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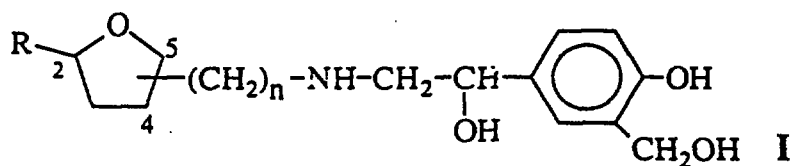
TITLE

Tetrahydrofuran derivatives

DESCRIPTION

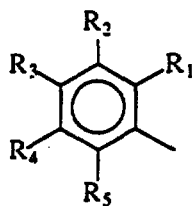
The invention relates to N-derivatives of (phenylethyl- β -ol) amine, their processes of preparation, and pharmaceutical compositions based thereon. These products are agonists of β -adrenergic receptors.

The invention provides a N-(2,4- or 2,5-disubstituted tetrahydrofuryl alkyl)-N-(phenylethyl- β -ol) amine derivative, under a racemic or enantiomer form, of general formula I



wherein

- R represents a straight or branched alkyl group comprising from 1 to 10 carbon atoms ; an heteroaryl group, a phenyl radical or a substituted phenyl radical of the formula



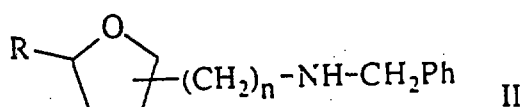
in which the radicals R_1 , R_2 , R_3 , R_4 and R_5 independently represent a hydrogen atom, a halogen atom, an alkoxy radical comprising from 1 to 5 carbon atoms, or an alkylsulphonyl radical comprising from 1 to 5 carbon atoms ;

- n is from 1 to 10 ;

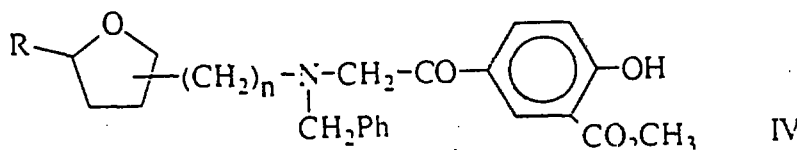
and pharmaceutically acceptable salts thereof. Such salts are formed from organic or mineral acids, such as hydrochloric, hydrobromic, sulphuric, fumaric or maleic acid.

The state of the art may be illustrated by British Patent Application No. 2230775, British Patent Application No. 2140800 and European Patent Application No. 422889; said patent applications refer to ether-like compounds, with an ether bond instead of the $-(CH_2)_n-$ chain of the compounds of the invention.

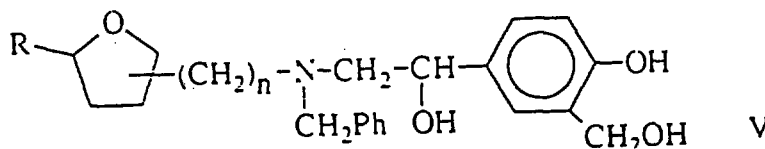
The invention also provides a process for the preparation of a tetrahydrofuran derivative of the general formula I, the process comprising condensing a 2-substituted (4 or 5)-benzylaminoalkyl-tetrahydrofuran compound of the general formula II



with methyl 5-bromoacetyl-salicylate III in a solvent in the presence of an organic base, reducing the resultant compound of the general formula IV



with a hydride as reducing agent in a solvent under an inert atmosphere, and debenzylating the resultant compound of the general formula V



by catalytic hydrogenation.

The condensation reaction is preferably effected in a protic solvent, such as dimethylsulphoxide, or in acetonitrile. The organic base is suitably triethylamine. The reaction may be performed at a temperature of from room temperature to the boiling point of the reaction mixture for 2 to 18 hours.

The hydride used in the reduction of the compound IV is preferably lithium aluminium hydride. For the reduction, an ethereal solvent such as tetrahydrofuran or diethyl ether is preferred. The reduction may proceed for 2 to 8 hours at a temperature of from 0°C to room temperature.

The catalytic hydrogenation which effects the debenzylation is preferably performed at from 2 to 5.5 bar, at a temperature of from room temperature to 40°C for 10 minutes to 5 hours; the catalyst is suitably PtO₂ or Pd/C. In a preferred embodiment, when R represents a heteroaryl group or a phenyl group substituted by one or more halogen atoms, the debenzylation is effected by hydrogenation over platinum dioxide at 4 to 5.5 bar at room temperature for 10 to 30 minutes. In another preferred embodiment, when R represents an alkyl group or a phenyl group substituted by one or more alkoxy or alkylsulphonyl groups, the debenzylation is effected by hydrogenation over palladium/carbon at 2 to 3.5 bar.

The above preparation process is illustrated by reaction scheme 1. The cis and trans isomers of compounds of the formula I can be obtained either by preparative HPLC of the racemic compounds, or starting from cis/trans isomers of intermediate compounds. These compounds can be separated at different stages in the synthesis, particularly when R stands for an aryl radical. Each of the cis and trans compounds is a mixture of two enantiomers which may be obtained by asymmetric synthesis.

The bromoketone III can be obtained by a Fries rearrangement of the phenolic ester of methyl salicylate, followed by bromination of the methyl ketone.

The starting compounds II are new compounds and may be obtained by various ways according to the positions of the substituents and the number of carbon atoms n in the alkyl chain. Benzylamine can be condensed with a cyclopentyl heterocycle substituted with a haloalkyl, or a corresponding mesylate of the alcohol.

Various processes for the preparation of the starting compound II are illustrated in reaction schemes 2 to 6. Reaction schemes 2, 3, 4 and 5 illustrate the synthesis of the starting compound II with a 2,5-disubstitution wherein n = 1, 2, 3 and n > 3 respectively: reaction scheme 6 describes the synthesis of the starting compound II with a 2,4-disubstitution wherein n = 1. In reaction scheme 5, n' represents an integer of from 1 to 7.

Finally, the invention provides a pharmaceutical composition comprising a tetrahydrofuran derivative of the general formula I as above defined, in racemic or enantiomeric form, or a pharmaceutically acceptable salt of such a tetrahydrofuran derivative, in admixture with a pharmaceutically acceptable diluent or carrier.

In the description of the preparation process of any starting compounds II as illustrated below and more specifically when R stands for a substituted phenyl radical, a letter is added, as a superscript, to the number of the compound to simplify and distinguish the different substituents for a given value of n. This convention, followed throughout, is as follows :

Substitution	R ₁	R ₂	R ₃	R ₄	R ₅	n	Indice
2,5-	H	H	H	H	H	1	a
2,5-	H	CH ₃ O	CH ₃ O	CH ₃ O	H	1	b
2,5-	CH ₃ O	CH ₃ O	CH ₃ O	H	H	1	c
2,5-	Cl	H	H	H	H	1	d
2,5-	H	Cl	H	H	H	1	e
2,5-	F	H	H	H	H	1	f
2,5-	H	CH ₃ O	C ₃ H ₇ O	CH ₃ SO ₂	H	1	g
2,5-	H	H	H	H	H	2	h
2,5-	H	CH ₃ O	CH ₃ O	CH ₃ O	H	2	i
2,5-	H	CH ₃ O	CH ₃ O	CH ₃ O	H	3	j
2,5-	Cl	H	H	H	H	3	k
2,5-	H	CH ₃ O	CH ₃ O	CH ₃ O	H	7	l
2,4-	H	CH ₃ O	CH ₃ O	CH ₃ O	H	1	m
2,4-	Cl	H	H	H	H	1	n

A) Process for the preparation of starting compound II disubstituted in the 2,5-position with n = 1

A-1) Process according to reaction scheme 2, for the preparation of compound II wherein R = aryl

10 5-aryl-5-hydroxy-pentene - group compounds 1

The aldehydes used are in general commercial. For the preparation of compound 1g, the aldehyde was obtained starting from iodovanilin according to the method of A.S. Thomson (Tetrahedron Letters, vol. 31, p. 6953, 1990).

The reaction was carried out under argon. To the Grignard reagent obtained from 11 g (80 mmol) of 4-bromobutene and 2 g (80 mmol) of magnesium in tetrahydrofuran (THF), 50 mmol of the appropriate aldehyde in 100 ml of THF was added at room temperature. The stirring was maintained for 1 hour. The reaction mixture was quenched with a 10 % aqueous solution of ammonium chloride and extracted with chloroform. After the usual workup, the residue was purified by flash chromatography (light petroleum / ethyl acetate 80:20 then 70:30) to give the alcohol **1** as a viscous product.

Compound **1_a** : $R_f = 0.37$ (EP/AcOEt 80:20)

Compound **1_b** : $R_f = 0.43$ (EP/AcOEt 50:50)

10 Compound **1_c** : $R_f = 0.39$ (EP/AcOEt 50:50)

Compound **1_d** : $R_f = 0.55$ (EP/AcOEt 95:5)

Compound **1_e** : $R_f = 0.35$ (EP/AcOEt 90:10)

Compound **1_f** : $R_f = 0.23$ (EP/AcOEt 90:10)

Compound **1_g** : $R_f = 0.27$ (EP/AcOEt 70:30)

15 The alcohols all show in $^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ), the following signals : 5.8 (m, 1H, $\text{CH}=\text{C}$) ; 5.0 (t, 2H, $\text{C}=\text{CH}_2$) ; 4.6 (t, 1H, CHOH) ; 2.1 (2m, 4H, $\text{CH}_2\text{-CH}_2$).

2-aryl-5-iodomethyl-tetrahydrofuran - group compounds **2**

20 A stirred solution of alcohol **1** (71 mmol) in 250 ml of ether and 70 ml of water was cooled to 0°C . 8.9 g (1.5 equivalents) of sodium bicarbonate (NaHCO_3) were added by small portionwise. The mixture was allowed to warm to room temperature and stirred overnight. A solution of sodium thiosulphate (10 %) was added. After decantation and washing, the organic phase was dried and concentrated. The thus obtained residue was purified by flash chromatography (light petroleum / ethyl acetate 80:20 then 30:70) to yield the compound **2** as a mixture (yield about 80-85 %). In some cases, the cis and trans isomers may be isolated.

Compound **2_a** : R_f (cis) = 0.25 R_f (trans) = 0.31 (EP/AcOEt 95:5)

Compound **2_b** : R_f (cis) = 0.29 R_f (trans) = 0.35 (EP/AcOEt 70:30)

Compound **2_c** : R_f (rac) = 0.39 (EP/AcOEt 80:20)

30 Compound **2_d** : R_f (rac) = 0.70 (EP/AcOEt 95:5)

Compound **2_e** : R_f (cis) = 0.36 R_f (trans) = 0.45 (EP/AcOEt 90:10)

Compound **2_f** : R_f (rac) = 0.48 (EP/AcOEt 95:5)

IR (cm^{-1}) : $\nu_{\text{C-O-C}} = 1600$; $\nu_{\text{OCH}_3} = 1120$

^1H -NMR (100 MHz, CDCl_3 TMS, δ), characteristic signals :

Trans compound : 5.0 (m, 1H, H_2) ; 4.3 (m, 1H, H_5) ; 3.3 (m, 2H CH_2I) ; 2.5-1.7 (m, 4H, $\text{CH}_2\text{-CH}_2$)

Cis compound : 4.9 (m, 1H, H_2) ; 4.1 (m, 1H, H_5).

- 5 When the phenyl radical is substituted by one or more alkylsulphonyl groups, the synthesis of compound II may be performed through the intermediates 3 and 4 as shown in reaction scheme 2.

2-(3'-methoxy-4'-propyloxy-5'-methylsulphonyl-phenyl)-5-hydroxymethyl tetrahydrofuran 3

- 10 A solution of anhydrous m-chloroperbenzoic acid (m-CPBA) (14.7 g, 85.2 mmol) in 100 ml of dry dichloromethane was added slowly at 0°C to a solution of 6.3 g (21.3 mmol) of alcohol 1g in 200 ml of anhydrous dichloromethane. Stirring was maintained at room temperature overnight, then a saturated solution of sodium thiosulphate was added. After decantation, the organic phase was washed with 1N
- 15 sodium hydroxide solution, then with water, and dried. After elimination of the solvent, the residue thus obtained was purified on a silica gel column (eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) to give a viscous product (5.12 g, yield 70 %).

TLC : $R_f = 0.43$ ($\text{CHCl}_3/\text{MeOH}$ 95:5)

IR (cm^{-1}) : $\nu_{\text{OH}} = 3500$; $\nu_{\text{CH}_3\text{SO}_2} = 1310$

- 20 ^1H NMR (100 MHz, CDCl_3 , TMS, δ), characteristic signals :

5 (m, 1H, H_2) ; 4.3 (m, 1H, H_5) ; 3.8 (m, 2H, CH_2OH) ; 3.2 (s, 3H, CH_3SO_2).

Mesylate of 2-(3'-methoxy-4'-propyloxy-5'-methylsulphonyl-phenyl)-5-hydroxymethyl tetrahydrofuran 4

- The mesylate 4 was obtained by action of mesyl chloride (MeSO_2Cl) on the compound
- 25 3, and used without purification in the following step.

TLC : $R_f = 0.54$ ($\text{CHCl}_3/\text{MeOH}$ 95:5)

^1H NMR (100 MHz, CDCl_3 , TMS, δ) : 4.3 (m, 3H, H_5 and CH_2OMes).

2-aryl-5-benzylaminomethyl-tetrahydrofuran - group compounds II

A solution of benzylamine (4 equivalents) and either the iodide **2** (42 mmol) or the mesylate **4** in 200 ml of anhydrous acetonitrile was refluxed for 5 hours, then evaporated to dryness and taken up in 250 ml of chloroform. After washing with water and drying, the solvent was eliminated. The thus obtained residue was purified by flash chromatography (eluent CHCl_3 then $\text{CHCl}_3/\text{MeOH}$ 95:5). The amine was obtained in a yield about 70-75 %.

Compound **II_a** : R_f (cis) = 0.16 R_f (trans) = 0.22 (AcOEt)

Compound **II_b** : R_f (cis) = 0.15 R_f (trans) = 0.24 ($\text{CHCl}_3/\text{MeOH}$ 95:5)

10 Compound **II_c** : R_f (rac) = 0.28 ($\text{CHCl}_3/\text{MeOH}$ 95:5)

Compound **II_d** : R_f (rac) = 0.42 ($\text{CHCl}_3/\text{MeOH}$ 90:10)

Compound **II_e** : R_f (cis) = 0.26 R_f (trans) = 0.25 ($\text{CHCl}_3/\text{MeOH}$ 96:4)

Compound **II_f** : R_f (rac) = 0.25 (AcOEt)

Compound **II_g** : R_f (rac) = 0.25 ($\text{CHCl}_3/\text{MeOH}$ 95:5)

15 IR (cm^{-1}) : ν_{NH} = 3300

$^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ), characteristics signals :

Trans compound : 4.9 (t, 1H, H_2) ; 4.3 (m, 1H, H_5) ; 3.8 (d, 2H, $\text{NCH}_2\emptyset$) ; 2.7 (d, 2H, CH_2N).

Cis compound : 4.1 (m, 1H, H_5) ; 2.8 (d, 2H, CH_2N).

20 The enantiomers of compound **II**(cis) and compound **II**(trans) may be obtained separately from the corresponding enantiomers **2**(cis) and **2**(trans) respectively, or **3**(cis) and **3**(trans) respectively, according to the process as described above (cf. A-1) Preparation of compound **II**).

25 Said enantiomers of compound **2** or **3** may be obtained by oxydation of the corresponding alcohol **1** followed by asymmetric reduction and cyclisation. The synthesis of such enantiomers is hereunder illustrated for the compound **II_b** according to the following successive steps 1' and 2'.

Step 1': 2-(3', 4', 5'-trimethoxyphenyl)-5-pentanone

30 A solution of alcohol **1_b** (4 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a mixture of pyridinium chlorochromate (1.5 eq.), sodium acetate (0.04 eq.) and celite (1.5 g) in anhydrous CH_2Cl_2 (8 ml) at 0° C under nitrogen atmosphere. The reaction mixture was allowed to room temperature and stirred for about 4 hours (followed by TLC). The

insoluble materials were eliminated by filtration. The filtrate was evaporated and the thus obtained residue was purified by flash chromatography (EP/AcOEt 70:30), to give the ketone as a white solid (yield 81 %).

Melting point : mp = 64° C ; TLC : R_f = 0.60 (EP/AcOEt 1:1)

5 IR (cm⁻¹) ν_{CO} = 1680 ; ν_O = 1590

¹H-NMR (100 MHz, CDCl₃, TMS, δ) :

7.3 (s, 2H, Ø) ; 5.9 (m, 1H, HC=C) ; 5.1 (m, 2H, =CH₂) ; 3.9 (s, 9H, OCH₃) ;
3.1 (m, 2H, -C(O)-CH₂) ; 2.5 (q, 2H, CH₂-C=)

Step 2': 2-(3' 4' 5'-trimethoxyphenyl)-5-(-)-hydroxypentene

10 This step was performed according to Brown H.C., J. Org. Chem. 50, 5446 (1985).

A solution of (-) DIP chloride (β-chlorodiisopinocampocyl borane) (1.4 eq.) in anhydrous THF (4.5 ml) was added dropwise to a solution of ketone (31.8 mM) in dry THF (45 ml) at 0° C under stirring. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated and the thus obtained
15 residue was taken up in diethyl ether and diethylethanolamine (2.2 eq.) was added. After 30 minutes, the insoluble material was filtered off and washed with pentane. Elimination of the filtrate gave a viscous product which was purified by flash chromatography (EP/AcOEt 3:1) to afford the (-) alcohol (yield 65 %).

TLC : R_f = 0.34 (EP/AcOEt 2:1)

20 [α]_D²³ = -32.6 (CHCl₃, 0.82 g/100 ml)

The (+) alcohol may be obtained according to the process as described above but by using (+) DIPCl instead of (-)-DIPCl.

[α]_D²³ = +30.49 (CHCl₃, 0.9 g/100 ml)

The compounds 2_b(+) trans and 2_b(-) trans may be obtained according to the process as
25 described above (A-1) Preparation of compound 2), starting from the appropriate alcohols 1_b(+) trans and 1_b(-) trans respectively.

Compound 2_b(+) trans : [α]_D²³ = + 47.05 (CHCl₃, 1.27 g/100 ml)

Compound 2_b(-) trans : [α]_D²³ = - 46 (CHCl₃, 1.8 g/100 ml)

The compounds II_b(+) trans and II_b(-) trans may be obtained according to the process as
30 described above (cf. A-1 : Preparation of compound II), starting from the appropriate compounds 2_b(+) trans and 2_b(-) trans respectively.

Compound II_b(+) trans : [α]_D²³ = + 34.545 (CHCl₃, 2.2 g/100 ml)

Compound II_b(-) trans : $[\alpha]_D^{23} = -35.1$ (CHCl₃, 2 g/100 ml)

A-2) Process for the preparation of compound II wherein R = heteroaryl

2-(4'-pyridyl)-5-hydroxy-pentene 1

This compound **1** was obtained as described above and purified by flash chromatography
5 (eluent : AcOEt) to yield a brown oil (60 %)

TLC : R_f = 0.19 (AcOEt)

IR (cm⁻¹) : $\nu_{\text{pyridine}} = 1620$ and 1590 .

¹H-NMR (100 MHz, CDCl₃, TMS, δ) : 8.5 (m, 2H, H _{α} N) ; 7.3 (m, 2H, H aromatic) ; 5.8 (m, 1H, HC=) ; 5 (m, 2H, C=CH₂) ; 4.7 (t, 1H, CHOH) ;
10 1.9-2.2 (m, 5H, OH and 2CH₂).

2-(4'-pyridyl)-5-iodomethyl-tetrahydrofuran 2

This compound was obtained from the corresponding alcohol **1**, as described above, and purified by flash chromatography (eluent EP/AcOEt 30:70 then 20:80) (70 %).

TLC : R_f = 0.22 (EP/AcOEt 30:70)

15 IR (cm⁻¹) : $\nu_{\text{pyridine}} = 1600$ and 1560 ; $\nu_{\text{C-O-C}} = 1050$

¹H-NMR (100 MHz, CDCl₃, TMS, δ) : 8.5 (m, 2H, H _{α} N) ; 7.3 (m, 2H, 2H aromatic) ; 5 (m, 1H, H₂) ; 4.3 (m, 1H, H₅) ; 3.4 (m, 2H, CH₂I) ; 2.5-1.7 (m, 4H, CH₂-CH₂).

2-(4'-pyridyl)-5-benzylaminomethyl-tetrahydrofuran II

20 This amine was obtained from the corresponding compound **2**, as described above, and purified by flash chromatography (eluent CHCl₃/MeOH 90:10 then 80:20 and 70:30).

TLC : R_f = 0.40 (CHCl₃/MeOH 70:30).

A-3) Starting compound II wherein R = alkyl

The successive steps for the preparation of the compounds **1**, **2** and **II** respectively, are
25 performed in the same conditions as described above (cf. A-1).

B) Process for the preparation of the starting compound II disubstituted in the 2,5-positions with n=2

B-1) Process according to reaction scheme 3, for the preparation of compound II wherein R = aryl

5 2-aryl-5-cyanomethyl-tetrahydrofuran - group compounds 5

A mixture of 2-aryl-5-iodomethyl tetrahydrofuran 2 and potassium cyanide (1.5 equivalents) in 20 ml of dimethylsulphoxide was heated at 80° C for 3 hours. After cooling, 30 ml of brine was added and the product was extracted with ether. The elimination of the solvent leaves a residue which crystallized or which was purified by chromatography on a silica gel column (eluent EP/AcOEt 50:50 then 40:60). The compounds 5 were obtained in a yield of the order of 70-75 %.

Compound 5_h : R_f (cis) = 0.32 R_f (trans) = 0.38 (EP/AcOEt 70:30)

Compound 5_i : R_f (cis) = 0.34 R_f (trans) = 0.41 (EP/AcOEt 40:60)

Compound 5_h cis and 5_i cis are viscous compounds. Compound 5_i trans :mp: 98-100°C.

15 IR (cm⁻¹) : ν_{C≡N} = 2240

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

Trans compound : 5.1 (m, 1H, H₂) ; 4.5 (m, 1H, H₅) ; 2.7 (m, 2H, CH₂CN).

Cis compound : 4.9 (m, 1H, H₂) ; 4.3 (m, 1H, H₅).

2-aryl-5-(β-amino-ethyl)-tetrahydrofuran - group compounds 6

20 The reduction of the nitrile 5 was effected with LiAlH₄ (3 equivalents) in THF at room temperature. After hydrolysis in basic conditions, the product was extracted with chloroform, dried and the solvent was eliminated. The viscous oil 6 thus obtained was used without purification. Crude yield 80 %.

Compound 6_h : R_f (cis) = 0.28 R_f (trans) = 0.35 (CHCl₃/MeOH/NH₃ 80:19:1)

25 Compound 6_i : R_f (cis) = 0.25 R_f (trans) = 0.31 (CHCl₃/MeOH/NH₃ 80:19:1)

IR (cm⁻¹) ν_{NH₂} = 3350 - 3300

¹H NMR (100 MHz, CDCl₃, TMS, δ), principal signals :

Trans compound : 4.8 (m, 1H, H₂) ; 4.3 (m, 1H, H₅) ; 2.9 (m, 2H, CH₂N).

Cis compound : 4.7 (m, 1H, H₂) ; 4.2 (m, 1H, H₅).

2-aryl-5-(β -benzoylamino-ethyl)-tetrahydrofuran - group compounds 7

5 A solution of benzoyl chloride (1 equivalent) in dichloromethane was added slowly at 0° C to a mixture of the amine 6 and triethylamine (1.1 equivalents) in dichloromethane. Stirring was maintained for 1 hour. After filtration, the solvent was eliminated and the product was purified on a silica gel column (eluent CHCl₃/MeOH 98:2 then 97:3) (yield 90 %).

Compound 7_h : R_f (cis) = 0.52 R_f (trans) = 0.60 (CHCl₃/MeOH 97:3)

Compound 7_i : R_f (cis) = 0.50 R_f (trans) = 0.57 (CHCl₃/MeOH 97:3)

IR (cm⁻¹) : ν_{NH} = 3300 ; ν_{CO} = 1710

10 ¹H-NMR (100 MHz, CDCl₃, TMS, δ), principal signals :

Trans compound : 7.7 (m, 2H, H α to CO) ; 4.9 (m, 1H, H₂) ; 4.4 (m, 1H, H₅) ; 3.4 (m, 2H, CH₂NCO).

Cis compound : 4.8 (m, 1H, H₂) ; 4.2 (m, 1H, H₅).

2-aryl-5-(β -benzylamino-ethyl)-tetrahydrofuran - group compounds II

15 Compounds II were obtained by reduction of the amide 7 with LiAlH₄ under reflux in THF. The product was purified by chromatography on a silica gel column (eluent CHCl₃ then CHCl₃/MeOH 95:5) (yield about 70 %).

Compound II_h : R_f (cis) = 0.28 R_f (trans) = 0.30 (CHCl₃/MeOH 90:10)

Compound II_i : R_f (cis) = 0.24 R_f (trans) = 0.29 (CHCl₃/MeOH 90:10)

20 IR (cm⁻¹) : ν_{NH} = 3300

¹H NMR (100 MHz, CDCl₃, TMS, δ), principal signals :

Trans compound : 4.9 (m, 1H, H₂) ; 4.3 (m, 1H, H₅) ; 3.7 (s, 2H, NCH₂Ø) ; 2.8 (m, 2H, CH₂N)

Cis compound : 4.8 (m, 1H, H₂) ; 4.1 (m, 1H, H₅).

25 B-2) Process for the preparation of compound II wherein R = alkyl or heteroaryl

The successive steps for the preparation of compounds 5, 6, 7 and II respectively, may be performed as described above (cf. B-1).

C) Process for the preparation of the starting compound II disubstituted in the 2,5-positions with n=3

C-1) Process according to reaction scheme 4. for the preparation of compound II wherein R = aryl

5 2-aryl-5-(β -dicarboxyethyl-ethyl)-tetrahydrofuran - group compounds 8

To a suspension of sodium hydride (1.1 equivalents) in 50 ml of anhydrous THF, a solution of ethyl malonate (1 equivalent) was added dropwise. Stirring was maintained for 1 hour at room temperature. 2-aryl-5-iodomethyl-tetrahydrofuran **2** (1 equivalent) dissolved in THF was then added at 0°C, and the mixture was heated under reflux for 30
10 hours. After cooling, the sodium iodide was filtered off. The solvent was evaporated off and the residue was dissolved in ether and washed. After the usual workup, the residue was purified by flash chromatography (eluent EP/AcOEt 90:10 then 80:20) to afford a colourless viscous oil in a yield about 60 %.

Compound **8_j** : R_f (cis) = 0.28 R_f (trans) = 0.31 (EP/AcOEt 70:30)

15 Compound **8_k** : R_f (rac) = 0.51 (EP/AcOEt 70:30)

IR(cm^{-1}) : ν_{CO} = 1740 and 1730.

$^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ) principal signals :

Trans compound : 4.9 (t, 1H, H_2) ; 4.2 (m, 5 H, H_5 and 2 OCH_2CH_3) ; 3.65 [t, 1H, $\text{CH}(\text{CO}_2\text{Et})_2$] ; 1.2 (m, 6H, 2 CH_3)

20 Cis compound : 4.8 (t, 1H, H_2).

2-aryl-5-(β -carboxy-ethyl)-tetrahydrofuran - group compounds 9

An ethanolic solution of potassium hydroxide (2.05 equivalents) was added slowly to a solution of the diester **8** in ethanol. After 1.5 hours (monosaponification, monitored by TLC), the mixture was refluxed overnight, evaporated to dryness, and taken up in water.
25 The aqueous phase was first extracted with chloroform, then acidified and extracted again with chloroform. The elimination of the solvent gave the diacid (yield 98 %). Decarboxylation was obtained by warming the diacid on an oil-bath at 120°C until the evolution of carbon dioxide ceased (about 1 hour). After cooling, the acid **9** was obtained in a quantitative yield.

30 IR (cm^{-1}) : $\nu_{\text{OH chelate}}$ = 3400-3300 ; ν_{CO} = 1730

¹H-NMR (100 MHz, CDCl₃, TMS, δ), principal signals :

Trans compound : 5.7 (1H, OH) ; 4.9 (t, 1H, H₂) ; 4.2 (q, 1H, H₅) ; 2.6 (m, 2H, CH₂CO)

Cis compound : 7.3 (1H, OH) ; 4.8 (t, 1H, H₂) ; 4.1 (m, 1H, H₅).

5 2-aryl-5-(γ hydroxy)-propyl-tetrahydrofuran - group compounds 10

The reduction of the acid **9** by LiAlH₄ (2.5 equivalents), at room temperature, lead to the alcohol **10**. The purification was performed on a silica gel column (eluent AcOEt/EP 90:10 then pure AcOEt). Yield : 79 %.

Compound 10j : R_f (cis) = 0.28 R_f (trans) = 0.32 (AcOEt/EP 90:10)

10 Compound 10k : R_f (rac) = 0.40 (AcOEt)

IR (cm⁻¹) : ν_{OH} = 3400

¹H NMR (100 MHz, CDCl₃, TMS, δ) principal signals :

Trans compound : 4.9 (t, 1H, H₂) ; 4.2 (m, 1H, H₅) ; 4.1 (m, 2H, CH₂OH) ; 2.8 (1H, OH).

15 Cis compound : 4.8 (t, 1H, H₂) ; 4.1 (m, 3H, H₅ and CH₂OH) ; 2.6 (1H, OH).

Mesylate of 2-aryl-5-(γ-hydroxy)-propyl)-tetrahydrofuran - group compounds 11

The mesylate was obtained by action of mesyl chloride in dichloromethane in the presence of triethylamine at room temperature. The product was used in the next step without purification.

20 Compound 11j : R_f (cis) = 0.52 R_f (trans) = 0.49 (AcOEt)

Compound 11k : R_f (rac) = 0.60 (AcOEt)

IR (cm⁻¹) : ν_{SO2} = 1360 and 1180

¹H NMR (100 MHz, CDCl₃, TMS, δ), principal signals :

25 Trans compound : 4.9 (t, 1H, H₂) ; 4.2 (m, 3H, H₅ and CH₂OMs) ; 2.9 (s, 3H, SO₂Me).

Cis compound : 4.8 (t, 1H, H₂) ; 4.2 (t, 2H, CH₂OMes) ; 4 (m, 1H, H₅).

Specific signals for compound 11k : 5.3 (m, 1H, H₂)

2-aryl 5-[N-benzyl δ-amino propyl] tetrahydrofuran - group compounds II

30 The condensation of the mesylate **11** and the benzylamine was carried out in boiling acetonitrile, according to the process already described (cf. A-1) Process according to

scheme 2, step 3). Purification by chromatography on a silica gel column (eluent $\text{CHCl}_3/\text{MeOH}$ 95:5 then 90:10) gave the compound **II** (approximative yield 60 %).

Compound **II_j** : $R_f(\text{cis}) = 0.48$ $R_f(\text{trans}) = 0.55$ ($\text{CHCl}_3/\text{MeOH}$ 80:20)

Compound **II_k** : $R_f(\text{rac}) = 0.51$ ($\text{CHCl}_3/\text{MeOH}$ 80:20)

5 C-2) Process for the preparation of compound **II** wherein R = alkyl or heteroaryl

The successive steps for the preparation of the compounds **8**, **9**, **10**, **11** and **II** respectively, may be performed as described above (cf. C-1).

D) Process for the preparation of the starting compound **II** disubstituted in the 2,5-positions with n = 7

10 D-1) Process according to reaction scheme 5, for the preparation of compound **II** wherein R = aryl

2-(bromohexyl-oxy)tetrahydropyran **13**

15 This compound was obtained by bromation of 2-(hydroxyhexyl-oxy)tetrahydropyran which may be prepared from 1-6 hexanediol and dihydropyran.

^1H NMR (100 MHz, CDCl_3 , TMS, δ), principal signals :

4.6 (m, 1H, O-CH-O) ; 3.7 (m, 2H, $2\text{H}_\alpha\text{O}$) ; 3.3 (t, 4H, OCH_2 and CH_2Br) ; 1.9-1.3 (m, 14H, 7CH_2).

2-(3', 4', 5'-trimethoxyphenyl)-5-[tetrahydropyran-2-oxyhexyl] tetrahydrofuran **14**

20 A mixture of Cu(I)I (0.7 mmol) and compound **2b** (trans) in 20 ml of dry THF, was cooled at -40°C , under nitrogen atmosphere. The Grignard reagent prepared from compound **13** in THF was added dropwise. The mixture was stirred at this temperature for 30 minutes, raised to room temperature then refluxed for 6 hours. After usual work up, the product was chromatographed (eluent AcOEt) to yield the compound **14_i** trans
25 (60 %). $R_f(\text{trans}) = 0.51$ (AcOEt)

^1H NMR (100 MHz, CDCl_3 , TMS, δ), principal signals :

6.8 (s, 2H, $\emptyset$) ; 5 (m, 2H, H_2) ; 4.6 (m, 1H, O-CH-O) ; 4.2 (m, 1H, H_5) ; 3.9 (d, 9H, $3\text{CH}_3\text{O}$) ; 3.3 (t, 2H, CH_2O) ; 2.6-1.7 (m, 16H, 2H_3 , 2H_4 , 6CH_2).

The following successive steps for the preparation of compounds 15 and II, may be performed as described above (cf. reaction scheme 4).

D-2) Process for the preparation of compound II wherein R = alkyl or heteroaryl

5 The successive steps for the preparation of the compounds 12, 13, 14, 15 and II respectively, may be performed as described above (cf. D-1).

E) Process for the preparation of the starting compound II disubstituted in the 2,4-positions with n = 1

E-1) Process according to reaction scheme 6, for the preparation compound II wherein R = aryl

10 Ethyl 4-aryl-4-oxo-2-cyano-butyrate - group compounds 16

To a suspension of sodium hydride (1.1 equivalents) in anhydrous THF, 5.8 g (52 mmol) of ethyl cyanoacetate, in 100 ml of THF, was added dropwise. The mixture was stirred 30 minutes more then cooled to 0° C and a solution of 52 mmol of bromomethyl-aryl-ketone in 150 ml of THF was added slowly. The mixture was
15 allowed to warm to room temperature then refluxed for 1 hour. A hydrolysis followed by an extraction with chloroform lead, after the usual workup, to a product. A purification by silica gel column chromatography (eluent EP/AcOEt 60:40) afforded compound 16.

Compound 16_m : R_f = 0.5 (EP/AcOEt 50:50)

20 Compound 16_n : R_f = 0.62 (EP/AcOEt 50:50)

IR (cm⁻¹) : ν_{CN} = 2240 ; ν_{CO₂Et} = 1730 ; ν_{CO} = 1680.

¹H-NMR (100 MHz, CDCl₃, TMS, δ), main signals :

4.3 (q, 2H, OCH₂CH₃) ; 4.1 (t, 1H, CH) ; 3.6 (m, 2H, COCH₂) ; 1.3 (t, 3H, CH₃).

4-aryl-2-cyano-1,4-diol-butane - group compounds 17

25 Compound 17 was obtained by reducing the ketone and ester moieties of the compound 16, with LiBH₄ (2.2 equivalents) in THF at room temperature. After the usual

treatments, a purification on a silica gel column (eluent AcOEt/EP 80:20 then 90:10 then AcOEt) provided the diol 17 (yield 75 %).

Compound 17_m : $R_f(\text{rac}) = 0.31$ (AcOEt)

Compound 17_n : $R_f(\text{rac}) = 0.39$ (AcOEt)

5 IR (cm⁻¹) : $\nu_{\text{OH}} = 3400$; $\nu_{\text{CN}} = 2240$

¹H NMR (100 MHz, CDCl₃, TMS, δ), main signals :

5.35 (t, 2H, CHOH) ; 3.8 (m, 2H, CH₂OH) ; 3.15 (m, 1H, CHCN) ; 2.7 (2H, 2OH exchangeable with D₂O) ; 1.9 (m, 2H, CH₂CHCN)

4-aryl-2-cyano-tetrahydrofuran - group compounds 18

10 A mixture of diol 17 (28 mmol) and 0.2 g of p-toluene-sulphonic acid in 100 ml of anhydrous benzene was refluxed in an apparatus fitted with a Dean and Stark trap, for 5 hours. After elimination of the solvent, the residue was purified by flash chromatography (eluent EP/AcOEt 60:0) to afford compound 18 as cis, trans isomers (yield 75-78 %).

15 Compound 18_m : $R_f(\text{cis}) = 0.36$ $R_f(\text{trans}) = 0.41$ (EP/AcOEt 50:50)

Compound 18_n : $R_f(\text{cis}) = 0.46$ $R_f(\text{trans}) = 0.58$ (EP/AcOEt 50:50)

IR (cm⁻¹) $\nu_{\text{CN}} = 2240$; $\nu_{\text{C-O-C}} = 1010$

¹H NMR (100 MHz, CDCl₃, TMS, δ)

Trans compound : 5 (t, 1H, H₂) ; 4.4 and 4.1 (2m, 2H, 2H₅) ; 3.3 (m, 1H, H₄) ;

20 2.6 and 2.2 (2m, 2H, H₃)

Cis compound : 4.8 (t, 1H, H₂) ; 4.3 and 4.1 (2m, 2H, 2H₅) ; 2.7 and 2.1 (2m, 2H, H₃).

4-aryl-2-aminomethyl-tetrahydrofuran - group compounds 19

The reduction of the nitrile 18 with LiAlH₄ lead to the amine 19 (yield 89 %).

25 Compound 19_m : $R_f(\text{rac}) = 0.49$ (CHCl₃/MeOH/NH₃, 80:19:1)

Compound 19_n : $R_f(\text{rac}) = 0.51$ (CHCl₃/MeOH/NH₃, 80:19:1)

IR (cm⁻¹) $\nu_{\text{NH}_2} = 3400$ and 3350

¹H NMR (100 MHz, CDCl₃, TMS, δ) (mixture) :

4.85 (m, 1H, H₂) ; 4.3-3.6 (m, 4H, 2H₅, CH₂N) ; 2.7 (m, 1H, H₄) ; 2.4 and

30 2 (2m, 2H, H₃) ; 1.5 (2H, NH₂ exchangeable with D₂O).

4-aryl-2-(N-benzyl-aminomethyl)-tetrahydrofuran - group compounds II

The amine **19** was condensed with benzoyl chloride and the thus obtained amide was reduced with LiAlH_4 . The product **II** thus obtained was purified on a silica gel column (eluent $\text{CHCl}_3/\text{MeOH}$ 98:2 then 95:5).

5 Compound **II_m** : $R_f(\text{rac}) = 0.38$ ($\text{CHCl}_3/\text{MeOH}$ 98:2)

Compound **II_n** : $R_f(\text{rac}) = 0.40$ ($\text{CHCl}_3/\text{MeOH}$ 98:2)

IR (cm^{-1}) : $\nu_{\text{NH}} = 3300$

^1H NMR (100 MHz, CDCl_3 , TMS, δ) :

7.3 (m, 5H, $\emptyset$) ; 4.8 (m, 1H, H_2) ; 4.3-3.5 (m, 6H, 2H_5 , CH_2NCH_2) ; 2.6 (1H,
10 NH) ; 2.5-2 (2m, 2H, H_3).

E-2) Process for the preparation compound II wherein R = alkyl or heteroaryl

The successive steps for the preparation of the compounds **16**, **17**, **18**, **19** and **II** respectively, may be performed as described above (cf. E-1).

The following Examples illustrate the invention.

15 **Example 1**

2-phenyl-5-[N-[β -(3'-hydroxymethyl-4'-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound **I**, with a 2,5-disubstitution in which $n = 1$ and R = phenyl

Step 1 :

20 **2-phenyl-5-[N-benzyl-N-(3'-methoxycarbonyl-4'-hydroxy-phenacyl)]-aminomethyl-tetrahydrofuran IV**

25 A solution of methyl-5-bromoacetyl salicylate **III** (1.05 equivalents) in 100 ml of anhydrous acetonitrile was added dropwise to a solution of the appropriate amine **II** (28 mmol) and triethylamine (1.1 equivalents) in 120 ml of acetonitrile. The mixture was stirred at room temperature 2.5 hours more, then concentrated to dryness and taken up in chloroform. After the usual workup, the residue was purified by flash chromatography (EP/AcOEt 90:10 to 70:30) to yield compound **IV** (71 %). $M = 473$ g
TLC : $R_f(\text{rac}) = 0.47$ (EP/AcOEt 60:40)

IR (cm⁻¹) : ν_{OH} = 3100 ; ν_{CO_2Me} = 1690 ; ν_{CO} = 1670

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H₂) ; 8.1 (2d, 1H, H₆) ; 7.3 (m, 5H, $\emptyset$) ; 6.9 (d, 1H, H₅) ; 4.8 (t, 1H, H₂) ; 4.4 (m, 1H, H₅) ; 3.85 (m, 7H, CO₂Me, NCH₂CO, NCH₂ $\emptyset$) ; 2.8 (d, 2H, CH₂N).

Cis compound : 4.2 (m, 1H, H₅) ; 2.9 (d, 2H, CH₂N).

Step 2 :

2-phenyl-5-[[N-benzyl-N-[[β -hydroxy- β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]-ethyl]-aminomethyl]-tetrahydrofuran V

10 To a suspension of LiAlH₄ (3 equivalents) in 50 ml of anhydrous tetrahydrofuran (THF), cooled to 0° C under nitrogen atmosphere, was added dropwise a solution of the compound IV as obtained above (16 mmol) in 100 ml of THF. The mixture was allowed to warm to room temperature and stirred 1.5 hours more. The reaction was quenched in basic medium. After extraction with chloroform and usual workup, the residue was purified by chromatography (AcOEt/EP 80:20 then AcOEt) to yield V (77 %). M = 447 g

TLC : R_f (rac) = 0.24 (CH₂Cl₂/MeOH 95:5)

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

Trans compound : 11.1 (1H, OH) ; 4.9 (t, 1H, H₂) ; 4.5 (m, 3H, H₅ and CH₂OH) ; 2.8-2.7 (m, 4H, CH₂NCH₂).

Cis compound : 4.8-4.5 (m, 4H, H₂, H₅ and CH₂OH).

Step 3 :

2-phenyl-5-[N-[[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran I

25 The compound I was obtained by hydrogenolysis of the compound V as obtained above, in methanol, in the presence of Pd/C 10 %, under a pressure of 2.7 bar for 2-4 hours. The catalyst was filtered off and the solvent eliminated. The product was purified by chromatography on a silica gel column (eluent CHCl₃/MeOH 95:5 then 90:10) to yield compound I (73 %). Purity was checked by thin layer chromatography (TLC) and HPLC. M = 343 g

TLC : R_f (rac) = 0.16 (CHCl₃/MeOH 80:20).

(RTM)

HPLC : reverse phase column C₁₈-5 μ , Nucleosil¹²⁵, CFCC 3F 10386 ; 150 x 4.6 mm :

T_{Rmin} = 12.5 (eluent MeOH/H₂O/TFA 25:75:0.5 % - Flow rate 1 ml/min)

IR (cm⁻¹), general absorption bands :

ν_{OH} and ν_{NH} = 3400-3300 ; $\nu_{\emptyset}$ = 1590 ; ν_{C-OH} = 1220 ; ν_{C-O-C} = 1040

5 ¹H-NMR : δ (ppm) (cf table 1)

The fumarate salt was prepared by heating, under reflux for 5 minutes, an equimolar mixture of the compound **I** as obtained above and fumaric acid in absolute ethanol.

Melting point (°C) : mp (rac) = 98

Example 2

10 2-(3',4',5'-trimethoxyphenyl)-5-[N-[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound **I**, with a 2,5-disubstitution in which n = 1 and R = 3,4,5-trimethoxyphenyl

Step 1 :

15 2-(3',4',5'-trimethoxyphenyl)-5-[N-benzyl-N-(3'-methoxycarbonyl)-4'-hydroxy-phenacyl]-aminomethyl tetrahydrofuran **IV**

The compound **IV** was obtained according to the process as described above (cf. example 1, step 1), starting from the appropriate starting compound **II** (71 %).

M = 549 g

TLC : R_f (cis) = 0.42 R_f (trans) = 0.38 (EP/AcOEt 60:40)

20 IR (cm⁻¹) : ν_{OH} = 3100 ; ν_{CO_2Me} = 1690 ; ν_{CO} = 1670

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H₂) ; 8.1 (2d, 1H, H₆) ; 7.3 (m, 5H, $\emptyset$) ; 6.9 (d, 1H, H₅) ; 4.8 (t, 1H, H₂) ; 4.4 (m, 1H, H₅) ; 3.85 (m, 7H, CO₂Me, NCH₂CO, NCH₂ $\emptyset$) ; 2.8 (d, 2H, CH₂N).

25 Cis compound : 4.2 (m, 1H, H₅) ; 2.9 (d, 2H, CH₂N).

Step 2 :

2-(3',4',5'-trimethoxyphenyl)-5-[[N-benzyl]-N-[β -hydroxy- β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]-ethyl]-aminomethyl]-tetrahydrofuran V

The compound V was obtained according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (77 %).

M = 523 g

TLC : R_f (cis) = 0.41 R_f (trans) = 0.43 (AcOEt)

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

Trans compound : 11.1 (1H, OH) ; 4.9 (t, 1H, H₂) ; 4.5 (m, 3H, H₅ and CH₂OH) ;
2.8-2.7 (m, 4H, CH₂NCH₂).

Cis compound : 4.8-4.5 (m, 4H, H₂, H₅ and CH₂OH).

Step 3 :

2-(3',4',5'-trimethoxyphenyl)-5-[N-[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran I

The compound I was obtained according to the process as described above (cf. example 1, step 3), starting from the compound V as obtained above (71 %).

M = 433 g

TLC : R_f (cis)=0.25 R_f (trans)=0.21 (CHCl₃/MeOH 80:20)

HPLC : reverse phase column C₁₈-5 μ , Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :

T_Rmin (cis)= 12.4 ; T_Rmin (trans) = 7.2 (eluent MeOH/H₂O/TFA 50:50:0.5 % - Flow rate 0.5 ml/min)

IR (cm⁻¹), general absorption bands :

ν_{OH} and ν_{NH} = 3400-3300 ; ν_{ϕ} = 1590 ; ν_{C-OH} = 1220 ; ν_{C-O-C} = 1040 ;

ν_{OCH_3} = 1130

¹H-NMR : δ (ppm) (cf table 1)

Compound I trans(+) [α]_D²³ = +32.147 (CHCl₃, 0.871 g/100 ml)

Compound I trans(-) [α]_D²³ = -34.2 (CHCl₃, 0.92 g/100 ml)

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting points (°C) : mp (cis) = 111-113 mp (trans) = 124

Example 3

2-(2',3',4'-trimethoxyphenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound I, with a 2,5-disubstitution in which $n = 1$ and $R = 2,3,4$ -trimethoxyphenyl

5 Step 1 :

2-(2',3',4'-trimethoxyphenyl)-5-[N-benzyl-N-(3'-methoxycarbonyl-4'-hydroxy-phenacyl)]-aminomethyl-tetrahydrofuran IV

The compound **IV** was obtained according to the process as described above (cf. example 1, step 1), starting from the appropriate starting compound **II** (76 %).

10 $M = 549$ g

TLC : R_f (rac) = 0.25 (EP/AcOEt 70:30)

IR (cm^{-1}) : $\nu_{\text{OH}} = 3100$; $\nu_{\text{CO}_2\text{Me}} = 1690$; $\nu_{\text{CO}} = 1670$

$^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ), characteristics signals :

15 Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H_2) ; 8.1 (2d, 1H, H_6) ; 7.3 (m, 5H, $\emptyset$) ; 6.9 (d, 1H, H_5) ; 4.8 (t, 1H, H_2) ; 4.4 (m, 1H, H_5) ; 3.85 (m, 7H, CO_2Me , NCH_2CO , $\text{NCH}_2\emptyset$) ; 2.8 (d, 2H, CH_2N).

Cis compound : 4.2 (m, 1H, H_5) ; 2.9 (d, 2H, CH_2N).

Step 2 :

20 **2-(2',3',4'-trimethoxyphenyl)-5-[N-benzyl-N-[β-hydroxy-β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-ethyl]-aminomethyl]-tetrahydrofuran V**

The compound **V** was obtained according to the process as described above (cf. example 1, step 2), starting from the compound **IV** as obtained above (80 %).

$M = 523$ g

TLC : R_f (rac) = 0.40 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:90)

25 $^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ), characteristics signals :

Trans compound : 11.1 (1H, OH) ; 4.9 (t, 1H, H_2) ; 4.5 (m, 3H, H_5 and CH_2OH) ; 2.8-2.7 (m, 4H, CH_2NCH_2).

Cis compound : 4.8-4.5 (m, 4H, H_2 , H_5 and CH_2OH).

Step 3 :

2-(2',3',4'-trimethoxyphenyl)-5-[N-[β -(3'-hydroxymethyl-4'-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran I

- 5 The compound I was obtained according to the process as described above (cf. example 1, step 3), starting from the compound V as obtained above. The cis and trans isomers are separated by preparative HPLC (70 %). M = 433 g

TLC : R_f (cis) = 0.37 R_f (trans) = 0.32 (CHCl₃/MeOH 80:20)

HPLC : reverse phase column C₁₈-5 μ , Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :

- 10 T_{Rmin} (cis) = 47 ; T_{Rmin} (trans) = 45 (eluent MeOH/H₂O/TFA 25:75:0.5 % - Flow rate 1 ml/min)

IR (cm⁻¹), general absorption bands :

ν_{OH} and ν_{NH} = 3400-3300 ; ν_{ϕ} = 1590 ; ν_{COH} = 1220 ; ν_{C-O-C} = 1040 ; ν_{OCH_3} = 1130

¹H-NMR : δ (ppm) (cf table 1)

- 15 The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : mp (trans) = 145

Example 4

2-(2'-chlorophenyl)-5-[N-[β -(3'-hydroxymethyl-4'-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

- 20 Compound I, with a 2,5-disubstitution in which n = 1 and R = 2-chlorophenyl

Step 1 :

2-(2'-chlorophenyl)-5-[N-benzyl-N-(3'-methoxycarbonyl-4'-hydroxy-phenacyl)]-aminomethyl-tetrahydrofuran IV

- 25 The compound IV was obtained according to the process as described above (cf. example 1, step 1), starting from the appropriate starting compound II (69 %).

M = 493.5 g

TLC : R_f (cis) = 0.26 R_f (trans) = 0.21 (EP/AcOEt 80:20)

IR (cm⁻¹) : ν_{OH} = 3100 ; ν_{CO_2Me} = 1690 ; ν_{CO} = 1670

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H_{2'}) ; 8.1 (2d, 1H, H₆) ; 7.3 (m, 5H, Ø) ; 6.9 (d, 1H, H_{5'}) ; 4.8 (t, 1H, H₂) ; 4.4 (m, 1H, H₅) ; 3.85 (m, 7H, CO₂Me, NCH₂CO, NCH₂Ø) ; 2.8 (d, 2H, CH₂N).

5 Cis compound : 4.2 (m, 1H, H₅) ; 2.9 (d, 2H, CH₂N).

Step 2 :

2-(2'-chlorophenyl)-5-[[N-benzyl-N-[β-hydroxy-β-(3'-hydroxymethyl)-4'-hydroxy-phenyl) ethyl]-aminomethyl]-tetrahydrofuran V

The compound V was obtained according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (75 %).

M = 467.5 g

TLC : R_f (cis) = 0.41 R_f (trans) = 0.44 (EP/AcOEt 10:90)

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

10 Trans compound : 11.1 (1H, OH) ; 4.9 (t, 1H, H₂) ; 4.5 (m, 3H, H₅ and CH₂OH) ;
15 2.8-2.7 (m, 4H, CH₂NCH₂).

Cis compound : 4.8-4.5 (m, 4H, H₂, H₅ and CH₂OH).

Step 3 :

20 2-(2'-chlorophenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl)-β-hydroxyethyl]-aminomethyl]-tetrahydrofuran I

The compound I was obtained according to the process as described above (cf. example 1, step 3), starting from the compound V as obtained above in presence of PtO₂ instead of Pt/C (73 %). M = 377.5 g

TLC : R_f (cis) = 0.18 R_f (trans) = 0.15 (CHCl₃/MeOH 80:20)

25 HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :
T_{Rmin} (Cis)= 38 ; T_{Rmin} (Trans)= 35 (eluent MeOH/H₂O/TFA 25:75:0.5 ‰ - Flow rate 1 ml/min)

IR (cm⁻¹), general absorption bands :

ν_{OH} and ν_{NH} = 3400-3300 ; ν_Ø = 1590 ; ν_{C=O} = 1220 ; ν_{C-O-C} = 1040

30 ¹H-NMR : δ (ppm) (cf table 1)

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : mp (cis) = 90 mp (trans) = 80

Example 5

2-(3'-chlorophenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound I, with a 2,5-disubstitution in which $n = 1$ and $R = 3$ -chlorophenyl

5 **Step 1 :**

2-(3'-chlorophenyl)-5-[N-benzyl-N-(3'-methoxycarbonyl-4'-hydroxy-phenacyl)]-aminomethyl]-tetrahydrofuran IV

The compound **IV** was obtained according to the process as described above (cf. example 1, step 1), starting from the appropriate starting compound **II** (79 %).

10 $M = 493.5$ g

TLC : R_f (cis) = 0.23 R_f (trans) = 0.29 (EP/AcOEt 80:20)

IR (cm^{-1}) : $\nu_{\text{OH}} = 3100$; $\nu_{\text{CO}_2\text{Me}} = 1690$; $\nu_{\text{CO}} = 1670$

$^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ), characteristics signals :

15 Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, $\text{H}_{2'}$) ; 8.1 (2d, 1H, H_6) ; 7.3 (m, 5H, $\emptyset$) ; 6.9 (d, 1H, $\text{H}_{5'}$) ; 4.8 (t, 1H, H_2) ; 4.4 (m, 1H, H_5) ; 3.85 (m, 7H, CO_2Me , NCH_2CO , $\text{NCH}_2\emptyset$) ; 2.8 (d, 2H, CH_2N).

Cis compound : 4.2 (m, 1H, H_5) ; 2.9 (d, 2H, CH_2N).

Step 2 :

20 **2-(3'-chlorophenyl)-5-[[N-benzyl-N-[β-hydroxy-β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-ethyl]-aminomethyl]-tetrahydrofuran V**

The compound **V** was obtained according to the process as described above (cf. example 1, step 2), starting from the compound **IV** as obtained above. $M = 467.5$ g

TLC : R_f (cis) = 0.35 R_f (trans) = 0.33 (EP/AcOEt 20:80)

$^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ), characteristics signals :

25 Trans compound : 11.1 (1H, OH) ; 4.9 (t, 1H, H_2) ; 4.5 (m, 3H, H_5 and CH_2OH) ; 2.8-2.7 (m, 4H, CH_2NCH_2).

Cis compound : 4.8-4.5 (m, 4H, H_2 , H_5 and CH_2OH).

Step 3 :

2-(3'-chlorophenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxyethyl]-aminomethyl]-tetrahydrofuran I

The compound **I** was obtained according to the process as described above (cf. example 1, step 3), starting from the compound **V** as obtained above in presence of PtO₂ instead of Pd/C (73 %). M = 377.5 g

TLC : R_f (cis) = 0.17 R_f (trans) = 0.14 (CHCl₃/MeOH 80:20)

HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :

T_Rmin (cis) = 35 ; T_Rmin (trans) = 32.5 (eluent MeOH/H₂O/TFA 25:75:0.5 % - Flow rate 1 ml/min)

IR (cm⁻¹), general absorption bands :

ν_{OH} and ν_{NH} = 3400-3300 ; ν_O = 1590 ; ν_{C OH} = 1220 ; ν_{C-O-C} = 1040

¹H-NMR : δ (ppm) (cf table 1)

The fumarate salt was prepared by using the compound **I** as obtained above and fumaric acid. Melting point (°C) : mp (cis) = 72 mp (trans) = 84

Example 6

2-(2'-fluorophenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound **I**, with a 2,5-disubstitution in which n = 1 and R = 2-fluorophenyl

Step 1 :

2-(2'-fluorophenyl)-5-[N-benzyl-N-(3'-methoxycarbonyl)-4'-hydroxy-phenacyl]-aminomethyl-tetrahydrofuran IV

The compound **IV** was obtained according to the process as described above (cf. example 1, step 1), starting from the appropriate starting compound **II** (78 %).

M = 477.5 g

TLC : R_f (rac) = 0.34 (EP/AcOEt 80:20)

IR (cm⁻¹) : ν_{OH} = 3100 ; ν_{CO₂Me} = 1690 ; ν_{CO} = 1670

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H_{2'}) ; 8.1 (2d, 1H, H₆) ; 7.3 (m, 5H, Ø) ; 6.9 (d, 1H, H_{5'}) ; 4.8 (t, 1H, H₂) ; 4.4 (m, 1H, H₅) ; 3.85 (m, 7H, CO₂Me, NCH₂CO, NCH₂Ø) ; 2.8 (d, 2H, CH₂N).

5 Cis compound : 4.2 (m, 1H, H₅) ; 2.9 (d, 2H, CH₂N).

Step 2 :

2-(2'-fluorophenyl)-5-[[N-benzyl-N-[β-hydroxy-β-(3'-hydroxymethyl-4'-hydroxy-phenyl) ethyl-aminomethyl]-tetrahydrofuran V

The compound V was obtained according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (78 %).
10 M = 451 g

TLC : R_f (rac) = 0.46 (EP/AcOEt 10:90)

¹H-NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

Trans compound : 11.1 (1H, OH) ; 4.9 (t, 1H, H₂) ; 4.5 (m, 3H, H₅ and CH₂OH) ;
15 2.8-2.7 (m, 4H, CH₂NCH₂).

Cis compound : 4.8-4.5 (m, 4H, H₂, H₅ and CH₂OH).

Step 3 :

2-(2'-fluorophenyl)-5-[N-[β-(3'-hydroxymethyl-4'-hydroxy-phenyl)-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran I

20 The compound I was obtained according to the process as described above (cf. example 1, step 3), starting from the compound V as obtained above in presence of PtO₂ instead of Pd/C (75 %). M = 361 g

TLC : R_f (rac) = 0.16 (CHCl₃/MeOH 80:20)

HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386; 150 x 4.6 mm :

25 T_Rmin (rac) = 16.5 (eluent MeOH/H₂O/TFA 25:75:0.5 ‰ - Flow rate 1 ml/min)

IR (cm⁻¹), general absorption bands :

ν_{OH} and ν_{NH} = 3400-3300 ; ν_Ø = 1590 ; ν_{C OH} = 1220 ; ν_{C-O-C} = 1040 ; ν_{C-F} = 1230

¹H-NMR : δ (ppm) (cf table 1)

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : mp (rac) = 170
30

Example 7

2-(3'-methoxy-4'-propyloxy-5'-methylsulfonyl-phenyl)-5-[N-[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound I, with a 2,5-disubstitution in which $n = 1$ and $R = 3$ -methoxy-4-propyloxy-5-methylsulfonyl phenyl.

Step 1 :

2-(3'-methoxy-4'-propyloxy-5'-methylsulfonyl-phenyl)-5-[N-benzyl-N-(3'-methoxycarbonyl-4'-hydroxy-phenacyl)]-aminomethyl-tetrahydrofuran IV

The compound IV was obtained according to the process as described above (cf. example 1, step 1), starting from the appropriate starting compound II (74 %).

$M = 625$ g

TLC : R_f (rac) = 0.33 (CH_2Cl_2)

IR (cm^{-1}) : $\nu_{\text{OH}} = 3100$; $\nu_{\text{CO}_2\text{Me}} = 1690$; $\nu_{\text{CO}} = 1670$

$^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ), characteristics signals :

Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H_2') ; 8.1 (2d, 1H, H_6) ; 7.3 (m, 5H, $\emptyset$) ; 6.9 (d, 1H, H_5') ; 4.8 (t, 1H, H_2) ; 4.4 (m, 1H, H_5) ; 3.85 (m, 7H, CO_2Me , NCH_2CO , $\text{NCH}_2\emptyset$) ; 2.8 (d, 2H, CH_2N).

Cis compound : 4.2 (m, 1H, H_5) ; 2.9 (d, 2H, CH_2N).

Step 2 :

2-(3'-methoxy-4'-propyloxy-5'-methylsulfonyl-phenyl)-5-[[N-benzyl-N-[β -hydroxy- β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]-ethyl]-aminomethyl]-tetrahydrofuran V

The compound V was obtained according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (76 %).

$M = 599$ g

TLC : R_f (rac) = 0.37 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5)

$^1\text{H-NMR}$ (100 MHz, CDCl_3 , TMS, δ), characteristics signals :

Trans compound : 11.1 (1H, OH) ; 4.9 (t, 1H, H_2) ; 4.5 (m, 3H, H_5 and CH_2OH) ; 2.8-2.7 (m, 4H, CH_2NCH_2).

Cis compound : 4.8-4.5 (m, 4H, H_2 , H_5 and CH_2OH).

Step 3 :

2-(3'-methoxy-4'-propyloxy-5'-methylsulfonyl-phenyl)-5-[N-[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran I

- The compound **I** was obtained according to the process as described above (cf. example 1, step 3), starting from the compound **V** as obtained above (75 %). The cis and trans isomers are separated by preparative HPLC. M = 509 g
- TLC : R_f (cis) = 0.23 R_f (trans) = 0.19 (CHCl₃/MeOH 80:20)
- HPLC : reverse phase column C₁₈-5 μ , Nucleosil 125, CFCC 3F 10386; 150 x 4.6 mm :
T_{Rmin}(cis) = 23 ; T_{Rmin} (trans) = 19 (eluent H₂O/MeOH/TFA 60:40:0.5 ‰ - Flow rate 0.6 ml/min)
- IR (cm⁻¹), general absorption bands :
 ν_{OH} and ν_{NH} = 3400-3300 ; $\nu_{\emptyset}$ = 1590 ; ν_{C-OH} = 1220; ν_{C-O-C} = 1040 ;
 ν_{SO_2Me} = 1305 ; ν_{OCH_3} = 1140
¹H-NMR : δ (ppm) (cf table 1)
- The fumarate salt was prepared by using the compound **I** as obtained above and fumaric acid. Melting point (°C) : mp (cis) = 156 mp (trans) = 126

Example 8

2-(3',4'-dimethoxyphenyl)-5-[N-[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

- Compound **I**, with a 2.5-disubstitution in which n = 1 and R = 3,4-dimethoxyphenyl.
- The steps 1 to 3 were performed as described above (cf. example 1, steps 1 to 3) to obtain the required compound. M = 403 g
- TLC : R_f (cis) = 0.27 ; R_f (trans) = 0.22 (CHCl₃/MeOH 80:20)
- HPLC : reverse phase column C₁₈-5 μ , Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :
T_{Rmin} (cis) = 13.6 ; T_{Rmin} (trans) = 6.5 (eluent MeOH/H₂O/TFA 50:50:0.5 ‰ - Flow rate 0.5 ml/min)
- ¹H-NMR : δ (ppm) (cf table 1)
- The fumarate salt was prepared by using the compound **I** as obtained above and fumaric acid. Melting point (°C) : mp (cis) = 118 mp (trans) = 129

Example 9

2-(4'-methoxyphenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl)-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound I, with a 2,5-disubstitution in which n = 1 and R = 4-methoxyphenyl.

- 5 The steps 1 to 3 were performed as described above (cf. example 1, steps 1 to 3) to obtain the required compound. M = 373 g
TLC : R_f (cis) = 0.22 ; R_f (trans) = 0.19 (CHCl₃/MeOH 80:20)
HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :
T_Rmin (cis) = 45 ; T_Rmin (trans) = 41 (eluent MeOH/H₂O/TFA 25:75:0.5 ‰ - Flow rate
10 1 ml/min)
¹H-NMR : δ (ppm) (cf table 1)

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : mp (cis) = 101 mp (trans) = 112

Example 10

- 15 2-(2',6'-dichlorophenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl)-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound I, with a 2,5-disubstitution in which n = 1 and R = 2,6-dichlorophenyl.

- The steps 1 to 3 were performed as described above (cf. example 4, steps 1 to 3) to obtain the required compound. M = 412 g
20 TLC : R_f (rac) = 0.19 (CHCl₃/MeOH 80:20)
HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :
T_Rmin = 39 (eluent MeOH/H₂O/TFA 25:75:0.5 ‰ - Flow rate 1 ml/min)
¹H-NMR : δ (ppm) (cf table 1)

- The fumarate salt was prepared by using the compound I as obtained above and fumaric
25 acid. Melting point (°C) : mp (rac) = 92

Example 11

2-propyl-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxyphenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound I, with a 2,5-disubstitution in which n = 1 and R = propyl.

- 5 The steps 1 to 3 were performed as described above (cf. example 1, steps 1 to 3) to obtain the required compound. M = 309 g
TLC : R_f (rac) = 0.12 (CHCl₃/MeOH 80:20)
HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :
T_Rmin = 8.3 (eluent MeOH/H₂O/TFA 25:75:0.5 ‰ - Flow rate 1 ml/min)
- 10 ¹H-NMR : δ (ppm) (cf table 1).

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : m_p (rac) = 127

Example 12

2-(4'-pyridyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

- 15 Compound I, with a 2,5-disubstitution in which n = 1 and R = 4'-pyridyl.

Step 1 :

2-(4'-pyridyl)-5-[N-benzyl-N-(3'-methoxycarbonyl)-4'-hydroxy-phenacyl]-aminomethyl-tetrahydrofuran IV

- 20 The compound IV was obtained according to the process as described above (cf. example 1, step 1), starting from the corresponding starting compound II (69 %).
M = 474 g.
TLC : R_f (rac) = 0.25 (CHCl₃/MeOH 90:10).

Step 2 :

2-(4'-pyridyl)-5-[[N-benzyl-N-[β -hydroxy- β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]-ethyl]-aminomethyl]-tetrahydrofuran V

The compound V was obtained according to the process as described above (cf. example 1, step 2), starting from the corresponding compound IV (78 %).

M = 448 g

TLC : R_f (rac) = 0.20 (CHCl₃/MeOH 80:20)

Step 3 :

2-(4'-pyridyl)-5-[N-[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran I

The compound I was obtained according to the process as described above (cf. example 1, step 3), starting from the corresponding compound V in presence of PtO₂ instead of Pd/C (72 %). M = 344 g

TLC : R_f (rac) = 0.18 (CHCl₃/MeOH 60:40)

HPLC : reverse phase column C₁₈-5 μ , Nucleosil 125, CFCC 3F 10386 ; 150 x 4.6 mm :

T_Rmin (rac) = 12 (eluent MeOH/H₂O/TFA 15:85:0.5 % - Flow rate 0.6 ml/min)

IR (cm⁻¹), general absorption bands :

ν_{OH} and ν_{NH} = 3400-3300 ; $\nu_{\emptyset}$ = 1590 ; ν_{C-OH} = 1220 ; ν_{C-O-C} = 1040 ;

$\nu_{pyridine}$ = 1600 and 1560

¹H-NMR : δ (ppm) (cf table 1)

Example 13

2-phenyl-5-[N-[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminoethyl]-tetrahydrofuran

Compound I, with a 2,5-disubstitution in which n = 2 and R = phenyl

Step 1 :

2-phenyl-5-[[N-benzyl-N-(3'-methoxycarbonyl)-4'-hydroxy-phenacyl]-aminoethyl]-tetrahydrofuran IV

The compound IV was obtained according to the process as described above (cf. example 1, step 1), starting from the appropriate compound II (73 %).

TLC : R_f (cis) = 0.47 R_f (trans) = 0.43 (EP/AcOEt 60:40)

IR (cm^{-1}) : $\nu_{\text{CO}_2\text{Me}}$ = 1690 ; ν_{CO} = 1675

^1H NMR (100 MHz, CDCl_3 , TMS, δ) principal signals :

Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H_2') ; 8.1 (2d, 1H, H_6') ; 7.3 (s, 5H, OCH_2) ; 4.9 (t, 1H, H_2) ; 4.2 (m, 1H, H_5) ; 4.1 (s, 5H, NCH_2CO and CO_2Me) ; 3.8 (2H, NCH_2O) ; 2.7 (t, 2H, CH_2N) ; 2.4-1.5 (m, 8H, H_3 , H_4 , 2 CH_2 of the chain)

Cis compound : 4.8 (t, 1H, H_2).

Step 2 :

10 2-phenyl-5-[[N-benzyl-N-[β -hydroxy- β -(3'-hydroxymethyl)-4'-hydroxy-phenyl] ethyl]-aminoethyl]-tetrahydrofuran V

The compound V was obtained according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (70 %).

$M = 445 \text{ g}$

15 TLC : R_f (cis) = 0.24 R_f (trans) = 0.28 ($\text{CHCl}_3/\text{MeOH}$ 95:5)

IR (cm^{-1}) : ν_{OH} = 3400

^1H NMR (100 MHz, CDCl_3 , TMS, δ) principal signals :

Trans compound : 4.9 (t, 1H, H_2) ; 4.7 (s, 2H, CH_2OH) ; 4.6 (m, 1H, H_5) ; 4.15 (m, 1H, CHOH) ; 3.9 and 3.5 (2d, 2H, NCH_2O)

20 Cis compound : 4.7 (m, 4H, H_5 , H_2 and CH_2OH).

Step 3 :

2-phenyl-5-[N-[β -(3'-hydroxymethyl)-4'-hydroxy-phenyl]- β -hydroxy-ethyl]-aminoethyl]-tetrahydrofuran I

25 The compound I was obtained according to the process as described above (cf. example 1, step 3), starting from the compound V as obtained above (71 %). $M = 355 \text{ g}$

TLC : R_f (cis) = 0.48 R_f (trans) = 0.40 ($\text{CHCl}_3/\text{MeOH}$ 80:20)

HPLC : reverse phase column C_{18} -5 μ , Nucleosil 125, CFCC 3F 10386, 150 x 4.6 mm :

$T_{R\text{min}}(\text{cis}) = 52$; $T_{R\text{min}}(\text{trans}) = 48$ (eluent : $\text{MeOH}/\text{H}_2\text{O}/\text{TFA}$ 25:75:0.5 % - Flow rate 1 ml/min)

30 ^1H -NMR : δ (ppm) (cf. table 2)

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : mp (cis) = 145 mp (trans) = 130

Example 14

2-(3',4',5'-trimethoxyphenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminoethyl]-tetrahydrofuran

5

Compound I, with a 2,5-disubstitution in which n = 2 and R = 3,4,5-trimethoxyphenyl

Step 1 :

2-(3',4',5'-trimethoxyphenyl)-5-[[N-benzyl-N-(3'-methoxycarbonyl)-4'-hydroxy-phenacyl]]-aminoethyl-tetrahydrofuran IV

- 10 The compound IV was obtained according to the process as described above (cf. example 1, step 1), starting from the appropriate compound II.

TLC : R_f (cis) = 0.40 R_f (trans) = 0.28 (EP/AcOEt 50:50)

IR (cm⁻¹) : ν_{CO₂Me} = 1690 ; ν_{CO} = 1675

¹H NMR (100 MHz, CDCl₃, TMS, δ) principal signals :

- 15 Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H_{2'}) ; 8.1 (2d, 1H, H_{6'}) ; 7.3 (s, 5H, ØCH₂) ; 4.9 (t, 1H, H₂) ; 4.2 (m, 1H, H₅) ; 4.1 (s, 5H, NCH₂CO and CO₂Me) ; 3.8 (2H, NCH₂Ø) ; 2.7 (t, 2H, CH₂N) ; 2.4-1.5 (m, 8H, H₃, H₄, 2CH₂ of the chain)

Cis compound : 4.8 (t, 1H, H₂).

- 20 **Step 2 :**

2-(3',4',5'-trimethoxyphenyl)-5-[[N-benzyl-N-[β-hydroxy-β-(3'-hydroxymethyl)-4'-hydroxy-phenyl] ethyl]-aminoethyl]-tetrahydrofuran V

The compound V was obtained according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (72 %).

- 25 M = 535 g

TLC : R_f (cis) = 0.60 R_f (trans) = 0.65 (CHCl₃/MeOH 80:20)

IR (cm⁻¹) : ν_{OH} = 3400

¹H NMR (100 MHz, CDCl₃, TMS, δ) principal signals :

- 30 Trans compound : 4.9 (t, 1H, H₂) ; 4.7 (s, 2H, CH₂OH) ; 4.6 (m, 1H, H₅) ; 4.15 (m, 1H, CHOH) ; 3.9 and 3.5 (2d, 2H, NCH₂Ø)

Cis compound : 4.7 (m, 4H, H₅, H₂ and CH₂OH)

Step 3 :

2-(3',4',5'-trimethoxyphenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminoethyl]-tetrahydrofuran I

- 5 The compound **I** was obtained according to the process as described above (cf. example 1, step 3), starting from the compound **V** as obtained above (74 %). M= 455 g
 TLC : R_f (cis) = 0.18 R_f (trans) = 0.13 (CHCl₃/MeOH 80:20)
 HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386, 150 x 4.6 mm :
 T_Rmin(cis) = 24 ; T_Rmin(trans) = 19.5 (eluent : MeOH/H₂O/TFA 25:75:0.5 ‰ - Flow
 10 rate 1 ml/min)
¹H-NMR : δ (ppm) (cf. table 2)

The fumarate salt was prepared by using the compound **I** as obtained above and fumaric acid. Melting point (°C) : mp (cis) = 180 mp (trans) = 220

Example 15

- 15 2-(3',4',5'-trimethoxyphenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminopropyl]-tetrahydrofuran

Compound **I**, with a 2,5-disubstitution in which n = 3 and R = 3,4,5-trimethoxyphenyl

Step 1 :

- 20 2-(3',4',5'-trimethoxyphenyl)-5-[N-benzyl-N-(3'-methoxycarbonyl)-4'-hydroxy-phenacyl]-aminopropyl]-tetrahydrofuran IV

The compound **IV** was prepared according to the process as described above (cf. example 1, step 1), starting from the appropriate compound **II** (75 %).

TLC: R_f (cis) = 0.38 R_f (trans) = 0.26 (EP/AcOEt 50:50)

IR (cm⁻¹) : ν_{CO₂Me} = 1690 ; ν_{CO} = 1675

- 25 ¹H NMR (100 MHz, CDCl₃, TMS, δ) principal signals :

Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H_{2'}) ; 8.1 (2d, 1H, H_{6'}) ; 7.3 (s, 5H, ØCH₂) ; 4.9 (t, 1H, H₂) ; 4.2 (m, 1H, H₅) ; 4.1 (s, 5H, NCH₂CO and CO₂Me) ; 3.8 (2H, NCH₂Ø) ; 2.7 (t, 2H, CH₂N) ; 2.4-1.5 (m, 8H, H₃, H₄, 2CH₂ of the chain)

Cis compound : 4.8 (t, 1H, H₂).

Step 2 :

2-(3',4',5'-trimethoxyphenyl)-5-[[N-benzyl-N-[β-hydroxy-β-(3'-hydroxymethyl)-4'-hydroxy-phenyl) ethyl]-aminopropyl]-tetrahydrofuran V

- 5 The compound V was prepared according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (78 %).

M = 547 g

TLC: R_f (cis) = 0.36 R_f (trans) = 0.38 (CHCl₃/MeOH 90:10)

IR (cm⁻¹) : ν_{OH} = 3400

- 10 ¹H NMR (100 MHz, CDCl₃, TMS, δ) principal signals :

Trans compound : 4.9 (t, 1H, H₂) ; 4.7 (s, 2H, CH₂OH) ; 4.6 (m, 1H, H₅) ; 4.15 (m, 1H, CHOH) ; 3.9 and 3.5 (2d, 2H, NCH₂Ø)

Cis compound : 4.7 (m, 4H, H₅, H₂ and CH₂OH).

Step 3 :

- 15 2-(3',4',5'-trimethoxyphenyl)-5-[-N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl)-β-hydroxy-ethyl]-aminopropyl]-tetrahydrofuran I

The compound I was prepared according to the process as described above (cf. example 1, step 3), starting from the compound V as obtained above (72 %).

M = 457 g

- 20 TLC: R_f (cis) = 0.18 R_f (trans) = 0.15 (CHCl₃/MeOH 80:20)

HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386, 150 x 4.6 mm :

T_Rmin(cis) = 38 ; T_Rmin(trans) = 30 (eluent : MeOH/H₂O/TFA 25:75:0.5 ‰ - Flow rate 1 ml/min)

¹H-NMR : δ (ppm) (cf. table 3)

- 25 The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : mp (cis) = 205 mp (trans) = 162

Example 16

2-(2'-chlorophenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminopropyl]-tetrahydrofuran

Compound I, with a 2,5-disubstitution in which $n = 3$ and $R = 2\text{-chlorophenyl}$

5 **Step 1 :**

2-(2'-chlorophenyl)-5-[N-benzyl-N-(3'-methoxycarbonyl-4'-hydroxy-phenacyl)-aminopropyl]-tetrahydrofuran IV

The compound **IV** was prepared according to the process as described above (cf. example 1, step 1), starting from the appropriate compound **II** (75 %).

10 TLC: $R_f(\text{rac}) = 0.40$ (EP/AcOEt 70:30)

IR (cm^{-1}): $\nu_{\text{CO}_2\text{Me}} = 1690$; $\nu_{\text{CO}} = 1675$

^1H NMR (100 MHz, CDCl_3 , TMS, δ) principal signals :

Trans compound : 11.2 (1H, OH) ; 8.5 (d, 1H, H_2') ; 8.1 (2d, 1H, H_6') ; 7.3 (s, 5H, OCH_2) ; 4.9 (t, 1H, H_2) ; 4.2 (m, 1H, H_5) ; 4.1 (s, 5H, NCH_2CO and
15 CO_2Me) ; 3.8 (2H, NCH_2O) ; 2.7 (t, 2H, CH_2N) ; 2.4-1.5 (m, 8H, H_3 , H_4 , 2CH_2 of the chain)

Cis compound : 4.8 (t, 1H, H_2).

Step 2 :

20 **2-(2'-chlorophenyl)-5-[N-benzyl-N-[β-hydroxy-β-(3'-hydroxymethyl)-4'-hydroxy-phenyl] ethyl]-aminopropyl]-tetrahydrofuran V**

The compound **V** was prepared according to the process as described above (cf. example 1, step 2), starting from the compound **IV** as obtained above (79 %).

$M = 491.5$ g

TLC: $R_f(\text{rac}) = 0.42$ ($\text{CHCl}_3/\text{MeOH}$ 95:5)

25 IR (cm^{-1}): $\nu_{\text{OH}} = 3400$

^1H NMR (100 MHz, CDCl_3 , TMS, δ) principal signals :

Trans compound : 4.9 (t, 1H, H_2) ; 4.7 (s, 2H, CH_2OH) ; 4.6 (m, 1H, H_5) ; 4.15 (m, 1H, CHOH) ; 3.9 and 3.5 (2d, 2H, NCH_2O)

Cis compound : 4.7 (m, 4H, H_5 , H_2 and CH_2OH).

Step 3 :

2-(2'-chlorophenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminopropyl]-tetrahydrofuran I

- The compound I was prepared according to the process as described above (cf. example 1, step 3), starting from the compound V as obtained above, in presence of PtO₂ instead of Pd/C (73 %). M = 401.5 g
TLC : R_f (rac) = 0.14 (CHCl₃/MeOH 80:20)
HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386, 150 x 4.6 mm :
T_Rmin(rac) = 19.4 (eluent : MeOH/H₂O/TFA 25:75:0.5 % - Flow rate 1 ml/min)
¹H-NMR : δ (ppm) (cf. table 3)

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : mp (rac) = 210

Example 17

- 2-(3',4',5'-trimethoxyphenyl)-5-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminoheptyl]-tetrahydrofuran**

Compound I, with a 2,5-disubstitution in which n = 7 and R = 3,4,5-trimethoxyphenyl.

- The steps 1 to 3 were performed as described above (cf. example 1, steps 1 to 3) to obtain the required compound. M = 513 g
TLC : R_f (trans) = 0.19 (CHCl₃/MeOH 80:20)
HPLC : reverse phase column C₁₈-5μ, Nucleosil 125, CFCC 3F 10386, 150 x 4.6 mm :
T_Rmin(trans) = 35 (eluent MeOH/H₂O/TFA 25:75:0.5 % - Flow rate 1 ml/min)
¹H-NMR : δ (ppm) (cf. table 4)

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. Melting point (°C) : mp (trans) = 156

- Example 18**

2-(3',4',5'-trimethoxyphenyl)-4-[N-β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound I, with a 2,4-disubstitution in which n = 1 and R = 3,4,5-trimethoxyphenyl

Step 1 :

2-(3',4',5'-trimethoxyphenyl)-4-[N-benzyl-N-(3'-methoxycarbonyl-4'-hydroxy-phenacyl)-aminomethyl]-tetrahydrofuran IV

The compound IV was prepared according to the process as described above (cf. example 1, step 1), starting from the appropriate amine II (yield 69 %).

TLC : Rf (rac) = 0.42 (EP/AcOEt 50:50)

IR (cm⁻¹) : ν_{CO} (ester and ketone) = 1690

¹H NMR (100 MHz, CDCl₃, TMS, δ) characteristics signals :

4.7 (m, 1H, H₂) ; 4,2-3.5 (m, 16H, 4CH₃O, NCH₂CO, NCH₂Ø) ; 2.7-1.7 (m, 5H, 2H₃, 1H₄ and CH₂N).

Step 2 :

2-(3',4',5'-trimethoxyphenyl)-4-[-N-benzyl-N-[β -(3'-hydroxymethyl-4'-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran V

The compound V was prepared according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (yield 70 %).

TLC : Rf (rac) = 0.27 (CHCl₃/MeOH 85:15)

IR (cm⁻¹) : ν_{OH} = 3450-3300

¹H NMR (100 MHz, CDCl₃, TMS, δ), characteristics signals :

11 (phenolic OH) ; 7.3-6.8 (m, 8H, Ø and H₉, H₁₀, H₁₁) ; 6.5 (d, 2H, Ø) ; 4.8 (m, 3H, OH, H₂ and H₁₂) ; 3.8 (m, 14H, 3CH₃O, 2H₅, NCH₂Ø and H₈) ; 2.6-1.9 (m, 8H, 3OH, H₆, H₇ and H₄).

Step 3 :

2-(3',4',5'-trimethoxyphenyl)-4-[N- β -(3'-hydroxymethyl-4'-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl]-tetrahydrofuran I

After hydrogenolysis of the compound V, the compound I thus obtained was purified by chromatography on a silica column (eluent CHCl₃/MeOH 95:5, 90:10 then 70:30) (74 %). M = 433 g

TLC : Rf (rac) = 0.23 (CHCl₃/MeOH 80: 20)

¹H-NMR : δ (ppm) (cf. table 5)

HPLC : reverse phase column C₁₈-5 μ , Nucleosil 125, CFCC 3F 10386, 150 x 4.6 mm : T_R min = 7.5 (eluent MeOH/H₂O/TFA 25:75:0.5 ‰ - Flow rate 1 ml/min).

The fumarate salt was prepared by using the compound I as obtained above and fumaric acid. M = 549 g ; Melting point (°C) : 118° C

Example 19

5 2-(2'-chlorophenyl)-4-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran

Compound I, with a 2,4-disubstitution in which n = 1 and R = 2-chlorophenyl

Step 1 :

2-(2'-chlorophenyl)-4-[N-benzyl-N-(3'-methoxycarbonyl-4'-hydroxy-phenacyl)]-aminomethyl]-tetrahydrofuran IV

- 10 The compound IV was prepared according to the process as described above (cf. example 1, step 1), starting from the appropriate compound II (yield 67 %).

TLC : R_f (rac) = 0.46 (EP/AcOEt 50:50)

IR (cm⁻¹) : ν_{CO} (ester and ketone) = 1690

¹H NMR (100 MHz, CDCl₃, TMS, δ) characteristics signals :

- 15 4.7 (m, 1H, H₂) ; 4.2-3.5 (m, 7H, CH₃O, NCH₂CO, NCH₂Ø) ; 2.7-1.7 (m, 5H, 2H₃, 1H₄ and CH₂N).

Step 2 :

2-(2'-chlorophenyl)-4-[-N-benzyl-N-[β-(3'-hydroxymethyl)-4'-hydroxyphenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran V

- 20 The compound V was prepared according to the process as described above (cf. example 1, step 2), starting from the compound IV as obtained above (yield 71 %).

TLC : R_f (rac) = 0.29 (CHCl₃/MeOH 85:15)

IR (cm⁻¹) : ν_{OH} = 3450-3300

¹H-NMR (100 MHz, CDCl₃, TMS, δ) characteristics signals :

- 25 11 (phenolic OH) ; 7.3-6.8 (m, 8H, Ø and H₉, H₁₀, H₁₁) ; 4.8 (m, 3H, OH, H₂ and H₁₂) ; 3.8 (m, 5H, 2H₅, NCH₂Ø and H₈) ; 2.6-1.9 (m, 8H, 3OH, H₆, H₇ and H₄).

Step 3 :

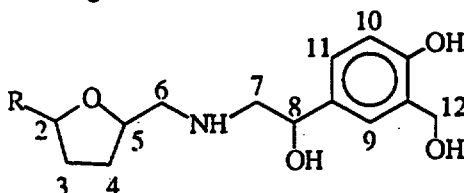
2-(2'-chlorophenyl)-4-[N-[β-(3'-hydroxymethyl)-4'-hydroxy-phenyl]-β-hydroxy-ethyl]-aminomethyl]-tetrahydrofuran I

- 5 The compound **I** was prepared according to the process as described above (cf. example 1, step 3), starting from the compound **V** as obtained above in presence of PtO_2 instead of Pd.
- TLC : R_f (rac) = 0.19 ($\text{CHCl}_3/\text{MeOH}$ 80:20)
- HPLC : reverse phase column C_{18} -5 μ , Nucleosil 125, CFCC 3F 10386, 150 x 4.6 mm :
- 10 T_R min = 38 (eluent $\text{MeOH}/\text{H}_2\text{O}/\text{TFA}$ 25:75:0.5 % - Flow rate 1 ml/min).
- $^1\text{H-NMR}$: δ (ppm) (cf. table 5)

The fumarate salt was prepared by using the compound **I** as obtained above and fumaric acid. $M = 493.5$ g ; Melting point ($^\circ\text{C}$) : 79°C

Table 1

- 15 $^1\text{H-NMR}$ (100 MHz, CD_3OD , TMS, δ) : the exchangeable protons are not visible.
 δ (ppm) according to the following formula :



- Example 1 : Racemic : 7.3 (s, 5H) ; 7.1-6.6 (m, 3H, H_9 , H_{10} , H_{11}) ; 4.9 (m, 1H, H_2) ; 4.6 (s, 2H, H_{12}) ; 4.4 (m, 2H, H_5 and H_8) ; 2.8 (m, 4H, H_6 and H_7) ; 2.3-1.7 (m, 4H, H_3 and H_4)
- Example 2 : Trans : 7.4-6.9 (m, 3H, H_9 , H_{10} , H_{11}) ; 6.8 (s, 2H, $\emptyset$) ; 5.2 (m, 3H, H_2 and H_{12}) ; 4.7 (m, 2H, H_5 and H_8) ; 3.9 (d, 9H, $3\text{CH}_3\text{O}$) ; 3.15 (m, 4H, H_6 and H_7) ; 2.5-1.9 (m, 4H, H_3 and H_4)
- Cis : 5 (m, 3H, H_2 and H_{12}) ; 4.5 (m, 1H, H_5)

- Example 3 : Trans : 7.2-6.9 (2m, 5H, H₉, H₁₀, H₁₁ and Ø) ; 5.3 (m, 1H, H₂) ; 5.1 (s, 2H, H₁₂) ; 4.9 (m, 1H, H₅) ; 4.7 (m, 1H, H₈) ; 3.9 (d, 9H, 3CH₃O) ; 3.15 (m, 4H, H₆ and H₇) ; 2.5-1.9 (m, 4H, H₃ and H₄)
Cis : 4.5 (m, 1H, H₅)
- Example 4 : Trans : 7.6-7.3 (m, 6H, H₉, H₁₁ and Ø) ; 6.9 (d, 1H, H₁₀) ; 5.5 (t, 1H, H₂) ; 4.9 (m, 3H, H₁₂ and H₈) ; 4.7 (m, 1H, H₅) ; 3.2 (m, 4H, H₆ and H₇) ; 2.6-1.9 (m, 4H, H₃ and H₄)
Cis : 5.4 (t, 1H, H₂) ; 4.5 (m, 1H, H₅) ; 3.3 (m, 4H, H₆ and H₇)
- Example 5 : Trans : 7.6-7.3 (m, 6H, H₉, H₁₁ and Ø) ; 6.9 (d, 1H, H₁₀) ; 5.3 (t, 1H, H₂) ; 4.8 (m, 4H, H₁₂, H₈ and H₅) ; 3.1 (m, 4H, H₆ and H₇) ; 2.6-1.7 (m, 4H, H₃ and H₄)
Cis : 4.4 (m, 1H, H₅) ; 3.3 (m, 4H, H₆ and H₇)
- Example 6 : Racemic : 7.5-7 (m, 6H, H₉, H₁₁ and Ø) ; 6.9 (d, 1H, H₁₀) ; 5.4 (m, 1H, H₂) ; 4.7 (m, 3H, H₈ and H₁₂) ; 4.6 (m, 1H, H₅) ; 3.1 (m, 4H, H₆ and H₇) ; 2.6-1.7 (m, 4H, H₃ and H₄)
- Example 7 : Trans : 7.6-7 (m, 4H, H₉, H₁₁ and Ø) ; 6.9 (d, 1H, H₁₀) ; 4.9 (m, 1H, H₂) ; 4.7 (m, 3H, H₁₂ and H₈) ; 4.5 (m, 1H, H₅) ; 4 (t, 2H, OCH₂) ; 3.8 (s, 3H, OCH₃) ; 3.2 (l, 3H, SO₂CH₃) ; 3 (m, 4H, H₆ and H₇) ; 2.6-1.6 (m, 6H, CH₂, H₃ and H₄) ; 0.9 (t, 3H, CH₃)
Cis : 4.7 (m, 1H, H₂) ; 4.3 (m, 1H, H₅) ; 3.2 (m, 7H, SO₂CH₃, H₆ and H₇)
- Example 8 : Trans : 7.4-7 (m, 3H, H₉, H₁₀, H₁₁) ; 6.8 (m, 3H, Ø) ; 5.2 (m, 3H, H₂ and H₁₂) ; 4.7 (m, 2H, H₅ and H₈) ; 3.8 (s, 6H, 2CH₃O) ; 3.2 (m, 4H, H₆ and H₇) ; 2.5-1.9 (m, 4H, H₃ and H₄)
Cis : 5 (m, 3H, H₂ and H₁₂) ; 4.5 (m, 1H, H₅)

Example 9 : Trans : 7.4-7 (m, 5H, H₉, H₁₀, H₁₁, Ø); 6.8 (d, 2H, H in **a** of OMe); 5.2 (m, 3H, H₂ and H₁₂); 4.7 (m, 2H, H₅ and H₈); 3.8 (s, 3H, OCH₃); 3.15 (m, 4H, H₆ and H₇); 2.15-1.9 (m, 4H, H₃ and H₄)

Cis : 5 (m, 3H, H₂ and H₁₂); 4.5 (m, 1H, H₅)

Example 10 : Racemic : 7.5-6.9 (m, 6H, H₉, H₁₀, H₁₁, Ø); 5.5 (t, 1H, H₂); 4.9 (m, 3H, H₁₂ and H₈); 4.6 (m, 1H, H₅); 3.2 (m, 4H, H₆ and H₇); 2.6-1.9 (m, 4H, H₃ and H₄)

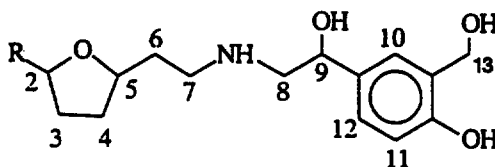
Example 11 : Racemic : 7-6.6 (m, 3H, H₉, H₁₀, H₁₁); 5 (s, 2H, H₁₂); 4.8 (m, 1H, H₈); 4.1-3.9 (m, 2H, H₂ and H₅); 3.2 (m, 4H, H₆ and H₇); 2.3-1.4 (m, 8H, 4CH₂); 0.9 (t, 3H, CH₃)

Example 12 : Racemic : 8.5 (m, 2H, 2H_αN); 7.4-6.9 (m, 5H, 2H pyridine, H₉, H₁₀, H₁₁); 5 (m, 1H, H₂); 4.8-4.5 (m, 4H, H₅, H₈ and 2H₁₂); 3.1 (m, 4H, H₆ and H₇); 2.6-1.9 (m, 4H, H₃ and H₄)

Table 2

¹H-NMR (100 MHz, CD₃OD, TMS, δ), characteristics signals :

δ (ppm) according to the following formula :



Example 13 : Trans : 7.3 (s, 5H); 7.1-6.6 (m, 3H, H₁₀, H₁₁, H₁₂); 5.1 (s, 2H, H₁₃); 5 (m, 2H, H₂ and H₉); 4.1 (m, 1H, H₅); 3.2 (m, 2H, H₈); 2.75 (m, 2H, H₇); 2-1.4 (m, 6H, H₃, H₄ and H₆)

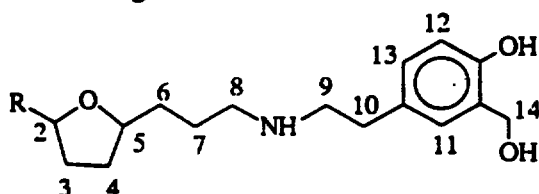
Cis : 4.9 (m, 2H, H₂ and H₉); 3.9 (m, 1H, H₅)

Example 14 : Trans : 7.4-6.9 (m, 3H, H₁₀, H₁₁, H₁₂) ; 6.8 (s, 2H, Ø) ; 5.2 (s, 2H, H₁₃) ; 5 (m, 1H, H₂) ; 4.8 (m, 1H, H₉) ; 4.6 (m, 1H, H₅) ; 3.9 (d, 9H, 3CH₃O) ; 3.2 (m, 2H, H₈) ; 2.5 (m, 2H, H₇) ; 2.2-1.7 (m, 6H, H₃, H₄, H₆)
Cis : 4.8 (m, 1H, H₈) ; 4.3 (m, 1H, H₅)

Table 3

¹H-NMR (100 MHz, CD₃OD, TMS, δ), characteristics signals :

5 δ (ppm) according to the following formula :

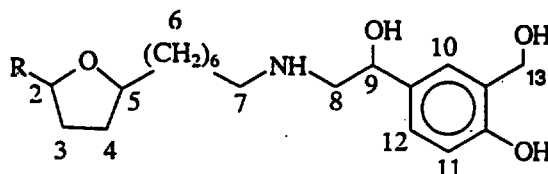


Example 15 : Trans : 7.5-6.9 (m, 3H, H₁₁, H₁₂, H₁₃) ; 6.7 (s, 2H, Ø) ; 5.1 (m, 2H, H₂ and H₁₀) ; 4.9 (s, 2H, H₁₄) ; 4.3 (m, 1H, H₅) ; 3.9 (d, 9H, 3CH₃O) ; 3.2 (m, 4H, H₈ and H₉) ; 2.6-1.7 (m, 8H, H₆, H₇, H₃ and H₄)
Cis : 5 (m, 4H, H₂, H₁₀ and H₁₄) ; 4.1 (m, 1H, H₅)

Example 16 : Racemic : 7.7-6.8 (m, 7H, H₁₁, H₁₂, H₁₃ and Ø) ; 5.4 (m, 1H, H₂) ; 5.1 (s, 2H, H₁₄) ; 4.9 (m, 1H, H₁₀) ; 4.3 (m, 1H, H₅) ; 3.2 (m, 4H, H₈ and H₉) ; 2.2-1.3 (m, 8H, H₆, H₇, H₃ and H₄)

Table 4

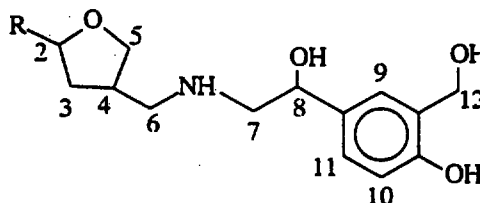
^1H -NMR (100 MHz, CD_3OD , TMS, δ), characteristics signals :
 δ (ppm) according to the following formula :



Example 17 : Trans : 7.4-6.9 (m, 3H, H_{10} , H_{11} , H_{12}) ; 6.7 (s, 2H, $\emptyset$) ; 5.1 (m, 2H, H_2 and H_9) ; 4.3 (m, 1H, H_5) ; 3.9 (d, 9H, $3\text{CH}_3\text{O}$) ; 3.2 (m, 4H, H_7 and H_8) ; 2.6-1.7 (m, 16H, H_3 , H_4 and 6CH_2)

Table 5

5 ^1H NMR (100 MHz, CD_3OD , TMS, δ) characteristics signals :
 δ (ppm) according to the following formula :



Example 18 : 7.5-6.8 (m, 3H, H_9 , H_{10} , H_{11}) ; 6.7 (d, 2H, $\emptyset$) ; 4.8 (m, 3H, H_2 and H_{12}) ; 4.3 (m, 1H, H_8) ; 3.8 (m, 11H, $3\text{CH}_3\text{O}$ and 2H_5) ; 2.8 (m, 4H, H_6 and H_7) ; 2.3 (m, 3H, H_3 and H_4).

Example 19 : 7.5-6.8 (m, 6H, H_9 , H_{11} and $\emptyset$) ; 6.9 (d, 1H, H_{10}) ; 5 (m, 3H, H_2 and H_{12}) ; 4.4 (m, 1H, H_8) ; 3.8 (m, 2H, 2H_5) ; 2.8 (m, 4H, H_6 and H_7) ; 2.3 (m, 3H, 2H_3 and H_4).

Toxicology

No toxicity was noticed for any of the compounds according to the invention when administered per se, at doses up to 50 mg/kg, to rats and mice. By the IP route, no death was noticed at 30 mg/kg for the same animals.

5 Pharmacology

Compounds of the invention are potent β_2 adrenoceptor agonists with a long duration of action on airways smooth muscles and act as bronchodilators in vivo.

In vitro, radioligand binding studies in lung membrane indicated that several of them have a better affinity for β adrenoceptors than Salbutamol, used as a reference. The Results are
10 summarised in Table A. Generally, the activity is better for the trans than the cis isomer.

In vivo

The different compounds showed a bronchodilator effect with a duration of action better than Salbutamol in its ability to inhibit acetylcholine induced bronchoconstriction.

Method :

15 Male Hartley Guinea Pigs (450-500 g) were anaesthetised with ethyl carbamate and prepared for recording bronchoconstriction according to Konzett and Rossler method (Naunym Schmiedebergers Arch. Exp. Path. Pharmacol (1940) 195, 71). To abolish
spontaneous respiration, an injection IV of vecuronium bromide (2 mg/kg) was made. Bronchoconstriction was induced by IV injection of Acetylcholine and the animals
20 received one dose of β_2 agonist compound (IV) 5 minutes later. Results are given with Salbutamol as reference and are summarised in Table B.

Moreover, the example 2 (cis) showed an α -antagonist activity (binding α , receptor $K_i = 61$ nM) and was an inhibitor of isolated aorta contraction induced by phenylephrine ($pA_2 : 7.75$).

25 Compounds of the invention compared to Salbutamol, are not more active but their actions last a longer time which is a very important advantage.

Presentation-Posology

In human therapy, a daily dose is of from 0.01 to 50 mg ; for oral administration, the pharmaceutical composition may take the form of, for instance, tablets or capsules ; by this route, the suitable doses are 0.01 mg to 50 mg. By IP route, the corresponding
5 daily doses are 0.01 mg to 20 mg.

Table A

	BINDING AFFINITY (K _i , nM)
Salbutamol	2500
Example 1	410
Example 2 (trans)	80
Example 2 (cis)	410
Example 2 (trans) (+)	50
Example 2 (trans) (-)	350
Example 3 (trans)	1600
Example 4 (trans)	400
Example 4 (cis)	347
Example 5 (trans)	750
Example 5 (cis)	760
Example 6	1800
Example 8 (trans)	1050
Example 8 (cis)	1100
Example 9 (trans)	590
Example 9 (cis)	810
Example 11	520
Example 12	350
Example 14 (cis)	1900
Example 15 (trans)	760
Example 15 (cis)	1900
Example 16	570
Example 18	1600

Table B

COMPOUNDS	DOSE μmol/kg, IV	BRONCHOCONSTRICTION PROTECTION			
		DURATION OF ACTION (mn)	5 mn	15 mn	30 mn
Salbutamol	0.13	10	+++	0	0
	0.42	30	+++	+++	0
Example 1	4.8	0	0	0	0
Example 2 (trans)	0.13	30	+++	++	+
	0.42	> 50	+++	+++	+++
Example 2 (cis)	4.6	5	+	0	0
Example 3 (trans)	1.53	5	+	0	0
	3.6	30	++	+	+
Example 4 (trans)	0.46	10	+++	0	0
	1.48	> 25	+++	++	++
Example 4 (cis)	0.46	10	++	0	0
	1.5	< 40	++	++	+
Example 5 (trans)	0.46	> 20	++	+	+
Example 5 (cis)	0.47	< 10	+	0	0
Example 6	0.47	< 30	++	+	+
Example 8 (trans)	0.13	30	++	+	+
	0.46	> 30	++	++	+
Example 8 (cis)	0.48	< 30	++	+	0
Example 9 (trans)	0.46	> 30	+++	++	+
Example 9 (cis)	0.46	20	++	+	0
Example 12	0.13	> 30	++	+	+
	0.42	> 30	++	++	+
Example 14 (cis)	1.50	30	+++	+	+
Example 15 (trans)	0.42	20	+++	++	0
	4.18	> 50	+++	+++	++
Example 16	1.6	> 15	+	+	0
Example 18	1.6	30	++	+	+

The score legends are as follows :

Score 0 : inhibition = < 20 %

Score + : inhibition = 20-50 %

5 Score ++ : inhibition = 50-75 %

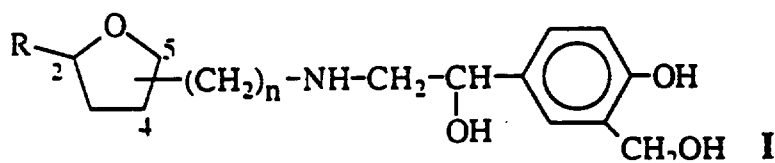
Score +++ : inhibition > 75 %.

5. 2-(2-chlorophenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
6. 2-(3-chlorophenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
7. 2-(2-fluorophenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
8. 2-(3-methoxy-4-propoxy-5-methylsulphonyl-phenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
9. 2-(3,4-dimethoxyphenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
10. 2-(4-methoxyphenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
11. 2-(2,6-dichlorophenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
12. 2-propyl-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
13. 2-(4-pyridyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
14. 2-phenyl-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminoethyl}-tetrahydrofuran.
15. 2-(3,4,5-trimethoxyphenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminoethyl}-tetrahydrofuran.
16. 2-(3,4,5-trimethoxyphenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminopropyl}-tetrahydrofuran.



CLAIMS

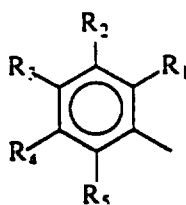
1. A tetrahydrofuran derivative, in racemic or enantiomeric form, having the general formula I



wherein

n is an integer of from 1 to 10, and

R represents a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, a heteroaryl group or a group of the general formula



wherein

each of the groups R_1 , R_2 , R_3 , R_4 and R_5 independently represents a hydrogen atom, a halogen atom, an alkoxy group having from 1 to 5 carbon atoms or an alkylsulphonyl group having from 1 to 5 carbon atoms;

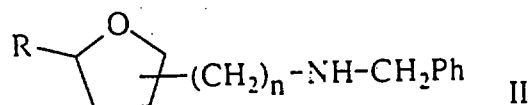
or a pharmaceutically acceptable salt thereof.

2. 2-phenyl-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
3. 2-(3,4,5-trimethoxyphenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
4. 2-(2,3,4-trimethoxyphenyl)-5-{N-[β -(3-hydroxymethyl-4-hydroxy-phenyl)- β -hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.

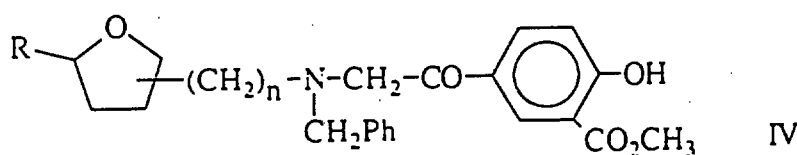


17. 2-(2-chlorophenyl)-5-{N-[β-(3-hydroxymethyl-4-hydroxy-phenyl)-β-hydroxy-ethyl]-aminopropyl}-tetrahydrofuran.
18. 2-(3,4,5-trimethoxyphenyl)-5-{N-[β-(3-hydroxymethyl-4-hydroxy-phenyl)-β-hydroxy-ethyl]-aminoheptyl}-tetrahydrofuran.
19. 2-(3,4,5-trimethoxyphenyl)-5-{N-[β-(3-hydroxymethyl-4-hydroxy-phenyl)-β-hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.
20. 2-(2-chlorophenyl)-4-{N-[β-(3-hydroxymethyl-4-hydroxy-phenyl)-β-hydroxy-ethyl]-aminomethyl}-tetrahydrofuran.

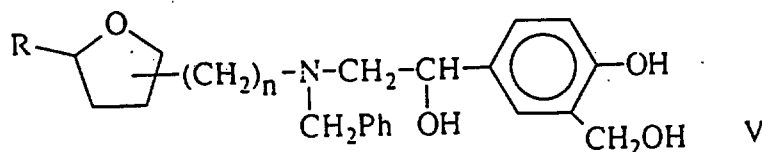
21. A process for the preparation of a tetrahydrofuran derivative according to claim 1, the process comprising
condensing a 2-substituted (4 or 5)-benzylaminoalkyl-tetrahydrofuran compound of the general formula II



wherein R and n are as defined in claim 1 with methyl 5-bromoacetyl-salicylate in a solvent in the presence of an organic base,
reducing the resultant compound of the general formula IV



wherein R and n are as defined in claim 1 with a hydride as reducing agent in a solvent under an inert atmosphere, and
debenzylating the resultant compound of the general formula V



wherein R and n are as defined in claim 1 by catalytic hydrogenation.



22. A process according to claim 21 in which the condensation is effected in a protic solvent or acetonitrile, in the presence of triethylamine at a temperature of from room temperature to the boiling point of the reaction mixture for 2 to 18 hours.
23. A process according to claim 21 or claim 22 in which the reduction with a hydride is effected in an ethereal solvent for 2 to 8 hours at a temperature of from 0°C to room temperature.
24. A process according to claim 23 in which the hydride is lithium aluminium hydride.
25. A process according to claim 23 or claim 24 in which the ethereal solvent is tetrahydrofuran or diethyl ether.
26. A process according to any of claims 21 to 25 in which the catalytic hydrogenation is effected at from 2 to 5.5 bar, at a temperature of from room temperature to 40°C for 10 minutes to 5 hours.
27. A process according to any of claims 21 to 26 in which the catalyst for the catalytic hydrogenation is platinum dioxide or palladium/carbon.
28. A process according to any of claims 21 to 27 in which R represents a heteroaryl group or a phenyl group substituted by one or more halogen atoms and the debenzylolation is effected by hydrogenation over platinum dioxide at 4 to 5.5 bar at room temperature for 10 to 30 minutes.
29. A process according to any of claims 21 to 27 in which R represents an alkyl group or a phenyl group substituted by one or more alkoxy or alkylsulphonyl groups and the debenzylolation is effected by hydrogenation over palladium/carbon at 2 to 3.5 bar.
30. A pharmaceutical composition comprising a tetrahydrofuran derivative I according to any of claims 1 to 20, in racemic or enantiomeric form, or a pharmaceutically acceptable salt of such a tetrahydrofuran derivative, in admixture with a pharmaceutically acceptable diluent or carrier.