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CA 2378087 C 2007/12/18

(11)(21) 2 378 087

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2000/07/13
(87) Date publication PCT/PCT Publication Date: 2001/01/25
(45) Date de délivrance/Issue Date: 2007/12/18
(85) Entrée phase nationale/National Entry: 2002/01/02
(86) N° demande PCT/PCT Application No.: HU 2000/000078
(87) N° publication PCT/PCT Publication No.: 2001/005791
(30) Priorité/Priority: 1999/07/15 (HUP 9902376)

(51) Cl.Int./Int.Cl. *C07D 209/96* (2006.01)

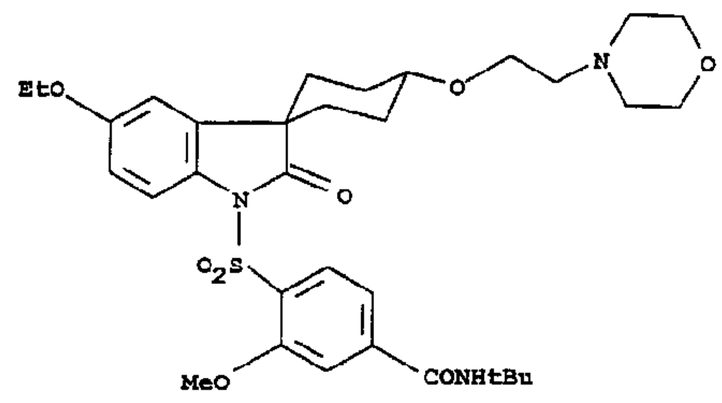
(72) Inventeurs/Inventors:
HEJA, GERGELY, HU;
CSIKOS, EVA, HU;
EROSNE TAKACSY, TUNDE POSA, HU;
GONCZI, CSABA, HU;
HALASZ, JUDIT, HU;
HERMECZ, ISTVAN, HU;
MAJLATH, CSILLA, HU;
...

(73) Propriétaire/Owner:
SANOFI-AVENTIS, FR

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : NOUVELLE TECHNIQUE DE PREPARATION DE N-(1,1-DIMETHYLETHYL)-4-[[5'-ETHOXY-4-CIS-[2-(4-MORFOLINO)ETHOXY]-2'-OXOSPIRO[CYCLOHEXAN-1,3'-[H]INDOL]-1'(2'H)-YL]-SULFONYL]-3-METHOXYBENZAMIDE ET SES SELS

(54) Title: NEW PROCESS FOR THE PREPARATION OF N-(1,1-DIMETHYLETHYL)-4-[[5'-ETHOXY-4-CIS-[2-(4-MORFOLINO)ETHOXY]-2'-OXOSPIRO[CYCLOHEXAN-1,3'-[H]INDOL]-1'(2'H)-YL]-SULFONYL]-3-METHOXYBENZAMIDE AND ITS SALTS



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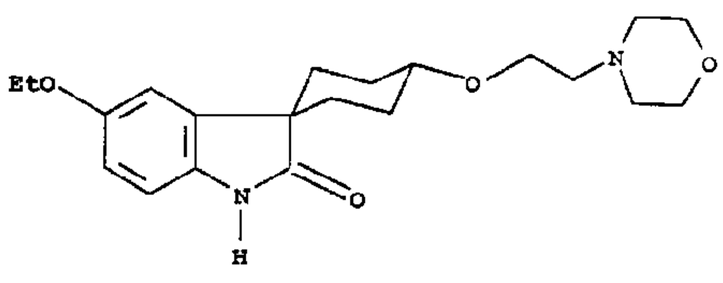

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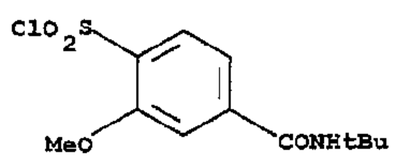

III.

(57) Abrégé/Abstract:
The invention relates to a process for the preparation of a compound of formula (I) and the salts thereof by reacting the compound of formula (II) with the compound of formula (III), which comprises carrying out the reaction in dimethyl sulfoxide, at a temperature

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(72) Inventeurs(suite)/Inventors(continued): NAGY, LAJOS, HU; SANTANE CSUTOR, ANDREA, HU; SAROSI, PETER, HU; SIMON, KALMAN, HU; SZOMOR, TIBORNE, HU; SZVOBODA, GYORGYNE, HU

(57) Abrégé(suite)/Abstract(continued):
between 10 °C and 40 °C, preferably at room temperature and transforming the resulting base of formula (I), if desired, into its salt by a method known per se.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05791 A3

(51) International Patent Classification[7]: C07D 209/96

(21) International Application Number: PCT/HU00/00078

(22) International Filing Date: 13 July 2000 (13.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P 9902376 15 July 1999 (15.07.1999) HU

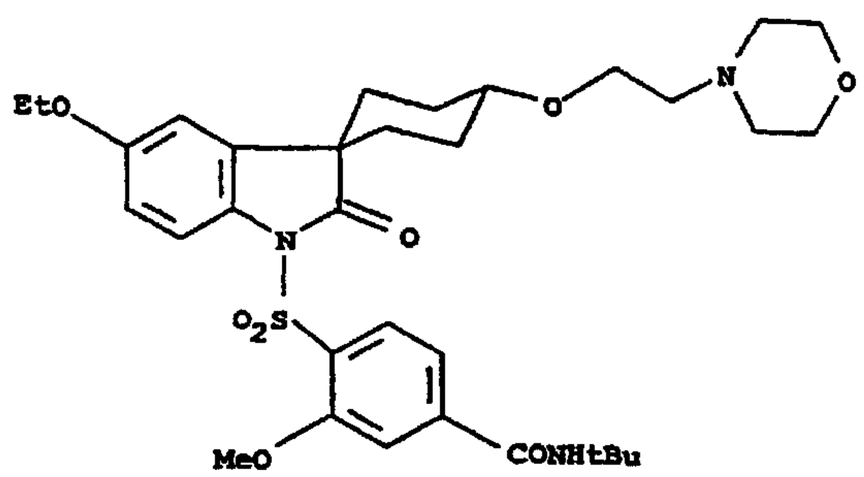
(71) Applicant *(for all designated States except US)*: **SANOFI-SYNTHELABO** [FR/FR]; 174, avenue de France, F-75013 Paris (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HÉJA, Gergely** [HU/HU]; Násznagy u. 27, H-1131 Budapest (HU). **CSIKÓS, Éva** [HU/HU]; Bérctető u. 4, H-1038 Budapest (HU). **ERŐSNÉ TAKÁCSY, Tünde** [HU/HU]; Pósa L. u. 24, H-1149 Budapest (HU). **GÖNCZI, Csaba** [HU/HU]; Lisznyai u. 5, H-1016 Budapest (HU). **HALÁSZ, Judit** [HU/HU]; Erdősor u. 11, H-1046 Budapest (HU). **HERMECZ, István** [HU/HU]; Ráday u. 32, H-1092 Budapest (HU). **MAJLÁTH, Csilla** [HU/HU]; Átlós u. 174, H-1204 Budapest (HU). **NAGY, Lajos** [HU/HU]; Vásárhelyi K. tér 16, H-2000 Szentendre (HU). **SÁNTÁNÉ CSUTOR, Andrea** [HU/HU]; Frankel L. u. 96, H-1023 Budapest (HU). **SÁROSI, Péter** [HU/HU]; Arany J. u. 70, H-1154 Budapest (HU). **SIMON, Kálmán** [HU/HU]; Ördögmalom út 6, H-1118 Budapest (HU). **SZOMOR, Tiborné** [HU/HU]; Attila u. 2, H-1013 Budapest (HU). **SZVOBODA, Györgyné** [HU/HU]; Váczi M. u. 21, H-2120 Dunakeszi (HU).

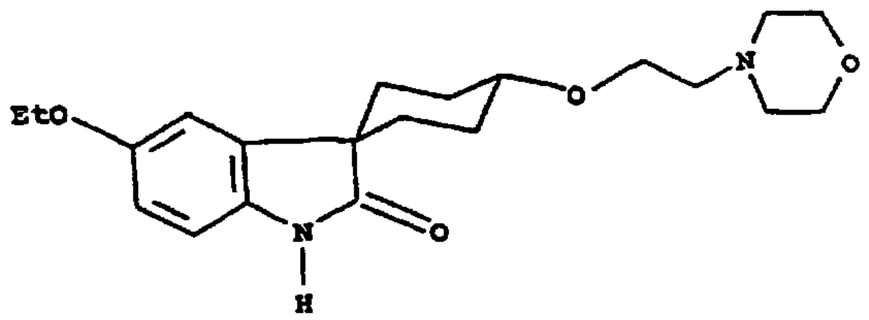
(74) Agents: **MIHÁLYI, György** et al.; Sanofi-Synthelabo, Tó u. 1-5, H-1045 Budapest (HU).

[Continued on next page]

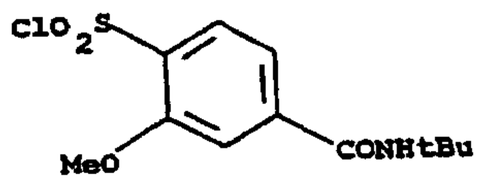
(54) Title: NEW PROCESS FOR THE PREPARATION OF N-(1,1-DIMETHYLETHYL)-4-[[5'-ETHOXY-4-*cis*-[2-(4-MORFOLINO)ETHOXY]-2'-OXOSPIRO[CYCLOHEXAN-1,3'-[*H*]INDOL]-1'(2'*H*)-yl]-SULFONYL]-3-METHOXYBENZAMIDE AND ITS SALTS



(I)



(II)



(III)

(57) Abstract: The invention relates to a process for the preparation of a compound of formula (I) and the salts thereof by reacting the compound of formula (II) with the compound of formula (III), which comprises carrying out the reaction in dimethyl sulfoxide, at a temperature between 10 °C and 40 °C, preferably at room temperature and transforming the resulting base of formula (I), if desired, into its salt by a method known per se.

WO 01/05791 A3

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(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) **Date of publication of the international search report:**
19 July 2001

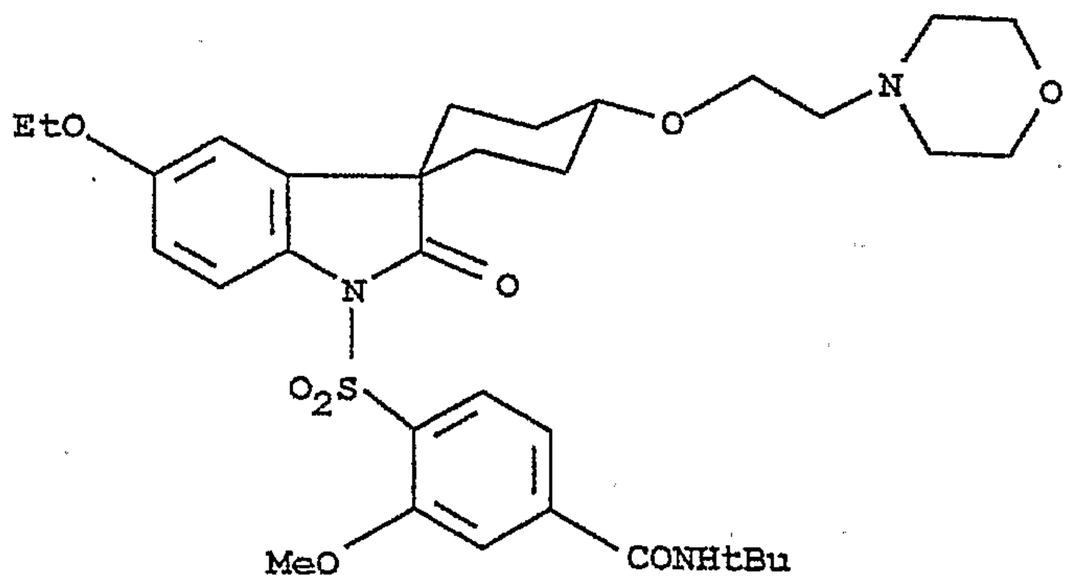
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Enclosure

WO01/05791 **PCT/HU00/00078**

New process for the preparation of N-(1,1-dimethylethyl)-4-[[5'-ethoxy-4-*cis*-[2-(4-morfolino)ethoxy]-2'-oxospiro[cyclohexan-1,3'-[3*H*]indol]-1'(2'*H*)-yl]-sulfonyl]-3-methoxybenzamide and its salts

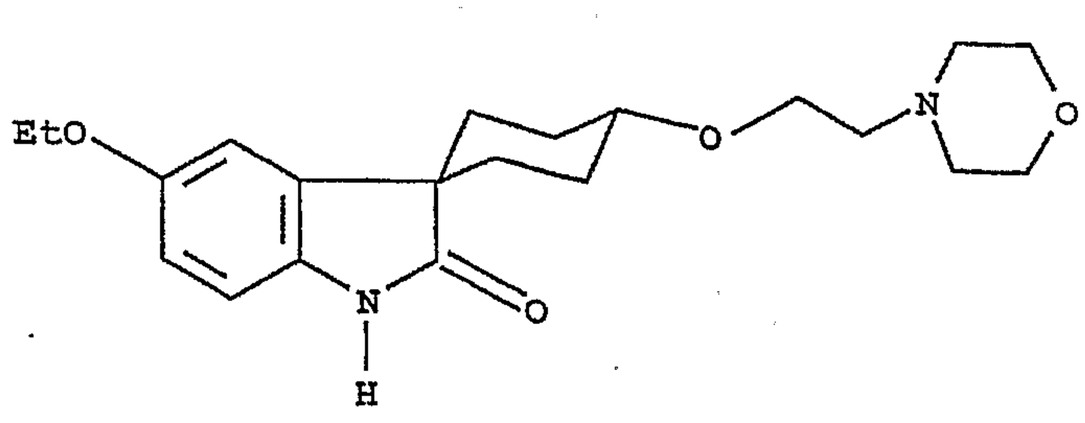
The subject of the present invention is a process for the preparation of N-(1,1-dimethylethyl)-4-[[5'-ethoxy-4-*cis*-[2-(4-morfolino)ethoxy]-2'-oxospiro[cyclohexan-1,3'-[3*H*]indol]-1'(2'*H*)-yl]-sulfonyl]-3-methoxybenzamide (SR 121463) of formula I



I.

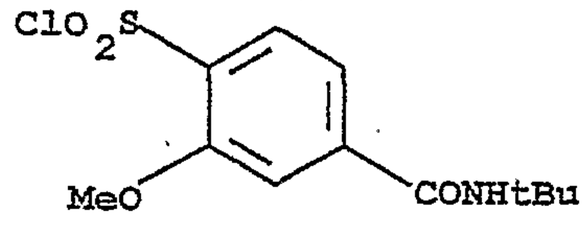
and its salts, compounds having vasopressine V_2 antagonistic effect.

According to patent application WO 9715556 the compound of formula I is prepared by reacting the spiro/cis-4-(beta-morfolino-ethyloxy)cyclohexan-1,3`-(5`-ethoxy)-[3*H*]indol-2`[1`*H*]one of formula II



II.

with the 2-methoxy-4-(N-t-butylaminocarbonyl)benzenesulfonyl chloride of formula III



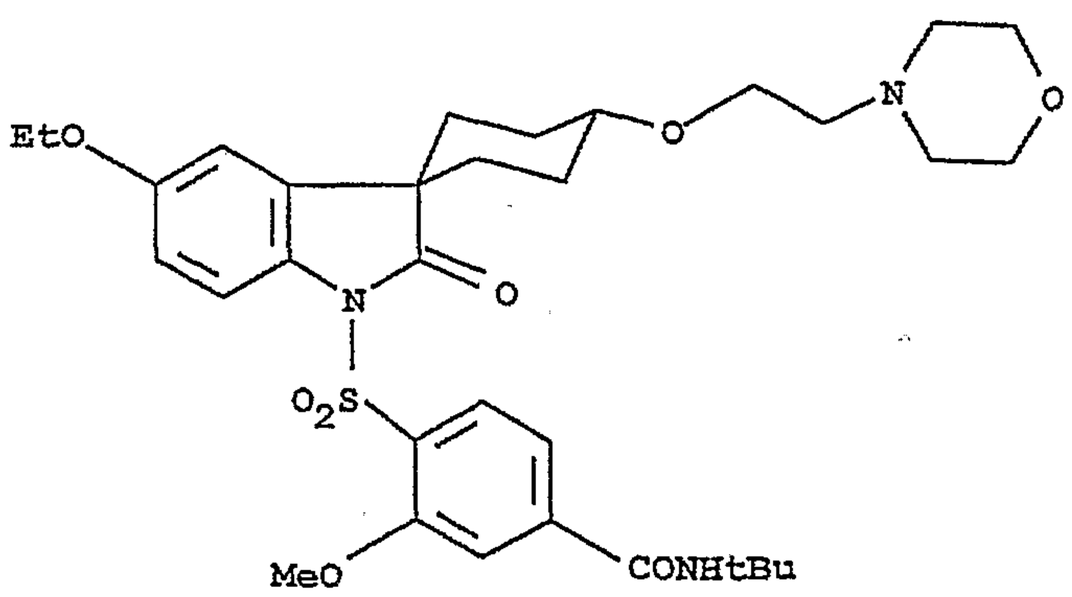
III.

using potassium-*t*-butylate in tetrahydrofurane.

Because of the applied solvent (tetrahydrofurane) and reaction temperature (between -60 °C and 40 °C) it is not easy to carry out the process under industrial conditions, the yield is low, the product is contaminated, its purification requires repeated crystallization.

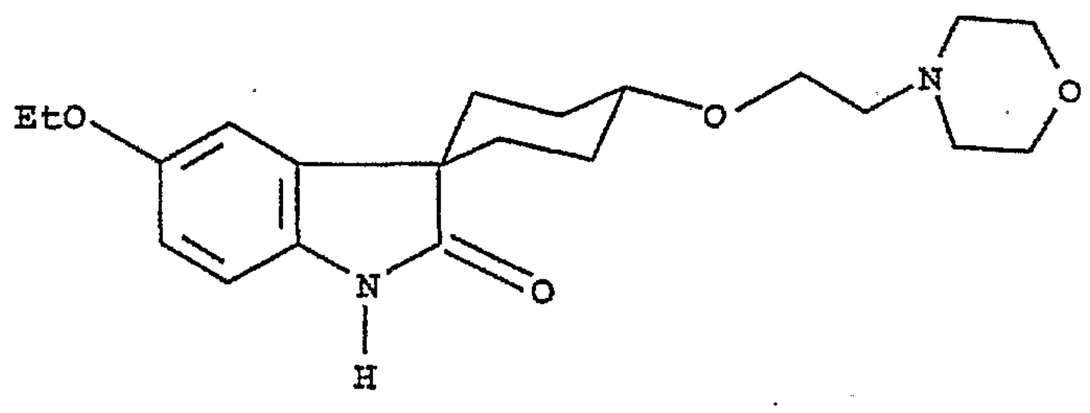
To our surprise, we have found that by stirring in dimethyl sulfoxide at room temperature the reaction proceeds in very good yield (85 - 92%). The work-up procedure is simple, while in the original process the product is obtained by extraction, in the present process the base precipitates on diluting the reaction mixture with water, and it can be filtered off. The purity of the resulting base is 93-96% and the salt formed from it is appropriately pure.

In accordance with the above, the subject of the invention is a process for the preparation of the compound of the formula I



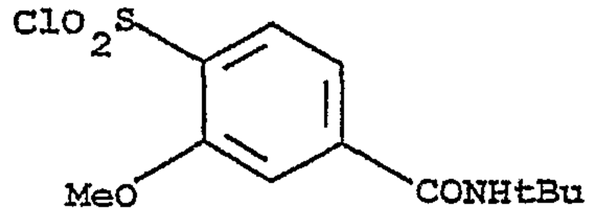
I.

and the salts thereof, by reacting the compounds of the formula II



II.

and III,



III.

which comprises carrying out the reaction in dimethyl sulfoxide at a temperature between 10°C and 40°C, preferably at room temperature and transforming the resulting base of formula I into its salt by a method known per se.

The process according to the invention is illustrated by the following examples:

Example 1.

In 180 ml of dimethyl sulfoxide 26,7 g of potassium *t*-butylate is dissolved. After 10 minutes of stirring 74,9 g of compound II is added to the mixture, at 20 - 25 °C, and the mixture is stirred until complete dissolution. Then rapidly, keeping the temperature below 25 °C, the compound of formula III is added to the mixture. The resulting light-brown suspension is stirred at 25 °C for 1.5 hours, then it is decomposed with 700 ml of ice-water. After 1 hour of stirring the precipitate is filtered off, suspended and washed with 2x500 ml of water, thoroughly sucked and washed with 2x 100 ml of 96 % ethanol. 117 g of compound of formula I is obtained, assay (by HPLC): 95,2 %. Yield: 90,8 %.

Example 2.

1 mol of the base of compound I is suspended in 3-5-fold amount of ethanol and to the mixture 0.5-1 mol of acid is added. After dissolution the solution is clarified by active carbon and filtered. On cooling the salt precipitates, it is filtered off, washed with a small amount of cold ethanol and dried. Yield ranges between 87-95% .

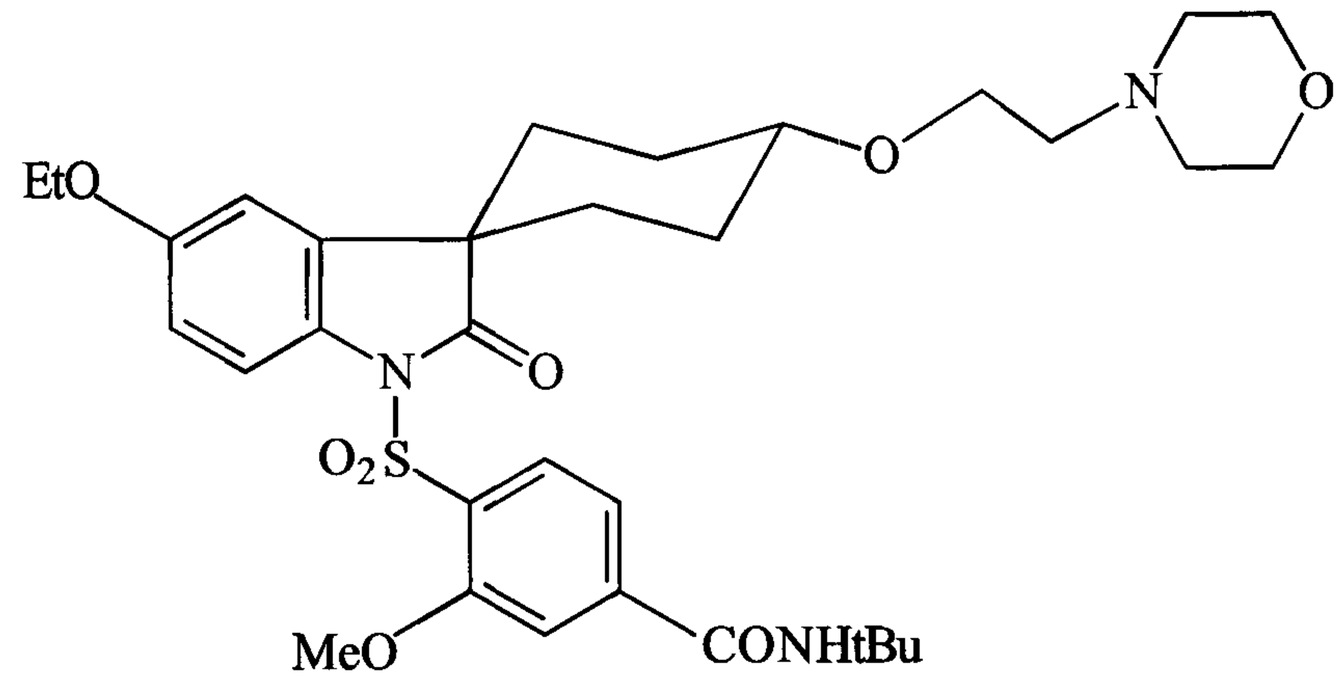
Dihydrogenphosphate monohydrate salt: mp.: 164.5°C

Hydrogen maleate salt: mp.: 184-185°C

Hydrogen fumarate salt: mp.: 182-183°C

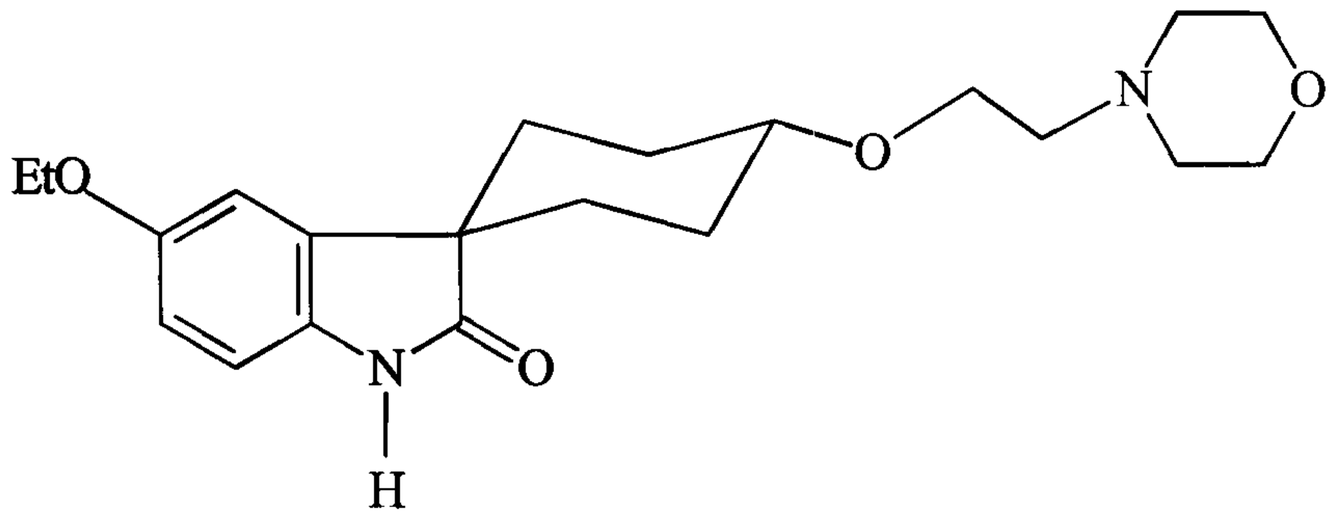
CLAIMS:

1. A process for preparation of a compound of formula I



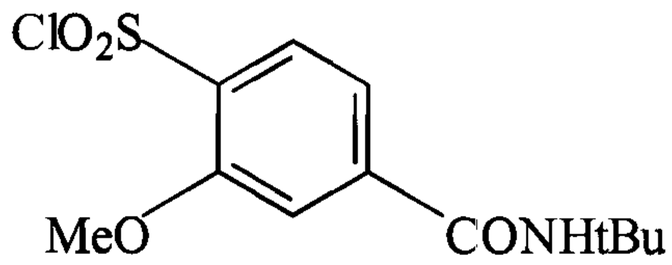
I

or a salt thereof by reacting a compound of formula II



II

with a compound of formula III,



III

in the presence of potassium t-butylate which comprises carrying out the reaction in dimethyl sulfoxide, at a temperature between 10°C and 40°C and optionally

transforming the resulting base of formula I, into the salt thereof.

2. The process of claim 1, wherein the temperature of the reaction is room temperature.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

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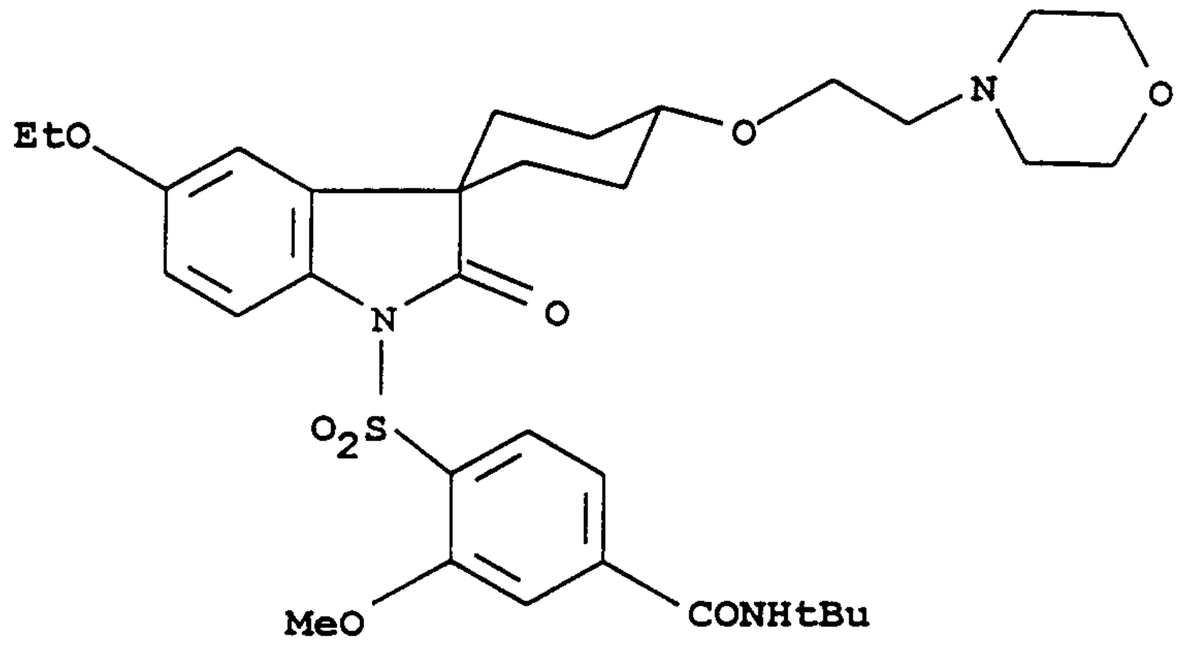
Figure 1



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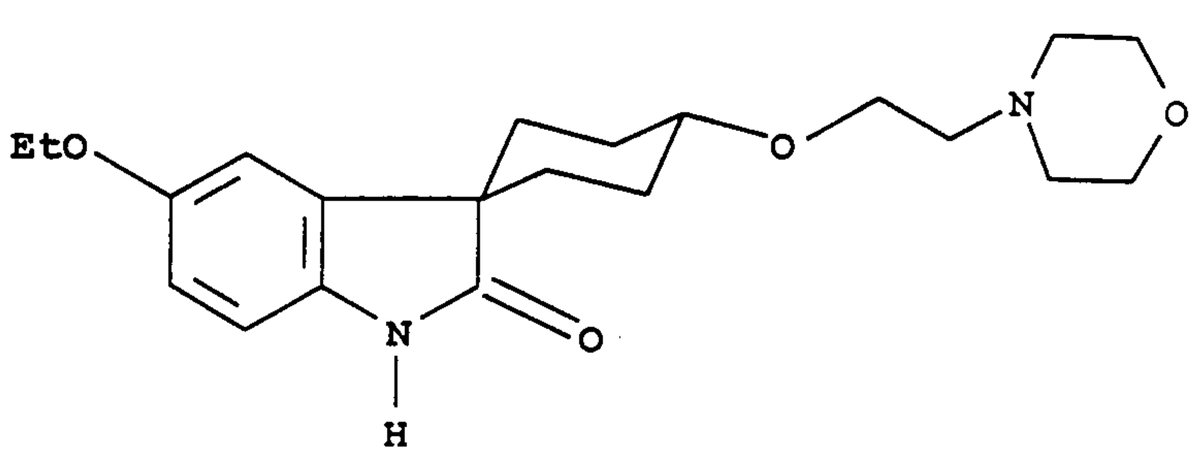

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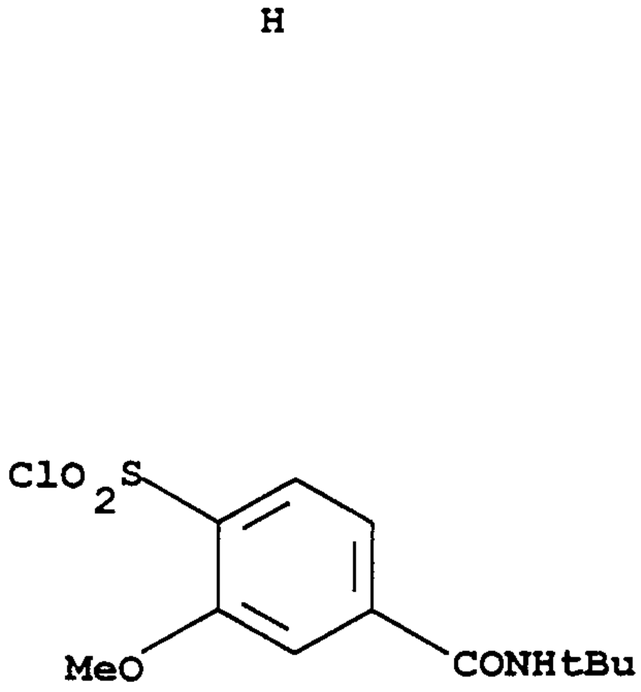

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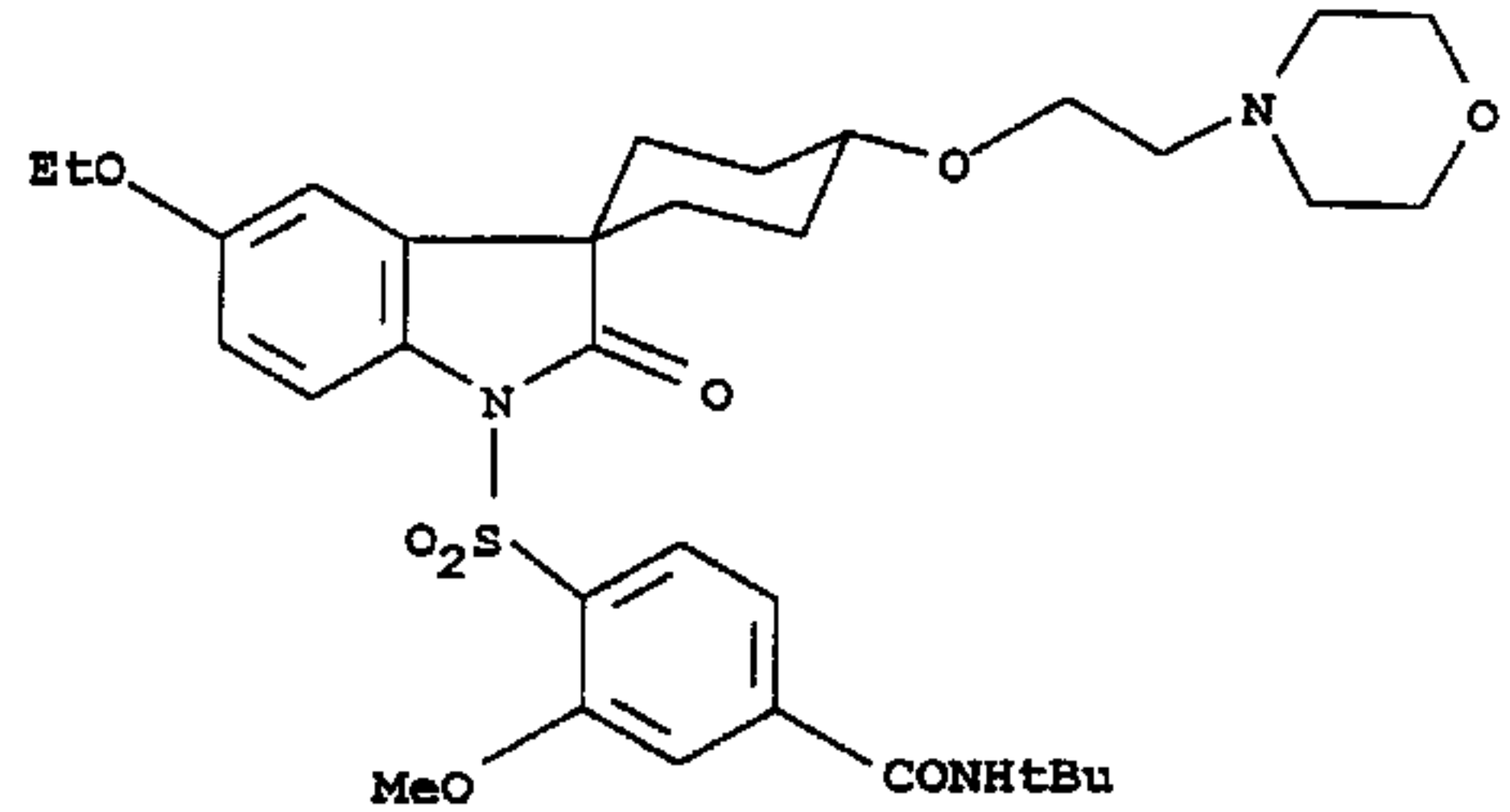

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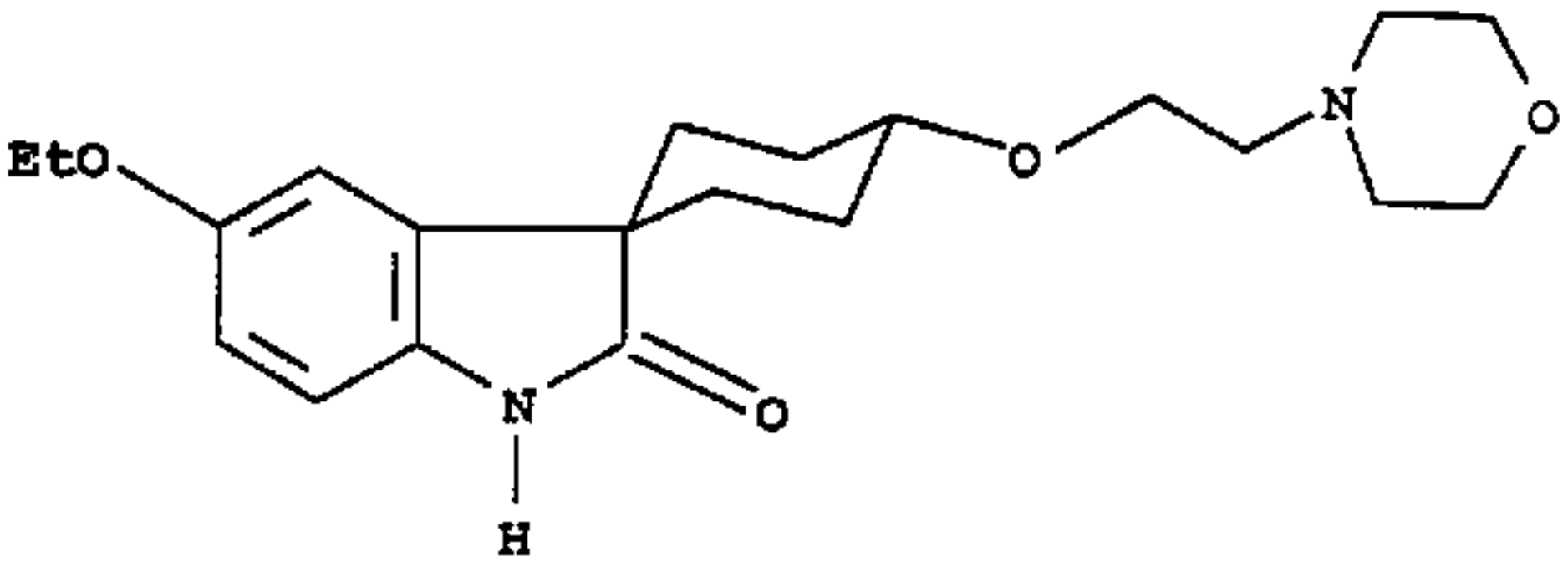

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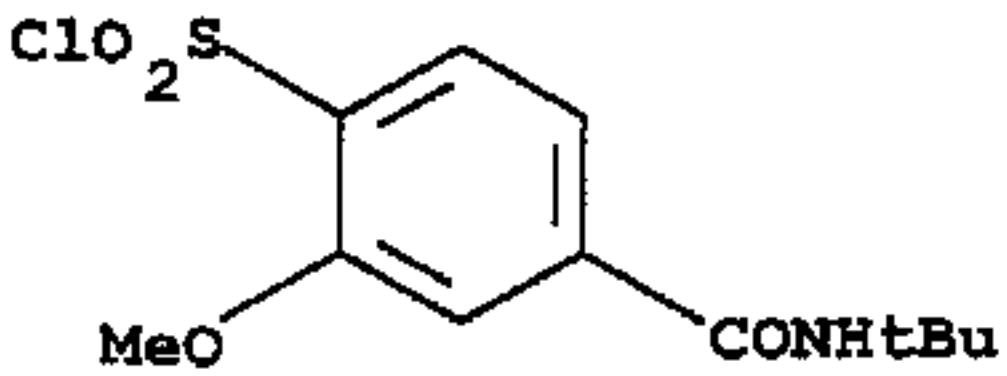

III.