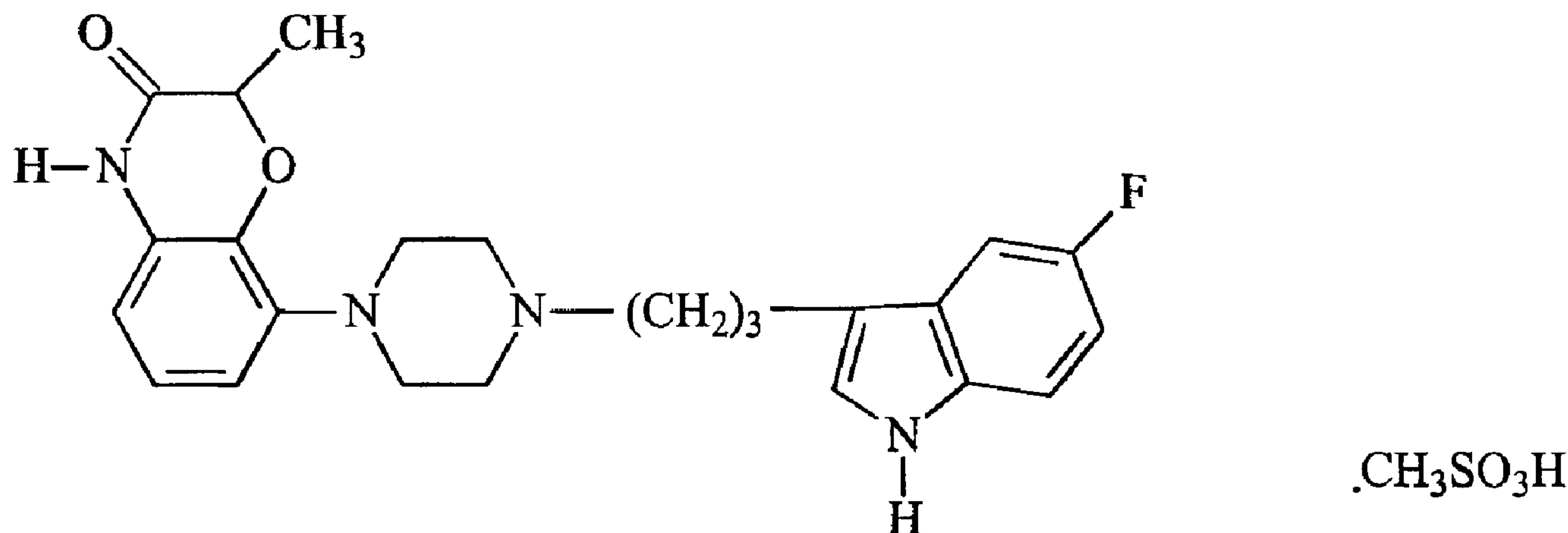




(86) Date de dépôt PCT/PCT Filing Date: 2002/02/19
(87) Date publication PCT/PCT Publication Date: 2002/08/29
(45) Date de délivrance/Issue Date: 2011/04/26
(85) Entrée phase nationale/National Entry: 2003/06/02
(86) N° demande PCT/PCT Application No.: EP 2002/001795
(87) N° publication PCT/PCT Publication No.: 2002/066473
(30) Priorité/Priority: 2001/02/21 (EP01200610.2)

(51) Cl.Int./Int.Cl. *C07D 413/14* (2006.01),
A61K 31/538 (2006.01), *A61P 25/18* (2006.01),
C07D 413/12 (2006.01)
(72) Inventeur/Inventor:
BAKKER, CORNELIS, NL
(73) Propriétaire/Owner:
SOLVAY PHARMACEUTICALS B.V., NL
(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : METHANESULFONATE DE 8'-3-(5-FLUORO-1H-INDOL-3-YL)PROPYL-1-PIPERAZINYL-2-METHYL-2H-1,4-BENZOXAZIN-3(4H)-ONE A HAUTE AFFINITE POUR LE RECEPTEUR D2 DE LA DOPAMINE ET LE SITE DE REABSORPTION DE LA SEROTONINE
(54) Title: 8-{4-[3-(5-FLUORO-1H-INDOL-3-YL)PROPYL]-PIPERAZIN-1-YL}-2-METHYL-4H-BENZO[1,4]OXAZIN-3-ONE MESYLATE WITH HIGH AFFINITY FOR THE DOPAMINE D2 RECEPTOR AND THE SEROTONIN REUPTAKE SITE



(57) Abrégé/Abstract:

The invention relates to the novel mesylate of a phenylpiperazine derivative of the formula (I). This salt has favourable properties as compared with the free base of this compound.



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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
29 August 2002 (29.08.2002)

PCT

(10) International Publication Number
WO 02/066473 A1(51) International Patent Classification⁷: **C07D 413/12**,
A61K 31/538, A61P 25/18

(21) International Application Number: PCT/EP02/01795

(22) International Filing Date: 19 February 2002 (19.02.2002)

(25) Filing Language: English

(26) Publication Language: English

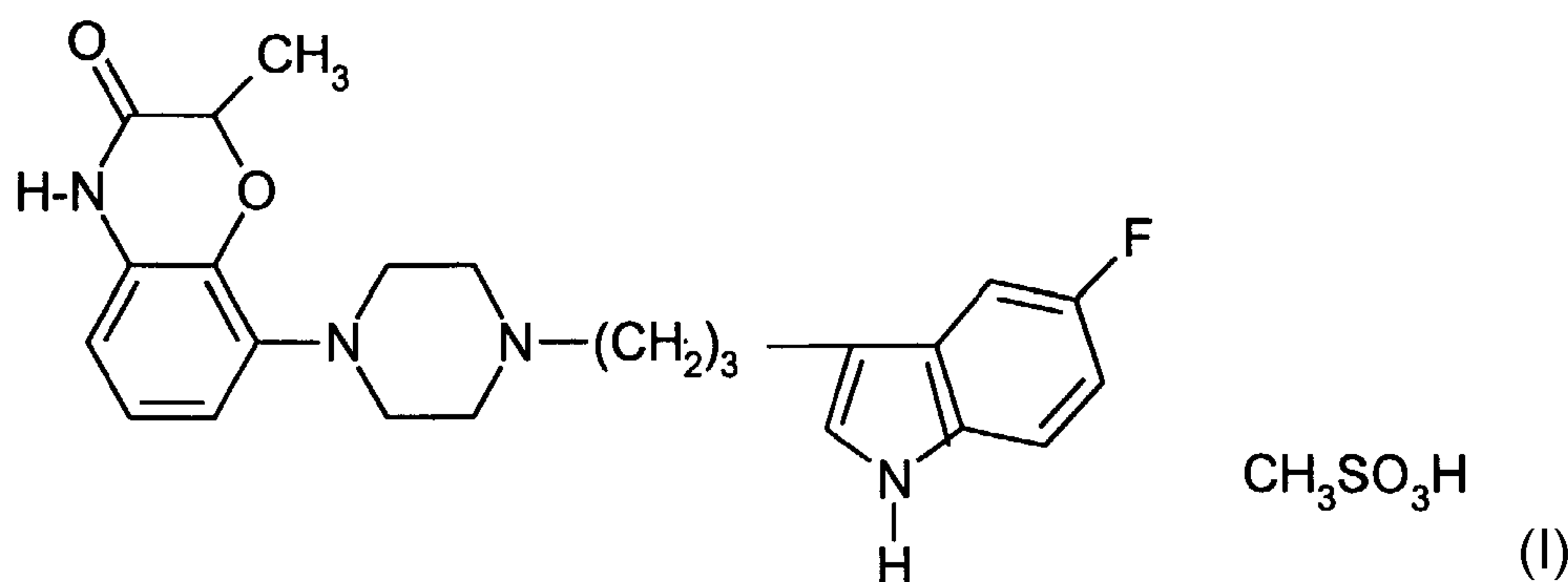
(30) Priority Data:
01200610.2 21 February 2001 (21.02.2001) EP(71) Applicant (for all designated States except US): **SOLVAY
PHARMACEUTICALS B.V.** [NL/NL]; C.J. van Houten-
laan 36, NL-1381 CP Weesp (NL).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BAKKER, Cornelis**
[NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp
(NL).(74) Agent: **MUIS, Maarten**; Octrooibureau Zoan B.V., P.O.
Box 140, NL-1380 AC Weesp (NL).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, 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, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, 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, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).**Published:**

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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

(54) Title: 8'-4'-3-(5-FLUORO-1H-INDOL-3-YL)PROPYL-1-PIPERAZINYL-2-METHYL-2H-1,4-BENZOXAZIN-
-3(4H)-ONE METHANESULFONATE WITH HIGH AFFINITY FOR THE DOPAMINE D2 RECEPTOR AND THE SEOTONIN
REUPTAKE SITE

(57) Abstract: The invention relates to the novel mesylate of a phenylpiperazine derivative of the formula (I). This salt has favourable properties as compared with the free base of this compound.



WO 02/066473 A1

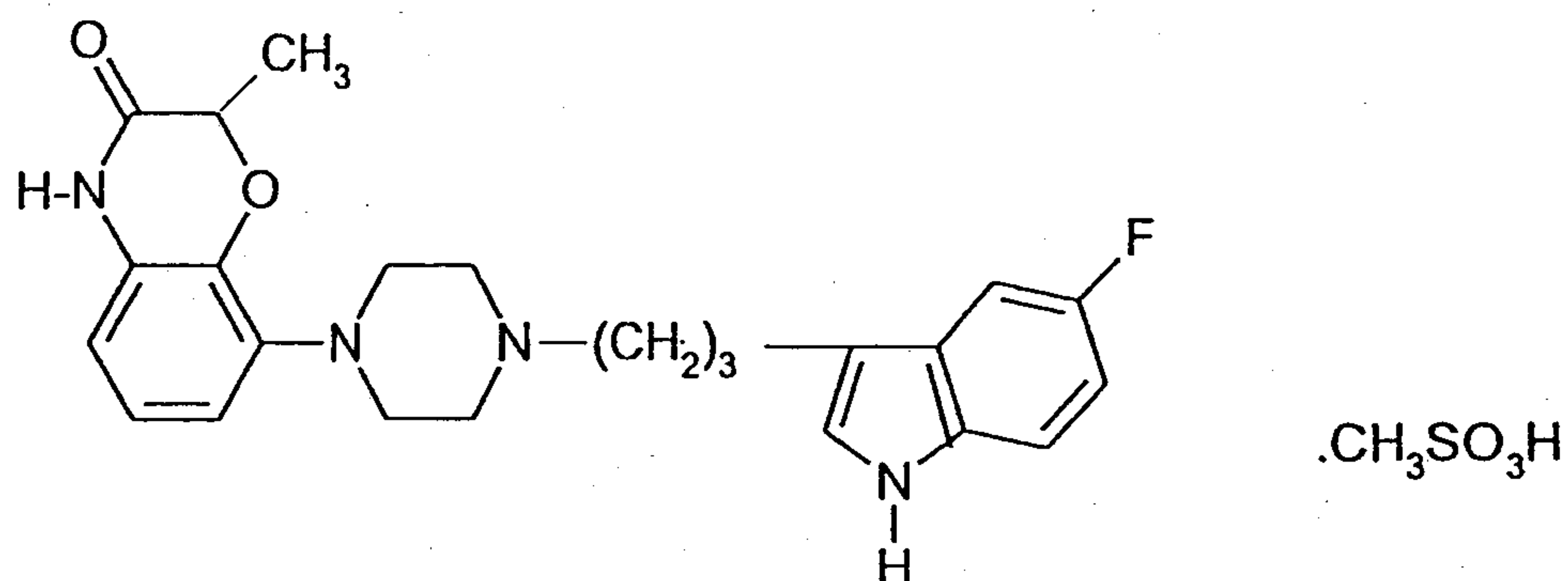
27072-200

1

**8-{4-[3-(5-FLUORO-1H-INDOL-3-YL)PROPYL]-
PIPERAZIN-1-YL}-2-METHYL-4H-BENZO[1,4]OXAZIN-3-ONE
MESYLATE WITH HIGH AFFINITY FOR THE DOPAMINE D₂
RECEPTOR AND THE SEROTONIN REUPTAKE SITE**

The invention relates to the novel phenylpiperazine derivative of the formula
(I):

5



WO 01/14330 relates to a group of novel
phenyl piperazines. The compounds of that group show high affinity for both the
dopamine D₂ receptor and the serotonin reuptake site. This combination is useful for
the treatment of schizophrenia and other psychotic disorders which enables a more
complete treatment of all disease symptoms (e.g. positive symptoms and negative
symptoms).

The compounds show activity as antagonists at dopamine D₂ receptors as they
potentially antagonize apomorphine-induced climbing behaviour in mice. The
compounds also show activity as inhibitors of serotonin reuptake, as they potentiate 5-
HTP induced behaviour in mice.

The compounds are active in therapeutic models sensitive to clinically relevant
antipsychotics (e.g. the conditioned avoidance response; Van der Heyden & Bradford,
Behav. Brain Res., 1988, 31:61-67) and antidepressants or anxiolytics (e.g.
suppression of stress-induced vocalization; van der Poel et al., Psychopharmacology,
1989, 97: 147-148).

In contrast to clinically relevant dopamine D₂ receptor antagonists the described
compounds have a low propensity to induce catalepsy in rodents and as such are likely
to induce less extrapyramidal side effects than existing antipsychotic agents.

27072-200

2

The inhibitory activity of serotonin reuptake inherent in these compounds may be responsible for the therapeutic effects observed in behavioural models sensitive to either antidepressants or anxiolytics.

- 5 The compounds can be used for the treatment of affections or diseases of the central nervous system caused by disturbances in either the dopaminergic or serotonergic systems, for example: aggression, anxiety disorders, autism, vertigo, depression, disturbances of cognition or memory, Parkinson's disease, and in particular schizophrenia and other psychotic disorders.

10

It has now been found that the mesylate of the above formula has particularly favourable properties in comparison with the free base (i.e. compound no. 89 of WO 01/14330).

- 15 This mesylate compound is much better soluble in water than the free base resulting in a good bio-availability.

The compound has a centre of chirality; both the racemic mixture and the individual enantiomers belong to the invention.

20

The compound can be brought into forms suitable for administration by means of suitable processes using auxiliary substances such as liquid and solid carrier materials.

- 25 The free base of compounds can be prepared as described in WO 01/14330.

The free base can be converted into the mesylate according to processes known per se for salt formation.

27072-200

2a

In a composition aspect, the invention provides a pharmaceutical composition comprising the above compound, as the active ingredient, and an auxiliary substance.

5 In a use aspect, the invention provides use of the above compound or composition, for the treatment of a CNS disorder.

In a further use aspect, the invention provides use of the above compound or composition, for the preparation of a medicament for the treatment of a CNS disorder.

10 In a commercial package aspect, the invention provides a commercial package comprising the above compound or composition, and associated therewith instructions for the use thereof in the treatment of a CNS disorder.

The invention is illustrated by means of the following Example.

Example

15 2.0 g (4.7 mmol) of the free base obtainable as described in WO 01/14330 (compound no. 89) is suspended in 40 ml of methanol. The suspension is warmed to 60 °C, and a solution of 0.45 g (4.7 mmol) of methanesulfonic acid in 10 ml of methanol is added in about two minutes. A clear solution is obtained. After stirring for 5 minutes at 60 °C the crystallization begins.
20 The solution is cooled slowly in 60 minutes to 20 °C, and stirred at that temperature for 30 minutes. Further cooling to 0

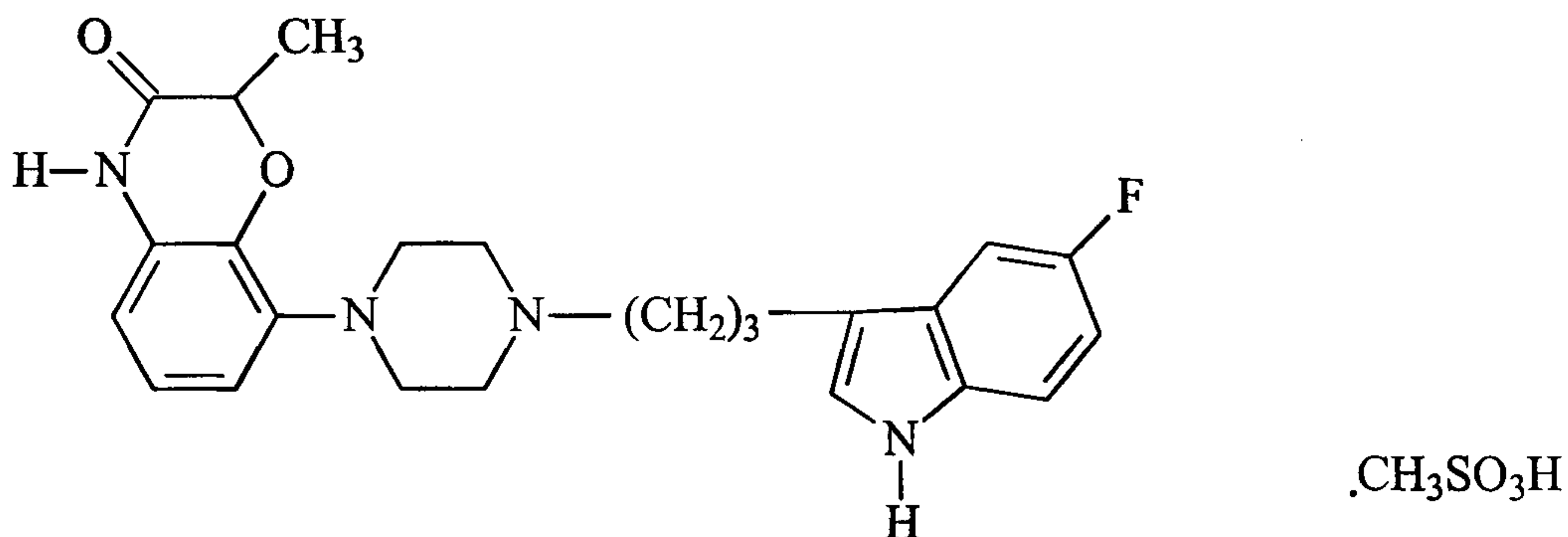
°C in 60 minutes and stirring for 90 minutes is carried out. The solid material is isolated by means of filtration, washed with 5 ml of methanol and dried during a night at 50 °C under reduced pressure. Yield 2.17 g (88%) of white coloured mesylate.

27072-200

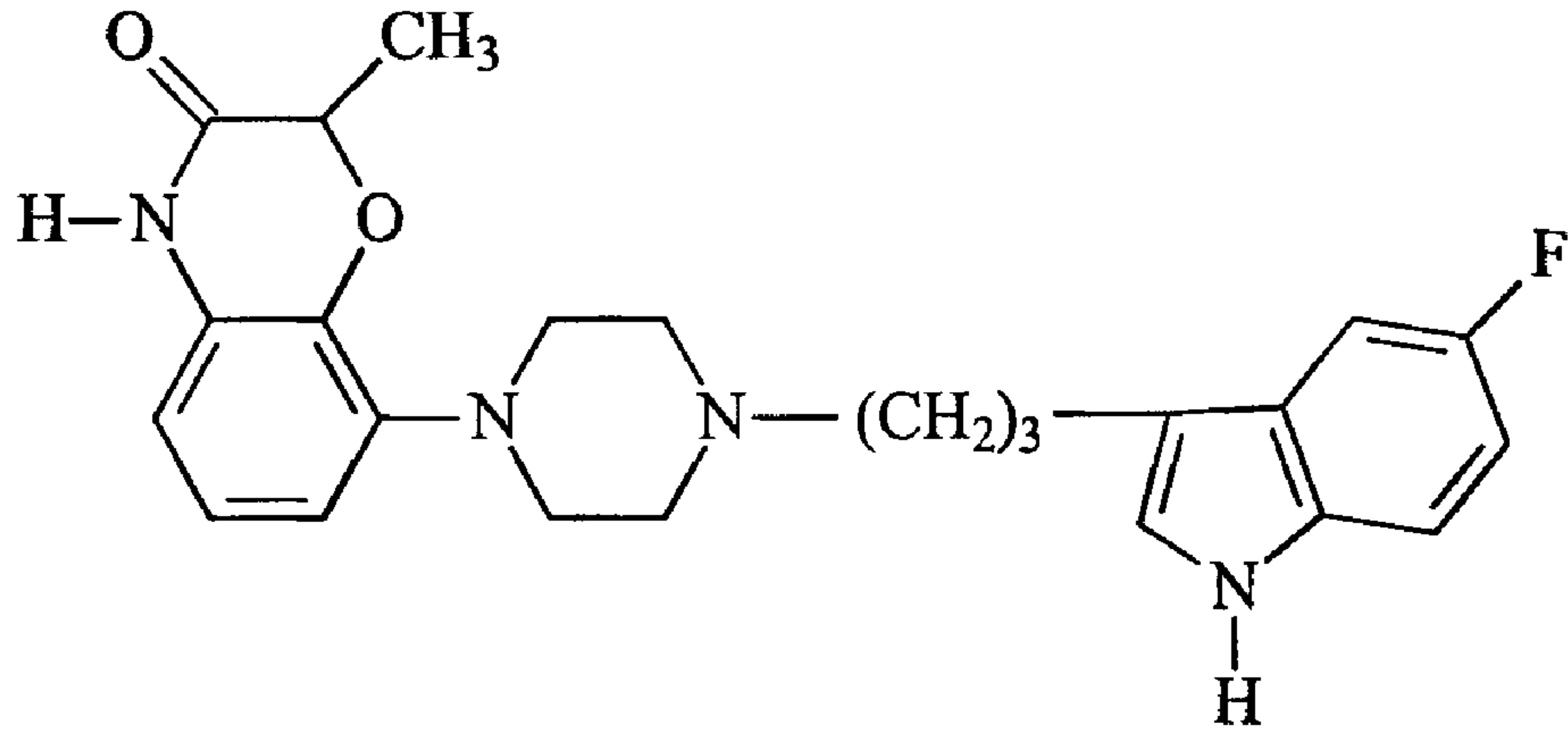
4

CLAIMS:

1. The compound of the formula:



2. A pharmaceutical composition comprising the compound of claim 1, as the active ingredient, and an auxiliary substance.
3. Use of the compound as claimed in claim 1, or the composition as claimed in claim 2, for the treatment of a CNS disorder.
4. Use of the compound as claimed in claim 1, or the composition as claimed in claim 2, for the preparation of a medicament for the treatment of a CNS disorder.
5. The compound as claimed in claim 1, or the composition as claimed in claim 2, for use in the treatment of a CNS disorder.
6. The compound as claimed in claim 1, or the composition as claimed in claim 2, for use in the preparation of a medicament for the treatment of a CNS disorder.
7. A commercial package comprising the compound as claimed in claim 1, or the composition as claimed in claim 2, and associated therewith instructions for the use thereof in the treatment of a CNS disorder.



$\cdot\text{CH}_3\text{SO}_3\text{H}$