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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERC
E. S. D.

Referencia : Expediente No. 00.092.734
Solicitante : H. LUNDBECK A/S.
Asunto : Solicitud de patente para:
"COMBINACIÓN DE UN INHIBIDOR DE LA RECAPTACION
DE SEROTONINA E IRINDALONA"
Fecha de solicitud : 5 de diciembre de 2000

TRAMITE 002 EVENTO 001 ACTUACION 329

1. Yo, Emilio FERRERO, obrando como apoderado de la solicitante en el asunto de la referencia, atentamente, presento con este escrito la copia certificada de la solicitud de patente estadounidense No. 60/169,245 del 6 de diciembre de 1999, junto con la respectiva traducción de su carátula y reivindicaciones de la cual se reclama prioridad en esta solicitud de patente.

2. Ruego a la Señora Jefe se sirva aceptar este escrito con sus anexos, y se continúe con el trámite de la solicitud.

Bogotá, 15 FEB. 2001
Señora Jefe,



EMILIO FERRERO
T.P.A. No. 31.929

WCA COLO 03003-801-006-9
JJC-ID-55

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United States Patent and Trademark Office

December 05, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/169,245

FILING DATE: December 06, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

L. Edelen

**L. EDELEN
Certifying Officer**

1c604 U.S. PTO



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60/169245
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805 Third Avenue
New York, New York 10022
212-527-7700

Docket No: 5432/OG455

Date: December 6, 1999

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Enclosed please find a provisional application for United States patent as identified below:

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PROVISIONAL PATENT APPLICATION COVER SHEET

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Title: THE COMBINATION OF A SEROTONIN REUPTAKE INHIBITOR AND
A 5-HT_{2A} ANTAGONIST, INVERSE AGONIST OR PARTIAL AGONIST

Including the items indicated:

1. Specification and 42 claims: 4 indep.; 12 dep.; 26 multiple dep.
2. ☐ Drawings, sheets (Fig.)
3. ☐ Assignment for recording to:
4. ☐ Verified Statement Claiming Small Entity Status

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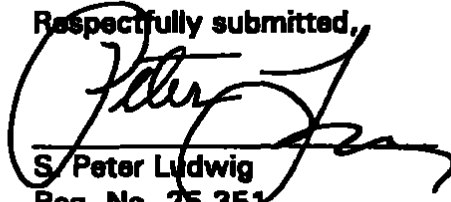
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December 6, 1999

Respectfully submitted,



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PROVISIONAL PATENT APPLICATION CORRESPONDENCE

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The combination of a serotonin reuptake inhibitor and a 5-HT_{2C} antagonist, inverse agonist or partial agonist

The present invention relates to the use of compounds and to compositions of compounds having selective serotonin reuptake inhibiting activity and 5-HT_{2C} antagonistic, partial agonistic, or inverse agonistic activity for the treatment of depression and other affective disorders. The combined serotonin reuptake inhibiting effect and the 5-HT_{2C} antagonistic, partial agonistic, or inverse agonistic effect may reside within the same chemical entity or in two separate chemical entities.

Background

Selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) have become first choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they are effective, well tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants.

Clinical studies on depression and anxiety disorders indicate that non-response to SSRIs is substantial, up to 30 %. Another, often neglected factor in antidepressant treatment is compliance. Two aspects of SSRI treatment may have a rather profound effect on the patient's motivation to continue pharmacotherapy. First, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Second, sexual dysfunction is a side effect common to all SSRIs. Without addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen.

In order to cope with non-response, psychiatrists sometimes make use of augmentation strategies. Augmentation of antidepressant therapy may be accomplished through the co-administration of mood stabilizers such as lithium carbonate or triiodothyronine or by the use of electroshock.

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In 1993, an augmentation strategy with pindolol was described by Artigas et al, in *Trends Pharmacol. Sci.*, 1993, 14, p 262-263. Unlike the aforementioned strategies, Artigas' idea is based on intracerebral microdialysis experiments in animals. In fact, latter neurochemical studies build on the desensitization hypothesis by Blier and coworkers stating that the delay in therapeutic effect of antidepressants is related to a gradual desensitization of 5-HT autoreceptors (Blier et al., *J. Clin. Psychopharmacol.*, 1987, 7 suppl. 6, 24S-35S). A key point in their hypothesis is that the effects of SSRIs on the release controlling autoreceptors limit the effect of uptake inhibition on the 5-HT release in terminal areas. This is supported by microdialysis experiments in rats, showing that the increase in extracellular 5-HT elicited by a single dose of an SSRI is augmented by co-administration of a 5-HT_{1A} autoreceptor antagonist (Invernizzi et al., *Brain Res.*, 1992, 584, p 322-324 and Hjorth, S., *J. Neurochem.*, 1993, 60, p 776-779).

The effect of combined administration of a compound that inhibits serotonin reuptake and a 5-HT_{1A} receptor antagonist has been evaluated in several studies (Imris, R.B. et al., *Eur. J. Pharmacol.*, 1987, 143, p. 1093-1094 and Gattardo, S.B., *Br. J. Pharmacol.*, 1995, 115, p 1064-1070, Blier, P., et al., *Trends in Pharmacol. Science*, 1994, 15, 220) in these studies it was found that 5-HT_{1A} receptor antagonists would abolish the initial brake on 5-HT neurotransmission induced by the serotonin reuptake inhibitors and thus produce an immediate boost of 5-HT transmission and a rapid onset of therapeutic action.

Several patent applications have been filed which cover the use of a combination of a 5-HT_{1A} antagonist and a serotonin reuptake inhibitor for the treatment of depression (see e.g. EP-A2-687 472 and EP-A2-714 663).

Another approach to increase terminal 5-HT would be through blockade of the 5-HT_{1B} autoreceptor. Microdialysis experiments in rats have indeed shown that increase of hippocampal 5-HT by citalopram is potentiated by GMC 2-29, an experimental 5-HT_{1B} receptor antagonist.

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In a recent clinical study, it was shown that pindolol and mianserin augment the efficacy of fluoxetine in the treatment of treatment resistant patients and that mianserin may shorten the latency of onset of antidepressive effect when combined with fluoxetine. The

effect of mianserin in this study can be explained by at least four different mechanisms relating to the effect of mianserin on noradrenaline turnover, α_2 -receptor blockade and its antagonistic effect at 5-HT_{2A/2C} receptors, (Maca, M., et al., *J.Clin. Psychopharmacol.*, 1999, 19, 2, p 177-182).

However, it has also been reported that in the mouse forced swimming test, prior administration of the selective 5-HT_{2A/2C} antagonist, ritanserin (4 mg/kg i.p.) or ketanserin (8 mg/kg i.p.) potentiated the effects of imipramine (mg/kg i.p.) and desipramine (16 mg/kg i.p.), but not of fluoxetine 16 mg/kg i.p.), citalopram (16 mg/kg i.p.) or fluvoxamine (8 mg/kg i.p.) (Redrobe, J.P., et al., *Eur J Pharmacol*, 1997, 325:129-135).

It has now surprisingly been found that the combination of a serotonin uptake inhibitor with a compound having 5-HT_{2C} antagonistic or inverse agonistic effect (compounds having a negative efficacy at the 5-HT_{2C} receptor) provides a considerable increase in the level of 5-HT in terminal areas, as measured in microdialysis experiments.

In particular, it was found that ketanserin, ritanserin, RS 102221, irindalone, Lu 27121 ((+)-trans-1-(5-chloro-3-(4-fluorophenyl)-1-indanyl)-4-(2-(3-isopropyl-2-imidazolidinon-1-yl)ethyl)piperazine, dimaleate), and Lu 29066 (2,5-dimethyl-3-(4-fluorophenyl)-1-[1-[2-(imidazolidin-2-on-1-yl)ethyl]-piperidin-4-yl]-1H-indole) in combination with SSRIs, synergistically act to increase the 5-HT release. As applied to humans, this would imply a shorter onset of antidepressant effect in the clinic.

5-HT_{2C} partial agonists may also be useful according to the present invention.

Further advantages of the combined administration of a SSRI and a compound with 5-HT_{2C} antagonistic or inverse agonistic effect may be the concurrent blockade of postsynaptic 5-HT_{2C} receptors which potentially diminishes the risk of SSRI-induced sexual dysfunctions and sleep disturbances.

Another advantage is that the putative anxiolytic effect of 5-HT_{2C} receptor antagonism may be interesting in view of the high comorbidity of depressive and anxiety-related symptoms.

Moreover, case reports indicate that blockade of postsynaptic 5-HT_{2A/2C} receptors is able to counteract the serotonin syndrome. In view of the large 5-HT increases by 5-HT_{2C} augmentation, this seems to be a most welcome safety mechanism.

The invention

The present invention thus provides:

The use of a compound which is a serotonin reuptake inhibitor and has affinity for the 5-HT_{2C} receptor, or a combination of a compound which is a serotonin reuptake inhibitor and another compound which is a 5-HT_{2C} receptor ligand, for the preparation of a pharmaceutical composition for the treatment of depression, anxiety disorders and other affective disorders, eating disorders such as bulimia, anorexia and obesity, social phobia, premenstrual syndrome and cognitive disorders.

Furthermore, the present invention provides a method for the treatment of depression, anxiety disorders and other affective disorders, eating disorders such as bulimia, anorexia and obesity, social phobia, premenstrual syndrome and cognitive disorders comprising administering to an individual in need thereof, a therapeutically effective amount of a compound which is a serotonin reuptake inhibitor and has affinity for the 5-HT_{2C} receptor, or a combination of a compound which is a serotonin reuptake inhibitor and another compound which is a 5-HT_{2C} receptor ligand,

The present invention also relates to a pharmaceutical composition comprising compound which is a serotonin reuptake inhibitor and has affinity for the 5-HT_{2C} receptor, or a combination of a compound which is a serotonin reuptake inhibitor and another compound which is a 5-HT_{2C} receptor ligand, and optionally pharmaceutically acceptable carriers or diluents.

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In a particular embodiment of the invention, the compound used as above is a selective serotonin reuptake inhibitor.

And in still another embodiment of the invention, the compound used as above is a partial agonist at the 5-HT_{1C} receptor.

In a particularly preferred embodiment, the compound used as above has a K_i value at the 5-HT_{2C} receptor which is lower or equal to that of Irindalona, ketanserin, Lu 29066, Lu 27121, RS 102221, mianserin, or ritanserin.

In one embodiment of the invention, the pharmaceutical compositions as above contain a serotonin uptake inhibitor selected from citalopram, desmethylcitalopram, fluoxetine or its

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In a particularly preferred embodiment, the serotonin uptake inhibitor is citalopram or dextrocitalopram.

Finally, the present invention relates to a method for the identification of compounds useful for the treatment of depression, anxiety disorders and other affective disorders, eating disorders such as bulimia, anorexia and obesity, social phobia, premenstrual syndrome and cognitive disorders comprising, in any order:

- and thereafter measuring the efficacy of the selected compounds at the 5-HT_{2C} receptor and selecting the compounds which are antagonists, inverse agonists, or partial agonists at the receptor.

The invention also relates to compounds identified by the method above.

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According to the present invention, a method of improving the onset of therapeutic action by concomitant administration of a first component

- a) which is a serotonin reuptake inhibitor; and
- b) a compound with affinity to the 5-HT_{2C} receptor which act to augment the effect of the serotonin reuptake inhibitor.

In particular, the present invention relates to medicaments that provides fast onset of antidepressant effect and /or effect in depressive patients which do not respond to SSRIs.

According to the present invention, the anxiety disorder to be treated can be general anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post trauma stress disorder, and social anxiety disorder.

In a particular embodiment of the invention, the serotonin reuptake inhibitor is a selective reuptake inhibitor, i.e. a compound with stronger inhibitory effect at the serotonin transporter compared to its effect at the dopamine and noradrenaline transporters.

Typical examples of SSRIs are compounds like citalopram, fluoxetine, fluvoxamine, sertraline, paroxetine and fenoxetine, indalpine, zimeldine, nafazodone and venlafaxine or where the compound is a racemate, its active enantiomers, i.e. dextrocitalopram. In Sánchez, C., et al, Cellular and Molecular Neurobiology, 1999, 19, 4, p 467 - 489, the effect of various antidepressants and their metabolites on serotonin reuptake and receptor binding is reviewed. The above SSRIs are mentioned with the purpose of providing representative examples and are not intended to restrict the scope of the present invention.

Particularly interesting pharmaceutical compositions are those synergistic compositions wherein the SSRI is selected from citalopram, dextrocitalopram, fluoxetine, fluvoxamine, sertraline, clomipramine, and paroxetine, in particular citalopram and dextrocitalopram.

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When used herein the term selective for the 5-HT_{2C} receptor means that the compound possess higher affinity for the 5-HT_{2C} receptor than to other serotonin receptors.

Ketanserin, which is a 5-HT_{2A} and 5-HT_{2C} receptor, is the generic name of the compound 3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-2,4(1H,3H)-quinazolinemedione. This compound and related compounds, their synthesis, as well as their antiserotonergic properties are described in U.S. Pat. No. 4,335,127.

Other 5-HT_{2C} receptor ligands which may be useful as active ingredients in the pharmaceutical compositions of the invention are: ritanserin, SB 242084, SB 200646A, SB 221284, SB 204741, SB 221284, irindalones, RS 102221, SB 206553, Lu 29066, Lu 27121, LY 53857 metargoline, mirtazapine, mianserine, piroperone, methysergide, serazapine, and Ro 600491.

Further 5-HT_{2C} receptor antagonists are described in WO 96/23769, WO96/39382, WO 97/08167 and WO 97/39001.

The K_i values at the 5-HT_{2C} receptor for some of these compounds as well as fluoxetine and nefazodone are given in the table below:

Compound	K _i (nM)
ketanserin	14
irindalones	19
Lu 29066	6.9
Lu 27121M	5.1
fluoxetine	80
nefazodone	33
RS 102221	0.56
ritanserin	0.19
mianserin	1.1

The K_i values given in the table above were determined using the 5-HT_{2C} binding assay described in the experimental section. It should be noted that other tests, modified tests,

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or tests carried out by other groups may result in figures that differ somewhat from the figures given in the table above.

Accordingly, it is only possible to compare with the K_i and IC_{50} values given in the present description, if the test method and test conditions used for generating the figures are the same, i.e. as described in the experimental section below.

These compounds and groups of compounds are listed with the purpose of providing representative examples and are not intended to restrict the scope of the present invention.

When a combined serotonin reuptake inhibitor and 5-HT_{2C} antagonist, inverse agonist or partial agonist is used according to the invention, the compound is preferably lacking affinity for the dopamine receptor, i.e. it has an IC_{50} value over 100 nM at this receptor.

The active ingredients may be used according to the invention in the free base form or in a pharmaceutically acceptable acid addition salt form, the latter being obtained by reaction of the base form with an appropriate acid. Exemplary of organic acid addition salts according to the invention are those with malic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of inorganic acid addition salts according to the invention are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids. The acid addition salts of the invention are preferably pharmaceutically acceptable salts formed with non-toxic acids. A particularly interesting acid addition salt form of the compound ketanserin is (+)-3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-2,4(1H,3H)-quinazolinedi-one R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1). A particularly interesting acid addition salt of citalopram is the hydrobromide.

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The term addition salt as used hereinabove also comprises the solvates which the active ingredients are able to form. Said solvates are meant to be included within the scope of the present invention. Examples of such solvates are e.g. the hydrates, alcoholates, and the like.

The pharmaceutical compositions according to the present invention unexpectedly show a synergistic effect on the central nervous system (CNS). As a consequence, a combination therapy using compositions with lower doses of each drug than used normally in monotherapy, may be effective, and occasional side-effects associated with the larger amounts used in monotherapy may be reduced or prevented altogether. Additionally, a combination therapy using a dose of each drug as used normally in monotherapy, has the advantage that an effective CNS effect may be obtained in the often large number of patients who do not respond to conventional monotherapy with SSRIs.

The amount of each of the active ingredients in the synergistic compositions according to the present invention is such that a synergistic effect is obtained upon administration. For example, the amount of the 5-HT_{2C} antagonist, partial agonist, or inverse agonist in said synergistic compositions may typically range from about 5 to about 150 mg, particularly from about 10 to about 80 mg and more particularly from about 20 to about 40 mg per dosage unit form. Serotonin reuptake inhibitors, including the SSRIs specifically mentioned hereinabove, differ both in molecular weight and in activity and, therefore, may be administered in fairly different quantities. As a consequence, the amount of selective serotonin reuptake inhibitor in said synergistic compositions depends on the nature of said selective serotonin reuptake inhibitor, and ranges in general from about 1 to about 300 mg, particularly from about 5 to about 150 mg and more particularly from about 10 to about 50 mg per dosage unit form.

In said synergistic compositions, the molar ratio between the 5-HT_{2C} antagonist or inverse agonist and the selective serotonin reuptake inhibitor in the free base form may vary depending both on the nature of the serotonin reuptake inhibitor and the application aimed at. The molar ratio of the 5-HT_{2C} antagonist or inverse agonist to the serotonin

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reuptake inhibitor will be such that a synergistic effect is obtained and in particular may be situated between 50:1 and 1:50, more particularly between 20:1 to 1:20 or between 10:1 and 1:10, most particularly between 5:1 and 1:5. In the synergistic compositions according to the present invention wherein a serotonin reuptake inhibitor with moderate activity, the molar ratio of the 5-HT_{2C} antagonist or inverse agonist to said serotonin reuptake inhibitor may be situated between 5:1 and 1:30, in particular between 1:1 to 1:5 and more particularly between 1:2 and 1:3, or between 1:1 and 1:1.5. If, on the contrary, a potent serotonin reuptake inhibitor is used in the synergistic compositions according to the present invention, the molar ratio of the 5-HT_{2C} antagonist or inverse agonist to said serotonin reuptake inhibitor may be situated between 50:1 and 1:5, in particular between 10:1 to 1:1 and more particularly between 5:1 and 3:1.

To prepare the pharmaceutical compositions of this invention, an effective amount of the active ingredients, in acid or base addition salt form or base form, is combined in intimate admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, 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, 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 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 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

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optionally comprises a penetration enhancing agent and/or a 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 ointment. Acid addition salts of the active ingredients are, due to their increased water solubility over the corresponding base form, obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions 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 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 segregated multiples thereof.

The 5-HT_{2C} antagonist, partial agonist, or inverse agonist may be administered before, during or after the administration of the serotonin reuptake inhibitor, provided that the time between the administration of the 5-HT_{2C} antagonist, partial agonist, or inverse agonist and the administration of the serotonin reuptake inhibitor is such that ingredients are allowed to act synergistically on the CNS. When simultaneous administration of the 5-HT_{2C} antagonist, partial agonist, or inverse agonist and a serotonin reuptake inhibitor is envisaged, a composition containing both a serotonin reuptake inhibitor and the 5-HT_{2C} antagonist, partial agonist or inverse agonist may be particularly convenient. Or, the 5-HT_{2C} antagonist, partial agonist or inverse agonist and the serotonin reuptake inhibitor may be administered separately in the form of suitable compositions. The latter can be prepared as described hereinabove.

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The present invention also comprises products containing the 5-HT_{2C} antagonist, partial agonist or inverse agonist and a serotonin reuptake inhibitor as a combined preparation for simultaneous, separate, or sequential use in psychiatric drug therapy. Such products may comprise, for example, a kit comprising a container with a suitable composition containing 5-HT_{2C} antagonist, partial agonist or inverse agonist or a pharmaceutically acceptable acid addition salt thereof and another container containing a composition with a serotonin reuptake inhibitor.

In the Netherlands, ketanserin® is registered as an antihypertensive drug. Extrapolating kinetic data from animals to humans indicates that the amount of ketanserin needed for augmentation compares to the dose used for hypertension. In healthy subjects, an oral dose of ketanserin is rapidly absorbed with peak levels attained after 0.5 to 2 hours. Binding to plasma proteins is 95 %. It is extensively metabolized and metabolites are preferentially excreted in urine. Approximately 3% of the drug penetrates into the brain. The most frequently reported side effects after oral administration are dizziness, tiredness, headache and depression. There are no indications for unwanted interactions between ketanserin and SSRIs.

Experimental section

5-HT_{2C} binding

K_i values at the 5-HT_{2C} were determined by testing the compounds according to the procedure described below:

SR-3T3 cells (ATCC CRL 9851) are grown to confluency and then scraped off in TBS (50 mM Tris, pH 7.7, 125 mM NaCl). The cell suspension is centrifuged and the pellet resuspended in 50 mM Tris, HCl, pH 7.7 and stored at -80°C. For experimental use, the frozen cell pellet is thawed and homogenized with an Ultra Turrax for 10-15 seconds. 1.5 mg cell preparation is incubated with 0.5 nM 3H-Mianserin for 60 minutes at 37 °C.

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Incubation is terminated by rapid filtration through Filtermat B filters and bound radioactivity is determined in a Tricarb scintillation counter.

5-HTT inhibition

IC₅₀ values for serotonin reuptake inhibition are measured as described in the test below:

Male rats (125-225 g) are decapitated and encephalon is dissected out and transferred to 0.9 % NaCl at 0 °C. The brain is weighed and homogenized at 0°C in a glass/teflon homogenizer in 40 volumes of 0.32 sucrose containing 1 nM Nialamid. The homogenate is centrifuged at 600 g for 10 minutes at 4 °C. The supernatant/S1 is centrifuged at 20000 g for 55 min. at 4 °C. Supernatant/S2 is discarded and the pellet is resuspended in 360 volumes of modified Krebs Ringer phosphate buffer, pH 7.4 (oxygenated for 10 minutes). The suspension is kept on ice. The tissue is incubated with ³H-5-HT for 15 minutes at 37 °C in Krebs Ringer buffer. The samples are filtered through 0.1 % PEI soaked Filtermat C filters to wash away ³H-5-HT in solution. Filters are washed with 10 µM 5-HT before and after sample filtration. Radioactivity captured in synaptosomes is counted in a Tricarb scintillation counter.

Microdialysis Experiments

Animals and drug administration

Male albino rats of a Wistar-derived strain (285-320 g; Harlan, Zeist, The Netherlands) were used for the experiments. The rats were housed in plastic cages (35 x 35 x 40 cm), and had free access to food and water. The experiments are concordant with the declarations of Helsinki and were approved by the Animal Care Committee of the Faculty of Mathematics and Natural Science of the University of Groningen.

The following drugs were used: Citalopram hydrobromide and internal standard (kindly donated by Lundbeck (Copenhagen, Denmark), courtesy Dr. Sanchez), rimanserin and

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ketanserin tartrate (RBI, Natick, USA). Citalopram and ketanserin were dissolved in saline, ritanserin was dissolved in 30 % alcohol/saline. Ketanserin and citalopram were injected subcutaneously (in different areas during co-administration), ritanserin was injected intraperitoneally. All drugs were administered in a volume of 1 ml per kg.

Surgery

Microdialysis experiments were performed using home made I-shaped probes, made of polyacrylonitrile / sodium methyl sulphonate copolymer dialysis fiber (I.d. 220 μ m, o.d. 0.31 μ m, AN 69, Hospal, Italy). The exposed length of the membranes was 4 mm. Proceeding surgery rats were anaesthetised either by means of an intraperitoneal injection of 400 mg/kg chloral hydrate (ritanserin experiments) or by an intraperitoneal injection of ketamine/xylazine, with midazolam as premedication (ketanserin experiments). Lidocaine-HCl, 10 % (m/v) was used for local anaesthesia. Rats were placed in a stereotaxic frame (Kopf, USA), and probes were inserted into the ventral hippocampus (coordinates: IA: +3.7 mm, lateral: +4.8 mm, ventral: -8.0 mm from the dura mater, Paxinos and Watson, 1982) and secured with dental cement.

In the pharmacokinetic experiments, blood was drawn through a cannula made of silicon tubing, which was inserted into the right jugular vein for 3.8 cm. The tubing was transferred subcutaneously to the skull of the rat, and a stainless steel inlet was connected to the tubing. The inlet was mounted on the skull with dental cement and surgical screws. After insertion, cannulas were filled with a FVP solution (55 % polyvinylpyrrolidone in 500 IE/ml heparin) in saline to prevent blood clotting.

Pharmacokinetic experiments

Rats were allowed to recover for at least 24 h. Blood samples (0.30 ml) were drawn at 0, 15, 30, 60, 120, 240 and 360 min after injection of either citalopram or ketanserin. Samples were transferred to 1.5 ml eppendorf vials, containing 5 μ l heparin (500 IE/ml

saline), mixed and immediately transferred to a chilled centrifuge (MSE, England), and centrifuged for 15 min at 3,000 rpm.

Microdialysis experiments

Rats were allowed to recover for at least 24 h. Probes were perfused with artificial CSF containing 147 mM NaCl, 3.0 mM KCl, 1.2 mM CaCl₂, and 1.2 mM MgCl₂, at a flow-rate of 1.5 µl / min (Harvard apparatus, South Natick, Ma., USA). Samples were collected on-line in a 20 µl loop and injected automatically onto the column every 15 min.

Analysis

Serotonin:

5-HT was analysed using HPLC with electrochemical detection. The HPLC pump (Shimadzu LC-10 AD liquid chromatograph) was connected to a reversed phase column (phenomenex hypersil 3 : 3 µm, 100 x 2.0 mm, C18, Bostar, Amstelveen, the Netherlands) followed by an electrochemical detector (Antec Leyden, Leiden, the Netherlands), working at a potential setting of 500 mV vs. Ag/AgCl reference. The mobile phase consisted of 5 g/l di-ammoniumsulphate, 500 mg/l ethylenediamine tetraacetic acid (EDTA), 50 mg/l heptane sulphonic acid and 30 µl/l of triethylamine, at a pH of 4.65 and 4.5 % (w/w) methanol and water. Flow-rate of the mobile phase was 0.4 ml/min. The detection limit was 0.5 fmol 5-HT per 20 µl sample (signal to noise ratio 3).

Citalopram:

Citalopram was measured according to Øyehaug et al. (1982), with minor modifications. Briefly, to 150 µl plasma samples 75 µl of the internal standard LU 10-202 (2 µM) and 30 µl of 0.1N NaOH were added. Samples were extracted twice by mechanically shaking for 3 minutes with 3 ml of diethyl ether. The ether layers were then transferred to 10 ml evaporating tubes, and 150 µl of 0.1 N HCl was added. The ether was evaporated in a water-bath at 40 °C under a stream of nitrogen. The HCl layer was washed once with 0.5 ml ether. 50 µl samples were injected onto the column.

With the experiments in which 5 ml plasma was obtained via the vacuumiser, a similar protocol was used, but the plasma sample was now extracted three times with 10 ml of ether.

An HPLC/auto-injector (1084B Liquid Chromatograph, Hewlett-Packard) was used, in combination with a fluorescence detector (470 Scanning Fluorescence detector, Waters, England) operating at an absorption wavelength of 240 nm, an emission wavelength of 296 nm, and a slit-width of 12 nm. Separation was performed using a Supelcosil HPLC column (5 μ m, C18, 250 x 46 mm, Supelco, the Netherlands), at ambient temperature. The mobile phase consisted of 46 % v/v acetonitrile, 54 % v/v potassium dihydrogen phosphate buffer (4.3 g/l), and 30 μ l/l triethylamine, at a pH value of 3.0. Flow-rate in this system was 0.75 ml/min. The detection limit of the assay was 8 nM (signal to noise = 2). Extraction of samples spiked with known concentrations of citalopram revealed that the extraction method had a recovery of 99 %.

Ketanserine:

Ketanserine was measured using liquid-liquid extraction, followed by reversed phase chromatography in conjunction with fluorescence detection. Briefly, to 150 μ l plasma samples 30 μ l of 0.1N NaOH were added. Samples were extracted twice by mechanically shaking for 3 minutes with 3 ml of diethyl ether. The ether layers were then transferred to 10 ml evaporating tubes, and 150 μ l of 0.1 N HCl was added. The ether was evaporated in a water-bath at 40 °C under a stream of nitrogen. The HCl layer was washed once with 0.5 ml ether. 50 μ l samples were injected onto the column.

An HPLC/auto-injector (1084B Liquid Chromatograph, Hewlett-Packard) was used, in combination with a fluorescence detector (470 Scanning Fluorescence detector, Waters, England) operating at an absorption wavelength of 240 nm, an emission wavelength of 370 nm, and a slit-width of 12 nm. Separation was performed using a Supelcosil HPLC column (5 μ m, C18, 250 x 46 mm, Supelco, the Netherlands), at ambient temperature. The mobile phase consisted of 35 % v/v acetonitrile, 65 % v/v potassium dihydrogen phosphate buffer (4.3 g/l), and 30 μ l/l triethylamine, at a pH value of 3.0. Flow-rate in this system was 1.0 ml/min. The detection limit of the assay was 6 nM (signal to noise =

2). Extraction of samples spiked with known concentrations of citalopram revealed that the extraction method had a recovery of 93 %.

Data presentation and statistics

Four consecutive microdialysis samples with less than 20 % variation were taken as control and set at 100 %. Data are presented as percentages of control level (mean $\pm$ SEM). Statistical analysis was performed using Sigmaplot for windows (Jandel Corporation). Treatment effects were compared using two way ANOVA for repeated measurements, followed by Dunnett's test. Level of significance level was set at $p < 0.05$. Pharmacokinetic data were fitted using Multifit (copyright Dr. J.H. Proost, Dept. of pharmacokinetics and drug delivery, University of Groningen, the Netherlands

Results

Pharmacological experiments:

Ritanserin co-administration:

Intraperitoneal administration of 10 $\mu\text{mol/kg}$ ritanserin did not have any effect on 5-HT levels in rat ventral hippocampus. Subcutaneous administration of 10 $\mu\text{mol/kg}$ citalopram significantly increased 5-HT levels compared to saline injection ($F(1,131) = 12.8$, $p < 0.05$). Post hoc analysis revealed significance from $t = 45$ to 150 minutes. 10 $\mu\text{mol/kg}$ ritanserin given 60 minutes prior to a subcutaneous injection of 10 $\mu\text{mol/kg}$ citalopram augmented the effect of citalopram significantly ($F(1,105) = 8.90$, $p < 0.05$). Post hoc analysis revealed significance from $t = 60$ to $t = 150$ minutes.

Ketanserin co-administration:

Ventral Hippocampus

Subcutaneous administration of 100 nmol/kg ketanserin had no effect on ventral hippocampal 5-HT levels. Subcutaneous administration of 10 $\mu\text{mol/kg}$ citalopram

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Administration of ketanserin did not show any effect on prefrontal cortex 5-HT levels. Subcutaneous administration of 10 $\mu\text{mol/kg}$ citalopram significantly increased 5-HT levels compared to saline injection ($F(1,159)=9.77, p<0.05$). Post hoc analysis revealed significance from t=45 to 150 minutes. Co-administration of 1nmol/kg of ketanserin did not augment the citalopram induced increase in cortical 5-HT levels ($F(1,117)=0.2781, p>0.05$). Co-administration of 10 nmol/kg ketanserin transiently enhanced the effect of citalopram. However, this effect did not reach significance ($F(1,127)=1.047, p>0.05$). Simultaneous administration of citalopram with 100 nmol/kg ketanserin showed a significant enhancement of the effect of citalopram ($F(1,127)=2.90, p<0.05$). Post-hoc analysis, however did not show any significant differences among the different time points.

Citalopram administration

Upon subcutaneous administration of 10 $\mu\text{mol/kg}$ citalopram initial plasma levels of around 0.7 μM developed, after which levels declined with an apparent half life of around 2 hours.

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877**Ketanserin administration**

Upon subcutaneous administration of 100 nmol/kg ketanserin initial plasma levels of around 0.2 μ M developed after 30 minutes. Levels declined with an apparent half life of around 1.5 hours.

The following combinations of compounds was also tested as described above:

Citalopram and irindalene, citalopram and RS 102221, citalopram and Lu 27121, citalopram and Lu 29066 and fluoxetine and ketanserin.

Results:

Subcutaneous administration of 1 μ mol/kg irindalene had no effect on rat ventral hippocampal 5-HT levels. Subcutaneous administration of 10 μ mol/kg citalopram significantly increased 5-HT levels compared to control. Simultaneous administration of 10 μ mol/kg citalopram with 1 μ mol/kg irindalene showed a significant enhancement of the effect of citalopram $F(1,129) = 5.91$.

Subcutaneous administration of 1 μ mol/kg RS 102221 had no effect on rat ventral hippocampal 5-HT levels. Subcutaneous administration of 10 μ mol/kg citalopram significantly increased 5-HT levels compared to control. Simultaneous administration of 10 μ mol/kg citalopram with 1 μ mol/kg RS 102221 showed a significant enhancement of the effect of citalopram $F(1,119) = 3.34$.

Subcutaneous administration of 1 μ mol/kg Lu 271212 had no effect on rat ventral hippocampal 5-HT levels. Subcutaneous administration of 10 μ mol/kg citalopram significantly increased 5-HT levels compared to control. Simultaneous administration of 10 μ mol/kg citalopram with 1 μ mol/kg Lu 27121 showed a significant enhancement of the effect of citalopram $F(1,120) = 4.25$.

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Subcutaneous administration of $1\mu\text{mol/kg}$ Lu 29066 had no effect on rat ventral hippocampal 5-HT levels. Subcutaneous administration of $10\mu\text{mol/kg}$ citalopram significantly increased 5-HT levels compared to control. Simultaneous administration of $10\mu\text{mol/kg}$ citalopram with $1\mu\text{mol/kg}$ Lu 29066 showed a significant enhancement of the effect of citalopram $F(1,120)=7.29$

Subcutaneous administration of 100 nmol/kg ketanserin had no effect on rat ventral hippocampal 5-HT levels. Simultaneous administration of 5 mg/kg fluoxetine with 100 nmol/kg ketanserin showed a significant enhancement of the effect of citalopram $F(1,69)=2.28$

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Claims:

1. The use of a compound which is a serotonin reuptake inhibitor and has affinity for the 5-HT_{2C} receptor, or a combination of a compound which is a serotonin reuptake inhibitor and another compound which is a 5-HT_{2C} receptor ligand, for the preparation of a pharmaceutical composition useful for the treatment of depression, anxiety disorders and other affective disorders, eating disorders such as bulimia, anorexia and obesity, social phobia, premenstrual syndrome and cognitive disorders.
2. The use according to claim 1 wherein a compound which is a serotonin reuptake inhibitor and has affinity for the 5-HT_{2C} receptor is used for the preparation of the pharmaceutical composition.
3. The use according to claim 1 wherein a combination of a compound which is a serotonin reuptake inhibitor and another compound which is a 5-HT_{2C} receptor ligand is used for the preparation of the pharmaceutical composition.
4. The use according to claims 1-3 wherein a selective serotonin reuptake inhibitor is used for the preparation of the pharmaceutical composition.
5. The use according to claims 1-3 wherein a compound which is selective for the 5-HT_{2C} receptor is used for the preparation of the pharmaceutical composition.
6. The use according to claims 1-5 wherein an antagonist or an inverse agonist at the 5-HT_{2C} receptor is used for the preparation of the pharmaceutical composition.
7. The use according to claims 1-5 wherein a partial agonist at the 5-HT_{2C} receptor is used for the preparation of the pharmaceutical composition.

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8. The use according to claims 1-7 wherein the compound or compounds used has a K_i value at the 5-HT_{2C} receptor which is below 30 nM and an IC_{50} value at the serotonin transporter which is below 20 nM.
9. The use according to claims 1-7 wherein the compound used has an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of irindalone to the 5-HT_{2C} receptor.
10. The use according to claims 1-7 wherein the compound used has an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of ketanserin to the 5-HT_{2C} receptor.
11. The use according to claims 1-7 wherein the compound used has an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of Lu 29066 to the 5-HT_{2C} receptor.
12. The use according to claims 1-7 wherein the compound used has an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of Lu 27121 to the 5-HT_{2C} receptor.
13. The use according to claims 1-7 wherein the compound used has an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of RB 102221 to the 5-HT_{2C} receptor.
14. The use according to claims 1-7 wherein the compound used has an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of mianserin to the 5-HT_{2C} receptor.
15. The use according to claims 1-7 wherein the compound used has an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of ritanserin to the 5-HT_{2C} receptor.

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16. The use according to claim 3 wherein the serotonin uptake inhibitor is selected from citalopram, dextrocitalopram, fluoxetine or its enantiomers, fluvoxamine, sertraline, paroxetine, fenoxetine, indalpine, nefazodone, venlafaxine and zimeldine.
17. The use according to claim 3 characterized in that the 5-HT_{2C} antagonist is selected from ketanserin, ritanserin, irindalone, RS 110221, Lu 27121, Lu 29066 and SB 206553.
18. The use according to claims 16-17 wherein the serotonin uptake inhibitor is citalopram or dextrocitalopram
19. The use according to claim 1 wherein the anxiety disorder is general anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post trauma stress disorder, or social anxiety disorder.
20. A pharmaceutical composition comprising compound which is a serotonin reuptake inhibitor and has affinity for the 5-HT_{2C} receptor, or a combination of a compound which is a serotonin reuptake inhibitor and another compound which is a 5-HT_{2C} receptor ligand, and optionally pharmaceutically acceptable carriers or diluents.
21. The pharmaceutical composition according to claim 20 comprising a compound which is a serotonin reuptake inhibitor that has affinity for the 5-HT_{2C} receptor
22. The pharmaceutical composition according to claim 20 comprising a combination of a compound which is a serotonin reuptake inhibitor and another compound which is a 5-HT_{2C} receptor ligand.
23. A pharmaceutical composition according to claims 20-23 comprising a selective serotonin reuptake inhibitor.

24. A pharmaceutical composition according to claims 20-22 comprising a compound which is an antagonist or an inverse agonist at the 5-HT_{2C} receptor.
25. A pharmaceutical composition according to claims 20-22 comprising a compound which is a partial agonist at the 5-HT_{2C} receptor.
26. A pharmaceutical composition according to claims 22-25 comprising a compound which is selective for the 5-HT_{2C} receptor.
27. A pharmaceutical composition according to claims 20-26 comprising a compound or compounds that has an IC₅₀ value below 20 nM at the serotonin transporter and a K_i value below 30 nM at the 5-HT_{2C} receptor.
28. A pharmaceutical composition according to claims 20-26 comprising a compound having an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of indalolone at this receptor.
29. A pharmaceutical composition according to claims 20-26 comprising a compound having an affinity to 5-HT_{2C} receptor which is higher or equal to the affinity of ketanserin at this receptor.
30. A pharmaceutical composition according to claims 20-26 comprising a compound having an affinity to 5-HT_{2C} receptor which is higher or equal to the affinity of Ln 29066 at this receptor.
31. A pharmaceutical composition according to claims 20-26 comprising a compound having an affinity to the 5-HT_{2C} receptor is higher or equal to the affinity of Ln 27121 at this receptor.
32. A pharmaceutical composition according to claims 20-26 comprising a compound having an affinity to the 5-HT_{2C} receptor is higher or equal to the affinity of RS 110221 at this receptor.

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33. A pharmaceutical composition according to claims 20-26 comprising a compound having an affinity to the 5-HT_{2C} receptor which is higher or equal to the affinity of mianserin at this receptor.
34. A pharmaceutical composition according to claims 20-26 comprising a compound having an affinity to the 5-HT_{2C} receptor is higher or equal to the affinity of ritanserin at this receptor.
35. A pharmaceutical composition according to claim 22 characterized in that the serotonin uptake inhibitor is selected from citalopram, dextrocitalopram, fluoxetine or its enantiomers, fluvoxamine, sertraline, paroxetine and fenoxetine, nefazodone, venlafaxine, indalpine and zimeldine.
36. A pharmaceutical composition according to claim 22 characterized in that the 5-HT_{2C} ligand is selected from ketanserin, risperidone, indalpine, RS 110221, La 27121, Lu 29066 and SB 206553.
37. A pharmaceutical composition according to claims 35-36 characterized in that the serotonin uptake inhibitor is citalopram or dextrocitalopram.
38. A pharmaceutical composition according to claim 20 wherein the pharmaceutical composition is adapted for simultaneous administration of the active ingredients.
39. A pharmaceutical composition according to claim 20 wherein the pharmaceutical composition is adapted for sequential administration of the active ingredients.
40. A method for the identification of compounds useful for the treatment of depression, anxiety disorders and other affective disorders, eating disorders such as bulimia, anorexia and obesity, social phobia, premenstrual syndrome and cognitive disorders comprising, in any order:

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- (a) measuring the ability of test compounds to inhibit serotonin reuptake and selecting the compounds that have an IC_{50} value below 20 nM;
 - (b) measuring the affinity of test compounds to the 5-HT_{2C} receptor and selecting the compounds that have K_i values below 30 nM;
- and thereafter measuring the efficacy of the selected compounds at the 5-HT_{2C} receptor and selecting the compounds which are antagonists or inverse agonists at the receptor.

41. A compound identified according to claim 40.

42. A method of improving the onset of therapeutic action by concomitant administration of a first component

- a) which is a serotonin reuptake inhibitor; and
- b) a compound with affinity to the 5-HT_{2C} receptor which act to augment the effect of the serotonin reuptake inhibitor.

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Abstract

The present invention relates to the use of compounds and compositions of compounds having serotonin reuptake inhibiting activity and 5-HT_{2C} antagonistic, partial agonistic or inverse agonistic activity for the treatment of depression and other affective disorders. The combined serotonin reuptake inhibiting effect and the 5-HT_{2C} antagonistic, partial agonistic or inverse agonistic effect may reside within the same chemical compound or in two different chemical compounds.

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Oficina de Patentes y Marcas de los Estados Unidos

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SOLICITUD NUMERO: 60/169,245

FECHA DE PRESENTACION: 6 de diciembre de 1999



**Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS**

**Firmado por
L. EDELEN**

Funcionario Certificador

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REIVINDICACIONES

1. El uso de un compuesto el cual es inhibidor de la recaptación de serotonina y tiene afinidad por el receptor 5-HT_{2c}, o una combinación de un compuesto el cual es inhibidor de la recaptación de serotonina y otro compuesto el cual es un ligando del receptor 5-HT_{2c}, para la preparación de una composición farmacéutica útil para el tratamiento de depresión, desórdenes de ansiedad y otros desórdenes afectivos, desórdenes alimenticios como bulimia, anorexia y obesidad, fobia social, síndromes premenstruales y desórdenes cognitivos.
2. El uso de acuerdo a la reivindicación 1 donde un compuesto el cuales un inhibidor de la recaptación de serotonina y tiene afinidad por el receptor 5-HT_{2c} es usado para la preparación de la composición farmacéutica.
3. El uso de acuerdo a la reivindicación 1 donde una combinación del compuesto el cual es un inhibidor de la recaptación de serotonina y otro compuesto el cual es un ligando del receptor 5-HT_{2c} es usado para la preparación farmacéutica.
4. El uso de acuerdo a las reivindicaciones 1 a 3 donde un inhibidor selectivo de la recaptación de serotonina es usado para la preparación de la composición farmacéutica.

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5. El uso de acuerdo a las reivindicaciones 1-3 donde un compuesto el cual es selectivo para el receptor 5-HT_{2c} es usado para la preparación de la composición farmacéutica.
6. El uso de acuerdo a las reivindicaciones 1-5 donde un antagonista o el inverso del antagonista en el receptor 5-HT_{2c} es usado para la preparación de la composición farmacéutica.
7. El uso de acuerdo a las reivindicaciones 1-5 donde un agonista parcial en el receptor 5-HT_{2c} es usado para la preparación de una composición farmacéutica.
8. El uso de acuerdo a las reivindicaciones 1-7 donde el compuesto o compuestos usados tiene un valor K_i en el receptor 5-HT_{2c} el cual es inferior a 30 nM y un valor IC₅₀ en el portador de serotonina el cual es inferior a 20 nM.
9. El uso de acuerdo a las reivindicaciones 1-7 donde el compuesto usado tiene una afinidad con el receptor 5-HT_{2c} la cual es mayor o igual a la afinidad de la irindalona con el receptor de 5-HT_{2c}.
10. El uso de acuerdo a las reivindicaciones 1-7 donde el compuesto usado tiene una afinidad con el receptor 5-HT_{2c} la cual es mayor o igual a la afinidad de la ketanserina con el receptor de 5-HT_{2c}.

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11. El uso de acuerdo a las reivindicaciones 1-7 donde el compuesto usado tiene una afinidad con el receptor 5-HT_{2c} la cual es mayor o igual a la afinidad de Lu 29066 con el receptor de 5-HT_{2c}.
12. El uso de acuerdo a las reivindicaciones 1-7 donde el compuesto usado tiene una afinidad con el receptor 5-HT_{2c} la cual es mayor o igual a la afinidad de Lu 27121 con el receptor de 5-HT_{2c}.
13. El uso de acuerdo a las reivindicaciones 1-7 donde el compuesto usado tiene una afinidad con el receptor 5-HT_{2c} la cual es mayor o igual a la afinidad de RS 102221 con el receptor de 5-HT_{2c}.
14. El uso de acuerdo a las reivindicaciones 1-7 donde el compuesto usado tiene una afinidad con el receptor 5-HT_{2c} la cual es mayor o igual a la afinidad de mianserina con el receptor de 5-HT_{2c}.
15. El uso de acuerdo a las reivindicaciones 1-7 donde el compuesto usado tiene una afinidad con el receptor 5-HT_{2c} la cual es mayor o igual a la afinidad de ritanserina con el receptor de 5-HT_{2c}.
16. El uso de acuerdo a la reivindicación 3 donde el inhibidor de la recaptación de serotonina se selecciona de citalopram, dextrocitalopram, fluoxetina, o sus enantómeros, fluvoxamina, sertralina, paroxetina, femoxetina, indalpina, nefazodon, venlafaxina y zimeldina.

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17. El uso de acuerdo a la reivindicación 3 caracterizado en que el antagonista de 5-HT_{2c} se selecciona de ketaserina, ritanserina, irindalona, RS 110221, Lu 27121, Lu 29066 y SB 206553.
18. El uso de acuerdo a las reivindicaciones 16-17 donde el inhibidor de la recaptación de serotonina es citalopram o dextrocitalopram.
19. El uso de acuerdo a la reivindicación 1 donde el desorden de ansiedad es desorden de ansiedad general, ansiedad de pánico, desorden compulsivo obsesivo, desorden de estrés agudo, desorden de estrés post trauma, o desorden de ansiedad social.
20. Una composición farmacéutica que comprende un compuesto el cual es un inhibidor de la recaptación de serotonina y tiene afinidad por el receptor 5-HT_{2c}, o una combinación de un compuesto el cual es un inhibidor de la recaptación de serotonina y otro compuesto el cual es un ligando del receptor 5-HT_{2c}, y opcionalmente portadores farmacéuticamente aceptables o diluyentes.
21. La composición farmacéutica de acuerdo a la reivindicación 20, que comprende un compuesto el cual es un inhibidor de la recaptación de serotonina que tiene afinidad por el receptor 5-HT_{2c}.
22. La composición farmacéutica de acuerdo con la reivindicación 20 que comprende la combinación de un compuesto el cual es un

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inhibidor de la recaptación de serotonina y otro compuesto el cual es un ligando del receptor 5-HT_{2c}.

23. Una composición farmacéutica de acuerdo a las reivindicaciones 20-23 que comprende un inhibidor selectivo de la recaptación de serotonina.

24. Una composición farmacéutica de acuerdo a las reivindicaciones 20-22 que comprende un compuesto el cual es un antagonista o un agonista inverso en el receptor 5-HT_{2c}.

25. Una composición farmacéutica de acuerdo a las reivindicaciones 20-22 que comprende un compuesto el cual es un agonista parcial en el receptor 5-HT_{2c}.

26. Una composición farmacéutica de acuerdo a las reivindicaciones 22-25 que comprende un compuesto el cual es selectivo para el receptor 5-HT_{2c}.

27. Una composición farmacéutica de acuerdo a las reivindicaciones 20-26 que comprende un compuesto o compuestos que tiene un valor IC₅₀ menor a 20nM en el portador de serotonina y un valor K_i inferior a 30nM en el receptor 5-HT_{2c}.

28. Una composición farmacéutica de acuerdo a las reivindicaciones 20-26 que comprende un compuesto que tiene una afinidad por el

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receptor 5-HT_{2c} el cual es mayor o igual a la afinidad de irindalona en ese receptor.

29. Una composición farmacéutica de acuerdo a las reivindicaciones 20-26 que comprenden un compuesto que tiene una afinidad al receptor 5-HT_{2c} el cual es mayor o igual a la afinidad de ketaserina en ese receptor.

30. Una composición farmacéutica de acuerdo a las reivindicaciones 20-26 que comprende un compuesto que tiene una afinidad al receptor 5-HT_{2c} el cual es mayor o igual a la afinidad del Lu 29066 en ese receptor.

31. Una composición farmacéutica de acuerdo a las reivindicaciones 20-26 que comprende un compuesto que tiene una afinidad al receptor 5-HT_{2c} el cual es mayor o igual a la afinidad del Lu 27121 en ese receptor.

32. Una composición farmacéutica de acuerdo a las reivindicaciones 20-26 que comprende un compuesto que tiene una afinidad al receptor 5-HT_{2c} el cual es mayor o igual a la afinidad de RS 110221 en ese receptor.

33. Una composición farmacéutica de acuerdo a las reivindicaciones 20-26 que comprende un compuesto que tiene una afinidad al receptor 5-HT_{2c} el cual es mayor o igual a la afinidad de la mianserina en ese receptor.

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34. Una composición farmacéutica de acuerdo a las reivindicaciones 20-26 que comprende un compuesto que tiene una afinidad al receptor 5-HT_{2c} el cual es mayor o igual a la afinidad de la ritanserina en ese receptor.
35. Una composición farmacéutica de acuerdo a la reivindicación 22 caracterizada en que el inhibidor de la recaptación de la serotonina se selecciona de citalopram, dextrocitalopram, fluoxetina o sus enantiómeros, fluvoxamina, sertralina, paroxetina, y femoxetina, nefazodone, venlafaxina, indalpina, y zimeldina.
36. Una composición farmacéutica de acuerdo a la reivindicación 22 caracterizada en que el ligando del 5-HT_{2c} se selecciona de ketanserina, rianserina, irindalona, RS 110221, Lu 27121, Lu 29066 y SB 206553.
37. Una composición farmacéutica de acuerdo a las reivindicaciones 35-36 caracterizado en que el inhibidor de la recaptación de serotonina es citalopram o dextrocitalopram.
38. Una composición farmacéutica de acuerdo a la reivindicación 20 donde la composición farmacéutica se adapta para administración simultánea de los ingredientes activos.

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39. Una composición farmacéutica de acuerdo a la reivindicación 20 donde la composición farmacéutica se adapta para administración secuencial de los ingredientes activos.

40. Un método para la identificación de los compuestos útil para el tratamiento de la depresión, desórdenes de ansiedad y otros desórdenes afectivos, desórdenes alimenticios como bulimia, anorexia, y obesidad, fobia social, síndrome premenstrual y desórdenes cognitivos que comprende en cualquier orden:

(a) medir la habilidad de los compuestos prueba para inhibir la recaptación de serotonina y seleccionar los compuestos que tienen un valor IC_{50} inferior a 20 nM;

(b) medir la afinidad de los compuestos prueba con el receptor 5-HT_{2c} y seleccionar los compuestos que tienen valores K_i inferiores a 30 nM;

y posteriormente medir la eficacia de los compuestos seleccionados en el receptor 5-HT_{2c} y seleccionar los compuestos los cuales son antagonistas o agonistas inversos en el receptor.

41. Un compuesto identificado de acuerdo a la reivindicación 40.

42. Un método para mejorar el acceso de la acción terapéutica por la administración concomitante de un primer componente

(a) el cual es un inhibidor de la recaptación de serotonina; y

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(b) un compuesto con afinidad al receptor 5-HT_{2c} el cual actúa para aumentar el efecto del inhibidor de la recaptación de serotonina.

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