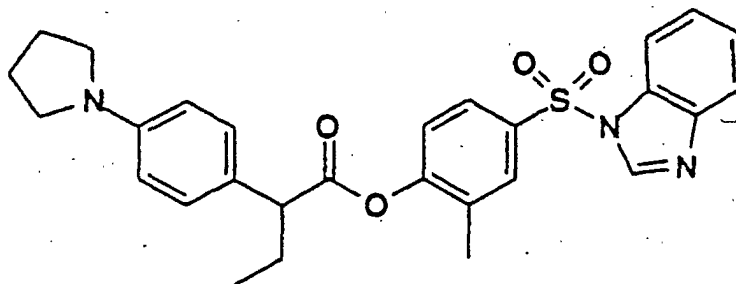


[0133] NMR (CDCl₃): δ 7.6-7.5 (m, 2H), 7.15 (d, J=8.6Hz, 2H), 7.0-6.9 (m, 2H), 6.82 (d, J=8.0Hz, 1H), 6.52 (d, J=8.6Hz, 2H), 6.29 (dd, J=2.0, 8.0Hz, 1H), 3.84 (t, J=8.0Hz, 2H), 3.58 (t, J=7.6Hz, 1H), 3.4-3.2 (m, 4H), 2.76 (t, J=7.6Hz, 2H), 2.3-1.8 (m, 9H), 0.97 (t, J=7.4Hz, 3H);

[0134] TLC : R_f 0.40 (hexane:ethyl acetate=2:1).

Example 1(15)

[0135] 4-(benzimidazol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



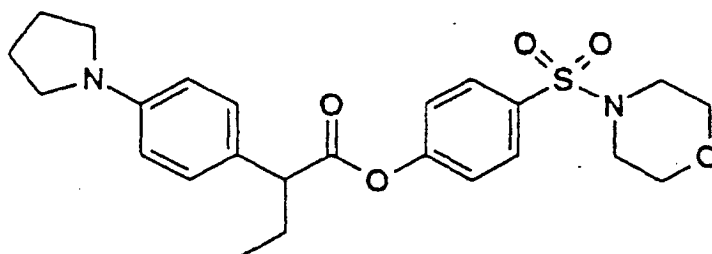
[0136] NMR (CDCl₃): δ 8.35 (1H, s), 7.79 (4H, m), 7.35 (2H, m), 7.17 (2H, d, J=8.8Hz), 7.08 (1H, d, J=9.4Hz), 6.52 (2H, d, J=8.8Hz), 3.57 (1H, t, J=7.8Hz), 3.26 (4H, m), 2.10 (1H, m), 2.00 (3H, s), 1.97 (4H, m), 1.88 (1H, m), 0.95 (3H,

t, J=7.4Hz);

[0137] TLC : Rf 0.49 (hexane:ethyl acetate=2:1).

Example 1(16)

[0138] 4-(morpholin-4-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

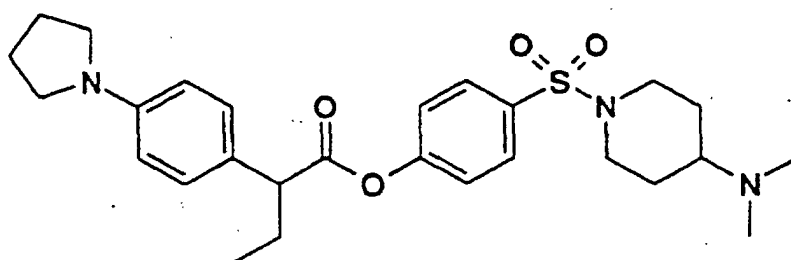


[0139] NMR (DMSO-d₆): δ 7.75 (2H, d, J=7Hz), 7.27 (2H, d, J=7Hz), 7.16 (2H, d, J=7Hz), 6.52 (2H, d, J=7Hz), 3.67 (1H, t, J=7Hz), 3.61 (4H, t-like), 3.20 (4H, t-like), 2.83 (4H, t-like), 2.04 (1H, m), 1.94 (4H, t-like), 1.79 (1H, m), 0.88 (3H, t, J=7Hz);

[0140] TLC : Rf 0.54 (hexane:ethyl acetate=1:1).

Example 1(21)

[0141] 4-(4-(N,N-dimethylamino)piperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

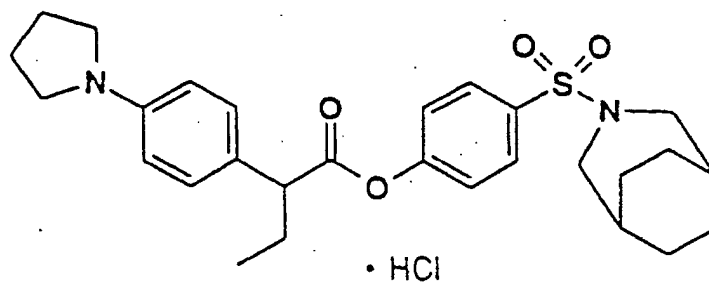


[0142] NMR (CDCl₃): δ 7.71 (2H, d, J=8.8Hz), 7.20 (2H, d, J=8.8Hz), 7.16 (2H, d, J=8.7Hz), 6.54 (2H, d, J=8.8Hz), 3.75 (2H, d, J=13.7Hz), 3.58 (1H, t, J=7.7Hz), 3.29 (4H, t, J=6.6Hz), 2.36-1.53 (19H, m), 0.98 (3H, t, J=7.4Hz);

[0143] TLC : Rf 0.25 (hexane:ethyl acetate=2:1).

Example 1(24)

[0144] 4-(3-azabicyclo[3.2.2]nonan-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

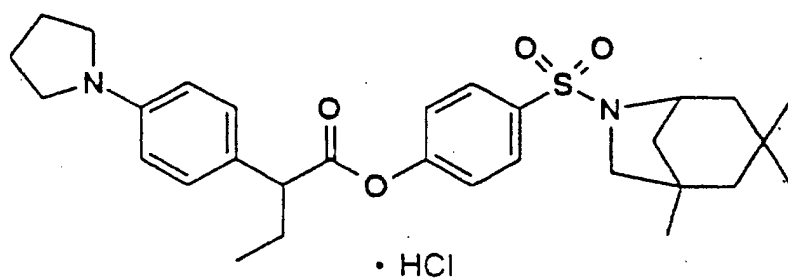


[0145] NMR (CDCl₃): δ 7.73 (2H, d, J=8.6Hz), 7.53 (2H, d, J=8.6Hz), 7.45 (2H, d, J=8.6Hz), 7.15 (2H, d, J=8.8Hz), 3.72 (1H, t, J=7.6Hz), 3.75-3.50 (4H, m), 3.22 (4H, d, J=4.2Hz), 2.40-2.20 (4H, m), 2.40-1.75 (2H, m), 2.10-2.00 (2H, m), 1.80-1.50 (8H, m), 0.99 (3H, t, J=7.4Hz);

[0146] TLC : R_f 0.57 (ethyl acetate:hexane=1:3).

Example 1(25)

[0147] 4-(1,3,3-trimethyl-6-azabicyclo[3.2.1]octan-6-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

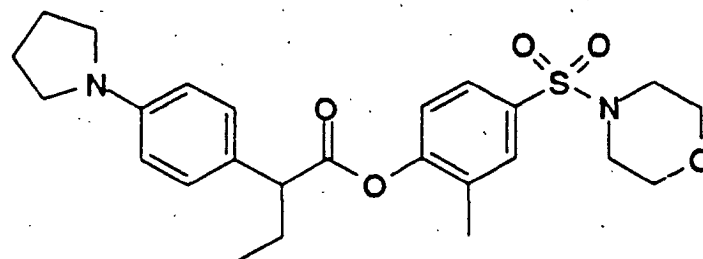


[0148] NMR (CDCl₃): δ 7.81 (2H, d, J=8.8Hz), 7.40 (2H, d, J=8.4Hz), 7.36-7.18 (2H, brs), 7.15 (2H, d, J=8.8Hz), 4.08 (1H, t-like), 3.69 (1H, t, J=7.8Hz), 3.64-3.38 (4H, m), 3.32 (1H, d, J=9.6Hz), 2.76 (1H, dd, J=9.6 and 1.4Hz), 2.36-2.08 (5H, m), 2.02-1.76 (2H, m), 1.52 (2H, d, J=14.4Hz), 1.34 (2H, d, J=12.4Hz), 1.22 (3H, s), 1.16-1.02 (1H, m), 0.99 (3H, t, J=7.4Hz), 0.94 (3H, s), 0.92 (3H, s);

[0149] TLC : R_f 0.54 (ethyl acetate:hexane=1:3).

Example 1(31)

[0150] 4-(morpholin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



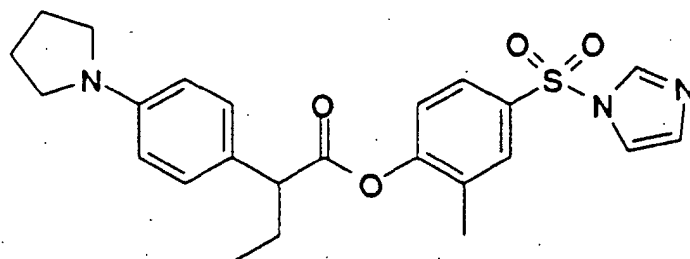
[0151] NMR (CDCl₃): δ 7.56-7.51 (2H, m), 7.26-7.21 (2H, m), 7.10 (1H, d, J=8Hz), 6.55 (2H, d, J=8Hz), 3.75-3.71 (4H, m), 3.62 (1H, t, J=8Hz), 3.32-3.26 (4H, m), 3.01-2.96 (4H, m), 2.37-1.73 (2H, m), 2.06 (3H, s), 2.04-1.96 (4H, m),

1.00 (3H, t, J=8Hz);

[0152] TLC : Rf 0.27 (hexane:ethyl acetate=3:1).

Example 1(32)

[0153] 4-(imidazol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

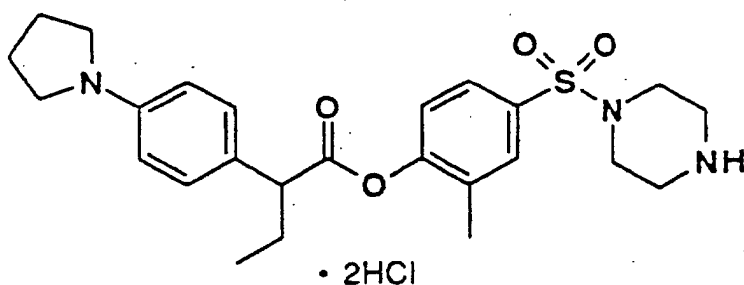


[0154] NMR(CDCl₃): δ 7.99 (1H, m), 7.75 (1H, s), 7.72 (1H, m), 7.27-7.08 (5H, m), 6.54 (2H, d, J=8.8Hz), 3.60 (1H, t, J=7.6Hz), 3.28 (4H, m), 2.14 (1H, m), 2.04 (3H, s), 2.01 (4H, m), 1.91 (1H, m), 0.97 (3H, t, J=7.4Hz);

[0155] TLC : Rf 0.36 (hexane:ethyl acetate=2:1).

Example 1(33)

[0156] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

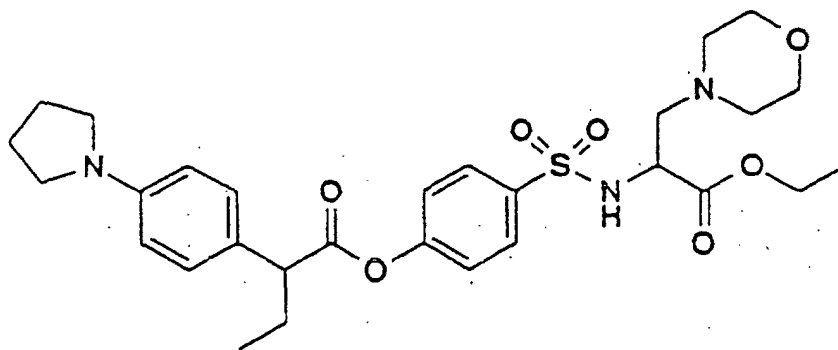


[0157] NMR (CD₃OD): δ 7.80-7.56 (6H, m), 7.18 (1H, d, J=8.2Hz), 4.00 (1H, t, J=7.6Hz), 3.90-3.72 (4H, m), 3.30 (8H, s-like), 2.43-2.15 (5H, m), 2.06 (3H, s), 2.15-1.84 (1H, m), 1.00 (3H, t, J=7.2Hz);

[0158] TLC : Rf 0.53 (chloroform:methanol:acetic acid=15:2:1).

Comparative Example 1(40)

[0159] 4-(N-1RS-(ethoxycarbonyl)-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

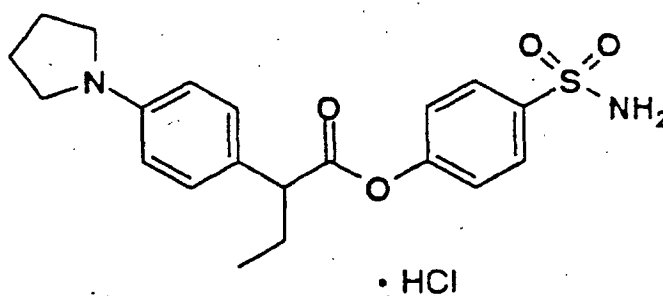


[0160] NMR (CDCl₃): δ 7.84 (2H, d, J=8.6Hz), 7.20 (2H, d, J=8.6Hz), 7.12 (2H, d, J=8.6Hz), 6.55 (2H, d, J=8.6Hz), 4.01 (3H, m), 3.57 (5H, m), 3.29 (4H, t, J=6.4Hz), 2.63 (2H, m), 2.36 (4H, m), 2.14 (1H, m), 2.01 (4H, m), 1.89 (1H, m), 1.17 (3H, t, J=7.0Hz), 0.97 (3H, t, J=7.4Hz);

[0161] TLC : R_f 0.34 (hexane:ethyl acetate=1:1).

Example 1(46)

[0162] 4-sulfamoylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

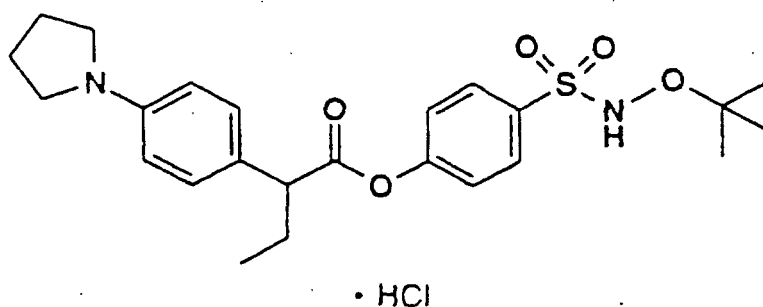


[0163] NMR (CD₃OD): δ 7.88 (2H, d, J=8.6Hz), 7.18 (2H, d, J=8.8Hz), 7.11 (2H, d, J=8.8Hz), 6.57 (2H, d, J=8.6Hz), 3.61 (1H, t, J=7.6Hz), 3.34-3.19 (4H, m), 2.26-2.00 and 2.00-1.70 (each 1H, m), 2.07-1.96 (4H, m), 0.96 (3H, t, J=7.4Hz);

[0164] TLC : R_f 0.22 (acetic acid:methanol:chloroform=1:2:40).

Example 1(49)

[0165] 4-(N-t-butyloxysulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



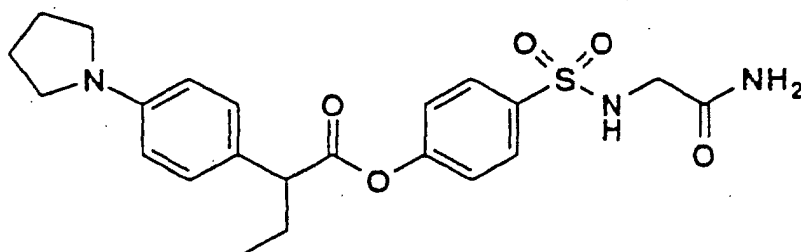
EP 0 769 498 B9 (W1B1)

[0166] NMR (CDCl₃): δ 7.88 (2H, d, J=8.8Hz), 7.24-7.15 (4H, m), 6.56 (2H, d, J=8.2Hz), 6.44 (1H, s), 3.59 (1H, t, J=7.2Hz), 3.33-3.26 (4H, m), 2.45-1.80 (6H, m), 1.21 (9H, s), 0.98 (3H, t, J=7.2Hz);

[0167] TLC : R_f 0.40 (hexane:ethyl acetate:acetic acid=5:2:0.1).

Comparative Example 1(56)

[0168] 4-(N-(carbamoylmethyl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

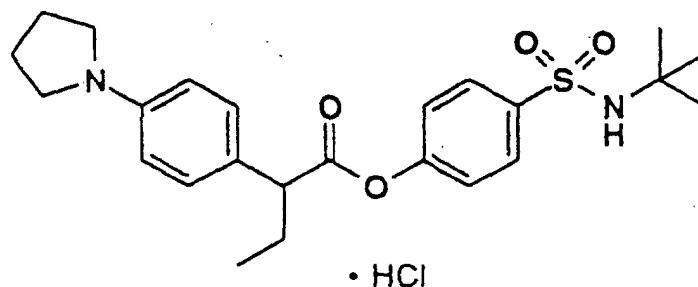


[0169] NMR (CDCl₃): δ 7.78 (2H, d, J=8.7Hz), 7.20 (2H, d, J=8.6Hz), 7.11 (2H, d, J=8.7Hz), 6.54 (2H, d, J=8.6Hz), 6.42-6.30 (1H, brs), 6.20-5.96 (2H, m), 3.58 (1H, t, J=7.8Hz), 3.50 (2H, s), 3.38-3.18 (4H, m), 2.26-1.74 (6H, m), 0.96 (3H, t, J=7.3Hz);

[0170] TLC : R_f 0.41 (chloroform:methanol=9:1).

Example 1 (57)

[0171] 4-(N-t-butylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

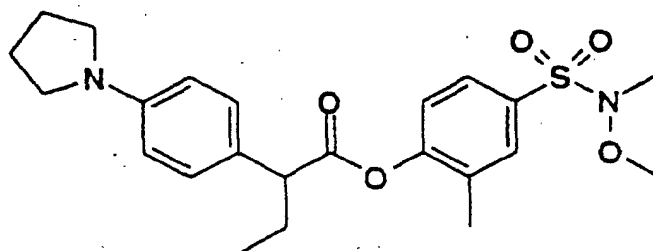


[0172] NMR (CDCl₃): δ 7.89 (2H, d, J=8.8Hz), 7.63 (2H, d, J=8.6Hz), 7.48 (2H, d, J=8.6Hz), 7.12 (2H, d, J=8.8Hz), 4.83 (1H, s), 3.74 (1H, t, J=7.6Hz), 3.80-3.50 (4H, m), 2.40-2.25 (4H, m), 2.40-2.10 and 2.05-1.75 (each 1H, m), 1.22 (9H, s), 1.00 (3H, t, J=7.4Hz);

[0173] TLC : R_f 0.55 (ethyl acetate:hexane=1:2).

Example 1(63)

[0174] 4-(N-methyl-N-methoxysulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

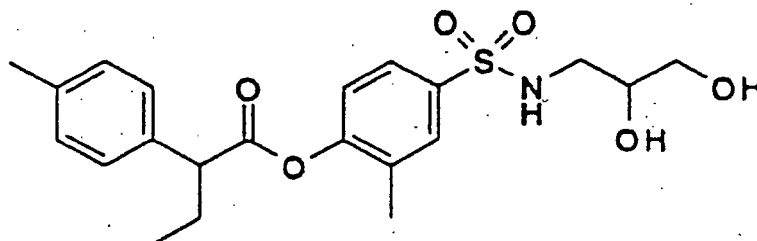


[0175] NMR (CDCl₃): δ 7.68 (1H, s), 7.66 (1H, d, J=8.4Hz), 7.22 (2H, d, J=8.6Hz), 7.11 (1H, d, J=8.4Hz), 6.55 (2H, d, J=8.6Hz), 3.78 (3H, s), 3.62 (1H, t, J=7.7Hz), 3.28 (4H, t, J=6.6Hz), 2.76 (3H, s), 2.3-2.1 (1H, m), 2.06 (3H, s), 2.1-1.9 (4H, m), 2.1-1.8 (1H, m), 0.99 (3H, t, J=7.3Hz);

[0176] TLC : R_f 0.36 (hexane:ethyl acetate=4:1).

Comparative Example 1(68)

[0177] 4-(N-2RS,3-dihydroxypropylsulfamoyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester

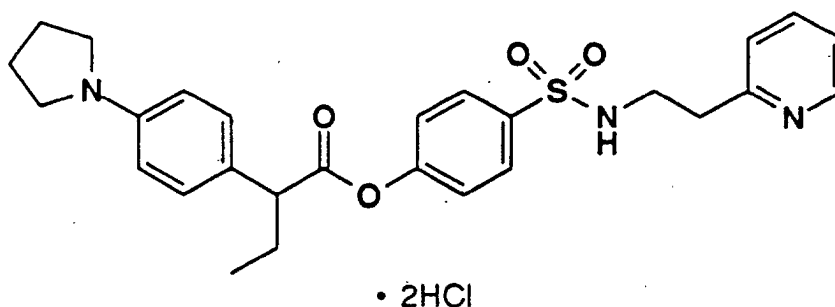


[0178] NMR (CDCl₃): δ 7.67-7.61 (2H, m), 7.27 (2H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 7.04 (1H, d, J=8Hz), 5.54 (1H, br), 3.80-3.46 (3H, m), 3.42 (1H, br), 3.70 (1H, t, J=8Hz), 3.11-2.87 (2H, m), 2.83 (1H, br), 2.35 (3H, s), 2.32-2.11 and 2.03-1.79 (each 1H, m), 1.98 (3H, s), 0.99 (3H, t, J=8Hz);

[0179] TLC : R_f 0.40 (chloroform:methanol:water=9:1:0.1).

Example 1(78)

[0180] 4-(N-2-(pyridin-2-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

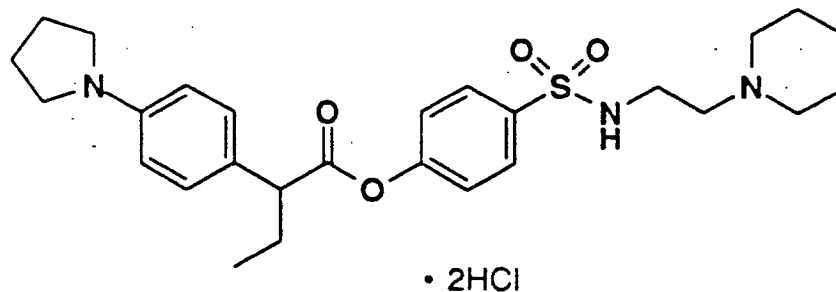


[0181] NMR (DMSO-d₆): δ 8.79 (1H, d, J=5.0Hz), 8.50 (1H, t, J=7.4Hz), 8.04 (1H, m), 7.90 (2H, m), 7.79 (2H, d, J=8.6Hz), 7.28 (2H, m), 7.21 (2H, d, J=8.4Hz), 6.90 (2H, m), 3.76 (1H, t, J=7.0Hz), 3.34 (4H, brs), 3.23 (4H, brs), 2.01 (5H, m), 1.80 (1H, m), 0.91 (3H, t, J=7.0Hz);

[0182] TLC : R_f 0.48 (chloroform:methanol:water=9:1:0.1).

Example 1(79)

[0183] 4-(N-2-(piperidin-1-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2hydrochloride

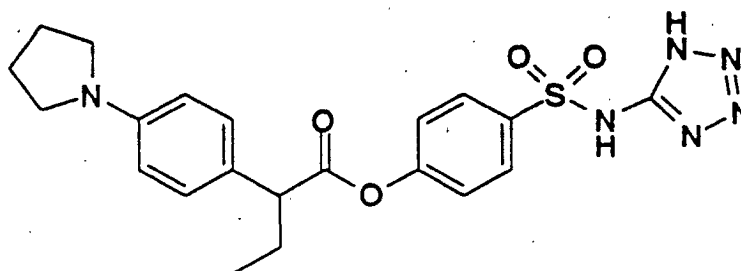


[0184] NMR (CD₃OD): δ 7.92 (2H, d, J=8.8Hz), 7.71 (2H, d, J=8.8Hz), 7.63 (2H, d, J=8.8Hz), 7.26 (2H, d, J=8.8Hz), 3.95 (1H, t, J=7.2Hz), 3.81 (4H, m), 3.55 (2H, brd, J=12.0Hz), 3.24 (4H, brs), 2.98 (2H, brt, J=12.0Hz), 2.32 (4H, m), 1.89 (7H, m), 1.55 (1H, m), 0.99 (3H, t, J=7.2Hz);

[0185] TLC : R_f 0.39 (chloroform:methanol:water=9:1:0.1).

Example 1(80)

[0186] 4-(N-(tetrazol-5-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

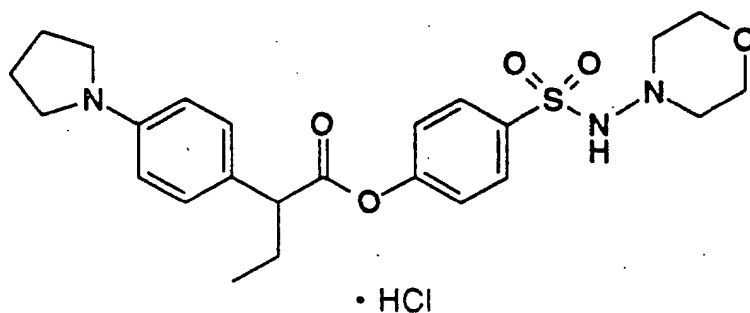


[0187] NMR (CD₃OD): δ 7.89 (2H, d, J=8.6Hz), 7.15 (2H, d, J=8.6Hz), 7.02 (2H, d, J=8.6Hz), 6.55 (2H, d, J=8.6Hz), 3.58 (1H, t, J=7.8Hz), 3.35-3.15 (4H, m), 2.20-1.95 and 1.95-1.70 (each 1H, m), 2.05-1.95 (4H, m), 0.93 (3H, t, J=7.2Hz);

[0188] TLC : R_f 0.46 (acetic acid:methanol:chloroform=1:5:25).

Example 1(81)

[0189] 4-(N-(morpholin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

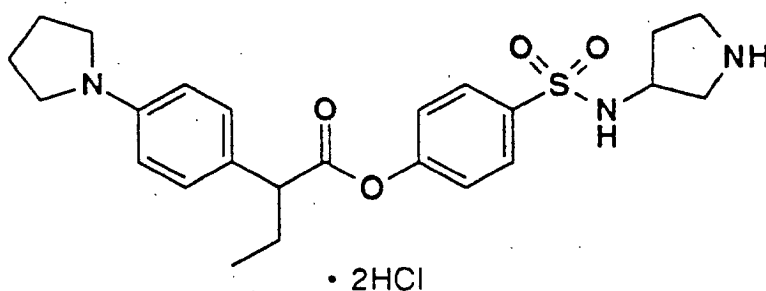


15 **[0190]** NMR (CDCl₃): δ 7.97 (2H, d, J=8.6Hz), 7.61 (2H, d-like), 7.48 (2H, d-like), 7.16 (2H, d, J=8.6Hz), 5.99 (1H, s), 3.74 (1H, t, J=7.8Hz), 3.76-3.63 (4H, m), 3.65-3.54 (4H, m), 2.70-2.58 (4H, m), 2.42-2.29 (4H, m), 2.37-2.10 and 2.04-1.77 (each 1H, m), 1.00 (3H, t, J=7.2Hz);

[0191] TLC : R_f 0.45 (methanol:chloroform=1:20).

Example 1(82)

20 **[0192]** 4-(N-(pyrrolidin-3-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

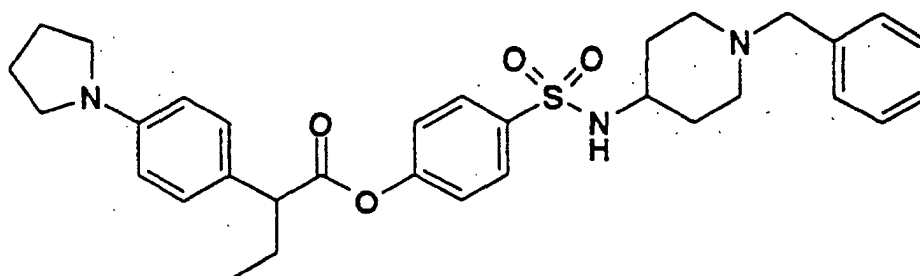


35 **[0193]** NMR (CDCl₃): δ 7.7-7.5 (4H, m), 7.42 (2H, d, J=8.6Hz), 6.96 and 6.92 (2H, d, J=8.6Hz), 4.35-4.13 (1H, m), 3.5-2.9 (10H, m), 2.40-2.25 (4H, m), 2.20-1.55 (4H, m), 0.94 (3H, t, J=7.2Hz);

[0194] TLC : R_f 0.35 (methanol:chloroform=1:10).

Example 1(83)

40 **[0195]** 4-(N-(1-benzylpiperidin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

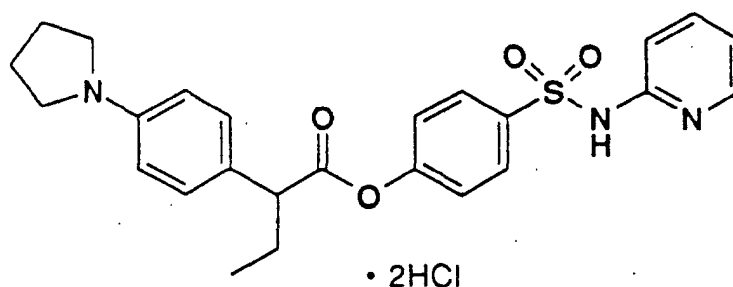


55 **[0196]** NMR (CDCl₃): δ 7.82 (2H, d, J=9.0Hz), 7.36-7.08 (5H, m), 7.21 (2H, d, J=9.0Hz), 7.13 (2H, d, J=8.8Hz), 6.55 (2H, d, J=8.8Hz), 4.50 (1H, d, J=5.7Hz), 3.58 (1H, t, J=5.0Hz), 3.43 (2H, s), 3.36-3.21 (4H, m), 3.21-3.02 (1H, m), 2.78-2.61 (2H, m), 2.28-1.65 (10H, m), 1.56-1.34 (1H, m), 0.97 (3H, t, J=7.2Hz);

[0197] TLC : R_f 0.60 (ethyl acetate:hexane=9:1).

Example 1(84)

[0198] 4-(N-(pyridin-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

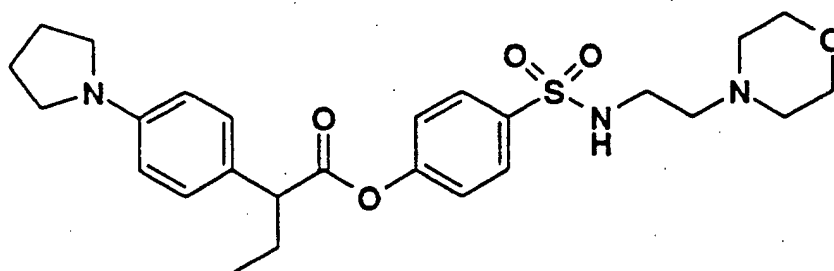


[0199] NMR (CDCl₃): δ 8.26 (1H, d, J=6.0Hz), 7.96 (2H, d, J=8.6Hz), 7.83 (1H, t, J=8.6Hz), 7.72 (2H, d, J=9.0Hz), 7.55 (1H, d, J=8.6Hz), 7.48 (2H, d, J=8.6Hz), 7.12 (2H, d, J=6.6Hz), 6.95 (1H, t, J=6.0Hz), 3.74 (1H, t, J=7.6Hz), 3.80-3.60 (4H, m), 2.44-2.24 (4H, m), 2.32-2.02 and 2.02-1.72 (each 1H, m), 0.97 (3H, t, J=7.2Hz);

[0200] TLC : R_f 0.51 (ethyl acetate:hexane=2:1).

Example 1(85)

[0201] 4-(N-2-(morpholin-4-yl)ethylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

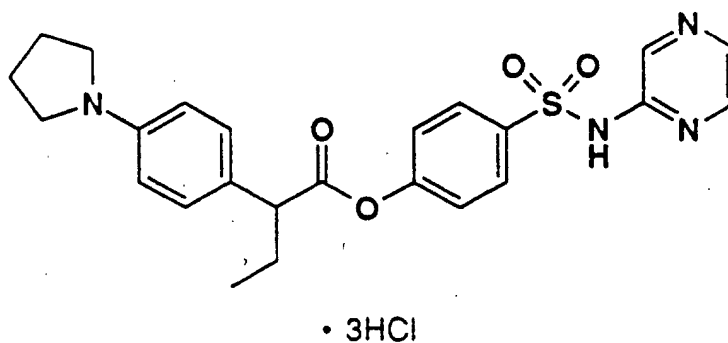


[0202] NMR (CDCl₃): δ 7.83 (2H, d, J=8.9Hz), 7.21 (2H, d, J=8.7Hz), 7.13 (2H, d, J=8.9Hz), 6.55 (2H, d, J=8.7Hz), 6.23-5.06 (1H, brs), 3.64-3.52 (5H, m), 3.36-3.20 (4H, m), 2.98 (2H, t, J=6.0Hz), 2.38 (2H, t, J=6.0Hz), 2.30-2.20 (4H, m), 2.20-1.70 (6H, m), 0.97 (3H, t, J=7.2Hz);

[0203] TLC : R_f 0.24 (ethyl acetate:hexane=7:3).

Example 1 (86)

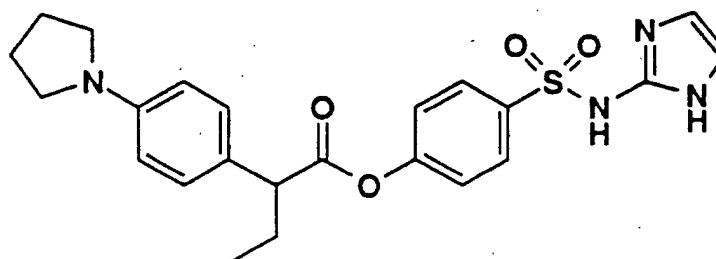
[0204] 4-(N-(pyrazin-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 3hydrochloride



[0205] NMR (CDCl₃): δ 8.46 (1H, s), 8.17 (2H, s), 8.01 (2H, d, J=8.2Hz), 7.7-7.4 (4H, m), 7.14 (2H, d, J=8.2Hz), 3.9-3.5 (5H, m), 2.5-2.2 (4H, m), 2.4-2.1 and 2.1-1.8 (each 1H, m), 0.98 (3H, t, J=7.2Hz);
[0206] TLC : R_f 0.18 (hexane:ethyl acetate=1:1).

Example 1(87)

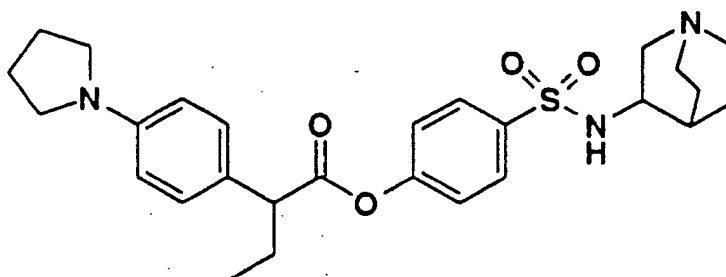
[0207] 4-(N-(imidazol-2-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



[0208] NMR (CDCl₃): δ 7.90 (2H, d, J=8.8Hz), 7.19 (4H, d, J=8.8Hz), 6.81 (1H, d, J=2.0Hz), 6.54 (1H, d, J=2.0Hz), 6.54 (2H, d, J=8.8Hz), 3.57 (1H, t, J=7.8Hz), 3.28 (4H, t-like), 2.30-2.00 and 2.00-1.70 (each 1H, m), 2.00 (4H, t-like), 0.96 (3H, t, J=7.4Hz);
[0209] TLC : R_f 0.67 (methanol:chloroform=1:10).

Example 1(88)

[0210] 4-(N-(quinuclidin-3RS-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



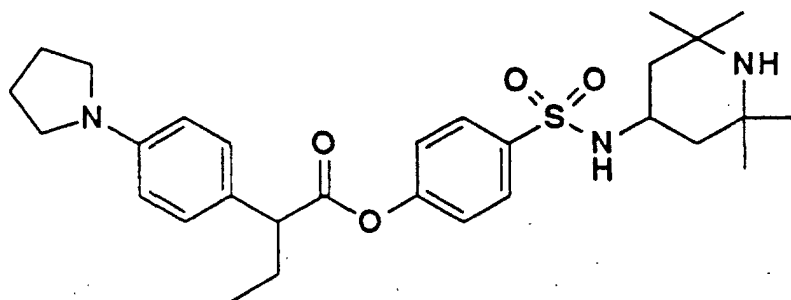
[0211] NMR (CDCl₃): δ 7.88 (2H, d, J=8.8Hz), 7.21 (2H, d, J=8.8Hz), 7.11 (2H, d, J=8.8Hz), 6.55 (2H, d, J=8.8Hz), 3.58 (1H, t, J=7.6Hz), 3.60-3.47 (1H, m), 3.35-3.20 (4H, m), 3.30-2.80 (6H, m), 2.10-1.95 (4H, m), 2.30-1.40 (7H, m),

0.98 (3H, t, J=7.2Hz);

[0212] TLC : Rf 0.43 (acetic acid:methanol:chloroform=1 :5:25).

Example 1(89)

[0213] 4-(N-(2,2,6,6-tetramethylpiperidin-4-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

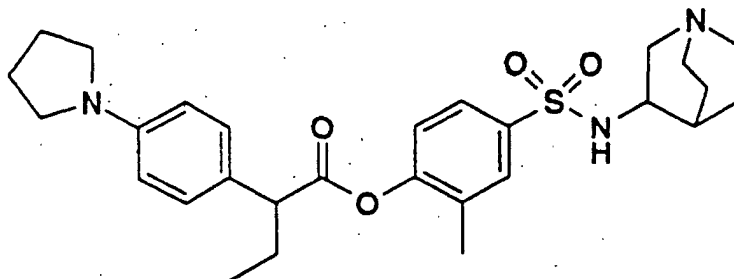


[0214] NMR (CDCl₃+CD₃OD): δ 7.85 (2H, d, J=8.8Hz), 7.22 (2H, d, J=8.6Hz), 7.14 (2H, d, J=8.8Hz), 6.57 (2H, d, J=8.6Hz), 3.59 (1H, t, J=7.8Hz), 3.60-3.42 (1H, m), 3.35-3.20 (4H, m), 2.30-1.75 (2H, m), 2.06-1.96 (4H, m), 1.63 (2H, dd, J=13.2 and 3.8Hz), 1.33-1.08 (2H, m), 1.19 (12H, s), 0.98 (3H, t, J=7.3Hz);

[0215] TLC : Rf 0.55 (chloroform:methanol:acetic acid=25:5:1).

Example 1(90)

[0216] 4-(N-(quinuclidin-3RS-yl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

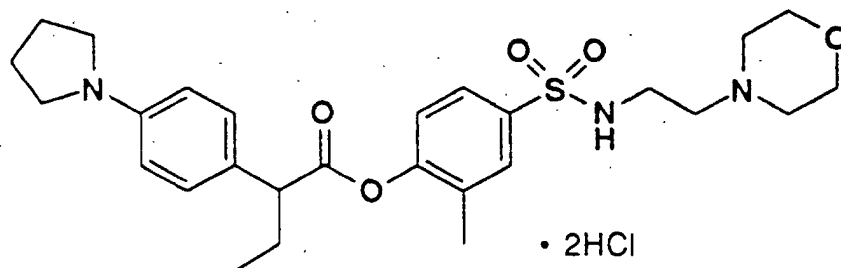


[0217] NMR (CDCl₃): δ 7.69 (1H, d, J=2Hz), 7.66 (1H, dd, J=8 and 2Hz), 7.30-7.13 (2H, m), 7.06 (1H, d, J=8Hz), 6.55 (2H, d, J=9Hz), 3.62 (1H, t, J=8Hz), 3.38-3.23 (5H, m), 3.23-3.05 (1H, m), 2.90-2.48 (5H, m), 2.32-2.08 (1H, m), 2.04 (3H, s), 2.08-1.03 (10H, m), 0.99 (3H, t, J=7Hz);

[0218] TLC : Rf 0.43 (chloroform:methanol:water=8:2:0.2).

Example 1(91)

[0219] 4-(N-2-(morpholin-4-yl)ethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

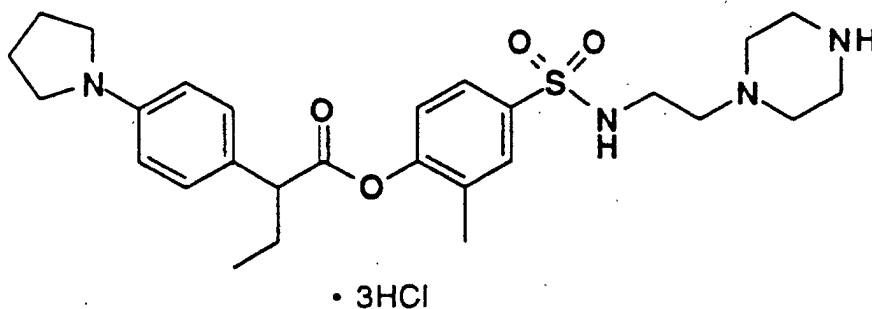


[0220] NMR (DMSO- d_6): δ 11.3-11.1 (1H, brs), 8.18 (1H, brs), 7.75 (1H, s), 7.70 (1H, d, $J=8.0$ Hz), 7.27 (2H, d, $J=8.6$ Hz), 7.18 (2H, d, $J=9.2$ Hz), 4.0-3.7 (5H, m), 3.4-3.0 (12H, m), 2.2-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.7 (1H, m), 1.98 (3H, s), 0.91 (3H, t, $J=7.3$ Hz);

[0221] TLC : Rf 0.50 (chloroform:methanol=9:1).

Example 1(92)

[0222] 4-(N-(2-(piperazin-4-yl)ethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 3hydrochloride

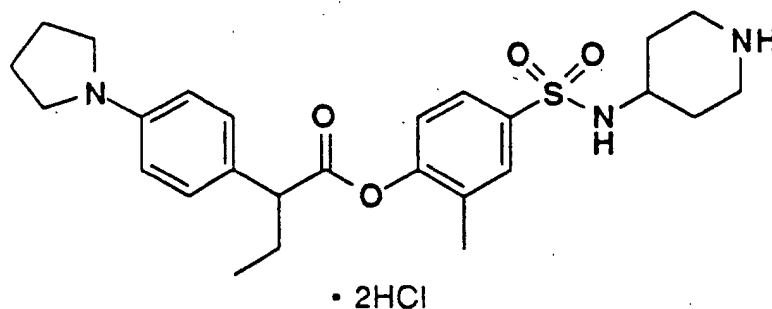


[0223] NMR (DMSO- d_6): δ 9.6-9.2 (2H, br), 7.71 (1H, s), 7.67 (1H, d, $J=8.0$ Hz), 7.18 (2H, d, $J=8.4$ Hz), 7.14 (1H, d, $J=8.0$ Hz), 6.53 (2H, d, $J=8.4$ Hz), 3.69 (1H, t, $J=7.3$ Hz), 3.7-2.6 (16H, br), 2.2-2.0 (1H, m), 2.0-1.9 (4H, brs), 1.96 (3H, s), 1.9-1.7 (1H, m), 0.90 (3H, t, $J=7.1$ Hz);

[0224] TLC : Rf 0.46 (chloroform:methanol:acetic acid=25:5:1).

Example 1(93)

[0225] 4-(N-(piperidin-4-yl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride



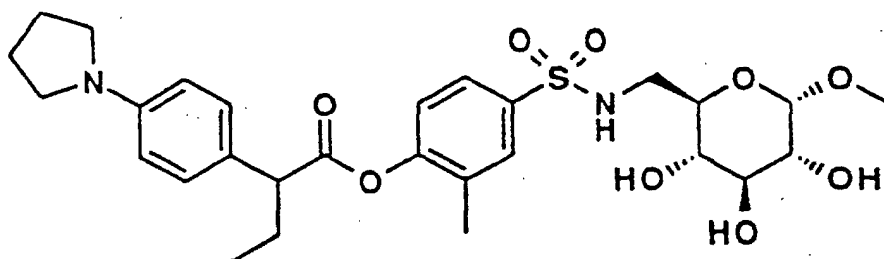
EP 0 769 498 B9 (W1B1)

[0226] NMR (DMSO- d_6): δ 9.1-8.7 (1H, br), 8.00 (1H, d, $J=7.2$ Hz), 7.71 (1H, s), 7.68 (1H, d, $J=8.4$ Hz), 7.26 (2H, d, $J=8.4$ Hz), 7.15 (1H, d, $J=8.4$ Hz), 6.79 (2H, d, $J=8.4$ Hz), 3.76 (1H, t, $J=7.8$ Hz), 3.4-3.2 (4H, brs), 3.2-3.0 (3H, br), 3.0-2.7 (2H, br), 2.2-1.9 (1H, m), 1.99 (4H, brs), 1.97 (3H, s), 1.9-1.5 (5H, m), 0.91 (3H, t, $J=7.3$ Hz);

[0227] TLC : R_f 0.46 (chloroform:methanol:acetic acid=25:5:1).

Example 1(103)

[0228] 4-(N-2R-methoxy-3R-hydroxy-4S-hydroxy-5R-hydroxyperhydropyran-6R-ylmethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

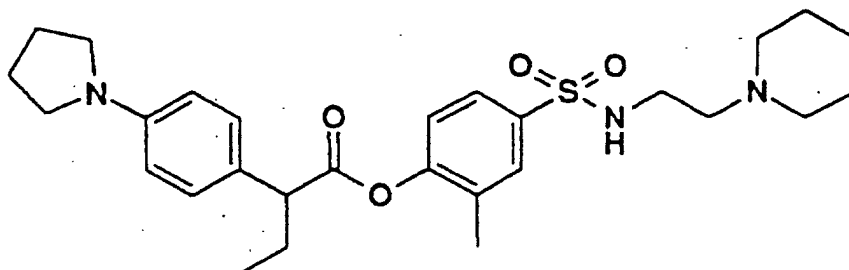


[0229] NMR (CDCl₃+6 drops of CD₃OD): δ 7.68-7.63 (m, 2H), 7.22 (d, $J=8.8$ Hz, 2H), 7.05 (d, $J=8.1$ Hz, 1H), 6.55 (d, $J=8.8$ Hz, 2H), 4.63 (d, $J=3.7$ Hz, 1H), 3.70-3.50 (m, 3H), 3.50-3.10 (m, 11H), 2.30-1.80 (m, 9H), 0.99 (t, $J=7.4$ Hz, 3H);

[0230] TLC : R_f 0.41 (chloroform:methanol=8:1).

Example 1(125)

[0231] 4-(2-(piperidin-1-yl)ethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

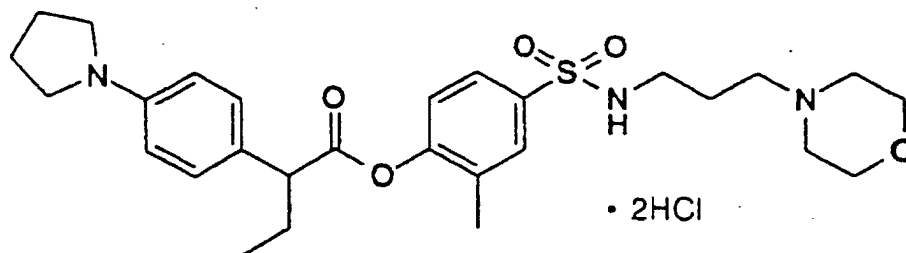


[0232] NMR (CDCl₃): δ 7.7-7.4 (m, 2H), 7.23 (d, $J=8.7$ Hz, 2H), 7.05 (d, $J=8.4$ Hz, 1H), 6.56 (d, $J=8.7$ Hz, 2H), 3.61 (t, $J=7.4$ Hz, 1H), 3.4-3.2 (m, 4H), 3.1-2.9 (m, 2H), 2.5-2.4 (m, 2H), 2.4-2.3 (m, 4H), 2.3-1.8 (m, 2H), 2.1-1.9 (m, 4H), 2.03 (s, 3H), 1.6-1.3 (m, 6H), 0.99 (t, $J=7.4$ Hz, 3H);

[0233] TLC : R_f 0.55 (chloroform:methanol=7:1).

Example 1(126)

[0234] 4-(3-(morpholin-4-yl)propylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

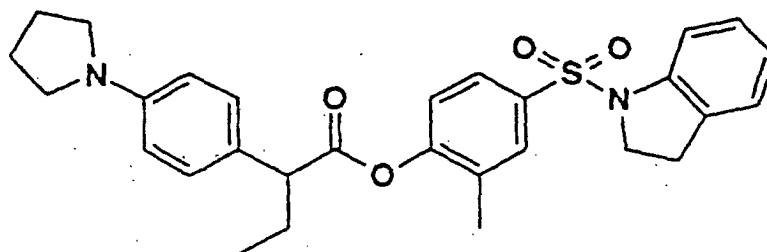


[0235] NMR (CDCl₃): δ 7.8-7.4 (m, 5H), 7.3-7.0 (m, 3H), 4.3-3.4 (m, 11H), 3.2-2.8 (m, 6H), 2.4-1.8 (m, 11H), 0.99 (t, J=7.2Hz, 3H);

[0236] TLC : R_f 0.56 (chloroform:methanol=9:1).

Example 1(127)

[0237] 4-(indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

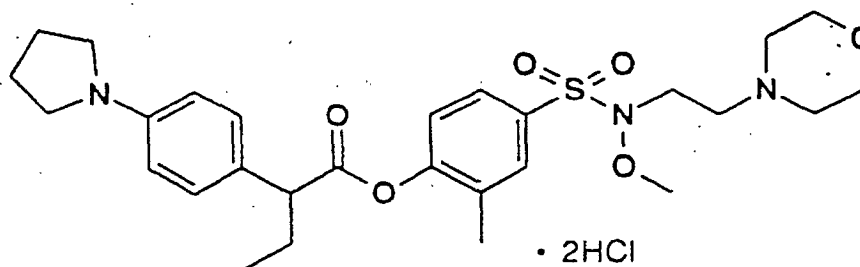


[0238] NMR (CDCl₃): δ 7.66-7.51 (3H, m), 7.24-6.88 (6H, m), 6.53 (2H, d, J=8.8Hz), 3.88 (2H, t, J=8.4Hz), 3.58 (1H, t, J=7.8Hz), 3.27 (4H, m), 2.89 (2H, t, J=8.4Hz), 2.29-1.72 (9H, m), 0.96 (3H, t, J=7.2Hz);

[0239] TLC : R_f 0.80 (hexane:ethyl acetate=1:1).

Example 1(129)

[0240] 4-(N-2-(morpholin-4-yl)ethyl-N-methoxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester hydrochloride

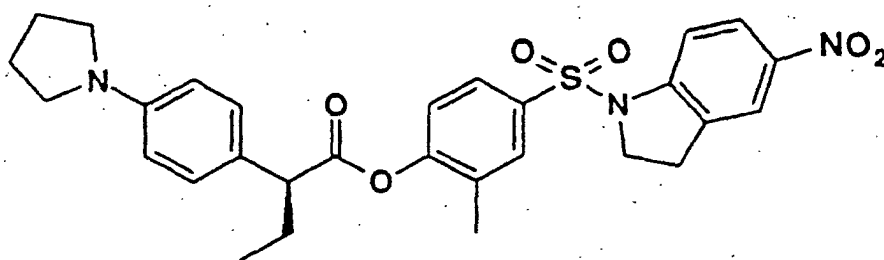


[0241] NMR (DMSO-d₆): δ 7.85-7.65 (2H, m), 7.27 (3H, d, J=8.0Hz), 6.95-6.70 (2H, brd), 4.05-3.70 (5H, m), 3.85 (3H, s), 3.50-2.95 (12H, m), 2.30-1.65 (6H, m), 2.02 (3H, s), 0.92 (3H, t, J=7.5Hz);

[0242] TLC : R_f 0.52 (hexane:ethyl acetate=2:1).

Example 1(130)

[0243] 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

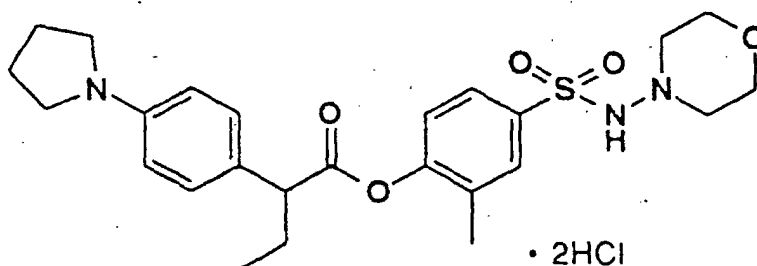


[0244] NMR (CDCl₃): δ8.10 (1H, d, J= 9.0Hz), 7.95 (1H, s), 7.72-7.56 (3H, m), 7.18 (2H, d, J=8.0Hz), 7.05 (1H, d, J=8.0Hz), 6.52 (2H, d, J=8.0Hz), 4.01 (2H, t, J=8.5Hz), 3.58 (1H, t, J=7.5Hz), 3.35-3.18 (4H, m), 3.08 (2H, t, J=8.5Hz), 2.30-1.70 (6H, m), 2.00 (3H, s), 0.96 (3H, t, J=7.5Hz);

[0245] TLC : R_f 0.60 (hexane:ethyl acetate=2:1).

Example 1(131)

[0246] 4-(morpholin-4-ylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

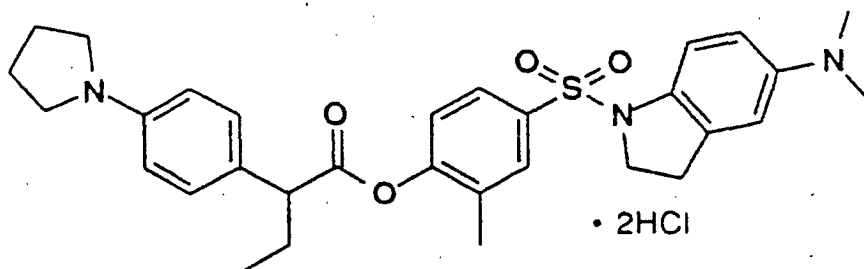


[0247] NMR (CD₃OD): δ7.84-7.70 (2H, m), 7.64 (4H, s-like), 7.13 (1H, d, J=8.2Hz), 3.97 (1H, t, J=7.4Hz), 3.87-3.66 (4H, m), 3.54 (4H, t, J=4.4Hz), 2.55 (4H, t, J=4.4Hz), 2.43-2.14 (5H, m), 2.14-1.80 (4H, m), 1.00 (3H, t, J=7.4Hz);

[0248] TLC : R_f 0.51 (hexane:ethyl acetate=1:1).

Example 1(133)

[0249] 4-(5-(N,N-dimethylamino)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2 hydrochloride



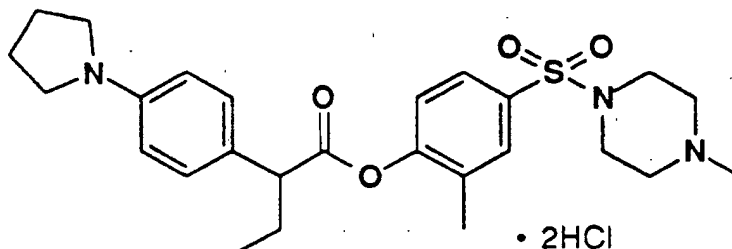
[0250] NMR (CD₃OD): δ7.78-7.64 (3H, m), 7.60 (4H, s-like), 7.52-7.42 (2H, m), 7.11 (1H, d, J=8.4Hz), 4.01 (2H, t,

J=8.5Hz), 3.93 (1H, t, J=8.4Hz), 3.87-3.70 (4H, m), 3.23 (6H, s), 3.06 (2H, t, J=8.5Hz), 2.40-2.10 (5H, m), 2.10-1.80 (4H, m), 0.97 (3H, t, J=7.2Hz);

[0251] TLC : Rf 0.24 (hexane :ethyl acetate=3:1).

Example 1(134)

[0252] 4-(4-methylpiperazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2 hydrochloride

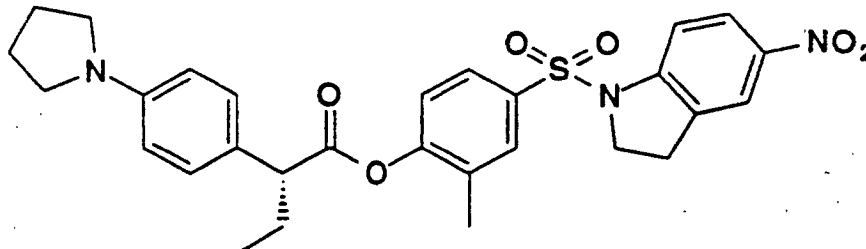


[0253] NMR (CD₃OD): δ7.75-7.59 (6H, m), 7.23 (1H, d, J=8.2Hz), 4.06-3.84 (3H, m), 3.84-3.68 (4H, m), 3.64-3.49 (2H, m), 3.32-3.11 (2H, m), 2.89 (3H, s), 2.84-2.64 (2H, m), 2.44-2.14 (5H, m), 2.13-1.82 (4H, m), 1.00 (3H, t, J=7.2Hz);

[0254] TLC : Rf 0.36 (ethyl acetate).

Example 1(135)

[0255] 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

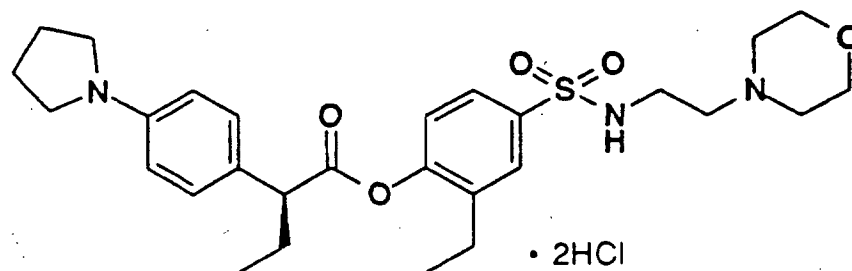


[0256] NMR (CDCl₃): δ8.10 (1H, dd, J=9.0, 2.2Hz), 7.95 (1H, d, J=2.2Hz), 7.66 (1H, d, J=9.0Hz), 7.66 (1H, s), 7.63 (1H, d, J=8.2Hz), 7.18 (2H, d, J=8.8Hz), 7.05 (1H, d, J=8.2Hz), 6.53 (2H, d, J=8.8Hz), 4.01 (2H, t, J=8.5Hz), 3.58 (1H, t, J=7.7Hz), 3.3-3.2 (4H, brs), 3.08 (2H, t, J=8.5Hz), 2.3-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.00 (3H, s), 2.0-1.8 (1H, m), 0.96 (3H, t, J=7.3Hz);

[0257] TLC : Rf 0.60 (hexane:ethyl acetate=2:1).

Example 1(136)

[0258] 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-ethylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

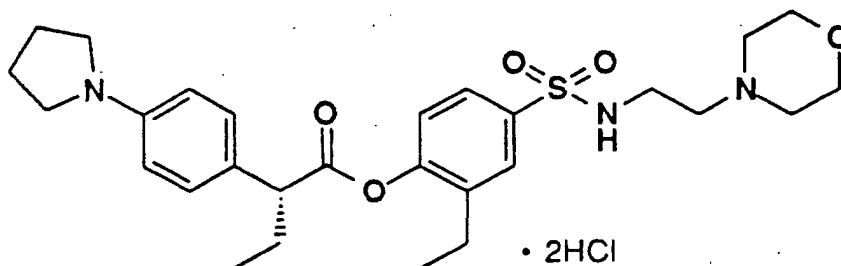


[0259] NMR (CD₃OD): δ7.83-7.58 (6H, m), 7.18 (1H, d, J=8.0Hz), 4.12-3.70 (9H, m), 3.53 (2H, d, J=12.0Hz), 3.38-3.08 (6H, m), 2.45-1.80 (8H, m), 1.00 (6H, t, J=7.5Hz);

[0260] TLC : R_f 0.41 (hexane:ethyl acetate=1:4).

Example 1(137)

[0261] 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-ethylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

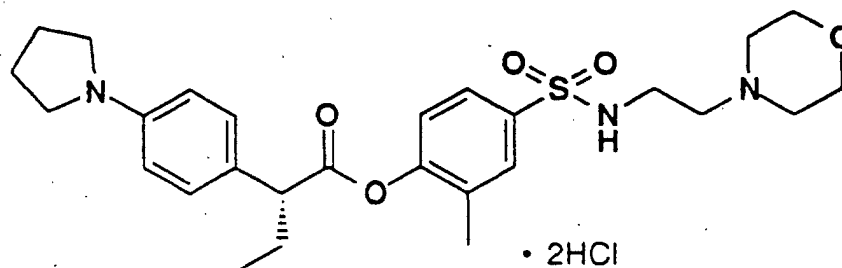


[0262] NMR (CD₃OD): δ7.83-7.58 (6H, m), 7.19 (1H, d, J=8.0Hz), 4.12-3.70 (9H, m), 3.53 (2H, d, J=12.0Hz), 3.40-3.08 (6H, m), 2.50-1.80 (8H, m), 0.99 (6H, t, J=7.5Hz);

[0263] TLC : R_f 0.41 (hexane:ethyl acetate=1:4).

Example 1(138)

[0264] 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

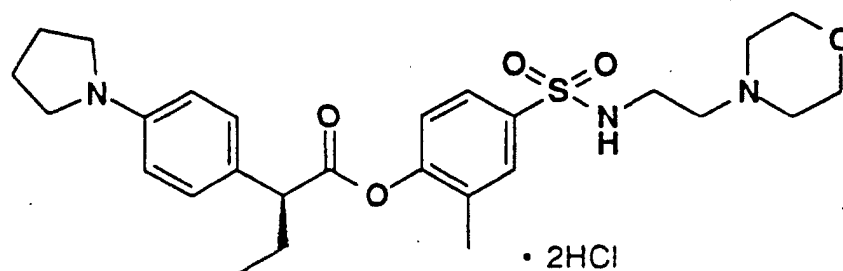


[0265] NMR (DMSO-d₆): δ11.0-10.8 (1H, brs), 7.75 (1H, s), 7.70 (1H, d, J=8.6Hz), 7.22 (2H, d, J=8.4Hz), 7.18 (1H, d, J=8.6Hz), 6.64 (2H, d, J=8.4Hz), 4.0-3.7 (5H, m), 3.4-3.0 (12H, m), 2.2-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.7 (1H, m), 1.97 (3H, s), 0.91 (3H, t, J=7.3Hz);

[0266] TLC : R_f 0.50 (chloroform:methanol=9:1).

Example 1(139)

[0267] 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

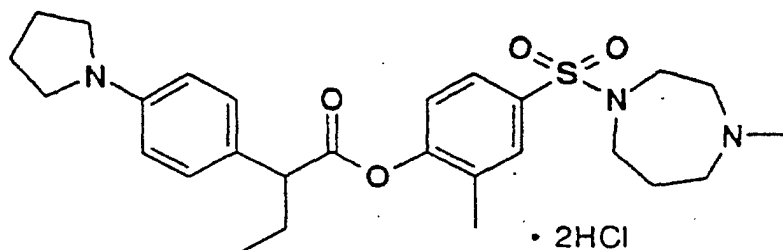


[0268] NMR (DMSO- d_6): δ 11.4-11.2 (1H, brs), 7.76 (1H, s), 7.70 (1H, d, $J=8.6$ Hz), 7.30 (2H, d, $J=8.4$ Hz), 7.18 (1H, d, $J=8.6$ Hz), 6.87 (2H, d, $J=8.4$ Hz), 4.0-3.7 (5H, m), 3.5-3.3 (6H, m), 3.3-3.0 (6H, m), 2.2-2.0 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.7 (1H, m), 1.98 (3H, s), 0.91 (3H, t, $J=7.2$ Hz);

[0269] TLC : R_f 0.50 (chloroform:methanol=9:1).

Example 1(140)

[0270] 4-(4-methyl-1,4-perhydropyridazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

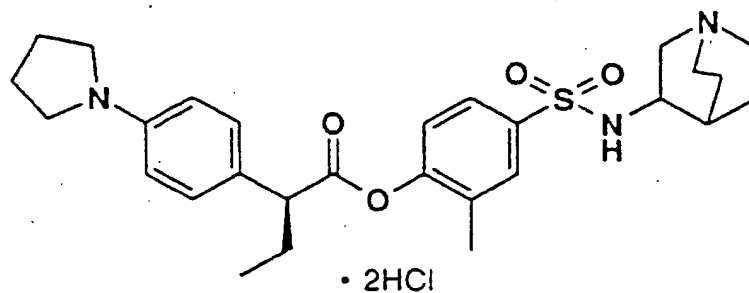


[0271] NMR (DMSO- d_6): δ 7.72 (1H, d, $J=2$ Hz), 7.66 (1H, dd, $J=2$ and 8Hz), 7.25 (2H, d, $J=8$ Hz), 7.19 (1H, d, $J=8$ Hz), 6.76 (2H, d-like), 3.76 (1H, t, $J=7$ Hz), 3.75-3.01 (12H, m), 2.76 and 2.74 (total 3H, each s), 2.21-1.66 (8H, m), 1.99 (3H, s), 0.91 (3H, t, $J=7$ Hz);

[0272] TLC : R_f 0.52 (chloroform:methanol:water=9:1:0.1).

Example 1(142)

[0273] 4-(quinuclidin-3RS-ylaminosulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride



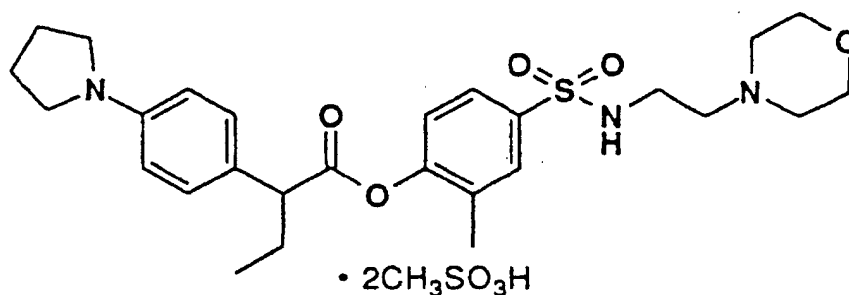
EP 0 769 498 B9 (W1B1)

[0274] NMR (DMSO- d_6): δ 8.35 (1H, d, $J=7$ Hz), 7.74-7.64 (2H, m), 7.26 (2H, d, $J=8$ Hz), 7.17 (1H, d, $J=8$ Hz), 6.82-6.70 (2H, br), 3.75 (1H, t, $J=7$ Hz), 3.61-3.43 (1H, br), 3.40-3.22 (5H, m), 3.18-2.94 (5H, m), 2.90-2.79 (1H, m), 2.17-1.60 (13H, m), 0.91 (3H, t, $J=7$ Hz);

[0275] TLC : R_f 0.35 (chloroform:methanol:water=8:2:0.2).

Example 1(143)

[0276] 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2methanesulfonic acid salt

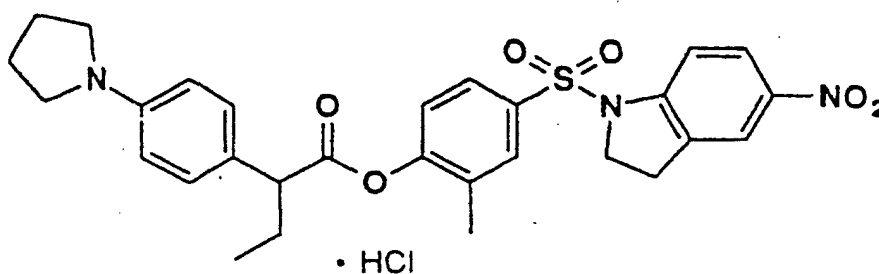


[0277] NMR (CD₃OD): δ 7.80-7.70 (2H, m), 7.67 (4H, s), 7.17 (1H, d, $J=8.0$ Hz), 4.10-3.70 (9H, m), 3.54 (2H, d, $J=12.0$ Hz), 3.40-3.10 (6H, m), 2.70 (6H, s), 2.40-1.80 (6H, m), 2.05 (3H, s), 1.00 (3H, t, $J=7.5$ Hz);

[0278] TLC : R_f 0.31 (chloroform:methanol:acetic acid=40:2:1).

Example 1(145)

[0279] 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

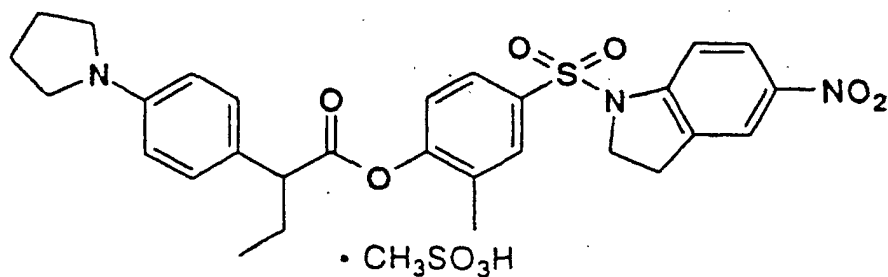


[0280] NMR (CDCl₃): δ 8.11 (1H, dd, $J=2.0, 9.0$ Hz), 7.96 (1H, d, $J=2.0$ Hz), 7.72-7.60 (3H, m), 7.55 (2H, d, $J=8.0$ Hz), 7.44 (2H, d, $J=8.0$ Hz), 7.06 (1H, d, $J=8.0$ Hz), 4.03 (2H, t, $J=8.5$ Hz), 3.75 (1H, t, $J=7.5$ Hz), 3.85-3.40 (4H, m), 3.10 (2H, t, $J=8.5$ Hz), 2.45-2.20 (4H, m), 2.40-1.75 (2H, m), 2.02 (3H, s), 0.98 (3H, t, $J=7.5$ Hz);

[0281] TLC : R_f 0.60 (hexane:ethyl acetate=2:1).

Example 1(146)

[0282] 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2 RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · methanesulfonic acid salt

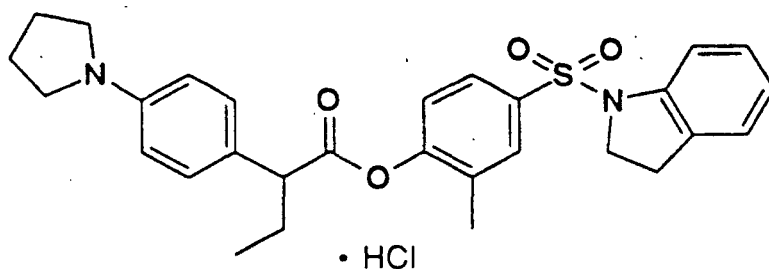


[0283] NMR (CDCl₃): δ 8.11 (1H, dd, J=2.5, 9.0Hz), 7.97 (1H, d, J=2.5Hz), 7.74-7.62 (3H, m), 7.57 (2H, d, J=8.5Hz), 7.49 (2H, d, J=8.5Hz), 7.07 (1H, d, J=8.0Hz), 4.03 (2H, t, J=8.5Hz), 3.77 (1H, t, J=7.5Hz), 4.10-3.30 (4H, m), 3.11 (2H, t, J=8.5Hz), 2.85 (3H, s), 2.50-2.20 (4H, m), 2.40-2.10 and 2.10-1.80 (each 1H, m), 2.04 (3H, s), 0.99 (3H, t, J=7.5Hz);

[0284] TLC : R_f 0.60 (hexane:ethyl acetate=2:1).

Example 1(147)

[0285] 4-(indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

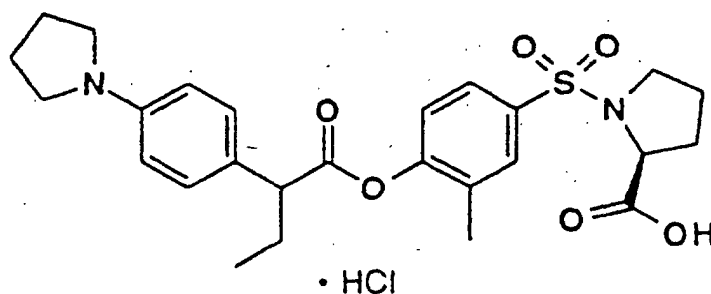


[0286] NMR (CDCl₃): δ 7.65-7.53 (3H, m), 7.32 (2H, d, J=8.4Hz), 7.24-6.90 (6H, m), 3.89 (2H, t, J=8.5Hz), 3.66 (1H, t, J=8.2Hz), 3.45 (4H, brs), 2.89 (2H, t, J=8.5Hz), 2.34-2.04 (5H, m), 1.97 (3H, s), 2.04-1.73 (1H, m), 0.97 (3H, t, J=7.2Hz);

[0287] TLC : R_f 0.42 (hexane:ethyl acetate=3:1).

Example 2

[0288] 4-(2S-carboxypyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



[0289] To a mixture solution of the compound prepared in example 1 (1.04 g) in dichloromethane(5 ml) and anisole (5 ml) were slowly added trifluoroacetic acid (5 ml) at 0 °C. The reaction mixture was stirred for 6h at room temperature. The reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (chloro-

form:methanol=20:1) to give N-{4-[2RS-(4-(1-pyrrolidinyl)phenyl)butyloxy]-3-methylphenyl sulfonyl}-L-proline. The obtained above compound was converted to hydrochloride salt by the following method. To a solution of N-{4-[2RS-(4-(1-pyrrolidinyl)phenyl)butyloxy]-3-methylphenyl sulfonyl}-L-proline in dioxane (5 ml) was added 4N hydrochloric acid in dioxane solution (1 ml) at 0 °C. The reaction mixture was stirred for 5 min, and reaction mixture was concentrated to give the title compound (1 g) having the following physical data.

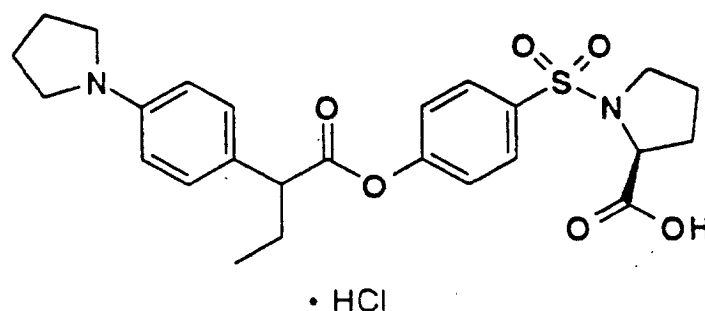
[0290] NMR (CDCl₃): δ 7.70 (1H, s), 7.67 (1H, d, J=8.0Hz), 7.59 (2H, d, J=8.5Hz), 7.49 (2H, d, J=8.5Hz), 7.07 (1H, d, J=8.0Hz), 4.26 (1H, dd, J=3.5, 7.0Hz), 3.78 (1H, t, J=7.5Hz), 3.75-3.60 (4H, m), 3.52-3.40 (1H, m), 3.33-3.14 (1H, m), 2.40-2.25 (4H, m), 2.40-1.65 (6H, m), 2.04 (3H, s), 1.00 (3H, t, J=7.5Hz);

[0291] TLC : R_f 0.39 (acetic acid:methanol:chloroform=1:2:40).

[0292] By the same procedure as Preparation example 1 and example 2 and by known methods converted to corresponding salts, acid addition salts or solvates, the compounds having the following physical data were given by using corresponding phenol derivatives instead of the compound prepared in reference example 4 and by using corresponding carboxylic acid derivatives instead of the compound prepared in reference example 7.

Example 2(1)

[0293] 4-(2S-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

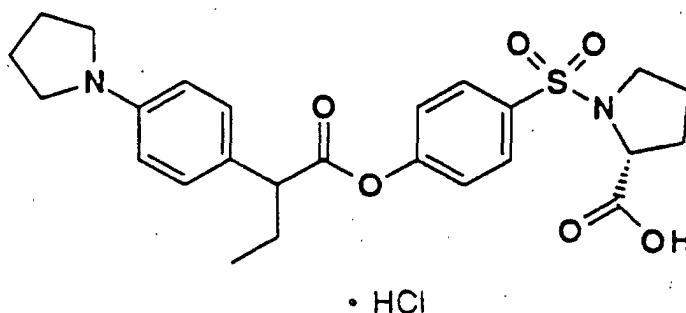


[0294] NMR (DMSO-d₆): δ 7.86 (2H, d, J=8Hz), 7.24 (4H, d, J=8Hz), 6.78 (2H, d, J=8Hz), 4.15-4.05 (1H, m), 3.73 (1H, t, J=7Hz), 3.40-3.05 (6H, m), 2.20-1.45 (10H, m), 0.89 (3H, t, J=7Hz);

[0295] TLC : R_f 0.26 (acetic acid:methanol:chloroform=1:2:60).

Example 2(2)

[0296] 4-(2R-carboxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester hydrochloride

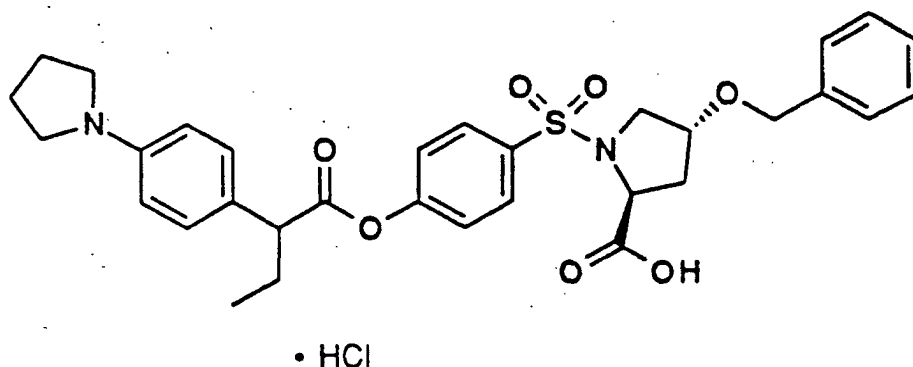


[0297] NMR (DMSO-d₆): δ 7.86 (2H, d, J=8.8Hz), 7.25 (4H, d, J=8.8Hz), 6.78 (2H, d, J=8.8Hz), 4.16-4.05 (1H, m), 3.74 (1H, t, J=7.2Hz), 3.44-3.06 (2H, m), 3.36-3.24 (4H, m), 2.22-1.46 (10H, m), 0.90 (3H, t, J=7.2Hz);

[0298] TLC : R_f 0.39 (acetic acid:methanol:chloroform=1:2:40).

Example 2(4)

[0299] 4-(2S-carboxy-4R-benzyloxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

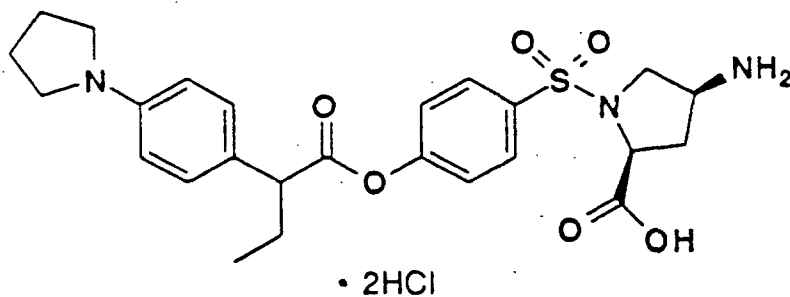


[0300] NMR (CDCl₃): δ 7.84 (2H, d, J=9Hz), 7.62 (2H, d, J=9Hz), 7.47 (2H, d, J=9Hz), 7.34-7.19 (3H, m), 7.17-7.00 (4H, m), 4.30 (1H, t, J=8Hz), 4.23 (2H, s), 4.15-4.03 (1H, m), 3.86-3.42 (7H, m), 2.47-2.05 (7H, m), 2.05-1.74 (1H, m), 0.97 (3H, t, J=7Hz);

[0301] TLC : R_f 0.35 (chloroform:methanol:acetic acid=40:2:1).

Example 2(5)

[0302] 4-(2S-carboxy-4S-aminopyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

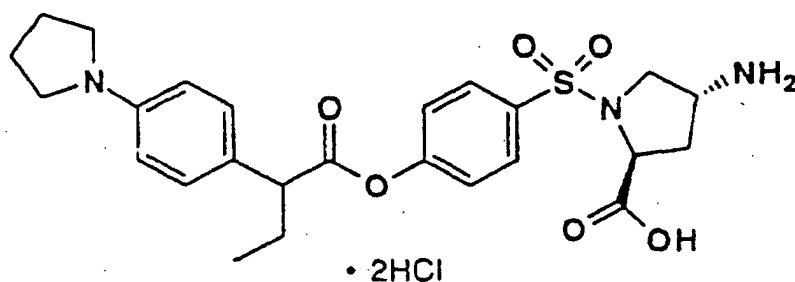


[0303] NMR (DMSO-d₆): δ 8.55-8.20 (2H, brs), 7.89 (2H, d, J=9Hz), 7.29 (2H, d, J=9Hz), 7.25 (2H, d, J=9Hz), 6.73 (2H, d, J=9Hz), 5.80-4.40 (1H, m), 4.18 (1H, t, J=7Hz), 3.74 (1H, t, J=7Hz), 3.64-3.10 (7H, m), 2.67-2.40 (1H, m), 2.20-1.65 (7H, m), 0.90 (3H, t, J=7Hz);

[0304] TLC : R_f 0.49 (ethyl acetate:acetic acid:water=6:2:1).

Example 2(6)

[0305] 4-(2S-carboxy-4R-aminopyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

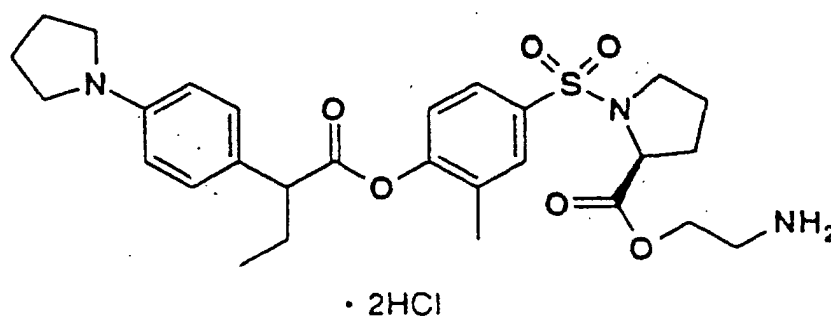


[0306] NMR (DMSO- d_6): δ 8.60-8.30 (2H, brs), 7.88 (2H, d, $J=9$ Hz), 7.28 (2H, d, $J=9$ Hz), 7.23 (2H, d, $J=9$ Hz), 6.72 (2H, d, $J=9$ Hz), 5.40-4.20 (1H, m), 4.40 (1H, dd, $J=9$ Hz, 4Hz), 3.90-3.50 (2H, m), 3.50-3.10 (6H, m), 2.33-1.60 (8H, m), 0.90 (3H, t, $J=7$ Hz);

[0307] TLC : R_f 0.42 (ethyl acetate :acetic acid:water=6:2:1).

Example 2(8)

[0308] 4-(2S-(2-aminoethoxycarbonyl)pyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

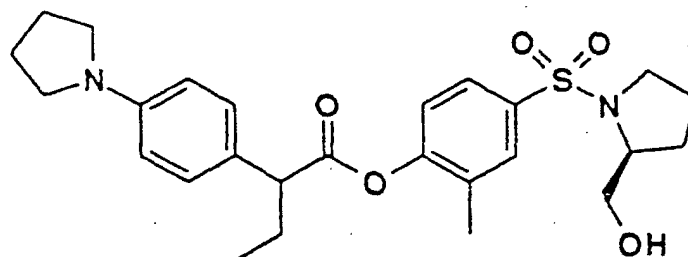


[0309] NMR (DMSO- d_6): δ 8.21 (2H, brs), 7.75 (1H, s), 7.69 (1H, d, $J=8.2$ Hz), 7.22 (3H, m), 6.70 (2H, d, $J=8.8$ Hz), 4.26 (3H, m), 3.50-3.36 (2H, m), 3.31 (4H, m), 3.20 (1H, m), 3.08 (2H, m), 2.12 (1H, m), 2.00 (3H, s), 1.96 (4H, m), 1.87 (4H, m), 1.66 (1H, m), 0.92 (3H, t, $J=7.2$ Hz);

[0310] TLC : R_f 0.31 (chloroform:methanol:acetic acid=12:1:1).

Preparation Example 2(10)

[0311] 4-(2S-hydroxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

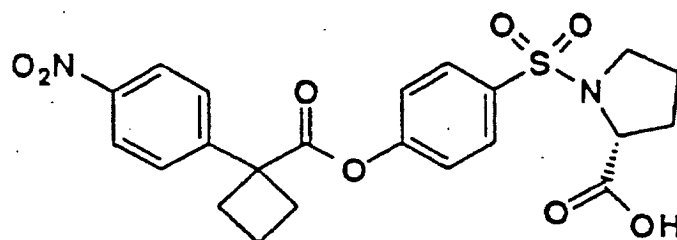


[0312] NMR (CDCl₃): δ 7.70-7.58 (2H, m), 7.22 (2H, d, $J=8.5$ Hz), 7.09 (1H, d, $J=8.0$ Hz), 6.55 (2H, d, $J=8.5$ Hz), 3.80-3.52 (3H, m), 3.62 (1H, t, $J=7.5$ Hz), 3.52-3.35 (1H, m), 3.35-3.12 (5H, m), 2.90-2.55 (1H, brs), 2.35-1.70 (2H, m),

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2.05 (3H, s), 2.05-1.95 (4H, m), 1.80-1.30 (4H, m), 0.99 (3H, t, J=7.5Hz);

[0313] TLC : Rf 0.36 (hexane:ethyl acetate=1:1).

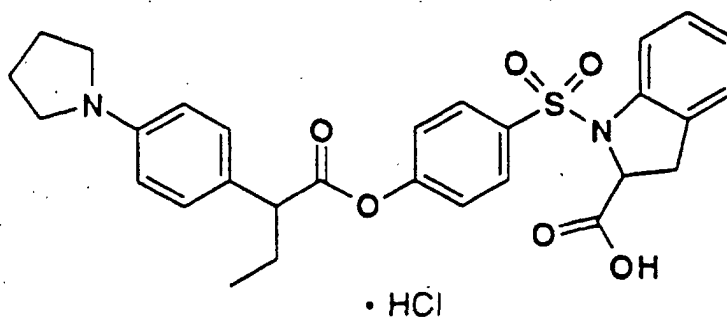


[0314] NMR (DMSO-d₆): δ 12.9-12.6 (1H, brs), 8.28 (2H, d, J=8.8Hz), 7.87 (2H, d, J=8.8Hz), 7.71 (2H, d, J=8.8Hz), 7.31 (2H, d, J=8.8Hz), 4.16-4.04 (1H, m), 3.43-3.10 (2H, m), 3.10-2.90 (2H, m), 2.75-2.55 (2H, q-like), 2.28-1.46 (6H, m);

[0315] TLC : Rf 0.46 (acetic acid:methanol:chloroform=1:2:40).

Example 2(31)

[0316] 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

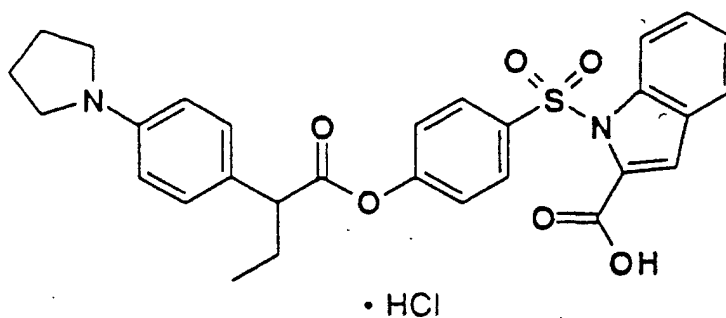


[0317] NMR (CDCl₃): δ 7.73 (2H, d, J=8.6Hz), 7.58 (1H, d, J=8.2Hz), 7.17 (2H, d, J=8.6Hz), 7.12-6.94 (5H, m), 6.53 (2H, d, J=8.8Hz), 4.73 (1H, dd, J=8.9Hz and 6.8Hz), 3.54 (1H, t, J=7.8Hz), 3.35-3.21 (4H, m), 3.17 (2H, d, J=6.8Hz), 2.25-1.70 (2H, m), 2.05-1.94 (4H, m), 0.95 (3H, t, J=7.2Hz);

[0318] TLC : Rf 0.46 (acetic acid:methanol:chloroform=1:2:40).

Example 2(32)

[0319] 4-(2-carboxyindol-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

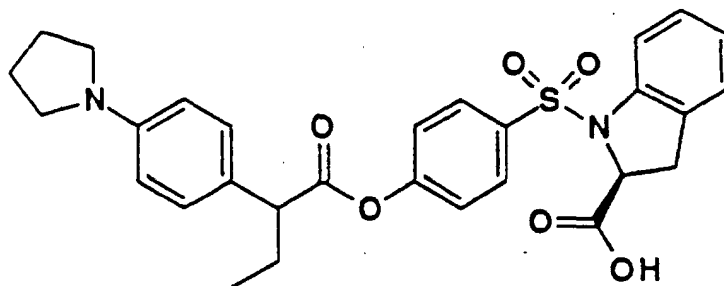


[0320] NMR (DMSO- d_6): δ 8.08 (2H, d, $J=8.8\text{Hz}$), 8.01 (1H, d, $J=8.4\text{Hz}$), 7.68 (1H, d, $J=8.0\text{Hz}$), 7.46 (1H, m), 7.40-7.16 (2H, m), 7.24 (2H, d, $J=8.8\text{Hz}$), 7.20 (2H, d, $J=8.6\text{Hz}$), 6.85-6.60 (2H, m), 3.69 (1H, t, $J=7.4\text{Hz}$), 3.40-3.15 (4H, m), 2.20-1.84 (5H, m), 1.84-1.60 (1H, m), 0.86 (3H, t, $J=7.4\text{Hz}$);

[0321] TLC : Rf 0.20 (chloroform:methanol:water=9:1:0.1).

Example 2(33)

[0322] 4-(2S-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

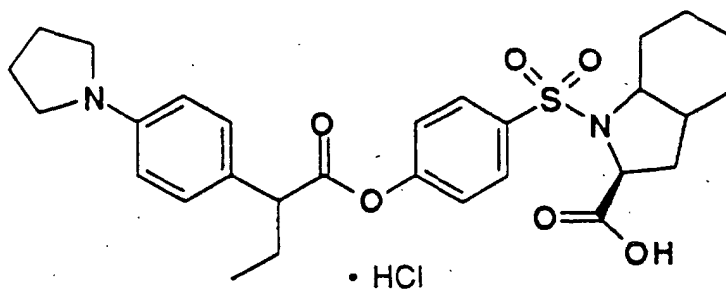


[0323] NMR (CDCl_3): δ 7.72 (2H, d, $J=8.6\text{Hz}$), 7.57 (1H, d, $J=7.8\text{Hz}$), 7.17 (2H, d, $J=8.6\text{Hz}$), 7.28-6.88 (5H, m), 6.53 (2H, d, $J=8.6\text{Hz}$), 4.72 (1H, dd, $J=5.8\text{Hz}$ and 9.1Hz), 3.54 (1H, t, $J=7.8\text{Hz}$), 3.35-3.22 (4H, m), 3.22-3.08 (2H, m), 2.25-1.70 (2H, m), 2.05-1.95 (4H, m), 0.95 (3H, t, $J=7.2\text{Hz}$);

[0324] TLC : Rf 0.46 (acetic acid:methanol:chloroform=1:2:40).

Example 2(34)

[0325] 4-(2S-carboxyperhydroindol-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

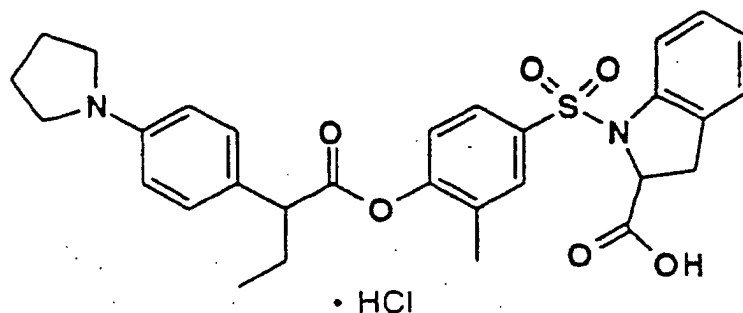


[0326] NMR (CDCl_3): δ 7.89 (2H, d, $J=8.8\text{Hz}$), 7.71 (2H, d, $J=8.6\text{Hz}$), 7.51 (2H, d, $J=8.6\text{Hz}$), 7.17 (2H, d, $J=8.8\text{Hz}$), 4.20 (1H, t, $J=8.6\text{Hz}$), 4.0-3.5 (6H, m), 2.5-2.2 (4H, m), 2.4-1.0 (13H, m), 0.99 (3H, t, $J=7.4\text{Hz}$);

[0327] TLC : Rf 0.60 (chloroform:methanol:acetic acid=40:2:1).

Example 2(35)

[0328] 4-(2RS-carboxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

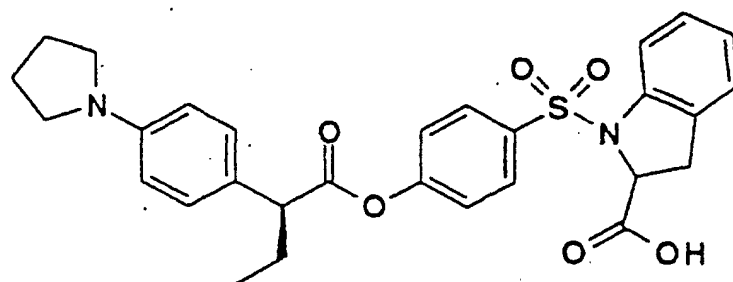


[0329] NMR (DMSO- d_6): δ 7.79 (1H, d-like), 7.67 (1H, dd, $J=2.2$ and 8.4Hz), 7.35-6.95 (7H, m), 6.71-6.67 (2H, m), 4.97 (1H, dd, $J=4.4$ and 10.7Hz), 3.71 (1H, t, $J=7.6$ Hz), 3.35-2.96 (6H, m), 2.14-1.68 (2H, m), 2.00-1.94 (4H, m), 1.91 (3H, s), 0.87 (3H, t, $J=7.2$ Hz);

[0330] TLC : R_f 0.45 (chloroform:methanol:water=8:2:0.2).

Example 2(37)

[0331] 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

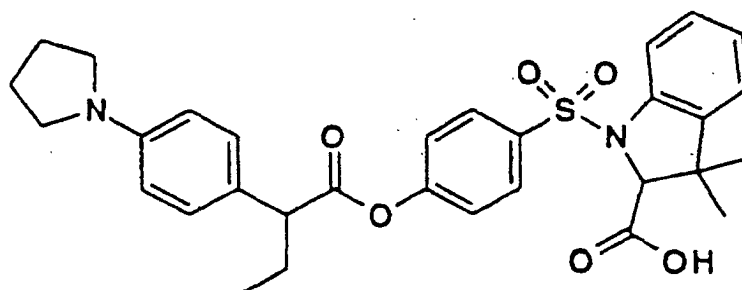


[0332] NMR (CDCl₃): δ 7.72 (2H, d, $J=8$ Hz), 7.59 (1H, d, $J=8$ Hz), 7.27-7.03 (7H, m), 6.54 (2H, d, $J=8$ Hz), 6.08 (1H, br), 4.77-4.69 (1H, m), 3.55 (1H, t, $J=8$ Hz), 3.31-3.24 (4H, m), 3.19-3.15 (2H, m), 2.20-1.76 (2H, m), 2.03-1.96 (4H, m), 0.95 (3H, t, $J=8$ Hz);

[0333] TLC : R_f 0.45 (chloroform:methanol:water=8:2:0.2).

Example 2(38)

[0334] 4-(2RS-carboxy-3,3-dimethylindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



[0335] NMR (CDCl₃): δ 7.83 (2H, d, $J=8.5$ Hz), 7.55 (1H, d, $J=8.0$ Hz), 7.25-6.93 (3H, m), 7.17 (2H, d, $J=8.5$ Hz), 7.09 (2H, d, $J=8.5$ Hz), 6.53 (2H, d, $J=8.5$ Hz), 4.36 (1H, s), 3.54 (1H, t, $J=8.0$ Hz), 3.35-3.10 (4H, m), 2.05-1.90 (4H, m),

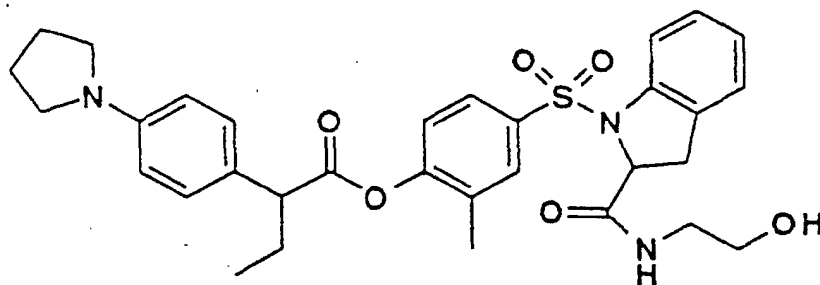
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2.25-1.70 (2H, m), 1.31 (3H, s), 1.04 (3H, s), 0.94 (3H, t, J=7.5Hz);

[0336] TLC : Rf 0.48 (chloroform:methanol:acetic acid=40:2:1).

Example 2(41)

[0337] 4-(2RS-(N-2-hydroxyethylcarbamoyl)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

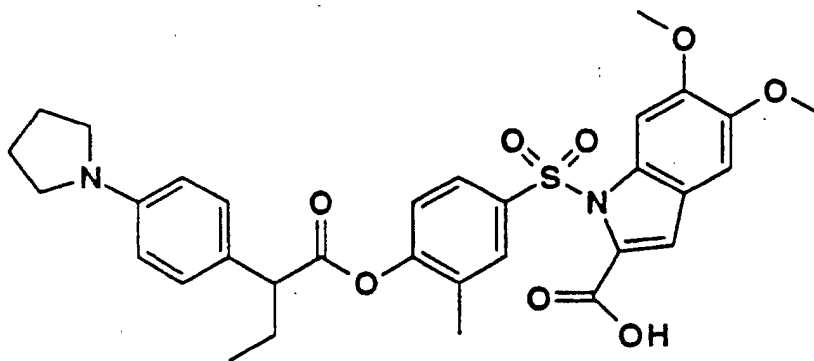


[0338] NMR (CDCl₃): δ 7.72 (1H, d, J=8.0Hz), 7.45-6.92 (9H, m), 6.51 (2H, d, J=8.6Hz), 4.57 (1H, dd, J=2.8, 10.6Hz), 3.77-3.52 (5H, m), 3.39-3.17 (5H, m), 2.88 (1H, dd, J=10.6, 16.8Hz), 2.23-1.78 (6H, m), 1.92 (3H, s), 0.96 (3H, t, J=7.4Hz);

[0339] TLC : Rf 0.43 (chloroform:methanol:acetic acid=25:5:1).

Example 2(42)

[0340] 4-(2-carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

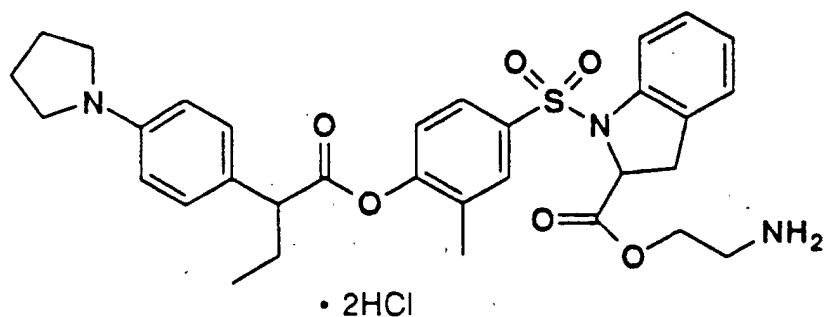


[0341] NMR (CDCl₃): δ 7.78-7.62 (3H, m), 7.35 (1H, s), 7.18 (2H, d, J=9Hz), 7.00 (1H, d, J=8Hz), 6.95 (1H, s), 6.52 (2H, d, J=9Hz), 4.00 (3H, s), 3.91 (3H, s), 3.70-3.10 (1H, brs), 3.57 (1H, t, J=7Hz), 3.35-3.18 (4H, m), 2.25-1.75 (9H, m), 0.96 (3H, t, J=7Hz).

[0342] TLC : Rf 0.19 (ethyl acetate:hexane:acetic acid=5:10:0.5).

Example 2(43)

[0343] 4-(2RS-(2-aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2hydrochloride

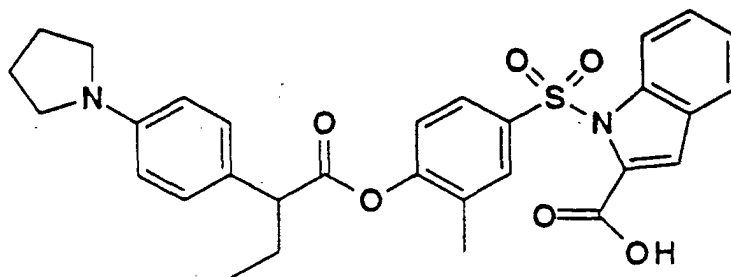


[0344] NMR (DMSO- d_6): δ 8.30 (2H, brs), 7.76 (1H, s), 7.66 (1H, d, $J=8.0$ Hz), 7.37 (1H, d, $J=8.0$ Hz), 7.23-7.00 (6H, m), 6.70 (2H, d, $J=8.0$ Hz), 5.08 (1H, dd, $J=6.2, 9.4$ Hz), 4.37-4.32 (2H, m), 3.69 (1H, t, $J=7.2$ Hz), 3.35-3.07 (8H, m), 2.14-1.69 (9H, m), 0.89 (3H, t, $J=7.2$ Hz);

[0345] TLC : Rf 0.46 (chloroform:methanol:acetic acid=25:5:1).

Example 2(44)

[0346] 4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

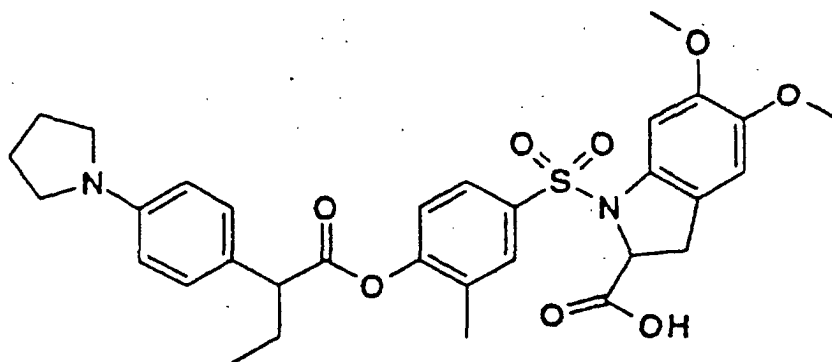


[0347] NMR (CDCl₃): δ 8.13 (1H, d, $J=9$ Hz), 7.90-7.78 (2H, m), 7.60 (1H, d, $J=9$ Hz), 7.46 (1H, td, $J=8.1$ Hz), 7.39 (1H, s), 7.35-7.25 (1H, m), 7.21 (2H, d, $J=9$ Hz), 6.75-6.50 (2H, m), 3.59 (1H, t, $J=7$ Hz), 3.38-3.23 (4H, m), 3.23-2.90 (1H, brs), 2.25-1.75 (6H, m), 0.96 (3H, t, $J=7$ Hz);

[0348] TLC : Rf 0.20 (ethyl acetate:hexane:acetic acid=5:10:0.5).

Example 2(45)

[0349] 4-(2RS-carboxy-5,6-dimethoxyindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

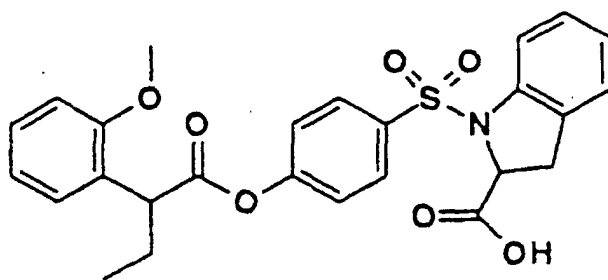


[0350] NMR (CDCl₃+CD₃OD): δ 7.6-7.4 (m, 2H), 7.26 (s, 1H), 7.19 (d, J=8.7Hz, 2H), 6.96 (dd, J=1.2, 8.4Hz, 1H), 6.58 (s, 1H), 6.54 (d, J=8.7Hz, 2H), 4.7-4.6 (m, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.58 (t, J=7.7Hz, 1H), 3.4-3.2 (m, 4H), 3.1-2.9 (m, 2H), 2.3-1.8 (m, 6H), 1.94 (s, 3H), 0.96 (t, J=7.4Hz, 3H);

[0351] TLC : R_f 0.45 (chloroform:methanol=4:1).

Comparative Example 2(62)

[0352] 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(2-methoxyphenyl)butanoic acid ester

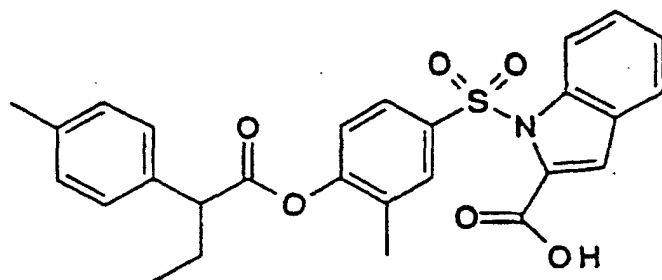


[0353] NMR (CDCl₃): δ 7.75 (2H, d, J=8.8Hz), 7.58 (1H, d, J=8.0Hz), 7.25 (2H, d, J=8.8Hz), 7.31-6.87 (7H, m), 4.74 (1H, t, J=8.0Hz), 4.04 (1H, t, J=7.2Hz), 3.84 (3H, s), 3.18 (2H, brd, J=7.2Hz), 2.22-2.05 (1H, m), 1.96-1.74 (1H, m), 0.95 (3H, t, J=7.6Hz);

[0354] TLC : R_f 0.48 (chloroform:methanol:acetic acid=40:2:1).

Comparative Example 2(69)

[0355] 4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester



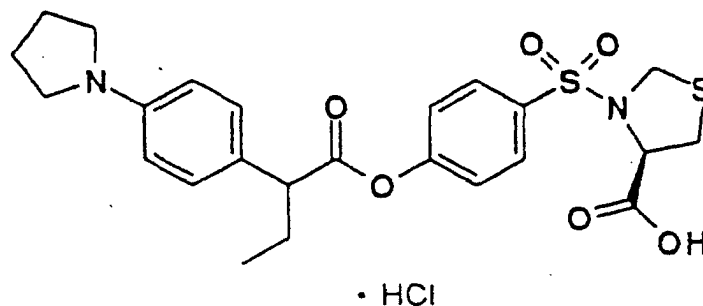
[0356] NMR (CDCl₃): δ 8.14 (1H, d, J=9Hz), 7.90-7.78 (2H, m), 7.60 (1H, d, J=9Hz), 7.52-7.41 (1H, m), 7.39 (1H,

s), 7.35-7.10 (5H, m), 7.03 (1H, d, J=9Hz), 4.00-3.60 (1H, br), 3.66 (1H, t, J=7Hz), 2.33 (3H, s), 2.30-2.07 (1H, m), 2.00-1.75 (1H, m), 1.97 (3H, s), 0.96 (3H, t, J=7Hz);

[0357] TLC : Rf 0.28 (ethyl acetate:hexane:acetic acid=5:10:0.5).

Example 2(77)

[0358] 4-(4S-carboxyperhydrothiazol-3-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

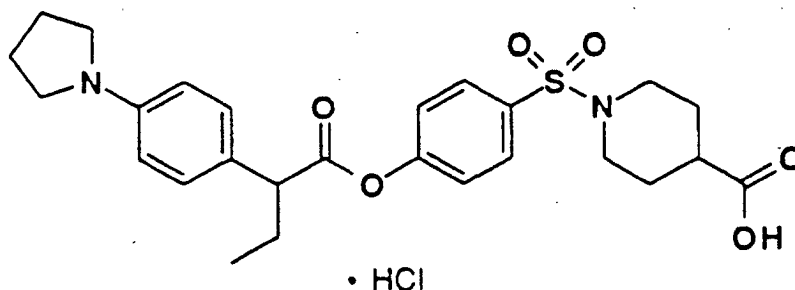


[0359] NMR (CDCl₃): δ 7.85 (2H, d, J=8.8Hz), 7.21 (2H, d, J=8.8Hz), 7.17 (2H, d, J=8.8Hz), 6.57 (2H, d, J=8.8Hz), 4.83 (1H, dd, J=7.0 and 3.4Hz), 4.67 (1H, d, J=9.0Hz), 4.40 (1H, d, J=9.0Hz), 3.59 (1H, t, J=7.6Hz), 3.40-3.18 (5H, m), 3.01 (1H, dd, J=11.4 and 7.0Hz), 2.30-2.05 and 2.05-1.75 (each 1H, m), 2.10-1.95 (4H, m), 0.98 (3H, t, J=7.6Hz);

[0360] TLC : Rf 0.36 (acetic acid:methanol:chloroform=1:2:40).

Example 2(78)

[0361] 4-(4-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

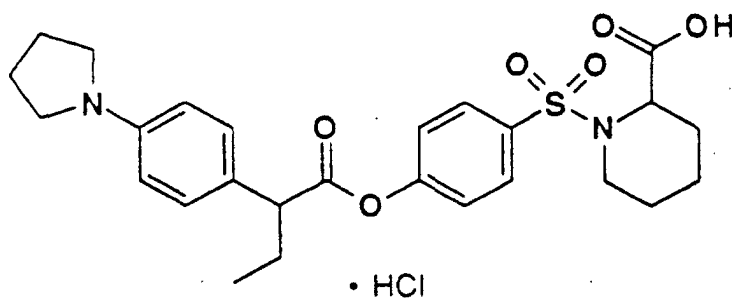


[0362] NMR (CDCl₃): δ 7.71 (2H, d, J=8.8Hz), 7.21 (2H, d, J=8.8Hz), 7.17 (2H, d, J=8.8Hz), 6.55 (2H, d, J=8.8Hz), 3.72-3.54 (2H, m), 3.59 (1H, t, J=7.6Hz), 3.36-3.20 (4H, m), 2.45 (2H, t-like), 2.38-1.70 (7H, m), 2.08-1.94 (4H, m), 0.98 (3H, t, J=7.4Hz);

[0363] TLC : Rf 0.34 (acetic acid:methanol:chloroform=1 : 2:40).

Example 2(79)

[0364] 4-(2RS-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

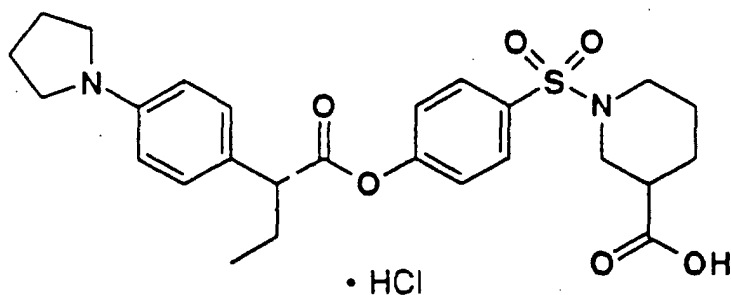


[0365] NMR (CDCl₃): δ 7.75 (2H, d, J=8.8Hz), 7.21 (2H, d, J=8.8Hz), 7.08 (2H, d, J=8.8Hz), 6.55 (2H, d, J=8.8Hz), 4.8-4.7 (1H, m), 3.8-3.7 (1H, m), 3.58 (1H, t, J=7.5Hz), 3.4-3.1 (5H, m), 2.3-1.2 (12H, m), 0.97 (3H, t, J=7.4Hz);

[0366] TLC : R_f 0.48 (acetic acid:methanol:chloroform=1:2:50).

Example 2(80)

[0367] 4-(3RS-carboxypiperidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester hydrochloride

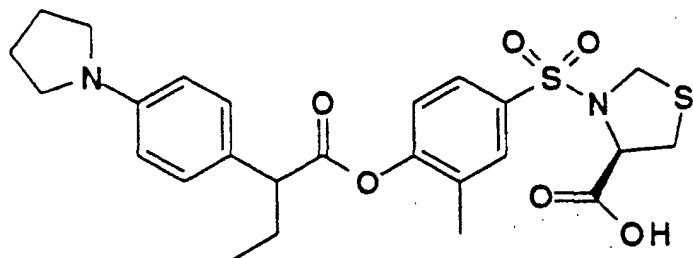


[0368] NMR (CDCl₃): δ 7.75 (2H, d, J=8.4Hz), 7.7-7.3 (4H, m), 7.19 (2H, d, J=8.4Hz), 4.0-3.4 (8H, m), 2.7-2.5 (2H, m), 2.5-2.1 (5H, m), 2.1-1.3 (5H, m), 1.00 (3H, t, J=7.4Hz);

[0369] TLC : R_f 0.32 (acetic acid:methanol:chloroform=1:2:100),

Example 2(81)

[0370] 4-(4S-carboxyperhydrothiazol-3-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



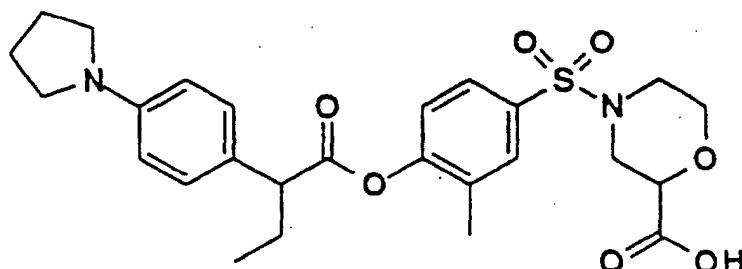
[0371] NMR (CDCl₃+CD₃OD): δ 7.69 (1H, s), 7.66 (1H, d, J=8.0Hz), 7.21 (2H, d, J=8.6Hz), 7.07 (1H, d, J=8.0Hz), 6.55 (2H, d, J=8.6Hz), 4.71 (1H, dd, J=7.2, 3.2Hz), 4.63 (1H, d, J=9.8Hz), 4.45 (1H, d, J=9.8Hz), 3.61 (1H, t, J=7.7Hz), 3.4-3.2 (5H, m), 2.84 (1H, dd, J=11.2, 7.2Hz), 2.3-2.1 (1H, m), 2.1-1.8 (4H, br), 2.02 (3H, s), 0.98 (3H, d, J=7.3Hz);

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[0372] TLC : R_f 0.55 (chloroform:methanol:acetic acid=25:5:1).

Example 2(82)

[0373] 4-(2RS-carboxymorpholin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

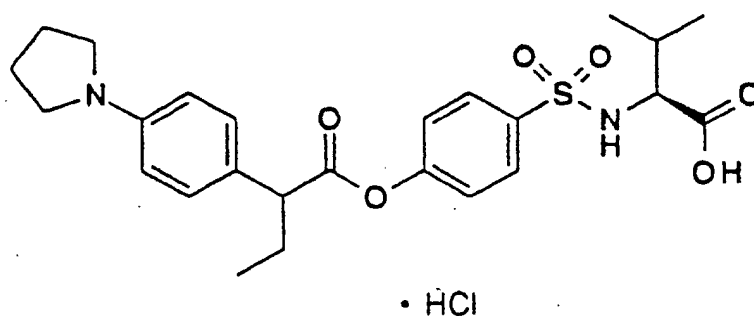


[0374] NMR (CD₃OD): δ 7.65-7.54 (2H, m), 7.20 (2H, d, J=8Hz), 7.15 (1H, d, J=8Hz), 6.58 (2H, d, J=8Hz), 4.03-3.80 (3H, m), 3.71-3.38 (3H, m), 3.37-3.15 (4H, m), 2.50-1.78 (11H, m), 0.97 (3H, t, J=7Hz);

[0375] TLC : R_f 0.25 (methanol:chloroform=3:17).

Example 2(92)

[0376] 4-(N-1S-carboxy-2-methylpropylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

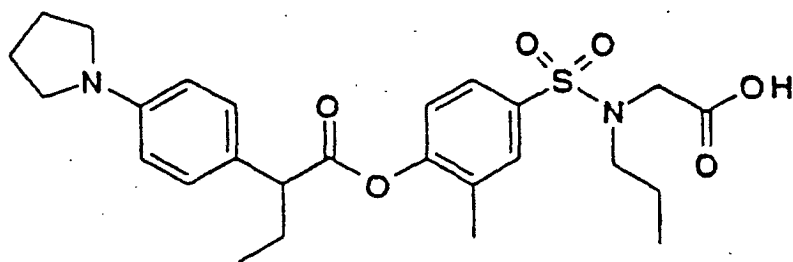


[0377] NMR (DMSO-d₆): δ 8.05 (1H, d, J=9Hz), 7.78 (2H, d, J=8Hz), 7.25 (2H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 6.86-6.70 (2H, m), 3.73 (1H, t, J=7Hz), 3.50 (1H, dd, J=9Hz, 6Hz), 3.38-3.20 (4H, m), 2.20-1.68 (7H, m), 0.88 (3H, t, J=7Hz), 0.80 (3H, d, J=7Hz), 0.76 (3H, d, J=7Hz);

[0378] TLC : R_f 0.34 (ethyl acetate).

Example 2(97)

[0379] 4-(N-propyl-N-carboxymethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

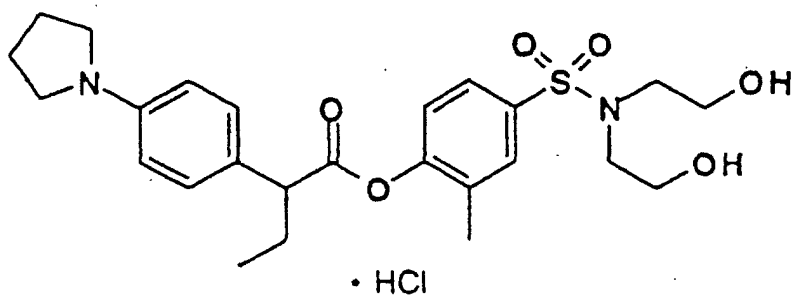


[0380] NMR (CDCl₃): δ 7.70-7.55 (2H, m), 7.23 (2H, d, J=8Hz), 7.01 (1H, d, J=8Hz), 6.55 (2H, d, J=8Hz), 4.20-3.80 (1H, br), 3.98 (2H, s), 3.60 (1H, t, J=7Hz), 3.35-3.07 (6H, m), 2.28-1.75 (9H, m), 1.60-1.38 (2H, m), 0.98 (3H, t, J=7Hz), 0.90 (3H, t, J=7Hz);

[0381] TLC : R_f 0.23 (chloroform:methanol=19:1).

Example 2(107)

[0382] 4-(N,N-bis(2-hydroxyethyl)sulfamoyl)-2-methyl 2RS-(4-pyrrolidinyl-1-yl)phenylbutanoic acid ester · hydrochloride

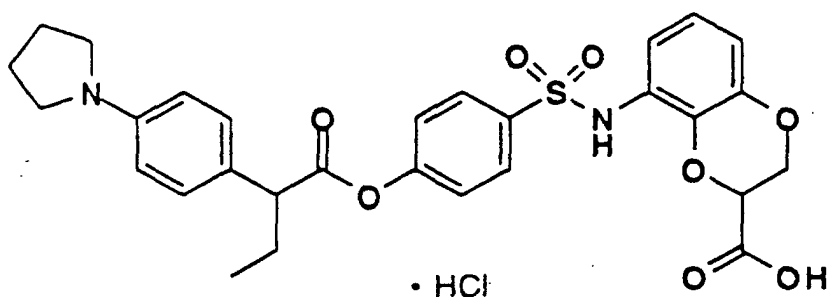


[0383] NMR (CD₃OD): δ 7.78-7.50 (6H, m), 7.15 (1H, d, J=8Hz), 3.96 (1H, t, J=7Hz), 3.95-3.80 (8H, m), 3.35-3.18 (4H, m), 2.40-2.15 (5H, m), 2.10-1.80 (1H, m), 2.02 (3H, s), 0.99 (3H, t, J=7Hz);

[0384] TLC : R_f 0.23 (hexane:ethyl acetate=1:1).

Example 2(109)

[0385] 4-(N-(3RS-carboxy-1,4-benzodioxan-5-yl)sulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



[0386] NMR (DMSO-d₆): δ 9.67 (1H, s), 7.80 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz), 7.13 (2H, d, J=9Hz), 6.84-6.57 (5H, m), 4.78 (1H, t, J=3Hz), 4.28 (1H, dd, J=11Hz, 3Hz), 4.13-4.00 (1H, m), 3.68 (1H, t, J=7Hz), 3.35-3.18 (4H, m),

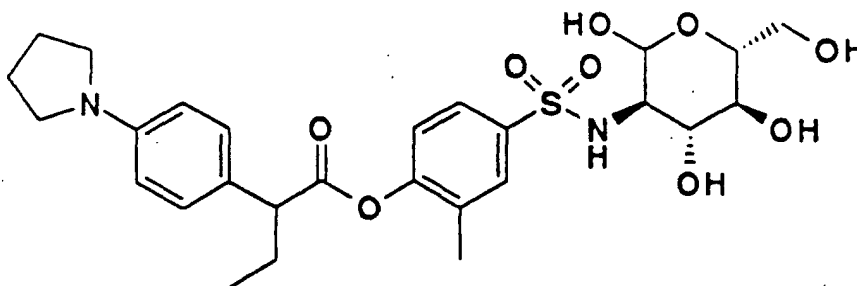
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2.15-1.88 (5H, m), 1.88-1.60 (1H, m), 0.88 (3H, t, J=7Hz);

[0387] TLC : R_f 0.18 (chloroform:methanol:acetic acid=40:2:1).

Example 2(110)

[0388] 4-(N-2RS-hydroxy-4R-hydroxy-5R-hydroxy-6R-hydroxymethylperhydropyran-3R-ylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

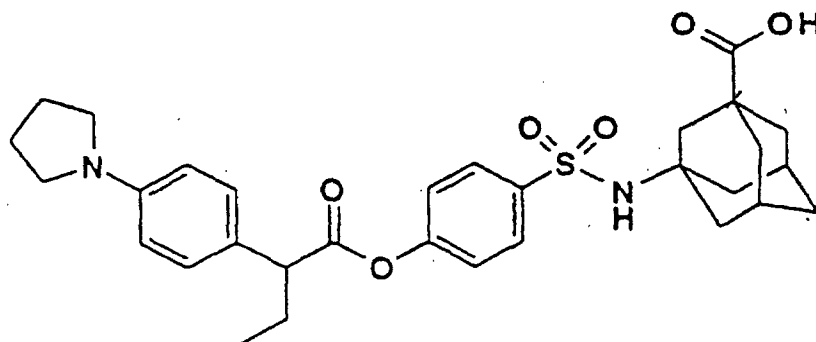


[0389] NMR (DMSO-d₆+3 drop of CD₃OD): δ 7.80-7.60 (2H, m), 7.20 (2H, d, J=8.5Hz), 7.05 (1H, d, J=8.5Hz), 6.60 (2H, d, J=8.5Hz), 4.78 (1H, d, J=3.5Hz), 3.70 (1H, t, J=7.5Hz), 3.65-3.35 (4H, m), 3.30-3.15 (4H, m), 3.03 (1H, t, J=9.0Hz), 2.90 (1H, dd, J=10.5, 3.5Hz), 2.20-1.60 (2H, m), 2.00-1.90 (4H, m), 1.94 (3H, s), 0.91 (3H, t, J=7.5Hz);

[0390] TLC : R_f 0.55 (chloroform:methanol:water=40:10:1).

Comparative Example 2(111)

[0391] 4-(N-3-carboxyadamantan-1-ylsulfamoyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

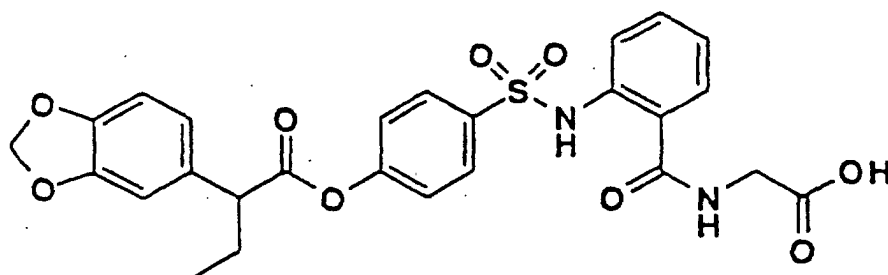


[0392] NMR (CDCl₃): δ 7.85 (2H, d, J=8.8Hz), 7.22 (2H, d, J=8.8Hz), 7.12 (2H, d, J=8.8Hz), 6.54 (2H, d, J=8.8Hz), 4.60 (1H, s), 3.59 (1H, t, J=7.4Hz), 3.40-3.15 (4H, m), 2.30-1.40 (20H, m), 0.98 (3H, t, J=7.6Hz);

[0393] TLC : R_f 0.60 (chloroform:methanol:acetic acid=40:2:1).

Comparative Example 2(120)

[0394] 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(1,3-benzodioxol-5-yl)butanoic acid ester

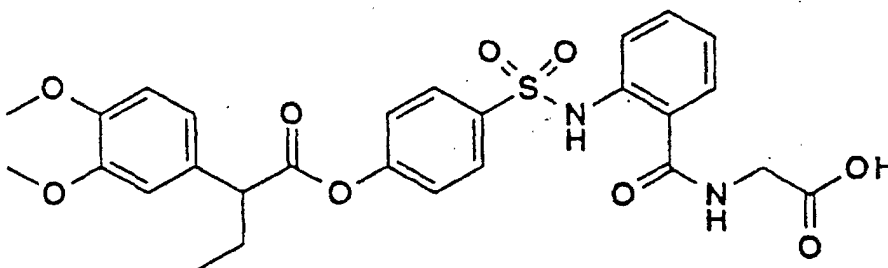


[0395] NMR (DMSO- d_6): δ 12.73 (1H, br), 11.62 (1H, br), 9.22 (1H, t, $J=6$ Hz), 7.82-7.71 (3H, m), 7.53-7.42 (2H, m), 7.26-7.10 (3H, m), 6.94-6.79 (3H, m), 6.01 (2H, s), 3.89 (2H, d, $J=5$ Hz), 3.75 (1H, t, $J=8$ Hz), 2.16-1.95 and 1.86-1.64 (each 1H, m), 0.86 (3H, t, $J=7$ Hz);

[0396] TLC : Rf 0.68 (acetic acid:methanol:chloroform=1:3:30).

Comparative Example 2(157)

[0397] 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(3,4-dimethoxyphenyl)butanoic acid ester

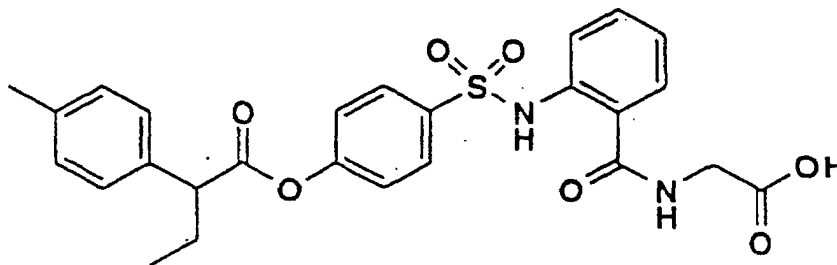


[0398] NMR (CDCl₃+CD₃OD): δ 7.45-7.41 (2H, m), 7.30-7.19 (2H, m), 7.18-7.01 (1H, m), 6.82-6.69 (3H, m), 6.56-6.52 (3H, m), 3.63 (2H, s), 3.53 (6H, s), 3.28 (1H, t, $J=7$ Hz), 1.98-1.42 (2H, m), 0.63 (3H, t, $J=7$ Hz);

[0399] TLC : Rf 0.64 (acetic acid:methanol:chloroform=1:3:30).

Comparative Example 2(173)

[0400] 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-methylphenyl)butanoic acid ester



[0401] NMR(DMSO- d_6): δ 10.61-10.32 (1H, m), 7.85-7.74 (3H, m), 7.36-7.04 (8H, m), 6.90-6.75 (1H, m), 3.92-3.83 (2H, m), 3.77 (1H, t, $J=7.6$ Hz), 2.29 (3H, s), 2.21-1.96 and 1.89-1.63 (each 1H, m), 0.87 (3H, t, $J=7.4$ Hz);

[0402] TLC : Rf 0.23 (chloroform:methanol:water=8:2:0.2).

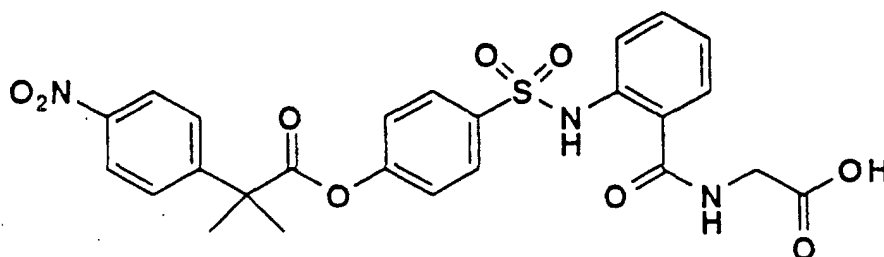
EP 0 769 498 B9 (W1B1)

[0403] NMR (CDCl₃ + CD₃OD): δ 8.24 (2H, d, J=8Hz), 7.85-7.55 (6H, m), 7.10 (4H, m), 3.95 (2H, s), 3.87 (1H, t, J=7Hz), 2.25 and 1.98 (each 1H, m), 0.99 (3H, t, J=7Hz);

[0404] TLC : R_f 0.33 (acetic acid:methanol:chloroform=1:3:30).

Example 2(175)

[0405] 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2-(4-nitrophenyl)-2-methylpropanoic acid ester

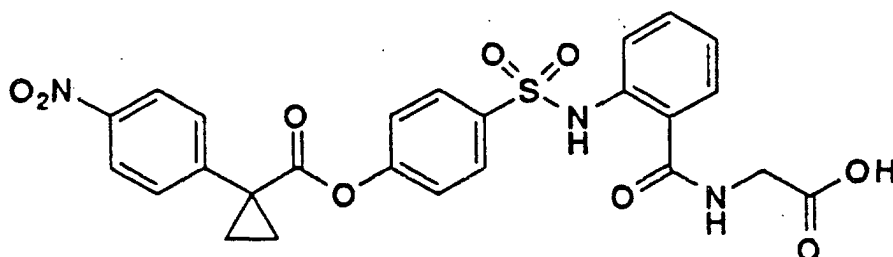


[0406] NMR (DMSO-d₆): δ 13.50-11.00 (2H, br), 9.30-9.16 (1H, m), 8.23 (2H, d, J=8Hz), 7.88-7.68 (5H, m), 7.55-7.40 (2H, m), 7.25 (2H, d, J=8Hz), 7.20-7.09 (1H, m), 3.89 (2H, d, J=6Hz), 1.68 (6H, s);

[0407] TLC : R_f 0.41 (acetic acid:methanol:chloroform=1:3:30).

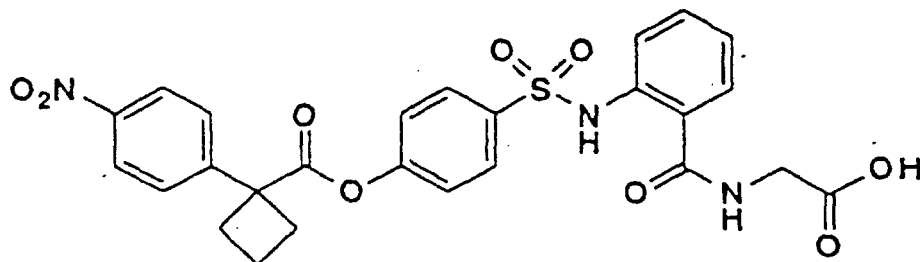
Example 2(176)

[0408] 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclopropanecarboxylic acid ester



Comparative Example 2(179)

[0409] 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 1-(4-nitrophenyl)cyclobutanecarboxylic acid ester



[0410] NMR (DMSO-d₆): δ 9.2-9.1 (1H, brt), 8.24 (2H, d, J=8Hz), 7.8-7.6 (5H, m), 7.5-7.4 (2H, m), 7.3-7.1 (3H, m),

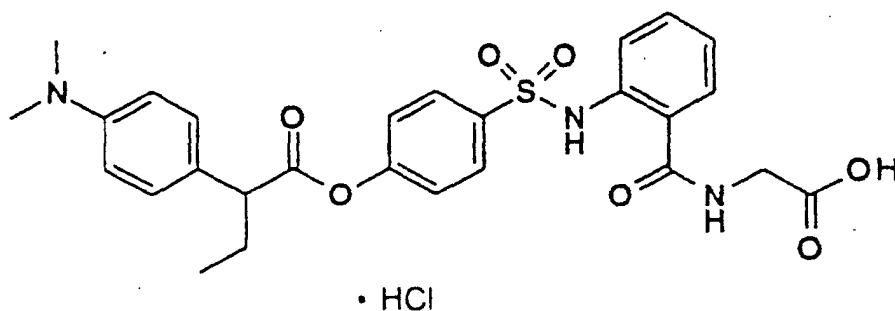
EP 0 769 498 B9 (W1B1)

3.88 (2H, d, J=5Hz), 3.0-2.8 (2H, br), 2.7-2.5 (2H, m), 2.2-1.8 (2H, m);

[0411] TLC : Rf 0.22 (acetic acid:methanol:chloroform=1:2:40).

Comparative Example 2(197)

[0412] 4-(N-2-(N'-carboxymethylcarbamoyl)phenylsulfamoyl)phenyl 2RS-(4-(N,N-dimethylamino)phenyl)butanoic acid ester · hydrochloride

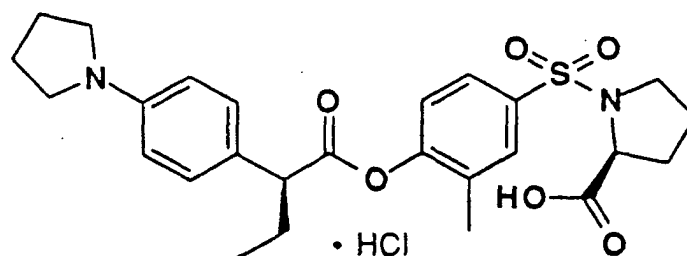


[0413] NMR (DMSO-d₆): δ 11.62 (1H, s), 9.25 (1H, t, J=6Hz), 7.80 (2H, d, J=9Hz), 7.76 (1H, d, J=8Hz), 7.50-7.44 (5H, m), 7.27-7.14 (4H, m), 3.89 (2H, d, J=6Hz), 3.86 (1H, t, J=8Hz), 3.04 (6H, s), 2.17-2.03 and 1.91-1.71 (each 1H, m). 0.88 (3H, t, J=7Hz);

[0414] TLC : Rf 0.48 (acetic acid:methanol:chloroform=1:3:30).

Example 2(232)

[0415] 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

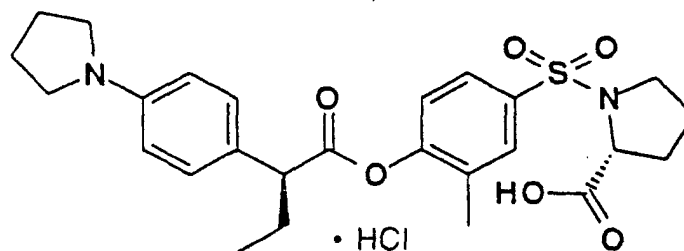


[0416] NMR (CD₃OD): δ 7.89-7.69 (2H, m), 7.54 and 7.41 (each 2H, d, J=8Hz), 7.15 (1H, d, J=8Hz), 4.28-4.16 (1H, m), 3.90 (1H, t, J=7Hz), 3.69-3.64 (4H, m), 3.51-3.40 and 3.31-3.21 (each 1H, m), 2.28-2.21 (5H, m), 2.02 (3H, s), 2.01-1.89 (4H, m), 1.80-1.65 (1H, m), 0.99 (3H, t, J=7Hz);

[0417] TLC : Rf 0.17 (chloroform:methanol:water=9:1:0.1).

Example 2(233)

[0418] 4-((2R-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

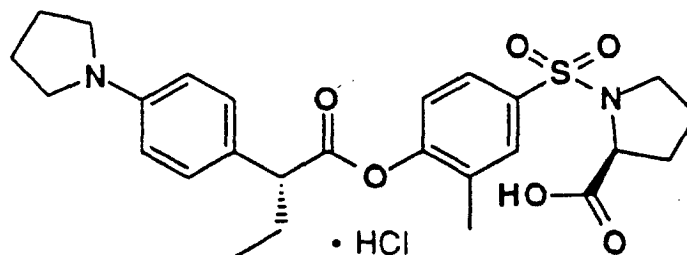


[0419] NMR (CD₃OD): δ 7.81-7.68 (2H, m), 7.56 and 7.45 (each 2H, d, J=8Hz), 7.15 (1H, d, J=8Hz), 4.28-4.16 (1H, m), 3.91 (1H, t, J=7Hz), 3.71-3.64 (4H, m), 3.50-3.40 and 3.33-3.22 (each 1H, m), 2.31-2.22 (5H, m), 2.03 (3H, s), 2.02-1.84 (4H, m), 1.80-1.64 (1H, m), 1.00 (3H, t, J=7Hz);

[0420] TLC : R_f 0.18 (chloroform:methanol:water=9:1:0.1).

Example 2(234)

[0421] 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

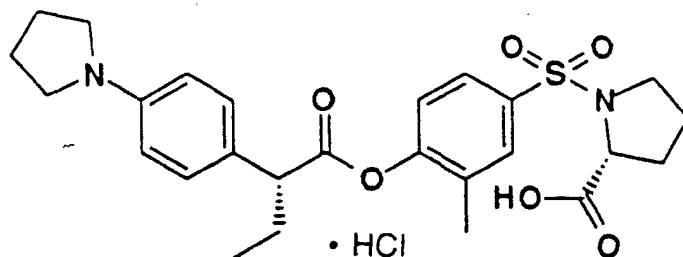


[0422] NMR (CD₃OD): δ 7.80-7.68 (2H, m), 7.50 and 7.31 (each 2H, d, J=8Hz), 7.14 (1H, d, J=8Hz), 4.22-4.16 (1H, m), 3.87 (1H, t, J=7Hz), 3.68-3.56 (4H, m), 3.50-3.42 and 3.35-3.20 (each 1H, m), 2.32-2.18 (5H, m), 2.02 (3H, s), 2.01-1.83 (4H, m), 1.79-1.65 (1H, m), 0.99 (3H, t, J=7Hz);

[0423] TLC : R_f 0.17 (chloroform:methanol:water=9:1:0.1).

Example 2(235)

[0424] 4-((2R-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

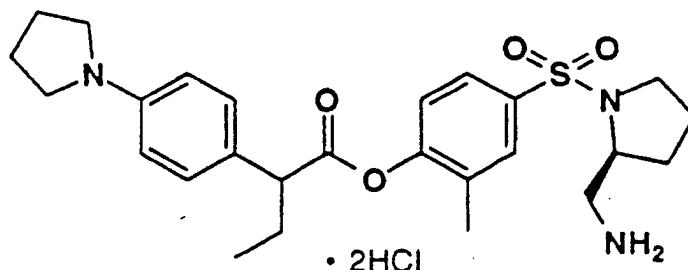


[0425] NMR (CD₃OD): δ 7.77-7.68 (2H, m), 7.57 and 7.48 (each 2H, d, J=8Hz), 7.15 (1H, d, J=8Hz), 4.22-4.17 (1H, m), 3.93 (1H, t, J=7Hz), 3.74-3.66 (4H, m), 3.52-3.42 and 3.35-3.21 (each 1H, m), 2.28-2.22 (5H, m), 2.02 (3H, s), 2.01-1.87 (4H, m), 1.80-1.64 (1H, m), 0.99 (3H, t, J=7Hz);

[0426] TLC : R_f 0.18 (chloroform:methanol:water=9:1:0.1).

Example 2(236)

[0427] 4-((2S-aminomethylpyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

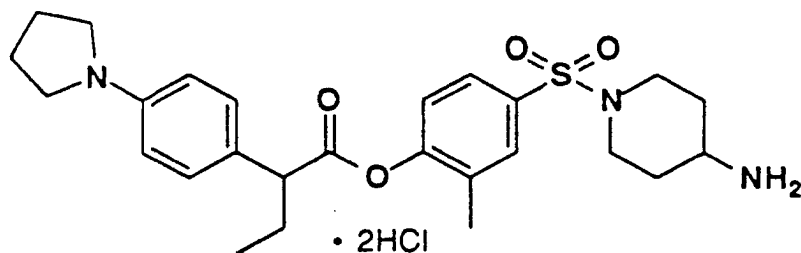


[0428] NMR (CD₃OD): δ 7.85-7.70 (2H, m), 7.64 (4H, s), 7.22 (1H, d, J=8.0Hz), 3.98 (1H, t, J=8.0Hz), 4.00-3.80 (1H, m), 3.85-3.70 (4H, m), 3.55-3.20 (2H, m), 3.15-2.95 (2H, m), 2.40-1.80 (2H, m), 2.35-2.25 (4H, m), 2.06 (3H, s), 2.00-1.40 (4H, m), 1.00 (3H, t, J=7.5Hz);

[0429] TLC : R_f 0.29 (chloroform:methanol:water=4:1:0.1).

Example 2(237)

[0430] 4-((4-aminopiperidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

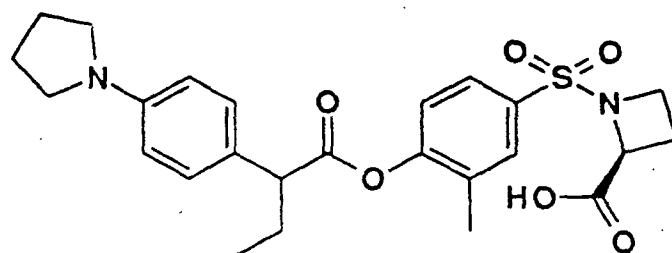


[0431] NMR (DMSO-d₆): δ 8.14 (2H, brs), 7.63 (1H, s), 7.60 (1H, d, J=8.4Hz), 7.21 (2H, d, J=8.4Hz), 7.20 (1H, d, J=8.4Hz), 6.64 (2H, d, J=8.4Hz), 3.8-3.5 (4H, br), 3.3-3.2 (5H, br), 3.2-3.0 (1H, br), 2.5-2.3 (2H, m), 2.2-2.0 (1H, m), 2.0-1.9 (4H, br), 1.98 (3H, s), 1.9-1.7 (1H, m), 1.7-1.5 (2H, m), 0.90 (3H, t, J=7.2Hz);

[0432] TLC : R_f 0.20 (chloroform:methanol=9:1).

Example 2(238)

[0433] 4-((2S-carboxyazetidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



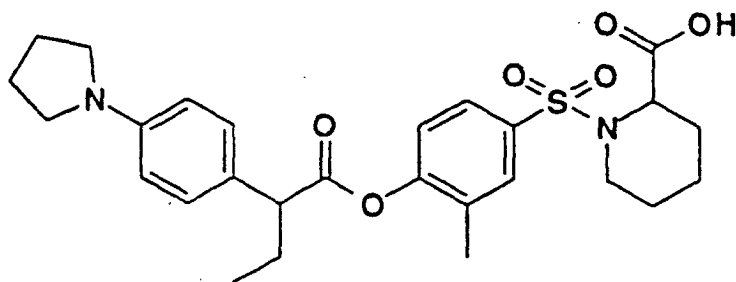
EP 0 769 498 B9 (W1B1)

[0434] NMR (CD₃OD): δ 7.72 (1H, s), 7.71 (1H, d, J=8.0Hz), 7.22 (2H, d, J=8.8Hz), 7.17 (1H, d, J=8.0Hz), 6.58 (2H, d, J=8.8Hz), 4.30 (1H, t, J=8.5Hz), 3.8-3.6 (3H, m), 3.4-3.2 (4H, m), 2.4-2.1 (3H, m), 2.1-2.0 (4H, brs), 2.0-1.8 (1H, m), 2.04 (3H, s), 1.00 (3H, t, J=7.4Hz);

[0435] TLC : R_f 0.59 (chloroform:methanol:acetic acid=25:5:1).

Example 2(239)

[0436] 4-((2RS-carboxypiperidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

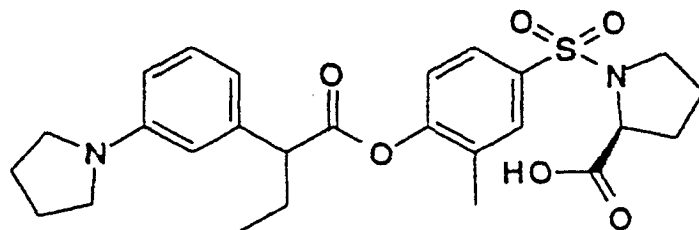


[0437] NMR (CDCl₃): δ 7.65 (1H, s), 7.63 (1H, d, J=8.2Hz), 7.21 (2H, d, J=8.6Hz), 6.99 (1H, d, J=8.2Hz), 6.53 (2H, d, J=8.6Hz), 4.7-4.6 (1H, brs), 4.7-4.1 (1H, br), 3.59 (1H, t, J=7.7Hz), 3.5-3.2 (6H, brs), 2.3-2.1 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.8 (1H, m), 1.98 (3H, s), 1.6-1.2 (6H, br), 0.96 (3H, t, J=7.4Hz);

[0438] TLC : R_f 0.12 (chloroform:methanol=9: 1).

Example 2(241)

[0439] 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(3-(pyrrolidin-1-yl)phenyl)butanoic acid ester

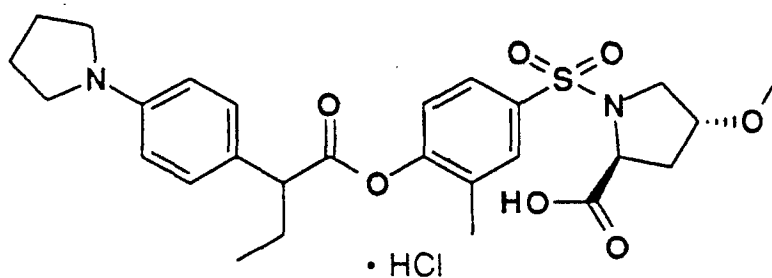


[0440] NMR (CDCl₃): δ 7.70-7.64 (2H, m), 7.20 (1H, t, J=7.8Hz), 7.09 (1H, d, J=7.8Hz), 6.66 (1H, d, J=7.8Hz), 6.53-6.47 (2H, m), 4.3-4.2 (1H, m), 3.8-3.4 (2H, m), 3.4-3.2 (5H, m), 2.3-1.7 (13H, m), 1.01 (3H, t, J=7.4Hz);

[0441] TLC : R_f 0.58 (chloroform:methanol:acetic acid=9:1:0.2).

Example 2(242)

[0442] 4-((2S-carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride

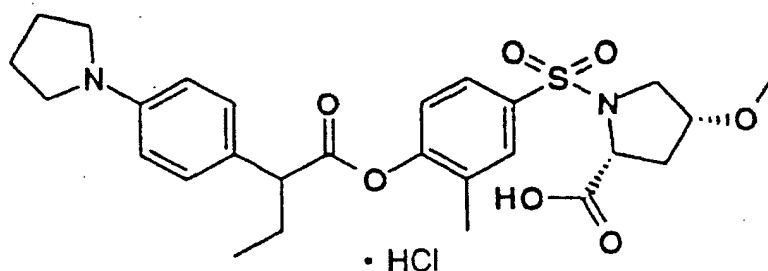


[0443] NMR (DMSO- d_6): δ 7.73 (1H, s), 7.66 (1H, d, J=8.6Hz), 7.26 (2H, d, J=8.8Hz), 7.15 (1H, d, J=8.6Hz), 6.78 (2H, d, J=8.8Hz), 5.00 (1H, brs), 4.02 (1H, t, J=7Hz), 3.82 (1H, m), 3.76 (1H, t, J=7Hz), 3.41 (2H, m), 3.31 (4H, m), 2.83 (3H, s), 2.15 (2H, m), 2.00 (4H, m), 1.98 (3H, s), 1.95 (2H, m), 0.92 (3H, t, J=7.4Hz);

[0444] TLC : R_f 0.34 (chloroform:methanol:water=4:1:0.1).

Example 2(243)

[0445] 4-((2R-carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • hydrochloride

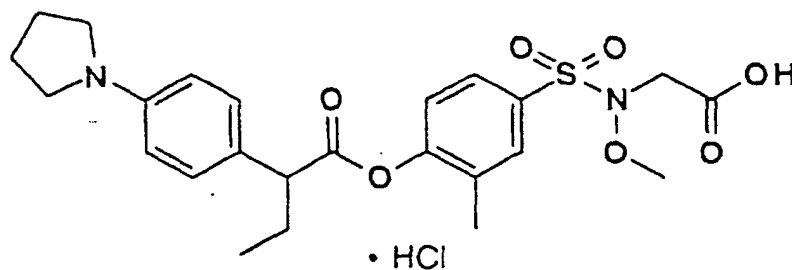


[0446] NMR (DMSO- d_6): δ 7.77 (1H, d, J=2.4Hz), 7.70 (1H, dd, J=8.4Hz, 2.4Hz), 7.26 (2H, d, J=8.2Hz), 7.16 (1H, d, J=8.4Hz), 6.75 (2H, d, J=8.2Hz), 4.80 (1H, brs), 4.31 (1H, dd, J=9.2Hz, 3.2Hz), 3.76 (2H, m), 3.33 (6H, m), 3.12 (3H, s), 2.12 (2H, m), 2.02 (4H, m), 1.98 (3H, s), 1.80 (2H, m), 0.91 (3H, t, J=7.2Hz);

[0447] TLC : R_f 0.47 (chloroform:methanol:water=4:1:0.1).

Example 2(246)

[0448] 4-(N-methoxy-N-carboxymethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • hydrochloride



[0449] NMR (CDCl₃): δ 7.66 (1H, s), 7.63 (1H, d, J=8.0Hz), 7.22 (2H, d, J=8.8Hz), 7.08 (1H, d, J=8.0Hz), 6.54 (2H, d, J=8.8Hz), 5.3-4.6 (1H, br), 3.81 (3H, s), 3.70 (2H, s), 3.69 (1H, t, J=7.8Hz), 3.3-3.2 (4H, brs), 2.2-2.0 (1H, m), 2.1-1.9

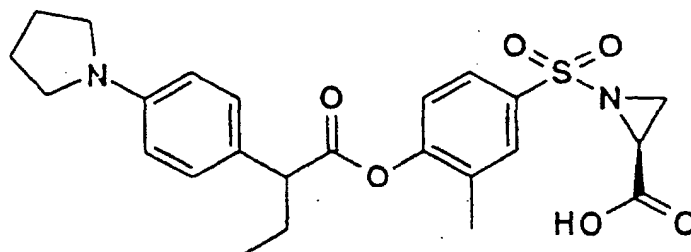
EP 0 769 498 B9 (W1B1)

(4H, brs), 2.01 (3H, s), 2.0-1.8 (1H, m), 0.97 (3H, t, J=7.4Hz);

[0450] TLC : Rf 0.44 (hexane:ethyl acetate=2:1).

Example 2(248)

[0451] 4-((2S-carboxyaziridin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

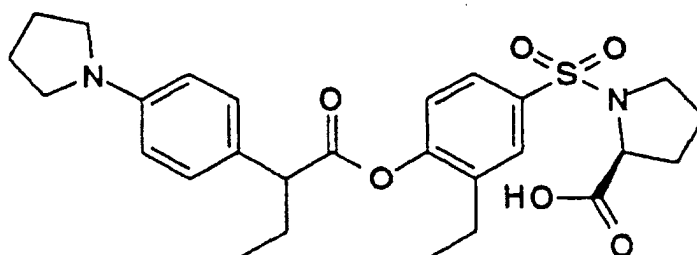


[0452] NMR (CDCl₃+CD₃OD): δ 7.74 (1H, s), 7.70 (1H, d, J=8.4Hz), 7.20 (2H, d, J=8.4Hz), 7.08 (1H, d, J=8.4Hz), 6.54 (2H, d, J=8.4Hz), 3.61 (1H, t, J=7.5Hz), 3.3-3.2 (4H, brs), 2.6-2.3(3H, brs), 2.3-2.1 (1H, m), 2.1-1.9 (4H, brs), 2.0-1.8 (1H, m), 1.99(3H, s), 0.97 (3H, t, J=7.4Hz);

[0453] TLC : Rf 0.28 (chloroform:methanol=4:1).

Example 2(251)

[0454] 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-ethylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

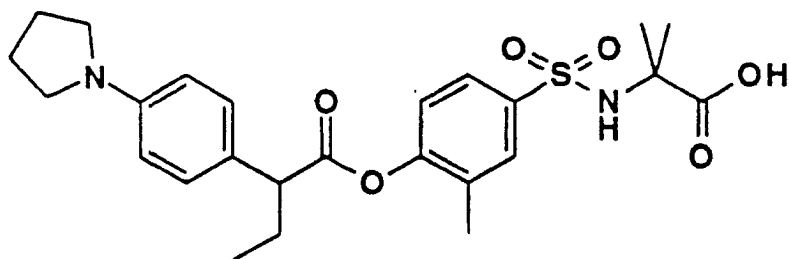


[0455] NMR (CDCl₃): δ 7.8-7.6 (m, 2H), 7.36 (d, J=8.4Hz, 2H), 7.07 (d, J=8.4Hz, 1H), 7.02 (d, J=8.4Hz, 2H), 4.3-4.2 (m, 1H), 3.70 (t, J=7.2Hz, 1H), 3.6-3.4 (m, 5H), 3.3-3.1 (m, 1H), 2.37 (q, J=7.6Hz, 2H), 2.3-1.6 (m, 10H), 1.03 (t, J=7.6Hz, 3H), 0.99 (t, J=7.6Hz, 3H);

[0456] TLC : Rf 0.33 (chloroform:methanol:acetic acid=50:2:1).

Example 2(254)

[0457] 4-(N-(1,1-dimethyl-1-carboxymethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

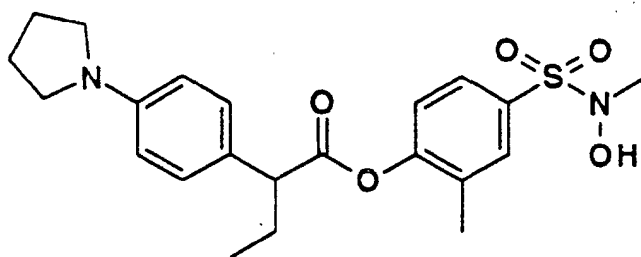


[0458] NMR (DMSO- d_6): δ 7.68 (1H, s-like), 7.64 (1H, dd, $J=2$ and 8Hz), 7.39 (1H, br), 7.18 (2H, d, $J=8$ Hz), 7.07 (1H, d, $J=8$ Hz), 6.53 (2H, d, $J=8$ Hz), 3.69 (1H, t, $J=7$ Hz), 3.24-3.18 (4H, m), 2.20-1.65 (2H, m), 1.98-1.91 (4H, m), 1.93 (3H, s), 1.18 (6H, s), 0.90 (3H, t, $J=7$ Hz);

[0459] TLC : Rf 0.19 (chloroform:methanol:water=9:1:0.1).

Example 2(255)

[0460] 4-(N-methyl-N-hydroxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

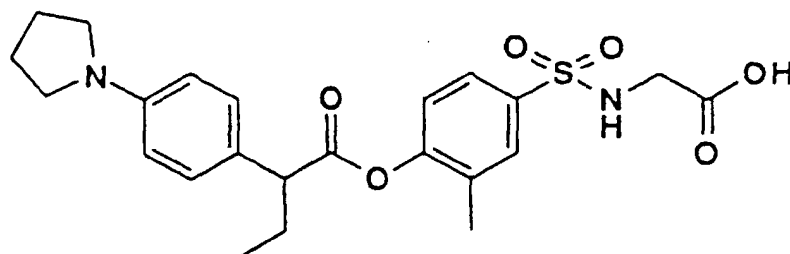


[0461] NMR (CDCl₃): δ 7.71 (1H, s), 7.69 (1H, d, $J=8.6$ Hz), 7.23 (2H, d, $J=8.8$ Hz), 7.13 (1H, d, $J=8.6$ Hz), 6.55 (2H, d, $J=8.8$ Hz), 6.54 (1H, s), 3.63 (1H, t, $J=7.7$ Hz), 3.3-3.2 (4H, brs), 2.81 (3H, s), 2.3-2.1 (1H, m), 2.1-1.9 (4H, brs), 2.06 (3H, s), 2.0-1.8 (1H, m), 0.99 (3H, t, $J=7.3$ Hz);

[0462] TLC : Rf 0.43 (hexane:ethyl acetate=2:1).

Example 2(257)

[0463] 4-(N-carboxymethylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

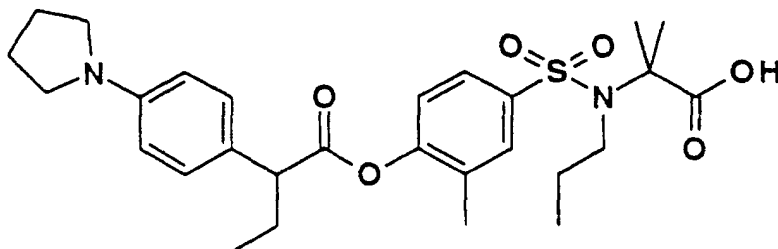


[0464] NMR (CDCl₃): δ 7.70-7.58 (2H, m), 7.25 (2H, d, $J=8$ Hz), 7.01 (1H, d, $J=8$ Hz), 6.65 (2H, d, $J=8$ Hz), 5.43-5.23 (1H, br), 5.18-4.80 (1H, br), 3.75 (2H, brs), 3.63 (1H, t, $J=7$ Hz), 3.40-3.20 (4H, m), 2.28-1.80 (9H, m), 0.98 (3H, t, $J=7$ Hz);

[0465] TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(258)

[0466] 4-(N-(1,1-dimethyl-1-carboxymethyl)-N-propylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

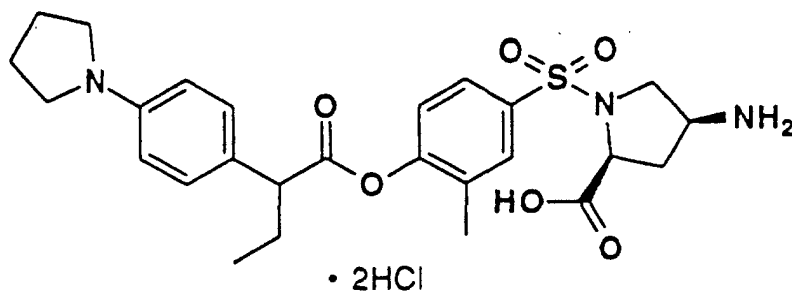


[0467] NMR (DMSO- d_6 + 2 drops of D₂O): δ 7.80 (1H, s-like), 7.78 (1H, dd, J=2 and 8Hz), 7.18 (2H, d, J=8Hz), 7.11 (1H, d, J=8Hz), 6.54 (2H, d, J=8Hz), 3.70 (1H, t, J=7Hz), 3.25-3.17 (4H, m), 3.12-3.04 (2H, m), 2.20-1.70 (2H, m), 1.99-1.92 (4H, m), 1.95 (3H, s), 1.57-1.42 (2H, m), 1.45 (6H, s), 0.91 (3H, t, J=7Hz), 0.71 (3H, t, J=7Hz);

[0468] TLC : R_f 0.57 (chloroform:methanol:water=9:1:0.1).

Example 2(259)

[0469] 4-((2S-carboxy-4S-aminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

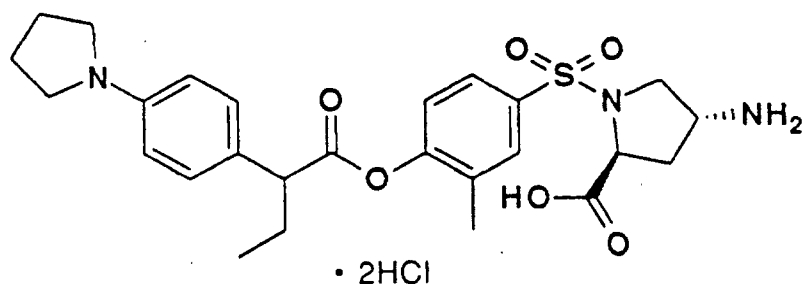


[0470] NMR (CD₃OD): δ 7.83-7.68 (2H, m), 7.63 (4H, s-like), 7.22 (1H, d, J=8.2Hz), 4.21 (1H, dd, J=9.2 and 3.4Hz), 3.98 (1H, t, J=7.8Hz), 3.90-3.43 (7H, m), 2.70-1.84 (8H, m), 2.06 (3H, s), 1.00 (3H, t, J=7.4Hz);

[0471] TLC : R_f 0.46 (ethyl acetate:acetic acid:water=6:2:1).

Example 2(260)

[0472] 4-((2S-carboxy-4R-aminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

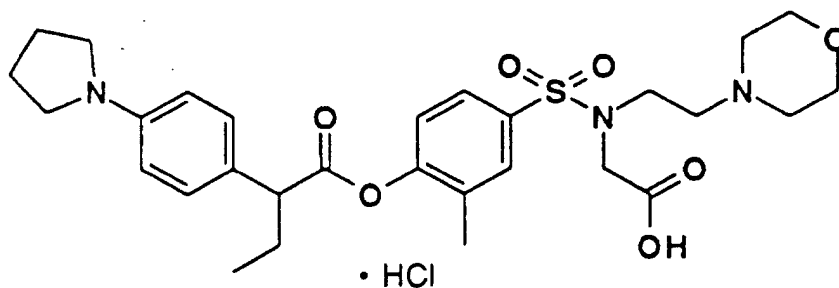


[0473] NMR (CD₃OD): δ 7.84-7.68 (2H, m), 7.63 (4H, s-like), 7.18 (1H, d, J=8.0Hz), 4.55 (1H, dd, J=8.4 and 4.2Hz), 4.07-3.90 (2H, m), 3.90-3.63 (5H, m), 3.47-3.26 (1H, m), 2.53-1.82 (8H, m), 2.05 (3H, s), 1.00 (3H, t, J=7.4Hz);

[0474] TLC : R_f 0.42 (ethyl acetate:acetic acid:water=6:2:1).

Example 2(261)

[0475] 4-(N-carboxymethyl-N-(2-(morpholin-4-yl)ethyl)aminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoate hydrochloride

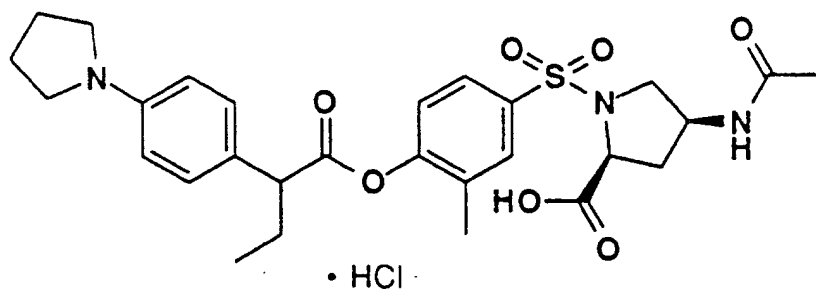


[0476] NMR (CDCl₃): δ 7.66-7.52 (2H, m), 7.21 (2H, d, J=8.5Hz), 7.09 (1H, d, J=8.5Hz), 6.55 (2H, d, J=8.5Hz), 3.95-3.80 (4H, m), 3.75 (2H, s), 3.61 (1H, t, J=7.5Hz), 3.45-3.20 (6H, m), 3.10-2.70 (6H, m), 2.30-1.75 (6H, m), 2.04 (3H, s), 0.99 (3H, t, J=7.5Hz);

[0477] TLC : R_f 0.24 (chloroform:methanol:water=9:1:0.1).

Example 2(262)

[0478] 4-((2S-carboxy-4S-acetylamino-1-pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoate hydrochloride



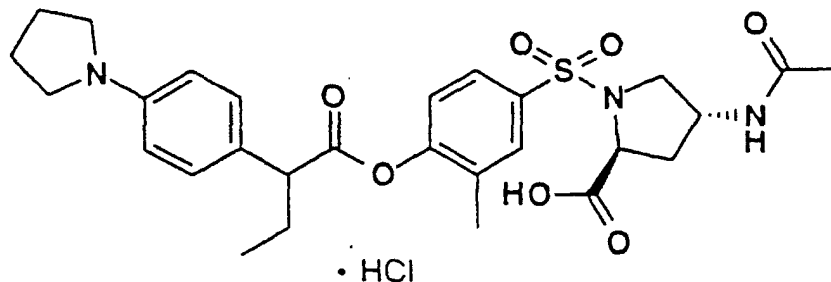
EP 0 769 498 B9 (W1B1)

[0479] NMR (DMSO- d_6): δ 8.02 (1H, d, $J=7.8$ Hz), 7.74 (1H, d, $J=2.2$ Hz), 6.69 (1H, dd, $J=8.4$ Hz, 2.2Hz), 7.17 (2H, d, $J=8.6$ Hz), 7.17 (1H, d, $J=8.4$ Hz), 6.54 (2H, d, $J=8.6$ Hz), 4.13 (1H, t, $J=7.8$ Hz), 3.82 (1H, m), 3.70 (1H, t, $J=7.6$ Hz), 3.50 (1H, m), 3.22 (4H, m), 3.06 (1H, m), 2.31 (1H, m), 2.07 (1H, m), 1.99 (3H, s), 1.96 (4H, m), 1.82 (2H, m), 1.75 (3H, s), 0.91 (3H, t, $J=7.4$ Hz);

[0480] TLC : Rf 0.18 (chloroform:methanol:water=4:1:0.1).

Example 2(264)

[0481] 4-((2S-carboxy-4R-acetylamino pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester hydrochloride

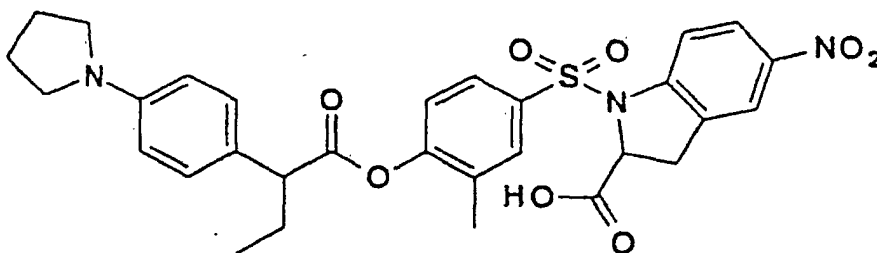


[0482] NMR (DMSO- d_6): δ 7.78 (1H, d, $J=5$ Hz), 7.68 (1H, s), 7.64 (1H, d, $J=8.0$ Hz), 7.19 (2H, d, $J=8.6$ Hz), 7.16 (1H, d, $J=8.0$ Hz), 6.56 (2H, d, $J=8.6$ Hz), 4.28 (1H, t, $J=7.8$ Hz), 4.12 (1H, m), 3.75 (1H, m), 3.48 (1H, m), 3.23 (4H, m), 3.06 (1H, m), 2.12 (1H, m), 2.03 (2H, m), 1.99 (3H, s), 1.96 (4H, m), 1.80 (1H, m), 1.54 (3H, s), 0.91 (3H, t, $J=7.2$ Hz);

[0483] TLC : Rf 0.19 (chloroform:methanol:water=4:1:0.1).

Example 2(265)

[0484] 4-((2RS-carboxy-5-nitroindolin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester

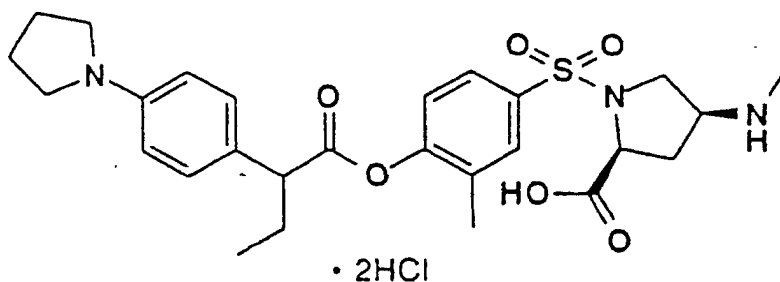


[0485] NMR (CDCl₃): δ 8.33 (1H, d, $J=2$ Hz), 7.89 (1H, dd, $J=8, 2$ Hz), 7.67 (1H, s), 7.62 (1H, d, $J=8$ Hz), 7.20 (1H, d, $J=8$ Hz), 7.18 (2H, d, $J=8$ Hz), 7.02 (1H, d, $J=8$ Hz), 6.55 (2H, d, $J=8$ Hz), 4.85 (1H, dd, $J=10, 5$ Hz), 4.60-4.25 (1H, br), 3.59 (1H, t, $J=7$ Hz), 3.40-3.15 (6H, m), 2.25-1.75 (9H, m), 0.95 (3H, t, $J=7$ Hz);

[0486] TLC : Rf 0.30 (chloroform:methanol:acetic acid=4:2:0.1).

Example 2(267)

[0487] 4-((2S-carboxy-4S-methylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2hydrochloride

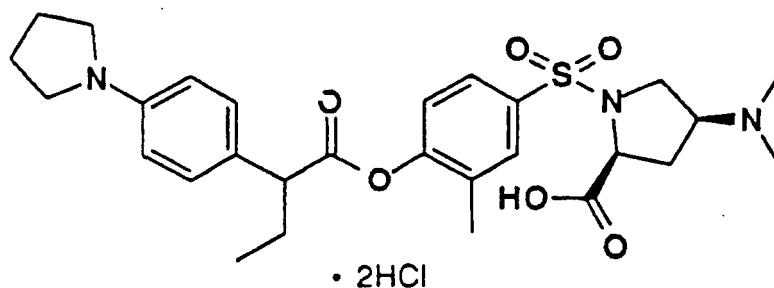


[0488] NMR (CD₃OD): δ 7.77 (1H, s), 7.75 (1H, d, J=8.0Hz), 7.37 (2H, d, J=8.6Hz), 7.19 (1H, d, J=8.0Hz), 6.98 (2H, d, J=8.6Hz), 4.18 (1H, m), 3.69 (3H, m), 3.59 (1H, m), 3.46 (4H, m), 2.72 (3H, s), 2.57 (1H, m), 2.21 (2H, m), 2.13 (4H, m), 2.02 (3H, s), 1.93 (1H, m), 0.98 (3H, t, J=7.4Hz);

[0489] TLC : R_f 0.28 (chloroform:methanol:water=4:1:0.1).

Example 2(268)

[0490] 4-((2S-carboxy-4S-(N,N-dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2hydrochloride

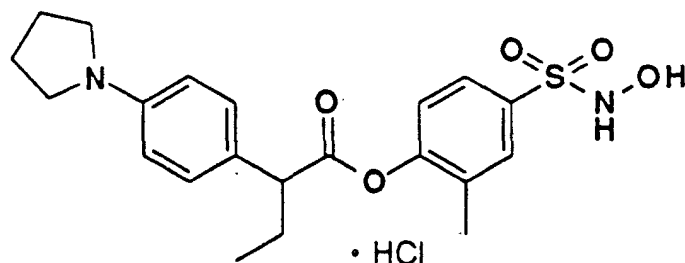


[0491] NMR (CD₃OD): δ 7.81 (1H, s), 7.78 (1H, d, J=8.2Hz), 7.62 (4H, s), 7.21 (1H, d, J=8.2Hz), 4.25 (1H, t, J=7Hz), 3.98 (1H, t, J=7Hz), 3.77 (4H, m), 3.65 (3H, m), 2.90 (6H, s), 2.80 (1H, m), 2.29 (4H, m), 2.24 (2H, m), 2.06 (3H, s), 1.99 (1H, m), 1.00 (3H, t, J=7.4Hz);

[0492] TLC : R_f 0.42 (chloroform:methanol:water=6:4:1).

Example 2(269)

[0493] 4-(N-hydroxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · hydrochloride



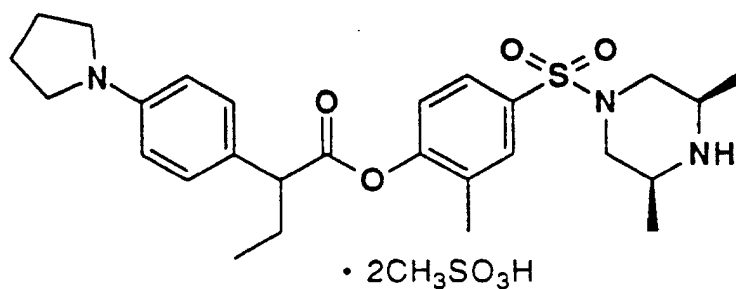
[0494] NMR (CDCl₃): δ 7.73 (1H, s), 7.68 (1H, d, J=8.6Hz), 7.23 (2H, d, J=8.0Hz), 7.2-7.0 (2H, br), 7.04 (1H, d, J=8.6Hz), 6.63 (2H, d, J=8.0Hz), 3.63 (1H, t, J=7.7Hz), 3.4-3.2 (4H, brs), 2.3-2.1 (1H, m), 2.1-1.9 (4H, brs), 2.00 (3H, s);

s), 2.0-1.8 (1H, m), 0.97 (3H, t, J=7.3Hz);

[0495] TLC : Rf 0.25 (hexane:ethyl acetate=2:1).

Example 2(270)

[0496] 4-((2S,6S-dimethylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2methanesulfonic acid salt

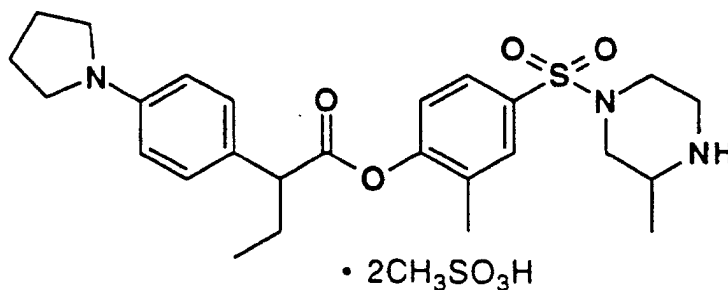


[0497] NMR (CDCl₃): δ 7.76-7.62 (6H, m), 7.23 (1H, d, J=8.5Hz), 4.01 (1H, t, J=7.5Hz), 4.00-3.75 (6H, m), 3.55-3.30 (2H, m), 2.68 (6H, s), 2.45-1.80 (8H, m), 2.07 (3H, s), 1.31 (6H, d, J=6.5Hz), 1.00 (3H, t, J=7.5Hz);

[0498] TLC : Rf 0.66 (chloroform:methanol:water=4:1:0.1).

Example 2(271)

[0499] 4-((2RS-methylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2methanesulfonic acid salt

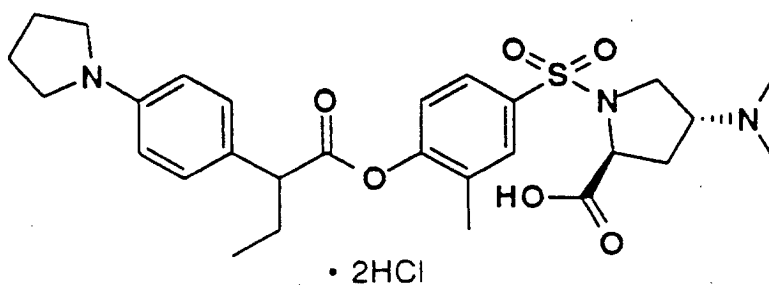


[0500] NMR (CDCl₃): δ 7.76-7.60 (6H, m), 7.23 (1H, d, J=8.0Hz), 4.01 (1H, t, J=7.5Hz), 3.90-3.72 (6H, m), 3.55-3.35 (2H, m), 3.32-3.13 (1H, m), 2.82-2.62 (1H, m), 2.67 (6H, s), 2.49 (1H, dd, J=13.0, 10.0Hz), 2.40-1.80 (6H, m), 2.07 (3H, s), 1.32 (3H, d, J=6.5Hz), 1.00 (3H, t, J=7.5Hz);

[0501] TLC : Rf 0.45 (chloroform:methanol:water=9:1:0.1).

Example 2(272)

[0502] 4-((2S-carboxy-4R-(N,N-dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2hydrochloride

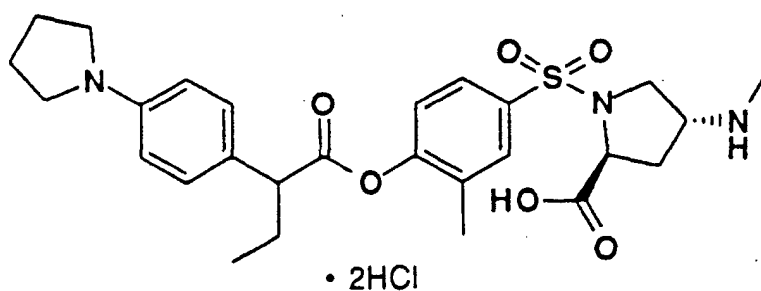


[0503] NMR (DMSO- d_6): δ 11.38 (1H, m), 7.77 (1H, s), 7.72 (1H, d, $J=8.2$ Hz), 7.19 (3H, m), 6.63 (2H, d, $J=8.6$ Hz), 4.38 (1H, m), 4.01 (1H, m), 3.82 (1H, m), 3.73 (1H, t, $J=7.4$ Hz), 3.49 (1H, t, $J=8.6$ Hz), 3.24 (4H, m), 2.70 (6H, s), 2.36 (2H, m), 2.11 (1H, m), 1.99 (3H, s), 1.97 (4H, m), 1.83 (1H, m), 0.91 (3H, t, $J=7.2$ Hz);

[0504] TLC : R_f 0.44 (chloroform:methanol:water=6:4:1).

Example 2(273)

[0505] 4-((2S-carboxy-4R-methylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2hydrochloride

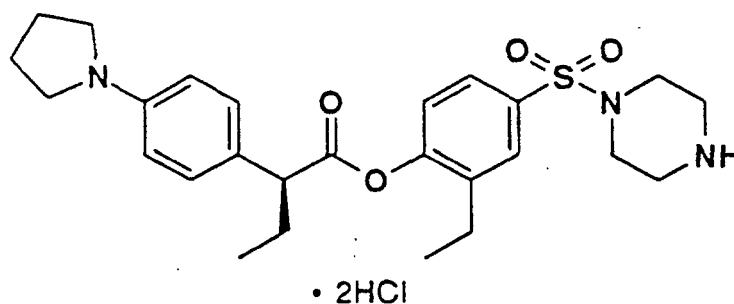


[0506] NMR (CD₃OD): δ 7.76 (1H, s), 7.73 (1H, d, $J=8.0$ Hz), 7.25 (2H, d, $J=8.4$ Hz), 7.13 (1H, d, $J=8.0$ Hz), 6.71 (2H, d, $J=8.4$ Hz), 4.53 (1H, m), 3.97 (1H, m), 3.86 (1H, m), 3.70 (1H, t, $J=8$ Hz), 3.41 (1H, m), 3.35 (4H, m), 2.70 (3H, s), 2.49 (1H, m), 2.31 (1H, m), 2.17 (1H, m), 2.06 (4H, m), 2.00 (3H, s), 1.92 (1H, m), 0.98 (3H, t, $J=7.2$ Hz);

[0507] TLC : R_f 0.46 (chloroform:methanol:water=6:4:1).

Example 2(274)

[0508] 4-(piperazin-4-ylsulfonyl)-2-ethylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • 2hydrochloride



[0509] NMR (CD₃OD): δ 7.75-7.50 (6H, m), 7.25 (1H, d, $J=9.0$ Hz), 3.97 (1H, t, $J=7.5$ Hz), 3.85-3.70 (4H, m), 3.35-3.15

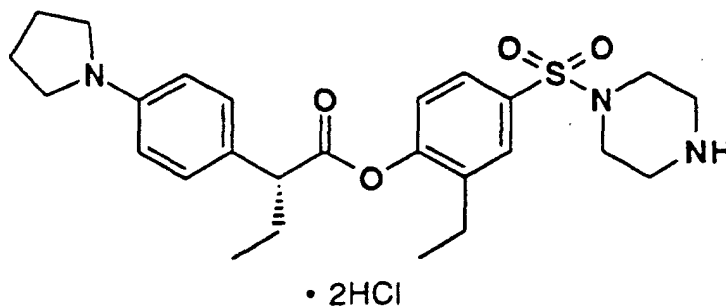
EP 0 769 498 B9 (W1B1)

(8H, m), 2.50-1.80 (8H, m), 1.00 (6H, t, J=7.5Hz);

[0510] TLC : R_f 0.46 (chloroform:methanol:water=9:1:0.1).

Example 2(275)

[0511] 4-(piperazin-4-ylsulfonyl)-2-ethylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

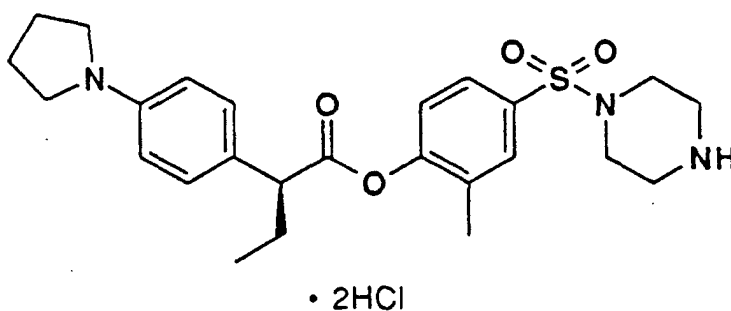


[0512] NMR (CD₃OD): δ 7.75-7.58 (6H, m), 7.25 (1H, d, J=9.0Hz), 3.98 (1H, t, J=7.5Hz), 3.90-3.70 (4H, m), 3.40-3.20 (8H, m), 2.50-1.80 (8H, m), 1.00 (6H, t, J=7.5Hz);

[0513] TLC : R_f 0.46 (chloroform:methanol:water=9:1:0.1).

Example 2(276)

[0514] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

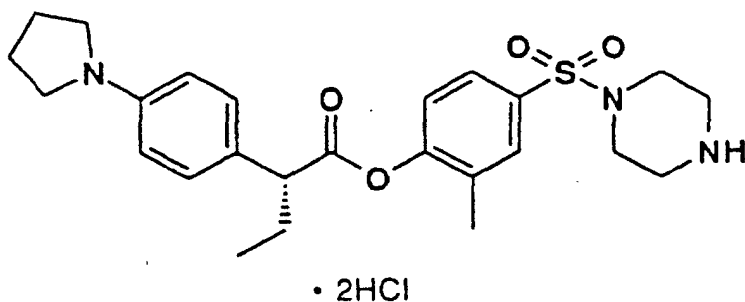


[0515] NMR (CD₃OD): δ 7.71 (6H, m), 7.22 (1H, d, J=8.0Hz), 4.00 (1H, t, J=8Hz), 3.81 (4H, m), 3.31 (8H, s), 2.33 (4H, m), 2.24 (1H, m), 2.07 (3H, s), 1.98 (1H, m), 1.01 (3H, t, J=7.4Hz);

[0516] TLC : R_f 0.66 (chloroform:methanol:water=4:1:0.1).

Example 2(277)

[0517] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester · 2hydrochloride

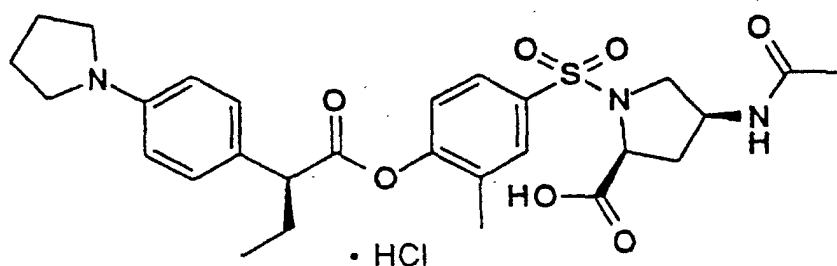


[0518] NMR (CD_3OD): δ 7.70 (6H, m), 7.22 (1H, d, $J=8.0\text{Hz}$), 4.00 (1H, t, $J=8\text{Hz}$), 3.81 (4H, m), 3.30 (8H, s), 2.32 (4H, m), 2.24 (1H, m), 2.06 (3H, s), 1.99 (1H, m), 1.00 (3H, t, $J=7.4\text{Hz}$);

[0519] TLC : Rf 0.66 (chloroform:methanol:water=4:1:0.1).

Example 2(279)

[0520] 4-((2S-carboxy-4-acetylamino pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester \cdot hydrochloride

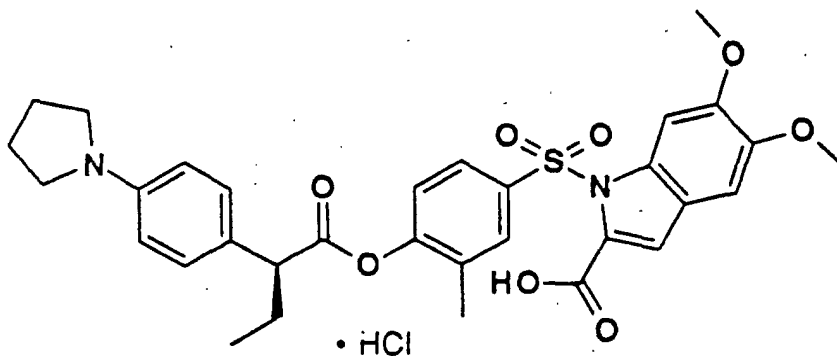


[0521] NMR ($\text{DMSO}-d_6$): δ 8.02 (1H, d, $J=6\text{Hz}$), 7.74 (1H, s), 7.69 (1H, d, $J=8.8\text{Hz}$), 7.24 (2H, d, $J=8.6\text{Hz}$), 7.18 (1H, d, $J=8.6\text{Hz}$), 6.69 (1H, d, $J=8.8\text{Hz}$), 4.15 (1H, t, $J=7\text{Hz}$), 3.75 (2H, m), 3.51 (1H, m), 3.28 (4H, m), 3.05 (1H, m), 2.33 (1H, m), 2.12 (1H, m), 1.99 (7H, s-like), 1.83 (2H, m), 1.75 (3H, s), 0.91 (3H, t, $J=7.4\text{Hz}$);

[0522] TLC : Rf 0.67 (chloroform:methanol:water=6:4:1).

Example 2(280)

[0523] 4-((2-carboxy-5,6-dimethoxyindol-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester \cdot hydrochloride



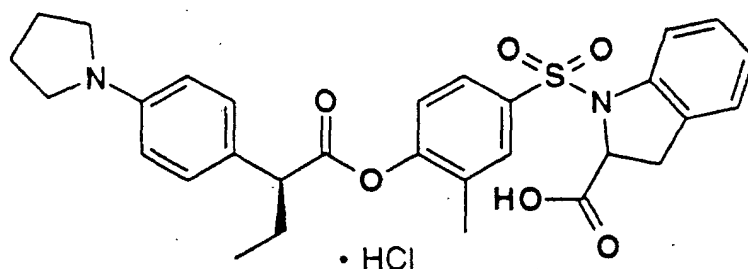
EP 0 769 498 B9 (W1B1)

[0524] NMR (DMSO- d_6): δ 7.87 (1H, d, $J=2.2$ Hz), 7.79 (1H, dd, $J=8.6$ Hz, 2.2Hz), 7.50 (1H, s), 7.25-7.13 (5H, m), 6.66 (2H, d, $J=8.0$ Hz), 3.88 (3H, s), 3.78 (3H, s), 3.71 (1H, t, $J=7.2$ Hz), 3.26 (4H, m), 2.08 (1H, m), 1.97 (4H, m), 1.93 (3H, s), 1.78 (1H, m), 0.88 (3H, t, $J=7.6$ Hz);

[0525] TLC : Rf 0.45 (chloroform:methanol:water=4:1:0.1).

Example 2(281)

[0526] 4-((2RS-carboxyindolin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • hydrochloride

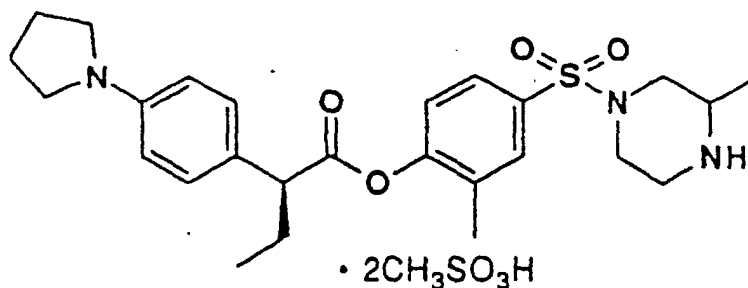


[0527] NMR (DMSO- d_6): δ 7.78 (1H, s), 7.67 (1H, dd, $J=2$ and 8Hz), 7.35-6.94 (7H, m), 6.80-6.64 (2H, br), 5.00-4.93 (1H, m), 3.70 (1H, t, $J=7$ Hz), 3.39-2.96 (6H, m), 2.17-1.64 (2H, m), 2.04-1.94 (4H, m), 1.91 (3H, s), 0.87 (3H, t, $J=7$ Hz);

[0528] TLC : Rf 0.30 (chloroform:methanol:water=4:1:0.1).

Example 2(282)

[0529] 4-((2RS-methylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • 2methanesulfonic acid salt

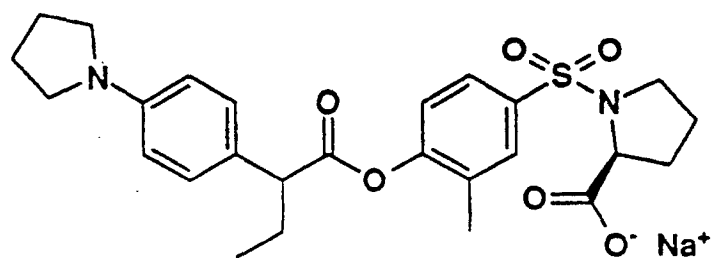


[0530] NMR (CD $_3$ OD): δ 7.75-7.60 (6H, m), 7.23 (1H, d, $J=8.5$ Hz), 4.00 (1H, t, $J=7.5$ Hz), 3.90-3.70 (6H, m), 3.55-3.35 (2H, m), 3.35-3.10 (1H, m), 2.80-2.65 (1H, m), 2.66 (6H, s), 2.47 (1H, t, $J=10.0$ Hz), 2.06 (3H, s), 1.31 (3H, d, $J=6.5$ Hz), 1.00 (3H, t, $J=7.5$ Hz);

[0531] TLC : Rf 0.45 (chloroform:methanol:water=9:1:0.1).

Example 2(284)

[0532] 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • sodium salt



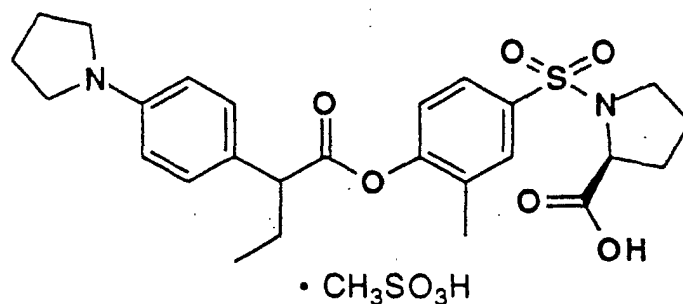
[0533] NMR (d_6 -DMSO): δ 7.78-7.64 (2H, m), 7.18 (2H, d, $J=8.0$ Hz), 7.08 (1H, d, $J=8.0$ Hz), 6.53 (2H, d, $J=8.0$ Hz),

3.95-3.80 (1H, m), 3.69 (1H, t, $J=7.5$ Hz), 3.50-3.00 (6H, m), 2.20-1.30 (10H, m), 1.96 (3H, s), 0.91 (3H, t, $J=7.5$ Hz);

[0534] TLC : Rf 0.32 (chloroform:methanol:water=9:1:0.1).

Example 2(285)

[0535] 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • methanesulfonic acid salt

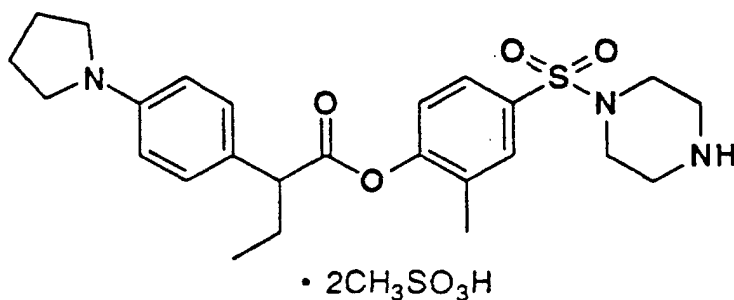


[0536] NMR ($CDCl_3$): δ 7.65 (4H, d, $J=8.5$ Hz), 7.54 (2H, d, $J=8.5$ Hz), 7.05 (1H, d, $J=8.5$ Hz), 4.30-4.15 (1H, m), 4.10-3.50 (4H, m), 3.80 (1H, t, $J=7.5$ Hz), 3.55-3.35 (1H, m), 3.30-3.10 (1H, m), 2.87 (3H, s), 2.50-1.60 (10H, m), 2.03 (3H, s), 0.99 (3H, t, $J=7.5$ Hz);

[0537] TLC : Rf 0.32 (chloroform:methanol:water=9:1:0.1).

Example 2(286)

[0538] 4-((piperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • 2methanesulfonic acid salt



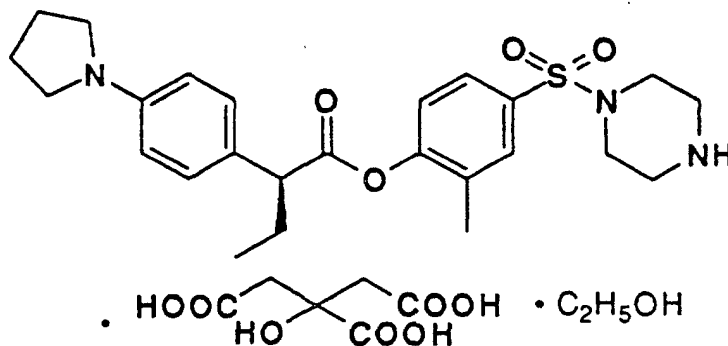
EP 0 769 498 B9 (W1B1)

[0539] NMR (CD₃OD): δ 7.75-7.60 (6H, m), 7.23 (1H, d, J=8.0Hz), 4.01 (1H, t, J=7.5Hz), 3.90-3.70 (4H, m), 3.35-3.20 (8H, m), 2.68 (6H, s), 2.40-1.80 (6H, m), 2.06 (3H, s), 1.00 (3H, t, J=7.5Hz);

[0540] TLC : R_f 0.14 (chloroform:methanol:acetic acid=40:2:1).

Example 2(287)

[0541] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl) butanoic acid ester • citric acid salt • ethanol salt

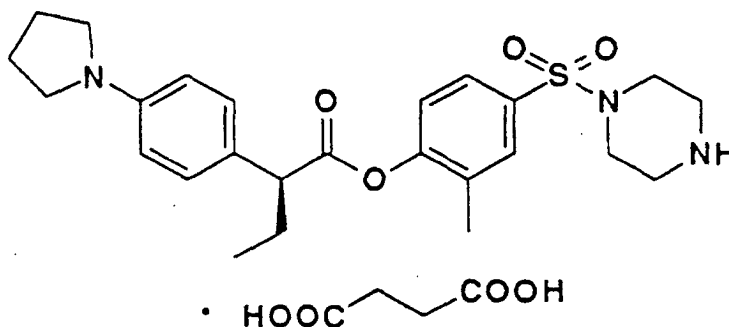


[0542] NMR (CD₃OD): δ 7.66 (1H, brs), 7.62 (1H, brd, J=8.0Hz), 7.20 (2H, d, J=8.5Hz), 7.18 (1H, d, J=8.0Hz), 6.58 (2H, d, J=8.5Hz), 3.67 (1H, t, J=7.5Hz), 3.60 (2H, q, J=7.0Hz), 3.40-3.15 (12H, m), 2.76 (4H, dd, J=8.0, 14.0Hz), 2.30-1.70 (9H, m), 1.17 (3H, t, J=7.0Hz), 0.97 (3H, t, J=7.5Hz);

[0543] TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(288)

[0544] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester • succinic acid salt

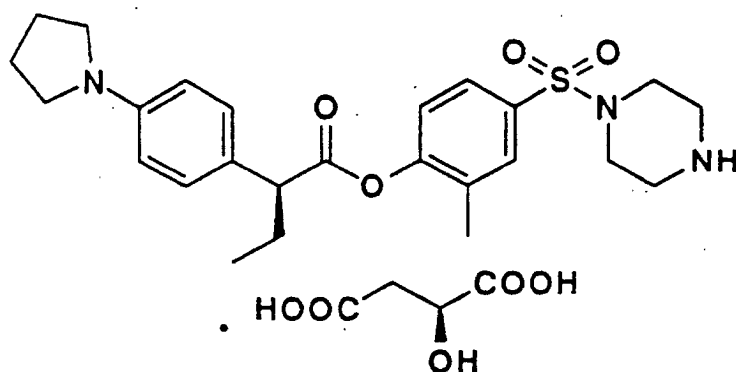


[0545] NMR (CD₃OD): δ 7.64 (1H, brs), 7.61 (1H, brd, J=8.0Hz), 7.19 (2H, d, J=8.5Hz), 7.17 (1H, d, J=8.0Hz), 6.57 (2H, d, J=8.5Hz), 3.64 (1H, t, J=7.5Hz), 3.40-3.20 (4H, m), 3.12 (8H, s), 2.51 (4H, s), 2.30-1.76 (9H, m), 0.97 (3H, t, J=7.5Hz);

[0546] TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(289)

[0547] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester • L-malic acid salt

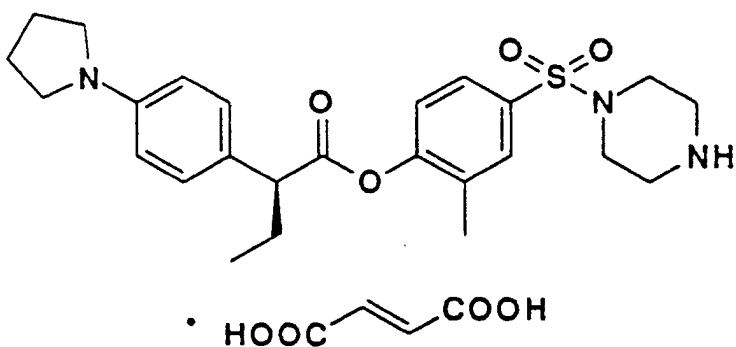


[0548] NMR (CD₃OD): δ 7.67 (1H, brs), 7.62 (1H, brd, J=8.0Hz), 7.22 (2H, d, J=8.5Hz), 7.19 (1H, d, J=8.0Hz), 6.58 (2H, d, J=8.5Hz), 4.28 (1H, dd, J=5.0, 7.5Hz), 3.68 (1H, t, J=7.5Hz), 3.40-3.05 (12H, m), 2.78 (1H, dd, J=5.0, 15.0Hz), 2.52 (1H, dd, J=7.5, 15.0Hz), 2.40-1.72 (9H, m), 0.98 (3H, t, J=7.5Hz);

[0549] TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(290)

[0550] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester • fumaric acid salt

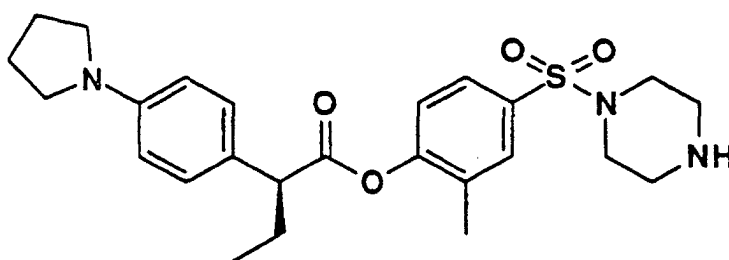


[0551] NMR (CD₃OD): δ 7.68 (1H, brs), 7.63 (1H, brd, J=8.0Hz), 7.21 (2H, d, J=8.5Hz), 7.19 (1H, d, J=8.0Hz), 6.82 (2H, s), 6.59 (2H, d, J=8.5Hz), 3.65 (1H, t, J=7.5Hz), 3.40-3.10 (12H, m), 2.30-1.70 (9H, m), 0.98 (3H, t, J=7.5Hz);

[0552] TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(291)

[0553] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester • oxalic acid salt



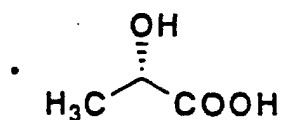
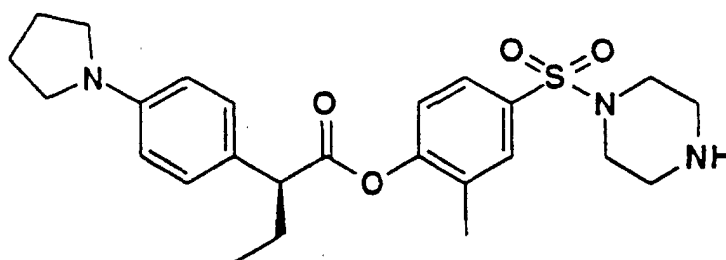
• (COOH)₂

[0554] NMR (CD₃OD): δ 7.68 (1H, s), 7.63 (1H, brd, J=8.0Hz), 7.20 (2H, d, J=8.5Hz), 7.19 (1H, d, J=8.0Hz), 6.60 (2H, d, J=8.5Hz), 3.66 (1H, t, J=7.5Hz), 3.45-3.10 (12H, m), 2.30-1.75 (9H, m), 0.98 (3H, t, J=7.5Hz);

[0555] TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(292)

[0556] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester • L-lactic acid salt

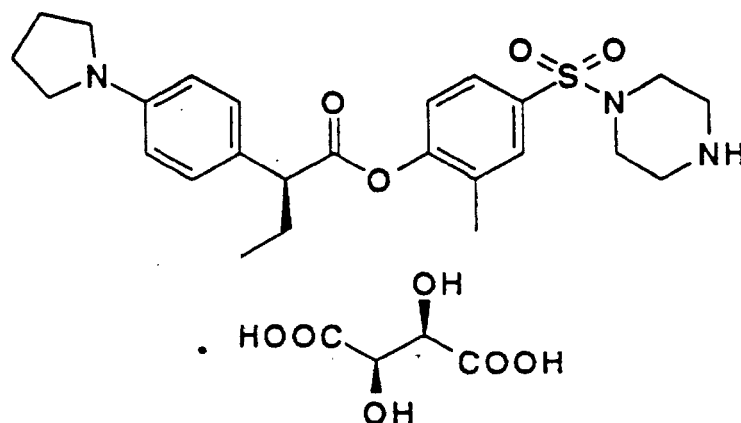


[0557] NMR (CD₃OD): δ 7.65 (1H, s), 7.61 (1H, brd, J=8.0Hz), 7.20 (2H, d, J=8.5Hz), 7.17 (1H, d, J=8.0Hz), 6.57 (2H, d, J=8.5Hz), 4.04 (1H, q, J=7.0Hz), 3.65 (1H, t, J=7.5Hz), 3.40-3.20 (4H, m), 3.14 (8H, s), 2.15 (3H, s), 2.20-1.75 (6H, m), 1.31 (3H, d, J=7.0Hz), 0.97 (3H, t, J=7.5Hz);

[0558] TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(293)

[0559] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester • L-tartaric acid salt

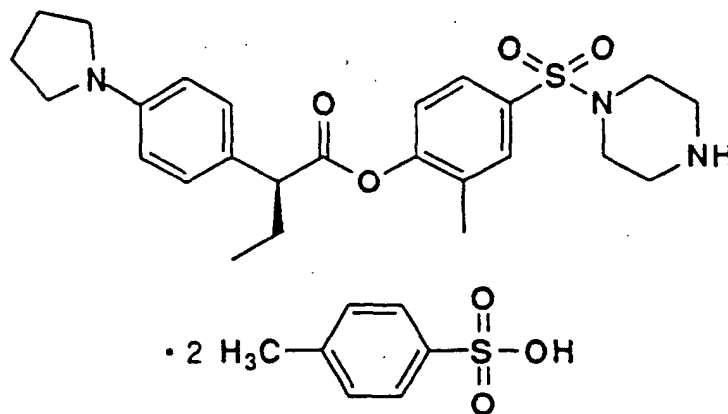


[0560] NMR (CD₃OD): δ 7.68 (1H, s), 7.64 (1H, brd, J=8.0Hz), 7.21 (2H, d, J=8.5Hz), 7.18 (1H, d, J=8.0Hz), 6.59 (2H, d, J=8.5Hz), 4.43 (2H, s), 3.68 (1H, t, J=7.5Hz), 3.45 - 3.10 (12H, m), 2.40 - 1.78 (9H, m), 0.98 (3H, t, J=7.5Hz);

[0561] TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(294)

[0562] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • 2 p-toluenesulfonic acid salt

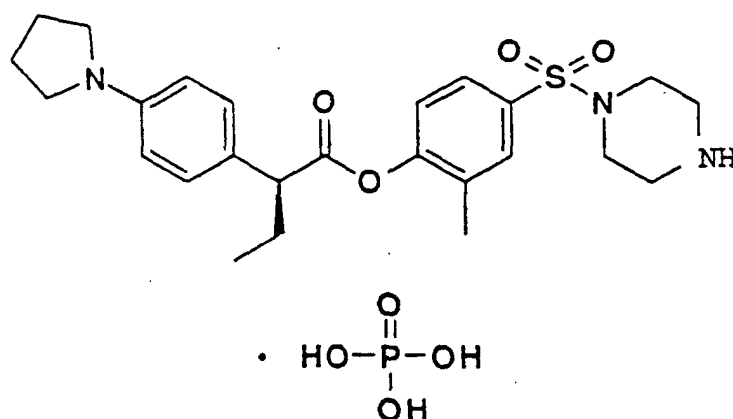


[0563] NMR (CD₃OD): δ 7.68 (6H, d, J=8.0Hz), 7.63 (4H, d, J=9.0Hz), 7.22 (5H, d, J=8.0Hz), 3.99 (1H, t, J=7.4Hz), 3.83 - 3.65 (4H, m), 3.30 (8H, m), 2.36 (6H, s), 2.36-2.20 (5H, m), 2.04 (3H, s), 1.95 (1H, m), 0.99 (3H, t, J=7.4Hz);

[0564] TLC : R_f 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(295)

[0565] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester • phosphoric acid salt

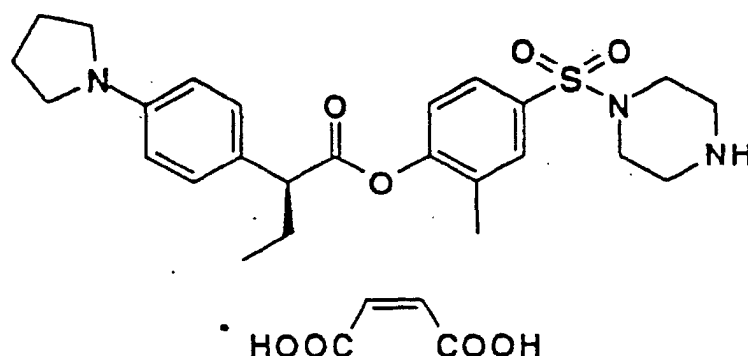


[0566] NMR (DMSO- d_6): δ 8.00-7.40 (3H, m), 7.67 (1H, brs), 7.62 (1H, brd, $J=8.8$ Hz), 7.25 (1H, d, $J=8.8$ Hz), 7.21 (2H, d, $J=8.8$ Hz), 6.56 (2H, d, $J=8.8$ Hz), 3.75 (1H, t, $J=7.4$ Hz), 3.23 (4H, brs), 2.94 (8H, brs), 2.01 (3H, s), 2.20-1.80 (6H, m), 0.93 (3H, t, $J=7.4$ Hz);

[0567] TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

Example 2(296)

[0568] 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl) phenyl)butanoic acid ester • maleic acid salt

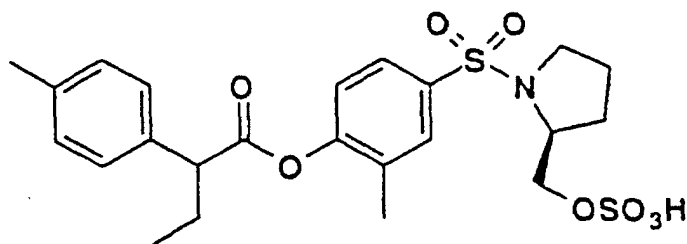


[0569] NMR (CD₃OD): δ 7.67 (1H, s), 7.62 (1H, brd, $J=8.0$ Hz), 7.20 (2H, d, $J=8.5$ Hz), 7.19 (1H, d, $J=8.0$ Hz), 6.58 (2H, d, $J=8.5$ Hz), 6.23 (2H, s), 3.65 (1H, t, $J=7.5$ Hz), 3.40-3.05 (12H, m), 2.30-1.78 (6H, m), 1.98 (3H, s), 0.97 (3H, t, $J=7.5$ Hz);

[0570] TLC : Rf 0.11 (chloroform:methanol:acetic acid=40:2:1).

Preparation Example3

[0571] 4-(2S-hydroxysulfonyloxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-methylphenyl)butanoic acid ester



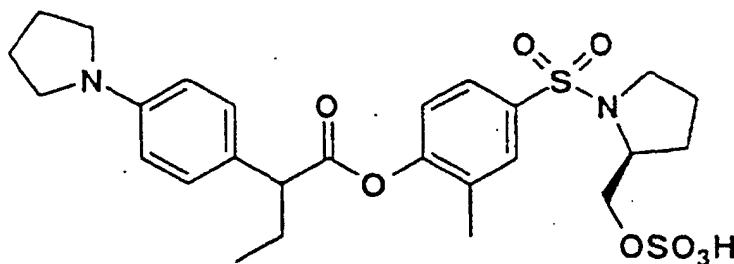
[0572] To a solution of the compound prepared in example 2(19) (690 mg) in pyridine (10 ml) was added sulfur trioxide pyridine complex (766 mg) and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (chloroform:methanol=10:1) to give the title compound (700 mg) having the following physical data.

[0573] NMR (DMSO- d_6): δ 7.74 (1H, d, $J=2.0$ Hz), 7.67 (1H, dd, $J=8.5, 2.0$ Hz), 7.30 (2H, d, $J=8.5$ Hz), 7.20 (2H, d, $J=8.5$ Hz), 7.18 (1H, d, $J=8.5$ Hz), 3.94-3.78 (2H, m), 3.76-3.60 (1H, m), 3.58 (1H, t, $J=7.0$ Hz), 3.3-3.2 (1H, m), 3.12-2.94 (1H, m), 2.31 (3H, s), 2.25-2.00 and 1.95-1.70 (each 1H, m), 1.97 (3H, s), 1.90-1.60 (2H, m), 1.60-1.30 (2H, m), 0.91 (3H, t, $J=7.5$ Hz);

[0574] TLC : R_f 0.39 (water:methanol:chloroform=1:10:40).

Example 3(1)

[0575] 4-(2S-hydroxysulfonyloxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester



[0576] By the same procedure as Preparation example 3, the title compound having the following physical data was given by using the compound prepared in Preparation example 2(10).

[0577] NMR (DMSO- d_6): δ 7.74 (1H, s), 7.67 (1H, d, $J=8.5$ Hz), 7.25-7.10 (3H, m), 6.55 (2H, d, $J=8.0$ Hz), 3.91 (1H, d, $J=8.5$ Hz), 3.80-3.50 (3H, m), 3.40-3.20 (1H, m), 3.35-3.20 (4H, m), 3.15-2.90 (1H, m), 2.20-1.60 (2H, m), 1.98 (3H, s), 2.05-1.90 (4H, m), 1.90-1.60 (2H, m), 1.60-1.30 (2H, m), 0.91 (3H, t, $J=7.5$ Hz);

[0578] TLC: R_f 0.38 (water:methanol:chloroform=1:10:40).

Formulation Examples

Formulation Example 1

[0579] The following components were admixed in conventional manner and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

4-(piperazin-4-yl sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2 hydrochloride	5.0g
Carboxymethylcellulose calcium (disintegrating agent)	0.2g
Magnesium stearate (lubricating agent)	0.1g
Microcrystalline cellulose	4.7g

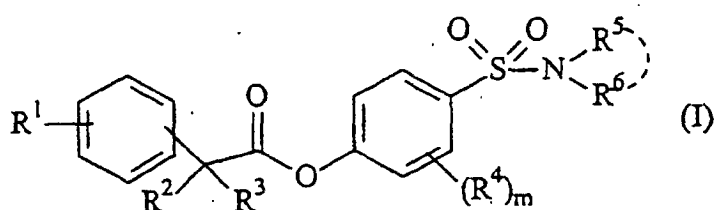
Formulation Example 2

[0580] The following components were admixed in conventional manner. The solution was sterilized in conventional manner, placed 5 ml portion into ampoules and freeze-dried to obtain 100 ampoules each containing 20 mg of the active ingredient.

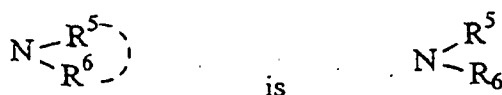
4-(piperazin-4-yl sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester 2	2.0g
hydrochloride	
mannitol	20 g
Distilled water	1000ml

Claims

1. A compound of the formula (I)



wherein R^1 is pyrrolidinyl;
 R^2 and R^3 each, independently, is hydrogen atom or C1-4 alkyl;
 R^4 is C1-4 alkyl;
 m is an integer from 0 to 4; and



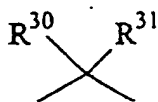
in which R^5 and R^6 each, independently, is

- 1) hydrogen atom,
- 2) hydroxy;
- 3) C1-8 alkyl,
- 4) C1-8 alkoxy,
- 5) -M- R^{16}

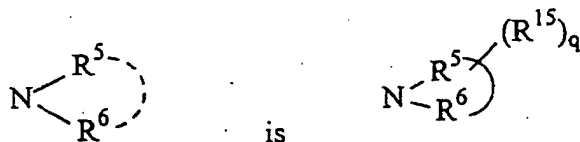
(in which M is single bond or C1-8 alkylene), and
 R^{16} is

- 5-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one to four nitrogen atoms, one or two oxygen atoms or one nitrogen atom and one sulfur atom or oxygen atom, unsubstituted or substituted by 1 to 4 substituents selected from C1-4 alkyl, C1-4 alkoxy, hydroxy, phenyl C1-4 alkyl, -COOR²⁶ (in which R^{26} is hydrogen atom, C1-8 alkyl, phenyl or phenyl C1-4 alkyl), hydroxy C1-4 alkyl or C2-4 alkoxyalkyl),
- 6) -J-COOR²⁹, in which R^{29} is hydrogen atom, and

J is



(in which
 R^{30} and R^{31} each, independently, is hydrogen atom or C1-8 alkyl; or

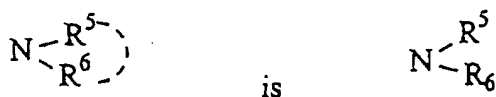


in which R^5 and R^6 , taken together with the nitrogen atom to which they are attached represent a 3-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one or two nitrogen atoms or one nitrogen atom and one sulfur atom or oxygen atom,
 q is an integer from 0 to 4, and
 R^{15} is

- 1) C1-4 alkyl,
- 2) C1-4 alkoxy,
- 3) phenyl C1-4 alkoxy,
- 4) nitro,
- 5) $-\text{COOR}^{36}$ (in which R^{36} is hydrogen atom, or C1-4 alkyl substituted by $-\text{NR}^{39}\text{R}^{40}$ (in which R^{39} and R^{40} each, independently, is hydrogen atom or C1-4 alkyl),
- 6) $-\text{NR}^{43}\text{R}^{44}$ (in which R^{43} and R^{44} each, independently, is hydrogen atom, C1-4 alkyl or C2-5 acyl),
- 7) $-\text{CONR}^{45}\text{R}^{46}$ (in which R^{45} and R^{46} each, independently, is hydrogen atom or C1-4 alkyl substituted by hydroxy,
- 8) C1-4 alkyl substituted by $-\text{OSO}_3\text{H}$;

or a non-toxic salt, acid addition salt or solvate thereof.

2. A compound according to claim 1, wherein



in which all symbols are as defined in claim 1.

3. A compound according to claim 1, wherein



in which all symbols are as defined in claim 1.

4. A compound according to claim 1, which is

21) 4-(N-methyl-N-methoxysulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,

35) 4-(N-(quinuclidin-3RS-yl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 36) 4-(N-2-(morpholin-4-yl)ethylsulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 38) 4-(N-(piperidin-4-yl)sulfamoyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 56) 4-(2-(morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 57) 4-(quinuclidin-3RS-ylaminosulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 101) 4-(N-(1,1-dimethyl-1-carboxymethyl)-N-propylaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 103) 4-(N-hydroxyaminosulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 or a non-toxic salt, acid addition salt or solvate thereof.

5. A compound according to claim 1, which is

11) 4-(6-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 14) 4-(7-aminoindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 15) 4-(benzimidazol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 31) 4-(morpholin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 33) 4-(piperazin-4-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 40) 4-(4-methylpiperazin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 41) 4-(5-nitroindolin-1-ylsulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 44) 4-(2S-carboxypyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 48) 4-(2S-carboxy-4R-benzyloxypyrrolidin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 56) 4-(2RS-carboxyindolin-1-ylsulfonyl)phenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 66) 4-(2RS-(N-2-hydroxyethylcarbamoyl)indolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 67) 4-(2-carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 68) 4-(2RS-(2-aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 69) 4-(2-carboxyindol-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 89) 4-((2R-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 90) 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2R-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 95) 4-((2RS-carboxypiperidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 98) 4-((2S-carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 99) 4-((2R-carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 104) 4-((2S-carboxypyrrolidin-1-yl)sulfonyl)-2-ethylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 107) 4-((2S-carboxy-4S-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 109) 4-((2S-carboxy-4R-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 113) 4-((2S,6S-dimethylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 114) 4-((2RS-methylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 115) 4-((2S-carboxy-4R-(N,N-dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 116) 4-((2S-carboxy-4R-methylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 117) 4-(piperazin-4-ylsulfonyl)-2-ethylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 125) 4-((2RS-methylpiperazin-4-yl)sulfonyl)-2-methylphenyl 2S-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 128) 4-(2S-hydroxysulfonyloxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl 2RS-(4-(pyrrolidin-1-yl)phenyl)butanoic acid ester,
 or a non-toxic salt, acid addition salt or solvate thereof

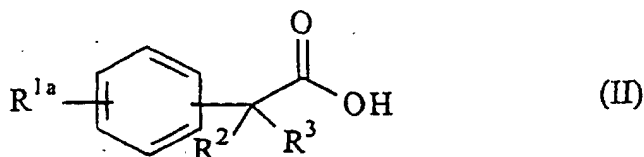
6. A pharmaceutical composition which comprises, as active ingredient, an effective amount of a compound of the formula (I) defined in claim 1, a non-toxic salt thereof, an acid addition salt thereof or a solvate thereof, with a carrier or coating.

7. A compound of the formula (I) defined in claim 1 or a non-toxic salt thereof or a non-toxic acid addition salt thereof

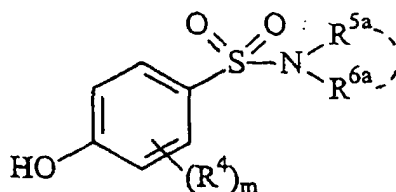
or solvate thereof for use in the manufacture of pharmaceutical composition as an inhibitor of Elastase.

8. A compound of the formula (I) defined in claim 1 or a non-toxic salt thereof or a non-toxic addition salt thereof or solvate thereof for use in the manufacture of a pharmaceutical composition for the prevention and/or the treatment of diseases induced by an abnormal enhancement of the degradation of elastin, collagen fiber and/or proteoglycan, resulting from the action of elastase on a mammalian animal, especially a human (e.g. chronic obstructive pulmonary disease such as emphysema, rheumatoid arthritis, atherosclerosis, adult respiratory distress syndrome (ARDS), glomerular nephritis, myocardial infarction, idiopathic ulcerative colitis or gingivitis).

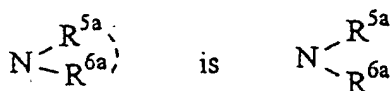
9. A process for the preparation of a compound of formula (I) as defined in claim 1 which process comprises esterifying a compound of the formula:



wherein R^{1a} is pyrrolidinyl;
and R^2 and R^3 are as defined in claim 1,
with a compound of formula (III)



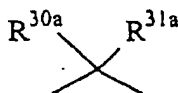
wherein R^4 and m are as defined in claim 1,



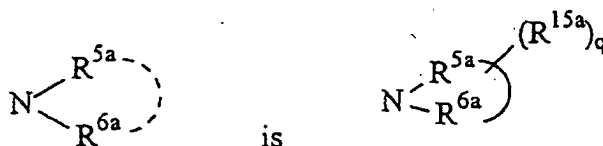
(in which R^{5a} and R^{6a} each, independently, is

- 1) hydrogen atom (with the proviso that, R^{5a} and R^{6a} do not represent hydrogen atom at the same time),
- 2) hydroxy,
- 3) hydroxy protected by a protecting group which is removable under acid conditions,
- 4) t-butoxycarbonyl,
- 5) benzyloxycarbonyl,
- 6) C1-8 alkyl,
- 7) C1-8 alkoxy,
- 8) $-M-R^{16a}$ (in which M is as defined in claim 1, and R^{16a} is 5-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one to four nitrogen atoms, one or two oxygen atoms or one nitrogen atom and one sulfur atom or oxygen atom, unsubstituted or substituted by 1 to 4 substituents selected from C1-4 alkyl, C1-4 alkoxy, hydroxy, phenyl C1-4 alkyl, $-\text{COOR}^{26}$ (in which R^{26} is as defined in claim 1), hydroxy C1-4 alkyl in which hydroxy is protected by a protecting group which is removable under acid conditions or C2-4 alkoxyalkyl),
- 9) $-\text{Ja}-\text{COOR}^{29}$ (in which R^{29} is as defined in claim 1,

Ja is



(in which
 R^{30a} and R^{31a} each, independently, is i) hydrogen atom or, ii) C1-8 alkyl, or



in which R^{5a} and R^{6a} taken together with the nitrogen atom to which they are attached represent a 3-15 membered mono- or bi-cyclic aromatic heterocyclic ring, saturated heterocyclic ring or partly saturated heterocyclic ring containing one or two nitrogen atoms or one nitrogen atom and one sulfur atom or oxygen atom,
 q is as defined in claim 1,
 R^{15a} is

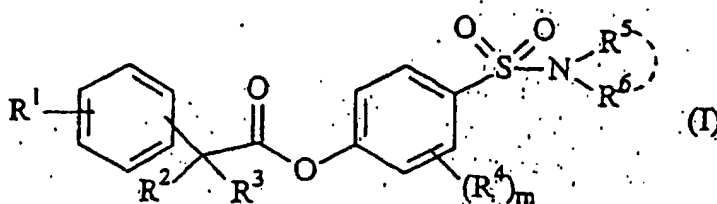
- 1) C1-4 alkyl,
- 2) C1-4 alkoxy,
- 3) phenyl C1-4 alkoxy,
- 4) nitro,
- 5) $-\text{COOR}^{36a}$ (in which R^{36a} is hydrogen atom, C1-4 alkyl substituted by $-\text{NR}^{39a}\text{R}^{40a}$ (in which R^{39a} and R^{40a} each, independently, is hydrogen atom (with the proviso that, R^{39a} and R^{40a} do not represent hydrogen atom at the same time, t-butoxycarbonyl, benzyloxycarbonyl or C1-4 alkyl),
- 6) $-\text{NR}^{43a}\text{R}^{44a}$ (in which R^{43a} and R^{44a} each, independently, is hydrogen atom (with the proviso that, R^{43a} and R^{44a} do not represent hydrogen atom at the same time), t-butoxycarbonyl, benzyloxycarbonyl, C1-4 alkyl or C2-5 acyl),
- 7) $-\text{CONR}^{45a}\text{R}^{46a}$ (in which R^{45a} and R^{46a} each, independently, is hydrogen atom, or C1-4 alkyl substituted by hydroxy or protected hydroxy),

or

may be prepared by esterifying a compound of formula (II) with a compound of formula (III) to obtain a compound having protected group(s) and then eliminating the protecting groups,
 or may be prepared by esterifying a compound of formula (II) with a compound of formula (III), if necessary, eliminating the protecting groups to obtain a compound having R^{15} represent C1-4 alkyl substituted by hydroxy, and then subjecting to sulfuric acid esterification and optionally converting a compound of formula (I) thus obtained into a non-toxic salt, acid addition salt or solvate thereof.

Patentansprüche

1. Verbindung der Formel (I)



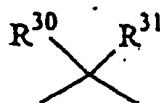
worin R^1 Pyrrolidinyl bedeutet;

R² und R³ jeweils unabhängig voneinander ein Wasserstoffatom oder C1-4-Alkyl bedeuten;
R⁴ C1-4-Alkyl bedeutet;
m eine ganze Zahl von 0 bis 4 ist; und

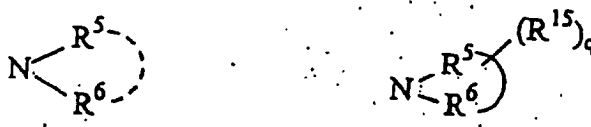


bedeutet,
wobei R⁵ und R⁶ jeweils unabhängig voneinander

- 1) ein Wasserstoffatom,
- 2) Hydroxy,
- 3) C1-8-Alkyl,
- 4) C1-8-Alkoxy,
- 5) -M-R¹⁶ (wobei M eine Einfachbindung oder C1-8-Alkylen ist), und R¹⁶ einen 5-15-gliedrigen mono- oder bicyclischen aromatischen heterocyclischen Ring, gesättigten heterocyclischen Ring oder teilweise gesättigten heterocyclischen Ring, der ein bis vier Stickstoffatome, ein oder zwei Sauerstoffatome oder ein Stickstoffatom und ein Schwefelatom oder Sauerstoffatom enthält, der unsubstituiert ist oder substituiert ist mit 1 bis 4 Substituenten, die ausgewählt sind aus C1-4-Alkyl, C1-4-Alkoxy, Hydroxy, Phenyl-C1-4-alkyl, -COOR²⁶ (wobei R²⁶ ein Wasserstoffatom, C1-8-Alkyl, Phenyl oder Phenyl-C1-4-alkyl ist), Hydroxy-C1-4-alkyl oder C2-4-Alkoxyalkyl, bedeutet),
- 6) -J-COOR²⁹, wobei R²⁹ ein Wasserstoffatom ist und J



(wobei R³⁰ und R³¹ jeweils unabhängig voneinander ein Wasserstoffatom oder C1-8-Alkyl sind) bedeutet, bedeuten; oder



bedeutet,

wobei R⁵ und R⁶ zusammen mit dem Stickstoffatom, an das sie gebunden sind, für einen 3-15-gliedrigen mono- oder bicyclischen aromatischen heterocyclischen Ring, gesättigten heterocyclischen Ring oder teilweise gesättigten heterocyclischen Ring, der ein oder zwei Stickstoffatome oder ein Stickstoffatom und ein Schwefelatom oder Sauerstoffatom enthält, stehen,
q eine ganze Zahl von 0 bis 4 ist und
R¹⁵

- 1) C1-4-Alkyl,
- 2) C1-4-Alkoxy,
- 3) Phenyl-C1-4-alkoxy,
- 4) Nitro,
- 5) -COOR³⁶ (wobei R³⁶ ein Wasserstoffatom oder C1-4-Alkyl, das mit NR³⁹R⁴⁰ (wobei R³⁹ und R⁴⁰ jeweils unabhängig voneinander ein Wasserstoffatom oder C1-4-Alkyl sind) substituiert ist, bedeutet),
- 6) -NR⁴³R⁴⁴ (wobei R⁴³ und R⁴⁴ jeweils unabhängig voneinander ein Wasserstoffatom, C1-4-Alkyl oder

C2-5-Acyl sind),

7) -CONR⁴⁵R⁴⁶ (wobei R⁴⁵ und R⁴⁶ jeweils unabhängig voneinander ein Wasserstoffatom oder C1-4-Alkyl, das mit Hydroxy substituiert ist, sind),

8) C1-4-Alkyl, das mit -OSO₃H substituiert ist, bedeutet;

oder ein nichttoxisches Salz, Säureadditionssalz oder Solvat derselben.

2. Verbindung nach Anspruch 1, wobei



bedeutet,

wobei alle Symbole wie in Anspruch 1 definiert sind.

3. Verbindung nach Anspruch 1, wobei



bedeutet,

wobei alle Symbole wie in Anspruch 1 definiert sind.

4. Verbindung nach Anspruch 1, nämlich

21) 4-(N-Methyl-N-methoxysulfamoyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

35) 4-(N-Chinuclidin-3RS-yl-sulfamoyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

36) 4-(N-2-(Morpholin-4-yl)ethylsulfamoyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

38) 4-(N-(Piperidin-4-yl)sulfamoyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

56) 4-(2-(Morpholin-4-yl)ethylaminosulfonyl)-2-methylphenyl-2S-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

57) 4-(Chinuclidin-3RS-ylaminosulfonyl)-2-methylphenyl-2S-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

101) 4-(N-(1,1-Dimethyl-1-carboxymethyl)-N-propylaminosulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

103) 4-(N-Hydroxyaminosulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

oder ein nichttoxisches Salz, Säureadditionssalz oder Solvat derselben.

5. Verbindung nach Anspruch 1, nämlich

11) 4-(6-Nitroindolin-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

14) 4-(7-Aminoindolin-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

15) 4-(Benzimidazol-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

31) 4-(Morpholin-4-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

33) 4-(Piperazin-4-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

40) 4-(4-Methylpiperazin-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

41) 4-(5-Nitroindolin-1-ylsulfonyl)-2-methylphenyl-2R-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

44) 4-(2S-Carboxypyrrolidin-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

48) 4-(2S-Carboxy-4R-benzylloxypyrrolidin-1-ylsulfonyl)phenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

56) 4-(2RS-Carboxyindolin-1-ylsulfonyl)phenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

66) 4-(2RS-(N-2-Hydroxyethylcarbamoyl)indolin-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

67) 4-(2-Carboxy-5,6-dimethoxyindol-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

68) 4-(2RS-(2-Aminoethyl)oxycarbonylindolin-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butan-

säureester,

69) 4-(2-Carboxyindol-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

89) 4-((2R-Carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl-2S-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

90) 4-((2S-Carboxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl-2R-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

95) 4-((2RS-Carboxypiperidin-1-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

98) 4-((2S-Carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

99) 4-((2R-Carboxy-4R-methoxypyrrolidin-1-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

104) 4-((2S-Carboxypyrrolidin-1-yl)sulfonyl)-2-ethylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

107) 4-((2S-Carboxy-4S-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

109) 4-((2S-Carboxy-4R-acetylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

113) 4-((2S,6S-Dimethylpiperazin-4-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

114) 4-((2RS-Methylpiperazin-4-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

115) 4-((2S-Carboxy-4R-(N,N-dimethylamino)pyrrolidin-1-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

116) 4-((2S-Carboxy-4R-methylaminopyrrolidin-1-yl)sulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

117) 4-(Piperazin-4-ylsulfonyl)-2-ethylphenyl-2S-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

125) 4-((2RS-Methylpiperazin-4-yl)sulfonyl)-2-methylphenyl-2S-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

128) 4-(2S-Hydroxysulfonyloxymethylpyrrolidin-1-ylsulfonyl)-2-methylphenyl-2RS-(4-(pyrrolidin-1-yl)phenyl)butansäureester,

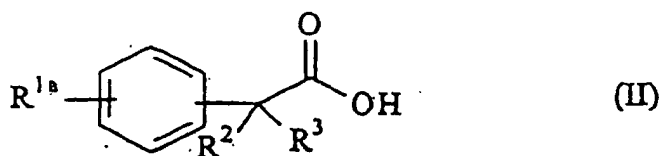
oder ein nichttoxisches Salz, Säureadditionssalz oder Solvat derselben.

6. Pharmazeutische Zusammensetzung, die als Wirkstoff eine wirksame Menge einer Verbindung der Formel (I) gemäß der Definition in Anspruch 1, eines nichttoxischen Salzes derselben, eines Säureadditionssalzes derselben oder eines Solvats derselben mit einem Träger oder einem Überzug umfasst.

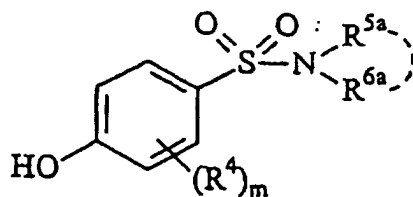
7. Verbindung der Formel (I) gemäß der Definition in Anspruch 1 oder ein nichttoxisches Salz derselben oder ein nichttoxisches Säureadditionssalz derselben oder Solvat derselben zur Verwendung bei der Herstellung einer pharmazeutischen Zusammensetzung als Inhibitor von Elastase.

8. Verbindung der Formel (I) gemäß der Definition in Anspruch 1 oder ein nichttoxisches Salz derselben oder ein nichttoxisches Säureadditionssalz derselben oder Solvat derselben zur Verwendung bei der Herstellung einer pharmazeutischen Zusammensetzung zur Prävention und/oder Behandlung von Erkrankungen, die durch eine anomale Verstärkung des Abbaus von Elastin, Kollagenfasern und/oder Proteoglykan als Ergebnis der Wirkung von Elastase auf einen Säuger, insbesondere einen Menschen, induziert wurden (beispielsweise eine chronische obstruktive Lungenerkrankung, wie ein Emphysem, rheumatoide Arthritis, Atherosklerose, Respiratory-Distress-Syndrom bei Erwachsenen (ARDS), glomeruläre Nephritis, Myokardinfarkt, idiopathische ulzeröse Kolitis oder Gingivitis).

9. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß der Definition in Anspruch 1, wobei das Verfahren das Verestern einer Verbindung der Formel:



worin R^{1a} Pyrrolidinyl ist; und R² und R³ wie in Anspruch 1 definiert sind;
mit einer Verbindung der Formel (III)



worin R^4 und m wie in Anspruch 1 definiert sind,

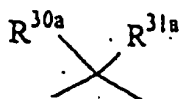


bedeutet,

(wobei R^{5a} und R^{6a} jeweils unabhängig voneinander

- 1) ein Wasserstoffatom (wobei R^{5a} und R^{6a} nicht gleichzeitig für ein Wasserstoffatom stehen),
- 2) Hydroxy,
- 3) Hydroxy, das durch eine unter sauren Bedingungen entfernbare Schutzgruppe geschützt ist,
- 4) tert-Butoxycarbonyl,
- 5) Benzyloxycarbonyl,
- 6) C1-8-Alkyl,
- 7) C1-8-Alkoxy,
- 8) -M- R^{16a} (wobei M wie in Anspruch 1 definiert ist und R^{16a} einen 5-15-gliedrigen mono- oder bicyclischen aromatischen heterocyclischen Ring, gesättigten heterocyclischen Ring oder teilweise gesättigten heterocyclischen Ring, der ein bis vier Stickstoffatome, ein oder zwei Sauerstoffatome oder ein Stickstoffatom und ein Schwefelatom oder Sauerstoffatom enthält, der unsubstituiert ist oder substituiert ist mit 1 bis 4 Substituenten, die ausgewählt sind aus C1-4-Alkyl, C1-4-Alkoxy, Hydroxy, Phenyl-C1-4-alkyl, -COOR²⁶ (wobei R^{26} wie in Anspruch 1 definiert ist), Hydroxy-C1-4-alkyl, wobei Hydroxy durch eine unter sauren Bedingungen entfernbare Schutzgruppe geschützt ist, oder C2-4-Alkoxyalkyl, bedeutet),
- 9) -J^a-COOR²⁹ (wobei R^{29} wie in Anspruch 1 definiert ist,

Ja



bedeutet (wobei R^{30a} und R^{31a} jeweils unabhängig voneinander i) ein Wasserstoffatom oder ii) C1-8-Alkyl sind)),
oder



bedeutet,

wobei R^{5a} und R^{6a} zusammen mit dem Stickstoffatom, an das sie gebunden sind, für einen 3-15-gliedrigen mono- oder bicyclischen aromatischen heterocyclischen Ring, gesättigten heterocyclischen Ring oder teilweise gesättigten heterocyclischen Ring, der 1 oder 2 Stickstoffatome oder ein Stickstoffatom und ein Schwefelatom oder

Sauerstoffatom enthält, stehen,
q wie in Anspruch 1 definiert ist,
R^{15a}

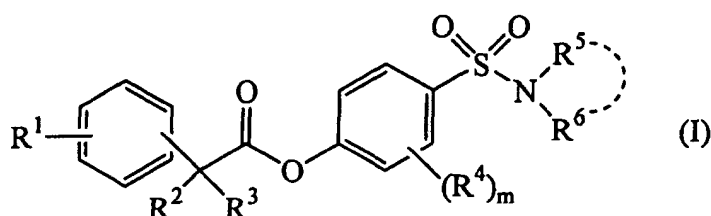
- 1) C1-4-Alkyl,
- 2) C1-4-Alkoxy,
- 3) Phenyl-C1-4-alkoxy,
- 4) Nitro,
- 5) -COOR^{36a} (wobei R^{36a} ein Wasserstoffatom, C1-4-Alkyl, das mit NR^{39a}R^{40a} substituiert ist (wobei R^{39a} und R^{40a} jeweils unabhängig voneinander ein Wasserstoffatom (wobei R^{39a} und R^{40a} nicht gleichzeitig für ein Wasserstoffatom stehen), tert-Butoxycarbonyl, Benzyloxycarbonyl oder C1-4-Alkyl bedeuten), bedeutet),
- 6) -NR^{43a}R^{44a} (wobei R^{43a} und R^{44a} jeweils unabhängig voneinander ein Wasserstoffatom (wobei R^{43a} und R^{44a} nicht gleichzeitig für ein Wasserstoffatom stehen), tert-Butoxycarbonyl, Benzyloxycarbonyl, C1-4-Alkyl oder C2-5-Acyl bedeuten),
- 7) -CONR^{45a}R^{46a} (wobei R^{45a} und R^{46a} jeweils unabhängig voneinander ein Wasserstoffatom oder C1-4-Alkyl, das mit Hydroxy oder geschütztem Hydroxy substituiert ist, bedeuten) bedeutet, umfasst,

oder eine Herstellung durch Verestern einer Verbindung der Formel (II) mit einer Verbindung der Formel (III) unter Bildung einer Verbindung mit einer geschützten Gruppe bzw. geschützten Gruppen und anschließendes Entfernen der Schutzgruppen erfolgen kann,

oder eine Herstellung durch Verestern einer Verbindung der Formel (II) mit einer Verbindung der Formel (III), ggf. Entfernen der Schutzgruppen unter Bildung einer Verbindung, wobei R¹⁵ für mit Hydroxy substituiertes C1-4-Alkyl steht, und anschließendes Durchführen einer Schwefelsäureveresterung und optionales Umwandeln einer auf diese Weise erhaltenen Verbindung der Formel (I) in ein nichttoxisches Salz, Säureadditionssalz oder Solvat derselben erfolgen kann.

Revendications

1. Composé de formule (I)

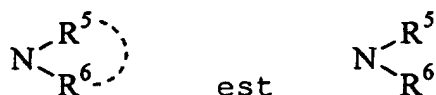


dans lequel R¹ est un pyrrolidinyle ;

R² et R³ indépendamment l'un de l'autre, sont un atome d'hydrogène ou un alkyle en C₁ à C₄ ;

R⁴ est un alkyle en C₁ à C₄ ;

m est un nombre entier compris entre 0 et 4 ; et



dans lequel R⁵ et R⁶ indépendamment l'un de l'autre, sont

- 1) un atome d'hydrogène,
- 2) un hydroxy,
- 3) un alkyle en C₁ à C₈,

4) un alkoxy en C₁ à C₈,

5) -M-R¹⁶

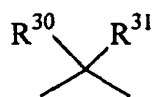
(dans lequel M est une liaison simple ou un alcoylène en C₁ à C₈), et

R¹⁶ est

un cycle hétérocyclique aromatique mono- ou bi-cyclique de 5 à 15 chaînons, un cycle hétérocyclique saturé ou un cycle hétérocyclique partiellement saturé contenant de un à quatre atomes d'azote, un ou deux atomes d'oxygène ou un atome d'azote et un atome de soufre ou un atome d'oxygène, non substitué ou substitué par 1 à 4 substituants choisis dans le groupe comprenant un alkyle en C₁ à C₄, un alkoxy en C₁ à C₄, un hydroxy, un phényl(alkyle en C₁ à C₄), -COOR²⁶ (dans lequel R²⁶ est un atome d'hydrogène, un alkyle en C₁ à C₈, un phényle ou un phényl(alkyle en C₁ à C₄), un hydroxy(alkyle en C₁ à C₄) ou un alkoxyalkyle en C₂ à C₄),

6) -J-COOR²⁹, dans lequel R²⁹ est un atome d'hydrogène, et

J est



(dans lequel

R³⁰ et R³¹ indépendamment l'un de l'autre, est un atome d'hydrogène ou un alkyle en C₁ à C₈ ; ou



dans lequel R⁵ et R⁶, pris ensemble avec l'atome d'azote auquel ils sont liés représentent un cycle hétérocyclique aromatique mono- ou bi-cyclique de 3 à 15 chaînons, un cycle hétérocyclique saturé ou un cycle hétérocyclique partiellement saturé contenant un ou deux atomes d'azote ou un atome d'azote et un atome de soufre ou un atome d'oxygène,

q est un nombre entier compris entre 0 et 4, et

R¹⁵ est

1) un alkyle en C₁ à C₄,

2) un alkoxy en C₁ à C₄,

3) un phényl(alkoxy en C₁ à C₄),

4) un nitro,

5) -COOR³⁶ (dans lequel R³⁶ est un atome d'hydrogène, ou un alkyle en C₁ à C₄ substitué par -NR³⁹R⁴⁰ (dans lequel R³⁹ et R⁴⁰ indépendamment l'un de l'autre, sont un atome d'hydrogène ou un alkyle en C₁ à C₄),

6) -NR⁴³R⁴⁴ (dans lequel R⁴³ et R⁴⁴ indépendamment l'un de l'autre, est un atome d'hydrogène, un alkyle en C₁ à C₄ ou un acyle en C₂ à C₅),

7) -CONR⁴⁵R⁴⁶ (dans lequel R⁴⁵ et R⁴⁶ indépendamment l'un de l'autre, est un atome d'hydrogène ou un alkyle en C₁ à C₄ substitué par un hydroxy),

8) un alkyle en C₁ à C₄ substitué par -OSO₃H ;

ou un sel non toxique, un sel d'addition à un acide ou un solvat de celui-ci.

2. Composé selon la revendication 1, dans lequel



dans lequel tous les symboles sont tels que définis dans la revendication 1.

3. Composé selon la revendication 1, dans lequel



dans lequel tous les symboles sont tels que définis dans la revendication 1.

4. Composé selon la revendication 1, lequel est

- 21) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(*N*-méthyl-*N*-méthoxysulfamoyl)-2-méthylphényle,
 - 35) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-[*N*-(quinuclidin-3-yl)sulfamoyl]-2-méthylphényle,
 - 36) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-[*N*-2-(morpholin-4-yl)éthylsulfamoyl]-2-méthylphényle,
 - 38) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-[*N*-(pipéridin-4-yl)sulfamoyl]-2-méthylphényle,
 - 56) le (2*S*)-2-[4'-(pyrrolidin-1"-yl)phényl]butanoate de 4-[2-(morpholin-4-yl)éthylaminosulfonyl]-2-méthylphényle,
 - 57) le (2*S*)-2-[4'-(pyrrolidin-1"-yl)phényl]butanoate de 4-(quinuclidin-3-ylaminosulfonyl)-2-méthylphényle,
 - 101) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-[*N*-(1,1-diméthyl-1-carboxyméthyl)-*N*-propylaminosulfonyl]-2-méthylphényle,
 - 103) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(*N*-hydroxyaminosulfonyl)-2-méthylphényle,
- ou un sel non toxique, un sel d'addition à un acide ou un solvat de celui-ci.

5. Composé selon la revendication 1, lequel est

- 11) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(6-nitroindolin-1-ylsulfonyl)-2-méthylphényle,
- 14) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(7-aminoindolin-1-ylsulfonyl)-2-méthylphényle,
- 15) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(benzimidazol-1-ylsulfonyl)-2-méthylphényle,
- 31) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(morpholin-4-ylsulfonyl)-2-méthylphényle,
- 33) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(pipérazin-4-ylsulfonyl)-2-méthylphényle,
- 40) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(4-méthylpipérazin-1-ylsulfonyl)-2-méthylphényle,
- 41) le (2*R*)-2-[4'-(pyrrolidin-1"-yl)phényl]butanoate de 4-(5-nitroindolin-1-ylsulfonyl)-2-méthylphényle,
- 44) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*)-4-(2'-carboxypyrrolidin-1'-ylsulfonyl)-2-méthylphényle,
- 48) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*,4'*R*)-4-(2'-carboxy-4'-benzyloxy-1'-ylsulfonyl)-2-méthylphényle,
- 56) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(2-carboxyindolin-1-ylsulfonyl)phényle,
- 66) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-[2-(*N*-hydroxyéthylcarbamoyl)indolin-1-ylsulfonyl]-2-méthylphényle,
- 67) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(2-carboxy-5,6-diméthoxyindol-1-ylsulfonyl)-2-méthylphényle,
- 68) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-[2-(2-aminoéthyl)oxycarbonylindolin-1-ylsulfonyl]-2-méthylphényle,
- 69) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(2-carboxyindol-1-ylsulfonyl)-2-méthylphényle,
- 89) le (2*S*)-2-[4'-(pyrrolidin-1"-yl)phényl]butanoate de (2'*R*)-4-(2'-carboxypyrrolidin-1'-ylsulfonyl)-2-méthylphényle,
- 90) le (2*R*)-2-[4'-(pyrrolidin-1"-yl)phényl]butanoate de (2'*S*)-4-(2'-carboxypyrrolidin-1'-ylsulfonyl)-2-méthylphényle,
- 95) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(2-carboxypipéridin-1-ylsulfonyl)-2-méthylphényle,
- 98) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*,4'*R*)-4-(2'-carboxy-4'-méthoxypyrrolidin-1'-ylsulfonyl)-2-méthylphényle,

2-méthylphényle,

99) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*R*,4'*R*)-4-(2'-carboxy-4'-méthoxypyrrolidin-1'-yl sulfonyl)-2-méthylphényle,

104) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*)-4-(2'-carboxypyrrolidin-1'-ylsulfonyl)-2-éthyl phényle,

107) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*,4'*S*)-4-(2'-carboxy-4'-acétylaminopyrrolidin-1'-yl sulfonyl)-2-méthylphényle,

109) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*,4'*R*)-4-(2'-carboxy-4'-acétylaminopyrrolidin-1'-yl sulfonyl)-2-méthylphényle,

113) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*, 6'*S*)-4-(2',6'-diméthylpipérazin-4'-ylsulfonyl)-2-méthylphényle,

114) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de 4-(2-méthylpipérazin-4-ylsulfonyl)-2-méthylphényle,

115) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*,4'*R*)-4-[2'-carboxy-4'-(*N,N*-diméthylamino) pyrrolidin-1'-ylsulfonyl]-2-méthylphényle,

116) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*,4'*R*)-4-(2'-carboxy-4'-méthylaminopyrrolidin-1'-ylsulfonyl)-2-méthylphényle,

117) le (2*S*)-2-[4'-(pyrrolidin-1"-yl)phényl] butanoate de 4-(pipérazin-4-ylsulfonyl)-2-éthylphényle,

125) le (2*S*)-2-[4'-(pyrrolidin-1"-yl)phényl] butanoate de 4-(2-méthylpipérazin-4-ylsulfonyl)-2-méthylphényle,

128) le 2-[4-(pyrrolidin-1-yl)phényl]butanoate de (2'*S*)-4-(2'-hydroxysulfonyloxyméthylpyrrolidin-1'-yl sulfonyl)-2-méthylphényle,

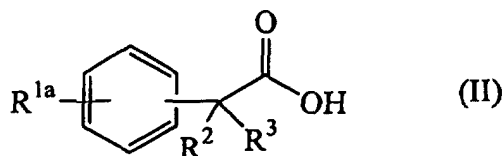
ou un sel non toxique, un sel d'addition à un acide ou un solvat de celui-ci.

6. Composition pharmaceutique qui comprend, en tant que substance active, une quantité efficace d'un composé de formule (I) tel que défini dans la revendication 1, un sel non toxique de celui-ci, un sel d'addition à un acide de celui-ci ou un solvat de celui-ci, avec un vecteur ou enrobée.

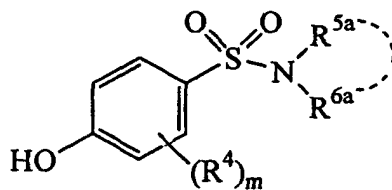
7. Composé de formule (I) tel que défini dans la revendication 1 ou un sel non toxique de celui-ci ou un sel non toxique d'addition à un acide de celui-ci ou un solvat de celui-ci pour l'utilisation dans la fabrication de composition pharmaceutique comme inhibiteur d'élastase.

8. Composé de formule (I) tel que défini dans la revendication 1 ou un sel non toxique de celui-ci ou un sel non toxique d'addition de celui-ci ou un solvat de celui-ci pour l'utilisation dans la fabrication de composition pharmaceutique pour la prévention et/ou le traitement de maladies induites par une augmentation anormale de la dégradation d'élastine, de fibres de collagène et/ou de protéoglycane, résultant de l'action de l'élastase sur un animal mammifère, particulièrement un humain (par exemple, la maladie pulmonaire obstructive chronique telle que l'emphysème, la polyarthrite rhumatoïde, l'athérosclérose, le syndrome de détresse respiratoire de l'adulte (SDRA), la glomérulonéphrite, l'infarctus du myocarde, la recto-colite hémorragique ou la gingivite).

9. Procédé pour la préparation d'un composé de formule (I) tel que défini dans la revendication 1 ledit procédé comprenant l'estérification d'un composé de formule :



dans lequel R^{1a} est un pyrrolidinyle ;
et R² et R³ sont tels que définis dans la revendication 1,
avec un composé de formule (III)



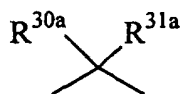
dans lequel R^4 et m sont tels que définis dans la revendication 1,



(dans lequel R^{5a} et R^{6a} indépendamment l'un de l'autre, est

- 1) un atome d'hydrogène (à la condition que, R^{5a} et R^{6a} ne représentent pas un atome d'hydrogène en même temps),
- 2) un hydroxy,
- 3) un hydroxy protégé par un groupe protecteur qui est labile en conditions acides,
- 4) un *t*-butoxycarbonyl,
- 5) un benzyloxycarbonyl,
- 6) un alkyle en C_1 à C_8 ,
- 7) un alkoxy en C_1 à C_8 ,
- 8) $-M-R^{16a}$ (dans lequel M est tel que défini dans la revendication 1, et R^{16a} est un cycle hétérocyclique aromatique mono- ou bi-cyclique de 5 à 15 chaînons, un cycle hétérocyclique saturé ou un cycle hétérocyclique partiellement saturé contenant un à quatre atomes d'azote, un ou deux atomes d'oxygène ou un atome d'azote et un atome de soufre ou un atome d'oxygène, non substitué ou substitué par 1 à 4 substituants choisis dans le groupe comprenant un alkyle en C_1 à C_4 , un alkoxy en C_1 à C_4 , un hydroxy, un phényl(alkyle en C_1 à C_4), $-COOR^{26}$ (dans lequel R^{26} est tel que défini dans la revendication 1), un hydroxy(alkyle en C_1 à C_4) dans lequel l'hydroxy est protégé par un groupe protecteur qui est labile en conditions acides ou un alkoxyalkyle en C_2 à C_4),
- 9) $-J^a-COOR^{29}$ (dans lequel R^{29} est tel que défini dans la revendication 1,

J^a est



(dans lequel

R^{30a} et R^{31a} indépendamment l'un de l'autre, est i) un atome d'hydrogène ou, ii) un alkyle en C_1 à C_8 , ou



dans lequel R^{5a} et R^{6a} , pris ensemble avec l'atome d'azote auquel ils sont liés représentent un cycle hétérocyclique aromatique mono- ou bi-cyclique de 3 à 15 chaînons, un cycle hétérocyclique saturé ou un cycle hétérocyclique

térocyclique partiellement saturé contenant un ou deux atomes d'azote ou un atome d'azote et un atome de soufre ou un atome d'oxygène,

q est tel que défini dans la revendication 1,

R^{15a} est

1) un alkyle en C₁ à C₄,

2) un alkoxy en C₁ à C₄,

3) un phényl(alkoxy en C₁ à C₄),

4) un nitro,

5) -COOR^{36a} (dans lequel R^{36a} est un atome d'hydrogène, un alkyle en C₁ à C₄ substitué par -NR^{39a}R^{40a} (dans lequel R^{39a} et R^{40a} indépendamment l'un de l'autre, est un atome d'hydrogène (à la condition que, R^{39a} et R^{40a} ne représentent pas un atome d'hydrogène en même temps, un *t*-butoxycarbonyle, un benzyloxycarbonyle ou un alkyle en C₁ à C₄),

6) -NR^{43a}R^{44a} (dans lequel R^{43a} et R^{44a} indépendamment l'un de l'autre, est un atome d'hydrogène (à la condition que, R^{43a} et R^{44a} ne représentent pas un atome d'hydrogène en même temps), un *t*-butoxycarbonyle, un benzyloxycarbonyle, un alkyle en C₁ à C₄ ou un acyle en C₂ à C₅,

7) -CONR^{45a}R^{46a} (dans lequel R^{45a} et R^{46a} indépendamment l'un de l'autre, sont un atome d'hydrogène, ou un alkyle en C₁ à C₄ substitué par un hydroxy ou un hydroxy protégé),

ou

peut être préparé en estérifiant un composé de formule (II) avec un composé de formule (III) pour obtenir un composé ayant un ou plusieurs groupes protégés, puis ensuite en éliminant les groupes protecteurs,

ou peut être préparé en estérifiant un composé de formule (II) avec un composé de formule (III), au besoin, en éliminant les groupes protecteurs pour obtenir un composé ayant R¹⁵ représentant un alkyle (en C₁ à C₄) substitué par un hydroxy, puis ensuite en soumettant à une estérification avec de l'acide sulfurique et facultativement en convertissant un composé de formule (I) ainsi obtenu en un sel non toxique, un sel d'addition à un acide ou un solvat de celui-ci.