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(54) Titre : NOUVEAU PROCEDE POUR PREPARER LA (-)-TRANS-N-p-FLUOROBENZOLYLMETHYL-4-(p-FLUOROPHENYL)-3-3,4-(METHYLENEDIOXY)PHENOXY METHYL PIPERIDINE
(54) Title: NEW PROCESS FOR PREPARING (-)-TRANS-N-p-FLUOROBENZOYLMETHYL-4-(p-FLUOROPHENYL)-3-[[3,4-(METHYLENEDIOXY)PHENOXY]METHYL]-PIPERIDINE

(57) **Abrégé/Abstract:**

The process consists in reacting (-)-trans-N-(p-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine acetate with 2-chloro- or 2-bromo-4'-fluoroacetophenone, and the resulting compound can be isolated as a pharmaceutically acceptable addition salt by reaction with the corresponding acid.



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(54) Title: NEW PROCESS FOR PREPARING (-)-TRANS-N-p-FLUOROBENZOYLMETHYL-4-(p-FLUOROPHENYL)-3-[[3,4-(METHYLENEDIOXY)PHENOXY]METHYL]-PIPERIDINE (57) Abstract The process consists in reacting (-)- <i>trans</i> -N-(<i>p</i> -fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine acetate with 2-chloro- or 2-bromo-4'-fluoroacetophenone, and the resulting compound can be isolated as a pharmaceutically acceptable addition salt by reaction with the corresponding acid.		

NEW PROCESS FOR PREPARING (-)-TRANS-N-*p*-FLUOROBENZOYLMETHYL-
4-(*p*-FLUOROPHENYL)-3-[[3,4-(METHYLENEDIOXY)PHENOXY]METHYL]-
PIPERIDINE

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The present invention relates to a new process for preparing
(-)-trans-N-*p*-fluorobenzoylmethyl-4-(*p*-fluorophenyl)-3-[[3,4-
(methylenedioxy)phenoxy]methyl]-piperidine as well as its
10 pharmaceutically acceptable addition salts.

WO 95/25732 describes the aforesaid compound and its
hydrochloride, which is the preferred salt for its
therapeutic use. These compounds inhibit 5-hydroxytryptamine
15 reuptake and are surprisingly less toxic than analogous
compounds commonly used in therapeutics. Consequently, they
are potentially useful in the treatment of depression.

In WO 95/25732 the compound (-)-trans-N-*p*-fluorobenzoyl-
20 methyl-4-(*p*-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]
methyl]-piperidine is prepared by reacting (-)-trans-4-(*p*-
fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-
piperidine hydrochloride with 2-chloro- or 2-bromo-4'-
fluoroacetophenone in an anhydrous alcohol medium, such as
25 that constituted by methanol or ethanol, and in the presence
of a mineral base, such as alkali metal carbonates or
bicarbonates, that facilitates the uptake reaction of the
formed hydracid.

Under these conditions, the reaction product must be separated from the decomposition products by column chromatography, which involves a considerably prolonged operating time as well as a decreased yield that hardly reaches 60%. In addition, the reaction by-products are difficult to remove and their presence has negative repercussions on the samples obtained.

Applicants have surprisingly found out that if instead of starting from (-)-trans-4-(p-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine hydrochloride salt the corresponding acetate is used, the solvent ratio can be decreased due to a higher solubility of the acetate in organic solvents. Furthermore, purification of the reaction product by column chromatography is unnecessary, and the resulting product can be directly isolated as a pharmaceutically acceptable addition salt, e.g. as hydrochloride. This provides a significantly higher yield and enhances the purity of the final product. These factors become determinant in the industrial production and constitute the main advantages of the new process disclosed in the present invention.

Thus, the present invention relates to a process for preparing (-)-trans-N-p-fluorobenzoylmethyl-4-(p-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine, as well as pharmaceutically acceptable addition salts thereof, which
5 comprises reacting (-)-trans-(p-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine acetate with 2-chloro (or bromo)-4'-fluoroacetophenone, preferably 2-chloro-4'-fluoroacetophenone, in an alcohol having 1 to 4 carbon atoms and in the presence of a base at an elevated temperature of the
10 mixture, and if desired, converting the resulting compound to a pharmaceutically acceptable addition salt by reaction with the corresponding acid.

Among solvents suitable to carry out the above alkylation
15 reaction, alkanols are preferred. Advantageously employed are those alkanols having one to four carbon atoms, such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol or 2-methylpropan-1-ol. Especially preferred are methanol and/or ethanol. Mixtures of the above solvents can be employed
20 as well.

Among bases suitable according to the present invention, inorganic bases, in particular mineral bases are preferred. Especially alkali metal carbonates and/or bicarbonates are
25 advantageously used to facilitate uptake reaction of the formed hydracid. Especially preferred are sodium carbonate and/or bicarbonate. Mixtures of bases can be employed as well.

It is advisable to perform the reaction at an elevated
30 temperature, preferably at the boiling temperature of the mixture.

According to the present invention the resulting (-)-trans-N-p-fluorobenzoylmethyl-4-(p-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine, i.e. the free base
35 form, can be converted to a pharmaceutically acceptable addition salt. Advantageously, the acid corresponding to the desired addition salt is reacted with said free base. Among the

pharmaceutically acceptable salts, the hydrochloride is preferred. Therefore, hydrochloric acid is preferably employed in the process according to the present invention.

- 5 According to the present process either the free base or a pharmaceutically acceptable addition salt thereof can be isolated. Preferably, a salt is isolated which can be conveniently achieved by its simple precipitation from the reaction mixture. Optionally, the resulting product may be
10 crystallized from a suitable solvent or solvent mixture, such as acetonitrile/diethyl ether.

The following example serves to illustrate the present invention without limiting it.

EXAMPLE 1: (-)-trans-N-p-fluorobenzoylmethyl-4-(p-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine hydrochloride

5 88.3 g (0.22 mole) of (-)-trans-(p-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine acetate (European Patent 223403) were dissolved in 700 ml of 96° ethanol. Then 70.2 g of sodium bicarbonate (0.836 mole) and 49.4 g of 2-chloro-4'-fluoroacetophenone (0.286 mole) were added. The
10 mixture was refluxed for 90 minutes. After cooling, the inorganic salts were filtered and the solid was washed with small volumes of 96° ethanol. The liquid phase was evaporated to dryness. The resin obtained was dissolved in 500 ml of diethyl ether, the solid formed was filtered and the liquid
15 was carefully poured, under vigorous stirring, onto a mixture containing 800 ml of 4M hydrochloric acid and 1.1 l of diethyl ether. The mixture was stirred for 1 hour. The resultant solid was washed with 800 ml of distilled water and crystallized from acetonitrile:diethyl ether (1:5, v/v). 95.3
20 g (yield: 88%) of crystalline solid were obtained as needles corresponding to (-)-trans-N-p-fluorobenzoyl-methyl-4-(p-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine hydrochloride. 99.7 % purity was determined by HPLC.

[α]_D at 0.5% (ethanol): -54°. IR (KBr) and ¹H-NMR (DMSO)
25 spectra, elemental analysis and melting point were in agreement with those of the sample obtained in the Example 1 of international Application WO 95/25732. The increase in the [α]_D value was due to the enhanced purity of the present sample.

CLAIMS

1. A process for preparing (-)-*trans*-N-*p*-fluoro-benzoylmethyl-4-(*p*- fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine, as well as pharmaceutically acceptable addition salts thereof, which comprises reacting (-)-*trans*-(*p*-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine acetate with 2-chloro- or 2-bromo-4'-fluoroacetophenone in an alkanol having one to four carbon
10 atoms and in the presence of a base at an elevated temperature, and, if desired, converting the resulting compound to a pharmaceutically acceptable addition salt by reaction with the corresponding acid.
2. A process as claimed in claim 1, wherein said 2-chloro- or 2-bromo-4'-fluoroacetophenone is 2-chloro-4'-fluoroacetophenone.
3. A process as claimed in claim 1 or claim 2, wherein the alkanol having one to four carbon atoms is methanol or ethanol.
- 20 4. A process as claimed in any one of claims 1 to 3, wherein the corresponding acid is hydrochloric acid.
5. A process as claimed in any one of claims 1 to 4, wherein (-)-*trans*-N-*p*-fluoro-benzoylmethyl-4-(*p*-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]-piperidine is isolated as a pharmaceutically acceptable salt.
6. A process as claimed in claim 5, wherein the pharmaceutically acceptable salt is the hydrochloride salt.

7. A process as claimed in any one of claims 1 to 6, wherein the base is a mineral base.

8. A process as claimed in claim 7, wherein the mineral base is an alkali metal carbonate or bicarbonate.

9. A process as claimed in any one of claims 1 to 8, wherein the reaction is carried out at the boiling temperature of the mixture.