



Combination therapy wherein a serotonin reuptake inhibitor is used

The present invention relates to the combination of a serotonin reuptake inhibitor and a GABA_B receptor antagonist. Accordingly, the present invention relates to the use of certain compounds, and to compositions of compounds having serotonin reuptake inhibiting activity and GABA_B antagonistic, partial agonistic or inverse agonistic activity for the treatment of depression and other affective disorders. The combined serotonin reuptake inhibiting effect and the GABA_B 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.

However, 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, which has a rather profound effect on the patient's motivation to continue pharmacotherapy.

First of all, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Secondly, 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.



In 1993, an augmentation strategy with pindolol was described by Artigas et al. in *Trends Pharmacol. Sci.* **1993**, *14*, p 262-263. Artigas' idea is based on intracerebral microdialysis experiments in animals. In fact, later neurochemical studies built on the desensitization hypothesis by Blier and co-workers stated 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 somatodendritic autoreceptors (5-HT_{1A}) limit the release of 5-HT in terminal areas and thus the effect of 5-HT uptake inhibition in those regions. 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 (Innis, R.B. et al. *Eur. J. Pharmacol.* **1987**, *143*, p. 1095-204 and Gartside, S.E., *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.

Several patent applications covering the combination of an SSRI and a 5-HT_{1B} antagonist or partial agonist have also been filed (WO 97/28141, WO 96/03400, EP-A-701819 and WO 99/13877).

5 γ-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the brain; up to 50% of all central synapses are GABA-ergic (Paredes R.G. & Agmo A., Neuroscience and Biobehavioural Reviews, vol 16: pp 145-170 (1992)).

Noradrenaline, dopamine and serotonin (5-HT) are all under inhibitory control of
10 GABA (Haefely W. The role of GABA in anxiolytic/antidepressant drug action. Elliott M.M., Heal D.J. & Marsden C.A. (eds), pp 151-168, John Wiley & Sons, New York (1992)). There are two subtypes of GABA receptors, GABA_A and GABA_B, which have been extensively studied and their influence on 5HT nerve function and release have been performed.

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Thus stimulation of the GABA_A receptor with the agonist muscimol reduced 5-HT cell activity & 5-HT release in the raphé nuclei (Tao R. & Auerbach S.B. J. Psychopharmacology vol 14(2): pp 100-113 (2000)) and blockade of GABA_A
20 receptors increases firing and subsequently elevates levels of extracellular 5-HT (see below - bicuculline & Tao R. *et al.*, British Journal of Pharmacology vol 119: pp 1375-1384 (1996)).

The GABA_B agonist baclofen produced a decrease in 5-HT in the raphé and reduction in the forebrain (Tao R. *et al.*, British Journal of Pharmacology vol 119: pp 1375-1384
25 (1996)) and when administered by itself the GABA_B antagonist, phaclofen, is devoid of effect on 5-HT levels in either the raphé (Abellán M.T. *et al.*, Neuroreport vol 11: pp941-945 (2000); Tao R. *et al.*, British Journal of Pharmacology vol 119: pp 1375-1384 (1996)) or in the forebrain (see below & Tao R. *et al.*, British Journal of Pharmacology vol 119: pp 1375-1384 (1996)). However, phaclofen, administered
30 either centrally into the hippocampus or systemically was shown to significantly increase the effects of citalopram on extracellular 5-HT levels, as demonstrated in the findings reported here.

The invention

It has now surprisingly been found that a GABA_B antagonist will augment the effect of an SSRI on extracellular 5-HT levels.

It is therefore suggested that the combination of an SSRI and a GABA_B antagonist or a molecule, which has both 5-HT reuptake inhibitory and GABA_B antagonistic properties, would have a better efficacy and faster onset than an SSRI alone.

Antagonism at any GABA_B splice variants, including but not limited to GABA_{BR1a} and GABA_{BR1b} is claimed.

The disclosure herein covers both SSRI + GABA_B antagonist in separate or the same molecule.

In a first aspect, there is provided the use of a compound, which is a serotonin reuptake inhibitor, and another compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist for the preparation of a pharmaceutical composition for the treatment of affective disorders selected from the group consisting of depression, anxiety disorders, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders selected from the group consisting of bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors.

In a second aspect, there is provided the use of a GABA_B receptor antagonist, inverse agonist or partial agonist for the preparation of a pharmaceutical composition to be used in combination with a serotonin reuptake inhibitor for the treatment of affective disorders selected from the group consisting of depression, anxiety disorders, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders selected from the group consisting of bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder. drug abuse or any other disorder responsive to serotonin reuptake inhibitors.

The disclosure herein also relates to the use of a GABA_B receptor antagonist, inverse agonist or partial agonist for the preparation of a pharmaceutical composition useful for augmenting and/or providing faster onset of the therapeutic effect of a serotonin reuptake inhibitor.

In a preferred embodiment, the disclosure herein relates to the use as above wherein the serotonin reuptake inhibitor is used for the treatment of depression, anxiety disorders and other affective disorders, including generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder or social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse and any other disorder responsive to a SRI.

In another embodiment, the disclosure herein relates to the use of

- a) a compound which is a serotonin reuptake inhibitor and a GABA_B receptor antagonist, inverse agonist or partial agonist, or
- b) a combination of a compound, which is a serotonin reuptake inhibitor, and a compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist,

for the preparation of a pharmaceutical composition or kit (kit-of-parts) useful for the treatment of depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors.

In two independent embodiments, the disclosure herein relates to the use of a compound, which is a serotonin reuptake inhibitor, and a compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist, for the preparation of a:

- (a) pharmaceutical composition, or

(b) kit

useful for the treatment of depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors.

In a third aspect, there is provided a pharmaceutical composition comprising a compound, which is a serotonin reuptake inhibitor, and another compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist, and optionally pharmaceutically acceptable carriers or diluents.

In a fourth aspect, there is provided a kit comprising:

- i) a GABA_B receptor antagonist, inverse agonist or partial agonist in a first-unit dosage form;
- ii) a serotonin reuptake inhibitor in a second-unit dosage form; and
- iii) a container means for containing said first-unit and second-unit dosage forms.

In a further embodiment, the disclosure herein relates to a pharmaceutical composition or kit comprising:

- a) a compound, which is a serotonin reuptake inhibitor, and a GABA_B receptor antagonist, inverse agonist or partial agonist, or
 - b) a combination of a compound, which is a serotonin reuptake inhibitor, and another compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist,
- and optionally pharmaceutically acceptable carriers or diluents.

In two further individual embodiments, the disclosure herein relates to either a pharmaceutical composition or a kit comprising a compound, which is a serotonin reuptake inhibitor, and another compound, which is a GABA_B receptor

antagonist, inverse agonist or partial agonist, and optionally pharmaceutically acceptable carriers or diluents.

In yet another embodiment, the disclosure herein relates to a method for the treatment of depression, anxiety disorders and other affective disorders, such as generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors comprising administering to a person in need thereof a therapeutically effective amount of

- a) a compound, which is a serotonin reuptake inhibitor, and a GABA_B receptor antagonist, inverse agonist or partial agonist, or
- b) a combination of a compound, which is a serotonin reuptake inhibitor and a compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist.

Whenever mentioned, each of the options

- a) a compound, which is a serotonin reuptake inhibitor, and a GABA_B receptor antagonist, inverse agonist or partial agonist, and
- b) a combination of a compound, which is a serotonin reuptake inhibitor and a (or another) compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist

are intended to be individual embodiments. Accordingly, each of them may be claimed individually.

Each of the medical indications depression, anxiety disorders and other affective disorders, including generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder or social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse and any other disorder responsive to a SRI is intended to be an individual embodiment. Accordingly, whenever mentioned in the disclosure herein, each of the indications specified above may be claimed individually.

Whenever the indications depression, anxiety disorders and other affective disorders, including generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder or social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse and any other disorder responsive to a SRI are mentioned in relation to use of a GABA_B receptor antagonist, inverse agonist or partial agonist and an SRI, a pharmaceutical composition, a kit, a method of

treatment and a method for the identification of compounds useful for treatment it is intended to be an individual embodiment. Accordingly, each of the indications specified above may individually be claimed together with said use of a GABA_B receptor antagonist, inverse agonist or partial agonist and an SRI, pharmaceutical composition, kit, method of treatment and method for the identification of compounds useful for treatment.

In a particular embodiment, a selective serotonin reuptake inhibitor is used as disclosed herein.

In another particular embodiment, a compound, which is selective for the GABA_B receptor is used as disclosed herein.

In a further embodiment, a compound, which is an antagonist, an inverse agonist at the GABA_B receptor is used as disclosed herein.

The pharmaceutical composition or kit as disclosed herein may be administered by simultaneous administration. The term "simultaneous administration" as used herein means, that the GABA_B receptor antagonist, inverse agonist or partial agonist and the SRI are administered with a time separation of no more than 15 minutes, such as at most 10 minutes, such as at most 5 minutes or such as at most 2 minutes. The GABA_B receptor antagonist, inverse agonist or partial agonist and the SRI may be contained in the "same unit dosage form" or in "discrete dosage forms". As used herein, the term "same unit dosage form" means a dosage form comprising both the SRI and the GABA_B receptor antagonist, inverse agonist or partial agonist. As used herein, the term "discrete dosage form" means that the GABA_B receptor antagonist, inverse agonist or partial agonist is comprised in one dosage form and that the SRI is comprised in another dosage form.

Simultaneous administration of GABA_B receptor antagonist, inverse agonist or partial agonist and the SRI is optionally combined with administration of supplementary doses of GABA_B receptor antagonist, inverse agonist or partial agonist. The supplementary doses of GABA_B receptor antagonist, inverse agonist or partial agonist

may be given for instance 1, 2, 3 or 4 times a day whereas the SRI and the GABA_B receptor antagonist, inverse agonist or partial agonist which are administered by “simultaneous administration” may be given one or more times a day, e.g. once daily or e.g. twice daily. Accordingly:

- 5 • the GABA_B receptor antagonist, inverse agonist or partial agonist and the SRI may be administered by simultaneous administration once daily and supplementary doses of GABA_B receptor antagonist, inverse agonist or partial agonist may be administered 1, 2, 3 or 4 times a day, such as 1, 2 or 3 times a day, such as once or twice daily, such as twice daily or such as once daily,
- 10 or
- the GABA_B receptor antagonist, inverse agonist or partial agonist and the SRI may be administered by simultaneous administration twice daily and supplementary doses of GABA_B receptor antagonist, inverse agonist or partial agonist may be administered 1, 2, 3 or 4 times a day, such as 1, 2 or 3 times a
- 15 day, such as once or twice daily, such as twice daily or such as once daily.

Alternatively, the pharmaceutical composition or kit as disclosed herein is administered by sequential administration. The term “sequential administration” as used herein means that 1 or more daily doses of GABA_B receptor antagonist, inverse agonist or partial agonist and 1 or more daily doses of SRI are administered with a

20 time separation between two administered doses of more than 15 minutes and less than 4 hours, such as more than 2 hours and less than 4 hours, such as more than 15 minutes and less than 2 hours, such as more than 1 hour and less than 2 hours, such as more than 30 minutes and less than 1 hour, such as more than 15 minutes and less

25 than 30 minutes. Either the SRI or the GABA_B receptor antagonist, inverse agonist or partial agonist may be administered first. The GABA_B receptor antagonist, inverse agonist or partial agonist and the SRI are contained in discrete dosage forms, optionally contained in the same container or package. Typically, 1, 2, 3, 4 or 5 daily doses of GABA_B receptor antagonist, inverse agonist or partial agonist and 1 or 2

30 daily doses of SRI may be administered. Accordingly:

- the GABA_B receptor antagonist, inverse agonist or partial agonist and the SRI may be administered once daily and the GABA_B receptor antagonist, inverse agonist or partial agonist may be administered 1, 2, 3, 4 or 5 times a day, such

as 1, 2, 3 or 4 times a day, such as 1, 2 or 3 times a day, such as once or twice daily, such as twice daily or such as once daily,

or

- the GABA_B receptor antagonist, inverse agonist or partial agonist and the SRI may be administered twice daily and the GABA_B receptor antagonist, inverse agonist or partial agonist may be administered 1, 2, 3, 4 or 5 times a day, such as 1, 2, 3 or 4 times a day, such as 1, 2 or 3 times a day, such as once or twice daily, such as twice daily or such as once daily.

Accordingly, the pharmaceutical composition or kit as disclosed herein may be adapted for simultaneous administration of the active ingredients, or it may be adapted for sequential administration of the active ingredients. When the pharmaceutical composition or kit is adapted for simultaneous administration, the active ingredients may be contained in the same unit dosage form. When the pharmaceutical composition or kit is adapted for sequential administration, the active ingredients are contained in discrete dosage forms, optionally contained in the same container or package. As used herein, an "active ingredient" means an SRI or a GABA_B receptor antagonist, inverse agonist or partial agonist.

A kit (kit-of-parts) comprises a preparation of the GABA_B receptor antagonist, inverse agonist or partial agonist in a first-unit dosage form, and the SRI in a second-unit dosage form, and container means for containing said first and second dosage forms.

In particular, the disclosure herein relates to the use of, and to pharmaceutical compositions or kits comprising the following combinations:

CGP 55845 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, vilazodone, duloxetine, nefazodone, imipramin, femoxetine and clomipramine,

CGP 62349 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

CGP 71982 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

- 5 CGP 76290 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

- 10 CGP 76291 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

- 15 CGP 35348 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

- 20 CGP 36742 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

- CGP 46381 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

- 25 CGP 52432 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

- 30 CGP 54626 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

CGP 55845, CGP 62349, CGP 71982, CGP 76290, CGP 76291, CGP 35348, CGP 36742, CGP 46381, CGP 52432 and CGP 54626 are disclosed in Bowery NG et al. *Pharmacological Reviews* 2002, 54 No. 2, p. 247-264.

SCH 50911 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

Phaclofen and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

Saclofen and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

2-hydroxysaclofen and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine,

GAS 360 and an SRI selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine .

In a fifth aspect, there is provided a method for the identification of compounds useful for the treatment of affective disorders selected from the group consisting of depression, anxiety disorders, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders selected from the group consisting of bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake

inhibitors, comprising, in any order:

- (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 $GABA_B$ receptor and selecting the compounds,

and thereafter measuring the efficacy of the selected compounds at the $GABA_B$ receptor and selecting the compounds which are antagonists, inverse agonists or partial agonists at the receptor.

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Preferred GABA_B ligands show affinity of below 1,5 µM, whereas other preferred
10 ligands show affinity of below 1,0 µM and yet other preferred ligands show affinity of
below 500 nM. Even more preferred are compounds with affinity below 100 nM.

Examples of assays for the selection / detection of GABA_B antagonists, inverse
agonists or partial agonists are for example the following:

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Binding assay for the detection of compounds with affinity for GABA_B receptors are
described in Karla et. al. *J. Med. Chem.* **1999**, 42(11), 2053-2059; or Frydenvang et.
al. *Chirality* **1994**; 6(7); 583-589;

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Efficacy assay for the detection of antagonists, partial agonists or inverse agonists at
the GABA_B receptors are for example: Kamatchi et. al. *Brain Res.* **1990**, 506(2), 181-
186; or Brauner-Osborne et. al. *Br. J. Pharmacol.* **1999**, 128(7), 1370-1374.

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The disclosure herein also covers compounds identified according to this method but
is not limited to theses assay methods.

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According to the disclosure herein, it has been found that co-administration of GABA_B
receptor antagonist or inverse agonist and a serotonin reuptake inhibitor produces a
significant increase in the level of serotonin in terminal areas, as measured in
microdialysis experiments, compared to the administration of the serotonin reuptake
inhibitor alone.

According to the disclosure herein, animal studies have shown that GABA_B receptor antagonist or inverse agonist may provide fast onset of therapeutic effect of serotonin reuptake inhibitors and potentiate the anxiolytic potential of serotonin reuptake inhibitors.

- 5 The use of a combination of GABA_B receptor antagonist, inverse agonist or partial agonist and a serotonin reuptake inhibitor may greatly reduce the amount of serotonin reuptake inhibitor necessary to treat depression and other affective disorders and may thus reduce the side effects caused by the serotonin reuptake inhibitor. In particular, the combination of a reduced amount of SRI and a GABA_B receptor antagonist,
10 inverse agonist or partial agonist may reduce the risk of SSRI-induced sexual dysfunction and sleep disturbances.

Co-administration of a GABA_B receptor antagonist, inverse agonist or partial agonist and a serotonin reuptake inhibitor may also be useful for the treatment of refractory
15 depression, i.e. depression, which cannot be treated appropriately by administration of a serotonin reuptake inhibitor alone. Typically, GABA_B receptor antagonist, inverse agonist or partial agonist may be used as add-on therapy for the augmentation of the response to SRIs in patients where at least 40-60% reduction in symptoms has not been achieved during the first 6 weeks of treatment with an SRI.

20 Compounds which are both serotonin reuptake inhibitors and GABA_B receptor antagonists, inverse agonists or partial agonists may have the same pharmacological advantages as the combination of a serotonin reuptake inhibitor and a GABA_B receptor antagonists, inverse agonists or partial agonists, with respect to reduction of side effects, fast onset and in the treatment of treatment resistant patients.

Many antidepressants with serotonin reuptake inhibiting effect have been described in the literature. Any pharmacologically active compound, which primarily or partly exert its therapeutic effect via inhibition of serotonin reuptake in the CNS, may
30 benefit from augmentation with a GABA_B receptor antagonist, inverse agonist or partial agonist.

The following list contains a number of serotonin reuptake inhibitors, which may benefit from augmentation with a GABA_B receptor antagonist, inverse agonist or partial agonist: citalopram, escitalopram, fluoxetine, R-fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, desmethylvenlafaxine, duloxetine, dapoxetine, vilazodone, nefazodone, imipramine, imipramine N-oxide, desipramine, pirandamine, dazepinil, nefopam, befuraline, fezolamine, femoxetine, clomipramine, cianoimipramine, litoxetine, cericlamine, seproxetine, WY 27587, WY 27866, imeldine, ifoxetine, indeloxazine, tiflucarbine, viqualine, milnacipran, bazinaprine, YM 922, S 33005, F 98214-TA, FI 4503, A 80426, EMD 86006, NS 2389, S33005, OPC 14523, alaproclate, cyanodothepine, trimipramine, quinupramine, dothiepin, amoxapine, nitroxazepine, McN 5652, McN 5707, VN 2222, L 792339, roxindole, YM 35992, Ol 77, Org 6582, Org 6997, Org 6906, amitriptyline, amitriptyline N-oxide, nortriptyline, CL 255.663, pirlindole, indatraline, LY 280253, LY 285974, LY 113.821, LY 214.281, CGP 6085 A, RU 25.591, napamezole, diclofensine, trazodone, BMY 42.569, NS 2389, serclorephine, nitroquipazine, ademethionine, sibutramine, desmethylsibutramine, didesmethylsibutramine, clovoxamine vilazodone. The compounds mentioned above may be used in the form of the base or a pharmaceutically acceptable acid addition salt thereof. Each of the serotonin reuptake inhibitors specified above is intended to be an individual embodiment. Accordingly, each of them and the use thereof may be claimed individually.

Compounds such as citalopram, escitalopram, fluoxetine, R-fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, desmethylvenlafaxine, duloxetine, dapoxetine, vilazodone, nefazodone, imipramine, imipramine N-oxide, desipramine, pirandamine, dazepinil, nefopam, befuraline, fezolamine, femoxetine, clomipramine, cianoimipramine, litoxetine, cericlamine, seproxetine, imeldine, ifoxetine, indeloxazine, tiflucarbine, viqualine, milnacipran, bazinaprine, alaproclate, cyanodothepine, trimipramine, quinupramine, dothiepin, amoxapine, nitroxazepine, roxindole, amitriptyline, amitriptyline N-oxide, nortriptyline, pirlindole, indatraline, napamezole, diclofensine, trazodone, serclorephine, nitroquipazine, ademethionine, sibutramine, desmethylsibutramine, didesmethylsibutramine, clovoxamine vilazodone,

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N-[(1-[(6-Fluoro-2-naphthalenyl)methyl]-4-piperidyl]amino]carbonyl]-3-pyridine
carboxamide (WY 27587),

[trans-6-(2-chlorophenyl)-1,2,3,5,6,10b-hexahydropyrrolo- (2,1-a)isoquinoline] (McN
5707),

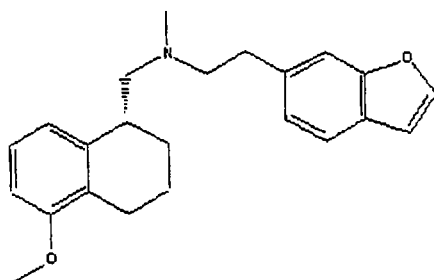
5 (dl-4-exo-amino-8-chloro-benzo-(b)-bicyclo[3.3.1]nona-2-6 alpha(10 alpha)-diene
hydrochloride)(Org 6997),

(dl)-(5 alpha,8 alpha,9 alpha)-5,8,9,10-Tetrahydro-5,9- methanobenzocycloocten-8-
amine hydrochloride (Org 6906),

-[2-[4-(6-fluoro-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]ethyl]-3-isopropyl-6-
10 (methylsulphonyl)-3,4-dihydro-1H-2,1,3-benzothiadiazine-2,2-dioxide (LY393558),

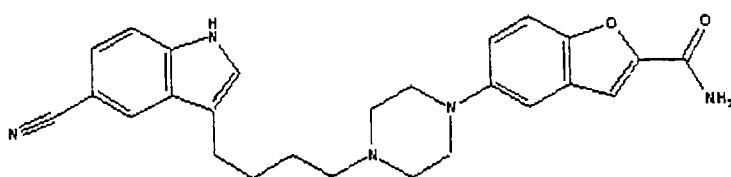
[4-(5,6-dimethyl-2-benzofuranyl)-piperidine] (CGP 6085),

dimethyl-[5-(4-nitro-phenoxy)-6,7,8,9-tetrahydro-5H-benzocyclohepten-7-yl]-amine
(RU 25.591),

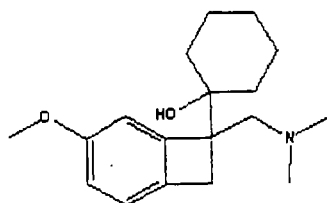


(A 80426),

15



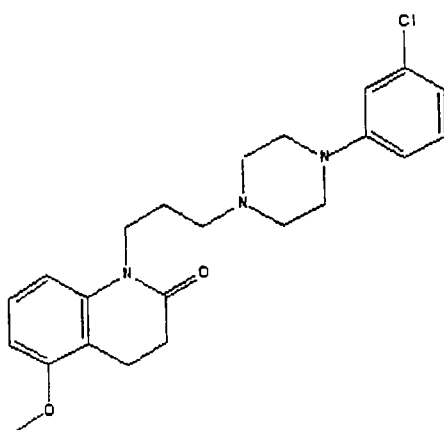
(EMD 86006),



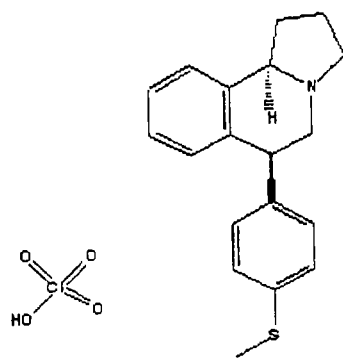
(S33005),

20

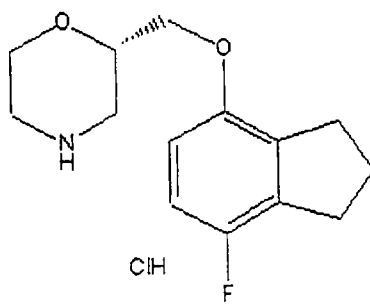
17



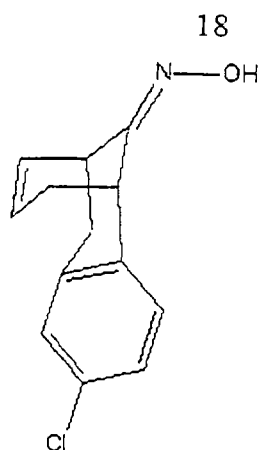
(OPC 14523),



(McN 5652),



(YM 35992),



are preferred. The compounds mentioned above may be used in the form of the base or a pharmaceutically acceptable acid addition salt thereof. Each of the serotonin reuptake inhibitors specified above is intended to be an individual embodiment.

5 Accordingly, each of them and the use thereof may be claimed individually.

Other therapeutic compounds, which may benefit from augmentation with GABA_B receptor antagonists, inverse agonist or partial agonists, include compounds, which cause an elevation in the extracellular level of 5-HT in the synaptic cleft, although
10 they are not serotonin reuptake inhibitors. One such compound is tianeptine.

Accordingly, other compounds than SRIs which cause an elevation in the extracellular level of serotonin, may be used instead of SRIs in every aspect of the disclosure herein.

15

The above list of serotonin reuptake inhibitors and other compounds, which cause an increase in the extracellular level of serotonin, may not be construed as limiting.

SRIs, which are particularly preferred according to the disclosure herein, include
20 citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine.

The term selective serotonin reuptake inhibitor (SSRI) means an inhibitor of the
25 monoamine transporters, which has stronger inhibitory effect at the serotonin transporter than the dopamine and the noradrenaline transporters. Particularly

preferred SSRIs as disclosed herein are citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, duloxetine, vilnazodone and paroxetine.

In particular individual embodiments, citalopram or escitalopram is used.

5

The following list contains a number of GABA_B antagonists, partial agonists or inverse agonists, which may be used according to the invention: CGP-71982, CGP-76290, CGP-76291, CGP-35348, CGP-36742, CGP-46381, CGP-52432, CGP-54626, CGP-55845, CGP-62349, SCH 50911, GAS-360, Phaclofen, Saclofen, 2-

10 hydroxysaclofen. Each of the GABA_B antagonists, partial agonists or inverse agonists specified above is intended to be an individual embodiment. Accordingly, each of them may be claimed individually.

In a preferred embodiment, a GABA_B receptor ligand selected from CGP 71982, CGP
15 76290, CGP 55845 and CGP 62349.

In particular individual embodiments, Phaclofen, 2-hydroxysaclofen or CGP-46381 is used.

20 Whenever mentioned, each of the terms "GABA_B antagonist, partial agonist or inverse agonist", "GABA_B receptor antagonist, partial agonist or inverse agonist", "GABA_B ligand", and "GABA_B receptor ligand" means GABA_B receptor antagonist, partial GABA_B receptor agonist and inverse GABA_B receptor agonist. Each of which is intended to be an individual embodiment. Accordingly, each of these embodiments
25 and the use thereof may be claimed individually.

A particular embodiment relates to a GABA_B receptor antagonist and the use thereof.

Pharmaceutical compositions

30 Each of the active ingredients disclosed herein may be administered alone or together or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions disclosed herein may be formulated with pharmaceutically acceptable carriers or diluents as

well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

- 5 The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the
10 preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the specific active ingredient or active ingredients chosen.

- Pharmaceutical compositions for oral administration include solid dosage forms such
15 as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they may be prepared with coatings such as enteric coatings or they may be formulated so as to provide controlled release of one or more active ingredient such as sustained or prolonged release according to methods well known in the art.

- 20 Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

- Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as
25 sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the disclosure herein.

- Other suitable administration forms include suppositories, sprays, ointments, cremes,
30 gels, inhalants, dermal patches, implants etc.

The pharmaceutical compositions of the disclosure herein or those which are manufactured as disclosed herein may be administered by any suitable route, for

example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

5

A typical oral dosage of each of the active ingredients is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The
10 exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

15 For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of the disclosure herein are generally utilized as the free substance or
20 as a pharmaceutically acceptable salt thereof. One example is a base addition salt of a compound having the utility of a free acid. When an active ingredient contains a free acid such salts are prepared in a conventional manner by treating a solution or suspension of a free acid of the active ingredient with a chemical equivalent of a pharmaceutically acceptable base.

25

For parenteral administration, solutions of one or more active ingredient in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The
30 aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Solutions for injections may be prepared by dissolving one or more active ingredients and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to a desired volume, sterilising the solution and filling it in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents.

Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, agar, pectin, acacia, stearic acid and lower alkyl ethers of cellulose corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like.

Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredient or ingredients used.

Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The pharmaceutical compositions formed by combining one or more active ingredients of the disclosure herein with the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

The active ingredients of the disclosure herein may be formulated in similar or dissimilar pharmaceutical compositions and unit forms thereof.

If a solid carrier is used for oral administration, the preparation may be tablette, placed in a hard gelatine capsule in powder or pellet form or it may be in the form of a

troche or lozenge.

The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

5

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

10

If desired, the pharmaceutical composition of the disclosure herein may comprise one or more active ingredients in combination with further pharmacologically active substances such as those described in the foregoing.

15

Short description of figures

Figure 1. Effect of local administration of bicuculline (50 μ M), followed by systemic administration of citalopram 10 μ mol/kg s.c.

20

Figure 2. Effect of local administration of phaclofen (50 μ M), followed by systemic administration of citalopram 10 μ mol/kg s.c.

Figure 3. Effect of co-administration of phaclofen (2 mg/kg s.c.), followed by systemic administration of citalopram (10 μ mol/kg s.c.).

25

Figure 4. Effect of administration of GABA_B antagonist 2-hydroxysaclofen (2mg/kg s.c.) on citalopram induced increase of 5-HT levels in rat ventral hippocampus.

F(1,172)=3.01, P<0.05. citalopram 10 μ mol/kg s.c., n=13, citalopram 10 μ mol/kg s.c. and 2-hydroxysaclofen 2 mg/kg s.c. n=3.

30

Figure 5. Effect of administration of GABA_B antagonist CGP 46381 (mg/kg s.c.) on citalopram induced increase of 5-HT levels in rat ventral hippocampus; citalopram 10

μmol/kg s.c., n=13, citalopram 10 μmol/kg s.c. and CGP 46381 2 mg/kg s.c. n=5; citalopram 10 μmol/kg s.c. and CGP 46381 0.5 mg/kg s.c. n=5; CGP 46381 10 mg/kg s.c. n=2.

- 5 *Figure 6.* Effect of administration of GABA_B antagonist Phaclofen (2mg/kg s.c.) on citalopram induced increase of 5-HT levels in rat prefrontal cortex. F(1,198)=3.25, P<0.05. citalopram 10 μmol/kg s.c., n=13, citalopram 10 μmol/kg s.c. and phaclofen 2 mg/kg s.c. n=4.

10

Materials and Methods

Animals

- 15 Male albino rats of a Wistar-derived strain (285-320 g; Harlan, Zeist, The Netherlands) were used for the experiments. Upon surgery, rats were housed individually in plastic cages (35 x 35 x 40 cm), and had free access to food and water. Animals were kept on a 12 h light schedule (light on 7:00 a.m.). The experiments are concordant with the declarations of Helsinki and were approved by the animal care
20 committee of the faculty of mathematics and natural science of the University of Groningen.

Drugs

- 25 The following drugs were used: Citalopram hydrobromide, 2hydroxysaclofen, CGP 46381 (Lundbeck A/S, Copenhagen, Denmark), Phaclofen and (+)-Bicuculline (Sigma, St Louis, USA).

Surgery

30

Microdialysis of brain serotonin levels was performed using home made I-shaped probes, made of polyacrylonitrile / sodium methyl sulfonate copolymer dialysis fiber (i.d. 220 μm, o.d. 0.31 μm, AN 69, Hospal, Italy). Preceding surgery rats were

anaesthetised using isoflurane (O₂/N₂O; 300/300ml/min). Lidocaine-HCl, 10 % (m/v) was used for local anaesthesia. Rats were placed in a stereotaxic frame (Kopf, USA), and probes were inserted into Ventral Hippocampus (V. Hippo, L +4.8 mm, IA: +3.7 mm, V: -8.0 mm) and median prefrontal cortex (PFC, L -0.9 mm; AP: +3.5 mm
5 relative to bregma; V: -6.0 mm (Paxinos and Watson, 1982). After insertion, probes were secured with dental cement.

Microdialysis experiments

10 Rats were allowed to recover for at least 24 h. Probes were perfused with artificial cerebrospinal fluid 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). 15 minute microdialysis samples were collected in HPLC vials containing 7.5 µl 0.02 M acetic acid for serotonin analysis.

15

Serotonin analysis:

Twenty-µl microdialysate samples were injected via an autoinjector (CMA/200 refrigerated microsampler, CMA, Sweden) onto a 100 x 2.0 mm C18 Hypersil 3 µm
20 column (Bester, Amstelveen, the Netherlands) and separated with a mobile phase consisting of 5 g/L di-ammoniumsulfate, 500 mg/L EDTA, 50 mg/L heptane sulphonic acid, 4 % methanol v/v, and 30 µl/L of triethylamine, pH 4.65 at a flow of 0.4 ml/min (Shimadzu LC-10 AD). 5-HT was detected amperometrically at a glassy carbon electrode at 500 mV vs Ag/AgCl (Antec Leyden, Leiden, The Netherlands).
25 The detection limit was 0.5 fmol 5-HT per 20 µl sample (signal to noise ratio 3).

Data presentation and statistics

Four consecutive microdialysis samples with less than 20 % variation were taken as
30 control and set at 100 %. Data are presented as percentages of control level (mean ± S.E.M.) in time. Statistical analysis was performed using Sigmastat for Windows (SPSS, Jandel Corporation). Treatments were compared versus controls using two

way analysis of variance (ANOVA) for repeated measurements, followed by Student Newman Keuls test. Level of significance level was set at $p < 0.05$.

Results

Local administration of GABA_A antagonist bicuculline, followed by systemic administration of citalopram (fig 1).

Local administration of 50 μ M bicuculline in ventral hippocampus increased serotonin levels by about 150 % (treatment vs. time; $F(1,79) = 5.20$, $P = 0.0003$). Post-hoc analysis revealed significance from $t = 45$ to 90 min.

The increase established by systemic administration of 10 μ mol/kg s.c. citalopram was not affected by local application of bicuculline (treatment; $F(1,10) = 4.64$, $P = 0.0567$).

Local administration of GABA_B antagonist phaclofen, followed by systemic administration of citalopram (fig 2).

Local infusion of GABA_B antagonist Phaclofen did not have any effect on basal levels of 5-HT in ventral hippocampus ($F(1,9) = 1.44$ $P = 0.26$). Systemic administration of citalopram during local administration of phaclofen induced augmented levels of 5-HT (Treatment $F(1,9) = 12.21$ $P = 0.0068$, Treatment vs. Time $F(1,112) = 5.03$ $P < 0.0001$). Significant differences during post-hoc analysis was attained from $t = 75$ to 150 min.

Simultaneous administration of phaclofen 2 mg/kg s.c. with citalopram 10 μ mol/kg s.c. (fig 3).

Co-administration of phaclofen 2 mg/kg s.c with citalopram 10 μ mol/kg s.c. elicited enhanced levels of 5-HT when compared to citalopram treatment alone (Treatment

F(1,7)=8.64 P=0.021, Treatment vs. Time, F(1,98)=6.38 P<0.0001). Post-hoc analysis showed different effects from t=75 to t=135.

- 5 *Simultaneous administration of 2-hydroxysaclofen (2 mg/kg s.c.) with citalopram 10 μ mol/kg s.c. on 5-HT levels (fig 4).*

Simultaneous administration of citalopram with GABA_B antagonist 2-hydroxysaclofen also induced augmented effects on 5-HT levels. Treatment
10 F(1,14)=4.80, P= 0.046, treatment versus time F(1,172)=3.01, P=0.0018.

Simultaneous administration of CGP 46381 with citalopram 10 μ mol/kg s.c. on 5-HT levels (fig 5).

15 Administration of a high dose of the GABA_B antagonist CGP 46381 (10 mg/kg s.c.) did not show any effect on 5-HT levels. However, when CGP 46381 (0.5 and 2 mg/kg) was co-administered with citalopram 10 μ mol/kg an augmented response on 5-HT levels was observed (0.5 mg CGP; treatment F(1,16)=4.94, p=0.04; treatment
20 vs. time (F(1,193)= 3.24, 0.00081); 2 mg cgp treatment F(1,16)=2.94, p=0.10; treatment vs. time (F(1,192)= 3.79, 0.001)

Simultaneous administration of phaclofen 2 mg/kg s.c. with citalopram 10 μ mol/kg s.c. on 5-HT levels in PFC(fig 6).

25 Co-administration of phaclofen 2 mg/kg s.c with citalopram 10 μ mol/kg s.c. elicited enhanced levels of 5-HT when compared to citalopram treatment alone (Treatment F(1,15)=4.61 P=0.048, Treatment vs. Time, F(1,198)=6.3.25 P<0.0008).

Claims:

1. The use of a compound, which is a serotonin reuptake inhibitor, and another compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist for the preparation of a pharmaceutical composition for the treatment of affective disorders selected from the group consisting of depression, anxiety disorders, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders selected from the group consisting of bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors.
2. The use of a GABA_B receptor antagonist, inverse agonist or partial agonist for the preparation of a pharmaceutical composition to be used in combination with a serotonin reuptake inhibitor for the treatment of affective disorders selected from the group consisting of depression, anxiety disorders, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders selected from the group consisting of bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors.
3. The use according to claim 2, wherein the pharmaceutical composition is useful for augmenting and/or providing faster onset of the therapeutic effect of a serotonin reuptake inhibitor.

4. The use according to any one of claims 1-3 wherein a selective serotonin reuptake inhibitor is used.
5. The use according to any one of claims 1-3 wherein a compound, which is selective for the GABA_B receptor, is used.
6. The use according to any one of claims 1-3 or 5 wherein an antagonist or an inverse agonist at the GABA_B receptor is used.
7. The use according to claim 6 wherein a GABA_B receptor antagonist is used.
8. The use according to any one of claims 1-4 wherein the SRI is elected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine.
9. The use according to any one of claims 1-3 or 5-7 wherein said GABA_B receptor antagonist, inverse agonist or partial agonist is a GABA_B ligand selected from the group consisting of CGP-71982, CGP-76290, CGP-76291, CGP-35348, CGP-36742, CGP- 46381, CGP-52432, CGP-54626, CGP-55845, CGP-62349, SCH 50911, GAS-360, Phaclofen, Saclofen and 2-hydroxysaclofen.
10. A pharmaceutical composition comprising a compound, which is a serotonin reuptake inhibitor, and another compound, which is a GABA_B receptor antagonist, inverse agonist or partial agonist, and optionally pharmaceutically acceptable carriers or diluents.

11. A pharmaceutical composition according to claim 10 wherein the serotonin reuptake inhibitor used is a selective serotonin reuptake inhibitor.
12. A pharmaceutical composition according to claim 10 wherein the GABA_B antagonist, inverse agonist or partial agonist is selective for the GABA_B receptor.
13. A pharmaceutical composition according to any one of claims 10 and 12, wherein said GABA_B receptor antagonist, inverse agonist or partial agonist is a GABA_B receptor antagonist.
14. A pharmaceutical composition according to any one of claims 10 and 11 characterized in that the serotonin uptake inhibitor is selected from citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, duloxetine, vilazodone, nefazodone, imipramin, femoxetine and clomipramine.
15. A pharmaceutical composition according to any one of claims 10 and 12-13 wherein said GABA_B receptor antagonist, inverse agonist or partial agonist is a GABA_B ligand selected from the group consisting of CGP-71982, CGP-76290, CGP-76291, CGP-35348, CGP-36742, CGP-46381, CGP-52432, CGP-54626, CGP-55845, CGP-62349, SCH 50911, GAS-360, Phaclofen, Saclofen and 2-hydroxysaclofen.
16. A pharmaceutical composition according to any one of claims 10-15, wherein said serotonin reuptake inhibitor and said GABA_B receptor antagonist, inverse agonist or partial agonist is administered by simultaneous administration.
17. A pharmaceutical composition according to claim 16 wherein said serotonin reuptake inhibitor and said GABA_B receptor antagonist, inverse agonist or partial agonist are contained in the same unit dosage form.
18. A pharmaceutical composition according to any one of claims 10-15, wherein said serotonin reuptake inhibitor and said GABA_B receptor antagonist, inverse agonist or partial agonist is administered by sequential administration.

19. The pharmaceutical composition according to any one of claims 16 and 18, wherein said serotonin reuptake inhibitor and said GABA_B receptor antagonist, inverse agonist or partial agonist are contained in discrete dosage forms.

20. A kit comprising:

- i) a GABA_B receptor antagonist, inverse agonist or partial agonist in a first-unit dosage form;
- ii) a serotonin reuptake inhibitor in a second-unit dosage form; and
- iii) a container means for containing said first-unit and second-unit dosage forms.

21. A method for the identification of compounds useful for the treatment of affective disorders selected from the group consisting of depression, anxiety disorders, generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder and social anxiety disorder, eating disorders selected from the group consisting of bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder, drug abuse or any other disorder responsive to serotonin reuptake inhibitors, comprising, in any order:

- (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 $GABA_B$ receptor and selecting the compounds,

and thereafter measuring the efficacy of the selected compounds at the $GABA_B$ receptor and selecting the compounds which are antagonists, inverse agonists or partial agonists at the receptor.

22. A method according to claim 21 wherein the compound has an affinity in step (b) of less than 500 nM.

23. A method according to claim 22, wherein the compound has an affinity in step (b) of less than 100 nM.

24. A compound identified according to a method of any one of claims 21-23.