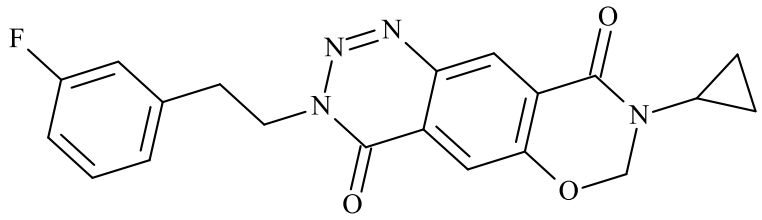
# NEW ASSOCIATION BETWEEN 8-CYCLOPROPYL-3-[2-(3-FLUOROPHENYL)ETHYL]-7,8-DIHYDRO-3*H*-[1,3]OXAZINO[6,5-*g*][1,2,3]BENZOTRIAZINE-4,9-DIONE AND AN ANTIDEPRESSANT AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

The present invention relates to a new association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione of formula (I):




(I)

or an addition salt thereof with a pharmaceutically acceptable acid or base, and an antidepressant for obtaining pharmaceutical compositions for use in the treatment of mood disorders, anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder.

8-Cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]-benzotriazine-4,9-dione is a glutamate AMPA (*α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid*) receptor positive allosteric modulator described in patent application WO 2008/085506. More precisely, the compound of formula (I) possesses procognitive properties, improves synaptic plasticity and exhibits neuroprotective properties, giving it an activity which is of interest in the treatment of disorders of the central nervous system.

The present invention relates to the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione of formula (I), or addition salts thereof with a pharmaceutically acceptable acid or base, and an antidepressant, as well as the properties thereof which are of interest for the treatment of mood disorders, especially major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorder and dysthymic

disorder, and also obsessive-compulsive disorder, post-traumatic stress disorder and anxiety disorders, especially generalised anxiety disorder, panic disorder, acute stress disorder and social anxiety disorder (social phobia).

According to the World Health Organisation, depression and bipolar disorders affect about 460 million people in the world (source: WHO, Mediacenter Fact sheet No. 396, October 2014). The World Mental Health Survey conducted in 17 countries by the WHO showed that about 5 % of the population reported a depressive episode in 2012. Globally, mental and substance dependence pathologies represent 7.4 % of all disability adjusted life years (DALYs) linked to a pathology. Depressive disorders are the leading cause of DALYS due to mental and substance dependence pathologies (40.5 %), followed by anxiety disorders (14.6 %) (Whiteford *et al*. *Lancet* 2013, 382, 1575-1586). Major depressive disorder is a highly prevalent disease which affected almost 17.2 million adult patients in the USA in 2014. This pathology is associated with a high economic, social and familial cost, which is exacerbated in patients who exhibit an inadequate response to a first antidepressant treatment. Although many antidepressants are currently available, not all medical needs are covered: in fact, about 50 % of patients do not respond to initial antidepressant treatment and two thirds of patients do not manage to obtain complete remission after appropriate antidepressant treatment, leading to a considerable risk of relapse, chronicity and suicide (Cameron *et al*. *Psychiatry Res.* 2014, 220(S1), S45-57).

The current antidepressants, such as selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, tricyclic antidepressants or selective catecholamine reuptake inhibitors, have similar mechanisms of action *via* an increase in the synaptic monoamine concentrations and cause, to varying degrees, undesirable effects such as gastrointestinal disorders, sexual dysfunction, weight gain and cardiovascular problems, as well as pharmacodependence. The time to onset of the therapeutic effects of standard antidepressants remains long (about 4 weeks), which constitutes a major challenge in the treatment of depression, where the suicide rate is high during the initial management period. Moreover, in most cases, discontinuation of these treatments results in the occurrence of a discontinuation syndrome, with a reoccurrence of certain depressive symptoms, which is difficult to manage for the clinician and for the patient.

Since the beginning of the 2000s, several works have shown that agents targeting the glutamatergic system could be an option for the development of new rapid-onset antidepressant treatments (Mathew *et al*. *Rev. Bras. Psiquiatr*. 2005, 27(3), 243-248; Alt *et al*. *Curr. Pharm. Design* 2005, 11, 1511-1527). Several studies have in fact shown the involvement of the glutamatergic system, especially *via* the neurotrophins such as BDNF, in the pathophysiology of depression. For example, an increase in the expression of BDNF has been observed during chronic antidepressant treatment (Nibuya *et al*. *J. Neurosci.* 1995, 15, 7539-47; Nibuya *et al*. *J. Neurosci.* 1996, 16, 2365-72), or BDNF has been seen to be effective in animal models predicting an antidepressant activity (Siuciak *et al*. *Pharmacol. Biochem. Behav.* 1997, 56, 131-7; Shirayama *et al*. *J. Neurosci.* 2002, 22, 3251-61). In addition, it has been shown that AMPA modulators increase the expression of neurotrophins such as BDNF in numerous preclinical models of depression *in vitro* and *in vivo* (Lauterborn *et al*. *J. Neurosci.* 2000, 20, 8-21; Legutko *et al*. *Neuropharmacology* 2001, 40, 1019-27; Mackowiak *et al*. *Neuropharmacology* 2002, 43, 1-10).

In patients suffering from depression who exhibit an inadequate response to their treatment, the therapeutic alternative recommended by the Guidelines is to change antidepressant or to add a second antidepressant having a different mechanism of action or to add another treatment such as an antipsychotic. In the first case, where the antidepressant is changed, a withdrawal syndrome has frequently been observed in the week following the discontinuation of treatment with the preceding antidepressant. Psychological symptoms are indicated most frequently (Dominguez *et al*. *Pharmacotherapy* 1995, 15, 778-780; Fava *et al*. *Am. J. Psychiatry* 1997, 154, 1760-1762; Judge *et al*. *Int. Clin. Psychopharmacol.* 2002, 17, 217-225). In addition, it has been shown that a gradual discontinuation of the initial antidepressant, carried out at the same time as the initiation of the new treatment, delayed but did not significantly reduce the discontinuation symptoms observed (Rosenbaum *et al*. *Biol. Psychiatry* 1998, 44, 77-87; Fava *et al*. 1997; Judge *et al*. 2002; Michelson *et al*. *Br. J. Psychiatry* 2000, 176, 363-368; Tint *et al*. *J. Psychopharmacol.* 2008, 22, 330-332; Lejoyeux *et al*. *J. Clin. Psychiatry* 1997, 58, 11-15; Price *et al*. *Br. J. Clin. Pharmacol.* 1996, 42, 757-763; Lejoyeux *et al*. *CNS Spect.* 2015, 20, 29-38). On the other hand, the therapeutic value of the association of two antidepressants remains very controversial, no antidepressant has as yet been approved as an association treatment in patients suffering from depression. Finally, even though it

brings about a therapeutic improvement, the combination of an antidepressant with an antipsychotic (three antipsychotics have been approved by the FDA in this indication) is of limited use for reasons of tolerance (Rogoz, *Pharmacol. Rep.* 2013, 65, 1535-1544; Wright *et al*. *Pharmacotherapy* 2013, 33, 344-59; Fleurence *et al*. *Psychopharmacol. Bull.* 2009, 42, 57-90).

Consequently, it appears to be important to have in the therapeutic arsenal for the management of depression a treatment which is effective for patients who exhibit an inadequate response to a first treatment and which has a rapid onset of action as soon as it is initiated and is well tolerated in association with the current antidepressants.

Surprisingly, the present invention has shown that the effects of the current antidepressants are potentiated by those of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione or its addition salts with a pharmaceutically acceptable acid or base. Accordingly, the coadministration of these two classes of compounds may permit an improvement in the depressive state of patients as compared with the simple administration of an antidepressant, without increasing the harmful effects associated with the initial treatment (especially gastrointestinal disorders, sexual dysfunction, weight gain, cardiovascular problems and pharmacodependence). In other words, therapeutic doses of antidepressants that are below those conventionally used in mono-administration therefore become envisageable, with equivalent or even superior antidepressant performances and fewer harmful effects.

More surprisingly, the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, administered in a subactive dose, and an antidepressant which is also administered in a subactive dose, shows a marked potentiation of the antidepressant effectiveness in animal models of depression.

These effects, which were not foreseeable, make it possible to envisage using associations between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*]-[1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and an antidepressant in the treatment of mood disorders, anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder. Advantageously, these effects make it possible to envisage also

using associations between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and an antidepressant in the treatment of mood disorders, anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder for patients who exhibit an inadequate response to a first treatment. The mood disorders according to the invention include depressive disorders, especially major depressive disorder, seasonal affective disorder and treatment-resistant depression, bipolar disorders, cyclothymic disorder and also dysthymic disorder. The anxiety disorders according to the invention include generalised anxiety disorder, panic disorder, acute stress disorder and social anxiety disorder. Major depressive disorder, treatment-resistant depression, generalised anxiety disorder and obsessive-compulsive disorder are targeted especially. Major depressive disorder is especially preferred. More especially, the present invention relates to associations between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and an antidepressant in the treatment of major depressive disorder for patients who exhibit an inadequate response to a first antidepressant treatment.

Preferably, 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione is used in the form of the base within the context of the invention.

Among the antidepressants according to the invention there will preferably be chosen from:

- selective serotonin reuptake inhibitors such as fluoxetine, paroxetine, sertraline, citalopram, escitalopram, indalpine, zimelidine, dapoxetine, vortioxetine, vilazodone or fluvoxamine;
- serotonin and noradrenaline reuptake inhibitors such as venlafaxine, milnacipran, duloxetine, nefazodone or desvenlafaxine;
- tricyclic antidepressants such as amitriptyline, amoxapine, clomipramine, dosulepine, doxepine, imipramine, maprotiline, opipramol, quinupramine or trimipramine;
- selective catecholamine reuptake inhibitors such as bupropion;
- melatonergic agonists and 5-$HT_{2c}$ antagonists such as agomelatine;
- thymoregulatory agents used in the treatment of depression such as lithium.

According to the invention, the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and agomelatine is especially preferred.

A preferred embodiment is the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and a selective serotonin reuptake inhibitor.

A preferred embodiment is the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and a serotonin and noradrenaline reuptake inhibitor.

Among the selective serotonin reuptake inhibitors according to the invention there will preferably be chosen fluoxetine, paroxetine, sertraline, citalopram, escitalopram, vilazodone or vortioxetine. Among the serotonin and noradrenaline reuptake inhibitors there will preferably be chosen venlafaxine, duloxetine or desvenlafaxine. Among the tricyclic antidepressants there will preferably be chosen clomipramine. Among the selective catecholamine reuptake inhibitors, bupropion is a preferred antidepressant.

More especially, the association of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione and an antidepressant chosen from fluoxetine, paroxetine, sertraline, citalopram, escitalopram, vilazodone, vortioxetine, venlafaxine, duloxetine, desvenlafaxine, clomipramine, agomelatine or bupropion is used in the treatment of mood disorders, especially major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorder and dysthymic disorder, and also obsessive-compulsive disorder, post-traumatic stress disorder and anxiety disorders, especially generalised anxiety disorder, panic disorder, acute stress disorder and social anxiety disorder.

A preferred embodiment is the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and an antidepressant chosen from fluoxetine, paroxetine, sertraline, citalopram or escitalopram.

A preferred embodiment is the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and fluoxetine.

A preferred embodiment is the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and paroxetine.

A preferred embodiment is the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and sertraline.

A preferred embodiment is the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and citalopram.

A preferred embodiment is the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof, and escitalopram.

The invention relates also to the use of the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or addition salts thereof with a pharmaceutically acceptable acid or base, and an antidepressant, for obtaining pharmaceutical compositions for the treatment of mood disorders, especially major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorder and dysthymic disorder, and also obsessive-compulsive disorder, post-traumatic stress disorder and anxiety disorders, especially generalised anxiety disorder, panic disorder, acute stress disorder and social anxiety disorder.

More especially, the invention relates to the use of the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-

dione, or addition salts thereof with a pharmaceutically acceptable acid or base, and an antidepressant chosen from fluoxetine, paroxetine, sertraline, citalopram, escitalopram, vilazodone, vortioxetine, venlafaxine, duloxetine, desvenlafaxine, clomipramine, agomelatine or bupropion, for obtaining pharmaceutical compositions for the treatment of mood disorders, especially major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorder and dysthymic disorder, and also obsessive-compulsive disorder, post-traumatic stress disorder and anxiety disorders, especially generalised anxiety disorder, panic disorder, acute stress disorder and social anxiety disorder.

The invention relates also to pharmaceutical compositions comprising the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*]-[1,2,3]benzotriazine-4,9-dione, or addition salts thereof with a pharmaceutically acceptable acid or base, and an antidepressant in combination with one or more pharmaceutically acceptable excipients.

Advantageously, the invention relates to pharmaceutical compositions comprising the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]-oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or addition salts thereof with a pharmaceutically acceptable acid or base, and an antidepressant chosen from fluoxetine, paroxetine, sertraline, citalopram, escitalopram, vilazodone, vortioxetine, venlafaxine, duloxetine, desvenlafaxine, clomipramine, agomelatine or bupropion, in combination with one or more pharmaceutically acceptable excipients.

A particular embodiment relates to pharmaceutical compositions comprising the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]-oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or addition salts thereof with a pharmaceutically acceptable acid, and an antidepressant in combination with one or more pharmaceutically acceptable excipients, for use in the treatment of mood disorders, especially major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorder and dysthymic disorder, and also obsessive-compulsive disorder, post-traumatic stress disorder and anxiety disorders,

especially generalised anxiety disorder, panic disorder, acute stress disorder and social anxiety disorder.

In the pharmaceutical compositions according to the invention, the fraction by mass of active ingredients (mass of the active ingredients over the total mass of the composition) is from 5 to 50 %.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for administration by the oral, parenteral and especially intravenous, per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory route and more specifically tablets, dragées, sublingual tablets, gelatin capsules, glossettes, capsules, lozenges, injectable preparations, aerosols, eye or nasal drops, suppositories, creams, ointments, dermal gels, transdermal patches, powders in sachets, etc.

In addition to the 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione and the antidepressant compound, the pharmaceutical compositions according to the invention comprise one or more excipients or carriers chosen from diluents, lubricants, binders, disintegrators, stabilisers, preservatives, absorbents, colourings, sweeteners, flavourings, etc.

Examples which may be mentioned, without implying any limitation, include:

- for the diluents: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerin;
- for the lubricants: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol;
- for the binders: aluminium and magnesium silicate, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone;
- for the disintegrators: agar, alginic acid and its sodium salt, effervescent mixtures.

The compounds of the association can be administered simultaneously or in succession. The preferred administration route is the oral route. The corresponding pharmaceutical compositions can permit the immediate or delayed release of the active ingredients. Moreover, the compounds of the association can be administered in the form of two

separate pharmaceutical compositions, each comprising one of the active ingredients, or alternatively in the form of a single pharmaceutical composition in which the active ingredients are mixed.

The preferred pharmaceutical compositions are tablets.

The dosage used varies according to the sex, age and weight of the patient, the administration route, the nature of the disorder and of any associated treatments and ranges from 1 to 200 mg of equivalents of free base of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione per 24 hours, preferably from 5 to 150 mg per day, more preferably from 5 to 100 mg per day and yet more preferably from 5 to 50 mg per day. The dose of the antidepressant will be equal to or less than that used when it is administered on its own. In the case of duloxetine, the dosage is from 10 to 120 mg per day. In the case of bupropion, the dosage is from 50 to 300 mg per day. In the case of escitalopram, the dosage is from 1 to 20 mg per day, more preferably from 10 to 20 mg per day. In the case of venlafaxine, the dosage is from 10 to 375 mg per day. In the case of sertraline, the dosage is from 10 to 200 mg per day, more preferably from 50 to 200 mg per day. In the case of vortioxetine, the dosage is from 1 to 40 mg per day. In the case of vilazodone, the dosage is from 1 to 80 mg per day. In the case of fluoxetine, the dosage is from 1 to 80 mg per day, more preferably from 20 to 80 mg per day. In the case of desvenlafaxine, the dosage is from 1 to 100 mg per day. In the case of paroxetine, the dosage is from 1 to 100 mg per day. In the case of clomipramine, the dosage is from 5 to 250 mg per day. In the case of agomelatine, the dosage is from 1 to 75 mg per day. In the case of citalopram, the dosage is from 10 to 100 mg per day, more preferably from 20 to 40 mg per day. In the case of paroxetine, the dosage is from 10 to 100 mg per day, more preferably from 20 to 75 mg per day.

In the preferred embodiments of the invention, the association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione and the antidepressant is administered in the following doses:

| | Composition 1 | Composition 2 | Composition 3 |
|---|---|---|---|
| 8-Cyclopropyl-3-[2-(3-fluorophenyl)-ethyl]-7,8-dihydro-3*H*-[1,3]oxazino-[6,5-*g*][1,2,3]benzotriazine-4,9-dione | 15 mg | 50 mg | 100 mg |
| Antidepressant chosen from: | | | |
| escitalopram | 10 mg | 10 mg | 10 mg |
| fluoxetine | 20 mg | 20 mg | 20 mg |
| citalopram | 20 mg | 20 mg | 20 mg |
| paroxetine | 20 mg | 20 mg | 20 mg |
| sertraline | 50 mg | 50 mg | 50 mg |

## PHARMACOLOGICAL STUDY

**EXAMPLE A: Marble burying test in the NMRI mouse**

Preclinical studies were conducted in an empirical model which is very sensitive to antidepressant treatments (Sanchez *et al*. *Psychopharmacology* 1997, 129, 197-205; Dekeyne, *Thérapie* 2005, 60, 477-484; Nicolas *et al*. *Eur. J. Pharmacol*. 2006, 547, 106-115). These studies showed the potential of an association of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione with antidepressants in the treatment of depression and anxiety such as major depressive disorder or treatment-resistant depression, or generalised anxiety disorders in patients who are inadequately managed by existing antidepressant treatments. Spontaneous marble burying in the mouse is an anxious-depressive behaviour which is considered to be relevant and the inhibition of which suggests that a treatment may have antidepressant and anxiolytic and/or anti-impulsive activity (Dekeyne, *Thérapie* 2005; Sanchez *et al*. 1997; Nicolas *et al*. 2006). 8-Cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, citalopram and paroxetine were evaluated in this test on their own after a single intraperitoneal administration and in coadministration with subactive doses of the 3 compounds and with active doses of citalopram and paroxetine in order to study a synergistic potential between these compounds.

The studies were carried out as follows:

Male mice of the NMRI strain weighing 18-25 g on the day of the experiment were placed individually in Macrolon boxes (30 x 18 x 19 cm) containing 5 cm of sawdust. Twenty-four "*cat's eye*" glass marbles were distributed evenly on the sawdust at the periphery of the box. The animals are treated by the intraperitoneal route either with 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione (3-10-30 mg/kg, i.p.) or with its carrier (control, 0.9 % NaCl and 2 % Tween 80), or with the antidepressants (citalopram and paroxetine at 1, 3 and 10 mg/kg, i.p.) or with their carriers (control, 0.9 % NaCl and 0.9 % NaCl and 2 % Tween 80, respectively), or with a

coadministration of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]-oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione (30 mg/kg, i.p.) and citalopram (1, 3 and 10 mg/kg, i.p.) or with the coadministration of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione (30 mg/kg, i.p.) and paroxetine (1, 3 and 10 mg/kg, i.p.) 30 minutes before the animals were placed in the cage filled with marbles. After 30 minutes' free exploration, the animals are removed from the box and the number of marbles buried to two thirds is counted. The results are analysed by ANOVA and then by the Dunett's test.

*Marble burying test in the NMRI mouse with 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H-*[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione on its own*

The results indicate that, over a range of doses (3, 10 and 30 mg/kg, i.p.), 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione does not significantly modify spontaneous marble burying in the NMRI mouse (-30 % (but not significant), -13 % and -17 %, respectively) (see Figure 1).

*Marble burying test in the mouse of citalopram on its own or in coadministration with 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H-*[1,3]oxazino[6,5-g][1,2,3]-benzotriazine-4,9-dione*

When given on its own, citalopram significantly reduces the number of marbles buried at a dose of 10 mg/kg i.p. and above (-35 % marbles buried, $p < 0.01$ *vs.* control group), suggesting an antidepressant effect (see Figure 2A).

The coadministration of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione at a subactive dose (30 mg/kg, i.p.) with citalopram at subactive (1 and 3 mg/kg, i.p.) and active (10 mg/kg, i.p.) doses significantly inhibits spontaneous marble burying behaviour in the mouse (-70 %, -76 % and -83 % buried marbles, respectively, *vs.* -23 %, -10 % and -35 % buried marbles, respectively, with citalopram on its own), showing a potentiation of the effect due to the coadministration of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]-oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione and citalopram (see Figure 2B).

*Marble burying test in the mouse of paroxetine on its own or of the coadministration with 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-g][1,2,3]-benzotriazine-4,9-dione*

When given on its own, paroxetine significantly reduces the number of marbles at a dose of 3 mg/kg and above (-44 % and -62 % buried marbles at doses of 3 and 10 mg/kg, respectively, $p < 0.05$ and $p < 0.01$ *vs.* control group), suggesting an antidepressant effect (see Figure 3A).

The coadministration of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]-oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione at a subactive dose (30 mg/kg, i.p.) with paroxetine at a subactive (1 mg/kg, i.p.) and active (3 and 10 mg/kg, i.p.) doses significantly inhibits spontaneous marble burying behaviour in the mouse (-78 %, -88 % and -94 % buried marbles, respectively, *vs.* -8 %, -44 % and -62 % buried marbles, respectively, with paroxetine on its own), showing a potentiation of the effect due to the coadministration of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]-oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione and paroxetine (see Figure 3B).

All these data show that the association of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione and an antidepressant at subactive doses induces a potentiation of the antidepressant effect and may therefore have, especially in patients who are inadequately managed by existing antidepressant treatments, a therapeutic potential in the treatment of mood disorders, especially major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorder and dysthymic disorder, and also obsessive-compulsive disorder, post-traumatic stress disorder and anxiety disorders, especially generalised anxiety disorder, panic disorder, acute stress disorder and social anxiety disorder.

**EXAMPLE B: Irwin's primary observation test**

The effects in terms of safety of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione and of citalopram (in the form of a hydrobromide), administered on their own or in association, were studied using Irwin's primary observation test in the Wistar rat (n = 6 individuals per group). Behavioural changes, physiological and neurotoxic symptoms, rectal temperature and also pupil diameter were recorded using a standardised observation grid derived from that of Irwin.

It was observed that 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]-oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione (from 10 to 100 mg/kg of base *per os*) and citalopram (at 100 mg/kg of base *per os*), given on their own or in coadministration acutely, did not induce any change in the rat according to the standardised observation grid.

At the dose of 100 mg/kg of base *per os*, citalopram administered on its own does not induce any notable effects on the behaviour of the animal, with the exception of a moderate redness appearing in the region of the plantar surface in all the animals between 3.5 and 7.5 hours after administration and a fall in temperature between 2 and 5.5 hours after administration in comparison with the control group.

No potentiation of the above-mentioned notable effects observed with citalopram at 100 mg/kg was observed when the antidepressant was coadministered with 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione (from 10 to 100 mg/kg of base *per os*). In addition, this good tolerance of the association of the two products was observed despite a slight increase in exposure in the animals treated with citalopram, according to the pharmacokinetic analyses.

In conclusion, the results presented above show a good safety profile of the combination of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]-benzotriazine-4,9-dione (at 10 and 100 mg/kg of base *per os*) with citalopram (at 100 mg/kg of base *per os*).

**EXAMPLE C: Clinical trial**

A phase II clinical trial (*vs.* placebo) is carried out in order to evaluate the effectiveness (using the Hamilton depression rating scale) and the tolerance of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione administered in doses of 15 and 50 mg per day, in association with a selective serotonin reuptake inhibitor (fluoxetine, citalopram or paroxetine in a dose of 20 mg per day or more; escitalopram in a dose of 10 mg per day or more; or sertraline in a dose of 50 mg per day or more) in 400 patients who are suffering from major depressive disorders and have had an inadequate response to treatment with the current selective serotonin reuptake inhibitor. This trial is divided into three parts comprising:

- a selection period of 3 to 14 days during which the patient continues treatment with the current selective serotonin reuptake inhibitor;
- a double blind treatment period of 8 weeks during which the patient is treated with the current selective serotonin reuptake inhibitor associated either with a placebo or with 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*]-[1,2,3]benzotriazine-4,9-dione administered in a dose of 15 or 50 mg per day; and
- an observation period of 2 weeks after discontinuation of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione during which the patient continues treatment with the selective serotonin reuptake inhibitor.

**EXAMPLE D: Pharmaceutical composition**

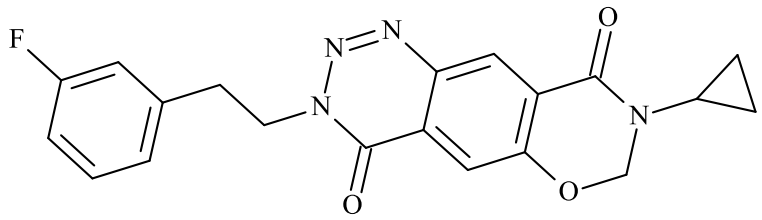
The formulae for the preparation of tablets each containing a dose of from 1 to 200 mg of equivalents of free base of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione per 24 hours, preferably from 5 to 150 mg per day, more preferably from 5 to 100 mg per day and yet more preferably from 5 to 50 mg per day, comprise a posological dose of antidepressant according to the invention; binders such as maize starch, maltodextrin, sodium starch glycolate; lubricants such as colloidal silica, magnesium stearate; diluents such as lactose monohydrate.

By way of example, the preparation formula for 1000 tablets each containing a dose of 15 mg of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*]-[1,2,3]benzotriazine-4,9-dione and 10 mg of escitalopram is as follows:

8-Cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]-benzotriazine-4,9-dione ..... 15 g
Escitalopram ..... 10 g
Maize starch ..... 20 g
Maltodextrin ..... 7.5 g
Colloidal silica ..... 0.2 g
Sodium starch glycolate ..... 3 g
Magnesium stearate ..... 1 g
Lactose monohydrate ..... 43.3 g

## CLAIMS

**1.** Association between 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]-oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione of formula (I):




(I)

or an addition salt thereof with a pharmaceutically acceptable acid or base, and an antidepressant.

**2.** Association according to claim 1, characterised in that 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione is used in the form of the base.

**3.** Association according to claim 1 or 2, characterised in that the antidepressant is a selective serotonin reuptake inhibitor, a serotonin and noradrenaline reuptake inhibitor, a tricyclic antidepressant, a selective catecholamine reuptake inhibitor, a melatonergic agonist and 5-$HT_{2c}$ antagonist, or a thymoregulatory agent.

**4.** Association according to claim 1 or 2, characterised in that the antidepressant is a selective serotonin reuptake inhibitor.

**5.** Association according to claim 1 or 2, characterised in that the antidepressant is a serotonin and noradrenaline reuptake inhibitor.

**6.** Association according to claim 3, characterised in that the antidepressant is fluoxetine, paroxetine, sertraline, citalopram, escitalopram, vilazodone, vortioxetine, venlafaxine, duloxetine, desvenlafaxine, clomipramine, agomelatine or bupropion.

**7.** Association according to claim 6, characterised in that the antidepressant is fluoxetine, paroxetine, sertraline, citalopram or escitalopram.

**8.** Association according to any one of claims 1 to 7, characterised in that 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione is administered in a daily dose of from 1 to 200 mg of equivalents of free base.

**9.** Pharmaceutical composition comprising as active ingredient 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione, or an addition salt thereof with a pharmaceutically acceptable acid or base, in association with an antidepressant according to any one of claims 1 to 8 in combination with one or more pharmaceutically acceptable excipients.

**10.** Pharmaceutical composition according to claim 9 for use in the treatment of mood disorders, anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder.

**11.** Pharmaceutical composition according to claim 10 for use in the treatment of major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorders, dysthymic disorders, generalised anxiety disorder, panic disorder, acute stress disorder, social anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder.

**12.** Use of an association according to any one of claims 1 to 8 for the manufacture of a medicament for the treatment of mood disorders, anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder.

**13.** Use of an association according to claim 12 for the manufacture of a medicament for the treatment of major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorders, dysthymic disorders, generalised anxiety disorder, panic disorder, acute stress disorder, social anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder.

**14.** Association according to any one of claims 1 to 8 for use in the treatment of mood disorders, anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder.

**15.** Association according to claim 14 for use in the treatment of major depressive disorder, seasonal affective disorder, treatment-resistant depression, bipolar disorders, cyclothymic disorders, dysthymic disorders, generalised anxiety disorder, panic disorder, acute stress disorder, social anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder.