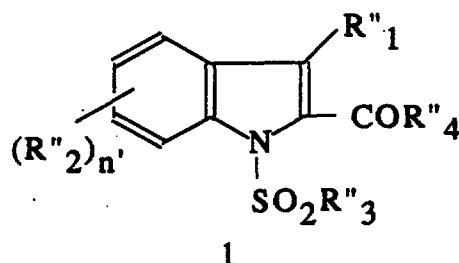


The present invention relates to N-sulfonyl-indoline derivatives, carrying an amide functional group, their preparation and the pharmaceutical compositions in which they are present.

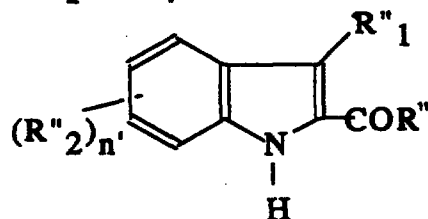
5 US Patent 3,838,167 describes some N-sulfonyl-indole derivatives of the formula:



in which

- R'1 is hydrogen, an alkyl or a substituted or unsubstituted phenyl;
- 10 - R'2 is a halogen, an alkyl, an alkoxy, a nitro or trifluoromethyl;
- R'3 is an alkyl, a phenyl or an alkylphenyl;
- R'4 is an alkyl, a substituted or unsubstituted phenyl, an alkoxy or a phenoxy;
- 15 - n' = 0, 1 or 2.

These compounds 1 are synthesis intermediates for the preparation of indole derivatives active on the central nervous system, of formula:



20 in which R'' is an alkyl, a substituted or unsubstituted phenyl or a hydroxyl.

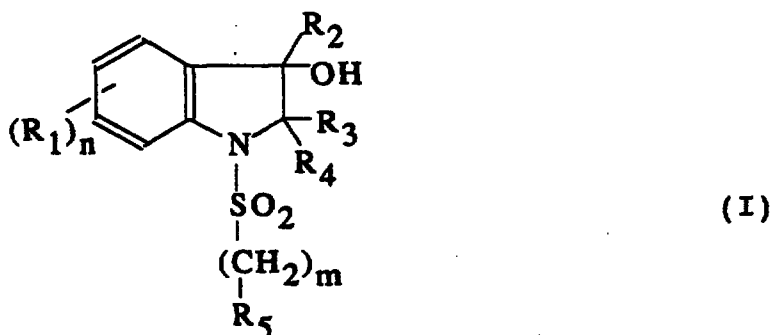
The indoline derivatives according to the present invention have an affinity for the vasopressin and oxytocin receptors.

25 Vasopressin is a hormone known for its antidiuretic effect and its effect in the regulation of the arterial

pressure. It stimulates several types of receptors: V_1 , V_2 , V_{1a} , V_{1b} and thus exerts cardiovascular, central, hepatic, antidiuretic, emetic and aggregating effects, as well as proliferative and mitotic effects, especially on the vascular and hepatic tissues. Vasopressin receptor antagonists can affect the regulation of the central or peripheral circulation, especially the coronary, renal and gastric circulations, as well as the metabolism of water and the release of adrenocorticotrophic hormone (ACTH). The vasopressin receptors, like those of oxytocin, are also found on the smooth muscle of the uterus. Oxytocin has a peptide structure similar to that of vasopressin. Its receptors are also found on the myoepithelial cells of the mammary gland and in the central nervous system. (Presse Médicale, 1987, 16 (10), 481-485, J. Lab. Clin. Med., 1989, 114 (6), 617-632 and Pharmacol. Rev., 1991, 43 (1), 73-108).

Thus the compounds according to the invention are useful especially in the treatment of complaints of the central nervous system, the cardiovascular system and the gastric sphere in humans and animals.

The present invention relates to compounds of formula:



25 in which

- 30
- R_1 is a halogen atom, a C_1 - C_4 alkyl, a hydroxyl, a C_1 - C_4 alkoxy, a benzyloxy group, a cyano group, a trifluoromethyl group, a nitro group or an amino group;
 - R_2 is a C_1 - C_6 alkyl, a C_3 - C_7 cycloalkyl, a C_5 - C_7 cycloalkene or a phenyl which is unsubstituted or monosubstituted or polysubstituted by a C_1 - C_4 alkyl, a



- 5 C₁-C₄ alkoxy, a halogen, a trifluoromethyl group or an amino group, or R₂ is a nitrophenyl which is unsubstituted or monosubstituted by a trifluoromethyl group or monosubstituted or polysubstituted by a C₁-C₄ alkyl or a halogen;
- 10 - R₃ is a hydrogen atom;
- R₄ is a carbamoyl group of formula CONR₆R₇;
- R₅ is a C₁-C₄ alkyl; a 1-naphthyl; a 2-naphthyl; a 5-dimethylamino-1-naphthyl; a phenyl which is unsubstituted or substituted by one or more substituents selected from a halogen atom, a C₁-C₄ alkyl, a trifluoromethyl group, an amino group which is free or substituted by one or 2 C₁-C₄ alkyls, a hydroxyl, a C₁-C₄ alkoxy, a C₂-C₄ alkenoxy, a C₁-C₄ alkylthio, a
- 15 trifluoromethoxy group, a benzyloxy group, a cyano group, a carboxyl group, a C₁-C₄ alkoxy-carbonyl group, a carbamoyl group which is free or substituted by one or two C₁-C₄ alkyls or a C₁-C₄ alkylamido group, or R₅ is a nitrophenyl which is unsubstituted or monosubstituted by a trifluoromethyl group or a C₂-C₄ alkenoxy or mono- or polysubstituted by a halogen, a C₁-C₄ alkyl, a C₁-C₄ alkoxy, a C₁-C₄ alkylthio, a trifluoromethoxy group or a benzyloxy group;
- 20 - R₆ is a C₁-C₆ alkyl or R₆ is similar to R₇;
- 25 - R₇ is a 4-piperidyl group or a 3-azetidiny group, the said groups being substituted or unsubstituted on the nitrogen by a C₁-C₄ alkyl, by a benzyloxycarbonyl or by a C₁-C₄ alkoxy-carbonyl; a group (CH₂)_x which is itself substituted by a 2-, 3- or 4-pyridyl group, by a
- 30 hydroxyl group or by an amino group which is free or substituted by one or two C₁-C₄ alkyls, a carboxyl group, a C₁-C₄ alkoxy-carbonyl group, a benzyloxycarbonyl group or a carbamoyl group which is free or substituted by one or 2 C₁-C₄ alkyls;
- 35 - or R₆ and R₇ together, with the nitrogen atom to which they are connected, form a heterocycle selected from:
· morpholine,
· thiomorpholine,



- thiazolidine or 2,2-dimethylthiazolidine, unsubstituted or substituted by R_8 ,
- piperazine, unsubstituted or substituted at the 4-position by a group R''_8 ,
- 5 • an unsaturated, 5-membered ring containing a single nitrogen atom and substituted by R_8 or a saturated, 3-, 4-, 5-, 6- or 7-membered ring containing a single nitrogen atom and substituted by R_8 and R_9 ;
- R_8 is R'_8 or a group $(CH_2)_r$ which is itself substituted
- 10 by a hydroxyl or by an amino which is free or substituted by one or two C_1-C_4 alkyls;
- R'_8 is a group $(CH_2)_q$ which is itself substituted by a carboxyl group, a C_1-C_4 alkoxycarbonyl group, a benzyloxycarbonyl group, a carbamoyl group which is
- 15 free or substituted by a hydroxyl or by one or 2 C_1-C_4 alkyls or an aminocarbothioyl group which is free or substituted by one or 2 C_1-C_4 alkyls;
- R''_8 is R'_8 or a group $(CH_2)_2NH_2$ which is free or substituted by one or two C_1-C_4 alkyls;
- 20 - R_9 is hydrogen, a halogen, a group $(CH_2)_rOR_{10}$, a group $(CH_2)_rNR_{11}R_{12}$, a group $(CH_2)_rCONR_{11}R'_{11}$ or an azido group;
- R_{10} is hydrogen, a C_1-C_4 alkyl, a mesyl or a tosyl;
- R_{11} , R'_{11} and R_{12} are each a hydrogen or a C_1-C_4 alkyl or
- 25 R_{11} is hydrogen and R_{12} is a benzyloxycarbonyl or a C_1-C_4 alkoxycarbonyl;
- n is 0, 1 or 2;
- m is 0, 1 or 2;
- q is 0, 1, 2 or 3 ;
- 30 - r is 0, 1, 2 or 3, with the limitation that r is not zero when R_8 or R_9 is at the alpha-position of the intracyclic amide nitrogen;
- s is 0 or 1;
- as well as their possible salts.

35 The salts of the compounds of formula (I) according to the present invention comprise those with inorganic or organic acids which make possible a suitable separation or crystallization of the compounds of formula (I), such



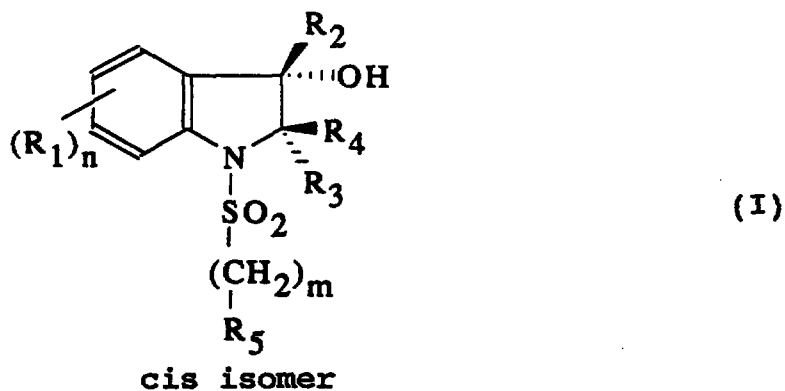
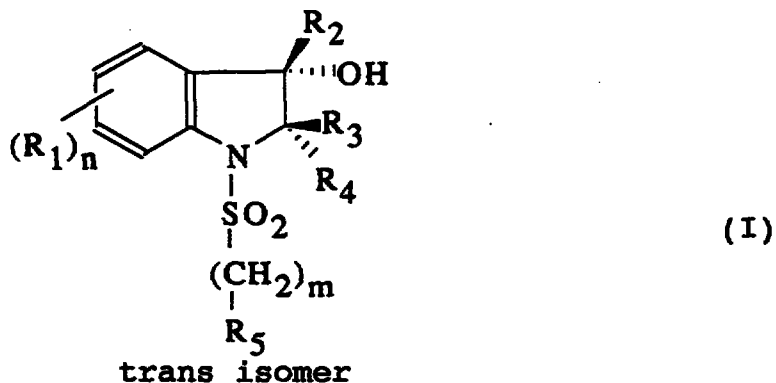
as picric acid, oxalic acid or an optically active acid, for example a mandelic acid or a camphosulfonic acid, and those which form pharmaceutically acceptable salts such as the hydrochloride, the hydrogensulfate, the dihydrogenphosphate, the methanesulfonate, the maleate, the fumarate or the 2-naphthalenesulfonate.

The salts of the compounds of formula (I) also comprise the salts with organic or inorganic bases, for example the salts of alkali or alkaline-earth metals such as the salts of sodium, potassium or calcium, the salts of sodium and potassium being preferred, or with an amine, such as trometamol, or even the salts of arginine or lysine or of any pharmaceutically acceptable amine.

The compounds (I) exhibit cis-trans isomerism around the 2,3 bond of the indoline. The different isomers form an integral part of the invention.

By convention, the compounds (I) in which R_2 and R_4 are on the same side of the ring are called the cis isomers.

By convention, the compounds (I) in which R_2 and R_4 are on opposite sides of the ring are called the trans isomers.





Moreover, the compounds according to the invention have 2 asymmetric carbon atoms or more when R_4 contains one 1 or 2 asymmetric carbons. The optical isomers of the compounds (I) form part of the invention.

5 In the present description and in the claims which follow, halogen is understood as meaning a fluorine, chlorine, bromine or iodine atom; alkyl group is understood as meaning linear or branched hydrocarbon groups.

10 Preferred compounds (I) according to the invention are those in which at least one of the following conditions is satisfied:

- R_1 is a chlorine or bromine atom or a methoxy group and $n = 0$;
- R_2 is a chlorophenyl, a methoxyphenyl or a cyclohexyl;
- 15 - R_4 is a group $CONR_6R_7$ in which R_6 and R_7 or NR_6R_7 have one of the following definitions;
 - NR_6R_7 is a pyrrolidino group which is substituted at the 2-position by a group $(CH_2)_q$ which is itself substituted by a carboxyl or carbamoyl group with
 - 20 $q = 0, 1, 2$ or 3 .
 - NR_6R_7 is a piperidino group which is substituted at the 4-position by an amino group, a C_1 - C_4 alkylamino or a C_1 - C_4 dialkylamino,
 - NR_6R_7 is a thiazolidino group which is substituted by
 - 25 a group $(CH_2)_q$ which is itself substituted by a carboxyl or carbamoyl group with $q = 0, 1, 2$ or 3 .
 - NR_6R_7 is a pyrrolidino group which is substituted at the 2-position by a group $(CH_2)_q$ which is itself substituted by a carboxyl or carbamoyl group with
 - 30 $q = 0, 1, 2$ or 3 and which is substituted at the 4-position by an amino group, a C_1 - C_4 alkylamino or a C_1 - C_4 dialkylamino;
- R_6 is a C_1 - C_4 alkyl and R_7 is a group $(CH_2)_r$ which is itself substituted by a carboxyl group or a carbamoyl
- 35 group with $r = 1, 2$ or 3 ;
- R_5 is a phenyl substituted at the 3- and 4-position or at the 2- and 4-position by a methoxy group, or R_5 is a phenyl substituted at the 4-position by a methyl



group;

- m = 0.

The compounds (I) which are in the form of the cis isomers are particularly preferred.

5 The following abbreviations are used in the description and the examples.

DCM: dichloromethane

AcOEt: ethyl acetate

MeOH: methanol

10 EtOH: ethanol

Ether: ethyl ether

DMF: dimethylformamide

THF: tetrahydrofuran

TEA: triethylamine

15 DMSO: dimethyl sulfoxide

DIPEA: diisopropylethylamine

DCC: N,N'-dicyclohexylcarbodiimide

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene

20 DBN: 1,5-diazabicyclo[4.3.0]non-5-ene

DMAP: 4-dimethylaminopyridine

DMPU: 1,3-dimethyl-2-oxohexahydropyrimidinone

TMEDA: tetramethylethylenediamine

LDA: lithium diisopropylamide

25 HMPA: hexamethylphosphoramide

HOBT: 1-hydroxybenzotriazole hydrate

BOP: benzotriazolyloxytrisdimethylaminophosphonium hexafluorophosphate

TFA: trifluoroacetic acid

30 Lawesson's reagent: 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide

M.p.: melting point

Saline solution: water saturated with sodium chloride

35 Dry ice: solid carbon dioxide

TLC: thin layer chromatography

HPLC: high performance liquid chromatography

NMR: nuclear magnetic resonance



s: singlet
m: multiplet
bs: broad singlet
d: doublet

5 Hydrochloric water: dilute hydrochloric acid, about 1N

80% NaH: dispersion of sodium hydride in mineral oil (Janssen Chemica)

Me: methyl

10 Et: ethyl

iPr: isopropyl, Pr: propyl

iPentyl: isopentyl

iBu: isobutyl

tBu:tert-butyl, Bu: butyl

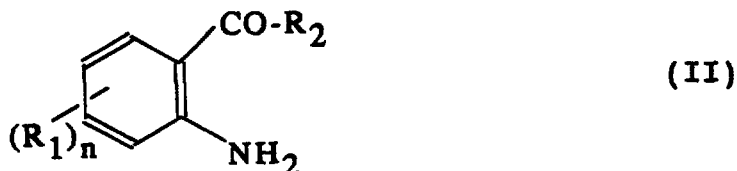
15 Bz: benzyl

Ph: phenyl

RT: room temperature

The present invention further relates to the process for preparing the compounds (I).

20 This process is characterized in that it comprises :
a) reacting a 2-aminophenone derivative of formula:

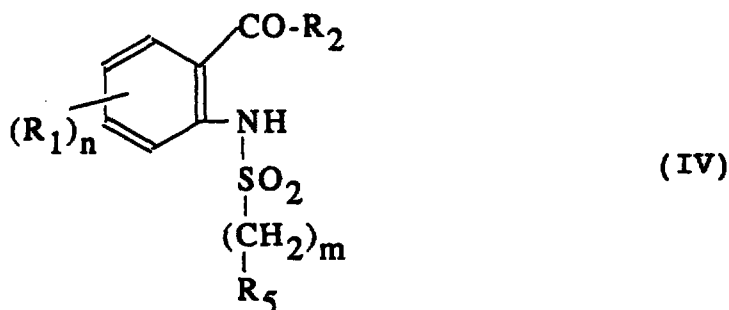


in which R_1 , R_2 and n have the meanings indicated above for I, with a sulfonyl derivative of formula:

25 $\text{Hal-SO}_2-(\text{CH}_2)_m-\text{R}_3$ (III)

in which

- Hal is a halogen, preferably chlorine or bromine,
 - m and R_3 have the meanings indicated above for (I);
- b) treating the resulting compound of formula:



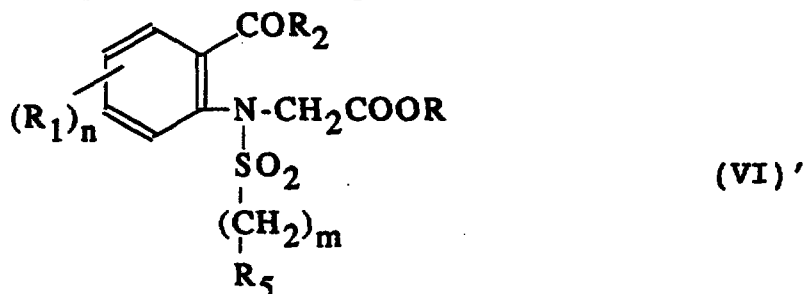
with a halogenated derivative of formula:



in which

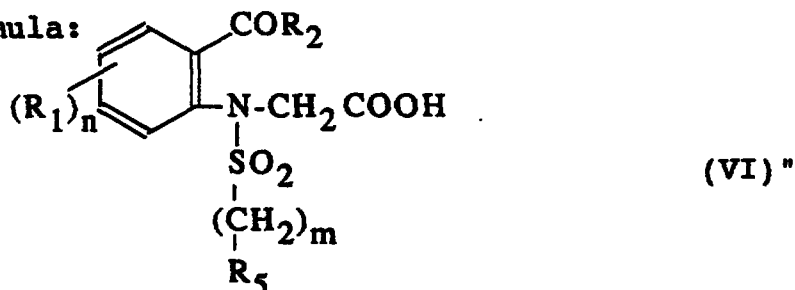
- 5 Hal' is a halogen, preferably bromine, and A represents either the group NR_5R , or the group OR in which R is a tert-butyl or a benzyl;

c) deprotecting the resulting ester of formula:



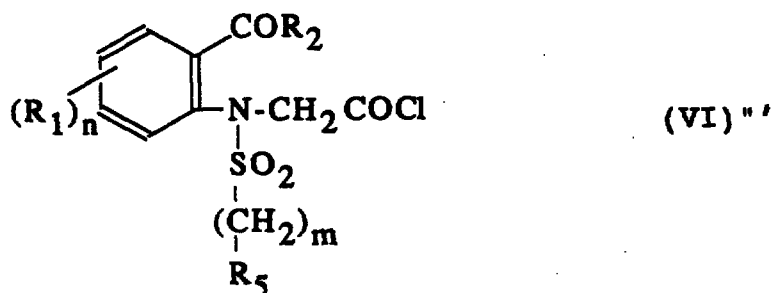
- 10 under suitable conditions, if applicable, when A is OR;

d) treating, if applicable, the resulting acid from Step c) of formula:



15

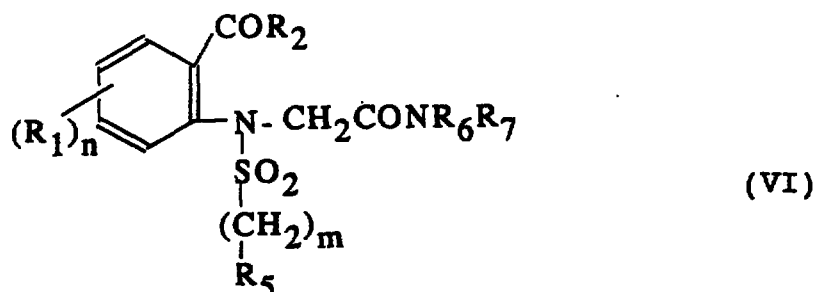
or its acid chloride of formula:





with a compound HNR_6R_7 according to suitable amide coupling techniques;

e) cyclizing the resulting compound from Step b) or from Step d) of formula:



in a basic medium in order to prepare the compound (I) according to the invention;

f) separating, if appropriate, the cis and trans isomers of the compound (I) and, if appropriate, separating the enantiomers.

The 2-aminophenone derivatives (II) are known or prepared by known methods, such as those described by A.K. Singh et al., Synth. Commun. 1986, 16 (4), 485 and G.N. Walker, J. Org. Chem., 1962, 27, 1929. The 2-amino-2'-trifluoromethylbenzophenones and the other trifluoromethylated derivatives are prepared according to US Patent 3,341,592.

2,4-dimethoxybenzenesulfonyl chloride is prepared according to J. Am. Chem. Soc., 1952, 74, 2008.

The sulfonyl derivatives of formula (III) are known or prepared by known methods. Thus, for example, 4-dimethylaminobenzenesulfonyl chloride is prepared according to C.N. Sukenik et al., J. Am. Chem. Soc., 1977, 99, 851-858; p-benzyloxybenzenesulfonyl chloride is prepared according to European patent application EP 229,566.

The alkoxybenzenesulfonyl chloride is prepared from the sodium alkoxybenzenesulfonate, which is itself prepared by reacting an alkyl halide with sodium hydroxybenzenesulfonate.

The halogenated derivatives of formula (V) are known or prepared by known methods, such as those described by A.I. Vogel: A Text Book of Practical Organic Chemistry: Longman, 3rd ed. 1956, p. 383, or G. Kirchner et al.,

J. Am. Chem. Soc., 1985, 107, 24, 7072.

Step a) of the process is carried out in pyridine by heating at a temperature between room temperature and the boiling point of the solvent for a period of time of
5 between a few hours and a few days. If appropriate, the reaction can be carried out in the presence of dimethylaminopyridine, which is used in a catalytic or stoichiometric amount.

Step b) of the process is carried out between the
10 sulfonamide of formula (IV) and an excess of the halogenated derivative of formula (V), in a solvent such as dimethylformamide or dimethyl sulfoxide, under an inert atmosphere, at a temperature of between 0°C and room temperature, for a time of between a few hours and
15 24 hours, in the presence of sodium hydride.

When the group $\text{-NR}_6\text{R}_7$ contains a second amine group, that is to say when R_6 and/or R_7 are substituted by an amino group, it is possible to choose to use a halogenated derivative (V) of formula $\text{Hal}'\text{-CH}_2\text{-CO}_2\text{R}$ in
20 which R is a tert-butyl or a benzyl, in order to prepare the intermediates of formula (VI)' and then (VI)". In this case, Step c) for the formation of the acid of formula (VI)" is carried out either by the action of hydrogen in the presence of a catalyst such as palladium
25 on charcoal when R is benzyl, or in acid medium, when R is tert-butyl, for example in the presence of TFA or in the presence of hydrobromic acid in acetic acid or even in the presence of ZnBr_2 in DCM.

Step d) is then carried out under the conventional
30 conditions for amide coupling, for example in the presence of BOP or HOBT and DCC.

The compounds HNR_6R_7 are known or prepared by known methods. By way of example, the stereospecific synthesis of (R)- and (S)-2-pyrrolidinylacetic acids is carried out
35 according to H. Rueger et al. in Heterocycles, 1982, 19 (9), 1677 from a proline derivative of suitable configuration. The preparation of methyl N-Boc-3,4-dehydro- α -prolinate is carried out according to J.R. Dormoy,



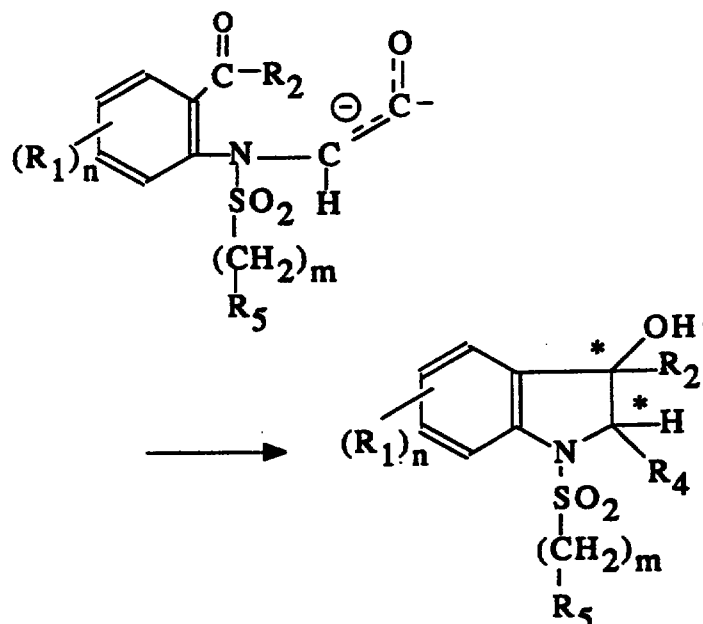
- 12 -

Synthesis, 1982, 753. The preparation of optically pure derivatives of pipelicolic acid is described, for example, in Tetrahedron, 1992, 48 (3) 431-442 and Tetrahedron, 1991, 47 (24) 4039-4062.

5 The preparation of the derivatives of aziridine-carboxylic acid is carried out according to K. Nakajima et al. in Bull. Chem. Soc. Jap., 1978, 51 (5), 1577.

Step e) of the process is closely related to an aldolization reaction: the methylene group in the α -position of the amide is deprotonated and the carbonyl group of the phenone then acts like an internal electrophile, resulting in cyclization with the appearance of two asymmetric carbons (C^*).

15 The reaction can be illustrated by the following scheme:



The principles of the aldol addition reaction have been reviewed by C.H. Heathcock in Asymmetric Synthesis, vol. 3: Stereodifferentiating addition reactions, part B, 111-112; Academic Press, 1984, edited by J.D. Morrison.

20 It is known that the aldol reaction of achiral amide anions gives rise to the formation of 2 racemic diastereoisomers of β -hydroxyamides in a ratio which depends largely on the experimental conditions used. The following may be mentioned among these conditions: the nature of the inorganic or organic base used, the nature



of the cations or counterions, the possible presence of additives in the reaction medium, the solvent, the reaction temperature and the structure of the compound undergoing this reaction.

5 When the groups R_8 and R_7 do not contain a group which is hydrolysable in alkaline medium, it is possible to use sodium hydroxide in water, in the presence of a cosolvent, with or without the addition of a phase transfer catalyst; it is also possible to use a
10 quaternary ammonium hydroxide, for example benzyltrimethylammonium hydroxide in methanol.

In order to carry out this aldolization reaction, it is also possible to use organic bases, for example:

- guanidines such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene,
15
- amidines such as 1,8-diazabicyclo[5.4.0]undec-5-ene or 1,5-diazabicyclo[4.3.0]non-5-ene,

in a solvent or a mixture of solvents selected for example from benzene, THF, dichloromethane, methanol and
20 dimethylformamide; the reaction is carried out under an inert atmosphere at between -10°C and 110°C ; the amount of base used is at least stoichiometric; the reaction can also be carried out without a solvent, at the temperature of the bath.

25 Preferentially, Step e) of the process according to the invention is carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-5-ene (DBU) in a solvent such as dichloromethane or methanol, at a temperature of between -10°C and the reflux temperature of the solvent.

30 It is also possible to use an alcoholate of a primary, secondary or tertiary alcohol with lithium, sodium, potassium, calcium or magnesium.

The alcoholate is used in a catalytic or stoichiometric amount in an anhydrous solvent, for example an
35 alcohol (if appropriate in the presence of a cosolvent such as THF), or else in a stoichiometric amount in THF, DMF or DMSO, if appropriate in the presence of crown ethers, for example dicyclohexyl-18-crown-6; the reaction



is carried out at between -15°C and 80°C .

The use of an amide of the type $\text{RR}'\text{NLi}$ or $\text{RR}'\text{NMgBr}$, in which R and R' are monovalent radicals, as a deprotonating agent is a method of forming enolates of amides, which are intermediates in the aldolization reaction; this method has recently been reviewed by R.E. Ireland et al., J. Org. Chem., 1991, 56, 650. The reaction solvent can be benzene, hexane or THF used in anhydrous form under an inert atmosphere. Adjuvants such as LiF, LiCl, LiBr, LiI, LiBu, TMEDA, DMPU, HMPA or a crown ether can be added. (M. Murakate et al., J. Chem. Soc. Commun., 1990, 1657). By way of example, there may be mentioned the use of lithium diisopropylamide at between -78°C and -30°C in anhydrous THF under an inert atmosphere or in THF in the presence of additives such as, for example, tetramethylenediamine, DMPU or HMPA. Examples of other known amides which can be used are lithium cyclohexylamide and lithium 2,2,6,6-tetramethylcyclohexylamide. It is also possible to prepare other amides by reacting the requisite amount of butyllithium in hexane with linear or cyclic secondary amines, the reaction taking place in one of the solvents mentioned above.

Finally, various publications describe amides of optically active secondary amines: L. Duhamel et al., Bull. Soc. Chim. France, 1984, II, 421; J.K. Whitesell et al., J. Org. Chem., 1980, 45, 755; M. Murakata et al., J. Chem. Soc. Chem. Commun., 1990, 1657; M. Yamaguchi, Tetrahedron Lett., 1986, 27 (8), 959; P.J. Cox and N.S. Simpkins, Tetrahedron: Asymmetry, 1991, 2 (1), 1.

The silylamides of lithium, sodium or potassium constitute another group of bases which can be used, among which there may be mentioned: $(\text{Me}_3\text{Si})_2\text{NLi}$, $(\text{Me}_2\text{PhSi})_2\text{NLi}$, $(\text{Et}_3\text{Si})_2\text{NLi}$, $(\text{Me}_3\text{Si})_2\text{NK}$, $(\text{Me}_3\text{Si})_2\text{NNa}$.

It is also possible to use mixed amides as described by Y. Yamamoto, Tetrahedron, 1990, 46, 4563, for example the lithium salt of N-(trimethylsilyl)benzylamine or an analog in which the benzylamine is replaced with a chiral



- 15 -

primary amine such as (R)- or (S)- α -methylbenzylamine.

When the compound of formula (I) to be prepared has 2 asymmetric carbon atoms, the use of chiral amides or alcoholates in Step e) makes possible an enantiomeric enrichment of each of the *cis* or *trans* stereoisomers. The proportion of each of the enantiomers is then determined by measurement on a chiral high performance liquid chromatography column.

When the compound of formula (I) to be prepared has 3 or 4 asymmetric carbon atoms, the cyclization Step c) can be accompanied by a diastereoisomeric enrichment and the use of a suitable chiral base makes it possible to modify this diastereoisomeric enrichment.

In Step f), the *cis* and *trans* geometric isomers of the compound (I) formed are extracted by conventional methods and separated by chromatography or fractional crystallization.

If appropriate, the optical isomers of each of the *cis* and *trans* isomers are separated, for example by preparative chromatography on a chiral column followed, if appropriate, by a fractional crystallization or by formation of an optically active salt in the presence of a suitably selected chiral acid or base.

Thus, when the compound according to the invention has 2 asymmetric carbon atoms, the enantiomers can be separated by chiral HPLC.

When the compound according to the invention has 3 or 4 asymmetric carbon atoms, the diastereoisomers can be separated by using chromatographic methods and fractional crystallization methods.

Several methods can be used to differentiate and characterize the *cis* isomer and the *trans* isomer of a compound (I). When R_3 is hydrogen, a comparative analysis is performed by high field NMR (250 MHz), coupled for example with the study of the Overhauser effect (N.O.E.) between, for example, the proton of the indoline ($R_3 = H$) and the proton of the hydroxyl.



- 16 -

The IR spectra of the cis isomer and the trans isomer in solution in DCM are different. The cis isomer most commonly has a strong, fine and symmetrical absorption band at around 3550-3520 cm^{-1} , due to the hydroxyl vibration, whereas the trans isomer has no resolved vibration band in this region.

By means of the data collected, it has been found that the cis isomer is generally the more mobile in TLC on an aluminum oxide plate (60F254 neutral, Type E, Merck), eluting with DCM containing variable proportions of AcOEt. Similarly, in chromatography on an alumina column (aluminum oxide 90, particle size 0.063-0.200 mm), the cis isomer is most commonly eluted first, the eluent being DCM containing variable proportions of AcOEt or MeOH.

Thus the cis or trans isomerism of a compound (I) according to the invention can most often be determined by an analytical method. It is also possible to utilize the analogy between similar compounds or between compounds prepared from one another.

The absolute configuration of some compounds according to the invention was determined by an X-ray analysis. By deduction therefrom, taking into account the value of the optical rotation, it is also possible to know the absolute configuration of other compounds obtained in an analogous fashion.

A compound (I) in which R_1 is an amino group and/or a compound in which R_2 is a phenyl group which is substituted by an amino can be prepared by the conversion of a compound (VI), obtained in Step b), in which R_1 is a nitro group and/or R_2 is a phenyl group which is substituted by a nitro, the other substituents having the meanings desired for (I), by catalytic hydrogenation, for example in the presence of palladium on charcoal, or rhodium on alumina or Raney nickel.

The compounds (I) in which the substituents R_6 and/or R_7 , or the group NR_6R_7 , contain a $\text{C}_1\text{-C}_4$ alkoxy carbonyl group make it possible to obtain, by hydrolysis of the ester,



the compounds (I) in which R_6 and/or R_7 or the group NR_6R_7 contain a carboxyl group, the other substituents of (I) being unchanged. Furthermore, the compounds in which R_6 and/or R_7 or NR_6R_7 contain a carboxyl group make it possible to obtain, by a conventional amide coupling reaction, the compounds (I) in which R_6 and/or R_7 or the group NR_6R_7 contain a carbamoyl group which is free or substituted by one or two C_1-C_4 alkyls, the other substituents being identical.

Finally, the compounds (I) in which R_6 and/or R_7 or the group NR_6R_7 contain a carbamoyl group make it possible to obtain, by a Hofmann rearrangement, the compounds (I) in which R_6 and/or R_7 or the group NR_6R_7 contain an amino group, the other substituents being identical (J. Org. Chem., 1979, 44 (10), 1746).

Thus, according to the present invention, the process for preparing compounds (I) in which R_6 and/or R_7 or the group NR_6R_7 contain an amino group which is free or substituted by one or two C_1-C_4 alkyls can have two variants:

i) Step b) of the process is carried out by treating the compound (IV) obtained in Step a) with a halogenated derivative (V) of formula $Hal'-CH_2CONR_6R_7$, in which R_6 and/or R_7 or the group NR_6R_7 contain a precursor group of the amine, for example a carboxyester, a carboxyl or a carbamoyl; the cyclization Step e) is then carried out and the precursor group of the amine is then converted into the amine, for example the carboxyester group of the compound (I) thus obtained is hydrolyzed into a carboxyl group, which is then converted into a carbamoyl group and then into an amino group by the Hofmann rearrangement.

ii) Step b) is carried out by treating the compound (IV) obtained in Step a) with an halogenated derivative (V) of formula $Hal'-CH_2COOR$ in which R is a benzyl or a tert-butyl; the ester of the compound (VI)' thus obtained is deprotected by a suitable treatment, according to Step c); a coupling is then carried out with the compound HNR_6R_7 , in which the amino group of R_6 and/or R_7 is, if

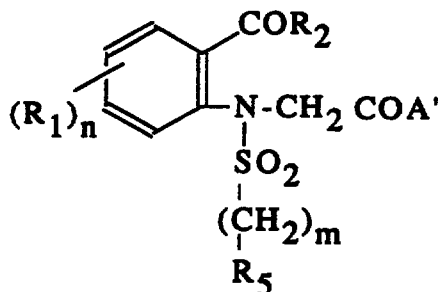


appropriate, protected; the compound (VI) thus obtained is then cyclized according to Step e); and, if appropriate, the compound (I) in which the amino group is free is prepared by deprotection of the amine.

5 The compounds (I) in which the groups R_6 and/or R_7 , or the group NR_6R_7 , contain a benzyloxycarbonyl or alkoxy-carbonyl group as substituent of an amine group make it possible to obtain the compounds (I) in which the amine group is free, the other substituents being identical.

10 The compounds of formula (VI), useful as intermediates for the preparation of compounds (I) according to the invention, are novel and form part of the invention. Likewise, the compounds (VI)' and (VI)" are novel and form part of the invention.

15 The present invention thus also relates to the compounds of formula:



6

in which

- A' is a group selected from: NR_6R_7 , OH, OtBu, OBz;
- 20 - R_1 is a halogen atom, a C_1 - C_4 alkyl, a hydroxyl, a C_1 - C_4 alkoxy, a benzyloxy group, a cyano group, a trifluoromethyl group, a nitro group or an amino group;
- 25 - R_2 is a C_1 - C_6 alkyl, a C_3 - C_7 cycloalkyl, a C_5 - C_7 cycloalkene or a phenyl which is unsubstituted or monosubstituted or polysubstituted by C_1 - C_4 alkyl, a C_1 - C_4 alkoxy, a halogen, a trifluoromethyl group or an amino group, or R_2 is a nitrophenyl which is unsubstituted or monosubstituted by a trifluoromethyl group or monosubstituted or polysubstituted by a C_1 - C_4 alkyl, a C_1 - C_4 alkoxy or a halogen;
- 30



- 5 - R_5 is a C_1-C_4 alkyl; a 1-naphthyl; a 2-naphthyl; a 5-dimethylamino-1-naphthyl; a phenyl which is unsubstituted or substituted by one or more substituents selected from a halogen atom, a C_1-C_4 alkyl, a trifluoromethyl group, an amino group which is free or substituted by one or 2 C_1-C_4 alkyls, a hydroxyl, a C_1-C_4 alkoxy, a C_2-C_4 alkenoxy, a C_1-C_4 alkylthio, a trifluoromethoxy group, a benzyloxy group, a cyano group, a carboxyl group, a C_1-C_4 alkoxy-carbonyl group, a carbamoyl group which is free or substituted by one or two C_1-C_4 alkyls or a C_1-C_4 alkylamido group, or R_5 is a nitrophenyl which is unsubstituted or monosubstituted by a trifluoromethyl group or a C_2-C_4 alkenoxy or mono- or polysubstituted by a halogen, a C_1-C_4 alkyl, a C_1-C_4 alkoxy, a C_1-C_4 alkylthio, a trifluoromethoxy group or a benzyloxy group;
- 10 - R_6 is a C_1-C_6 alkyl or R_6 is similar to R_7 ;
- 15 - R_7 is a 4-piperidyl group or a 3-azetidiny group, the said groups being substituted or unsubstituted on the nitrogen by a C_1-C_4 alkyl, by a benzyloxycarbonyl or by a C_1-C_4 alkoxy-carbonyl; a group $(CH_2)_r$ which is itself substituted by a 2-, 3- or 4-pyridyl group, by a hydroxyl group or by an amino group which is free or substituted by one or two C_1-C_4 alkyls, a carboxyl group, a C_1-C_4 alkoxy-carbonyl group, a benzyloxycarbonyl group or a carbamoyl group which is free or substituted by one or 2 C_1-C_4 alkyls;
- 20 - or R_6 and R_7 together, with the nitrogen atom to which they are connected, form a heterocycle selected from:
- 25 . morpholine,
- 30 . thiomorpholine,
- . thiazolidine or 2,2-dimethylthiazolidine, unsubstituted or substituted by R_8 ,
- . piperazine, unsubstituted or substituted at the 4-position by a group R''_8 ,
- 35 . an unsaturated, 5-membered ring containing a single nitrogen atom and substituted by R_8 or



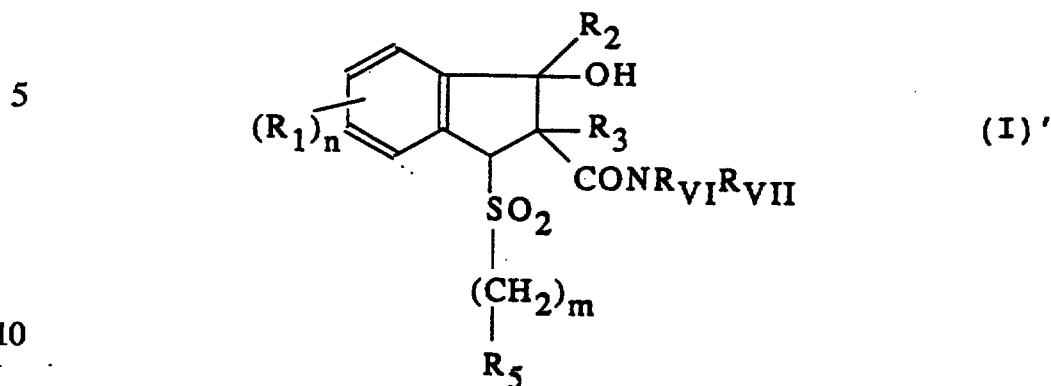
- 20 -

- a saturated, 3-, 4-, 5-, 6- or 7-membered ring containing a single nitrogen atom and substituted by R_8 and R_9 ;
- R_8 is R'_8 or a group $(CH_2)_r$ which is itself substituted by a hydroxyl or by an amino which is free or substituted by one or two C_1-C_4 alkyls;
 - R'_8 is a group $(CH_2)_q$ which is itself substituted by a carboxyl group, a C_1-C_4 alkoxy carbonyl group, a benzyloxycarbonyl group, a carbamoyl group which is free or substituted by a hydroxyl or by one or 2 C_1-C_4 alkyls or an aminocarbothioyl group which is free or substituted by one or 2 C_1-C_4 alkyls;
 - R''_8 is R'_8 or a group $(CH_2)_2NH_2$ which is free or substituted by one or two C_1-C_4 alkyls;
 - R_9 is hydrogen, a halogen, a group $(CH_2)_rOR_{10}$, a group $(CH_2)_rNR_{11}R_{12}$, a group $(CH_2)_rCONR_{11}R'_{11}$ or an azido group;
 - R_{10} is hydrogen, a C_1-C_4 alkyl, a mesyl or a tosyl;
 - R_{11} , R'_{11} and R_{12} are each a hydrogen or a C_1-C_4 alkyl or R_{11} is hydrogen and R_{12} is a benzyloxycarbonyl or a C_1-C_4 alkoxy carbonyl;
 - n is 0, 1 or 2;
 - m is 0, 1 or 2;
 - q is 0, 1, 2 or 3 ;
 - r is 0, 1, 2 or 3, with the limitation that r is not zero when R_8 or R_9 is at the alpha-position of the intracyclic amide nitrogen;
 - s is 0 or 1;

According to another aspect of the present invention, the compounds (I) according to the invention in which either R_7 or the group NR_8R_9 contains a carboxyl group are useful for the preparation of analogous decarboxylated compounds.



According to this aspect, the invention relates to the use of the compounds of formula (I)'



in which R_1, R_2, R_3, R_5, m and n have the meanings indicated above for (I),

- R_{VI} is a C_1-C_6 alkyl,

15 - R_{VII} is a group $(CH_2)_r COOH$ with $r = 1, 2$ or 3 ,

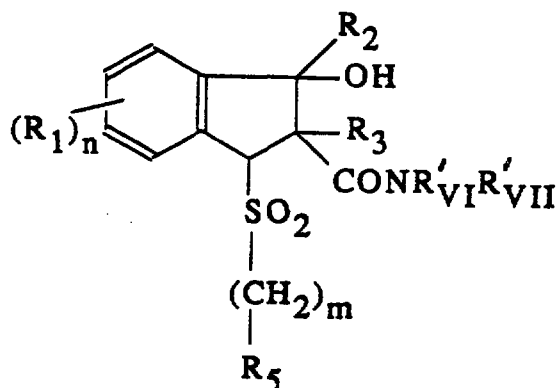
- or R_{VI} and R_{VII} together, with the nitrogen atom to which they are connected, constitute a heterocycle selected from :

- 20 . thiazolidine or 2,2-dimethylthiazolidine, substituted by a $(CH_2)_q COOH$ group,
- . piperazine substituted at the 4-position by a $(CH_2)_q COOH$ group,
- . an unsaturated, 5-membered ring containing a single nitrogen atom and substituted by a $(CH_2)_q COOH$ group
- 25 or a saturated, 3-, 4-, 5-, 6- or 7-membered ring containing a single nitrogen atom and substituted by a $(CH_2)_q COOH$ group,

with $q = 0, 1, 2$ or 3

for the preparation of a compound of formula (I)"

30 having the same configuration around the 2,3 bond of the indoline as the starting material



5

in which

- R_1 , R_2 , R_3 , R_5 , m and n are as defined above,
- R'_{VI} is a C_1 - C_6 alkyl,
- R'_{VII} is a group $(CH_2)_rH$,
- or R'_{VI} and R'_{VII} together, with the nitrogen atom to which they are connected, constitute a heterocycle selected from :
 - . thiazolidine or 2,2-dimethylthiazolidine, substituted by a $(CH_2)_qH$ group,
 - . piperazine substituted at the 4-position by a $(CH_2)_qH$ group,
 - . an unsaturated, 5-membered ring containing a single nitrogen atom and substituted by a $(CH_2)_qH$ group or a saturated, 3-, 4-, 5-, 6- or 7-membered ring containing a single nitrogen atom and substituted by a $(CH_2)_qH$ group.

The free-radical decarboxylation reaction is carried out according to D. H. R. Barton et al. in J. Chem. Soc; Chem. Commun.; 1984, 1298.

The affinity of the compounds according to the invention for the vasopressin receptors was determined in vitro using the method described in J. Biol. Chem., 1985, 260 (5), 2844-2851. This method consists in studying the displacement of tritiated vasopressin bound to the V_1 sites of rat liver membranes. The 50% inhibitory concentrations (IC_{50}) of the compounds according to the invention for the binding of tritiated vasopressin are



low, ranging down to 10^{-9} M.

Furthermore, the inhibition of the platelet aggregation induced by vasopressin was measured on a human platelet rich plasma (human PRP) using the method described in Thrombosis Res., 1987, 45, 7-16. The compounds according to the invention inhibit the aggregation induced by 50 to 100 nM concentrations of vasopressin with low ID_{50} values (inhibitory doses) which range down to 10^{-9} M. These results show the antagonistic activity of the compounds according to the invention towards the V_1 receptors.

The affinity of the compounds (I) according to the invention for the V_2 receptors was measured by a method adapted from P. Crause et al., Molecular and Cellular Endocrinology, 1982, 28, 529-541.

The compounds according to the invention of cis configuration around the 2,3 bond of the indoline have a marked selectivity for the V_1 receptors.

The affinity of the compounds (I) according to the invention for the oxytocin receptors was determined in vitro by the displacement of tritiated oxytocin bound to the receptors of a membrane preparation of gestating rat glands. The IC_{50} values of the compounds according to the invention are low, of between 10^{-5} M and 10^{-8} M.

The compounds according to the invention are active after administration by various routes, especially orally.

No sign of toxicity is observed with these compounds at the pharmacologically active doses.

Thus the compounds according to the invention can be used in the treatment or prevention of various vasopressin-dependent complaints, especially cardiovascular complaints such as hypertension, cardiac insufficiency, thrombosis or coronary vasospasm, in particular in smokers; complaints of the central nervous system, for example cerebral edemas, psychotic states, appetite disorders or memory disorders; complaints of the renal system, such as renal vasospasm or necrosis of the



renal cortex; and complaints of the gastric system, for example ulcers or else the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

5 The compounds according to the invention can also be used as antiemetics, especially in motion sickness, and as antiproliferative agents, for example in cancer or atherosclerosis.

10 In woman, the compounds according to the invention can also be used for the treatment of dysmenorrhea or premature labor.

The present invention further relates to pharmaceutical compositions containing an effective dose of a compound according to the invention, or of a pharmaceutically acceptable salt, and suitable excipients. Said excipients are chosen according to the pharmaceutical form and the desired mode of administration.

15 In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal or rectal administration, the active principles of formula I above, or their possible salts, can be administered to animals and humans in unit forms of administration, mixed with conventional pharmaceutical carriers, for the prophylaxis or treatment of the above disorders or diseases. Appropriate unit forms of administration include forms for oral administration, such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, forms for sublingual, buccal, intratracheal or intranasal administration, forms for subcutaneous, intramuscular or intravenous administration and forms for rectal administration. For topical application, the compounds according to the invention can be used in creams, ointments or lotions.

35 To obtain the desired prophylactic or therapeutic effect, the dose of active principle can vary between 0.01 and 50 mg per kg of body weight and per day.



Each unit dose can contain from 0.5 to 1000 mg, preferably from 1 to 500 mg, of active ingredients in combination with a pharmaceutical carrier. This unit dose can be administered 1 to 5 times per day so as to
5 administer a daily dosage of 0.5 to 5000 mg, preferably 1 to 2500 mg.

If a solid composition in the form of tablets is prepared, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose,
10 magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose, a cellulose derivative or other appropriate substances or they can also be treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of
15 active principle continuously.

A preparation in the form of gelatin capsules is obtained by mixing the active ingredient with a diluent and pouring the resulting mixture into soft or hard gelatin capsules.

20 A preparation in the form of a syrup or elixir or for administration in the form of drops can contain the active ingredient in combination with a sweetener, which is preferably calorie-free, and methylparaben and propylparaben as antiseptics, as well as with a flavoring
25 and an appropriate color.

Water-dispersible granules or powders can contain the active ingredient mixed with dispersants or wetting agents or with suspending agents such as polyvinylpyrrolidone, as well as with sweeteners or taste
30 correctors.

Rectal administration is effected using suppositories which are prepared with binders melting at the rectal temperature, for example cocoa butter or polyethylene glycols.

35 Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersants and/or wetting agents, for example



propylene glycol or butylene glycol.

The active principle can also be formulated as microcapsules, if appropriate with one or more carriers or additives.

5 Apart from the products of formula I above or one of the pharmaceutically acceptable salts, the compositions of the present invention can contain other active principles which may be useful in the treatment of the disorders or diseases indicated above.

10 Thus the present invention relates to pharmaceutical compositions containing a plurality of active principles in association, one of which is a compound according to the invention.

The following examples illustrate the invention.

15 The compounds are characterized by their melting point (M.p. °C) (or their boiling point B.p.) and/or their NMR spectrum recorded at 200 MHz in DMSO, and/or their optical rotation (α_D) measured at 25°C (except when otherwise indicated).

20 The measured value of the optical rotation is dependent on the amount of residual solvent present in the prepared product.

25 Except when otherwise indicated, the designation "cis isomer" or "trans isomer" signifies that the isolated compound is a mixture of enantiomers, either of cis configuration or of trans configuration.

The optical purity of the compounds is studied by high performance liquid chromatography (HPLC).

EXAMPLE 1

30 N-methyl-N-methoxycarbonylmethyl-5-bromo-3-(2-fluorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer.

A) Methyl N-bromoacetylsarcosinate.

35 This compound is prepared according to T.D. Harris et al. in J. Heterocyclic Chem., 1981, 18, 423.

B) 5-Bromo-2-(3,4-dimethoxyphenylsulfonamido)-2'-fluorobenzophenone.



20 g of 2-amino-5-bromo-2'-fluorobenzophenone are heated at 85°C for 48 hours in 120 ml of dry pyridine in the presence of 20 g of 3,4-dimethoxyphenylsulfonyl chloride. The mixture is cooled, poured into ice-cold water, the solid is filtered off, the solid is extracted with AcOEt, the organic phase is washed with water, a solution of hydrochloric acid (1N), water and then saline water. After drying over magnesium sulfate and evaporating the solvent under vacuum, a solid is obtained which is recrystallized from DCM/isopropyl ether.

m = 28 g

M.p. = 125-128°C.

C) 5-Bromo-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(N'-methyl-N'-(methoxycarbonylmethyl)carbonylmethyl)]amino-2'-fluorobenzophenone.

3.5 g of the compound prepared in Step B are dissolved in anhydrous DMF at 0°C under argon and 250 mg of 80% sodium hydride are added; after 15 minutes, 4.85 g of the compound prepared in Step B are added and the mixture is left stirring at RT for 12 hours. The reaction mixture is poured into water, the solid is filtered off and then the solid is dissolved in AcOEt, the organic phase is washed with water and then with saline water and the solvent is evaporated under vacuum. The oil obtained is filtered on silica by eluting with a DCM/AcOEt (85/15 ; v/v) mixture. It is recrystallized from a DCM/isopropyl ether/MeOH mixture.

m = 3.2 g

M.p. = 136-137°C.

D) N-methyl-N-methoxycarbonylmethyl-5-bromo-3-(2-fluorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer.

3.2 g of product obtained in the preceding step are dissolved in DCM (3 ml), 750 mg of DBU are added and the mixture is left stirring at RT for 24 hours. The reaction mixture is poured onto a silica column; by eluting with DCM/AcOEt (90/10 ; v/v), a product is obtained which is the mixture of the two isomers (cis and trans) of the



expected compound. This product is triturated in a hexane/isopropyl ether mixture and the solid obtained is filtered. The filtration liquors are chromatographed on an alumina column which was preequilibrated in a DCM/AcOEt (70/30 ; v/v) mixture. The least polar compound is eluted with a DCM/AcOEt (60/40 ; v/v) mixture and is then recrystallized from a DCM/hexane/isopropyl ether mixture.

M.p. = 95°C with evolution of gas.

EXAMPLES 2 and 3

2-[(4-Benzyloxycarbonyl)-1-piperazinyl]carbonyl-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer and trans isomer.

A) 1-Bromacetyl-4-(benzyloxycarbonyl)piperazine.

A mixture of 22 g of 4-benzyloxycarbonylpiperazine and 10.1 g of triethylamine in 200 ml of ether is cooled to 0°C. 20.2 g of bromoacetyl bromide in 100 ml of ether are added over 30 minutes and the mixture is left to return to RT. After 4 hours, the reaction mixture is washed with water, dried, concentrated and then chromatographed on silica. The mixture DCM/AcOEt (95/5 ; v/v) elutes the expected compound which is recrystallized from DCM/isopropyl ether.

m = 9 g

M.p. = 100-101°C.

B) 2',5-Dichloro-2-(3,4-dimethoxyphenylsulfonamido)benzophenone.

5.6 g of 2-amino-2',5-dichlorobenzophenone and 5 g of 3,4-dimethoxyphenylsulfonyl chloride are heated in pyridine at 100°C overnight. The pyridine is evaporated to dryness, water is added and extraction is carried out with ethyl acetate containing a small amount of DCM. After washing more than once with water and drying over sodium sulfate, the extract is evaporated under vacuum and 7.7 g of the expected product are recrystallized in a DCM/AcOEt mixture.

M.p. = 164°C.



C) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(4-benzyloxycarbonyl-1-piperazinylcarbonylmethyl)]amino-benzophenone.

2.3 g of the benzophenone prepared in Step B are placed in 10 ml of DMF and treated with 200 mg of 80% sodium hydride in oil. After 30 minutes, 5.3 g of the compound prepared in Step A are added and the mixture is stirred for 60 hours at RT. The mixture is poured into water, the precipitate is filtered, taken up in DCM, dried and then concentrated and chromatographed on silica. The DCM/AcOEt (90/10 ; v/v) mixture elutes the expected product which crystallizes from a DCM/isopropyl ether mixture.

m = 2 g

M.p. = 173-175°C.

D) 2-[(4-Benzyloxycarbonyl)-1-piperazinyl]carbonyl-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer and trans isomer.

1 g of the compound obtained in the preceding step is suspended in 20 ml of methanol and 20 ml of THF and is treated with 75 mg of sodium methylate. After 2 hours, the mixture is neutralized by the addition of a small amount of dry ice, is concentrated to dryness and then taken up in water; the mixture is then extracted with DCM, the extract is dried and concentrated. The crude product is chromatographed on alumina, and the DCM/AcOEt (80/20; v/v) mixture elutes the 2 isomers successively.

The least polar isomer is recrystallized from a DCM/hexane mixture. This compound is the cis isomer.

m = 262 mg

M.p. = 169-179°C.

The most polar isomer is recrystallized from the DCM/isopropyl ether mixture.

m = 200 mg

M.p. = 209-211°C.

EXAMPLE 4

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-(1-piperazinylcarbonyl)indoline,



cis isomer.

200 mg of the cis isomer prepared in the preceding example are dissolved in 10 ml of ethanol and 5 ml of THF and are hydrogenolyzed at RT in the presence of 10% Pd/C.

5 After 30 minutes, the mixture is filtered on Celite[®], the filtration liquors are concentrated and then chromatographed on silica. The MeOH/DCM (10/90 ; v/v) mixture elutes the expected product which is recrystallized from a DCM/isopropyl ether mixture.

10 m = 110 mg
M.p. 230-233°C.

EXAMPLES 5 and 6

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-morpholinocarbonylindoline, cis
15 isomer and trans isomer.

A) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(morpholinocarbonylmethyl)]aminobenzophenone.

5 g of 2',5-dichloro-2-(3,4-dimethoxyphenyl-sulfonamido)benzophenone are treated with 350 mg of 80%
20 sodium hydride in 30 ml of DMF at RT for 20 minutes. 4.5 g of morpholinebromoacetamide are added and then the mixture is stirred at RT for 48 hours. The mixture is poured into water, the precipitate is filtered, it is dissolved in DCM, the solution is dried and concentrated.
25 The product formed is recrystallized from a DCM/isopropyl ether mixture. 5.4 g are obtained.

M.p. = 173-176°C.

B) 5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-morpholinocarbonylindoline, cis
30 isomer.

1 g of the product obtained in the preceding step is dissolved in the methanol (10 ml) and THF (20 ml) mixture and is treated with 92 mg of sodium methylate at RT for 1 hour. The mixture is neutralized with dry ice, the
35 solvents are partly evaporated, the mixture is taken up in water, extracted with DCM and the extract is dried, concentrated and chromatographed on alumina. The DCM/AcOEt (70/30; v/v) mixture elutes the least polar



isomer which is recrystallized from a DCM/isopropyl ether mixture.

m = 215 mg: cis isomer

M.p. = 260-264°C.

- 5 C) 5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-morpholinocarbonylindoline, trans isomer.

By the chromatography of the preceding step, a more polar product is collected by eluting with the AcOEt/MeOH (90/10) ; v/v) mixture. After recrystallizing from a DCM/isopropyl ether mixture, there is obtained:

m = 513 mg: trans isomer

M.p. = 240-241°C.

EXAMPLE 7

- 15 N-Methyl-N-carboxymethyl-5-bromo-3-(2-fluorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indoline-carboxamide, cis isomer.

200 mg of the compound prepared in Example 1 are dissolved in 3 ml of MeOH and 1 ml of water containing 13 mg of sodium hydroxide. After stirring for 24 hours at RT, one drop of concentrated sodium hydroxide solution is added to bring the reaction to an end and then, after 15 minutes, the mixture is acidified to pH 3 by addition of a potassium hydrogensulfate solution. Water is added, the mixture is extracted with AcOEt and the extract is washed with water and dried over magnesium sulfate and the solvent is evaporated under vacuum. The product obtained is recrystallized from DCM/isopropyl ether.

M.p. = 206-208°C.

30 EXAMPLES 8 and 9

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-(4-ethylcarboxylatepiperidino-carbonyl)indoline, cis isomer, trans isomer.

A) Ethyl N-bromoacetyl-4-piperidinecarboxylate.

- 35 This product is prepared from ethyl 4-piperidine-carboxylate, which is commercially available.



B) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(4-ethylcarboxylatepiperidinocarbonylmethyl)]aminobenzophenone.

8 g of 2',5-dichloro-2-(3,4-dimethoxyphenylsulfonyl-
 5 amido)benzophenone are dissolved in 100 ml of DMF and
 then 541 mg of sodium hydride are added. After stirring
 for 30 minutes, 9.5 g of the compound of Step A are added
 and the mixture is left stirring for 18 hours at RT. The
 10 mixture is concentrated under vacuum, taken up in water,
 extracted with ethyl acetate and the extract is dried and
 concentrated. The oil obtained is chromatographed on
 silica, eluting with the AcOEt/DCM/hexane
 (40/10/50 ; v/v/v) mixture. The expected product
 crystallizes from ether.

15 m = 3.5 g
 M.p. = 128°C.

C) 5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-
 sulfonyl)-3-hydroxy-2-(4-ethylcarboxylatepiperidino-
 carbonyl)indoline, cis isomer, trans isomer.

20 A mixture containing 3.4 g of the compound prepared
 in the preceding step and 869 mg of DBU in 10 ml of
 chloroform is brought to 60°C for 18 hours. The reaction
 mixture is then filtered on an alumina column, eluting
 with a DCM/AcOEt (90/10; v/v) mixture in order to obtain
 25 the cis isomer.

m = 700 mg
 M.p. = 110°C.

Pure ethyl acetate elutes the trans isomer.

m = 610 mg
 30 M.p. = 187°C.

EXAMPLES 10 and 11

N-methyl-N-(2-pyridylethyl)-5-chloro-3-(2-chloro-
 phenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-
 indolinecarboxamide, cis isomer, trans isomer.

35 A) N-[2-(2-chlorophenylcarbonyl)-5-chlorophenyl]-N-(3,4-
 dimethoxyphenylsulfonyl)glycine acid.

a) 2',5-Dichloro-2-(3,4-dimethoxyphenylsulfonyl-
 benzophenone.



This compound is prepared in Example 2-3, Step B.

b) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-benzyloxycarbonylmethyl]aminobenzophenone.

172 g of the product prepared previously are dissolved in 800 ml of DMF and cooled to 0°C. 11.7 g of 80% sodium hydride is added progressively under nitrogen and then, after 30 minutes, 256 g of benzyl bromoacetate are added and the mixture is left stirring for 24 hours at RT. The DMF is evaporated, the residue is taken up in water, extracted with DCM, and the extract dried and concentrated. The expected product crystallizes from isopropyl ether and is then recrystallized from a DCM/isopropyl ether mixture.

m = 136.5 g

M.p. = 102-104°C.

c) N-[2-(2-Chlorophenylcarbonyl)-5-chlorophenyl]-N-(3,4-dimethoxyphenylsulfonyl)glycine acid.

50 g of the benzyl ester obtained previously are dissolved in 500 ml of AcOEt and 2.5 g of 5% Pd/C are added under nitrogen. The solution is vigorously stirred and a stream of hydrogen is passed in for 5 hours. At the end of the hydrogenation, the product crystallizes. The mixture is filtered on Celite®, the cake is washed copiously with hot DCM and then the organic phase is concentrated. The expected product crystallizes and is then recrystallized from the DCM/isopropyl ether mixture.

m = 33.7 g

M.p. = 177-178°C.

B) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(N'-(2-(2-pyridyl)ethyl)-N'-methyl)carbamoylmethyl]amino-benzophenone.

2 g of the acid prepared in Step A are placed in 30 ml of DCM and 1.13 g of 2-(2-methylaminoethyl)-pyridine, then 844 mg of triethylamine and finally 1.92 g of BOP are added and then the mixture is left stirring for 18 hours at RT. The mixture is taken up with water, the organic phase is separated, washed with a sodium carbonate solution, dried and concentrated. After



chromatography on silica, the expected product is collected by eluting with the DCM/MeOH (95/5); v/v mixture.

m = 2 g

5 M.p. = 150°C.

C) N-methyl-N-(2-pyridylethyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide.

10 A mixture containing 1.7 g of the product obtained in the preceding step and 442 mg of DBU in DCM is heated at 55°C for 18 hours. The reaction mixture is chromatographed on alumina. The AcOEt/DCM (40/60); v/v mixture elutes the cis isomer:

m = 410 mg

15 M.p. = 191°C.

Pure AcOEt elutes the trans isomer:

m = 790 mg

M.p. = 154°C.

EXAMPLE 12

20 2-(4-Carboxypiperidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-indoline, cis isomer.

500 mg of the cis isomer prepared in Example 9 are placed in 5 ml of methanol in the presence of 48 mg of sodium hydroxide in 1 ml of water. After stirring for 18 hours, the mixture is poured into water, acidified with dilute hydrochloric acid, then extracted with DCM and the extract dried and concentrated. The solid obtained is purified by chromatography on silica, eluting with the DCM/MeOH (95/5; v/v) mixture and the product obtained is then crystallized from a DCM/isopropyl ether mixture.

m = 250 mg

M.p. = 150°C.

EXAMPLES 13 and 14

35 N-Methyl-N-(1-methyl-4-piperidyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer and trans isomer.



- 35 -

A) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(N'-methyl-N'-(methyl-4-piperidyl)carbamoylmethyl)amino]benzophenone.

2 g of the acid prepared in Example 10-11, Step A in 50 ml of DCM are mixed with 650 mg of 4-methylamino-1-methylpiperidine in the presence of 1.90 g of BOP. After stirring for 2 hours at RT, the organic phase is washed with carbonated water, dried and concentrated. The residue is then chromatographed on silica, eluting with the DCM/MeOH (90/10 ; v/v) mixture. 1.2 g of the expected product are obtained.

M.p. = 165-166°C.

B) N-Methyl-N-(methyl-4-piperidyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer and trans isomer.

650 mg of the product obtained in the preceding step are treated overnight with 100 mg of sodium methylate in 5 ml of methanol. Dry ice is added, the solvent is evaporated, the residue is taken up in carbonated water, extracted with DCM and the extract dried and concentrated and then chromatographed on silica. The methanol/DCM (5/95 ; v/v) mixture elutes the 2 isomers successively. Each is then recrystallized from a DCM/isopropyl ether mixture.

The trans isomer is the least polar under these conditions,

m = 205 mg

M.p. = 181°C.

Cis isomer: m = 150 mg

M.p. = 97°C: contains 0.25 M of isopropyl ether.

EXAMPLES 15 and 16

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-[4-methyl-1-piperazinylcarbonyl]-indoline, cis isomer and trans isomer.

A) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((4-methyl-1-piperazinyl)carbamoylmethyl)]aminobenzophenone.



This compound is obtained by the action of N-methyl-piperazine on the acid prepared in Example 10-11 Step A.

M.p. = 165-167°C.

5 B) 5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-[4-methyl-1-piperazinylcarbonyl]-indoline, cis isomer and trans isomer.

The compound of the preceding step is cyclized by proceeding as in Example 12-13. The 2 isomers formed are separated by chromatography on alumina. The DCM/AcOEt
10 (75/25; v/v) mixture elutes the least polar product: the cis isomer, which is recrystallized from a DCM/isopropyl ether mixture.

M.p. = 120°C: contains 0.25 M of isopropyl ether.

The DCM/MeOH mixture elutes the most polar compound,
15 the trans isomer which is then recrystallized from methanol.

M.p. = 189°C.

EXAMPLES 17 and 18

20 N-Isopropyl-N-methoxycarbonylethyl-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer and trans isomer.

A) N-Isopropyl-N-(methoxycarbonylethyl)bromoacetamide.

90 g of isopropylamine are added dropwise to 130 g of a solution, cooled to -10°C, of methyl acrylate in
25 300 ml of methanol. After 72 hours at RT, the mixture is evaporated and the residue is then distilled. The oil obtained (168.3 g) is methyl 3-(N-isopropyl)-aminopropionate.

B.p. = 73-78°C at 15 mm Hg.

30 29 g of the compound obtained in 100 ml DCM are mixed with 20.2 g of bromoacetyl bromide in 100 ml of DCM at 0°C. After 12 hours at RT, the solvent is evaporated, the residue is taken up in water, extracted with ethyl acetate and the extract dried and concentrated. The oil
35 obtained is used as it is in the following step.

B) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(N'-isopropyl-N'-methoxycarbonylethyl)carbamoylmethyl]-aminobenzophenone.



This compound is obtained by following the usual procedure, by reacting the product prepared in Step A with 2',5-dichloro-2-(3,4-dimethoxyphenylsulfonamido)-benzophenone in the presence of sodium hydride.

5 M.p. = 135-137°C (recrystallization: DCM/isopropyl ether).

C) N-Isopropyl-N-methoxycarbonylethyl-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer and trans isomer.

10 This product is obtained by cyclizing the compound prepared in Step B, in the presence of DBU. The cis isomer is separated by chromatography on alumina, eluting with a DCM/AcOEt (90/10; v/v) mixture. The product is then crystallized from an AcOEt/hexane mixture.

15 M.p. = 153-155°C.

The trans isomer is obtained by eluting the alumina column with ethyl acetate. The product is then recrystallized from a methanol/isopropyl ether mixture.

M.p. = 182-185°C.

20 EXAMPLES 19 and 20

N-Methyl-N-methoxycarbonylmethyl-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer and trans isomer.

25 The 2 isomers of this compound are prepared according to the procedure described in Example 1. They are separated by chromatography on alumina. The DCM/AcOEt (80/20 ; v/v) mixture elutes the cis isomer. This crystallizes from a DCM/isopropyl ether mixture in the form of a white powder containing 0.25 mole of isopropyl ether. It is converted to a foam by heating in vacuum.

30 The NMR spectrum of the cis isomer (Example 19) is given in Figure 1.

The trans isomer is eluted with pure AcOEt. It is recrystallized from DCM/isopropyl ether.

35 M.p. = 176-178°C.

The NMR spectrum of the trans isomer (Example 20) is given in Figure 2.



EXAMPLES 21 and 22

N-Methyl-N-carboxymethyl-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer and trans isomer.

5 These compounds are each prepared from the compounds described in Examples 19 and 20 according to the procedure described in Example 8.

Cis isomer: M.p. = 220-222°C after recrystallizing from a DCM/isopropyl ether/MeOH mixture.

10 Trans isomer: M.p. = 222-225°C after recrystallizing from a DCM/isopropyl ether mixture.

EXAMPLES 23 and 24

N-Methyl-N-carbamoylmethyl-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer and trans isomer.

15 Each isomer is obtained from the corresponding isomer of the acid prepared in Example 21-22.

605 mg of the trans isomer of the acid obtained in the preceding example are dissolved in 10 ml of DCM, and 435 mg of BOP and 260 mg of DIPEA are added. After 5 minutes at RT, 6 ml of 20% aqueous ammonia solution are added with vigorous stirring and the mixture is left stirring for 4 hours. A sodium carbonate solution is added and the mixture is then extracted with DCM. The organic phase is washed successively with water, a sodium hydrogensulfate solution, and water and is then dried over magnesium sulfate. After evaporating, the residue is chromatographed on silica gel and is eluted with an AcOEt/MeOH (95/5; v/v) mixture. The product obtained is crystallized twice from a DCM/EtOH mixture at 0°C.

30 M.p. = 236°C.

The NMR spectrum of the trans isomer (Example 23) is given in Figure 3.

35 Using the same procedure, the cis isomer is prepared.

The expected product crystallizes from DCM/isopropyl ether. The micronized compound, dried in vacuum at 70°C for 8 hours, contains 0.25 mole of isopropyl ether.



The NMR spectrum of the cis isomer (Example 24) is given in Figure 4.

EXAMPLES 25 and 26

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-1-(4-hydroxy-1-piperidyl)carbonyl-indoline, trans isomer.

This compound is prepared from N-[2-(2-chlorophenyl-carbonyl)-5-chlorophenyl]-N-(3,4-dimethoxyphenyl-sulfonyl)glycine acid described in Example 11-12, Step A.

10 The process is then carried out as in Example 11-12 for the addition of 4-hydroxypiperidine, in the presence of BOP and triethylamine. The product obtained is then cyclized according to the usual method in the presence of DBU. The 2 isomers are separated by chromatography on
15 alumina. The DCM/MeOH (99/1; v/v) mixture elutes the cis isomer.

The product crystallizes from a DCM/hexane/MeOH mixture and the solid obtained is then triturated in DCM/hexane to provide an amorphous powder.

20 The cis isomer is characterized by its NMR spectrum at 388°K.

1-1.8 ppm:m:4H:CH₂ at positions 3 and 5 of the piperidine
2.8-3.65 ppm:m:5H:CH₂ at positions 2 and 6 of the piperidine and CH at position 4

25 3.75 ppm:2s:6H:2OCH₃
4.15 ppm:d:1H:OH on piperidine
5.45 ppm:s:1H:CH (indoline)
6.1 ppm:s:1H:OH indoline
6.8-7.6 ppm:m:10H:H aromatic

30 DMSO:2.4 ppm
DOH:2.75 ppm

The DCM/MeOH (97/3; v/v) mixture elutes the trans isomer which is recrystallized from DCM/isopropyl ether.

M.p. = 232-234°C.

35 SYNTHESSES in the (L)-Proline series: Examples 27, 28, 39 and 30.



EXAMPLES 27 and 27a

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-[(2S)-(2-methoxycarbonyl)pyrrolidinocarbonyl]indoline, (cis isomers : 2 compounds).

5 A) Methyl (L)-N-(bromoacetyl)prolinate.

20 g of triethylamine and 20 g of bromoacetyl bromide in 30 ml of DCM are added simultaneously to a solution of 16.7 g of methyl (L)-prolinate hydrochloride in 20 ml of DCM while maintaining the temperature at -5°C and the mixture is then stirred at RT for 24 hours. Water is added, and the mixture is washed with a solution of KHSO₄, with water, with a sodium bicarbonate solution and with water and is then dried over magnesium sulfate. After evaporating, an oil is obtained which is dried under vacuum. This oil, pure by TLC, is used as it is in the following step.

B) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((2S)-(2-methoxycarbonyl)pyrrolidinocarbonylmethyl)]-aminobenzo-phenone.

4.66 g of 2',5-dichloro-2-(3,4-dimethoxyphenyl-sulfonamido)benzophenone are dissolved in 40 ml of anhydrous DMF under argon, at 0°C, 340 mg of 80% sodium hydride are added and then, after 30 minutes, 6.5 g of the compound obtained in Step A. After 4 days at RT, the mixture is poured into water, extracted with AcOEt, the extract washed with water, with saline water and then dried over magnesium sulfate and evaporated under vacuum. A solid containing a small amount of the starting brominated derivative is eluted with a DCM/AcOEt (85/15; v/v) mixture by chromatography on silica gel. A sample is recrystallized from DCM/isopropyl ether.

m = 1.2 g

M.p. = 141-142°C

$\alpha_D^{25} = -43.7^\circ$ (c = 1; MeOH/THF: 8/2; v/v)

35	Analysis	Calculated	C:54.81	H:4.44	N:4.41
		Found	54.40	4.54	4.55



C) 5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-[(2S)-(2-methoxycarbonyl)pyrrolidinocarbonyl]indoline, (cis isomerism).

1.1 g of the compound obtained in the preceding step are heated in 4 ml of methylene chloride for 24 hours with one equivalent of DBU. HPLC analysis of an aliquot shows the existence of the expected 4 isomers. After 24 hours, the reaction mixture is poured onto an alumina column, pre-equilibrated in the DCM/AcOEt (90/10; v/v) mixture and is eluted with the DCM/AcOEt (90/10; v/v to 70/30; v/v) mixture. 510 mg of a mixture of the 2 least polar compounds are obtained in the ratio 4/1 (measured by HPLC).

1°) Two successive crystallizations from DCM/isopropyl ether while cold provide the major compound.

m = 180 mg

$\alpha_D^{25} = -247^\circ (c = 0.4; \text{chloroform})$

M.p. = 187-190°C.

2°) The crystallization mother liquors of the preceding compound are chromatographed on alumina by eluting with DCM/AcOEt (85/15; v/v). The preceding compound is thus separated from the second, the latter is dissolved in the minimum amount of DCM and is then precipitated by addition of the minimum amount of hexane.

$\alpha_D^{26} = +136 (c = 0.24; \text{chloroform})$

EXAMPLE 28

2-((2S)-2-Carboxypyrrolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer.

430 mg of the compound prepared in Example 27 are dissolved in 6 ml of methanol, 41 mg of sodium hydroxide in 1 ml of water are added and the mixture is stirred for 24 hours at RT. The mixture is acidified to pH 3 with a few drops of a potassium acidsulfate solution and is extracted with ethyl acetate. The extract is washed with water and is then dried over magnesium sulfate. Chromatography is carried out on a silica column prepared in a DCM/pentane (80/20; v/v) mixture. The unreacted ester



(compound of example 27) is eluted by a DCM/AcOEt (70/30 ; v/v) mixture. The AcOEt/MeOH (80/20 ; v/v) mixture elutes the expected acid which is then recrystallized from DCM/isopropyl ether.

5 M.p. = 232-234 °C $\alpha_D^{23} = -254^\circ (c = 0.3 ; \text{chloroform})$.

EXAMPLES 29 and 29a

2-((2S)-2-Carbamoylpyrrolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-indoline, (cis isomers : 2 compounds).

10 230 mg of the compound prepared in Example 28 are dissolved in 5 ml of DCM, 50 mg of DIPEA and then 165 mg of BOP are added and the mixture is left for 5 minutes at RT. The mixture is cooled in an ice bath and a stream of gaseous ammonia is then bubbled through for 1 minute and,
15 after 15 minutes, for a further 1 minute. Water and then a large volume of ethyl acetate are added in order to obtain two phases. The organic solution is washed with a sodium carbonate solution, water, a potassium hydrogen-sulfate solution, water and then saline water. After
20 drying, the residue is chromatographed on silica by eluting with a DCM/MeOH (93/7; v/v) mixture. The product obtained is triturated in a DCM/isopropyl ether/hexane mixture. It contains 1/3 mole of isopropyl ether.

$\alpha_D^{25} = -189^\circ (c = 0.23; \text{chloroform})$.

25 The compound of Example 29 can be prepared according to another procedure.

A) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((2S-2-carbamoylpyrrolidinocarbonylmethyl)]aminobenzo-phenone.

30 33.9 g of the acid prepared in Example 10-11, Step A are dissolved in 300 ml of chloroform. 15 g of thionyl chloride are added and the mixture is brought to reflux for 1 hour and a half. The mixture is evaporated to dryness, the residue is then taken up in DCM and
35 evaporated again. The mixture is dissolved in 300 ml of DCM, brought to 0°C and 10.5 g of (L)-prolinamide hydrochloride are added, and then 18 g of DIPEA in 20 ml of DCM are slowly added without allowing the temperature of the reaction mixture to exceed 3°C. After one night at



DCM are slowly added without allowing the temperature of the reaction mixture to exceed 3°C. After one night at RT, the reaction mixture is washed with sodium bicarbonate (2 times) and then with potassium hydrogen-sulfate (2 times); the reaction mixture is dried and concentrated. The crude product obtained is dissolved in the minimum amount of DCM and added dropwise to isopropyl ether (1.2 l) with stirring. After stirring for 2 hours, the precipitate obtained is filtered and then dried under vacuum for 6 hours at 60°C. 42 g are collected.

$$\alpha_D^{25} = -40.8 \text{ (c = 1.007; chloroform)}.$$

B) 2-((2S)-2-Carbamoylpyrrolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, (cis isomerism: 2 compounds).

5 g of the product prepared in the preceding step are dissolved in 50 ml of methanol. The solution is cooled to -10°C; 1.35 g of DBU is added and the mixture is maintained for 60 hours at -10°C. A compound crystallizes; it is filtered (cis compound 1). The crystallization liquors are neutralized with KHSO₄ and the mixture is evaporated to dryness. It is taken up in water, extracted 2 times with DCM, and the extracts are dried and concentrated. The crude product obtained is chromatographed on silica by eluting with an AcOEt/DCM (28/72; v/v) mixture. A mixture is collected which is dissolved in the minimum amount of methanol while hot; the insoluble material is filtered off the liquors are then placed overnight at -4°C and the cis compound 2 crystallizes.

$$m = 1.25 \text{ g}$$

$$\alpha_D^{25} = -196^\circ \text{ (c = 0.351; chloroform)}.$$

The analysis of the NMR spectrum shows the presence of one mole of MeOH per mole of product. The recrystallization of the product from ethanol makes it possible to remove the solvent in the crystals.

$$\text{M.p.} = 154-162^\circ\text{C}$$

$$\alpha_D^{25} = -204^\circ \text{ (c = 0.3; chloroform)}$$

$$\alpha_D^{25} = -131^\circ \text{ (c = 0.27; chloroform/methanol: 8/2; v/v)}$$



This compound is identical, the solvent excepted, to that prepared by the first procedure of the present example.

The compound which crystallized in Step B) above,
5 called cis compound 1, is recrystallized from methanol.

M.p. = 190°C

$\alpha_D = +115^\circ$ (c = 0.3; chloroform)

EXAMPLE 30

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-
10 sulfonyl)-3-hydroxy-2-[(2S)-2-(hydroxymethyl)pyrrolidino-
carbonyl]indoline, cis isomers.

A) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(2-
(hydroxymethyl)pyrrolidinocarbonylmethyl)]aminobenzo-
phenone.

15 This compound is obtained by reacting (L)-prolinol
with the acid prepared in Example 10-11, Step A, by
following the usual procedure.

B) 5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-
sulfonyl)-3-hydroxy-2-[(2S)-2-(hydroxymethyl)pyrrolidino-
20 carbonyl]indoline, cis isomer.

1.5 g of the compound of the preceding step is
cyclized in the presence of 380 mg of DBU in 2 ml of DCM.
After 3 days at RT, 1 ml of DCM is added and the mixture
is then heated at 40°C overnight. The formation of 3
25 major compounds is observed by TLC on silica (eluent
AcOEt).

The least polar fraction is eluted by chromatography
on silica using DCM/AcOEt (60/40 to 80/20; v/v). A
chromatography on alumina is then carried out by eluting
30 with DCM/MeOH (99/1; v/v). The fraction obtained is
homogeneous by TLC. The product is recrystallized three
times from DCM/isopropyl ether. The expected product is
obtained with an HPLC purity greater than 99%.

m = 155 mg

35 M.p. = 194-197°C

$\alpha_D^{25} = -195^\circ$ (c = 0.2; chloroform).

SYNTHESES in the (D)-Proline series: Example 31.

EXAMPLE 31



SYNTHESES in the (D)-Proline series: Example 31.

EXAMPLE 31

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-[(2R)-2-(methoxycarbonyl)pyrrolidinocarbonyl]indoline, cis isomer.

A) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((2R)-2-(methoxycarbonyl)pyrrolidinocarbonylmethyl)]-aminobenzo-phenone.

This compound is obtained from the acid prepared in Example 10-11, Step A (3 g) to which are added 1.2 g of methyl (D)-prolinate and 2.8 g of BOP in 10 ml of DCM in the presence of 1.15 g of triethylamine. The mixture is left for 1 hours at RT and is then diluted with DCM, the organic phase is washed with sodium carbonate and with potassium hydrogensulfate, dried and concentrated. The crude product is chromatographed on silica, eluting with a DCM/AcOEt (95/5; v/v) mixture. The product obtained is then recrystallized from a DCM/isopropyl ether mixture.

M.p. = 140-141°C.

$\alpha_D^{25} = +28.5^\circ (c = 0.27; \text{chloroform}).$

B) 5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-[(2R)-2-(methoxycarbonyl)pyrrolidinocarbonyl]indoline, cis isomer.

1.5 g of the preceding compound is brought to reflux overnight in 5 ml of DCM in the presence of 360 mg of DBU. The mixture is chromatographed on alumina. The mixture DCM/AcOEt (95/5; v/v) elutes the least polar fraction (m = 300 mg) which is recrystallized 2 times in a DCM/isopropyl ether mixture.

M.p. = 186-188°C

$\alpha_D^{25} = +245^\circ (c = 0.4; \text{chloroform}).$

This compound is the enantiomer obtained from (D)-proline of that described in Example 27.

EXAMPLE 32 and 32a

N-Methyl-N-methoxycarbonylmethyl-5-chloro-3-(2-chlorophenyl)-1-(4-ethoxyphenylsulfonyl)-3-hydroxy-2-indoline-carboxamide, trans isomer and cis isomer.



A) 2',5-Dichloro-2-[N-(4-ethoxyphenylsulfonyl)-N-(N'-methyl-N'-(methoxycarbonylmethyl)carbamylmethyl)amino]benzophenone.

5.7 g of 2',5-dichloro-2-(4-ethoxyphenylsulfonamido)-benzophenone are dissolved, under argon, in 40 ml of DMF and 400 mg of 80% sodium hydride are added at 0°C; after 15 minutes, 4.3 g of methyl N-(bromoacetyl)sarcosinate are added. After 48 hours, the expected product is extracted in the usual way and is then purified by chromatography on silica by eluting with DCM/AcOEt (90/10; v/v) and recrystallizing in a DCM/isopropyl ether mixture.

M.p. = 158-160°C

B) N-Methyl-N-methoxycarbonylmethyl-5-chloro-3-(2-chlorophenyl)-1-(4-ethoxyphenylsulfonyl)-3-hydroxy-2-indoline-carboxamide, trans isomer.

1 g of the compound obtained in the preceding step is dissolved in 4 ml of DCM and treated for 90 minutes at RT with 312 mg of TBD. A solution of potassium hydrogen-sulfate is added, the DCM is evaporated under vacuum, the mixture is extracted with AcOEt and the extract is washed and dried over magnesium sulfate. The expected product is obtained by chromatography on silica gel by eluting with DCM/AcOEt (90/10; v/v).

m = 590 mg

M.p. = 168-171°C after recrystallizing from DCM/hexane.

C) N-Methyl-N-methoxycarbonylmethyl-5-chloro-3-(2-chlorophenyl)-1-(4-ethoxyphenylsulfonyl)-3-hydroxy-2-indoline-carboxamide, cis isomer.

2.96 g of the compound obtained in Step A are suspended in 20 ml of methanol and 10 ml of THF; 100 mg of sodium methylate are added and the mixture is then left for 7 hours in the refrigerator. Water is added, the mixture neutralized with a potassium hydrogensulfate solution and a part of the methanol is evaporated under vacuum. After extracting with AcOEt, the residue is chromatographed on alumina and is then eluted with a



DCM/AcOEt (80/20; v/v) mixture. 850 mg of the expected product are obtained which are recrystallized from a DCM/isopropyl ether mixture.

The NMR spectrum is given in Figure 6.

- 5 By using methods similar to those described above, intermediate compounds (VI) for the synthesis of compounds (I) according to the invention were prepared.

The compounds (VI) prepared are described in Table 1 below.

- 10 The compounds (I) prepared are described in Table 2 below.

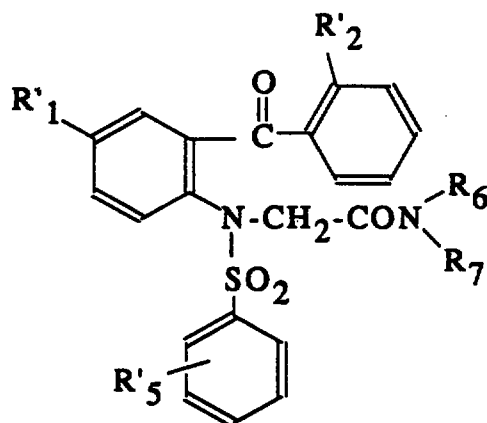
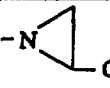




Table 1

	R' ₁	R' ₅	R' ₂	$\begin{array}{c} \text{R}_6 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}_7 \end{array}$	M.p. (°C) or IR Solvent
5	Br-	3,4-CH ₃ O	F-	$\begin{array}{c} \text{CH}_3 \\ \\ \text{-N-CH}_2\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5 \end{array}$	82-83 DCM/isopropyl ether
10	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{CH}_3 \\ \\ \text{-N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	164-166 DCM/isopropyl ether
	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{CH}_3 \quad \text{Et} \\ \quad \\ \text{-N-CH}_2\text{CH}_2\text{N-Et} \end{array}$	128 DCM/isopropyl ether
15	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{-N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	105 DCM/isopropyl ether
20	Cl-	2,4-CH ₃ O	Cl-	$\text{-N} \begin{array}{c} \diagup \quad \diagdown \\ \text{C}_4\text{H}_8 \end{array} \text{N-CO}_2\text{CH}_2\text{C}_6\text{H}_5$	142-143 MeOH
	CH ₃ O-	3,4-CH ₃	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{-N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	IR (1)
25	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{iPentyl} \\ \\ \text{-N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	85 Isopropyl ether/DCM
	Br-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{-N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	IR (2)
30	Cl-	3,4-CH ₃ O	Cl-	$\text{-N} \begin{array}{c} \diagup \quad \diagdown \\ \text{C}_4\text{H}_6\text{S} \end{array}$	199 DCM/isopropyl ether
	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Pr} \\ \\ \text{N-CH}_2\text{CO}_2\text{CH}_3 \end{array}$	135 Isopropyl ether/ DCM/AcOH
35	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Pr} \\ \\ \text{N-CH}_2\text{CH}_2\text{-CO}_2\text{CH}_3 \end{array}$	113 DCM/isopropyl ether



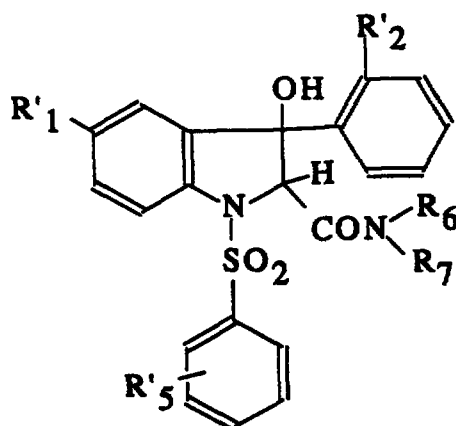
5	Cl-	3,4-CH ₃ O	Cl-	Et -N-CH ₂ -CO ₂ CH ₃	160 isopropyl ether
	Cl-	3,4-CH ₃ O	Cl-		197-198
	Cl-	3,4-CH ₃ O	Cl-		(3)

10 IR (1) (DCM) 1740 cm⁻¹ fine
1680 cm⁻¹ broad
IR (2) (DCM) 1735 cm⁻¹ fine
1660-1680 cm⁻¹ split

(3) This compound is characterized by its optical rotation:

15 $\alpha_D^{25} = -36.8^\circ$ (c = 0.44; chloroform).

Table 2

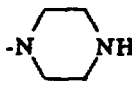
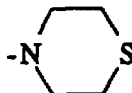
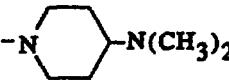


20 For each compound of formula (I) which has the substituents R'₁, R'₅, R'₂ and NR₆R₇ of the table below, the cis isomerism is shown and then the trans isomerism, except when otherwise indicated.



Example	R' ₁	R' ₅	R' ₂	$\begin{array}{c} \text{R}_6 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}_7 \end{array}$	M.p. (°C) or NMR Solvent
5 33 34	Br-	3,4-CH ₃ O	F-	$\begin{array}{c} \text{CH}_3 \\ \\ \text{N-CH}_2\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5 \end{array}$	87-95 NMR
10 35 36	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{CH}_3 \\ \\ \text{N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	100-103 154-157 DCM/isopropyl ether
37 cis	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{CH}_3 \\ \\ \text{N-CH}_2\text{CH}_2\text{CO}_2\text{H} \end{array}$	140-144 DCM/isopropyl ether
15 38 mixture	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{CH}_3 \quad \text{Et} \\ \quad \\ \text{N-CH}_2\text{CH}_2\text{N-Et} \end{array}$	222-225 DCM/isopropyl ether
39 40	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	NMR NMR
20 41 cis	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{N-CH}_2\text{CH}_2\text{CO}_2\text{H} \end{array}$	166 DCM/isopropyl ether
25 42 43	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{N} \text{---} \text{C}_6\text{H}_{10} \text{---} \text{N} \\ \diagdown \\ \text{CH}_3 \end{array}$	119 AcOEt/isopropyl ether 228 MeOH
30 44 cis	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{CH}_2\text{C}_6\text{H}_5 \\ \\ \text{N-CH}_2\text{CH}_2\text{N} \begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{CH}_3 \end{array} \end{array}$	179 DCM/isopropyl ether
45 46	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{N} \text{---} \text{C}_6\text{H}_{10} \text{---} \text{N-CH}_2\text{CO}_2\text{Et} \end{array}$	109 DCM/isopropyl ether 196 DCM/isopropyl ether
35 47 48	Cl-	2,4-CH ₃ O	Cl-	$\begin{array}{c} \text{N} \text{---} \text{C}_6\text{H}_{10} \text{---} \text{N-CO}_2\text{CH}_2\text{C}_6\text{H}_5 \end{array}$	134 (iPr) ₂ O 195 DCM/isopropyl ether

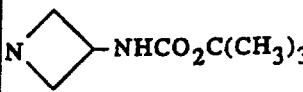
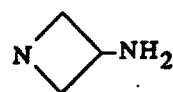
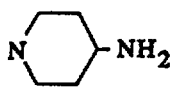
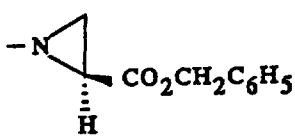


5	49 cis	Cl-	3,4-CH ₂ O	Cl-	Et -N-CH ₂ CH ₂ CONH ₂	236 isopropyl ether
	50 51	CH ₃	3,4-CH ₃	Cl-	Et -N-CH ₂ CH ₂ CO ₂ CH ₃	154 isopropyl ether 87 isopropyl ether
10	52 cis	Cl-	2,4-CH ₃ O	Cl-		194 MeOH/isopropyl ether
15	53 cis	Cl-	3,4-CH ₃ O	Cl-	iPentyl -N-CH ₂ CH ₂ CO ₂ CH ₃	195 isopropyl ether/DCM
	54 55	Br-	2,4-CH ₃ O	Cl-	Et -N-CH ₂ CH ₂ CO ₂ CH ₃	138-140 isopropyl ether 140 isopropyl ether
20	56 57	Cl-	3,4-CH ₃ O	Cl-		242-245 DCM/isopropyl ether 225 MeOH/isopropyl ether
25	58 58 a	Cl-	2,4-CH ₃ O	Cl-		228 MeOH/isopropyl ether 221 DCM/MeOH
30	59 59a	Cl-	3,4-CH ₃ O	Cl-	Et -N-CH ₂ CH ₂ CH ₂ CO ₂ CH ₃	131-134 DCM/isopropyl ether/ hexane 121 DCM/ether/hexane
35						



5	60 61	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{iBu} \\ \\ \text{N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	162-166 DCM/isopropyl ether 130 DCM/isopropyl ether/ hexane
10	62 63	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Pr} \\ \\ \text{-N-CH}_2\text{CO}_2\text{CH}_3 \end{array}$	176 isopropyl ether/DCM NMR
15	64 65	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Pr} \\ \\ \text{-N-CH}_2\text{CH}_2\text{CO}_2\text{CH}_3 \end{array}$	148 isopropyl ether/DCM 122 isopropyl ether/DCM
20	66 67	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{N-CH}_2\text{CO}_2\text{CH}_3 \end{array}$	NMR 168 isopropyl ether
25	68 cis	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{iBu} \\ \\ \text{N-(CH}_2)_2\text{CO}_2\text{H} \end{array}$	179-182 DCM/isopropyl ether
30	69 cis	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{N-CH}_2\text{CO}_2\text{H} \end{array}$	139 DCM/isopropyl ether
35	70 cis	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Pr} \\ \\ \text{N-CH}_2\text{CO}_2\text{H} \end{array}$	130 isopropyl ether
	71 cis	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{N-(CH}_2)_3\text{CO}_2\text{H} \end{array}$	136 DCM/isopropyl ether
	72 cis	Cl-	3,4-CH ₃ O	Cl-	$\begin{array}{c} \text{Et} \\ \\ \text{N-CH}_2\text{-CONH}_2 \end{array}$	135 DCM/isopropyl ether



5	73 74	Cl-	3,4-CH ₃ O	Cl-		197 MeOH/isopropyl ether 211 MeOH
10	75 cis	Cl-	3,4-CH ₃ O	Cl-		NMR
15	76 cis	Cl-	3,4-CH ₃ O	Cl-		Fumarate 152-156 DCM/isopropyl ether
	76a 76b	Cl-	3,4-CH ₃ O	Cl-		137 isopropyl ether/MeOH/ hexane 183-185 hexane

20 - Example 34

analysis: calculated C:55.54 H: 4.24 N:3.93
found 55.72 4.57 3.83

NMR spectra at 200 MHz (DMSO: 2.5 ppm)

- Example 34: Figure 5

25 - Example 38

0.7-1.1 ppm: m:6H:2CH₃(Et)

2-4 ppm:m:17H:2CH₂(Et), 2CH₂-N, N-CH₃, 2OCH₃

5.2-5.7 ppm:3s:1H:H (indoline)

6.2-8.2 ppm:m:11H:OH + aromatics

30 - Example 39

0.3-1.2 ppm:m:3H:CH₃ (Et)

1.5-4.3 ppm:m:15H:CH₂-CO, CH₂ (Et), CH₂-N, 2OCH₃, CO₂CH₃

5.2-5.6 ppm:3s:1H:H (indoline)

6.2-8.2 ppm:m:11H:OH + aromatics

35 - Example 40

0.8-1.1 ppm:m:3H:CH₃ (Et)

2.2-3.9 ppm:m:15H:CH₂CO, CH₂(Et), CH₂N, CO₂CH₃, 2OCH₃

5.3-5.7 ppm:2s:1H:H (indoline)



- 6.6-8.2 ppm:m:11H:OH + aromatics
 - Example 63
 0.4-1 ppm: split t:3H:CH₂-CH₂-CH₃
 5 ppm:m:2H:CH₂-CH₂-CH₃
 5 2.5-4.4 ppm:m:13H:CH₂-CH₂-CH₃, NCH₂COOCH₃, 2OCH₃
 5.2-5.8 ppm; bs :1H:H (indoline)
 6.5-8.3 ppm:m:11H:OH + aromatics
 - Example 66
 0 to 1.5 ppm:m:3H:CH₂-CH₃
 10 2.3-5.8 ppm:m:14H:CH₂-CH₃, NCH₂COOCH₃, 2OCH₃, H (indoline)
 6.1-8.3 ppm:m:11H:OH + aromatics
 - Example 75
 1.95 ppm:bs:2H:NH₂
 2.7 to 5.3 ppm:m:12H:2OCH₃, 2NCH₂, H(indoline), CHNH₂
 15 6 to 8.3 ppm:m:11H:OH + aromatics
 - Example 76a
 $\alpha_D^{25} = +102^\circ$ (c = 0.35; chloroform)
 - Example 76b
 $\alpha_D^{25} = -158^\circ$ (c = 0.2; chloroform).
 20 Some compounds according to the invention described
 in Table 2 are useful in the preparation of other com-
 pounds according to the invention. For example, compound
 41 was obtained from compound 39 by treatment in basic
 medium in methanol MeOH/H₂O. Compound 49 was prepared from
 25 compound 41 by treatment with aqueous ammonia in the
 presence of DIPEA and BOP.
EXAMPLE 77
 N-Ethyl-N-(2-aminoethyl)-5-chloro-3-(2-chlorophenyl)-1-
 (3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indoline-
 30 carboxamide, (cis isomerism).
 500 mg of compound 49 are dissolved in 10 ml of
 acetonitrile and 10 ml of water and 252 mg of pyridine
 and 380 mg of bis(trifluoroacetoxy)iodobenzene are added.
 After stirring for 2 hours, the mixture is taken up in a
 35 solution of hydrochloric acid, extracted with ether,
 alkalized with dilute sodium hydroxide solution,
 extracted with DCM and the extract is dried and con-
 centrated. An oil is obtained and the expected product



then crystallizes from ether.

m = 150 mg

M.p. = 164°C

EXAMPLE 78

5 N-Ethyl-N-[(1S)-1-(ethoxycarbonyl)ethyl]-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, (cis isomerism).

A) N-[2-(2-Chlorophenylcarbonyl)-5-chlorophenyl]-N-(3,4-dimethoxyphenylsulfonyl)glycine acid chloride.

10 A mixture containing 11 g of the acid prepared in Example 10-11, Step A) and 5 g of thionyl chloride in 10 ml of chloroform is heated for 1 hour at 60°C. The mixture is left to return to RT, concentrated under vacuum and the residue taken up in DCM (2 times). A
15 yellow oil is obtained which is used as it is in the following step.

IR: 1800 cm⁻¹ (C=O)

20 B) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-(N'-ethyl-N'-((1S)-1-(ethoxycarbonyl)ethyl)ethoxycarbamoylmethyl)]aminobenzophenone.

The preparation of this compound was carried out according to J. Org. Chem., 1985, 50, 945-950.

5.15 g of (L)-Boc(N-Et)AlaOEt is treated with 10 ml of TFA at 0°C in order to remove the Boc group. The
25 mixture is concentrated under vacuum, taken up in 20 ml of DCM, cooled to -78°C and 2 equivalents of TEA and the acid chloride prepared in the preceding step, dissolved in DCM, are added. After 18 hours at RT, the mixture is extracted with DCM, the extract is washed with water and
30 then chromatographed on silica by eluting with a DCM/AcOEt (90/10; v/v) mixture. The expected product crystallizes from isopropyl ether.

M.p. = 112°C

m = 8 g

35 C) N-Ethyl-N-[(1S)-1-(ethoxycarbonyl)ethyl]-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, (cis isomerism).



- 56 -

The compound obtained in the preceding step is stirred at RT for 18 hours in 10 ml of THF and 20 ml of ethanol, in the presence of 1.46 g of DBU. The mixture is concentrated under vacuum, the residue is taken up in DCM, washed with water, concentrated and the product chromatographed on alumina by eluting with AcOEt/DCM (10/90; v/v).

NMR

0-0.9 ppm: split d:3H:CH-CH₃
0.9-1.7 ppm:m:6H:2CH₃ (ethyl)
2.6 to 5.8 ppm:m:12H:2OCH₃, NCH₂, OCH₂, NCH, COCH
6.1 to 8.3 ppm:m:11H:OH - 10H aromatics

EXAMPLES 79 and 80

N,N-Di[2-(methoxycarbonyl)ethyl]-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer and trans isomer.

A) N,N-Di[2-(methoxycarbonyl)ethyl]benzylamine.

Preparation according to J. Am. Chem. Soc., 1950, 72, 3298.

107 g of benzylamine in 200 ml of ethanol are cooled in an ice bath and 172.2 g of methyl acrylate in 250 ml of ethanol are slowly added. After 13 days at RT, the solvent is evaporated under vacuum and a part of the oily residue is then distilled.

B.p. = 135-140°C at 0.6 mm Hg

m = 30 g

IR: 1730 cm⁻¹

B) N,N-Di[2-(methoxycarbonyl)ethyl]amine.

27.9 g of the amine obtained in the preceding step, placed in 500 ml of methanol, are mixed with 3 g of 5% palladium on charcoal and are treated under hydrogen pressure for 1 hour. The mixture is filtered on Celite®, rinsed with methanol and the solvent evaporated under vacuum; the residual oil is used as it is in the following step.

C) N,N-Di[2-(methoxycarbonyl)ethyl]bromoacetamide.

A mixture containing 14.3 g of the amine prepared in the preceding step, 100 ml of DCM and 10.6 ml of TEA is



- 57 -

cooled in an ice bath; 15.3 g of bromoacetyl bromide are added dropwise and the mixture is then left stirring for 48 hours at RT. The mixture is extracted with DCM, the extract is washed with water and then a chromatography is carried out on silica by eluting with a DCM/MeOH (97/3 ; v/v) mixture. The expected product is obtained in the form of an oil.

m = 15.9 g

IR: 1650 cm^{-1} and 1730 cm^{-1} .

- 10 D) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-[N',N'-di(2-(methoxycarbonyl)ethyl)carbamoylmethyl]]-aminobenzo-phenone.

14.3 g of 2',5-dichloro-2-(3,4-dimethoxyphenyl-sulfonamido)benzophenone are placed in 180 ml of DMF and 1.1 g of sodium hydride are added in portions. After stirring for 1 hour at RT, the mixture is cooled in an ice bath and 14.3 g of the product prepared in the preceding step are added and the mixture is left stirring for 72 hours at RT. The mixture is extracted with DCM, the extract is washed with water and then chromatographed on silica by eluting with a DCM/AcOEt (93/7; v/v) mixture.

m = 28.4 g

M.p. = 130°C.

- 25 E) N,N-Di[2-(methoxycarbonyl)ethyl]-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomer.

12 g of the compound prepared in the preceding step and 0.930 g of sodium methylate in 150 ml of methanol are mixed at 0°C and the mixture is then left stirring overnight at RT. The reaction mixture is neutralized by addition of 5% KHSO_4 and the solvent is then evaporated under vacuum. The residue is chromatographed on alumina by eluting with a DCM/AcOEt (8/2; v/v) mixture. 2.4 g of the expected product are recovered which are crystallized from methanol.

M.p. = 175°C.



- 58 -

F) N,N-Di[2-(methoxycarbonyl)ethyl]-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, trans isomer.

5 The chromatography of the preceding step is continued and elution is carried out with a DCM/MeOH (9.5/0.5; v/v) mixture. 1.82 g of the trans isomer is obtained which crystallizes from isopropyl ether.

M.p. = 85°C.

EXAMPLES 81, 82 and 83

10 2-((2R)-2-Carbamoylthiazolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, (cis isomerism: 2 compounds and trans isomerism).

A) (L)-4-Thiazolidinecarboxamide.

15 This compound is prepared according to J. Med. Chem., 1981, 24, 692.

B) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((2R)-2-carbamoylthiazolidinocarbonylmethyl)]-aminobenzophenone.

20 This compound is obtained by the usual methods from the acid prepared in Example 10-11, Step A).

M.p. = 125°C after crystallizing from ether.

25 C) 2-((2R)-2-Carbamoylthiazolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline.

30 4.3 g of the product obtained in Step B) are cyclized in 90 ml of MeOH at RT in the presence of 1 g of DBU. The mixture is concentrated, the residue is taken up in water and DCM, the layers are separated, the organic layer is washed with KHSO₄ and then dried and concentrated. The residue is chromatographed on alumina by eluting with DCM/MeOH (97/3; v/v). The compound is obtained in the cis form (mixture of 2 diastereoisomers): 1.5 g, and then in the trans form (mixture of 2 diastereoisomers): m = 1 g.

35 a) The cis fraction is crystallized from MeOH/DCM in order to obtain cis compound 1.



M.p. = 176°C after crystallizing from isopropyl ether.

$\alpha_D = +57^\circ$ (c = 0.1; chloroform).

b) The crystallization liquors of the preceding product are chromatographed on silica by eluting with AcOEt/DCM (30/70; v/v). The cis compound 2 obtained is recrystallized from ether.

M.p. = 205°C

$\alpha_D = -185^\circ$ (c = 0.3; chloroform).

c) The trans fraction (mixture of 2 diastereoisomers) is recrystallized from isopropyl ether.

M.p. = 170°C

EXAMPLES 84, 85, 86 and 86a

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-[(2S)-2-(N,N-dimethylthiocarbamoyl)pyrrolidinocarbonyl]indoline, cis isomerism (2 compounds), (trans isomerism: 2 compounds).

A) (L)-(N'-Boc)-N,N-Dimethylprolinethioamide.

This compound is prepared according to J. Med. Chem., 1989, 2178.

2.36 g of (N'-Boc)-N,N-dimethylprolinamide are heated in anhydrous toluene under argon at 80°C for 4 hours in the presence of 2.3 g of Lawesson's reagent. After 24 hours, the solvent is evaporated and isopropanol is added. The precipitate formed is separated, the isopropanol is evaporated and the residue is chromatographed on silica by eluting with hexane/AcOEt (30/70; v/v). The product obtained is recrystallized while cold from DCM/isopropyl ether (30/70 ; v/v).

M.p. = 62°C

B) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((2S)-2-(N',N'-dimethylthiocarbamoyl)pyrrolidinocarbonylmethyl)]aminobenzophenone.

3 g of the product prepared in the preceding step are dissolved in 10 ml of DCM and treated at 0°C for 2 hours with 10 ml of TFA. The mixture is evaporated to dryness, then 20 ml of DCM and 6.1 g of the acid prepared in Example 10-11, Step A) are added at 0°C and the



mixture is neutralized with 3 g of DIPEA. 5.15 g of BOP are dissolved in 30 ml of DCM and this solution is added to the preceding solution at 0°C over 30 minutes; the pH is maintained at neutral by the addition of DIPEA and the mixture is left stirring for 3 hours at 0°C. After one night at RT, the mixture is extracted in the usual way and then chromatographed on silica by eluting with DCM/AcOEt (85/15; v/v). The product obtained is recrystallized from isopropyl ether.

M.p. = 182-185°C

$\alpha_D = -72^\circ$ (c = 0.32; chloroform).

C) 5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-sulfonyl)-3-hydroxy-2-[(2S)-2-(N,N-dimethylthiocarbamoyl)pyrrolidinocarbonyl]indoline (cis isomerism : 2 compounds, and trans isomerism: 2 compounds).

3.8 g of the compound obtained in the preceding step are dissolved in 15 ml of DCM and the mixture is heated at reflux for 36 hours in the presence of 850 mg of DBU. The different isomers formed are separated by successive chromatographic runs on silica.

a) Using DCM/AcOEt (85/15; v/v), the expected compound is eluted first in the form of a mixture of 2 cis diastereoisomers. The least soluble diastereoisomer is crystallized 2 times from a DCM/isopropyl ether/methanol mixture and is then recrystallized from the minimum amount of DMF at 60°C followed by addition of 2 volumes of ethanol.

M.p. = 270°C

$\alpha_D = -278^\circ$ (c = 1; chloroform).

b) The crystallization liquors of the preceding mixture are taken up in and the second cis diastereoisomer crystallizes from a DCM/isopropyl ether mixture.

M.p. = 249-251°C

$\alpha_D = +42^\circ$ (c = 0.22; chloroform).

c) The chromatography fractions eluted last, as well as the crystallization mother liquors of fractions a) and b), are combined, and are chromatographed again on silica by eluting with hexane/AcOEt (20/80; v/v). Isolated first



is a fraction which is recrystallized 3 times from a DCM/isopropyl ether mixture and an insoluble material is removed on a paper between each recrystallization. The trans isomer 1 is thus obtained.

5 M.p. = 191-193

$\alpha_D = +74.5^\circ$ (c = 0.2; chloroform).

d) The second fraction contains trans isomer 2 which is recrystallized from a DCM/isopropyl ether mixture and crystallizes with 1/3 mole of isopropyl ether.

10 M.p. = 170°C

$\alpha_D = -266$ (c = 0.14; chloroform).

EXAMPLES 87, 88 and 89

2-((2S)-2-Carbamoylpyrrolidinocarbonyl)-5-chloro-3-cyclohexyl-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-indoline, (cis isomerism: 2 compounds, trans isomerism).

15 A) 5-Chloro-2-[N-(3,4-dimethoxyphenylsulfonyl)amino]-cyclohexylphenone.

A solution of 35.6 g of 2-amino-5-chlorocyclohexylphenone and 39.5 g of 3,4-dimethoxyphenylsulfonyl chloride in 340 ml of pyridine is left stirring for 24 hours at RT. The solvent is evaporated under vacuum and the residue is then washed with water and with an acid solution (0.5 N HCl). The expected product crystallizes from ethanol.

25 M.p. = 135°C

m = 56.1 g.

B) 2-[(N-Benzyloxycarbonylmethyl-N-(3,4-dimethoxyphenylsulfonyl))amino]-5-chlorocyclohexylphenone.

3.2 g of sodium hydride are added in portions to 52.6 g of the compound prepared in the preceding step in 520 ml of DMF and the mixture is left stirring for 1 hour at RT. After cooling in the ice bath, 21 ml of benzyloxycarbonylmethyl bromide are added dropwise and the mixture is left stirring for 24 hours at RT. The solvent is evaporated under vacuum and the residue is taken up in water. It is extracted with DCM and the extract is washed with water; the product obtained is used as it is in the following step.



C) N-(5-Chloro-2-(cyclohexylcarbonyl)phenyl)-N-(3,4-dimethoxyphenylsulfonyl)glycine.

The compound obtained in the preceding step is placed with 3.9 g of 5% palladium on charcoal in 700 ml of acetic acid under hydrogen (1 atmosphere). At the end of the reaction, the palladium is filtered on Celite® and rinsed with hot acetic acid; the solvent is evaporated under vacuum and the residue is taken up in water. It is extracted with DCM and the extract is washed with water and then with a concentrated NaHCO₃ solution. The residue obtained is chromatographed on silica by eluting with a DCM/MeOH (97/3; v/v) mixture. The expected product crystallizes from ethanol.

M.p. = 160°C

15 m = 22.4 g.

D) 5-Chloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((2S)-2-carbamoylpyrrolidinocarbonylmethyl)]-aminocyclohexylphenone.

A mixture containing 9.92 g of the acid prepared in the preceding step, 3 g of (L)-prolinamide hydrochloride and 3.5 ml of DIPEA in 75 ml of DCM is cooled to 0°C. 8.84 g of BOP in solution in DCM are added and the pH is maintained at 7 by addition of DIPEA. The mixture is left stirring for 24 hours at RT. The mixture is extracted with DCM, and the extract washed with a saturated NaHCO₃ solution, a saline solution, a 5% KHSO₄ solution and again with a saline solution. The product is chromatographed on silica by eluting with a DCM/MeOH (96/4; v/v) mixture. The expected product solidifies in isopropyl ether.

30 M.p. = 110°C

m = 7.3 g

$\alpha_D = -53.9^\circ$ (c = 1; chloroform)

E) 2-((2S)-2-Carbamoylpyrrolidinocarbonyl)-5-chloro-3-cyclohexyl-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-indoline, cis isomerism (2 compounds), trans isomerism.

5.9 g of the compound prepared in the preceding step and 1.67 g of DBU are placed in 60 ml of methanol with stirring at 0°C for 48 hours. The solvent is evaporated



under vacuum, water is added, the mixture is extracted with DCM and the extract is then washed with a 5% KHSO₄ solution. The product is chromatographed on alumina by eluting with DCM/MeOH (98/2; v/v).

5 a) The least polar fraction contains the 2 cis isomers. This fraction is recrystallized from methanol. The first compound thus obtained (cis 1) is pure by HPLC. M.p. = 185°C.

By recrystallization of the mother liquors from
10 MeOH, a second compound is obtained (cis 2). HPLC purity: 75% (it contains 25% cis 1). M.p. = 132°C.

b) The most polar fraction contains the trans isomer in the form of an apparently single compound which is
15 obtained by recrystallizing from methanol. M.p. = 240°C

$\alpha_D = -55.1^\circ$ (c = 1; chloroform).

EXAMPLE 89a

2-((2S)-2-Carbamoylpyrrolidinocarbonyl)-5-chloro-3-
20 cyclohexyl-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomerism (2 compounds), trans isomerism.

By using a procedure similar to that described for Examples 87, 88 and 89, an analogous compound in the (D)-proline series is prepared.

25 The compound obtained after crystallizing from a DCM/MeOH mixture has the trans configuration.

M.p. = 238°C

$\alpha_D = +164^\circ$ (c = 0.245; chloroform/methanol, 8.2, v/v).

The NMR spectrum of this compound and of that
30 described in Step E b) of the preceding example are identical.

EXAMPLE 90

5-Chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-2-[(2S)-2-(N-methylaminocarbonyl)pyrrolidinocarbonyl]-3-hydroxyindoline, cis isomer.
35

920 mg of the compound prepared in Example 28 are placed, with stirring, in 20 ml of DCM containing 371 mg of BOP for 15 minutes, a stream of monomethylamine is



- 64 -

bubbled through for 10 minutes and the stirring is maintained for an additional 30 minutes. The mixture is taken up in water, the layers separated, the organic layer washed with potassium hydrogensulfate and with sodium carbonate, dried and concentrated. The residue is chromatographed on silica by eluting with DCM/methanol (97.5/2.5; v/v). The expected product is collected which crystallizes from an isopropyl ether/DCM mixture.

m = 750 mg

10 M.p. = 158°C

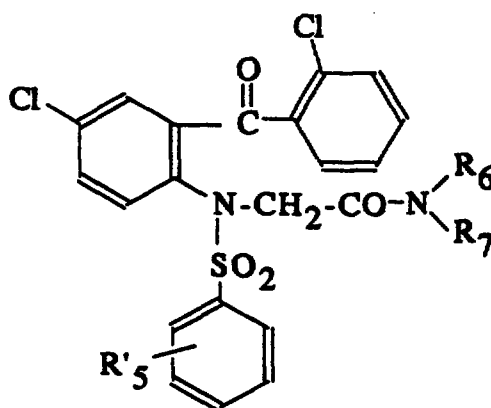
$\alpha_D = -216^\circ$ (c = 0.3; chloroform).

By operating as in the previously described examples (Examples 27 to 31 and 90) and by using derivatives of (L)-proline (except when otherwise indicated), other intermediate compounds (VI) for the synthesis of the compounds (I) according to the invention were prepared.

The compounds (VI) prepared are described in Table 3 below.

20 The Compounds (I) prepared are described in Table 4 below.

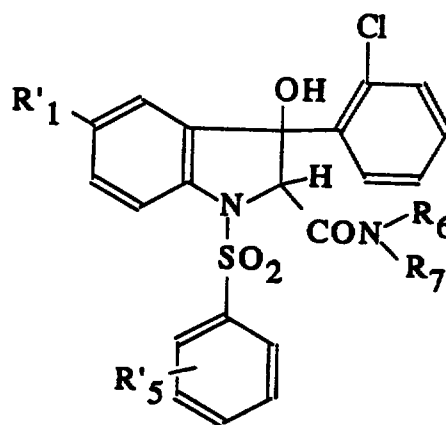
Table 3





	R'_5	$\begin{array}{c} \text{---} N \text{---} R_6 \\ \text{---} R_7 \end{array}$	M.p. ($^{\circ}C$)	α_D^{25} (chloroform)
5	3,4- CH_3O	(D) $\begin{array}{c} \text{---} N \text{---} \\ H \text{---} \\ \vdots \\ CONH_2 \end{array}$		+45 $c = 1.015$
10	3,4- CH_3O	$\begin{array}{c} \text{---} N \text{---} \\ H \text{---} \\ \vdots \\ COOCH_3 \end{array}$	161-163 DCM/isopropyl ether	-70.8 $c = 0.48$
	2,4- CH_3O	$\begin{array}{c} \text{---} N \text{---} \\ H \text{---} \\ \vdots \\ COOCH_3 \end{array}$	145-148	-17.5 $c = 3.36$
15	3,4- CH_3O	$\begin{array}{c} \text{---} N \text{---} \\ H \text{---} \\ \vdots \\ COOCH_2 \text{---} \text{C}_6\text{H}_5 \end{array}$	≈ 110 DCM/isopropyl ether	
	3,4- CH_3O	$\begin{array}{c} \text{---} N \text{---} \\ H \text{---} \\ \vdots \\ CH_2COOCH_3 \end{array}$	148 isopropyl ether/MeOH	

Table 4



	Example	R'_1	R'_5	$\begin{array}{c} \text{---} N \text{---} R_6 \\ \text{---} R_7 \end{array}$	M.p. ($^{\circ}C$)	α_D^{25} (chloroform)
25	91 cis 1	Cl	3,4- CH_3O	(D) $\begin{array}{c} \text{---} N \text{---} \\ H \text{---} \\ \vdots \\ CONH_2 \end{array}$	115 MeOH	+ 188 $c = 0.33$
	92 cis 2	Cl			204 MeOH/DMF	-114* $c = 0.31$



5	93 cis	Cl	3,4-CH ₃ O		198-201 DCM/isopropyl ether	
	94 cis	Cl	2,4-CH ₃ O		205-207 DCM/isopropyl ether	
10	95 cis	Cl	2,4-CH ₃ O		221 DCM/isopropyl ether	-242 c = 0.254
15	96 cis	Cl	3,4-CH ₃ O			-234 c = 0.32
	97 cis	Cl	3,4-CH ₃ O			-214 c = 0.32
20	98 cis 1	Cl	3,4-CH ₃ O		105-115 DCM/isopropyl ether	+174.6 c = 0.3
	99 cis 2				175 DCM/isopropyl ether	-214.6 c = 0.3
25	100 trans 1					-155 c = 0.2
	101 trans 2				177 DCM/isopropyl ether	+95.2 c = 0.2
30	102 cis 1	Cl	3,4-CH ₃ O		135 isopropyl ether	-162



5

10

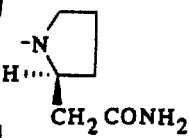
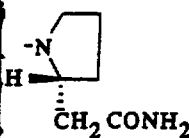
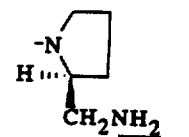
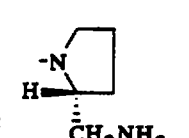
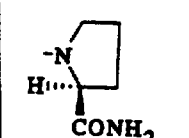
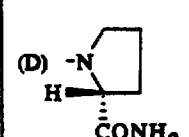
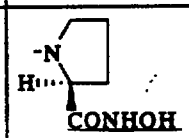
15

20

25

30

35

103 cis 1	Cl	3,4-CH ₃ O		145 DCM/isopropyl ether	-167 c = 0.4
103a cis 1 cis 2	Cl	3,4-CH ₃ O			
104 cis 1	Cl	3,4-CH ₃ O		210 ether	-177.5 c = 0.2
104a cis 1 cis 2	Cl	3,4-CH ₃ O			
105	CH ₃ O	3,4-CH ₃ O		200 EtOH	-195 c = 0.2
106				215 MeOH	+127 c = 0.2
107	CH ₃ O	3,4-CH ₃ O		198	-63.3 c = 0.117 (CHCl ₃ /MeOH 8/2;v/v)
108	Cl	2,4-CH ₃ O		274 DCM/MeOH	-225 c = 0.372 (CHCl ₃ /MeOH 8/2;v/v)
108a cis	Cl	3,4-CH ₃ O			-198.7 c = 0.24



*: Example 92: Other measured optical rotation:

$\alpha_D^{25} = -39.5$ ($c = 0.17$; $\text{CHCl}_3/\text{MeOH}$: 8/2:v/v).

The compound of Example 107 is the enantiomer of that of Example 106.

5 The compound of Example 108a was prepared from the compound of Example 28 by reacting with hydroxylamine hydrochloride in DMF and by activating with the reagent BOP in the presence of DIPEA.

10 Some compounds according to the invention, described in Table 4 above, are useful for the preparation of other compounds. Thus, the compound of Example 99 makes it possible to obtain the compound of Example 101, then that of Example 103 and finally that of Example 104.

EXAMPLE 109

15 2-((2S,4S)-4-Azido-2-(methoxycarbonyl)pyrrolidino-carbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer.

A) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidino-carbonylmethyl)]amino-benzophenone.

20 15 g of the acid prepared in Example 10-11, Step A) and 6.25 g of methyl (2S,4R)-4-hydroxyprolinate hydrochloride are heated to 0°C in 150 ml of DCM in the presence of 7.4 g of DIPEA. A solution of 12.7 g of BOP
25 in 30 ml of DCM is added dropwise over 30 minutes and the amount of DIPEA necessary to neutralize the solution is added. After one night at RT, the mixture is extracted in the usual way and chromatographed on silica by elution with a DCM/AcOEt (60/40; v/v) mixture. The expected
30 product crystallizes from a DCM/ether/isopropyl ether mixture.

M.p. = 128-131°C

$\alpha_D = +8.5^\circ$ ($c = 0.38$; chloroform).

B) 2',5-Dichloro-2-[N-(3,4-dimethoxyphenylsulfonyl)-N-((2S,4R)-4-mesyloxy-2-(methoxycarbonyl)pyrrolidino-carbonylmethyl)]aminobenzophenone.

2 g of the compound obtained in the preceding step are dissolved at 0°C in 10 ml of DCM. 550 mg of



triethylamine and then 550 mg of methanesulfonyl chloride are added and the mixture is left at 0°C for 20 hours. Water is added and the organic layer is washed with 0.5 N hydrochloric water, with water and then with a sodium bicarbonate solution, dried over magnesium sulfate and evaporated. The oil obtained is used as it is in the following step.

5 C) 2-[N-((2S,4S)-4-azido-2-(methoxycarbonyl)pyrrolidinocarbonylmethyl)-N-(3,4-dimethoxyphenylsulfonyl)]amino-
10 2',5-dichlorobenzophenone.

11 g of the product prepared in the preceding step are heated in 60 ml of DMSO at 80-90°C in the presence of 2.7 g of sodium azide for 18 hours. The mixture is poured into water, extracted with ethyl acetate, the organic layer washed with water, dried and chromatographed on silica by eluting with a pentane/AcOEt (50/50; v/v) mixture. An oil (10 g) is obtained.

$\alpha_D = -25.5$ ($c = 0.39$; chloroform, $T = 26^\circ\text{C}$).

D) 2-((2S,4S)-4-Azido-2-(methoxycarbonyl)pyrrolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer.

3.38 g of the product obtained in the preceding step are cyclized under the usual conditions in the presence of DBU. The expected product is obtained which is recrystallized from DCM/isopropyl ether.

$m = 755$ mg

M.p. 200-202°C

$\alpha_D = -176^\circ$ ($c = 0.21$; chloroform, $T = 26^\circ\text{C}$).

EXAMPLE 110

30 2-[(2S,4S)-4-(N-Benzyloxycarbonyl-N-methyl)amino-2-(methoxycarbonyl)pyrrolidinocarbonyl]-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer.

A) Methyl ester of (N-Boc)-4-hydroxyproline.

35 The starting material is the hydrochloride of the methyl ester of (2S,4R)-4-hydroxyproline.

19 g of this compound are suspended in 100 ml of THF, 22.9 g of (Boc)₂O are added and then the mixture is



cooled to 0°C. 21.2 g of triethylamine in 25 ml of THF are added dropwise and then the mixture is stirred for 12 hours at 0°C and 4 hours at 60°C. Water is added, the mixture is extracted with ethyl acetate, the organic layer is washed with water, with a potassium hydrogen-sulfate solution (4 times), with water and then with saline water. The solvent is evaporated and an oil (21.6 g) is isolated which contains a small amount of (Boc)₂O.

10 B) Methyl ester of (2S,4R)-(N-Boc)-4-mesyloxyproline.

A solution of 22.9 g of the product prepared in the preceding step in 250 ml of DCM is cooled to 0°C. 22.9 g of mesyl chloride in 10 ml of DCM are added dropwise, then 9.4 g of triethylamine in 100 ml of DCM are added dropwise and the mixture is left to return to RT overnight. The mixture is evaporated to dryness, water is added, the mixture is extracted with AcOEt, the organic layer is washed with water and saline water and dried over magnesium sulfate. After a second evaporation, an oil is obtained which is used as it is in the following step.

C) Methyl ester of (2S,4S)-(N-Boc)-4-azidoproline.

This compound is prepared from that obtained in Step B. 15.2 g of the methyl ester of (N-Boc)-4-mesyloxy-2-hydroxyproline are dissolved in 70 ml of DMSO and the solution is heated at 90°C for 5 hours in the presence of 3.05 g of sodium azide. The mixture is cooled, water is added, the mixture is extracted with AcOEt, the organic layer is washed with water and saline water and dried over MgSO₄. The oil obtained is purified by chromatography on silica by eluting with the AcOEt/hexane (40/60; v/v) mixture.

$$\alpha_D = -37.8^\circ (c = 3; \text{chloroform})$$

lit. $\alpha_D = -36.6^\circ (c = 2.8; \text{chloroform})$ D.J. Abraham et al., J. Med. Chem., 1983, 549, 26.

D) Methyl ester of (2S,4S)-(N-Boc)-4-aminoproline.

8.45 g of the compound obtained in Step A are dissolved in 100 ml of methanol, 500 mg of 10% Pd/C are



added and the mixture is hydrogenated at 40°C for 18 hours. The catalyst is filtered off, half the methanol is evaporated, 100 ml of 0.5 N HCl are added, the remainder of the methanol is then evaporated and the unreacted starting material is extracted with AcOEt. The aqueous phase is treated with sodium carbonate and the fraction containing the expected product (m = 4.35 g) is extracted with AcOEt.

E) Methyl ester of (2S,4S)-(N-Boc)-4-(N'-benzyloxy-carbonylamino)proline.

The crude product obtained in the preceding step is dissolved in 15 ml of ether and 15 ml of DCM at 0°C. 2.3 g of DIPEA and then 3.03 g of benzyl chloroformate in 5 ml of DCM are added, over 70 minutes at 0°C. After 3 hours, the solvents are evaporated at RT under vacuum; water and ethyl acetate are added and the organic phase is washed successively with a potassium hydrogensulfate solution (3 times), with water (3 times), with a sodium carbonate solution (3 times), with water (3 times) and with saline water. The product is chromatographed on silica by eluting with hexane/AcOEt (40/60; v/v) mixture in order to obtain the expected product.

$$\alpha_D = -16.4 \text{ (c = 0.3; chloroform).}$$

F) Methyl ester of (2S,4S)-(N-Boc)-4-(N'-benzyloxy-carbonyl-N'-methyl)aminoproline.

2 g of the compound obtained in the preceding step are dissolved in 20 ml of DMF at 0°C, under argon, in the presence of 2.25 g of methyl iodide. 170 mg of 80% sodium hydride are added in portions and then the mixture is stirred at 0°C for 90 minutes. The mixture is extracted with water and ethyl acetate; the organic phase is washed with water and then saline water. The product is chromatographed on silica by eluting with a hexane/AcOEt (50/50; v/v) mixture. 1.55 g of the expected product is obtained.

$$\alpha_D = -38.8 \text{ (c = 0.38; chloroform).}$$



G) 2',5-Dichloro-2-[(2S,4S)-N-(3,4-dimethoxyphenylsulfonyl)-N-(4-(N'-benzyloxycarbonyl-N'-methyl)amino-2-(methoxycarbonyl)pyrrolidinocarbonylmethyl)]-amino-benzophenone.

5 This product is obtained by the usual methods.

$\alpha_D = -22.4$ ($c = 0.37$; chloroform).

H) 2-[(2S,4S)-4-(N-Benzyloxycarbonyl-N-methyl)amino-2-(methoxycarbonyl)pyrrolidinocarbonyl]-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-indoline, cis isomer.

10

This product is obtained by cyclizing in the presence of DBU according to the usual methods. The crystals formed are crystallized from DCM/isopropyl ether.

15

M.p. = 129°C

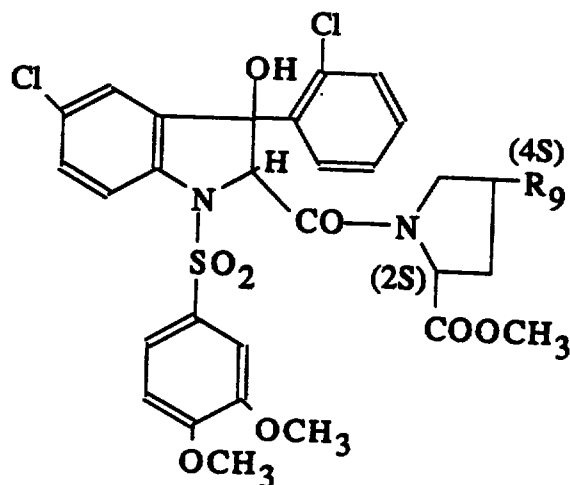
$\alpha_D = -129$ ($c = 0.321$; chloroform).

The isomeric purity by HPLC is 99%.

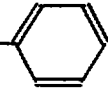
The compounds prepared in Examples 109 and 110 are used to prepare the compounds according to the invention described in Table 5 below:

20

Table 5

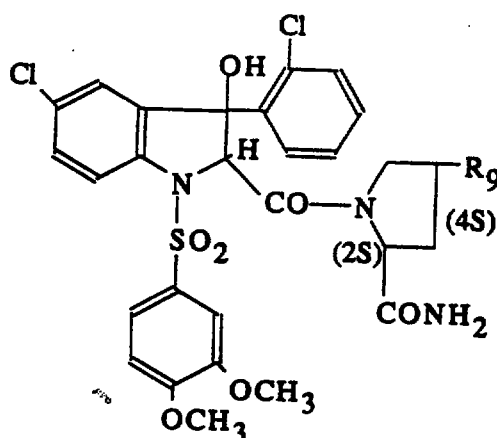




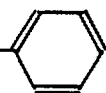
Example	R ₉	α _D (chloroform)
111 cis	-NH ₂	-189.6 c = 0.4
112 cis	-NHCOOCH ₂ - 	-174 c = 0.24
113 cis	-NHCH ₃	-152.6 c = 0.28
114 cis	-N(CH ₃) ₂	-191 c = 0.19

The compound of Example 112 makes it possible to successively prepare the compounds of Examples 115 and 116 described in Table 6 below and the compound of Example 114 makes it possible to prepare the compound of Example 116a.

Table 6





Example	R ₉	$\alpha_D(\text{chloroform})$
5 115 cis	$-\text{NHCOOCH}_2$ 	-151 c = 0.27
116 cis	$-\text{NH}_2$	-161.4 c = 0.26
10 116a cis	$-\text{N}(\text{CH}_3)_2$	

The compound of Example 116a can be prepared either by conversion of the compound of Example 114, or from (2S,4S)-(N-Boc)-4-(dimethylamino)prolinamide, the preparation of which is carried out as follows:

1) Methyl (2S,4S)-(N-Boc)-4-aminoprolinate is prepared from methyl (2S,4S)-4-azidoprolinate according to T.R. Webl in J. Org. Chem., 1991, 56, 3009.

2) Methyl (2S,4S)-(N-Boc)-4-(dimethylamino)-prolinate.

4 g of the compound prepared in 1) are dissolved in 50 ml of acetonitrile, 12.8 ml of 30% formalin are added and then, over 5 minutes, 3 g of sodium cyanoborohydride. After the reactants have been in contact for 2 hours, acetic acid is added to bring the solution to a pH of 6. After 3 hours, the acetonitrile is evaporated, water, potassium carbonate and solid sodium chloride are added and the mixture is extracted with 4 volumes of ethyl acetate. The organic phase is evaporated, the residue is dissolved in 1 N hydrochloric acid and extraction is carried out with AcOEt. Solid sodium carbonate and then solid sodium chloride are added to the aqueous phase and extraction is carried out with AcOEt. After evaporating, the residue is chromatographed on silica gel by eluting with a DCM/MeOH (95/5; v/v) mixture and an oil which solidifies is isolated.

m = 2.1 g

IR (DCM): 1755 cm^{-1} , 1695 cm^{-1} .



3) 534 mg of the ester prepared in 2) are dissolved in 4 ml of MeOH and are treated with sodium hydroxide (116 mg) in 1 ml of water for 48 hours at RT. The mixture is acidified with 0.5 N hydrochloric acid to a pH of 3.5 and is evaporated to dryness. An azeotropic drying of the residue is carried out in the presence of benzene (5 times) and then the residue is dried under vacuum for 8 hours. 2 ml of DMF and 3 ml of DCM are then added and the mixture is cooled to 0°C. 865 mg of BOP, and DIPEA, are added to bring the reaction mixture to neutrality. After 15 minutes, a stream of gaseous ammonia is bubbled through 2 times for 30 minutes. After 2 hours at RT, the DCM is evaporated, carbonated water and sodium chloride are added and the mixture is extracted with 4 volumes of AcOEt. After evaporating, the residue is chromatographed on silica. The mixture (DCM/MeOH/NH₄OH; 84.5/15/0.5; v/v/v) elutes a solid (m = 185mg) which is recrystallized from a DCM/isopropyl ether mixture.

M.p. = 183-186°C.

$\alpha_D^{25} = -63.1^\circ$ (c = 0.24; chloroform).

EXAMPLE 117

Decarboxylation of N-(2-carboxyethyl)-N-ethyl-3-(2-chlorophenyl)-5-chloro-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxy-2-indolinecarboxamide, cis isomerism.

630 mg of the compound prepared in Example 41 are placed in solution in 20 ml of THF under an argon atmosphere and then 101 mg of N-methylmorpholine at -15°C and 118 mg of isobutyl chloroformate are added. After stirring for 5 minutes, 127 mg of N-hydroxy-2-pyridinethione and 101 mg of TFA are added, the mixture is held at -15°C with stirring for 15 minutes, 900 mg of tert-butylmercaptan are then added and the mixture is left to return to RT. The reaction mixture is then irradiated for 1 hour 30 with a tungsten filament lamp (150 watts). The mixture is concentrated, taken up in water, extracted with DCM and the extract dried and concentrated. The residue is chromatographed on silica by eluting with DCM/AcOEt (95/5; v/v). The expected product



is obtained.

m = 300 mg

M.p. = 215°C.

This compound is similar to that of Example 125 described in the European Patent Application EP 469984. It has the cis configuration around the 2,3 bond of the indoline as in the starting material.

EXAMPLE 118

Decarboxylation of 2-((2R)-2-(carboxymethyl)pyrrolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer.

The operation is carried out as in the preceding example from the compound described in Example 102.

The product obtained is recrystallized from a DCM/isopropyl ether mixture.

M.p. = 215-220°C

$\alpha_D = -214.5^\circ$ (c = 0.2; chloroform).

This compound is 2-((2S)-2-methylpyrrolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomerism.

EXAMPLE 119

Decarboxylation of 2-(2-carboxypyrrolidinocarbonyl)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer.

The operation is carried out as in the preceding example by using the compound prepared in Example 28 as the starting material. The product obtained is recrystallized from an isopropyl ether/DCM mixture.

M.p. = 263°C

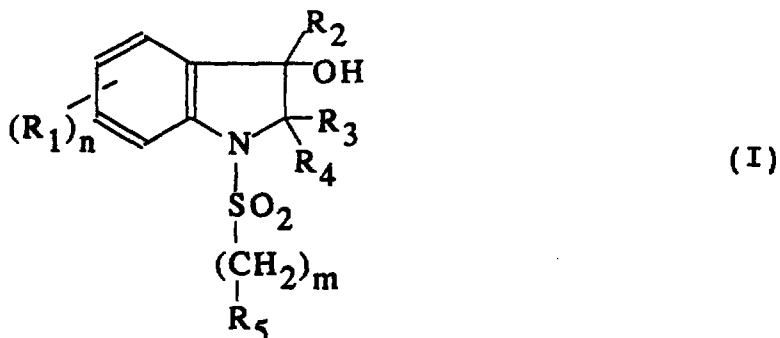
$\alpha_D = -201.5^\circ$ (c = 0.2; chloroform).

This compound is 2-pyrrolidinocarbonyl-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulfonyl)-3-hydroxyindoline, cis isomer.



WHAT IS CLAIMED IS:

1. A compound of formula:



in which

- 5 - R_1 is a halogen atom, a C_1 - C_4 alkyl, a hydroxyl, a C_1 - C_4 alkoxy, a benzyloxy group, a cyano group, a trifluoromethyl group, nitro group or an amino group;
- 10 - R_2 is a C_1 - C_6 alkyl, a C_3 - C_7 cycloalkyl, a C_5 - C_7 cycloalkene or a phenyl which is unsubstituted or monosubstituted or polysubstituted by a C_1 - C_4 alkyl, a C_1 - C_4 alkoxy, a halogen, a trifluoromethyl group or an amino group, or R_2 is a nitrophenyl which is unsubstituted or monosubstituted by a trifluoromethyl group or monosubstituted or polysubstituted by a C_1 - C_4 alkyl or a halogen;
- 15 - R_3 is a hydrogen atom;
- R_4 is a carbamoyl group of formula $CONR_6R_7$;
- 20 - R_5 is a C_1 - C_4 alkyl; a 1-naphthyl; a 2-naphthyl; a 5-dimethylamino-1-naphthyl; a phenyl which is unsubstituted or substituted by one or more substituents selected from a halogen atom, a C_1 - C_4 alkyl, a trifluoromethyl group, an amino group which is free or substituted by one or two C_1 - C_4 alkyls, a hydroxyl, a C_1 - C_4 alkoxy, a C_2 - C_4 alkenoxy, a C_1 - C_4 alkylthio, a trifluoromethoxy group, a benzyloxy group, a cyano group, a carboxyl group, a C_1 - C_4 alkoxy carbonyl group, a carbamoyl group which is free or substituted by one or two C_1 - C_4 alkyls or a
- 25 C_1 - C_4 alkylamido group, or R_5 is a nitrophenyl which is unsubstituted or monosubstituted by a trifluoro-
- 30



methyl group or a C₂-C₄ alkenoxy or mono- or poly-substituted by a halogen, a C₁-C₄ alkyl, a C₁-C₄ alkoxy, a C₁-C₄ alkythio, a trifluoromethoxy group or a benzyloxy group;

- 5 - R₆ is a C₁-C₆ alkyl or R₆ is similar to R₇;
 - R₇ is a 4-piperidyl group or a 3-azetidiny group, the said groups being substituted or unsubstituted on the nitrogen by a C₁-C₄ alkyl, by a benzyloxy-carbonyl or by a C₁-C₄ alkoxy-carbonyl; a group (CH₂)_r
10 which is itself substituted by a 2-, 3- or 4-pyridyl group, by a hydroxyl group or by an amino group which is free or substituted by one or two C₁-C₄ alkyls, a carboxyl group, a C₁-C₄ alkoxy-carbonyl group, a benzyloxy-carbonyl group or a carbamoyl
15 group which is free or substituted by one or 2 C₁-C₄ alkyls;
 - or R₆ and R₇ together, with the nitrogen atom to which they are connected, form a heterocycle selected from:
20 . morpholine,
 . thiomorpholine,
 . thiazolidine or 2,2-dimethylthiazolidine, unsubstituted or substituted by R₈,
 . piperazine, unsubstituted or substituted at the
25 4-position by a group R"₈,
 . an unsaturated, 5-membered ring containing a single nitrogen atom and substituted by R₈ or a saturated, 3-, 4-, 5-, 6- or 7-membered ring containing a single nitrogen atom and substituted
30 by R₈ and R₉;
 - R₈ is R'₈ or a group (CH₂)_r which is itself substituted by a hydroxyl or by an amino which is free or substituted by one or two C₁-C₄ alkyls;
 - R'₈ is a group (CH₂)_q which is itself substituted by
35 a carboxyl group, a C₁-C₄ alkoxy-carbonyl group, a benzyloxy-carbonyl group, a carbamoyl group which is free or substituted by a hydroxyl or by one or 2 C₁-C₄ alkyls or an aminocarbothioyl group which is





- free or substituted by one or 2 C_1-C_4 alkyls;
- R''_8 is R'_8 or a group $(CH_2)_2NH_2$ which is free or substituted by one or two C_1-C_4 alkyls;
 - R_9 is hydrogen, a halogen, a group $(CH_2)_rOR_{10}$, a group $(CH_2)_rNR_{11}R_{12}$, a group $(CH_2)_sCONR_{11}R'_{11}$ or an azido group;
 - R_{10} is hydrogen, a C_1-C_4 alkyl, a mesyl or a tosyl;
 - R_{11} , R'_{11} and R_{12} are each a hydrogen or a C_1-C_4 alkyl or R_{11} is hydrogen and R_{12} is a benzyloxycarbonyl or a C_1-C_4 alkoxy carbonyl;
 - n is 0, 1 or 2;
 - m is 0, 1 or 2;
 - q is 0, 1, 2 or 3 ;
 - r is 0, 1, 2 or 3, with the limitation that r is not zero when R_8 or R_9 is at the alpha-position of the intracyclic amide nitrogen;
 - s is 0 or 1;
- as well as its possible salts.
2. A compound as claimed in claim 1 in which R_1 is a chlorine or bromine atom or a methoxy group and $n = 0$.
3. A compound as claimed in either of claims 1 and 2 in which R_2 is a chlorophenyl or a methoxyphenyl or a cyclohexyl.
4. A compound as claimed in any one of claims 1 to 3 in which R_3 is a phenyl substituted at the 3- and 4-positions or at the 2- and 4-positions by a methoxy group, or else R_3 is a phenyl substituted at the 4-position by a methyl.
5. A compound as claimed in any one of claims 1 to 4 in which $m = 0$.
6. A compound as claimed in any one of claims 1 to 5 in which R_4 is $CONR_6R_7$ and NR_6R_7 is a pyrrolidino group

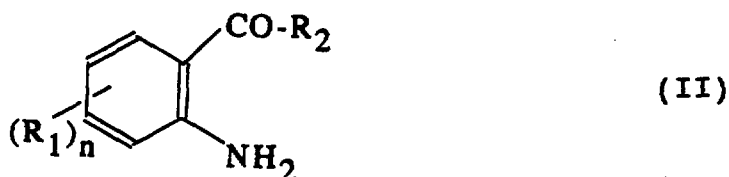




substituted at the 2-position by a group $(CH_2)_q$ which is itself substituted by a carboxyl group, or a carbamoyl group with $q = 0, 1, 2$ or 3 .

- 5 7. A compound as claimed in one of claims 1 to 5 in which R_4 is $CONR_6R_7$ and NR_6R_7 is a piperidino group substituted at the 4-position by an amino group, a C_1-C_4 alkylamino or a C_1-C_4 dialkylamino.
- 10 8. A compound as claimed in any one of claims 1 to 5 in which R_4 is $CONR_6R_7$ and NR_6R_7 is a thiazolidino group substituted by a group $(CH_2)_q$ which is itself substituted by a carboxyl group or a carbamoyl group with $q = 0, 1, 2$ or 3 .
- 15 9. A compound as claimed in any one of claims 1 to 5 in which R_4 is $CONR_6R_7$ and NR_6R_7 is a pyrrolidino group substituted at the 2-position by a group $(CH_2)_q$ which is itself substituted by a carboxyl group or a carbamoyl group and substituted at the 4-position by an amino group, a C_1-C_4 alkylamino or a C_1-C_4 dialkylamino.
- 20 10. A compound as claimed in any one of claims 1 to 5 in which R_4 is $CONR_6R_7$, R_6 being a C_1-C_4 alkyl and R_7 being a group $(CH_2)_r$ which is itself substituted by a carboxyl group or a carbamoyl group with $r = 1, 2$ or 3 .
- 25 11. A compound as claimed in any one of claims 1 to 10 in the form of a cis isomer in which R_2 and R_4 are on the same side of the indoline ring.
- 30 12. A process for preparing a compound (I) as claimed in claim 1, characterized in that it comprises :
a) reacting a 2-aminophenone derivative of formula:





in which R_1 , R_2 and n have the meanings indicated above for I, with a sulfonyl derivative of formula:



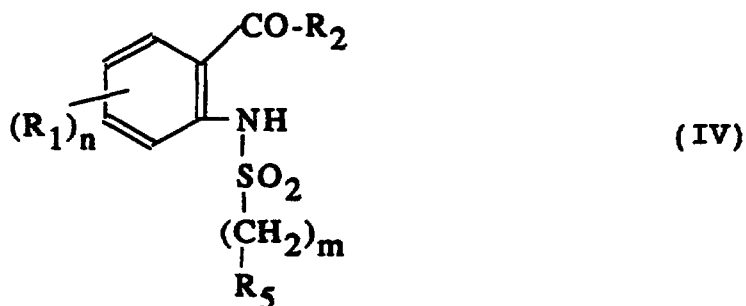
5

in which

- Hal is a halogen, preferably chlorine or bromine,
- m and R_5 have the meanings indicated above for (I) in claim 1;

b) treating the resulting compound of formula:

10



with a halogenated derivative of formula:

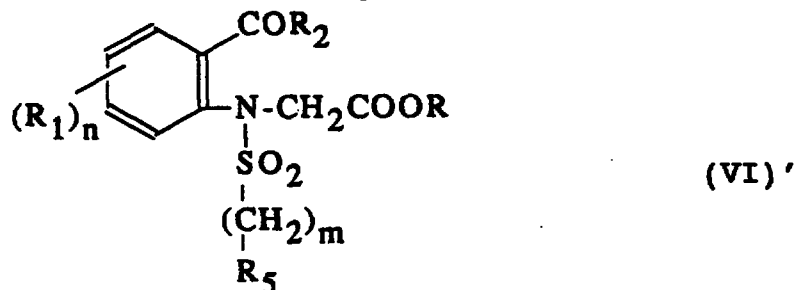


in which

15

Hal' is a halogen, preferably bromine, and A represents either the group NR_6R_7 or the group OR in which R is a tert-butyl or a benzyl;

c) deprotecting the resulting ester of formula:

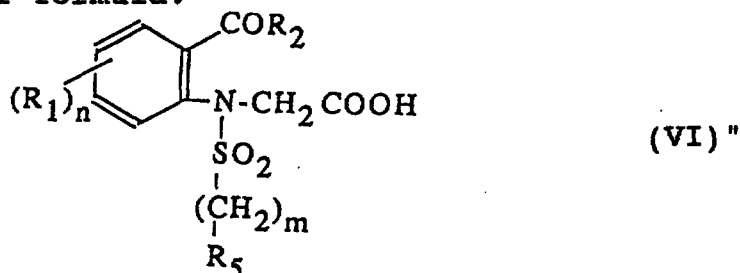


20

under suitable conditions, if applicable, when A is OR;

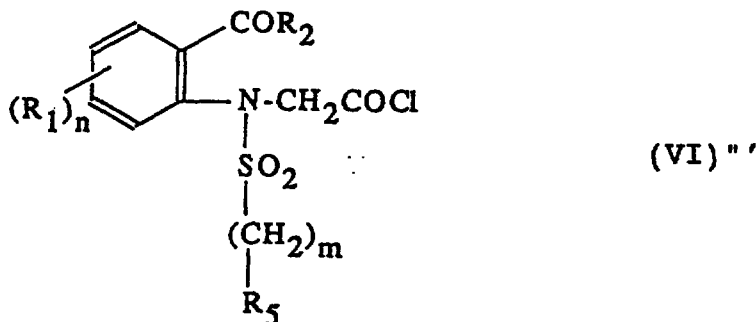


- d) treating, if applicable, the resulting acid from Step c) of formula:



5

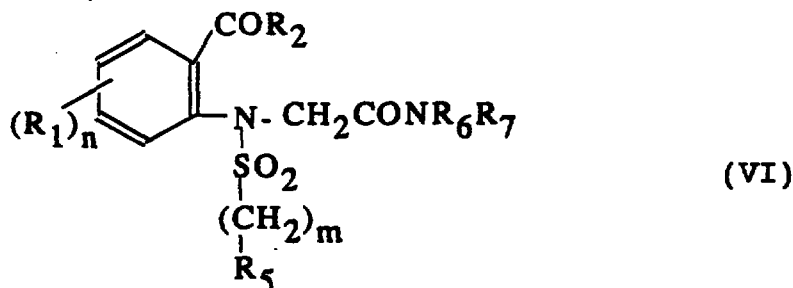
or its acid chloride of formula:



10

with a compound HNR_6R_7 , according to suitable amide coupling techniques;

- e) cyclizing the resulting compound from Step b) or from Step d) of formula:

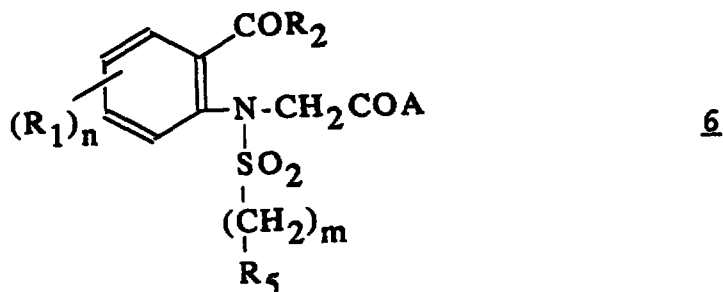


15

in a basic medium in order to prepare the compound (I) as claimed in claim 1;

- f) separating, if appropriate, the cis and trans isomers of the compound (I) and, if appropriate, separating the enantiomers.

13. A compound of formula:





in which

A' is a group selected from: NR_6R_7 , OH, OtBu, OBz;

- 5 - R_1 is a halogen atom, a $\text{C}_1\text{-C}_4$ alkyl, a hydroxyl, a $\text{C}_1\text{-C}_4$ alkoxy, a benzyloxy group, a cyano group, a trifluoromethyl group, a nitro group or an amino group;
- 10 - R_2 is a $\text{C}_1\text{-C}_6$ alkyl, a $\text{C}_3\text{-C}_7$ cycloalkyl, a $\text{C}_5\text{-C}_7$ cycloalkene or a phenyl which is unsubstituted or monosubstituted or polysubstituted by $\text{C}_1\text{-C}_4$ alkyl, a $\text{C}_1\text{-C}_4$ alkoxy, a halogen, a trifluoromethyl group or an amino group, or R_2 is a nitrophenyl which is unsubstituted or monosubstituted by a trifluoromethyl group or monosubstituted or polysubstituted by a $\text{C}_1\text{-C}_4$ alkyl, a $\text{C}_1\text{-C}_4$ alkoxy or a halogen;
- 15 - R_3 is a $\text{C}_1\text{-C}_4$ alkyl; a 1-naphthyl; a 2-naphthyl; a 5-dimethylamino-1-naphthyl; a phenyl which is unsubstituted or substituted by one or more substituents selected from a halogen atom, a $\text{C}_1\text{-C}_4$ alkyl, a trifluoromethyl group, an amino group which is free or substituted by one or two $\text{C}_1\text{-C}_4$ alkyls, a hydroxyl, a $\text{C}_1\text{-C}_4$ alkoxy, a $\text{C}_2\text{-C}_4$ alkenoxy, a $\text{C}_1\text{-C}_4$ alkylthio, a trifluoromethoxy group, a benzyloxy group, a cyano group, a carboxyl group, a $\text{C}_1\text{-C}_4$ alkoxycarbonyl group, a carbamoyl group which is free or substituted by one or two $\text{C}_1\text{-C}_4$ alkyls or a $\text{C}_1\text{-C}_4$ alkylamido group, or R_3 is a nitrophenyl which is unsubstituted or monosubstituted by a trifluoromethyl group or a $\text{C}_2\text{-C}_4$ alkenoxy or mono- or polysubstituted by a halogen, a $\text{C}_1\text{-C}_4$ alkyl, a $\text{C}_1\text{-C}_4$ alkoxy, a $\text{C}_1\text{-C}_4$ alkylthio, a trifluoromethoxy group or a benzyloxy group;
- 20 - R_6 is a $\text{C}_1\text{-C}_6$ alkyl or R_6 is similar to R_7 ;
- 25 - R_7 is a 4-piperidyl group or a 3-azetidiny group, the said groups being substituted or unsubstituted on the nitrogen by a $\text{C}_1\text{-C}_4$ alkyl, by a benzyloxy-carbonyl or by a $\text{C}_1\text{-C}_4$ alkoxycarbonyl; a group $(\text{CH}_2)_x$ which is itself substituted by a 2-, 3- or 4-pyridyl group, by a hydroxyl group or by an amino group
- 30
- 35



- which is free or substituted by one or two C_1-C_4 alkyls, a carboxyl group, a C_1-C_4 alkoxy carbonyl group, a benzyloxy carbonyl group or a carbamoyl group which is free or substituted by one or 2 C_1-C_4 alkyls;
- 5 or R_6 and R_7 together, with the nitrogen atom to which they are connected, form a heterocycle selected from:
- morpholine,
 - 10 • thiomorpholine,
 - thiazolidine or 2,2-dimethylthiazolidine, unsubstituted or substituted by R_8 ,
 - piperazine, unsubstituted or substituted at the 4-position by a group R''_8 ,
 - 15 • an unsaturated, 5-membered ring containing a single nitrogen atom and substituted by R_8 or
 - a saturated, 3-, 4-, 5-, 6- or 7-membered ring containing a single nitrogen atom and substituted by R_8 and R_9 ;
 - 20 - R_8 is R'_8 or a group $(CH_2)_r$ which is itself substituted by a hydroxyl or by an amino which is free or substituted by one or two C_1-C_4 alkyls;
 - R'_8 is a group $(CH_2)_q$ which is itself substituted by a carboxyl group, a C_1-C_4 alkoxy carbonyl group, a benzyloxy carbonyl group, a carbamoyl group which is
 - 25 free or substituted by a hydroxyl or by one or 2 C_1-C_4 alkyls or an aminocarbothioyl group which is free or substituted by one or 2 C_1-C_4 alkyls;
 - R''_8 is R'_8 or a group $(CH_2)_2NH_2$ which is free or
 - 30 substituted by one or two C_1-C_4 alkyls;
 - R_9 is hydrogen, a halogen, a group $(CH_2)_rOR_{10}$, a group $(CH_2)_rNR_{11}R_{12}$, a group $(CH_2)_rCONR_{11}R'_{11}$ or an azido group;
 - R_{10} is hydrogen, a C_1-C_4 alkyl, a mesyl or a tosyl;
 - 35 - R_{11} , R'_{11} and R_{12} are each a hydrogen or a C_1-C_4 alkyl or R_{11} is hydrogen and R_{12} is a benzyloxy carbonyl or a C_1-C_4 alkoxy carbonyl;
 - n is 0, 1 or 2;

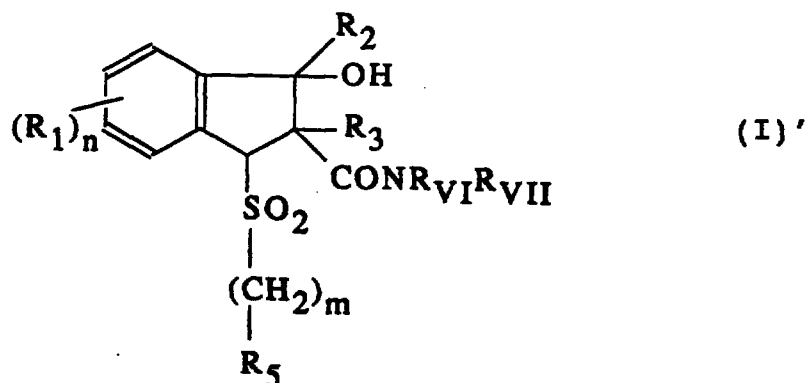




- m is 0, 1 or 2;
- q is 0, 1, 2 or 3 ;
- r is 0, 1, 2 or 3, with the limitation that r is not zero when R₈ or R₉ is at the alpha-position of the intracyclic amide nitrogen;
- s is 0 or 1.

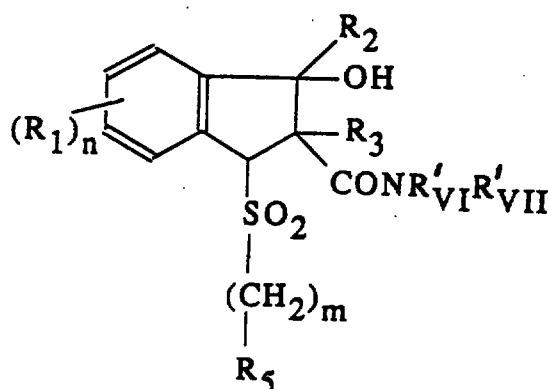
5

14. The use of a compound of formula:



- 10 in which R₁, R₂, R₃, R₅, m and n have the meanings given for (I) in claim 1 and
- R_{VI} is a C₁-C₆ alkyl,
 - R_{VII} is a group (CH₂)_rCOOH with r = 1, 2 or 3,
 - or R_{VI} and R_{VII} together, with the nitrogen atom to
- 15 which they are connected, constitute a heterocycle selected from :
- . thiazolidine or 2,2-dimethylthiazolidine, substituted by a (CH₂)_qCOOH group,
 - . piperazine substituted at the 4-position by a
- 20 (CH₂)_qCOOH group,
- . an unsaturated, 5-membered ring containing a single nitrogen atom and substituted by a (CH₂)_qCOOH group or a saturated, 3-, 4-, 5-, 6- or 7-membered ring containing a single nitrogen atom and substituted by
- 25 a (CH₂)_qCOOH group,
- with q = 0, 1, 2 or 3
- for the preparation of a compound of formula (I)" having the same configuration around the 2,3 bond of the indoline as the starting material





(I) "

5

in which

- R_1 , R_2 , R_3 , R_5 , m and n are as defined above,
- R'_{VI} is a C_1-C_6 alkyl,
- R'_{VII} is a group $(CH_2)_rH$,
- or R'_{VI} and R'_{VII} together, with the nitrogen atom to which they are connected, constitute a heterocycle selected from :
 - . thiazolidine or 2,2-dimethylthiazolidine, substituted by a $(CH_2)_qH$ group,
 - . piperazine substituted at the 4-position by a $(CH_2)_qH$ group,
 - . an unsaturated, 5-membered ring containing a single nitrogen atom and substituted by a $(CH_2)_qH$ group or a saturated, 3-, 4-, 5-, 6- or 7-membered ring containing a single nitrogen atom and substituted by a $(CH_2)_qH$ group.

25

15. A pharmaceutical composition in which a compound as claimed in one of claims 1 to 10 is present as the active principle.

30

16. A pharmaceutical composition in which a compound as claimed in any one of claims 1 to 10 is present in association with another active principle.

