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3-SUSTITUTOS - (1-2-3)- COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.

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71. SOLICITANTE

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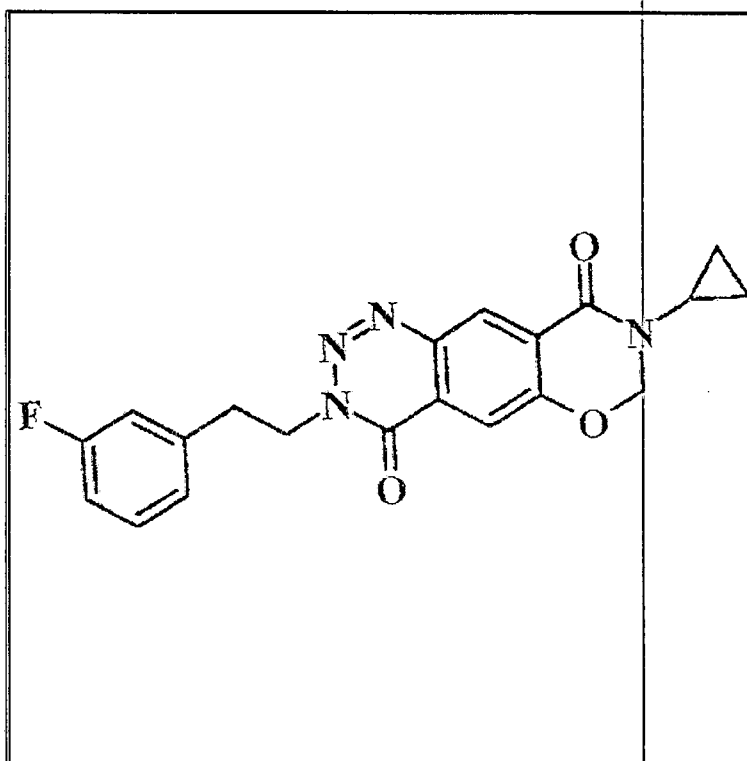
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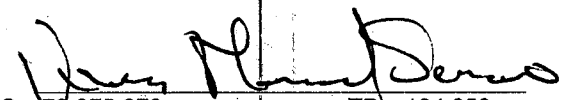
ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
- ☐ Comprobante de pago de la tasa por concepto de reivindicación de prioridad.
- ☒ Poderes, si fuere el caso.
- ☒ Certificado de existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Copia certificada de la primera solicitud, si se reivindica prioridad.
- ☐ Traducción simple de la primera solicitud, si se reivindica prioridad.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☒ Descripción de la invención.
- ☒ Una o más reivindicaciones.
- ☒ Dibujos y/o planos necesarios.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de la comunidad de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12 y 6x6 cm.
- ☒ Resumen y extracto para publicación.



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FIRMA:


C.C. 79.875.670 TP. 124.953

ANEXO No. 1

DESCRIPCIÓN DE LA INVENCION - REIVINDICACIONES Y RESUMEN. (en inglés)

**3 - SUSTITUTOS - [1-2-3] - COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC..**

3-SUBSTITUTED-[1,2,3]-BENZOTRIAZINONE COMPOUND FOR ENHANCING GLUTAMATERGIC SYNAPTIC RESPONSES

Field of the Invention

5

This invention relates to a compound, pharmaceutical compositions and methods for use in the prevention and treatment of cerebral insufficiency, including enhancement of receptor functioning at synapses in brain networks responsible for higher order behaviors. These brain networks, which are involved in cognitive abilities, are related to memory impairment, such as is observed in ageing and a variety of dementias, in imbalances in neuronal activity between different brain regions, as is suggested in disorders such as Parkinson's disease, schizophrenia, attention deficit and affective or mood disorders, and in disorders wherein a deficiency in neurotrophic factors is implicated. In a particular aspect, the present invention relates to compounds useful for treatment of such conditions, and methods of using these compounds for such treatment.

15

Related Applications

This application claims the benefit of priority of U.S. provisional applications US60/878,503, filed January 3, 2007 and US60/921,433, filed April 2, 2007, relevant portions of which applications are incorporated by reference herein.

20

Background of the Invention

The release of glutamate at synapses at many sites in mammalian forebrain stimulates two classes of postsynaptic, ionotropic receptors. These classes are usually referred to as AMPA/quisqualate and N-methyl-D-aspartic acid (NMDA) receptors. AMPA/quisqualate receptors mediate a voltage independent fast excitatory post-synaptic current (the fast EPSC), whereas NMDA receptors generate a voltage-dependent, slow excitatory current. Studies carried out in slices of hippocampus or cortex, indicate that the AMPA receptor mediated fast EPSC is generally the dominant component by far at most glutamatergic synapses.

30

AMPA receptors are not evenly distributed across the brain but rather are largely restricted to

the telencephalon and cerebellum. These receptors are found in high concentrations in the superficial layers of neocortex, in each of the major synaptic zones of hippocampus, and in the striatal complex, as reported by Monaghan *et al.*, in *Brain Research* 324:160-164 (1984). Studies in animals and humans indicate that these structures organize complex

5 perceptual-motor processes and provide the substrates for higher-order behaviors. Thus, AMPA receptors mediate transmission in those brain networks responsible for a host of cognitive activities.

For the reasons set forth above, drugs that modulate and thereby enhance the functioning of

10 AMPA receptors could have significant benefits for cognitive and intellectual performance. Such drugs should also facilitate memory encoding. Experimental studies, such as those reported by Arai and Lynch, *Brain Research* 598:173-184 (1992), indicate that increasing the size of AMPA receptor-mediated synaptic response(s) enhances the induction of long-term potentiation (LTP). LTP is a stable increase in the strength of synaptic contacts that follows

15 repetitive physiological activity of a type known to occur in the brain during learning.

Compounds that enhance the functioning of the AMPA form of glutamate receptors facilitate the induction of LTP and the acquisition of learned tasks in rodents and humans as measured in a number of paradigms. See, for example, Granger *et al.*, *Synapse* 15:326-329 (1993);

20 Staubli *et al.*, *PNAS* 91:777-781 (1994); Arai *et al.*, *Brain Res.* 638:343-346 (1994); Staubli *et al.*, *PNAS* 91:11158-11162 (1994); Shors *et al.*, *Neurosci. Let.* 186:153-156 (1995); Larson *et al.*, *J. Neurosci.* 15:8023-8030 (1995); Granger *et al.*, *Synapse* 22:332-337 (1996); Arai *et al.*, *JPET* 278:627- 638 (1996); Lynch *et al.*, *Internat. Clin. Psychopharm.* 11: 13-19 (1996); Lynch *et al.*, *Exp. Neurology* 145:89-92 (1997); Ingvar *et al.*, *Exp. Neurology* 146:553-559

25 (1997); Hampson, *et al.*, *J. Neurosci.* 18:2748-2763 (1998); Porrino *et al.*, *PLoS Biol* 3(9):1-14 (2006) and Lynch and Rogers, US Patent 5,747,492. There is a considerable body of evidence showing that LTP is a substrate of memory. For example, compounds that block LTP interfere with memory formation in animals, and certain drugs that disrupt learning in humans antagonize the stabilization of LTP, as reported by del Cerro and Lynch,

30 *Neuroscience* 49: 1-6 (1992). Learning a simple task induces LTP in hippocampus that occludes LTP generated by high frequency stimulation (Whitlock *et al.*, *Science* 313:1093-1097 (2006)) and a mechanism that maintains LTP sustains spatial memory (Pastalkova, *et*

al., Science **313**:1141-1144 (2006)). Of significant importance to the field of learning is the finding that *in vivo* treatments with a positive AMPA-type glutamate receptor modulator restores stabilization of basal dendritic LTP in middle-aged animals (Rex, *et al.*, *J. Neurophysiol.* **96**:677-685 (2006)).

- 5 Excitatory synaptic transmission provides a major pathway by which neurotrophic factors are increased within specific brain regions. As such, potentiation of AMPA receptor function by modulators has been found to increase levels of neurotrophins, particularly brain derived neurotrophic factor, or BDNF. See, for example, Lauterborn, *et al.*, *J. Neurosci.* **20**:8-21 (2000); Gall, *et al.*, U.S. Patent 6,030,968; Lauterborn, *et al.*, JPET **307**:297-305 (2003); and
- 10 Mackowiak, *et al.*, *Neuropharmacology* **43**:1-10 (2002). Other studies have linked BDNF levels to a number of neurological disorders, such as Parkinson's disease, Attention Deficit Hyperactivity Disorder (ADHD), autism, Fragile-X Syndrome, and Rett Syndrome (RTT). See, for example, O'Neill, *et al.*, *Eur. J. Pharmacol.* **486**:163-174 (2004); Kent, *et al.*, *Mol. Psychiatry* **10**:939-943 (2005); Riikonen, *et al.*, *J. Child Neurol.* **18**:693-697 (2003) and
- 15 Chang, *et al.*, *Neuron* **49**:341-348 (2005). Thus, AMPA receptor potentiators may be useful for the treatment of these, as well as other, neurological diseases that are the result of a glutamatergic imbalance or a deficit in neurotrophic factors.

A prototype for a compound that increases AMPA receptor function was described by Ito *et al.*, *J. Physiol.* **424**:533-543 (1990). These authors found that the nootropic drug aniracetam (N-anisoyl-2-pyrrolidinone) increases currents mediated by brain AMPA receptors expressed in *Xenopus* oocytes without affecting responses by γ -aminobutyric acid (GABA), kainic acid (KA), or NMDA receptors. Infusion of aniracetam into slices of hippocampus was also

20 shown to substantially increase the size of fast synaptic potentials without altering resting

25 membrane properties. It has since been confirmed that aniracetam enhances synaptic responses at several sites in hippocampus, and that it has no effect on NMDA-receptor mediated potentials (Staubli *et al.*, *Psychobiology* **18**:377-381 (1990) and Xiao *et al.*, *Hippocampus* **1**:373-380 (1991)).

- 30 Aniracetam has been found to have an extremely rapid onset and washout, and can be applied repeatedly with no apparent lasting effects, which are desirable features for behaviorally-relevant drugs. Aniracetam does present several disadvantages, however. The

peripheral administration of aniracetam is not likely to influence brain receptors. The drug works only at high concentrations (approx. 1000 μ M), and about 80% of the drug is converted to anisoysl-GABA following peripheral administration in humans (Guenzi and Zanetti, *J. Chromatogr.* **530**:397-406 (1990)). The metabolite, anisoysl-GABA, has been found to have less synaptic activity than aniracetam. In addition to these issues, aniracetam has putative effects on a plethora of other neurotransmitter and enzymatic targets in the brain, which makes uncertain the mechanism of any claimed therapeutic drug effect. See, for example, Himori, *et al.*, *Pharmacology Biochemistry and Behavior* **47**:219-225 (1994); Pizzi *et al.*, *J. Neurochem.* **61**:683-689 (1993); Nakamura and Shirane, *Eur. J. Pharmacol.* **380**: 81-89 (1999); Spignoli and Pepeu, *Pharmacol. Biochem. Behav.* **27**:491-495 (1987); Hall and Von Voigtlander, *Neuropharmacology* **26**:1573-1579(1987); and Yoshimoto *et al.*, *J. Pharmacobiodyn.* **10**:730-735(1987).

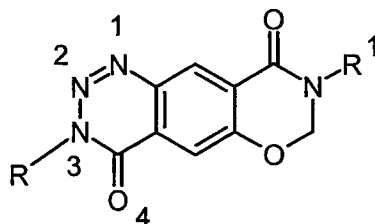
A class of AMPA receptor-modulating compounds that does not display the low potency and inherent instability characteristic of aniracetam has been described (Lynch and Rogers, US Patent 5,747,492). These compounds, termed "Ampakines"[®], can be substituted benzamides, which include, for example, 1-(quinoxaline-6-ylcarbonyl)piperidine (CX516; Ampalex[®]). Typically, they are chemically more stable than aniracetam and show improved bioavailability. CX516 is active in animal tests used to detect efficacious drugs for the treatment of memory disorders, schizophrenia, and depression. In three separate clinical trials, CX516 showed evidence for efficacy in improving various forms of human memory (Lynch *et al.*, *Internat. Clin. Psychopharm.* **11**:13-19 (1996); Lynch *et al.*, *Exp. Neurology* **145**:89-92 (1997); Ingvar *et al.*, *Exp. Neurology* **146**:553-559 (1997)).

Another class of Ampakines, benzoxazines, has been discovered to have very high activity in *in vitro* and *in vivo* models for assessing the probability of producing cognition enhancement (Rogers and Lynch; US Patent # 5,736,543). The substituted benzoxazines are rigid benzamide analogues with different receptor modulating properties from the flexible benzamide, CX516.

Certain substituted benzofurazan and benzothiadiazole compounds have been found to be significantly and surprisingly more potent in the animal model of schizophrenia than

previous compounds, and are also effective in cognition enhancement. These compounds are structurally similar to those disclosed in Lynch and Rogers, US Patent # 5,736,543.

Previously disclosed structures that contained the 1,3-benzoxazine-4-one pharmacophore were substituted on the benzene portion by heteroatoms, such as nitrogen or oxygen (US Patents # 5,736,543 and 5,962,447), by substituted alkyl groups (US Patents # 5,650,409 and 5,783,587), or unsubstituted (WO 99/42456). Yet another class of 1,3-benzoxazine compounds contained a carbonyl external to the oxazine ring (US Patent # 6,124,278), but not as a substituent on the benzene ring structure. Now, a new class of triazinone compounds has been discovered that display significant activity on hippocampal synaptic responses and neuronal whole cell currents mediated by AMPA receptors. 3-Substituted benzo[1,2,3]triazin-4-one compounds are potent AMPA receptor modulators that are significantly more metabolically stable than the corresponding bis-benzoxazinones.



The biological activity of the triazinones was unexpected and the potency at the AMPA receptor is surprisingly high; the most potent triazinones in this class double AMPA receptor currents at concentrations as low as 3 nM. A benzo[1,2,3]triazin-4-one compound as a AMPA receptor modulator is disclosed herein.

Summary of the Invention

The present invention includes, in one aspect, a compound as shown by structure I, and is described in Section II of the detailed description, which follows. Administration of compounds of this class has been found to increase synaptic responses mediated by AMPA receptors. The compound of the present invention is significantly and unexpectedly more potent than previously described compounds in increasing AMPA receptor function in primary neuronal cultures and in slices of rat hippocampus, and in enhancing cognitive performance, such as performance in a delayed match to sample task. This unexpected

activity translates into pharmaceutical compounds and corresponding methods of use, including treatment methods, which utilize significantly lower concentrations (on a mole-to-mole basis) of the present compounds compared to prior art compositions.

- 5 The ability of the compound of the invention to increase AMPA receptor-mediated responses makes the compounds useful for a variety of purposes. These include facilitating the learning of behaviors dependent upon glutamate receptors, treating conditions in which AMPA receptors or synapses utilizing these receptors are reduced in numbers or efficiency, and enhancing excitatory synaptic activity in order to restore an imbalance between brain sub-
- 10 regions or increase the levels of neurotrophic factors.

In another aspect, the invention includes a method for the treatment of a mammalian subject suffering from a hypoglutamatergic condition, or from a deficiency in the number or strength of excitatory synapses, or in the number of AMPA receptors, such that memory or other

15 cognitive functions are impaired. Such conditions may also cause a cortical/striatal imbalance, leading to schizophrenia or schizophreniform behavior. According to the method, such a subject is treated with an effective amount of a compound as shown by structure I, and is described in Section II of the detailed description, following, in a pharmaceutically acceptable carrier.

20 These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying drawings.

25 **Detailed Description of the Invention**

I. Definitions

The terms below have the following definitions unless indicated otherwise. Other terms that are used to describe the present invention have the same definitions as those terms are

30 generally used by those skilled in the art.

The term "alkyl" is used herein to refer to a fully saturated monovalent radical containing

carbon and hydrogen, and which may be a straight chain, branched or cyclic. Examples of alkyl groups are methyl, ethyl, n-butyl, n-heptyl, isopropyl, 2-methylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylethyl and cyclohexyl.

- 5 The term "alkenyl" is used herein to refer to a monovalent radical containing carbon and hydrogen that contains one or two sites of unsaturation, and which may be a straight chain, branched or cyclic. Examples of alkyl groups are ethenyl, n-butenyl, n-heptenyl, isopropenyl, cyclopentenyl, cyclopentenylethyl and cyclohexenyl.

- 10 The term "substituted alkyl" refers to alkyl as just described including one or more functional groups such as lower alkyl containing 1-6 carbon atoms, aryl, substituted aryl, acyl, halogen (i.e., alkyl halos, e.g., CF_3), hydroxy, alkoxy, alkoxyalkyl, amino, alkyl and dialkyl amino, acylamino, acyloxy, aryloxy, aryloxyalkyl, carboxyalkyl, carboxamido, thio, thioethers, both saturated and unsaturated cyclic hydrocarbons, heterocycles and the like.

- 15 The term "aryl" refers to a substituted or unsubstituted monovalent aromatic radical having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl). Other examples include heterocyclic aromatic ring groups having one or more nitrogen, oxygen, or sulfur atoms in the ring, such as oxazolyl, isoxazolyl, pyrazolyl, thiazolyl, thiadiazolyl, tetrazolyl, pyridazinyl, pyrimidyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl, 20 benzothiazolyl, quinolyl, isoquinolyl, imidazolyl, furyl, pyrrolyl, pyridyl, thienyl and indolyl.

- The term "substituted" as used in the term "substituted aryl, substituted aromatic, substituted heteroaryl, or substituted heteroaromatic" herein signifies that one or more substituents may be present, said substituents being selected from atoms and groups, which when present do not prevent the compound from functioning as a potentiator of AMPA receptor function. Examples of substituents that may be present in a substituted aromatic or heteroaromatic group include, but are not limited to, groups such as $(\text{C}_1\text{-C}_7)$ alkyl, $(\text{C}_1\text{-C}_7)$ acyl, aryl, heteroaryl, substituted aryl and heteroaryl, halogen, cyano, nitro, $(\text{C}_1\text{-C}_7)$ alkylhalos (e.g., 25 CF_3), hydroxy, $(\text{C}_1\text{-C}_7)$ alkoxy, alkoxyalkyl, amino, alkyl and dialkyl amino, acylamino, acyloxy, aryloxy, aryloxyalkyl, carboxyalkyl, carboxamido, thio, thioethers, both saturated and unsaturated $(\text{C}_3\text{-C}_8)$ cyclic hydrocarbons, $(\text{C}_3\text{-C}_8)$ heterocycles and the like.
- 30

"Heterocycle" or "heterocyclic" refers to a carbocyclic ring wherein one or more carbon atoms have been replaced with one or more heteroatoms such as nitrogen, oxygen or sulfur.

Examples of heterocycles include, but are not limited to, piperidine, pyrrolidine, morpholine, thiomorpholine, piperazine, tetrahydrofuran, tetrahydropyran, 2-pyrrolidinone, δ -velerolactam, δ -velerolactone and 2-ketopiperazine.

The term "substituted heterocycle" refers to a heterocycle as just described that contains one or more functional groups such as lower alkyl, acyl, aryl, cyano, halogen, hydroxy, alkoxy, alkoxyalkyl, amino, alkyl and dialkyl amino, acylamino, acyloxy, aryloxy, aryloxyalkyl, carboxyalkyl, carboxamido, thio, thioethers, both saturated and unsaturated cyclic hydrocarbons, heterocycles and the like.

The term "compound" is used herein to refer to any specific chemical compound disclosed herein. Within its use in context, the term generally refers to a single compound, but in certain instances may also refer to stereoisomers and/or optical isomers (including racemic mixtures) of disclosed compounds.

The term "effective amount" refers to the amount of a selected compound of formula I that is used to enhance glutamatergic synaptic response by increasing AMPA receptor activity. The precise amount used will vary depending upon the particular compound selected and its intended use, the age and weight of the subject, route of administration, and so forth, but may be easily determined by routine experimentation. In the case of the treatment of a condition or disease state, an effective amount is that amount which is used to effectively treat the particular condition or disease state.

The term "pharmaceutically acceptable carrier" refers to a carrier or excipient which is not unacceptably toxic to the subject to which it is administered. Pharmaceutically acceptable excipients are described at length by E.W. Martin, in "Remington's Pharmaceutical Sciences."

A "pharmaceutically acceptable salt" of an amine compound, such as those contemplated in

the current invention, is an ammonium salt having as counterion an inorganic anion such as chloride, bromide, iodide, sulfate, sulfite, nitrate, nitrite, phosphate, and the like, or an organic anion such as acetate, malonate, pyruvate, propionate, fumarate, cinnamate, tosylate, and the like.

5

The term "patient" or "subject" is used throughout the specification to describe an animal, generally a mammalian animal, including a human, to whom treatment or use with the compounds or compositions according to the present invention is provided. For treatment or use with/or of those conditions or disease states which are specific for a specific animal (especially, for example, a human subject or patient), the term patient or subject refers to that particular animal.

10

The term "sensory motor problems" is used to describe a problem which arises in a patient or subject from the inability to integrate external information derived from the five known senses in such a way as to direct appropriate physical responses involving movement and action.

15

The term "cognitive task" or "cognitive function" is used to describe an endeavor or process by a patient or subject that involves thought or knowing. The diverse functions of the association cortices of the parietal, temporal and frontal lobes, which account for approximately 75% of all human brain tissue, are responsible for much of the information processing that goes on between sensory input and motor output. The diverse functions of the association cortices are often referred to as cognition, which literally means the process by which we come to know the world. Selectively attending to a particular stimulus, recognizing and identifying these relevant stimulus features and planning and experiencing the response are some of the processes or abilities mediated by the human brain which are related to cognition.

20

25

The term "brain network" is used to describe different anatomical regions of the brain that communicate with one another via the synaptic activity of neuronal cells.

30

The term "AMPA receptor" refers to an aggregate of proteins found in some membranes,

which allows positive ions to cross the membrane in response to the binding of glutamate or AMPA (DL- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), but not NMDA.

The term "excitatory synapse" is used to describe a cell-cell junction at which release of a chemical messenger by one cell causes depolarization of the external membrane of the other cell. An excitatory synapse describes a postsynaptic neuron which has a reversal potential that is more positive than the threshold potential and consequently, in such a synapse, a neurotransmitter increases the probability that an excitatory post synaptic potential will result (a neuron will fire producing an action potential). Reversal potentials and threshold potentials determine postsynaptic excitation and inhibition. If the reversal potential for a post synaptic potential ("PSP") is more positive than the action potential threshold, the effect of a transmitter is excitatory and produces an excitatory post synaptic potential ("EPSP") and the firing of an action potential by the neuron. If the reversal potential for a post synaptic potential is more negative than the action potential threshold, the transmitter is inhibitory and may generate inhibitory post synaptic potentials (IPSP), thus reducing the likelihood that a synapse will fire an action potential. The general rule for postsynaptic action is: if the reversal potential is more positive than threshold, excitation results; inhibition occurs if the reversal potential is more negative than threshold. See, for example, Chapter 7, NEUROSCIENCE, edited by Dale Purves, Sinauer Associates, Inc., Sunderland, MA 1997.

The term "motor task" is used to describe an endeavor taken by a patient or subject that involves movement or action.

The term "perceptual task" is used to describe an act by a patient or subject of devoting attention to sensory inputs.

The term "synaptic response" is used to describe biophysical reactions in one cell as a consequence of the release of chemical messengers by another cell with which it is in close contact.

The term "hypoglutamatergic condition" is used to describe a state or condition in which transmission mediated by glutamate (or related excitatory amino acids) is reduced to below normal levels. Transmission consists of the release of glutamate, binding to post synaptic

receptors, and the opening of channels integral to those receptors. The end point of the hypoglutamatergic condition is reduced excitatory post synaptic current. It can arise from any of the three above noted phases of transmission. Conditions or disease states which are considered hypoglutamatergic conditions and which can be treated using the compounds, compositions and methods according to the present invention include, for example, loss of memory, dementia, depression, attention disorders, sexual dysfunction, movement disorders, including Parkinson's disease, schizophrenia or schizophreniform behavior, memory and learning disorders, including those disorders which result from aging, trauma, stroke and neurodegenerative disorders, such as those associated with drug-induced states, neurotoxic agents, Alzheimer's disease, and aging. These conditions are readily recognized and diagnosed by those of ordinary skill in the art.

The term "cortico-striatal imbalance" is used to describe a state in which the balance of neuronal activities in the interconnected cortex and underlying striatal complex deviates from that normally found. 'Activity' can be assessed by electrical recording or molecular biological techniques. Imbalance can be established by applying these measures to the two structures or by functional (behavioral or physiological) criteria.

The term "affective disorder" or "mood disorder" describes the condition when sadness or elation is overly intense and continues beyond the expected impact of a stressful life event, or arises endogenously. As used herein, the term "effective disorder" embraces all types of mood disorders as described in, for example, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM IV), pages 317-391.

The term "schizophrenia" is used to describe a condition which is a common type of psychosis, characterized by a disorder in the thinking processes, such as delusions and hallucinations, and extensive withdrawal of the individual's interest from other people and the outside world, and the investment of it in his or her own. Schizophrenia is now considered a group of mental disorders rather than a single entity, and distinction is made between reactive and process schizophrenias. As used herein, the term schizophrenia or "schizophreniform" embraces all types of schizophrenia, including ambulatory schizophrenia, catatonic schizophrenia, hebephrenic schizophrenia, latent schizophrenia, process

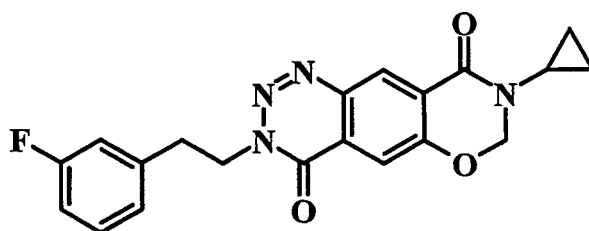
schizophrenia, pseudoneurotic schizophrenia, reactive schizophrenia, simple schizophrenia, and related psychotic disorders which are similar to schizophrenia, but which are not necessarily diagnosed as schizophrenia *per se*. Schizophrenia and other psychotic disorders may be diagnosed using guidelines established in, for example, *Diagnostic and Statistical*
5 *Manual of Mental Disorders*, Fourth Edition (DSM IV) Sections 293.81, 293.82, 295.10, 295.20, 295.30, 295.40, 295.60, 295.70, 295.90, 297.1, 297.3, 298.8.

The term "brain function" is used to describe the combined tasks of perceiving, integrating, filtering and responding to external stimuli and internal motivational processes.

10 The term "impaired" is used to describe a function working at a level that is less than normal. Impaired functions can be significantly impacted such that a function is barely being carried out, is virtually non-existent or is working in a fashion that is significantly less than normal. Impaired functions may also be sub-optimal. The impairment of function will vary in severity
15 from patient to patient and the condition to be treated.

II. Compounds that Increase AMPA Receptor Function

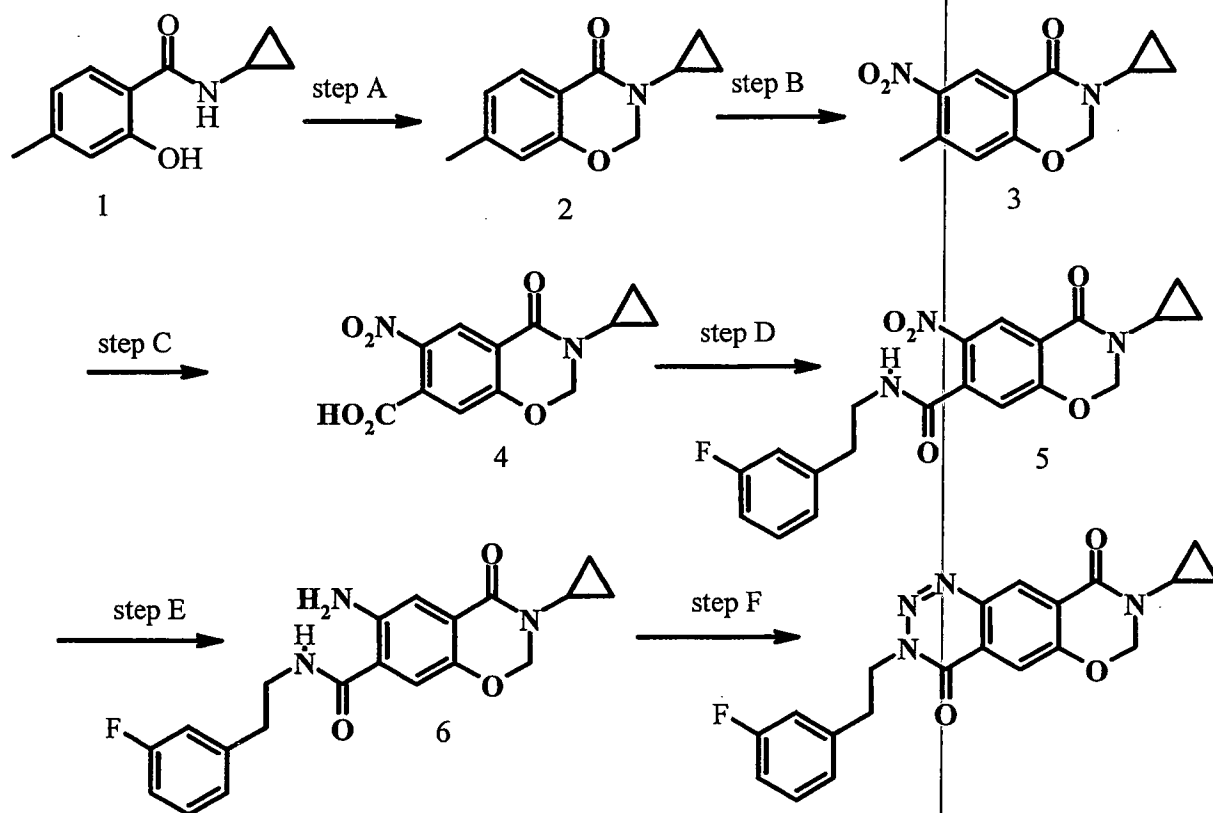
The present invention is directed, in one aspect, to a compound having the property of
20 enhancing AMPA receptor function. The specified compound of this invention having the structure I, below:



I

The synthesis of the invention compound, 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-
25 dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione, is preferably carried out by the following synthetic scheme, wherein the synthesis of the substituted salicylamide is well-known in the field of organic synthesis:

5



SCHEME 1

10

In Scheme 1, step A may be carried out under standard conditions, among them acid catalyzed insertion of a formaldehyde synthon. For example, the salicylamide (1) is dissolved and heated in a suitable organic solvent together with trioxane and sulfuric or hydrochloric acid. Step B is a nitration reaction that can be carried out under mild conditions known to those skilled in organic synthesis and detailed in such volumes at Reagents for Organic Synthesis (Fieser and Fieser) and Organic Syntheses (see web site at <http://www.orgsyn.org/>). Step C involves the 2-step oxidation of the methyl group of compound 3 to a carboxylic acid

15

17
via an intermediate aldehyde employing *N,N*-dimethylformamide dimethyl acetal and sodium periodate followed by oxone. Step D involves coupling of a primary amine to the nitro acid, which can be accomplished using a variety of coupling reagents known to a skilled chemist. Some non-limiting examples commonly used are thionyl chloride, oxalyl chloride or carbonyl diimidazole. Step E is a reduction of an aryl nitro to an aniline and can be effected by
5 reduction using a variety of catalysts including, but not limited to, Pd or Pt or Raney Ni and hydrogen or Zn/Cu. Step F forms the triazinone ring and can be carried out by the addition of isoamyl nitrite in DMF.

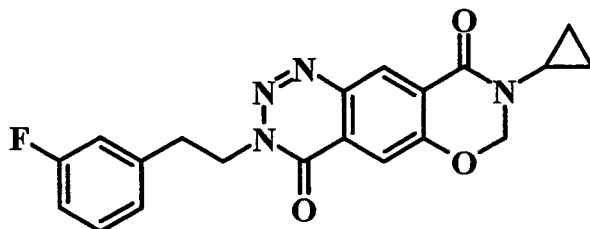
10 All compositions disclosed in the present application may be synthesized by the above-described methods using analogous synthetic steps to those specifically presented in the examples described herein as well as those known in the art. Also claimed are all addition salts with a pharmaceutically acceptable acid or base thereof.

15 III. Method of Treatment

According to one aspect of the invention, a method is provided for treating a mammalian subject suffering from a hypoglutamatergic condition, or from deficiencies in the number or
20 strength of excitatory synapses or in the number of AMPA receptors. In such a subject, memory or other cognitive functions may be impaired or cortical/striatal imbalance may occur, leading to loss of memory, dementia, depression, attention disorders, sexual dysfunction, movement disorders, schizophrenia or schizophreniform behavior. Memory disorders and learning disorders, which are treatable according to the present, invention
25 include those disorders that result from aging, trauma, stroke and neurodegenerative disorders. Examples of neurodegenerative disorders include, but are not limited to, those associated with drug-induced states, neurotoxic agents, Alzheimer's disease, and aging. These conditions are readily recognized and diagnosed by those of ordinary skill in the art and treated by administering to the patient an effective amount of one or more compounds
30 according to the present invention.

In the present invention, the method of treatment comprises administering to the subject in

need of treatment, in a pharmaceutically acceptable carrier, an effective amount of 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione having the formula:



or a pharmaceutically acceptable addition salt of an acid or base thereof.

As noted above, treatment of a subject according to the method of the invention is useful for enhancing AMPA receptor activity, and thus may be used to facilitate the learning of behaviors dependent upon AMPA receptors, and to treat conditions, such as memory impairment, in which AMPA receptors, or synapses utilizing these receptors, are reduced in numbers or efficiency. The method is also useful for enhancing excitatory synaptic activity in order to restore an imbalance between brain sub-regions, which may manifest itself in schizophrenia or schizophreniform behavior, or other behavior as described above. The compounds administered in accordance with the method have been found to be more effective than previously described compounds in enhancing AMPA receptor activity, as shown in the *in vitro* and *in vivo* tests described below.

IV. Biological Activity: Enhancement of AMPA Receptor Function

Synaptic responses mediated by AMPA receptors are increased according to the method of the invention, using the compound described herein. The compound is demonstrated to be substantially more potent than previously-described compounds in increasing AMPA mediated whole cell currents in cultured neurons. The *in vitro* assay is described as follows. Cortical cells were prepared from day 18-19 embryonic Sprague-Dawley rats and recorded after 3 days in culture. The extracellular solution (ECS) contained (in mM): NaCl (145), KCl (5.4), HEPES (10), MgCl₂ (0.8), CaCl₂ (1.8), glucose (10), sucrose (30); pH. 7.4. In order to block the voltage-gated sodium currents, 40 nM TTX was added to the recording solution. The intracellular solution contained (in mM): K-gluconate (140), HEPES (20), EGTA (1.1),

phosphocreatine (5), MgATP (3), GTP (0.3), MgCl₂ (5), and CaCl₂ (0.1); pH: 7.2. All test compound and glutamate solutions were made-up in the extracellular solution.

The whole-cell current was measured with patch-clamp amplifier (Axopatch 200B), filtered at 2 kHz, digitized at 5 kHz and recorded on a PC with pClamp 8. The cells were voltage-clamped at -80 mV. Solutions were applied by DAD-12 system. A baseline response for each cell was recorded using a 1 s pulse of 500 μ M glutamate dissolved in ECS. Responses to test compound were then determined by application of a 10 s pulse of test compound followed by a 1 s pulse of the same concentration of test compound plus 500 μ M glutamate and then 10 s of saline. This pulse sequence was repeated until a stable reading was obtained, or until sufficient data points were measured to allow extrapolation to a calculated maximum change.

The mean value of plateau current between 600 ms to 900 ms after application of glutamate or test compound plus glutamate was calculated and used as the parameter to measure the drug effect. The plateau responses in the presence of varying concentrations of test compound were divided by the baseline response in order to calculate the percentage increase. Compounds are deemed active in this test if, at a test concentration of 3 μ M or less, they produce a greater than 100% increase in the value of the steady-state current measured due to application of glutamate alone. The concentration at which the glutamate induced current is increased by 100% is commonly referred to as the EC_{2x} value.

The compound of this invention, 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione displayed an EC_{2x} value of 0.1 μ M.

V. Administration, Dosages, and Formulation

As noted above, the compound and method of the invention increase AMPA receptor-mediated responses, and are useful for the treatment of hypoglutamatergic conditions. The compound is also useful for treatment of conditions such as impairment of memory or other cognitive functions, brought on by a deficiency in the number or strength of excitatory synapses, or in the number of AMPA receptors. The compound may also be used

in the treatment of schizophrenia or schizophreniform behavior resulting from a cortical/striatal imbalance, and in facilitation of learning of behaviors dependent upon AMPA receptors.

- 5 In subjects treated with the present compound, pharmaceutical compositions and methods memory or other cognitive functions may be impaired, or cortical/striatal imbalance may occur, leading to loss of memory, dementia, depression, attention disorders, sexual dysfunction, movement disorders, schizophrenia or schizophreniform behavior. Memory disorders and learning disorders, which are treatable according to the present invention, include those disorders that result from aging, trauma, stroke and neurodegenerative disorders. Examples of neurodegenerative disorders include, but are not limited to, those associated with drug-induced states, neurotoxic agents, Alzheimer's disease, and aging. These conditions are readily recognized and diagnosed by those of ordinary skill in the art and treated by administering to the patient an effective amount of one or more compounds according to the present invention.

- Generally, dosages and routes of administration of the compound will be determined according to the size and condition of the subject, according to standard pharmaceutical practices. Dose levels employed can vary widely, and can readily be determined by those of skill in the art. Typically, amounts in the milligram up to gram quantities are employed. The composition may be administered to a subject by various routes, e.g. orally, transdermally, perineurally or parenterally, that is, by intravenous, subcutaneous, intraperitoneal, or intramuscular injection, among others, including buccal, rectal and transdermal administration. Subjects contemplated for treatment according to the method of the invention include humans, companion animals, laboratory animals, and the like.

- Formulations containing the compound according to the present invention may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, capsules, powders, sustained-release formulations, solutions, suspensions, emulsions, suppositories, creams, ointments, lotions, aerosols, patches or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

Pharmaceutical compositions according to the present invention typically include a conventional pharmaceutical carrier or excipient and may additionally include other medicinal agents, carriers, adjuvants, additives and the like. Preferably, the composition will be about 0.5 to 75% by weight of a compound or compounds of the invention, with the remainder consisting essentially of suitable pharmaceutical excipients. For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. If desired, the composition may also contain minor amounts of non-toxic auxiliary substances such as wetting agents, emulsifying agents, or buffers.

Liquid compositions can be prepared by dissolving or dispersing the compounds (about 0.5% to about 20% by weight or more), and optional pharmaceutical adjuvants, in a carrier, such as, for example, aqueous saline, aqueous dextrose, glycerol, or ethanol, to form a solution or suspension. For use in oral liquid preparation, the composition may be prepared as a solution, suspension, emulsion, or syrup, being supplied either in liquid form or a dried form suitable for hydration in water or normal saline.

When the composition is employed in the form of solid preparations for oral administration, the preparations may be tablets, granules, powders, capsules or the like. In a tablet formulation, the composition is typically formulated with additives, e.g. an excipient such as a saccharide or cellulose preparation, a binder such as starch paste or methyl cellulose, a filler, a disintegrator, and other additives typically used in the manufacture of medical preparations.

An injectable composition for parenteral administration will typically contain the compound in a suitable i.v. solution, such as sterile physiological salt solution. The composition may also be formulated as a suspension in a lipid or phospholipid, in a liposomal suspension, or in an aqueous emulsion.

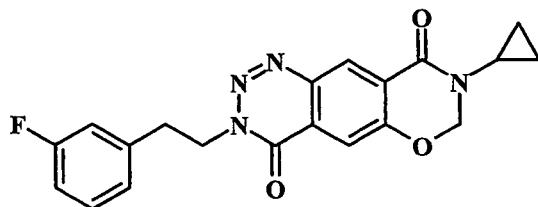
Methods for preparing such dosage forms are known or will be apparent to those skilled in the art; for example, see Remington's Pharmaceutical Sciences (17th Ed., Mack Pub. Co.,

1985). The composition to be administered will contain a quantity of the selected compound in a pharmaceutically effective amount for effecting increased AMPA receptor currents in a subject.

- 5 The following examples illustrate but are not intended in any way to limit the invention. Unless otherwise stated, all temperatures are given in degrees Celsius. Unless otherwise stated, all NMR spectra are ¹H NMR spectra and were obtained in deuteriochloroform or deuterated DMSO as solvent using tetramethylsilane as an internal standard. The name of the example compound conforms to IUPAC nomenclature as provided by the computer software
- 10 ChemSketch by ACD Labs.

Example 1

8-Cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione



- 15 4-Methylsalicylic acid (21.3 g, 140 mmol) was dissolved in methylene chloride (120 mL) followed by CDI (22.7 g, 140 mmol) in portions. The mixture was stirred at room temperature for 24 hr, and then briefly heated to boiling. A solution of cyclopropylamine (8.0
- 20 g, 140 mmol) in triethylamine (5 mL, 36 mmol) was added to the mixture, which was stirred for 3 days. Water (200 mL) was added and the pH was adjusted to 2 using 12 M hydrochloric acid. The phases were separated and the aqueous phase was extracted with chloroform (200 mL). The combined organic phases were washed with sodium bicarbonate solution (100 mL) and dried over sodium sulfate. Concentration gave 22.7 g of amide as an off white solid.
- 25 The amide (22.7 g, 119 mmol) and trioxane (36 g, 0.4 mol) were dissolved in chloroform (250 mL), which was stirred at room temperature. Sodium sulfate (32 g) and concentrated sulfuric acid (80 drops) were added and the mixture was refluxed for 30 min, after which an additional 40 drops of conc. sulfuric acid were added. After 90 min, the solids were removed

by filtration and washed with ethyl acetate. The combined solvents were removed under vacuum to give 30 g of oil. The oil was purified using flash chromatography (250 g silica gel, ethyl acetate:hexane 30:70, then 40:60) to give 20.1 g of 7-methylbenzoxazinone as a colorless oil.

- 5 The benzoxazinone (16 g, 79 mmol) was dissolved in methylene chloride (200 mL) to which acetic acid (30 mL) was added. The mixture was cooled to $\sim 0^{\circ}\text{C}$ using an ice bath and nitric acid (14 mL, 90%) was added drop wise over 15 min, which produced an orange solution. The reaction mixture was stirred for 90 min and then poured over crushed ice/water (300 mL). A sodium hydroxide solution was slowly added until the pH reached 5. The reaction
- 10 mixture was extracted with chloroform (200 mL), dried over sodium sulfate and concentrated under vacuum to ~ 40 mL. Ethyl acetate (200 mL) was added and the mixture was concentrated under vacuum to ~ 60 mL. The formed crystals were filtered off to give 8.1 g (33 mmol, yield=41%) the desired 6-nitro isomer as an off white solid. The mother liquor was concentrated and more product crystallized (1.2 g) as an off white solid. Subsequently,
- 15 another 5 g of mixed isomers were isolated from the mother liquor, this mix was used in the following step.

- The mixed isomer solids from the previous step (5 g, 20 mmol) were suspended in N,N-dimethylformamide dimethyl acetal (30 mL) and DMF (10 mL) and heated to 125°C for 16 hr. The solvent was removed under vacuum to yield a dark brown residue. The residue was
- 20 dissolved in THF (100 mL). Sodium periodate (11 g, 51 mmol) was dissolved in water (100 mL) and added to the reaction mixture, which was stirred for 15 min at room temperature. The beige slurry was extracted with chloroform (200 mL), which was dried over sodium sulfate and diluted with ethyl acetate (200 mL). The solvents were allowed to slowly evaporate, which resulted in the crystallization of the desired isomer (2.0g, 7.6 mmol) as an
- 25 off white solid).

- The nitro aldehyde intermediate (524 mg, 2.0 mmol) was dissolved in DMF (10 mL) at 40°C . After the solution was cooled to ambient, oxone (1.47 g, 2.4 mmol) was added and the mixture was stirred overnight. Addition of water (25 mL) and ethyl acetate (30 mL) produced two phases, which were separated and the organic phase was filtered and washed with water.
- 30 The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed twice with water, dried over magnesium sulfate and concentrated under vacuum to

give a wet, yellow residue (0.54 g, 1.9 mmol), which was used without further purification.

A solution of the nitro acid intermediate (0.54 g, 1.9 mmol) in methylene chloride was combined with thionyl chloride (1.4 mL, 20 mmol) together with a few drops of DMF stirred at ambient temperature overnight. The mixture was concentrated under vacuum and redissolved in methylene chloride (10 mL). 3-Fluorophenethylamine (0.56 mL, 4.3 mmol) and triethylamine (1.1 mL, 7.9 mmol) were dissolved in methylene chloride (15 mL) to which the freshly prepared solution of the acid chloride was added. After being stirred for 2 hr, the solution was washed with aqueous HCl (1 M) and sat. sodium bicarbonate and dried over magnesium sulfate. The product solution was concentrated under vacuum to give a yellow solid, which was triturated in ethyl acetate to give light beige crystals (0.53 g, 1.3 mmol).

The beige solid from the previous step (0.53 g, 1.3 mmol) was dissolved in a mixture of THF (20 mL) and methanol (20 mL) and added to freshly prepared Zn/Cu reagent (10 g, see below). Formic acid (10 drops) was added and the mixture was stirred at ambient temperature overnight, after which TLC showed completion of the reaction. After addition of DMF (2 mL), the mixture was stirred for 10 min, and then filtered through silica gel (2 cm). The silica was washed with THF/methanol (1:1) and the combined filtrate and wash was concentrated under vacuum. Chloroform was added and evaporated to remove any residual water. DMF (2 mL) and an excess of isoamyl nitrite (5 mL) were added and the mixture was stirred for 2.5 hr after which TLC showed the reaction was complete. Addition of diethyl ether (5 mL) caused precipitation of the product, which was washed with ethyl acetate and air dried to give 0.29 g of a yellow solid with the following properties: MP 181 – 182 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.78 (1H, s), 7.82 (1H, s), 7.3-6.8 (4H, m), 5.33 (2H, s), 4.67 (2H, m), 3.21 (2H, m), 2.76 (1H, m), 1.02 (2H, m) and 0.86 ppm (2H, m).

The Zn/Cu reagent (used above) was freshly prepared in the following manner: Conc. HCl (3 mL) was added to 10 g zinc in 100 mL water during vigorous stirring. The stirring continued for 2 min (clumps start to form), after which the water was decanted off. An additional 100 mL of water was added with vigorous stirring. Any remaining clumps were crushed with a spatula. Conc. HCl (3 mL) was added and the stirring was continued for 2 min. After removing the water by decantation, the solid was washed with an additional 100 mL of water. Water (50 mL) was added to the solid and the stirring was continued while a solution of

CuSO₄ (300 mg in 50 mL water) was added slowly. After the zinc turned black, the water was removed by decantation. The residue was sequentially washed with methanol (50 mL) and THF (50 mL).

EXAMPLE 2

In Vivo Physiological Testing

The physiological effects of the invention compound were tested *in vivo* in anesthetized animals according to the following procedures.

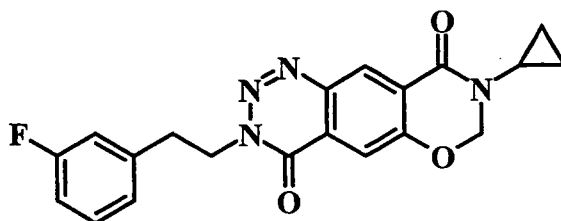
Animals are maintained under anesthesia by phenobarbital administered using a Hamilton syringe pump. Stimulating and recording electrodes are inserted into the perforant path and dentate gyrus of the hippocampus, respectively. Once electrodes are implanted, a stable baseline of evoked responses are elicited using single monophasic pulses (100 μ s pulse duration) delivered at 3/min to the stimulating electrode. Field EPSPs are monitored until a stable baseline is achieved (about 20-30 min), after which a solution of test compound in HPCD is injected intraperitoneally and evoked field potentials are recorded. Evoked potentials are recorded for approximately 2 h following drug administration or until the amplitude of the field EPSP returns to baseline. In the latter instance, it is common that an iv administration is also carried out with an appropriate dose of the same test compound.

8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione produced an increase in the amplitude of the field EPSP of 10% at a dose of 5 mg/kg following iv administration.

While the invention has been described with reference to specific methods and embodiments, it will be appreciated that various modifications may be made without departing from the invention.

WHAT IS CLAIMED:

1. A compound of the formula:



or a pharmaceutically acceptable addition salt of an acid or base thereof.

2. A compound of the formula in claim 1 that is:

8-Cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione, or a pharmaceutically acceptable addition salt of an acid or base thereof.

3. A method for the treatment of a mammalian subject, wherein the subject suffers from a hypoglutamatergic condition or a deficiency in the number or strength of excitatory synapses or in the number of AMPA receptors, such that memory or other cognitive functions are impaired, said method comprising administering to said subject, in a pharmaceutically acceptable carrier, an effective amount of a compound according to any of claim 1 or 2.

4. A method for the treatment of a mammal wherein the subject suffers from a hypoglutamatergic condition or deficiencies in the number or strength of excitatory synapses or in the number of AMPA receptors such that a cortical/striatal imbalance occurs leading to schizophrenia or schizophreniform behavior, said method comprising administering to said subject, in a pharmaceutically acceptable carrier, an effective amount of a compound according to any of claims 1 or 2.

5. The method according to claim 4 wherein said condition is schizophrenia.

6. The method according to claim 3 wherein said condition is Parkinson's disease.
7. The method according to claim 3 wherein said condition is Alzheimer's disease.
- 5 8. A pharmaceutical composition comprising an effective amount of a compound according any of claims 1-2 in combination with a pharmaceutically acceptable carrier, additive or excipient.
9. The composition according to claim 8 wherein said compound comprises about 0.5%
10 to about 75% by weight of said composition and said carrier, additive or excipient comprises about 25% to about 95.5% of said composition.
10. Use of a compound according to any of claims 1-2 in the manufacture of a
15 medicament for use in the treatment of a mammalian subject, wherein the subject suffers from a hypoglutamatergic condition or a deficiency in the number or strength of excitatory synapses or in the number of AMPA receptors, such that memory or other cognitive functions are impaired.
11. Use of a compound according to any of claims 1 and 2 in the manufacture of a
20 medicament for use in the treatment of schizophrenia.
12. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for use in the treatment of Parkinson's disease.
- 25 13. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for use in the treatment of ADHD.
14. Use of a compound according to any of claims 1 and 2 in the manufacture of a
30 medicament for use in the treatment of Rett Syndrome.
15. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for use in the treatment of Fragile-X Syndrome.

16. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for the treatment of Alzheimer's disease.

ABSTRACT

This invention relates to the prevention and treatment of cerebral insufficiency, including enhancement of receptor functioning in synapses in brain networks responsible for higher order behaviors. These brain networks are involved in cognitive abilities related to memory impairment, such as is observed in a variety of dementias, and in imbalances in neuronal activity between different brain regions, as is suggested in disorders such as Parkinson's disease, schizophrenia and affective disorders. In a particular aspect, the present invention relates to a compound useful for treatment of such conditions, and methods of using this compound for such treatment.

30

ANEXO No. 2

REPORTE DE LA BÚSQUEDA INTERNACIONAL

**3 – SUSTITUTOS – [1-2-3] – COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC.**

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference C21-079PCT	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 07/26416	International filing date (<i>day/month/year</i>) 28 December 2007 (28.12.2007)	(Earliest) Priority Date (<i>day/month/year</i>) 03 January 2007 (03.01.2007)
Applicant CORTEX PHARMACEUTICALS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 07/26416

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 57/00; A61K 31/675, 31/535 (2008.04)

USPC - 514/93

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC-514/93Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-514/228.8, 230.5, 242 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Google, WEST:terms-benzotriazinone; AMPA; 1,2,3-benzotriazine and benzoxazine; AMPA receptor; Parkinson's disease; Fragile-X;
ADHD; neurological composition
SciFinder-substructure and similarity search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,962,477 A (ROGERS et al.) 05 October 1999 (05.10.1999) Abstract; col 4, ln 64; col 5, ln 33, ln 50; col 10, Example 6	1-16
Y	US 6,303,542 B1 (LI et al.) 16 October 2001 (16.10.2001) col 1, formula I	1-16
Y	MURRAY et al. LY503430, a novel AMPA receptor potentiator with functional, neuroprotective and neurotrophic effects in rodent models of Parkinson's disease. J Pharmacol Exp Ther, 2003, Vol 306, pp 752-62, Abstract	6, 12
Y	RUSSELL. Increased AMPA Receptor Function in Slices Containing the Prefrontal Cortex of Spontaneously Hypertensive Rats. Metabolic Brain Disease, 2001, Vol 16, pp 143-149, Abstract	13
Y	WO 2003/099299 A1 (CHEEMA et al.) 04 December 2003 (04.12.2003) p 10, ln 5-17	14
Y	PONTARELLI. New drug that enhances glutamate transmission in brain being evaluated for fragile X, 2002, downloaded 10.04.2008, URL: http://www.innovations-report.com/html/reports/medicine_health/report-12386.html , para 8	15

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 April 2008 (10.04.2008)

Date of mailing of the international search report

01 MAY 2008

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

33

ANEXO No. 3

SOLICITUD - PETITORIO DE LA PATENTE PCT

**3 - SUSTITUTOS - [1-2-3] - COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC.**

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) C21-079PCT

Box No. I TITLE OF INVENTION

3-Substituted-[1,2,3]-Benzotriazinone Compound For Enhancing Glutamatergic Synaptic Responses

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CORTEX PHARMACEUTICALS, INC.
15241 Barranca Parkway
Irvine, CA 92718

Telephone No.

949-727-3157

Facsimile No.

949-727-3657

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LES LABORATOIRES SERVIER
12, Place de La Defense
92415 COURBEVOIE Cedex
FRANCE

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

FR

State (that is, country) of residence:

FR

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Henry D. COLEMAN
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
United States of America

Telephone No.

203-366-3560

Facsimile No.

203-335-6899

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CORDI, Alexis
8 bis, Rue Ledru-Rollin
F-92150 SURESNES
FRANCE

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
FR

State (that is, country) of residence:
FR

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ROGERS, Gary
28821 Shady Lane
Laguna Beach, CA 92651

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No. V DESIGNATIONS							
The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. However, ☐ DE Germany is not designated for any kind of national protection ☐ KR Republic of Korea is not designated for any kind of national protection ☐ RU Russian Federation is not designated for any kind of national protection <i>(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)</i>							
Box No. VI PRIORITY CLAIM							
The priority of the following earlier application(s) is hereby claimed:							
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:					
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office			
item (1) 3 January 2007 (03.01.2007)	60/878,503	US					
item (2) 2 April 2007 (02.04.2007)	60/921,433	US					
item (3)							
☐ Further priority claims are indicated in the Supplemental Box.							
The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) <i>(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)</i> identified above as: ☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box <i>* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):</i> 							
Box No. VII INTERNATIONAL SEARCHING AUTHORITY							
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / USPTO Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">Date (day/month/year)</td> <td style="width: 33%;">Number</td> <td style="width: 33%;">Country (or regional Office)</td> </tr> </table>					Date (day/month/year)	Number	Country (or regional Office)
Date (day/month/year)	Number	Country (or regional Office)					
Box No. VIII DECLARATIONS							
The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):				Number of declarations			
☐	Box No. VIII (i)	Declaration as to the identity of the inventor	:				
☐	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:				
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:				
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:				
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:				

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Box No. IX CHECK LIST; LANGUAGE OF FILING																																					
This international application contains: (a) in paper form, the following number of sheets: request (including declaration sheets) : 4 description (excluding sequence listing and/or tables related thereto) : 22 claims : 3 abstract : 1 drawings : 0 Sub-total number of sheets : 30 sequence listing : tables related thereto : <i>(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)</i> Total number of sheets : 30 (b) ☐ only in computer readable form (Section 801(a)(i)) (i) ☐ sequence listing (ii) ☐ tables related thereto (c) ☐ also in computer readable form (Section 801(a)(ii)) (i) ☐ sequence listing (ii) ☐ tables related thereto Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the ☐ sequence listing: ☐ tables related thereto: <i>(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)</i>	This international application is accompanied by the following item(s) <i>(mark the applicable check-boxes below and indicate in right column the number of each item)</i>: <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 80%;"></th> <th style="width: 20%; text-align: right;">Number of items</th> </tr> </thead> <tbody> <tr> <td>1. ☒ fee calculation sheet</td> <td style="text-align: right;">1</td> </tr> <tr> <td>2. ☐ original separate power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;">:</td> </tr> <tr> <td>4. ☐ copy of general power of attorney; reference number, if any:</td> <td style="text-align: right;">:</td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;">:</td> </tr> <tr> <td>6. ☐ priority document(s) identified in Box No. VI as item(s):</td> <td style="text-align: right;">:</td> </tr> <tr> <td>7. ☐ translation of international application into (language):</td> <td style="text-align: right;">:</td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;">:</td> </tr> <tr> <td>9. ☐ sequence listing in computer readable form (indicate type and number of carriers)</td> <td style="text-align: right;">:</td> </tr> <tr> <td style="padding-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :</td> <td style="text-align: right;">:</td> </tr> <tr> <td style="padding-left: 20px;">(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :</td> <td style="text-align: right;">:</td> </tr> <tr> <td style="padding-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :</td> <td style="text-align: right;">:</td> </tr> <tr> <td>10. ☐ tables in computer readable form related to sequence listing (indicate type and number of carriers)</td> <td style="text-align: right;">:</td> </tr> <tr> <td style="padding-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) :</td> <td style="text-align: right;">:</td> </tr> <tr> <td style="padding-left: 20px;">(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) :</td> <td style="text-align: right;">:</td> </tr> <tr> <td style="padding-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :</td> <td style="text-align: right;">:</td> </tr> <tr> <td>11. ☐ other (specify):</td> <td style="text-align: right;">:</td> </tr> </tbody> </table>		Number of items	1. ☒ fee calculation sheet	1	2. ☐ original separate power of attorney	:	3. ☐ original general power of attorney	:	4. ☐ copy of general power of attorney; reference number, if any:	:	5. ☐ statement explaining lack of signature	:	6. ☐ priority document(s) identified in Box No. VI as item(s):	:	7. ☐ translation of international application into (language):	:	8. ☐ separate indications concerning deposited microorganism or other biological material	:	9. ☐ sequence listing in computer readable form (indicate type and number of carriers)	:	(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :	:	(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :	:	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :	:	10. ☐ tables in computer readable form related to sequence listing (indicate type and number of carriers)	:	(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) :	:	(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) :	:	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :	:	11. ☐ other (specify):	:
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(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :	:																																				
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10. ☐ tables in computer readable form related to sequence listing (indicate type and number of carriers)	:																																				
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11. ☐ other (specify):	:																																				
Figure of the drawings which should accompany the abstract:	Language of filing of the international application:																																				
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i> Henry D. COLEMAN / Reg. No. 32,559																																					

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid
For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

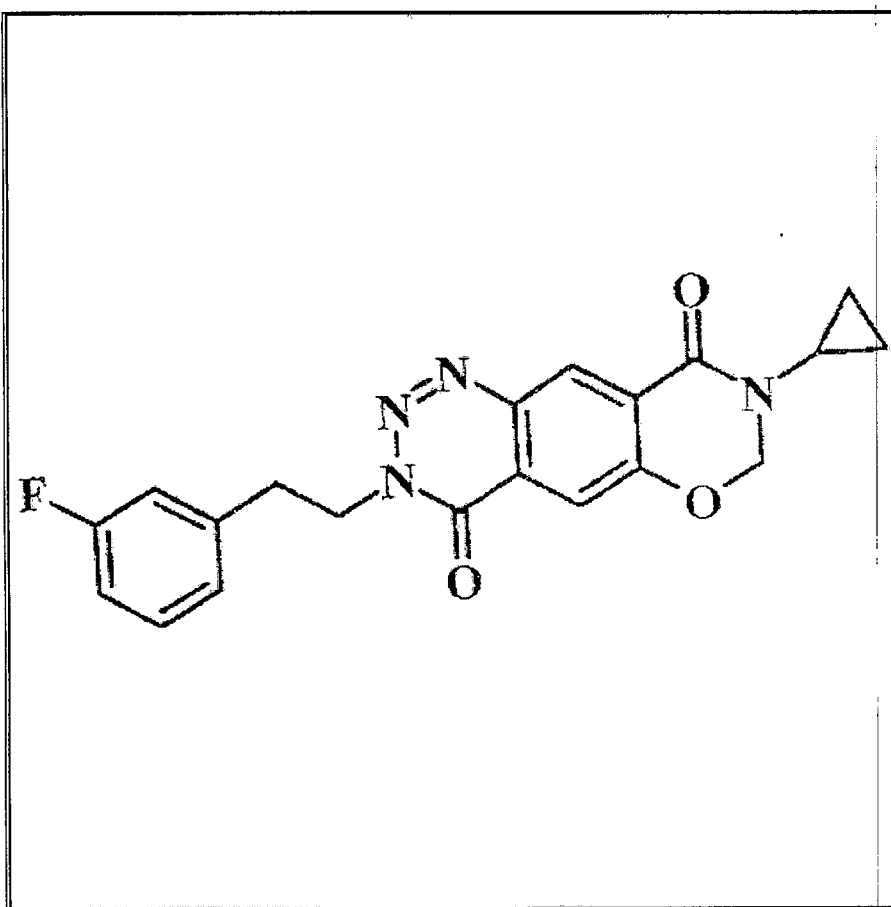
30

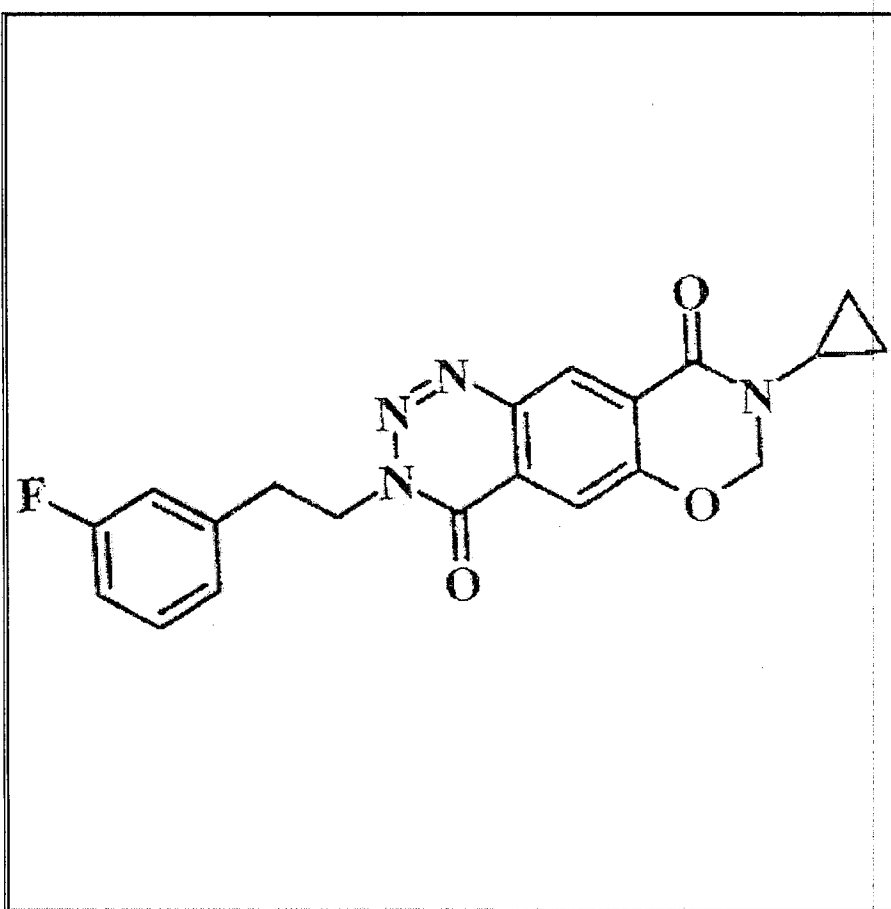
ANEXO No. 4

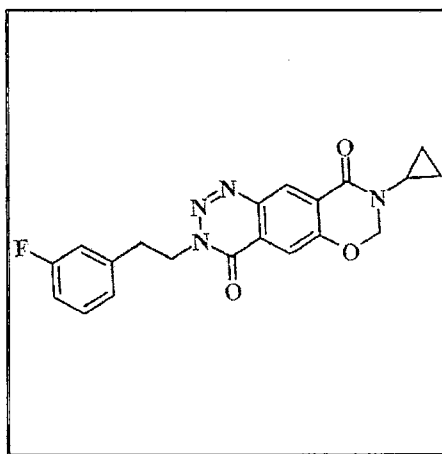
ARTE FINAL 12X12 Y 6X6 CM.

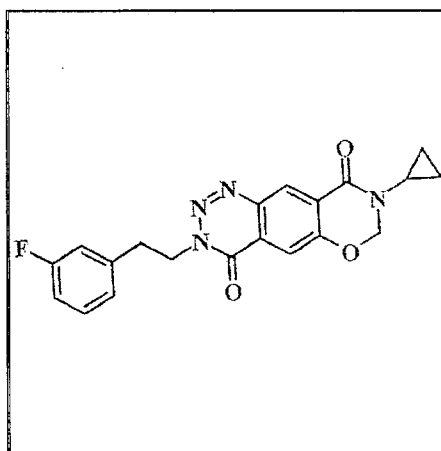
**3 – SUSTITUTOS – [1-2-3] – COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC.**









ANEXO No. 5

**COMPROBANTE DE PAGO DE LA TASA DE
PRESENTACIÓN DE LA SOLICITUD**

**3 – SUSTITUTOS – [1-2-3] – COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC.**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 47,894
FECHA : JULIO 2 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-068410-00000-0000

Fecha: 2009-07-02 15:53:32 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 90

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALEXANDER BARRETO	CONSIGNACION	BANCO DE BOGOTA	062754387	16958900	02/07/2009	540,000.00
ALEXANDER BARRETO	CONSIGNACION	BANCO DE BOGOTA	062754387	16958911	02/07/2009	222,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL :	\$ 540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXO No. 6

**PUBLICACIÓN DE LA SOLICITUD DE PATENTE
PCT - WO 2008/085506 A1**

**3 - SUSTITUTOS - [1-2-3] - COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC.**

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 July 2008 (17.07.2008)

PCT

(10) International Publication Number
WO 2008/085506 A1

(51) International Patent Classification:
A01N 57/00 (2006.01) A61K 31/675 (2006.01)

(74) Agent: COLEMAN, Henry, D.; Coleman Sudol Sapone, P.C., 714 Colorado Avenue, Bridgeport, CT 06605-1601 (US).

(21) International Application Number:
PCT/US2007/026416

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date:
28 December 2007 (28.12.2007)

(25) Filing Language: English

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(30) Priority Data:
60/878,503 3 January 2007 (03.01.2007) US
60/921,433 2 April 2007 (02.04.2007) US

(71) Applicants (for all designated States except US): COR-
TEX PHARMACEUTICALS, INC. [US/US]; 15241
Barranca Parkway, Irvine, CA 92718 (US). LES LABO-
RATOIRES SERVIER [FR/FR]; 12, place de la Defense,
F-92415 Courbevoie Cedex (FR).

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CORDI, Alexis [FR/FR]; 8 bis, rue Ledru-Rollin, F-92150 Suresnes (FR). ROGERS, Gary [US/US]; 28821 Shady Lane, Laguna Beach, CA 92651 (US).

Published:
— with international search report

(54) Title: 3-SUBSTITUTED-[1,2,3]-BENZOTRIAZINONE COMPOUND FOR ENHANCING GLUTAMATERGIC SYNAP-
TIC RESPONSES

(57) Abstract: This invention relates to the prevention and treatment of cerebral insufficiency, including enhancement of receptor functioning in synapses in brain networks responsible for higher order behaviors. These brain networks are involved in cognitive abilities related to memory impairment, such as is observed in a variety of dementias, and in imbalances in neuronal activity between different brain regions, as is suggested in disorders such as Parkinson's disease, schizophrenia and affective disorders. In a particular aspect, the present invention relates to a compound useful for treatment of such conditions, and methods of using this compound for such treatment.

WO 2008/085506 A1

**3-SUBSTITUTED-[1,2,3]-BENZOTRIAZINONE COMPOUND FOR ENHANCING
GLUTAMATERGIC SYNAPTIC RESPONSES**

Field of the Invention

5 This invention relates to a compound, pharmaceutical compositions and methods for use in the prevention and treatment of cerebral insufficiency, including enhancement of receptor functioning at synapses in brain networks responsible for higher order behaviors. These brain networks, which are involved in cognitive abilities, are related to memory impairment, such as is observed in ageing and a variety of dementias, in imbalances in neuronal activity between different brain regions, as is suggested in disorders such as Parkinson's disease, schizophrenia, attention deficit and affective or mood disorders, and in disorders wherein a deficiency in neurotrophic factors is implicated. In a particular aspect, the present invention relates to compounds useful for treatment of such conditions, and methods of using these compounds for such treatment.

Related Applications

This application claims the benefit of priority of U.S. provisional applications US60/878,503, filed January 3, 2007 and US60/921,433, filed April 2, 2007, relevant portions of which applications are incorporated by reference herein.

Background of the Invention

25 The release of glutamate at synapses at many sites in mammalian forebrain stimulates two classes of postsynaptic, ionotropic receptors. These classes are usually referred to as AMPA/quisqualate and N-methyl-D-aspartic acid (NMDA) receptors. AMPA/quisqualate receptors mediate a voltage independent fast excitatory post-synaptic current (the fast EPSC), whereas NMDA receptors generate a voltage-dependent, slow excitatory current. Studies carried out in slices of hippocampus or cortex, indicate that the AMPA receptor mediated fast EPSC is generally the dominant component by far at most glutamatergic synapses.

AMPA receptors are not evenly distributed across the brain but rather are largely restricted to

the telencephalon and cerebellum. These receptors are found in high concentrations in the superficial layers of neocortex, in each of the major synaptic zones of hippocampus, and in the striatal complex, as reported by Monaghan *et al.*, in *Brain Research* 324:160-164 (1984).

Studies in animals and humans indicate that these structures organize complex

5 perceptual-motor processes and provide the substrates for higher-order behaviors. Thus, AMPA receptors mediate transmission in those brain networks responsible for a host of cognitive activities.

For the reasons set forth above, drugs that modulate and thereby enhance the functioning of

10 AMPA receptors could have significant benefits for cognitive and intellectual performance.

Such drugs should also facilitate memory encoding. Experimental studies, such as those reported by Arai and Lynch, *Brain Research* 598:173-184 (1992), indicate that increasing the size of AMPA receptor-mediated synaptic response(s) enhances the induction of long-term potentiation (LTP). LTP is a stable increase in the strength of synaptic contacts that follows

15 repetitive physiological activity of a type known to occur in the brain during learning.

Compounds that enhance the functioning of the AMPA form of glutamate receptors facilitate the induction of LTP and the acquisition of learned tasks in rodents and humans as measured in a number of paradigms. See, for example, Granger *et al.*, *Synapse* 15:326-329 (1993);

20 Staubli *et al.*, *PNAS* 91:777-781 (1994); Arai *et al.*, *Brain Res.* 638:343-346 (1994); Staubli *et al.*, *PNAS* 91:11158-11162 (1994); Shors *et al.*, *Neurosci. Let.* 186:153-156 (1995); Larson *et al.*, *J. Neurosci.* 15:8023-8030 (1995); Granger *et al.*, *Synapse* 22:332-337 (1996); Arai *et al.*, *JPET* 278:627- 638 (1996); Lynch *et al.*, *Internat. Clin. Psychopharm.* 11: 13-19 (1996); Lynch *et al.*, *Exp. Neurology* 145:89-92 (1997); Ingvar *et al.*, *Exp. Neurology* 146:553-559

25 (1997); Hampson, et al., *J. Neurosci.* 18:2748-2763 (1998); Porrino et al., *PLoS Biol* 3(9):1-14 (2006) and Lynch and Rogers, US Patent 5,747,492. There is a considerable body of evidence showing that LTP is a substrate of memory. For example, compounds that block LTP interfere with memory formation in animals, and certain drugs that disrupt learning in humans antagonize the stabilization of LTP, as reported by del Cerro and Lynch,

30 *Neuroscience* 49: 1-6 (1992). Learning a simple task induces LTP in hippocampus that occludes LTP generated by high frequency stimulation (Whitlock *et al.*, *Science* 313:1093-1097 (2006)) and a mechanism that maintains LTP sustains spatial memory (Pastalkova, et

al., Science **313**:1141-1144 (2006)). Of significant importance to the field of learning is the finding that *in vivo* treatments with a positive AMPA-type glutamate receptor modulator restores stabilization of basal dendritic LTP in middle-aged animals (Rex, *et al.*, *J. Neurophysiol.* **96**:677-685 (2006)).

- 5 Excitatory synaptic transmission provides a major pathway by which neurotrophic factors are increased within specific brain regions. As such, potentiation of AMPA receptor function by modulators has been found to increase levels of neurotrophins, particularly brain derived neurotrophic factor, or BDNF. See, for example, Lauterborn, *et al.*, *J. Neurosci.* **20**:8-21 (2000); Gall, *et al.*, U.S. Patent 6,030,968; Lauterborn, *et al.*, JPET **307**:297-305 (2003); and
- 10 Mackowiak, *et al.*, *Neuropharmacology* **43**:1-10 (2002). Other studies have linked BDNF levels to a number of neurological disorders, such as Parkinson's disease, Attention Deficit Hyperactivity Disorder (ADHD), autism, Fragile-X Syndrome, and Rett Syndrome (RTT). See, for example, O'Neill, *et al.*, *Eur. J. Pharmacol.* **486**:163-174 (2004); Kent, *et al.*, *Mol. Psychiatry* **10**:939-943 (2005); Riikonen, *et al.*, *J. Child Neurol.* **18**:693-697 (2003) and
- 15 Chang, *et al.*, *Neuron* **49**:341-348 (2006). Thus, AMPA receptor potentiators may be useful for the treatment of these, as well as other, neurological diseases that are the result of a glutamatergic imbalance or a deficit in neurotrophic factors.

- A prototype for a compound that increases AMPA receptor function was described by Ito *et al.*, *J. Physiol.* **424**:533-543 (1990). These authors found that the nootropic drug aniracetam (N-anisoyl-2-pyrrolidinone) increases currents mediated by brain AMPA receptors expressed
- 20 in *Xenopus* oocytes without affecting responses by γ -aminobutyric acid (GABA), kainic acid (KA), or NMDA receptors. Infusion of aniracetam into slices of hippocampus was also shown to substantially increase the size of fast synaptic potentials without altering resting
- 25 membrane properties. It has since been confirmed that aniracetam enhances synaptic responses at several sites in hippocampus, and that it has no effect on NMDA-receptor mediated potentials (Staubli *et al.*, *Psychobiology* **18**:377-381 (1990) and Xiao *et al.*, *Hippocampus* **1**:373-380 (1991)).

- 30 Aniracetam has been found to have an extremely rapid onset and washout, and can be applied repeatedly with no apparent lasting effects, which are desirable features for behaviorally-relevant drugs. Aniracetam does present several disadvantages, however. The

peripheral administration of aniracetam is not likely to influence brain receptors. The drug works only at high concentrations (approx. 1000 μ M), and about 80% of the drug is converted to anisoyl-GABA following peripheral administration in humans (Guenzi and Zanetti, *J. Chromatogr.* **530**:397-406 (1990)). The metabolite, anisoyl-GABA, has been found to have less synaptic activity than aniracetam. In addition to these issues, aniracetam has putative effects on a plethora of other neurotransmitter and enzymatic targets in the brain, which makes uncertain the mechanism of any claimed therapeutic drug effect. See, for example, Himori, *et al.*, *Pharmacology Biochemistry and Behavior* **47**:219-225 (1994); Pizzi *et al.*, *J. Neurochem.* **61**:683-689 (1993); Nakamura and Shirane, *Eur. J. Pharmacol.* **380**: 81-89 (1999); Spignoli and Pepeu, *Pharmacol. Biochem. Behav.* **27**:491-495 (1987); Hall and Von Voigtlander, *Neuropharmacology* **26**:1573-1579(1987); and Yoshimoto *et al.*, *J. Pharmacobiodyn.* **10**:730-735(1987).

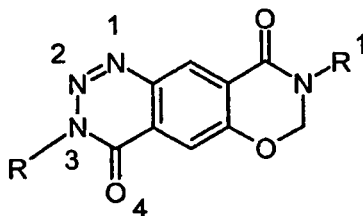
A class of AMPA receptor-modulating compounds that does not display the low potency and inherent instability characteristic of aniracetam has been described (Lynch and Rogers, US Patent 5,747,492). These compounds, termed "Ampakines"[®], can be substituted benzamides, which include, for example, 1-(quinoxaline-6-ylcarbonyl)piperidine (CX516; Ampalex[®]). Typically, they are chemically more stable than aniracetam and show improved bioavailability. CX516 is active in animal tests used to detect efficacious drugs for the treatment of memory disorders, schizophrenia, and depression. In three separate clinical trials, CX516 showed evidence for efficacy in improving various forms of human memory (Lynch *et al.*, *Internat. Clin. Psychopharm.* **11**:13-19 (1996); Lynch *et al.*, *Exp. Neurology* **145**:89-92 (1997); Ingvar *et al.*, *Exp. Neurology* **146**:553-559 (1997)).

Another class of Ampakines, benzoxazines, has been discovered to have very high activity in *in vitro* and *in vivo* models for assessing the probability of producing cognition enhancement (Rogers and Lynch; US Patent # 5,736,543). The substituted benzoxazines are rigid benzamide analogues with different receptor modulating properties from the flexible benzamide, CX516.

Certain substituted benzofurazan and benzothiadiazole compounds have been found to be significantly and surprisingly more potent in the animal model of schizophrenia than

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previous compounds, and are also effective in cognition enhancement. These compounds are structurally similar to those disclosed in Lynch and Rogers, US Patent # 5,736,543.

Previously disclosed structures that contained the 1,3-benzoxazine-4-one pharmacophore were substituted on the benzene portion by heteroatoms, such as nitrogen or oxygen (US Patents # 5,736,543 and 5,962,447), by substituted alkyl groups (US Patents # 5,650,409 and 5,783,587), or unsubstituted (WO 99/42456). Yet another class of 1,3-benzoxazine compounds contained a carbonyl external to the oxazine ring (US Patent # 6,124,278), but not as a substituent on the benzene ring structure. Now, a new class of triazinone compounds has been discovered that display significant activity on hippocampal synaptic responses and neuronal whole cell currents mediated by AMPA receptors. 3-Substituted benzo[1,2,3]triazin-4-one compounds are potent AMPA receptor modulators that are significantly more metabolically stable than the corresponding bis-benzoxazinones.



The biological activity of the triazinones was unexpected and the potency at the AMPA receptor is surprisingly high; the most potent triazinones in this class double AMPA receptor currents at concentrations as low as 3 nM. A benzo[1,2,3]triazin-4-one compound as a AMPA receptor modulator is disclosed herein.

Summary of the Invention

The present invention includes, in one aspect, a compound as shown by structure I, and is described in Section II of the detailed description, which follows. Administration of compounds of this class has been found to increase synaptic responses mediated by AMPA receptors. The compound of the present invention is significantly and unexpectedly more potent than previously described compounds in increasing AMPA receptor function in primary neuronal cultures and in slices of rat hippocampus, and in enhancing cognitive performance, such as performance in a delayed match to sample task. This unexpected

activity translates into pharmaceutical compounds and corresponding methods of use, including treatment methods, which utilize significantly lower concentrations (on a mole-to-mole basis) of the present compounds compared to prior art compositions.

- 5 The ability of the compound of the invention to increase AMPA receptor-mediated responses makes the compounds useful for a variety of purposes. These include facilitating the learning of behaviors dependent upon glutamate receptors, treating conditions in which AMPA receptors or synapses utilizing these receptors are reduced in numbers or efficiency, and enhancing excitatory synaptic activity in order to restore an imbalance between brain sub-
- 10 regions or increase the levels of neurotrophic factors.

- In another aspect, the invention includes a method for the treatment of a mammalian subject suffering from a hypoglutamatergic condition, or from a deficiency in the number or strength of excitatory synapses, or in the number of AMPA receptors, such that memory or other
- 15 cognitive functions are impaired. Such conditions may also cause a cortical/striatal imbalance, leading to schizophrenia or schizophreniform behavior. According to the method, such a subject is treated with an effective amount of a compound as shown by structure I, and is described in Section II of the detailed description, following, in a pharmaceutically acceptable carrier.

- 20 These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying drawings.

25 **Detailed Description of the Invention**

I. Definitions

- The terms below have the following definitions unless indicated otherwise. Other terms that are used to describe the present invention have the same definitions as those terms are
- 30 generally used by those skilled in the art.

The term "alkyl" is used herein to refer to a fully saturated monovalent radical containing

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carbon and hydrogen, and which may be a straight chain, branched or cyclic. Examples of alkyl groups are methyl, ethyl, n-butyl, n-heptyl, isopropyl, 2-methylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylethyl and cyclohexyl.

5 The term "alkenyl" is used herein to refer to a monovalent radical containing carbon and hydrogen that contains one or two sites of unsaturation, and which may be a straight chain, branched or cyclic. Examples of alkyl groups are ethenyl, n-butenyl, n-heptenyl, isopropenyl, cyclopentenyl, cyclopentenylethyl and cyclohexenyl.

10 The term "substituted alkyl" refers to alkyl as just described including one or more functional groups such as lower alkyl containing 1-6 carbon atoms, aryl, substituted aryl, acyl, halogen (i.e., alkyl halos, e.g., CF₃), hydroxy, alkoxy, alkoxyalkyl, amino, alkyl and dialkyl amino, acylamino, acyloxy, aryloxy, aryloxyalkyl, carboxyalkyl, carboxamido, thio, thioethers, both saturated and unsaturated cyclic hydrocarbons, heterocycles and the like.

15 The term "aryl" refers to a substituted or unsubstituted monovalent aromatic radical having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl). Other examples include heterocyclic aromatic ring groups having one or more nitrogen, oxygen, or sulfur atoms in the ring, such as oxazolyl, isoxazolyl, pyrazolyl, thiazolyl, thiadiazolyl, tetrazolyl, 20 pyridazinyl, pyrimidyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, imidazolyl, furyl, pyrrolyl, pyridyl, thienyl and indolyl.

The term "substituted" as used in the term "substituted aryl, substituted aromatic, substituted heteroaryl, or substituted heteroaromatic" herein signifies that one or more substituents may 25 be present, said substituents being selected from atoms and groups, which when present do not prevent the compound from functioning as a potentiator of AMPA receptor function. Examples of substituents that may be present in a substituted aromatic or heteroaromatic group include, but are not limited to, groups such as (C₁-C₇) alkyl, (C₁-C₇) acyl, aryl, heteroaryl, substituted aryl and heteroaryl, halogen, cyano, nitro, (C₁-C₇) alkylhalos (e.g., 30 CF₃), hydroxy, (C₁-C₇) alkoxy, alkoxyalkyl, amino, alkyl and dialkyl amino, acylamino, acyloxy, aryloxy, aryloxyalkyl, carboxyalkyl, carboxamido, thio, thioethers, both saturated and unsaturated (C₃-C₈) cyclic hydrocarbons, (C₃-C₈) heterocycles and the like.

"Heterocycle" or "heterocyclic" refers to a carbocyclic ring wherein one or more carbon atoms have been replaced with one or more heteroatoms such as nitrogen, oxygen or sulfur.

Examples of heterocycles include, but are not limited to, piperidine, pyrrolidine, morpholine, thiomorpholine, piperazine, tetrahydrofuran, tetrahydropyran, 2-pyrrolidinone, δ -velerolactam, δ -velerolactone and 2-ketopiperazine.

The term "substituted heterocycle" refers to a heterocycle as just described that contains one or more functional groups such as lower alkyl, acyl, aryl, cyano, halogen, hydroxy, alkoxy, alkoxyalkyl, amino, alkyl and dialkyl amino, acylamino, acyloxy, aryloxy, aryloxyalkyl, carboxyalkyl, carboxamido, thio, thioethers, both saturated and unsaturated cyclic hydrocarbons, heterocycles and the like.

The term "compound" is used herein to refer to any specific chemical compound disclosed herein. Within its use in context, the term generally refers to a single compound, but in certain instances may also refer to stereoisomers and/or optical isomers (including racemic mixtures) of disclosed compounds.

The term "effective amount" refers to the amount of a selected compound of formula I that is used to enhance glutamatergic synaptic response by increasing AMPA receptor activity. The precise amount used will vary depending upon the particular compound selected and its intended use, the age and weight of the subject, route of administration, and so forth, but may be easily determined by routine experimentation. In the case of the treatment of a condition or disease state, an effective amount is that amount which is used to effectively treat the particular condition or disease state.

The term "pharmaceutically acceptable carrier" refers to a carrier or excipient which is not unacceptably toxic to the subject to which it is administered. Pharmaceutically acceptable excipients are described at length by E.W. Martin, in "Remington's Pharmaceutical Sciences."

A "pharmaceutically acceptable salt" of an amine compound, such as those contemplated in

the current invention, is an ammonium salt having as counterion an inorganic anion such as chloride, bromide, iodide, sulfate, sulfite, nitrate, nitrite, phosphate, and the like, or an organic anion such as acetate, malonate, pyruvate, propionate, fumarate, cinnamate, tosylate, and the like.

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The term "patient" or "subject" is used throughout the specification to describe an animal, generally a mammalian animal, including a human, to whom treatment or use with the compounds or compositions according to the present invention is provided. For treatment or use with/or of those conditions or disease states which are specific for a specific animal (especially, for example, a human subject or patient), the term patient or subject refers to that particular animal.

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The term "sensory motor problems" is used to describe a problem which arises in a patient or subject from the inability to integrate external information derived from the five known senses in such a way as to direct appropriate physical responses involving movement and action.

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The term "cognitive task" or "cognitive function" is used to describe an endeavor or process by a patient or subject that involves thought or knowing. The diverse functions of the association cortices of the parietal, temporal and frontal lobes, which account for approximately 75% of all human brain tissue, are responsible for much of the information processing that goes on between sensory input and motor output. The diverse functions of the association cortices are often referred to as cognition, which literally means the process by which we come to know the world. Selectively attending to a particular stimulus, recognizing and identifying these relevant stimulus features and planning and experiencing the response are some of the processes or abilities mediated by the human brain which are related to cognition.

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The term "brain network" is used to describe different anatomical regions of the brain that communicate with one another via the synaptic activity of neuronal cells.

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The term "AMPA receptor" refers to an aggregate of proteins found in some membranes,

which allows positive ions to cross the membrane in response to the binding of glutamate or AMPA (DL- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), but not NMDA.

The term "excitatory synapse" is used to describe a cell-cell junction at which release of a chemical messenger by one cell causes depolarization of the external membrane of the other cell. An excitatory synapse describes a postsynaptic neuron which has a reversal potential that is more positive than the threshold potential and consequently, in such a synapse, a neurotransmitter increases the probability that an excitatory post synaptic potential will result (a neuron will fire producing an action potential). Reversal potentials and threshold potentials determine postsynaptic excitation and inhibition. If the reversal potential for a post synaptic potential ("PSP") is more positive than the action potential threshold, the effect of a transmitter is excitatory and produces an excitatory post synaptic potential ("EPSP") and the firing of an action potential by the neuron. If the reversal potential for a post synaptic potential is more negative than the action potential threshold, the transmitter is inhibitory and may generate inhibitory post synaptic potentials (IPSP), thus reducing the likelihood that a synapse will fire an action potential. The general rule for postsynaptic action is: if the reversal potential is more positive than threshold, excitation results; inhibition occurs if the reversal potential is more negative than threshold. See, for example, Chapter 7, NEUROSCIENCE, edited by Dale Purves, Sinauer Associates, Inc., Sunderland, MA 1997.

The term "motor task" is used to describe an endeavor taken by a patient or subject that involves movement or action.

The term "perceptual task" is used to describe an act by a patient or subject of devoting attention to sensory inputs.

The term "synaptic response" is used to describe biophysical reactions in one cell as a consequence of the release of chemical messengers by another cell with which it is in close contact.

The term "hypoglutamatergic condition" is used to describe a state or condition in which transmission mediated by glutamate (or related excitatory amino acids) is reduced to below normal levels. Transmission consists of the release of glutamate, binding to post synaptic

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receptors, and the opening of channels integral to those receptors. The end point of the hypoglutamatergic condition is reduced excitatory post synaptic current. It can arise from any of the three above noted phases of transmission. Conditions or disease states which are considered hypoglutamatergic conditions and which can be treated using the compounds, compositions and methods according to the present invention include, for example, loss of memory, dementia, depression, attention disorders, sexual dysfunction, movement disorders, including Parkinson's disease, schizophrenia or schizophreniform behavior, memory and learning disorders, including those disorders which result from aging, trauma, stroke and neurodegenerative disorders, such as those associated with drug-induced states, neurotoxic agents, Alzheimer's disease, and aging. These conditions are readily recognized and diagnosed by those of ordinary skill in the art.

The term "cortico-striatal imbalance" is used to describe a state in which the balance of neuronal activities in the interconnected cortex and underlying striatal complex deviates from that normally found. 'Activity' can be assessed by electrical recording or molecular biological techniques. Imbalance can be established by applying these measures to the two structures or by functional (behavioral or physiological) criteria.

The term "affective disorder" or "mood disorder" describes the condition when sadness or elation is overly intense and continues beyond the expected impact of a stressful life event, or arises endogenously. As used herein, the term "effective disorder" embraces all types of mood disorders as described in, for example, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM IV), pages 317-391.

The term "schizophrenia" is used to describe a condition which is a common type of psychosis, characterized by a disorder in the thinking processes, such as delusions and hallucinations, and extensive withdrawal of the individual's interest from other people and the outside world, and the investment of it in his or her own. Schizophrenia is now considered a group of mental disorders rather than a single entity, and distinction is made between reactive and process schizophrenias. As used herein, the term schizophrenia or "schizophreniform" embraces all types of schizophrenia, including ambulatory schizophrenia, catatonic schizophrenia, hebephrenic schizophrenia, latent schizophrenia, process

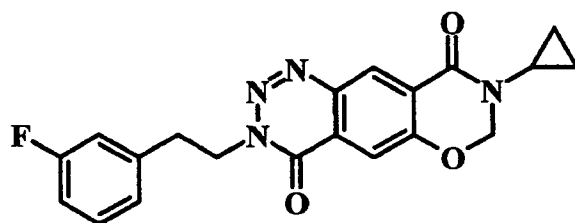
schizophrenia, pseudoneurotic schizophrenia, reactive schizophrenia, simple schizophrenia, and related psychotic disorders which are similar to schizophrenia, but which are not necessarily diagnosed as schizophrenia *per se*. Schizophrenia and other psychotic disorders may be diagnosed using guidelines established in, for example, *Diagnostic and Statistical*
5 *Manual of Mental Disorders*, Fourth Edition (DSM IV) Sections 293.81, 293.82, 295.10, 295.20, 295.30, 295.40, 295.60, 295.70, 295.90, 297.1, 297.3, 298.8.

The term "brain function" is used to describe the combined tasks of perceiving, integrating, filtering and responding to external stimuli and internal motivational processes.

10 The term "impaired" is used to describe a function working at a level that is less than normal. Impaired functions can be significantly impacted such that a function is barely being carried out, is virtually non-existent or is working in a fashion that is significantly less than normal. Impaired functions may also be sub-optimal. The impairment of function will vary in severity
15 from patient to patient and the condition to be treated.

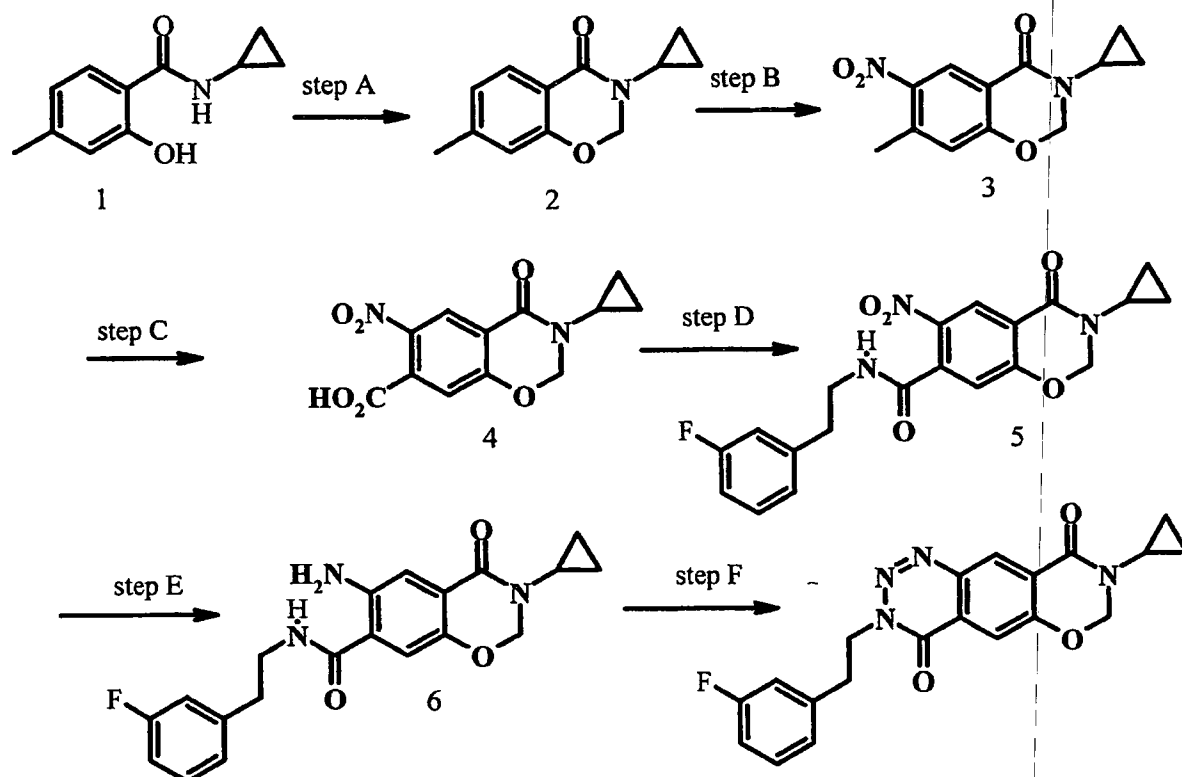
II. Compounds that Increase AMPA Receptor Function

The present invention is directed, in one aspect, to a compound having the property of
20 enhancing AMPA receptor function. The specified compound of this invention having the structure I, below:



I

The synthesis of the invention compound, 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione, is preferably carried out by
25 the following synthetic scheme, wherein the synthesis of the substituted salicylamide is well-known in the field of organic synthesis:



SCHEME 1

In Scheme 1, step A may be carried out under standard conditions, among them acid catalyzed insertion of a formaldehyde synthon. For example, the salicylamide (1) is dissolved and heated in a suitable organic solvent together with trioxane and sulfuric or hydrochloric acid. Step B is a nitration reaction that can be carried out under mild conditions known to those skilled in organic synthesis and detailed in such volumes at Reagents for Organic Synthesis (Fieser and Fieser) and Organic Syntheses (see web site at <http://www.orgsyn.org/>). Step C involves the 2-step oxidation of the methyl group of compound 3 to a carboxylic acid

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via an intermediate aldehyde employing *N,N*-dimethylformamide dimethyl acetal and sodium periodate followed by oxone. Step D involves coupling of a primary amine to the nitro acid, which can be accomplished using a variety of coupling reagents known to a skilled chemist. Some non-limiting examples commonly used are thionyl chloride, oxalyl chloride or carbonyl diimidazole. Step E is a reduction of an aryl nitro to an aniline and can be effected by
5 reduction using a variety of catalysts including, but not limited to, Pd or Pt or Raney Ni and hydrogen or Zn/Cu. Step F forms the triazinone ring and can be carried out by the addition of isoamyl nitrite in DMF.

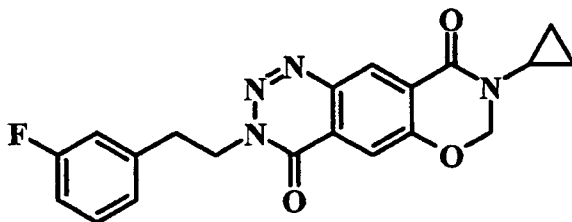
10 All compositions disclosed in the present application may be synthesized by the above-described methods using analogous synthetic steps to those specifically presented in the examples described herein as well as those known in the art. Also claimed are all addition salts with a pharmaceutically acceptable acid or base thereof.

15 III. Method of Treatment

According to one aspect of the invention, a method is provided for treating a mammalian subject suffering from a hypoglutamatergic condition, or from deficiencies in the number or
20 strength of excitatory synapses or in the number of AMPA receptors. In such a subject, memory or other cognitive functions may be impaired or cortical/striatal imbalance may occur, leading to loss of memory, dementia, depression, attention disorders, sexual dysfunction, movement disorders, schizophrenia or schizophreniform behavior. Memory disorders and learning disorders, which are treatable according to the present, invention
25 include those disorders that result from aging, trauma, stroke and neurodegenerative disorders. Examples of neurodegenerative disorders include, but are not limited to, those associated with drug-induced states, neurotoxic agents, Alzheimer's disease, and aging. These conditions are readily recognized and diagnosed by those of ordinary skill in the art and treated by administering to the patient an effective amount of one or more compounds
30 according to the present invention.

In the present invention, the method of treatment comprises administering to the subject in

need of treatment, in a pharmaceutically acceptable carrier, an effective amount 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 having the formula:



or a pharmaceutically acceptable addition salt of an acid or base thereof.

As noted above, treatment of a subject according to the method of the invention is useful for enhancing AMPA receptor activity, and thus may be used to facilitate the learning of behaviors dependent upon AMPA receptors, and to treat conditions, such as memory impairment, in which AMPA receptors, or synapses utilizing these receptors, are reduced in numbers or efficiency. The method is also useful for enhancing excitatory synaptic activity in order to restore an imbalance between brain sub-regions, which may manifest itself in schizophrenia or schizophreniform behavior, or other behavior as described above. The compounds administered in accordance with the method have been found to be more effective than previously described compounds in enhancing AMPA receptor activity, as shown in the *in vitro* and *in vivo* tests described below.

IV. Biological Activity: Enhancement of AMPA Receptor Function

Synaptic responses mediated by AMPA receptors are increased according to the method of the invention, using the compound described herein. The compound is demonstrated to be substantially more potent than previously-described compounds in increasing AMPA mediated whole cell currents in cultured neurons. The *in vitro* assay is described as follows.

Cortical cells were prepared from day 18-19 embryonic Sprague-Dawley rats and recorded after 3 days in culture. The extracellular solution (ECS) contained (in mM): NaCl (145), KCl (5.4), HEPES (10), MgCl₂ (0.8), CaCl₂ (1.8), glucose (10), sucrose (30); pH. 7.4. In order to block the voltage-gated sodium currents, 40 nM TTX was added to the recording solution. The intracellular solution contained (in mM): K-gluconate (140), HEPES (20), EGTA (1.1),

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phosphocreatine (5), MgATP (3), GTP (0.3), MgCl₂ (5), and CaCl₂ (0.1); pH: 7.2. All test compound and glutamate solutions were made-up in the extracellular solution.

5 The whole-cell current was measured with patch-clamp amplifier (Axopatch 200B), filtered at 2 kHz, digitized at 5 kHz and recorded on a PC with pClamp 8. The cells were voltage-clamped at - 80 mV. Solutions were applied by DAD-12 system. A baseline response for each cell was recorded using a 1 s pulse of 500 μ M glutamate dissolved in ECS. Responses to test compound were then determined by application of a 10 s pulse of test compound followed by a 1 s pulse of the same concentration of test compound plus 500 μ M glutamate and then 10 s of saline. This pulse sequence was repeated until a stable reading was obtained, or until sufficient data points were measured to allow extrapolation to a calculated maximum change.

15 The mean value of plateau current between 600 ms to 900 ms after application of glutamate or test compound plus glutamate was calculated and used as the parameter to measure the drug effect. The plateau responses in the presence of varying concentrations of test compound were divided by the baseline response in order to calculate the percentage increase. Compounds are deemed active in this test if, at a test concentration of 3 μ M or less, they produce a greater than 100% increase in the value of the steady-state current measured due to application of glutamate alone. The concentration at which the glutamate induced current is increased by 100% is commonly referred to as the EC_{2x} value.

25 The compound of this invention, 8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione displayed an EC_{2x} value of 0.1 μ M.

V. Administration, Dosages, and Formulation

30 As noted above, the compound and method of the invention increase AMPA receptor-mediated responses, and are useful for the treatment of hypoglutamatergic conditions. The compound is also useful for treatment of conditions such as impairment of memory or other cognitive functions, brought on by a deficiency in the number or strength of excitatory synapses, or in the number of AMPA receptors. The compound may also be used

in the treatment of schizophrenia or schizophreniform behavior resulting from a cortical/striatal imbalance, and in facilitation of learning of behaviors dependent upon AMPA receptors.

- 5 In subjects treated with the present compound, pharmaceutical compositions and methods memory or other cognitive functions may be impaired, or cortical/striatal imbalance may occur, leading to loss of memory, dementia, depression, attention disorders, sexual dysfunction, movement disorders, schizophrenia or schizophreniform behavior. Memory disorders and learning disorders, which are treatable according to the present invention,
- 10 include those disorders that result from aging, trauma, stroke and neurodegenerative disorders. Examples of neurodegenerative disorders include, but are not limited to, those associated with drug-induced states, neurotoxic agents, Alzheimer's disease, and aging. These conditions are readily recognized and diagnosed by those of ordinary skill in the art and treated by administering to the patient an effective amount of one or more compounds
- 15 according to the present invention.

- Generally, dosages and routes of administration of the compound will be determined according to the size and condition of the subject, according to standard pharmaceutical practices. Dose levels employed can vary widely, and can readily be determined by those of
- 20 skill in the art. Typically, amounts in the milligram up to gram quantities are employed. The composition may be administered to a subject by various routes, e.g. orally, transdermally, perineurally or parenterally, that is, by intravenous, subcutaneous, intraperitoneal, or intramuscular injection, among others, including buccal, rectal and transdermal administration. Subjects contemplated for treatment according to the method of the invention
- 25 include humans, companion animals, laboratory animals, and the like.

- Formulations containing the compound according to the present invention may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, capsules, powders, sustained-release formulations, solutions, suspensions, emulsions,
- 30 suppositories, creams, ointments, lotions, aerosols, patches or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

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Pharmaceutical compositions according to the present invention typically include a conventional pharmaceutical carrier or excipient and may additionally include other medicinal agents, carriers, adjuvants, additives and the like. Preferably, the composition will be about 0.5 to 75% by weight of a compound or compounds of the invention, with the remainder consisting essentially of suitable pharmaceutical excipients. For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. If desired, the composition may also contain minor amounts of non-toxic auxiliary substances such as wetting agents, emulsifying agents, or buffers.

Liquid compositions can be prepared by dissolving or dispersing the compounds (about 0.5% to about 20% by weight or more), and optional pharmaceutical adjuvants, in a carrier, such as, for example, aqueous saline, aqueous dextrose, glycerol, or ethanol, to form a solution or suspension. For use in oral liquid preparation, the composition may be prepared as a solution, suspension, emulsion, or syrup, being supplied either in liquid form or a dried form suitable for hydration in water or normal saline.

When the composition is employed in the form of solid preparations for oral administration, the preparations may be tablets, granules, powders, capsules or the like. In a tablet formulation, the composition is typically formulated with additives, e.g. an excipient such as a saccharide or cellulose preparation, a binder such as starch paste or methyl cellulose, a filler, a disintegrator, and other additives typically used in the manufacture of medical preparations.

An injectable composition for parenteral administration will typically contain the compound in a suitable i.v. solution, such as sterile physiological salt solution. The composition may also be formulated as a suspension in a lipid or phospholipid, in a liposomal suspension, or in an aqueous emulsion.

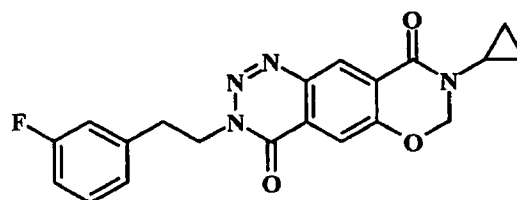
Methods for preparing such dosage forms are known or will be apparent to those skilled in the art; for example, see Remington's Pharmaceutical Sciences (17th Ed., Mack Pub. Co.,

1985). The composition to be administered will contain a quantity of the selected compound in a pharmaceutically effective amount for effecting increased AMPA receptor currents in a subject.

- 5 The following examples illustrate but are not intended in any way to limit the invention. Unless otherwise stated, all temperatures are given in degrees Celsius. Unless otherwise stated, all NMR spectra are ¹H NMR spectra and were obtained in deuteriochloroform or deuterated DMSO as solvent using tetramethylsilane as an internal standard. The name of the example compound conforms to IUPAC nomenclature as provided by the computer software
- 10 ChemSketch by ACD Labs.

Example 1

8-Cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione



- 15 4-Methylsalicylic acid (21.3 g, 140 mmol) was dissolved in methylene chloride (120 mL) followed by CDI (22.7 g, 140 mmol) in portions. The mixture was stirred at room temperature for 24 hr, and then briefly heated to boiling. A solution of cyclopropylamine (8.0 g, 140 mmol) in triethylamine (5 mL, 36 mmol) was added to the mixture, which was stirred for 3 days. Water (200 mL) was added and the pH was adjusted to 2 using 12 M hydrochloric acid. The phases were separated and the aqueous phase was extracted with chloroform (200 mL). The combined organic phases were washed with sodium bicarbonate solution (100 mL) and dried over sodium sulfate. Concentration gave 22.7 g of amide as an off white solid.
- 20
- 25 The amide (22.7 g, 119 mmol) and trioxane (36 g, 0.4 mol) were dissolved in chloroform (250 mL), which was stirred at room temperature. Sodium sulfate (32 g) and concentrated sulfuric acid (80 drops) were added and the mixture was refluxed for 30 min, after which an additional 40 drops of conc. sulfuric acid were added. After 90 min, the solids were removed

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by filtration and washed with ethyl acetate. The combined solvents were removed under vacuum to give 30 g of oil. The oil was purified using flash chromatography (250 g silica gel, ethyl acetate:hexane 30:70, then 40:60) to give 20.1 g of 7-methylbenzoxazinone as a colorless oil.

- 5 The benzoxazinone (16 g, 79 mmol) was dissolved in methylene chloride (200 mL) to which acetic acid (30 mL) was added. The mixture was cooled to $\sim 0^{\circ}\text{C}$ using an ice bath and nitric acid (14 mL, 90%) was added drop wise over 15 min, which produced an orange solution. The reaction mixture was stirred for 90 min and then poured over crushed ice/water (300 mL). A sodium hydroxide solution was slowly added until the pH reached 5. The reaction
- 10 mixture was extracted with chloroform (200 mL), dried over sodium sulfate and concentrated under vacuum to ~ 40 mL. Ethyl acetate (200 mL) was added and the mixture was concentrated under vacuum to ~ 60 mL. The formed crystals were filtered off to give 8.1 g (33 mmol, yield=41%) the desired 6-nitro isomer as an off white solid. The mother liquor was concentrated and more product crystallized (1.2 g) as an off white solid. Subsequently,
- 15 another 5 g of mixed isomers were isolated from the mother liquor, this mix was used in the following step.

- The mixed isomer solids from the previous step (5 g, 20 mmol) were suspended in N,N-dimethylformamide dimethyl acetal (30 mL) and DMF (10 mL) and heated to 125°C for 16 hr. The solvent was removed under vacuum to yield a dark brown residue. The residue was
- 20 dissolved in THF (100 mL). Sodium periodate (11 g, 51 mmol) was dissolved in water (100 mL) and added to the reaction mixture, which was stirred for 15 min at room temperature. The beige slurry was extracted with chloroform (200 mL), which was dried over sodium sulfate and diluted with ethyl acetate (200 mL). The solvents were allowed to slowly evaporate, which resulted in the crystallization of the desired isomer (2.0g, 7.6 mmol) as an
- 25 off white solid).

- The nitro aldehyde intermediate (524 mg, 2.0 mmol) was dissolved in DMF (10 mL) at 40°C . After the solution was cooled to ambient, oxone (1.47 g, 2.4 mmol) was added and the mixture was stirred overnight. Addition of water (25 mL) and ethyl acetate (30 mL) produced two phases, which were separated and the organic phase was filtered and washed with water.
- 30 The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed twice with water, dried over magnesium sulfate and concentrated under vacuum to

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give a wet, yellow residue (0.54 g, 1.9 mmol), which was used without further purification.

A solution of the nitro acid intermediate (0.54 g, 1.9 mmol) in methylene chloride was combined with thionyl chloride (1.4 mL, 20 mmol) together with a few drops of DMF stirred at ambient temperature overnight. The mixture was concentrated under vacuum and redissolved in methylene chloride (10 mL). 3-Fluorophenethylamine (0.56 mL, 4.3 mmol) and triethylamine (1.1 mL, 7.9 mmol) were dissolved in methylene chloride (15 mL) to which the freshly prepared solution of the acid chloride was added. After being stirred for 2 hr, the solution was washed with aqueous HCl (1 M) and sat. sodium bicarbonate and dried over magnesium sulfate. The product solution was concentrated under vacuum to give a yellow solid, which was triturated in ethyl acetate to give light beige crystals (0.53 g, 1.3 mmol).

The beige solid from the previous step (0.53 g, 1.3 mmol) was dissolved in a mixture of THF (20 mL) and methanol (20 mL) and added to freshly prepared Zn/Cu reagent (10 g, see below). Formic acid (10 drops) was added and the mixture was stirred at ambient temperature overnight, after which TLC showed completion of the reaction. After addition of DMF (2 mL), the mixture was stirred for 10 min, and then filtered through silica gel (2 cm). The silica was washed with THF/methanol (1:1) and the combined filtrate and wash was concentrated under vacuum. Chloroform was added and evaporated to remove any residual water. DMF (2 mL) and an excess of isoamylnitrite (5 mL) were added and the mixture was stirred for 2.5 hr after which TLC showed the reaction was complete. Addition of diethyl ether (5 mL) caused precipitation of the product, which was washed with ethyl acetate and air dried to give 0.29 g of a yellow solid with the following properties: MP 181 – 182 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.78 (1H, s), 7.82 (1H, s), 7.3-6.8 (4H, m), 5.33 (2H, s), 4.67 (2H, m) 3.21 (2H, m) 2.76 (1H, m) 1.02 (2H, m) and 0.86 ppm (2H, m).

The Zn/Cu reagent (used above) was freshly prepared in the following manner: Conc. HCl (3 mL) was added to 10 g zinc in 100 mL water during vigorous stirring. The stirring continued for 2 min (clumps start to form), after which the water was decanted off. An additional 100 mL of water was added with vigorous stirring. Any remaining clumps were crushed with a spatula. Conc. HCl (3 mL) was added and the stirring was continued for 2 min. After removing the water by decantation, the solid was washed with an additional 100 mL of water. Water (50 mL) was added to the solid and the stirring was continued while a solution of

CuSO₄ (300 mg in 50 mL water) was added slowly. After the zinc turned black, the water was removed by decantation. The residue was sequentially washed with methanol (50 mL) and THF (50 mL).

5

EXAMPLE 2

In Vivo Physiological Testing

10 The physiological effects of the invention compound were tested *in vivo* in anesthetized animals according to the following procedures.

Animals are maintained under anesthesia by phenobarbital administered using a Hamilton syringe pump. Stimulating and recording electrodes are inserted into the perforant path and dentate gyrus of the hippocampus, respectively. Once electrodes are implanted, a stable baseline of evoked responses are elicited using single monophasic pulses (100 μ s pulse duration) delivered at 3/min to the stimulating electrode. Field EPSPs are monitored until a stable baseline is achieved (about 20-30 min), after which a solution of test compound in HPCD is injected intraperitoneally and evoked field potentials are recorded. Evoked potentials are recorded for approximately 2 h following drug administration or until the amplitude of the field EPSP returns to baseline. In the latter instance, it is common that an iv administration is also carried out with an appropriate dose of the same test compound.

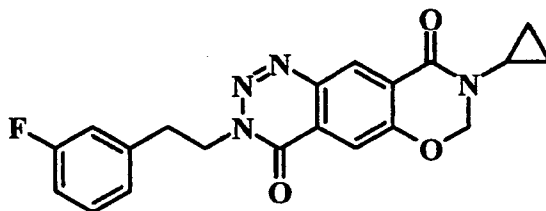
8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione produced an increase in the amplitude of the field EPSP of 10% at a dose of 5 mg/kg following iv administration.

While the invention has been described with reference to specific methods and embodiments, it will be appreciated that various modifications may be made without departing from the invention.

30

WHAT IS CLAIMED:

1. A compound of the formula:



or a pharmaceutically acceptable addition salt of an acid or base thereof.

2. A compound of the formula in claim 1 that is:

8-Cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazine-4,9-dione, or a pharmaceutically acceptable addition salt of an acid or base thereof.

3. A method for the treatment of a mammalian subject, wherein the subject suffers from a hypoglutamatergic condition or a deficiency in the number or strength of excitatory synapses or in the number of AMPA receptors, such that memory or other cognitive functions are impaired, said method comprising administering to said subject, in a pharmaceutically acceptable carrier, an effective amount of a compound according to any of claim 1 or 2.

4. A method for the treatment of a mammal wherein the subject suffers from a hypoglutamatergic condition or deficiencies in the number or strength of excitatory synapses or in the number of AMPA receptors such that a cortical/striatal imbalance occurs leading to schizophrenia or schizophreniform behavior, said method comprising administering to said subject, in a pharmaceutically acceptable carrier, an effective amount of a compound according to any of claims 1 or 2.

5. The method according to claim 4 wherein said condition is schizophrenia.

6. The method according to claim 3 wherein said condition is Parkinson's disease.
7. The method according to claim 3 wherein said condition is Alzheimer's disease.
- 5 8. A pharmaceutical composition comprising an effective amount of a compound according any of claims 1-2 in combination with a pharmaceutically acceptable carrier, additive or excipient.
- 10 9. The composition according to claim 8 wherein said compound comprises about 0.5% to about 75% by weight of said composition and said carrier, additive or excipient comprises about 25% to about 95.5% of said composition.
- 15 10. Use of a compound according to any of claims 1-2 in the manufacture of a medicament for use in the treatment of a mammalian subject, wherein the subject suffers from a hypoglutamatergic condition or a deficiency in the number or strength of excitatory synapses or in the number of AMPA receptors, such that memory or other cognitive functions are impaired.
- 20 11. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for use in the treatment of schizophrenia.
12. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for use in the treatment of Parkinson's disease.
- 25 13. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for use in the treatment of ADHD.
14. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for use in the treatment of Rett Syndrome.
- 30 15. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for use in the treatment of Fragile-X Syndrome.

16. Use of a compound according to any of claims 1 and 2 in the manufacture of a medicament for the treatment of Alzheimer's disease.

ANEXO No. 7

**CERTIFICADO DE LA FECHA DE
PRESENTACIÓN DE LA SOLICITUD DE
PRIORIDAD EXPEDIDA POR LA AUTORIDAD
CORRESPONDIENTE
(en inglés)**

**3 – SUSTITUTOS – [1-2-3] – COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC.**

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

COLEMAN, Henry, D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 07 August 2008 (07.08.2008)		
Applicant's or agent's file reference C21-079PCT		IMPORTANT NOTICE
International application No. PCT/US2007/026416	International filing date (day/month/year) 28 December 2007 (28.12.2007)	
		Priority date (day/month/year) 03 January 2007 (03.01.2007)
Applicant CORTEX PHARMACEUTICALS, INC. et al		

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
17 July 2008 (17.07.2008)

None

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

LU, TZ, UG

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of **19 months** from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **20 MONTHS** from the priority date.

In practice, **time limits other than the 20-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For **regular updates on the applicable time limits** (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's **sole responsibility** to monitor all these time limits.

RECEIVED**AUG 14 2008**

COLEMAN SUDOL SAPONE, P.C

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Beate Giffo-Schmitt
Facsimile No. +41 22 338 82 70	e-mail: pt03.pct@wipo.int

RECEIVED

PATENT COOPERATION TREATY

PCT/US2007/026416

AUG 18 2008

COLEMAN SUDOL SAPONE, P.C

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

COLEMAN, Henry, D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 07 August 2008 (07.08.2008)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference C21-079PCT	
International application No. PCT/US2007/026416	International filing date (day/month/year) 28 December 2007 (28.12.2007)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address MUELLER, Rudolf 19431 Rue de Valore, No. 25A Foothill Ranch, CA 92610 United States of America	State of Nationality DE	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Mazoillier Auguste e-mail pt03.pct@wipo.int Telephone No. +41 22 338 74 03
---	--

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

COLEMAN, Henry, D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 07 May 2009 (07.05.2009)		
Applicant's or agent's file reference C21-079PCT		IMPORTANT NOTICE
International application No. PCT/US2007/026416	International filing date (day/month/year) 28 December 2007 (28.12.2007)	
Applicant CORTEX PHARMACEUTICALS, INC. et al		Priority date (day/month/year) 03 January 2007 (03.01.2007)

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does not apply**, please see Form PCT/IB/308(First Notice) issued previously.

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
17 July 2008 (17.07.2008)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MY, MZ, NA, NG, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AO, AP, AT, BA, BB, BG, BH, BR, BW, BZ, CA, CH, CR, CU, CZ, DE, DK, DM, DO, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, ID, IL, IN, IS, JP, KE, KM, KN, KZ, LA, LC, LK, LR, LS, LT, LY, MA, ME, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, RS, SC, SD, SE, SG, SK, SL, SM, SV, TJ, TN, TR, TT, UA, UZ, VC, VN, ZA, ZM, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **30 MONTHS** from the priority date.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For **regular updates on the applicable time limits** (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's **sole responsibility** to monitor all these time limits.

RECEIVED**MAY 20 2009**

COLEMAN SUDOL SAPONE, P.C.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Beate Giffo-Schmitt
Facsimile No. +41 22 338 82 70	e-mail: pt03.pct@wipo.int

ANEXO No. 8

INFORMACIÓN DE LOS INVENTORES.

**3 – SUSTITUTOS – [1-2-3] – COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC.**

Los inventores son los siguientes, tal y como obra en el contrato de cesión:

Inventor / cedente	Domicilio
Alexis CORDI	8 bis rue Ledru-Rollin 92150 Suresnes (FR)
Gary ROGERS	28821 Shady Lane, Laguna Beach, CA 92651 (USA)
Rudolf MUELLER	19431 rue de Valore, No. 56B, Foothill Ranch, CA 92610 (USA)

ANEXO No. 9

**PODER Y CERTIFICADO NOTARIAL DE LA
SOCIEDAD LES LABORATOIRES SERVIER
(CONTENIDO EN LA ESCRITURA PÚBLICA)**

**3 – SUSTITUTOS – [1-2-3] – COMPONENTES DE LA BENZOTRIAZINONE
PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

**LES LABORATOIRES SERVIER
CORTEX PHARMACEUTICALS, INC.**

REPÚBLICA DE COLOMBIA

36

NOTARIA

DEL CIRCULO DE BOGOTÁ

Teléfonos: PBX: (57-1) 257 6232 - FAX: (57-1) 257 6230

Calle 85 No. 10 - 74

E-mail: notaria36@gmail.com

COPIA NUMERO 43

DE LA ESCRITURA NUMERO: 1585
FECHA: 03 DE MAYO DEL AÑO 2007

ACTO O CONTRATO:
PROTOCOLIZACION Y SUSTITUCION DE PODER
OTORGANTES:
VERNOT HERNANDEZ CLAUDETTE MONIQUE y otros
GOMEZ OBREGON JOSE ALEJANDRO y otros



Certificado No. SC4403-1



Ma. del Pilar Moreno de Alvarado
NOTARIA

Nº

1585

AA

29817665



03 MAYO 2007

ESCRITURA PUBLICA NUMERO: **1585**

MIL QUINIENTOS OCHENTA Y CINCO ----

FECHA: TRES (03) DE MAYO -----

DE DOS MIL SIETE (2.007). -----

I. Acto. -----

PROTOCOLIZACIÓN DE PODER Y

SUSTITUCIÓN. -----

II.- Otorgante: -----

CLAUDETTE MONIQUE VERNOT HERNÁNDEZ, CON CÉDULA DE CIUDADANÍA NÚMERO 51.722.517 DE BOGOTÁ, D.C. Y T.P. NÚMERO 57.111 DEL C.S.J. -----

A: JUAN MANUEL SERRANO CASTILLO, CON CÉDULA DE CIUDADANÍA NÚMERO 19.205.192 DE BOGOTÁ, Y T.P. NÚMERO 124.953 DEL C.S.J. -----

Y ANDRÉS FELIPE ZAPATA OCAMPO, CON CÉDULA DE CIUDADANÍA NÚMERO 79.598.546 DE BOGOTÁ, Y T.P. NÚMERO 107.240 DEL C.S.J. -----

En la Ciudad de Bogotá, Distrito Capital, Departamento de Cundinamarca, República de Colombia, a los tres (03) días del mes Mayo de dos mil siete (2.007), ante el Despacho de la Notaría Treinta y seis (36) del Círculo de Bogotá D.C, cuyo(a) Titular es **MARÍA DEL PILAR MORENO DE ALVARADO** se otorgó Escritura Pública que se consigna en los siguientes términos:-----

I.- PROTOCOLIZACIÓN PODER. -----

Compareció: **CLAUDETTE MONIQUE VERNOT HERNÁNDEZ**, mayor de edad, vecina de esta ciudad de Bogotá, D.C., identificada con la cédula de ciudadanía número 51.722.517 expedida en Bogotá, y T.P. Número 57.111 DEL C.S.J., de estado civil casada con sociedad conyugal vigente, quien obra en nombre propio en calidad de PROTOCOLIZANTE y manifestó:

PRIMERO: Que presenta para su guarda y protocolización en esta Notaría

fuero 20/08
20/21/22/23
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28.29.30.31
en mayo

13.14.15.16.17.18.19.20.21.22.23.24.25.26.27.28.29.30.31
en mayo

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10.11.12.13.14.15.16.17.18.19.20.21.22.23.24.25.26.27.28.29.30.31
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los siguientes documentos: -----

- 1.- Poder General otorgado por la sociedad LES LABORATORIES SERVIER, a CLAUDETTE VERNOT y GUSTAVO PALACIO el cual obra en 1 folio, debidamente diligenciado y apostillado en fotocopia auténtica. -----
2. Inscripción en el Registro de Comercio y de Sociedad – Extracto del 14 de Febrero de 2.007, debidamente traducido y apostillado en fotocopias auténticas, el cual obra en ocho (8) folios útiles. -----

SEGUNDO: En consecuencia, la suscrita Notaria declara protocolizado dicho documento para que surta los efectos legales y puedan los interesados solicitar las copias que de ellos se necesite. -----

II.- SUSTITUCIÓN DE PODER.

Compareció (nuevamente): **CLAUDETTE MONIQUE VERNOT HERNÁNDEZ**, mayor de edad, vecina de esta ciudad de Bogotá, D.C., identificada con la cédula de ciudadanía número 51.722.517 expedida en Bogotá, y T.P. Número 57.111 DEL C.S.J., de estado civil casada con sociedad conyugal vigente, quien obra en nombre propio, obrando en mi calidad de Representante Legal de LES LABORATORIES SERVIER, sociedad organizada y existente de conformidad con las leyes de Francia y con domicilio en París –, por el presente sustituyo el poder a mi conferido a favor de: **JUAN MANUEL SERRANO CASTILLO**, mayor de edad, vecino de esta ciudad, identificado con la cédula de ciudadanía número 79.875.670 expedida en Bogotá, D.C., y **ANDRÉS FELIPE ZAPATA OCAMPO**, mayor de edad, vecino de esta ciudad, identificado con la cédula de ciudadanía número 79.598.546 expedida en Bogotá, D.C., para que en su nombre y representación ejecute y celebre, los actos y contratos, relacionados en el poder general otorgado a ella por **LES LABORATOIRES SERVIER**. ----

EL COMPARECIENTE HACE CONSTAR QUE: -----

- 1.- Ha verificado cuidadosamente sus nombres y apellidos, estado civil, el número de su documento de identificación y aprueba este instrumento sin reserva alguna, en la forma como quedó redactado. -----

PODER GENERAL

Yo, abajo firmado,
Actuando como _____
de _____
domiciliada en _____

GENERAL POWER OF ATTORNEY

I, the undersigned, LES LABORATOIRES SERVIER
Acting as _____
of _____
domiciled in 12, Place de la Défense 92415 COURBEVOIE Cedex
FRANCE

por el presente conferimos poder a CLAUDETTE VERNOT, tpa. 57.111; GUSTAVO PALACIO, tpa. 82082; domiciliados en la Carrera 11 No. 84-42 Interior (9), Bogotá, Colombia, para: (1) Administren los bienes de la poderdante, recauden sus productos y celebre toda clase de contratos relativos a la administración de ellos; (2) exijan, cobren o perciban cualesquiera cantidad de dinero o de otras especies, que se adeuden a la poderdante, expidan los recibos y haga las cancelaciones correspondientes; (3) paguen a los acreedores de la poderdante y hagan con ellos los arreglos sobre los términos de pago de sus respectivas acreencias; (4) exijan y admitan cauciones, reales o personales, para asegurar los créditos reconocidos, o que se reconozcan a favor de la poderdante; (5) por cuenta de los créditos reconocidos o que se reconozcan a la poderdante, admitan a los deudores en pago bienes distintos de los que estén obligados a dar, y para que rematen tales bienes en juicio; (6) exijan cuentas a quienes tienen obligación de rendirlas a la poderdante, aprobarlas o improbarlas, pagar o percibir, según el caso, el saldo respectivo, y otorgar el finiquito correspondiente; (7) enajenen a título oneroso los bienes muebles o inmuebles de la poderdante y que estos tengan ya adquiridos o adquieran en lo futuro; (8) aseguren las obligaciones contraídas por la poderdante o que se contraigan en su nombre con prenda de sus bienes muebles; (9) transijan los pleitos, dudas o diferencias que ocurran, relativos a los derechos y a las obligaciones de la poderdante; (10) tomen para la poderdante dinero en mutuo y estipulen la tasa de interés, ya a plazo fijo, ya como crédito flotante; (11) representen a la poderdante en las sociedades anónimas o de otra clase de que la poderdante sea accionista; para que constituyan sociedades de cualquier clase o las transformen; para que lleve la voz y emita el voto en las respectivas asambleas o juntas de accionistas; y para que paguen los instalamentos y reciban los dividendos o utilidades que correspondan a la poderdante; (12) representen a la poderdante ante cualquier corporaciones, funcionarios o empleados del orden judicial o del administrativo en cualesquiera juicios y actuaciones, actos, diligencias o gestiones en que la poderdante tenga que intervenir directa o indirectamente, sea como demandante, o como demandada, o como coadyuvante de cualesquiera de las partes; sea para iniciar o seguir tales juicios, actuaciones, actos diligencias o gestiones, (13) en general asuman la personería de la poderdante siempre que lo estimen conveniente de manera que en ningún tiempo quede sin representación en asuntos que le interesan; y (14) para obtener la protección de la poderdante en sus asuntos, a cuyo efecto autorizamos a la dicha apoderada para que nos represente ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial; (15) y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir o no los hechos del proceso, desistir, cancelar, recibir y repudiar.

hereby grant to CLAUDETTE VERNOT, tpa. 57.111; GUSTAVO PALACIO, tpa. 82082; domiciled at Carrera 11 No. 84-42 Interior (9), Bogotá, Colombia, Power of Attorney to (1) administer the assets of the grantor, receive its products and enter into all kind of contracts relating to its administration; (2) request, collect or receive any monies or goods due to the grantor giving the necessary receipts and cancellations; (3) pay the creditors of the grantor and agree with them the terms of payment of their respective credit; (4) request and receive bonds, real or personal, in order to assure the credits recognized or to be recognized to the grantor; (5) to receive on account of recognized credits in favour of the grantor other different goods than those to which the obligation refer, and to make a forced sale of them in Court; (6) to request accounts from those obliged to render them to the grantor, to approve or disapprove them, pay or receive the balance according to case and to give the quitance thereof; (7) to sell for a consideration the assets of the grantor, whether movables or real estate, either those already in its possession or those to be acquired in the future; (8) to guarantee the obligations of the grantor or those taken on its name with chattel mortgage of its movables; (9) to settle the suits, doubts or differences, occurring with respect to rights and obligations of the grantor; (10) to receive money loans for the grantor stipulating the interest thereof, being them at term or as an exigible credit; (11) represent the grantor in corporations or other companies where the grantor is shareholder or partner; to form corporations or companies of any kind, or transform them; to represent and vote in the corresponding shareholders meetings; and to pay the installments and receive the dividends or profits of the grantor; (12) represent the grantor before any corporations, officials or employees of the Courts or the administration in any suits and proceedings in acts where the grantor has to intervene as plaintiff or defendant or as coadjutant of any party; be it to institute or follow up with those suits or proceedings or acts; (13) in general, to represent the grantor whenever it is considered convenient so as to assure that the grantor would not remain unrepresented in the matters of its interest; and (14) to obtain the protection of the grantor in your matters, which purpose we authorize the said attorneys to represent us before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial; and (15) that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit of the facts of the case, desist, cancel, receive and renounce.

Dado y firmado hoy / Given and signed this 6 March 2002

in Caracas

by _____

Odile OSTERMANN proxy for LES LABORATOIRES SERVIER

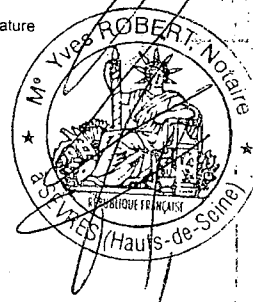
Signature

certification

matérial de

la signature de Mme OSTERMANN

apposée ci-contre



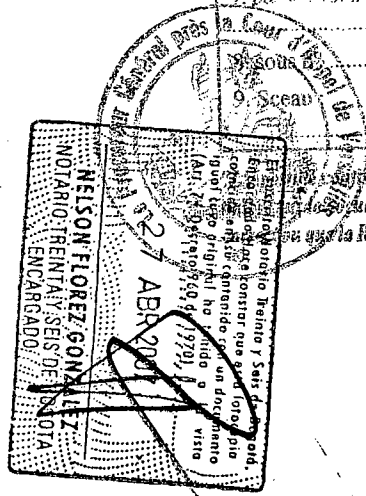


APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. République Française **COLOMBIE**
Le présent acte public
2. a été signé par **M. YVES ROBERT**
3. agissant en qualité de **NOTAIRE A**
4. est revêtu du sceau de **SEVRES**

Attesté

5. à **VERSAILLES**
6. le **2 AVR. 2007**
7. par le **Notaire Public près la Cour d'Appel de Versailles**
8. **7823/07**
9. Sceau
10. Signature *[Signature]*



"L'apostille certifie seulement l'authenticité de la signature, du sceau ou du contenu du document. Elle ne signifie pas que le contenu du document est approuvé par la République française." "



Traducción oficial de una **Apostilla en Francés**. República Francesa; Colombia; acta notarial firmada por el Abogado Yves Robert; actuando en calidad de Notario; con el sello de la oficina del Notario de Sèvres; certificado en Versalles; el 2 de abril de 2007; por el Procurador General del Tribunal de Casación de Versalles; bajo el número 7823/07; firma (ilegible).

"La Apostilla confirma únicamente la autenticidad de la firma, del sello o de la estampilla en el documento; ella no significa que el contenido del documento es correcto o que la República Francesa aprueba su contenido"

(Sello)

Procurador General del Tribunal de Casación de Versalles

Certifico que la anterior es traducción fiel y completa de la Apostilla y sello en referencia, la cual se sella con el sello del traductor Germán Fonseca Chaparro, Resolución Minjusticia No.2110 del 12 de diciembre de 2003. Bogotá, D. C., 25 de abril de 2007.

GERMAN FONSECA CHAPARRO

TRADUCTOR E INTERPRETE OFICIAL

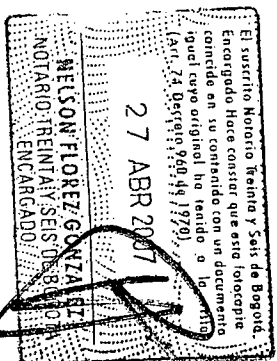
ESPAÑOL - FRANCÉS - ESPAÑOL

RESOLUCION MINJUSTICIA NO. 2110

DICIEMBRE 12 DE 2003

MINISTERIO DE
RELACIONES EXTERIORES
597589
JEFES DE
DEPARTAMENTO DE
ASUNTO DE
FONSECA

NO SE ASUME
RESPONSABILIDAD DEL TEXTO
2007 ABR 27 P 2:39
JEFE DE LEGALIZACIONES
BOGOTÁ D.C.



Extrait Kbis

IMMATRICULATION AU REGISTRE DU COMMERCE ET DES SOCIÉTÉS

Extrait au 14 Février 2007

IDENTIFICATION

Dénomination sociale : LES LABORATOIRES SERVIER
Sigle : (VOIR OBSERVATIONS)
Numéro d'identification : 085 480 796 R.C.S. NANTERRE
Numéro de gestion : 1988 B 02123
Date d'immatriculation : 01 Juin 1988

RENSEIGNEMENTS RELATIFS A LA PERSONNE

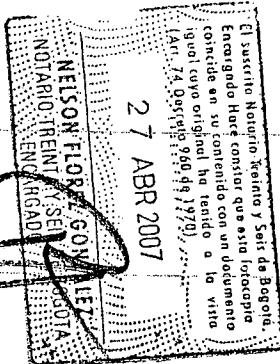
Forme juridique : Société par actions simplifiée
Au capital de : 34 590 852,00 Euros
Adresse du siège : 22 Rue-Garnier 92200 Neuilly Sur Seine
Durée de la société : Jusqu'au 30 NOVEMBRE 2047
Date d'arrêté des comptes : 30 Septembre
Constitution - Dépôt de l'acte constitutif : Au Greffe du Tribunal de Commerce de ORLEANS le 28 Janvier 1949
Publication : LES PETITES AFFICHES DE L'ORLEANAIS du 29 Janvier 1949
Transfert de : ORLEANS
Dépôt de l'acte : Au Greffe du Tribunal de Commerce de NANTERRE le 03 Novembre 1995 sous le numéro 25805
Publication au Greffe du nouveau siège : Journal Gazette-du palais du 24 Octobre 1995

ADMINISTRATION

Président : SERVIER SAS
(324 444 991 R.C.S. NANTERRE)
6 Des Pleiades 92415 Courbevoie Cedex
Forme juridique Société par actions simplifiée
représentée par
Monsieur SERVIER JACQUES
né(e) le 09/02/1922 à VATAN 36150
de nationalité Française
- DEMEURANT : 92 RUE CHARLES LAFFITTE 92200 NEUILLY
SUR SEINE

Vice président : Monsieur LE RIDANT ALAIN VICTOR LUCIEN HENRI
né(e) le 31/10/1935 à EPINAY SUR ORGE 91360
de nationalité Française
demeurant 47 Boulevard Du Cdt Charcot 92200 Neuilly

Vice président : Madame BANZET MARIE-NOELLE
né(e) le 20/12/1951 à COURBEVOIE 92400
de nationalité Française
demeurant 9 Rue Freville Le Vingt 92310 Sevres





Extrait Kbis

IMMATRICULATION AU REGISTRE DU COMMERCE ET DES SOCIÉTÉS

Extrait au 14 Février 2007

Pharmacien responsable

Monsieur LE RIDANT ALAIN
né(e) le 30/10/1935 à EPINAY SUR ORGE 91360
de nationalité Française
demeurant 47 Boulevard Du Cdt Charcot 92200 Neuilly Sur Seine

Commissaire aux comptes titulaire

Monsieur DUVERNOIS STEPHANE
né(e) le 13/07/1953 à PARIS 75
de nationalité Française
démorant 111 Rue Cardinet 75017 Paris

Commissaire aux comptes suppléant

DUVERNOIS ET ASSOCIES, SA
(412 029 357 R.C.S. PARIS)
111 Rue Cardinet 75017 Paris
Forme juridique société anonyme

RENSEIGNEMENTS RELATIFS A L'ACTIVITE COMMERCIALE

Origine de la société :

Transfert du siège et de l'établissement principal
905 ROUTE DE SARAN 45520 GIDY
à compter du 20 Octobre 1995

Origine du fonds :

Création d'un fonds de commerce

Activité :

Exploitation de laboratoires de produits chimiques ou pharmaceutiques

Nom commercial :

SERVIER-ARDEX-EUTHERAPIE-BIOPHARMA-ORIL

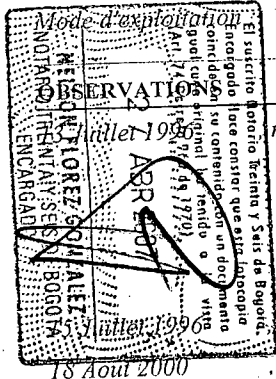
Adresse de l'établissement principal :

22 Rue Garnier 92200 Neuilly Sur Seine

Commencement d'activité le :

01 Décembre 1948

Exploitation directe



numéro 24322

Fusion avec les sociétés : Ardix 1 rue Carle Hebert 92400
Courbevoie Rcs Nanterre b 318 109 907 _ laboratoires
Biopharmaceutiques de France (Biopharma) 29 rue du pont 92200
Neuilly sur seine Rcs Nanterre b 542 073 499 et Euthérapie 27.29 rue
du pont 92200 Neuilly sur seine Rcs Nanterre b 642 020 036 à
compter du 29 mars 1996

Sigle : Servier - Ardix - Euthérapie - Biopharma -

Fusion-absorption de la société Oril sa (b 582080172 Rcs Nanterre) -
à compter du : 29-06-2000--

17 Octobre 2001 , numéro 73636

Fusion absorption de la société Adir et compagnie (329 211,650 Rcs Nanterre) à compter du 31 août 2001 -

ETABLISSEMENTS DANS LE RESSORT DU GREFFE

Adresse :

192 Avenue Charles De Gaulle 92200 Neuilly Sur Seine

Extrait Kbis

IMMATRICULATION AU REGISTRE DU COMMERCE ET DES SOCIÉTÉS

Extrait au 14 Février 2007

Nom commercial : SERVIER-ARDIX-EUTHERAPIE-BIOPHARMA-ORIL
Activité : Toutes opérations administratives se rapportant directement ou indirectement à l'exploitation de laboratoires de produits chimiques ou pharmaceutiques
Commencement d'activité le : 29 Juin 2000
Origine du fonds de commerce : Fonds de commerce acquis par apport
Précédent exploitant : ORIL
n° identification B582080172

Déclaration de créances :

Au greffe de NANTERRE

Mode d'exploitation :

Exploitation directe

Adresse :

12 Place De La Defense 92400 Courbevoie

Nom commercial :

SERVIER-ARDIX-EUTHERAPIE-BIOPHARMA-ORIL

Activité :

EXPLOITATION DE LABORATOIRES DE PRODUITS CHIMIQUES OU PHARMACEUTIQUES

Commencement d'activité le :

17 Mai 2002

Origine du fonds de commerce :

Création d'un fonds de commerce

Mode d'exploitation :

Exploitation directe

Adresse :

6 Place Des Pléiades 92415 Courbevoie Cedex

Activité :

Toutes opérations administratives se rapportant directement ou indirectement à l'exploitation de laboratoires pharmaceutiques

Commencement d'activité le :

01 Septembre 2006

Origine du fonds de commerce :

Création d'un fonds de commerce

Mode d'exploitation :

Exploitation directe

ETABLISSEMENTS HORS LE RESSORT DU GREFFE

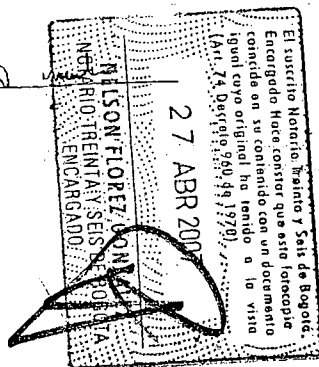
Greffe de ORLEANS (4502)

Numéro de gestion 1996 B 00646

Etablissement Secondaire

Extrait délivré à NANTERRE, le 15 février 2007 sur 3 page(s)

Le Greffier,



Fin de l'extrait



APOSTILLE

Convention de La Haye du 5 octobre 1961

COLOMBIE

NOM

GRÉFFIER

REPUBLICAIN DE

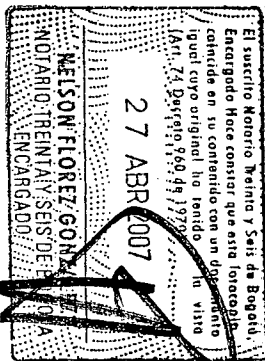
COGNANCE

Attesté

VERSAILLES

2 AVR. 2007

7820/07



confirmant seulement l'authenticité de la signature, du sceau ou
l'identité du document. Elle ne signifie pas que le contenu du document est
approuvé par la République française.



84

1585

Secretaría del Tribunal de Comercio de NANTERRE
4 Rue Pablo Neruda
92020 NANTERRE CEDEX

085 480 796 R.C.S NANTERRE
Nuestras referencias: ALT
(1988 B 02123)

(Sello)
Tribunal de Comercio-Secretaría
(Manuscrito)
43826 Colombia

Extracto Kbis

INSCRIPCIÓN EN EL REGISTRO DE COMERCIO Y DE SOCIEDADES
Extracto del 14 de Febrero de 2007

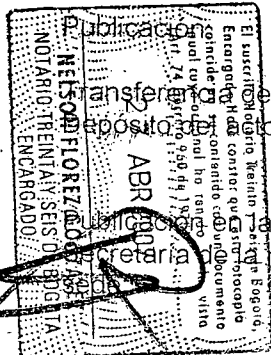
IDENTIFICACIÓN

Denominación social: **LES LABORATOIRES SERVIER**
Sigla: (VER OBSERVACIONES)
Número de identificación: 085 480 796 R.C.S. NANTERRE
Número de trámite: 1988 B 02123
Fecha de inscripción: 1 de junio de 1988

INFORMACIONES RELACIONADAS CON LA PERSONA:

Forma jurídica: sociedad simplificada por acciones
Con un capital de: 34. 590. 852,00 Euros
Dirección de la sede: 22 Rue Garnier 92200 Neuilly Sur Seine
Duración de la sociedad: Hasta el 30 DE NOVIEMBRE de 2047
Fecha de corte de cuentas: 30 de septiembre
Constitución-Depósito del acto constitutivo:

En la Secretaría del Tribunal de Comercio de ORLEÁNS el 28 de enero de 1949
LES PETITES AFFICHES DE L'ORLÉANAIS del 29 de enero de 1949
ORLÉANS
En la Secretaría del Tribunal de Comercio de NANTERRE el 3 de noviembre de 1995 bajo el número 25805



Diario Gazette du Palais del 24 de octubre de 1995

GERMAN FONSECA CHARRRO

TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - FRANCES - ESPAÑOL

RESOLUCION MINJUSTICIA No. 2110

DICIEMBRE 12 DE 2003

Toda reproducción del presente extracto no posee valor el original expedido por la

ADMINISTRACIÓN

Presidente:

SERVIER SAS
(324 444 991 R.C.S. NANTERRE)
6 Des Pleiades 92415 Courbevoie Cedex
Forma Jurídica sociedad simplificada por acciones
representada por
el Señor SERVIER JACQUES
nacido el 09/02/1922 en VATHY 36150
de nacionalidad Francesa
- DOMICILIADO EN: 92 RUE CHARLES LAFFITTE
92200 NEUILLY SUR SEINE

Vicepresidente

Señor LE RIDANT ALAIN VICTOR LUCIEN HENRI
nacido el 31/10/1935 en ÉPINAY SUR ORGE 91360
de nacionalidad Francesa
domiciliado en 47 Boulevard Du Cdt Charcot 92200
NEUILLY

Vicepresidente

Señora BANZET MARIE-NOELLE
nacida el 20/12/1951 en COURBEVOIE 92400
de nacionalidad Francesa
domiciliada en 9 Rue Freville Le Vingt 92310 Sevres

Notario Público en el Estado de Bogotá
NOTARIO TREINTY SEIS DE BOGOTÁ
EN FARGADO

GERMAN FONSECA CHAPARRA
 TRADUCTOR E INTERPRETE OFICIAL
 ESPAÑOL - FRANCES - ESPAÑOL
 RESOLUCION MINJUSTICIA NO. 2110
 DICIEMBRE 12 DE 2003

El suscrito Notario, Reimundo J. Sait, de Bogotà,
Entregado hace constar que este Notario
Contenido en su contenido con un documento
Igual en su original, ha tenido a la vista
(Art. 74, Decreto 950 de 1968)

27 APR 2007

NEILSON FLOREZ GONZALEZ
NOTARIO TREINTAYSEIS D. BOGOTIA
ENCARGADO

87

NO 1585

(Biopharma) 29 rue du pont 92200 Neuilly sur Seine
Rcs Nanterre b 542 073 499 y Euthérapie 27.29 rue du
pont 92200 Neuilly sur Seine Rcs Nanterre b 642 020
036 a partir del 29 de marzo de 1996

15 de julio de 1996
Número 24348
18 de agosto de 2000
Número 56121

Sigla: Servier - Ardix - Euthérapie - Biopharma -

Fusión - absorción de la sociedad Oril sa (b 582080172
Rcs Nanterre) a partir del: 29-06-2000

17 de octubre de 2001
Número 73636

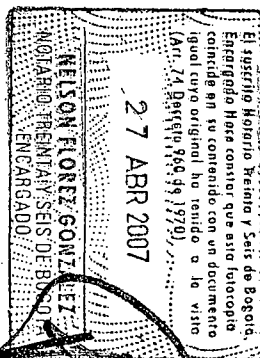
Fusión absorción de la sociedad Adir y compañía (329
211 650 Rcs Nanterre) a partir del 31 de agosto de
2001

ESTABLECIMIENTOS DE COMPETENCIA DE LA SECRETARÍA

Dirección: 192 Avenue Charles De Gaulle 92200 Neuilly Sur Seine


GERMAN FONSECA CHAPARRO
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - FRANCES - ESPAÑOL
RESOLUCION MINJUSTICIA NO. 2110
DICIEMBRE 12 DE 2003


Nelson Flores Gonzalez
NOTARIO
ENCARGADO


El suscrito Notario Público y Secretario de Bogotá,
Encargado para constar que este documento
contiene sin su contenido con un documento
igual cuyo original ha tenido a la vista
(Art. 74 Decreto 1664 de 1970)
27 ABR 2007
NELSON FLORES GONZALEZ
NOTARIO
ENCARGADO

1585

Secretaría del Tribunal de Comercio de NANTERRE
4 Rue Pablo Neruda
92020 NANTERRE CEDEX

085 480 796 R.C.S NANTERRE
Nuestras referencias: ALT
(1988 B 02123)

(Sello)
Tribunal de Comercio-Secretaría

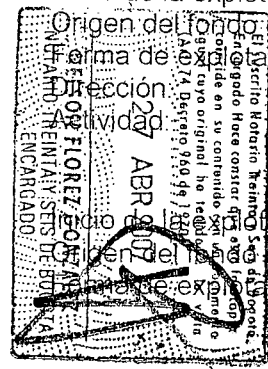
Extracto Kbis

INSCRIPCIÓN EN EL REGISTRO DE COMERCIO Y DE SOCIEDADES
Extracto del 14 de Febrero de 2007

Denominación comercial: SERVIER-ARDIX-EUTHÉRAPIE-BIOPHARMA-ORIL
Actividad: Todas las operaciones administrativas relacionadas directamente o indirectamente con la explotación de los laboratorios de productos químicos o farmacéuticos
Inicio de la explotación: 29 de junio de 2000
Origen del fondo comercial: Fondo de comercio adquirido por aporte
Anterior explotador: ORIL
nº de identificación B582080172

Declaración de acreencias:
En la Secretaría de NANTERRE
Forma de explotación: Explotación directa
Dirección: 12 Place De la Défense 92400 Courbevoie
Denominación comercial: SERVIER-ARDIX-EUTHÉRAPIE-BIOPHARMA-ORIL
Actividad: EXPLOTACIÓN DE LOS LABORATORIOS DE PRODUCTOS QUÍMICOS O FARMACÉUTICOS
Inicio de la explotación: 17 de mayo de 2002

Origen del fondo comercial: Creación de un fondo de comercio
Forma de explotación: Explotación directa
Dirección: 6 Place Des Pléiades 92415 Courbevoie Cedex
Actividad: Todas las operaciones administrativas relacionadas directamente o indirectamente con la explotación de los laboratorios de productos químicos o farmacéuticos
Inicio de la explotación: 1 de septiembre de 2006
Origen del fondo comercial: Creación de un fondo de comercio
Forma de explotación: Explotación directa



GERMAN FONSECA CHAPARRO

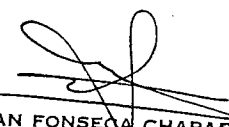
Traducción oficial de una **Apostilla en Francés**. República Francesa; Colombia; acta notarial firmada por ilegible; actuando en calidad de Secretario; con el sello del Tribunal de Comercio de Nantema; certificado en Versalles; el 2 de Abril de 2007; por el Procurador General del Tribunal de Casación de Versalles; bajo el número 7820/07; firma (ilegible); en 3 páginas.

"La Apostilla confirma únicamente la autenticidad de la firma, del sello o de la estampilla en el documento; ella no significa que el contenido del documento es correcto o que la República Francesa aprueba su contenido"

(Sello)

Procurador General del Tribunal de Casación de Versalles

Certifico que la anterior es traducción fiel y completa de la Apostilla y sello en referencia, la cual se sella con el sello del traductor Germán Fonseca Chaparro, Resolución Minjusticia No.2110 del 12 de diciembre de 2003. Bogotá D. C., 25 de abril de 2007.


GERMAN FONSECA CHAPARRO

TRADUCTOR E INTERPRETE OFICIAL

ESPAÑOL - FRANCÉS - ESPAÑOL

RESOLUCION MINJUSTICIA NO. 2110

DICIEMBRE 12 DE 2003

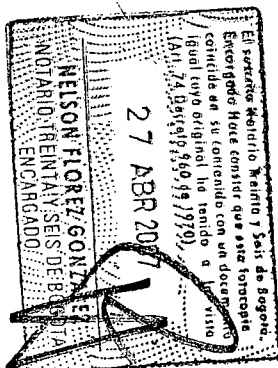
RELACIONES EXTRANJERAS
FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

597594

JEFES DE LEGALIZACIONES
BOGOTÁ D.C.

2007 ABR 27 P 2:41

NO SE ASUME
RESPONSABILIDAD DEL TEXTO





2.- Las declaraciones consignadas en este instrumento corresponden a la verdad y en consecuencia, asume la responsabilidad de lo manifestado en caso de utilizarse esta escritura con fines ilegales. -----

3.- Conoce la ley y sabe que el notario responde de la regularidad formal de los instrumentos que autoriza, pero no de la veracidad de las declaraciones de los otorgantes, ni de la autenticidad de los documentos que forma parte de este instrumento. -----

4.- Solo solicitare correcciones o modificaciones al texto de la presente escritura en la forma y en los casos previstos por la Ley. -----

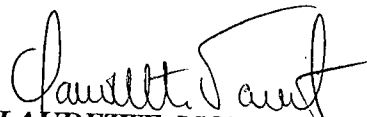
ADVERTENCIA, OTORGAMIENTO Y AUTORIZACIÓN. Leído el presente instrumento por la compareciente y advertida sobre las formalidades legales, lo aprobó y firma conmigo el Notario que suscribe. Derechos notariales resolución número 7880 de 2006. -----

\$38.110.00 -----

Se emplearon las hojas de papel notarial números: AA

29817666 /

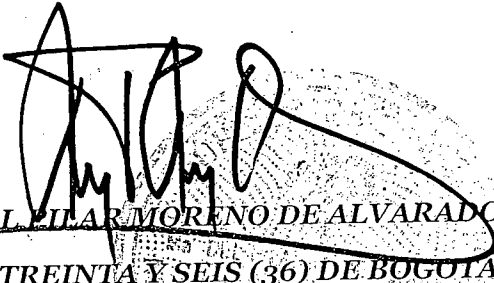
29817666 -----


CLAUDETTE MONIQUE VERNOT HERNÁNDEZ

C.C.No. 51.722.517 de Bogotá

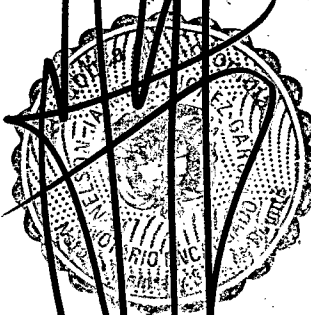
TEL.: 5310652




MARÍA DEL PILAR MORENO DE ALVARADO.
NOTARIA TREINTA Y SEIS (36) DE BOGOTÁ.

Elaborada por: Juan F.

Escritura Pública No. 15.85 de fecha 3 mayo 2007
ES FIEL Y emanada de los COPIA TOMADA DE SU
ORIGINAL EN Def 17 HOJAS CON DESTINO A
Intercomunicación
EXPEDIDA EN BOGOTÁ 16 SEP 2008





REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE

PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Firma Responsable

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Fecha.



No. 09-068410- -00000-0000

Fecha: 2009-07-02 15:53:32 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 90

Carrera 13 No. 27-00 Piso 5, 7y10'

Conmutador: 3 82 0840

Fax: 3505220

E-mail: info@sic.gov.co

www.sic.gov.co

Bogotá D.C. - Colombia

Bogotá D.C., 15 de octubre de 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-068410- -00001-0000

Fecha: 2009-10-15 15:31:49 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 46

Señora Jefe

ALIX CARMENZA CESPEDES DE VERGEL

DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E.

S.

D.

ARTURO CHAÑES

Referencia: Patente de Invención 3-SUSTITUTOS - (1-2-3)-
COMPONENTES DE LA BENZOTRIAZINONE PARA
AUMENTAR LA RESPUESTA SINÁPTICA
GLUTAMATÉRGICA. PCT/US2007/026416
Complemento de información
Radicado 2009-068410

JUAN MANUEL SERRANO CASTILLO, mayor de edad, domiciliado en esta ciudad, identificado con la cédula de ciudadanía No. 79'875.670 de Bogotá, abogado en ejercicio, portador de la tarjeta profesional No. 124.953 del C. S. de la J., actuando en calidad de apoderado de la sociedad **LES LABORATOIRES SERVIER y CORTEX PHARMACEUTICALS, INC.**, estando dentro del término legal me dirijo respetuosamente a su Despacho para aportar los siguientes documentos como complemento de información a la solicitud de la referencia:

1. Poder especial conferido por la sociedad CORTEX PHARMACEUTICALS, INC., en español e inglés debidamente apostillado.
2. Certificado notarial de la sociedad CORTEX PHARMACEUTICALS, INC., en español e inglés debidamente apostillado, en el que consta la existencia y representación legal de dicha compañía.
3. Copia simple del certificado de incorporación de la sociedad CORTEX PHARMACEUTICALS, INC. en inglés y la apostilla en la que consta que dicha copia es fiel y correcta del certificado regularizado presentado ante el Secretario de Estado del Estado de Delaware el 11 de abril de 1989. la apostilla se encuentra en inglés y se aporta su respectiva traducción oficial al español. (Este documento soporta lo informado en el certificado notarial mencionado en el numeral 2º de este mismo escrito.

- 2
4. Contrato de cesión de derechos sobre la patente de la referencia suscrito por los inventores Alexis CORDI, Gary ROGERS y Rudolf Mueller a favor de LES LABORATOIRES SERVIER y CORTEX PHARMACEUTICALS, INC., en español e inglés debidamente apostillado.
 5. Documento que acredita el campo de invención, solicitudes relacionadas, antecedentes de la invención, resumen de la invención, descripción detallada de la invención, ejemplos, reivindicación y resumen.
 6. Notificación de la patente, Reporte internacional preliminar de patentabilidad.

Ruego a su Despacho que proceda a realizar el estudio de forma de la solicitud de la referencia.

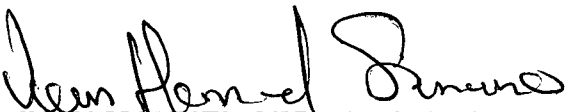
Anexos

Se anexan los documentos mencionados en 44 folios.

Notificaciones

Recibo notificaciones en la secretaría de su Despacho, en el casillero que para el efecto me ha sido asignado, o en la Carrera 11 No. 86 – 32 (oficina 101) de esta ciudad.

De Usted, atentamente,


JUAN MANUEL SERRANO CASTILLO
C.C. No. 79'875.670 de Bogotá D.C.
T.P. No. 124.953 del C.S. de la J.

3-SUBSTITUTED-(1,2,3)- BENZOTRIAZINONE COMPOUND FOR ENHANCING GLUTAMATERGIC SYNAPTIC RESPONSES
3-SUSTITUTOS - (1,2,3) - COMPONENTES DE LA BENZOTRIAZINONE PARA AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATERGICA

PODER

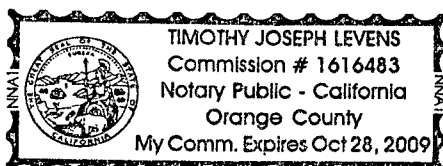
POWER OF ATTORNEY

Yo, Mark A. Varney abajo
firmado, CEO
Actuando como CEO
de Cortex Pharmaceuticals, Inc.

domiciliada en 15241 Barranca Parkway; Irvine CA 92718, USA.

por el presente conferimos poder a JUAN MANUEL SERRANO CASTILLO, tpa. 124953; PABLO ANDRÉS VELASCO ORDÓÑEZ, tpa. 129.348; domiciliados en la Carrera 11 No.84-42 Interior (9), Bogotá, Colombia, para (1) representen a la poderdante ante cualquiera corporaciones, funcionarios o empleados del orden judicial o del administrativo en cualesquiera juicios y actuaciones, actos, diligencias o gestiones en que la poderdante tenga que intervenir directa o indirectamente, sea como demandante, o como demandada, o como coadyuvante de cualesquiera de las partes; sea para iniciar o seguir tales juicios, actuaciones, actos diligencias o gestiones, y (2) para obtener la protección de la poderdante en sus asuntos, a cuyo efecto autorizamos a la dicha apoderada para que nos represente ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial; particularmente para adelantar todas las gestiones tendientes a la obtención de los derechos de propiedad intelectual que se soliciten ante la Superintendencia de Industria y Comercio (3) y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir y renunciar.

Dado y firmado hoy 16 July 2009
En Irvine, California
Por
Firma Mark A. Varney



I, the undersigned, **CORTEX PHARMACEUTICALS, INC.**

Acting as CEO
of Cortex Pharmaceuticals, Inc.

domiciled 15241 Barranca Parkway; Irvine, CA 92718 in USA

hereby grant to JUAN MANUEL SERRANO CASTILLO, tpa. 124953; PABLO ANDRÉS VELASCO ORDÓÑEZ, tpa. 129.348; domiciled at Carrera 11 No.84-42 Interior (9), Bogotá, Colombia, Power of Attorney to; (1) to represent the grantor before any corporations, officials or employees of the Courts or the administration in any suits and proceedings or acts where the grantor has to intervene as plaintiff or defendant or as adjuvant of any party; be it to institute or follow up with those suits or proceedings or acts; (2) to obtain the protection of the grantor in your matters, which purpose we authorize the said attorneys to represent us before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial; in special to conduce all the steps necessary to obtain registries related with Intellectual Property requested before the Superintendence of Industry and Commerce (3) and that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit of the facts of the case, desist, cancel, receive and renounce.

Given and signed this 16 July 2009
In Irvine, California

By Mark A. Varney
proxy for **CORTEX PHARMACEUTICALS, INC.**
Signature

STATE OF CALIFORNIA, COUNTY OF ORANGE
On 7-16-09 before me, TIMOTHY JOSEPH LEVENS, notary public, personally appeared MARK A. VARNEY

who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies); and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct. WITNESS my hand and official seal.

SIGNATURE Timothy Joseph Levens

95

State of California

SECRETARY OF STATE

Requested for use in Colombia.

Not for use within the United States of America.

The purpose of the Apostille is to certify the authenticity of the signature of the official signing the document, the capacity in which the official signing the document has acted, and, where appropriate, the identity of the seal or stamp.

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*
This public document
2. *has been signed by Olivia Martin*
3. *acting in the capacity of Deputy Clerk-Recorder, County of Orange, State of California*
4. *bears the seal/stamp of the County of Orange,*
State of California

CERTIFIED

5. *At Los Angeles, California*
6. *the 16th day of July 2009*
7. *by Deputy Secretary of State, State of California*
8. *No. 703055*
9. *Seal/Stamp*



10. Signature

Jana Bowen
Secretary of State

BY *Sharon K. Hawken*



5

Estado de California

[Sello redondo: Gran Sello del Estado de California]

SECRETARIO DE ESTADO

Solicitada para usarse en Colombia.

No debe usarse en los Estados Unidos de América.

La finalidad de la Apostilla consiste en certificar la autenticidad de la firma del funcionario que suscribe el documento, la calidad en que ha actuado el funcionario que suscribe el documento, y, cuando proceda, la identidad del sello o de la estampilla.

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América

El presente documento público

2. Ha sido firmado por Olivia Martin

3. Actuando en calidad de Secretaria Encargada-Registradora del Condado de Orange, Estado de California

4. Lleva el sello / la estampilla del Condado de Orange.

MINISTERIO DE
RELACIONES
EXTERIORES
138614
2010-08-10
COAHUILA DE ZARAGOZA
DOCUMENTO DESEMPLEA
LAS FUNCIONES DESIGNADAS

CERTIFICADO

5. En Los Ángeles, California

6. El 16 de julio de 2009

7. Por el Secretario de Estado (Encargado) del Estado de California

8. No. 703055

9. Sello / Estampilla: [Sello dorado redondo superpuesto: El Gran Sello del Estado de California]

10. Firma [firma facsimilar de Debra Bowen, Secretaria de Estado; Por: Firma facsimilar ilegible]

NO ASUME
RESPONSABILIDAD
DEL TEXTO
2009 SEP 25 P 1:18
JEFE DE LEGALIZACIONES
BOGOTA D.C.

Jorge E. Castilla Viana
Traductor Oficial
Res Minjusticia
No. 2789 de Nov. 14 de 1986

92

Colombia
Cortex - 078
6

CERTIFICADO NOTARIAL

El suscrito _____
debidamente nombrado Notario Público, por la
presente certifico que:

He visto los siguientes documentos:

1. Escritura de constitución de la sociedad
CORTEX PHARMACEUTICALS, INC.
de conformidad con las leyes de USA
2. Documento en el que se señala que
_____ esta autorizada por
CORTEX PHARMACEUTICALS, INC.
para representarla y actuar en su nombre.

Los documentos anteriores prueban lo siguiente:

1. Que **CORTEX PHARMACEUTICALS, INC.** fue constituida y existe de conformidad con las leyes de USA.
2. Que la dirección registrada de las oficinas de **CORTEX PHARMACEUTICALS, INC.** es **15241 Barranca Parkway . Irvine, CA 92718 (USA)**
3. Que **CORTEX PHARMACEUTICALS, INC.** está desarrollando sus actividades empresariales y que el propósito por el que se otorga el presente poder está comprendido en el objeto social de la compañía.
4. Que _____ está autorizada para otorgar el presente poder.

En fe de lo cual, suscribo el presente en mi nombre y estampo el sello de la mencionada Notaría. (Si aplica estampar el sello)

Ciudad _____
País _____
Firma _____

Nota: Tanto el poder como el certificado notarial deben ser: 1) otorgados ante Notaría; 2) la firma del Notario debe ser certificada por la corporación respectiva que está en capacidad de afirmar que el Notario que firma dicho documento se encuentra registrado o certificado, y; 3) se requiere la legalización o apostilla de los documentos.

NOTARIAL CERTIFICATE

Timothy Joseph Levens
I _____, Notary Public, certify:

That I have seen the following documents:

1. Deed of incorporation of **CORTEX PHARMACEUTICALS, INC.** according to the laws of USA.
2. Document evidencing that **MARK A VARNY** are duly authorized by **CORTEX PHARMACEUTICALS, INC.** to represent it and to act on its behalf.

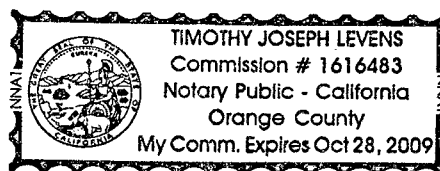
That the above documents prove:

1. That **CORTEX PHARMACEUTICALS, INC.** was incorporated and exists in accordance with the laws of USA.
2. That the registered domicile of **CORTEX PHARMACEUTICALS, INC.** is **15241 Barranca Parkway . Irvine, CA 92718 (USA)**
3. That **CORTEX PHARMACEUTICALS, INC.** is developing its corporate or company activities and that the purpose for which the present power of attorney is granted is comprised within the company's purposes.
4. That **Mark A Varny** is authorized to grant the present power of attorney.

In faith of which, I signed the present in my behalf and stamp the seal of the mentioned Notary (If applied to stamp seal)

City **IRVINE**
Country **ORANGE**
Signed *[Signature]*

Note: Both the power of attorney and the notarial certificate need to be executed: 1) Before the Notary public; 2) the signature of the Notary public needs to be certified by the corporation or association entitled to certify that the Notary public is duly registered and certified; and 3) should be legalized or apostilled.



03



TOM DALY
CLERK-RECORDER

PROPERTY RECORDS
BIRTH AND DEATH RECORDS
MARRIAGE LICENSES/RECORDS
PASSPORTS
FICTITIOUS BUSINESS NAMES
NOTARY REGISTRATION
ORANGE COUNTY ARCHIVES

NOTARY AUTHENTICATION

State of California
County of Orange}

I, Tom Daly, County Clerk-Recorder of the County of Orange, State of California, in and for said County DO HEREBY CERTIFY THAT Timothy Joseph Levens was, on October 29, 2005 a duly commissioned, qualified and acting NOTARY PUBLIC, in the State of California, County of Orange, empowered to act as such Notary in any part of this State and authorized to take the acknowledgment or proof of powers of attorney, mortgages, deeds, grants, transfers, and other instruments of writing executed by any person, and to take depositions and affidavits and administer oaths and affirmations in all matters incident to the duties of the office or to be used before any court, judge, officer, or board.

I FURTHER CERTIFY that the seal affixed or impressed on the attached document is the official seal of said Notary Public and it appears that the name subscribed thereon is the genuine signature of the person aforesaid, his (or her) signature being of record in this office.

In Witness Whereof, I execute this certificate and have hereunto set my hand and affixed the seal of said County on 16th Day of July, 2009

Tom Daly, Orange County Clerk - Recorder

(Seal)

By  _____, Deputy Clerk
Olivia Martin

NORTH COUNTY BRANCH OFFICE
HISTORIC DOWNTOWN FULLERTON
201 N. HARBOR BOULEVARD
FULLERTON, CALIFORNIA 92832

ORANGE COUNTY
HALL OF FINANCE AND RECORDS
12 CIVIC CENTER PLAZA, ROOM 101
SANTA ANA, CALIFORNIA 92701

SOUTH COUNTY BRANCH OFFICE
LAGUNA HILLS CIVIC CENTER
24031 EL TORO ROAD
LAGUNA HILLS, CALIFORNIA 92653

7



99

[Sello redondo, Condado de Orange, California]

TOM DALY
SECRETARIO - REGISTRADOR

AUTENTICACIÓN NOTARIAL

Estado de California

Condado de Orange

Yo, Tom Daly, Secretario-Registrador del Condado de orange, Estado de California en dicho Condado y para dicho Condado, CERTIFICO POR LA PRESENTE QUE el 29 de octubre de 2005 Timothy Joseph Levens era NOTARIO PÚBLICO debidamente capacitado y en funciones en el Estado de California, Condado de Orange, facultado para actuar en tal calidad de Notario en cualquier lugar de este estado y autorizado para recibir reconocimientos o pruebas de poderes, hipotecas, concesiones, traspasos y demás instrumentos escritos otorgados por cualquier persona, y tomar atestiguaciones y declaraciones juramentadas, tomar juramentos y afirmaciones en todos los asuntos incidentales a las responsabilidades del cargo, o que deban usarse ante cualquier tribunal, juez, funcionario, o junta.

CERTIFICO, ADEMÁS, que el sello fijado o impreso en el documento adjunto es el sello oficial de dicho Notario Público y que parece que el nombre suscrito en el mismo es la firma genuina de la persona antedicha y que su firma está registrada en este despacho.

En Constancia, otorgo el presente certificado y en él he estampado mi firma y fijado el sello de dicho Condado hoy, 16 de julio de 2009.

Tom Daly, Secretario-Registrador del condado de Orange

(Sello)

Por [Firmado], Secretaria Encargada

Olivia Martin

SUCURSAL NORTH COUNTY
HISTORIC DOWNTOWN FULLERTON
201 N. HARBOR BOULEVARD
FULLERTON, CALIFORNIA 92382

CONDADO DE ORANGE
HALL OF FINANCE AND RECORDS
12 CIVIC CENTER PLAZA, ROOM 101
SANTA ANA, CALIFORNIA 92701

SUCURSAL SOUTH COUNTY
LAGUNA HILLS CIVIC CENTER
24031 EL TORO ROAD
LAGUNA HILLS, CALIFORNIA 92653

(714) 834-2500 * Fax: (714) 834-2675 * www.OCRERECORDER.COM * www.OCARCHIVES.COM

[Firma]
JORGE E. CASTILLA VIANA
Traductor Oficial
Res Minjusticia
No. 2789 de Nov. 14 de 1986

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
El presente documento público
2. Ha sido firmado por Jeffrey W. Bullock
3. Actuando en calidad de Secretario de Estado de Delaware
4. Lleva el sello / la estampilla del Despacho del Secretario de Estado

CERTIFICADO

5. En Dover, Delaware
6. El diez de julio de 2009 a. D.
7. Por el Secretario de Estado, Departamento de Estado de Delaware
8. No. 0390187
9. Sello / Estampilla: [Sello redondo superpuesto: Despacho del Secretario, Delaware 1793-1855]
10. Firma [firma facsimilar de J. W. Bullock, Secretario de Estado]

COPIA DE LA APOSTILLA
DOCUMENTO DESEMPENADO
LAS FUNCIONES INMEDIATAS
138615
Jorge Castilla

2009 SEP 25 P 11:18
JEFE DE LEGALIZACIONES
BOGOTA D.C.
Jorge

MINISTERIO DE
RELACIONES
EXTERIORES

NO ASUME
RESPONSABILIDAD
DEL TEXTO

JORGE E. CASTILLA VIANA
Traductor Oficial
Res Minjusticia
No. 2789 de Nov. 14 de 1986

Delaware

El Primer Estado

PÁGINA 1

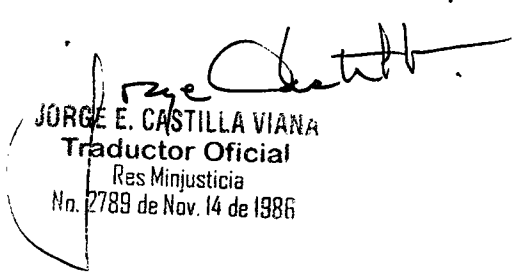
YO, JEFFREY W. BULLOCK, SECRETARIO DE ESTADO DEL ESTADO DE DELAWARE, CERTIFICO POR LA PRESENTE QUE LA ADJUNTA ES COPIA FIEL Y CORRECTA DEL CERTIFICADO REGULARIZADO DE "CORTEX PHARMACEUTICALS, INC.", PRESENTADO EN ESTE DESPACHO EL ONCE DE ABRIL DE 1989, A. D., A LAS 10:01 EN PUNTO A. M.

[Sello redondo superpuesto: Despacho del Secretario, Delaware, 1793-1855]

[Firma facsimilar de Jeffrey W. Bullock, Secretario de Estado]

2117188 8100 AUTENTICACIÓN: 7411899
090689459 FECHA: 07-10-09

Ud. Puede verificar el presente certificado en Internet,
En corp.Delaware.gov/authver.shtml


JORGE E. CASTILLA VIANA
Traductor Oficial
Res Minjusticia
Nº. 2789 de Nov. 14 de 1986

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America

This public document:

2. has been signed by Jeffrey W. Bullock

3. acting in the capacity of Secretary of State of Delaware

4. bears the seal/stamp of Office of Secretary of State

Certified

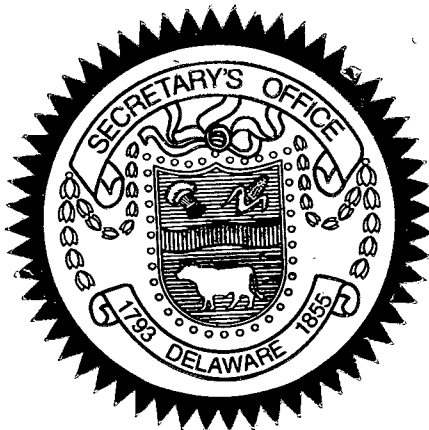
5. at Dover, Delaware

6. the tenth day of July, A.D. 2009

7. by Secretary of State, Delaware Department of State

8. No. 0390187

9. Seal/Stamp:



10. Signature:

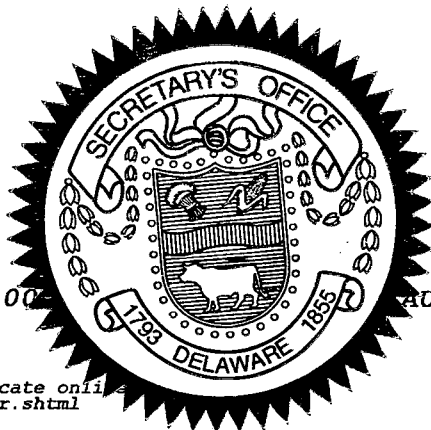
msar
Secretary of State

Delaware

PAGE 1

The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE RESTATED CERTIFICATE OF "CORTEX PHARMACEUTICALS, INC.", FILED IN THIS OFFICE ON THE ELEVENTH DAY OF APRIL, A.D. 1989, AT 10:01 O'CLOCK A.M.



2117188 8100

090689459

You may verify this certificate online at corp.delaware.gov/authver.shtml

AUTHENTICATION: 7411899

DATE: 07-10-09

Jeffrey W. Bullock, Secretary of State

899101070

RESTATED CERTIFICATE OF INCORPORATION
OF
CORTEX PHARMACEUTICALS, INC.,
a Delaware corporation

10:01 AM
FILED

APR 11 1989

Michael J. Gahan
SECRETARY OF STATE

CORTEX PHARMACEUTICALS, INC., a corporation organized and existing under the General Corporation Law of the State of Delaware, does hereby certify that:

(1) The name of the corporation is Cortex Pharmaceuticals, Inc. (the "Corporation"). The Corporation was originally incorporated under the name X-Age, Inc., and the original Certificate of Incorporation of the Corporation was filed with the Secretary of State of the State of Delaware on February 10, 1987.

(2) This Restated Certificate of Incorporation restates and integrates and does not further amend the provisions of the Certificate of Incorporation of the Corporation, as heretofore amended or supplemented, and there is no discrepancy between those provisions and the provisions of this Restated Certificate of Incorporation.

(3) The text of the Restated Certificate of Incorporation, as heretofore amended or supplemented, is hereby restated to read in its entirety as follows:

"FIRST: The name of this corporation is Cortex Pharmaceuticals, Inc.

SECOND: The address of the registered office of the Corporation in the State of Delaware is Corporation Trust Center, 1209 Orange Street in the City of Wilmington, County of New Castle. The name of the Corporation's registered agent at that address is The Corporation Trust Company.

THIRD: The purpose of the Corporation is to engage in any lawful act or activity for which corporations may be organized under the General Corporation Law of the State of Delaware.

FOURTH: (A) (1) The aggregate number of shares which the Corporation shall have authority to issue is 35,000,000, of which 5,000,000 shares of the par value of \$.001 per share shall be designated "Preferred Stock" and 30,000,000 shares of the par value of \$.001 per share shall be designated "Common Stock."

(2) Authority is hereby expressly granted to the Board of Directors from time to time to issue the Preferred Stock as Preferred Stock of any series and, in connection with

the creation of each such series, to fix by the resolution or resolutions providing for the issue of shares thereof, the number of shares of such series and the designations, powers, preferences, rights, qualifications, limitations, and restrictions of such series, to the full extent now or hereafter permitted by the laws of the State of Delaware.

(B) 9% Cumulative Convertible Preferred Stock

A series of Preferred Stock, consisting of 1,250,000 shares of the authorized but unissued Preferred Stock of the Corporation is hereby created. The designation, powers, preferences, rights, qualifications, limitations, and restrictions of this series, are as follows:

(1) Designation of Series. The designation of the series of preferred stock created hereby shall be 9% Cumulative Convertible Preferred Stock, par value .001 per share (the "9% Preferred Stock"). The shares of the 9% Preferred Stock shall be fully-paid and nonassessable.

The number of shares of 9% Preferred Stock may be decreased (but not below the number of shares then outstanding) or increased by a certificate executed, acknowledged, filed, and recorded in accordance with the General Corporation Law of the State of Delaware setting forth a statement that a specified decrease or increase, as the case may be, thereof had been authorized and directed by a resolution or resolutions adopted by the Board of Directors pursuant to authority expressly vested in it by the provisions of the certificate of incorporation of the Corporation.

(2) Dividends. The fixed dividend rate for the 9% Preferred Stock shall be \$.09 per share per annum, and no more, and dividends shall be cumulative from June 15, 1989 payable in equal semiannual amounts on the fifteenth day of June and December in each year for the semiannual dividend periods ending respectively on the dates immediately preceding such dates, commencing on June 15, 1989.

(3) Conversion. The holders of shares of 9% Preferred Stock shall have the right, at their option, to convert such shares into shares of Common Stock at any time on the following terms and conditions:

(a) Each share of 9% Preferred Stock shall be convertible at the option of the holder thereof at the office of the Corporation or at the office of the transfer agent, if any, for the 9% Preferred Stock into shares of duly authorized, fully paid, and non-assessable shares of Common Stock at the conversion price of \$1.50 per share of Common Stock (the "Conversion Rate"), subject to adjustment as provided in

Section (B)(3)(c) of this Article FOURTH. The number of shares of Common Stock to be delivered upon conversion of the 9% Preferred Stock shall be determined by dividing the liquidation amount (\$1.00 per share) of the shares surrendered by the Conversion Rate at the time of surrender, calculated to the nearest 1/100th of a share (fractions of less than 1/100 being disregarded). The Corporation shall make no payment or adjustment on the account of any unpaid cumulative dividends on the shares of 9% Preferred Stock surrendered for conversion or on account of any dividends on the Common Stock. In case of the call for redemption by the Corporation of any shares of 9% Preferred Stock, such right of conversion shall cease and terminate, as to the shares designated for redemption, from and after the dates specified for redemption pursuant to the provisions of Section (B)(5) of this Article FOURTH.

(b) Before any holder of shares of 9% Preferred Stock shall be entitled to convert the same into Common Stock, he shall surrender the certificate or certificates therefor, duly endorsed, at the office of the Corporation or the transfer agent therefor, if any, and shall give written notice to the Corporation that he elects to convert all or part of the shares represented by the certificate or certificates and shall state in writing therein the name or names in which he wishes the certificate or certificates for Common Stock to be issued. The Corporation will, as soon as practicable thereafter, issue and deliver to such holder of shares of 9% Preferred Stock, or to his nominee or nominees, certificates for the number of full shares of Common Stock to which he shall be entitled as aforesaid, together with cash in lieu of any fraction of a share as hereinafter provided. If surrendered certificates for 9% Preferred Stock are converted only in part, the Corporation will issue and deliver to the holder, or to his nominee or nominees, a new certificate or certificates representing the aggregate of the unconverted shares of 9% Preferred Stock. Shares of 9% Preferred Stock shall be deemed to have been converted as of the date of the surrender of such shares for conversion as provided above, and the person or persons entitled to receive the Common Stock issuable upon such conversion shall be treated for all purposes as the record holder or holders of such Common Stock on such date.

(c) The Conversion Rate shall be subject to adjustment as follows:

(i) In case the Corporation shall (w) pay a dividend or make a distribution on its outstanding shares of Common Stock in shares of its capital stock (whether shares of its Common Stock or of capital stock of any other class), (x) subdivide its outstanding shares of Common Stock, (y) combine its outstanding shares of Common Stock into a smaller number of shares, or (z) issue by

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reclassification of its shares of Common Stock any shares of capital stock of the Corporation, the Conversion Rate in effect immediately prior to such action shall be adjusted so that the holder of any shares of 9% Preferred Stock thereafter surrendered for conversion shall be entitled to receive the number of shares of capital stock of the Corporation which he would have owned immediately following such action had such shares of 9% Preferred Stock been converted immediately prior thereto. An adjustment made pursuant to this subsection (i) shall become effective retroactively immediately after the record date in the case of a dividend or distribution and shall become effective immediately after the effective date in the case of a subdivision, combination, or reclassification.

(ii) In case the Corporation shall issue to holders of shares of its outstanding Common Stock generally any rights, options, or warrants entitling them to subscribe for or purchase (w) shares of its Common Stock, (x) any assets of the Corporation, (y) any securities of the Corporation (except its Common Stock) or of any corporation other than the Corporation, or (z) any rights, options, or warrants entitling them to subscribe for or to purchase any of the foregoing securities, whether or not such rights, options, or warrants are immediately exercisable (hereinafter collectively called a "Distribution on Common Stock"), the Corporation shall issue to the holders of outstanding shares of 9% Preferred Stock the Distribution on Common Stock to which they would have been entitled if they had converted the shares of 9% Preferred Stock held by them into Common Stock immediately prior to the record date for the purpose of determining stockholders entitled to receive such Distribution on Common Stock.

(d) De Minimus Changes. No adjustment in the Conversion Rate shall be required unless such adjustment would require an increase or decrease of at least 1% in the Conversion Rate; provided, however, that any adjustments which by reason of this Section (B)(3)(d) of this Article FOURTH are not required to be made shall be carried forward and taken into account in any subsequent adjustment. All calculations under Section (B)(3)(c) of this Article FOURTH shall be made to the nearest cent or to the nearest one hundredth of a share, as the case may be.

(e) Notice of Adjustment. Whenever the Conversion Rate is adjusted, as herein provided, the Corporation shall promptly cause a notice setting forth the adjusted Conversion Rate to be mailed to the holders of the 9% Preferred Stock.

(f) No Fractional Shares to be Issued. No fractional shares or scrip representing fractional shares of Common Stock shall be issued upon conversion of 9% Preferred Stock. Instead of any fractional share of Common Stock which would otherwise be issuable upon conversion of 9% Preferred Stock (or specified portions thereof), the Corporation shall pay in cash to the holders of such 9% Preferred Stock in respect of such fraction of a share an amount equal to the same fraction of the fair market value per share of Common Stock as determined by the Board of Directors in its sole discretion.

(g) Effect of Sale, Merger, or Consolidation.
In the event of any capital reorganization of the Corporation, or of any reclassification (other than a change in par value) of the Common Stock, or of any conversion of the Common Stock into securities of another corporation, or the consolidation of the Corporation with, or the merger of the Corporation into, any other corporation where the Corporation is not the surviving corporation or in the event of the sale of all or substantially all of the properties and assets of the Corporation to any other corporation (each such event hereinafter being referred to as a "Capital Change"), a share of 9% Preferred Stock shall be convertible after such Capital Change, upon the terms and conditions herein specified, for the number of shares of stock or other securities or property of the Corporation, or of the corporation into which shares of Common Stock are converted or resulting from such consolidation or surviving such merger or to which such sale shall be made, as the case may be, to which the shares of Common Stock issuable (at the time of such Capital Change) upon conversion of such share of 9% Preferred Stock would have been entitled upon such Capital Change. In any such case, if necessary, the provisions set forth in this Section (B)(3) of Article FOURTH with respect to the rights and interests thereafter of the holders of the 9% Preferred Stock shall be appropriately adjusted so as to be reasonably applicable to any shares of stock or other securities or property thereafter deliverable on the conversion of the 9% Preferred Stock. The subdivision or combination of shares of Common Stock at any time outstanding into a greater or lesser number of shares of Common Stock shall not be deemed to be a reclassification of the Common Stock for the purpose of this Section (B)(3)(g) of this Article FOURTH. The Corporation shall not effect any consolidation, merger, or sale resulting in a Capital Change, unless prior to or simultaneously with the consummation thereof, any successor corporation or corporation purchasing such assets shall assume, by written instrument, the obligation to deliver to the holder of each share of 9% Preferred Stock such shares of stock, securities, or assets as the holders of 9% Preferred Stock may be entitled to receive upon exercise of the 9% Preferred Stock in accordance with the foregoing provisions, and the other obligations of the Corporation hereunder.

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(h) Notice of Reclassification or
Recapitalization, etc.

In case:

(i) the Corporation shall authorize the issuance to all holders of Common Stock of rights or warrants to subscribe for or purchase shares of its capital stock or of any other right;

(ii) the Corporation shall authorize the distribution to all holders of Common Stock of evidences of its indebtedness or assets or the change or adoption of a dividend policy;

(iii) of any subdivision, combination, or reclassification of Common Stock, or of any consolidation or merger to which the Corporation is a party and for which approval of any stockholders of the Corporation is required, or of the sale or transfer of all or substantially all of the assets of the Corporation; or

(iv) of the voluntary or involuntary dissolution, liquidation, or winding up of the Corporation;

then the Corporation shall mail to the holders of 9% Preferred Stock at least 10 days prior to the applicable record date hereinafter specified in clauses (x) and (y) below, a notice stating (x) the date as of which the holders of Common Stock of record to be entitled to receive any such rights, warrants, or distribution are to be determined, or (y) the date on which any such subdivision, combination, reclassification, consolidation, merger, sale, transfer, dissolution, liquidation, winding up, or other action is expected to become effective, and the date as of which it is expected that holders of Common Stock of record shall be entitled to exchange their Common Stock for securities or other property, if any, deliverable upon such subdivision, combination, reclassification, consolidation, merger, sale, transfer, dissolution, liquidation, winding up, or other action. The failure to give the notice required by this Section (B)(3)(h) of this Article FOURTH or any defect therein shall not affect the legality or validity of any distribution, right, warrant, subdivision, combination, reclassification, consolidation, merger, sale, transfer, dissolution, liquidation, winding up, or other action, or the vote upon any of the foregoing.

(i) Reservation of Shares for Issuance Upon Conversion. The Corporation covenants that it will at all times reserve and keep available out of its authorized Common Stock, free from preemptive rights, solely for the purpose of issuance upon conversion of the 9% Preferred Stock as herein

provided, such number of shares of Common Stock as shall then be issuable upon the conversion of all outstanding shares of the 9% Preferred Stock. The Corporation covenants that all shares of Common Stock which shall be so issuable upon conversion of the 9% Preferred Stock as herein provided shall, when issued, be duly authorized, validly issued, and fully paid and nonassessable, free of all liens and charges and not subject to preemptive rights and that, upon conversion of the 9% Preferred Stock, the appropriate capital stock accounts of the Corporation shall be duly credited.

(j) Payment of Taxes on Shares Issued Upon Conversion. The issuance of certificates for shares of Common Stock upon the conversion of shares of the 9% Preferred Stock shall be made without charge to the converting holders for any tax in respect of the issuance of such certificates and such certificates shall be issued in the respective names of, or in such names as may be directed by, the holders of the shares of the 9% Preferred Stock converted; provided, however, that the Corporation shall not be required to pay any tax which may be payable in respect of any transfer involved in the issuance and delivery of any such certificate in a name other than that of the shares of the 9% Preferred Stock converted, and the Corporation shall not be required to issue or deliver such certificates unless or until the person or persons requesting the issuance thereof shall have paid to the Corporation the amount of such tax or shall have established to the satisfaction of the Company that such tax has been paid.

(4) Redemption of 9% Preferred Stock by Holders

(a) Right to Redeem 9% Preferred Stock. Subject to and upon compliance with the provisions of this Section (B)(4) of this Article FOURTH, at any time during the six-month period following the date of the written notice referred to in Section (B)(4)(c) of this Article FOURTH, the holder of shares of 9% Preferred Stock shall have the option, but not the obligation, to require the Corporation to redeem his shares of 9% Preferred Stock at a price of \$1.00 per share of 9% Preferred Stock to be redeemed. A holder of shares of 9% Preferred Stock wishing to require the Corporation to redeem such shares shall surrender the shares which are to be so redeemed to the Corporation or to such agent as may be appointed by the Corporation for such purpose at any time during such six-month period during usual business hours accompanied by a written notice of election to redeem and, if so required by the Corporation, by a written instrument or instruments of transfer in form satisfactory to the Corporation duly executed by the holder or his attorney duly authorized in writing.

(b) Payment of Redemption Price. As promptly as practicable after the surrender, as herein provided, of shares of 9% Preferred Stock for redemption, the Corporation shall pay or cause to be paid to or upon the written order of the holder of the shares of 9% Preferred Stock so surrendered an amount equal to \$1.00 multiplied by the number of shares so surrendered in accordance with the provisions of Section (B)(4)(a) of this Article FOURTH. Such redemption shall be deemed to have occurred at the time that such shares of 9% Preferred Stock shall have been surrendered for redemption in accordance herewith and the rights of the holder of such shares of 9% Preferred Stock as a holder of 9% Preferred Stock shall cease at such time. In the case of any shares of 9% Preferred Stock which are redeemed in part only, upon such redemption the Corporation shall execute and deliver to the holder thereof, as requested by such holder, a new certificate for shares of 9% Preferred Stock of authorized denominations equal to the unredeemed portion of such shares of 9% Preferred Stock.

(c) Notice of Right of Redemption. Within 30 days after the Corporation determines that, as of the last day of any calendar quarter, the total stockholders' equity of the Corporation exceeds \$5,000,000 (as determined in accordance with generally accepted accounting principles applied in a consistent manner with prior periods), the Corporation shall give notice thereof to the holders of the 9% Preferred Stock. Such notice shall specify the redemption price and the period of time during which holders of 9% Preferred Stock may cause such shares to be redeemed by the Corporation as described in Section (B)(4) of this Article FOURTH.

(5) Redemption of 9% Preferred Stock by the Corporation

(a) Right to Redeem 9% Preferred Stock. The 9% Preferred Stock may be redeemed, at the option of the Corporation, in whole or in part, at any time at a price of \$1.00 per share. If the Corporation desires to redeem the shares of 9% Preferred Stock, the Corporation shall give the holders thereof notice of such redemption, which notice shall set forth the number of shares to be redeemed and the place and date fixed for redemption, which date shall be not less than 30 nor more than 60 days after the date of such notice. On the date fixed for redemption, the holders of shares of 9% Preferred Stock shall surrender the certificates therefor against payment of the redemption amount. If the shares of 9% Preferred Stock are to be redeemed in part, each such redemption shall be applied pro rata to the shares of 9% Preferred Stock then outstanding.

(b) Payment of Redemption Price. As promptly as practicable after the surrender, as herein provided, of shares

of 9% Preferred Stock for redemption, the Corporation shall pay or cause to be paid to or upon the written order of the holder of the shares of 9% Preferred Stock so surrendered an amount equal to \$1.00 multiplied by the number of shares so surrendered in accordance with the provisions of Section (B)(5)(a) of this Article FOURTH. Such redemption shall be deemed to have occurred at the time that such shares of 9% Preferred Stock shall have been surrendered for redemption in accordance herewith and the rights of the holder of such shares of 9% Preferred Stock as a holder of 9% Preferred Stock shall cease at such time. In the case of any shares of 9% Preferred Stock which are redeemed in part only, upon such redemption the Corporation shall execute and deliver to the holder thereof, as requested by such holder, a new certificate for shares of 9% Preferred Stock of authorized denominations equal to the unredeemed portion of such shares of 9% Preferred Stock.

(6) Voting. Other than any voting rights created by applicable law, the holders of shares of 9% Preferred Stock shall not be entitled to vote at any election of directors or any other matter upon which holders of the Common Stock have the right to vote or to receive notice of any meeting of stockholders.

(7) Preference on Liquidation, etc. In the event of any voluntary or involuntary liquidation, distribution of all or substantially all of the assets, dissolution, or winding-up of the Corporation (any such event being hereinafter referred to as a "Liquidation Transaction"), any payment or distribution of the assets of the Corporation (whether capital or surplus), or the proceeds thereof, shall be made to or set apart in the following order of preference: (i) the holders of shares of 9% Preferred Stock shall be entitled to receive payment of \$1.00 per share of 9% Preferred Stock held by them, plus any accrued and unpaid dividends on the 9% Preferred Stock, if any (and no more), and, if the assets of the Corporation shall be insufficient to pay in full the preferential amounts set forth in this clause (i), then such assets shall be distributed among such holders ratably in accordance with the respective amounts which would be payable on such shares if all amounts payable thereon were paid in full; and (ii) after payment in full of the preferential amounts set forth in clause (i) above, the holders of shares of Common Stock shall be entitled to receive ratably payment or distribution of the remaining assets per share of Common Stock.

FIFTH: Election of directors need not be by written ballot.

SIXTH: The Board of Directors is authorized to adopt, amend, or repeal By-Laws of the Corporation, except as and to the extent provided in the By-Laws.

SEVENTH: Any person who was or is a party or is threatened to be made a party to any threatened, pending, or completed action, suit, or proceeding, whether civil, criminal, administrative, or investigative (whether or not by or in the right of the Corporation) by reason of the fact that he is or was a director, officer, incorporator, employee, or agent of the Corporation, or is or was serving at the request of the Corporation as a director, officer, incorporator, employee, partner, trustee, or agent of another corporation, partnership, joint venture, trust, or other enterprise (including an employee benefit plan), shall be entitled to be indemnified by the Corporation to the full extent then permitted by law against expenses (including attorneys' fees), judgments, fines (including excise taxes assessed on a person with respect to an employee benefit plan), and amounts paid in settlement incurred by him in connection with such action, suit, or proceeding. Such right of indemnification shall inure whether or not the claim asserted is based on matters which antedate the adoption of this Article SEVENTH. Such right of indemnification shall continue as to a person who has ceased to be a director, officer, incorporator, employee, partner, trustee, or agent and shall inure to the benefit of the heirs and personal representatives of such a person. The indemnification provided by this Article SEVENTH shall not be deemed exclusive of any other rights which may be provided now or in the future under any provision currently in effect or hereafter adopted by the By-Laws, by any agreement, by vote of stockholders, by resolution of disinterested directors, by provision of law, or otherwise.

EIGHTH: No director of the Corporation shall be liable to the Corporation or any of its stockholders for monetary damages, for breach of fiduciary duty as a director, except for liability (i) for any breach of the director's duty of loyalty to the Corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the Delaware General Corporation Law, or (iv) for any transaction from which the director derived an improper personal benefit.

NINTH: Whenever a compromise or arrangement is proposed between this Corporation and its creditors or any class of them and/or between this Corporation and its stockholders or any class of them, any court of equitable jurisdiction within the State of Delaware may, on the application in a summary way of this Corporation or of any creditor or stockholder thereof or on the application of any receiver or receivers appointed for this Corporation under the provisions of Section 291 of Title 8 of the Delaware Code or on the application of trustees in dissolution or of any receiver or receivers appointed for this Corporation under the provisions of Section 279 of Title 8 of

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the Delaware Code order a meeting of the creditors or class of creditors, and/or of the stockholders or class of stockholders of this Corporation, as the case may be, to be summoned in such manner as the said court directs.

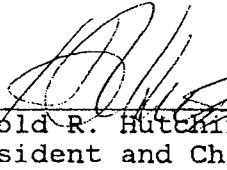
If a majority in number representing three-fourths in value of the creditors or class of creditors, and/or of the stockholders or class of stockholders of this Corporation, as the case may be, agree to any compromise or arrangement and to any reorganization of this Corporation as consequence of such compromise or arrangement, the said compromise or arrangement and the said reorganization shall, if sanctioned by the court to which the said application has been made, be binding on all the creditors or class of creditors, and/or on all the stockholders or class of stockholders, of this Corporation, as the case may be, and also on this Corporation."

(4) The foregoing Restated Certificate of Incorporation has been duly adopted in accordance with the applicable provisions of Section 245 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, this Restated Certificate of Incorporation has been signed under the seal of the Corporation by Harold R. Hutchings, M.D., its President and Chief Executive Officer, and attested to by D. Scott Hagen, its Assistant Secretary, this 7th day of April, 1989.

CORTEX PHARMACEUTICALS, INC.

[SEAL]

By: 
Harold R. Hutchings, M.D.,
President and Chief Executive
Officer

ATTEST:

By: 
D. Scott Hagen,
Assistant Secretary

Traducción oficial de una **Apostilla en Francés**. República Francesa; Colombia; acta notarial firmada por el Abogado Yves Robert; actuando en calidad de Notario; con el sello de la oficina del Notario de Sèvres; certificado en Versalles; el 20 de agosto de 2009; por el Procurador General del Tribunal de Casación de Versalles; bajo el número 19176/2009; firma (ilegible).

"La Apostilla confirma únicamente la autenticidad de la firma, del sello o de la estampilla en el documento; ella no significa que el contenido del documento es correcto o que la República Francesa aprueba su contenido"

(Sello)

Procurador General del Tribunal de Casación de Versalles

Certifico que la anterior es traducción fiel y completa de la Apostilla y sello en referencia, la cual se sella con el sello del traductor Germán Fonseca Chaparro, Resolución Minjusticia No.2110 del 12 de diciembre de 2003. Bogotá, D. C., 22 de septiembre de 2009.


GERMAN FONSECA CHAPARRO
 TRADUCTOR E INTERPRETE OFICIAL
 ESPAÑOL - FRANCÉS - ESPAÑOL
 RESOLUCION MINJUSTICIA NO. 2110
 DICIEMBRE 12 DE 2003

NO ASUME
 RESPONSABILIDAD
 DEL TEXTO

2009 SEP 25 P 1:19

DELEGACIONES
 BOGOTA D.C.

MINISTERIO DE
 RELACIONES
 EXTERIORES

138616
 Germán Fonseca
 CUYA FIRMATALE EN EL
 DOCUMENTO REPRESENTA
 LAS FUNCIONES INDICADAS

25

**3-SUSTITUTOS – (1-2-3)- COMPONENTES DE LA BENZOTRIAZINONE PARA
AUMENTAR LA RESPUESTA SINÁPTICA GLUTAMATÉRGICA.**

*Colombia
Cortex 079*

CESIÓN DE DERECHOS

Por la presente se deja constancia del Contrato de Cesión de Derechos celebrado por y entre **Alexis CORDI, Gary ROGERS, Rudolf Mueller**, domiciliados a efectos del presente documento respectivamente en Francia, E. U. A. y E. U. A., por una parte, y por otra:

- **LES LABORATOIRES SERVIER**, domiciliados a efectos del presente documento en Francia y debidamente representados por Christine BRUNEL,
- y
- **CORTEX PHARMACEUTICALS, INC.**, domiciliados a efectos del presente documento en E. U. A., debidamente representados por Mark A. Varney

en los siguientes términos y condiciones:
PREÁMBULO

1. **Alexis CORDI, Gary ROGERS, Rudolf Mueller** son los autores de la patente
2. **Alexis CORDI, Gary ROGERS, Rudolf Mueller** han decidido ceder todos sus derechos en la patente a la que se refiere la cláusula anterior.
3. LES LABORATOIRES SERVIER y **CORTEX PHARMACEUTICALS, INC.**, desean adquirir los derechos de explotación económica del diseño al que se refiere la cláusula 1).

ACUERDOS

1. **Alexis CORDI, Gary ROGERS, Rudolf Mueller** ceden a favor de **LES LABORATOIRES SERVIER** y de **CORTEX PHARMACEUTICALS, INC.**, sin reservas ni limitaciones de ninguna índole, todos sus derechos en la patente a la que se refiere la cláusula 1) del Preámbulo.
2. La cesión se hace a título gratuito.
3. Ambas partes acuerdan que ESTRATEGIA JURÍDICA podrá presentar la solicitud de registro de la patente a la que se refiere la cláusula 1) del Preámbulo ante la Superintendencia de Industria y Comercio de Colombia.

En constancia, el presente documento se celebra en *Suresnes el 16 de julio de 2009.*

Cedente	Cesionario
1. <i>[Firmado]</i> Alexis CORDI 92150 Suresnes (Francia)	2. <i>[Firmado]</i> Gary ROGERS Laguna Beach, CA92651 (E. U. A.)

Jorge E. Castilla Viana
Traductor Oficial
Res. Minjusticia
No. 2789 de Nov. 14 de 1986

Cedente		Cesionario	
3. <i>[Firmado]</i> Rudolf MUELLER Foothill Ranch, CA92610 (E. U. A.)		1. <i>[Firmado]</i> Christine BRUNEL, Apoderada de LES LABORATOIRES SERVIER	
		Cesionario	
		1. <i>[Firmado]</i> Mark. A. VARNEY Apoderado de CORTEX PHARMACEUTICALS, INC.	
<i>[Firma y Sello de M^e. François GUILLERMAN, Notario de SÈVRES (Hauts-de-Seine), República Francesa</i>			
Visto para la certificación material de las firmas de los Sres. Alexis CORDI, Gary ROGERS, Rudolf MUELLER, Christine BRUNEL, Mark Varney, ESTAMPADAS EN ESTE DOCUMENTO.			

[El documento lleva adjunta una apostilla y sellos en francés, con la correspondiente traducción].


JORGE I. CASTILLA VIANA
Traductor Oficial
Res. Minjusticia
No. 2789 de Nov. 14 de 1986

SYNAPTIC RESPONSES
ASSIGNMENT OF RIGHTS

Columbia
Corpus 079

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Witnesseth hereby, the Assignment of Rights Agreement entered into by and between **Alexis CORDI, Gary ROGERS, Rudolf MUELLER** domiciled for these purposes respectively in France, USA and USA on the one hand and on the other hand :

- LES LABORATOIRES SERVIER, domiciled for these purposes in France, duly represented by Christine BRUNEL

and

- CORTEX PHARMACEUTICALS, INC. domiciled for these purposes in USA, duly represented by Mark A. Varney

in the following terms and conditions:

PREAMBLE

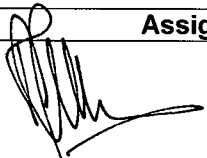
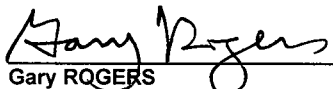
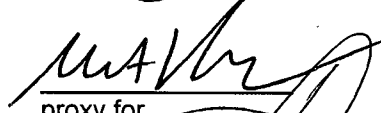
1. Alexis CORDI, Gary ROGERS, Rudolf MUELLER are the authors of the patent
2. Alexis CORDI, Gary ROGERS, Rudolf MUELLER have decided to assign all their rights over the patent referred in the above-mentioned clause.
3. LES LABORATOIRES SERVIER and CORTEX PHARMACEUTICALS, INC. wishes to acquire the rights for the economic exploitation of the design referred to in clause 1).

AGREEMENTS

1. Alexis CORDI, Gary ROGERS, Rudolf MUELLER assign in favor of LES LABORATOIRES SERVIER, and CORTEX PHARMACEUTICALS, INC. without reserve and limitation whatsoever, all their rights over the patent referred to in clause 1) of the Preamble.
2. The assignment is made on gratuitous basis.
3. Both parties agree that ESTRATEGIA JURIDICA can file the application for registration of the patent referred to in clause 1) of the Preamble, before the Superintendencia de Industria y Comercio de Colombia.

Suresnes July 16, 2009

In witness whereof, this document is executed at On, 2009.

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Assignor	Assignee
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	Assignee
	2.  Mark A. Varney proxy for CORTEX PHARMACEUTICAL, INC.

Vu pour la certification

matérielle de

la signature de Alexis CORDI, Gary ROGERS, Rudolf MUELLER

apposée ci-contre Christine BRUNEL, Mark VARNEY



APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1. République française

Le présent acte public

2. a été signé par

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4. est revêtu du sceau/la signature de

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5. à

6. le

7. par le Procureur général près la Cour d'appel de Versailles

8. sous le n°

9. scellé :

10. Signature :



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de l'acte sur le document. Elle ne signifie pas que le contenu du document est
vrai ou que la République française approuve son contenu.

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**COMPUESTO [1,2,3]-BENZOTRIAZINONA SUSTITUIDO EN 3 PARA INCREMENTAR
LAS RESPUESTAS SINÁPTICAS GLUTAMATÉRGICAS**

Campo de la Invención

- 5
- Esta invención se refiere a un compuesto, composiciones farmacéuticas y métodos para utilizarse en la prevención y tratamiento de insuficiencia cerebral, incluyendo incremento del funcionamiento de receptores en las sinapsis en las redes cerebrales responsables de los comportamientos de orden superior. Estas redes cerebrales, que están implicadas en las
- 10 capacidades cognitivas, están relacionadas con el deterioro de la memoria, tal como se observa en el envejecimiento y una variedad de demencias, en desequilibrios de la actividad neuronal entre diferentes regiones cerebrales, como se sugiere en trastornos tales como enfermedad de Parkinson, esquizofrenia, déficit de atención y trastornos afectivos o del humor, y en trastornos en los que está implicada una deficiencia de factores neurotróficos.
- 15 En un aspecto particular, la presente invención se refiere a compuestos útiles para el tratamiento de dichas condiciones, y a métodos para utilizar estos compuestos para dicho tratamiento.

Solicitudes Relacionadas

- 20
- Esta solicitud reivindica el beneficio de prioridad de las solicitudes provisionales U.S. US60/878,503, presentada el 3 de enero, 2007 y US60/921,433, presentada el 2 de abril, 2007, incorporándose partes relevantes de dichas aplicaciones en la presente memoria por referencia.

- 25
- Antecedentes de la Invención**
- La liberación de glutamato en las sinapsis en muchos sitios del cerebro anterior de los mamíferos estimula dos clases de receptores ionotrópicos postsinápticos. Estas clases se
- 30 refieren habitualmente como receptores AMPA/quiscualato y ácido N-metil-D-aspartico (NMDA). Los receptores AMPA/quiscualato median una corriente independiente de voltaje excitadora rápida post-sináptica (excitatory post-synaptic current) (la EPSC rápida), mientras que los receptores NMDA generan una corriente dependiente de voltaje excitadora lenta. Los

estudios realizados en rebanadas de hipocampo o corteza, indican que la EPSC rápida mediada por el receptor AMPA es generalmente el componente dominante por mucho en la mayoría de las sinapsis glutamatérgicas.

- 5 Los receptores AMPA no están distribuidos homogéneamente a lo largo del cerebro sino que están muy restringidos al telencéfalo y el cerebelo. Estos receptores se encuentran en altas concentraciones en las capas superficiales de la neocorteza, en cada una de las zonas sinápticas principales del hipocampo, y en el complejo estriatal, como muestran Monaghan *et al.*, en *Brain Research* **324**:160-164 (1984). Los estudios en animales y seres humanos
- 10 indican que estas estructuras organizan procesos perceptuales-motores complejos y proporcionan los sustratos para los comportamientos de orden superior. Así, los receptores AMPA median la transmisión en aquellas redes cerebrales responsables de multitud de actividades cognitivas.
- 15 Debido las razones expuestas anteriormente, los fármacos que modulan y, por lo tanto, incrementan el funcionamiento de los receptores AMPA podrían tener beneficios significativos para el rendimiento cognitivo e intelectual. Dichos fármacos también deberían facilitar la codificación de la memoria. Los estudios experimentales, tales como los mostrados por Arai y Lynch, *Brain Research* **598**:173-184 (1992), indican que el incremento del tamaño
- 20 de la o las respuestas sinápticas mediadas por el receptor AMPA incrementa la inducción de potenciación a largo plazo (LTP). LTP es un incremento estable de la fuerza de los contactos sinápticos que se producen después de una actividad fisiológica reiterada de un tipo que se sabe que ocurre en el cerebro durante el aprendizaje.
- 25 Los compuestos que incrementan el funcionamiento de la forma AMPA de los receptores de glutamato facilitan la inducción de LTP y la adquisición de tareas aprendidas en roedores y seres humanos como se mide en varios paradigmas. Véanse, por ejemplo, Granger *et al.*, *Synapse* **15**:326-329 (1993); Staubli *et al.*, *PNAS* **91**:777-781 (1994); Arai *et al.*, *Brain Res.* **638**:343-346 (1994); Staubli *et al.*, *PNAS* **91**:11158-11162 (1994); Shors *et al.*, *Neurosci. Let.* **186**:153-156 (1995); Larson *et al.*, *J. Neurosci.* **15**:8023-8030 (1995); Granger *et al.*, *Synapse* **22**:332-337 (1996); Arai *et al.*, *JPET* **278**:627-638 (1996); Lynch *et al.*, *Internat. Clin. Psychopharm.* **11**: 13-19 (1996); Lynch *et al.*, *Exp. Neurology* **145**:89-92 (1997); Ingvar *et*
- 30

al., Exp. Neurology **146**:553-559 (1997); Hampson, et al., *J. Neurosci.* **18**:2748-2763 (1998); Porrino et al., *PLoS Biol* **3**(9):1-14 (2006) y Lynch y Rogers, Patente US 5.747.492. Existe un grupo considerable de datos que muestra que LTP es un sustrato de memoria. Por ejemplo, los compuestos que bloquean LTP interfieren con la formación de la memoria en animales, y determinados fármacos que interrumpen el aprendizaje en los seres humanos antagonizan la estabilización de LTP, como muestran del Cerro y Lynch, *Neuroscience* **49**: 1-6 (1992). El aprendizaje de una tarea simple induce LTP en el hipocampo que obstruye el LTP generado por la estimulación de alta frecuencia (Whitlock *et al.*, *Science* **313**:1093-1097 (2006)) y un mecanismo que mantiene LTP sustenta la memoria espacial (Pastalkova, *et al.*, *Science* **313**:1141-1144 (2006)). En el campo del aprendizaje tiene una importancia significativa el descubrimiento de que los tratamientos *in vivo* con un modulador positivo del receptor de glutamato de tipo AMPA restaura la estabilización de LTP dendrítica basal en animales de mediana edad (Rex, *et al.*, *J. Neurophysiol.* **96**:677-685 (2006)).

La transmisión sináptica excitadora proporciona una vía principal por la que los factores neurotróficos se incrementan en regiones cerebrales específicas. Como tal, se ha encontrado que la potenciación de la función del receptor AMPA por moduladores incrementa los niveles de neurotrofinas, particularmente el factor neurotrófico derivado del cerebro (brain derived neurotrophic factor), o BDNF. Véanse, por ejemplo, Lauterborn, *et al.*, *J. Neurosci.* **20**:8-21 (2000); Gall, *et al.*, Patente U.S. 6.030.968; Lauterborn, *et al.*, *JPET* **307**:297-305 (2003); y Mackowiak, *et al.*, *Neuropharmacology* **43**:1-10 (2002). Otros estudios han asociado los niveles de BDNF con varios trastornos neurológicos, tales como enfermedad de Parkinson, Trastorno de Hiperactividad con Déficit de Atención (ADHD), autismo, Síndrome de X Frágil, y Síndrome de Rett (RTT). Véanse, por ejemplo, O'Neill, *et al.*, *Eur. J. Pharmacol.* **486**:163-174 (2004); Kent, *et al.*, *Mol. Psychiatry* **10**:939-943 (2005); Riikonen, *et al.*, *J. Child Neurol.* **18**:693-697 (2003) y Chang, *et al.*, *Neuron* **49**:341-348 (2006). Así, los potenciadores del receptor AMPA pueden ser útiles para el tratamiento de estas, así como de otras, enfermedades neurológicas que son el resultado de un desequilibrio glutamatérgico o un déficit de factores neurotróficos.

Un prototipo para un compuesto que incrementa la función del receptor AMPA fue descrito por Ito *et al.*, *J. Physiol.* **424**:533-543 (1990). Estos autores encontraron que el fármaco nootrópico aniracetam (N-anisoil-2-pirrolidinona) incrementa las corrientes mediadas por los

receptores AMPA cerebrales expresados en oocitos de *Xenopus* sin afectar las respuestas por el ácido γ -aminobutírico (GABA), ácido kaínico (KA), o los receptores NMDA. También se mostró que la infusión de aniracetam en rebanadas de hipocampo incrementa sustancialmente el tamaño de los potenciales sinápticos rápidos sin alterar las propiedades de

5 reposo de la membrana. Desde entonces se ha confirmado que el aniracetam incrementa las respuestas sinápticas en varios sitios en el hipocampo, y que no tiene efecto en los potenciales mediados por el receptor NMDA (Staubli *et al.*, *Psychobiology* **18**:377-381 (1990) y Xiao *et al.*, *Hippocampus* **1**:373-380 (1991)).

- 10 Se ha encontrado que el aniracetam tiene una liberación y eliminación extremadamente rápidas, y puede aplicarse repetidamente sin efectos duraderos aparentes, lo que son características deseables para fármacos comportamentalmente relevantes. El aniracetam presenta, sin embargo, varias desventajas. La administración periférica de aniracetam probablemente no influya en los receptores cerebrales. El fármaco funciona sólo a altas
- 15 concentraciones (aprox. 1.000 μ M), y aproximadamente 80% del fármaco se convierte en anisoil-GABA después de la administración periférica a los seres humanos (Guenzi y Zanetti, *J. Chromatogr.* **530**:397-406 (1990)). Se ha encontrado que el metabolito anisoil-GABA, tiene menos actividad sináptica que el aniracetam. Además de estas cuestiones, el aniracetam tiene efectos potenciales en una plétora de otras dianas neurotransmisoras y
- 20 enzimáticas en el cerebro, lo que hace dudoso el mecanismo de cualquier efecto terapéutico reivindicado del fármaco. Véanse, por ejemplo, Himori, *et al.*, *Pharmacology Biochemistry and Behavior* **47**:219-225 (1994); Pizzi *et al.*, *J. Neurochem.* **61**:683-689 (1993); Nakamura y Shirane, *Eur. J. Pharmacol.* **380**: 81-89 (1999); Spignoli y Pepeu, *Pharmacol. Biochem. Behav.* **27**:491-495 (1987); Hall y Von Voigtlander, *Neuropharmacology* **26**:1573-
- 25 1579(1987); y Yoshimoto *et al.*, *J. Pharmacobiodyn.* **10**:730-735(1987).

Se ha descrito una clase de compuestos moduladores del receptor AMPA que no muestra la baja potencia y la característica de inestabilidad inherente al aniracetam (Lynch y Rogers, Patente US 5.747.492). Estos compuestos, denominados "Ampakines"[®], pueden ser

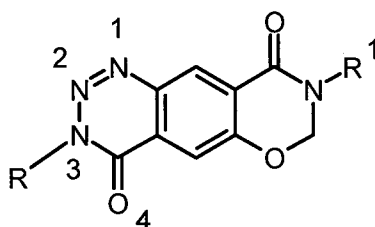
30 benzamidas sustituidas, que incluyen, por ejemplo, 1-(quinoxalina-6-ilcarbonil)piperidina (CX516; Ampalex[®]). Típicamente, son químicamente más estables que el aniracetam y muestran una biodisponibilidad mejorada. CX516 es activo en ensayos de animales

utilizados para detectar fármacos eficientes para el tratamiento de trastornos de la memoria, esquizofrenia, y depresión. En tres ensayos clínicos independientes, CX516 mostró evidencia de eficacia mejorando varias formas de memoria humana (Lynch *et al.*, *Internat. Clin. Psychopharm.* **11**:13-19 (1996); Lynch *et al.*, *Exp. Neurology* **145**:89-92 (1997); Ingvar *et al.*, *Exp. Neurology* **146**:553-559 (1997)).

Se ha descubierto que otra clase de Ampakines, benzoxazinas, tiene una actividad muy alta en modelos *in vitro* e *in vivo* para evaluar la probabilidad de producir un incremento en la cognición (Rogers y Lynch; Patente US # 5.736.543). Las benzoxazinas sustituidas son análogos de benzamida rígidos con diferentes propiedades moduladoras de receptor respecto a la benzamida flexible, CX516.

Se ha encontrado que determinados compuestos benzofurazano y benzotiadiazol sustituidos son significativamente y sorprendentemente más potentes en el modelo animal de esquizofrenia que los compuestos previos, y también son eficaces en el incremento de la cognición. Estos compuestos son estructuralmente similares a los descritos en Lynch y Rogers, Patente US # 5.736.543.

Estructuras descritas previamente que contenían el farmacóforo 1,3-benzoxazina-4-ona se sustituyeron en la parte benceno con heteroátomos, tales como nitrógeno u oxígeno (Patentes US # 5.736.543 y 5.962.447), con grupos alquilo sustituidos (Patentes US # 5.650.409 y 5.783.587), o no sustituidos (WO 99/42456). Otra clase más de compuestos 1,3-benzoxazina contenían un carbonilo externo al anillo oxazina (Patente US # 6.124.278), pero no como un sustituyente en la estructura del anillo de benceno. Ahora, se ha descubierto una nueva clase de compuestos triazinona que muestran una actividad significativa en las respuestas sinápticas del hipocampo y en las corrientes neuronales en células completas mediadas por los receptores AMPA. Los compuestos benzo[1,2,3]triazin-4-ona sustituidos en 3 son moduladores potentes del receptor AMPA que son significativamente más estables metabólicamente que las bis-benzoxazinonas correspondientes.



La actividad biológica de la triazinona fue inesperada y la potencia en el receptor AMPA es sorprendentemente alta; duplicando las triazinonas más potentes de esta clase las corrientes en el receptor AMPA a concentraciones tan bajas como 3 nM. En la presente memoria se describe un compuesto benzo[1,2,3]triazin-4-ona como un modulador del receptor AMPA.

Resumen de la Invención

La presente invención incluye, en un aspecto, un compuesto como se muestra por la estructura I, y se describe en la Sección II de la descripción detallada, que sigue. Se ha encontrado que la administración de compuestos de esta clase incrementa las respuestas sinápticas mediadas por los receptores AMPA. El compuesto de la presente invención es significativamente e inesperadamente más potente que los compuestos descritos previamente incrementando la función del receptor AMPA en cultivos neuronales primarios y en rebanadas de hipocampo de rata, e incrementando el rendimiento cognitivo, tal como rendimiento en una tarea demorada de igualación a la muestra. Esta actividad inesperada se traduce en compuestos farmacéuticos y métodos correspondientes de utilización, incluyendo métodos de tratamiento, que utilizan concentraciones significativamente menores (en un base mol-a-mol) de los compuestos presentes comparado con composiciones de la técnica anterior.

La capacidad del compuesto de la invención para incrementar las respuestas mediadas por el receptor AMPA hace a los compuestos útiles para una variedad de propósitos. Éstos incluyen facilitar el aprendizaje de comportamientos dependientes de los receptores de glutamato, tratar condiciones en las que los receptores AMPA o las sinapsis que utilizan estos receptores están reducidas en número o eficacia, e incrementar la actividad sináptica excitadora con el fin de restaurar un desequilibrio entre las subregiones cerebrales o incrementar los niveles de factores neurotróficos.

En otro aspecto, la invención incluye un método para el tratamiento de un sujeto mamífero que padece una condición hipoglutamatérgica, o una deficiencia en el número o fuerza de sinapsis excitadoras, o en el número de receptores AMPA, de manera que la memoria u otras funciones cognitivas están deterioradas. Dichas condiciones también pueden causar un

5 desequilibrio cortical/estriatal, dando lugar a esquizofrenia o comportamiento esquizofreniforme. Según el método, dicho sujeto se trata con una cantidad eficaz de un compuesto como se muestra por la estructura I, y se describe en la Sección II de la descripción detallada, siguiente, en un vehículo farmacéuticamente aceptable.

- 10 Éstos y otros objetivos y características de la invención serán mucho más evidentes cuando se lea la descripción detallada siguiente de la invención conjuntamente con los dibujos adjuntos.

Descripción Detallada de la Invención

15 I. Definiciones

Los términos siguientes tienen las definiciones siguientes a no ser que se indique otra cosa. Otros términos que se utilizan para describir la presente invención tienen las mismas definiciones que aquellos términos utilizados generalmente por los expertos en la técnica.

- 20 El término "alquilo" se utiliza en la presente memoria para referirse a un radical monovalente completamente saturado que contiene carbono e hidrógeno, y que puede ser una cadena lineal, ramificada o cíclica. Los ejemplos de grupos alquilo son metilo, etilo, n-butilo, n-heptilo, isopropilo, 2-metilpropilo, ciclopropilo, ciclopropilmetilo, ciclobutilo, ciclopentilo,
- 25 ciclopentiletilo y ciclohexilo.

- El término "alquenilo" se utiliza en la presente memoria para referirse a un radical monovalente que contiene carbono e hidrógeno que contiene uno o más sitios de insaturación, y que puede ser una cadena lineal, ramificada o cíclica. Los ejemplos de grupos
- 30 alquilo son etenilo, n-butenilo, n-heptenilo, isopropenilo, ciclopentenilo, ciclopenteniletilo y ciclohexenilo.

El término "alquilo sustituido" se refiere a alquilo como se acaba de describir que incluye uno o más grupos funcionales tales como alquilo inferior que contiene 1-6 átomos de carbono, arilo, arilo sustituido, acilo, halógeno (es decir, alquil halos, p. ej., CF_3), hidroxilo, alcoxi, alcoxialquilo, amino, alquil y dialquil amino, acilamino, aciloxi, ariloxi, ariloxialquilo, carboxialquilo, carboxamido, tio, tioéteres, hidrocarburos cíclicos tanto saturados como insaturados, heterociclos y semejantes.

El término "arilo" se refiere a un radical aromático monovalente sustituido o no sustituido que tiene un único anillo (p. ej., fenilo) o múltiples anillos condensados (p. ej., naftilo). Otros ejemplos incluyen grupos de anillo aromático heterocíclico que tienen uno o más átomos de nitrógeno, oxígeno, o azufre en el anillo, tal como oxazolilo, isoxazolilo, pirazolilo, tiazolilo, tiadiazolilo, tetrazolilo, piridacinilo, pirimidilo, benzofurilo, benzotienilo, bencimidazolilo, benzoxazolilo, benzotiazolilo, quinolilo, isoquinolilo, imidazolilo, furilo, pirrolilo, piridilo, tienilo e indolilo.

El término "sustituido" tal y como se utiliza en el término "arilo sustituido, aromático sustituido, heteroarilo sustituido, o heteroaromático sustituido" en la presente memoria significa que pueden estar presentes uno o más sustituyentes, seleccionándose dichos sustituyentes de átomos y grupos, que cuando están presentes no evitan que el compuesto funcione como un potenciador de la función del receptor AMPA. Los ejemplos de sustituyentes que pueden estar presentes en un grupo aromático o heteroaromático sustituido incluyen, pero no están limitados a, grupos tales como alquilo ($\text{C}_1\text{-C}_7$), acilo ($\text{C}_1\text{-C}_7$), arilo, heteroarilo, arilo y heteroarilo sustituido, halógeno, ciano, nitro, alquilhalos ($\text{C}_1\text{-C}_7$) (p. ej., CF_3), hidroxilo, alcoxi ($\text{C}_1\text{-C}_7$), alcoxialquilo, amino, alquil y dialquil amino, acilamino, aciloxi, ariloxi, ariloxialquilo, carboxialquilo, carboxamido, tio, tioéteres, hidrocarburos cíclicos ($\text{C}_3\text{-C}_8$) tanto saturados como insaturados, heterociclos ($\text{C}_3\text{-C}_8$) y semejantes.

"Heterociclo" o "heterocíclico" se refiere a un anillo carbocíclico en el que uno o más átomos de carbono ha sido reemplazados por uno o más heteroátomos tales como nitrógeno, oxígeno o azufre. Los ejemplos de heterociclos incluyen, pero no están limitados a, piperidina, pirrolidina, morfolina, tiomorfolina, piperacina, tetrahidrofurano, tetrahidropirano, 2-pirrolidinona, δ -velerolactama, δ -velerolactona y 2-ketopiperacina.

El término "heterociclo sustituido" se refiere a un heterociclo como se acaba de describir que contiene uno o más grupos funcionales tales como alquilo inferior, acilo, arilo, ciano, halógeno, hidroxilo, alcoxi, alcoxialquilo, amino, alquil y dialquil amino, acilamino, aciloxi, ariloxi, ariloxialquilo, carboxialquilo, carboxamido, tio, tioéteres, hidrocarburos cíclicos tanto saturados como insaturados, heterociclos y semejantes.

El término "compuesto" se utiliza en la presente memoria para referirse a cualquier compuesto químico específico descrito en la presente memoria. En su utilización en contexto, el término se refiere generalmente a un único compuesto, pero en determinados casos también puede referirse a estereoisómeros y/o isómeros ópticos (incluyendo mezclas racémicas) de los compuestos descritos.

El término "cantidad eficaz" se refiere a la cantidad de un compuesto seleccionado de fórmula I que se utiliza para incrementar la respuesta sináptica glutamatérgica mediante el incremento de la actividad del receptor AMPA. La cantidad precisa utilizada variará dependiendo del compuesto particular seleccionado y su utilización pretendida, la edad y el peso del sujeto, ruta de administración, y así sucesivamente, pero puede determinarse fácilmente por experimentación rutinaria. En el caso del tratamiento de una condición o estado patológico, una cantidad eficaz es aquella cantidad que se utiliza para tratar eficazmente la condición o estado patológico particular.

El término "vehículo farmacéuticamente aceptable" se refiere a un vehículo o excipiente que no es inaceptablemente tóxico para el sujeto al que se administra. Los excipientes farmacéuticamente aceptables están descritos extensamente en E.W. Martin, en "Remington's Pharmaceutical Sciences."

Una "sal farmacéuticamente aceptable" de un compuesto amina, tales como los contemplados en la actual invención, es una sal amonio que tiene como contraión un anión inorgánico tal como cloruro, bromuro, yoduro, sulfato, sulfito, nitrato, nitrito, fosfato, y semejantes, o un anión orgánico tal como acetato, malonato, piruvato, propionato, fumarato, cinamato, tosilato, y semejantes.

El término “paciente” o “sujeto” se utiliza a lo largo de la especificación para describir un animal, generalmente un animal mamífero, incluyendo un ser humano, al que se proporciona tratamiento o utilización con los compuestos o composiciones según la presente invención.

- 5 Para tratamiento o utilización con/o de aquellas condiciones o estados patológicos que son específicos para un animal específico (especialmente, por ejemplo, un sujeto o paciente humano), el término paciente o sujeto se refiere a ese animal particular.

- 10 El término “problemas motores sensoriales” se utiliza para describir un problema que surge en un paciente o sujeto a partir de la incapacidad para integrar información externa derivada de los cinco sentidos conocidos de manera que se dirigen las respuestas físicas apropiadas que implican movimiento y acción.

- 15 El término “tarea cognitiva” o “función cognitiva” se utiliza para describir un esfuerzo o proceso por un paciente o sujeto que implica pensamiento o conocimiento. Las diversas funciones de las cortezas de asociación de los lóbulos parietal, temporal y frontal, que representan aproximadamente 75% de todo el tejido cerebral humano, son responsables de la mayor parte del procesamiento de la información que se produce entre la entrada sensorial y la respuesta motora. Las diversas funciones de las cortezas de asociación se refieren
20 frecuentemente como cognición, que significa literalmente el proceso por el que llegamos a conocer lo que nos rodea. La atención selectiva a un estímulo particular, el reconocimiento e identificación de estas características relevantes del estímulo y planear y experimentar la respuesta son algunos de los procesos o capacidades mediados por el cerebro humano que están relacionados con la cognición.

- 25 El término “red cerebral” se utiliza para describir diferentes regiones anatómicas del cerebro que se comunican entre sí a través de la actividad sináptica de las células neuronales.

- 30 El término “receptor AMPA” se refiere a un agregado de proteínas encontrado en algunas membranas, que permite a los iones positivos cruzar la membrana en respuesta a la unión del glutamato o AMPA (ácido DL- α -amino-3-hidroxi-5-metil-4-isoxazolpropiónico), pero no NMDA.

El término “sinapsis excitadora” se utiliza para describir una unión célula-célula en la que la liberación de un mensajero químico por una célula causa la despolarización de la membrana externa de la otra célula. Una sinapsis excitadora describe una neurona postsináptica que tiene un potencial de inversión que es más positivo que el potencial umbral y consecuentemente, en dicha sinapsis, un neurotransmisor incrementa la probabilidad de que resulte un potencial post sináptico excitador (una neurona se disparará produciendo un potencial de acción). Los potenciales de inversión y los potenciales umbral determinan la excitación e inhibición postsinápticas. Si el potencial de inversión para un potencial post sináptico (“PSP”) es más positivo que el umbral del potencial de acción, el efecto de un transmisor es excitador y produce un potencial post sináptico excitador (“EPSP”) y el disparo de un potencial de acción por la neurona. Si el potencial de inversión para un potencial post sináptico es más negativo que el umbral del potencial de acción, el transmisor es inhibitorio y puede generar potenciales post sinápticos inhibitorios (IPSP), reduciendo así la probabilidad de que una sinapsis dispare un potencial de acción. La regla general para la acción postsináptica es: si el potencial de inversión es más positivo que el umbral, resulta una excitación; la inhibición ocurre si el potencial de inversión es más negativo que el umbral. Véase, por ejemplo, Capítulo 7, NEUROSCIENCE, editado por Dale Purves, Sinauer Associates, Inc., Sunderland, MA 1997.

El término “tarea motora” se utiliza para describir un esfuerzo efectuado por un paciente o sujeto que implica movimiento o acción.

El término “tarea perceptual” se utiliza para describir un acto por un paciente o sujeto de prestar atención a entradas sensoriales.

El término “respuesta sináptica” se utiliza para describir reacciones biofísicas en una célula como consecuencia de la liberación de mensajeros químicos por otra célula con la que está en contacto estrecho.

El término “condición hipoglutamatérgica” se utiliza para describir un estado o condición en la que la transmisión mediada por el glutamato (o aminoácidos excitadores relacionados) está

reducida por debajo de los niveles normales. La transmisión consiste en la liberación de glutamato, unión a los receptores post sinápticos, y apertura de los canales integrales a esos receptores. El punto final de la condición hipoglutamatérgica es una corriente post sináptica excitadora reducida. Puede surgir a partir de cualquiera de las tres fases de transmisión

5 indicadas anteriormente. Las condiciones o estados patológicos que se consideran condiciones hipoglutamatérgicas y que pueden tratarse utilizando los compuestos, composiciones y métodos según la presente invención incluyen, por ejemplo, pérdida de memoria, demencia, depresión, trastornos de la atención, disfunción sexual, trastornos del movimiento, incluyendo enfermedad de Parkinson, esquizofrenia o comportamiento
10 esquizofreniforme, trastornos de la memoria y del aprendizaje, incluyendo aquellos trastornos que resultan del envejecimiento, trauma, ictus y trastornos neurodegenerativos, tales como aquellos asociados con los estados inducidos por drogas, agentes neurotóxicos, enfermedad de Alzheimer, y envejecimiento. Estas condiciones son reconocidas y diagnosticadas fácilmente por los expertos en la técnica.

15 El término “desequilibrio cortico-estriatal” se utiliza para describir un estado en el que el equilibrio de las actividades neuronales en la corteza y el complejo estriatal subyacente interconectado se aleja del que se encuentra normalmente. La 'actividad' puede evaluarse por registro eléctrico o técnicas de biología molecular. El desequilibrio puede establecerse
20 aplicando estas medidas a las dos estructuras o por criterios funcionales (comportamental o fisiológico).

El término “trastorno afectivo” o “trastorno del humor” describe la condición en la que la tristeza o alegría es demasiado intensa y continúa más allá del impacto esperado de un evento
25 vital estresante, o surge endógenamente. Tal y como se utiliza en la presente memoria, el término “trastorno afectivo” engloba todos los tipos de trastornos del humor como se describe, por ejemplo, en *Diagnostic and Statistical Manual of Mental Disorders*, Cuarta Edición (DSM IV), páginas 317-391.

30 El término “esquizofrenia” se utiliza para describir una condición que es un tipo común de psicosis, caracterizada por un trastorno en los procesos de pensamiento, tales como ilusiones y alucinaciones, y renuncia extensa del interés del individuo por otra gente y el mundo exterior, y la inversión de éste por él o ella solo. La esquizofrenia se considera ahora un grupo

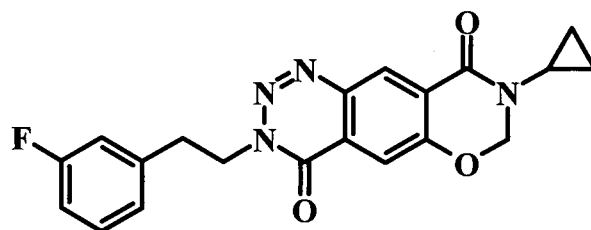
de trastornos mentales en lugar de una entidad única, y se hace una distinción entre esquizofrenias reactivas y en proceso. Tal y como se utiliza en la presente memoria, el término esquizofrenia o “esquizofreniforme” engloba todos los tipos de esquizofrenia, incluyendo esquizofrenia ambulatoria, esquizofrenia catatónica, esquizofrenia hebefrénica, esquizofrenia latente, esquizofrenia en proceso, esquizofrenia pseudoneurótica, esquizofrenia reactiva, esquizofrenia simple, y trastornos psicóticos relacionados que son similares a la esquizofrenia, pero que no se diagnostican necesariamente como esquizofrenia *per se*. La esquizofrenia y otros trastornos psicóticos pueden diagnosticarse utilizando las directrices establecidas, por ejemplo, en *Diagnostic and Statistical Manual of Mental Disorders*, Cuarta Edición (DSM IV) Secciones 293.81, 293.82, 295.10, 295.20, 295.30, 295.40, 295.60, 295.70, 295.90, 297.1, 297.3, 298.8.

El término “función cerebral” se utiliza para describir las tareas combinadas de percibir, integrar, filtrar y responder a estímulos externos y procesos motivacionales internos.

El término “deteriorado” se utiliza para describir una función que trabaja a un nivel que es menor del normal. Las funciones deterioradas pueden estar significativamente afectadas de manera que una función apenas se realiza, es virtualmente inexistente o trabaja de una manera que es significativamente menor de la normal. Las funciones deterioradas también pueden ser sub-óptimas. El deterioro de la función variará su gravedad de un paciente a otro y la condición que se va a tratar.

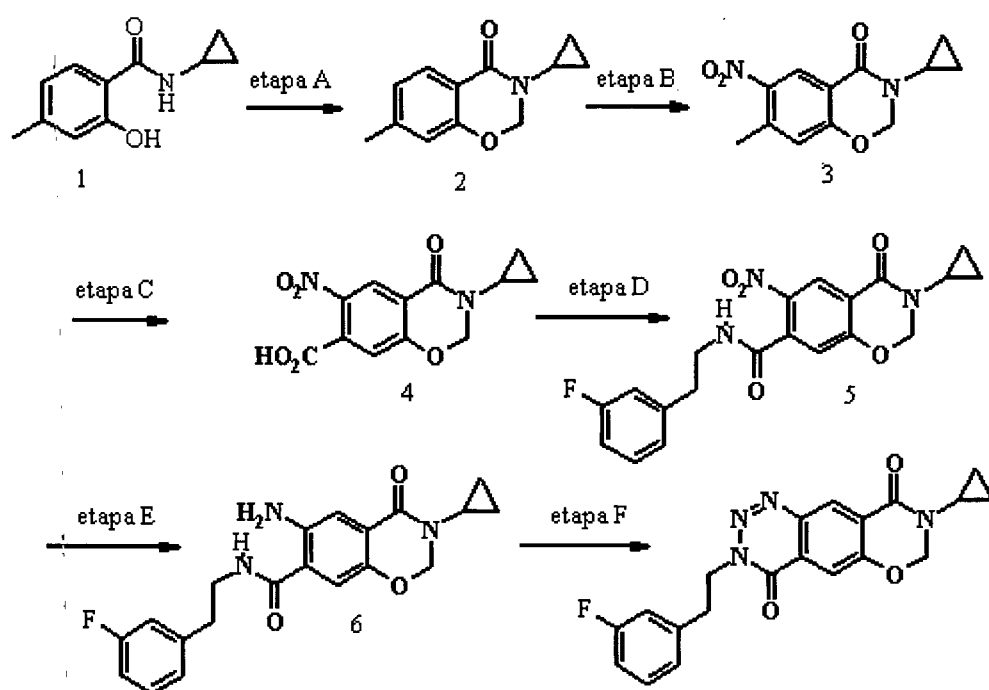
II. Compuestos que Incrementan la Función del Receptor AMPA

La presente invención está dirigida, en un aspecto, a un compuesto que tiene la propiedad de incrementar la función del receptor AMPA. El compuesto especificado de esta invención que tiene la estructura I, siguiente:



I

La síntesis del compuesto de la invención, 8-ciclopropil-3-[2-(3-fluorofenil)etil]-7,8-dihidro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazina-4,9-diona, se realiza preferiblemente por el esquema sintético siguiente, en el que la síntesis de la salicilamida sustituida es muy conocida en el campo de la síntesis orgánica:



ESQUEMA 1

En el Esquema 1, la etapa A puede realizarse bajo condiciones estándar, entre ellas la inserción catalizada por un ácido de un síntón formaldehído. Por ejemplo, la salicilamida (1) se disuelve y calienta en un disolvente orgánico adecuado junto con trioxano y ácido sulfúrico

- o ácido clorhídrico. La etapa B es una reacción de nitración que puede realizarse bajo condiciones suaves conocidas por los expertos en la síntesis orgánica y detalladas en sendos volúmenes en Reagents for Organic Synthesis (Fieser y Fieser) y Organic Syntheses (véase el sitio web en <http://www.orgsyn.org/>). La etapa C implica la oxidación en 2 etapas del grupo metilo del compuesto 3 a un ácido carboxílico a través de un intermedio aldehído empleando *N,N*-dimetilformamida dimetil acetal y peryodato de sodio seguido de oxona. La etapa D implica el acoplamiento de una amina primaria al ácido nitro, que puede conseguirse utilizando una variedad de reactivos de acoplamiento conocidos por un químico experto. Algunos ejemplos no limitativos utilizados comúnmente son cloruro de tionilo, cloruro de oxalilo o carbonil diimidazol. La etapa E es una reducción de un aril nitro a una anilina y puede efectuarse por reducción utilizando una variedad de catalizadores incluyendo, pero sin limitarse a, Pd o Pt o Ni de Raney e hidrógeno o Zn/Cu. La etapa F forma el anillo triazinona y puede realizarse por la adición de nitrito de isoamilo en DMF.
- 15 Todas las composiciones descritas en la presente solicitud pueden sintetizarse por los métodos descritos anteriormente utilizando etapas sintéticas análogas a las presentadas específicamente en los ejemplos descritos en la presente memoria así como las conocidas en la técnica. También se reivindican todas las sales de adición con un ácido o base farmacéuticamente aceptable de éstas.

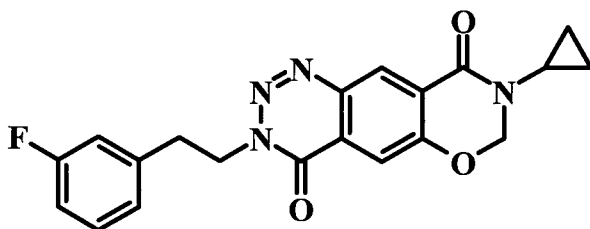
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III. Método de Tratamiento

- Según un aspecto de la invención, se proporciona un método para tratar un sujeto mamífero que padece una condición hipoglutamatergica, o deficiencias en el número o fuerza de sinapsis excitadoras o en el número de receptores AMPA. En dicho sujeto, la memoria u otras funciones cognitivas pueden estar deterioradas o puede ocurrir un desequilibrio cortical/estriatal, dando lugar a la pérdida de memoria, demencia, depresión, trastornos de la atención, disfunción sexual, trastornos del movimiento, esquizofrenia o comportamiento esquizofreniforme. Los trastornos de la memoria y los trastornos del aprendizaje, que son tratables según la presente invención incluyen aquellos trastornos que resultan del envejecimiento, trauma, ictus y trastornos neurodegenerativos. Los ejemplos de trastornos

neurodegenerativos incluyen, pero no están limitados a, aquellos asociados con estados inducidos por drogas, agentes neurotóxicos, enfermedad de Alzheimer, y envejecimiento. Estas condiciones son reconocidas y diagnosticadas fácilmente por los expertos en la técnica y tratadas por la administración al paciente de una cantidad eficaz de uno o más compuestos según la presente invención.

En la presente invención, el método de tratamiento comprende administrar al sujeto que necesita el tratamiento, en un vehículo farmacéuticamente aceptable, una cantidad eficaz de 8-ciclopropil-3-[2-(3-fluorofenil)etil]-7,8-dihidro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazina-4,9-diona que tiene la fórmula:



o una sal de adición farmacéuticamente aceptable de un ácido o base de ésta.

Como se ha indicado anteriormente, el tratamiento de un sujeto según el método de la invención es útil para incrementar la actividad del receptor AMPA, y así puede utilizarse para facilitar el aprendizaje de comportamientos dependientes de los receptores AMPA, y para tratar condiciones, tales como deterioro de la memoria, en la que los receptores AMPA, o las sinapsis que utilizan estos receptores, están reducidos en número o eficacia. El método también es útil para incrementar la actividad sináptica excitadora con el fin de restaurar un desequilibrio entre las sub-regiones cerebrales, que puede manifestarse en sí mismo en esquizofrenia o comportamiento esquizofreniforme, u otro comportamiento como se ha descrito anteriormente. Se ha encontrado que los compuestos administrados según el método son más eficaces que los compuestos descritos previamente incrementando la actividad del receptor AMPA, como se muestra en los ensayos *in vitro* e *in vivo* descritos a continuación.

IV. Actividad Biológica: Incremento de la Función del Receptor AMPA

Las respuestas sinápticas mediadas por los receptores AMPA se incrementan según el método de la invención, utilizando el compuesto descrito en la presente memoria. Se

5 demuestra que el compuesto es sustancialmente más potente que los compuestos descritos previamente incrementando las corrientes en células completas mediadas por AMPA en neuronas cultivadas. El ensayo *in vitro* se describe como sigue.

Se prepararon células corticales a partir de ratas Sprague-Dawley embrionarias de 18-19 días y se registró después de 3 días en cultivo. La disolución extracelular (ECS) contenía (en
10 mM): NaCl (145), KCl (5,4), HEPES (10), MgCl₂ (0,8), CaCl₂ (1,8), glucosa (10), sacarosa (30); pH. 7,4. Con el fin de bloquear las corrientes de sodio dependientes de voltaje, se añadió 40 nM TTX a la disolución de registro. La disolución intracelular contenía (en mM): K-gluconato (140), HEPES (20), EGTA (1,1), fosfocreatina (5), MgATP (3), GTP (0,3), MgCl₂ (5), y CaCl₂ (0,1); pH: 7,2. Todas las disoluciones del compuesto de ensayo y de
15 glutamato se hicieron en la disolución extracelular.

La corriente en células completas se midió con amplificador de pinzamiento zonal (Axopatch 200B), se filtró a 2 kHz, se digitalizó a 5 kHz y se registró en un PC con pClamp 8. Las células se pinzaron por voltaje a - 80 mV. Se aplicaron las disoluciones por un sistema
20 DAD-12. Se registró una respuesta basal para cada célula utilizando un pulso de 1 s de 500 µM de glutamato disuelto en ECS. Se determinaron las respuestas al compuesto de ensayo por aplicación de un pulso de 10 s del compuesto de ensayo seguido de un pulso de 1 s de la misma concentración del compuesto de ensayo más 500 µM glutamato y 10 s de salino. Esta secuencia de pulsos se repitió hasta que se obtuvo una lectura estable, o hasta que se
25 midieron suficientes puntos de datos para permitir la extrapolación a un cambio máximo calculado.

El valor medio de la corriente plató entre 600 ms y 900 ms después de la aplicación de glutamato o compuesto de ensayo más glutamato se calculó y se utilizó como el parámetro
30 para medir el efecto del fármaco. Las respuestas plató en presencia de concentraciones variables del compuesto de ensayo se dividieron por la respuesta basal con el fin de calcular el porcentaje del incremento. Los compuestos se consideran activos en este ensayo si, a una

concentración de ensayo de 3 μ M o menos, producen un incremento mayor de 100% en el valor de la corriente estacionaria medido debido a la aplicación de glutamato solo. La concentración a la que la corriente inducida por glutamato se incrementa un 100% se refiere comúnmente como el valor CE2x.

5

El compuesto de esta invención, 8-ciclopropil-3-[2-(3-fluorofenil)etil]-7,8-dihidro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazina-4,9-diona mostró un valor CE2x de 0,1 μ M.

V. Administración, Dosificaciones, y Formulación

10

Como se ha indicado anteriormente, el compuesto y método de la invención incrementan las respuestas mediadas por el receptor AMPA, y son útiles para el tratamiento de condiciones hipoglutamatérgicas. El compuesto también es útil para el tratamiento de condiciones tales como deterioro de la memoria u otras funciones cognitivas, causado por una deficiencia en el número o fuerza de las sinapsis excitadoras, o en el número de receptores AMPA. El compuesto también puede utilizarse en el tratamiento de la esquizofrenia o comportamiento esquizofreniforme que resulta de un desequilibrio cortical/estriatal, y en la facilitación del aprendizaje de comportamientos dependientes de los receptores AMPA.

15

En los sujetos tratados con el presente compuesto, composiciones farmacéuticas y métodos la memoria u otras funciones cognitivas pueden estar deterioradas, o puede ocurrir un desequilibrio cortical/estriatal, dando lugar a la pérdida de memoria, demencia, depresión, trastornos de la atención, disfunción sexual, trastornos del movimiento, esquizofrenia o comportamiento esquizofreniforme. Los trastornos de la memoria y los trastornos del aprendizaje, que son tratables según la presente invención, incluyen aquellos trastornos que resultan del envejecimiento, trauma, ictus y trastornos neurodegenerativos. Los ejemplos de trastornos neurodegenerativos incluyen, pero no están limitados a, aquellos asociados con estados inducidos por drogas, agentes neurotóxicos, enfermedad de Alzheimer, y envejecimiento. Estas condiciones son reconocidas y diagnosticadas fácilmente por los expertos en la técnica y tratadas por la administración al paciente de una cantidad eficaz de uno o más compuestos según la presente invención.

25

30

Generalmente, las dosificaciones y rutas de administración del compuesto se determinarán según el tamaño y condición del sujeto, según prácticas farmacéuticas estándar. Los niveles de dosis empleados pueden variar ampliamente, y pueden ser determinados fácilmente por los expertos en la técnica. Típicamente, se emplean cantidades en cantidades de miligramo hasta gramo. La composición puede administrarse a un sujeto por varias rutas, p. ej. oralmente, transdérmicamente, perineuralmente o parenteralmente, esto es, por inyección intravenosa, subcutánea, intraperitoneal, o intramuscular, entre otras, incluyendo administración bucal, rectal y transdérmica. Los sujetos contemplados para el tratamiento según el método de la invención incluyen seres humanos, animales de compañía, animales de laboratorio, y semejantes.

Las formulaciones que contienen el compuesto según la presente invención pueden tomar la forma de sólido, semi-sólido, polvo liofilizado, o formas de dosificación líquidas, tales como, por ejemplo, comprimidos, cápsulas, polvos, formulaciones de liberación sostenida, disoluciones, suspensiones, emulsiones, supositorios, cremas, pomadas, lociones, aerosoles, parches o semejantes, preferiblemente en formas de dosificación unitaria para la administración simple de dosificaciones precisas.

Las composiciones farmacéuticas según la presente invención incluyen típicamente un vehículo o excipiente farmacéutico convencional y pueden incluir adicionalmente otros agentes medicinales, vehículos, adyuvantes, aditivos y semejantes. Preferiblemente, la composición será aproximadamente 0,5 a 75% en peso de un compuesto o compuestos de la invención, con el resto que consiste esencialmente en excipientes farmacéuticos adecuados. Para la administración oral, dichos excipientes incluyen grados farmacéuticos de manitol, lactosa, almidón, estearato de magnesio, sacarina sódica, talco, celulosa, glucosa, gelatina, sacarosa, carbonato de magnesio, y semejantes. Si se desea, la composición también puede contener cantidades pequeñas de sustancias auxiliares no tóxicas tales como agentes humectantes, agentes emulsionantes, o tampones.

Las composiciones líquidas pueden prepararse disolviendo o dispersando los compuestos (aproximadamente 0,5% a aproximadamente 20% en peso o más), y adyuvantes farmacéuticos opcionales, en un vehículo, tal como, por ejemplo, disolución salina acuosa,

dextrosa acuosa, glicerol, o etanol, para formar una disolución o suspensión. Para la utilización en una preparación líquida oral, la composición puede prepararse como una disolución, suspensión, emulsión, o jarabe, suministrándose bien en forma líquida o una forma seca adecuada para hidratación en agua o en disolución salina normal.

5

Cuando la composición se emplea en la forma de preparaciones sólidas para administración oral, las preparaciones pueden ser comprimidos, gránulos, polvos, cápsulas o semejantes. En una formulación en comprimidos, la composición se formula típicamente con aditivos, p. ej. un excipiente tal como una preparación de sacárido o celulosa, un aglutinante tal como una pasta de almidón o metil celulosa, un material de relleno, un disgregante, u otros aditivos utilizados típicamente en la fabricación de preparaciones médicas.

10

Una composición inyectable para administración parenteral contendrá típicamente el compuesto en una disolución i.v. adecuada, tal como disolución salina fisiológica estéril. La composición también puede formularse como una suspensión en un lípido o fosfolípido, en una suspensión liposomal, o en una emulsión acuosa.

15

Los métodos para preparar dichas formas de dosificación son conocidos o serán evidentes para los expertos en la técnica; por ejemplo, véase Remington's Pharmaceutical Sciences (17a Ed., Mack Pub. Co., 1985). La composición que se va a administrar contendrá una cantidad del compuesto seleccionado en una cantidad farmacéuticamente eficaz para efectuar el incremento de las corrientes del receptor AMPA en un sujeto.

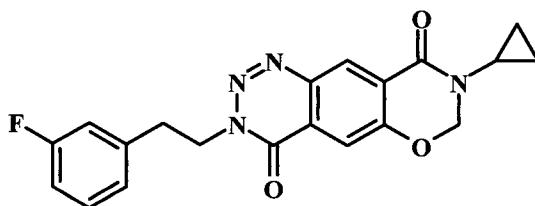
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Los ejemplos siguientes ilustran pero no se pretende de ninguna forma que limiten la invención. A no ser que se indique otra cosa, todas las temperaturas se proporcionan en grados Celsius. A no ser que se indique otra cosa, todos los espectros de RMN son espectros ^1H RMN y se han obtenido en deuterocloroformo o DMSO deuterado como disolvente utilizando tetrametilsilano como estándar interno. El nombre del compuesto del ejemplo sigue la nomenclatura IUPAC según proporciona el programa informático ChemSketch de ACD Labs.

25

30

Ejemplo 1

8-Ciclopropil-3-[2-(3-fluorofenil)etil]-7,8-dihidro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazina-4,9-diona

5

Se disolvió ácido 4-Metilsalicílico (21,3 g, 140 mmoles) en cloruro de metileno (120 mL) seguido de CDI (22,7 g, 140 mmoles) en partes. La mezcla se agitó a temperatura ambiente durante 24 hr, y se calentó brevemente hasta la ebullición. Se añadió una disolución de ciclopropilamina (8,0 g, 140 mmoles) en trietilamina (5 mL, 36 mmoles) a la mezcla, que se agitó durante 3 días. Se añadió agua (200 mL) y el pH se ajustó a 2 utilizando ácido clorhídrico 12 M. Las fases se separaron y la fase acuosa se extrajo con cloroformo (200 mL). Las fases orgánicas combinadas se lavaron con disolución de bicarbonato de sodio (100 mL) y se secaron sobre sulfato de sodio. La concentración proporcionó 22,7 g de amida como un sólido blanquecino.

15 La amida (22,7 g, 119 mmoles) y trioxano (36 g, 0,4 moles) se disolvieron en cloroformo (250 mL), que se agitó a temperatura ambiente. Se añadieron sulfato de sodio (32 g) y ácido sulfúrico concentrado (80 gotas) y la mezcla se puso a reflujo durante 30 min, después de lo cual se añadieron 40 gotas adicionales de ácido sulfúrico concentrado. Después de 90 min, los sólidos se recogieron por filtración y se lavaron con acetato de etilo. Los disolventes combinados se eliminaron en vacío para proporcionar 30 g de aceite. El aceite se purificó utilizando cromatografía flash (250 g de gel de sílice, acetato de etilo:hexano 30:70, y 40:60) para proporcionar 20,1 g de 7-metilbenzoxazinona como un aceite incoloro.

20 La benzoxazinona (16 g, 79 mmoles) se disolvió en cloruro de metileno (200 mL) al que se añadió ácido acético (30 mL). La mezcla se enfrió hasta ~0 °C utilizando un baño de hielo y se añadió ácido nítrico (14 mL, 90%) gota a gota durante 15 min, lo que produjo una disolución naranja. La mezcla de reacción se agitó durante 90 min y se vertió sobre hielo picado/agua (300 mL). Se añadió lentamente una disolución de hidróxido de sodio hasta que el pH alcanzó 5. La mezcla de reacción se extrajo con cloroformo (200 mL), se secó sobre

sulfato de sodio y se concentró en vacío hasta ~40 mL. Se añadió acetato de etilo (200 mL) y la mezcla se concentró en vacío hasta ~ 60 mL. Los cristales formados se recogieron por filtración para proporcionar 8,1 g (33 mmoles, rendimiento=41%) del isómero 6-nitro deseado como un sólido blanquecino. El licor madre se concentró y cristalizó más producto (1,2 g) como un sólido blanquecino. Posteriormente, se aislaron otros 5 g de isómeros mezclados a partir del licor madre, esta mezcla se utilizó en la etapa siguiente.

Los isómeros sólidos mezclados de la etapa anterior (5 g, 20 mmoles) se suspendieron en N,N-dimetilformamida dimetil acetal (30 mL) y DMF (10 mL) y se calentaron hasta 125 °C durante 16 hr. El disolvente se eliminó en vacío para rendir un resto marrón oscuro. El resto se disolvió en THF (100 mL). Se disolvió peryodato de sodio (11 g, 51 mmoles) en agua (100 mL) y se añadió a la mezcla de reacción, que se agitó durante 15 min a temperatura ambiente. La suspensión de sólidos beige se extrajo con cloroformo (200 mL), que se secó sobre sulfato de sodio y se diluyó con acetato de etilo (200 mL). Se dejó que los disolventes se evaporaran lentamente, lo que resultó en la cristalización del isómero deseado (2,0g, 7,6 mmoles) como un sólido blanquecino).

El intermedio nitro aldehído (524 mg, 2,0 mmoles) se disolvió en DMF (10 mL) a 40 °C. Después de que la disolución se hubo enfriado hasta la ambiente, se añadió oxona (1,47 g, 2,4 mmoles) y la mezcla se agitó toda la noche. La adición de agua (25 mL) y acetato de etilo (30 mL) produjo dos fases, que se separaron y la fase orgánica se filtró y se lavó con agua. La fase acuosa se extrajo con acetato de etilo y las fases orgánicas combinadas se lavaron dos veces con agua, se secaron sobre sulfato de magnesio y se concentraron en vacío para proporcionar un resto amarillo húmedo (0,54 g, 1,9 mmoles), que se utilizó sin más purificación.

Una disolución del intermedio ácido nitro (0,54 g, 1,9 mmoles) en cloruro de metileno se combinó con cloruro de tionilo (1,4 mL, 20 mmoles) junto con unas pocas gotas de DMF agitada a temperatura ambiente toda la noche. La mezcla se concentró en vacío y se redisolvió en cloruro de metileno (10 mL). Se disolvieron 3-fluorofenetilamina (0,56 mL, 4,3 mmoles) y trietilamina (1,1 mL, 7,9 mmoles) en cloruro de metileno (15 mL) al que se añadió la disolución recién preparada del cloruro de ácido. Después de agitarla durante 2 hr, la disolución se lavó con HCl acuoso (1 M) y bicarbonato de sodio saturado y se secó sobre

sulfato de magnesio. La disolución del producto se concentró en vacío para proporcionar un sólido amarillo, que se trituró en acetato de etilo para proporcionar cristales beige claros (0,53 g, 1,3 mmoles).

El sólido beige de la etapa anterior (0,53 g, 1,3 mmoles) se disolvió en una mezcla de THF (20 mL) y metanol (20 mL) y se añadió al reactivo Zn/Cu recién preparado (10 g, véase más adelante). Se añadió ácido fórmico (10 gotas) y la mezcla se agitó a temperatura ambiente toda la noche, después de lo cual una TLC mostró la finalización de la reacción. Después de la adición de DMF (2 mL), la mezcla se agitó durante 10 min, y se filtró a través de gel de sílice (2 cm). La sílice se lavó con THF/metanol (1:1) y el filtrado combinado y el lavado se concentró en vacío. Se añadió cloroformo y se evaporó para eliminar cualquier agua residual. Se añadieron DMF (2 mL) y un exceso de isoamilnitrito (5 mL) y la mezcla se agitó durante 2,5 hr después de lo cual una TLC mostró que la reacción había finalizado. La adición de dietil éter (5 mL) causó la precipitación del producto, que se lavó con acetato de etilo y se secó al aire para proporcionar 0,29 g de un sólido amarillo con las propiedades siguientes:

MP 181 – 182 °C; ^1H RMN (300 MHz, CDCl_3) δ 8,78 (1H, s), 7,82 (1H, s), 7,3-6,8 (4H, m), 5,33 (2H, s), 4,67 (2H, m) 3,21 (2H, m) 2,76 (1H, m) 1,02 (2H, m) y 0,86 ppm (2H, m).

El reactivo Zn/Cu (utilizado anteriormente) se preparó fresco de la siguiente manera: se añadió HCl concentrado (3 mL) a 10 g de cinc en 100 mL de agua con agitación vigorosa. La agitación continuó durante 2 min (se empezaron a formar grumos), después de lo cual el agua se eliminó por decantación. Se añadieron 100 mL adicionales de agua con agitación vigorosa. Todos los grumos remanentes se trituraron con una espátula. Se añadió HCl concentrado (3 mL) y la agitación se continuó durante 2 min. Después de eliminar el agua por decantación, el sólido se lavó con 100 mL adicionales de agua. Se añadió agua (50 mL) al sólido y la agitación se continuó mientras se añadía lentamente una disolución de CuSO_4 (300 mg en 50 mL de agua). Después de que el cinc se volviera negro, el agua se eliminó por decantación. El resto se lavó secuencialmente con metanol (50 mL) y THF (50 mL).

EJEMPLO 2

Ensayo Fisiológico In Vivo

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Los efectos fisiológicos del compuesto de la invención se ensayaron *in vivo* en animales anestesiados según los procedimientos siguientes.

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Los animales se mantuvieron bajo anestesia con fenobarbital administrado utilizando una bomba de jeringa Hamilton. Se insertaron electrodos estimulantes y de registro en la vía perforante y el giro dentado del hipocampo, respectivamente. Una vez que los electrodos estuvieron implantados, se incitó una línea base estable de respuestas evocadas utilizando pulsos monofásicos únicos (duración del pulso 100 μ s) administrados a 3/min al electrodo estimulante. Se monitorizaron los EPSP del Campo hasta que se consigue una línea base estable (aproximadamente 20-30 min), después de lo cual se inyecta intraperitonealmente una disolución del compuesto de ensayo en HPCD y se registran los potenciales evocados del campo. Los potenciales evocados se registran durante aproximadamente 2 h después de la administración del fármaco o hasta que la amplitud del EPSP del campo vuelva a la línea base. En el último caso, es común que también se realice una administración iv con una dosis apropiada del mismo compuesto de ensayo.

20

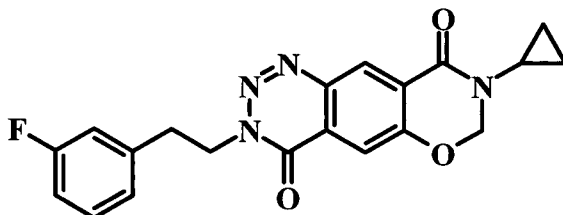
8-ciclopropil-3-[2-(3-fluorofenil)etil]-7,8-dihidro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazina-4,9-diona produjo un incremento de la amplitud del EPSP de campo de 10% a una dosis de 5 mg/kg después de administración iv.

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Aunque la invención se ha descrito con referencia a métodos y realizaciones específicas, se apreciará que pueden hacerse varias modificaciones sin apartarse de la invención.

REIVINDICACIONES:

1. Un compuesto de la fórmula:



5

o una sal de adición farmacéuticamente aceptable de un ácido o base de éste.

2. Un compuesto de la fórmula en la reivindicación 1 que es:

8-Ciclopropil-3-[2-(3-fluorofenil)etil]-7,8-dihidro-3H-[1,3]oxazino[6,5-g][1,2,3]benzotriazina-4,9-diona o una sal de adición farmacéuticamente aceptable de un ácido o base de éste.

10

3. Un método para el tratamiento de un sujeto mamífero, en el que el sujeto padece una condición hipoglutamatérgica o una deficiencia en el número o fuerza de sinapsis excitadoras o en el número de receptores AMPA, de manera que la memoria u otras funciones cognitivas están deterioradas, comprendiendo dicho método administrar a dicho sujeto, en un vehículo farmacéuticamente aceptable, una cantidad eficaz de un compuesto según cualquiera de las reivindicaciones 1 ó 2.

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4. Un método para el tratamiento de un mamífero en el que el sujeto padece una condición hipoglutamatérgica o deficiencias en el número o fuerza de sinapsis excitadoras o en el número de receptores AMPA de manera que ocurre un desequilibrio cortical/estriatal dando lugar a esquizofrenia o comportamiento esquizofreniforme, comprendiendo dicho método administrar a dicho sujeto, en un vehículo farmacéuticamente aceptable, una cantidad eficaz de un compuesto según cualquiera de las reivindicaciones 1 ó 2.

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5. El método según la reivindicación 4 en el que dicha condición es esquizofrenia.

6. El método según la reivindicación 3 en el que dicha condición es la enfermedad de Parkinson.
- 5 7. El método según la reivindicación 3 en el que dicha condición es la enfermedad de Alzheimer.
8. Una composición farmacéutica que comprende una cantidad eficaz de un compuesto según cualquiera de las reivindicaciones 1-2 en combinación con un vehículo,
10 aditivo o excipiente farmacéuticamente aceptable.
9. La composición según la reivindicación 8 en la que dicho compuesto comprende aproximadamente 0,5% a aproximadamente 75% en peso de dicha
composición y dicho vehículo, aditivo o excipiente comprende
15 aproximadamente 25% a aproximadamente 95,5% de dicha composición.
10. Utilización de un compuesto según cualquiera de las reivindicaciones 1-2 en la fabricación de un medicamento para utilizarse en el tratamiento de un sujeto
mamífero, en la que el sujeto padece una condición hipoglutamatergica o una
20 deficiencia en el número o fuerza de sinapsis excitadoras o en el número de receptores AMPA, de manera que la memoria u otras funciones cognitivas están deterioradas.
11. Utilización de un compuesto según cualquiera de las reivindicaciones 1 y 2 en la
25 fabricación de un medicamento para utilizarse en el tratamiento de la esquizofrenia.
12. Utilización de un compuesto según cualquiera de las reivindicaciones 1 y 2 en la
30 fabricación de un medicamento para utilizarse en el tratamiento de la enfermedad de Parkinson.

13. Utilización de un compuesto según cualquiera de las reivindicaciones 1 y 2 en la fabricación de un medicamento para utilizarse en el tratamiento de ADHD.
- 5 14. Utilización de un compuesto según cualquiera de las reivindicaciones 1 y 2 en la fabricación de un medicamento para utilizarse en el tratamiento del Síndrome de Rett.
- 10 15. Utilización de un compuesto según cualquiera de las reivindicaciones 1 y 2 en la fabricación de un medicamento para utilizarse en el tratamiento del Síndrome de X Frágil.
- 15 16. Utilización de un compuesto según cualquiera de las reivindicaciones 1 y 2 en la fabricación de un medicamento para utilizarse en el tratamiento de la enfermedad de Alzheimer.

RESUMEN

- Esta invención se refiere a la prevención y tratamiento de insuficiencia cerebral, incluyendo
- 5 incremento del funcionamiento de receptores en las sinapsis en las redes cerebrales responsables de comportamientos de orden superior. Estas redes cerebrales están implicadas en las capacidades cognitivas relacionadas con la alteración de la memoria, tal como se observa en una variedad de demencias, y en desequilibrios de la actividad neuronal entre diferentes regiones cerebrales, como se sugiere en trastornos tales como la enfermedad de Parkinson, esquizofrenia y trastornos afectivos.
- 10 En un aspecto particular, la presente invención se refiere a un compuesto útil para el tratamiento de dichas condiciones, y a métodos para utilizar este compuesto para dicho tratamiento.

From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)

(PCT Rule 44bis.1(c))

To:

COLEMAN, Henry, D.
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601
ETATS-UNIS D'AMERIQUEDate of mailing (*day/month/year*)
16 July 2009 (16.07.2009)Applicant's or agent's file reference
C21-079PCT

IMPORTANT NOTICE

International application No.
PCT/US2007/026416International filing date (*day/month/year*)
28 December 2007 (28.12.2007)Priority date (*day/month/year*)
03 January 2007 (03.01.2007)

Applicant

CORTEX PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

RECEIVED

JUL 27 2009

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference C21-079PCT	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2007/026416	International filing date (<i>day/month/year</i>) 28 December 2007 (28.12.2007)	Priority date (<i>day/month/year</i>) 03 January 2007 (03.01.2007)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CORTEX PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report 07 July 2009 (07.07.2009)
Facsimile No. +41 22 338 82 70	Authorized officer Beate Giffo-Schmitt
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 07/26416

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed.
- ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:
- a. type of material
- ☐ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☐ on paper
- ☐ in electronic form
- c. time of filing/furnishing
- ☐ contained in the international application as filed
- ☐ filed together with the international application in electronic form
- ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 07/26416

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box No. V 2. Citations and explanations:

Claims 6 and 12 lack an inventive step under PCT Article 33(3) as being obvious over Rogers in view of Li and in further view of the article entitled "LY503430, a novel AMPA receptor potentiator with functional, neuroprotective and neurotrophic effects in rodent models of Parkinson's disease" by Murray et al. (hereinafter 'Murray').

Regarding claim 6, Rogers and Li together disclose the method of claim 3. Rogers and Li do not specifically disclose the condition is Parkinson's disease. However, Murray further discloses the use of compounds that potentiate the AMPA receptor for the treatment of Parkinson's disease (Abstract). It would have been obvious to one skilled in the art to combine Rogers and Li's method of claim 3 with Murray's treatment of Parkinson's disease since compounds that potentiate the AMPA receptor have a positive effect on Parkinson's disease markers.

Regarding claim 12, Rogers and Li together disclose the compound of claim 1. Rogers and Li do not specifically disclose the use of said compound for the treatment of Parkinson's disease. However, Rogers does disclose the use of 2,3-dihydro-1H-pyrrolo[2,1-b][1,3]benzoxazine-9(3aH)-ones for potentiating the AMPA receptor (Abstract); and Murray further discloses the use of compounds that potentiate the AMPA receptor for the treatment of Parkinson's disease (Abstract). It would have been obvious to one skilled in the art to combine Rogers and Li's compound of claim 1 with Murray's treatment of Parkinson's disease since compounds that potentiate the AMPA receptor have a positive effect on Parkinson's disease markers.

Claim 13 lacks an inventive step under PCT Article 33(3) as being obvious over Rogers in view of Li and in further view of the article entitled "Increased AMPA Receptor Function in Slices Containing the Prefrontal Cortex of Spontaneously Hypertensive Rats" by Russell.

Regarding claim 13, Rogers and Li together disclose the compound of claim 1. Furthermore, Rogers discloses the use of said compound for potentiating the AMPA receptor (Abstract). Rogers and Li do not specifically disclose the use of said compound in the manufacture of a medicament for use in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). However, Russell further discloses increased AMPA receptor function in spontaneously hypertensive rats, which are used as genetic models for attention-deficit hyperactivity disorder (Abstract). It would have been obvious to one skilled in the art to combine Rogers and Li's compound of claim 1 with Russell's treatment of ADHD since increased AMPA receptor activity is positively correlated with hyperactivity and thereby ligands that attenuate the AMPA receptor have potential for the treatment of hyperactivity disorders such as ADHD.

Claim 14 lacks an inventive step under PCT Article 33(3) as being obvious over Rogers in view of Li and in further view of WO 2003/099299 A1 to Cheema et al. (hereinafter 'Cheema').

Regarding claim 14, Rogers and Li together disclose the compound of claim 1. Furthermore, Rogers discloses the use of said compound for potentiating the AMPA receptor (Abstract). Rogers and Li do not specifically disclose the use of said compound in the manufacture of a medicament for use in the treatment of Rett syndrome. However, Cheema further discloses the attenuation of the AMPA receptor for the treatment of Rett syndrome (p 10, ln 5-17). It would have been obvious to one skilled in the art to combine Rogers and Li's compound of claim 1 with Cheema's treatment of Rett syndrome since ligands that attenuate the AMPA receptor have potential for the treatment of motor neuron degeneration such as Rett's syndrome.

Claim 15 lacks an inventive step under PCT Article 33(3) as being obvious over Rogers in view of Li and in further view of the article entitled "New drug that enhances glutamate transmission in brain being evaluated for fragile X" by Pontarelli.

Regarding claim 15, Rogers and Li together disclose the compound of claim 1. Furthermore, Rogers discloses the use of said compound for potentiating the AMPA receptor (Abstract). Rogers and Li do not specifically disclose the use of said compound in the manufacture of a medicament for use in the treatment of Fragile-X Syndrome. However, Pontarelli further discloses a compound that enhances AMPA receptor activity for the treatment of fragile X syndrome (para 8). It would have been obvious to one skilled in the art to combine Rogers and Li's compound of claim 1 with Pontarelli's treatment of fragile X syndrome, since low AMPA receptor activity is observed in the brains of those with fragile X syndrome and thereby restoring AMPA receptor activity with compounds that potentiate the AMPA receptor may lead to a decrease of symptoms associated with this disease.

Claims 1-16 have industrial applicability as defined in PCT Article 33(4) because the subject matter can be made or used in industry.