

**DIVISIÓN DE NUEVAS CREACIONES**

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EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

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NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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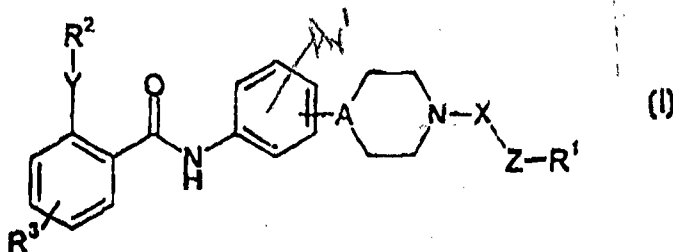
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: BENZAMIDE DERIVATIVES AND THEIR USE AS APOB-100 SECRETION INHIBITORS



## (57) Abstract

The invention relates to therapeutic benzamide compounds of formula (I) wherein A represents N or CH; X is selected from the following groups: (i) -C<sub>1-6</sub>alkylene-, optionally containing one or two double bonds and optionally substituted by one or more hydroxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub>acyl or C<sub>1-6</sub>acyloxy groups, (ii) oxo, sulfonyl, thioxy, (iii) -C<sub>1-6</sub>alkylenecarbonyl-, -C<sub>1-6</sub>alkylenesulfonyl-, -C<sub>1-6</sub>alkylenethio-, (iv) -C<sub>2-6</sub>alkyleneoxy-, -C<sub>2-6</sub>alkylenethio-, -C<sub>2-6</sub>alkylene(N-H or N-C<sub>1-6</sub>alkyl)amino-, (v) -C<sub>1-6</sub>alkylenecarboxy-, -C<sub>1-6</sub>alkylenethioamido-, -C<sub>1-6</sub>alkylene(N-H or N-C<sub>1-6</sub>alkyl)carboxamido-, and (vi) -C<sub>2-6</sub>alkyleneoxycarbonyl-, -C<sub>2-6</sub>alkylenethiocarbonyl-, -C<sub>2-6</sub>alkylene(N-H or N-C<sub>1-6</sub>alkyl)aminocarbonyl-; Z represents a direct link or -C<sub>1-6</sub>alkylene-, optionally containing one double bond and optionally substituted by one or more hydroxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub>acyl or C<sub>1-6</sub>acyloxy groups; R<sup>1</sup> is selected from the following groups: (i) hydrogen, C<sub>1-3</sub>perfluoroalkyl, (ii) C<sub>6-10</sub> aryl, C<sub>3-8</sub>cycloalkyl and fused benz derivatives thereof, C<sub>7-10</sub>polycycloalkyl, C<sub>4-8</sub>cycloalkenyl, C<sub>7-10</sub>polycycloalkenyl, (iii) a heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, and (iv) where either X is C<sub>1-6</sub>alkylene and Z is a direct link, or Z is C<sub>1-6</sub>alkylene; R<sup>1</sup> additionally may represent a halogen, cyano, nitro or C<sub>1-6</sub>acyl group, wherein, when R<sup>1</sup> contains one or more rings, said rings may each independently bear 0 to 4 substituents. Y represents a direct or oxy link, -C<sub>1-6</sub>alkylene-, -oxyC<sub>1-6</sub>alkylene- or a heterocyclyl consisting of monocyclic radicals. R<sup>2</sup> represents phenyl, C<sub>3-8</sub>cycloalkyl, or a heterocyclyl consisting of monocyclic radicals, and where each R<sup>2</sup> is optionally substituted by one or more groups independently selected from halogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>3-8</sub>cycloalkyl, C<sub>1-3</sub>perfluoroalkyl, C<sub>1-4</sub>perfluoroalkoxy, hydroxycarbonyl, C<sub>1-6</sub>alkoxycarbonyl, cyano, nitro, C<sub>1-4</sub>alkylaminosulfonyl; R<sup>3</sup> represents hydrogen or one or more groups independently selected from halogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-3</sub>perfluoroalkyl or C<sub>1-3</sub>perfluoroalkoxy; or a physiologically acceptable salt, solvate or derivative thereof, pharmaceutical compositions, to processes for their preparation and their use in the treatment of conditions mediated by ApoB-100 regulation.

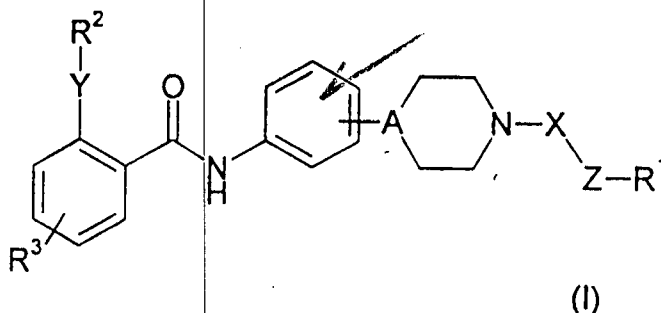
# BENZAMIDE DERIVATIVES AND THEIR USE AS APOB-100 SECRETION INHIBITORS

This invention relates to novel compounds which inhibit hepatic production of apoprotein B-100 (apoB-100), and to processes for their preparation, pharmaceutical compositions containing them and their medical use.

ApoB-100 is the main protein component of low density lipoprotein-cholesterol (LDL-C). High LDL-C plasmatic levels are a major risk factor for atherosclerosis and coronary artery diseases. ApoB-100 plasmatic levels correlate with LDL-C plasmatic levels and also constitute a cardiovascular risk factor in themselves. ApoB-100 is exclusively produced by hepatocytes and reducing hepatic production of ApoB-100 should induce a decrease of LDL-C plasmatic levels.

Compounds having ApoB-100 inhibition properties have been described in WO96/40640, which is incorporated herein by reference.

The present invention provides a compound of formula (I)



wherein

A represents N or CH;

X is selected from the following groups:

- (i) -C<sub>1-6</sub>alkylene- optionally containing one or two double bonds and optionally substituted by one or more hydroxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> acyl or C<sub>1-6</sub> acyloxy groups,
- (ii) oxo, sulfonyl, thioxo,
- (iii) -C<sub>1-6</sub>alkylenecarbonyl-, -C<sub>1-6</sub>alkylenesulfonyl-, -C<sub>1-6</sub>alkylenethioxo-,

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- (iv)  $-C_{2-6}$ alkyleneoxy-,  $-C_{2-6}$ alkylenethio-,  $-C_{2-6}$ alkylene(N-H or N- $C_{1-6}$ alkyl)amino-,  
 (v)  $-C_{1-6}$ alkylenecarboxy-,  $-C_{1-6}$ alkylenethioamido-,  $-C_{1-6}$ alkylene(N-H or N- $C_{1-6}$ alkyl)carboxamido-, and  
 5 (vi)  $-C_{2-6}$ alkyleneoxycarbonyl-,  $-C_{2-6}$ alkylenethiocarbonyl-,  $-C_{2-6}$ alkylene(N-H or N- $C_{1-6}$ alkyl)aminocarbonyl-;

Z represents a direct link or  $-C_{1-6}$ alkylene-, optionally containing one double bond and optionally substituted by one or more hydroxy,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ acyl or  $C_{1-6}$ acyloxy groups ;

$R^1$  is selected from the following groups:

- (i) hydrogen,  $C_{1-3}$ perfluoroalkyl,  
 (ii)  $C_{6-10}$ aryl,  $C_{3-8}$ cycloalkyl and fused benz derivatives thereof,  
 15  $C_{7-10}$ polycycloalkyl,  $C_{4-8}$ cycloalkenyl,  $C_{7-10}$ polycycloalkenyl,  
 (iii) a heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, and  
 20 (iv) where either X is  $C_{1-6}$ alkylene and Z is a direct link, or Z is  $C_{1-6}$ alkylene,  $R^1$  additionally may represent a halogen, cyano, nitro or  $C_{1-6}$ acyl group,

25 wherein, when  $R^1$  contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from

- (i) halogen, hydroxy, cyano, nitro, formyl,  $C_{1-6}$ alkylsulfonylamino,  
 (ii)  $C_{1-6}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{1-3}$ perfluoroalkyl,  
 30 (iii)  $C_{1-6}$ alkoxy, methylenedioxy,  $C_{1-3}$ perfluoroalkoxy,  $C_{1-6}$ alkylthio,  
 (iv) amino,  $C_{1-6}$ alkylamino, di- $C_{1-6}$ alkylamino,  
 (v) phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy,  
 (vi) hydroxycarbonyl,  $C_{1-6}$ alkoxycarbonyl,  
 (vii) aminocarbonyl,  $C_{1-6}$ alkylaminocarbonyl, di- $C_{1-6}$ alkylaminocarbonyl, di- $C_{1-6}$ alkylaminocarbonyl,  $C_{1-6}$ alkoxy,  $C_{1-3}$ perfluoroalkylaminocarbonyl,  
 35

C=O

- (viii)  $C_{1-6}$ acyl,  $C_{1-6}$ acyloxy,  $C_{1-6}$ acyloxy $C_{1-6}$ alkyl,  $C_{1-6}$ acylamino, and  
(ix) an aromatic heterocyclyl consisting of monocyclic radicals, wherein said radicals contain 5-6 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and where each of the said heterocyclyl groups is optionally substituted by one or more groups independently selected from halogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-3}$ perfluoroalkyl and  $C_{1-3}$ perfluoroalkoxy;

Y represents a direct or oxy link,  $-C_{1-6}$ alkylene-,  $-oxyC_{1-6}$ alkylene- or a heterocyclyl consisting of monocyclic radicals, wherein said radicals contain 5 ring atoms, and wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur and wherein the ring may be independently saturated, partially unsaturated, or aromatic;

$R^2$  represents phenyl,  $C_{3-8}$ cycloalkyl, or a heterocyclyl consisting of monocyclic radicals, wherein said radicals contain a total of from 5-6 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the ring may be independently saturated, partially unsaturated, or aromatic, and where each  $R^2$  is optionally substituted by one or more groups independently selected from halogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{3-8}$ cycloalkyl,  $C_{1-3}$ perfluoroalkyl,  $C_{1-3}$ perfluoroalkoxy, hydroxycarbonyl,  $C_{1-6}$ alkoxycarbonyl, cyano, nitro,  $C_{1-4}$ alkylaminosulfonyl;

$R^3$  represents hydrogen or one or more groups independently selected from halogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-3}$ perfluoroalkyl or  $C_{1-3}$ perfluoroalkoxy; or a physiologically acceptable salt, solvate or derivative thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic and inorganic acids for example, citrates, hydrochlorides, hydrobromides, or sulphates. Particularly preferred salts are citrates or hydrochloride salts.

The solvates may, for example, be hydrates.

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4'-Isopropyl-6-methyl-biphenyl-2-carboxylic acid [4-(4-carbamoylmethyl-piperazin-1-yl)-phenyl]-amide ;

4'-Isopropyl-6-methyl-biphenyl-2-carboxylic acid (4-(4-(3-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzyl)-piperazine-1-yl)-phenyl)-amide ;

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)-piperazin-1-yl)-phenyl]-amide ;

4'-Isopropyl-5-methyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)-piperazin-1-yl)-phenyl]-amide ;

10 5-Methyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-(4-(1H-pyrrol-2-ylmethyl)-piperazin-1-yl)-phenyl]-amide ;

or a physiologically acceptable salt, solvate or derivative thereof.

15 The term "physiologically functional derivative" as used herein refers to any physiologically acceptable derivative of a compound of the present invention, for example, an ester, which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) such a compound or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles And Practice, 20 which is incorporated herein by reference.

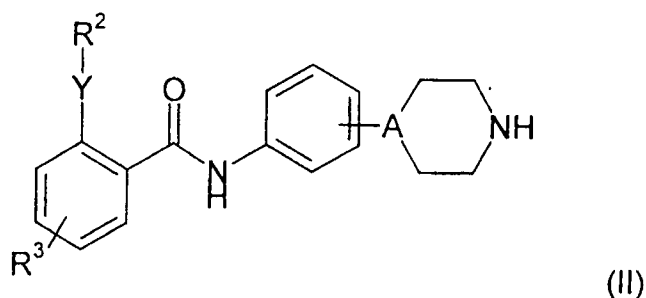
25 The compounds of the invention are inhibitors of hepatic production of apoB-100 and are thus of use in the treatment of conditions resulting from elevated circulating levels of apoB-100.

30 The ability of the compounds of the invention to inhibit the production of apoB-100 by human hepatocytes in vitro is determined using primary human hepatocytes as a model system. The specificity of the compounds of the invention is established by comparing the effects on apoB-100, apoprotein A-1, and fibrinogen production. A specificity of at least 100 is preferred.

35 The in vivo profile of the compounds was determined by acute oral administration of the compounds of the invention to DBA/2 mice and Wistar rats with measurement of apoB-100 plasmatic levels as percentage of control values. Active compounds are further evaluated in Wistar rats by repeated oral

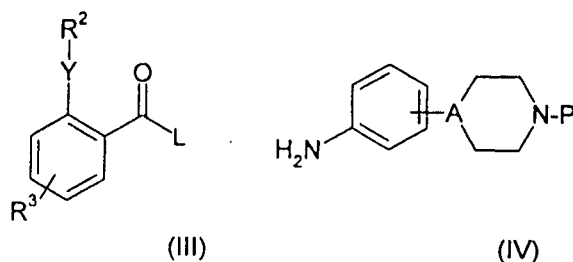
In the following description, the groups X, Y, Z, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as previously defined for compounds of formula (I), unless specified otherwise.

5 According to a general process (A), a compound of formula (I) may be prepared by reacting a compound of formula (II) with a compound of formula R<sup>1</sup>-Z-X-L



10 where L represents a suitable halide leaving group, e.g. chloride, under standard displacement conditions, or where X is an oxo group, L may additionally represent a hydroxy group, the reaction being effected under standard acid and amine coupling conditions.

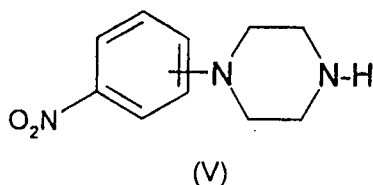
15 A compound of formula (II) may be prepared by reaction of a compound of formula (III) with a compound of formula (IV)



20 where L is defined above and P is a suitable amine protecting group, e.g. tert-butoxycarbonyl (Boc), under standard coupling conditions for an acid and amine coupling, followed by deprotection of the protecting group under suitable conditions, e.g. acidic removal of a Boc group.

A compound of formula (IV), where A represents N, may be prepared by the two step reaction of a compound of formula (V)

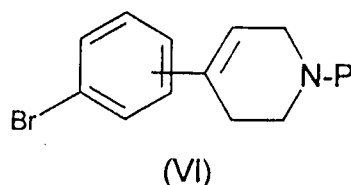
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comprising incorporation of the protecting group P using standard methodology followed by reduction of the nitro group, e.g. under hydrogenation conditions.

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A compound of formula (IV), where A represents CH, may be prepared from a compound of formula (VI)



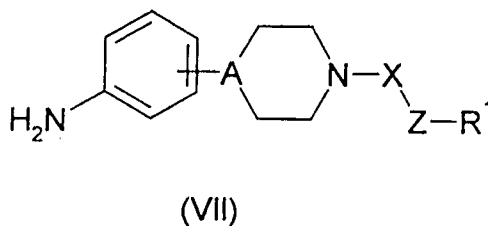
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by reaction with a suitable compound of formula  $H_2N-P'$  where  $P'$  is a suitable protecting group which is labile under hydrogenation conditions, such as a benzyl group, using a suitable coupling agent or agents such as tris(dibenzylidene acetone)dipalladium, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (binap) and sodium tert-butoxide in a suitable solvent such as toluene, followed by removal of the protecting group and reduction of the double bond under hydrogenation conditions.

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According to a second method (B), compounds of formula (I) may be prepared by reaction of compounds of formula (III) and compounds of formula (VII)



where L is defined above, under standard coupling conditions.

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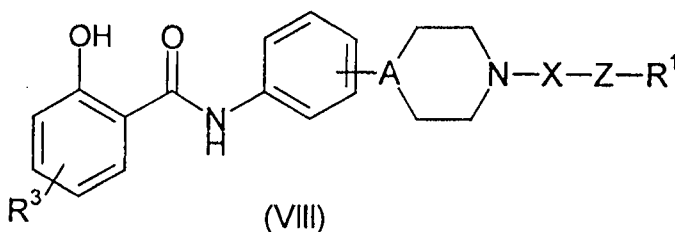
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Compounds of formula (VII) may be prepared by reaction of a compound of formula (V) with a compound of formula  $R^1-Z-X-L$ , where L is defined above, followed by reduction of the nitro group under hydrogenation or reductive tin chloride conditions.

5

According to a third process (C), a compound of formula (I) where Y is  $-O-C_{1-4}$ alkylene- may be prepared by reaction of a compound of formula (VIII) with a compound of formula  $R^2-C_{1-4}$ alkylene-L, where L is defined above,

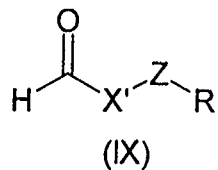
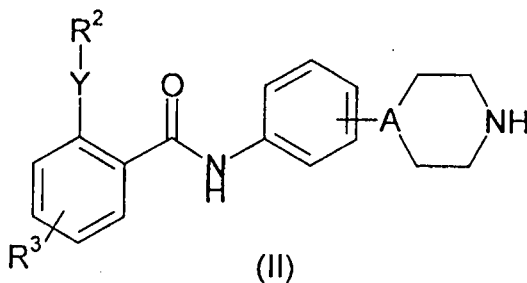


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Compounds of formula (VIII) may be prepared according to the process outlined in process B.

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According to a fourth general process (D), a compound of formula (I), where at least part of X represents an alkylene link to the piperidine or piperazine group, may be prepared by reacting a compound of formula (II) with a compound of formula (IX)



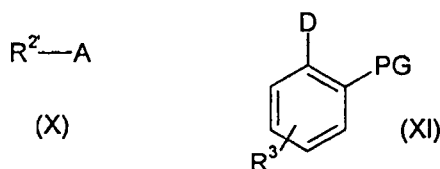
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where  $X'$  represents X minus a methylene group, under standard reductive amination conditions, e.g. using sodium triacetoxyborohydride in a solvent such as dichloroethane.

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According to a fifth process (E), a compound of formula (I) may be prepared from a different compound of formula (I), using standard techniques well known in the art. For example, compounds of formula (I) where R<sup>1</sup> comprises a group containing an amide group may be prepared from the compound of formula (I) where the corresponding position comprises a carboxylic acid group, which in turn may be prepared from the compound of formula (I) where the corresponding position comprises a carboxylic ester group. Well known methods in the art may be employed to facilitate the transformation of an ester to an acid and then to an amide.

A compound of formula (III), where Y is a direct link, R<sup>2</sup> is a phenyl or an aromatic heterocyclyl and L is a hydroxy group, may be prepared firstly by coupling a boronic acid with a suitable leaving group, represented by a compound of formula (X) and a compound of formula (XI)



where R<sup>2</sup> represents phenyl or an aromatic heterocyclyl, PG represents a protected carboxylic acid and A and D represent either the boronic acid or the suitable leaving group, such as triflate or bromide, followed by deprotection of the protecting group under standard conditions, such as base removal of an ester group. Where L represents a halide leaving group, the carboxylic acid product can be treated with a suitable reagent, such as thionyl chloride, to give the corresponding chloride leaving group.

Where R<sup>1</sup> is a phenyl, substituted by an aromatic heterocyclyl, the aromatic heterocyclyl may be introduced by any well known methods in the art. For instance, where the substituent is a methyl substituted oxadiazole, this may be formed by treatment of a suitable benzamide derivative with a suitable reagent, such as dimethylacetamide dimethylacetal at elevated temperature, followed by cyclisation of the intermediate compound with hydroxylamine.

The various general methods described above may be useful for the introduction of the desired groups at any stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

Compounds of formula  $R^1-Z-X-L$ , (III), (V) and (VI), (IX), (X) and (XI) are known or may be prepared by standard methods well known in the art and/or herein described.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compound of formula (I) using conventional methods.

The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent to give the corresponding solvates.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with the enantiomeric mixture of a compound of general formula (I). The resulting mixture of isomeric salts may be separated, for example, by fractional crystallisation into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

The invention is further illustrated by the following intermediates and examples. All temperatures are in degrees centigrade.

Abbreviations:

MS - LCMS mass spectrography, HOBt-1-Hydroxybenzotriazole, AcOEt-Ethyl acetate, EDCI-1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, BINAP-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, THF- Tetrahydrofuran, MeOH- Methanol, EtOH- Ethanol, Et<sub>3</sub>N- Triethylamine

Intermediate 1

5-Methoxy-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester

To a stirred solution of 4-methoxy-2-(trifluoro-methanesulfonyloxy)-benzoic acid methyl ester (6.28 g) in toluene (100 mL) was added LiCl (2.54 g) and Pd(PPh<sub>3</sub>)<sub>4</sub> (1.15 g). After few minutes at room temperature, a 2M solution of Na<sub>2</sub>CO<sub>3</sub> (26 mL) was added followed by a solution of 4-trifluoromethylphenyl boronic acid (4.17 g) in EtOH (30 mL). The resulting mixture was stirred under reflux for 6 hours. The mixture was cooled to room temperature and the phases were separated. The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with hexane/AcOEt (90/10) to give the title compound (5.7 g) as white crystals.  
m.p. : 93-94°C.

Similarly prepared were :

Intermediate 2

4'-Isopropyl-5-methyl-biphenyl-2-carboxylic acid methyl ester as an oil (10 g),  
GCMS : m/z 268 (M+)  
from 4-methyl-2-(trifluoro-methanesulfonyloxy)-benzoic acid methyl ester (11.9 g) and 4-isopropylphenyl boronic acid (7.2 g).

Intermediate 3

5-Methyl-4'-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester as a pale yellow oil (4.2 g),  
GCMS : m/z 294(M+)  
from 4-methyl-2-(trifluoro-methanesulfonyloxy)-benzoic acid methyl ester (4.7 g)