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(54) Title: NEW ASYMMETRIC PROCESS FOR THE PREPARATION OF DIARYLMETHYLPIPERAZINES DERIVATIVES AND NOVEL ASYMMETRIC DIARYLMETHYLAMINES AS INTERMEDIATES

(57) Abstract: An asymmetric synthesis of diarylmethylpiperazines is described. The synthetic route enables preparation of a variety of enantiomerically pure amines with different *N*-alkyl groups. The invention includes an asymmetric addition of organometallic compounds to chiral sulfinimine to give adducts in predominantly one diastereomer can subsequently be transferred into pure enantiomers of by cleavage of the chiral auxilliary which is followed by synthesis of the piperazine ring by alkylation procedures.



WO 02/070492 A1

New asymmetric process for the preparation of diarylmethylpiperazines derivatives and novel asymmetric diarylmethylamines as intermediates.

#### FIELD OF THE INVENTION

5 The present invention relates to a novel asymmetric process for the preparation of diarylmethylpiperazines derivatives and to novel asymmetric diarylmethylamines as intermediates.

#### BACKGROUND OF THE INVENTION AND PRIOR ART

10 Diarylmethylamines are an important class of amines present in many compounds with biological activity, for example diarylmethylpiperazines, and constitutes key intermediates in the synthesis of these compounds. Most preparations of enantiomerically pure diarylmethyl-amines and -piperazines rely on resolution of diastereomers by crystallization where half of the material is discarded.

15

There are few reports on asymmetric synthesis of diarylmethylpiperazines. The present invention describes a simple and practical process for asymmetric synthesis of diarylmethylpiperazines in high yield and enantiomeric purity with asymmetric diarylmethylamines as intermediates. The process relies on diastereoselective addition of  
20 organometallic compounds to chiral sulfinimines.

20

Diarylmethylpiperazines derivatives are known from *inter alia* WO 93/15062, WO 95/04051, and WO 97/23466 to have analgesic effect. The diarylmethylpiperazines derivatives are prepared starting from an N-unsubstituted piperazine derivative which is  
25 thereafter alkylated to give the desired diarylmethylpiperazines.

25

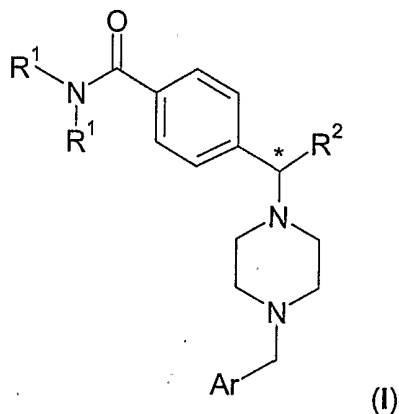
#### DESCRIPTION OF THE INVENTION

An asymmetric synthesis of diarylmethylpiperazines is described. The synthetic route enables preparation of a variety of enantiomerically pure amines with different N-alkyl  
30 groups. The invention includes an asymmetric addition of organometallic compounds to chiral sulfinimine to give adducts in predominantly one diastereomeric form. After purification by chromatography or crystallisation the pure diastereomer can subsequently

30

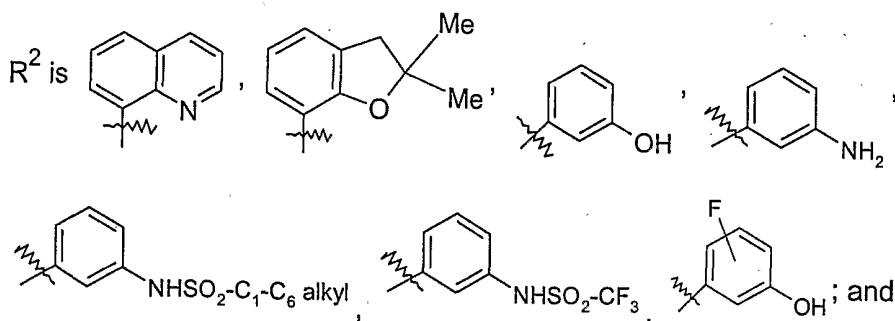
be transferred into the corresponding pure enantiomers of by cleavage of the chiral auxilliary which is followed by synthesis of the piperazine ring by alkylation procedures.

The present invention thus relates to a novel asymmetric process for the preparation of  
5 compounds of the general formula (I)



wherein

10  $R^1$  is  $C_1$ - $C_6$  alkyl,



Ar is selected from any one of phenyl, pyridinyl, thienyl, furanyl, imidazolyl, or triazolyl.

15 As used herein, the term " $C_1$ - $C_6$  alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said  $C_1$ - $C_6$  alkyl include, but is no limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

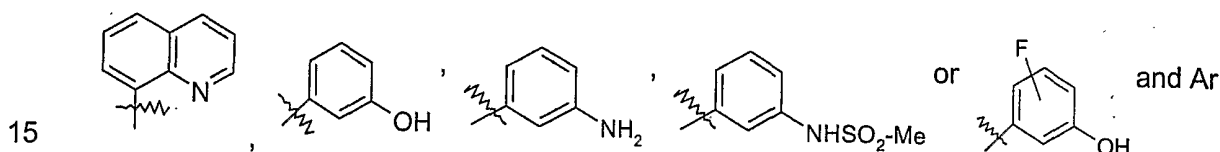
20 The term " $C_1$ - $C_6$  alkoxy" denotes a group O- $C_1$ - $C_6$  alkyl, wherein  $C_1$ - $C_6$  alkyl is as defined above.

The term "halogen" includes fluoro, chloro, bromo and iodo.

The term "hydride donating reagent", is a compound that can deliver a hydride to an imine thereby giving the corresponding amine. Examples of such hydride donating reagent  
 5 include, but is not limited to, sodium borohydride, sodium cyanoborohydride and sodium triacetoxymborohydride,

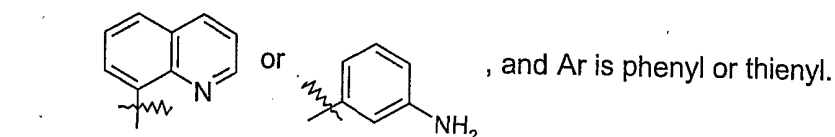
The asymmetric center is denoted "\*" in all figures. The present invention thus relates to enantiomerically pure compounds of Figure I, as either the isolated *R*-enantiomer or the  
 10 corresponding isolated *S*-enantiomer. Isolated enantiomers prepared according to the present invention can also be shown by indicating the optical rotation of an exemplified compound, e.g. (+)-6.

In a preferred embodiment of the present invention,  $R^1$  is ethyl or isopropyl,  $R^2$  is



is phenyl, pyridyl, thienyl, or furanyl.

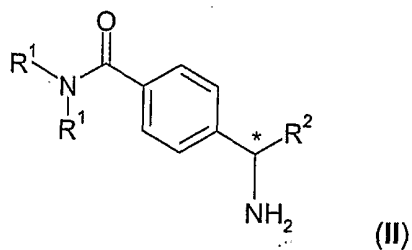
In a more preferred embodiment of the present invention,  $R^1$  is ethyl or isopropyl,  $R^2$  is



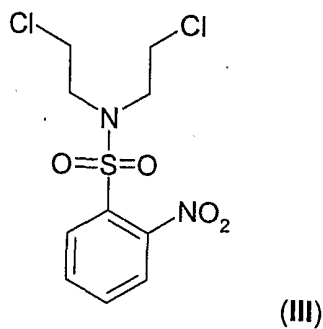
Each  $R^2$  and Ar heteroaromatic ring may optionally and independently be further substituted by up to three additional substituents selected from C<sub>1</sub>-C<sub>6</sub> alkyl, NO<sub>2</sub>, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, chloro, fluoro, bromo, and iodo. Preferred substituent is methyl. The  
 25 substitutions on the heteroaromatic ring may be in any position on said ring systems.

#### STEP 1

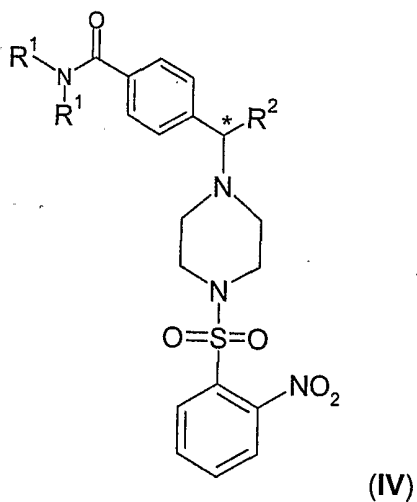
The novel asymmetric process of the present invention comprises the step of reacting a enantiomerically pure compound of the general formula (II)



wherein  $R^1$  and  $R^2$  are as defined above, with N,N-bis(2-chloroethyl)-2-nitrobenzeneamide of formula (III)



to give compounds of the general formula (IV)

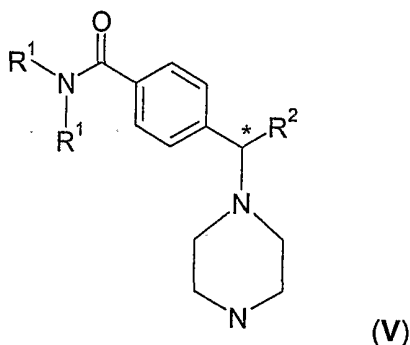


wherein  $R^1$  and  $R^2$  are as defined above. The reaction is carried out in a solvent at elevated temperature, such as reflux, in the presence of a base, such as a tertiary amine, for 10 to 50 hours. A molar excess of N,N-bis(2-chloroethyl)-2-nitrobenzenesulfonamide is used, e.g. 1.5 to 6, and is preferably added in portions to give a complete reaction.

Use of the 2-nitrobenzenesulfonate group is advantageous since it surprisingly can be cleaved off using conditions. These mild conditions are milder than the corresponding condition for other groups, such as the toluenesulfonate (tosylate) group. Mild  
5 deprotection conditions gives a cleaner reaction profile, less by-products, easier purification and increased yield. 2-nitrobenzenesulfonate group is thus the preferred N-protecting group to be used according to the present invention.

## STEP 2

10 The 2-nitrobenzenesulfonyl group of compounds of the general formula (IV) is thereafter cleaved by standard conditions, i.e. by using a sulfur nucleophile, such as thiophenol or mercaptoacetic acid, in the presence of a base, such as potassium carbonate, to give compounds of the general formula (V)



15

wherein R<sup>1</sup> and R<sup>2</sup> are as defined above

## STEP 3

20 Compounds of general formula (V) is thereafter alkylated under standard conditions using either;

i) a compound of the general formula Ar-CH<sub>2</sub>-X, wherein Ar is as defined above and X is halogen, preferably bromide, and a suitable base, or

25 ii) a compound of the general formula Ar-CHO, wherein Ar is as defined above, and a suitable reducing agent

to give compounds of the general formula (I), as defined above.

Suitable bases to be used in the standard alkylation step *i)* above includes, but is not limited to, triethylamine and potassium carbonate.

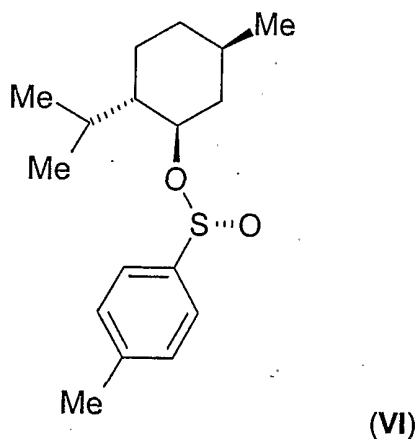
Suitable reducing agents to be used in the standard reduction step *ii)* includes, but is not limited to, sodium cyanoborohydride and sodium triacetoxyborohydride.

Non limiting examples of step 1 to 3 is shown below in Scheme 1.

The asymmetric key intermediate of the general formula (II) defined above is prepared by a process comprising the following steps.

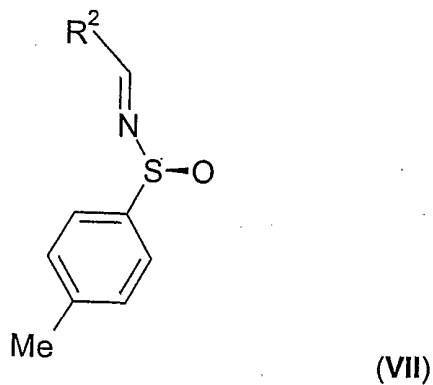
#### STEP 4

(1R,2S,5R)-(-)-Menthyl (S)-p-toluenesulfinate of the formula (VI)



15

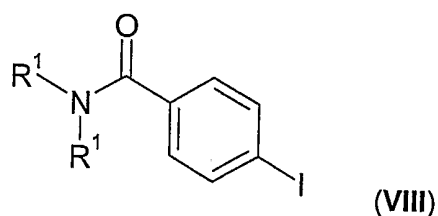
is reacted with lithium hexamethyldisilazan and a compound of the general formula  $R^2$ -CHO, wherein  $R^2$  is as defined above, to give a sulfimines of the general formula (VII)



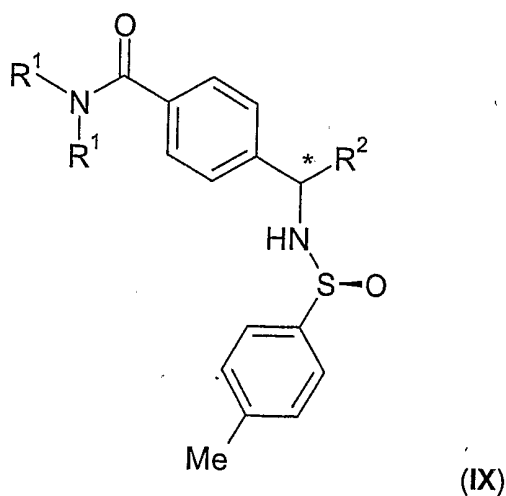
wherein  $R^2$  is as defined above. The reaction is carried out in an inert solvent, such THF, at around  $-78^\circ\text{C}$  under nitrogen atmosphere and for a few hours. A molar excess, such as 1.5 to 2 eq., of lithium hexamethyldisilazan is added first at the temperature is then increased to about room temperature for a few hours, e.g. 1-4 hours. The reaction is thereafter cooled again to around  $-78^\circ\text{C}$  and a molar excess of the aldehyde, e.g. 1 to 1.5 eq., is added and left for a few hours, e.g. 1 to 4 hours.

## STEP 5

10 p-Iodo-benzamide derivatives of the general formula (VIII)



wherein  $R^1$  is as defined above, is reacted with an alkyl lithium reagent, such as butyl lithium, in an inert solvent, such as THF, and low temperature, such as  $-78^\circ\text{C}$  and the sulfinimide prepared in step 4 above is added and allow to react for few minutes, such as 5 to 15 minutes, to give a diastereomeric mixture of the compounds of the general formula (IX)

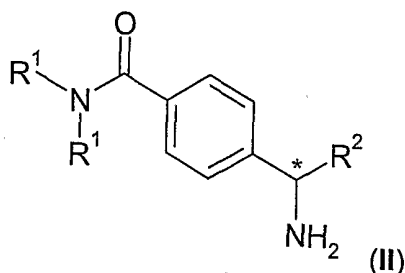


wherein  $R^1$  and  $R^2$  are as defined above.

The diastereomeric ratio of the products of step 5 is 70/30, preferably 80/20 and more preferably 90/10. The two diastereomers can thereafter be purified (from the other  
5 diastereomer) by standard techniques like crystallization or chromatography.

#### STEP 6

The purified diastereomer of the general formula (IX), prepared in step 5 above, is thereafter solvolized, e.g. methanolysis, by brief acid treatment to give the intermediate  
10 compound of the general formula (II)



wherein  $R^1$  and  $R^2$  are as defined above.

15

The enantiomeric excess (ee) of compounds of the general formula (II) prepared according to steps 4 to 6 of the present invention is >90%, preferably >95% and more preferably >98%.

20

If (1R,2S,5R)-(+)-menthyl (R)-p-toluenesulfinate is used in step 4 above and subsequent steps 5 and 6 are performed as the described the other optical isomer (enantiomer) of the compound of the general formula (II) will be obtained.

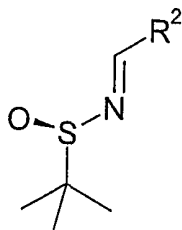
Non-limiting examples of steps 4 to 6 are shown below in Scheme 1.

25

In another embodiment of the present invention, asymmetric key intermediate compounds of general formula (II) is prepared by a process comprising the following steps.

## STEP 7

An aldehyde of the structure  $R^2$ -CHO, wherein  $R^2$  are as defined above, is reacted with (R)-(+)-2-methyl-2-propanesulfinamide to give a compound of the general formula (X)



5

(X)

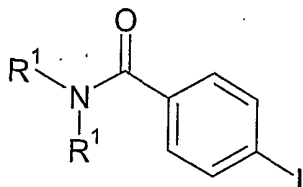
, wherein  $R^2$  is as defined above.

The reaction is carried out using excess titanium tetraethoxide, e.g. 1.1 to 2 eq., in a solvent, such as THF, at elevated temperature, such as 40 - 80°C, for a number of hours, such as 2 - 18 hours.

10

## STEP 8

p-Iodo-benzamide derivatives of the general formula (VIII)

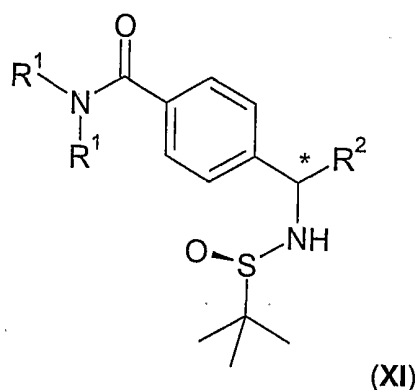


15

(VIII)

wherein  $R^1$  is as defined above, is reacted with an alkyl lithium reagent, such as butyl lithium, in an inert solvent, such as THF, and low temperature, such as -78°C and the sulfinamide prepared in step 7 above is added and allow to react for few minutes, such as 5 to 15 minutes, to give a diastereomeric mixture of the compounds of the general formula (XI)

20



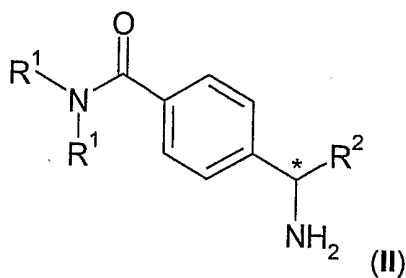
wherein  $R^1$  and  $R^2$  are as defined above.

- 5 The diastereomeric ratio of the products of step 8 is 70/30, preferably 80/20 and more preferably 90/10. The two diastereomers can thereafter be purified (from the other diastereomer) by standard techniques like crystallization or chromatography.

#### STEP 9

10

The purified diastereomer of the general formula (XI), prepared in step 8 above, is thereafter solvolized, e.g. methanolysis, by brief acid treatment to give the intermediate compound of the general formula (II)



15

wherein  $R^1$  and  $R^2$  are as defined above.

- 20 The enantiomeric excess (ee) of compounds of the general formula (II) prepared according to step 7 to 9 of the present invention is >90%, preferably >95% and more preferably >98%.

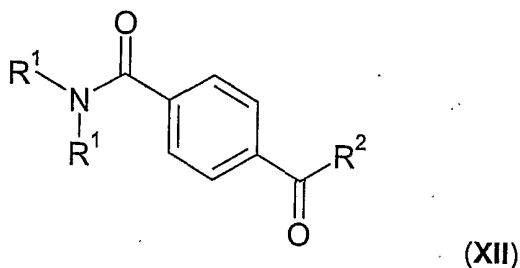
If (R)-(-)-2-methyl-2-propanesulfinamide is used in step 7 above and subsequent steps 8 and 9 are performed as described the other optical isomer (enantiomer) of the compound of the general formula (II) will be obtained.

- 5 Non-limiting examples of steps 7 to 9 are shown below in Scheme 2.

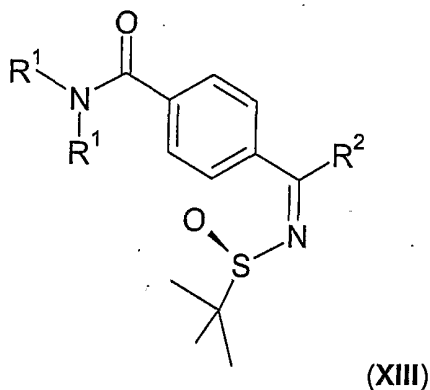
In another embodiment of the present invention, asymmetric key intermediate compounds of general formula (II) is prepared by a process comprising the following steps.

10 STEP 10

A ketone of the general formula (XII)



- 15 wherein  $R^1$  and  $R^2$  are as defined above, is reacted with (R)-(+)-2-methyl-2-propanesulfinamide as described in step 7 above to give compounds of the general formula (XIII)



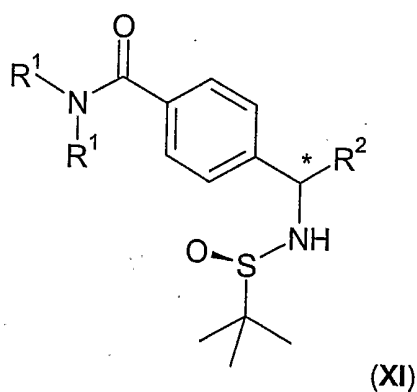
20

wherein  $R^1$  and  $R^2$  are as defined above.

## STEP 11

Compounds of the general formula (XIII) is thereafter reduced using a hydride donating reagent, such as sodium borohydride, under standard conditions, to give a diastereomeric mixture of the compounds of the general formula (XI)

5

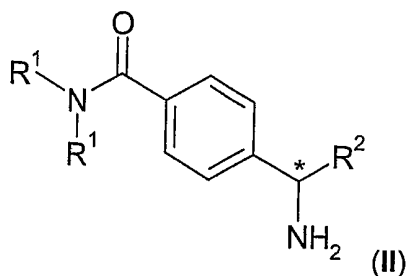


wherein  $R^1$  and  $R^2$  are as defined above.

- 10 The diastereomeric ratio of the products of step 11 is 70/30, preferably 80/20 and more preferably 90/10. The two diastereomers can thereafter be purified (from the other diastereomer) by standard techniques like crystallization or chromatography.

## STEP 12

- 15 The purified diastereomer of the general formula (XI), prepared in step 11 above, is thereafter treated as described in step 9 above to give key intermediate compound of general formula (II)



- 20 wherein  $R^1$  and  $R^2$  are as defined above.

The enantiomeric excess (ee) of compounds of the general formula (II) prepared according to step 10 to 12 of the present invention is >90%, preferably >95% and more preferably >98%.

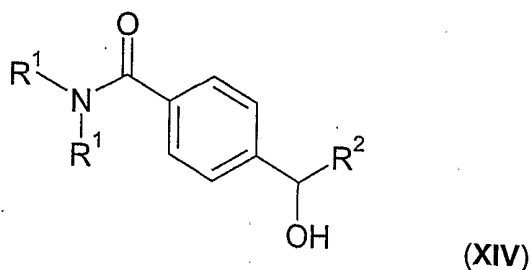
- 5 If (R)-(-)-2-methyl-2-propanesulfinamide is used in step 10 above and subsequent steps 11 and 12 are performed as described the other optical isomer (enantiomer) of the compound of the general formula (II) will be obtained.

Non-limiting examples of steps 10 to 12 are shown below in Scheme 3.

10

## STEP 13

- Ketone of the general formula (XII) above is prepared by treating a compound of general formula (VIII) above with an alkyl lithium reagent, such as butyl lithium, in an inert solvent, such as THF, and low temperature, such as -78°C and thereafter adding a compound of
- 15 the general formula  $R^2$ -CHO, wherein  $R^2$  is as defined above, and allow it to react for few minutes, such as 5 to 15 minutes to give a compound of general formula (XIV)



- wherein  $R^1$  and  $R^2$  are as defined above, which is thereafter oxidized under standard conditions, e.g. using pyridinium dichromate, to the corresponding ketone of the general
- 20 formula (XII), as defined above.

It will be appreciated by those skilled in the art that in the process described above the functional groups of starting materials or intermediate compounds may need to be protected by protecting groups.

25

Functional groups which it is desirable to protect include hydroxy and amino groups. Protecting groups may be added and removed in accordance with techniques which are well known to those skilled in the art. The use of protecting groups is described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene & P.G.M. Wutz,

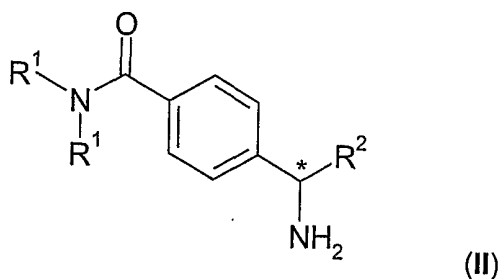
Wiley-Interscience (1991). The protective group may also be a polymer resin such as Wang resin or a 2-chlorotrityl chloride resin.

The present invention is thus more practical, easier to perform under controlled conditions, less sensitive to reaction conditions, more general, gives a higher yield than any other asymmetric process for making diarylmethylpiperazines and diarylmethylamines.

INTERMEDIATES

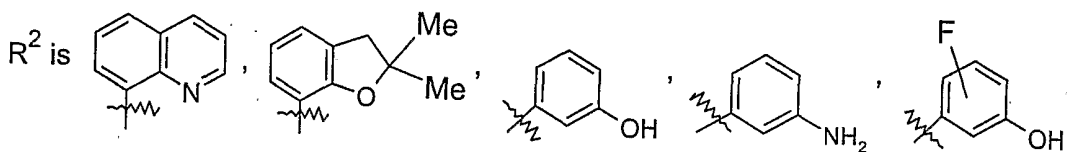
Another object of the present invention is to provide new intermediate compounds for use in the described process.

Thus, one aspect of the present invention is a compound of the general formula (II)



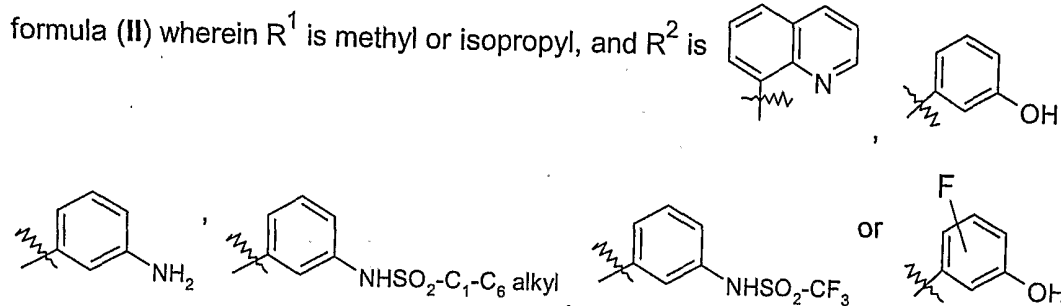
wherein

R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, and

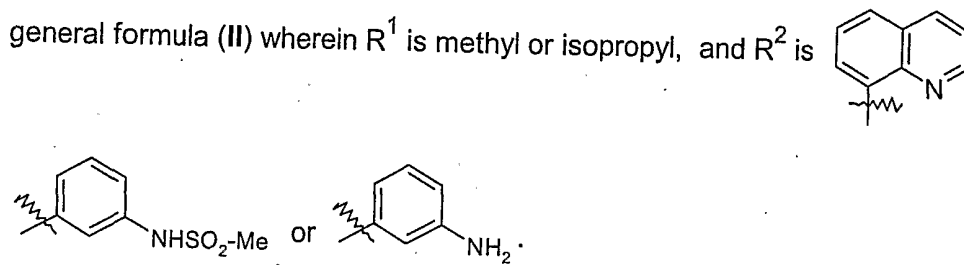


20 as a useful intermediate in the described process.

A preferred intermediate compound of the present invention is a compound of the general



5 A more preferred intermediate compound of the present invention is a compound of the

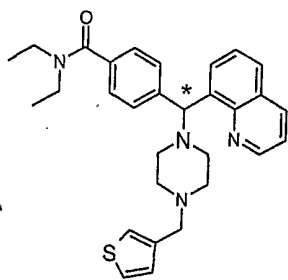


Each R<sup>2</sup> ring may optionally and independently be further substituted by up to three

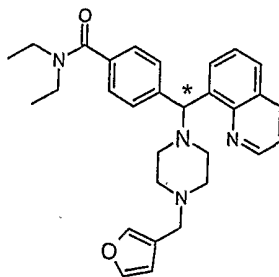
10 additional substituents selected from C<sub>1</sub>-C<sub>6</sub> alkyl, NO<sub>2</sub>, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, chloro, fluoro, bromo, and iodo. The substitutions may be in any position on said ring systems;

NOVEL COMPOUNDS

15 The following novel compounds have been prepared by the present invention.



(+)-19



(+)-20

The invention is illustrated, but in no way limited, by the following examples.

## EXAMPLES

5

### STEP 1

**(-)-N,N-diethyl-4-[[4-[(2-nitrophenyl)sulfonyl]-1-piperazinyl](8-quinolinyl)methyl]benzamide (8).**

(-)-6 (0.14 g, 0.42 mmol) was dissolved in toluene (2 mL) with Et<sub>3</sub>N (1 mL). N,N-bis(2-chloroethyl)-2-nitrobenzenesulfonamide (0.20 g, 0.61 mmol) was added and the reaction stirred at 110°C. Two more additions of N,N-bis(2-chloroethyl)-2-nitrobenzenesulfonamide were made during 36 h before the reaction was complete. Purification by chromatography on silica gave (-)-8 (90 mg, 36 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.2, 1.1 (m, 6H), 2.60 (m, 4H), 3.1-3.6 (m, 8H), 6.10 (s, 1H), 7.20-8.15 (m, 13H), 8.92 (m, 1H).

15

### STEP 2

**(-)-N,N-diethyl-4-[1-piperazinyl(8-quinolinyl)methyl]benzamide (9).**

(-)-8 (90 mg, 0.15 mmol) was dissolved in DMF (6 mL) and K<sub>2</sub>CO<sub>3</sub> (0.25 g, 1.8 mmol) and thiophenol (66 μL, 0.6 mmol) was added. Stirring was continued for 2 h at 25°C.

Purification by reverse phase chromatography (LiChroprep RP-18). Extraction (CH<sub>2</sub>Cl<sub>2</sub> / K<sub>2</sub>CO<sub>3</sub> (aq)) and evaporation gave (-)-9 (40 mg, 66 %). IR (KBr, ν<sub>max</sub>) 3297, 2982, 2716, 2474, 1611, 1434, 1380, 1288, 1098 cm<sup>-1</sup>. MS (amine): 402, 318, 246, 217, 109. <sup>1</sup>H NMR (amine, CDCl<sub>3</sub>): δ 1.2, 1.1 (2s, 6H), 2.94, 2.51 (2m, 8H), 3.5-3.1 (m, 5H), 6.05 (s, 1H), 8.94-7.20 (m, 10H).

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### STEP 3

**(+)-4-[(4-benzyl-1-piperazinyl)(8-quinolinyl)methyl]-N,N-diethylbenzamide (10).**

A sample of (+)-9 (0.40 g, 1.0 mmol) and triethylamine (0.28 mL, 2.0 mmol) was dissolved in MeCN (5 mL). Benzyl bromide (0.24 mL, 2.0 mmol) was added with stirring at 25°C.

After 12 h the solution was concentrated and purified by reverse phase chromatography (LiChroprep RP-18). After extraction (CH<sub>2</sub>Cl<sub>2</sub> / K<sub>2</sub>CO<sub>3</sub>(aq)) the free base was obtained (+)-10 (0.47 g, 95 %) IR (2X HCl, KBr) : 2388, 1606, 1434, 1356, 1287 (cm<sup>-1</sup>). <sup>1</sup>H NMR (free

30

amine,  $\text{CDCl}_3$ )  $\delta$  = 1.05 (m, 6H), 2.5 (m, 8H), 3.1-3.6 (m, 6H), 6.04 (s, 1H), 7.18 -8.98 (m, 15H). Anal. ( $\text{C}_{32}\text{H}_{38}\text{Cl}_2\text{N}_4\text{O}$ ) C, H, N.

## STEP 4

5 **(+)-(S)-4-methyl-N-[(E)-8-quinolinylmethylidene]benzenesulfinamide (3).**

(1R,2S,5R)-(-)-Menthyl (S)-p-toluenesulfinate (6.0 g, 20 mmol) was dissolved in THF (100 mL) and cooled to  $-78^\circ\text{C}$  under nitrogen. Lithium hexamethyldisilazan (1.0 M, 26 mL, 26 mmol) was added dropwise and solution was stirred at  $25^\circ\text{C}$  for 2 h. The solution was cooled again to  $-78^\circ\text{C}$  and 8-quinolylaldehyde (3.5 g, 22 mmol) was added dissolved in THF (2 mL). After stirring 2 h at  $-78^\circ\text{C}$ , water was added and the mixture was extracted with ether / water. The organic phase was dried ( $\text{MgSO}_4$ ), evaporated *in vacuo*, and the residue purified by chromatography on silica to give **3** (4.1 g, 67 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.40 (s, 3H), 7.32 (m, 2H), 7.48 (m, 1H), 7.61 (m, 1H), 7.71 (m, 2H), 7.99 (m, 1H), 8.19 (m, 1H), 8.45 (m, 1H), 9.01 (m, 1H), 10.27 (s, 1H).

15

## STEP 5

**(+)-N,N-diethyl-4-[[[(S)-(4-methylphenyl)sulfinyl]amino}(8-quinoliny)methyl]-benzamide (5).**

*N,N*-diethyl 4-iodo-benzamide (3.1 g, 10 mmol) was dissolved in dry toluene/THF (9:1, 200 mL) and cooled to  $-78^\circ\text{C}$  under nitrogen. *n*-BuLi (7.8 mL, 1.3 M in hexane, 10 mmol) was added dropwise during 5 to 10 min. After further 5 min, **3** (1.0 g, 3.4 mmol) was added dissolved in toluene (1 mL). The solution was stirred 10 min, then  $\text{NH}_4\text{Cl}$  (aq.) was added. Concentration, aqueous workup and chromatography on silica gave a total of 0.70 g (44 %) of a 70:30 mixture of diastereomers. The pure major isomer **5** (0.37 g) was obtained by one more chromatography.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.2 (m, 6H), 2.4 (s, 3H), 3.4 (m, 4H), 6.35 (d,  $J = 7.5$  Hz, 1H), 6.61 (d,  $J = 7.5$  Hz, 1H), 7.15-7.55 (m, 11H), 7.75 (m, 1H), 8.12 (m, 1H), 8.75 (m, 1H).

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## STEP 6

30 **(-)-4-[amino(8-quinoliny)methyl]-N,N-diethylbenzamide [(-)-6].**

Treatment of **5** (0.37 g, 0.79 mmol) with trifluoroacetic acid (123  $\mu\text{L}$ , 1.6 mmol) in MeOH (5 mL) at  $25^\circ\text{C}$ , for 12 h. Concentration *in vacuo* and reverse phase chromatography gave **6** (0.15 g, 53 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.2 (m, 6H), 2.2 (s, 2H), 3.4 (m, 4H), 6.40 (s, 1H), 7.30-7.58 (m, 7H), 7.71 (m, 1H), 8.15 (m, 1H), 8.92 (m, 1H).

## STEP 7

**(R)-(+)-2-methyl-N-[(E)-8-quinolinylmethylidene]-2-propanesulfonamide (14).**

(R)-(+)-2-methyl-2-propanesulfonamide (0.14 g, 1.2 mmol) and 8-quinolylaldehyde (0.19 g, 1.2 mmol) was dissolved in THF (5 mL) and titanium tetratoxide (1 mL, ~2.4 mmol) was added. The solution was heated at 65°C for 12 h, then concentrated in vacuo. Purification by chromatography on silica to give **14** (0.29 g, 93 %). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.31 (s, 9H), 7.49 (m, 1H), 7.66 (m, 1H), 8.01 (m, 1H), 8.21 (m, 1H), 8.49 (m, 1H), 9.02 (m, 1H), 10.09 (s, 1H).

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## STEP 8

**4-[[*tert*-butylsulfinyl]imino](8-quinolinyl)methyl]-N,N-diethylbenzamide (15).**

N,N-diethyl 4-iodo-benzamide (0.18 g, 0.6 mmol) was dissolved in dry THF (4 mL) and cooled to -78°C under nitrogen. n-BuLi (0.46 mL, 1.3 M in hexane, 0.6 mmol) was added dropwise during 5 to 10 min. After further 5 min, the solution was added with canula to **14** (78 mg, 0.30 mmol) dissolved in THF (2 mL) and cooled to -78 °C. The solution was stirred 10 min, then NH<sub>4</sub>Cl (aq.) was added. Concentration, aqueous workup and chromatography on silica gave a product (135 mg) containing **15** as a 80:20 mixture of diastereomers and some unreacted N,N-diethyl 4-iodo-benzamide.

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## STEP 9

**(+)-4-[amino(8-quinolinyl)methyl]-N,N-diethylbenzamide ((+)-6).**

Treatment of **15** (135 mg, ~0.30 mmol) with HCl in ether (0.3 mL, 0.6 mmol) in MeOH (2 mL) at 25°C, for 5 min. Concentration *in vacuo*, dilution with water, washing with EtOAc. The solution was then made basic with K<sub>2</sub>CO<sub>3</sub>(aq), extracted with and evaporated to give **(+)-6** (53 mg, 53 % from **14**). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.2 (m, 6H), 2.2 (s, 2H), 3.4 (m, 4H), 6.40 (s, 1H), 7.30-7.58 (m, 7H), 7.71 (m, 1H), 8.15 (m, 1H), 8.92 (m, 1H).

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Treatment of **(+)-6** with (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride gave the diastereomeric derivative. <sup>1</sup>H NMR (major diastereomer) (CDCl<sub>3</sub>): δ 1.0-1.2 (2m, 6H), 3.1, 3.5 (2m, 4H), 3.43 (s, 3H), 6.82 (d, J= 9.0, 1H), 7.10-7.40 (m, 9H), 7.52 (m, 1H), 7.71 (m, 1H), 7.79 (m, 1H), 8.14 (m, 1H), 8.68 (m, 1H), 9.83 (d, J= 9.0, 1H).

30

## STEP 10

**(-)-4-[[[(tert-butylsulfinyl)imino](8-quinolinyl)methyl]-N,N-diethylbenzamide (18).**

**13** (0.25 g, 2.0 mmol) and **17** (0.66 g, 2.0 mmol) was dissolved in THF (20 mL) and titanium tetraethoxide (2.5 mL, 4 mmol) was added. The solution was heated at 65°C for 3 days, then concentrated *in vacuo*. Purification by chromatography on silica to give **18** (0.44 g, 50 %).  $[\alpha]_D^{20} = -144^\circ$  (c 1.32, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.10, 1.25 (2m, 6H), 1.31 (s, 9H), 3.20, 3.55 (2m, 4H), 7.30-7.80 (m, 7H), 7.97 (m, 1H), 8.24 (m, 1H), 8.86 (m, 1H).

STEP 11

**4-[[[(tert-butylsulfinyl)imino](8-quinolinyl)methyl]-N,N-diethylbenzamide (15).**

**18** (25 mg, 0.06 mmol) was dissolved in dry THF (1 mL) together with titanium tetraethoxide (18 μL, 0.12 mmol) and added to a suspension of sodium borohydride (9 mg, 0.23 mmol) in THF (1 mL) at -50°C under nitrogen. The temperature was slowly raised to 0°C, 4 h and then the solution was worked up by addition of NH<sub>4</sub>Cl (aq.).

Concentration gave a crude product which was purified by chromatography on silica to give **15** (10 mg, 40%) as a mixture of diastereomers. <sup>1</sup>H NMR (major diastereomer) (CDCl<sub>3</sub>): δ 1.0-1.2 (2m, 6H), 1.23 (s, 9H), 3.1, 3.5 (2m, 4H), 6.30 (m, 1H), 7.20-7.50 (m, 9H), 7.58 (m, 1H), 7.60 (m, 1H), 8.10 (m, 1H), 8.79 (m, 1H).

STEP 12

**(-)-4-[amino(8-quinolinyl)methyl]-N,N-diethylbenzamide [(-)-6].**

Treatment of **15** with HCl in MeOH for 10 min and extractive workup gave (-)-**6**. NMR data identical to **6** made previously. Treatment of (-)-**6** with (R)-(-)-α-methoxy-α-

(trifluoromethyl)phenylacetyl chloride gave the diastereomeric derivative in a 9:1 ratio as determined by NMR. <sup>1</sup>H NMR (major diastereomer) (CDCl<sub>3</sub>): δ 1.0-1.2 (2m, 6H), 3.1, 3.5 (2m, 4H), 3.42 (s, 3H), 6.82 (d, J= 9.0, 1H), 7.10-7.50 (m, 9H), 7.55 (m, 1H), 7.64 (m, 1H), 7.79 (m, 1H), 8.19 (m, 1H), 8.78 (m, 1H), 9.90 (d, J= 9.0, 1H).

STEP 13

**N,N-diethyl-4-(8-quinolinylcarbonyl)benzamide (17).**

N,N-diethyl-4-iodobenzamide (**4**) (0.67 g, 2.2 mmol) was dissolved in dry THF (25 mL) and cooled to -78°C under nitrogen. n-BuLi (1.3 mL, 1.6 M in hexane, 2.2 mmol) was added dropwise during 5 min. After further 10 min, 8-formylquinoline (0.17 g, 1.1 mmol)

was added dissolved in THF (1 mL). The solution was stirred 1 h, then NH<sub>4</sub>Cl (aq.) was added. After concentration, aqueous workup and chromatography on silica a total of 0.29 g (78 %) N,N-diethyl-4-[hydroxy(8-quinolinyl)methyl]benzamide (**16**). was obtained. MS: 334, 262, 234, 215, 204, 178, 156, 129.

- 5 **16** (3.0 g, 9.0 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and powdered pyridinium dichromate (PDC) (5.0 g, 13 mmol) was added portionwise at 25°C. Two more portions of PDC (0.5 g) were added after 3 h and 12 h. After 24 h, the solution was diluted with heptane and filtered through silica gel. Elution with EtOAc and evaporation *in vacuo* gave **17** (1.8 g, 60%). MS: 332, 303, 275, 260, 232, 204, 176, 156, 128, 115. <sup>1</sup>H NMR (CDCl<sub>3</sub>):
- 10 δ 1.1, 1.3 (2m, 6H), 3.22, 3.55 (2m, 4H), 7.39 (d, *J*=8 Hz, 2H), 7.43 (m, 1H), 7.65 (m, 1H), 7.75 (m, 1H), 7.86 (d, *J*=8 Hz, 2H), 7.98 (m, 1H), 8.23 (m, 1H), 8.83 (m, 2H).

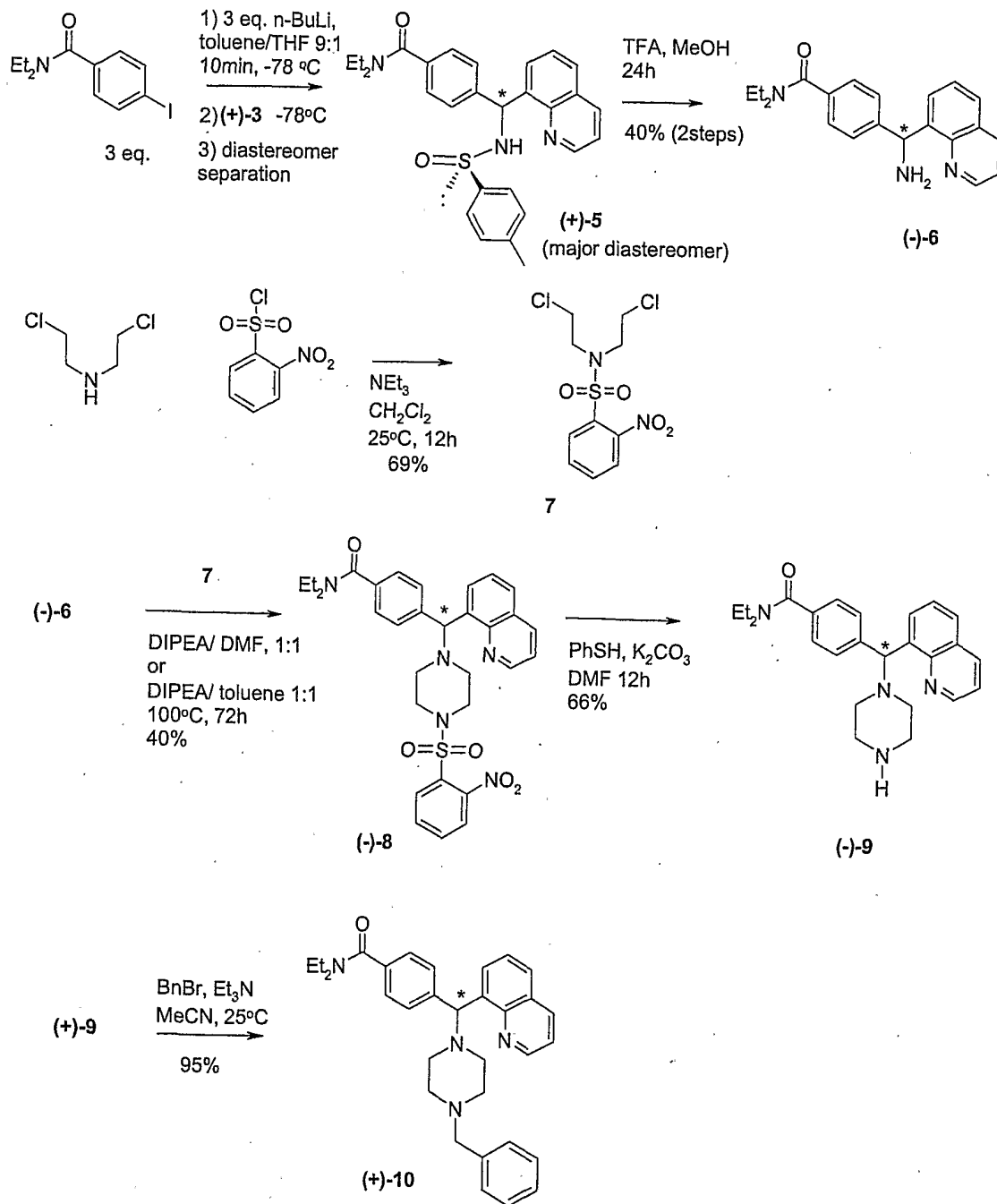
**(+)-N,N-diethyl-4-{8-quinolinyl[4-(3-thienylmethyl)-1-piperazinyl]methyl}benzamide ((+)-19)**

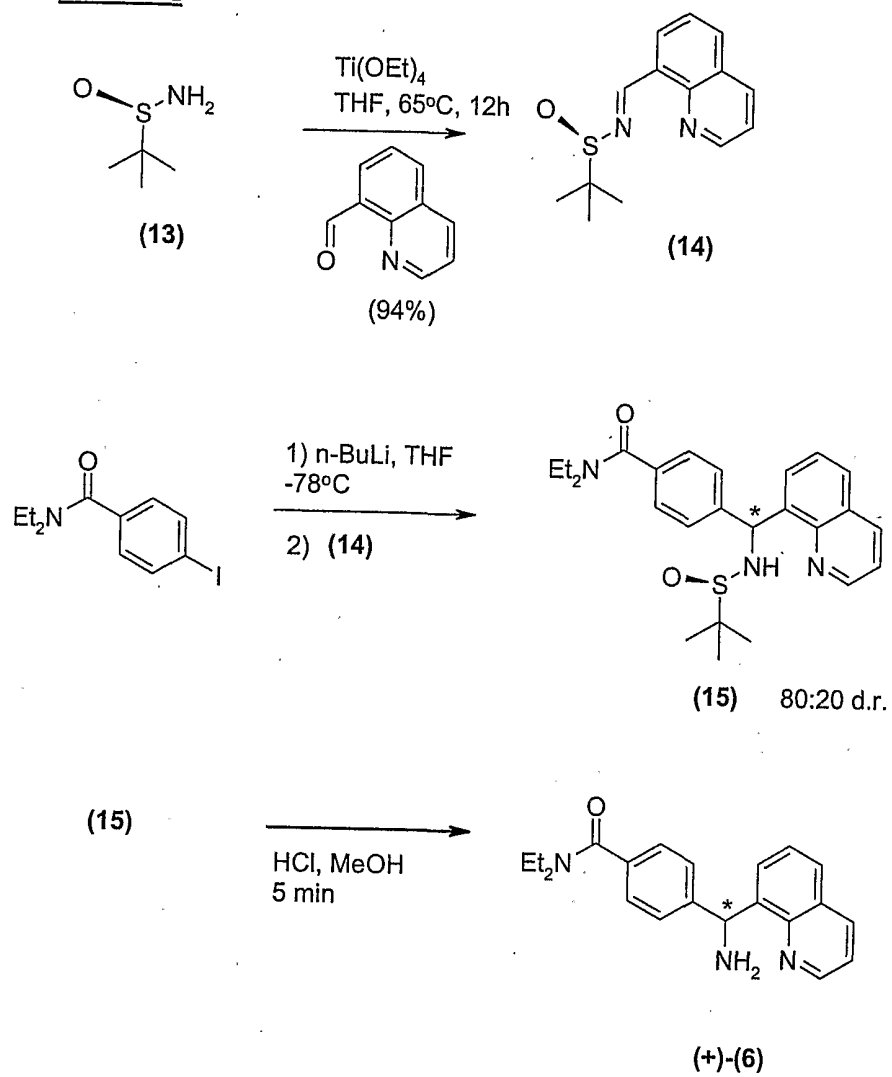
- 15 Compound **(+)-9** (0.60 mg, 1.5 mmol) and 3-thiophenecarboxaldehyde (0.28 mL, 3.0 mmol) was dissolved in MeOH (5 mL) and AcOH was added (43 μL, 0.75 mmol). After stirring 1 h, NaBH<sub>3</sub>CN (94 mg, 1.5 mmol) was added in portions over 6 h. After stirring over night, the solution was concentrated and the product purified by reverse phase chromatography (LiChroprep RP-18, 10-80 % MeCN in water, 0.1 % TFA) to give **(+)-19**
- 20 as the bis-trifluoroacetate (0.57 g, 77 %). [α]<sub>D</sub><sup>20</sup> = +84.5° (c 0.87, MeOH). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ = 1.1, 1.2 (2m, 6H), 3.2-3.5 (m, 12H), 4.35 (s, 2H), 6.19 (s, 1H), 7.20 (m, 1H), 7.28 (d, *J* = 8Hz, 2H), 7.50 (m, 1H), 7.55 (m, 1H), 7.58-7.66 (m, 2H), 7.70 (d, *J* = 8Hz, 2H), 7.83 (m, 1H), 8.07 (m, 1H), 8.28 (m, 1H), 8.94 (m, 1H).

25 **(+)-N,N-diethyl-4-[[4-(3-furylmethyl)-1-piperazinyl](8-quinolinyl)methyl]benzamide ((+)-20)**

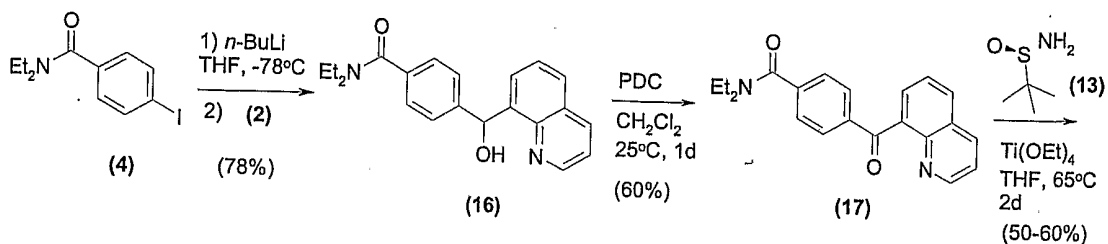
- Procedure as **(+)-19**. Reaction of **(+)-9** (50 mg, 0.12 mmol) with 3-furancarboxaldehyde (21 μL, 0.24 mmol) gave **(+)-20** as the bis-trifluoroacetate (58 mg, 68 %). [α]<sub>D</sub><sup>20</sup> = +78.2° (c 0.60, MeOH). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ = 1.1, 1.2 (2m, 6H), 3.1-3.6 (m, 12H), 4.21 (s, 2H),
- 30 6.19 (s, 1H), 6.58 (s, 1H), 7.28 (d, *J* = 8Hz, 2H), 7.50 (m, 1H), 7.61 (m, 2H), 7.70 (d, *J* = 8Hz, 2H), 7.74 (s, 1H), 7.83 (m, 1H), 8.07 (m, 1H), 8.28 (m, 1H), 8.94 (m, 1H).

Scheme 1.

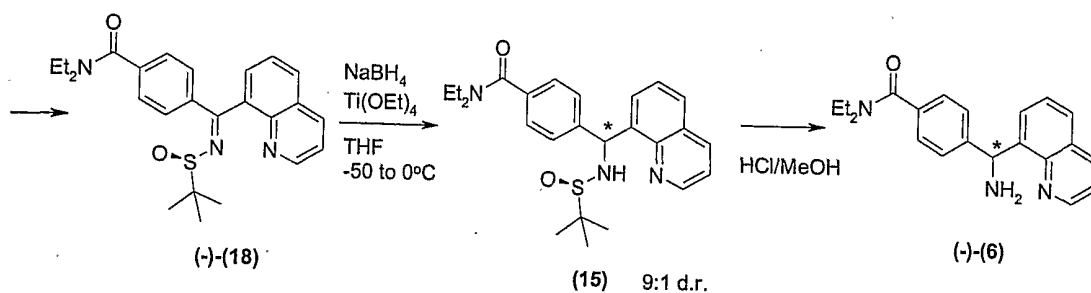


**Scheme 2**

Scheme 3.

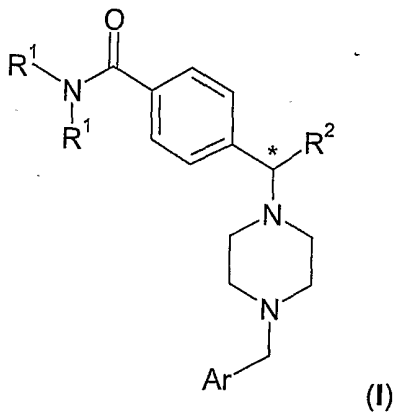


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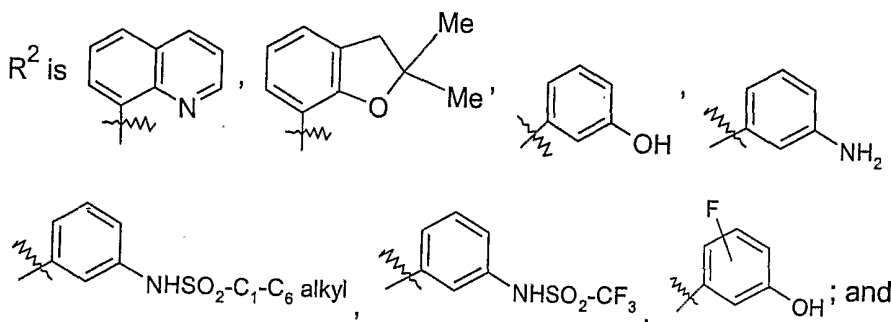
CLAIMS

1. A process for preparing a compound of the general formula (I)



5 wherein

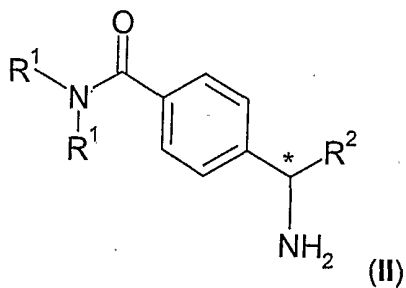
R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl,



Ar is selected from any one of phenyl, pyridinyl, thienyl, furanyl, imidazolyl, or triazolyl, comprising the steps of;

10

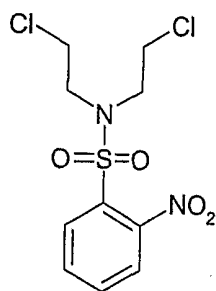
A) reacting a enantiomerically pure compound of the general formula (II)



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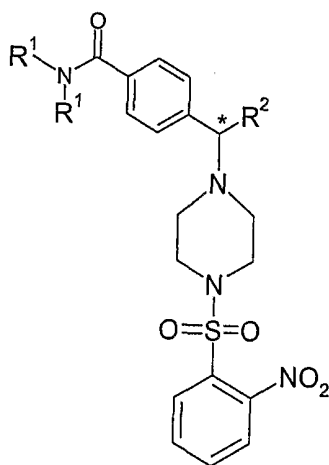
wherein R<sup>1</sup> and R<sup>2</sup> are as defined above, with N,N-bis(2-chloroethyl)-2-nitrobenzamide of formula (III)

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(III)

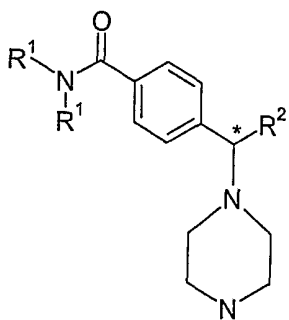
to give compounds of the general formula (IV)



(IV)

wherein  $R^1$  and  $R^2$  are as defined above,

B) Cleaving the 2-nitrobenzenesulfonyl group of compounds of the general formula (IV) by standard conditions to give compounds of the general formula (V)



(V)

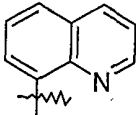
wherein  $R^1$  and  $R^2$  are as defined above, and

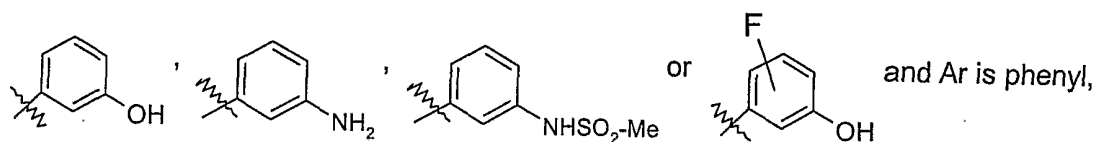
C) Alkylating a compound of general formula (V) under standard conditions using either;

- i) a compound of the general formula  $\text{Ar-CH}_2\text{-X}$ , wherein Ar is as defined above and X is halogen, and a suitable base, or  
 ii) a compound of the general formula  $\text{Ar-CHO}$ , wherein Ar is as defined above, and a suitable reducing agent

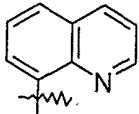
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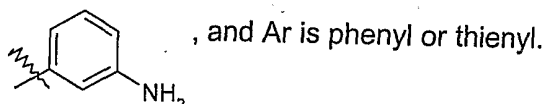
to give compounds of the general formula (I), as defined above.

2. A process according to claim 1, wherein  $\text{R}^1$  is methyl or isopropyl,  $\text{R}^2$  is 

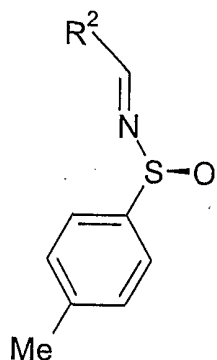


10 pyridyl, thienyl, or furanyl.

3. A process according to claim 1, wherein  $\text{R}^1$  is methyl or isopropyl,  $\text{R}^2$  is  or



- 15 4. A process according to claim 1, wherein a compound of the general formula (II) is prepared by  
 A) reacting (1R,2S,5R)-(-)-menthyl (S)-p-toluenesulfinate or (1R,2S,5R)-(+)-menthyl (R)-p-toluenesulfinate with lithium hexamethyldisilazan and a compound of the general formula  $\text{R}^2\text{-CHO}$ , wherein  $\text{R}^2$  is as defined in claim 1, to give a sulfimine of the general  
 20 formula (VII)

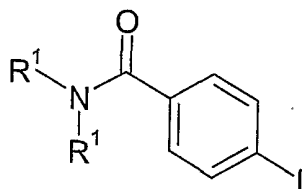


(VII)

or its enantiomer, wherein  $R^2$  is as defined in claim 1,

B) reacting a p-iodo-benzamide derivative of the general formula (VIII)

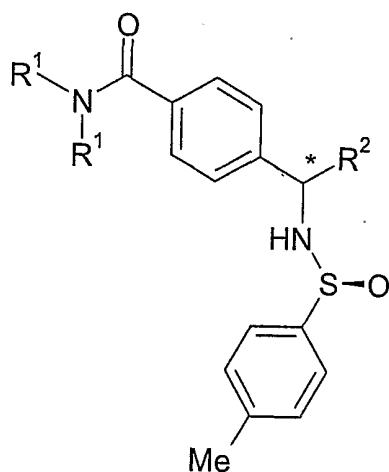
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(VIII)

wherein  $R^1$  is as defined in claim 1, with an alkyl lithium reagent and a sulfinimide prepared in step A above is thereafter added to give a compound of the general formula

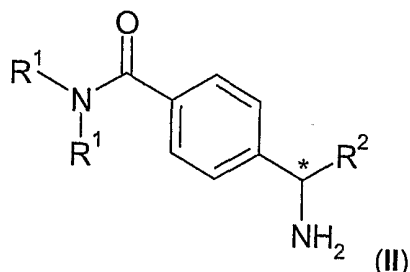
10 (IX)



(IX)

wherein  $R^1$  and  $R^2$  are as defined in claim 1,

C) methanolysing by brief acid treatment of a compound of the general formula (IX) to give a compound of the general formula (II)

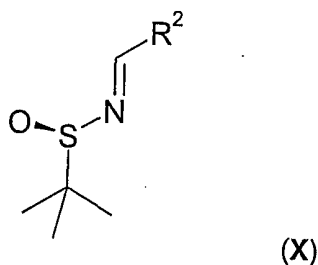


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wherein  $R^1$  and  $R^2$  are as defined in claim 1.

5. A process according to claim 1, wherein a compound of the general formula (II) is prepared by,

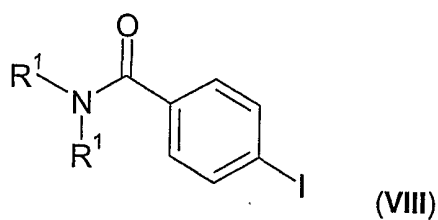
- 10 A) reacting an aldehyde of the structure  $R^2$ -CHO, wherein  $R^2$  are as defined in claim 1, with (R)-(+)-2-methyl-2-propanesulfinamide or (S)-(-)-2-methyl-2-propanesulfinamide to give a compound of the general formula (X)



15

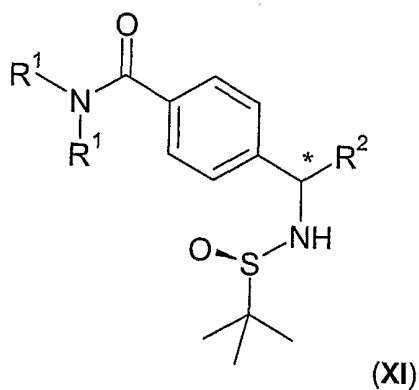
or its enantiomer, wherein  $R^2$  are as defined in claim 1,

- B) reacting a p-iodo-benzamide derivative of the general formula (VIII)



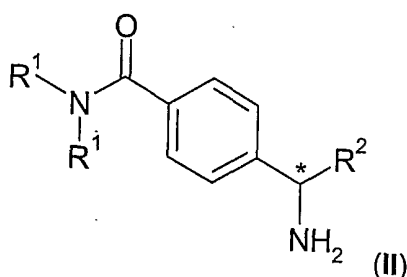
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wherein  $R^1$  is as defined in claim 1, with an alkyl lithium reagent and thereafter a sulfinamide prepared in step A above is added to give a compound of the general formula (XI)



wherein  $R^1$  and  $R^2$  are as defined in claim 1,

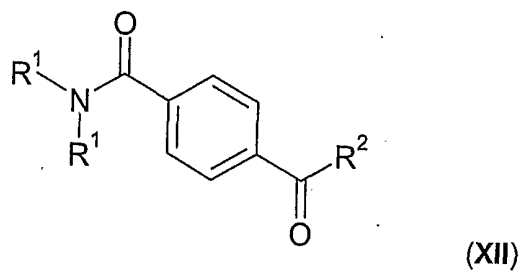
10 C) methanolysing by brief acid treatment a compound of the general formula (XI) to give a compound of the general formula (II)



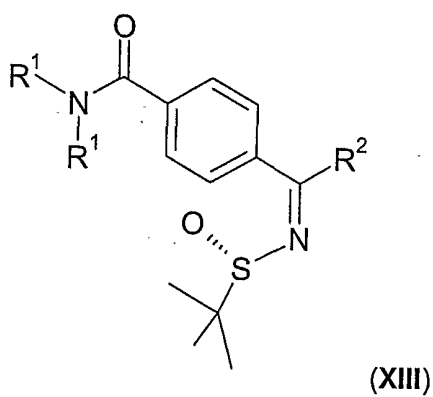
15 wherein  $R^1$  and  $R^2$  are as defined in claim 1.

6. A process according to claim 1, wherein a compound of the general formula (II) is prepared by,

A) reacting a ketone of the general formula (XII)

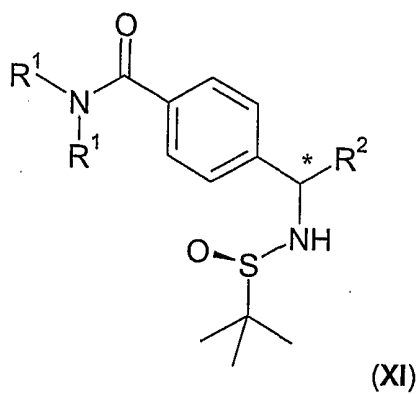


wherein  $R^1$  and  $R^2$  are as defined in claim 1, with (R)-(+)-2-methyl-2-propanesulfinamide or (S)-(-)-2-methyl-2-propanesulfinamide to give a compound of the general formula (XIII)



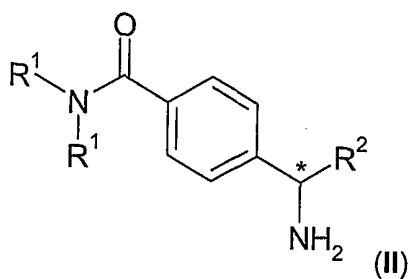
or its enantiomer, wherein  $R^1$  and  $R^2$  are as defined in claim 1,

B) reducing a compound of the general formula (XIII) using a hydride donating reagent, to give a compound of the general formula (XI)



wherein  $R^1$  and  $R^2$  are as defined in claim 1,

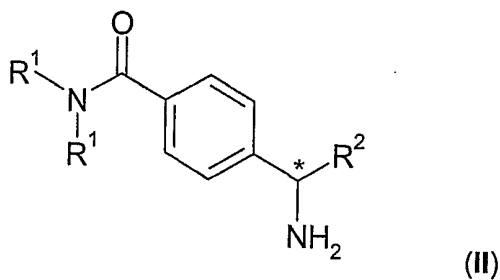
C) ) methanolyzing by brief acid treatment a compound of the general formula (XI) to give a compound of the general formula (II)



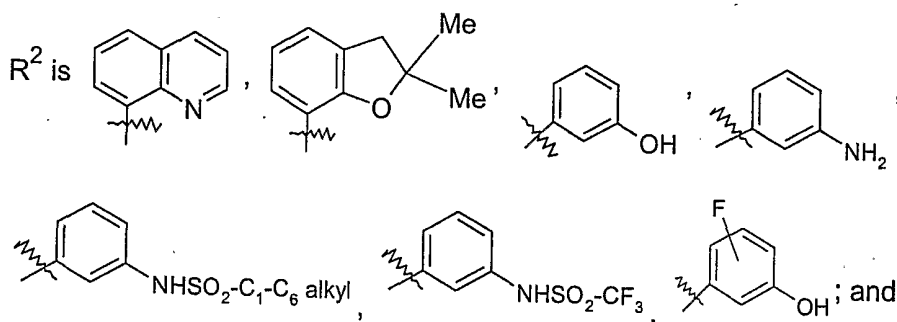
wherein R<sup>1</sup> and R<sup>2</sup> are as defined in claim 1.

5

7. A process for preparing a compound of the general formula (II)



10 wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl and

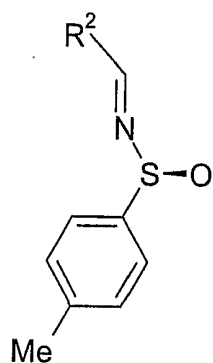


comprising the steps of,

A) reacting (1R,2S,5R)-(-)-menthyl (S)-p-toluenesulfinate or (1R,2S,5R)-(+)-menthyl (R)-p-toluenesulfinate with lithium hexamethyldisilazan and a compound of the general

15

formula R<sup>2</sup>-CHO, wherein R<sup>2</sup> is as defined above, to give a sulfimine of the general formula (VII)

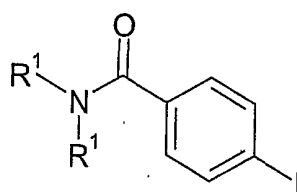


(VII)

or its enantiomer, wherein  $R^2$  is as defined above,

B) reacting a p-iodo-benzamide derivative of the general formula (VIII)

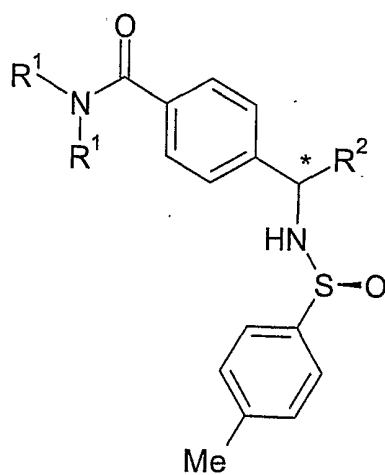
5



(VIII)

wherein  $R^1$  is as defined above, with an alkyl lithium reagent and a sulfonamide prepared in step A above is thereafter added to give a compound of the general formula (IX)

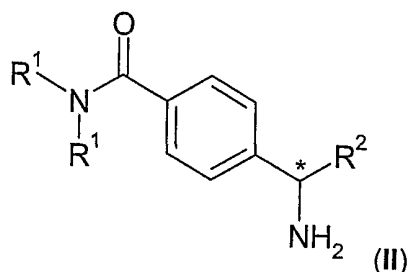
10



(IX)

wherein  $R^1$  and  $R^2$  are as defined above,

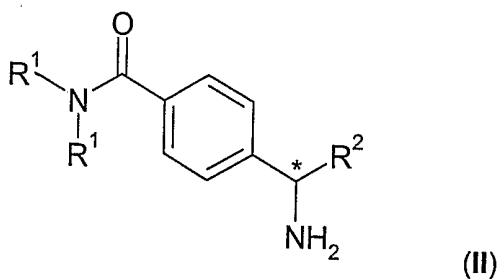
C) methanolysing by brief acid treatment a compound of the general formula (IX) to give a compound of the general formula (II)



5

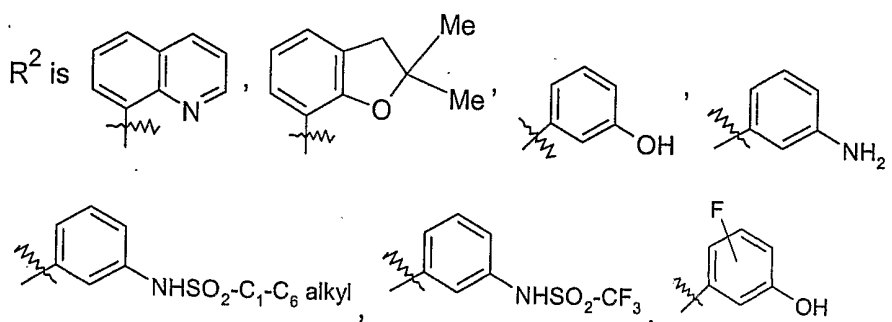
wherein R<sup>1</sup> and R<sup>2</sup> are as defined above.

8. A process for preparing a compound of the general formula (II)



10

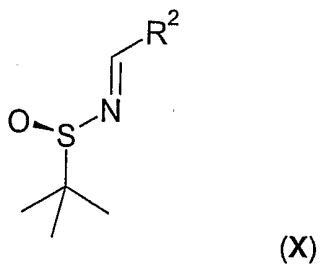
wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl and



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comprising the steps of,

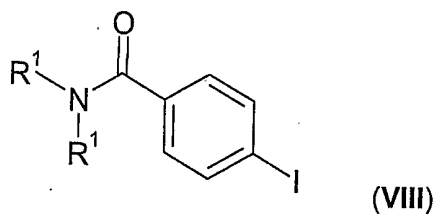
A) reacting an aldehyde of the structure R<sup>2</sup>-CHO, wherein R<sup>2</sup> is as defined above, with (R)-(+)-2-methyl-2-propanesulfinamide or (S)-(-)-2-methyl-2-propanesulfinamide to give a compound of the general formula (X)



or its enantiomer, wherein R<sup>2</sup> is as defined above,

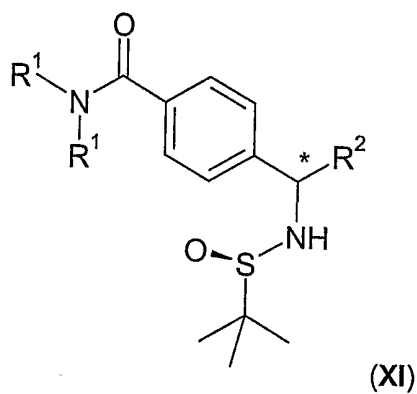
B) reacting a p-iodo-benzamide derivative of the general formula (VIII)

5



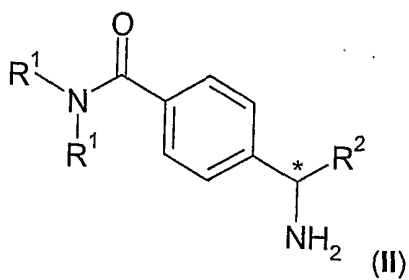
wherein R<sup>1</sup> is as defined above, with an alkyl lithium reagent and thereafter a sulfinamide prepared in step A above is added to give a compound of the general formula (XI)

10



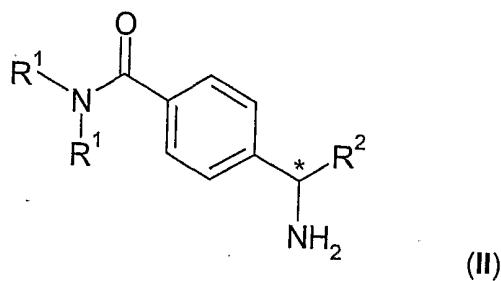
wherein R<sup>1</sup> and R<sup>2</sup> are as defined above,

15 C) methanolyzing by brief acid treatment a compound of the general formula (XI) to give a compound of the general formula (II)

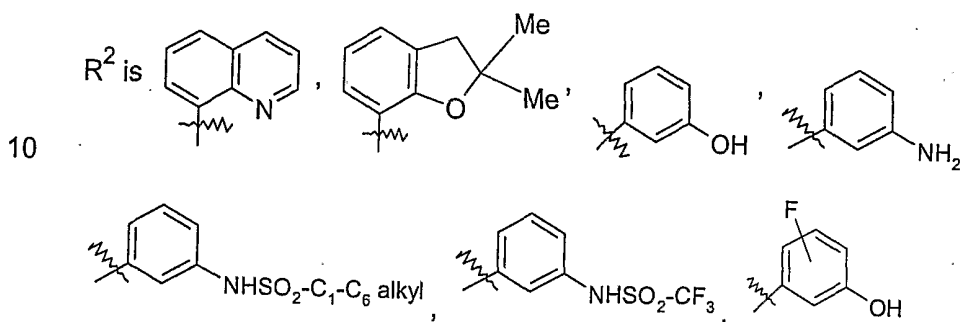


wherein R<sup>1</sup> and R<sup>2</sup> are as defined above.

5 9. A process for preparing a compound of the general formula (II)

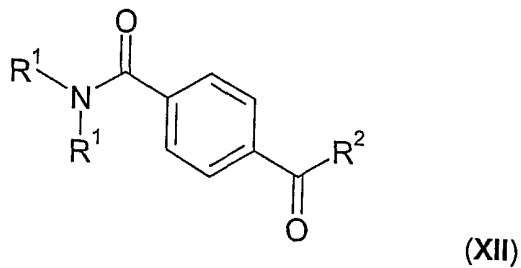


wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl and

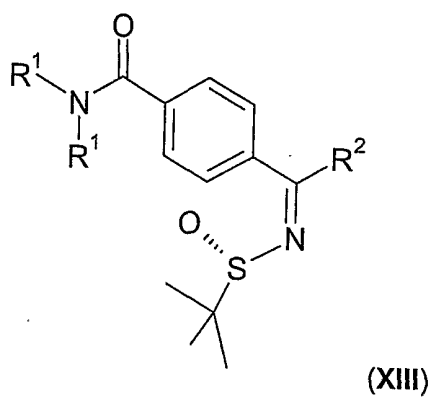


comprising the steps of,

A) reacting a ketone of the general formula (XII)



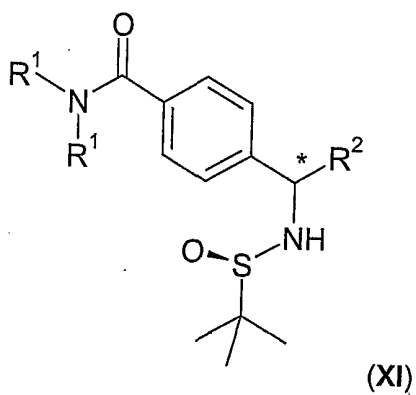
wherein  $R^1$  and  $R^2$  are as defined above, with (R)-(+)-2-methyl-2-propanesulfinamide or (S)-(-)-2-methyl-2-propanesulfinamide to give a compound of the general formula (XIII)



5

or its enantiomer, wherein  $R^1$  and  $R^2$  are as defined above,

B) reducing a compound of the general formula (XIII) using a hydride donating reagent, to give a compound of the general formula (XI)

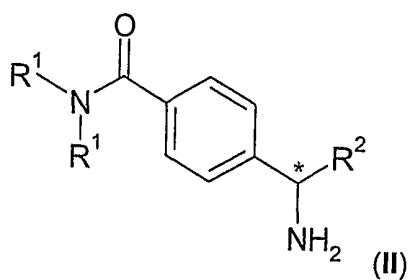


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wherein  $R^1$  and  $R^2$  are as defined above,

C) ) methanolysing by brief acid treatment a compound of the general formula (XI) to give a compound of the general formula (II)

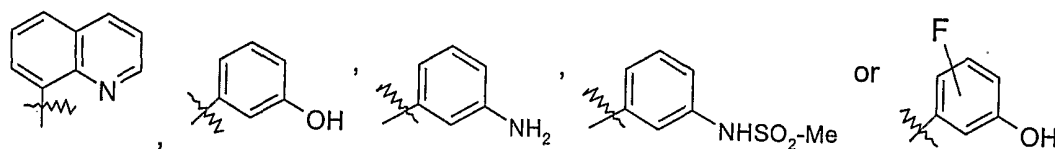
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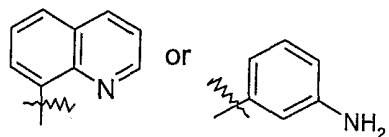
wherein R<sup>1</sup> and R<sup>2</sup> are as defined above.

10. A process according to claims 7 to 9, wherein R<sup>1</sup> is methyl or isopropyl, and R<sup>2</sup> is

5

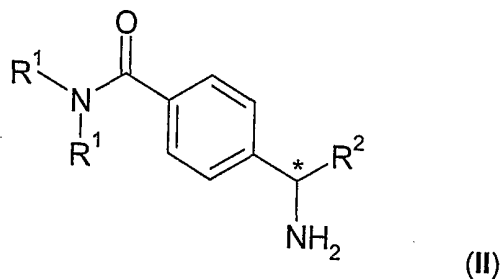


11. A process according to claims 7 to 9, wherein R<sup>1</sup> is methyl or isopropyl, and R<sup>2</sup> is



10

12. A compound of the general formula (II)



15 wherein

R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, and



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00376

| A. CLASSIFICATION OF SUBJECT MATTER  |  |   |
|--|--|---|
| IPC7: C07D 241/04, C07D 401/06, C07D 215/12, C07D 307/79, C07D 401/14,<br>C07D 403/14, C07D 405/06, C07D 405/14 C07D 409/06, C07D 409/14, C07C 237/32,<br>According to International Patent Classification (IPC) or to both national classification and IPC A61K 31/496, A61P 25/04  |  |   |
| B. FIELDS SEARCHED   |  |   |
| Minimum documentation searched (classification system followed by classification symbols)  |  |   |
| IPC7: C07D, C07C, A61K, A61P   |  |   |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  |  |   |
| SE,DK,FI,NO classes as above   |  |   |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)   |  |   |
| CHEM. ABS DATA   |  |   |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT   |  |   |
| Category*  | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No.   |
| A  | WO 9723466 A1 (ASTRA PHARMA INC.), 3 July 1997<br>(03.07.97)<br><br>--             | 1-15  |
| P,A  | WO 0145637 A2 (ASTRAZENECA AB), 28 June 2001<br>(28.06.01)<br><br>--               | 1-15  |
| E,A  | WO 0174805 A1 (ASTRAZENECA AB), 11 October 2001<br>(11.10.01)<br><br>--<br>-----   | 1-15  |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.   |  |   |
| * Special categories of cited documents:<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier application or patent but published on or after the international filing date<br>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br>"&" document member of the same patent family |  |   |
| Date of the actual completion of the international search  |  | Date of mailing of the international search report                          |
| 25 June 2002   |  | 27-06-2002  |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86   |  | Authorized officer<br><br>Eva Johansson/EÖ<br>Telephone No. +46 8 782 25 00 |

## INTERNATIONAL SEARCH REPORT

Information on patent family members

01/05/02

International application No.

PCT/SE 02/00376

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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|   |                     | SE 9904673 D               | 00/00/00            |
| WO 0174805 A1                             | 11/10/01            | AU 4498301 A               | 15/10/01            |
|   |                     | AU 6031600 A               | 02/01/01            |
|   |                     | SE 0001209 D               | 00/00/00            |