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(54) Title: CINNOLINE COMPOUNDS, THEIR PREPARATION, AND THEIR USE

(57) Abstract: The present invention relates to cinnoline compounds, particularly 4-amino-N-cyclopropyl- 7-fluoro-8-(3,6-dimethoxypyridazin-4-yl)cinnoline-3-carboxamide and salts thereof. The claimed invention also relates to compositions comprising such a compound, as well as uses of and processes for production of said compounds. The claimed cinnoline compounds are GABAA modulators useful in the treatment of anxiety disorders, cognitive disorders, mood disorders, schizophrenia and pain.



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CINNOLINE COMPOUNDS, THEIR PREPARATION, AND THEIR USE

CROSS-REFERENCE TO RELATED PATENT APPLICATION

5 [1] This patent claims the benefit of priority to U.S. Provisional Patent Application No. 61/234,762 (filed 18 August, 2009). The entire text of the above patent application is incorporated by reference into this patent.

FIELD OF THE INVENTION

10 [2] This invention generally relates to cinnoline compounds, particularly 4-amino-N-cyclopropyl-7-fluoro-8-(3,6-dimethoxypyridazin-4-yl)cinnoline-3-carboxamide and salts thereof. This invention also relates to pharmaceutical compositions comprising such a compound, uses of such a compound (including, for example, treatment methods and medicament preparations), and processes for making such a compound.

BACKGROUND

15 [3] Various cinnoline compounds, including selected 4-amino- and 4-oxo-cinnoline-3-carboxamides, are discussed in, for example, East German Patent 123525 (Verfahren zur Herstellung von substituierten 4-Aminocinnolinen); U.S. Pat. No. 4,379,929 to Conrad et al; U.S. Pat. Nos. 4,886,800 and 4,925,844 to Resch; Daunis et al., "Preparation et proprietes de cinnolones-3 et cinnolones-4," Bull. de la Societe Chimique de France, 8:3198-3202 (1972); Lunt et al. "A New Cinnoline Synthesis," J. Chem. Soc. (C), 687-695 (1968); Gewald, et al., "Synthese von 4-Aminocinnolinen aus (Arylhyaazono) (cyan)-essigsaeurederivaten," Liebigs Ann. Chem., 1390-1394 (1984);
20 and U.S. Pat. No. 3,657,241 to Kurihara. Additionally, selected cinnoline compounds, including 3-acyl-4-substituted cinnoline derivatives, are discussed in Liebigs Ann. Chem. 1390-1394 (1984) supra and Sandison, et al., "A New Heterocyclisation Reaction Leading to Cinnolin-4(IH)-one Derivatives," J. Chem. Soc. Chem. Comm., 752-753 (1974).
25 Additionally, cinnoline compounds are discussed in EP205272 and EP 328282. The foregoing references, however, fail to disclose or suggest the compounds of the present invention or their use as CNS depressants.

30 [4] γ -Aminobutyric acid (GABA) is a common inhibitory neurotransmitter in the mammalian brain, and is estimated to be present at about one third of all synapses. When GABA binds to a GABA receptor, it affects the ability of neurons
35 expressing the receptors to conduct neural impulses. In the adult mammalian nervous

system, GABA typically inhibits neuron firing (depolarization). Neurons in the brain express three main types of GABA receptors: GABA type A receptors (GABAA), GABA type B receptors (GABAB), and GABA type C receptors (GABAC). GABAA receptors function as ligand-gated ion channels to mediate fast inhibitory synaptic transmissions that regulate neuronal excitability involved in such responses as seizure threshold, skeletal muscle tone, and emotional status. GABAA receptors are targets of many sedating drugs, such as benzodiazepines, barbiturates, and neurosteroids.

[5] The intrinsic inhibitory signal of GABA is transduced principally by GABAA receptors. GABAA receptors are pentameric, ligand-gated chloride ion (Cl^-) channels belonging to a superfamily of ligand-gated ionotropic receptors that includes the nicotinic acetylcholine receptor. GABAA receptors are heterogeneous, with at least 16 different subunits producing potentially thousands of different receptor types.

[6] GABAA receptor subunits aggregate into complexes that form chloride ion selective channels and contain sites that bind GABA along with a variety of pharmacologically active substances. When GABA binds to this receptor, the anion channel is activated, causing it to open and allowing chloride ions (Cl^-) to enter the neuron. This influx of Cl^- ions hyperpolarizes the neuron, making it less excitable. The resultant decrease in neuronal activity following activation of the GABAA receptor complex can rapidly alter brain function to such an extent that consciousness and motor control may be impaired.

[7] The numerous possible combinations of GABAA receptor subunits and the widespread distribution of these receptors in the nervous system likely contribute to the diverse and variable physiological functions of GABAA receptors, which have been implicated in many neurological and psychiatric disorders and related conditions, including: stroke, head trauma, epilepsy, pain, migraine, mood disorders, anxiety, post traumatic stress disorder, obsessive compulsive disorders, schizophrenia, seizures, convulsions, tinnitus, neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's Chorea, Parkinson's disease, depression, bipolar disorders, mania, trigeminal and other neuralgia, neuropathic pain, hypertension, cerebral ischemia, cardiac arrhythmia, myotonia, substance abuse, myoclonus, essential tremor, dyskinesia and other movement disorders, neonatal cerebral hemorrhage, and spasticity. GABAA receptors also are believed to play a role in cognition, consciousness, and sleep.

[8] Currently available drugs for modulating GABAA receptor activity include barbiturates (*e.g.*, pentobarbital and secobarbital) and benzodiazepines (*e.g.*, diazepam, chlordiazepoxide, and midazolam). Barbiturates can directly activate GABAA receptors, significantly increasing Cl⁻ currents in the absence of further intervention by GABA itself and can also indirectly augment GABAergic neural transmission. In contrast, benzodiazepines act as indirect allosteric modulators, and are largely incapable of increasing Cl⁻ currents in the absence of GABA, but enhance GABA-activated increases in Cl⁻ conductance. This latter property is thought to be responsible for the usefulness of benzodiazepines for treating a number of disorders, including generalized anxiety disorder, panic disorder, seizures, movement disorders, epilepsy, psychosis, mood disorders, and muscle spasms, as well as the relative safety of benzodiazepines compared to barbiturates.

[9] Both barbiturates and benzodiazepines generally tend to be addictive and can cause drowsiness, poor concentration, ataxia, dysarthria, motor incoordination, diplopia, muscle weakness, vertigo, and mental confusion. These side effects can interfere with an individual's ability to perform daily routines such as driving, operating heavy machinery, or performing other complex motor tasks while under therapy, making barbiturates and benzodiazepines less than optimal for treating chronic disorders involving GABA and GABAA receptors.

[10] GABAA receptors and GABAergic neural transmissions are implicated as targets for therapeutic intervention in a myriad of neurological and psychiatric disorders. Adverse side effects (*e.g.*, addictive properties, dizziness, and sedation) make some of the currently available GABA and GABAA receptor modulating drugs less than optimal (or completely unsuitable) in many therapeutic contexts.

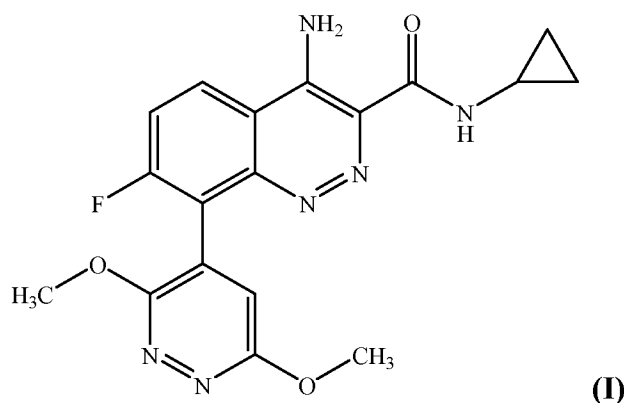
[11] The use of various cinnoline compounds for modulating the function and activity of GABA and GABA receptors in mammalian subjects and/or to target GABAergic neural transmission to treat anxiety disorders, cognitive disorders, and mood disorders is discussed in US Patent Nos. 7,425,556 and 7,465,795 and US Patent Appl. Publ. Nos. US2009/0018112 and 2009/0036554 to Chapdelaine et al. And the use of various cinnoline compounds for modulating the function and activity of GABA and GABA receptors in mammalian subjects and/or to target GABAergic neural transmission to treat schizophrenia, particularly cognitive disorders associated with schizophrenia, is discussed in US Patent Appl. Publ. No. US2008/0318925 to Arriza et al.

[12] Despite the foregoing, there continues to be a need for alternative compositions, methods, and tools that are useful in broad clinical applications to modulate the function and activity of GABA and GABA receptors in mammalian subjects (*e.g.*, humans) and/or to target GABAergic neural transmission. This need includes a need for
5 alternative compositions that exhibit, for example, one or more of the following: increased potency, increased efficacy, a desired therapeutic effect at lower receptor occupancy, a pharmacokinetic profile allowing for a desirable dosing regimen (*e.g.*, once daily dosing), a controlled rate of brain exposure, a desirable ratio of the C_{max} to the minimum effective concentration, improved GABAA3 functional activity, improved stability on the shelf
10 (*e.g.*, hydrolytic, thermal, chemical, or photochemical stability), improved tolerability for a wider range of patients, and an improved safety profile.

SUMMARY OF THE INVENTION

[13] This invention comprises, *inter alia*, cinnoline compounds; methods of
15 treatment using the cinnoline compounds (*e.g.*, use of the cinnoline compounds as central nervous system (CNS) depressants (*e.g.*, anxiolytics) and pharmacological tools); use of the cinnoline compounds to make medicaments; compositions comprising the cinnoline compounds (*e.g.*, pharmaceutical compositions); methods for manufacturing the cinnoline compounds; and intermediates used in such manufacturing methods.

[14] Briefly, this invention is directed, in part, to the compound of Formula I or
20 a salt thereof. The compound of Formula I corresponds to:



**4-amino-N-cyclopropyl-7-fluoro-
8-(3,6-dimethoxypyridazin-4-yl)cinnoline-3-carboxamide.**

[15] This invention also is directed, in part, to a pharmaceutical composition that
25 comprises the above compound of Formula I or salt thereof. In general, the composition also comprises at least one pharmaceutically acceptable inert ingredient. Such inert ingredients are sometimes collectively identified in this patent as “carriers, diluents, or

excipients.” The composition may further comprise one or more additional active ingredients. For example, such a composition may comprise more than one salt of the compound of Formula I. The composition also may, for example, alternatively or additionally comprise one or more active ingredients other than the compound of Formula

5 I or a salt thereof.

[16] This invention also is directed, in part, to methods for treating an anxiety disorder, cognitive disorder, mood disorder, schizophrenia, or pain in a mammal. These methods comprise administering to the mammal the above-described compound of Formula I or a pharmaceutically acceptable salt thereof. Such methods encompass the administration of the compound of Formula I or salt thereof alone. They also encompass administering other ingredients as well. For example, the compound of Formula I or salt thereof will typically be administered as part of a pharmaceutical composition that also comprises one or more carriers, diluents, or excipients. The compound of Formula I or salt thereof also may be administered with one or more additional active ingredients. For

10 example, more than one salt of the compound of Formula I may be administered. Alternatively or additionally, one or more active ingredients other than the compound of Formula I or salt thereof may be administered.

[17] In some embodiments, the compound of Formula I or salt thereof is administered in combination with a cognitive enhancing agent, memory enhancing agent, choline esterase inhibitor, or selective serotonin reuptake inhibitor. Such embodiments encompass administering the compound of Formula I or a salt thereof with one cognitive enhancing agent, memory enhancing agent, choline esterase inhibitor, or selective serotonin reuptake inhibitor. They also encompass administering other ingredients as well. For example, the compound of Formula I or salt thereof and the cognitive enhancing agent, memory enhancing agent, choline esterase inhibitor, or selective serotonin reuptake inhibitor will typically be administered as part of one or more pharmaceutical compositions that also comprise one or more carriers, diluents, or excipients. The compound of Formula I or salt thereof and the cognitive enhancing agent, memory enhancing agent, choline esterase inhibitor, or selective serotonin reuptake inhibitor also

20 may be administered with one or more additional active ingredients. For example, more than one salt of the compound of Formula I may be administered. Alternatively or additionally, more than one cognitive enhancing agent, memory enhancing agent, choline esterase inhibitor, or selective serotonin reuptake inhibitor may be administered. And, alternatively or additionally, one or more active ingredients other than the compound of

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Formula I, a salt thereof, a cognitive enhancing agent, a memory enhancing agent, a choline esterase inhibitor, or a selective serotonin reuptake inhibitor may be administered.

[18] In general, when the compound of Formula I or a salt thereof is administered as the only active ingredient to treat a targeted disorder, the administered amount of the compound of Formula I or salt thereof is therapeutically effective to treat the targeted disorder in the mammal. When, in contrast, the compound of Formula I or a salt thereof is administered in combination with one or more other active ingredients, the amount of the compound of Formula I or salt and the amount(s) of the other active ingredient(s) are, together, therapeutically effective to treat the targeted disorder in the mammal.

[19] This invention also is directed, in part, to a method for modulating activity of a GABAA receptor (*e.g.*, a GABAA1 receptor, GABAA2 receptor, GABAA3 receptor, or GABAA5 receptor). The method comprises contacting the GABAA receptor with the above-described compound of Formula I or a salt thereof. This method encompasses contacting one or more GABAA receptors with the compound of Formula I or a pharmaceutically acceptable salt thereof alone. It also encompasses contacting one or more GABAA receptors with other ingredients as well. For example, the GABAA receptor(s) may be contacted with one or more inert ingredients. The GABAA receptor(s) alternatively or additionally may be contacted with more than one salt of the compound of Formula I. And the GABAA receptor(s) alternatively or additionally may be contacted with one or more active ingredients other than the compound of Formula I or a salt thereof.

[20] This invention also is directed, in part, to a method for making the above-described compound of Formula I or a salt thereof. The method comprises reacting 4-amino-8-bromo-N-cyclopropyl-7-fluorocinnoline-3-carboxamide with 3,6-dimethoxypyridazin-4-ylboronic acid. In some embodiments, the reaction is conducted in the presence of a metal catalyst (*e.g.*, a palladium catalyst), tri-*t*-butylphosphonium tetrafluoroborate, and/or a solvent that comprises an organic solvent.

[21] This invention also is directed, in part, to the above-described compound of Formula I or a pharmaceutically acceptable salt thereof for use in therapy.

[22] This invention also is directed, in part, to the use of the above-described compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition (or "medicament"). In general, the composition also comprises at least one pharmaceutically acceptable inert ingredient. Such a composition

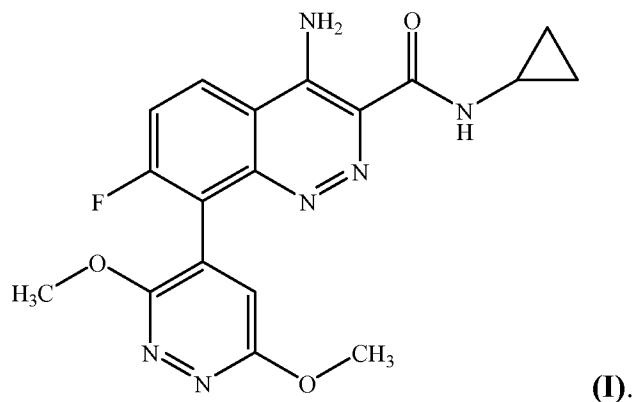
may further comprise one or more additional active ingredients as well. For example, such a composition may comprise more than one salt of the compound of Formula I. The composition also may, for example, alternatively or additionally comprise one or more active ingredients other than the compound of Formula I or a salt thereof.

5 [23] Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this specification.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

10 [24] This description of illustrative embodiments is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its specific examples, while indicating embodiments of this invention, are intended for purposes of illustration only. This invention, therefore, is not limited to the
15 illustrative embodiments described in this specification, and may be variously modified.

 [25] As noted above, this invention is directed, in part, to the compound of Formula I or a salt thereof. The compound of Formula I corresponds to:



20 It is believed that this invention provides one or more of the following advantages over previously known GABA and GABAA receptor modulating drugs: increased potency, increased efficacy, a desired therapeutic effect at lower receptor occupancy, a pharmacokinetic profile allowing for a desirable dosing regimen, a controlled rate of brain exposure, a desirable ratio of the C_{max} to the minimum effective concentration, improved GABAA3 functional activity, improved stability on the shelf, improved tolerability for a
25 wider range of patients, and an improved safety profile.

 [26] The salts of the compound of Formula I are typically acid addition salts. In general, an acid addition salt can be prepared using various inorganic or organic acids.

Such salts can typically be formed by, for example, mixing the compound of Formula I with an acid (typically a stoichiometric amount of acid) using various methods known in the art. This mixing may occur in water, an organic solvent (*e.g.*, ether, ethyl acetate, ethanol, isopropanol, or acetonitrile), or an aqueous/organic mixture.

5 [27] A salt may be advantageous due to one or more of its chemical or physical properties, such as stability in differing temperatures and humidities, or a desirable solubility in water, oil, or other solvent. In some instances, a salt may be used to aid in the isolation or purification of the compound. In some embodiments (particularly where the salt is intended for administration to an animal, or is a reagent for use in making a
10 compound or salt intended for administration to an animal), the salt is pharmaceutically acceptable.

 [28] Examples of inorganic acids that typically may be used to form acid addition salts include hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. In some embodiments, the salt comprises a salt derived from
15 hydrochloric or phosphoric acid. Examples of organic acids include, for example, sulfonates, such as mesylate (*i.e.*, methanesulfonate), ethanesulfonate, benzenesulfonate, 2-hydroxyethanesulfonate, cyclohexylaminosulfonate, camphorsulfonate, and 2-naphthalesulfonate. In some embodiments, the salt comprises a salt derived from an acid that has a pK_a of less than about 3.7.

20 [29] Formula I is intended to encompass any tautomer that may form. A “tautomer” is any other structural isomer that exists in equilibrium resulting from the migration of a hydrogen atom, *e.g.*, amide-imidic acid tautomerism.

 [30] It is contemplated that the amine of the compound of Formula I or a salt thereof may form an N-oxide. Such an N-oxide is intended to be encompassed by the
25 compound of Formula I or salt thereof. An N-oxide can generally be formed by treating an amine with an oxidizing agent, such as hydrogen peroxide or a per-acid (*e.g.*, a peroxycarboxylic acid). *See, e.g.*, Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience. N-oxides also can be made by reacting the amine with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent, such as
30 dichloromethane. *See* L. W. Deady, *Syn. Comm.*, 7, pp. 509-514 (1977).

 [31] It is contemplated that the compound of Formula I could form isolatable atropisomers in certain solvents at certain temperatures. Formula I is intended to encompass any such atropisomers. Atropisomers can generally be isolated using, for example, chiral LC.

[32] The compound of Formula I and salts thereof are intended to encompass any isotopically-labeled (or “radio-labeled”) derivatives of the compound of Formula I and salts thereof. Such a derivative is a derivative of the compound of Formula I or a salt thereof wherein one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of radionuclides that may be incorporated include ^2H (also written as D for deuterium), ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , and ^{18}F . The radionuclide that is used will depend on the specific application of that radio-labeled derivative. For example, for *in vitro* receptor labeling and competition assays, ^3H or ^{14}C are often useful. For radio-imaging applications, ^{11}C or ^{18}F are often useful. In some embodiments, the radionuclide is ^3H . In some embodiments, the radionuclide is ^{14}C . In some embodiments, the radionuclide is ^{11}C . And in some embodiments, the radionuclide is ^{18}F .

[33] The compound of Formula I and salts thereof are intended to cover all solid state forms of the compound of Formula I and salts thereof. The compound of Formula I and salts thereof also are intended to encompass all solvated (*e.g.*, hydrated) and unsolvated forms of the compound of Formula I and salts thereof.

[34] The compound of Formula I and salts thereof also are intended to encompass coupling partners in which the compound of Formula I or a salt thereof is linked to a coupling partner by, for example, being chemically coupled to the compound or salt or physically associated with it. Examples of coupling partners include a label or reporter molecule, a supporting substrate, a carrier or transport molecule, an effector, a drug, an antibody, or an inhibitor. Coupling partners can be covalently linked to the compound of Formula I or a salt thereof via an appropriate functional group on the compound, such as a hydroxyl, carboxyl, or amino group. Other derivatives include formulating the compound of Formula I or a salt thereof with liposomes.

[35] The term “pharmaceutically acceptable” is used to characterize a moiety (*e.g.*, a salt, dosage form, carrier, diluent, or excipient) as being appropriate for use in accordance with sound medical judgment. In general, a pharmaceutically acceptable moiety has one or more benefits that outweigh any deleterious effect that the moiety may have. Deleterious effects may include, for example, excessive toxicity, irritation, allergic response, and other problems and complications.

[36] This invention provides, in part, for methods to treat various disorders in animals, particularly mammals. Mammals include, for example, humans. Mammals also

include, for example, companion animals (*e.g.*, dogs, cats, and horses), livestock animals (*e.g.*, cattle and swine); lab animals (*e.g.*, mice and rats); and wild, zoo, and circus animals (*e.g.*, bears, lions, tigers, apes, and monkeys).

[37] The compound of Formula I has been observed to bind to GABAA
5 receptors. It also has been observed to bind to GABAA receptors by displacement of benzodiazepines. Accordingly, it is believed that the compound and salts of this invention can be used to modulate activities of GABAA receptors.

[38] Examples of tests that can be conducted to demonstrate the anxiolytic activity of the compound and salts of this invention include binding assays of GABAA
10 receptors. In some embodiments, the binding assay may be directed to a subtype of GABAA receptors, such as GABAA1 receptors (*i.e.*, those containing the α_1 subunit), GABAA2 receptors (*i.e.*, those containing the α_2 subunit), GABAA3 receptors (*i.e.*, those containing the α_3 subunit), and GABAA5 receptors (*i.e.*, those containing the α_5 subunit). Anxiolytic activity is indicated by a displacement of the flunitrazepam, such as is
15 exhibited by benzodiazepines, or by enhancement of the binding, such as is exhibited by cartazolate and tracazolate.

[39] Presently available GABAA modulator anxiolytics are believed to work via interactions at the classical benzodiazepine binding site. Many of these anxiolytics lack functional GABAA receptor subtype-selectivity (*i.e.*, selectivity of the potentiation
20 normalized to benzodiazepine). The subtype-selective GABAA receptor modulators may offer more advantages. For example, a growing body of work suggests that desirable anxiolytic activity is driven primarily by interactions with GABAA receptors containing the α_2 subunit. Sedation, a side-effect common to all marketed benzodiazepines, is believed to be mediated by interactions at GABAA receptors containing the α_1 subunit.
25 To develop anxiolytics with minimal liabilities due to interactions with other subunits, an electrophysiological assay may be used to screen modulatory effects of a compound on different GABA subunit combinations heterologously expressed in *Xenopus* oocytes. More specifically, GABAA receptors can be heterologously expressed in *Xenopus* oocytes by injecting cRNA corresponding to human α_1 , α_2 , α_3 , α_5 , β_2 , β_3 , and γ_2 subunits of the
30 GABAA receptor genes. The specific subunit combinations (subtypes) may be as follows: $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, and $\alpha_5\beta_3\gamma_2$. The EC_{10} of GABA is approximated for each cell. Stability of GABA-mediated (EC_{10}) current is established. Modulatory effect of a test compound may be determined and compared across subtypes. This assay can generally be conducted with reproducibility, which, in turns, allows discrimination of modulatory

activity down to minimal effect of about 25% potentiation (before normalization to standard) for all four subtypes. Thus, the assay can characterize modulatory effects and determine subtype selectivity of test compounds on major subtypes of GABAA receptors.

[40] Because the compound and salts of this invention can generally be used to modulate activities of GABAA receptors or to selectively modulate functional activities of a subtype of GABAA receptors, the compound and salts of this invention are envisioned to be useful for treating disorders mediated by GABAA receptors or a subtype of GABAA receptors. Such disorders, include, for example, cognitive disorders, anxiety disorders, mood disorders, and schizophrenia. They also include stroke, head trauma, epilepsy, pain, migraine, post traumatic stress disorder, obsessive compulsive disorders, seizures, convulsions, tinnitus, neurodegenerative disorders (*e.g.*, Alzheimer's disease), amyotrophic lateral sclerosis, Huntington's Chorea, Parkinson's disease, depression, bipolar disorders, mania, trigeminal and other neuralgia, neuropathic pain, hypertension, cerebral ischemia, cardiac arrhythmia, myotonia, substance abuse, myoclonus, essential tremor, dyskinesia and other movement disorders, neonatal cerebral hemorrhage, spasticity, and sleeping disorders.

[41] In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt thereof is used to treat an anxiety disorder. The method comprises administering to a mammal a therapeutically effective amount of a compound of Formula I or pharmaceutically acceptable salt thereof. In some embodiments, the anxiety disorder comprises, for example, one or more of the following: panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, and generalized anxiety disorder due to a general medical condition.

[42] In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt thereof is used to treat a cognitive disorder. The method comprises administering to a mammal a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. In some embodiments, the cognitive disorder comprises one or more of the following: Alzheimer's disease, dementia, dementia due to Alzheimer's disease, and dementia due to Parkinson's disease.

[43] In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt thereof is used to treat a mood disorder. The method comprises administering to a mammal a therapeutically effective amount of a compound of Formula I

or a pharmaceutically acceptable salt thereof. In some embodiments, the mood disorder comprises a depressive disorder including, for example, one or more of the following: major depressive disorder, dysthymic disorder, bipolar depression and/or bipolar mania, bipolar I with or without manic, depressive or mixed episodes, bipolar II, cyclothymic disorder, mood disorder due to a general medical condition, manic episodes associated with bipolar disorder, and mixed episodes associated with bipolar disorder.

[44] In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt thereof is used to treat schizophrenia. The method comprises administering to a mammal a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. In some such embodiments, the compound of Formula I or a pharmaceutically acceptable salt thereof is used to treat a cognitive disorder associated with schizophrenia. It is believed that existing non-selective GABAergic agents are generally not optimal for treating information/cognitive processing deficits in schizophrenia due to the unacceptable competing side effects, such as overt sedation and memory impairment. In contrast, it is believed that the compound of Formula I is capable of more optimally selectively modifying function at the specific GABAergic synapses affected by the schizophrenic disease state. It is contemplated that the compound of Formula I, and any of its salts acting selectively at GABAA $\alpha 2$ subunits, may be used to treat cognitive deficits in schizophrenia.

[45] The therapeutic effect of the compound of Formula I or a salt thereof in treating cognitive deficits associated with schizophrenia may be demonstrated by testing one or more of the compound or its salt using the method outlined in **Example 5**, which involves altering the power spectrum of frequencies comprising the spontaneous electroencephalogram (EEG) in behaving rats. The EEG protocol in **Example 5** shows that spontaneous EEG from behaving animals in the presence of the compound of Formula I with functionally selective $\alpha 2$ and $\alpha 3$ pharmacologies exhibits dose-dependent increases in high frequency oscillations in both the high beta and gamma ranges with no significant increases at lower frequencies. In contrast, the functionally $\alpha 1$ -selective compound, zolpidem, exhibits no significant increase at gamma frequencies, and the functionally non-selective GABA compound, Lorazepam, leads to broad changes in spontaneous EEG across a range of oscillation frequencies. The functionally selective nature of $\alpha 2$ and $\alpha 3$ on high frequency EEG *in vivo* indicates that the compound of Formula I may be useful in attenuating the high frequency EEG deficits seen in schizophrenic patients, and, to the

extent that these EEG deficits reflect impaired cognitive function, that the compound of Formula I may be used to treat cognitive deficits in schizophrenia.

[46] Anxiety disorders, cognitive disorders, mood disorders, and schizophrenia are defined in, for example, the *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, Washington, DC, American Psychiatric Association, 2000.

[47] In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt thereof is used to treat pain. Pain may include, for example, neuropathic pain. The method comprises administering to a mammal a therapeutically effective amount of a compound of Formula I or pharmaceutically acceptable salt thereof.

[48] It is contemplated that the compound of Formula I or a pharmaceutically acceptable salt thereof may be administered orally, buccally, vaginally, rectally, via inhalation, via insufflation, intranasally, sublingually, topically, or parenterally (*e.g.*, intramuscularly, subcutaneously, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly, or by injection into the joints).

[49] Pharmaceutical compositions comprising the compound of Formula I or a pharmaceutically acceptable salt thereof can vary widely. For example, it is contemplated that the compositions may be formulated for a variety of suitable routes and means of administration, including oral, rectal, nasal, topical, buccal, sublingual, vaginal, inhalation, insufflation, or parenteral administration. It is contemplated that such compositions may, for example, be in the form of solids, aqueous or oily solutions, suspensions, emulsions, creams, ointments, mists, gels, nasal sprays, suppositories, finely divided powders, and aerosols or nebulisers for inhalation. In some embodiments, the composition comprises a solid or liquid dosage form that may be administered orally.

[50] Solid form compositions may include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier may comprise one or more substances. Such substances are generally inert. A carrier also may act as, for example, a diluent, flavoring agent, solubilizer, lubricant, preservative, stabilizer, suspending agent, binder, or disintegrating agent. It also may act as, for example, an encapsulating material. Examples of often suitable carriers include pharmaceutical grade mannitol, lactose, magnesium carbonate, magnesium stearate, talc, lactose, sugar (*e.g.*, glucose and sucrose), pectin, dextrin, starch, tragacanth, cellulose, cellulose derivatives (*e.g.*, methyl cellulose and sodium carboxymethyl cellulose), sodium saccharin, low-melting wax, and cocoa butter.

[51] In powders, the carrier is typically a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is typically mixed with the carrier having the desirable binding properties in suitable proportions and compacted into the desired shape and size.

5 [52] For preparing suppository compositions, a low-melting wax (*e.g.*, a mixture of fatty acid glycerides and cocoa butter) is typically first melted, followed by dispersing the active ingredient therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

[53] Liquid compositions can be prepared by, for example, dissolving or
10 dispersing the compound or a salt of this invention in a carrier, such as, for example, water, saline aqueous dextrose, glycerol, or ethanol. Aqueous solutions for oral administration can be prepared by dissolving the compound of Formula I or a pharmaceutically acceptable salt thereof in water with a solubilizer. Colorants, flavoring agents, stabilizers, and thickening agents, for example, also may be added. Aqueous
15 suspensions for oral use can be made by dispersing the compound or salt of this invention in a finely divided form in water, together with a viscous material, such as, for example, one or more natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, or other suspending agents. If desired, the liquid composition also may contain other non-toxic auxiliary inert ingredients, such as, for example, wetting or emulsifying
20 agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Such compositions also may contain other ingredients, such as, for example, one or more pharmaceutical adjuvants.

[54] As note above, the inert ingredients present in a pharmaceutical
25 composition of this invention are sometimes collectively referred to as “carriers, diluents, and excipients.” Methods for making pharmaceutical compositions and the use of carriers, diluents, and excipients are well known in the art. *See, e.g.*, for example, *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, PA, 15th Edition, 1975.

[55] The optimum dosage and frequency of administration will depend on the
30 particular condition being treated; the species of the mammalian patient; the severity of the condition being treated; the age, size and weight, and general physical condition of the particular mammalian patient; brain/body weight ratio; other medication the mammalian patient may be taking; the route of administration; the formulation; and various other

factors known to physicians (in the context of human patients), veterinarians (in the context of non-human patients), and others skilled in the art.

[56] When the compound of Formula I or a pharmaceutically acceptable salt thereof is administered as a sole therapy for treating a disorder, a “therapeutically effective amount” is an amount sufficient to reduce or completely alleviate symptoms or other detrimental effects of the disorder; cure the disorder; reverse, completely stop, or slow the progress of the disorder; reduce the risk of the disorder getting worse; or delay or reduce the risk of onset of the disorder.

[57] In some embodiments, the optimum amount of the compound of Formula I or pharmaceutically acceptable salt thereof is from about 10 pg/kg of body weight to about 100 mg/kg of body weight per day. In some embodiments, the optimum amount is from about 100 ng/kg to about 10 mg/kg per day. In some embodiments, the optimum amount is from about 0.1 to about 20 mg/kg per day, from about 0.1 to about 2 mg/kg per day, or from about 0.2 to about 1 mg/kg per day. In some embodiments, a dosage range described above is used to treat an anxiety disorder, cognitive disorder, mood disorder, schizophrenia, or pain.

[58] It is contemplated that the pharmaceutical compositions can be in one or more unit dosage forms. Accordingly, the composition may be divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be, for example, a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these in packaged forms. The unit dosage form alternatively can be a packaged preparation in which the package contains discrete quantities of the composition, such as, for example, packeted tablets, capsules, or powders in vials or ampoules. Unit dosage forms may be prepared by, for example, various methods well known in the art of pharmacy.

[59] The dosage can be given once daily or in divided doses, such as, for example, from 2 to 4 times per day. In some embodiments, the dose is conventionally formulated in an oral dosage form by compounding from about 5 to about 250 mg per unit of dosage with, for example, one or more inert or active ingredients using accepted pharmaceutical practices, such as those described in U.S. Pat. No. 3,755,340.

[60] In some embodiments, the compound of Formula I or a salt thereof is administered concurrently, simultaneously, sequentially, or separately with one or more other pharmaceutically active compounds. In some such embodiments, the other pharmaceutically active compound(s) is/are selected from the following:

- (i) antidepressants, such as, for example, amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, elzasonan, escitalopram, fluvoxamine, fluoxetine, gepirone, imipramine, ipsapirone, maprotiline, nortriptyline, nefazodone, paroxetine, phenelzine, protriptyline, reboxetine, robalzotan, sertraline, sibutramine, thionisoxetine, tranlycypromaine, trazodone, trimipramine, venlafaxine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;
- (ii) atypical antipsychotics, such as, for example, quetiapine and pharmaceutically active isomer(s) and metabolite(s) thereof; amisulpride, aripiprazole, asenapine, benzisoxidil, bifeprunox, carbamazepine, clozapine, chlorpromazine, debenzapine, divalproex, duloxetine, eszopiclone, haloperidol, iloperidone, lamotrigine, lithium, loxapine, mesoridazine, olanzapine, paliperidone, perlapine, perphenazine, phenothiazine, phenylbutylpiperidine, pimozide, prochlorperazine, risperidone, quetiapine, sertindole, sulpiride, suproclonine, suriclone, thioridazine, trifluoperazine, trimetozine, valproate, valproic acid, zopiclone, zotepine, ziprasidone and equivalents thereof;
- (iii) antipsychotics, such as, for example, amisulpride, aripiprazole, asenapine, benzisoxidil, bifeprunox, carbamazepine, clozapine, chlorpromazine, debenzapine, divalproex, duloxetine, eszopiclone, haloperidol, iloperidone, lamotrigine, loxapine, mesoridazine, olanzapine, paliperidone, perlapine, perphenazine, phenothiazine, phenylbutylpiperidine, pimozide, prochlorperazine, risperidone, sertindole, sulpiride, suproclonine, suriclone, thioridazine, trifluoperazine, trimetozine, valproate, valproic acid, zopiclone, zotepine, ziprasidone and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;
- (iv) Alzheimer's therapies, such as, for example, donepezil, memantine, tacrine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;
- (v) Parkinson's therapies, such as, for example, deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal

nitric oxide synthase and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(vi) migraine therapies, such as, for example, almotriptan, amantadine, bromocriptine, butalbital, cabergoline, dichloralphenazone, eletriptan, frovatriptan, lisuride, naratriptan, pergolide, pramipexole, rizatriptan, ropinirole, sumatriptan, zolmitriptan, zomitriptan, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(vii) stroke therapies, such as, for example, abciximab, activase, disufenton sodium, citicoline, crobenetine, desmoteplase, repinotan, traxoprodil and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(viii) over active bladder urinary incontinence therapies, such as, for example, darafenacin, falvoxate, oxybutynin, propiverine, robalzotan, solifenacin, tolterodine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(ix) neuropathic pain therapies, such as, for example, gabapentin, lidoderm, pregablin and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(x) nociceptive pain therapies, such as, for example, celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, diclofenac, loxoprofen, naproxen, paracetamol and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof;

(xi) insomnia therapies, such as, for example, allobarbital, alonimid, amobarbital, benzoctamine, butabarbital, capuride, chloral, cloperidone, clorethate, dexclamol, ethchlorvynol, etomidate, glutethimide, halazepam, hydroxyzine, mecloqualone, melatonin, mephobarbital, methaqualone, midaflur, nisobamate, pentobarbital, phenobarbital, propofol, roletamide, triclofos, secobarbital, zaleplon, zolpidem and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof; and

(xii) mood stabilizers, such as, for example, carbamazepine, divalproex, gabapentin, lamotrigine, lithium, olanzapine, quetiapine, valproate, valproic acid, verapamil, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

[61] In some embodiments, the other pharmaceutically active ingredient(s) comprises a cognitive enhancing agent. In some such embodiments, the targeted disorder comprises an anxiety disorder, cognitive disorder, mood disorder, or schizophrenia.

5 [62] In some embodiments, the other pharmaceutically active ingredient(s) comprises a memory enhancing agent. In some such embodiments, the targeted disorder comprises an anxiety disorder, cognitive disorder, mood disorder, or schizophrenia.

[63] In some embodiments, the other pharmaceutically active ingredient(s) comprises a choline esterase inhibitor. In some such embodiments, the target disorder comprises an anxiety disorder, cognitive disorder, mood disorder, or schizophrenia.

10 [64] In some embodiments, the other pharmaceutically active ingredient(s) comprises anti-inflammatory agent. In some such embodiments, the targeted disorder comprises an anxiety disorder, cognitive disorder, mood disorder, schizophrenia, or pain.

[65] In some embodiments, the other pharmaceutically active ingredient(s) comprises an atypical antipsychotic agent. Atypical antipsychotic agents include, for
15 example, Olanzapine (marketed as Zyprexa), Aripiprazole (marketed as Abilify), Risperidone (marketed as Risperdal), Quetiapine (marketed as Seroquel), Clozapine (marketed as Clozaril), Ziprasidone (marketed as Geodon), and Olanzapine/Fluoxetine (marketed as Symbyax). In some such embodiments, the targeted disorder comprises an anxiety disorder, cognitive disorder, mood disorder, or schizophrenia.

20 [66] In some embodiments, the other pharmaceutically active ingredient(s) comprises a selective serotonin reuptake inhibitor (or “serotonin-specific reuptake inhibitor” or SSRI). Such agents include, for example, fluoxetine (marketed as, for example, Prozac), paroxetine (marketed as, for example, Paxil), citalopram (marketed as, for example, Celexa), dapoxetine, mesembrine, excitalopram (marketed as, for example,
25 Lexapro), fluvoxamine (marketed as, for example, Luvox), zimelidine (marketed as, for example, Zelmid), and sertraline (marketed as, for example, Zoloft).

[67] In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt thereof is administered as part of a combination therapy with chemotherapy. In some such embodiments, the targeted disorder comprises dementia
30 treatment.

[68] In some embodiments in which a combination therapy is used, the amount of the compound of Formula I or salt thereof and the amount of the other pharmaceutically active agent(s) are, when combined, therapeutically effective to treat a targeted disorder in the mammal. In this context, the combined amounts are “therapeutically effective

amount” if they are, when combined, sufficient to reduce or completely alleviate symptoms or other detrimental effects of the disorder; cure the disorder; reverse, completely stop, or slow the progress of the disorder; reduce the risk of the disorder getting worse; or delay or reduce the risk of onset of the disorder. Typically, such amounts may be determined by one skilled in the art by, for example, starting with the dosage range described in this patent for the compound of Formula I or salt thereof and an approved or otherwise published dosage range(s) of the other pharmaceutically active compound(s).

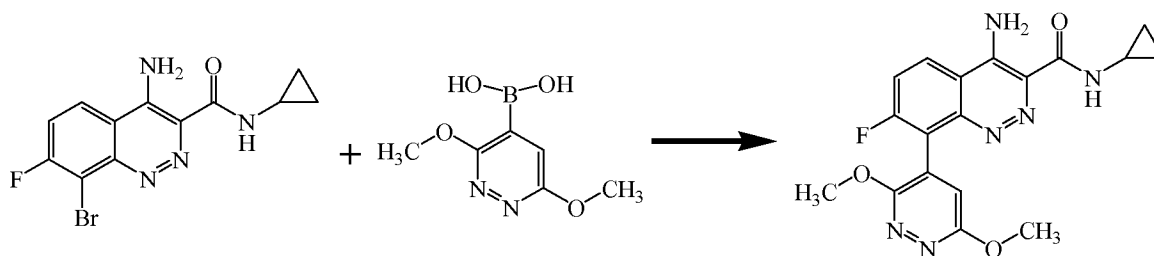
[69] When used in a combination therapy, it is contemplated that the compound of Formula I or a pharmaceutically acceptable salt thereof and the other active ingredients may be administered in a single composition, completely separate compositions, or a combination thereof. It also is contemplated that the active ingredients may be administered concurrently, simultaneously, sequentially, or separately. The particular composition(s) and dosing frequency(ies) of the combination therapy will depend on a variety of factors, including, for example, the route of administration, the condition being treated, the species of the mammalian patient, any potential interactions between the active ingredients when combined into a single composition, any interactions between the active ingredients when they are administered to the mammalian patient, and various other factors known to physicians (in the context of human patients), veterinarians (in the context of non-human patients), and others skilled in the art.

EXAMPLES

[70] The following examples are merely illustrative of embodiments of the invention, and not limiting to the remainder of this disclosure in any way.

Compound Preparation

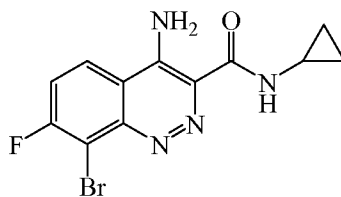
[71] **Example 1. Preparation of 4-amino-N-cyclopropyl-8-(3,6-dimethoxyphenyl)-7-fluorocinnoline-3-carboxamide.**



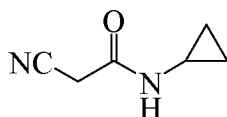
A vigorously stirred mixture of 4-amino-8-bromo-N-cyclopropyl-7-fluorocinnoline-3-carboxamide (16.0 g, 49.21 mmol), 3,6-dimethoxypyridazin-4-ylboronic acid (13.7 g, 74.47 mmol), tri-*t*-butylphosphonium tetrafluoroborate (1.47 g, 5.07 mmol), tris(dibenzylideneacetone)dipalladium(0) (2.25 g, 2.46 mmol), and potassium fluoride (8.0 g, 137.70 mmol) in a solvent mixture of acetonitrile (240 mL) and water (140 mL) was gradually brought to mild reflux, and then maintained at reflux for 3 hr. Afterward, the mixture was allowed to cool to room temperature, diluted with water (100 mL), and extracted with chloroform (2x400 mL). The resulting organic layers were combined, washed with half-saturated brine (150 mL), dried over sodium sulfate, and concentrated to give a crude semisolid product. The crude product was triturated with ether (300 mL), filtered, washed with ether, and air-dried to give a tan solid. This material was subjected to chromatography on silica gel eluting with a 0-8% CH₃OH/DCM gradient to give a pale yellowish solid. To a stirred solution of this material in dry THF (400 mL) at mild reflux temperature was added, in one portion, siliabond thiol Pd scavenger resin (2.7 g). Heating was continued for 6hr. The cooled mixture was diluted with ethanol (100 mL) and filtered the scavenger resin. The filtrate was then concentrated to dryness to give an off-white solid. This material was recrystallized from hot ethanol/water (1:1, 250 mL). The resulting solid was collected by filtration, washed with ethanol/water (1:1, 100 mL), and dried *in vacuo* at 85°C for 2 days to give the title compound (9.4 g, 49.5 %) as a white solid. NMR: ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 0.62 - 0.66 (m, 2 H) 0.86 - 0.90 (m, 2 H) 2.93 - 2.99 (m, 1 H) 3.97 (s, 3 H) 4.11 (s, 3 H) 7.05 (s, 1 H) 7.54 (dd, *J* = 9.2, 8.4 Hz, 1 H) 8.00 (dd, *J* = 9.3, 5.1 Hz, 1 H) 8.43 (br. s., 1 H). MS ^{m/z}: 385 (M+H).

[72] The reagents in the above reaction have been prepared as follows:

[73] **Reagent 1. Preparation of 4-amino-8-bromo-N-cyclopropyl-7-fluorocinnoline-3-carboxamide.**

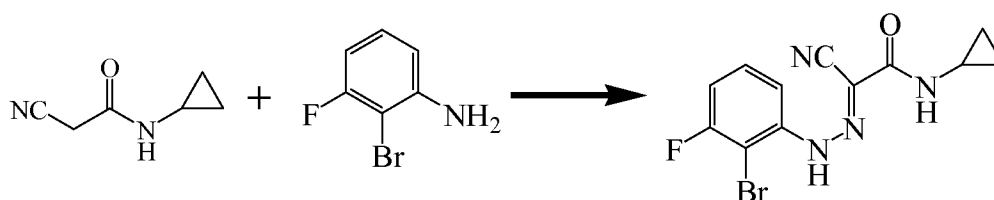


[74] **Part A. Preparation of 2-cyano-N-cyclopropylacetamide.**



A flask containing 113.1g of ethyl cyanoacetate was placed in a 38°C constant temperature bath. Cyclopropylamine (147.8g) was added over 50 min. The reaction was stirred for 1.5 hr. The mixture was evaporated to give a yellow solid. The solid was triturated with stirring under 3:1 hexane/diethyl ether for 10 min. The solids were filtered and washed once with 3:1 hexane / diethyl ether and were then dried under vacuum to give the title compound (113.2g; 91% yield); NMR spectrum (CDCl₃) δ ppm 0.54-0.63(m,2H) 0.79-0.88(m,2H) 2.68-2.85(m,J=7.1,7.1,3.7,3.5,3.5Hz, 1H) 3.26-3.41(m,2H) 6.24(br. S., 1H). *See also*, US Patent Appl. Publ. US2007/142328.

[75] Part B1. Preparation of 2-(2-bromo-3-fluorophenyl)hydrazono)-N-cyclopropyl-2-isocyanoacetamide.



To conduct the reaction, two mixtures were first prepared:

Mixture A: To a solution of 2-bromo-3-fluoroaniline (50.0g, 0.26 mol) in glacial acetic acid (72 mL) was added water (144 mL). The resulting suspension was cooled to 20°C. Concentrated HCl (77 mL) was added over 15 min as the mixture was cooled further to 3°C. A cold solution of sodium nitrite (20.08 g, 0.29 mol) in water (70 mL) was then added over 70 min keeping the temperature below 5°C.

Mixture B: To a solution of 2-cyano-N-cyclopropylacetamide (36.13 g, 0.29 mol) in 200 proof ethanol (870 mL) was added a solution of sodium acetate (303.9 g, 3.7 mol) in water (1.6 L). The resulting mixture was cooled to 5°C.

Mixture A was added to Mixture B to give an orange-yellow precipitate. The resulting suspension was stirred for 18 hr in an ice bath. Water (1 L) was added, and stirring was continued for 0.5 hr. The resulting solids were filtered, washed twice with water, and dried *in vacuo* to a constant weight to give the title compound (79.9 g, 93%) ; NMR: ¹H NMR (CDCl₃) δ 0.59-0.78 (m, 2H) 0.84-1.04 (m, 2H) 2.70-3.00 (m, 1H) 6.38 (br. s., 1H) 6.91 (td, J = 8.2,1.4Hz, 1H) 7.30-7.36 (m, 1H) 7.48 (d, J = 8.4Hz, 1H) 14.35 (br. s., 1H).

[76] Part B2. Alternative preparation of 2-(2-bromo-3-fluorophenyl)hydrazono)-N-cyclopropyl-2-isocyanoacetamide. To conduct the reaction, two mixtures were first prepared:

Mixture A: To a mechanically-stirred and ice-cooled suspension of 2-bromo-3-fluoroaniline hydrochloride (17.8 g, 78.60 mmol) in a solvent mixture of acetic acid (63 mL), water (32 mL), and concentrated HCl (24 mL) was added dropwise a solution of sodium nitrite (5.97 g, 86.46 mmol) in water (30 mL), maintaining the internal temperature below 5°C. The resulting orange solution was stirred at 0°C for an additional 15 min.

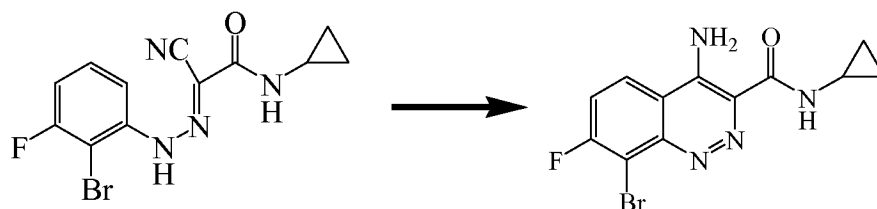
Mixture B: To a mechanically stirred solution of 2-cyano-N-cyclopropylacetamide (10.73 g, 86.46 mmol) in ethanol (235 mL) was added a solution of sodium acetate (90 g, 1.10 mol) in water (460 mL).

The resulting mixture was cooled to 0°C.

Ice-cooled Mixture A was poured into a mechanically-stirred and ice-cooled Mixture B at 0°C, maintaining the internal temperature below 5°C during the addition. The resulting mixture was stirred at 0°C overnight. Afterward, the yellow suspension was filtered, washed with water (200 mL x 3) and hexane (200 mL x 3), and dried *in vacuo* at 50°C

overnight to give the title compound (23.80 g, 93%). ¹H NMR (300.132 MHz, CDCl₃) δ ppm 0.61 - 0.73 (m, 2 H) 0.89 - 1.00 (m, 2 H) 2.79 - 2.90 (m, 1 H) 6.36 (br. s., 1 H) 6.91 (td, J = 8.1, 1.5 Hz, 1 H) 7.31 (td, J = 8.2, 5.7 Hz, 1 H) 7.47 (d, J = 8.4 Hz, 1 H) 14.35 (br. s., 1 H).

[77] Part C1. Preparation of 4-amino-8-bromo-N-cyclopropyl-7-fluorocinnoline-3-carboxamide.

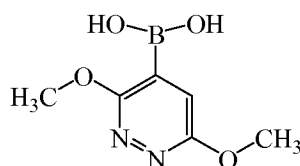


To a stirred suspension of 2-(2-bromo-3-fluorophenyl)hydrazono)-N-cyclopropyl-2-isocyanoacetamide (146.25g, 0.45 mol) in dry toluene (2.2 L) preheated to 60°C was added in a single portion aluminum chloride (126.0g, 0.95 mol). The resulting mixture was heated at 60-65°C for 20 hr. Afterward, the mixture was cooled in an ice bath, and diluted with THF (3 L). The resulting red solution was treated with 2N sodium hydroxide (1.8 L) while maintaining the temperature below 35°C. The layers were then separated, and the water layer was extracted with THF. The combined organic layers were dried over magnesium sulphate and evaporated to dryness. The resulting solids were triturated with diethyl ether at ambient temperature, filtered, and dried *in vacuo* to give the title

compound (79.6g, 54%); NMR: ^1H NMR (DMSO) δ ppm 0.73 (d, $J = 5.7$ Hz, 4H) 2.84-3.08 (m, 1H) 7.76 (t, $J = 8.9$ Hz, 1H) 8.52 (dd, $J = 9.3, 5.5$ Hz, 1H) 9.11 (d, $J = 4.8$ Hz, 1H). MS APCI, $m/z = 325/327$ ($M+H$, $M+2+H$).

[78] **Part C2. Alternative preparation of 4-amino-8-bromo-N-cyclopropyl-7-fluorocinnoline-3-carboxamide.** To a mechanically stirred suspension of 2-(2-bromo-3-fluorophenyl)hydrazono)-N-cyclopropyl-2-isocyanoacetamide (13.75 g, 42.29 mmol) in dry toluene (1.0 L) was added in portions aluminum chloride (11.84 g, 88.81 mmol). The resulting mixture was heated at 70°C for 2.5 hr, allowed to cool to room temperature, and quenched by adding Rochelle's salt (saturated aqueous potassium sodium tartrate, 300 mL). Afterward, the mixture was stirred at room temperature overnight. The aqueous layer was separated, and the organic layer was treated with fresh Rochelle's salt (300 mL) while stirring at room temperature for 1 hr. After separating the resulting layers, the organic suspension was washed with water (300 mL x 2) and filtered to give the title compound (6.45g, 46.9%). Additionally, the organic filtrate was concentrated to 100 mL, and diluted with ether (1L). The resulting solids were filtered and dried to give the title compound (5.08g, 36.9%). The total yield was 83.8%. ^1H NMR (300.132 MHz, CDCl_3) δ ppm 0.57 - 0.77 (m, 2 H) 0.84 - 1.01 (m, 2 H) 2.98 (td, $J = 7.2, 3.8$ Hz, 1 H) 7.47 (dd, $J = 9.2, 7.7$ Hz, 1 H) 7.84 (dd, $J = 9.3, 5.1$ Hz, 1 H) 8.52 (br. s., 1 H). MS APCI, $m/z = 325/327$ ($M+H$, $M+2+H$).

[79] **Reagent 2. Preparation of 3,6-dimethoxypyridazin-4-ylboronic acid.**



[80] **Part A Preparation of 3,6-dimethoxypyridazine.** A 5L, 3-neck flask was charged with 500.0g (3.356 moles) of 2,6-dichloropyridazine, followed by 1000 mL of methanol. The resulting pale yellow solution was treated with 2300 mL of a 25% (by weight) solution of NaOCH_3 in methanol over 3 hr. The resulting mixture was heated at gentle reflux for 20 hr. Afterward, the mixture was cooled to 40°C and poured into 6000 mL water/2000 mL CH_2Cl_2 . The aqueous layer was extracted with CH_2Cl_2 (2x1L). The combined organics were then dried over MgSO_4 to give a white crystalline solid. The solid was further dried *in vacuo* to give the title compound (458.3g ;97.5% yield). NMR spectrum (DMSO) δ ppm 3.94 (s, 6H) 7.17 (s, 2H).

[81] Part B. Preparation of 3,6-dimethoxypyridazin-4-ylboronic acid.

A 3L 3-neck flask was charged with 550 mL of THF. The mixture was cooled to -20°C. Next, 216mL of a 2.5M n-BuLi solution was added in a fast stream, resulting in an exotherm to 3°C. The mixture was re-cooled to -20°C, and 76.1mL of neat diisopropylamine was added while keeping the temperature below 0°C. The resulting mixture was to -70°C. A solution of 36.26g (0.259 mol) of 3,6-dimethoxypyridazine in 300 mL of THF was then added while maintaining the mixture at -70°C or below. After 30 min, 70 mL (0.303 mol) of neat triisopropyl borate was added while allowing the temperature to rise to -65°C. The mixture was then allowed to warm to -20°C. At that point, the reaction was quenched with 270 mL of water over 60 min, resulting in a final temperature of 24°C. An additional 270 mL of water was added in a single portion. The resulting mixture was stirred overnight. Afterward, 1100 mL of solvent was removed and 500 mL of water was added to give an amber solution (trace amount of solids). The aqueous layer (pH 13) was extracted with diethyl ether (2 X 300 mL), and then treated with 65mL of 48% HBr until the pH decreased to 5-6. The suspension was stirred for 2 hr, and the resulting solids were filtered and washed once with water. The solids were then dried *in vacuo* to a constant weight to give the title compound (42.1g; 88% yield). NMR spectrum (DMSO) δ ppm 3.96 (s, 6H) 7.08 (s, 1H) 8.40 (br.s, 2H).

[82] Example 2. Preparation of 4-amino-N-cyclopropyl-8-(3,6-

dimethoxypyridazin-4-yl)-7-fluorocinnoline-3-carboxamide methanesulfonic acid salt. To a solution of 4-amino-N-cyclopropyl-8-(3,6-dimethoxypyridazin-4-yl)-7-fluorocinnoline-3-carboxamide (0.78 g, 2.03 mmol) in methanol (14 ml) at ambient temperature was added dropwise a solution of methanesulfonic acid (0.162 ml, 2.5 mmol) in methanol (0.5 ml). The resulting solution was concentrated to afford a yellowish solid, which, in turn, was triturated with EtOAc (15 ml), collected by filtration, washed with fresh EtOAc (15 ml), and dried *in vacuo* at 60°C for 14 hr to give the title compound (0.786 g, 81%) as a pale yellow solid. NMR: ¹H NMR (500 MHz, *MeOD*) δ ppm 0.67 - 0.72 (m, 2 H) 0.83 - 0.90 (m, 2 H) 2.69 (s, 3 H) 2.88 - 2.94 (m, *J*=7.4, 7.4, 3.9, 3.7 Hz, 1 H) 3.99 (s, 3 H) 4.13 (s, 3 H) 7.42 (s, 1 H) 7.83 (t, *J*=9.0 Hz, 1 H) 8.70 (dd, *J*=9.5, 5.1 Hz, 1 H). MS ^m/_z: 385 (M+H).

*Biological Assays***[83] Example 3. GABAA Binding.**

[84] GABAA1, GABAA2, GABAA3, and GABAA5 binding K_i 's were obtained for the compound of Formula I using a procedure tracking the procedure described in US Patent 7,425,556, Columns 199-204. The observed binding K_i 's are as follows:

GABAA1	0.11 ± 0.035 nM
GABAA2	0.65 ± 0.45 nM
GABAA3	0.99 ± 0.16 nM
GABAA5	35.3 ± 8.5 nM

[85] Example 4. Relative Potentiation of GABAA Binding.

[86] The relative potentiations for GABAA1, GABAA2, GABAA3, and GABAA5 were obtained for the compound of Formula I using a procedure tracking the procedure described in US Patent 7,425,556, Columns 198-199. The observed relative potentiations obtained from the concentration response curves are as follows:

	% Potentiation Normalized to Diazepam at 1 μ M
GABAA1	-0.01
GABAA2	0.25
GABAA3	0.28
GABAA5	0.4

[87] Example 5. EEG Protocol. The compound of Formula I was analyzed using an EEG protocol tracking the protocol described in US Publ. Patent Appl. US2008/0318925, pp. 148-150. Spontaneous EEG from behaving animals in the presence of the compound of Formula I with functionally selective α_2 and α_3 pharmacologies exhibited dose-dependent increases in high frequency oscillations in both the high beta and gamma ranges with no significant increases at lower frequencies.

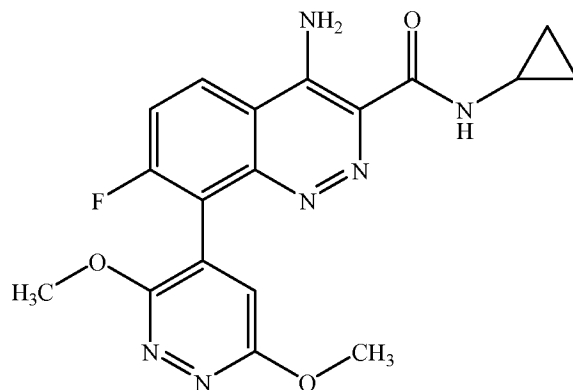
* * * * *

[88] The words "comprise," "comprises," and "comprising" in this patent (including the claims) are to be interpreted inclusively rather than exclusively. This interpretation is intended to be the same as the interpretation that these words are given under United States patent law.

[89] The above description of illustrative embodiments is intended only to acquaint others skilled in the art with the invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This
5 invention, therefore, is not limited to the above embodiments, and may be variously modified.

We claim:

1. A compound of Formula I or a salt thereof, wherein the compound of Formula I corresponds to:



(I).

2. A compound or salt according to claim 1, wherein the salt comprises a pharmaceutically acceptable salt.

3. A salt according to claim 1, wherein the salt comprises a sulfonate salt.

4. A salt according to claim 3, wherein the salt comprises a methanesulfonate salt.

5. A salt according to claim 1, wherein the salt comprises a salt derived from an inorganic acid.

6. A pharmaceutical composition, wherein the pharmaceutical composition comprises:

the compound of Formula I or pharmaceutically acceptable salt thereof according to claim 2; and
a pharmaceutically acceptable carrier, diluent, or excipient.

7. A method for treating an anxiety disorder in a mammal, wherein the method comprises administering to the mammal a therapeutically effective amount of the compound of Formula I or pharmaceutically acceptable salt thereof according to claim 2.

8. The method according to claim 7, wherein the anxiety disorder comprises panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia,

agoraphobia without history of panic disorder, specific phobia, social phobia, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, or generalized anxiety disorder due to a general medical condition.

5

9. The method according to claim 7, wherein the mammal is a human.

10. A method for treating an anxiety disorder in a mammal, wherein:

the method comprises administering to the mammal:

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the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2, and

a cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor; and

when combined, the amount of the compound of Formula I or a pharmaceutically

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acceptable salt thereof and the amount of the cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor are therapeutically effective to treat the anxiety disorder in the mammal.

11. A method for treating an anxiety disorder in a mammal, wherein:

20

the method comprises administering to the mammal:

the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2, and

a selective serotonin reuptake inhibitor; and

when combined, the amount of the compound of Formula I or a pharmaceutically

25

acceptable salt thereof and the amount of the selective serotonin reuptake inhibitor are therapeutically effective to treat the anxiety disorder in the mammal.

12. A method for treating a cognitive disorder in a mammal, wherein the method comprises administering to the mammal a therapeutically effective amount of the

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compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2.

13. The method according to claim 12, wherein the cognitive disorder is

Alzheimer's disease, dementia, dementia due to Alzheimer's disease, or dementia due to Parkinson's disease.

14. The method according to claim 12, wherein the mammal is a human.

15. A method of treating a cognitive disorder in a mammal, wherein:

5 the method comprises administering to the mammal:

the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2, and

a cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor; and

10 when combined, the amount of the compound of Formula I or a pharmaceutically acceptable salt thereof and the amount of the cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor are therapeutically effective to treat the cognitive disorder in the mammal.

15 16. A method for treating a cognitive disorder in a mammal, wherein:

the method comprises administering to the mammal:

the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2, and

a selective serotonin reuptake inhibitor; and

20 when combined, the amount of the compound of Formula I or a pharmaceutically acceptable salt thereof and the amount of the selective serotonin reuptake inhibitor are therapeutically effective to treat the cognitive disorder in the mammal.

25 17. A method of treating a mood disorder in a mammal, wherein the method comprises administering to the mammal a therapeutically effective amount of the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2.

18. The method according to claim 17, wherein the mood disorder comprises a depressive disorder.

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19. The method according to claim 18, wherein the depressive disorder comprises major depressive disorder, dysthymic disorder, bipolar depression and/or bipolar mania, bipolar I with or without manic, depressive or mixed episodes, bipolar II, cyclothymic

disorder, mood disorder due to a general medical condition, manic episodes associated with bipolar disorder, or mixed episodes associated with bipolar disorder.

20. The method according to claim 17, wherein the mammal is a human.

5

21. A method of treating a mood disorder in a mammal, wherein:

the method comprises administering to the mammal:

the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2, and

10

a cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor; and

when combined, the amount of the compound of Formula I or a pharmaceutically acceptable salt thereof and the amount of the cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor are therapeutically effective to treat the mood disorder in the mammal.

15

22. A method for treating a mood disorder in a mammal, wherein:

the method comprises administering to the mammal:

the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2, and

20

a selective serotonin reuptake inhibitor; and

when combined, the amount of the compound of Formula I or a pharmaceutically acceptable salt thereof and the amount of the selective serotonin reuptake inhibitor are therapeutically effective to treat the mood disorder in the mammal.

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23. A method of treating schizophrenia in a mammal, wherein the method comprises administering to the mammal a therapeutically effective amount of the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2.

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24. The method according to claim 23, wherein the treatment of schizophrenia comprises treating a cognitive disorder associated with schizophrenia.

25. The method according to claim 23, wherein the mammal is a human.

26. A method of treating schizophrenia in a mammal, wherein:

the method comprises administering to the mammal:

the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2, and

5 a cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor; and

when combined, the amount of the compound of Formula I or a pharmaceutically acceptable salt thereof and the amount of the cognitive enhancing agent, memory enhancing agent, or choline esterase inhibitor, are therapeutically effective to treat
10 schizophrenia in the mammal.

27. A method for treating schizophrenia in a mammal, wherein:

the method comprises administering to the mammal:

the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2, and

15 a selective serotonin reuptake inhibitor; and

when combined, the amount of the compound of Formula I or a pharmaceutically acceptable salt thereof and the amount of the selective serotonin reuptake inhibitor are therapeutically effective to treat the schizophrenia in the mammal.

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28. A method of treating pain in a mammal, wherein the method comprises administering to the mammal a therapeutically effective amount of the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2.

25 29. The method according to claim 28, wherein the mammal is a human.

30. A method of modulating activity of a GABAA receptor, wherein the method comprises contacting the GABAA receptor with the compound of Formula I or salt thereof according to claim 1 or 2.

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31. A method according to claim 30, wherein the GABAA receptor comprises a GABAA1 receptor, GABAA2 receptor, GABAA3 receptor, or GABAA5 receptor.

32. A method according to claim 30, wherein the GABAA receptor comprises a GABAA2 receptor.

33. A method according to claim 30 or 32, wherein the GABAA receptor
5 comprises a GABAA3 receptor.

34. A method for making the compound of Formula I or a salt thereof according to claim 1 or 2, wherein the method comprises reacting 4-amino-8-bromo-N-cyclopropyl-7-fluorocinnoline-3-carboxamide with 3,6-dimethoxypyridazin-4-ylboronic acid.
10

35. The method according to claim 34, wherein the reaction is conducted in the presence of a metal catalyst.

36. The method according to claim 35, wherein the catalyst comprises a palladium
15 catalyst.

37. The method according to claim 36, wherein the palladium catalyst comprises tris(dibenzylideneacetone)dipalladium(0).

20 38. The method according to any one of claims 34-37, wherein the reaction is conducted in the presence of tri-t-butylphosphonium tetrafluoroborate.

39. The method according to any one of claims 34-38, wherein the reaction is conducted in a solvent that comprises an organic solvent.
25

40. The method according to claim 39, wherein the solvent comprises acetonitrile.

41. The method according to claim 39 or 40, wherein the solvent further comprises water.
30

42. The compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 1 for use in therapy.

43. Use of the compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 2 for the manufacture of a medicament for use in the treatment of a disorder in which GABAA receptor activity is implicated.

5 44. Use according to claim 43, wherein the disorder comprises an anxiety disorder in a mammal.

 45. Use according to claim 44, wherein the anxiety disorder comprises panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia,
10 agoraphobia without history of panic disorder, specific phobia, social phobia, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, or generalized anxiety disorder due to a general medical condition.

15 46. Use according to claim 43, wherein the disorder comprises a cognitive disorder in a mammal.

 47. Use according to claim 46, wherein the cognitive disorder is Alzheimer's disease, dementia, dementia due to Alzheimer's disease, or dementia due to Parkinson's
20 disease.

 48. Use according to claim 43, wherein the disorder comprises a mood disorder in a mammal.

25 49. Use according to claim 48, wherein the mood disorder comprises a depressive disorder.

 50. Use according to claim 49, wherein the depressive disorder comprises major depressive disorder, dysthymic disorder, bipolar depression and/or bipolar mania, bipolar I
30 with or without manic, depressive or mixed episodes, bipolar II, cyclothymic disorder, mood disorder due to a general medical condition, manic episodes associated with bipolar disorder, or mixed episodes associated with bipolar disorder.

51. Use according to claim 43, wherein the disorder comprises schizophrenia in a mammal.

52. Use according to claim 51, wherein the treatment of schizophrenia comprises
5 treating a cognitive disorder associated with schizophrenia.

53. Use according to claim 43, wherein the disorder comprises pain in a mammal.

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/SE2010/050892
A. CLASSIFICATION OF SUBJECT MATTER**IPC: see extra sheet**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:A61K, A61P, C07D

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

SE, DK, FI, NO classes as above

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

EPO-Internal, PAJ, WPI data, CHEM ABS Data**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20070142382 A1 (CHAPDELAINE MARC J ET AL), 21 June 2007 (2007-06-21); paragraphs [0002], [0012]-[0019], [0089], [0284]-[0286], [0306], [0324]-[0325], [0333], [0380]-[0382]; pages 116, 121, 129, 151; claims 1-22; examples 93, 96-97, 130-131, 161, 163-164	1-53
X	WO 2008155573 A1 (ASTRAZENECA AB ET AL), 24 December 2008 (2008-12-24); page 16, line 12 - line 15; page 38, line 11 - page 39, line 8; page 44, line 30 - line 33; pages 178, 181, 185, 198; claims 1-23; examples 93, 96-97, 130-131, 161, 163-164	1-53
X	WO 2007073283 A1 (ASTRAZENECA AB ET AL), 28 June 2007 (2007-06-28); page 38, line 15 - page 39, line 8; page 44, line 30 - line 33; pages 177, 180, 184, 189, 197; claims 1-67; examples 93, 96-97, 130-131, 161, 163-164	1-53
A	EP 0328282 A2 (ICI AMERICA INC), 16 August 1989 (1989-08-16); figure la; claims 1-4	1-53

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search

17-11-2010

Date of mailing of the international search report

17-11-2010
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CORRECTED

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050892

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4886880 A (HAHN HOLGER ET AL), 12 December 1989 (1989-12-12); column 1, line 6 - line 13; claims 1-9; example 72 -- -----	1-53

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050892

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7-33
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 7-33 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of: second sheet

International Patent Classification (IPC)

C07D 403/04 (2006.01)

A61K 31/502 (2006.01)

A61P 25/04 (2006.01)

A61P 25/18 (2006.01)

A61P 25/22 (2006.01)

A61P 25/24 (2006.01)

A61P 25/28 (2006.01)

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Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE2010/050892

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