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Declarations under Rule 4.17:

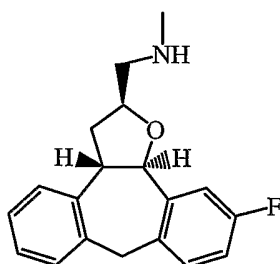
- as to applicant's entitlement to apply for and be granted
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CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: ANTIPSYCHOTIC AGENT WITH SOCIALIZING PROPERTIES



(I)

(57) Abstract: This invention concerns the use of the combination of a pre-
dominant 5HT_{2c} antagonist and a D₂ antagonist for use as an antipsychotic
with socializing properties. The invention more specifically concerns the
use of a compound of formula (I), its pharmaceutically acceptable salts,
more preferably the tartrate and mandelate salts for the preparation of a
medicament with socializing properties for the treatment of schizophrenia.

ANTIPSYCHOTIC AGENT WITH SOCIALIZING PROPERTIES

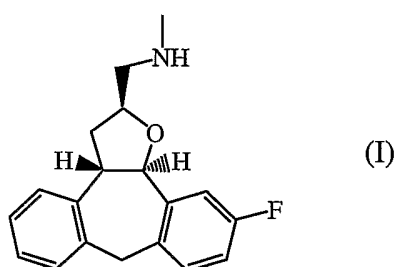
Field of the Invention

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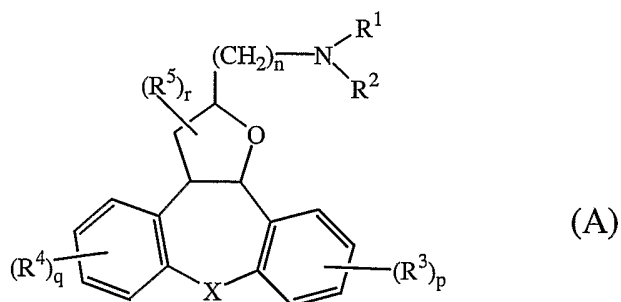
This invention concerns the use of the combination of a predominant 5HT_{2c} antagonist and a D₂ antagonist for use as an antipsychotic with socializing properties. The invention more specifically concerns the use of a compound of formula (I), its pharmaceutically acceptable salts, more preferably the tartrate and mandelate salts for

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the preparation of a medicament with socializing properties for treating schizophrenia.

15 Background prior art

WO 97/38991 discloses compounds of general formula (A)



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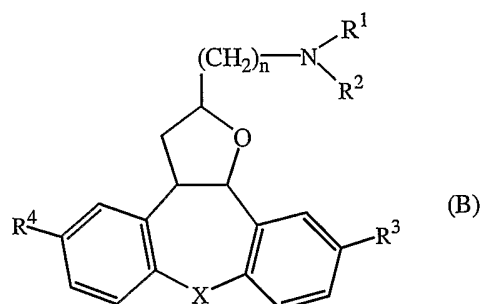
the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereoisomeric forms thereof. The compounds of formula (A) may be used as therapeutic agents in the treatment or the prevention of CNS disorders, cardiovascular

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disorders or gastrointestinal disorders.

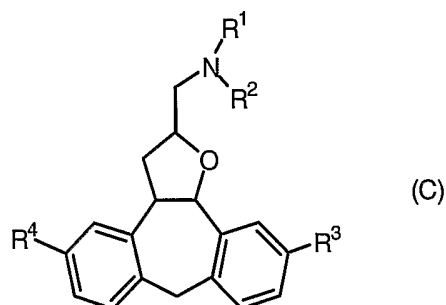
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WO 99/19317 discloses compounds of formula (B)



- 5 the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof. The compounds of formula (B) may be used as therapeutic agents.

- 10 WO 03/040122 discloses novel mandelate salts of a substituted tetracyclic tetrahydrofuran derivative according to Formula (C)



- 15 the *N*-oxide forms and the stereochemically isomeric forms thereof. The novel mandelate salt is not light-sensitive and is far more stable than the prior art salts at room temperature, enhanced temperature and at relative high humidities and in aqueous media. Also disclosed are pharmaceutical compositions comprising mandelate salts according to the invention, mandelate salts according to the invention for use as a medicine, a process for preparing the mandelate salts according to the invention and the use of the mandelate salts and pharmaceutical compositions comprising mandelate salts according to the invention for the treatment or the prevention of CNS disorders, cardiovascular disorders and gastrointestinal disorders.

- 25 The above mentioned patent applications all mention either generically or specifically the compound of the present invention. A preferred compound of the present invention is described in WO 03/040122 as a tartrate salt of the intermediate 16.

Description of the Invention

It is unexpectedly found that next to the pharmacological properties already described
5 in the mentioned art, the present compound unexpectedly also has socializing
properties next to its antipsychotic activity, due to the pharmacological profile.

The compound of formula (I) is a predominant 5HT_{2c} antagonist. Central 5HT_{2c}
antagonism is the basis for its ability to antagonize the anxiety-like effects induced by
10 the serotonin agonist meta-chlorophenylpiperazine (mCPP) in animals.
mCPP antagonism starts already at low doses of compound of formula (I) and is
complete (i.e., resulting in full normalisation of the behavior) at doses just below those
inducing the behavioral depression that results from the progressively increasing
occupancy of central D₂ receptors (Figure 1). Based on this predominant mCPP
15 antagonism in rats, the compound of formula (I) can be differentiated from other
available antipsychotics. mCPP also induces symptoms of anxiety in man, which show
a prolonged duration in schizophrenic patients as compared with healthy subjects. In
schizophrenics, moreover, mCPP increases positive symptoms. The anxiolytic activity
suggested by mCPP antagonism in animals may thus contribute to therapeutic effects in
20 schizophrenia, in particular to effects against negative and affective symptoms.

The compound of formula (I) has been found to induce 'socializing' effects in dogs.
These 'socializing' effects are predominantly related to anxiolytic and/or 'disinhibiting'
effects arising from central 5HT_{2c} antagonism.

25 The most preferred compounds are the (+)-L-tartrate salt and the (S) mandelate salt
form of the ($\pm$)(2 α ,3 α ,12b β)-forms of the structure of formula (I) (11-fluoro-
3,3a,8,12b-tetrahydro-*N*-methyl-2*H*-dibenzo-[3,4:6,7]cyclohepta-[1,2-*b*]furan-2
methanamine), more specifically the 2*R*-(2 α ,3 α ,12b β) isomer of the structure of
30 formula (I).

Those of skill in the treatment of such diseases could determine the effective
therapeutic daily amount from the test results presented hereinafter. An effective
therapeutic daily amount would be from about 0.01 mg/kg to about 10 mg/kg body
35 weight, more preferably from about 0.05 mg/kg to about 1 mg/kg body weight.

For ease of administration, the subject compounds may be formulated into various
pharmaceutical forms for administration purposes. To prepare the pharmaceutical

compositions of this invention, a therapeutically effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration.

- 5 These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, 10 elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise 15 sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of formula (I) may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for 20 example, peanut oil, sesame oil, cottonseed oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a 25 suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an 30 ointment. Acid or base addition salts of compounds of formula (I) due to their increased water solubility over the corresponding base or acid form, are more suitable in the preparation of aqueous compositions.

- It is especially advantageous to formulate the aforementioned pharmaceutical com- 35 positions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity

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of active ingredient calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and
5 segregated multiples thereof.

Experimental part

Compound 1 in the tests described hereunder is the (+)-L-tartrate salt of intermediate
10 16 as described in WO 03/040122 (2R-(2 α ,3 α ,12b β)-11-fluoro-3,3a,8,12b-tetrahydro-*N*-methyl-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]furan-2-methanamine).

Pharmacological test

15 Animals

Male Beagle dogs (Harlan CPB, The Netherlands) were housed under standard laboratory conditions. During the experiments, the dogs were individually housed in stainless steel cages (L x W x H: 130 x 80 x 80 cm). They were uniquely identified by an ear tattoo number (received at the time of weaning). The animals were fasted
20 overnight but were given free access to fresh tap water via drinking nipples in the back of the cage.

Test compounds

The test compounds were prepared as solutions either in distilled water (Compound 1),
25 in distilled water containing one equivalent (haloperidol) or two equivalents (risperidone) tartaric acid, or in 10 % hydroxypropyl- β -cyclodextrin containing two equivalents tartaric acid (olanzapine). The preparations were stored at room temperature in closed containers protected from light and coded A, B, C, D, E or F. It should be notified, however, that, despite coding, olanzapine solutions could be easily
30 recognized by the yellow color. The solutions were intravenously (i.v.) administered in a volume of 0.5 ml/kg.

Observation study

All experiments were performed by four unbiased technicians that were well
35 acquainted with the dogs under study. The dogs were housed individually in standard observation cages. Pairs of dogs were randomly assigned to each treatment group. Each of six pairs of dogs received an intravenous injection of a coded solution (A, B,

C, D, E or F) containing either saline (0.9 % NaCl) or a particular concentration of one of the test compounds. The presence of social behavior was scored (0: absent; 1: social attention; 2: social whining; 3: social playing) up to 4 h after injection. Inter-subject aggressive behavior was also scored (-1: doubtful; -2: present; -3: pronounced) and the presence of other behavioral abnormalities was noted. In order to enable the scoring of social behavior, each pair of dogs was taken out of the experimental cages separately from the other dogs at 0.5 h, 1 h, 2 h and 4 h after injection and allowed to walk together throughout the experimental room and adjacent corridor. The starting dose for each compound was 0.31 mg/kg, i.v. Based on the results, lower doses (selected from the geometrical series 0.005-0.02-0.08-0.31 mg/kg) were given down to a dose that was considered to be (almost) free of any socializing or other behavioral effect. At least this dose and a four times higher dose (inducing a clear behavioral effect) were tested on 5 pairs of dogs. ED₅₀ values and corresponding 95% confidence limits were estimated according to the method of Finney for categorical data. After the initial experiments, only pairs of dogs that did not show inter-subject aggressive behavior were included. This was tested in each experiment just before drug treatment by putting the dogs of each pair together in the experimental room. In each experiment, saline and five other formulations (not necessarily different compounds) were tested.

Results

Initial results

The first experiment was really disappointing: one group of dogs (that received haloperidol, 0.31 mg/kg) was scored +3 for social interaction and another pair of dogs (that received Compound 1, 0.31 mg/kg) was scored -3 for social interaction. After discussion with the observers it came out that the score +3 for the haloperidol group was given because these animals immediately lied down on the ground, close together, after they were taken out of their individual cages. The score -3 for the Compound 1 group was given because the two dogs started to fight when they were put together. However, they also said that this pair of dogs (receiving Compound 1) was initially (as long as both dogs were still inside the cages) thought to be the most social one because of the whining they displayed towards other dogs, indicating their apparent longing to meet them. When tried in a second experiment, it appeared moreover that the fighting behavior observed after Compound 1 was normal (dominant-submissive) agonistic behavior for these two dogs and thus not drug-related. Based on these initial results, it was decided to (1) not longer include pairs of dogs that display inter-subject aggressive behavior on beforehand, (2) not longer use "laying on the ground, close together" as an

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index of social behavior, and (3) include "social whining" as a measure of social behavior.

Control animals

- 5 All dogs (n = 56; 28 pairs) receiving saline were scored normal. Some of them were a little bit anxious whereas others displayed social whining but all of them showed behavior that was normal for each individual dog without any time-dependent changes after the intravenous injection.

10 Effects of Compound 1

- At 0.31 mg/kg, all dogs treated with Compound 1 without any exception were recognized among 6 pairs of dogs based on the occurrence of social whining. These dogs also showed slight sedation but no other behavioral abnormalities. At the lower dose of 0.08 mg/kg, social whining or sedation was not longer reported. At this dose, 15 however, all dogs Compound 1 treated could still be recognized on the basis of "social attention", i.e. the dogs clearly showed more attention for each other. This social attention was also observed in 6 and 2 out of 10 dogs treated with the lower doses of 0.02 and 0.005 mg/kg, respectively. It was very convincing that the observers were able to recognize in one experiment two different doses (0.02 and 0.08) of Compound 1 20 whereas they had the impression that only one of the coded bottles could contain Compound 1 [in all preceding experiments saline and five different compounds (Compound 1, haloperidol, risperidone, olanzapine and an other experimental compound) had been tested]. In other words, Compound 1 dose-dependently increased social attention (ED₅₀: 0.013 mg/kg) and social whining (ED₅₀: 0.21 mg/kg) and, apart 25 from slight sedation (ED₅₀: 0.16 mg/kg), it did not induce behavioral side effects.

Effects of haloperidol

- Haloperidol induced dose-dependent sedation (ED₅₀: 0.030 mg/kg) and catalepsy (in 2 and 4 out of 10 dogs tested at 0.02 and 0.08 mg/kg, respectively); compulsive biting 30 was observed in 2 out of 10 dogs tested at 0.08 mg/kg. Social attention was not and social whining was only occasionally observed (in 2 out of 10 dogs tested at 0.08 mg/kg).

Effect of risperidone

- 35 Risperidone dose-dependently induced sedation (ED₅₀: 0.017 mg/kg); compulsive scratching was occasionally observed (in 4 out of 10 dogs tested at 0.02 mg/kg).

Effect of olanzapine

Olanzapine dose-dependently induced sedation [ED₅₀: 0.16 mg/kg]; at 0.31 mg/kg, 4 out of 10 dogs displayed compulsive scratching and biting behavior and 3 dogs tended to show aggressive behavior (score -1 for social behavior).

5

Conclusion

It can be concluded that Compound 1 can be differentiated from saline, haloperidol, risperidone and olanzapine, based on socializing effects in dogs. Disregarding its exact nature and mechanism of action, this apparent socializing effect might be a valuable property in the treatment of schizophrenic patients.

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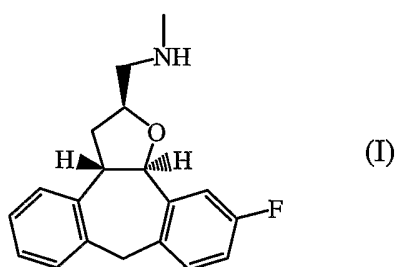
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CLAIMS

1. Use of a combination of a 5HT_{2c} antagonist and a D₂ antagonist for the preparation of a medicament with socializing properties for the treatment of schizophrenia.

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2. Use as claimed in claim 1 wherein the combination of the 5HT_{2c} antagonist and the D₂ antagonist is a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

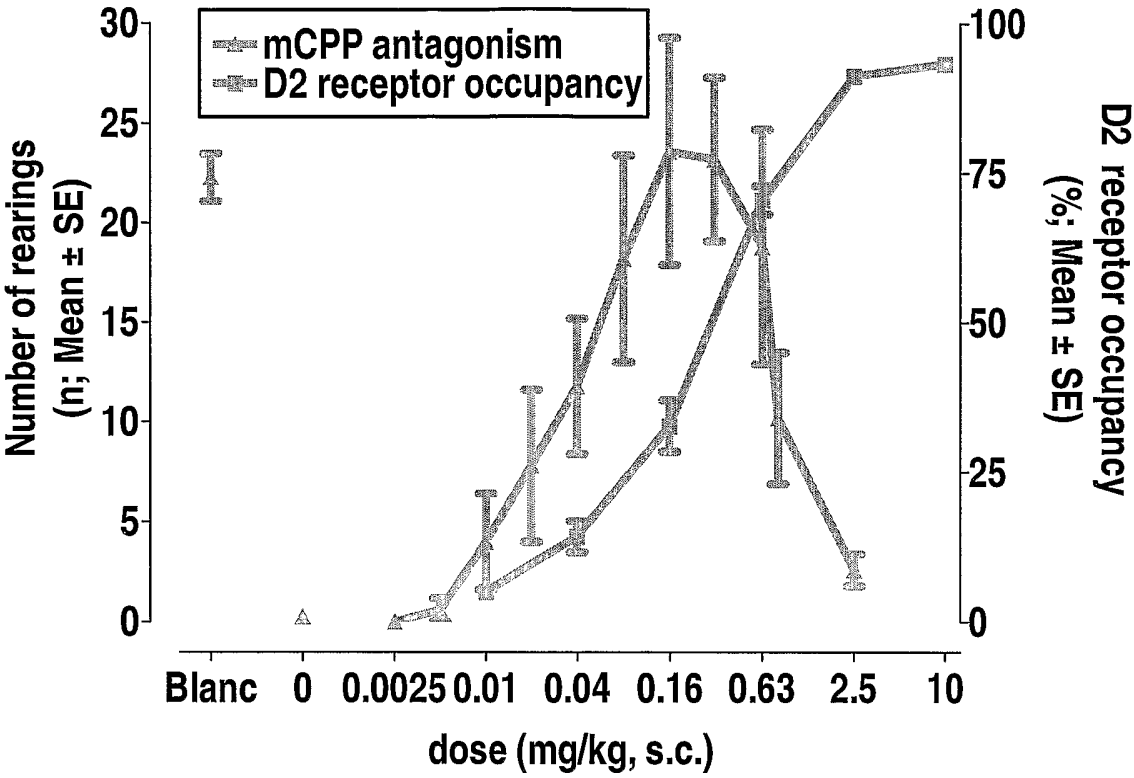


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3. Use as claimed in claim 2 wherein the pharmaceutically acceptable salt is the (+)-L-tartrate or the S-mandelate salt.

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Figure 1



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/007838

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/343 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/04289 A (BLACKBURN THOMAS PAUL ; SMITHKLINE BEECHAM PLC (GB)) 5 February 1998 (1998-02-05) claims 1,7 page 3, lines 7-9	1
X	WO 03/048146 A (MEDAER BART PETRUS ANNA MARIA ; MAO HUA (BE); KOZLECKI TOMASZ (BE); CO) 12 June 2003 (2003-06-12) page 10, lines 24,25 page 11, line 9 table 1	1-3
X	WO 03/040122 A (MEDAER BART PETRUS ANNA MARIA ; WEERTS JOHAN ERWIN EDMOND (BE); JANSSE) 15 May 2003 (2003-05-15) claim 4 page 6, lines 15,16	1-3
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

5 November 2004

Date of mailing of the international search report

15/11/2004

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/007838

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SEEGER T F ET AL: "ZIPRASIDONE (CP-88,059): A NEW ANTIPSYCHOTIC WITH COMBINED DOPAMINEAND SEROTONIN RECEPTOR ANTAGONIST ACTIVITY" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 275, no. 1, 1995, pages 101-113, XP002051730 ISSN: 0022-3565 abstract -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/007838

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