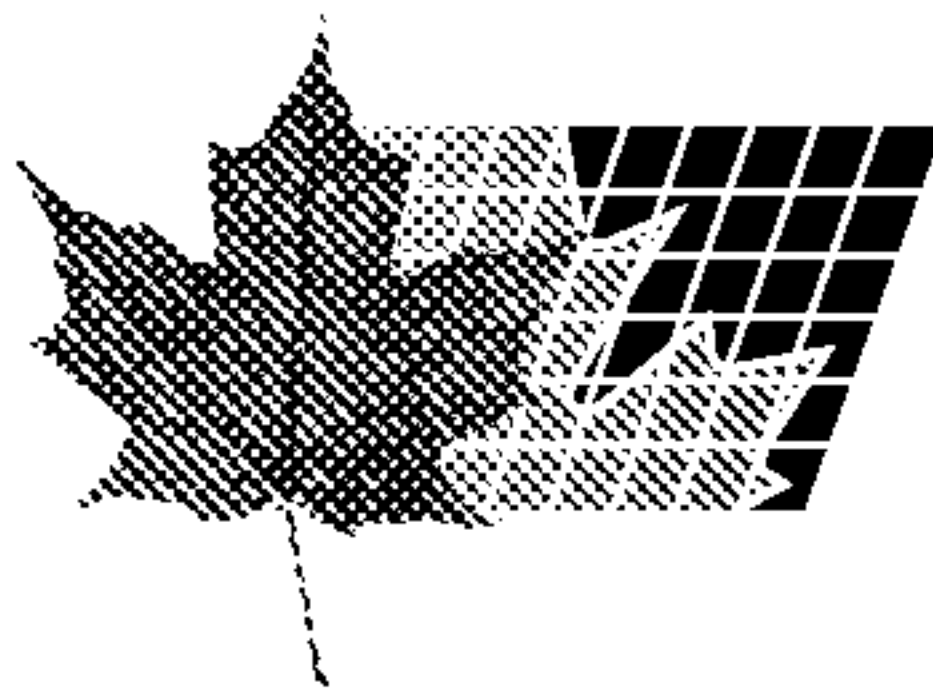




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(51) Int.Cl.⁷ C07C 309/65, A61K 31/255
(30) 1998/08/19 (198 37 627.8) DE
(54) **NOUVEAUX ESTERS D'AMINOACIDES
D'ARYLSULFONAMIDES ET LEURS ANALOGUES**
(54) **NOVEL ARYL SULPHONAMIDE AMINO ACID ESTERS AND
ANALOGUES**

(57) The present invention relates to novel aryl sulphonamide amino acid esters and analogues, methods for the production and use thereof in the prophylaxis and treatment of neurodegenerative diseases, especially in the treatment of apoplexia cerebri, craniocerebral trauma, pain and spasticity.

Novel amino acid esters of arylsulphonamides and analogues**A b s t r a c t**

The present invention relates to novel amino acid esters of arylsulphonamides and analogues, to processes for their preparation and to their use for the prophylaxis and treatment of neurodegenerative disorders, in particular for the treatment of cerebral apoplexy, craniocerebral trauma, pain and spasticity.

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Novel amino acid esters of arylsulphonamides and analogues

The present invention relates to novel amino acid esters of arylsulphonamides and analogues, to processes for their preparation and to their use for the prophylaxis and treatment of neurodegenerative disorders, in particular for the treatment of cerebral apoplexy, craniocerebral trauma, pain and spasticity.

Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) and, to a small extent, also Δ^8 -THC are the biologically active constituents in extracts of the plant *Cannabis sativa* (marihuana, hashish) and are responsible for the effects on the human central nervous system (CNS). Potential historical and contemporary therapeutic uses of cannabis preparations include, inter alia, analgesia, emesis, anorexia, glaucoma and mobility disorders.

Until now, two subtypes of cannabinoid receptors and a splice variant have been identified. The CB1 receptor (Nature 1990, 346, 561) and a splice variant CB1a (J. Biol. Chem. 1995, 270, 3726) are mainly localized in the central nervous system. The CB2 receptor was found mainly in peripheral tissue, in particular in leucocytes, spleen and macrophages (Eur. J. Biochem. 1995, 232, 54).

CB1 and CB2 receptors have seven transmembrane regions and belong to the family of G protein receptors. Both receptors are negatively coupled via G_i/G_o protein to adenylate cyclase and possibly negatively coupled to the presynaptic release of glutamate (J. Neurosci. 1996, 16, 4322). CB1 receptors are moreover positively coupled to potassium channels and also negatively coupled to N- and Q-type calcium channels.

Four classes of CB1 receptor agonists are known to date: classical cannabinoids, such as, for example, Δ^9 -THC, non-classical cannabinoids, aminoalkylindoles and eicosanoids. The latter include the generally accepted endogenous CB1 receptor agonist anandamide.

It is additionally known that cerebral apoplexy is a consequence of a sudden circulatory disorder of a human brain region with subsequent functional losses, with corresponding neurological and/or psychological symptoms. The causes of cerebral apoplexy can lie in cerebral haemorrhages (e.g. after a vascular tear in

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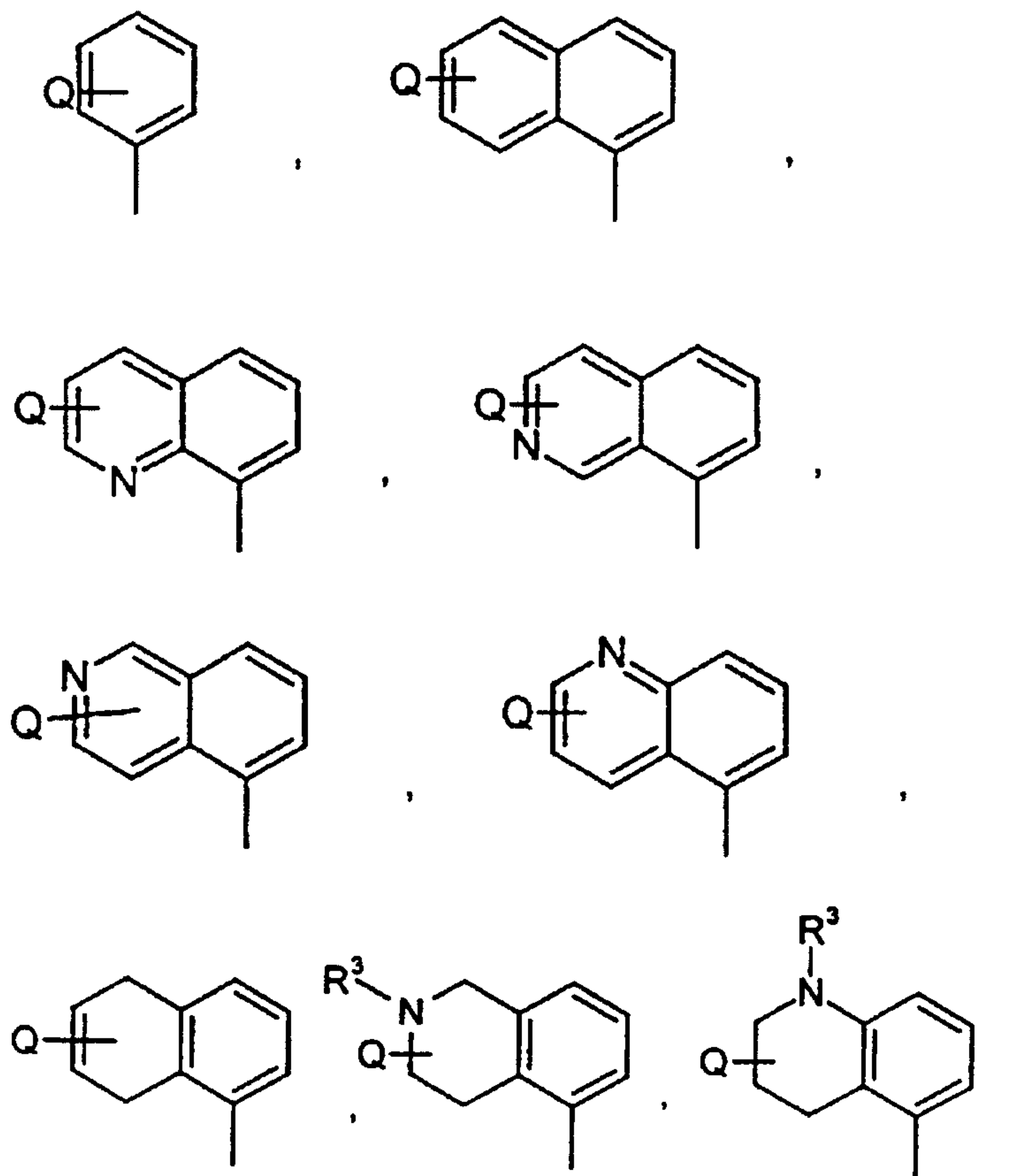
hypertension, arteriosclerosis and appoplectic aneurysm) and ischaemias (e.g. due to a drop in blood pressure or embolism). The functional losses in the brain lead to a degeneration or destruction of brain cells (Journal of Cerebral Blood Flow and Metabolism 1981, 1, 155); Chem. Eng. News 1996 (May 13), 41; Trends
 5 Pharmacol. Sci. 1996, 17, 227). Craniocerebral trauma is understood as meaning covered and open cranial injuries with involvement of the brain.

The present invention relates to compounds of the general formula (I)



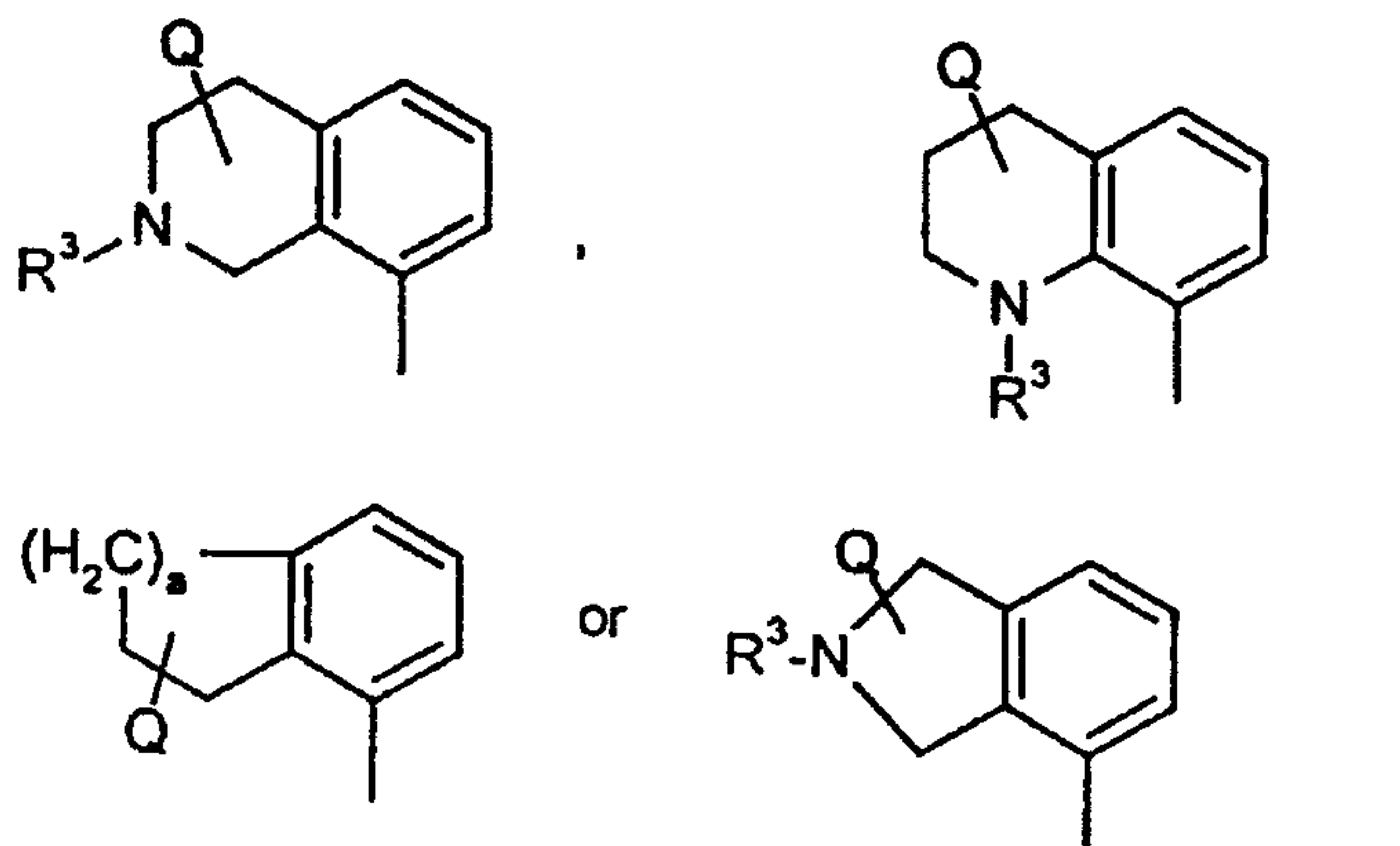
in which

15 R^1 represents a radical of the formula



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in which

a represents a number 1 or 2,

5

 R^3 represents hydrogen, (C₂-C₆)-alkenyl, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

and where all of the phenyl ring systems listed above are optionally substituted, optionally geminally, by one or more identical or different substituents selected from the group consisting of:

10

halogen, carboxyl, hydroxyl, phenyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl, (C₁-C₈)-alkyl, which for its part may be substituted by halogen, (C₁-C₆)-alkylsulphonyloxy, azide, amino, mono(C₁-C₆)-alkylamino, di(C₁-C₆)-alkylamino or hydroxyl,

15

a group of the formula $-(CO)_b-NR^4R^5$,

in which

20

b represents a number 0 or 1,

R^4 and R^5 are identical or different and independently of one another represent hydrogen, phenyl, (C₁-C₆)-acyl, cyclo(C₄-C₇)-acyl benzoyl or (C₁-C₆)-alkyl, which is optionally substituted by amino, mono(C₁-C₆)-alkylamino, di(C₁-C₆)-alkylamino,

25

or

 R^4 and R^5 together with the nitrogen atom form a 5- or 6-membered

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saturated heterocycle which may optionally contain one or more further heteroatom(s) from the group consisting of S and O and/or one or more radical(s) of the formula $-NR^8$,

5 in which

R^8 represents hydrogen, (C_1-C_6) -alkyl or (C_1-C_6) -acyl,

and

10

a group of the formula $-NR^6-SO_2-R^7$

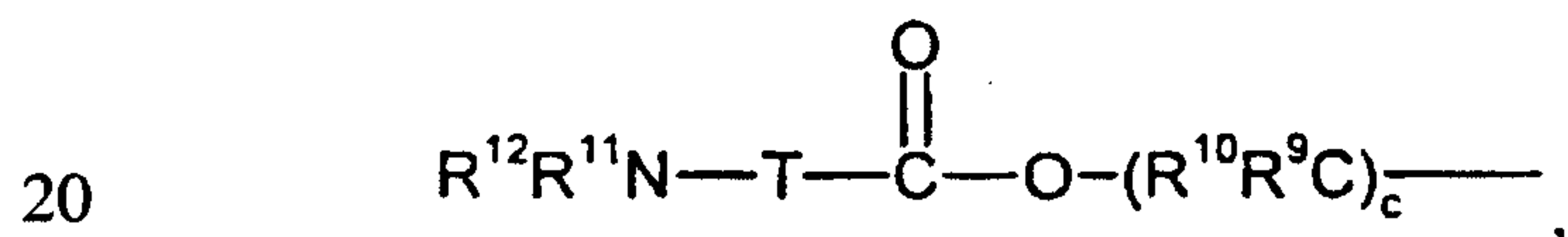
in which

15

R^6 represents hydrogen, phenyl, (C_1-C_6) -alkyl or (C_1-C_6) -acyl,

R^7 represents phenyl or (C_1-C_6) -alkyl,

Q represents a radical of the formula



in which

25

c represents a number 1, 2, 3, 4, 5 or 6,

R^9 and R^{10} are identical or different and represent hydrogen or (C_1-C_6) -alkyl,

30

T represents a radical of the formula $-(CH_2)_d-$,

in which

d represents a number 1, 2, 3, 4, 5, 6, 7 or 8,

35

or

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T represents a moiety of an amino acid radical of the formula



5

in which

R^{13} and R^{14} are identical or different and represent hydrogen or methyl,

10

or

R^{13} represents hydrogen or methyl

and

15

R^{14} represents (C₃-C₈)-cycloalkyl or (C₆-C₁₀)-aryl or hydrogen, or (C₁-C₈)-alkyl,

20

where the (C₁-C₈)-alkyl is optionally substituted by methythio, hydroxyl, mercapto, guanidyl or by a group of the formula -NR¹⁵R¹⁶ or -NR¹⁷-OC-,

in which

25

R^{15} and R^{16} independently of one another represent hydrogen, (C₁-C₈)-alkyl or phenyl

and

30

R^{17} represents hydroxyl, benzyloxy, (C₁-C₈)-alkoxy or the group -NR¹⁵R¹⁶ listed above,

or the (C₁-C₈)-alkyl is optionally substituted by (C₃-C₆)-cycloalkyl or phenyl, which for its part is substituted by hydroxyl, halogen or (C₁-C₆)-alkoxy or amino,

35

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or the (C₁-C₈)-alkyl is optionally substituted by imidazolyl or indolyl, in which the corresponding -NH functions are optionally protected by (C₁-C₆)-alkyl or by an amino protective group,

5

R¹¹ and R¹² are identical or different and represent hydrogen, (C₁-C₆)-alkyl or a typical amino protective group,

or

10

R¹¹ and R¹² together with the nitrogen atom form a 5- to 6-membered saturated heterocycle, which may optionally contain a further heteroatom from the group consisting of S and O or a radical of the formula -NR¹⁸,

15

in which

R¹⁸ represents hydrogen, (C₁-C₆)-alkyl or phenyl,

20 A and E are identical or different and represent a bond or represent (C₁-C₄)-alkylene,

D represents an oxygen atom or represents a radical of the formula -S(O)_e- or -N(R¹⁹)-,

25

in which

e represents a number 0, 1 or 2,

30 R⁹ represents hydrogen, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

G represents doubly attached (C₆-C₁₀)-aryl or represents a doubly attached 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, which are optionally substituted by one or more identical or different substituents selected from the group consisting of:

35

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hydroxyl, trifluoromethyl, carboxyl, halogen, (C₁-C₆)-alkyl, hydroxy(C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl,
 5 and groups of the formulae -CO-O-(CH₂)_f-NR²⁰R²¹, -NR²²-SO₂R²³, -
 (CH₂)_g-(CO)_h-NR²⁴R²⁵ and -OR²⁶,

in which

10 f represents a number 1, 2, 3 or 4,

g and h are identical or different and represent a number 0 or 1,

15 R²⁰ and R²¹ have the meaning of R⁴ and R⁵ given above and are identical to
 or different from this meaning,

R²² has the meaning of R⁶ given above and is identical to or different
 from this meaning,

20 R²³ has the meaning of R⁷ given above and is identical to or different
 from this meaning,

R²⁴ and R²⁵ have the meaning of R⁴ and R⁵ given above and are identical to
 or different from this meaning,

25 or independently of one another represent a radical of the formula



30 in which

i represents a number 1, 2, 3 or 4,

and

35 R²⁷ and R²⁸ have the meaning of R⁴ and R⁵ given above and are
 identical to or different from this meaning,

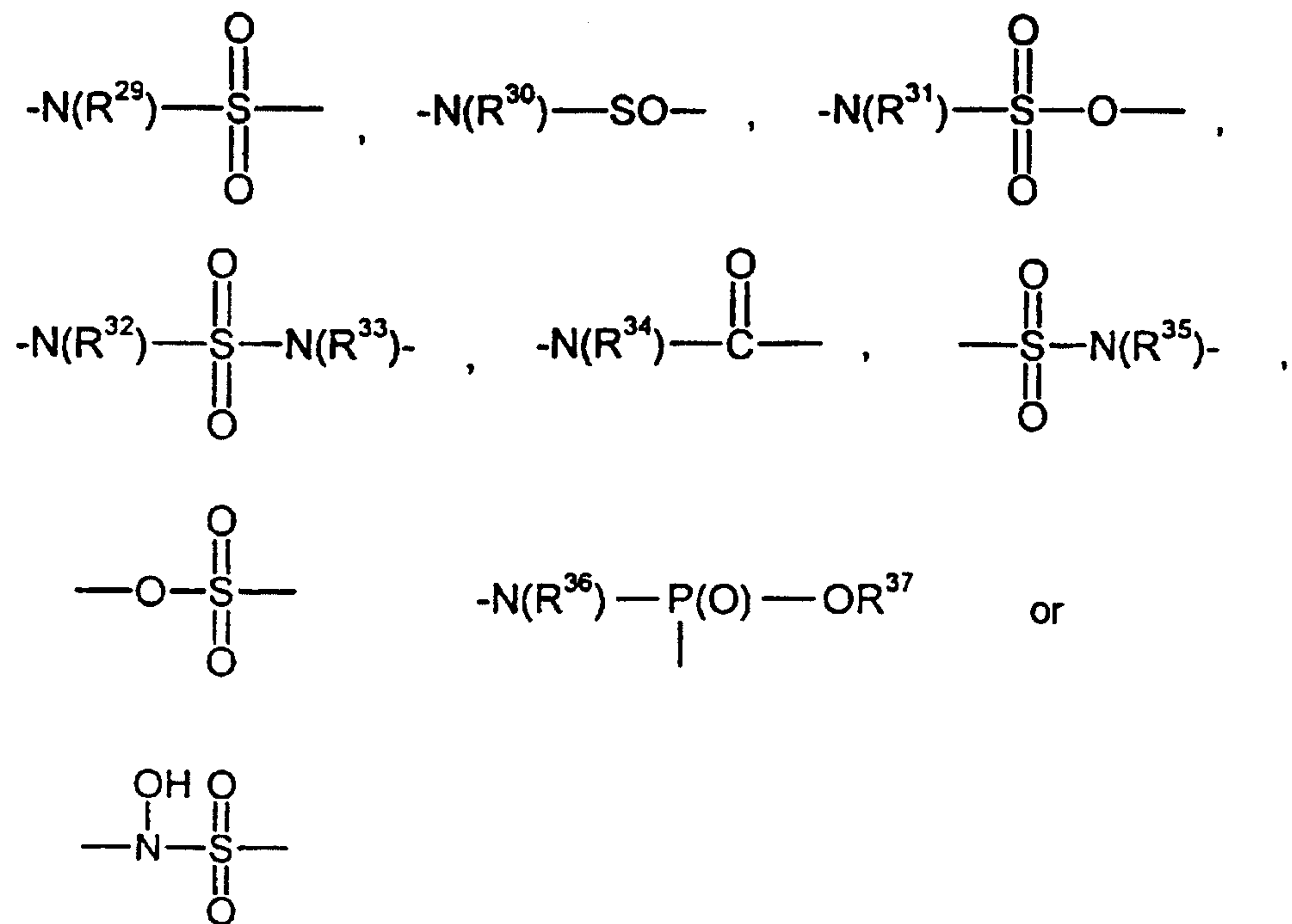
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R^{26} represents (C_6-C_{10}) -aryl,

L represents a radical of the formula -O-, -NH-,

5



10

where the left-hand side of the radicals is attached to G,

and in which R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} , R^{36} and R^{37} are identical or different and represent hydrogen or (C_1-C_4) -alkyl,

15

or

R^{29} represents a radical of the formula $-SO_2R^2$,

20

R^2 represents (C_6-C_{10}) -aryl or represents a 5- to 7-membered saturated or aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, which are optionally substituted by one or more identical or different substituents selected from the group consisting of:

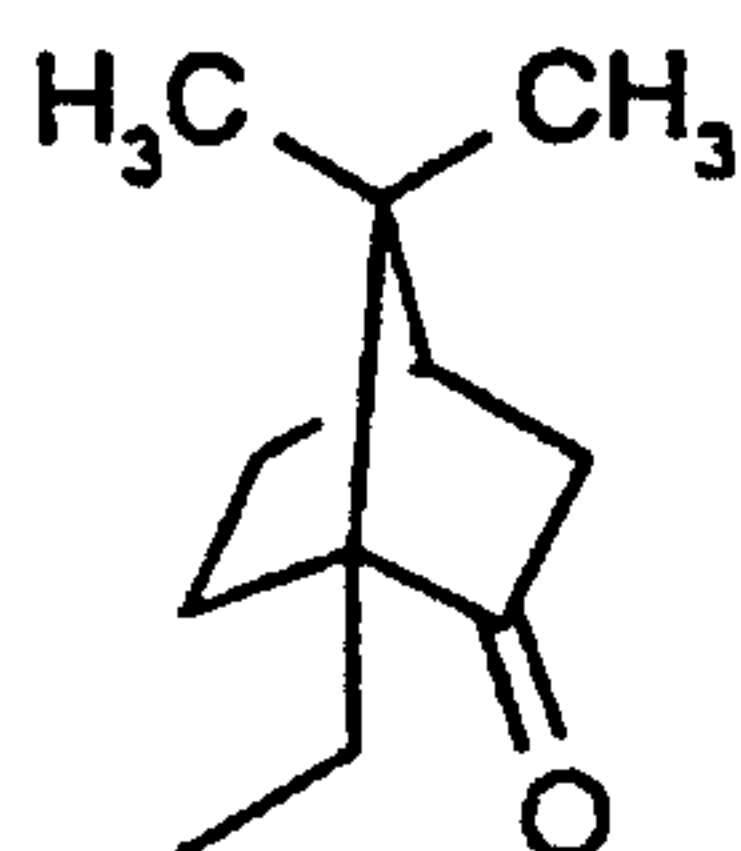
25

halogen, trifluoromethyl, nitro, amino and (C_1-C_6) -alkyl,
or

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represents the radical of the formula

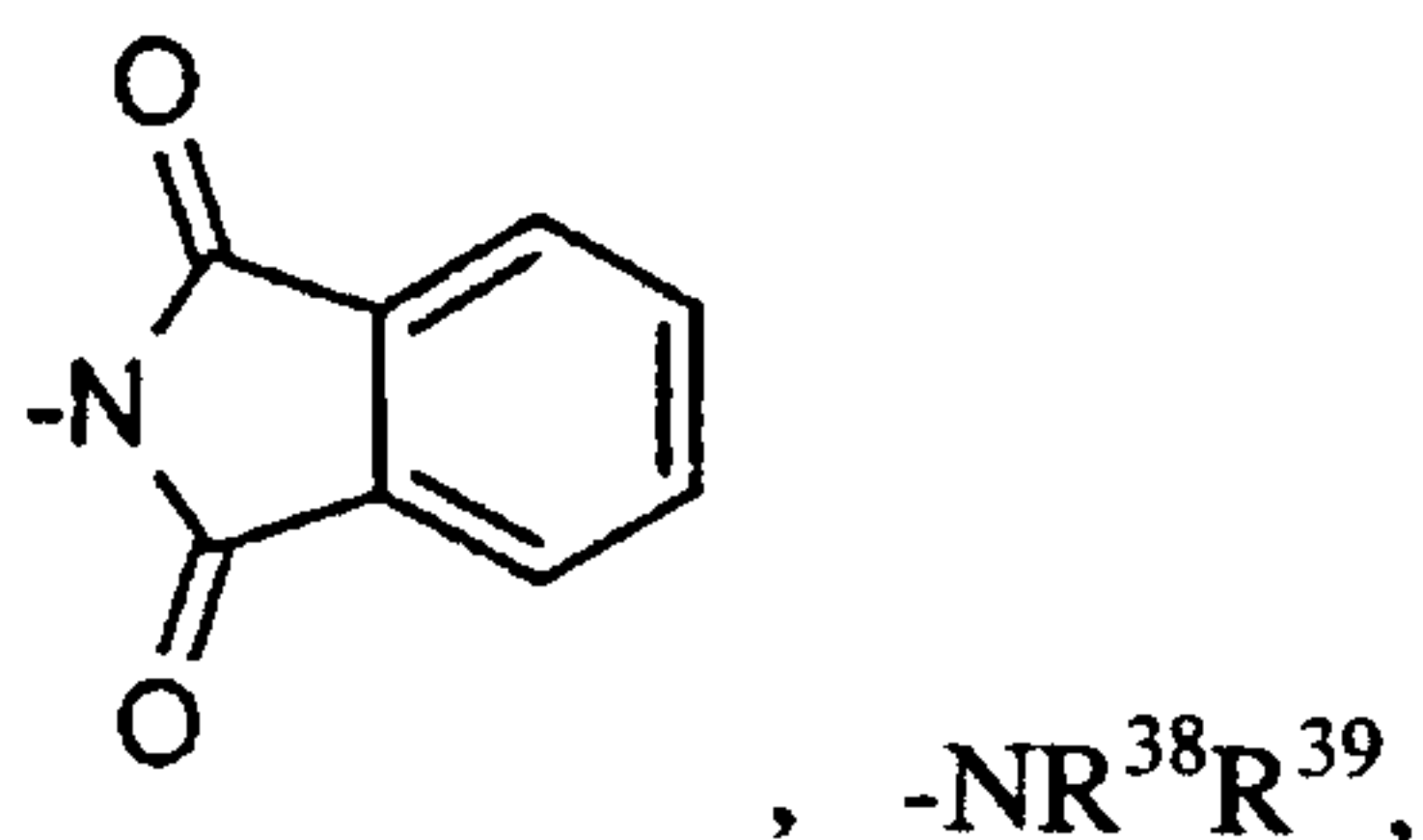


or morpholine, or

represents C₃-C₈-cycloalkyl, or

5 represents (C₁-C₁₂)-alkyl, (C₂-C₁₂)-alkenyl or (C₂-C₁₂)-alkinyl, which are optionally substituted by one or more identical or different substituents selected from the group consisting of:

10 halogen, trifluoromethyl, hydroxyl, cyano, azido, (C₁-C₆)-alkoxy, (C₁-C₆)-perfluoroalkoxy, partially fluorinated (C₁-C₆)-alkoxy, a radical of the formula



in which

15 R³⁸ and R³⁹ have the meaning of R⁴ and R⁵ given above and are identical to or different from this meaning,

phenyl, optionally substituted by one or more identical or different substituents selected from the group consisting of:

20 halogen, nitro, hydroxyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and a group of the formula -NR⁴⁰R⁴¹,

in which

25 R⁴⁰ and R⁴¹ are identical or different and represent hydrogen or (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

and a 5- to 6-membered aromatic heterocycle having up to three heteroatoms from the group consisting of S, N and O, optionally substituted

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by one or more identical or different substituents selected from the group consisting of:

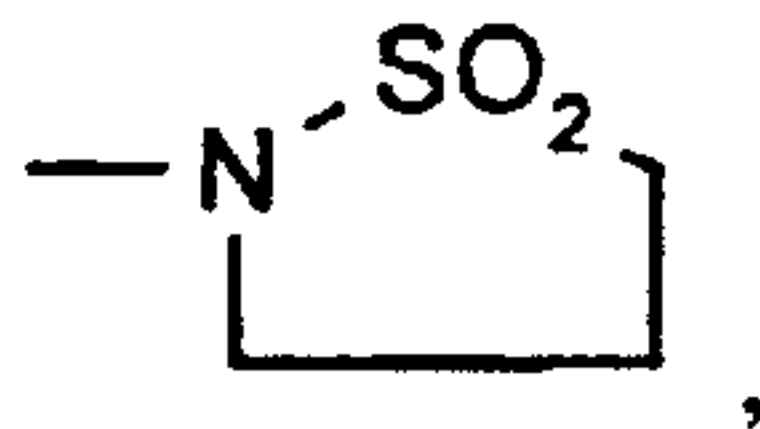
5 halogen, nitro, hydroxyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and a group of the formula -NR⁴⁰R⁴¹,

in which

10 R⁴⁰ and R⁴¹ are as defined above,

or

L and R² together represent a radical of the formula



15 and pharmaceutically acceptable salts thereof.

In the context of the invention, amino protective group are the customary amino protective groups used in peptide chemistry.

These preferably include: benzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 20 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl, vinyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 25 3,4,5-trimethoxybenzyloxycarbonyl, cyclohexoxycarbonyl, 1,1-dimethylethoxycarbonyl, adamantylcarbonyl, phthaloyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloro-tert-butoxycarbonyl, menthyloxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloroacetyl, 2-bromoacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, 30 benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, phthalimido, isovaleroyl or benzyloxymethylene, 4-nitrobenzyl, 2,4-dinitrobenzyl or 4-nitrophenyl.

35 The compounds according to the invention can exist in stereoisomeric forms which are either like image and mirror image (enantiomers) or which are not like image

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and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and to their respective mixtures. These mixtures of the enantiomers and diastereomers can be separated in a known manner into the stereoisomerically uniform components.

5

The compounds according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

10 In the context of the present invention, preference is given to physiologically acceptable salts. Physiologically acceptable salts of the compounds according to the invention can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particular preference is given, for example, to salts with hydrochloric acid, hydrobromic acid, sulphuric acid,
15 phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Physiologically acceptable salts can also be metal or ammonium salts of the
20 compounds according to the invention. Particular preference is, for example, given to sodium, potassium, magnesium or calcium salts, and to ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine or 2-phenylethylamine.

25

The present invention also includes ammonium compounds which can be prepared by converting the free amines by alkylation.

30 In the context of the present invention, the substituents generally have the following meaning:

(C₁-C₁₂)-Alkyl generally represents, depending on the abovementioned substituents, a straight-chain or branched hydrocarbon radical having 1 to 12 carbon atoms. Examples which may be mentioned are methyl, ethyl, propyl,
35 isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, isoheptyl, octyl

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and isooctyl. Preference is given to (C₁-C₈)-alkyl having 1 to 8 carbon atoms, for example methyl, ethyl, propyl or isopropyl.

5 (C₁-C₁₂)-Alkenyl generally represents, depending on the abovementioned substituents, a straight-chain or branched hydrocarbon radical having 2 to 6 and 2 to 20 carbon atoms and one or more, preferably one or two, double bonds. Preference is given to the lower alkyl radical having 2 to 4 and 2 to 10 carbon atoms and one double bond. Particular preference is given to an alkenyl radical having 2 to 3 and 2 to 8 carbon atoms and one double bond. Examples which may
10 be mentioned are allyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, isopentenyl, hexenyl, isohexenyl, heptenyl, isoheptenyl, octenyl and isooctenyl.

15 (C₂-C₁₂)-Alkynyl generally represents, depending on the abovementioned substituents, a straight-chain or branched hydrocarbon radical having 2 to 12 carbon atoms and one or more, preferably one or two, triple bonds. Preference is given to the lower alkyl radical having 2 to about 10 carbon atoms and one triple bond. Particular preference is given to an alkyl radical having 2 to 8 carbon atoms and one triple bond. Examples which may be mentioned are acetylene, 2-butyne, 2-pentyne and 2-hexyne.

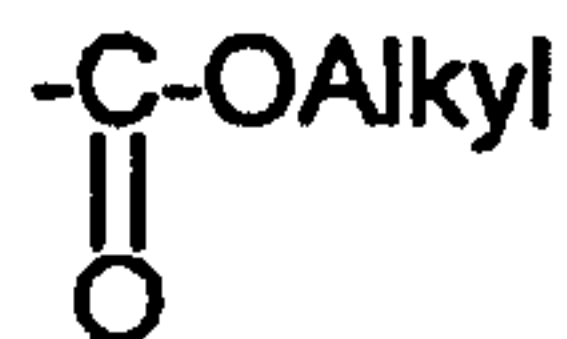
20 (C₁-C₆)-Acyl generally represents, depending on the abovementioned substituents, straight-chain or branched lower alkyl having 1 to 6 carbon atoms, which are attached via a carbonyl group. Particular preference is given to alkyl radicals having up to 4 carbon atoms. Very particular preference is, for example, given to
25 alkyl radicals having up to 3 carbon atoms. Examples which may be mentioned are: acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl and isobutylcarbonyl.

30 (C₁-C₆)-Alkoxy generally represents, depending on the abovementioned substituents, a straight-chain or branched hydrocarbon radical having 1 to 6 carbon atoms, which is attached via an oxygen atom. Preference is given to lower alkoxy having 1 to 4 carbon atoms. Particular preference is given to an alkoxy radical having 1 to 3 carbon atoms. Examples which may be mentioned are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, isopentoxy, hexoxy,
35 isohexoxy, heptoxy, isoheptoxy, octoxy or isooctoxy.

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(C₁-C₆)-Alkoxy carbonyl can be represented, for example, by the formula



- Here, alkyl represents a straight-chain or branched hydrocarbon radical having 1 to 6 carbon atoms. Preference is given to lower alkoxy carbonyl having 1 to 4 carbon atoms in the alkyl moiety. The following alkoxy carbonyl radicals may be mentioned by way of example: methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxy carbonyl or isobutoxy carbonyl.
- 10 (C₃-C₈)-Cycloalkyl generally represents a cyclic hydrocarbon radical having 3 to 8 carbon atoms. Preference is given to cyclopropyl, cyclopentyl and cyclohexyl. Examples which may be mentioned are cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.
- 15 cyclo(C₄-C₇)-Acyl generally represents, depending on the abovementioned substituents, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl or cyclohexylcarbonyl.
- 20 (C₆-C₁₀)-Aryl generally represents an aromatic radical having 6 to 10 carbon atoms. Preferred aryl radicals are phenyl and naphthyl.
- 25 (C₁-C₆)-Perfluoroalkoxy in the context of the invention represents an alkoxy radical having 1 to 6 carbon atoms and 3 to 13 fluorine atoms. Preference is given to an alkoxy radical having 1 to 5 carbon atoms and 3 to 9 fluorine atoms.
- 30 (C₁-C₆)-Partially fluorinated alkoxy in the context of the invention represents an alkoxy radical having 1 to 6 carbon atoms and 3 to 5 fluorine atoms. Preference is given to an alkoxy radical having 1 to 4 carbon atoms and 3 fluorine atoms. Particular preference is given to an alkoxy radical having 1 to 3 carbon atoms and which is substituted by trifluoromethyl.
- Halogen in the context of the invention represents fluorine, chlorine, bromine and iodine.

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Aromatic, saturated and unsaturated heterocycles in the context of the invention, depending on the abovementioned substituents, in general represent a 5- to 7-membered or 5- to 6-membered, preferably 5- to 6-membered, heterocycle which may contain up to 3 heteroatoms from the group consisting of S, N and O and which may optionally also be attached via a nitrogen atom. Examples which may be mentioned are: pyridyl, thienyl, furyl, pyrrolyl, pyrrolidinyl, piperazinyl, pyrimidyl, thiazolyl, oxazolyl, imidazolyl, morpholine or piperidyl. Preference is given to pyridyl, furyl, morpholine, piperidyl and piperazinyl.

Leaving groups in the sense of the invention are groups which can be replaced by a nucleophile in a nucleophilic substitution (Streitwieser, A., Jr.; Heathcock, C.H. Organische Chemie, Verlag Chemie, 1980, p. 169ff.). Preferred leaving groups are halides and sulphonic acid esters/anhydrides. A particularly preferred leaving group is chloride.

(C₃-C₆)-Ketone in the context of the invention represents a saturated or unsaturated ketone having 3 to 6 carbon atoms. Examples which may be mentioned are: acetone, butanone, but-1-en-3-one, but-1-in-3-one, pentan-3-one, pentan-2-one, pent-1-en-3-one, pent-1-in-3-one, penta-1,4-dien-3-one, 3-methylbutan-2-one, cyclopropyl methyl ketone, cyclopentanone, hexan-2-one, hexan-3-one, cyclohexanone, 2-methylcyclopentanone, 2-ethylcyclobutanone.

(C₁-C₆)-Aldehyde in the context of the invention represents a saturated or unsaturated aldehyde having 1 to 6 carbon atoms. Examples which may be mentioned are: formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, cyclopropylcarbaldehyde, but-2-enal, but-2-in-al, pentanal, isopentanal, pivaldehyde, cyclobutylcarbaldehyde, 2-methylcyclopropyl-carbaldehyde, pent-2-enal, pent-4-enal, hexanal, 2-cyclobutylacetaldehyde.

Preference is given to compounds of the formula (I)

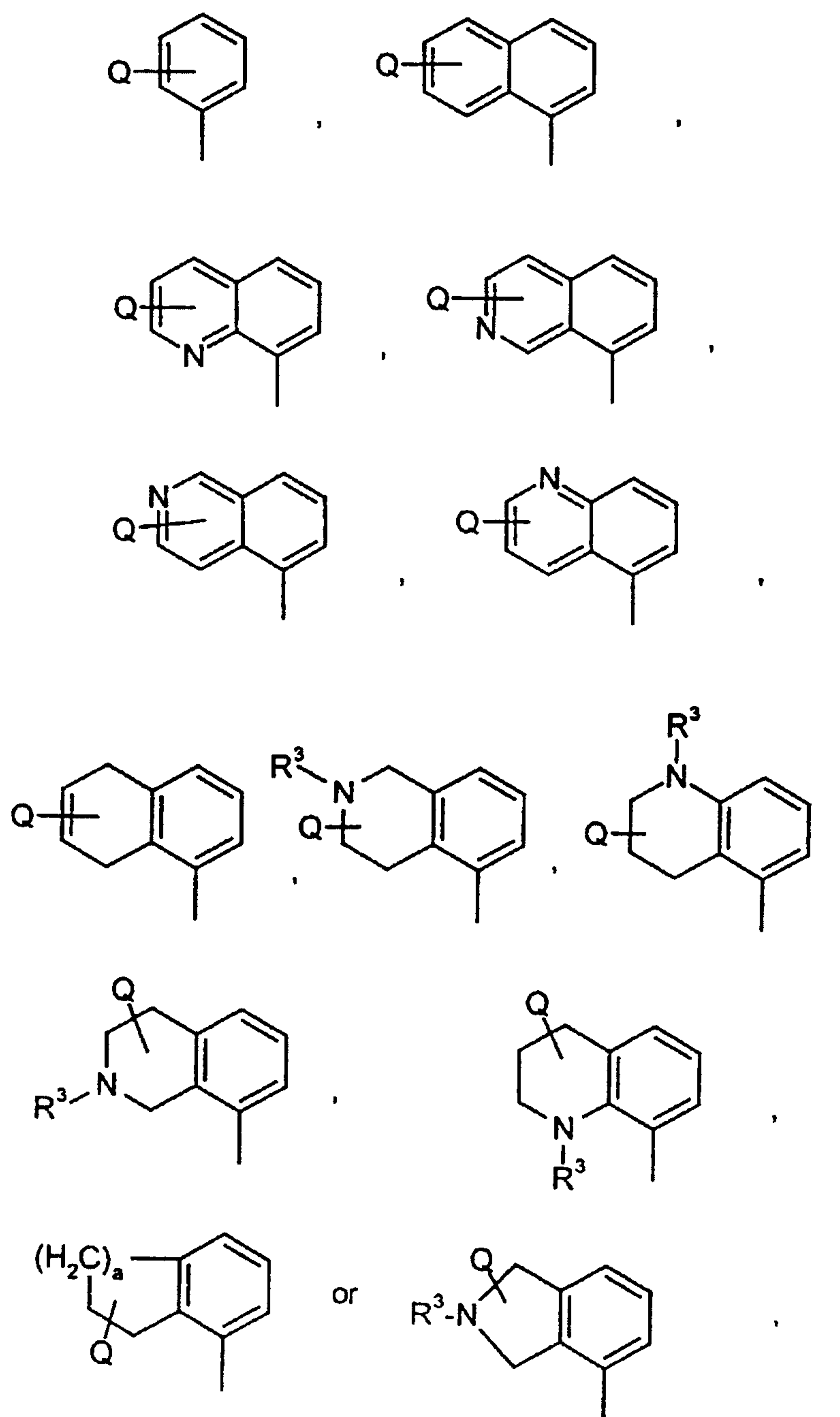


in which

R^1 represents a radical of the formula

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5 in which

a represents a number 1 or 2,

R³ represents hydrogen, (C₂-C₆)-alkenyl, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

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and where all of the phenyl ring systems listed above are optionally substituted, optionally geminally, by one or more identical or different substituents selected from the group consisting of:

5 halogen, carboxyl, hydroxyl, phenyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl, (C₁-C₈)-alkyl, which for its part may be substituted by halogen, (C₁-C₆)-alkylsulphonyloxy, azide, amino, mono(C₁-C₆)-alkylamino, di(C₁-C₆)-alkylamino or hydroxyl,

10 a group of the formula $-(CO)_b-NR^4R^5$,

in which

15 b represents a number 0 or 1,

R⁴ and R⁵ are identical or different and independently of one another represent hydrogen, phenyl, (C₁-C₆)-acyl, cyclo(C₄-C₇)-acyl benzoyl or (C₁-C₆)-alkyl, which is optionally substituted by amino, mono(C₁-C₆)-alkylamino, di(C₁-C₆)-alkylamino,

20

or

25 R⁴ and R⁵ together with the nitrogen atom form a 5- or 6-membered saturated heterocycle which may optionally contain one or more further heteroatom(s) from the group consisting of S and O and/or one or more radical(s) of the formula $-NR^8$,

in which

30 R⁸ represents hydrogen, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

and

a group of the formula $-NR^6-SO_2-R^7$

35

in which

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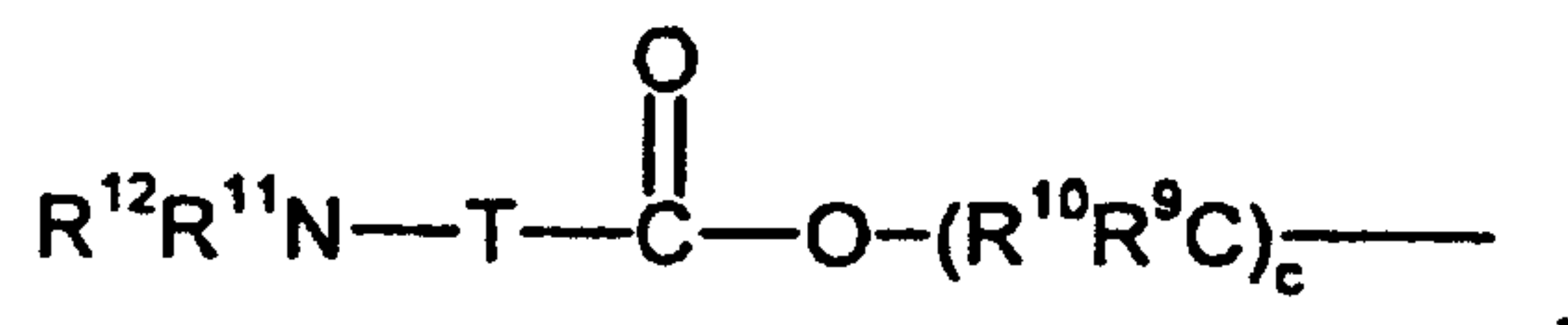
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R^6 represents hydrogen, phenyl, (C_1-C_6) -alkyl or (C_1-C_6) -acyl,

R^7 represents phenyl or (C_1-C_6) -alkyl,

5

Q represents a radical of the formula



in which

10

c represents a number 1, 2, 3, 4, 5 or 6,

R^9 and R^{10} are identical or different and represent hydrogen or (C_1-C_6) -alkyl,

15

T represents a radical of the formula $-(CH_2)_d-$,

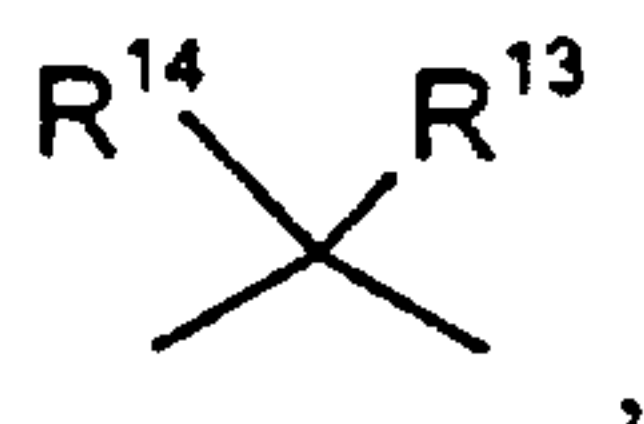
in which

20

d represents a number 1, 2, 3, 4, 5, 6, 7 or 8,

or

T represents a moiety of an amino acid radical of the formula



25

in which

R^{13} and R^{14} are identical or different and represent hydrogen or methyl,

30

or

R^{13} represents hydrogen or methyl

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and

5 R^{14} represents (C₃-C₈)-cycloalkyl or (C₆-C₁₀)-aryl or hydrogen, or (C₁-C₈)-alkyl,

where the (C₁-C₈)-alkyl is optionally substituted by methylthio, hydroxyl, mercapto, guanidyl or by a group of the formula -NR¹⁵R¹⁶ or -NR¹⁷-OC-,

10 in which

R^{15} and R^{16} independently of one another represent hydrogen, (C₁-C₈)-alkyl or phenyl

15 and

R^{17} represents hydroxyl, benzyloxy, (C₁-C₈)-alkoxy or the group -NR¹⁵R¹⁶ listed above,

20 or the (C₁-C₈)-alkyl is optionally substituted by (C₃-C₆)-cycloalkyl or phenyl, which for its part is substituted by hydroxyl, halogen or (C₁-C₆)-alkoxy or amino,

25 or the (C₁-C₈)-alkyl is optionally substituted by imidazolyl or indolyl, in which the corresponding -NH functions are optionally protected by (C₁-C₆)-alkyl or by an amino protective group,

R^{11} and R^{12} are identical or different and represent hydrogen or (C₁-C₆)-alkyl,

30

or

35 R^{11} and R^{12} together with the nitrogen atom form a 5- to 6-membered saturated heterocycle, which may optionally contain a further heteroatom from the group consisting of S and O or a radical of the formula -NR¹⁸,

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in which

R^{18} represents hydrogen, (C₁-C₆)-alkyl or phenyl,

5

A and E are identical or different and represent a bond or represent (C₁-C₄)-alkylene,

10 D represents an oxygen atom or represents a radical of the formula -S(O)_e- or -N(R¹⁹)-,

in which

e represents a number 0, 1 or 2,

15

R^9 represents hydrogen, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

20 G represents doubly attached (C₆-C₁₀)-aryl or represents a doubly attached 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, which are optionally substituted by one or more identical or different substituents selected from the group consisting of:

25 hydroxyl, trifluoromethyl, carboxyl, halogen, (C₁-C₆)-alkyl, hydroxy(C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl, and groups of the formulae -CO-O-(CH₂)_f-NR²⁰R²¹, -NR²²-SO₂R²³, -(CH₂)_g-(CO)_h-NR²⁴R²⁵ and -OR²⁶,

in which

30

f represents a number 1, 2, 3 or 4,

g and h are identical or different and represent a number 0 or 1,

35 R^{20} and R^{21} have the meaning of R^4 and R^5 given above and are identical to or different from this meaning,

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R^{22} has the meaning of R^6 given above and is identical to or different from this meaning,

5 R^{23} has the meaning of R^7 given above and is identical to or different from this meaning,

R^{24} and R^{25} have the meaning of R^4 and R^5 given above and are identical to or different from this meaning,

10

or independently of one another represent a radical of the formula



15

in which

i represents a number 1, 2, 3 or 4,

and

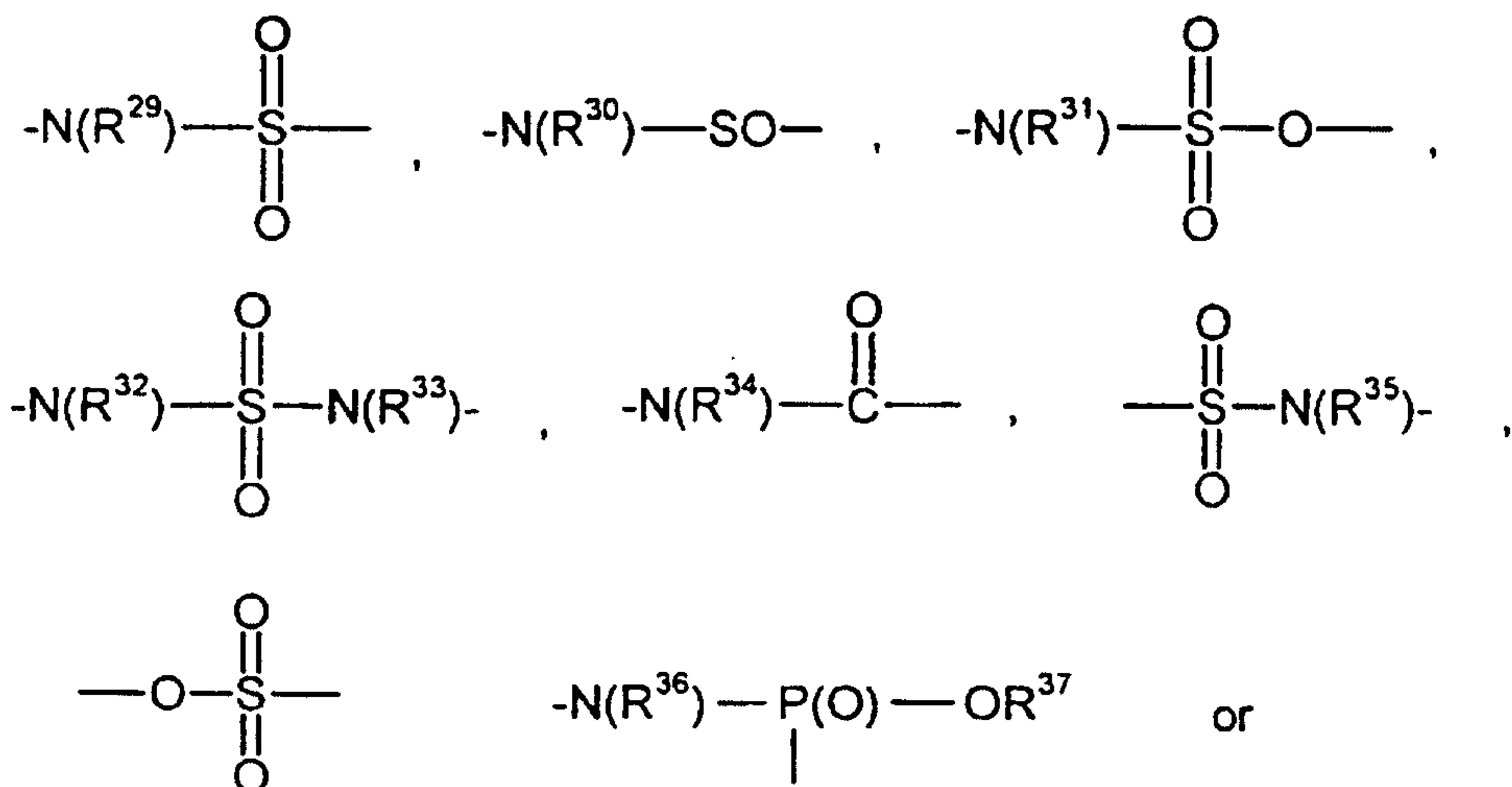
20

R^{27} and R^{28} have the meaning of R^4 and R^5 given above and are identical to or different from this meaning,

R^{26} represents (C_6-C_{10}) -aryl,

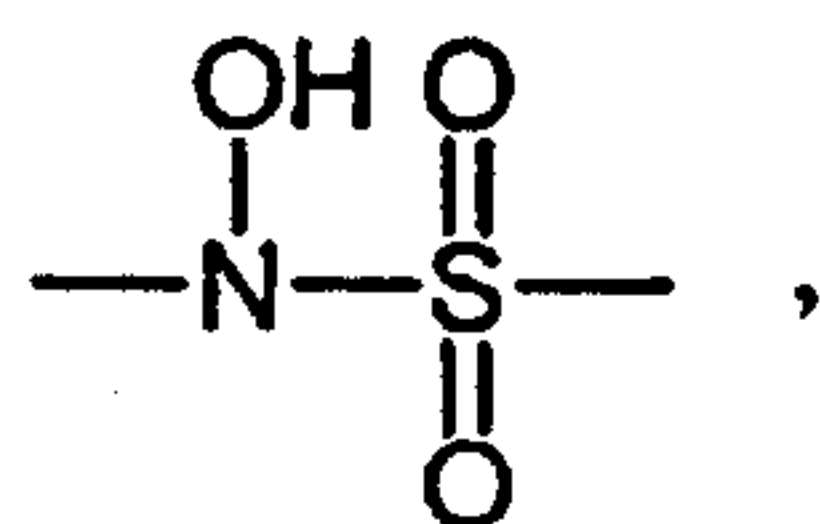
25

L represents a radical of the formula -O-, -NH-,



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where the left-hand side of the radicals is attached to G,

5 and in which R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} , R^{36} and R^{37} are identical or different and represent hydrogen or (C₁-C₄)-alkyl,

or

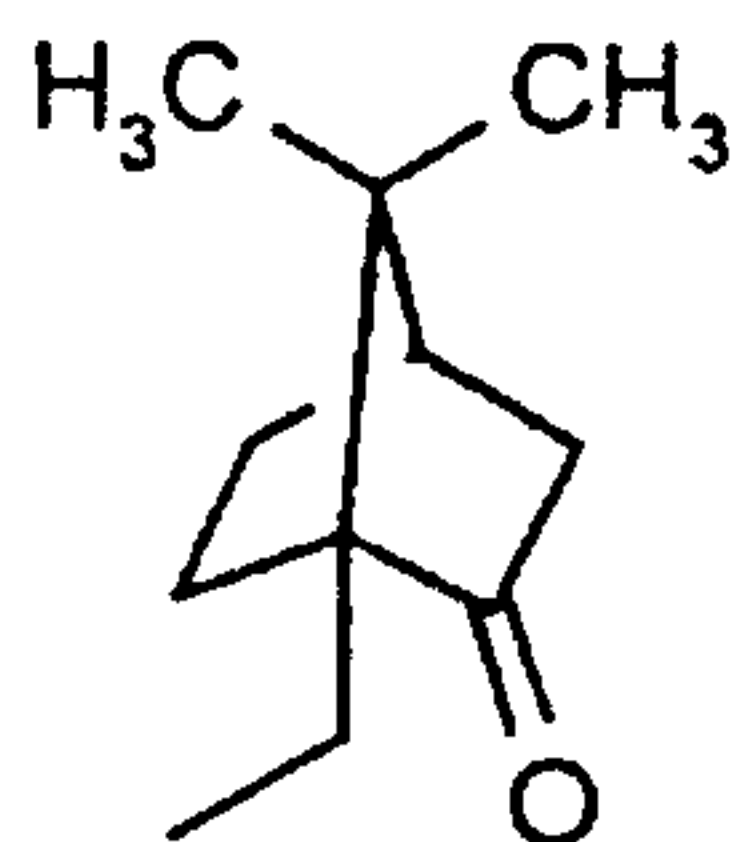
10 R^{29} represents a radical of the formula —SO_2R^2 ,

R^2 represents (C₆-C₁₀)-aryl or represents a 5- to 7-membered saturated or aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, which are optionally substituted by one or more identical or
15 different substituents selected from the group consisting of:

halogen, trifluoromethyl, nitro, amino and (C₁-C₆)-alkyl,

or

represents the radical of the formula



20

or morpholine, or

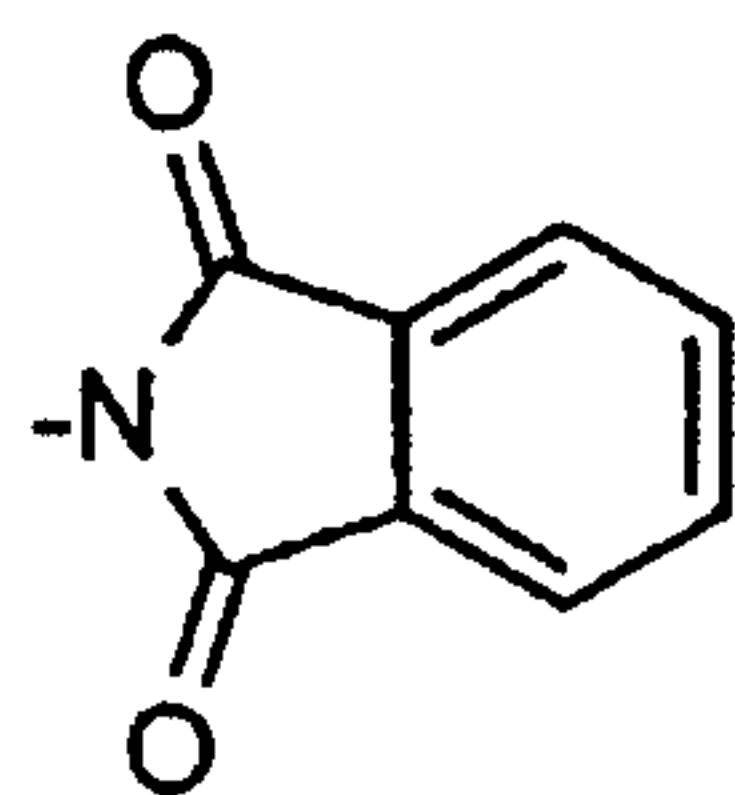
represents C₃-C₈-cycloalkyl, or

represents (C₁-C₁₂)-alkyl, (C₂-C₁₂)-alkenyl or (C₂-C₁₂)-alkinyl, which are optionally substituted by one or more identical or different substituents
25 selected from the group consisting of:

halogen, trifluoromethyl, hydroxyl, cyano, azido, (C₁-C₆)-alkoxy, (C₁-C₆)-perfluoroalkoxy, partially fluorinated (C₁-C₆)-alkoxy, a radical of the formula

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, $-NR^{38}N^{39}$,

in which

5 R^{38} and R^{39} have the meaning of R^4 and R^5 given above and are identical to or different from this meaning,

phenyl, optionally substituted by one or more identical or different substituents selected from the group consisting of:

10 halogen, nitro, hydroxyl, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy and a group of the formula $-NR^{40}R^{41}$,

in which

15 R^{40} and R^{41} are identical or different and represent hydrogen or (C_1-C_6) -alkyl or (C_1-C_6) -acyl,

and a 5- to 6-membered aromatic heterocycle having up to three heteroatoms from the group consisting of S, N and O, optionally substituted
20 by one or more identical or different substituents selected from the group consisting of:

halogen, nitro, hydroxyl, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy and a group of the
25 formula $-NR^{40}R^{41}$,

in which

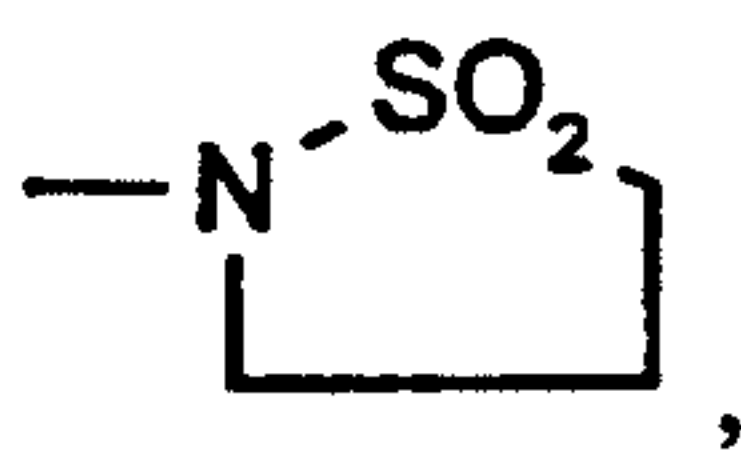
R^{40} and R^{41} are as defined above,

30 or

L and R^2 together represent a radical of the formula

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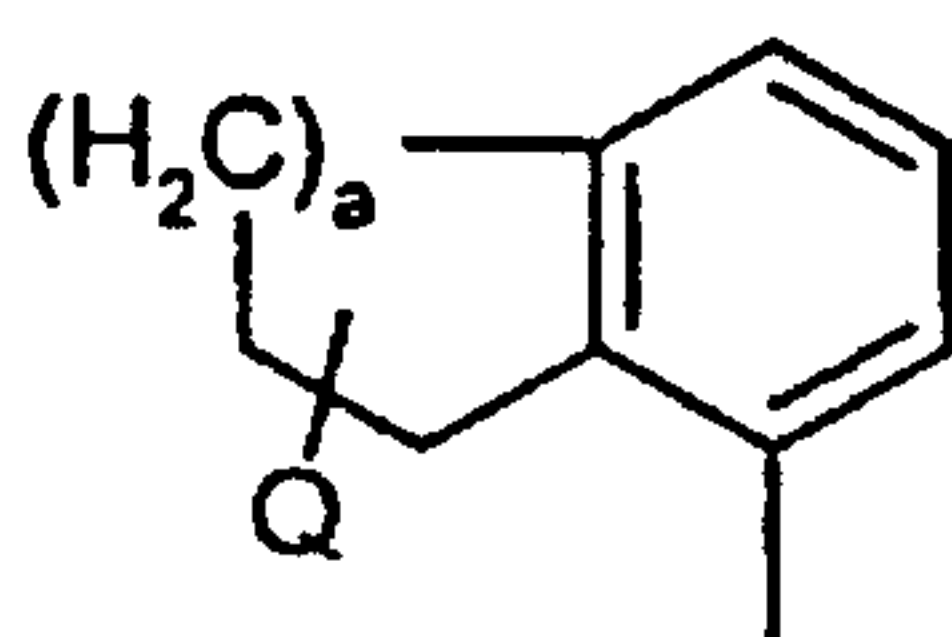
and pharmaceutically acceptable salts thereof.

Preference is given to compounds of the formula (I),

5

in which

R^1 represents a radical of the formula



10

in which

a represents a number 1 or 2,

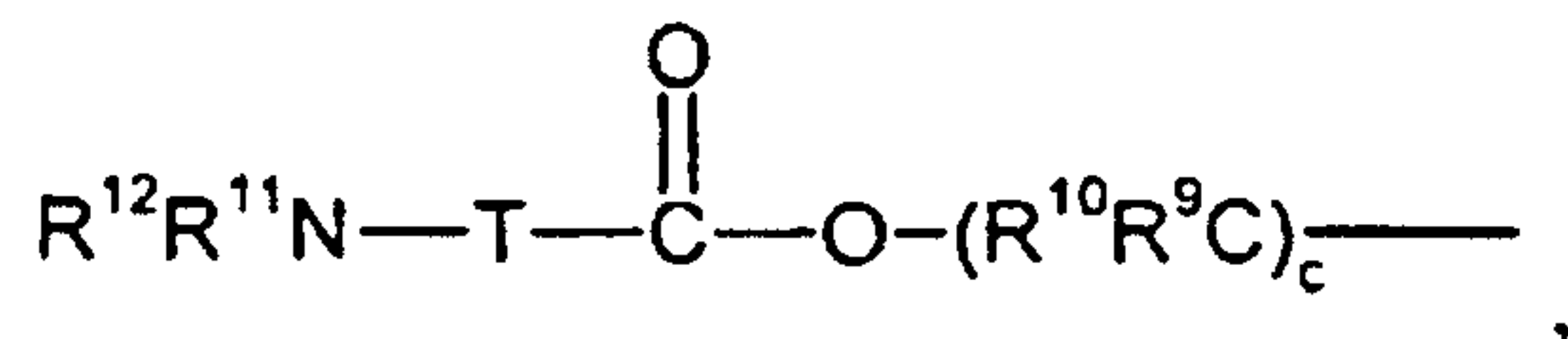
15

and where the phenyl radical listed above is optionally substituted, optionally geminally, by one or more identical or different substituents selected from the group consisting of:

20

fluorine, chlorine, carboxyl, hydroxyl, (C_1-C_4) -alkoxy, (C_1-C_5) -alkoxycarbonyl or (C_1-C_6) -alkyl, which for its part may be substituted by fluorine, chlorine or hydroxyl,

Q represents a radical of the formula



25

in which

c represents a number 1, 2, 3, 4, 5 or 6,

30

R^9 and R^{10} are identical or different and represent hydrogen or (C_1-C_6) -alkyl,

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T represents a radical of the formula $-(\text{CH}_2)_d-$,

in which

5 d represents a number 1, 2, 3, 4, 5 or 6,

or

T represents a moiety of an amino acid radical of the formula



in which

15 R^{13} represents hydrogen or methyl

and

20 R^{14} represents cyclopropyl, cyclopentyl, cyclohexyl, phenyl or hydrogen, or represents $(\text{C}_1\text{-C}_6)\text{-alkyl}$,

where the $(\text{C}_1\text{-C}_8)\text{-alkyl}$ is optionally substituted by methythio, hydroxyl, mercapto, guanidyl or by a group of the formula $-\text{NR}^{15}\text{R}^{16}$ or $-\text{NR}^{17}\text{-OC-}$,

in which

25

R^{15} and R^{16} independently of one another represent hydrogen, $(\text{C}_1\text{-C}_6)\text{-alkyl}$ or phenyl

and

30

R^{17} represents hydroxyl, benzyloxy, $(\text{C}_1\text{-C}_6)\text{-alkoxy}$ or the group $-\text{NR}^{15}\text{R}^{16}$ listed above,

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or the (C₁-C₆)-alkyl is optionally substituted by cyclopropyl, cyclopentyl, cyclohexyl or phenyl, which for its part is optionally substituted by hydroxyl, fluorine, chlorine, bromine or (C₁-C₄)-alkoxy or amino,

5 ,and

R¹¹ and R¹² are identical or different and represent hydrogen or (C₁-C₄)-alkyl,

10 or

R¹¹ and R¹² together with the nitrogen atom form a morpholinyl, piperidinyl or piperazinyl ring,

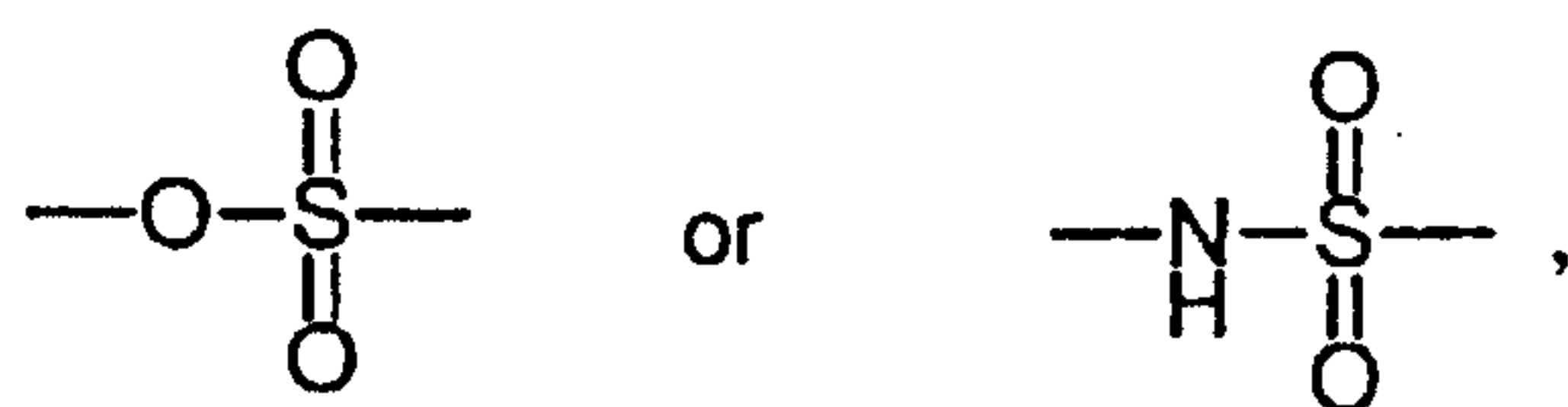
15 A and E are identical or different and represent a bond or represent (C₁-C₄)-alkylene,

D represents an oxygen atom,

20 G represents doubly attached phenyl, naphthyl, pyrimidyl, pyradizinyll or pyridyl, which are optionally substituted by one or more identical or different substituents selected from the group consisting of:
hydroxyl, trifluoromethyl, carboxyl, halogen, (C₁-C₄)-alkyl, hydroxy(C₁-C₄)alkyl, (C₁-C₄)-alkoxy and (C₁-C₄)-alkoxycarbonyl

25

L represents a radical of the formula



where the left-hand side of the radicals is attached to G,

30

R² represents (C₁-C₁₀)-alkyl which is optionally substituted by one or more identical or different substituents selected from the group consisting of:

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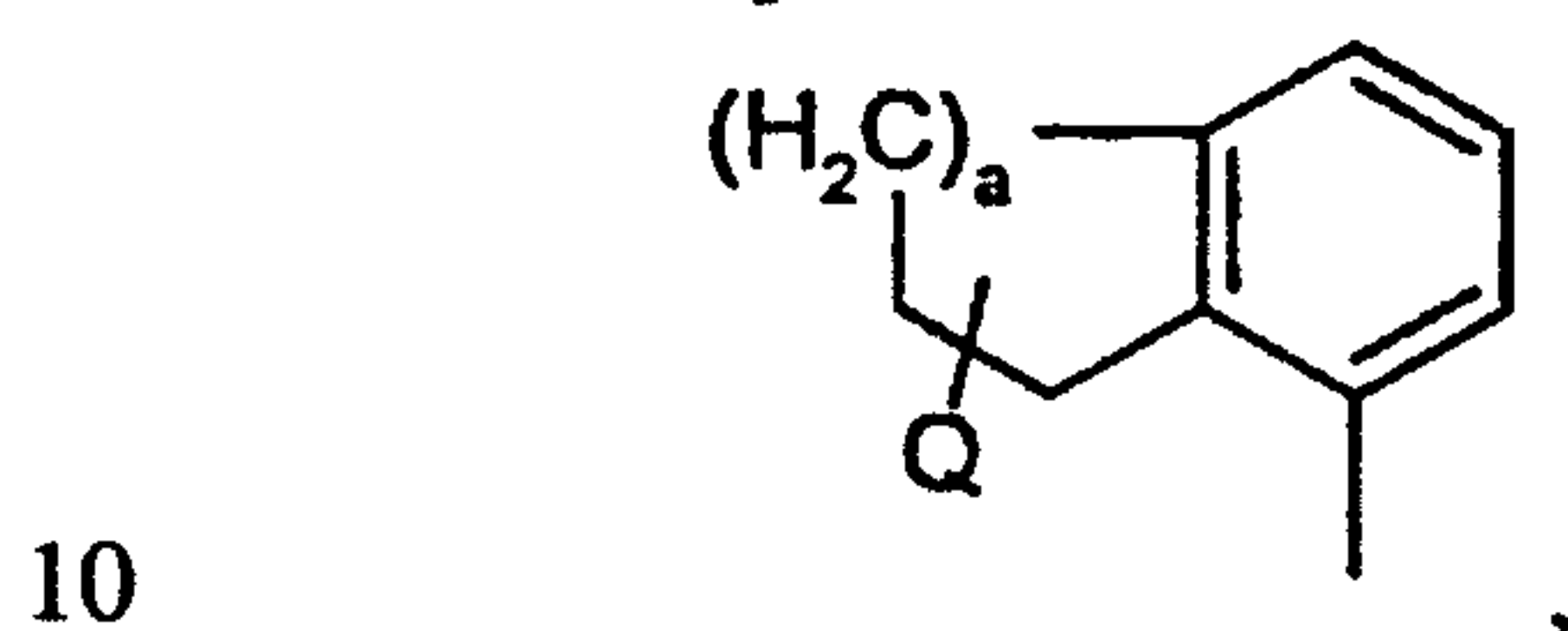
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fluorine, chlorine, bromine, phenyl, trifluoromethyl, hydroxyl, azido, (C₁-C₄)-alkoxy, (C₁-C₅)-perfluoroalkoxy or partially fluorinated (C₁-C₄)-alkoxy

5 and pharmaceutically acceptable salts thereof.

Particular preference is given to compounds of the formula (I), in which

R¹ represents a radical of the formula



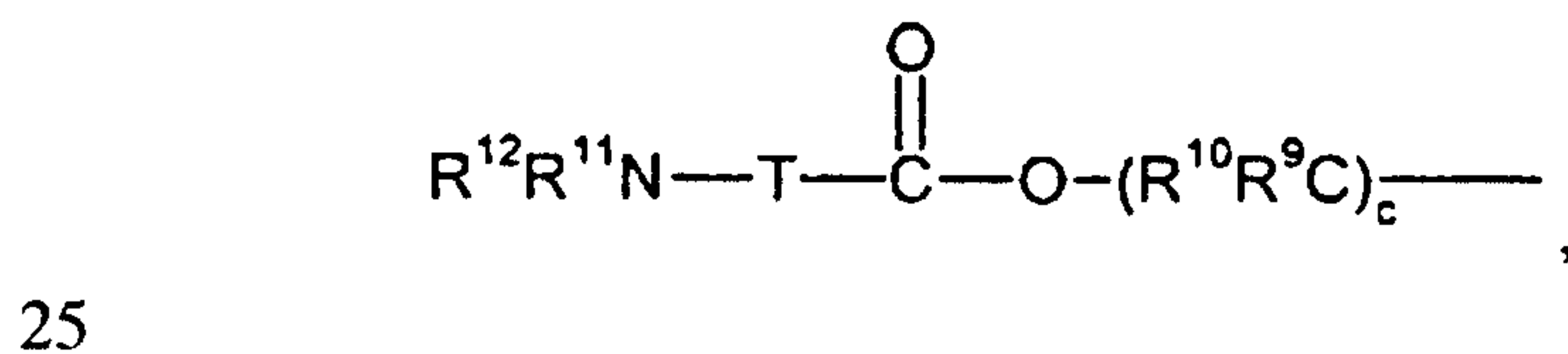
in which

15 a represents a number 1 or 2,

and where the phenyl radical listed above is optionally substituted by one or more identical or different substituents selected from the group consisting of:

20 chlorine, fluorine, hydroxyl, (C₁-C₃)-alkoxy or (C₁-C₄)-alkyl, which for its part may be substituted by hydroxyl,

Q represents a radical of the formula



in which

c represents a number 1, 2, 3 or 4,

30 R⁹ and R¹⁰ are identical or different and represent hydrogen or (C₁-C₃)-alkyl,

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T represents a radical of the formula $-(CH_2)_d-$,

in which

5 d represents a number 1, 2, 3, 4, 5 or 6,

or

T represents a moiety of an amino acid radical of the formula



in which

15 R^{13} represents hydrogen or methyl

and

R^{14} represents cyclopentyl, cyclohexyl, phenyl or hydrogen, or
20 represents (C_1-C_4) -alkyl,

where the (C_1-C_4) -alkyl is optionally substituted by methythio, hydroxyl,
mercapto, guanidyl or by a group of the formula $-NR^{15}R^{16}$ or $-NR^{17}-$
OC-,

25 in which

R^{15} and R^{16} independently of one another represent hydrogen, (C_1-C_8) -alkyl
or phenyl

30 and

R^{17} represents hydroxyl, benzyloxy, (C_1-C_3) -alkoxy or amino,

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or the (C₁-C₄)-alkyl is optionally substituted by cyclopentyl, cyclohexyl or phenyl, which for its part is substituted by hydroxyl, fluorine, chlorine or (C₁-C₃)-alkoxy or amino,

5 and

R¹¹ and R¹² are identical or different and represent hydrogen or (C₁-C₃)-alkyl,

10 or

R¹¹ and R¹² together with the nitrogen atom form a morpholinyl ring,

A and E represent a bond,

15

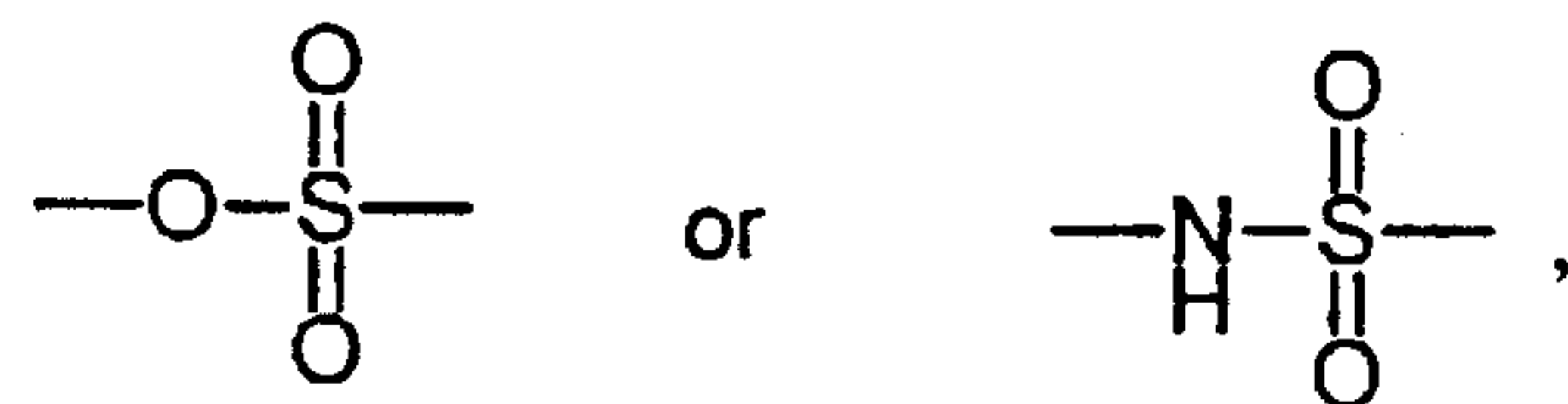
D represents an oxygen atom,

G represents doubly attached phenyl which are optionally substituted by one or more identical or different substituents selected from the group consisting of:

20

hydroxyl, trifluoromethyl, carboxyl, fluorine, chlorine, bromine, (C₁-C₃)-alkyl, hydroxy(C₁-C₃)alkyl or (C₁-C₃)-alkoxy

25 L represents a radical of the formula



where the left-hand side of the radicals is attached to G,

30 R² represents (C₁-C₈)-alkyl, which is optionally substituted by one or more identical or different substituents selected from the group consisting of:

fluorine, chlorine, bromine, phenyl, trifluoromethyl or trifluoromethyl-substituted (C₁-C₄)-alkoxy,

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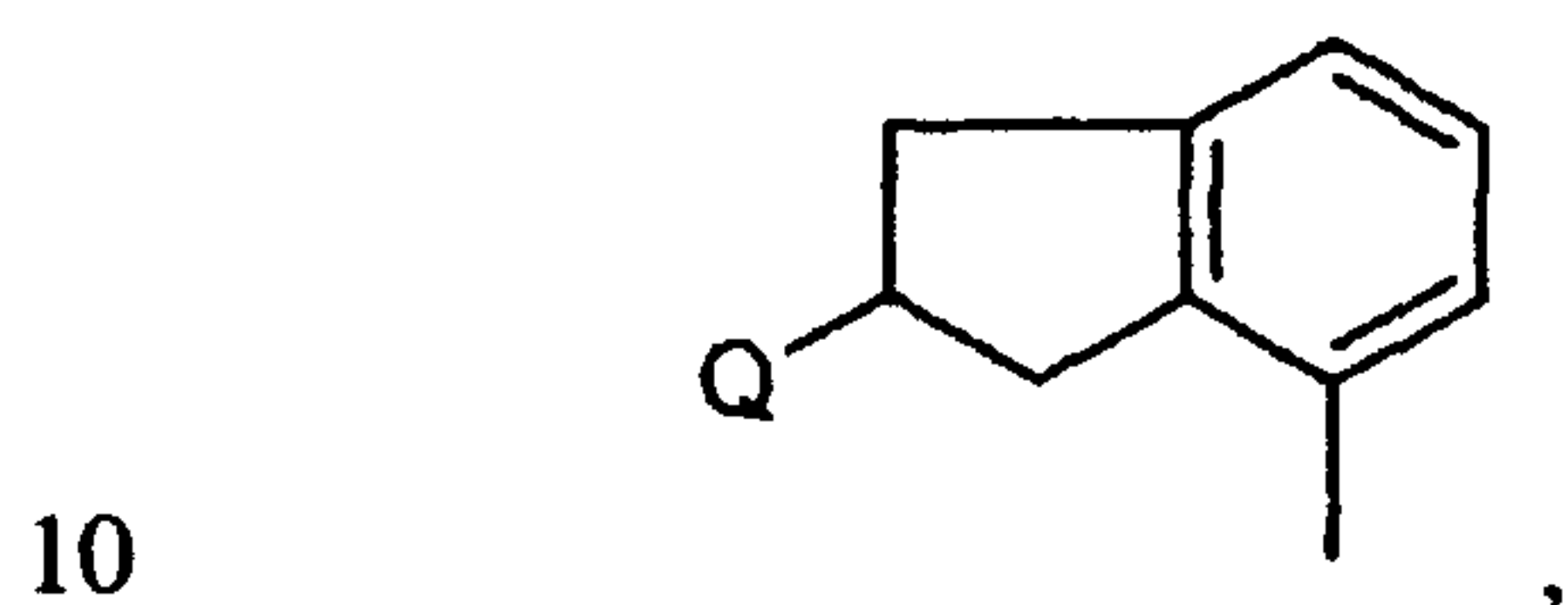
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and pharmaceutically acceptable salts thereof.

Very particular preference is given to compounds of the formula (I) according to
5 the invention,

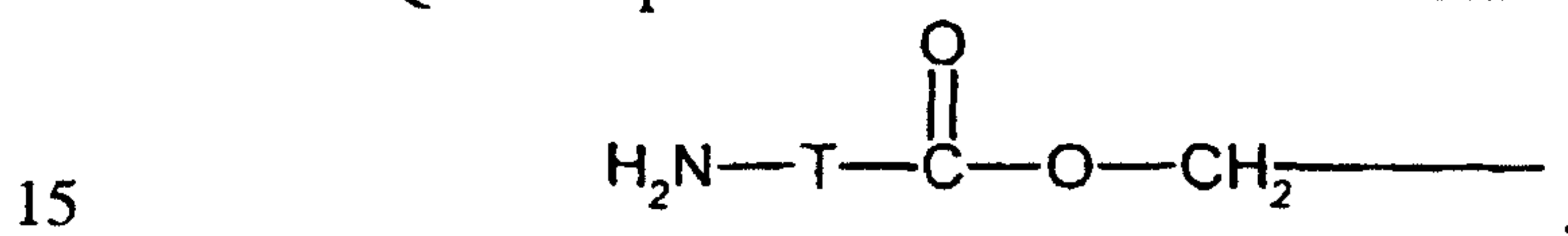
in which

R¹ represents a radical of the formula



in which

Q represents a radical of the formula



in which

T represents a radical of the formula -(CH₂)_d-,

20

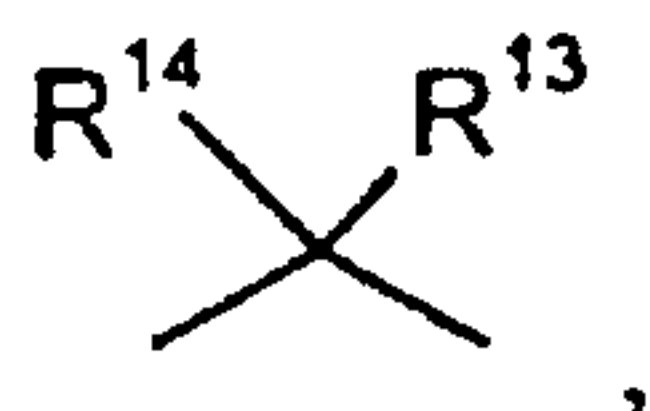
in which

d represents a number 1, 2, 3, 4, 5 or 6,

25

or

T represents a moiety of an amino acid radical of the formula



in which

30

R¹³ represents hydrogen,

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and

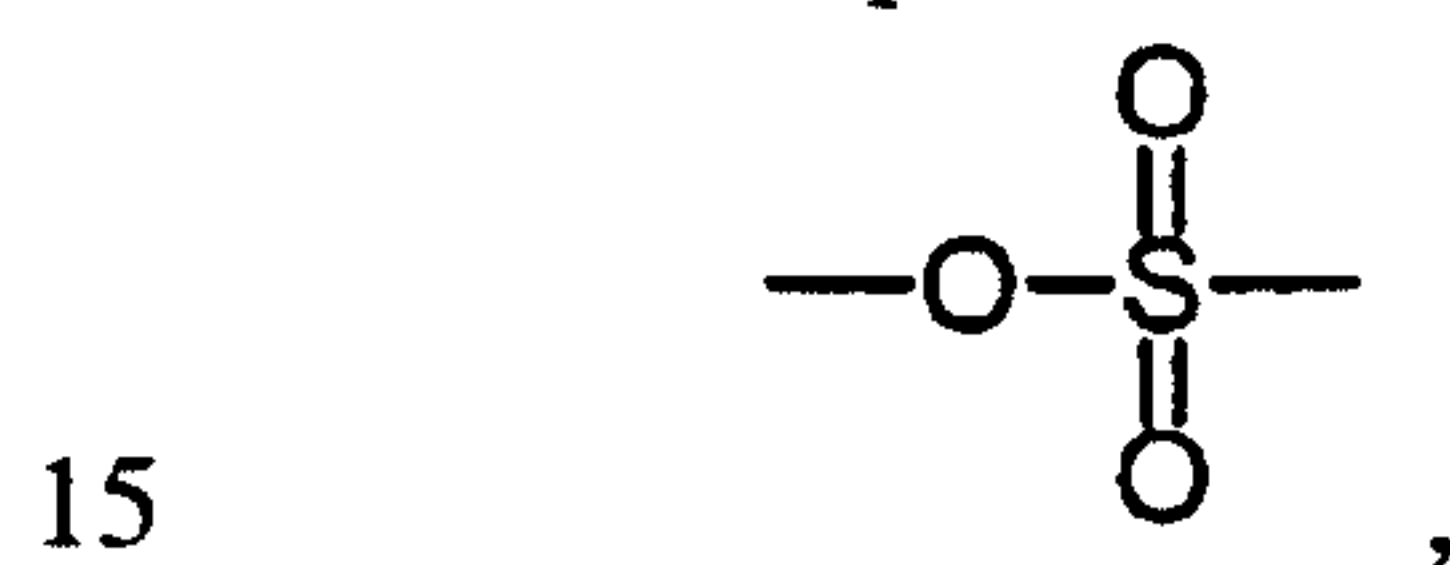
5 R^{14} represents hydrogen, (C₁-C₄)-alkyl, benzyl or a radical of the formula -CH₂OH,

A and E represent a bond,

10 D represents an oxygen atom,

G represents phenyl, which is optionally substituted by fluorine, chlorine or bromine,

L represents a radical of the formula



where the left-hand side of the radical is attached to G,

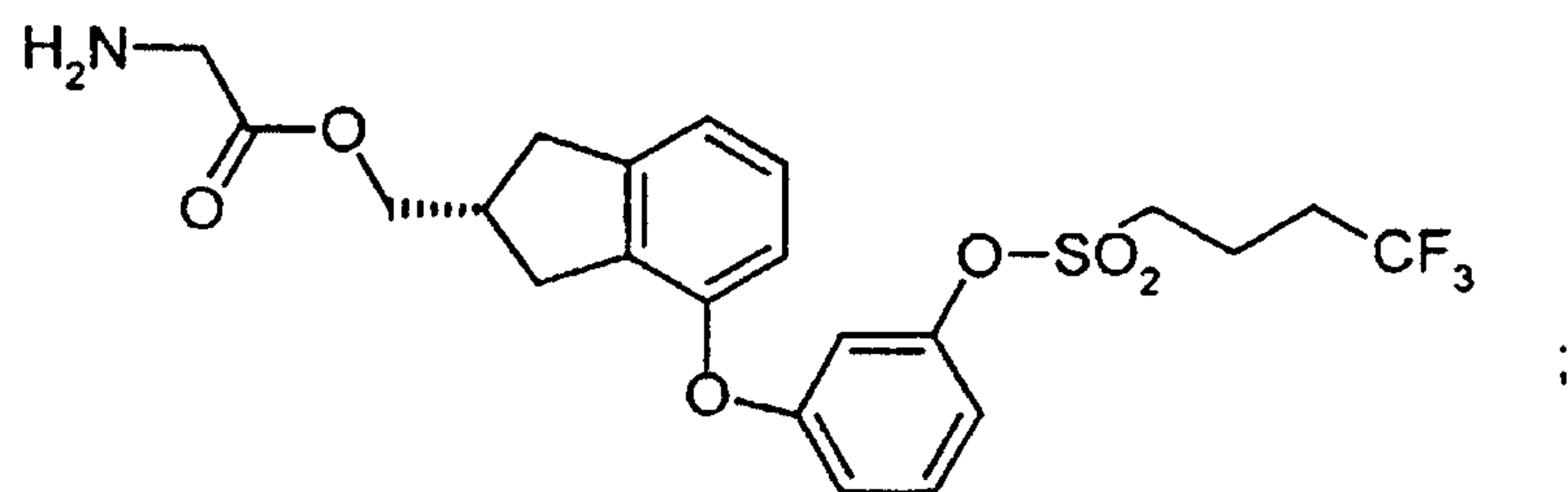
20 R^2 represents (C₁-C₄)-alkyl, which is optionally substituted by fluorine or trifluoromethyl,

and pharmaceutically acceptable salts thereof.

25 Particular preference is also given to compounds selected from the group consisting of

(R)-3-(2-glycinyloxymethyl-indanyl-4-oxy)-phenyl
butanesulphonate

4,4,4-trifluoro-1-

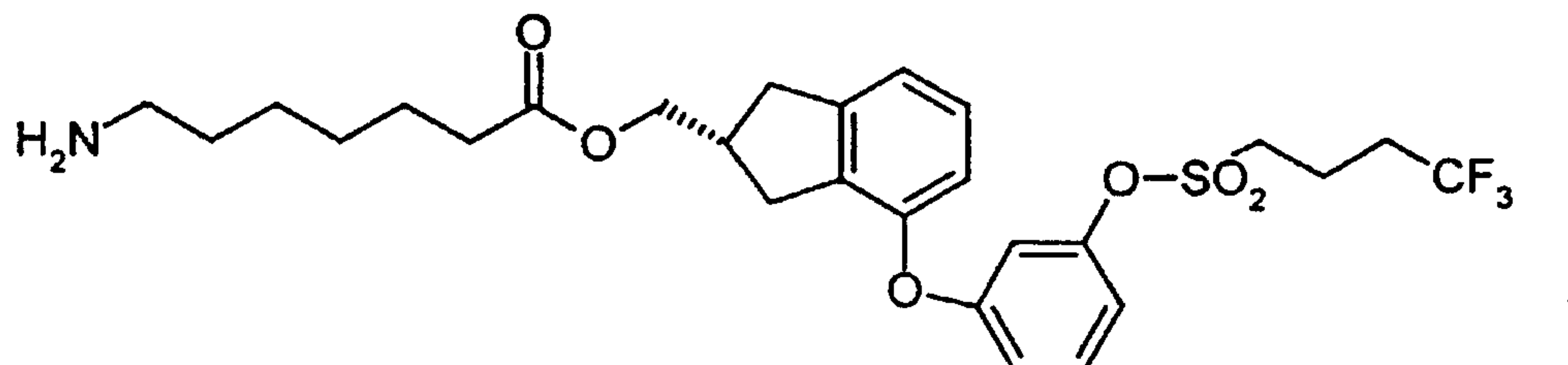


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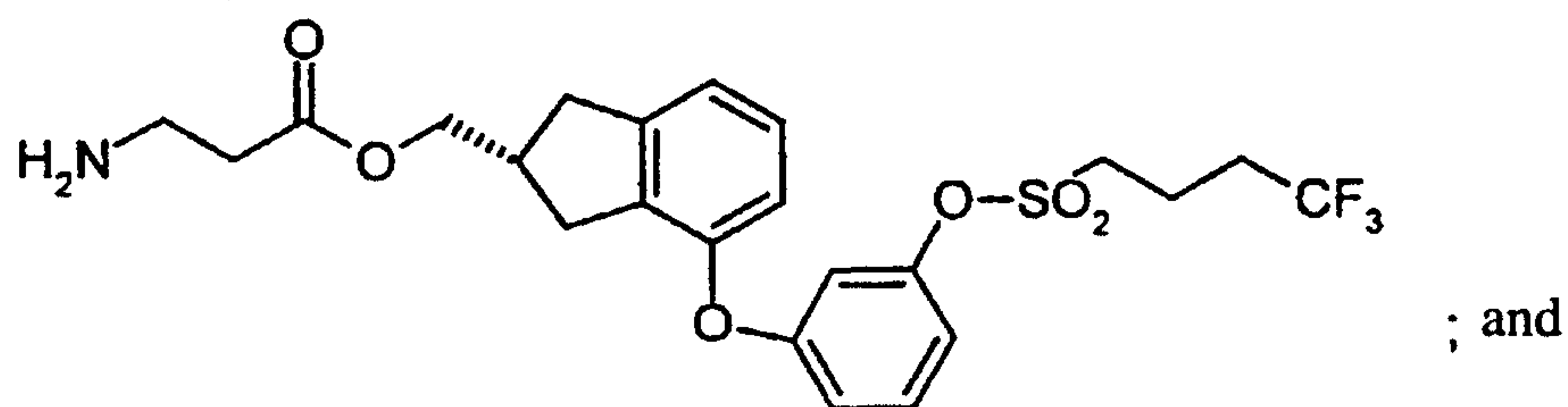
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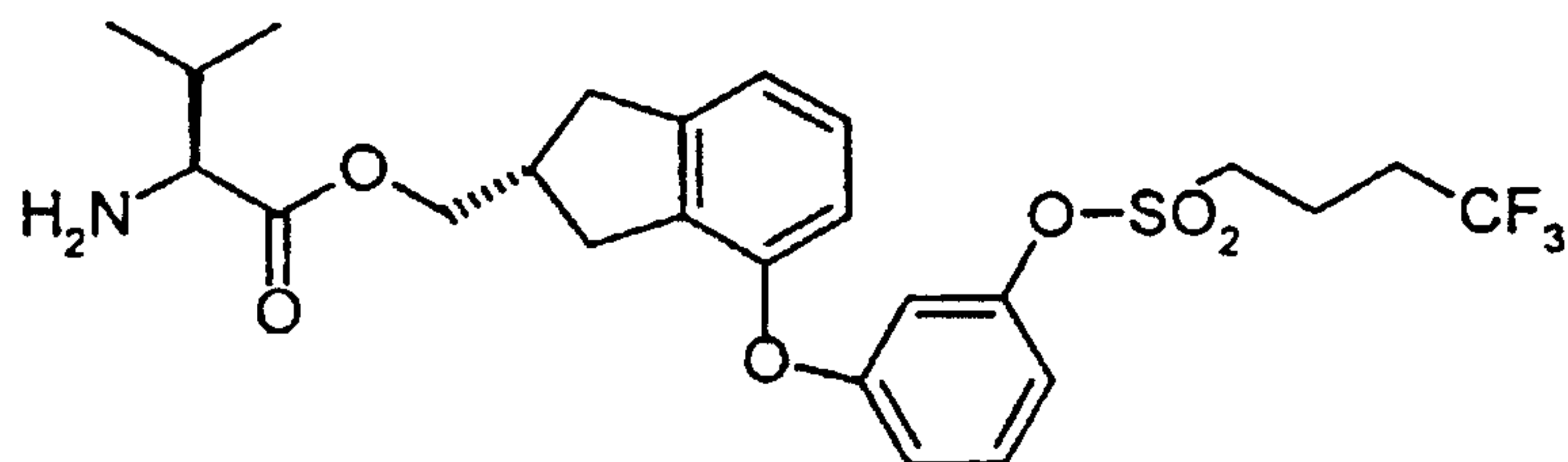
(R)-3-[2-(7-aminoheptanoyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



5 (R)-3-[2-(3-aminopropanoyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



10 (R)-3-[2-((S)-valinyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



and pharmaceutically acceptable salts thereof.

Moreover, we have found a process for preparing the compounds of the general formula (I) according to the invention, characterized in that compounds of the general formula (II)



in which

A, D, E, G, L, R^2 , R^9 and R^{10} and have the abovementioned meaning

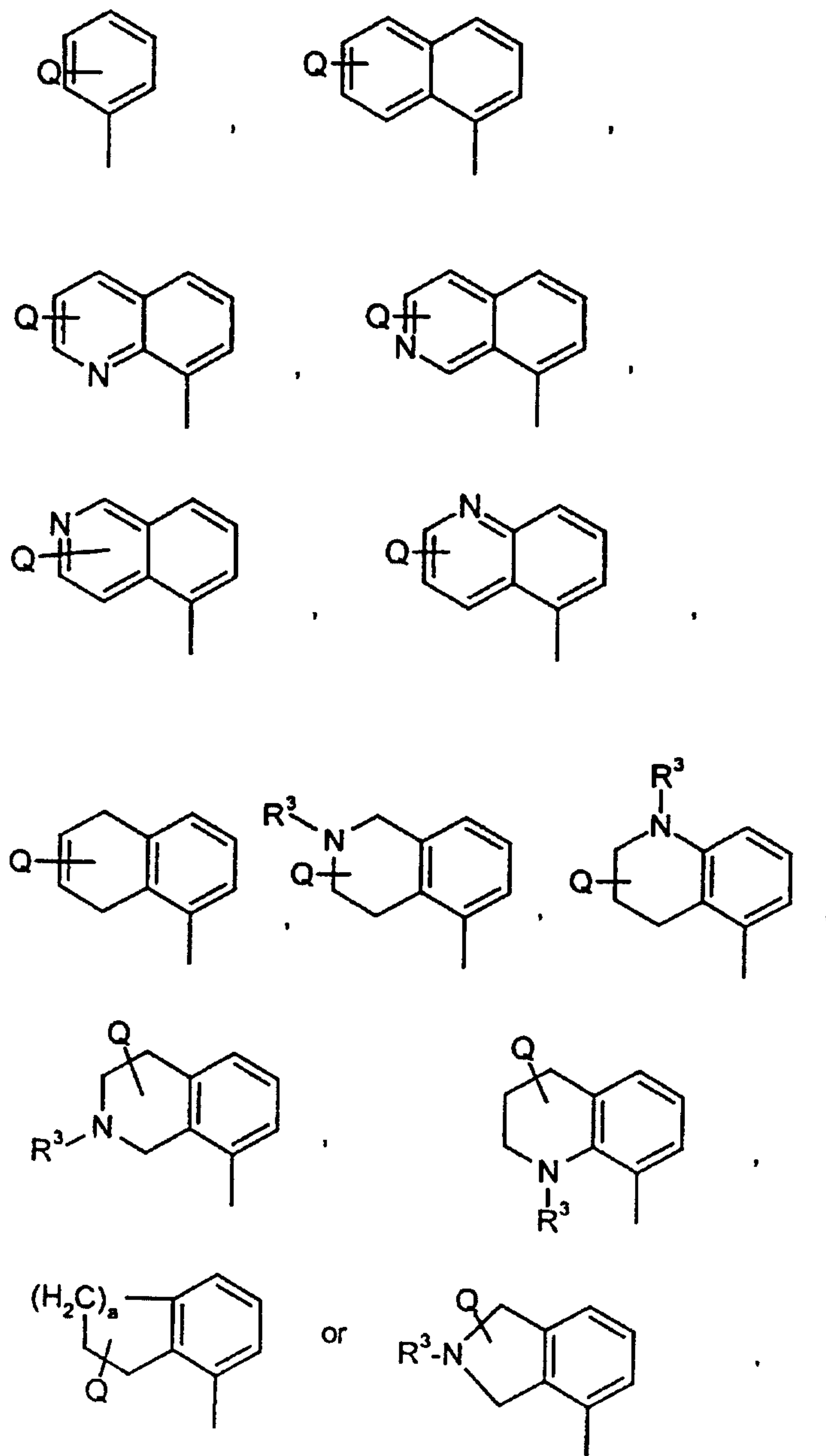
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and

R^{1'} represents a radical of the formula

5



10 in which

a represents a number 1 or 2,

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R^3 represents hydrogen, (C₂-C₆)-alkenyl, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

and where all phenyl ring systems listed above are optionally substituted,
optionally geminally, by one or more identical or different substituents
5 selected from the group consisting of:

halogen, carboxyl, hydroxyl, phenyl, (C₁-C₆)-alkoxy, (C₁-C₆)-
alkoxycarbonyl, (C₁-C₈)-alkyl, which for its part may be substituted by
halogen, C₁-C₆-alkylsulphonyloxy, azide, amino, mono(C₁-C₈)-alkylamino,
10 di(C₁-C₆)-alkylamino or hydroxyl,

a group of the formula $-(CO)_b-NR^4R^5$,

in which

15

b represents a number 0 or 1,

R^4 and R^5 are identical or different and independently of one another
represent hydrogen, phenyl, (C₁-C₆)-acyl, cyclo(C₄-C₇)-acyl,
20 benzoyl or (C₁-C₆)-alkyl, which is optionally substituted by amino,
mono(C₁-C₆)-alkylamino, di(C₁-C₆)-alkylamino,

or

25 R^4 and R^5 together with the nitrogen atom form a 5- or 6-membered
saturated heterocycle which may optionally contain one or more
further heteroatom(s) from the group consisting of S and O and/or
one or more radical(s) of the formula $-NR^8$,

30 in which

R^8 represents hydrogen, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

and

35

a group of the formula $-NR^6-SO_2-R^7$

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in which

R^6 represents hydrogen, phenyl, (C_1-C_6) -alkyl or (C_1-C_6) -acyl,

R^7 represents phenyl or (C_1-C_6) -alkyl,

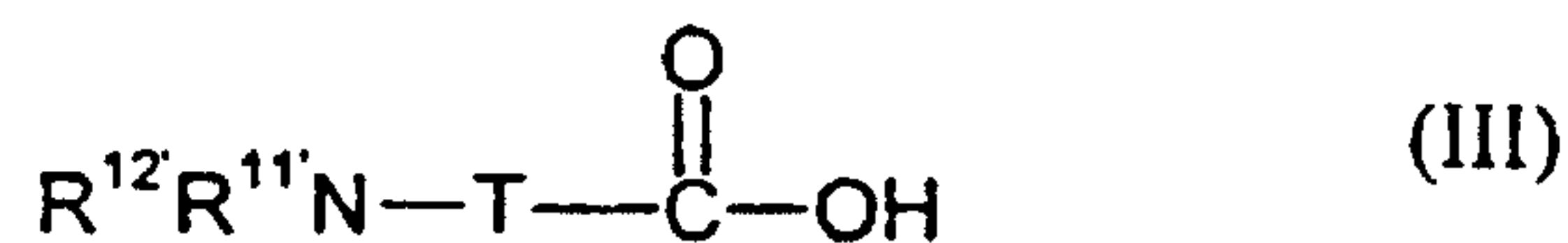
and

Q' represents a radical of the formula $HO-(R^{10}R^9C)_c-$,

in which

c , R^9 and R^{10} have the meaning given above,

are reacted with compounds of the general formula (III)



in which

$R^{11'}$ represents hydrogen

and

$R^{12'}$ represents one of the amino protective groups listed above, preferably represents tert-butyloxycarbonyl,

in inert solvents, if appropriate in the presence of a base and an auxiliary,

and the amino protective group is removed by customary methods,

and the amino group is then, if appropriate, reductively alkylated or dialkylated with an aldehyde or ketone,

or alkylated or dialkylated with a halide,

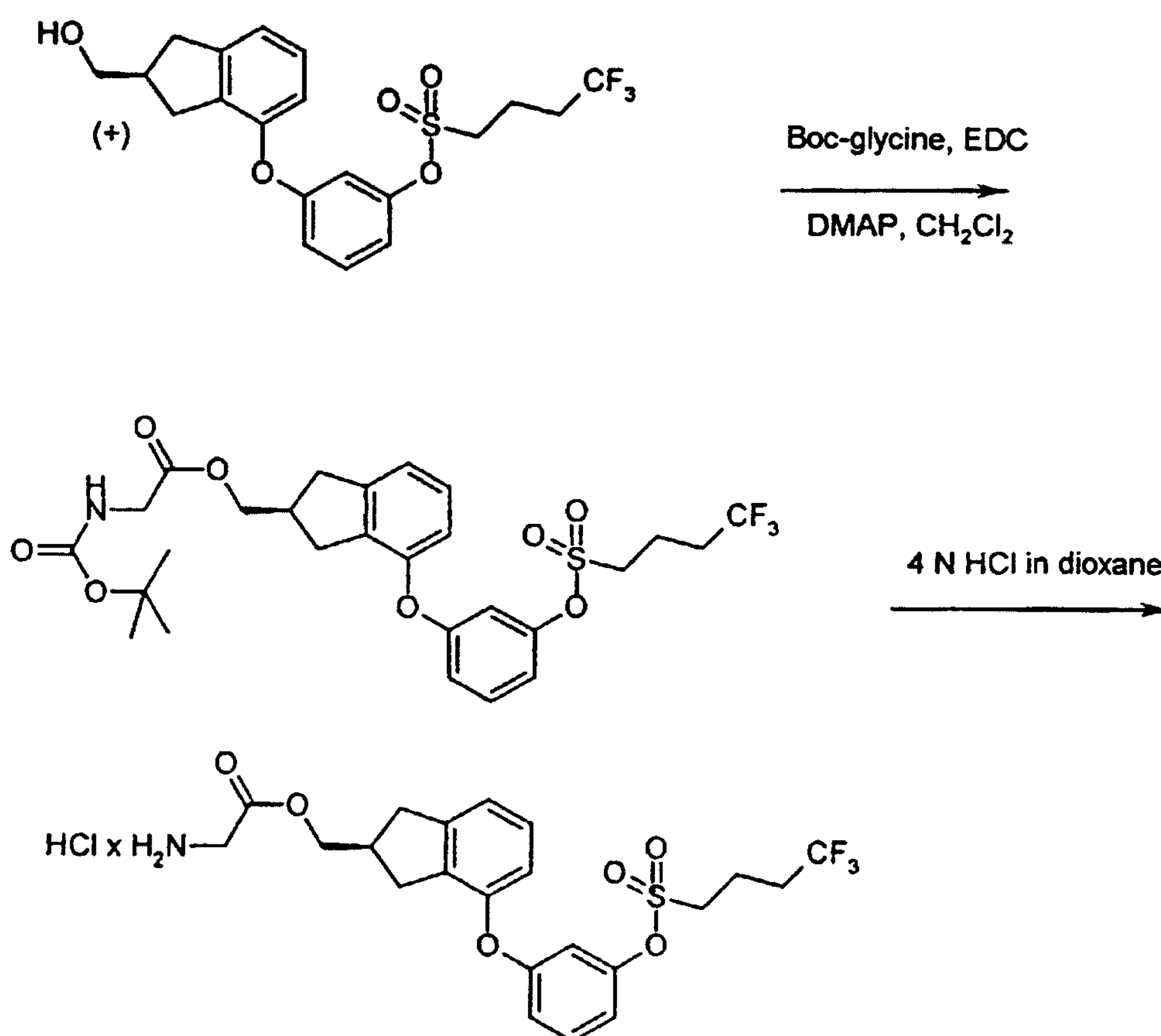
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followed, if appropriate, by derivatizations according to customary methods, such as, for example, an alkylation or esterification, depending on the substituents listed above.

5

The process according to the invention can be illustrated in an exemplary manner by the formula scheme below:



10

For all process steps, suitable solvents are the customary inert solvents which do not change under the reaction conditions. These preferably include organic solvents, such as ethers, for example diethyl ether, glycol monomethyl ether or glycol dimethyl ether, dioxane or tetrahydrofuran, or hydrocarbons, such as benzene, p-cresol, toluene, xylene, cyclohexane or mineral oil fractions, or halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, or dimethyl sulphoxide, dimethylformamide, hexamethylphosphoric triamide, ethyl acetate, pyridine, triethylamine or picoline. It is also possible to use mixtures of the solvents mentioned, if appropriate also with water. Particular

15

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preference is given to methylene chloride, tetrahydrofuran, dioxane and dioxane/water.

5 Suitable bases are organic amines-(C₁-C₆)-trialkylamines, such as, for example, triethylamine, or heterocycles, such as pyridine, methylpiperidine, piperidine or N-methylmorpholine. Preference is given to triethylamine and N-methylmorpholine.

10 The bases are generally employed in an amount of from 0.1 mol to 5 mol, preferably from 1 mol to 3 mol, in each case based on 1 mol of the compounds of the general formula (II).

15 The reactions can be carried out at atmospheric pressure, but also under elevated or reduced pressure (for example from 0.5 to 3 bar). In general, the reactions are carried out at atmospheric pressure.

The reactions are carried out in a temperature range of from 0 C to 100 C, preferably at from 0 C to 30 C and at atmospheric pressure.

20 The amino protective groups are removed in a manner known per se.

25 The auxiliaries used for the peptide couplings in question are preferably condensing agents, which can also be bases, in particular when the carboxyl group is activated as anhydride. Preference is given here to the customary condensing agents, such as carbodiimides, for example N,N'-diethyl-, N,'-dipropyl-, n,n'-diisopropyl-, N,N'-dicyclohexylcarbodiimide, N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride, or carbonyl compounds, such as carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulphate or 2-tert-butyl-5-methyl-isoxazolium perchlorate, or acylamino compounds, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis-(2-oxo-3-oxazolidinyl) phosphoryl chloride or benzotriazolyloxy-tri(dimethylamino)-phosphonium hexafluorophosphate, or 1-hydroxybenzotriazole and, as bases, alkali metal carbonates, for example sodium carbonate or potassium carbonate or sodium bicarbonate or potassium bicarbonate, or organic bases, such as
35 trialkylamines, for example triethylamine, N-ethylmorpholine, N-methylpiperidine

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or diisopropylethylamine. Particular preference is given to dicyclohexylcarbodiimide, N-methylmorpholine and 1-hydroxybenzotriazole.

Alkylation is generally carried out using alkylating agents, such as, for example,
 5 alkyl halides, sulphonic acid esters or substituted or unsubstituted dialkyl or diaryl sulphonates, preferably using methyl iodide or dimethyl sulphate.

Alkylation is generally carried out in one of the abovementioned solvents, preferably in dimethylformamide in a temperature range of from 0°C to +70°C,
 10 preferably from 0°C to +30°C and atmospheric pressure.

The compounds of the general formula (III) are known per se or can be prepared by customary methods.

15 The compounds of the general formula (II) can be prepared by
 [A] reacting compounds of the general formula (IV)



20 in which

$R^{11'}$ has the meaning of $R^{1'}$ given above, but instead of Q' , the substituent Q'' is introduced,

in which Q'' represents a group of the formula $(C_1-C_3)\text{-alkyl-O}_2\text{C-}$
 25 $(R^{10}R^9C)_c$,

in which c'' represents a number 0, 1, 2, 3, 4 or 5,

and

R^9 and R^{10} have the meaning given above,

30 A, D, E and G have the meaning given above

and

M represents oxygen or $-N(R^{42})-$,

35

in which

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R^{42} represents hydrogen or (C₁-C₄)-alkyl,

with compounds of the general formula (V)

5



in which

10 R^2 has the meaning given above,

R^{43} represents halogen, preferably chlorine or iodine,

15 W represents a radical of the formula -SO₂-, -SO-, -CO-, -P(O)(OR³⁷)- or a single bond,

in which

20 R^{37} has the meaning given above,

to give compounds of the general formula (V')



25 in which

$R^{1''}$, A, D, E, G, M, W and R^2 have the meaning given above,

in inert solvents, if appropriate in the presence of a base,

30

followed by final reduction to give compounds of the general formula (IIa)



35 in which

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R^1 , A, D, E, G, M, W and R^2 have the meaning given above,

or

5 [B] reacting compounds of the general formula (IV)

initially with trialkylsilyl chlorosulphonates, preferably trimethylsilyl
chlorosulphonate, admixing with an acid and then reacting with a chlorinating
agent, preferably phosphorus pentachloride, to give a compound of the general
10 formula (VI)



in which

15

$R^{1''}$, A, D, E, G and M have the meaning given above,

followed by reaction with compounds of the general formula (VII)

20



in which

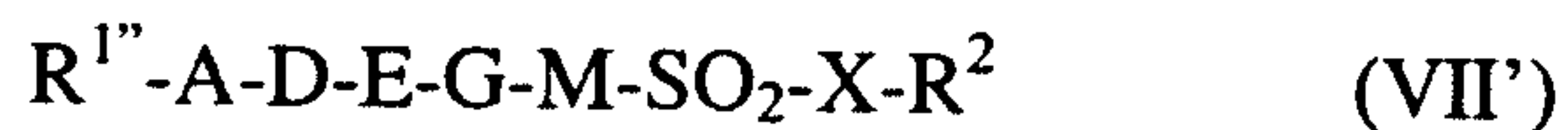
R^2 has the meaning given in Claim 1 and

25

X represents oxygen or nitrogen,

to give compounds of the general formula (VII')

30



in which

$R^{1''}$, A, D, E, G, M, X and R^2 have the meaning given above,

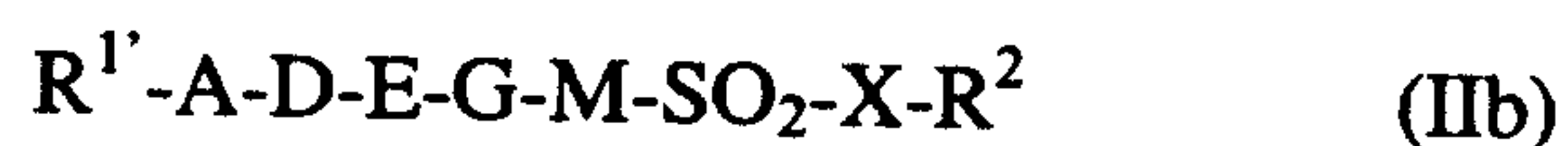
35

in inert solvents in the presence of $Bzl-NEt_3^+Cl^-$ and a base,

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followed by final reduction to give compounds of the general formula (IIb)



5

in which

$R^{1'}$, A, D, E, G, M, X and R^2 have the meaning given above,

10 or

[C] reacting compounds of the general formula (VIII)



15

in which

$R^{1''}$ and A have the meaning given above and

20 D' represents oxygen, sulphur or $-N(R^{19})-$

in which

R^{19} has the meaning given in Claim 1,

25

with compounds of the general formula (IX)



30 in which

E, G and R^2 have the meaning given above and

R^{44} represents a leaving group, preferably halogen, particularly preferably
35 fluorine, chlorine or bromine,

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to give compounds of the general formula (IX')



5 in which

$R^{1''}$, A, D', E, G and R^2 have the meaning given above,

followed by final reduction to give compounds of the general formula (IIc)

10



in which

15 $R^{1'}$, A, D', E, G and R^2 have the meaning given above,

or

[D] reacting compounds of the general formula (IId)

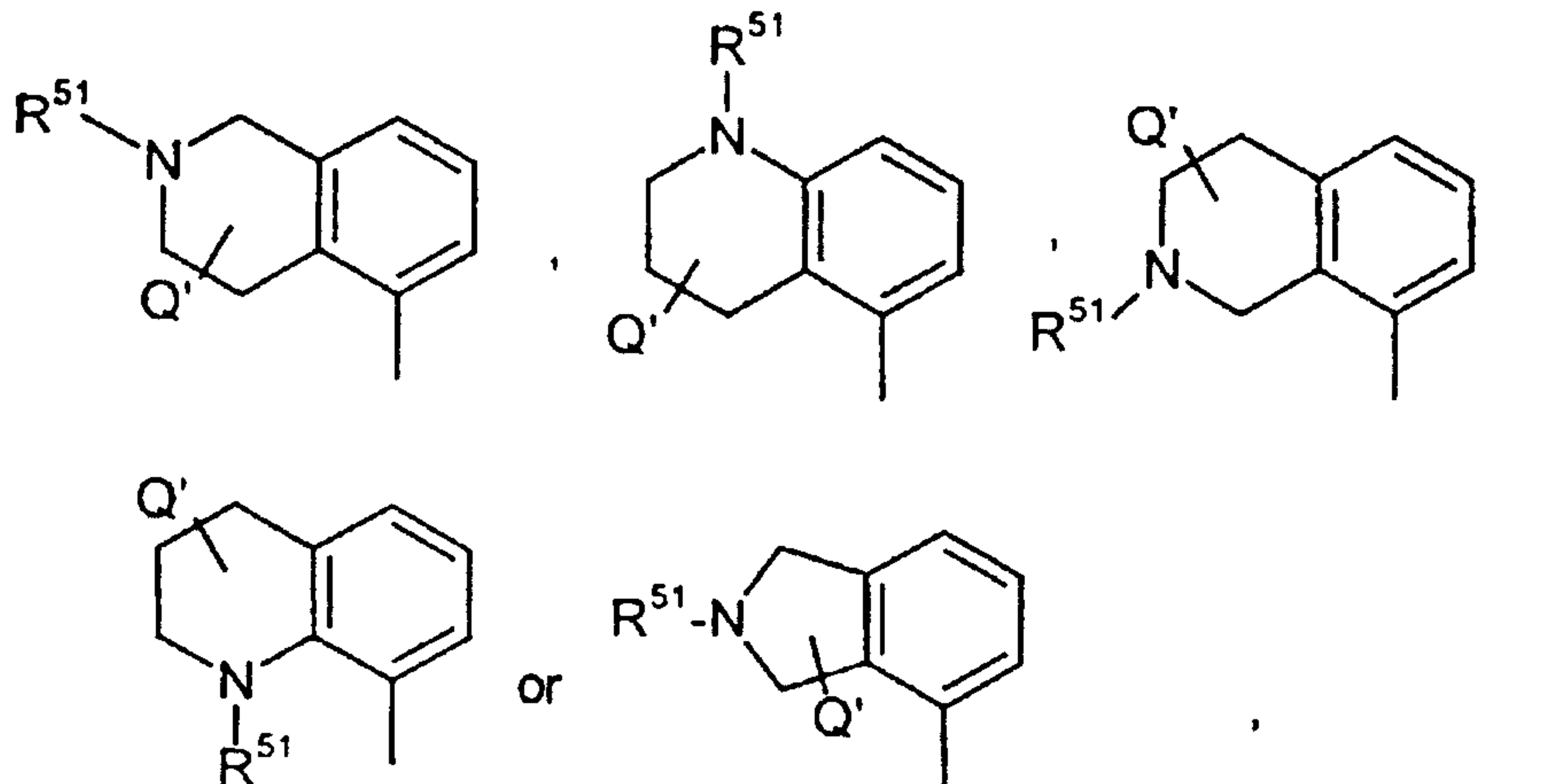
20



in which

25 A, D, E, G, L and R^2 have the meaning given above and

R^{47} represents a radical of the formula



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in which

R^{51} represents (C₁-C₆)-alkyl,

5

and

Q' has the meaning given above,

10 with chloroformates, preferably 1-(1-chloro)ethyl chloroformate or methyl chloroformate, and then with alcohols, preferably methanol, if appropriate in the presence of a base, to give compounds of the general formula (Ie)

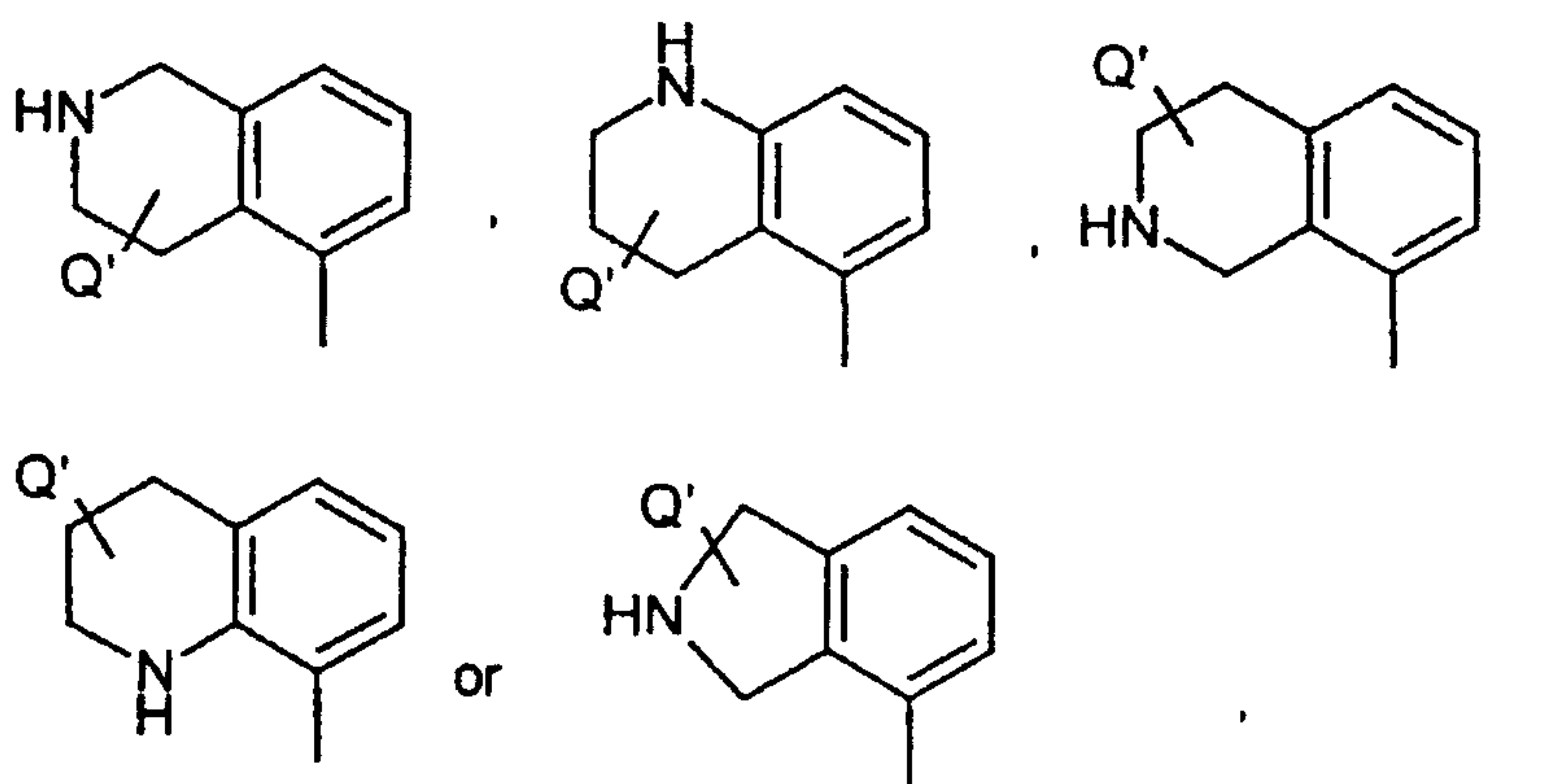


15

in which

A, D, E, G, L and R^2 have the meaning given above and

20 R^{48} represents a radical of the formula



in which

25 Q' has the meaning given above,

or

[E] reacting compounds of the general formula (Ie)

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with (C₁-C₆)-ketones or (C₁-C₆)-aldehydes in the presence of a reducing agent, preferably sodium cyanoborohydride, if appropriate in the presence of an acid, to give compounds of the general formula (II_f)

5



in which

10 A, D, E, G, L and R² have the meaning given above and

R⁴⁹ represents (C₃-C₆)-alkenyl or (C₁-C₆)-alkyl,

or

15

[F] [lacuna] compounds of the general formula (II_e) with compounds of the general formula (X)



20

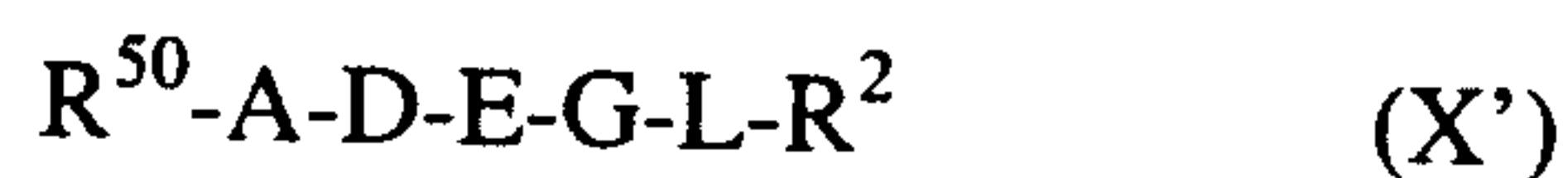
in which

R³ has the meaning given in Claim 1,

25 R⁴⁵ represents a leaving group, preferably halogen,

in inert solvents, if appropriate in the presence of a base, to give compounds of the general formula (X')

30



in which

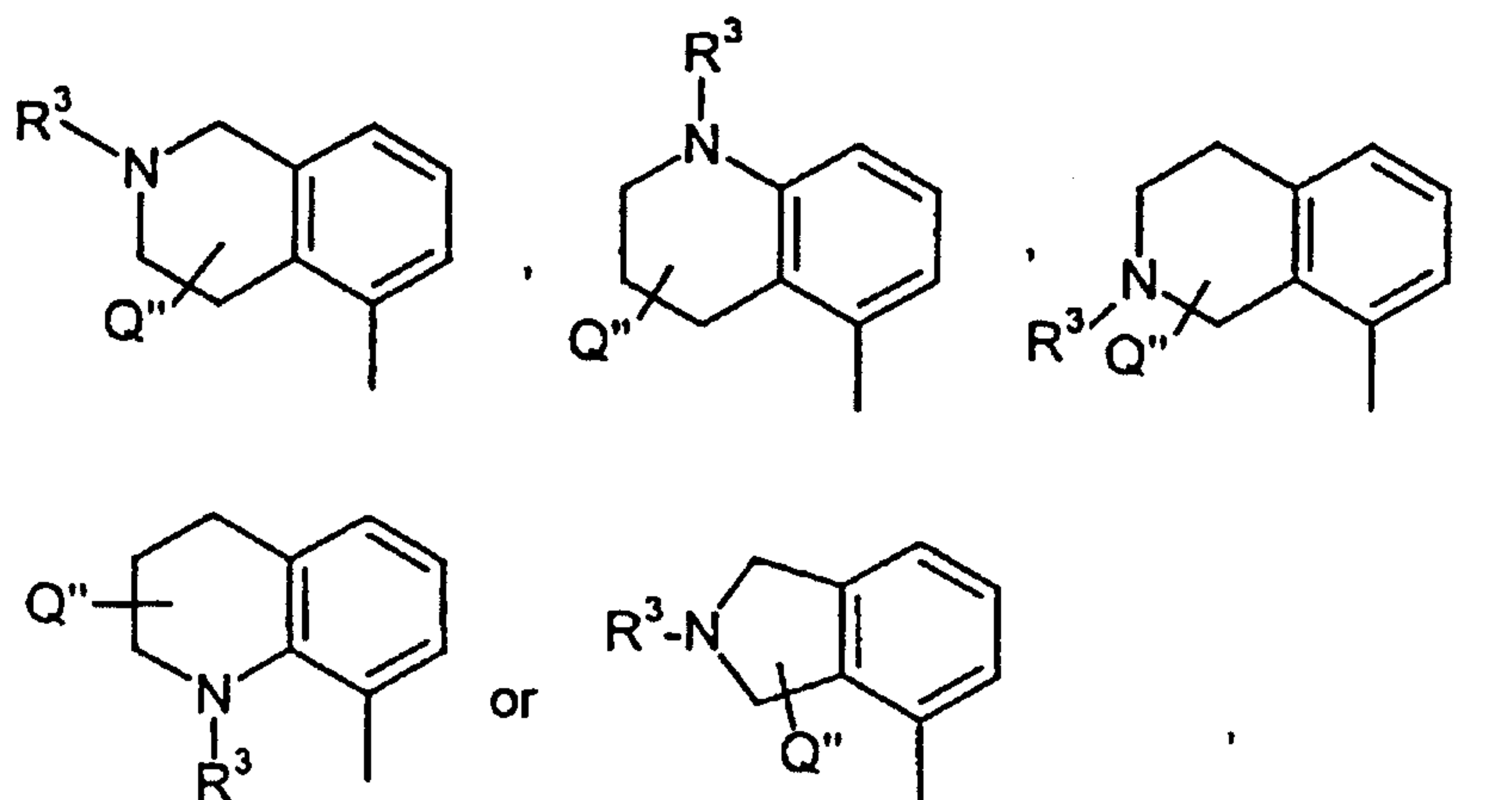
A, D, E, G, L and R² have the meaning given above and

35

R⁵⁰ represents a radical of the formula

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in which

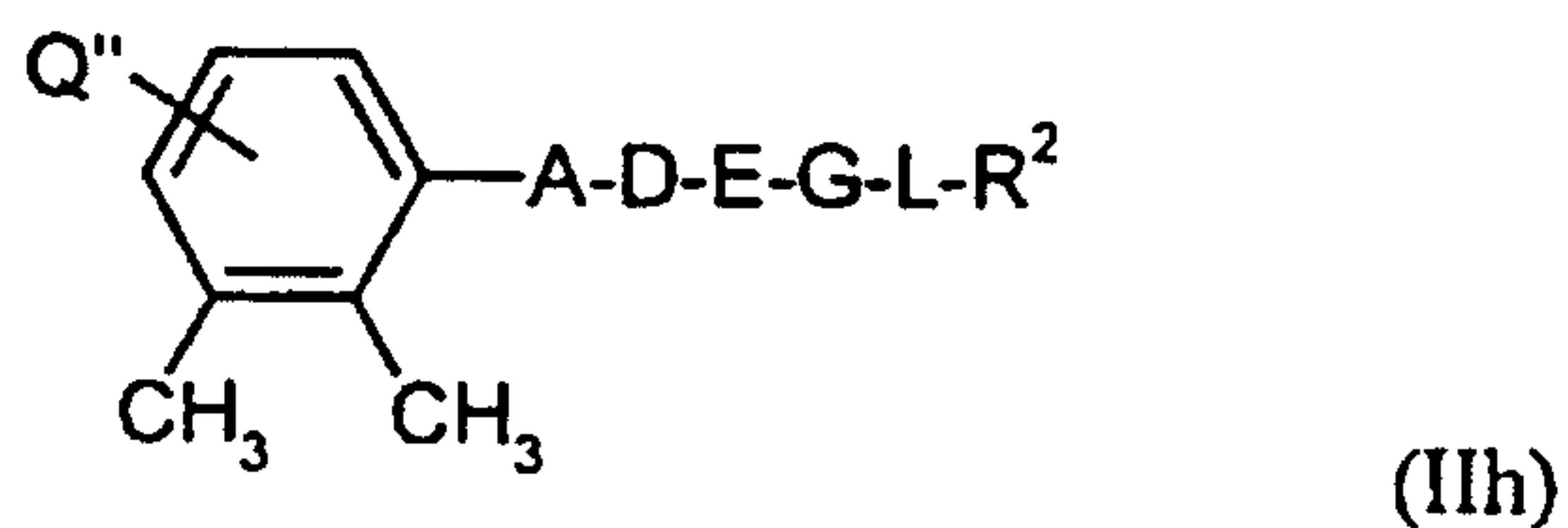
5 Q'' and R^3 have the meaning given above,

followed by final reduction to give compounds of the general formula (II_d),

or

10

[G] converting compounds of the general formula (II_h)

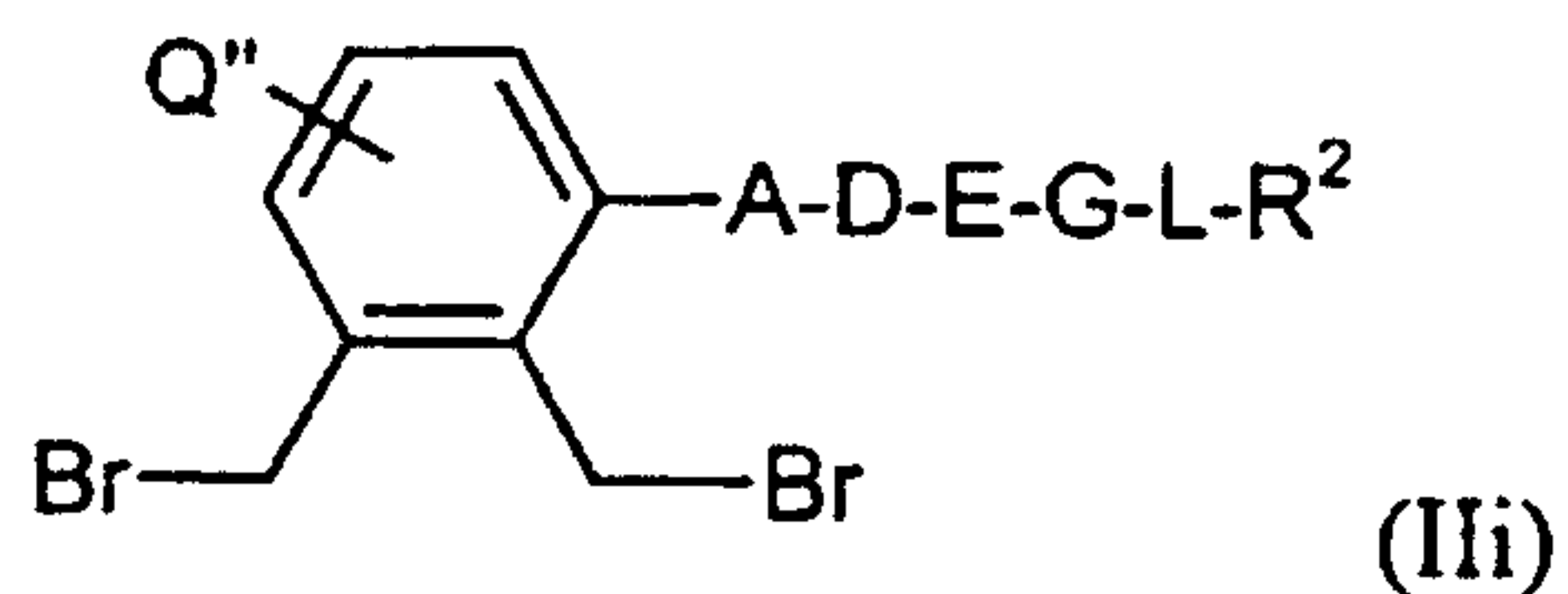


in which

15

Q'' , A, D, E, G, L and R^2 have the meaning given above,

by free-radical bromination, for example using N-bromosuccinimide, in an inert solvent into compounds of the general formula (II_i)



20

in which

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Q'', A, D, E, G, L and R² have the meaning given above,

and subsequently reacting them with compounds of the general formulae (XI) or
5 (XII)



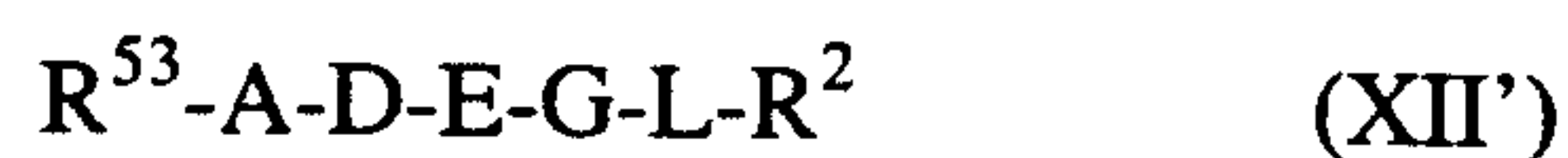
in which

10

R⁵² represents (C₁-C₆)-alkyl and

R³ has the meaning given above,

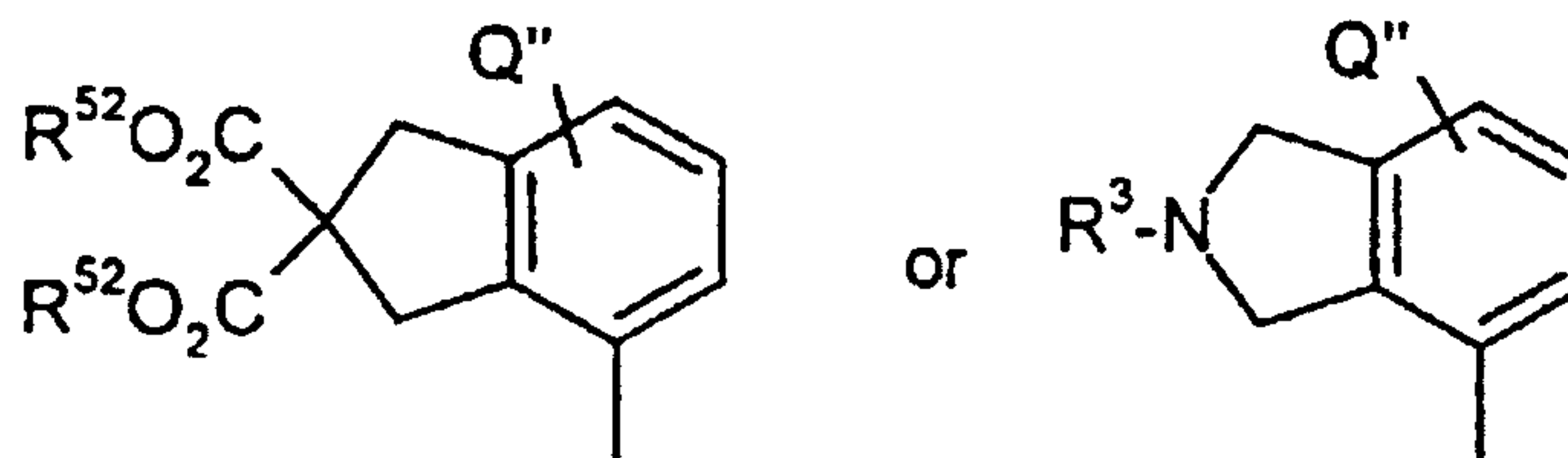
15 in inert solvents, if appropriate in the presence of a base, to give compounds of the general formula (XII')



20 in which

A, D, E, G, L and R² have the meaning given above and

R⁵³ represents



25

in which

Q'', R⁵² and R³ have the meaning given above,

30

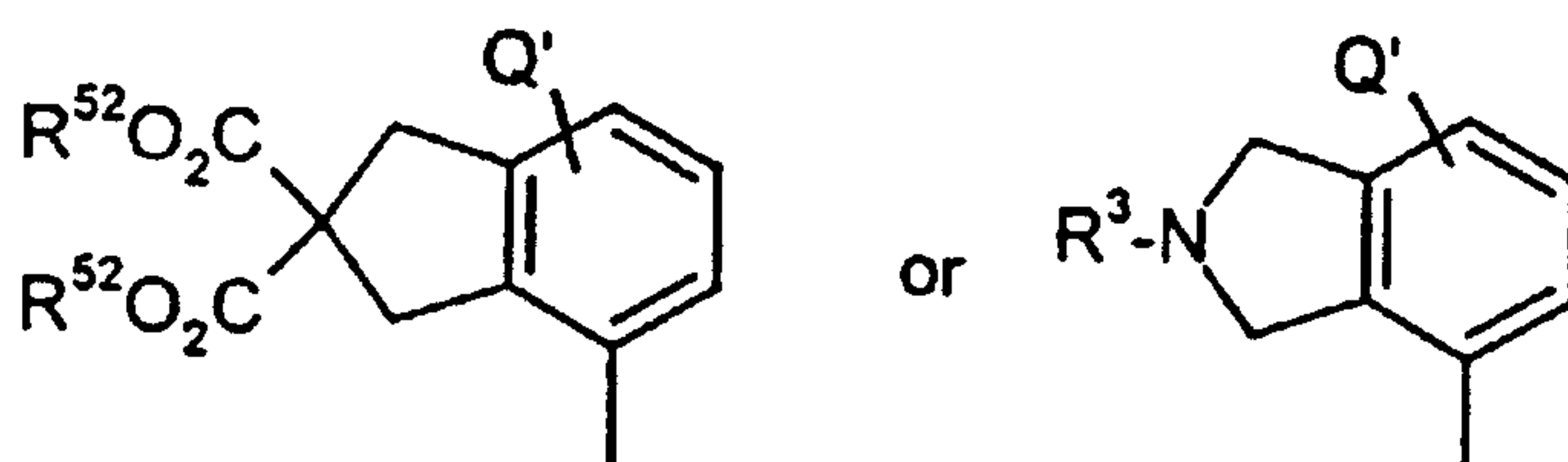
followed by final reduction to give compounds of the general formula (IIj)



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in which

 $R^{53'}$ represents

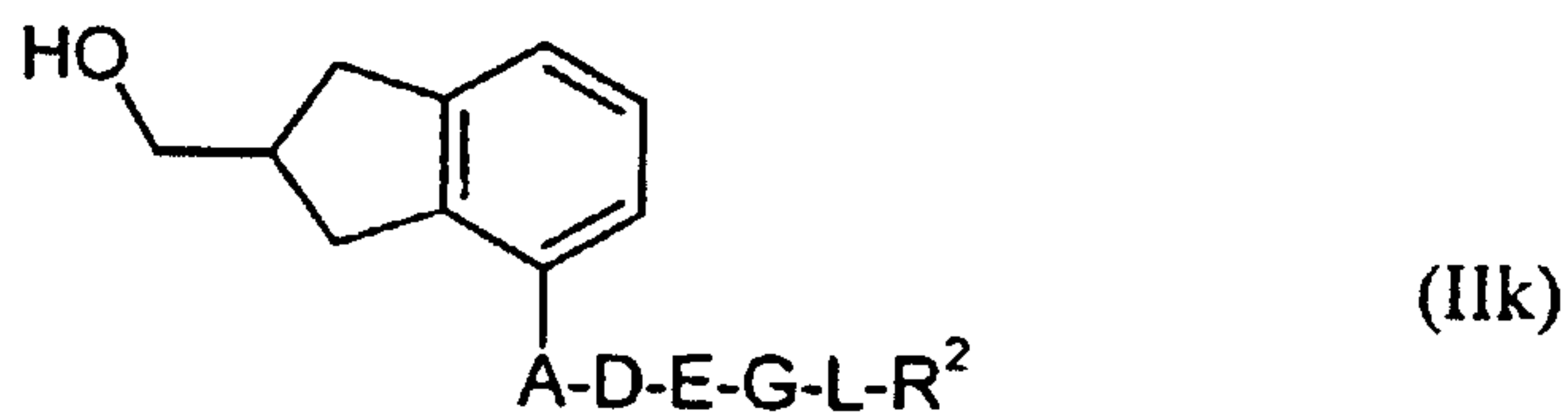
5

in which

 Q' , R^{52} and R^3 have the meaning given above,10 A, D, E, G, L and R^2 have the meaning given above,

or

[H] The compounds of the general formula (IIk)



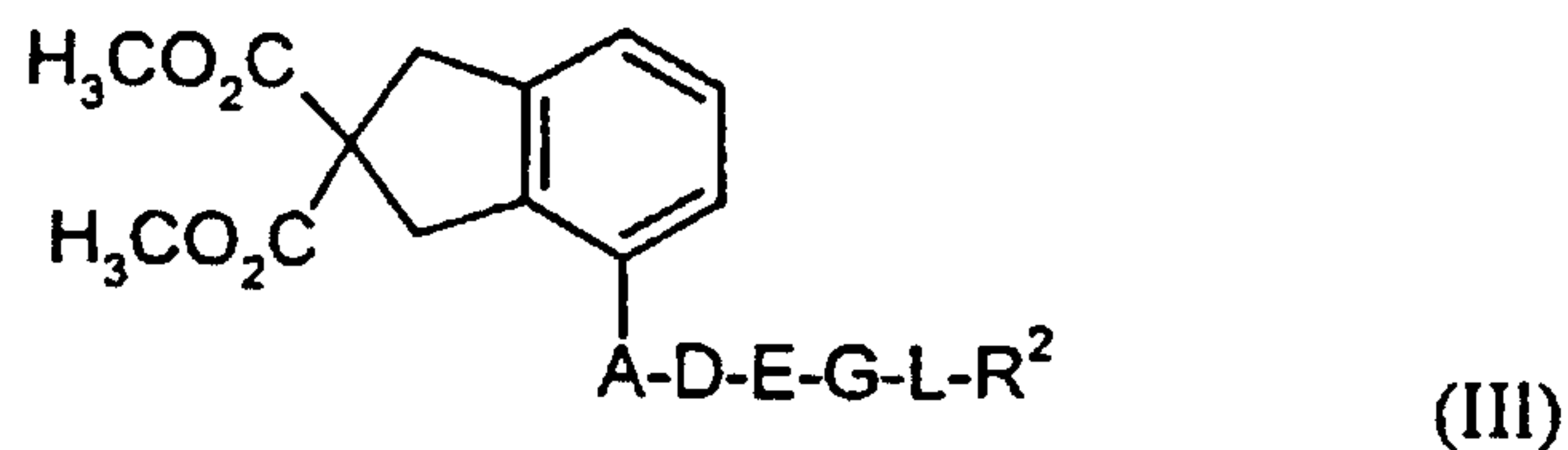
15

in which

A, D, E, G, L and R^2 have the meaning given above,

20

can be prepared by a novel process, characterized in that the compounds of the general formula (III)



in which

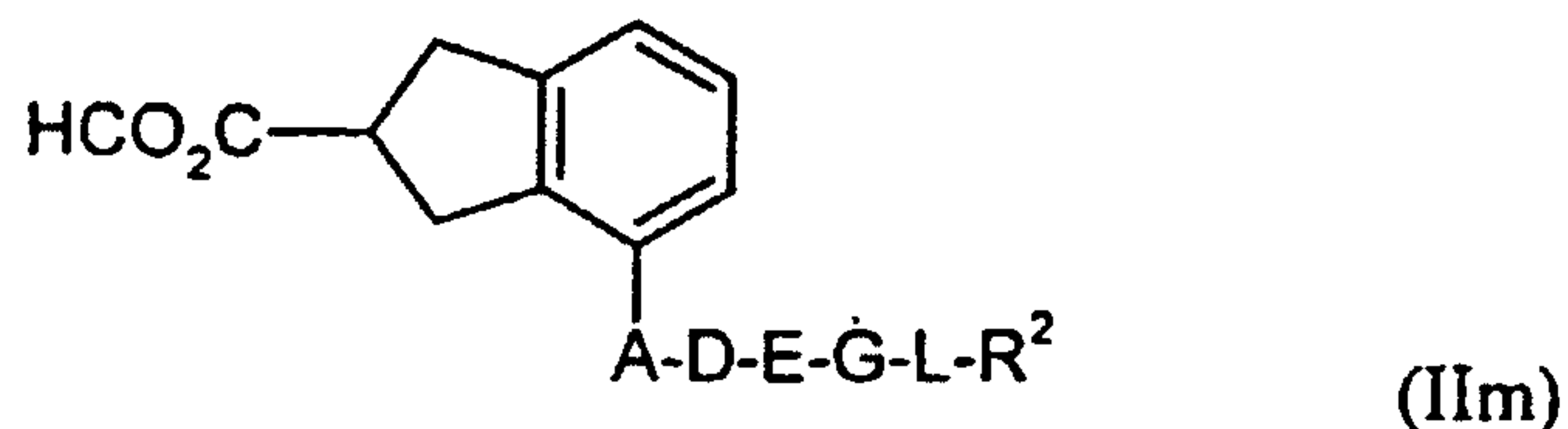
25

A, D, E, G, L and R^2 have the meaning given above

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are converted, by using HBr and acetic acid, into the compounds of the general formula (II_m)



5 in which

A, D, E, G, L and R₂ have the meaning given above,

and, in a last step, a reduction with BH₃ x S(CH₃)₂ in tetrahydrofuran is carried out,

and, in the case of the pure enantiomers, an HPLC separation is carried out by customary methods,

and, if appropriate, the substituents listed above are introduced by customary methods and derivatized,

and, in the case that D = -SO- or -SO₂-, an oxidation is carried out on the corresponding thioethers (D = S) by customary methods,

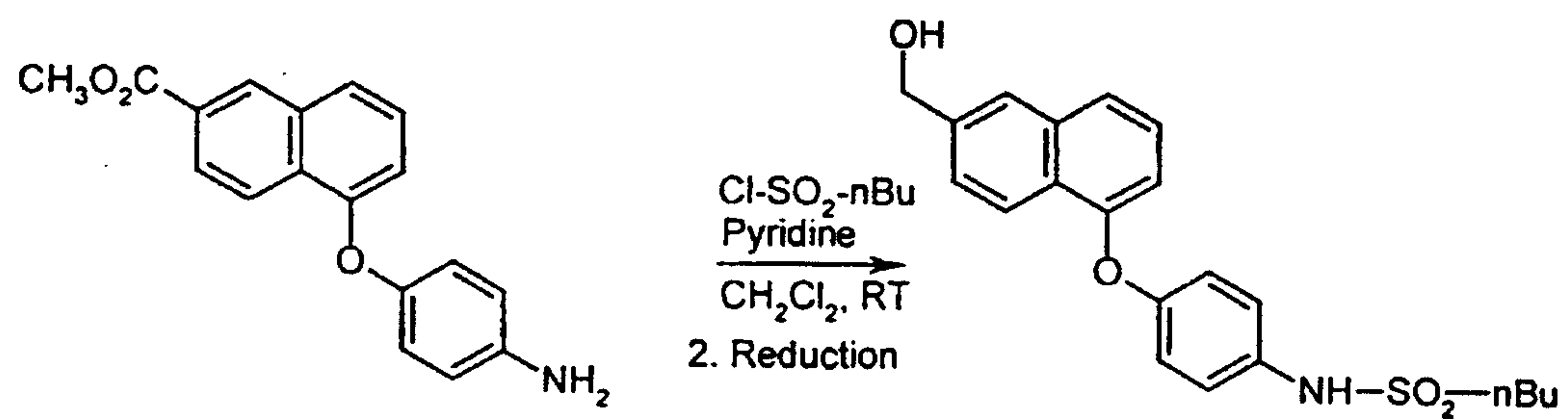
and, in the case of the ammonium compounds, an alkylation is carried out on the corresponding amines.

The processes according to the invention can be illustrated in an exemplary manner by the formula schemes below:

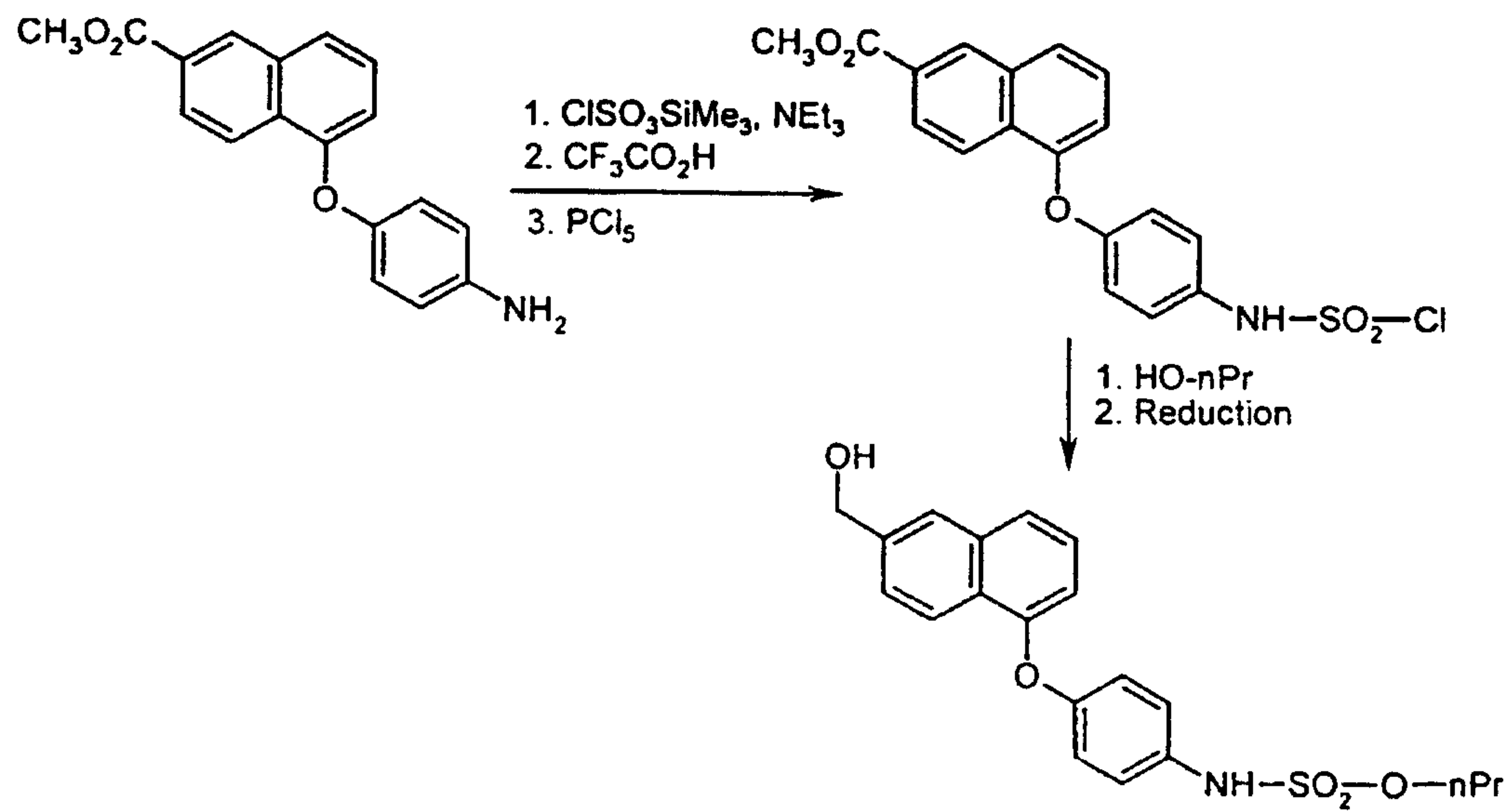
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[A]



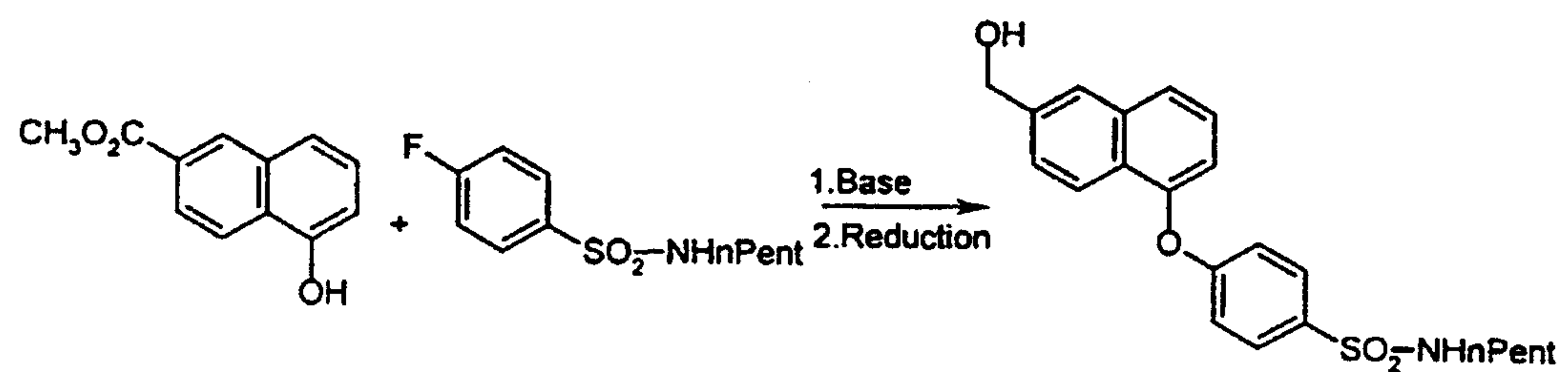
[B]



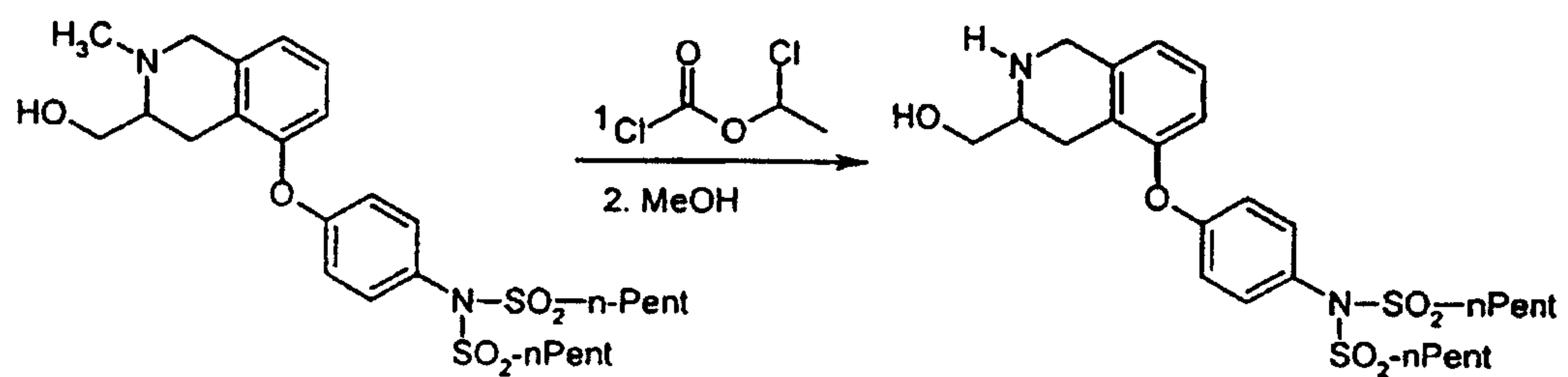
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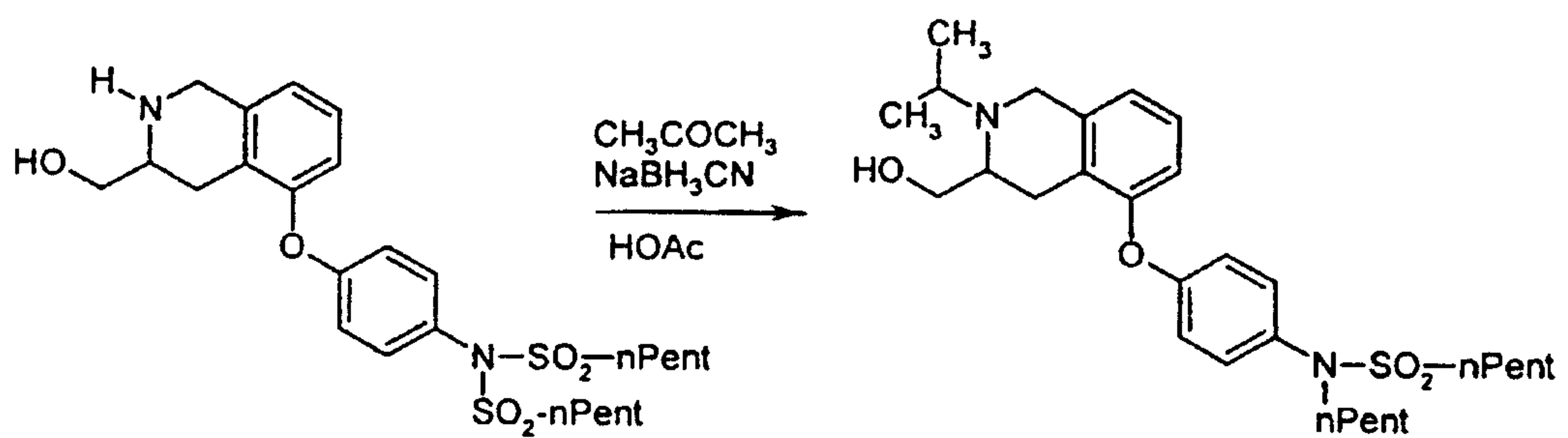
[C]



[D]



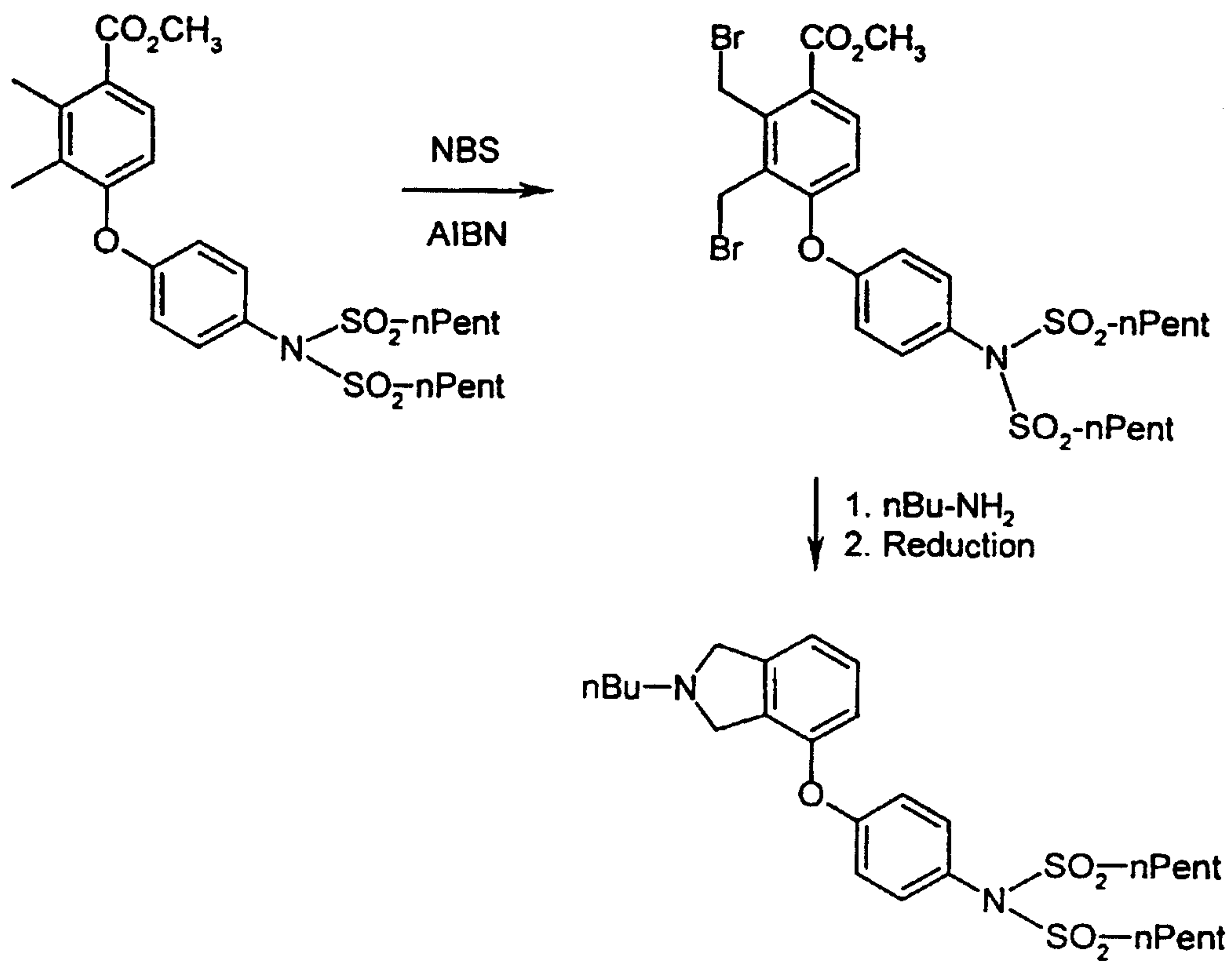
[E]



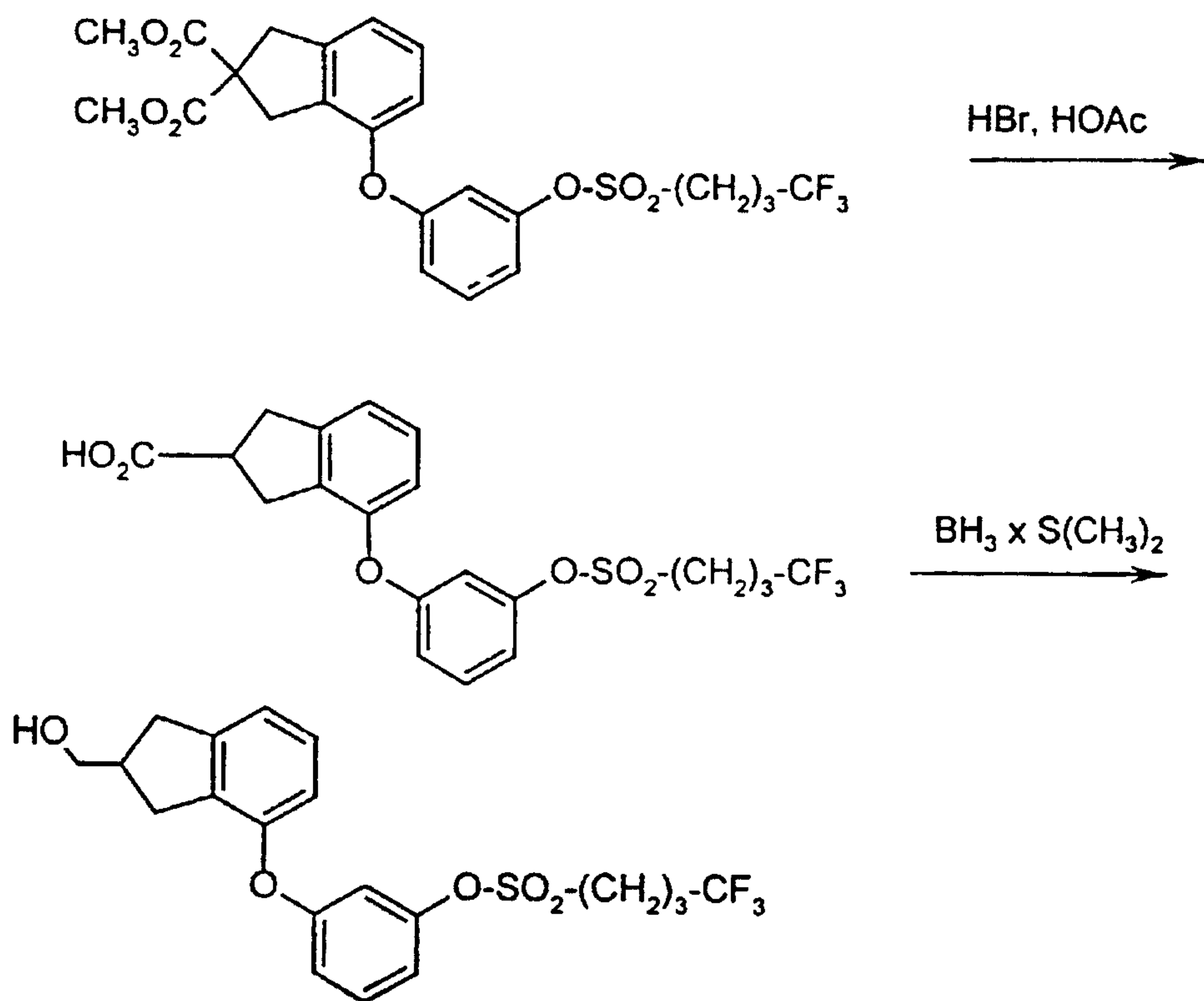
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[G]



[H]



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Suitable solvents are ethers, such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or hydrocarbons, such as benzene, toluene, xylene, hexane, cyclohexane or mineral oil fractions, or halogenated hydrocarbons, such as dichloromethane, trichloromethane, carbon tetrachloride, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, or triethylamine, pyridine, dimethyl sulphoxide, dimethylformamide, hexamethylphosphoric triamide, acetonitrile, acetone or nitromethane. It is also possible to use mixtures of the solvents mentioned. Dichloromethane is preferred.

10 In general, suitable bases are alkali metal hydrides or alkoxides, such as, for example, sodium hydride or potassium tert-butoxide, or cyclic amines, such as, for example, piperidine, pyridine, dimethylaminopyridine, or C₁-C₄-alkylamines, such as, for example, triethylamine. Triethylamine, sodium hydride, pyridine and/or dimethylaminopyridine are preferred.

15 Suitable bases are additionally the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides, such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates, such as sodium carbonate or potassium carbonate, or sodium bicarbonate, or alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide or potassium tert-butoxide. Potassium carbonate and sodium hydroxide are particularly preferred.

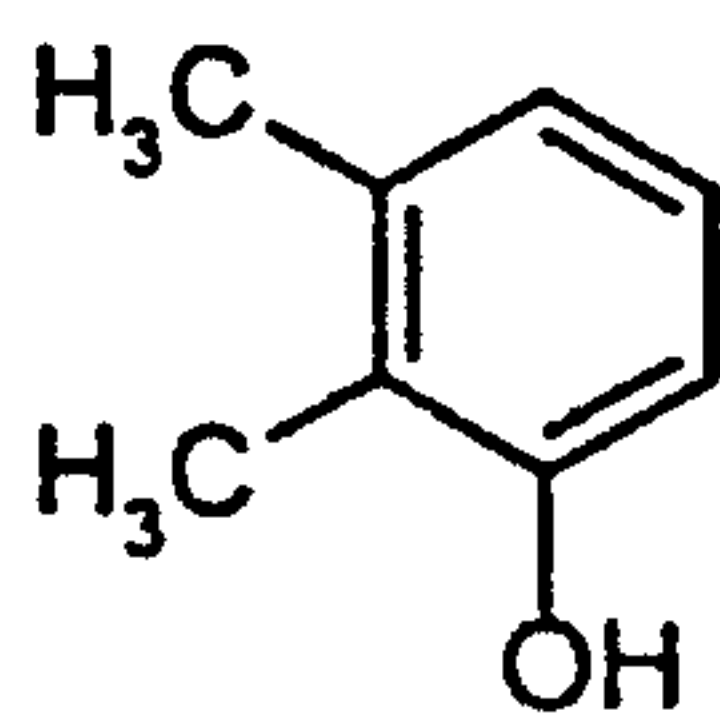
25 In one variant, the reaction is carried out in pyridine to which a catalytic amount of DMAP has been added. If appropriate, it is also possible to add toluene.

The processes are generally carried out at atmospheric pressure. However, it is also possible to carry out the processes under elevated pressure or under reduced pressure (for example in a range of from 0.5 to 5 bar).

30 Some of the compounds of the general formula (IIh) are known, or they are novel and can [lacuna] by reacting the compounds of the general formulae (XIII) and (XIV)

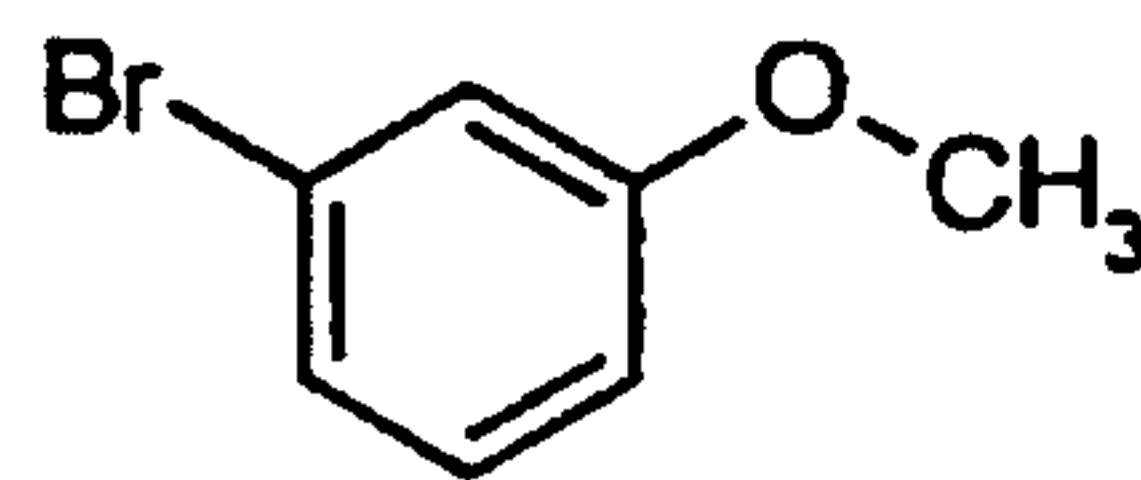
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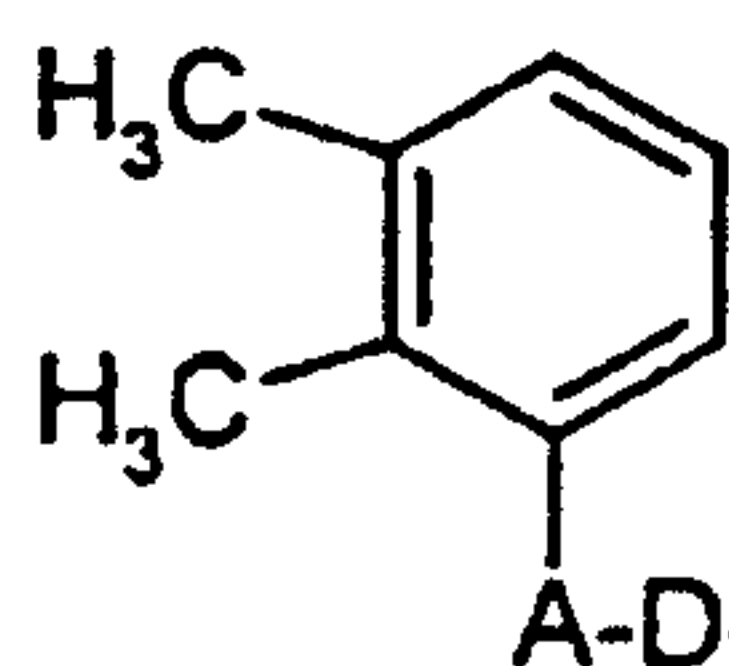
(XIII)

and



(XIV)

in the presence of CuO (cat.), potassium carbonate and pyridine, to give compounds of the general formula (XV)



(XV)

5

in which

A, D, E, G, L and R² have the meaning given above,

10

followed by final liberation of the hydroxyl function using hydrobromic acid and glacial acetic acid.

DOS (German Published Specification) 1 942 264 describes the preparation of fluorinated alkanesulphonyl chlorides, US 5 149 357 describes, inter alia, the preparation of a 4,4,4-trifluorobutanesulphonamide, but without disclosing the preparation of the corresponding sulphonyl chloride.

15

The fluorinated sulphonyl chlorides were prepared analogously to DOS (German Published Specification) 1 942 264.

20

The compounds of the general formulae (V), (VII), (X), (XI), (XII), (XIII) and (XIV) are known per se or can be prepared by customary methods.

The compounds of the general formulae (IIa), (V'), (VI), (VII'), (IIb), (VIII), (IX), (IX'), (IIc), (IId), (IIe), (IIf), (X'), (III), (IIj), (IIk), (III), (IIm) and (XV) can be prepared as described above.

25

The alkylation to prepare the ammonium compounds is generally carried out using alkylating agents, such as, for example, alkyl halides, sulphonic acid esters or

30

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substituted or unsubstituted dialkyl or diaryl sulphonates, preferably using methyl iodide or dimethyl sulphate.

5 The alkylation is generally carried out in one of the abovementioned solvents, preferably in dimethylformamide, in a temperature range of from 0°C to +70°C, preferably from 0°C to +30°C and atmospheric pressure.

10 Preference is given to compounds of the general formula (I) whose solubility in 0.9% strength aqueous sodium chloride solution at 25°C is above 10 mg/l, particularly preferably above 100 mg/l.

Moreover, preference is given to those amino acid esters of the general formula (I) 15 in are hydrolysed *in vivo* to give the corresponding alcohol of the general formula (II).

Surprisingly, the novel amino acid esters of aryl sulphonamides and their analogues show an unforeseeable, useful spectrum of pharmacological action.

20 They are distinguished as highly effective agonists of the CB1 receptor and in some cases of the CB2 receptor. They can be employed alone or in combination with other medicaments for the treatment and/or prevention of neuronal damage of varying cause, such as, for example, due to ischaemic, thrombic and/or thromboembolic, and haemorrhagic stroke, and conditions after direct and indirect injuries in the area of the brain and of the skull; furthermore for the treatment and/or prevention of cerebral 25 ischaemias after all operative interventions in the brain or peripheral organs or body parts and conditions of pathogenic or allergic nature accompanying or preceding them, which can lead primarily and/or secondarily to neuronal damage. Likewise, the compounds according to the invention are also suitable for the therapy of primary and/or secondary pathogenic conditions of the brain, for example during or after 30 cerebral vasospasms, migraine, spasticity hypoxia and/or anoxia of previously unmentioned origin, perinatal asphyxia, autoimmune disorders, metabolic and organ disorders which can be accompanied by damage to the brain and also damage to the brain as a result of primary brain disorders, for example convulsive conditions and athero- and/or arteriosclerotic changes; for the treatment of chronic or psychiatric 35 conditions such as, for example, depression, neurodegenerative disorders such as, for example, Alzheimer's, Parkinson's or Huntington's disease, multiple sclerosis,

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amyotrophic lateral sclerosis, neurodegeneration due to acute and/or chronic viral or bacterial infections and multiinfarct dementia.

5 They can moreover be employed in medicaments for the treatment of states of pain, emesis, nausea, glaucoma, asthma, anorexia, convulsions, rheumatism, sedation and mobility disorders.

10 The substances according to the invention are also suitable for the treatment of disorders which are caused by bacterial and/or viral infections and are based on direct and/or indirect alterations of the immune system or on dysregulations with participation of the immune system, such as, for example, in local or systemic autoimmune diseases (e.g. lupus erythematosus in all its variants), inflammatory and/or autoimmunological diseases of the joints (e.g. primary chronic polyarthritis, trauma-related inflammation), inflammatory and/or autoimmunologically related
15 diseases of the bone and muscle apparatus, inflammatory and/or autoimmunologically related pathogenic processes of the internal organs (e.g. Crohn's disease, glomerulonephritis) and of the external organs (e.g. allergic reactions due to aerogenic intake of antigens) and of the central nervous system (e.g. multiple sclerosis, Alzheimer's disease, psychiatric disorders) as well as of the sense organs,
20 primary and/or secondary and/or autoimmunological disorders of the haematogenic system and of the immune system (e.g. rejection reactions, AIDS) themselves, and also in skin disorders of inflammatory and/or immunological origin in humans and animals. These substances furthermore act on the indirect symptoms of these disorders such as, for example, pain.

25

Their use for the treatment of pain, spasticity, cerebral ischaemias and craniocerebral trauma is preferred.

30 To determine the solubility, a precipitation method was used:

10 mg of the test substance are completely dissolved in 50 µl of DMSO (stock solution). From this solution, 20 µl are added to 2000 µl of physiological saline. This solution in turn is shaken at 25°C in a Thermomixer Comfort (from Eppendorf) at 1400 rpm for 1 hour, for equilibration.

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The precipitated fractions of the test substance are centrifuged off at 14,000 rpm for 5 min, using a Biofuge 15 from Heraeus. 1300 µl of the supernatant are again centrifuged using a Microfuge from Beckmann, at 45,000 rpm = 125,000 g.

- 5 10 µl of this centrifugation supernatant are then diluted with 1000 µl of DMSO, and this solution is measured by HPLC. (Hewlett Packard 1090, method: gradient of 100% PBS buffer pH=4 over 15 min to 10% buffer/90% acetonitrile, column: RP18)

- 10 The measured peak area of the HPLC determination is converted into the substance concentration using a calibration curve. For the calibration curve, 20 µl of the stock solution are successively diluted with DMSO in such a manner that 5 concentrations of from 2.5 mg/l to 2000 mg/l are obtained. These solutions are likewise measured by HPLC (method see above) and the peak areas are plotted against the concentrations.

15

Using this method for the determination of the solubility, Example 5 had a solubility of 720 mg/l.

CB1 - Luciferase reporter gene test

20

1. **Cloning of the rat cannabinoid receptor CB1**

- 25 Total RNA from rat brain (the tissue was taken from freshly killed animals and shock-frozen in liquid nitrogen) was isolated by acidic guanidinium thiocyanate/phenol/chloroform extraction (J. Biol. Chem. 1979, 18, 5294) and converted into cDNA by means of reverse transcriptase and random primers (in each case from Invitrogen). The polymerase chain reaction (PCR, conditions: 4 min 94°C, 1H; 1 min 94°C; 2 min 53°C; 1 min 72°C, 50 cycles; 1 min 94°C, 2 min 53°C, 4 min 72°C, 1H) was carried out in a Perkin Elmer thermocycler using the enzyme
- 30 Taq polymerase (Perkin Elmer); the oligonucleotide primers employed (bases 99 to 122: 5'63', "down"; 1556-1575: 3'75', "up") were derived from the published sequence of the rat cannabinoid receptor (Nature 1990, 346, 561) and were synthesized on a DNA synthesizer, model 1380 from Applied Biosystems. One part of the PCR reaction was separated in a 1% strength agarose gel in 1H TBE buffer and
- 35 then stained with ethidium bromide, only one band having the expected length being visible (approximately 1.5 kb). This PCR product was subcloned into the TA cloning

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vector (Invitrogen) and the nucleotide sequence of the insert was determined by the dideoxynucleotide chain termination reaction using T7DNA polymerase (Sequenase, USA/Amersham). The insert has a length of 1477 base pairs and contains an open reading frame of 1419 base pairs which corresponds to a protein of 473 amino acids.

5 The number of base pairs, the position of the open reading frame and the number of amino acids agree with the published sequence. Computer analyses were carried out with the aid of the GCG software suite (Genetic Computer Group). The cDNA insert was subcloned into the expression vector pRc/CMV (Invitrogen) after partial digestion with HindIII and NotI (Biolabs). This construct (plasmid CMV-RH) was

10 employed for transfection experiments.

2. Stable transfection of the CHO_{luc9} reporter cells

CHO_{luc9} cells were cultured in 50% Dulbecco's modified Eagle medium/50% F-12

15 (DMEM/F12) which contained 10% foetal calf serum (FCS). Transfections were prepared in 6-well plates. 7.5 µg of Qiagen-purified CMV-RH plasmid DNA were added per 10⁵ cells with the DOTAP transfection system, corresponding to the experimental protocol of the manufacturer (Boehringer Mannheim). Transfected cells were selected using 1 mg/ml G418 and individual clones were obtained by limiting

20 dilution in 96-well plates. Cell lines which express the cannabinoid receptor were identified for the inhibition of reporter gene expression after incubation with the cannabinoid receptor agonist, WIN-55,212-2, in the presence of forskolin. Several stably transfected and subcloned cell lines were further characterized by means of RT-PCR, as described under 1.

25

3. Test optimization and pharmacological characterization of the CHO_{CB1} reporter cell line

With the aim of high sensitivity and reproducibility, low variance and high suitability

30 for carrying out on the robotic system, the luciferase test was optimized by variation of several test parameters, such as, for example, cell density, duration of the growth phase and the test incubation, forskolin concentration, medium composition. The following test protocol was used for pharmacological characterization of the cells and for robot-assisted substance screening: the stock cultures were cultured in 50%

35 Dulbecco's modified Eagle medium/50% F-12 (DMEM/F12) with 10% FCS at 37°C under 10% CO₂ and in each case split 1:10 after 2 to 3 days. Test cultures were

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inoculated into 96-well plates at 5000 cells per well and cultured at 37°C for 70 hours. The cultures were then carefully washed with phosphate-buffered saline and reconstituted using serum-free ultra-CHO medium (Bio-Whittaker). The substances dissolved in DMSO were diluted 1H in medium and pipetted into the test cultures (maximum DMSO final concentration in the test batch: 0.5%). 20 minutes later, forskolin was added and the cultures were then incubated at 37°C in an incubator for 3 hours. The supernatants were then removed and the cells were lysed by addition of 25 µl of lysis reagent (25 mM triphosphate, pH 7.8 with 2 mM DTT, 10% glycerol, 3% TritonX100). Directly after this, luciferase substrate solution (2.5 mM ATP, 0.5 mM luciferin, 0.1 mM coenzyme A, 10 mM tricine, 1.35 mM MgSO₄, 15 mM DTT, pH 7.8) was added, the mixture was briefly shaken and the luciferase activity was measured using a Hamamatzu camera system.

For inactivation of G_i proteins, the test cultures were treated with 5 ng/ml (final conc.) of Pertussis toxin for 16 hours before the test.

The IC₅₀ values were calculated using the GraphPadPrism program (Hill equation, specific: one-site competition).

Activity in the rat CB1 receptor luciferase receptor gene test

Example	IC ₅₀ (nmol/l)
1	0.35
2	0.13
5	0.11
6	0.85
7	0.4
8	0.2

hCB2 - Luciferase reporter gene test

CHOluc9 cells were stably transfected using the human CB2 receptor. Transfection, clone selection and test development were carried out analogously to the studies using the rat CB1 receptor. The following test protocol was used for the pharmacological characterization of the cells and for substance testing:

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- The stock cultures were cultured in 50% Dulbecco's modified Eagle medium/50% F-12 (DMEM/F12) with 10% FCS at 37°C under 10% CO₂ and in each case split 1:10 after 2 to 3 days. Test cultures were inoculated into 96-well plates at 5000 cells per well in DMEM/F12 medium with 5% FCS and cultured at 37°C for 70 hours.
- 5 The medium was then removed from the cultures and replaced by serum-free ultra-CHO medium (Bio-Whittaker). The substances dissolved in DMSO (200H final concentration) were pipetted into the test cultures (maximum DMSO final conc. in the test mixture: 0.5%) and 20 min later forskolin was added. The cultures were then incubated at 37°C in an incubator for 3.5 hours. The supernatants were then removed
- 10 and the cells were lysed by addition of 25 µl of lysis reagent (25 mM triphosphate, pH 7.8 with 2 mM DTT, 10% glycerol, 3% Triton X100). Directly afterwards, 50 µl of luciferase substrate solution, double-concentrated, (5 mM ATP, 1 mM luciferin, 0.2 mM coenzyme A, 10 mM tricine, 1.35 mM MgSO₄, 15 mM DTT, pH 7.8) were added, the mixture was briefly shaken, and the luciferase activity was determined
- 15 using a photomultiplier camera measuring system (Hamamatsu).

The IC₅₀ values were calculated using the GraphPad PrismTM program (Hill equation; specific: one-site competition).

20 **Binding studies on rat cortex membranes**

- Membrane protein is prepared from different tissues or from cells by standard methods. Buffers, labelled ligand, DMSO or test substance are pipetted together, then 100 µg of protein are added, and the mixture is mixed well and incubated in a
- 25 waterbath at 30°C for 60 min. After expiry of the incubation time, the reaction is stopped by addition of ice-cold incubation buffer to each tube. After filtering off, washing is carried out with 3/4 ml of incubation buffer. The filters are transferred to minivials and the radioactivity is determined in a scintillation counter.

30 **Inhibition of glutamate release**

- After decapitation of a rat, the skull is opened, and the brain is lifted out and cut along the median fissure. The hippocampus is exposed, separated from the remaining tissue, cut into 350 µm thick sections and incubated at 37°C in straining vessels for
- 35 60 min. Followed by basal value and stimulation 1 with 75 mM KCl (S1), the sections are incubated with test substance and then stimulation is repeated with KCl

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and test substance (S2). Glutamate concentration of the samples to be investigated is then measured by means of an enzymatic reaction (GLDH) and fluorometric measurement of NADH. By means of a calibration curve, the glutamate content of the sample is determined, and with knowledge of the protein content the glutamate content/mg of protein can be calculated. The ratio S2/S1 is compared; glutamate release inhibitors reduce this ratio in a concentration-dependent manner.

Using the test method below, it is possible to determine the *in vitro* conversion of the amino acid esters according to the invention into the corresponding alcohols.

10

Determination of the stability of substances in the blood of various species (rat, dog, human)

The principle of the method

15 The test substance is incubated in heparinized blood of each test species. At suitable intervals, aliquots of the mixture are taken and pipetted into an initial charge of acetonitrile. After centrifugation, the supernatant is evaporated and the residue is taken up in a solvent suitable for analysis.

20 **Material**

Laboratory centrifuge:	Sigma 4K10 (Sigma Laborzentrifugen, Osterode, Germany)
Shaker:	KS500 (Janke und Kunkel, IKA Labortechnik, Staufen, Germany)
Waterbath, Thermomix®	1442D (Braun-Melsungen, Melsungen, Germany)
Evaporation apparatus	BAYER AG

30

Procedure

To determine the stability of a test substance *in vitro*, the substance, which is dissolved in a small volume of a suitable solvent, is incubated in a concentration of, for example, 2 µg/ml in 5 ml of blood at 37°C for 5 hours. At suitable intervals, 100 µl of the mixture are pipetted into 500 µl of the initial charge of acetonitrile and mixed. Following centrifugation at 3000 rpm, the supernatant is removed and

35

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evaporated to dryness in a waterbath at 40°C. The residue is taken up in a solvent suitable for analysis.

	Solvent:	10 µl of EtOH/5 ml of blood
5	Shaker speed:	250 rpm
	Centrifugation	3000 rpm
	Centrifugation time:	10 min
	Blood volume:	5 ml
	Blood aliquots:	100 µl
10	Incubation times:	0, 2, 5, 10, 15, 30, 45 minutes, 1, 2, 3, 5 hours

Using the test methods below, it is possible to determine the *in vivo* conversion of the amino acid esters according to the invention into the corresponding alcohols.

15 Pharmacokinetics of the substances in the rat**1. Intravenous infusion**

The substance is, via a lateral tail vein, infused directly into the blood stream via a venous catheter (Introcan[®], 22G1, Braun, Melsungen, Germany). A calibrated
20 10 ml syringe is used for accurate administration of the selected dose and the volume. For the infusion, pump No. 540210 from TSE, Bad Homburg, FRG, is used.

2. Drawing of samples and work-up25 **Blood and plasma**

Blood samples of animals fitted with a catheter (Vena jugularis) are collected in heparinized tubes. The blood is centrifuged and the plasma is prepared in a suitable manner for analysis. Until analysis, the plasma is stored at < -15°C.

30 Pharmacokinetics of the substances in the dog**1. Intravenous infusion**

Following cannulation of a surface vein of the foreleg or hindleg, the substance is infused directly into the blood stream. The venous catheter (for example Introcan[®]
35 20 G/1¼, B. Braun, Melsungen, Germany) is linked with a calibrated syringe, which is attached to the infusion pump.

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2. Taking of samples and work-up**Blood and plasma**

5 Blood samples are taken by puncture of a surface vein of the foreleg or hindleg or a jugular vein. The extremity used for the infusion is not used for taking blood samples. The blood is centrifuged and the plasma is stored at $< -15^{\circ}\text{C}$ until analysis.

Hypothermia

10

1. Agonism testing:

15 Five minutes after determination of the basal body temperature via an oesophageal temperature probe, the test substance is administered (i.v.). A control group receives only the solvent of the test substances, likewise i.v. The body temperature is measured 7.5, 15, 30 and 60 minutes after i.v. administration. The group size per dose is 5-7 animals (rats).

2. Antagonism testing:

20 The specific CB1 antagonist *SR 141716A*, or, to the control group, only the solvent (Solutol/0.9% NaCl), is administered intraperitoneally 60 minutes before administration of test substance. The basal body temperature is measured five minutes before administration of *SR 141716A* via oesophageal temperature probe. The further procedure corresponds to the "agonism testing" method. The group size per dose is 5-7 animals (rats).

25

Rat hypothermia - agonism testing

Example	ED. _{1°C} ^{a)} [mg/kg]
5	0.03

a) Effective dose for 1°C body temperature reduction

30 b) Hypothermia is significantly reduced by administration of the specific CB1 antagonist *SR 141716 A* (see "Antagonism testing" method)

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Permanent focal cerebral ischaemia in the rat (MCA-O)

Under isoflurane anaesthesia, the median cerebral artery is exposed on one side and the latter and its side branches are irreversibly sealed by means of electrocoagulation.

5 As a result of the intervention a cerebral infarct is formed. During the operation, the body temperature of the animal is kept at 37°C. After wound closure and wearing off of the anaesthesia, the animals are again released into their cage. The administration of substance is carried out according to different time schemes and via different administration routes (i.v., i.p.) after occlusion. The infarct size is determined after 7

10 days. To do this, the brain is removed, worked up histologically and the infarct volume is determined with the aid of a computer-assisted analysis system.

Subdural haematoma in the rat (SDH)

15 Under anaesthesia, the animals are injected with their own blood subdurally on one side. An infarct is formed under the haematoma. Substance administration is carried out according to different time schemes and via different administration routes (i.v., i.p.). The determination of the infarct size is carried out as described in the model of permanent focal ischaemia in the rat (MCA-O).

20

The novel active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert non-toxic, pharmaceutically suitable excipients or solvents. In this case the therapeutically active compound

25 should in each case be present in a concentration from approximately 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

30 The formulations are prepared, for example, by extending the active compounds using solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, it optionally being possible, for example, to use organic solvents as auxiliary solvents if water is used as a diluent.

Administration is carried out in a customary manner, preferably orally, transdermally

35 or parenterally, in particular perlingually or intravenously.

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In general, it has proved advantageous in the case of intravenous administration to administer amounts from approximately 0.01 to 10 mg/kg, preferably approximately 0.1 to 10 mg/kg, of body weight to achieve effective results.

- 5 In spite of this, if appropriate it may be necessary to depart from the amounts mentioned, namely depending on the body weight or on the type of administration route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus in
10 some cases it may be adequate to manage with less than the abovementioned minimum amounts, while in other cases the upper limit mentioned has to be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into several individual doses over the course of the day.

Starting materials

15

Example 1A

4,4,4-Trifluorobutyl thiocyanate



- 20 At 0°C, a stirred solution of 4,4,4-trifluorobutanol (35 g; 0.027 mol) and triethylamine (28.3 g; 0.280 mol) in 200 ml of dichloromethane was admixed dropwise with a solution of methanesulphonyl chloride (32.1 g; 0.280 mol) in 100 ml of dichloromethane. After the addition had ended, the mixture was stirred for a further 30 min and then poured on ice, and the phases were then separated.
25 The organic phase was dried over magnesium sulphate and concentrated under reduced pressure. This gave 55 g of crude 4,4,4-trifluorobutyl-methanesulphonate as an orange oil.

- 30 The mesylate (55 g) and sodium thiocyanate (30.6 g; 0.30 mol) were boiled under reflux in acetone (300 ml) for 6 h. After cooling to room temperature, the mixture was poured on ice, the phases were separated and the organic phase was dried over magnesium sulphate. Filtration and concentration under reduced pressure gave 41 g (89% of theory) of 4,4,4-trifluorobutyl thiocyanate as an oil.

¹⁹F-NMR (376 MHz, CDCl₃; CFCl₃ δ [ppm]: -66.3

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¹H-NMR (400 MHz, CDCl₃, TMS) δ [ppm]: 2.15 (m, 2H); 2.3 (m, 2H); 3.05 (t, J = 7.1 Hz, 2H)

Example 2A

5

4,4,4-Trifluorobutanesulphonyl chloride



10 At from 20 to 40°C, chlorine was introduced into a solution of Example 1 A (40 g; 0.236 mol) in aqueous acetic acid (150 ml of acetic acid and 70 ml of water), and the progress of the reaction was monitored by gas chromatography. After completion of the chlorination, excess chlorine was flushed out by passing through a stream of nitrogen, 200 ml of water were added and the reaction mixture was
15 extracted repeatedly with dichloromethane. The combined organic phases were dried over magnesium sulphate, the magnesium sulphate was filtered off and the filtrate was concentrated under reduced pressure. This gave 44 g (89% of theory) of 4,4,4-trifluorobutanesulphonyl chloride as a yellow oil.

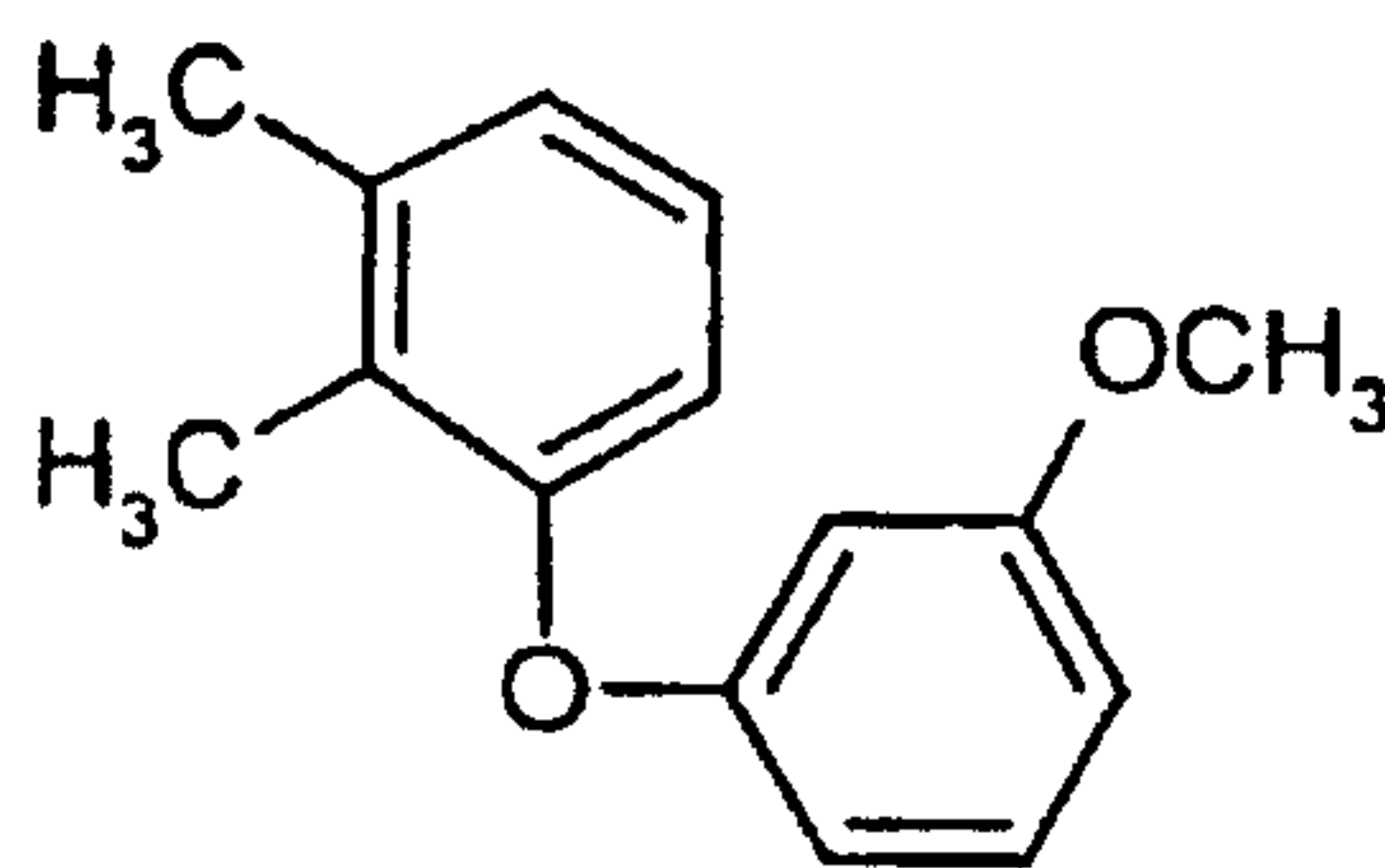
¹⁹F-NMR (376 MHz, CDCl₃; CFCl₃) δ [ppm]: -66.65 (t, J = 10 Hz)

20 ¹H-NMR (400 MHz, CDCl₃, TMS) δ [ppm]: 3.8 (m, 2H); 2.35 (m, 4H)

Example 3A

3-(2,3-Dimethylphenoxy)-anisole

25



A solution of 2,3-dimethylphenol (341.0 g; 2.79 mol) and 3-bromoanisole (548.2 g; 2.93 mol) in pyridine (3000 ml) is admixed with K₂CO₃ (771.5 g; 5.58 mol) and
30 copper-(II) oxide (44.4 g; 0.56 mol) and stirred under reflux under argon for 36 h. Copper-(II) oxide (20 g; 0.25 mol) is added, and the solution is then stirred under reflux for a further 24 h. After cooling, the mixture is filtered, the residue is

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washed with dichloromethane and the filtrate is concentrated under reduced pressure. The residue is taken up in diethyl ether (3000 ml) and washed with water (300 ml). Precipitated solid is filtered off with suction and, after phase separation, the organic phase is washed with 2 N HCl (3 x 300 ml), water (300 ml), 10% aqueous sodium hydroxide solution (3 x 300 ml) and water (300 ml). The ether phase is dried (MgSO₄) and concentrated under reduced pressure. The residue is distilled under reduced pressure.

Yield: 441.5 g (68% of theory)

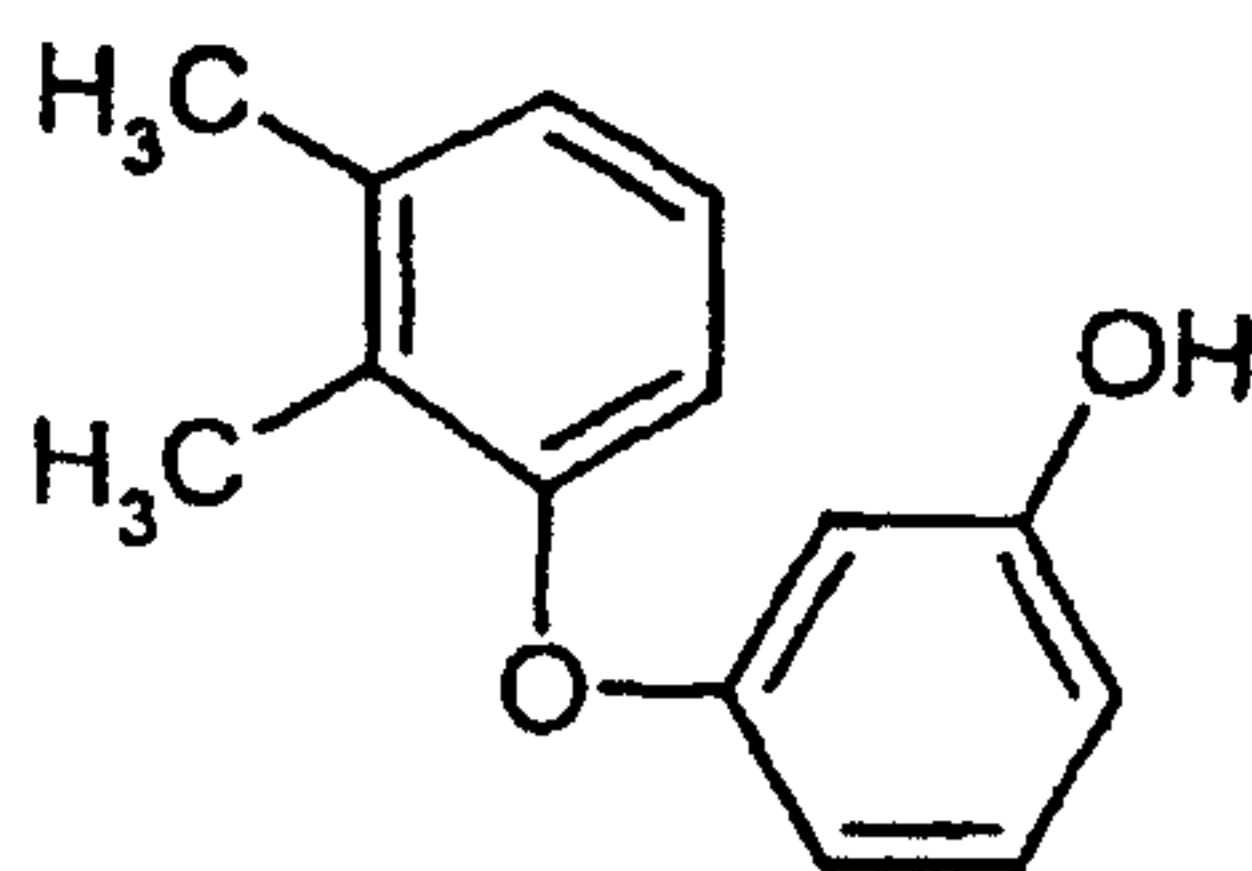
B.p.: 112°C/0.1 mbar

10 MS (DCI, NH₃): m/z = 246 (M + NH₄)

Example 4A

3-(2,3-Dimethylphenoxy)-phenol

15



Example 3A (109.6 g; 480 mmol) is initially charged in 48% aqueous hydrogen bromide (900 ml) and acetic acid (1500 ml), and the mixture is stirred under reflux overnight. The mixture is then concentrated under reduced pressure and the residue is taken up in water and extracted three times with ethyl acetate. The combined organic phases are washed twice with water, dried (MgSO₄) and concentrated under reduced pressure. The residue is chromatographed over silica gel using toluene:EA (10:1).

20 Yield: 86.5 g (83% of theory)

R_f = 0.15 (toluene)

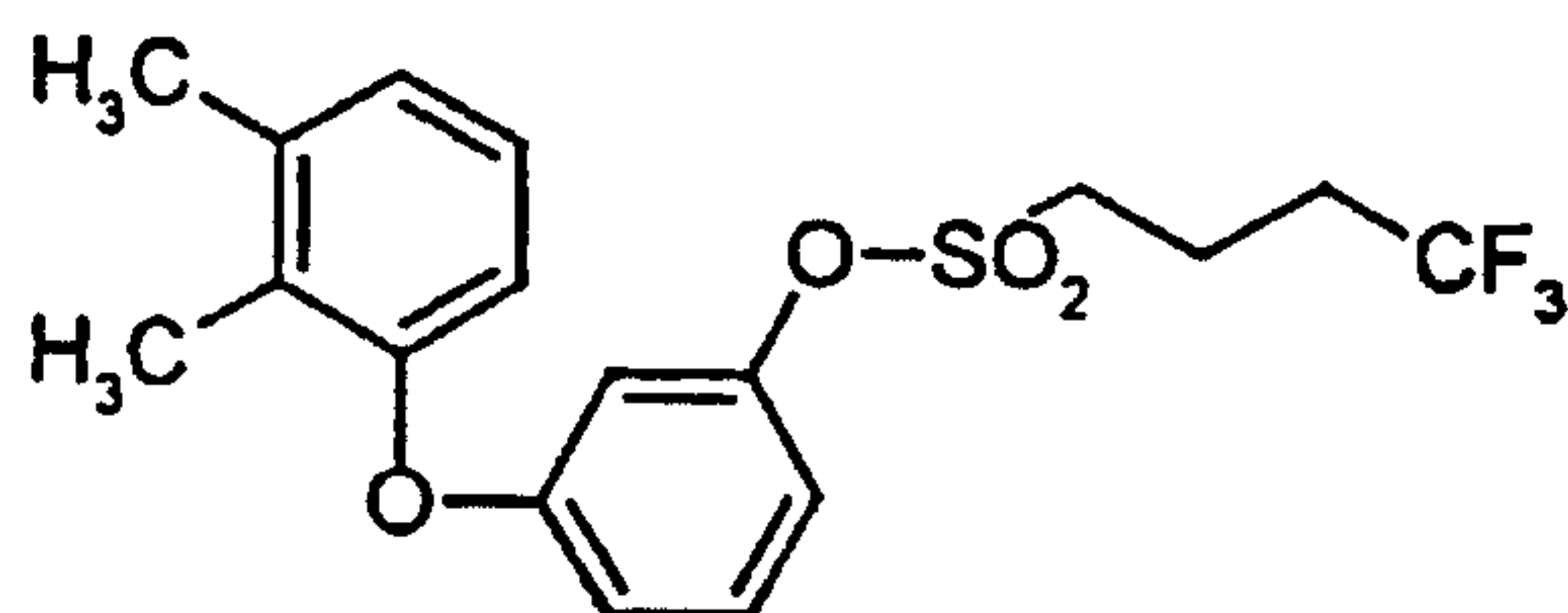
MS (ESI): m/z = 215 (M+H)

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Example 5A

3-(2,3-Dimethyl-phenyloxy)-phenyl 4,4,4-trifluoro-1-butanesulphonate



5

The preparation is carried out analogously to the preparation of Example 1 starting from Example 4A (4.54 g; 21.2 mmol).

Yield: 7.80 g (95% of theory)

10 $R_f = 0.51$ (toluene)

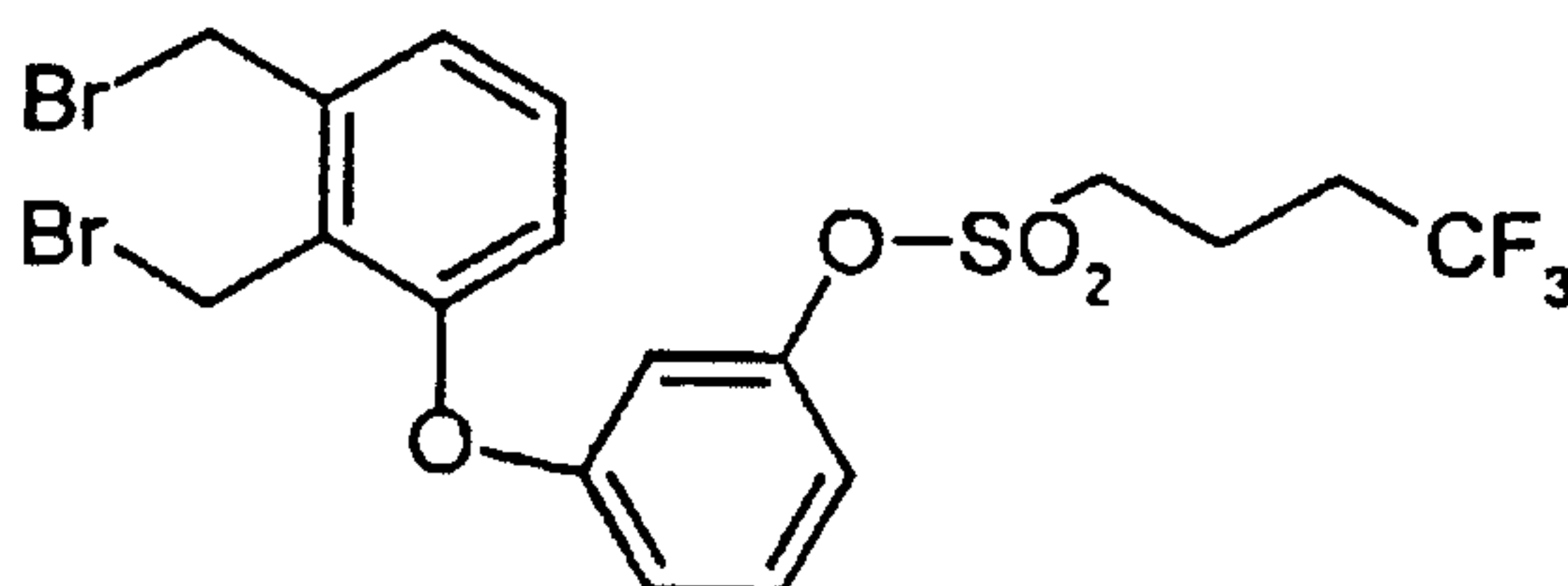
MS (DCI/ NH_3): $m/z = 406$ ($\text{M} + \text{NH}_4$)

Example 6A

15 3-(2,3-bis-Bromomethylphenyloxy)-phenyl

4,4,4-trifluoromethyl-1-

butanesulphonate



- 20 A solution of Example 5A (6.76 g; 17.4 mmol) in carbon tetrachloride (150 ml) is admixed with N-bromosuccinimide (6.50 g; 36.5 mmol), heated at reflux and, with stirring, irradiated with a 300 W lamp for 5 h. After cooling, precipitated succinimide is filtered off with suction and the filtrate is concentrated under reduced pressure. The residue is chromatographed over silica gel using toluene.
- 25 This gives a mixture (about 5:1) of Example 6A and 3-(2-bromomethyl-3-dibromomethylphenyloxy)phenyl 4,4,4-trifluoro-1-butanesulphonate (9.9 g) which was used further without further purification.

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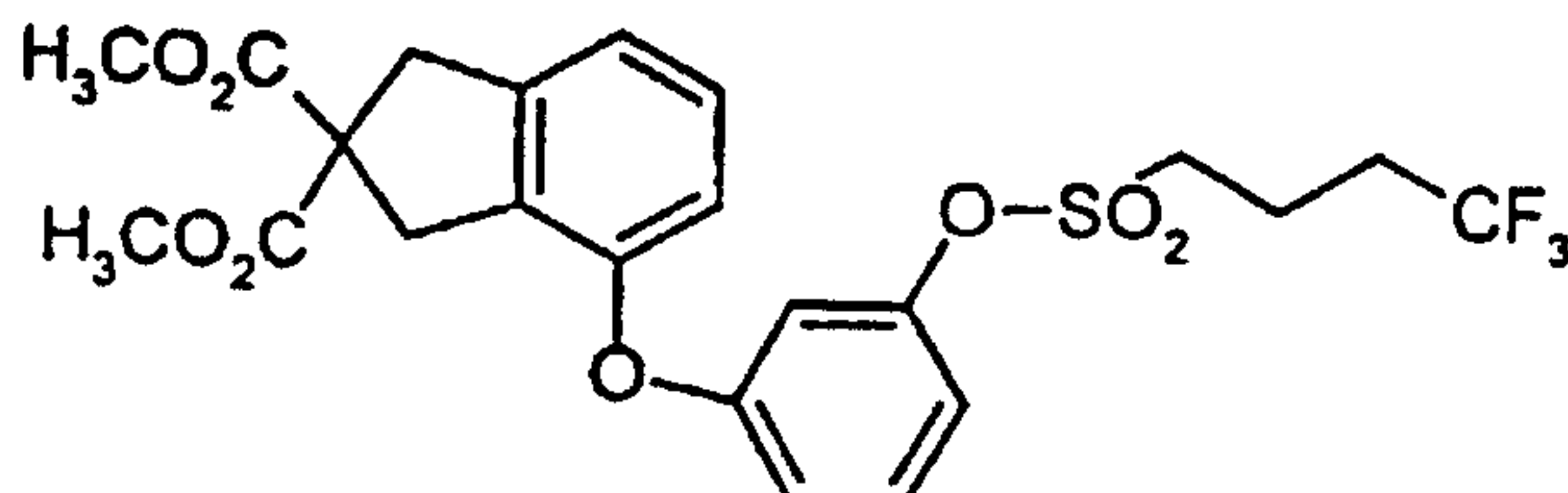
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Example 7A

3-(2,2-bis-Methoxycarbonyl-indanyl-4-oxy)phenyl
butanesulphonate

4,4,4-trifluoro-1-

5



The about 5:1 mixture, obtained in Example 6A, of 3-(2,3-bis-bromomethylphenyloxy)-phenyl 4,4,4-trifluoro-1-butane-sulphonate and 3-(2-bromomethyl-3-dibromomethylphenyloxy)-phenyl 4,4,4-trifluoro-1-butan-1-yl sulfonate (6.00 g) is dissolved in 2-butanone (150 ml). Dimethyl malonate (1.136 g; 8.6 mmol) and potassium carbonate (5.35 g; 38.7 mmol) are added, and the reaction mixture is then stirred under reflux overnight. After cooling, the undissolved salts are filtered off with suction and the filtrate is concentrated under reduced pressure. The residue is chromatographed over silica gel using toluene : ethyl acetate (20:1).

Yield: 1.95 g (35% of theory)

$R_f = 0.45$ (toluene : ethyl acetate = 20:1)

MS (DCI/ NH_3): $m/z = 534$ ($\text{M} + \text{NH}_4$)

20

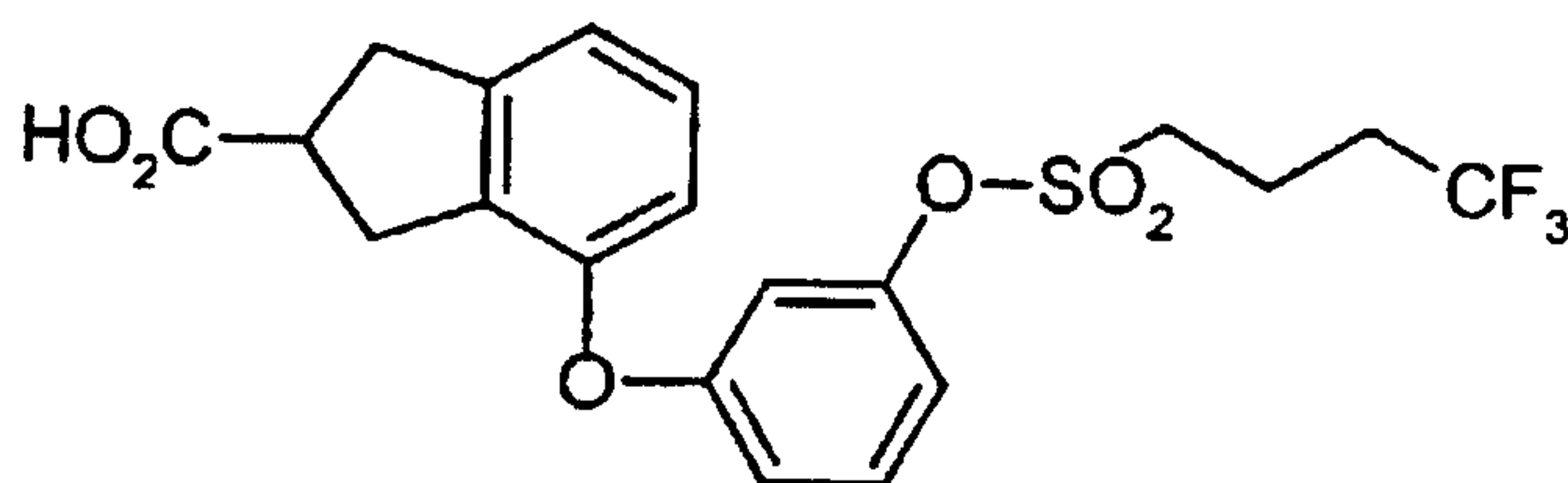
3-(1-Bromo-2,2-bis-methoxycarbonyl-indanyl-4-oxy)-phenyl 4,4,4-trifluoro-1-butan-1-yl sulfonate (0.82 g; 16% of theory; $R_f = 0.52$ (toluene : ethyl acetate = 20:1); MS (DCI/ NH_3): $m/z = 612, 614$ ($\text{M} + \text{NH}_4$) is obtained as byproduct.

25 Example 8A

(R,S)-3-(2-Hydroxycarbonyl-indanyl-4-oxy)-phenyl
butanesulphonate

4,4,4-trifluoro-1-

30



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Under argon, a solution of Example 7A (66.0 g; 128 mmol) in acetic acid (900 ml) and hydrogen bromide; 48% strength in water (350 ml) is heated at reflux for 5.5 h. The mixture is then concentrated under reduced pressure and the residue is taken
 5 up in ethyl acetate and washed with water (1 x 250 ml; 2 x 150 ml). The organic phase is dried (Na₂SO₄) and concentrated under reduced pressure.

Yield: 55.4 g (88% of theory)

Content according to HPLC: 90 area%

MS (DCI, NH₃): m/z = 462 (M + NH₄)

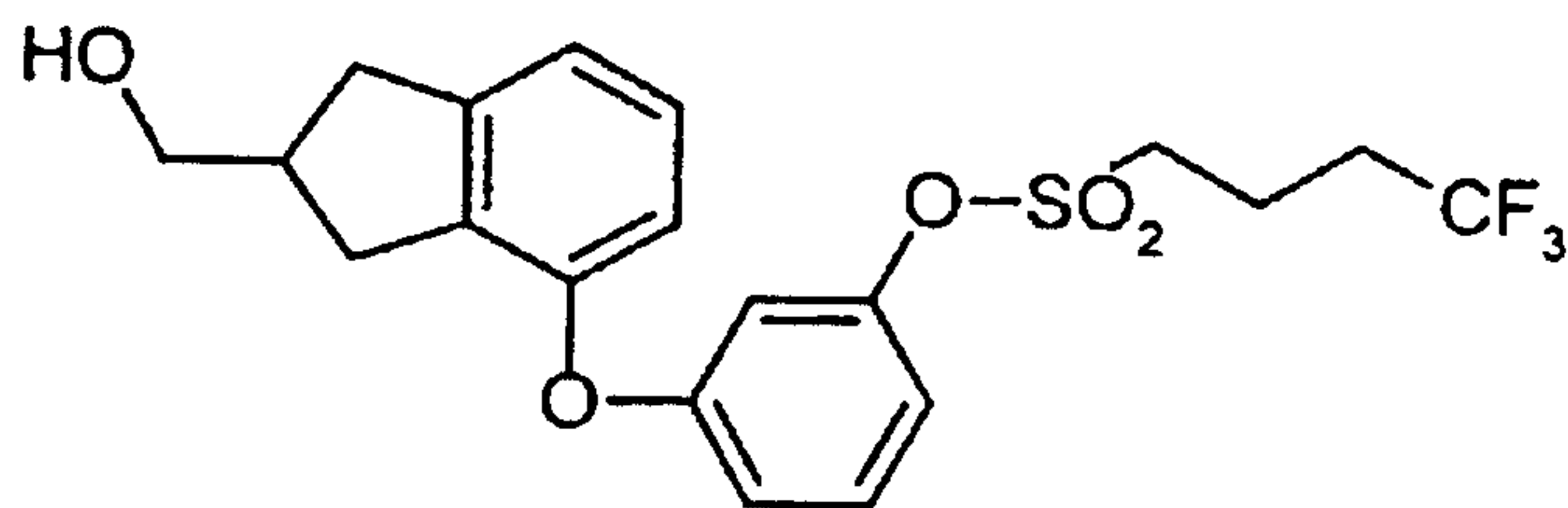
10

Example 9A

(R,S)-3-(2-Hydroxymethyl-indanyl-4-oxy)-phenyl
 butanesulphonate

4,4,4-trifluoro-1-

15



Borane-dimethyl sulphide complex, 2 M in THF (63.0 ml; 126 mmol) is added dropwise at room temperature and under argon to the solution of Example 8A
 20 (53.9 g; 109 mmol; 90% according to HPLC) in THF (1500 ml), and the mixture is stirred at RT for 1 h. Water (8 ml) is added, and the THF is then removed under reduced pressure and the residue is taken up in ethyl acetate (800 ml) and washed with water (2 x 150 ml). The organic phase is dried (MgSO₄) and concentrated under reduced pressure. The residue is chromatographed over silica gel using
 25 toluene : ethyl acetate (10:1).

Yield: 34.0 g (72% of theory)

R_f = 0.39 (tol : EA = 3:1)

MS (DCI, NH₃): m/z = 448 (M + NH₄)

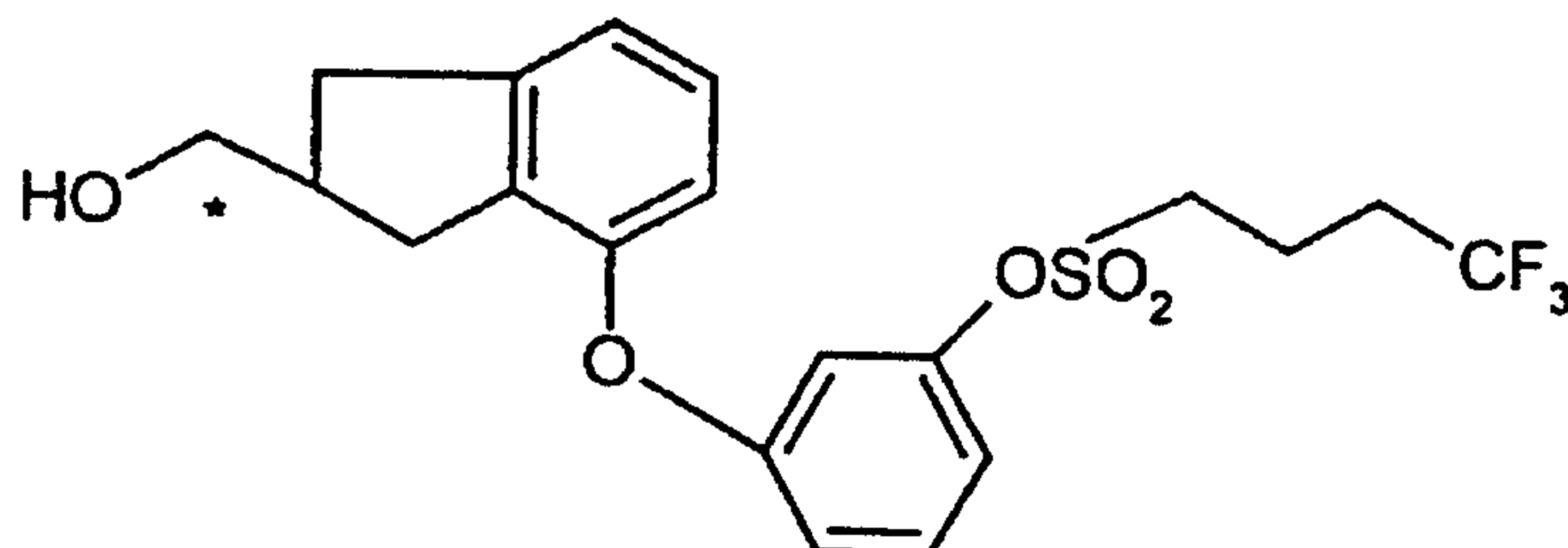
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Example 10A and 11A

(S)- and (R)-3-(2-hydroxymethyl-indanyl-4-oxy)-phenyl 1-(4,4,4-trifluoro-1-butanesulphonate

5



(S)-(+)-Enantiomer A (Example 10A) and (R)-(-)-enantiomer B (Example 11A)

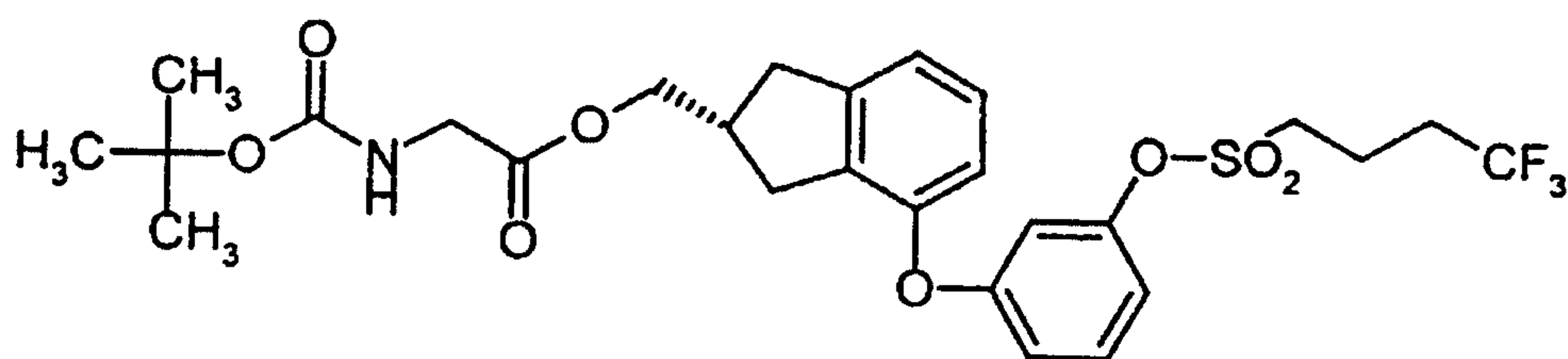
- 10 The compound from Example 9A (490 mg; 1.14 mmol) is separated by preparative HPLC (Chiracel OD, 10 μ m, 250 x 20 mm, flow rate 10 ml/min, mobile phase 80%, petroleum benzine 40-70°C/20% isopropanol, T = 10°C) into the (S)-enantiomer (Example 10A) and the (R)-enantiomer (Example 11A).
- 15 Example 10A:
Yield: 111 mg (23% of theory)
M.p.: 60-61°C
Retention time: 12.5 min
 $[\alpha]_D^{20}$ (c = 1, MeOH) = + 10.70
- 20 The absolute (S)-configuration of Example 10A was determined by X-ray analysis.
Example 11A:
Yield: 105 mg (21% of theory)
M.p.: 60-61°C
Retention time: 15.4 min
- 25 $[\alpha]_D^{20}$ (c = 1, MeOH) = - 10.35

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Preparation ExamplesExample 1

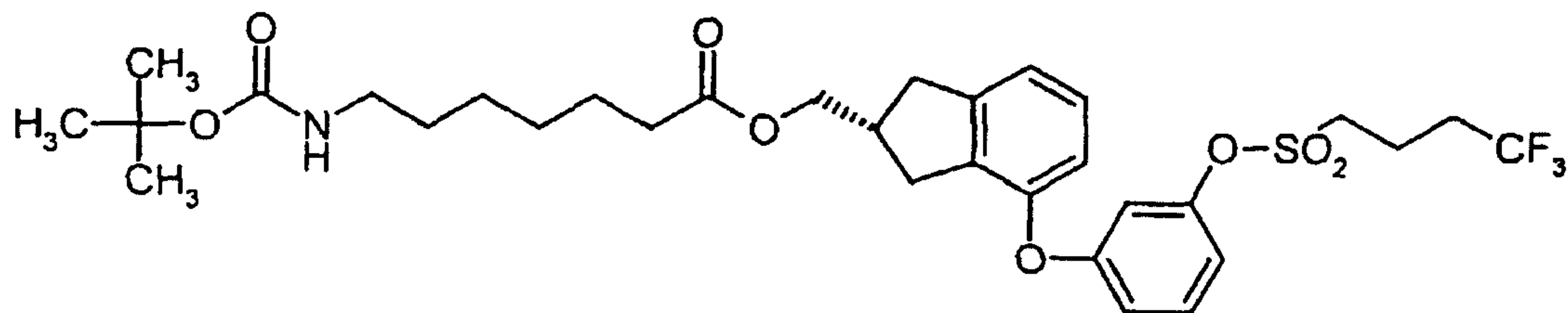
- 5 (R)-3-[2-(N-tert-butyloxycarbonylglycinyloxy)methyl-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



- 10 With ice-cooling and under argon, N-tert-butyloxycarbonylglycine (230 mg; 1.31 mmol) , N-ethyl-N'-3-(dimethylaminopropyl)-carbodiimide hydrochloride (277 mg; 1.44 mmol) and 4-dimethylaminopyridine (16 mg; 0.13 mmol) are added to the solution of Example 11A (565 mg; 1.31 mmol) in dichloromethane (20 ml), and the mixture is stirred at RT for 18 h. The mixture is then diluted with
- 15 dichloromethane (30 ml), washed with water (60 ml), sat. aqueous NaHCO₃ solution (60 ml) and water (60 ml), dried (Na₂SO₄) and concentrated under reduced pressure. The residue is chromatographed over silica gel using tol : EA = 10:1.
Yield: 651 mg (85% of theory)
R_f = 0.39 (tol : EA = 5:1)
- 20 MS (DCI, NH₃): m/z = 605 (M+NH₄)

Example 2

- 25 (R)-3-[2-(7-N-tert-Butyloxycarbonylaminoheptanoyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



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The preparation is carried out analogously to the preparation of Example 12A starting from Example 11A (196 mg; 0.46 mmol) and 7-N-tert-butyloxycarbonylaminohexanoic acid (285 mg; 1.16 mmol).

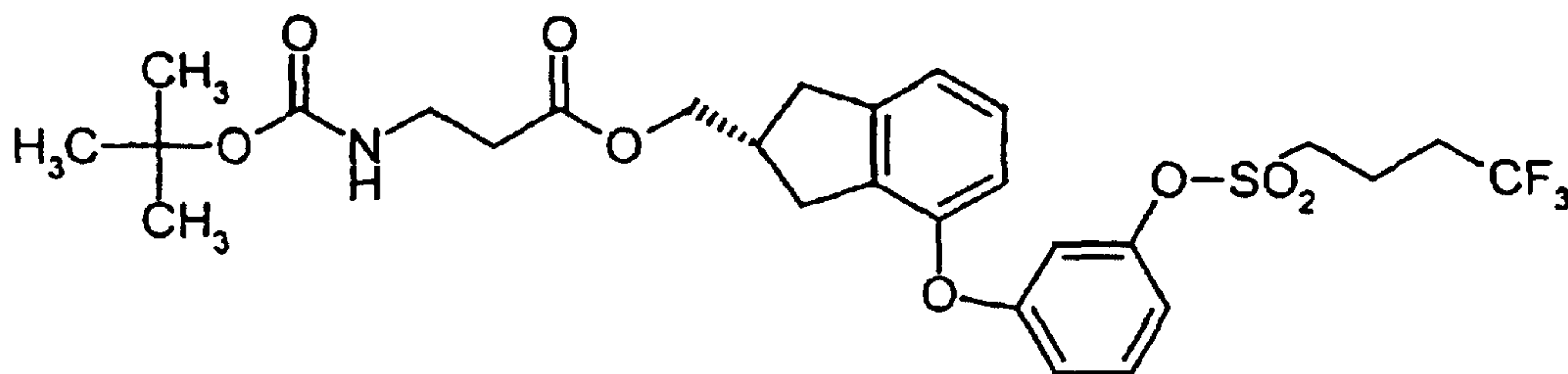
Yield: 265 mg (87% of theory)

5 $R_f = 0.19$ (tol : EA = 10:1)

MS (DCI, NH_3): $m/z = 675$ ($\text{M} + \text{NH}_4$)

Example 3

10 (R)-3-[2-(3-N-tert-Butyloxycarbonylaminopropanoyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



15 The preparation was carried out analogously to the preparation of Example 1 starting from Example 11A (600 mg; 1.39 mmol) and N-tert-butyloxycarbonyl- β -alanine (290 mg; 1.53 mmol).

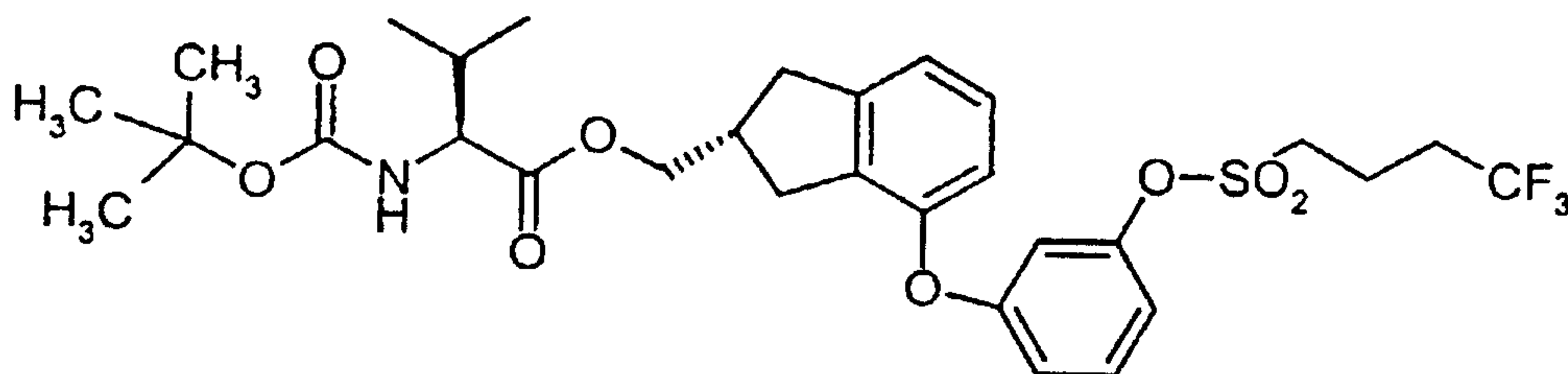
Yield: 499 mg (59% of theory)

$R_f = 0.41$ (tol : EA = 5:1)

20 MS (ESI): $m/z = 602$ ($\text{M} + \text{H}$)

Example 4

25 (R)-3-[2-((S)-N-tert-Butyloxycarbonylvalinyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



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The preparation was carried out analogously to the preparation of Example 1 starting from Example 11A (600 mg; 1.39 mmol) and N-tert-butyloxycarbonyl-(S)-valine (394 mg; 1.86 mmol).

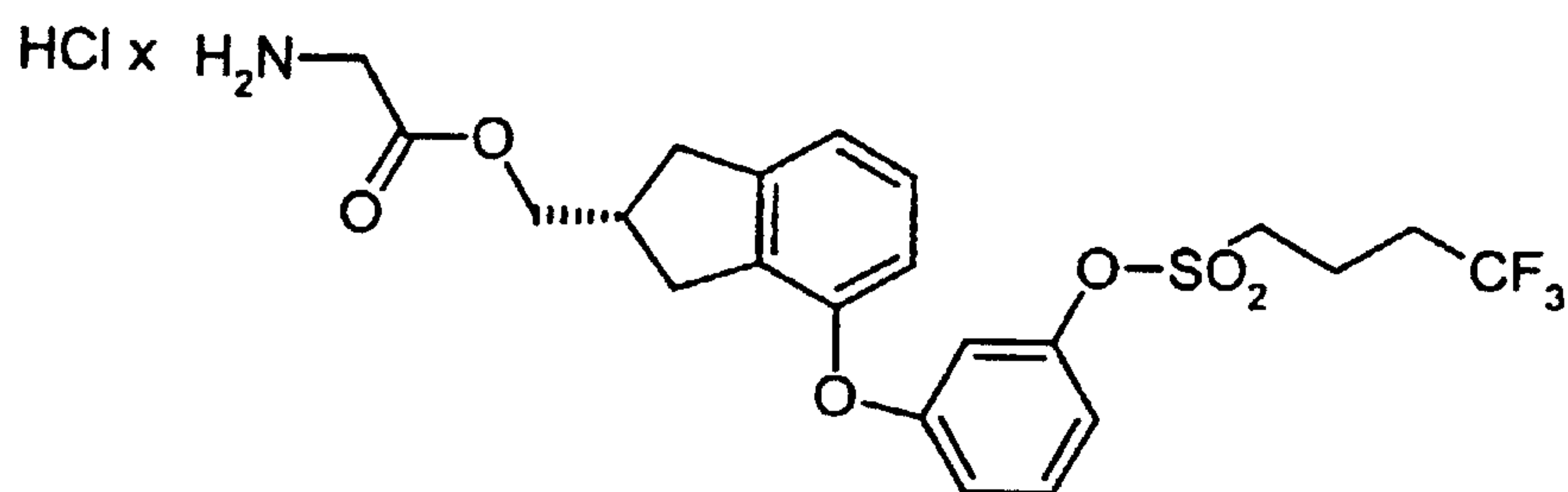
Yield: 745 mg (85% of theory)

5 $R_f = 0.58$ (tol : EA = 5:1)

MS (ESI): m/z 652 ($M+Na$)

Example 5

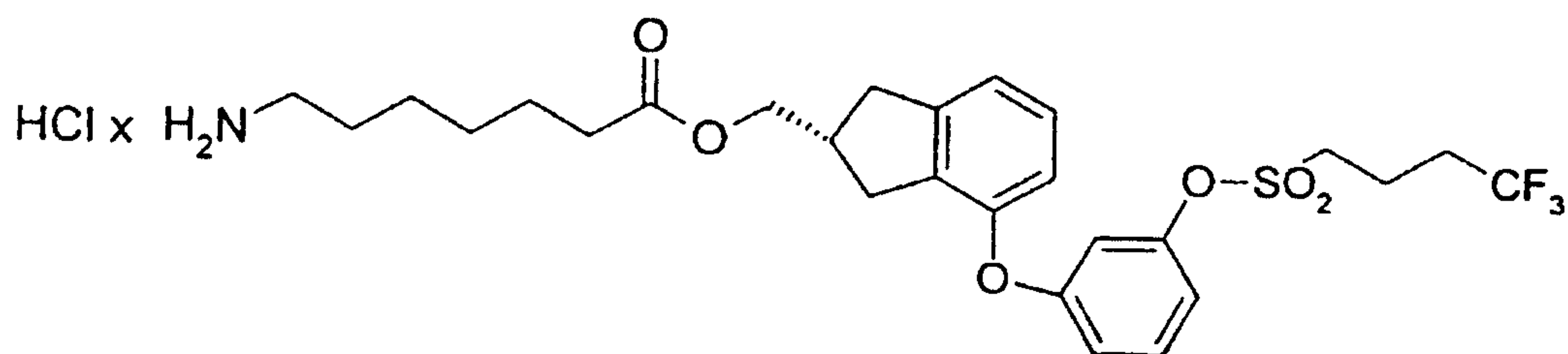
- 10 (R)-3-(2-Glycinyloxymethyl)-indanyl-4-oxy)-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate hydrochloride



- 15 At RT and under argon, a solution of 4 N HCl in 1,4-dioxane (5 ml) is added dropwise to a solution of Example 1 (537 mg; 0.91 mmol) in 1,4-dioxane (4 ml). The mixture is stirred at RT overnight, the solvent is removed under reduced pressure and the residue is triturated with diethyl ether/petroleum ether.
Yield: 479 mg (100% of theory)
- 20 MS (ESI): m/z 488 ($M+H$)
 $R_f = 0.21$ (dichloromethane : methanol : triethylamine = 20 : 1 : 0.2)

Example 6

- 25 (R)-3-[2-(7-Aminoheptanoyloxymethyl)-indanyl-4-oxy)-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate hydrochloride



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The preparation is carried out analogously to the preparation of Example 5 starting from Example 2 (225 mg; 0.34 mmol).

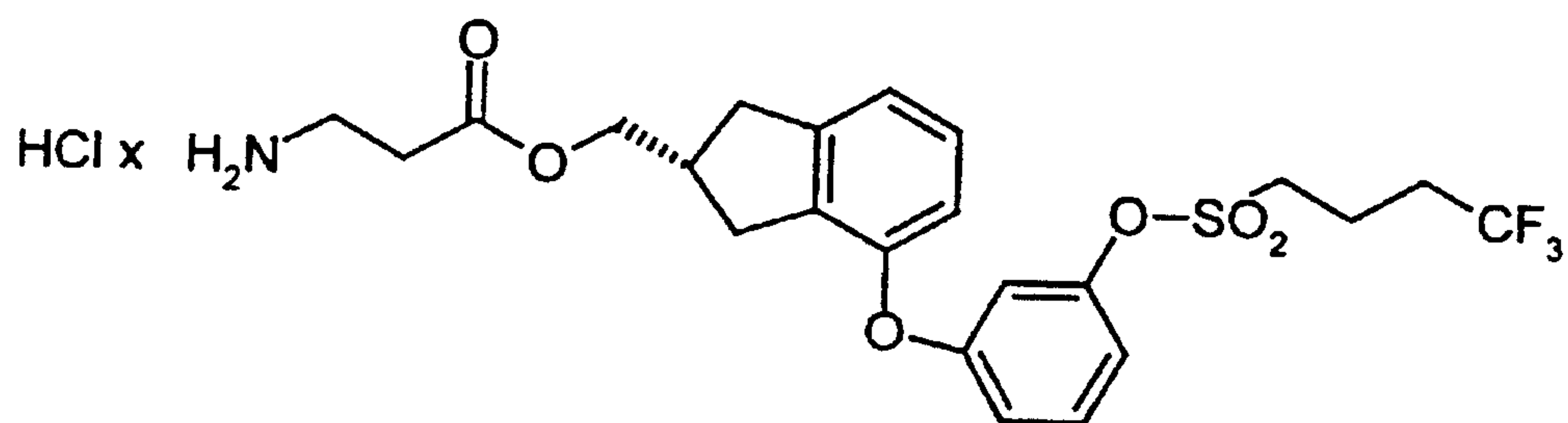
Yield: 202 mg (99% of theory)

5 MS (ESI): m/e 558 (M+H)

$R_f = 0.19$ (dichloromethane : methanol : triethylamine = 20 : 1 : 0.2)

Example 7

10 (R)-3-[2-(3-Aminopropanoyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate hydrochloride



15 The preparation is carried out analogously to the preparation of Example 5 starting from Example 3 (417 mg; 0.69 mmol).

Yield: 374 mg (100% of theory)

MS (DCI/NH₃): m/z 502 (M+H)

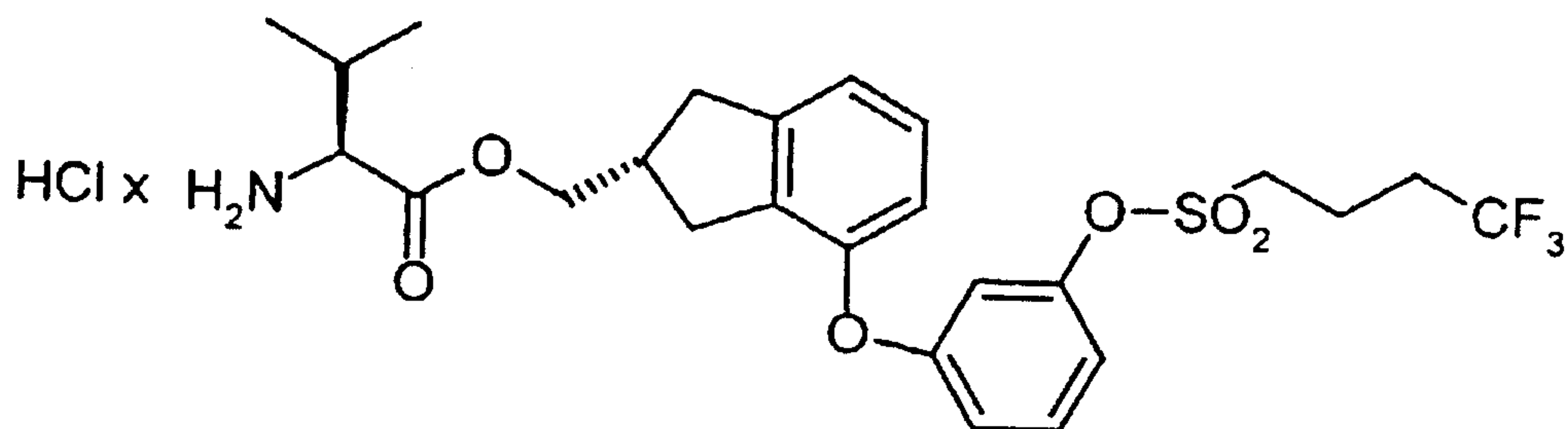
$R_f = 0.19$ (dichloromethane : methanol : triethylamine = 20 : 1 : 0.2)

20

Example 8

(R)-3-[2-((S)-Valinyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate hydrochloride

25



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The preparation was carried out analogously to the preparation of Example 5 starting from Example 4 (706 mg; 1.12 mmol).

Yield: 621 mg (98% of theory)

MS (DCI/NH₃): m/z 530 (M+H)

5 R_f = 0.30 (dichloromethane : methanol : triethylamine = 20 : 1 : 0.2)

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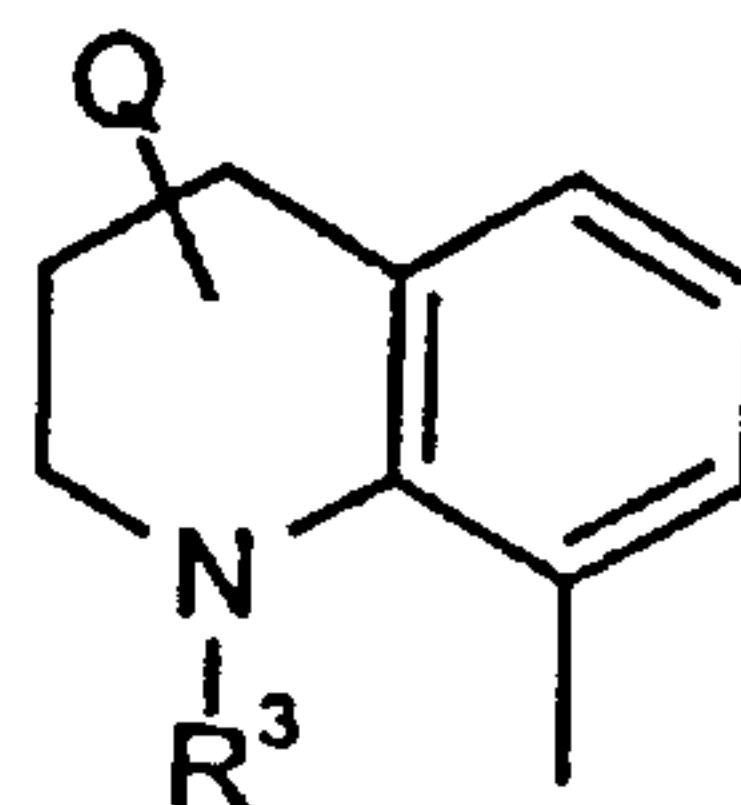
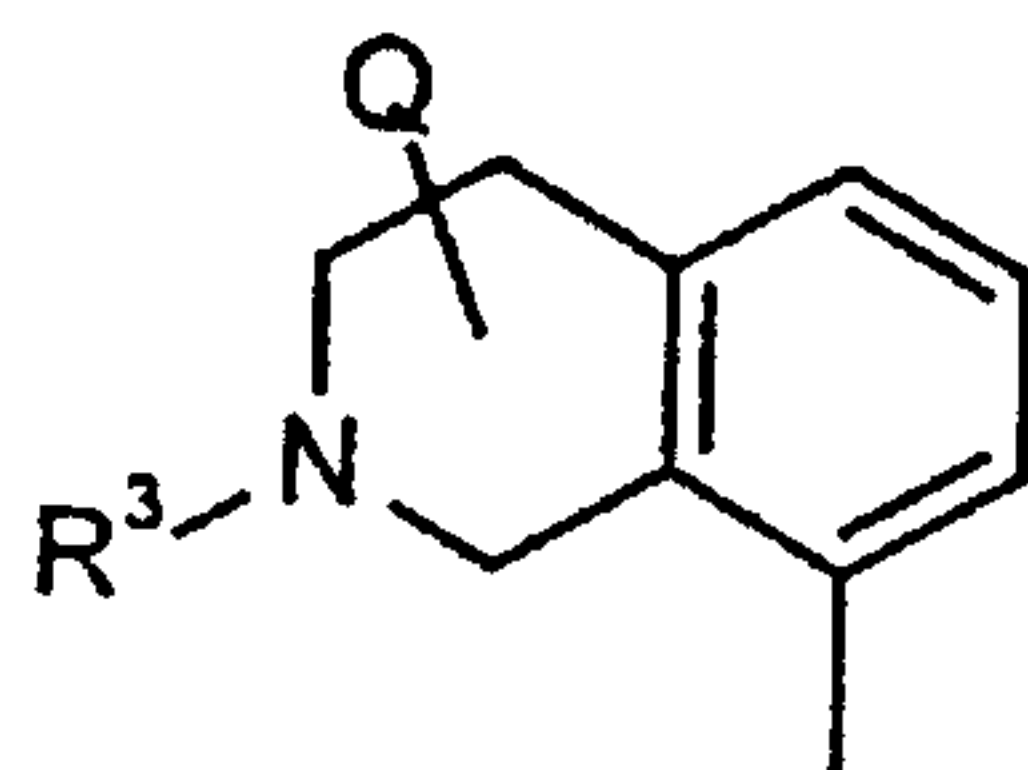
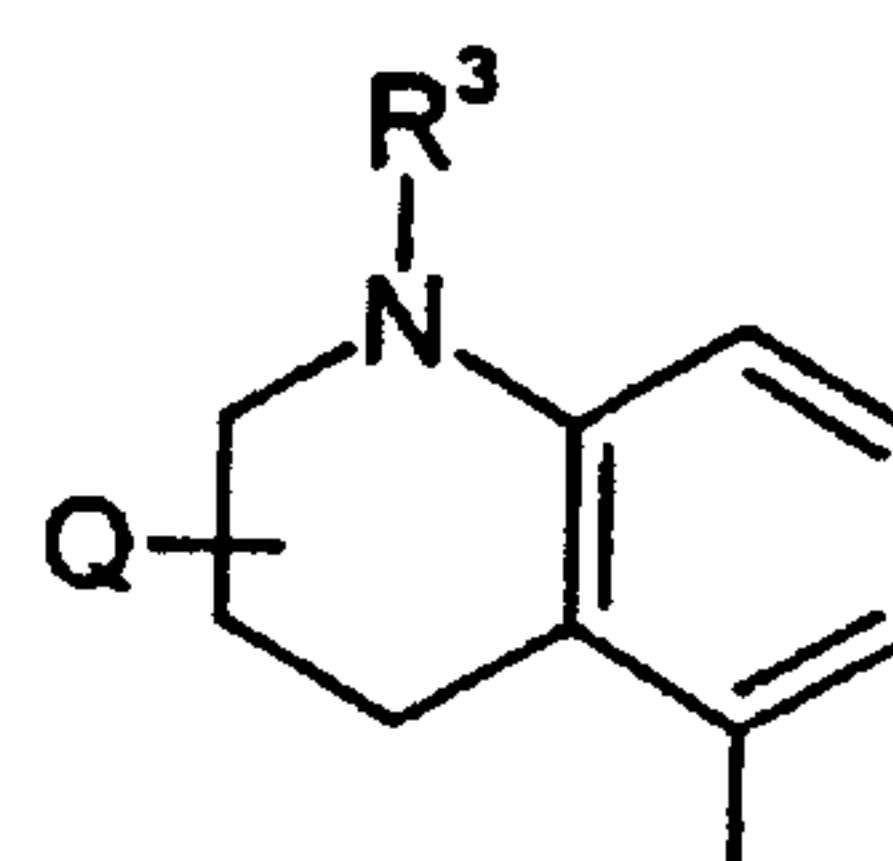
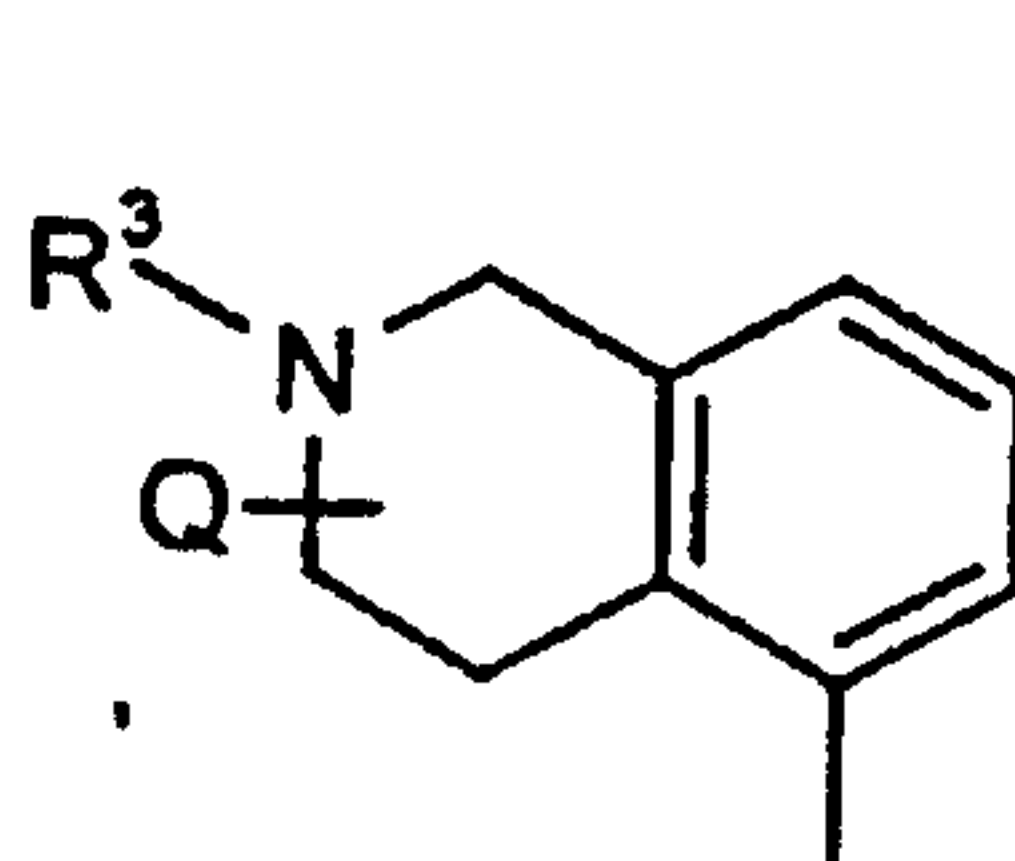
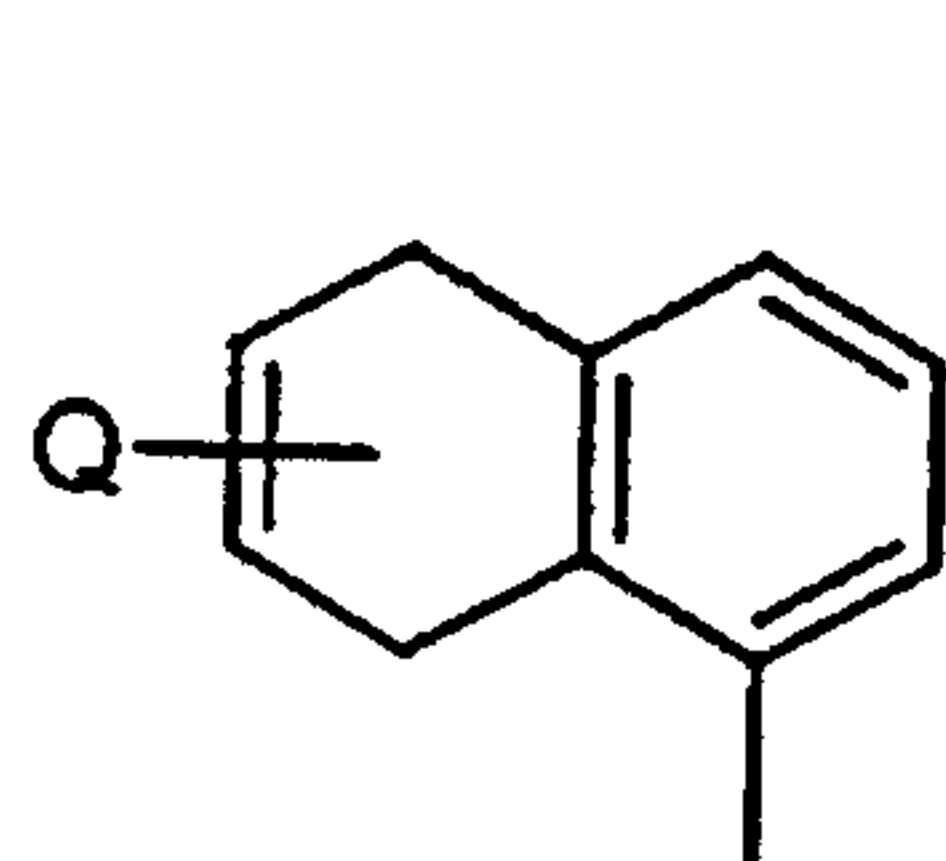
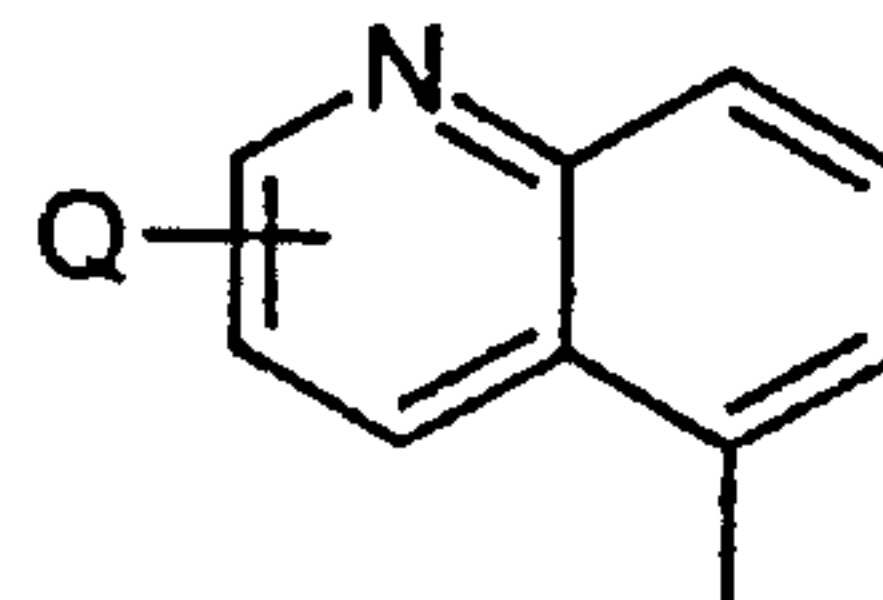
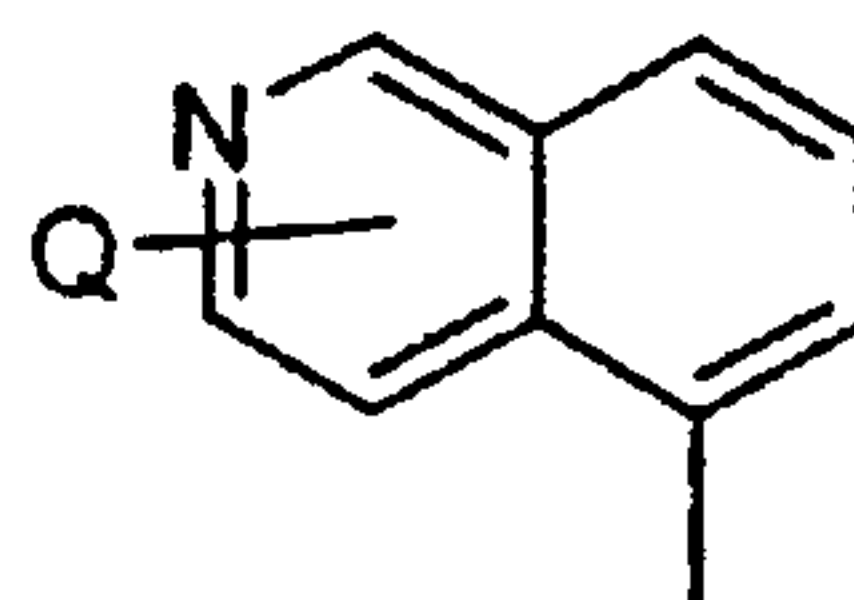
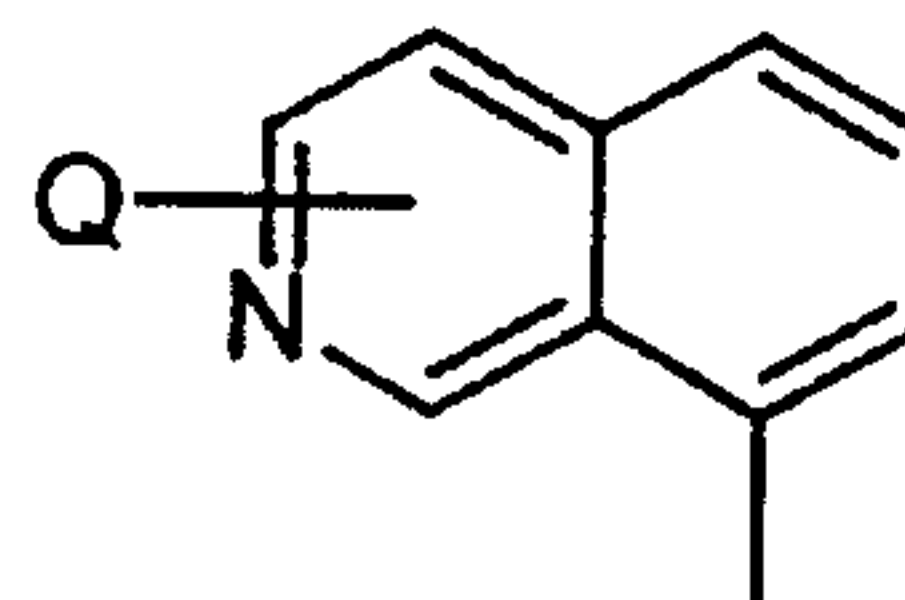
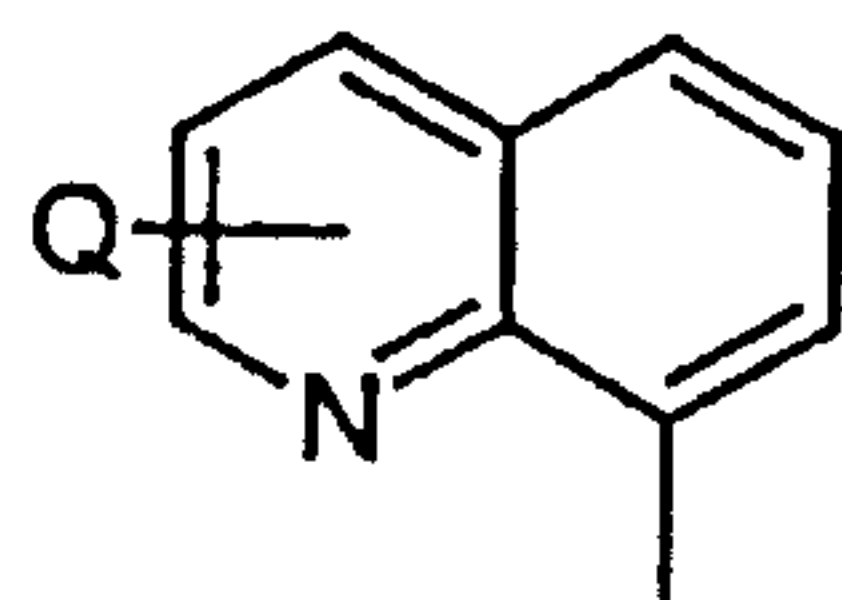
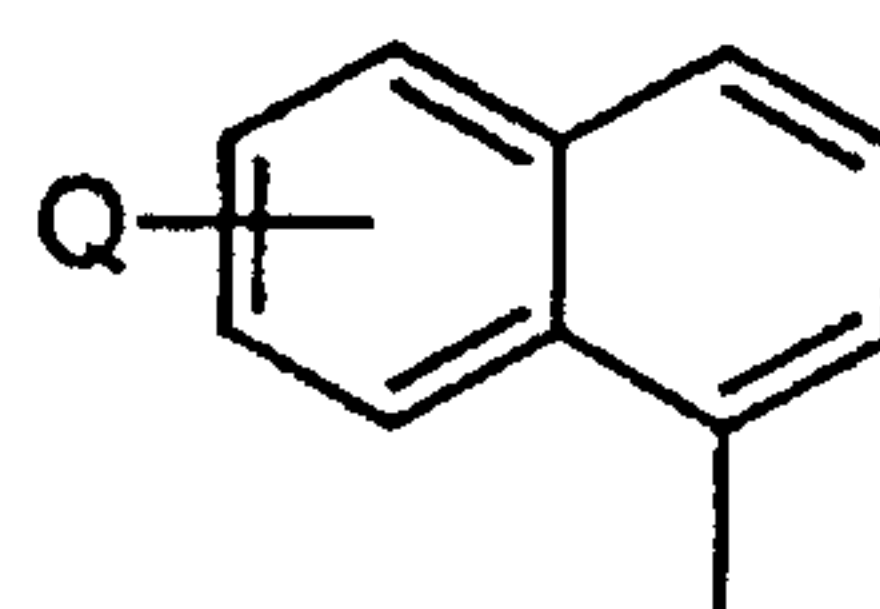
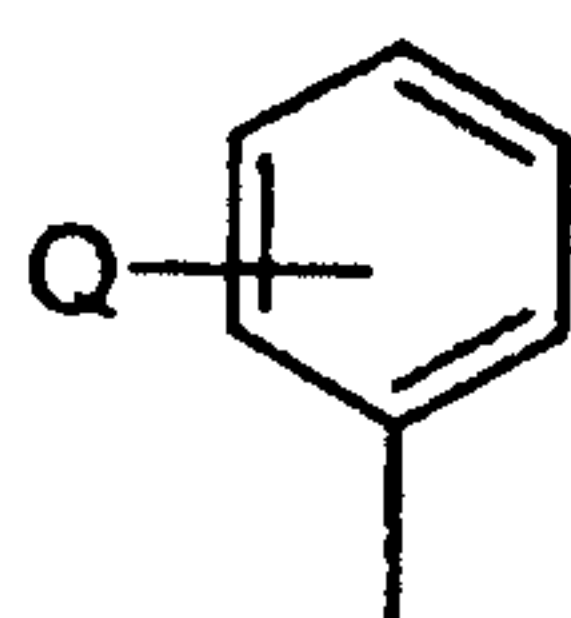
Patent claims

1. Compounds of the general formula (I)



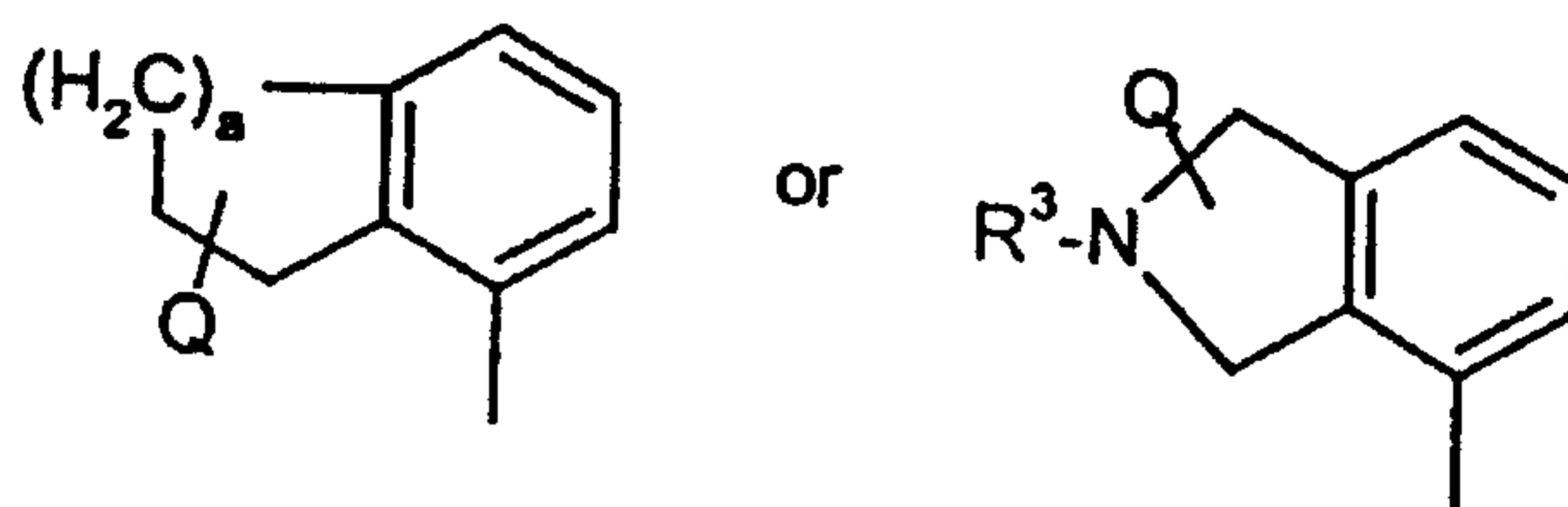
in which

10 R^1 represents a radical of the formula



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in which

5 a represents a number 1 or 2,

R^3 represents hydrogen, (C₂-C₆)-alkenyl, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

10 and where all of the phenyl ring systems listed above are optionally substituted, optionally geminally, by one or more identical or different substituents selected from the group consisting of:
 halogen, carboxyl, hydroxyl, phenyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl, (C₁-C₈)-alkyl, which for its part may be substituted by halogen, (C₁-C₆)-alkylsulphonyloxy, azide, amino, mono(C₁-C₆)-alkylamino, di(C₁-C₆)-alkylamino or hydroxyl,
 15 a group of the formula $-(CO)_b-NR^4R^5$,

in which

20 b represents a number 0 or 1,

R^4 and R^5 are identical or different and independently of one another represent hydrogen, phenyl, (C₁-C₆)-acyl, cyclo(C₄-C₇)-acyl benzoyl or (C₁-C₆)-alkyl, which is optionally substituted by amino,
 25 mono(C₁-C₆)-alkylamino, di(C₁-C₆)-alkylamino,

or

30 R^4 and R^5 together with the nitrogen atom form a 5- or 6-membered saturated heterocycle which may optionally contain one or more further heteroatom(s) from the group consisting of S and O and/or one or more radical(s) of the formula $-NR^8$,

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in which

R^8 represents hydrogen, (C_1-C_6) -alkyl or (C_1-C_6) -acyl,

5 and

a group of the formula $-NR^6-SO_2-R^7$

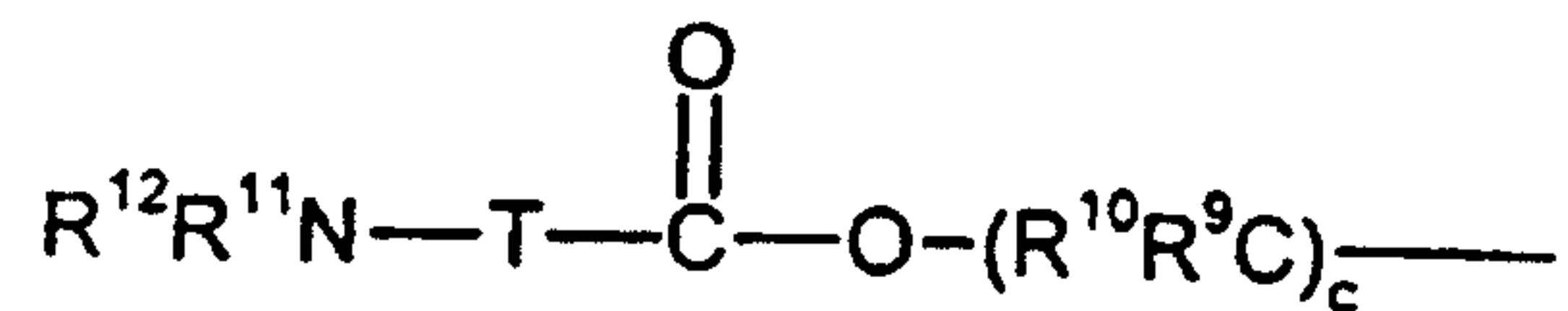
in which

10

R^6 represents hydrogen, phenyl, (C_1-C_6) -alkyl or (C_1-C_6) -acyl,

R^7 represents phenyl or (C_1-C_6) -alkyl,

15 Q represents a radical of the formula



in which

20

c represents a number 1, 2, 3, 4, 5 or 6,

R^9 and R^{10} are identical or different and represent hydrogen or (C_1-C_6) -alkyl,

25

T represents a radical of the formula $-(CH_2)_d-$,

in which

30

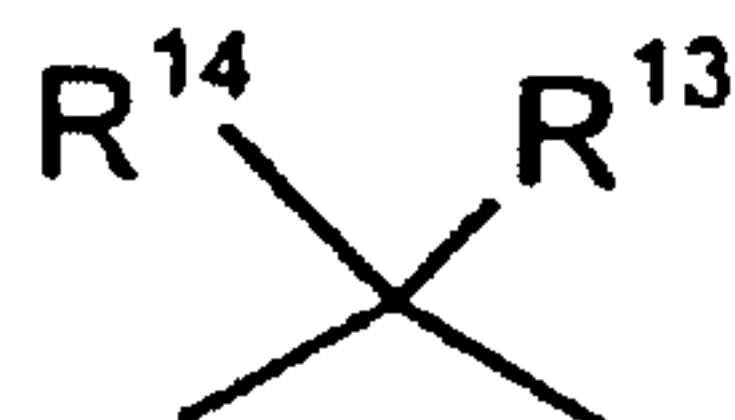
d represents a number 1, 2, 3, 4, 5, 6, 7 or 8,

or

T represents a moiety of an amino acid radical of the formula

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in which

5 R^{13} and R^{14} are identical or different and represent hydrogen or methyl,

or

10 R^{13} represents hydrogen or methyl

and

15 R^{14} represents (C₃-C₈)-cycloalkyl or (C₆-C₁₀)-aryl or hydrogen, or (C₁-C₈)-alkyl,

20 where the (C₁-C₆)-alkyl is optionally substituted by methythio, hydroxyl, mercapto, guanidyl or by a group of the formula -NR¹⁵R¹⁶ or -NR¹⁷-OC-,

in which

25 R^{15} and R^{16} independently of one another represent hydrogen, (C₁-C₈)-alkyl or phenyl

and

30 R^{17} represents hydroxyl, benzyloxy, (C₁-C₈)-alkoxy or the group -NR¹⁵R¹⁶ listed above,

35 or the (C₁-C₈)-alkyl is optionally substituted by (C₃-C₆)-cycloalkyl or phenyl, which for its part is substituted by hydroxyl, halogen or (C₁-C₆)-alkoxy or amino,

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or the (C₁-C₈)-alkyl is optionally substituted by imidazolyl or indolyl, in which the corresponding -NH functions are optionally protected by (C₁-C₆)-alkyl or by an amino protective group,

5

R¹¹ and R¹² are identical or different and represent hydrogen, (C₁-C₆)-alkyl or a typical amino protective group,

or

10

R¹¹ and R¹² together with the nitrogen atom form a 5- to 6-membered saturated heterocycle, which may optionally contain a further heteroatom from the group consisting of S and O or a radical of the formula -NR¹⁸,

15

in which

R¹⁸ represents hydrogen, (C₁-C₆)-alkyl or phenyl,

20

A and E are identical or different and represent a bond or represent (C₁-C₄)-alkylene,

D represents an oxygen atom or represents a radical of the formula -S(O)_e- or -N(R¹⁹)-,

25

in which

e represents a number 0, 1 or 2,

30

R⁹ represents hydrogen, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

G represents doubly attached (C₆-C₁₀)-aryl or represents a doubly attached 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, which are optionally substituted by one or more

35

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identical or different substituents selected from the group consisting of:

5 hydroxyl, trifluoromethyl, carboxyl, halogen, (C₁-C₆)-alkyl, hydroxy(C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl, and groups of the formulae -CO-O-(CH₂)_f-NR²⁰R²¹, -NR²²-SO₂R²³, -(CH₂)_g-(CO)_h-NR²⁴R²⁵ and -OR²⁶,

in which

10 f represents a number 1, 2, 3 or 4,

g and h are identical or different and represent a number 0 or 1,

15 R²⁰ and R²¹ have the meaning of R⁴ and R⁵ given above and are identical to or different from this meaning,

R²² has the meaning of R⁶ given above and is identical to or different from this meaning,

20 R²³ has the meaning of R⁷ given above and is identical to or different from this meaning,

25 R²⁴ and R²⁵ have the meaning of R⁴ and R⁵ given above and are identical to or different from this meaning,

or independently of one another represent a radical of the formula

30 $-(CH_2)_i-NR^{27}R^{28},$

in which

i represents a number 1, 2, 3 or 4,

35 and

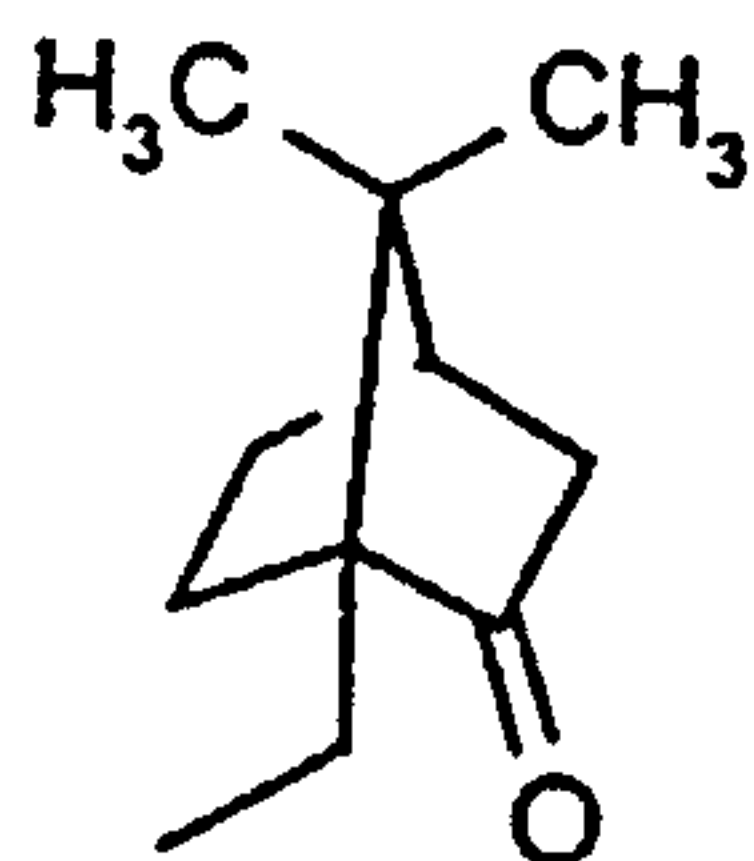
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halogen, trifluoromethyl, nitro, amino and (C₁-C₆)-alkyl,

or

represents the radical of the formula



5

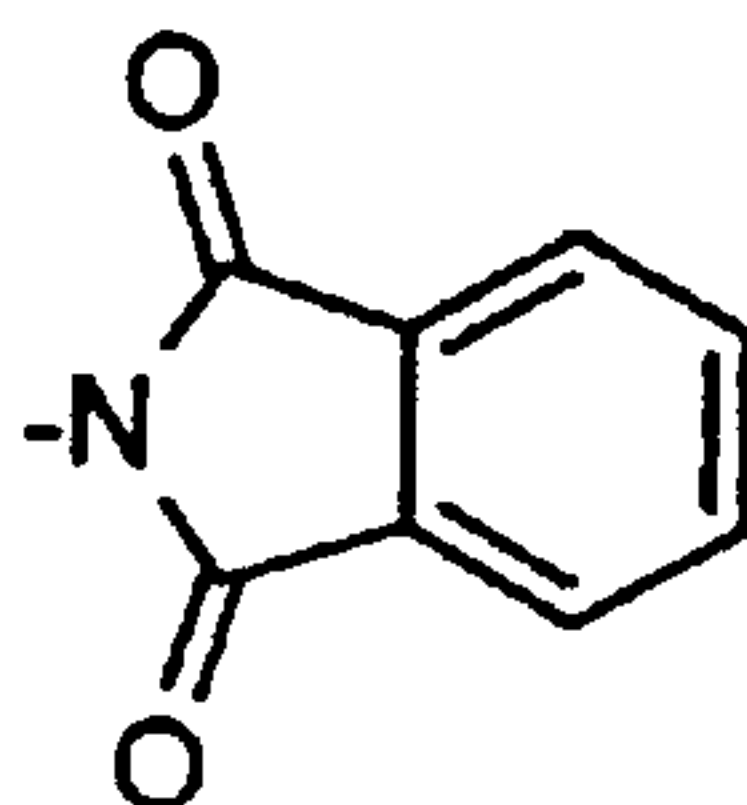
or morpholine, or

represents C₃-C₈-cycloalkyl, or

represents (C₁-C₁₂)-alkyl, (C₂-C₁₂)-alkenyl or (C₂-C₁₂)-alkinyl, which are optionally substituted by one or more identical or different substituents selected from the group consisting of:

10

halogen, trifluoromethyl, hydroxyl, cyano, azido, (C₁-C₆)-alkoxy, (C₁-C₆)-perfluoroalkoxy, partially fluorinated (C₁-C₆)-alkoxy, a radical of the formula



, -NR³⁸R³⁹,

in which

15

R³⁸ and R³⁹ have the meaning of R⁴ and R⁵ given above and are identical to or different from this meaning,

phenyl, optionally substituted by one or more identical or different substituents selected from the group consisting of:

20

halogen, nitro, hydroxyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and a group of the formula -NR⁴⁰R⁴¹,

in which

25

R⁴⁰ and R⁴¹ are identical or different and represent hydrogen or (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

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and a 5- to 6-membered aromatic heterocycle having up to three heteroatoms from the group consisting of S, N and O, optionally substituted by one or more identical or different substituents selected from the group consisting of:

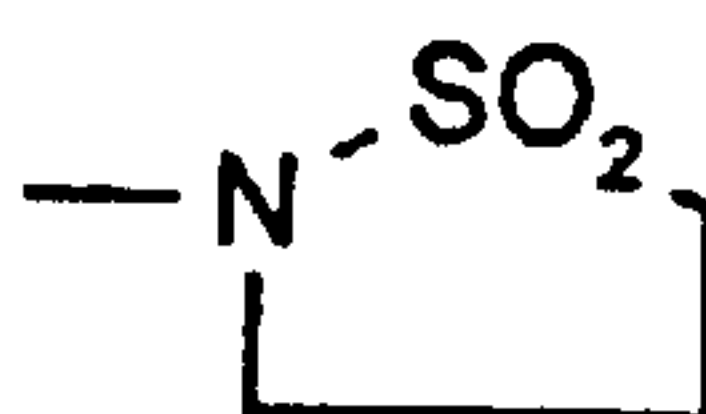
5 halogen, nitro, hydroxyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy and a group of the formula -NR⁴⁰R⁴¹,

in which

10 R⁴⁰ and R⁴¹ are as defined above,

or

L and R² together represent a radical of the formula



15

and pharmaceutically acceptable salts thereof.

2. Compounds of the general formula (I) according to Claim 1,

20 in which

R¹¹ and R¹² are identical or different and represent hydrogen or (C₁-C₆)-alkyl,

25 or

R¹¹ and R¹² together with the nitrogen atom form a 5- to 6-membered saturated heterocycle which may optionally contain a further heteroatom from the group consisting of S and O or a radical of the

30

in which

R¹⁸ represents hydrogen, (C₁-C₆)-alkyl or phenyl,

35

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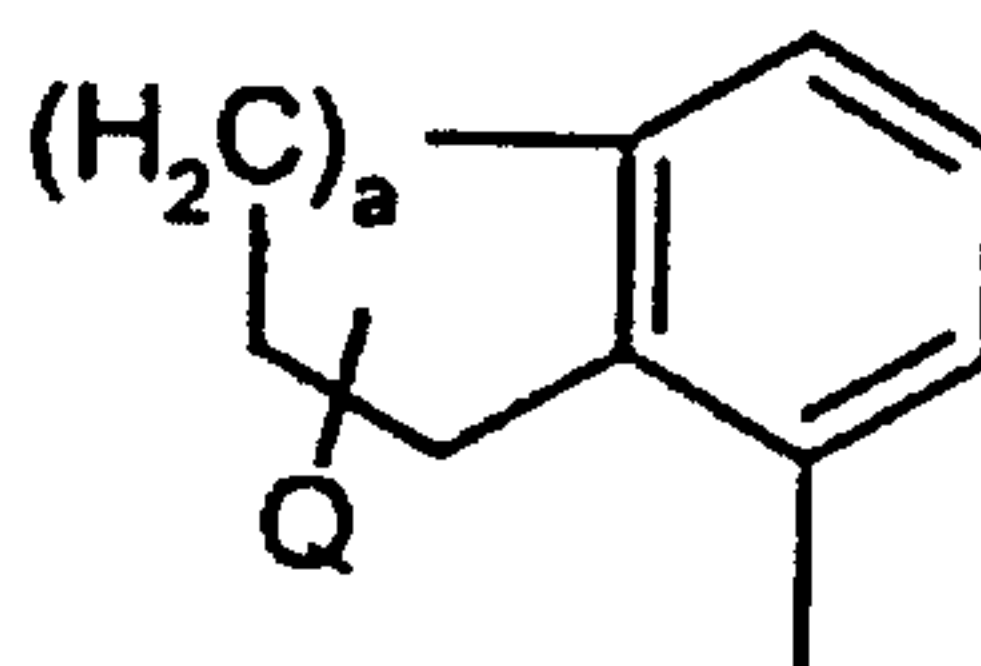
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and pharmaceutically acceptable salts thereof.

3. Compounds of the general formula (I) according to Claim 1,

5 in which

R^1 represents a radical of the formula



10 in which

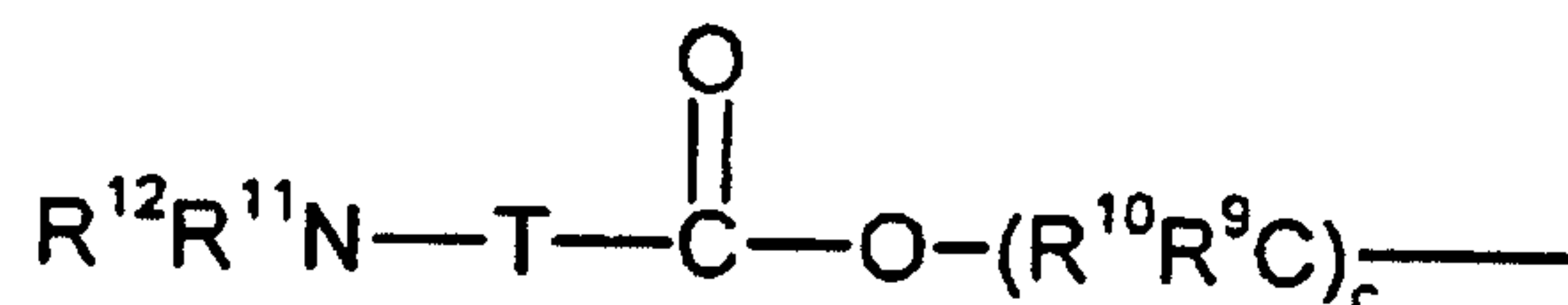
a represents a number 1 or 2,

15 and where the phenyl radical listed above is optionally substituted, optionally geminally, by one or more identical or different substituents selected from the group consisting of:

fluorine, chlorine, carboxyl, hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₅)-alkoxycarbonyl or (C₁-C₆)-alkyl, which for its part may be substituted by fluorine, chlorine or hydroxyl,

20

Q represents a radical of the formula



in which

25

c represents a number 1, 2, 3, 4, 5 or 6,

R^9 and R^{10} are identical or different and represent hydrogen or (C₁-C₆)-alkyl,

30

T represents a radical of the formula $-(CH_2)_d-$,

in which

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d represents a number 1, 2, 3, 4, 5 or 6,

or

5

T represents a moiety of an amino acid radical of the formula



in which

10

R^{13} represents hydrogen or methyl

and

15

R^{14} represents cyclopropyl, cyclopentyl, cyclohexyl, phenyl or hydrogen, or
represents (C₁-C₆)-alkyl,

20

where the (C₁-C₆)-alkyl is optionally substituted by methythio, hydroxyl, mercapto, guanidyl or by a group of the formula
-NR¹⁵R¹⁶ or -NR¹⁷-OC-,

in which

25

R^{15} and R^{16} independently of one another represent
hydrogen, (C₁-C₆)-alkyl or phenyl

and

30

R^{17} represents hydroxyl, benzyloxy, (C₁-C₆)-alkoxy or the group -NR¹⁵R¹⁶ listed above,

35

or the (C₁-C₆)-alkyl is optionally substituted by cyclopropyl, cyclopentyl, cyclohexyl or phenyl, which for its part is substituted by hydroxyl, fluorine, chlorine, bromine or (C₁-C₄)-alkoxy or amino,

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and

5 R^{11} and R^{12} are identical or different and represent hydrogen or (C₁-C₄)-alkyl,

or

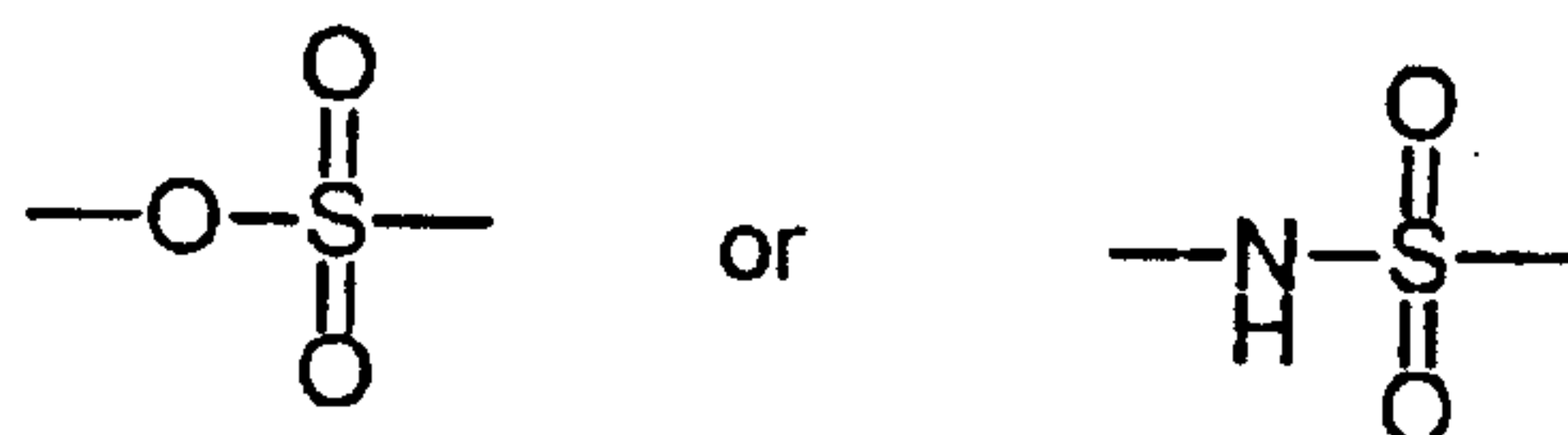
10 R^{11} and R^{12} together with the nitrogen atom form a morpholinyl, piperidinyl or piperazinyl ring,

A and E are identical or different and represent a bond or represent (C₁-C₄)-alkylene,

15 D represents an oxygen atom,

G represents doubly attached phenyl, naphthyl, pyrimidyl, pyradizinyll or pyridyl, which are optionally substituted by one or more identical or different substituents selected from the group consisting of:
20 hydroxyl, trifluoromethyl, carboxyl, halogen, (C₁-C₄)-alkyl, hydroxy(C₁-C₄)alkyl, (C₁-C₄)-alkoxy and (C₁-C₄)-alkoxycarbonyl

L represents a radical of the formula



25

where the left-hand side of the radicals is attached to G,

30 R^2 represents (C₁-C₁₀)-alkyl which is optionally substituted by one or more identical or different substituents selected from the group consisting of:
fluorine, chlorine, bromine, phenyl, trifluoromethyl, hydroxyl, azido, (C₁-C₄)-alkoxy, (C₁-C₅)-perfluoroalkoxy or partially fluorinated (C₁-C₄)alkoxy

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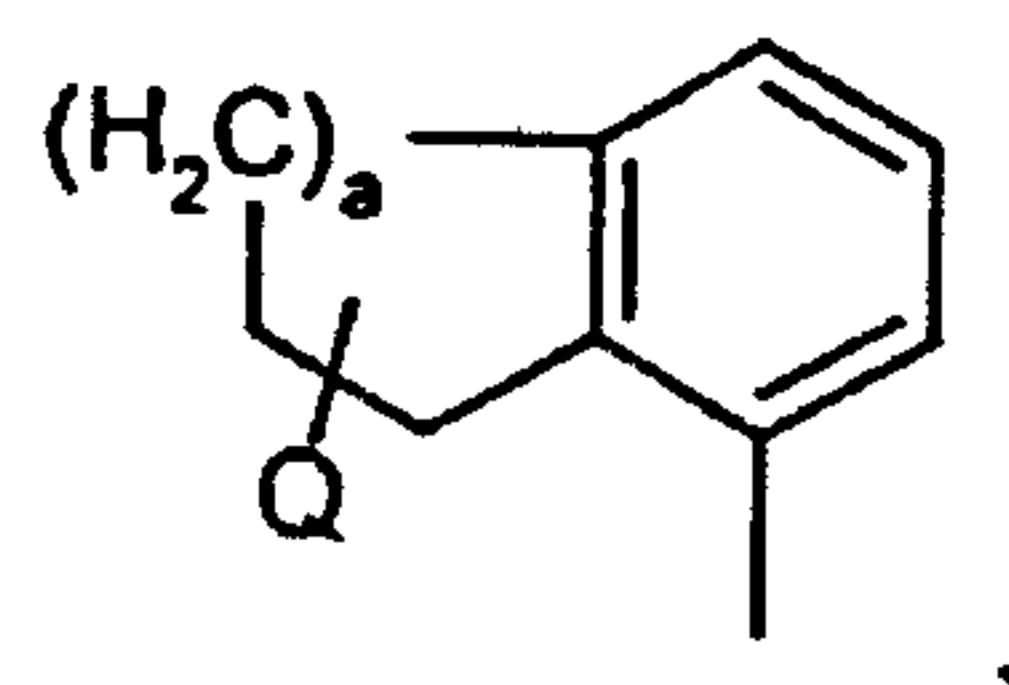
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and pharmaceutically acceptable salts thereof.

4. Compounds of the general formula (I), according to Claim 1

5 in which

R^1 represents a radical of the formula



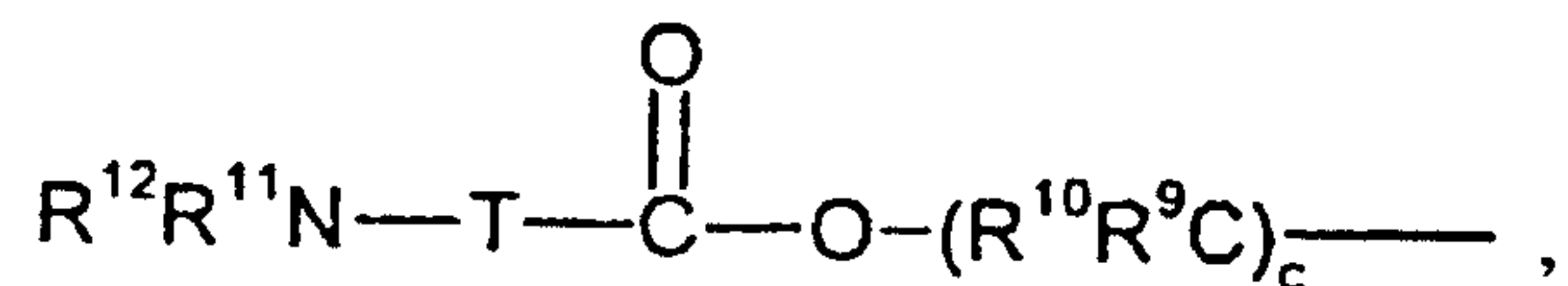
10 in which

a represents a number 1 or 2,

15 and where the phenyl radical listed above is optionally substituted by one or more identical or different substituents selected from the group consisting of:

chlorine, fluorine, hydroxyl, (C₁-C₃)-alkoxy or (C₁-C₄)-alkyl, which for its part may be substituted by hydroxyl,

20 Q represents a radical of the formula



in which

25 c represents a number 1, 2, 3 or 4,

R^9 and R^{10} are identical or different and represent hydrogen or (C₁-C₃)-alkyl,

30 T represents a radical of the formula $-(CH_2)_d-$,

in which

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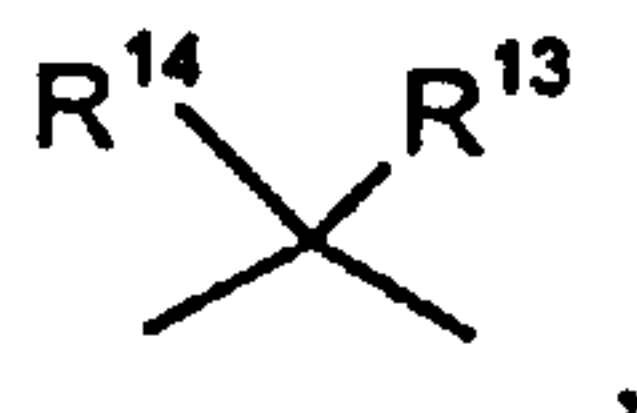
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d represents a number 1, 2, 3, 4, 5 or 6,

or

5

T represents a moiety of an amino acid radical of the formula



in which

10 R^{13} represents hydrogen or methyl

and

15 R^{14} represents cyclopentyl, cyclohexyl, phenyl or hydrogen, or
represents (C₁-C₄)-alkyl,

where the (C₁-C₄)-alkyl is optionally substituted by methythio, hydroxyl,
mercapto, guanidyl or by a group of the formula -NR¹⁵R¹⁶ or
-NR¹⁷-OC-,

20

in which

R^{15} and R^{16} independently of one another represent hydrogen, (C₁-C₈)-alkyl
or phenyl

25

and

R^{17} represents hydroxyl, benzyloxy, (C₁-C₃)-alkoxy or amino,

30

or the (C₁-C₄)-alkyl is optionally substituted by cyclopentyl, cyclohexyl or
phenyl, which for its part is substituted by hydroxyl, fluorine,
chlorine or (C₁-C₃)-alkoxy or amino,

and

35

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R^{11} and R^{12} are identical or different and represent hydrogen or (C₁-C₃)-alkyl,

or

5

R^{11} and R^{12} together with the nitrogen atom form a morpholinyl ring,

A and E represent a bond,

10

D represents an oxygen atom,

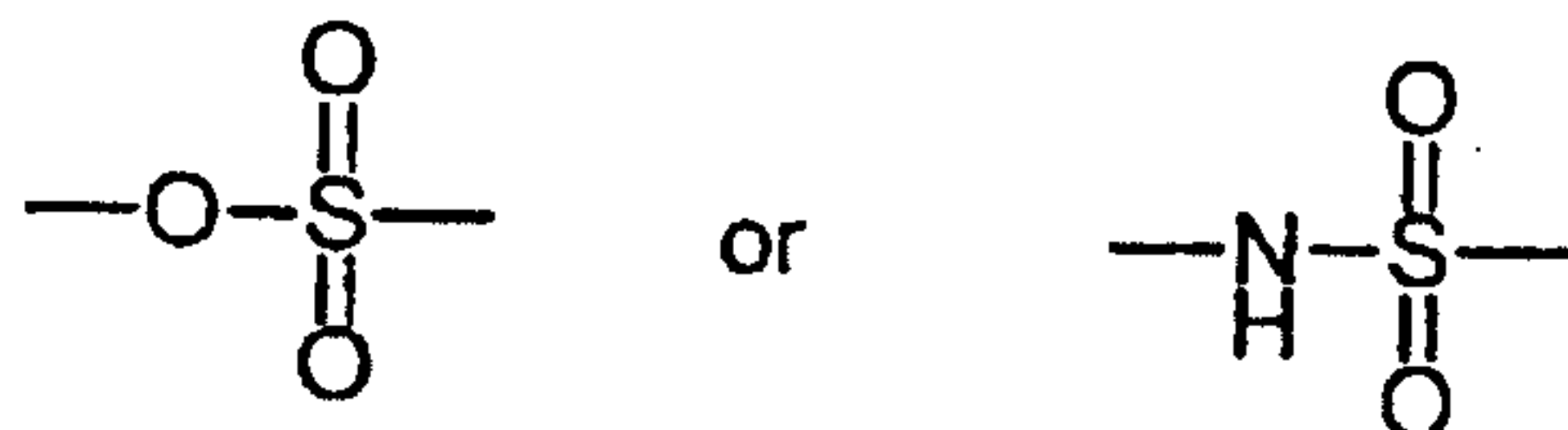
G represents doubly attached phenyl which are optionally substituted by one or more identical or different substituents selected from the group consisting of:

15

hydroxyl, trifluoromethyl, carboxyl, fluorine, chlorine, bromine, (C₁-C₃)-alkyl, hydroxy(C₁-C₃)alkyl or (C₁-C₃)-alkoxy

L represents a radical of the formula

20



where the left-hand side of the radicals is attached to G,

25

R^2 represents (C₁-C₈)-alkyl, which is optionally substituted by one or more identical or different substituents selected from the group consisting of:

fluorine, chlorine, bromine, phenyl, trifluoromethyl or trifluoromethyl-substituted (C₁-C₄)-alkoxy,

30

and pharmaceutically acceptable salts thereof.

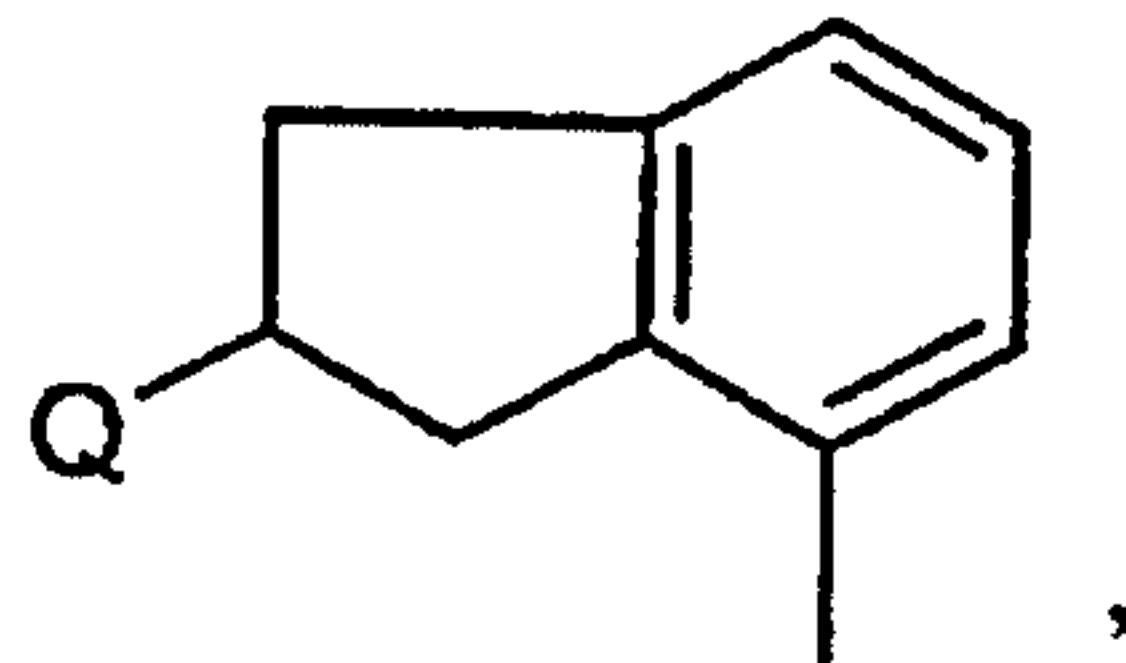
5. Compounds of the general formula (I), according to Claim 1,

in which

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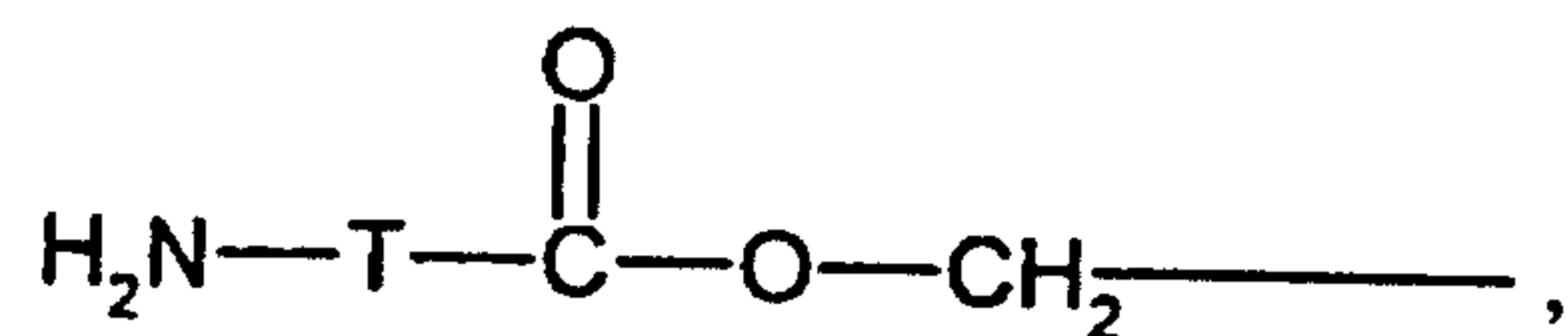
R^1 represents a radical of the formula



in which

5

Q represents a radical of the formula



in which

10

T represents a radical of the formula $-(CH_2)_d-$,

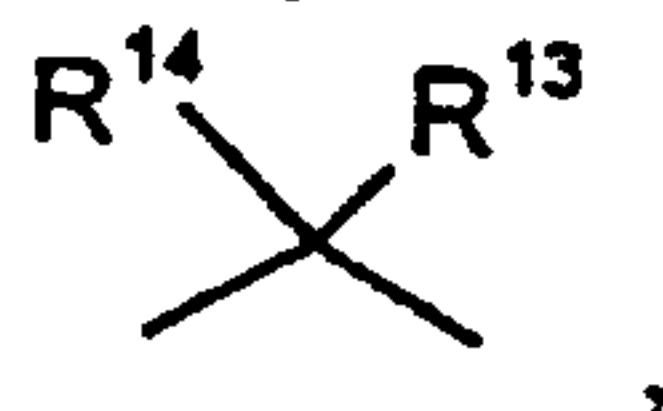
in which

15

d represents a number 1, 2, 3, 4, 5 or 6,

or

T represents a moiety of an amino acid radical of the formula



20

in which

R^{13} represents hydrogen,

and

25

R^{14} represents hydrogen, (C_1-C_4) -alkyl, benzyl or a radical of the formula $-CH_2OH$,

A and E represent a bond,

30

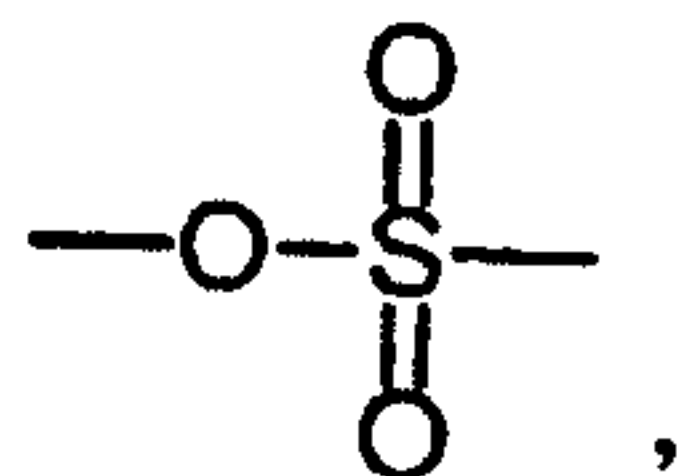
D represents an oxygen atom,

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G represents phenyl, which is optionally substituted by fluorine, chlorine or bromine,

5 L represents a radical of the formula



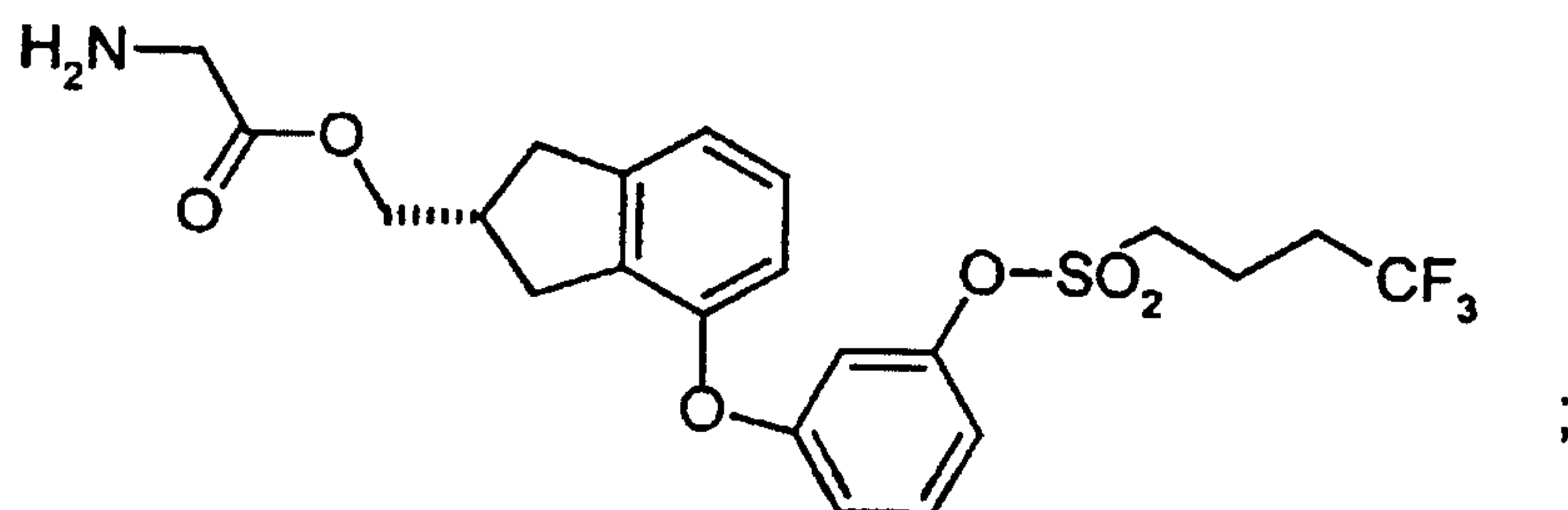
where the left-hand side of the radical is attached to G,

10 R² represents (C₁-C₄)-alkyl, which is optionally substituted by fluorine or trifluoromethyl,

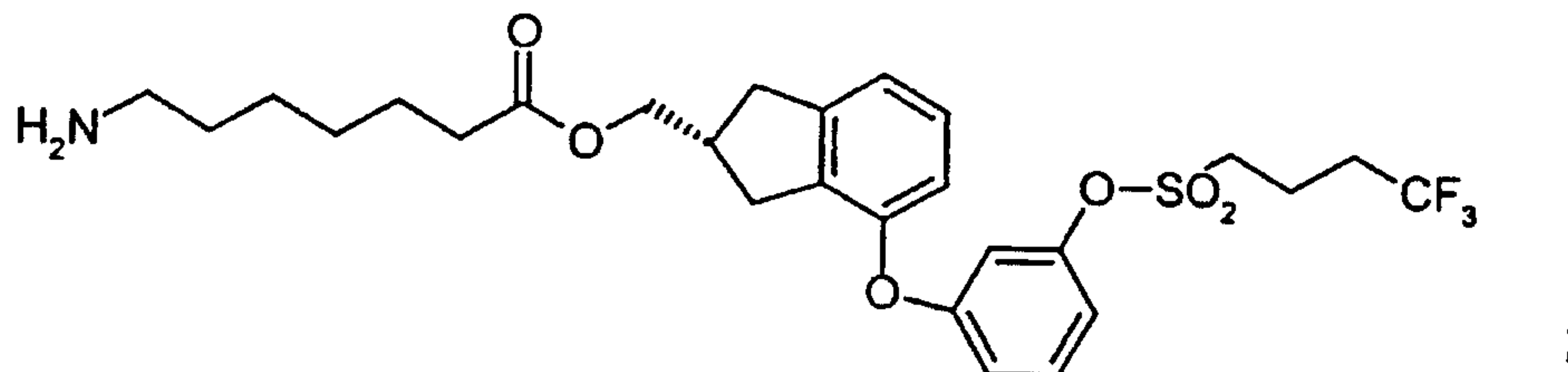
and pharmaceutically acceptable salts thereof.

15 6. Compounds selected from the group consisting of

(R)-3-(2-glycinyloxymethyl-indanyl-4-oxy)-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



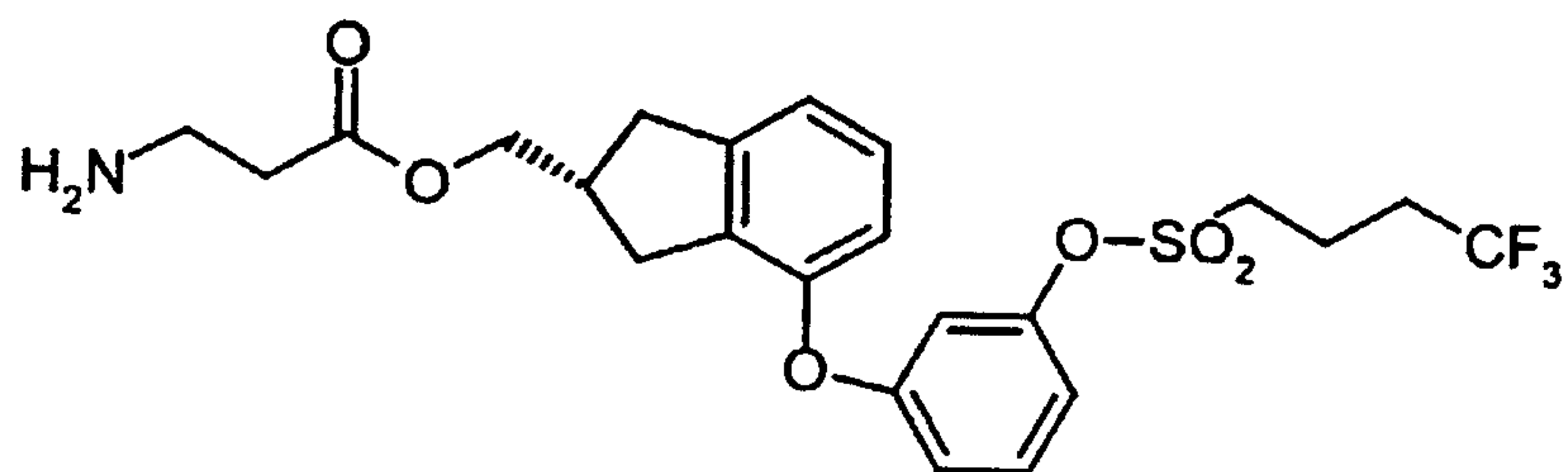
20 (R)-3-[2-(7-aminoheptanoyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate



(R)-3-[2-(3-aminopropanoyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butan-1-ylsulphonate

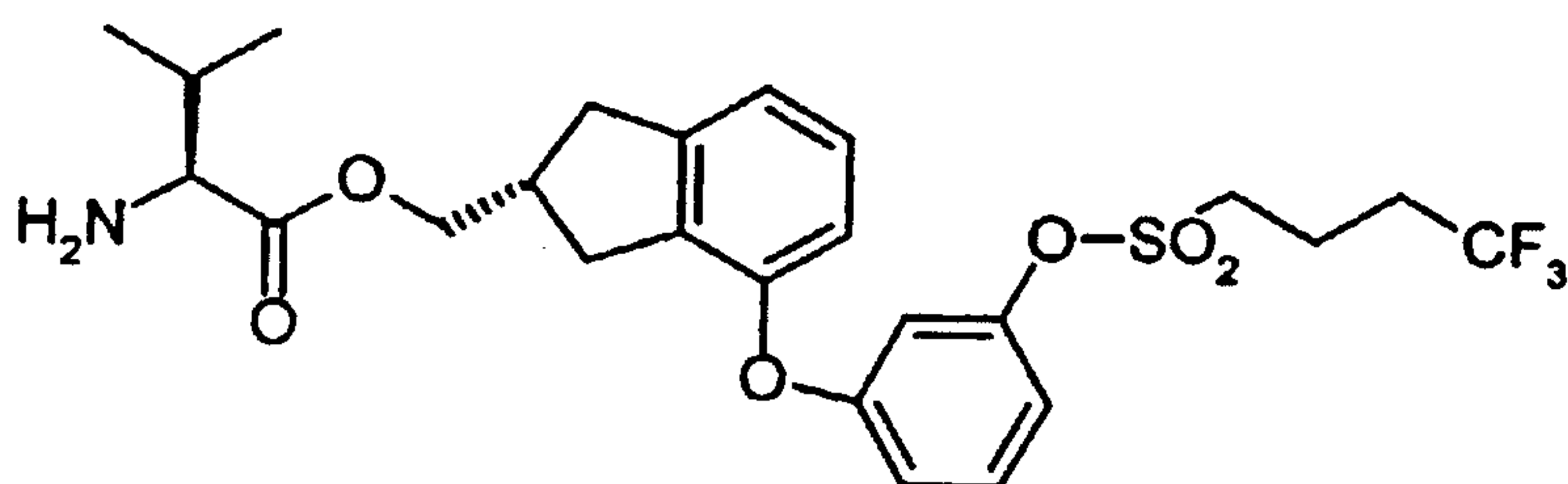
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; and

(R)-3-[2-((S)-valinyloxymethyl)-indanyl-4-oxy]-phenyl 4,4,4-trifluoro-1-butanesulphonate



5

and pharmaceutically acceptable salts thereof.

7. Process for preparing the compounds of the general formula (I) according to the invention, characterized in that compounds of the general formula (II)

10



in which

15

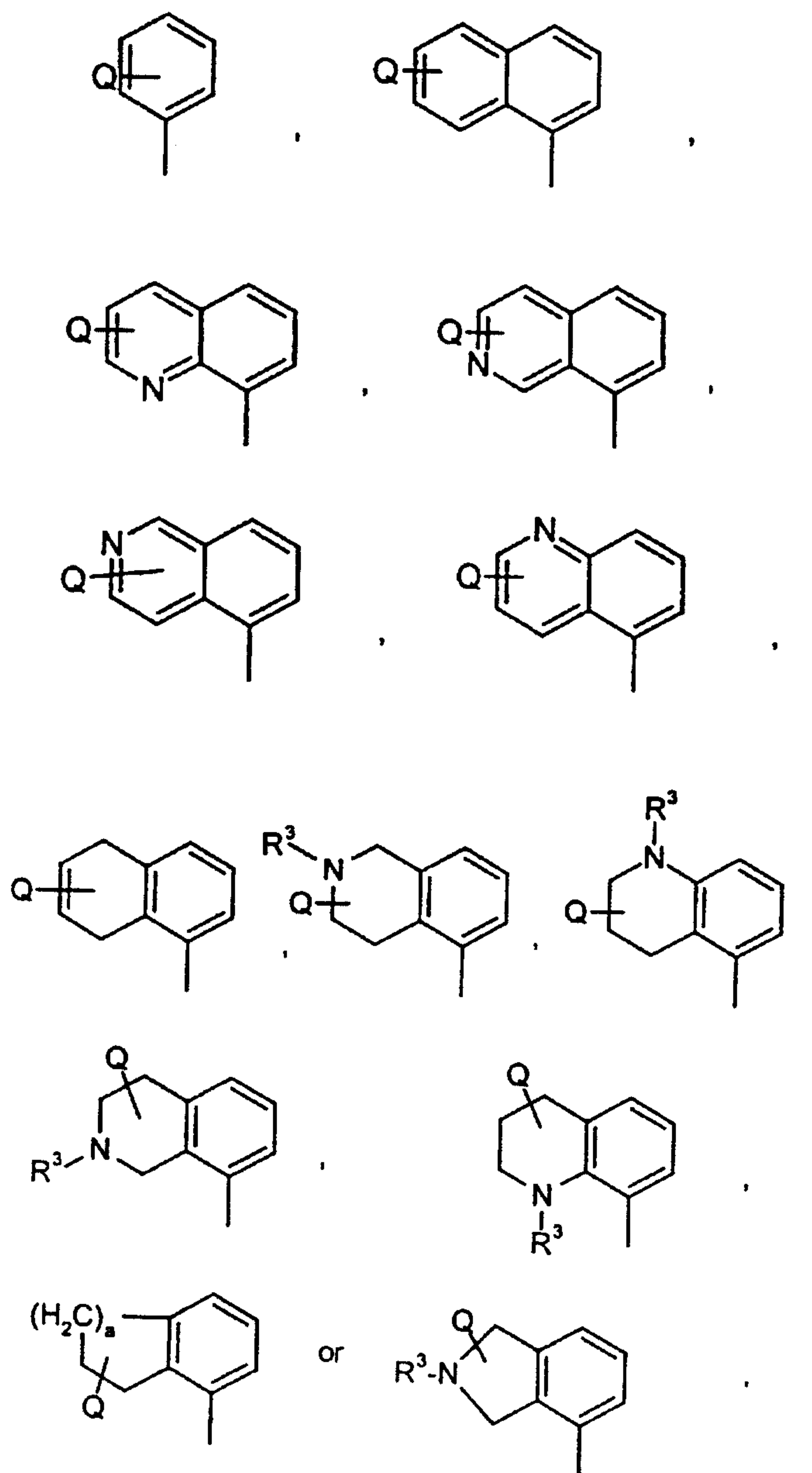
A, D, E, G, L, R^2 , R^9 and R^{10} and have the abovementioned meaning

and

$R^{1'}$ represents a radical of the formula

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5 in which

a represents a number 1 or 2,

R³ represents hydrogen, (C₂-C₆)-alkenyl, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

and where all phenyl ring systems listed above are optionally substituted, optionally geminally, by one or more identical or different substituents selected from the group consisting of:

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5 halogen, carboxyl, hydroxyl, phenyl, (C₁-C₆)-alkoxy, (C₁-C₆)-
alkoxycarbonyl, (C₁-C₈)-alkyl, which for its part may be substituted
by halogen, C₁-C₆-alkylsulphonyloxy, azide, amino, mono(C₁-C₆)-
alkylamino, di(C₁-C₆)-alkylamino or hydroxyl,
a group of the formula $-(CO)_b-NR^4R^5$,

in which

10 b represents a number 0 or 1,

R⁴ and R⁵ are identical or different and independently of one another
represent hydrogen, phenyl, (C₁-C₆)-acyl, cyclo(C₄-C₇)-acyl,
benzoyl or (C₁-C₆)-alkyl, which is optionally substituted by amino,
mono(C₁-C₆)-alkylamino, di(C₁-C₆)-alkylamino,

15

or

20 R⁴ and R⁵ together with the nitrogen atom form a 5- or 6-membered
saturated heterocycle which may optionally contain one or more
further heteroatom(s) from the group consisting of S and O and/or
one or more radical(s) of the formula $-NR^8$,

in which

25 R⁸ represents hydrogen, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

and

30 a group of the formula $-NR^6-SO_2-R^7$

in which

R⁶ represents hydrogen, phenyl, (C₁-C₆)-alkyl or (C₁-C₆)-acyl,

35 R⁷ represents phenyl or (C₁-C₆)-alkyl,

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and

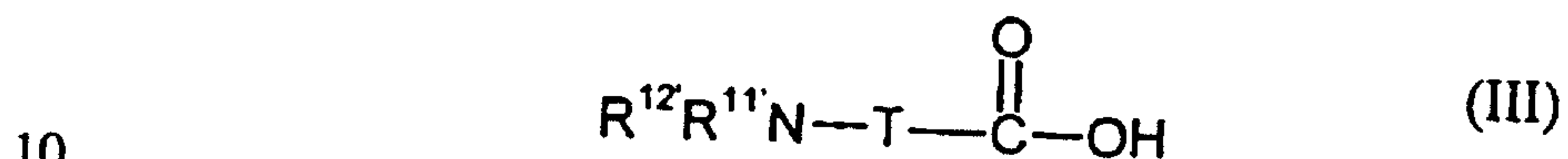
Q' represents a radical of the formula $\text{HO}-(\text{R}^{10}\text{R}^9\text{C})_c-$,

5

in which

c, R^9 and R^{10} have the meaning given above,

are reacted with compounds of the general formula (III)



10

in which

 $\text{R}^{11'}$ represents hydrogen

15

and

 $\text{R}^{12'}$ represents one of the amino protective groups listed above, preferably represents tert-butyloxycarbonyl,

20

in inert solvents, if appropriate in the presence of a base and an auxiliary,

and the amino protective group is removed by customary methods,

25

and the amino group is then, if appropriate, reductively alkylated or dialkylated with an aldehyde or ketone,

or alkylated or dialkylated with a halide,

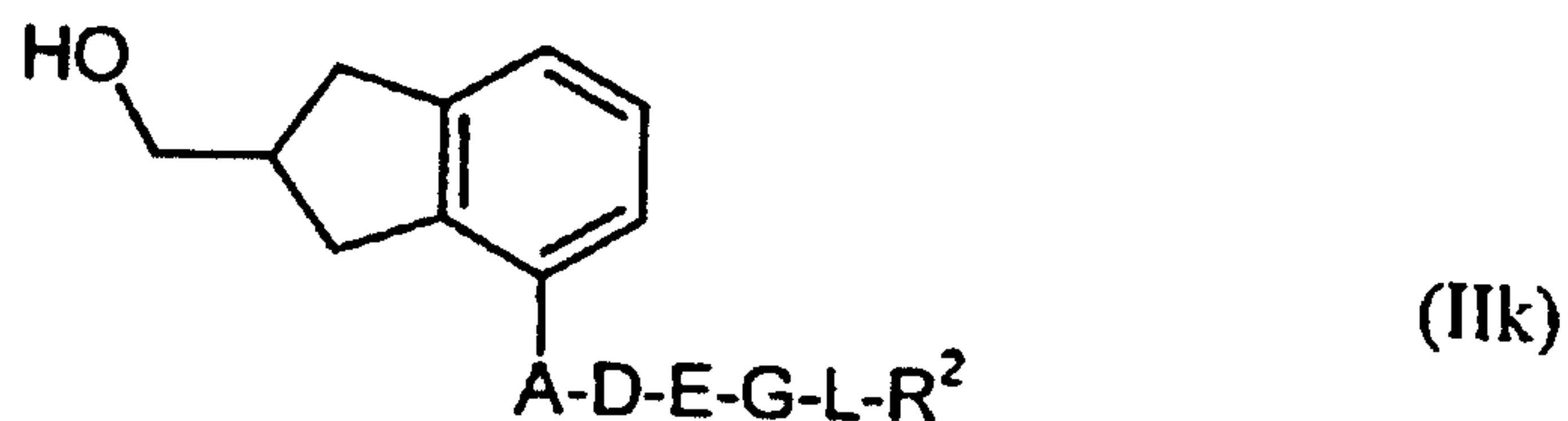
30

followed, if appropriate, by derivatizations according to customary methods, such as, for example, an alkylation or esterification, depending on the substituents listed above.

8. Process for preparing compounds of the general formula (IIk)

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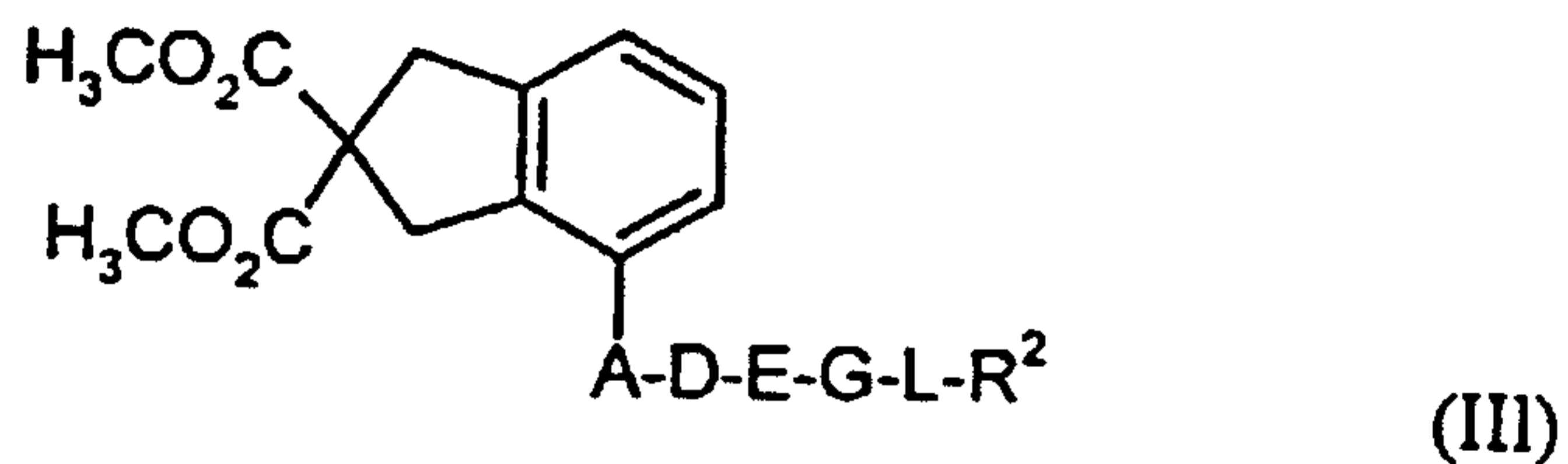


in which

A, D, E, G, L and R^2 have the meaning given above,

5

characterized in that the compounds of the general formula (III)

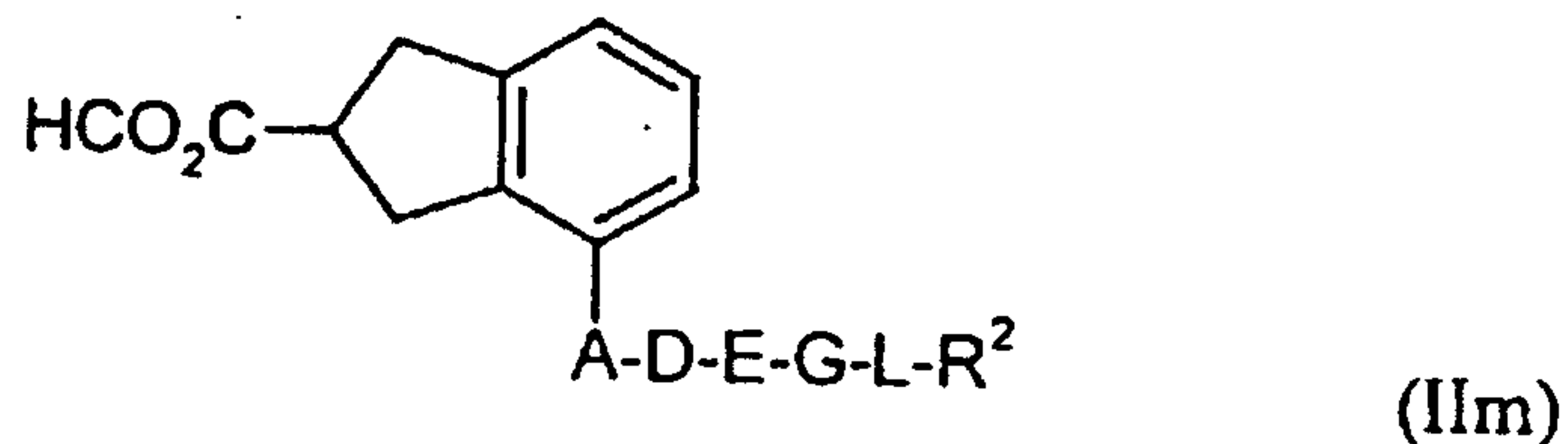


in which

10

A, D, E, G, L and R^2 have the meaning given above

are converted, by using HBr and acetic acid, into the compounds of the general formula (IIIm)



15

in which

A, D, E, G, L and R^2 have the meaning given above,

20

and, in a last step, a reduction with $\text{BH}_3 \times \text{S}(\text{CH}_3)_2$ in tetrahydrofuran is carried out,

and, in the case of the pure enantiomers, an HPLC separation by customary methods is carried out.

25

9. Pharmaceutical preparations which comprise, as active component, at least one compound according to any of Claims 1 to 6 in combination with at

Le A 33 201-Foreign countries

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least one pharmaceutically acceptable essentially non-toxic vehicle or excipient.

- 5 10. Compounds according to any of Claims 1 to 6 for use as medicaments in the treatment of humans and animals.
- 10 11. Use of the compounds according to any of Claims 1 to 6 for preparing a medicament for the prevention and/or treatment of neurodegenerative disorders.
12. Use of the compounds according to any of Claims 1 to 6 for preparing a medicament for the prevention and/or treatment of cerebral ischaemias and craniocerebral trauma.
- 15 13. Use of the compounds according to any of Claims 1 to 6 for the treatment of states of pain, emesis, nausea, glaucoma, asthma, anorexia, convulsions, rheumatism, sedation and mobility disorders.
- 20 14. Use of the compounds according to any of Claims 1 to 6 for the treatment of bacterial or viral infections, autoimmune diseases, inflammatory or autoimmunologically related diseases of the joints of the bone and muscle apparatus, of the internal and external organs, of the central nervous system, of the sense organs and of the haematogenic system in humans and animals.
- 25 15. Use of the compounds according to any of Claims 1 to 6 for the treatment of migraine and spasticity.

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