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(54) Title: NOVEL METHODS

(57) Abstract: The disclosure provides methods the treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis, and for protecting or reinforcing the blood-brain barrier, comprising administering to a patient in need thereof, a therapeutically effective amount of a 5-HT_{2A}.



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NOVEL METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to, and the benefit of, U.S. Provisional Application Ser. No. 63/343,192, filed on May 18, 2022, the contents of which are hereby incorporated by reference in its entirety.

TECHNICAL FIELD

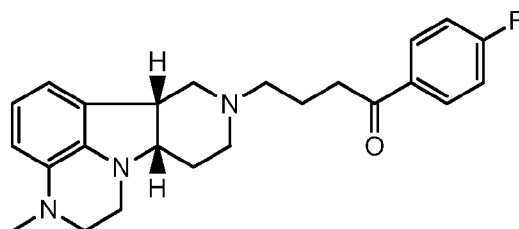
[0001] The present disclosure relates to use of a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, for example a substituted heterocycle fused gamma-carbolines as described herein, in free, pharmaceutically acceptable salt or prodrug form, for the treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis, and for protecting or reinforcing the blood-brain barrier.

BACKGROUND OF THE INVENTION

[0002] Substituted heterocycle fused gamma-carbolines such as lumateperone are known to be 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligands, which are useful in treating central nervous system disorders. These compounds antagonize the serotonin-2A (5-HT_{2A}) receptor, and/or modulate dopamine receptor signaling at the level of key intra-cellular phosphoproteins. Such compounds are principally known to be useful for the treatment of positive and negative symptoms of schizophrenia. At dopamine D2 receptors, these compounds have dual properties and act as both post-synaptic antagonists and pre-synaptic partial agonists. They also stimulate phosphorylation of glutamatergic NMDA NR2B, or GluN2B, receptors in a mesolimbic specific manner. It is believed that this regional selectivity in the brain areas thought to mediate the efficacy of antipsychotic drugs, together with the serotonergic, glutamatergic, and dopaminergic interactions, may result in antipsychotic efficacy for positive, negative, affective and cognitive symptoms associated with schizophrenia. The compounds also exhibit serotonin reuptake inhibition, providing antidepressant activity for the treatment of schizoaffective disorder, co-morbid depression, and/or as a stand-alone treatment for major depressive disorder. The 5-HT_{2A}

or 5-HT_{2A}/D2 receptor ligands as described are also useful for the treatment of bipolar disorder and other psychiatric and neurodegenerative disorders, particularly behavioral disturbances associated with dementia, autism and other CNS diseases. These features may be able to improve the quality of life of patients with schizophrenia and enhance social function to allow them to more fully integrate into their families and their workplace. These compounds display differential dose-dependent effects, selectively targeting the 5-HT_{2A} receptor at low doses, while progressively interacting with the D2 receptor at higher doses. As a result, at lower doses, they are useful in treating sleep, aggression and agitation. At a high-dose, they can treat acute exacerbated and residual schizophrenia, bipolar disorders, and mood disorders.

[0003] Lumateperone, having the formula:



is a novel therapeutic agent with potent ($K_i=0.5\text{nM}$) 5-HT_{2A} receptor antagonism, activity as a mesolimbic/mesocortical-selective dopamine receptor protein phosphorylation modulator consistent with presynaptic D2 receptor partial agonism and postsynaptic D2 receptor antagonism ($K_i=32\text{nM}$) in vivo, high D1 receptor affinity ($K_i=52\text{nM}$), and inhibition of the serotonin transporter (SERT) ($K_i=26\text{--}62\text{nM}$, using different assays for SERT activity).

Lumateperone has been approved in the United States for the treatment for schizophrenia and bipolar depression in adults, and it is in clinical development for the treatment of other neuropsychiatric disorders, such as major depressive disorder (MDD), agitation in dementia, including Alzheimer's Disease.

[0004] Lumateperone and related compounds have been disclosed in U.S. Pat. No. 6,548,493; 7,238,690; 6,552,017; 6,713,471; U.S. RE39,680, and U.S. RE39,679, as novel compounds useful for the treatment of disorders associated with 5-HT_{2A} receptor modulation such as anxiety, depression, psychosis, schizophrenia, sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain, and social phobias. WO 2000/077002 and

U.S. Pat. No. 7,071,186, also disclose methods of making substituted heterocycle fused gamma-carbolines and uses of these gamma-carbolines as serotonin agonists and antagonists useful for the control and prevention of central nervous system disorders such as addictive behavior and sleep disorders. WO 2009/145900 and U.S. 8,598,119, and WO 2013/155504 and U.S. 11,053,245, and WO 2013/155506 and U.S. 11,124,514, each incorporated herein by reference, disclose the use of specific substituted heterocycle fused gamma-carbolines for the treatment of a combination of psychosis and depressive disorders as well as sleep, depressive and/or mood disorders in patients with psychosis or Parkinson's disease, for the treatment of post-traumatic stress disorder, impulse control disorders and related disorders, and for the treatment or prophylaxis of disorders associated with dementia, particularly behavioral or mood disturbances such as agitation, irritation, aggressive/assaultive behavior, anger, physical or emotional outbursts and psychosis and sleep disorders associated with dementia. WO 2009/114181 and U.S. 8,648,077, each incorporated herein by reference, disclose methods of preparing toluenesulfonic acid addition salt crystals of particular substituted heterocycle fused gamma-carbolines, e.g., toluenesulfonic acid addition salt of 4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4': 4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone.

[0005] WO 2011/133224 and U.S. 8,993,572, each incorporated herein by reference, disclose prodrugs/metabolites of substituted heterocycle fused gamma-carboline for improved formulation, e.g., extended/controlled release formulation. This application discloses that heterocycle fused gamma-carboline N-substituted with a 4-fluorophenyl(4-hydroxy)butyl moiety are shown to have high selectivity for the serotonin transporter (SERT) relative to the heterocycle fused gamma-carboline containing 4-fluorophenylbutanone.

[0006] WO 2009/145900 and U.S. 8,598,119 also disclose that selected substituted heterocycle fused gamma-carboline compounds have nanomolar affinity for the serotonin reuptake transporter (SERT) and so are selective serotonin reuptake inhibitors.

[0007] As disclosed in WO2015/154025, US 2017/0183350, U.S. 10,077,267, WO 2017/165843, US 2019/0231780, U.S. 10,688,097, WO 2019/183546, and US 2021/0008065, each incorporated herein by reference, deuterated forms of lumateperone and related compounds have been shown to have improved metabolic stability.

[0008] WO2019/178484 and US 2021/0060009, the contents of each of which are incorporated by reference in their entireties, disclose the use of lumateperone and related analogs for the treatment of acute depression and acute anxiety. Unlike traditional antidepressants, including selective serotonin reuptake inhibitors (SSRIs), such as sertraline (Zoloft, Lustral), escitalopram (Lexapro, Cipralex), fluoxetine (Prozac), paroxetine (Seroxat), and citalopram (Celexa), which generally take weeks or months to achieve their full effects (SSRIs typically have an onset of action 3-4 weeks after initiation of daily dosing), lumateperone is believed to achieve rapid efficacy, in as little as a week or less, and even an immediate onset of action (e.g., hours to days after initial dosing). In this regard, lumateperone and its analogs share the functional benefits of ketamine. Ketamine has recently been tested as a rapid-acting antidepressant for treatment-resistant depression, in bipolar disorder and major depressive disorder, but it has significant side effects and risk of overdose, and it is not orally active. Lumateperone has shown promise as an orally-available, rapid-acting treatment for depression and anxiety, alone or in conjunction with other anti-anxiety or anti-depressant drugs, such as in treating acute depression and acute anxiety with the rapid onset characteristic of ketamine, but without ketamine's side effects or lack of oral activity. It is believed that these effects are mediated through indirect dopamine D1 receptor-dependent enhancement of NMDA and AMPA currents coupled with activation of the mTOR (e.g., mTORC1) signaling pathway and paralleled by anti-inflammatory properties.

[0009] In addition, unlike benzodiazepine class agents, lumateperone and related compounds appear to be non-addictive, and therefore, particularly suitable for the treatment of acute depressive episodes, including suicidal ideation and severe acute depression and/or severe acute anxiety. Lumateperone has already been approved by the U.S. FDA for the treatment of schizophrenia and bipolar disorder, under the brand name Caplyta®, and it is undergoing clinical study for the treatment of major depressive disorder and other disorders.

[0010] Immunological disturbances have been reported in subsets of patients suffering from generalized anxiety, major depressive disorder (MDD) and/or schizophrenia. *See, e.g.,* Mechawar & Savitz, "Neuropathology of mood disorders: do we see the stigmata of inflammation?" *Translational Psychiatry* 6:e946-e946 (2016); Zhang et al., "Brain-derived Neurotrophic Factor (BDNF)-TrkB Signaling in Inflammation-related Depression and Potential Therapeutic Targets," *Curr. Neuropharmacol.* 14:721-731 (2016); Herman & Pasinetti,

“Principles of inflammasome priming and inhibition: Implications for psychiatric disorders,” *Brain Behav. Immun.* 73:66-84 (2018); Beurel et al., “The Bidirectional Relationship of Depression and Inflammation: Double Trouble,” *Neuron* 107:234-256 (2020). In addition, exposure to infectious agents and subsequent heightened immune activity can also lead to transient depressive symptoms (e.g., anhedonia, fatigue, lethargy, and depressed mood). See, e.g., Nazimek et al., “The role of macrophages in anti-inflammatory activity of antidepressant drugs,” *Immunobiology* 222:823-830 (2017); Beurel et al., (2020). This concept is supported by studies in which direct administration of pro-inflammatory factors induced stress-like and/or depressive-like effects in patients or animals (Mechawar & Savitz, 2016) and studies showing that adverse symptoms are reversed by direct blockade of certain immune pathways such as interleukin (IL)-1b (Koo & Duman, “IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress,” *Proc. Nat. Acad. Sci. USA* 105:751-756 (2008); Koo & Duman, “Evidence for IL-1 receptor blockade as a therapeutic strategy for the treatment of depression,” *Curr. Opin. Invest. Drugs* 10:664-671 (2009)).

[0011] Viral infections and psychiatric illness have long been suspected of being linked. As early as the late 1800’s, influenza epidemics were noted to be temporally associated with increases in psychiatric illness. More recently, evidence suggests that chronic inflammation of the central nervous system (CNS) is often reported to be associated with psychiatric states. To date, there have been several studies suggesting a cause-and-effect relationship between viral infections of the CNS, including herpes simplex 1 and 2 and measles, and psychiatric symptoms, including depression and schizophrenia. It has even been suggested that some psychiatric illnesses that were previously never suspected of having an infectious component, may in-fact be examples of very mild encephalitis.

[0012] One of the most common causes of viral encephalitis is the herpes simplex virus (HSV). Significant work has been done to examine psychological outcomes of HSV encephalitis, and the results show that a significant number of HSV patients develop neuropsychological deficits, such as impairments in attention, executive function, retrograde memory, working memory, and visuo-spatial processing, as well as mood disorders, including depression and anxiety. Some of these effects have been found to last long beyond the acute phase of infection. It has also been shown that some of these deficits correlated to cerebral damage visible by MRI (magnetic resonance imaging), such as medial temporal lobe damage.

[0013] West Nile Virus (WNV) infection can also involve neuroinvasive disease, resulting in encephalitis or meningitis. Depression has reported as a prominent outcome in such patients. An 8-year study following WNV survivors showed higher than expected rates of mild to severe depression in patients with no prior history of depression.

[0014] The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) introduced a new category of “psychopathological states due to a general medical condition,” which included delirium, dementia, amnesia, psychosis, mood disorder (e.g., depression), anxiety disorder, sexual dysfunction, and sleep disorder. These have been associated with severe infections, such as bacterial or viral encephalitis and meningitis.

[0015] Pro-inflammatory cytokines, such as TNF-alpha and IL-6, are primarily secreted by peripheral monocytes and macrophages, and are thought to be secreted by CNS microglial cells as well. These cytokines activate other cellular components of the inflammatory response to infection. In addition, the anti-inflammatory cytokines IL-4 and IL-10 are also secreted by monocytes and macrophages, and perhaps microglial cells as well. C-reactive protein (CRP) is a common marker of an ongoing inflammatory response. Recent evidence has shown that major depressive disorder (MDD) is also associated with higher levels of TNF-alpha, IL-6, IL-1-beta, IL-2, and interferon-gamma. In addition, interferon-alpha has been shown to induce severe depressive symptoms in about one-third of patients, including suicidality. However, it has not been clear whether this inflammatory state is a cause of MDD or an effect of MDD.

[0016] In the last twenty years, it has been discovered that a significant cause of encephalitis is an autoimmune reaction against neural proteins, especially against the NMDA receptor and the leucine-rich glioma 1 (LGL-1) receptor protein. This autoimmune encephalitis (AIE) presents a variety of neurological and psychiatric symptoms, including amnesia, confusion, seizures, cognitive deficits, and mood disorders. At least ten different synaptic antineuronal and antiglial antibodies have been identified, and many more are suspected to exist. The mainstay of AIE treatment remains intravenous immune globulin treatment to clear autoimmune antibodies, such as rituximab.

[0017] Although 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligands are known to be useful for treating schizophrenia, and mood disorders such as depression and anxiety, generally, including the acute treatment of depression or anxiety, such compounds have not been previously suggested or

disclosed for the treatment of psychiatric disorders caused by encephalitis or for the treatment of affective symptoms of encephalitis.

[0018] New and improved methods for treating psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis are urgently needed. New and improved methods for protecting and reinforcing the blood-brain barrier are also urgently needed.

BRIEF SUMMARY OF THE INVENTION

[0019] We have surprisingly found that substituted heterocycle fused gamma-carbolines as described herein, particularly lumateperone, are effective in reducing aberrantly elevated levels of proinflammatory cytokines in both brain and serum, alters key pathways involved in tissue integrity and the maintenance of the blood-brain barrier (BBB), conferred anxiolytic and antianhedonic properties in rats, and reinforced BBB protection during inflammatory and stress challenges. This suggests that such compounds will be effective in the treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis.

[0020] The present disclosure thus provides a method for the treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for the treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis, the method comprising administering an therapeutically effective amount of (i) a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, for example, a substituted heterocycle fused gamma-carboline, as described herein, in free base, pharmaceutically acceptable salt, or prodrug form, to a patient in need thereof.

[0021] In another aspect, the present disclosure provides a method for protecting or reinforcing the blood-brain barrier, comprising administering to a patient in need thereof, a therapeutically effective amount of (i) a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, for example, a substituted heterocycle fused gamma-carboline, as described herein, in free base, pharmaceutically acceptable salt, or prodrug form, to a patient in need thereof.

[0022] In some embodiments, the present disclosure provides the above methods, wherein such methods further comprise the concurrent administration of a PDE1 inhibitor, for example, the compounds of Formula II, as disclosed herein. Such compounds are disclosed in, for example, U.S. Patent 9,545,406, the contents of which is hereby incorporated by reference in its

entirety, as having utility in the treatment of central nervous system diseases, disorders and injuries, and as neuroprotective and/or neural regenerative agents. Such compounds are further disclosed in, for example, WO 2018/049417, the contents of which is hereby incorporated by reference in its entirety, as having utility in the treatment of diseases and disorders characterized by neuroinflammation.

DETAILED DESCRIPTION

[0023] Lumateperone is a therapeutic agent with potent binding to the 5-HT_{2A} receptor ($K_i=0.5\text{nM}$) and moderate binding to the D₁ and D₂ receptors and the serotonin transporter (SERT). Functionally, receptor binding can generally result in either agonist activity, partial agonist activity, or antagonist activity. Lumateperone has been found to exhibit potent antagonist activity at the 5-HT_{2A} receptor and SERT, and mixed agonist/antagonist activity at the D₁ and D₂ receptors (depending on cell type). In particular, lumateperone shows activity as a mesolimbic/mesocortical-selective dopamine receptor protein phosphorylation modulator consistent with presynaptic D₂ receptor partial agonism and postsynaptic D₂ receptor antagonism ($K_i = 32\text{nM}$) in vivo, with high D₁ receptor affinity ($K_i = 52\text{nM}$), and inhibition of serotonin transporter activity (SERT) ($K_i=26\text{-}62\text{nM}$, using different assays for SERT activity). Lumateperone also indirectly enhances NMDA- and AMPA-mediated neurotransmission (Titulaer et al., “Lumateperone increases glutamate release in the rat medial prefrontal cortex,” *Eur. Neuropsychopharmacol.* 53:S556-S557 (2022)). Lumateperone is approved in the United States as a treatment for schizophrenia and for bipolar depression, and it is being studied for the treatment of major depressive disorder, agitation in dementia, including Alzheimer’s Disease, and other psychiatric disorders.

[0024] It has been unexpectedly found that lumateperone has the potential to ameliorate pathological levels of inflammation in brain, microglia, and serum, and to preserve the integrity of the BBB following immunological insult and stress in rodents. When administered over a range of doses at different time points, lumateperone reduces key pro-inflammatory markers elevated by an inflammogen (e.g., lipopolysaccharide, LPS) or by acute restraint stress. Surprisingly, the cytokines IL-1 β , IL-6, and TNF- α that are normalized by lumateperone treatment are known to be elevated in patients with psychiatric disorders, and in human post-mortem tissues including prefrontal cortex from suicide victims.

[0025] Lumateperone treatment reduces expression of the *Nlrp3* inflammasome, which is a large multiprotein complex containing NLRP3, a cytosolic sensor involved in innate immunity. Although the inflammasome has no baseline activity, once activated by stress, infections, or other stimuli, the complex is believed to generate active forms of the inflammatory cytokines IL-1 β and IL-18. In preclinical studies, *Nlrp3*-null mutant mice were reported to be resilient to the effects of stress on depression-like behavior, and *Nlrp3* expression was increased in peripheral blood mononuclear cells (PBMCs) from untreated patients with MDD.

[0026] The present disclosure shows that lumateperone treatment decreases *Nlrp3* transcript levels under conditions evoking pathological inflammation, which may contribute, in part, to the antidepressant-like action of lumateperone. In addition, it is shown that lumateperone has anxiolytic-like effects and reverses anhedonia in rats.

[0027] Stress and inflammation are thought to compromise BBB integrity and functionality in many pathological states. The BBB regulates ion and nutrient exchange between the brain and blood while protecting brain tissue from harmful agents. Malfunctioning BBB can result in chemical exposure and infections, and there have been reports suggesting that the BBB may be compromised in persons with psychiatric disorders, such as schizophrenia or depression, or in neurodegenerative diseases, such as Alzheimer's disease (substantial evidence has documented BBB disruption in these diseases).

[0028] The present disclosure provides evidence of an increased RNA copy number of hippocampal *Cldn5* in naïve mice after receiving lumateperone two hours prior to measurement, and confirms these results in the brain of acutely stressed or LPS-treated mice. Claudins such as *Cldn5* are small proteins (20-27 kDa) expressed in the tight junctions between brain endothelial cells, and they help to maintain BBB integrity. In mice, *Cldn5* ablation enhances BBB permeability and allows infiltration of large proteins up to ~69kD (e.g., IL-6) into brain parenchyma; this result has been associated with depressive-like behavior and behavioral impairments characteristic of schizophrenia and depression. Lumateperone-mediated upregulation of *Cldn5* gene expression is thus consistent with enhanced protein expression observed in mice treated with other chronic antipsychotic or antidepressant medications. Whereas chronic but not acute imipramine treatment rescued social avoidance and restored *Cldn5* levels that were altered by social defeat stress, acute lumateperone treatment is unexpectedly efficacious in improving similar behavioral states.

[0029] This finding highlights another potential difference between classic antidepressant treatment and lumateperone treatment. Since it is observed that reduced sodium fluorescein (NaFl) brain uptake and differences in anti-inflammatory cytokine expression between the central nervous system and the periphery, without being bound by theory, it is believed that *Cldn5* may change early after lumateperone administration resulting, in the preservation of BBB integrity and limiting the infiltration of large proteins (e.g., IL-6), infectious agents, and other potential pro-inflammatory stimuli into the CNS. Moreover, TNF- α /NF κ -B signaling increases BBB permeability by decreasing tight junction protein expression of *Cldn5*.

[0030] Classical antidepressants are also reported to modulate levels of ICAM-1, which is involved in leukocyte brain infiltration and BBB hyperpermeability. Levels of ICAM-1, a cell adhesion molecule and a member of the immunoglobulin gene superfamily, have been shown to be increased in the orbitofrontal cortex of patients with depression. The present disclosure shows that lumateperone acutely decreases *Icam1* expression in preclinical models. These findings are also consistent with literature showing that ICAM1 upregulation favors leukocyte migration through the endothelium and blood vessel wall regulating the BBB. Collectively, the results described herein suggest that lumateperone regulates a repertoire encompassing signaling networks involved in a variety of biological processes relevant to maintenance of BBB integrity and control deleterious inflammatory states.

[0031] Increased BBB integrity is also known to activate microglia and lead to changes in microglia phenotype. In the CNS, microglia are an important component of the local brain immune response. It is disclosed herein that in acute inflammatory conditions, lumateperone significantly increases expression of genes related to microglia physiological functions and anti-inflammatory phenotype, and decreases expression of microglia markers related to immune modulation. It is unexpectedly shown that enriched hippocampal microglia recapitulated the anti-inflammatory responses seen in whole brain homogenates. One of the genes overexpressed in hippocampi from LPS-treated mice was *Csf1*. This gene encodes the ligand for the microglia receptor CSF1R which is involved in maintaining microglia viability and immunologic surveillance. LPS-induced increases in *Csf1* expression are found to be significantly reduced with lumateperone coadministration. Furthermore, the results described herein show that lumateperone upregulates the anti-inflammatory cytokine IL-10, which could add to the repertoire of inflammation-resolving mechanisms following abnormal levels of stress and

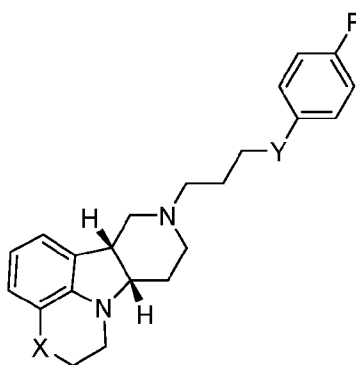
inflammation, possibly by influencing microglia function. Overall, the data described herein shows that the ability of lumateperone to alter microglial gene expression and to reduce *Csf1* gene expression following an inflammatory challenge may prevent activation of microglial function after exposure to proinflammatory stimuli.

[0032] Stress and agents that elicit neuroinflammation are strongly implicated in the etiology of diverse brain diseases including neurodegenerative disorders, psychiatric disorders (e.g., schizophrenia), and mood disorders (e.g., bipolar disorder, depression, and anxiety). Many infectious agents, including herpes simplex virus 1 and 2, Epstein-Barr virus, and cytomegalovirus (CMV), can be elevated in individuals with psychiatric conditions including bipolar disorder and schizophrenia. Further, viruses such as CMV can trigger psychiatric pathology in part by directly elevating pro-inflammatory cytokines including TNF- α and IL-6. Coronaviruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) which leads to coronavirus disease 2019 (COVID-19) infection, elicit hyperimmune responses (cytokine storm) that may precipitate psychiatric episodes in infected patients, although the precise precipitating event (e.g., stress or the virus itself) remains to be elucidated. It is notable, however, that the SARS-CoV-2 virus crosses the BBB of mice and passes the olfactory mucosa in humans, which supports potential routes/mechanisms for virus entry into brain tissue. Consequently, without being bound by theory, it is believed that therapeutics with anti-inflammatory benefit, such as lumateperone and its analogs, may provide further benefit in normalizing aberrant neuroinflammatory events and mitigating their impact on brain dysfunction, particularly with reference to maintenance of BBB integrity.

[0033] Without being bound by theory, it is believed that perturbation of the BBB may underlie the development of a variety of psychiatric disorders, including schizophrenia, autism spectrum disorder (ASD), and affective disorders. Increased permeability of the BBB appears to be a common factor in these disorders, leading to increased infiltration of peripheral material into the brain culminating in neuroinflammation and oxidative stress. Loss of BBB integrity is an early and prominent pathological feature of neuroinflammatory disorders. BBB permeability is increased in response to many proinflammatory stimuli, such as lipopolysaccharide, tumor necrosis factor α (TNF α), IL-6, MCP-1 and IL-1 β , with concomitant downregulation of tight junction proteins, such as claudin-5 (Cldn5). In response to danger signals, brain endothelial cells become activated and are characterized by upregulated expression of cell adhesion molecules

such as ICAM-1 and VCAM-1, and down regulation of claudin-5, to facilitate leukocyte entry to the CNS and facilitate an immune response. Therefore, measurement of the presence, absence or concentrations of these various biomarker signals can indicate the presence of neuroinflammation and breakdown of BBB integrity.

[0034] In a particular embodiment, the present disclosure provides a method (Method 1) for the treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis, comprising administering to a patient in need thereof, a therapeutically effective amount of a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, for example, a compound of Formula I:



Formula I

wherein:

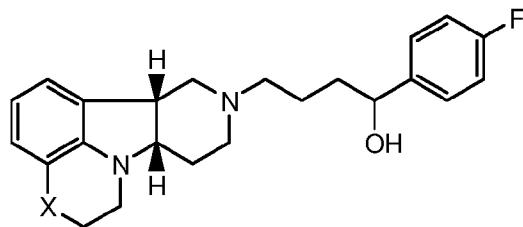
X is -N(H)-, -N(CH₃)- or -O-;

Y is -C(=O)-, -C(H)(OH)- or -C(H)(OR₁)-;

R₁ is -C(O)-C₁₋₂₁alkyl (e.g., -C(O)-C₁₋₅alkyl, -C(O)-C₆₋₁₅alkyl or -C(O)-C₁₆₋₂₁alkyl), preferably said alkyl is a straight chain, optionally saturated or unsaturated and optionally substituted with one or more hydroxy or C₁₋₂₂alkoxy (e.g., ethoxy) groups, for example R₁ is -C(O)-C₆alkyl, -C(O)-C₇alkyl, -C(O)-C₉alkyl, -C(O)-C₁₁alkyl, -C(O)-C₁₃alkyl or -C(O)-C₁₅alkyl, wherein such compound hydrolyzes to form the residue of a natural or unnatural, saturated or unsaturated fatty acid, e.g., the compound hydrolyzes to form the hydroxy compound on the one hand and octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid or hexadecanoic acid on the other hand, optionally in deuterated form,

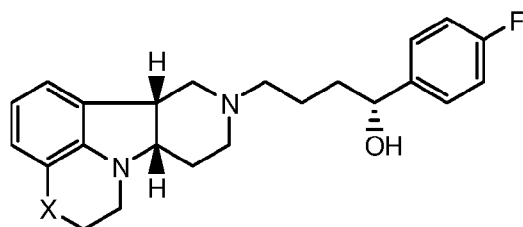
in free base, pharmaceutically acceptable salt, or prodrug form. For example, Method 1 may be as follows:

- 1.1. Method 1, wherein X in the compound of Formula I is $-N(H)-$, $-N(CH_3)-$ or $-O-$;
- 1.2. Method 1 or 1.1, wherein X in the compound of Formula I is $-N(H)-$;
- 1.3. Method 1 or 1.1, wherein X in the compound of Formula I is $-N(CH_3)-$;
- 1.4. Method 1 or 1.1, wherein X in the compound of Formula I is $-O-$;
- 1.5. Method 1 or any of formulae 1.1-1.4, wherein Y in the compound of Formula I is $-C(=O)-$, $-C(H)(OH)-$ or $-C(H)(OR_1)-$;
- 1.6. Method 1 or any of formulae 1.1-1.4, wherein Y in the compound of Formula I is $-C(=O)-$;
- 1.7. Method 1 or any of formulae 1.1-1.4, wherein Y in the compound of Formula I is $-C(H)(OH)-$;
- 1.8. Method 1 or any of formulae 1.1-1.4, wherein Y in the compound of Formula I is $-C(H)(OR_1)-$;
- 1.9. Method 1, or any of 1.1-1.5 or 1.8, wherein R_1 in the compound of Formula I is $-C(O)-C_{1-21}alkyl$ (e.g., $-C(O)-C_{1-5}alkyl$, $-C(O)-C_{6-15}alkyl$ or $-C(O)-C_{16-21}alkyl$), preferably said alkyl is a straight chain, optionally saturated or unsaturated and optionally substituted with one or more hydroxy or $C_{1-22}alkoxy$ (e.g., ethoxy) groups, for example R_1 is $-C(O)-C_6alkyl$, $-C(O)-C_7alkyl$, $-C(O)-C_9alkyl$, $-C(O)-C_{11}alkyl$, $-C(O)-C_{13}alkyl$ or $-C(O)-C_{15}alkyl$ wherein such compound hydrolyzes to form the residue of a natural or unnatural, saturated or unsaturated fatty acid, e.g., the compound hydrolyzes to form the hydroxy compound on the one hand and octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid or hexadecanoic acid on the other hand; e.g., wherein R_1 in the compound of Formula I is $-C(O)-C_{6-15}alkyl$, e.g., $-C(O)-C_9alkyl$; or wherein R_1 in the compound of Formula I is $-C(O)-C_{1-5}alkyl$, e.g., $-C(O)-C_3alkyl$;
- 1.10. Method 1 or any of 1.1-1.5 or 1.7, wherein the Compound of Formula I is:



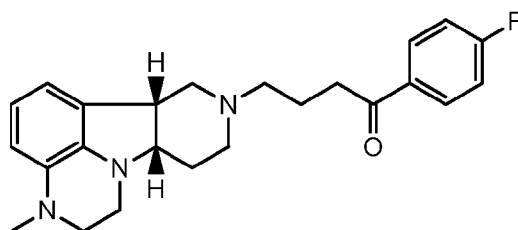
;

1.11. Method 1 or any of 1.1-1.5 or 1.7, wherein the Compound of Formula I is:



;

1.12. Method 1, or any of 1.1, 1.3, 1.5, or 1.6, wherein the Compound of Formula I is lumateperone:



;

1.13. Method 1, or any of 1.1-1.12, e.g., Method 1.12, wherein the Compound of Formula I is in the form of a pharmaceutically acceptable salt, e.g., a tosylate salt;

1.14. Method 1, or any of 1.1-1.12, e.g., Method 1.12, wherein the Compound of Formula I is in the form of the free base;

1.15. Method 1 or any of 1.1-1.14 wherein the Compound of Formula I is in deuterated form, e.g., wherein the deuterium:protium ratio for a specified carbon-bound hydrogen atom is significantly higher, e.g., at least 2x, for example at least 10x higher, than the natural isotope ratios;

1.16. Method 1.15 wherein the Compound of Formula I is a deuterated form of lumateperone, for example, selected from:

wherein D represents a hydrogen position with substantially greater than natural deuterium incorporation (i.e., substantially greater than 0.0156%), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90% or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%, in free base or pharmaceutically acceptable salt form, e.g. tosylate salt form;

- 1.17. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is a compound of Formula I in free base or pharmaceutically acceptable salt form, e.g. tosylate salt form, administered in a daily dose equivalent to 1 to 100 mg of free base, e.g., in an amount equivalent to 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 20 mg, or 1 to 10 mg, of free base;
- 1.18. Method 1.17 wherein the method comprises once daily administration of a unit dosage for oral administration, for example a tablet or capsule, comprising the compound of Formula I in free base or pharmaceutically acceptable salt form, e.g., in tosylate salt form, in an amount equivalent 1 to 100 mg of free base, e.g., in an amount equivalent to 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 30 mg, or 1 to 20 mg, or 1 to 10 mg, or 1 to 5 mg, or 40 to 60 mg, or 20 to 40 mg, or 10 to 20 mg, or about 60 mg, or about 40 mg, or about 30 mg, or about 20 mg, or about 10 mg, or about 5 mg, of free base, and a pharmaceutically acceptable diluent or carrier;
- 1.19. Method 1.17 wherein the method comprises once daily administration of a unit dosage for oral transmucosal administration, e.g., a sublingual or buccal orally disintegrating tablet, wafer, or film, comprising the compound of Formula I in free base or pharmaceutically acceptable salt form, e.g., in tosylate salt form, in an amount equivalent to 0.5 to 30 mg of free base, e.g., in an amount equivalent to 1 to 30 mg, or 1 to 20 mg, or 1 to 15 mg, or 1 to 10 mg, or 20 to 30 mg, or 10 to 20 mg, or about 5 mg, or about 10 mg, or about 15 mg, or about 20 mg, of free base, and a pharmaceutically acceptable diluent or carrier;
- 1.20. Any foregoing method wherein the condition to be treated is alleviated within one week, e.g., within three days, e.g., within one day;
- 1.21. Any foregoing method, wherein the method is a method of treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis;
- 1.22. Any foregoing method, wherein the method is a method for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis;

- 1.23. Method 1.21 or 1.22, wherein the encephalitis is viral encephalitis;
- 1.24. Method 1.23, wherein the encephalitis is caused by, or suspected to be caused by, Herpes simplex Virus 1, Herpes Simplex Virus 2, West Nile Virus, Nipah Virus, human immunodeficiency virus, rabies virus, Epstein-Barr Virus, cytomegalovirus, coronavirus (e.g., MERS-CoV, SARS-CoV, SARS-Cov2), or influenza virus (e.g., influenza A, such as H1N1, H2N2, H3N2, H5N1, H7N7);
- 1.25. Method 1.23 or 1.24, wherein the patient has acute viral encephalitis;
- 1.26. Method 1.21 or 1.22, wherein the encephalitis is bacterial encephalitis;
- 1.27. Method 1.26, wherein the encephalitis is caused by, or believed to be caused by, toxoplasmosis, rickettsia, mycoplasma, Borrelia (e.g., Lyme disease), or malaria;
- 1.28. Method 1.21 or 1.22, wherein the encephalitis is autoimmune encephalitis;
- 1.29. Method 1.28, wherein the encephalitis is caused by, or believed to be caused by, autoantibodies against the NMDA receptor, the AMPA receptor, the voltage-gated potassium channel (VGKC), the LGL1 protein, the GABA receptor, the glycine receptor, the glutamate receptor, or the CASPR2 receptor;
- 1.30. Any foregoing method, wherein the psychiatric disorder and/or the psychiatric symptom is depression (e.g., acute depression, depression of MDD, depression of bipolar disorder), anxiety, (e.g., acute anxiety), psychosis (e.g., schizophrenia), post-traumatic stress-disorder, anhedonia, memory loss, impairment of executive functioning, difficulty concentrating, seizures, difficulty sleeping, hallucination, change in personality, or any combination thereof;
- 1.31. Any foregoing method wherein the psychiatric disorder and/or the psychiatric symptom is depression (e.g., acute depression, depression of MDD, depression of bipolar disorder);
- 1.32. Any foregoing method wherein the psychiatric disorder and/or the psychiatric symptom is anxiety (e.g., acute anxiety);
- 1.33. Any foregoing method wherein the psychiatric disorder and/or the psychiatric symptom is anhedonia;
- 1.34. Any foregoing method wherein the patient is diagnosed as having suicidal ideation and/or suicidal tendencies;
- 1.35. Any foregoing method, wherein the patient has no prior history of psychiatric disorders or psychiatric symptoms;

- 1.36. Any foregoing method wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered in combination (e.g., a fixed combination in a unit dosage form, or a free combination administered sequentially or simultaneously or within a 24-hour period) with a therapeutically effective amount of an anxiolytic or antidepressant agent;
- 1.37. Method 1.36 wherein the anxiolytic or antidepressant agent is selected from one or more compounds in free base or pharmaceutically acceptable salt form, selected from selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and atypical antipsychotics, e.g. one or more compounds in free base or pharmaceutically acceptable salt form, selected from:
- (a) Selective serotonin reuptake inhibitors (SSRIs), e.g., Citalopram (Celexa), Escitalopram (Lexapro, Cipralex), Paroxetine (Paxil, Seroxat), Fluoxetine (Prozac), Fluvoxamine (Luvox) Sertraline (Zoloft, Lustral);
 - (b) Serotonin-norepinephrine reuptake inhibitors (SNRIs), e.g., Desvenlafaxine (Pristiq), Duloxetine (Cymbalta), Levomilnacipran (Fetzima), Milnacipran (Ixel, Savella), Tofenacin (Elamol, Tofacine), Venlafaxine (Effexor);
 - (c) Tricyclic antidepressants (TCAs), e.g., Amitriptyline (Elavil, Endep), Amitriptylinoxide (Amioxid, Ambivalon, Equilibrin), Clomipramine (Anafranil), Desipramine (Norpramin, Pertofrane), Dibenzepin (Noveril, Victoril), Dimetacrine (Istonil), Dosulepin (Prothiaden), Doxepin (Adapin, Sinequan), Imipramine (Tofranil), Lofepramine (Lomont, Gamanil), Melitracen (Dixeran, Melixeran, Trausabun), Nitroxazepine (Sintamil), Nortriptyline (Pamelor, Aventyl), Noxiptiline (Agedal, Elronon, Nogedal), Pipofezine (Azafen/Azaphen), Protriptyline (Vivactil), Trimipramine (Surmontil);
 - (d) Benzodiazepines, e.g., selected from 2-keto compounds (e.g., clorazepate, diazepam, flurazepam, halazepam, prazepam); 3-hydroxy compounds (lorazepam, lormetazepam, oxazepam, temazepam); 7-nitro compounds (e.g., clonazepam, flunitrazepam, nimetazepam, nitrazepam); triazolo compounds (e.g., adinazolam, alprazolam, estazolam, triazolam); and imidazo compounds (climazolam, loprazolam, midazolam);

- 1.38. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g., the compound of Formula I is administered intra-nasally, subcutaneously, intramuscularly, intravenously, orally, sub-lingually, intra-peritoneally, or buccally, such as an oral rapidly dissolving tablet, wafer, or film, which dissolves in the oral cavity for transmucosal absorption;
- 1.39. Any foregoing method, wherein the method further comprises the concurrent administration of an anti-depressant agent (e.g., selected from a selective serotonin reuptake inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor), a serotonin receptor antagonist, or any combination thereof), e.g., administered simultaneously, separately or sequentially;
- 1.40. Any foregoing method, wherein the method further comprises the concurrent administration of an NMDA receptor antagonist, for example, selected from ketamine (e.g., *S*-ketamine and/or *R*-ketamine), hydroxynorketamine, memantine, dextromethorphan, dextroalorphan, dextrophan, amantadine, and agmatine, or any combination thereof, e.g., administered simultaneously, separately or sequentially;
- 1.41. Any foregoing method, wherein the method further comprises the concurrent administration of a NMDA receptor allosteric modulator, e.g., a NMDA receptor glycine-site modulator, such as rapastinel, nebostinel, apimostinel, D-cycloserine, or any combination thereof, e.g., administered simultaneously, separately or sequentially;
- 1.42. Any foregoing method, wherein the method provides the patient with an acute response to treatment with the therapeutic agent or agents (e.g., the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, the Compound of Formula I, or the combination of the Compound or Formula I and the Compound of Formula II, and/or any additional antidepressant agents);
- 1.43. Method 1.42, wherein the patient shows an acute response to treatment within less than 3 weeks, for example, less than 2 weeks, or less than 1 week, or from 1 to 7 days, or 1 to 5 days, or 1 to 3 days, or 1 to 2 days, or about 1 day, or less than 2 days, or less than 1 day (e.g., 12-24 hours, 6-12 hours, or 3-6 hours);
- 1.44. Any foregoing method, wherein the patient has not responded to, or has not responded adequately to, or who suffers undesirable side effects from, treatment with another

antidepressant agent, for example, any one or more of a selective serotonin reuptake inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor, or a serotonin receptor antagonist;

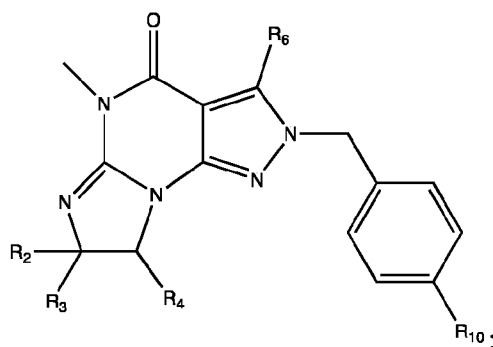
- 1.45. Any foregoing method, wherein the psychiatric disorder or symptoms is not associated with schizophrenia or dementia;
- 1.46. Any foregoing method, wherein the patient does not suffer from (or has not previously been diagnosed with) schizophrenia or dementia;
- 1.47. Any foregoing method, wherein the method protects or reinforces the blood-brain barrier;
- 1.48. Any foregoing method, wherein the patient has elevated levels of pro-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, or elevated levels of C-reactive protein (CRP) of Csf1, and/or depressed levels of anti-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- β , IFN- α , IL-4, and IL-10;
- 1.49. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the 5-HT_{2A} receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);
- 1.50. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the D2 receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);
- 1.51. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the D1 receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);

- 1.52. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the serotonin transporter (SERT), e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said transporter (agonism or antagonism);
- 1.53. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in free base or pharmaceutically acceptable salt form, optionally in a deuterated form;
- 1.54. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in a tosylate salt form (e.g., monotosylate salt), optionally in a deuterated form, and optionally in crystalline or amorphous tosylate salt form;
- 1.55. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in free base form, optionally in a deuterated form;
- 1.56. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered in the form of a long-acting injectable (LAI) composition, e.g., for intramuscular or subcutaneous injection;
- 1.57. Method 1.56, wherein the dose of the LAI composition is sufficient to provide the equivalent of a daily dose of 1 to 100 mg of free base, e.g., 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 20 mg, or 1 to 10 mg, of free base, released over a period of time ranging from about 1 week to about 3 months, e.g., about 1 week to about 8 weeks, or about 1 week to about 6 weeks, or about 1 week to about 4 weeks, or about 1 week to about 3 weeks, or about 1 week to about 2 weeks;
- 1.58. Method 1.56 or 1.57, wherein the LAI composition comprises the compound of Formula I dissolved, dispersed, suspended, or encapsulated in a polymeric matrix;
- 1.59. Method 1.58, wherein the polymeric matrix comprises one or more biocompatible and biodegradable polymers as defined herein, e.g., poly(hydroxycarboxylic acids), poly(amino acids), cellulose polymers, modified cellulose polymers, polyamides, and polyesters;
- 1.60. Method 1.59, wherein the one or more polymers comprises polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly-beta-hydroxybutyric acid, poly(lactic acid-glycolic acid) copolymer, 2-hydroxybutyric acid-glycolic acid copolymer, polylactic acid-

polyethylene glycol copolymer, polyglycolic acid-polyethylene glycol copolymer, PEG-PLGA copolymer or block copolymer, PEG-PLGA copolymer or block copolymer, poly(alkyl alpha-cyanoacrylate) such as poly(butyl cyanoacrylate) or poly(2-octyl cyanoacrylate), poly(ortho ester), polycarbonate, polyortho-carbonate, a polyamino acid, (for example poly-gamma.-L-alanine, poly-.gamma.-benzyl-L-glutamic acid or poly-y-methyl-L-glutamic acid), and/or hyaluronic acid ester;

- 1.61. Method 1.60, wherein the one or more polymers comprises polyortho esters (POE), polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, or a poly(lactic acid-glycolic acid) copolymer;
- 1.62. Method 1.60, wherein the one or more polymers comprises a poly(lactic acid-glycolic acid) copolymer, e.g., poly-d,l-lactide-co-glycolide (PLGA), for example, a PLGA copolymer with a lactide-to-glycolide molar ratio of about 50:50 to 90:10, or 50:50 to 85:15, or 50:50 to 75:25, and/or a molecular weight of 5,000 to 500,000 Daltons, or 5,000 to 150,000 Daltons, or 20,000 to 200,000 Daltons, or 24,000 to 38,000 Daltons;
- 1.63. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered as monotherapy, e.g., it is not administered concurrently or in conjunction with an anti-depressant, anti-psychotic, or anti-anxiety agent;
- 1.64. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered without the direct supervision of a health care professional (e.g., the compound is self-administered by the patient);
- 1.65. Any foregoing method, wherein the method does not comprise supervision or observation of the patient by a health care professional during or after (e.g., within 2 hours after) administration of a dose of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 1.66. Any foregoing method, wherein the method does not put the patient at risk for sedation, dissociation, abuse, misuse, or suicidal ideation;
- 1.67. Any foregoing method, wherein the method does not result in hypertension (e.g., systolic and/or diastolic hypertension) within four hours after administration of a dose of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g., an increase of more than 10 mm Hg, or more than 20 mm Hg, or more than 30 mm Hg, or more than 40 mm Hg, in systolic and/or diastolic blood pressure within 30 minutes to 4 hours after said dose;
- 1.68. Any foregoing method, wherein the method does not result in cognitive decline;

- 1.69. Any foregoing method, wherein the patient has (e.g., has been diagnosed with), or is at risk of, aneurysmal vascular disease (e.g., thoracic aorta, abdominal aorta, intracranial, or peripheral arterial aneurysms), arteriovenous malformation or intracerebral hemorrhage;
- 1.70. Any foregoing method, wherein the patient is under concurrent treatment with an oral antidepressant selected from duloxetine, escitalopram, sertraline, or venlafaxine;
- 1.71. Any foregoing method, wherein the patient is not under concurrent treatment with an oral antidepressant selected from duloxetine, escitalopram, sertraline, or venlafaxine;
- 1.72. Any foregoing method, wherein the patient is unresponsive to, or cannot be treated with ketamine (e.g., S-ketamine), e.g., because it is contraindicated in said patient;
- 1.73. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered to the patient concurrently with a PDE1 (cyclic nucleoside phosphodiesterase 1) inhibitor (e.g., administered simultaneously, separately, or sequentially), in free base or pharmaceutically acceptable salt form;
- 1.74. Method 1.73, wherein the PDE1 inhibitor is a compound according to Formula II:



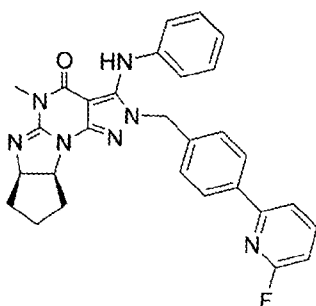
wherein R₂ is H and R₃ and R₄ together form a tri- or tetra-methylene bridge [pref. with the carbons carrying R₃ and R₄ having the R and S configuration respectively]; or R₂ and R₃ are each methyl and R₄ is H; or R₂ and R₄ are H and R₃ is isopropyl [pref. the carbon carrying R₃ having the R configuration];

R₆ is (optionally halo-substituted) phenylamino or (optionally halo-substituted) benzylamino;

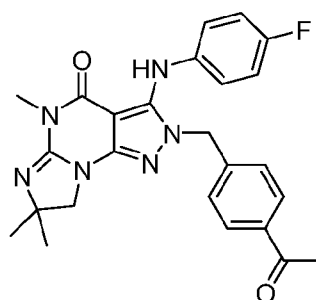
R₁₀ is (optionally halo-substituted) phenyl, (optionally halo-substituted) pyridyl (for example 3-fluoropyrid-2-yl), thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl), or C₁-alkylcarbonyl (e.g., methylcarbonyl);

in free base or pharmaceutically acceptable salt form;

- 1.75. Method 1.74, wherein, in the Compound of Formula II, R₆ is phenylamino or 4-fluorophenylamino;
- 1.76. Method 1.74, wherein, in the Compound of Formula II, R₁₀ is 3-fluoropyrid-2-yl or methylcarbonyl;
- 1.77. Method 1.74, wherein, in the Compound of Formula II, R₆ is phenylamino or 4-fluorophenylamino and R₁₀ is 3-fluoropyrid-2-yl or methylcarbonyl;
- 1.78. Any Methods 1.74-1.77, wherein the Compound of Formula II is

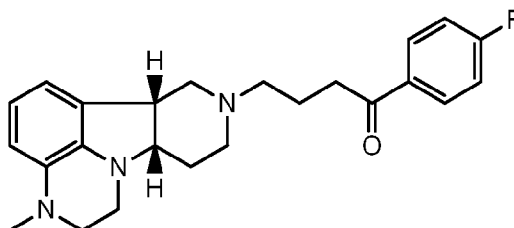


or

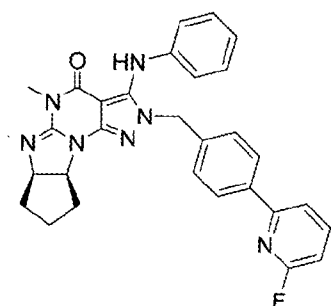


in free base or pharmaceutically acceptable salt form;

- 1.79 Method 1.77, wherein the Compound of Formula II is in the form of the monophosphate salt;
- 1.80 Any of Methods 1.74-1.79, wherein the Compound of Formula I is:



in free base or pharmaceutically acceptable salt form, e.g., tosylate salt form, optionally in a deuterated form; and the Compound of Formula II is:



in free base or pharmaceutically acceptable salt form, e.g., monophosphate salt form;

- 1.81 Any of Methods 1.74-1.80, comprising administration of a pharmaceutical composition comprising therapeutically effective amounts of both a Compound of Formula I and a Compound of Formula II;
- 1.82 Any preceding method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is a compound of Formula I, in free base or pharmaceutically acceptable salt form, optionally in deuterated form, and wherein the compound is administered in the form of a long-acting injectable (LAI) composition comprising the compound of Formula I dissolved or dispersed or in a pharmaceutically acceptable carrier and a polymeric matrix comprising polymers selected from polyortho esters (POE), polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, or a poly(lactic acid-glycolic acid) copolymer;
- 1.83 Method 1.82, wherein the pharmaceutically acceptable carrier comprises water (e.g., an aqueous buffer) and/or an organic solvent (e.g., a water-miscible organic solvent);
- 1.84 Method 1.82 or 1.83, wherein the polymers comprise a polylactic acid and/or a polyglycolic acid polymer;
- 1.85 Method 1.82 or 1.83, wherein the polymers comprise a poly(lactic acid-glycolic acid) copolymer, e.g., poly-d,l-lactide-co-glycolide (PLGA), for example, a PLGA copolymer with a lactide-to-glycolide molar ratio of about 50:50 to 90:10, or 50:50 to 85:15, or 50:50 to 75:25, and/or a molecular weight of 5,000 to 500,000 Daltons, or 5,000 to 150,000 Daltons, or 20,000 to 200,000 Daltons, or 24,000 to 38,000 Daltons;

- 1.86 Any of Methods 1.82-1.85, wherein the LAI composition is administered by, or formulated for administration by, intramuscular or subcutaneous injection;
- 1.87 Method 1, or any of 1.1-1.86, wherein the patient has no prior history of depression;
- 1.88 Method 1, or any of 1.1-1.87, wherein the patient shows evidence of cerebral damage or cerebral disease on magnetic resonance imaging (MRI) prior to administration of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 1.89 Method 1, or any of 1.1-1.88, wherein the patient has a positive serum antibody or antigen test for one or more of Herpes simplex Virus 1, Herpes Simplex Virus 2, West Nile Virus, Nipah Virus, human immunodeficiency virus, rabies virus, Epstein-Barr Virus, cytomegalovirus, coronavirus (e.g., MERS-CoV, SARS-CoV, SARS-Cov2, or influenza virus (e.g., influenza A, such as H1N1, H2N2, H3N2, H5N1, H7N7), prior to administration of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 1.90 Method 1, or any of 1.1-1.89, wherein the patient has a positive serum antibody test for autoantibodies against the NMDA receptor, the AMPA receptor, the voltage-gated potassium channel (VGKC), the LGL1 protein, the GABA receptor, the glycine receptor, the glutamate receptor, or the CASPR2 receptor;
- 1.91 Any foregoing method, wherein the patient has elevated levels of one or more biomarkers indicative of CNS inflammation, e.g., selected from TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, ICAM-1, VCAM-1, YKL-40, Nlrp3, and Flt-1, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF);
- 1.92 Any foregoing method, wherein the patient has changes in levels of one or more biomarkers indicative of CNS inflammation and/or loss of BBB integrity, e.g., increased levels of ICAM-1, VCAM-1, E-selectin, P-selectin, or soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), or reduced levels of Cldn5, Occludin, and ZO-1, in the serum or CSF;
- 1.93 Any foregoing method, wherein the patient has depressed levels of one or more anti-inflammatory biomarkers indicative of CNS inflammatory dysfunction, e.g., TNF- β , IFN- α , IL-4, and IL-10, in the blood, plasma, serum, peripheral blood mononuclear cells

- (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF);
- 1.94 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has a reduced level of one or more biomarkers indicative of CNS inflammation, e.g., TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, ICAM-1, VCAM-1, YKL-40, Nlrp3, and Flt-1, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;
- 1.95 Method 1.94, wherein the patient has at least a 5%, 10%, 15%, 20%, or 25%, 30%, 35%, 40%, 45%, or 50%, reduction in the level of the one or more biomarkers indicative of CNS inflammation, e.g., within 28 days of the initiation of treatment;
- 1.96 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has favorable changes in levels of one or more biomarkers indicative of CNS inflammation and/or loss of BBB integrity, e.g., decreased levels of ICAM-1, VCAM-1, E-selectin, P-selectin, or soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), or increased levels of Cldn5, Occludin, and ZO-1, in the serum or CSF, compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;
- 1.97 Method 1.96, wherein the patient has at least a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, reduction or increase in the level of the one or more biomarkers indicative of CNS inflammation, e.g., within 28 days of the initiation of treatment;
- 1.98 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has an increased level of one or more anti-inflammatory biomarkers indicative of CNS inflammatory dysfunction, e.g., TNF- β , IFN- α , IL-4, and IL-10, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;

- 1.99 Method 1.98, wherein the patient has an increase of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, in the levels of the one or more anti-inflammatory biomarkers indicative CNS inflammatory dysfunction, e.g., within 28 days of the initiation of treatment, e.g., within 28 days of the initiation of treatment;
- 1.100 Any foregoing method, wherein the method further comprises the step of testing one or more body fluids or tissues from the patient for the presence and/or concentration of one or more biomarkers indicative of CNS inflammation or CNS inflammatory dysfunction or loss of BBB integrity prior to the initiation of treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), and/or subsequent to the initiation of said treatment, and optionally comparing the pre-treatment and one or more post-treatment results thereof to quantify the effectiveness of the treatment in the patient and/or to adjust the treatment regimen;
- 1.101 Method 1.100, wherein the biomarkers are selected from one or more of TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, YKL-40, Nlrp3, Flt-1, ICAM-1, VCAM-1, E-selectin, P-selectin, Cldn5, Occludin, and ZO-1, soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), TNF- β , IFN- α , IL-4, and IL-10;
- 1.102 Method 1.100 or 1.101, wherein the one or more body fluids or tissues are selected from blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), or brain biopsy tissue samples;
- 1.103 Any foregoing method, wherein the method further comprises the step of non-invasively testing the central nervous system of the patient for the presence and/or concentration of one or more biomarkers indicative of CNS inflammation or CNS inflammatory dysfunction prior to the initiation of treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), and/or subsequent to the initiation of said treatment, and optionally comparing the pre-treatment and one or more post-treatment results thereof to quantify the effectiveness of the treatment in the patient and/or to adjust the treatment regimen;
- 1.104 Method 1.103, wherein the biomarkers are selected from one or more of TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, YKL-40,

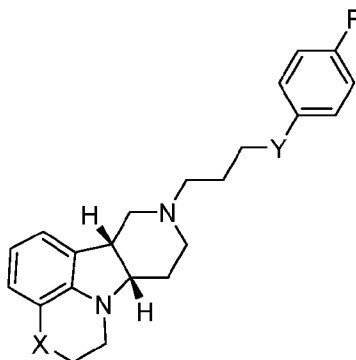
Nlrp3, Flt-1, ICAM-1, VCAM-1, E-selectin, P-selectin, Cldn5, Occludin, and ZO-1, soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), TNF- β , IFN- α , IL-4, and IL-10;

- 1.105 Method 1.103 or 1.104, wherein the step comprises an imaging method, such as magnetic resonance imaging (MRI), positron emission tomography (PET), functional MRI (fMRI), to evaluate the presence and/or concentration of said biomarkers;
- 1.106 Any of Methods 1.100-1.105, wherein the method comprises the step of initiating, altering, or terminating, the treatment regimen (e.g., the selected 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, the dose thereof, the route of administration thereof, the frequency of administration thereof, the form of administration thereof, and/or the combination of the selected 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand with any another therapeutic agent), based on the observed changes in the levels of one or more of said biomarkers.

[0035] In another aspect, the disclosure provides a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g., a compound of Formula I, as hereinbefore described, for example lumateperone, in free base or salt form, optionally in deuterated form, for use in the treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis, e.g., for use in any of Methods 1, et seq.

[0036] In another aspect, the disclosure provides the use of a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g. a compound of Formula I, as hereinbefore described, for example lumateperone, in free base or salt form, optionally in deuterated form, in the manufacture of a medicament for treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis, e.g., for any of Methods 1, et seq.

[0037] In a particular embodiment, the present disclosure provides a method (Method 2) for protecting or reinforcing the blood-brain barrier, comprising administering to a patient in need thereof, a therapeutically effective amount of a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, for example, a compound of Formula I:



wherein:

X is $-\text{N}(\text{H})-$, $-\text{N}(\text{CH}_3)-$ or $-\text{O}-$;

Y is $-\text{C}(=\text{O})-$, $-\text{C}(\text{H})(\text{OH})-$ or $-\text{C}(\text{H})(\text{OR}_1)-$;

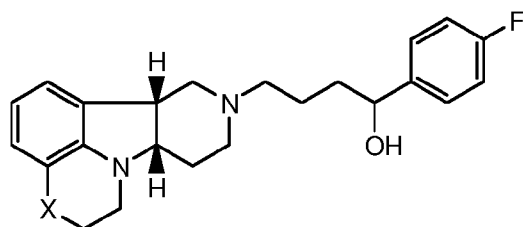
R_1 is $-\text{C}(\text{O})-\text{C}_{1-21}\text{alkyl}$ (e.g., $-\text{C}(\text{O})-\text{C}_{1-5}\text{alkyl}$, $-\text{C}(\text{O})-\text{C}_{6-15}\text{alkyl}$ or $-\text{C}(\text{O})-\text{C}_{16-21}\text{alkyl}$), preferably said alkyl is a straight chain, optionally saturated or unsaturated and optionally substituted with one or more hydroxy or $\text{C}_{1-22}\text{alkoxy}$ (e.g., ethoxy) groups, for example R_1 is $-\text{C}(\text{O})-\text{C}_6\text{alkyl}$, $-\text{C}(\text{O})-\text{C}_7\text{alkyl}$, $-\text{C}(\text{O})-\text{C}_9\text{alkyl}$, $-\text{C}(\text{O})-\text{C}_{11}\text{alkyl}$, $-\text{C}(\text{O})-\text{C}_{13}\text{alkyl}$ or $-\text{C}(\text{O})-\text{C}_{15}\text{alkyl}$, wherein such compound hydrolyzes to form the residue of a natural or unnatural, saturated or unsaturated fatty acid, e.g., the compound hydrolyzes to form the hydroxy compound on the one hand and octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid or hexadecanoic acid on the other hand,

optionally in deuterated form,

in free base, pharmaceutically acceptable salt or prodrug form. For example, Method 2 may be as follows:

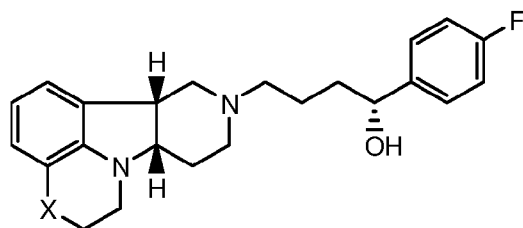
- 2.1. Method 2, wherein X in the compound of Formula I is $-\text{N}(\text{H})-$, $-\text{N}(\text{CH}_3)-$ or $-\text{O}-$;
- 2.2. Method 2 or 2.1, wherein X in the compound of Formula I is $-\text{N}(\text{H})$;
- 2.3. Method 2 or 2.1, wherein X in the compound of Formula I is $-\text{N}(\text{CH}_3)-$;
- 2.4. Method 2 or 2.1, wherein X in the compound of Formula I is $-\text{O}-$;
- 2.5. Method 2 or any of formulae 2.1-2.4, wherein Y in the compound of Formula I is $-\text{C}(=\text{O})-$, $-\text{C}(\text{H})(\text{OH})-$ or $-\text{C}(\text{H})(\text{OR}_1)-$;
- 2.6. Method 2 or any of formulae 1.1-1.4, wherein Y in the compound of Formula I is $-\text{C}(=\text{O})-$;

- 2.7. Method 2 or any of formulae 2.1-2.4, wherein Y in the compound of Formula I is –C(H)(OH)–;
- 2.8. Method 2 or any of formulae 2.1-2.4, wherein Y in the compound of Formula I is –C(H)(OR₁)–;
- 2.9. Method 2, or any of 2.2-2.5, or 2.8, wherein R₁ in the compound of Formula I is –C(O)–C₁₋₂₁alkyl (e.g., –C(O)–C₁₋₅alkyl, –C(O)–C₆₋₁₅alkyl or –C(O)–C₁₆₋₂₁alkyl), preferably said alkyl is a straight chain, optionally saturated or unsaturated and optionally substituted with one or more hydroxy or C₁₋₂₂alkoxy (e.g., ethoxy) groups, for example R₁ is –C(O)–C₆alkyl, –C(O)–C₇alkyl, –C(O)–C₉alkyl, –C(O)–C₁₁alkyl, –C(O)–C₁₃alkyl or –C(O)–C₁₅alkyl wherein such compound hydrolyzes to form the residue of a natural or unnatural, saturated or unsaturated fatty acid, e.g., the compound hydrolyzes to form the hydroxy compound on the one hand and octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid or hexadecanoic acid on the other hand); e.g., wherein R₁ in the compound of Formula I is –C(O)–C₆₋₁₅alkyl, e.g., –C(O)–C₉alkyl; or wherein R₁ in the compound of Formula I is –C(O)–C₁₋₅alkyl, e.g., –C(O)–C₃alkyl;
- 2.10. Method 2 or any of 2.1-2.5 or 2.7, wherein the Compound of Formula I is:



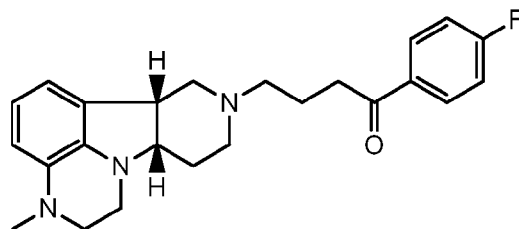
;

- 2.11. Method 2 or any of 2.1-2.5 or 2.7, wherein the Compound of Formula I is:



;

- 2.12. Method 2, or any of 2.1, 2.3, 2.5, or 2.6, wherein the Compound of Formula I is lumateperone:



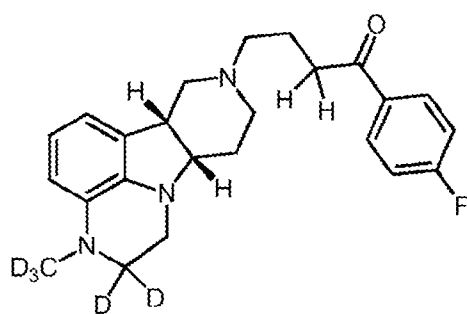
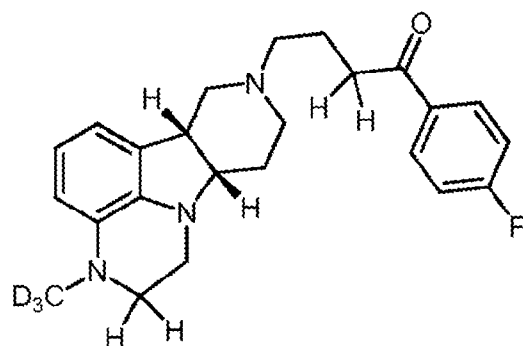
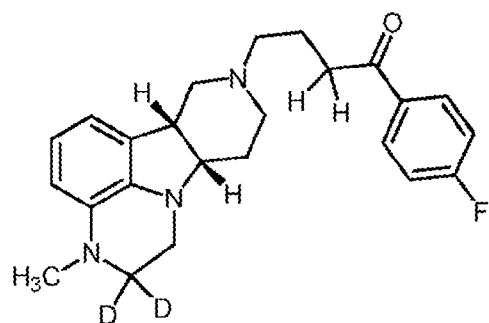
;

2.13. Method 2, or any of 2.1-2.12, e.g., Method 2.12, wherein the Compound of Formula I is in the form of a pharmaceutically acceptable salt, e.g., a tosylate salt;

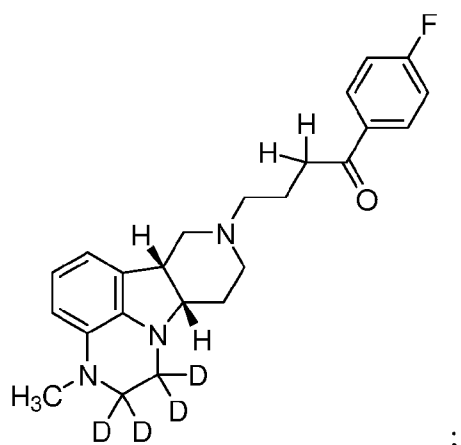
2.14. Method 2, or any of 2.1-2.12, e.g., Method 2.12, wherein the Compound of Formula I is in the form of the free base;

2.15. Method 2 or any of 2.1-2.14, wherein the Compound of Formula I is in deuterated form, e.g., wherein the deuterium:protium ratio for a specified carbon-bound hydrogen atom is significantly higher, e.g., at least 2x, for example at least 10x higher, than the natural isotope ratios;

2.16. Method 2.15 wherein the Compound of Formula I is a deuterated form of lumateperone, for example, selected from:



and



;

- wherein D represents a hydrogen position with substantially greater than natural deuterium incorporation (i.e., substantially greater than 0.0156%), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90% or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%, in free base or pharmaceutically acceptable salt form, e.g. tosylate salt form;
- 2.17. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D₂ receptor ligand is a compound of Formula I in free base or pharmaceutically acceptable salt form, e.g. in tosylate salt form, administered in a daily dose equivalent to 1 to 100 mg of free base, e.g., in an amount equivalent to 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 20 mg, or 1 to 10 mg, of free base;
- 2.18. Method 2.17 wherein the method comprises once daily administration of a unit dosage for oral administration, for example a tablet or capsule, comprising the compound of Formula I in free base or pharmaceutically acceptable salt form, e.g. in tosylate salt form in an amount equivalent to 1 to 100 mg of free base, e.g., in an amount equivalent to 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 30 mg, or 1 to 20 mg, or 1 to 10 mg, or 1 to 5 mg, or 40 to 60 mg, or 20 to 40 mg, or 10 to 20 mg, or about 60 mg, or about 40 mg, or about 30 mg, or about 20 mg, or about 10 mg, or about 5 mg, of free base, and a pharmaceutically acceptable diluent or carrier;
- 2.19. Method 2.17 wherein the method comprises once daily administration of a unit dosage for oral transmucosal administration, e.g., a sublingual or buccal orally disintegrating tablet, wafer, or film, comprising the compound of Formula I in free base or pharmaceutically acceptable salt form, e.g., in tosylate salt form, in an amount equivalent to 0.5 to 30 mg of free base, e.g., in an amount equivalent to 1 to 30 mg, or 1 to 20 mg, or 1 to 15 mg, or 1 to 10 mg, or 20 to 30 mg, or 10 to 20 mg, or about 5 mg, or about 10 mg, or about 15 mg, or about 20 mg, of free base, and a pharmaceutically acceptable diluent or carrier;
- 2.20. Any foregoing method, wherein the patient has a viral, bacterial, or autoimmune encephalitis, e.g., caused by, or suspected to be caused by, Herpes simplex Virus 1, Herpes Simplex Virus 2, West Nile Virus, Nipah Virus, human immunodeficiency virus, rabies virus, Epstein-Barr Virus, cytomegalovirus, coronavirus (e.g., MERS-CoV, SARS-CoV, SARS-Cov2), influenza virus (e.g., influenza A, such as H1N1, H2N2, H3N2, H5N1, H7N7), toxoplasmosis, rickettsia, mycoplasma, Borrelia (e.g., Lyme disease), malaria, or

autoantibodies against the NMDA receptor, the AMPA receptor, the voltage-gated potassium, channel (VGKC), the LGL1 protein, the GABA receptor, the glycine receptor, the glutamate receptor, or the CASPR2 receptor;

- 2.21. Any foregoing method wherein the patient is diagnosed as having suicidal ideation and/or suicidal tendencies;
- 2.22. Any foregoing method wherein the patient is diagnosed with a psychiatric disorder or psychiatric symptoms, e.g., depression (e.g., acute depression, depression of MDD, depression of bipolar disorder), anxiety, (e.g., acute anxiety), psychosis (e.g., schizophrenia), post-traumatic stress-disorder, anhedonia, memory loss, impairment of executive functioning, difficulty concentrating, seizures, difficulty sleeping, hallucination, change in personality, or any combination thereof;
- 2.23. Any foregoing method, wherein the patient is showing acute signs of psychiatric illness in the absence of a prior history of psychiatric disorders or psychiatric symptoms;
- 2.24. Any foregoing method, wherein the patient is at risk of damage or compromise of the blood-brain barrier, e.g., due to CNS inflammation, CNS infection (e.g., encephalitis), neurodegenerative disease, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, or due to cerebral trauma (e.g., traumatic brain injury, such as concussive injury);
- 2.25. Any foregoing method, wherein the patient has elevated levels of pro-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, or elevated levels of C-reactive protein (CRP) or Csf1, and/or depressed levels of anti-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- β , IFN- α , IL-4, and IL-10;
- 2.26. Any foregoing method wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered in combination (e.g., a fixed combination in a unit dosage form, or a free combination administered sequentially or simultaneously or within a 24-hour period) with a therapeutically effective amount of an anxiolytic or antidepressant agent;
- 2.27. Method 2.26 wherein the anxiolytic or antidepressant agent is selected from one or more compounds in free base or pharmaceutically acceptable salt form, selected from selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs),

tricyclic antidepressants (TCAs), and atypical antipsychotics, e.g. one or more compounds in free base or pharmaceutically acceptable salt form, selected from:

- (a) Selective serotonin reuptake inhibitors (SSRIs), e.g., Citalopram (Celexa), Escitalopram (Lexapro, Cipralex), Paroxetine (Paxil, Seroxat), Fluoxetine (Prozac), Fluvoxamine (Luvox) Sertraline (Zoloft, Lustral);
- (b) Serotonin-norepinephrine reuptake inhibitors (SNRIs), e.g., Desvenlafaxine (Pristiq), Duloxetine (Cymbalta), Levomilnacipran (Fetzima), Milnacipran (Ixel, Savella), Tofenacin (Elamol, Tofacine), Venlafaxine (Effexor);
- (c) Tricyclic antidepressants (TCAs), e.g., Amitriptyline (Elavil, Endep), Amitriptylinoxide (Amioxid, Ambivalon, Equilibrin), Clomipramine (Anafranil), Desipramine (Norpramin, Pertofrane), Dibenzepin (Noveril, Victoril), Dimetacrine (Istonil), Dosulepin (Prothiaden), Doxepin (Adapin, Sinequan), Imipramine (Tofranil), Lofepramine (Lomont, Gamanil), Melitracen (Dixeran, Melixeran, Trausabun), Nitroxazepine (Sintamil), Nortriptyline (Pamelor, Aventyl), Noxiptiline (Agedal, Elronon, Nogedal), Pipofezine (Azafen/Azaphen), Protriptyline (Vivactil), Trimipramine (Surmontil);
- (d) Benzodiazepines, e.g., selected from 2-keto compounds (e.g., clorazepate, diazepam, flurazepam, halazepam, prazepam); 3-hydroxy compounds (lorazepam, lormetazepam, oxazepam, temazepam); 7-nitro compounds (e.g., clonazepam, flunitrazepam, nimetazepam, nitrazepam); triazolo compounds (e.g., adinazolam, alprazolam, estazolam, triazolam); and imidazo compounds (climazolam, loprazolam, midazolam);

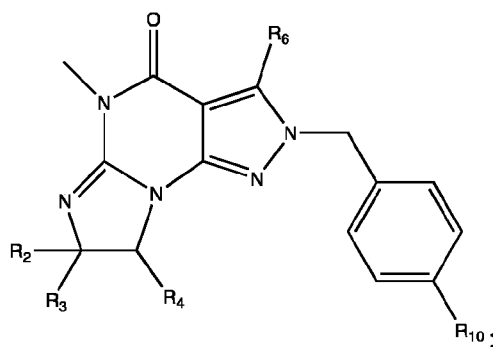
- 2.28. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D₂ receptor ligand, e.g., the compound of Formula I, is administered intra-nasally, subcutaneously, intramuscularly, intravenously, orally, sub-lingually, intra-peritoneally or buccally, such as an oral rapidly dissolving tablet, wafer, or film, which dissolves in the oral cavity for transmucosal absorption;
- 2.29. Any foregoing method, wherein the method further comprises the concurrent administration of an anti-depressant agent (e.g., selected from a selective serotonin reuptake

- inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor), a serotonin receptor antagonist, or any combination thereof), e.g., administered simultaneously, separately or sequentially;
- 2.30. Any foregoing method, wherein the method further comprises the concurrent administration of an NMDA receptor antagonist, for example, selected from ketamine (e.g., *S*-ketamine and/or *R*-ketamine), hydroxynorketamine, memantine, dextromethorphan, dextroalorphan, dextrophan, amantadine, and agmatine, or any combination thereof, e.g., administered simultaneously, separately or sequentially;
- 2.31. Any foregoing method, wherein the method further comprises the concurrent administration of a NMDA receptor allosteric modulator, e.g., a NMDA receptor glycine-site modulator, such as rapastinel, nebostinel, apimostinel, D-cycloserine, or any combination thereof, e.g., administered simultaneously, separately or sequentially;
- 2.32. Any foregoing method, wherein the method provides the patient with an acute response to treatment with the therapeutic agent or agents (e.g., the 5-HT_{2A} or 5-HT_{2A}/D₂ receptor ligand, the Compound of Formula I, or the combination of the Compound of Formula I and the Compound of Formula II, and/or any additional antidepressant agents);
- 2.33. Method 2.32, wherein the patient shows an acute response to treatment within less than 3 weeks, for example, less than 2 weeks, or less than 1 week, or from 1 to 7 days, or 1 to 5 days, or 1 to 3 days, or 1 to 2 days, or about 1 day, or less than 2 days, or less than 1 day (e.g., 12-24 hours, 6-12 hours, or 3-6 hours);
- 2.34. Any foregoing method, wherein the patient has not responded to, or has not responded adequately to, or who suffers undesirable side effects from, treatment with another antidepressant agent, for example, any one or more of a selective serotonin reuptake inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor), or a serotonin receptor antagonist;
- 2.35. Any foregoing method, wherein the patient does not suffer from (or has not previously been diagnosed with) schizophrenia or dementia;

- 2.36. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the 5-HT_{2A} receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);
- 2.37. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the D2 receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);
- 2.38. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the D1 receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);
- 2.39. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the serotonin transporter (SERT), e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said transporter (agonism or antagonism);
- 2.40. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in free base or pharmaceutically acceptable salt form, optionally in a deuterated form;
- 2.41. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in a tosylate salt form (e.g., monotosylate salt), optionally in a deuterated form, and optionally in crystalline or amorphous tosylate salt form;
- 2.42. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in free base form, optionally in a deuterated form;

- 2.43. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered in the form of a long-acting injectable (LAI) composition, e.g., for intramuscular or subcutaneous injection;
- 2.44. Method 2.43, wherein the dose of the LAI composition is sufficient to provide the equivalent of a daily dose of 1 to 100 mg of free base, e.g., 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 20 mg, or 1 to 10 mg, of free base, released over a period of time ranging from about 1 week to about 3 months, e.g., about 1 week to about 8 weeks, or about 1 week to about 6 weeks, or about 1 week to about 4 weeks, or about 1 week to about 3 weeks, or about 1 week to about 2 weeks;
- 2.45. Method 2.43 or 2.44, wherein the LAI composition comprises the compound of Formula I dissolved, dispersed, suspended, or encapsulated in a polymeric matrix;
- 2.46. Method 2.45, wherein the polymeric matrix comprises one or more biocompatible and biodegradable polymers as defined herein, e.g., poly(hydroxycarboxylic acids), poly(amino acids), cellulose polymers, modified cellulose polymers, polyamides, and polyesters;
- 2.47. Method 2.46, wherein the one or more polymers comprises polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly-beta-hydroxybutyric acid, poly(lactic acid-glycolic acid) copolymer, 2-hydroxybutyric acid-glycolic acid copolymer, polylactic acid-polyethylene glycol copolymer, polyglycolic acid-polyethylene glycol copolymer, PEG-PLGA copolymer or block copolymer, poly(alkyl alpha-cyanoacrylate) such as poly(butyl cyanoacrylate) or poly(2-octyl cyanoacrylate), poly(ortho ester), polycarbonate, polyortho-carbonate, a polyamino acid, (for example poly-gamma.-L-alanine, poly-.gamma.-benzyl-L-glutamic acid or poly-y-methyl-L-glutamic acid), and/or hyaluronic acid ester;
- 2.48. Method 2.46, wherein the one or more polymers comprises polyortho esters (POE), polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, or a poly(lactic acid-glycolic acid) copolymer;
- 2.49. Method 2.46, wherein the one or more polymers comprises a poly(lactic acid-glycolic acid) copolymer, e.g., poly-d,l-lactide-co-glycolide (PLGA), for example, a PLGA copolymer with a lactide-to-glycolide molar ratio of about 50:50 to 90:10, or 50:50 to 85:15, or 50:50 to 75:25, and/or a molecular weight of 5,000 to 500,000 Daltons, or 5,000 to 150,000 Daltons, or 20,000 to 200,000 Daltons, or 24,000 to 38,000 Daltons;

- 2.50. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered as monotherapy, e.g., it is not administered concurrently or in conjunction with an anti-depressant, anti-psychotic, or anti-anxiety agent;
- 2.51. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered without the direct supervision of a health care professional (e.g., the compound is self-administered by the patient);
- 2.52. Any foregoing method, wherein the method does not comprise supervision or observation of the patient by a health care professional during or after (e.g., within 2 hours after) administration of a dose of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 2.53. Any foregoing method, wherein the method does not put the patient at risk for sedation, dissociation, abuse, misuse, or suicidal ideation;
- 2.54. Any foregoing method, wherein the method does not result in hypertension (e.g., systolic and/or diastolic hypertension) within four hours after administration of a dose of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g., an increase of more than 10 mm Hg, or more than 20 mm Hg, or more than 30 mm Hg, or more than 40 mm Hg, in systolic and/or diastolic blood pressure within 30 minutes to 4 hours after said dose;
- 2.55. Any foregoing method, wherein the method does not result in cognitive decline;
- 2.56. Any foregoing method, wherein the patient has (e.g., has been diagnosed with), or is at risk of, aneurysmal vascular disease (e.g., thoracic aorta, abdominal aorta, intracranial, or peripheral arterial aneurysms), arteriovenous malformation or intracerebral hemorrhage;
- 2.57. Any foregoing method, wherein the patient is under concurrent treatment with an oral antidepressant selected from duloxetine, escitalopram, sertraline, or venlafaxine;
- 2.58. Any foregoing method, wherein the patient is not under concurrent treatment with an oral antidepressant selected from duloxetine, escitalopram, sertraline, or venlafaxine;
- 2.59. Any foregoing method, wherein the patient is unresponsive to, or cannot be treated with ketamine (e.g., S-ketamine), e.g., because it is contraindicated in said patient;
- 2.60. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered to the patient concurrently with a PDE1 (cyclic nucleoside phosphodiesterase 1) inhibitor (e.g., administered simultaneously, separately or sequentially), in free base or pharmaceutically acceptable salt form;
- 2.61. Method 2.60, wherein the PDE1 inhibitor is a compound according to Formula II:



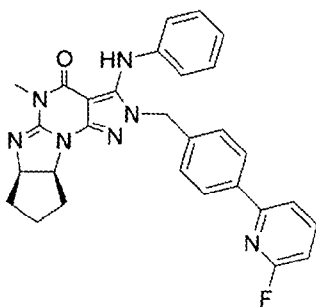
wherein R_2 is H and R_3 and R_4 together form a tri- or tetra-methylene bridge [pref. with the carbons carrying R_3 and R_4 having the R and S configuration respectively]; or R_2 and R_3 are each methyl and R_4 is H; or R_2 and R_4 are H and R_3 is isopropyl [pref. the carbon carrying R_3 having the R configuration];

R_6 is (optionally halo-substituted) phenylamino or (optionally halo-substituted) benzylamino;

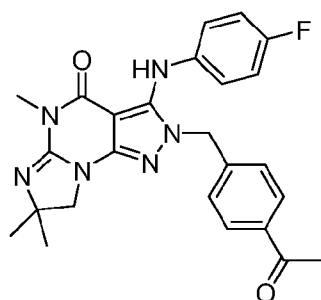
R_{10} is (optionally halo-substituted) phenyl, (optionally halo-substituted) pyridyl (for example 3-fluoropyrid-2-yl), thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl), or C_1 -alkylcarbonyl (e.g., methylcarbonyl);

in free base or pharmaceutically acceptable salt form

- 2.62. Method 2.61, wherein, in the Compound of Formula II, R_6 is phenylamino or 4-fluorophenylamino;
- 2.63. Method 2.61, wherein, in the Compound of Formula II, R_{10} is 3-fluoropyrid-2-yl or methylcarbonyl;
- 2.64. Method 2.61, wherein, in the Compound of Formula II, R_6 is phenylamino or 4-fluorophenylamino and R_{10} is 3-fluoropyrid-2-yl or methylcarbonyl;
- 2.65. Any Methods 2.61-2.64, wherein the Compound of Formula II is



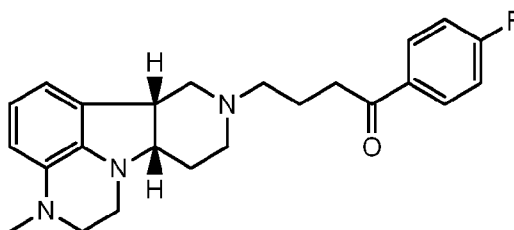
or



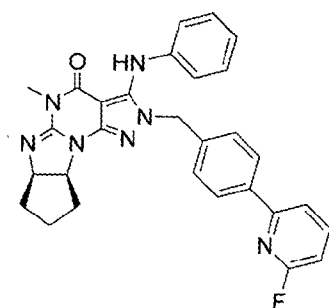
in free base or pharmaceutically acceptable salt form.

2.66 Method 2.65, wherein the Compound of Formula II is in the form of the monophosphate salt;

2.67 Any of Methods 2.61-2.66, wherein the Compound of Formula I is:



in free base or pharmaceutically acceptable salt form, e.g., tosylate salt form, optionally in a deuterated form; and the Compound of Formula II is:



in free base or pharmaceutically acceptable salt form, e.g., monophosphate salt form;

2.68 Any of Methods 2.61-2.67, comprising administration of a pharmaceutical composition comprising therapeutically effective amounts of both a Compound of Formula I and a Compound of Formula II;

- 2.69 Any preceding method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is a compound of Formula I, in free base or pharmaceutically acceptable salt form, optionally in deuterated form, and wherein the compound is administered in the form of a long-acting injectable (LAI) composition comprising the compound of Formula I dissolved or dispersed or in a pharmaceutically acceptable carrier and a polymeric matrix comprising polymers selected from polyortho esters (POE), polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, or a poly(lactic acid-glycolic acid) copolymer;
- 2.70 Method 2.69, wherein the pharmaceutically acceptable carrier comprises water (e.g., an aqueous buffer) and/or an organic solvent (e.g., a water-miscible organic solvent);
- 2.71 Method 2.69 or 2.70, wherein the polymers comprise a polylactic acid and/or a polyglycolic acid polymer;
- 2.72 Method 2.69 or 2.70, wherein the polymers comprise a poly(lactic acid-glycolic acid) copolymer, e.g., poly-d,l-lactide-co-glycolide (PLGA), for example, a PLGA copolymer with a lactide-to-glycolide molar ratio of about 50:50 to 90:10, or 50:50 to 85:15, or 50:50 to 75:25, and/or a molecular weight of 5,000 to 500,000 Daltons, or 5,000 to 150,000 Daltons, or 20,000 to 200,000 Daltons, or 24,000 to 38,000 Daltons;
- 2.73 Any of Methods 2.69-2.72, wherein the LAI composition is administered by, or formulated for administration by, intramuscular or subcutaneous injection;
- 2.74 Method 2, or any of 2.1-2.74, wherein the patient has no prior history of depression;
- 2.75 Method 2, or any of 2.1-2.75, wherein the patient shows evidence of cerebral damage or cerebral disease on magnetic resonance imaging (MRI) prior to administration of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 2.76 Method 2, or any of 2.1-2.75, wherein the patient has a positive serum antibody or antigen test for one or more of Herpes simplex Virus 1, Herpes Simplex Virus 2, West Nile Virus, Nipah Virus, human immunodeficiency virus, rabies virus, Epstein-Barr Virus, cytomegalovirus, coronavirus (e.g., MERS-CoV, SARS-CoV, SARS-Cov2, or influenza virus (e.g., influenza A, such as H1N1, H2N2, H3N2, H5N1, H7N7), prior to administration of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 2.77 Method 2, or any of 2.1-2.76, wherein the patient has a positive serum antibody test for autoantibodies against the NMDA receptor, the AMPA receptor, the voltage-gated

- potassium, channel (VGKC), the LGL1 protein, the GABA receptor, the glycine receptor, the glutamate receptor, or the CASPR2 receptor;
- 2.78 Any foregoing method, wherein the patient has elevated levels of one or more biomarkers indicative of CNS inflammation, e.g., selected from TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, ICAM-1, VCAM-1, YKL-40, Nlrp3, and Flt-1, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF);
- 2.79 Any foregoing method, wherein the patient has changes in levels of one or more biomarkers indicative of CNS inflammation and/or loss of BBB integrity, e.g., increased levels of ICAM-1, VCAM-1, E-selectin, P-selectin, or soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), or reduced levels of Cldn5, Occludin, and ZO-1, in the serum or CSF;
- 2.80 Any foregoing method, wherein the patient has depressed levels of one or more anti-inflammatory biomarkers indicative of CNS inflammatory dysfunction, e.g., TNF- β , IFN- α , IL-4, and IL-10, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF);
- 2.81 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has a reduced level of one or more biomarkers indicative of CNS inflammation, e.g., TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, ICAM-1, VCAM-1, YKL-40, Nlrp3, and Flt-1, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;
- 2.82 Method 1.94, wherein the patient has at least a 5%, 10%, 15%, 20%, or 25%, 30%, 35%, 40%, 45%, or 50%, reduction in the level of the one or more biomarkers indicative of CNS inflammation, e.g., within 28 days of the initiation of treatment;
- 2.83 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has a

- favorable changes in levels of one or more biomarkers indicative of CNS inflammation and/or loss of BBB integrity, e.g., increased levels of ICAM-1, VCAM-1, E-selectin, P-selectin, or soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), or reduced levels of Cldn5, Occludin, and ZO-1, in the serum or CSF, compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;
- 2.84 Method 2.83, wherein the patient has at least a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, reduction or increase in the level of the one or more biomarkers indicative of CNS inflammation and/or loss of BBB integrity, e.g., within 28 days of the initiation of treatment;
- 2.85 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has an increased level of one or more anti-inflammatory biomarkers indicative of CNS inflammatory dysfunction, e.g., TNF- β , IFN- α , IL-4, and IL-10, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;
- 2.86 Method 2.85, wherein the patient has an increase of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, in the levels of the one or more anti-inflammatory biomarkers indicative CNS inflammatory dysfunction, e.g., within 28 days of the initiation of treatment, e.g., within 28 days of the initiation of treatment;
- 2.87 Any foregoing method, wherein the method further comprises the step of testing one or more body fluids or tissues from the patient for the presence and/or concentration of one or more biomarkers indicative of CNS inflammation or CNS inflammatory dysfunction prior to the initiation of treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), and/or subsequent to the initiation of said treatment, and optionally comparing the pre-treatment and one or more post-treatment results thereof to quantify the effectiveness of the treatment in the patient and/or to adjust the treatment regimen;
- 2.88 Method 2.87, wherein the biomarkers are selected from one or more of TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, YKL-40, Nlrp3, Flt-1, ICAM-1, VCAM-1, E-selectin, P-selectin, Cldn5, Occludin, and

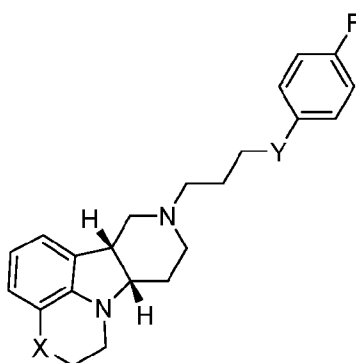
- ZO-1, soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), TNF- β , IFN- α , IL-4, and IL-10;
- 2.89 Method 2.87 or 2.88, wherein the one or more body fluids or tissues are selected from blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), or brain biopsy tissue samples;
- 2.90 Any foregoing method, wherein the method further comprises the step of non-invasively testing the central nervous system of the patient for the presence and/or concentration of one or more biomarkers indicative of CNS inflammation or CNS inflammatory dysfunction prior to the initiation of treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), and/or subsequent to the initiation of said treatment, and optionally comparing the pre-treatment and one or more post-treatment results thereof to quantify the effectiveness of the treatment in the patient and/or to adjust the treatment regimen;
- 2.91 Method 2.90, wherein the biomarkers are selected from one or more of TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, YKL-40, Nlrp3, Flt-1, ICAM-1, VCAM-1, E-selectin, P-selectin, Cldn5, Occludin, and ZO-1, soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), TNF- β , IFN- α , IL-4, and IL-10;
- 2.92 Method 2.90 or 2.91, wherein the step comprises an imaging method, such as magnetic resonance imaging (MRI), positron emission tomography (PET), functional MRI (fMRI), to evaluate the presence and/or concentration of said biomarkers;
- 2.93 Any of Methods 2.90-2.92, wherein the method comprises the step of initiating, altering, or terminating, the treatment regimen (e.g., the selected 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, the dose thereof, the route of administration thereof, the frequency of administration thereof, the form of administration thereof, and/or the combination of the selected 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand with any another therapeutic agent), based on the observed changes in the levels of one or more of said biomarkers.

[0038] In another aspect, the disclosure provides a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g. a compound of Formula I, as hereinbefore described, for example lumateperone, in free base

or salt form, optionally in deuterated form, for use in protecting or reinforcing the blood-brain barrier, e.g., for use in any of Methods 2, et seq.

[0039] In another aspect, the disclosure provides the use of a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g. a compound of Formula I, as hereinbefore described, for example lumateperone, in free base or salt form, optionally in deuterated form, in the manufacture of a medicament for protecting or reinforcing the blood-brain barrier, e.g., for any of Methods 2, et seq.

[0040] In a particular embodiment, the present disclosure provides a method (Method 3) for the treatment of psychiatric disorders in a patient in need thereof, wherein the patient has elevated levels of pro-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, or elevated levels of C-reactive protein (CRP), or Csf1, and/or depressed levels of anti-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- β , IFN- α , IL-4, and IL-10, the method comprising administering a therapeutically effective amount of a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand to the patient, for example, a compound of Formula I:



Formula I

wherein:

X is -N(H)-, -N(CH₃)- or -O-;

Y is -C(=O)-, -C(H)(OH)- or -C(H)(OR₁)-;

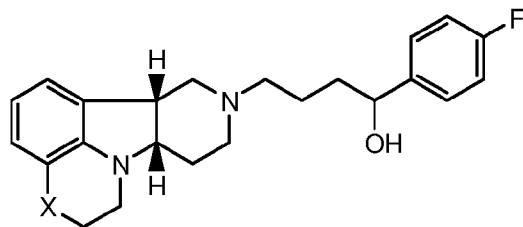
R₁ is -C(O)-C₁₋₂₁alkyl (e.g., -C(O)-C₁₋₅alkyl, -C(O)-C₆₋₁₅alkyl or -C(O)-C₁₆₋₂₁alkyl), preferably said alkyl is a straight chain, optionally saturated or unsaturated and optionally substituted with one or more hydroxy or C₁₋₂₂alkoxy (e.g., ethoxy) groups, for example R₁ is -C(O)-C₆alkyl, -C(O)-C₇alkyl, -C(O)-C₉alkyl, -C(O)-C₁₁alkyl, -C(O)-C₁₃alkyl or -C(O)-C₁₅alkyl, wherein such compound hydrolyzes to form the

residue of a natural or unnatural, saturated or unsaturated fatty acid, e.g., the compound hydrolyzes to form the hydroxy compound on the one hand and octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid or hexadecanoic acid on the other hand,

optionally in deuterated form,

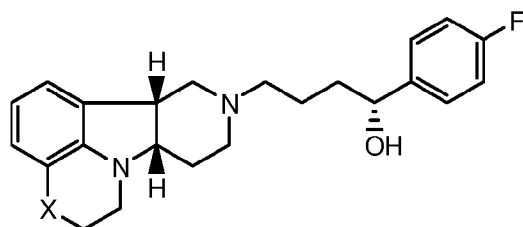
in free base, pharmaceutically acceptable salt, or prodrug form. For example, Method 3 may be as follows:

- 3.1. Method 3, wherein X in the compound of Formula I is $-N(H)-$, $-N(CH_3)-$ or $-O-$;
- 3.2. Method 3 or 3.1, wherein X in the compound of Formula I is $-N(H)-$;
- 3.3. Method 3 or 3.1, wherein X in the compound of Formula I is $-N(CH_3)-$;
- 3.4. Method 3 or 3.1, wherein X in the compound of Formula I is $-O-$;
- 3.5. Method 3 or any of formulae 3.1-3.4, wherein Y in the compound of Formula I is $-C(=O)-$, $-C(H)(OH)-$ or $-C(H)(OR_1)-$;
- 3.6. Method 3 or any of formulae 3.1-3.4, wherein Y in the compound of Formula I is $-C(=O)-$;
- 3.7. Method 3 or any of formulae 3.1-3.4, wherein Y in the compound of Formula I is $-C(H)(OH)-$;
- 3.8. Method 3 or any of formulae 3.1-3.4, wherein Y in the compound of Formula I is $-C(H)(OR_1)-$;
- 3.9. Method 3, or any of 3.1-3.5 or 3.8, wherein R_1 in the compound of Formula I is $-C(O)-C_{1-21}alkyl$ (e.g., $-C(O)-C_{1-5}alkyl$, $-C(O)-C_{6-15}alkyl$ or $-C(O)-C_{16-21}alkyl$), preferably said alkyl is a straight chain, optionally saturated or unsaturated and optionally substituted with one or more hydroxy or $C_{1-22}alkoxy$ (e.g., ethoxy) groups, for example R_1 is $-C(O)-C_6alkyl$, $-C(O)-C_7alkyl$, $-C(O)-C_9alkyl$, $-C(O)-C_{11}alkyl$, $-C(O)-C_{13}alkyl$ or $-C(O)-C_{15}alkyl$ wherein such compound hydrolyzes to form the residue of a natural or unnatural, saturated or unsaturated fatty acid, e.g., the compound hydrolyzes to form the hydroxy compound on the one hand and octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid or hexadecanoic acid on the other hand; e.g., wherein R_1 in the compound of Formula I is $-C(O)-C_{6-15}alkyl$, e.g., $-C(O)-C_9alkyl$; or wherein R_1 in the compound of Formula I is $-C(O)-C_{1-5}alkyl$, e.g., $-C(O)-C_3alkyl$;
- 3.10. Method 3 or any of 3.1-3.5, or 3.7-3.9, wherein the Compound of Formula I is:



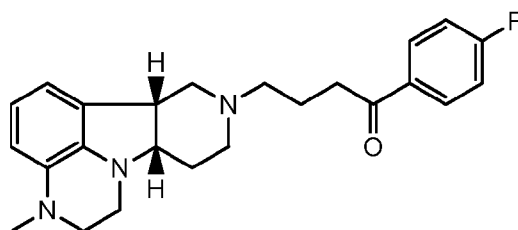
;

3.11. Method 3 or any of 3.1-3.5 or 3.7, wherein the Compound of Formula I is:



;

3.12. Method 3, or any of 3.1, 3.3, 3.5, or 3.6, wherein the Compound of Formula I is lumateperone:



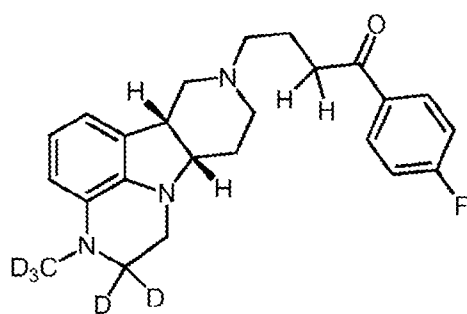
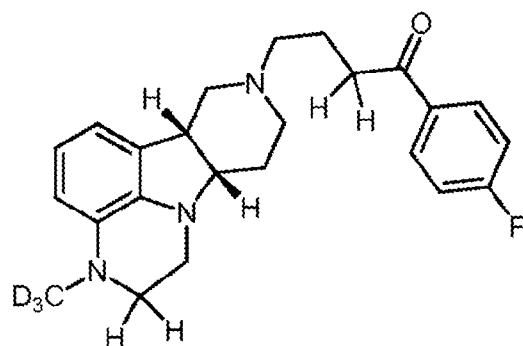
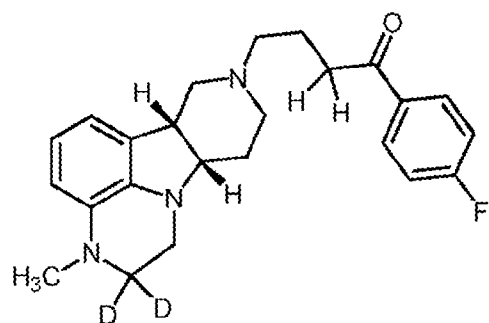
;

3.13. Method 3, or any of 3.1-1.12, e.g., Method 1.12, wherein the Compound of Formula I is in the form of a pharmaceutically acceptable salt, e.g., a tosylate salt;

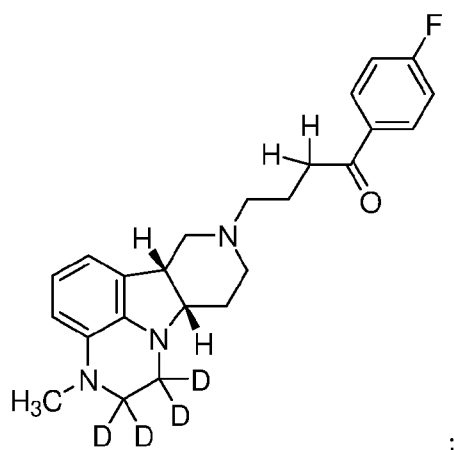
3.14. Method 3, or any of 3.1-1.12, e.g. Method 1.12, wherein the Compound of Formula I is in the form of the free base;

3.15. Method 3 or any of 3.1-1.14 wherein the Compound of Formula I is in deuterated form, e.g., wherein the deuterium:protium ratio for a specified carbon-bound hydrogen atom is significantly higher, e.g., at least 2x, for example at least 10x higher, than the natural isotope ratios;

3.16. Method 3.15 wherein the Compound of Formula I is a deuterated form of lumateperone, for example, selected from:



and



- wherein D represents a hydrogen position with substantially greater than natural deuterium incorporation (i.e., substantially greater than 0.0156%), e.g., greater than 60%, or greater than 70%, or greater than 80%, or greater than 90% or greater than 95%, or greater than 96%, or greater than 97%, or greater than 98%, or greater than 99%, in free base or pharmaceutically acceptable salt form, e.g. tosylate salt form;
- 3.17. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D₂ receptor ligand is a compound of Formula I in free base or pharmaceutically acceptable salt form, e.g. tosylate salt form, administered in a daily dose equivalent to 1 to 100 mg of free base, e.g., in an amount equivalent to 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 20 mg, or 1 to 10 mg, of free base;
- 3.18. Method 3.17 wherein the method comprises once daily administration of a unit dosage for oral administration, for example a tablet or capsule, comprising the compound of Formula I in free base or pharmaceutically acceptable salt form, e.g., in tosylate salt form, in an amount equivalent 1 to 100 mg of free base, e.g., in an amount equivalent to 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 30 mg, or 1 to 20 mg, or 1 to 10 mg, or 1 to 5 mg, or 40 to 60 mg, or 20 to 40 mg, or 10 to 20 mg, or about 60 mg, or about 40 mg, or about 30 mg, or about 20 mg, or about 10 mg, or about 5 mg, of free base, and a pharmaceutically acceptable diluent or carrier;
- 3.19. Method 3.17 wherein the method comprises once daily administration of a unit dosage for oral transmucosal administration, e.g., a sublingual or buccal orally disintegrating tablet, wafer, or film, comprising the compound of Formula I in free base or pharmaceutically acceptable salt form, e.g., in tosylate salt form, in an amount equivalent to 0.5 to 30 mg of free base, e.g., in an amount equivalent to 1 to 30 mg, or 1 to 20 mg, or 1 to 15 mg, or 1 to 10 mg, or 20 to 30 mg, or 10 to 20 mg, or about 5 mg, or about 10 mg, or about 15 mg, or about 20 mg, of free base, and a pharmaceutically acceptable diluent or carrier;
- 3.20. Any foregoing method wherein the condition to be treated is alleviated within one week, e.g., within three days, e.g., within one day;
- 3.21. Any foregoing method, wherein the patient has or is diagnosed with a viral, bacterial, or autoimmune encephalitis;
- 3.22. Method 3.21, wherein the patient's psychiatric disorder is caused by, or is suspected to be caused by, the viral, bacterial, or autoimmune encephalitis;

- 3.23. Method 3.21 or 3.22, wherein the encephalitis is viral encephalitis;
- 3.24. Method 3.23, wherein the viral encephalitis is caused by, or suspected to be caused by, Herpes simplex Virus 1, Herpes Simplex Virus 2, West Nile Virus, Nipah Virus, human immunodeficiency virus, rabies virus, Epstein-Barr Virus, cytomegalovirus, coronavirus (e.g., MERS-CoV, SARS-CoV, SARS-Cov2), or influenza virus (e.g., influenza A, such as H1N1, H2N2, H3N2, H5N1, H7N7);
- 3.25. Method 3.21, 3.22 or 3.23, wherein the viral encephalitis is acute viral encephalitis;
- 3.26. Method 3.21, wherein the encephalitis is bacterial encephalitis;
- 3.27. Method 3.26, wherein the encephalitis is caused by, or believed to be caused by, toxoplasmosis, rickettsia, mycoplasma, Borrelia (e.g., Lyme disease), or malaria;
- 3.28. Method 3.21, wherein the encephalitis is autoimmune encephalitis;
- 3.29. Method 3.28, wherein the encephalitis is caused by, or believed to be caused by, autoantibodies against the NMDA receptor, the AMPA receptor, the voltage-gated potassium, channel (VGKC), the LGL1 protein, the GABA receptor, the glycine receptor, the glutamate receptor, or the CASPR2 receptor;
- 3.30. Any of Methods 3.21-3.29, wherein the patient has no prior history of psychiatric disorders or psychiatric symptoms before the diagnosis of encephalitis;
- 3.31. Any of Methods 3.21-3.29, wherein the patient has no prior history of one or more of depression, anxiety, psychosis, post-traumatic stress-disorder, anhedonia, dementia, memory loss, impairment of executive function, difficulty concentrating, seizures, difficulty sleeping, hallucination, or change in personality, before the diagnosis of encephalitis;
- 3.32. Any foregoing method, wherein the psychiatric disorder is depression (e.g., acute depression, depression of MDD, depression of bipolar disorder), anxiety, (e.g., acute anxiety), psychosis (e.g., schizophrenia), post-traumatic stress-disorder, anhedonia, memory loss, impairment of executive functioning, difficulty concentrating, seizures, difficulty sleeping, hallucination, change in personality, or any combination thereof;
- 3.33. Any foregoing method wherein the psychiatric disorder is depression (e.g., acute depression, depression of MDD, depression of bipolar disorder);
- 3.34. Any foregoing method wherein the psychiatric disorder is anxiety (e.g., acute anxiety);
- 3.35. Any foregoing method wherein the psychiatric disorder is anhedonia;

- 3.36. Any foregoing method wherein the patient is diagnosed as having suicidal ideation and/or suicidal tendencies;
- 3.37. Any foregoing method wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered in combination (e.g., a fixed combination in a unit dosage form, or a free combination administered sequentially or simultaneously or within a 24-hour period) with a therapeutically effective amount of an anxiolytic or antidepressant agent;
- 3.38. Method 3.37 wherein the anxiolytic or antidepressant agent is selected from one or more compounds in free base or pharmaceutically acceptable salt form, selected from selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and atypical antipsychotics, e.g. one or more compounds in free base or pharmaceutically acceptable salt form, selected from:
- (a) Selective serotonin reuptake inhibitors (SSRIs), e.g., Citalopram (Celexa), Escitalopram (Lexapro, Cipralex), Paroxetine (Paxil, Seroxat), Fluoxetine (Prozac), Fluvoxamine (Luvox) Sertraline (Zoloft, Lustral);
 - (b) Serotonin-norepinephrine reuptake inhibitors (SNRIs), e.g., Desvenlafaxine (Pristiq), Duloxetine (Cymbalta), Levomilnacipran (Fetzima), Milnacipran (Ixel, Savella), Tofenacin (Elamol, Tofacine), Venlafaxine (Effexor);
 - (c) Tricyclic antidepressants (TCAs), e.g., Amitriptyline (Elavil, Endep), Amitriptylinoxide (Amioxid, Ambivalon, Equilibrin), Clomipramine (Anafranil), Desipramine (Norpramin, Pertofrane), Dibenzepin (Noveril, Victoril), Dimetacrine (Istonil), Dosulepin (Prothiaden), Doxepin (Adapin, Sinequan), Imipramine (Tofranil), Lofepramine (Lomont, Gamanil), Melitracen (Dixeran, Melixeran, Trausabun), Nitroxazepine (Sintamil), Nortriptyline (Pamelor, Aventyl), Noxiptiline (Agedal, Elronon, Nogedal), Pipofezine (Azafen/Azaphen), Protriptyline (Vivactil), Trimipramine (Surmontil);
 - (d) Benzodiazepines, e.g., selected from 2-keto compounds (e.g., clorazepate, diazepam, flurazepam, halazepam, prazepam); 3-hydroxy compounds (lorazepam, lormetazepam, oxazepam, temazepam); 7-nitro compounds (e.g., clonazepam, flunitrazepam,

nimetazepam, nitrazepam); triazolo compounds (e.g., adinazolam, alprazolam, estazolam, triazolam); and imidazo compounds (climazolam, loprazolam, midazolam);

- 3.39. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g., the compound of Formula I is administered intra-nasally, subcutaneously, intramuscularly, intravenously, orally, sub-lingually, intra-peritoneally, or buccally, such as an oral rapidly dissolving tablet, wafer, or film, which dissolves in the oral cavity for transmucosal absorption;
- 3.40. Any foregoing method, wherein the method further comprises the concurrent administration of an anti-depressant agent (e.g., selected from a selective serotonin reuptake inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor), a serotonin receptor antagonist, or any combination thereof), e.g., administered simultaneously, separately or sequentially;
- 3.41. Any foregoing method, wherein the method further comprises the concurrent administration of an NMDA receptor antagonist, for example, selected from ketamine (e.g., *S*-ketamine and/or *R*-ketamine), hydroxynorketamine, memantine, dextromethorphan, dextroallorphan, dextrorphan, amantadine, and agmatine, or any combination thereof, e.g., administered simultaneously, separately or sequentially;
- 3.42. Any foregoing method, wherein the method further comprises the concurrent administration of a NMDA receptor allosteric modulator, e.g., a NMDA receptor glycine-site modulator, such as rapastinel, nebostinel, apimostinel, D-cycloserine, or any combination thereof, e.g., administered simultaneously, separately or sequentially;
- 3.43. Any foregoing method, wherein the method provides the patient with an acute response to treatment with the therapeutic agent or agents (e.g., the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, the Compound of Formula I, or the combination of the Compound of Formula I and the Compound of Formula II, and/or any additional antidepressant agents);
- 3.44. Method 3.43, wherein the patient shows an acute response to treatment within less than 3 weeks, for example, less than 2 weeks, or less than 1 week, or from 1 to 7 days, or 1 to 5

days, or 1 to 3 days, or 1 to 2 days, or about 1 day, or less than 2 days, or less than 1 day (e.g., 12-24 hours, 6-12 hours, or 3-6 hours);

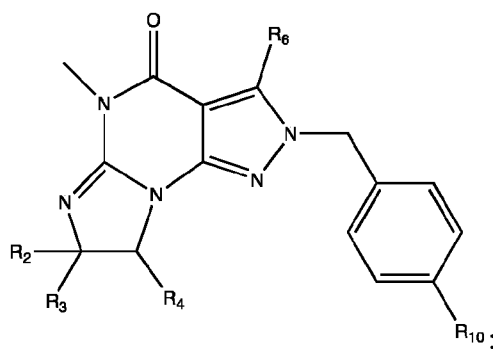
- 3.45. Any foregoing method, wherein the patient has not responded to, or has not responded adequately to, or who suffers undesirable side effects from, treatment with another antidepressant agent, for example, any one or more of a selective serotonin reuptake inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor, or a serotonin receptor antagonist;
- 3.46. Any foregoing method, wherein the psychiatric disorder is not associated with schizophrenia or dementia;
- 3.47. Any foregoing method, wherein the patient does not suffer from (or has not previously been diagnosed with) schizophrenia or dementia;
- 3.48. Any foregoing method, wherein the method protects or reinforces the blood-brain barrier;
- 3.49. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the 5-HT_{2A} receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);
- 3.50. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the D2 receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);
- 3.51. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at the D1 receptor, e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism);
- 3.52. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand has an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at

the serotonin transporter (SERT), e.g., an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said transporter (agonism or antagonism);

- 3.53. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in free base or pharmaceutically acceptable salt form, optionally in a deuterated form;
- 3.54. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in a tosylate salt form (e.g., monotosylate salt), optionally in a deuterated form, and optionally in crystalline or amorphous tosylate salt form;
- 3.55. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is lumateperone, in free base form, optionally in a deuterated form;
- 3.56. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered in the form of a long-acting injectable (LAI) composition, e.g., for intramuscular or subcutaneous injection;
- 3.57. Method 3.56, wherein the dose of the LAI composition is sufficient to provide the equivalent of a daily dose of 1 to 100 mg of free base, e.g., 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 20 mg, or 1 to 10 mg, of free base, released over a period of time ranging from about 1 week to about 3 months, e.g., about 1 week to about 8 weeks, or about 1 week to about 6 weeks, or about 1 week to about 4 weeks, or about 1 week to about 3 weeks, or about 1 week to about 2 weeks;
- 3.58. Method 3.56 or 3.57, wherein the LAI composition comprises the compound of Formula I dissolved, dispersed, suspended, or encapsulated in a polymeric matrix;
- 3.59. Method 3.58, wherein the polymeric matrix comprises one or more biocompatible and biodegradable polymers as defined herein, e.g., poly(hydroxycarboxylic acids), poly(amino acids), cellulose polymers, modified cellulose polymers, polyamides, and polyesters;
- 3.60. Method 3.59, wherein the one or more polymers comprises polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly-beta-hydroxybutyric acid, poly(lactic acid-glycolic acid) copolymer, 2-hydroxybutyric acid-glycolic acid copolymer, polylactic acid-polyethylene glycol copolymer, polyglycolic acid-polyethylene glycol copolymer, PEG-PLGA copolymer or block copolymer, poly(alkyl alpha-cyanoacrylate) such as poly(butyl

- cyanoacrylate) or poly(2-octyl cyanoacrylate), poly(ortho ester), polycarbonate, polyortho-carbonate, a polyamino acid, (for example poly-gamma.-L-alanine, poly-.gamma.-benzyl-L-glutamic acid or poly-y-methyl-L-glutamic acid), and/or hyaluronic acid ester;
- 3.61. Method 3.60, wherein the one or more polymers comprises polyortho esters (POE), polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, or a poly(lactic acid-glycolic acid) copolymer;
- 3.62. Method 3.60, wherein the one or more polymers comprises a poly(lactic acid-glycolic acid) copolymer, e.g., poly-d,l-lactide-co-glycolide (PLGA), for example, a PLGA copolymer with a lactide-to-glycolide molar ratio of about 50:50 to 90:10, or 50:50 to 85:15, or 50:50 to 75:25, and/or a molecular weight of 5,000 to 500,000 Daltons, or 5,000 to 150,000 Daltons, or 20,000 to 200,000 Daltons, or 24,000 to 38,000 Daltons;
- 3.63. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered as monotherapy, e.g., it is not administered concurrently or in conjunction with an anti-depressant, anti-psychotic, or anti-anxiety agent;
- 3.64. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered without the direct supervision of a health care professional (e.g., the compound is self-administered by the patient);
- 3.65. Any foregoing method, wherein the method does not comprise supervision or observation of the patient by a health care professional during or after (e.g., within 2 hours after) administration of a dose of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 3.66. Any foregoing method, wherein the method does not put the patient at risk for sedation, dissociation, abuse, misuse, or suicidal ideation;
- 3.67. Any foregoing method, wherein the method does not result in hypertension (e.g., systolic and/or diastolic hypertension) within four hours after administration of a dose of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g., an increase of more than 10 mm Hg, or more than 20 mm Hg, or more than 30 mm Hg, or more than 40 mm Hg, in systolic and/or diastolic blood pressure within 30 minutes to 4 hours after said dose;
- 3.68. Any foregoing method, wherein the method does not result in cognitive decline;
- 3.69. Any foregoing method, wherein the patient has (e.g., has been diagnosed with), or is at risk of, aneurysmal vascular disease (e.g., thoracic aorta, abdominal aorta, intracranial, or peripheral arterial aneurysms), arteriovenous malformation or intracerebral hemorrhage;

- 3.70. Any foregoing method, wherein the patient is under concurrent treatment with an oral antidepressant selected from duloxetine, escitalopram, sertraline, or venlafaxine;
- 3.71. Any foregoing method, wherein the patient is not under concurrent treatment with an oral antidepressant selected from duloxetine, escitalopram, sertraline, or venlafaxine;
- 3.72. Any foregoing method, wherein the patient is unresponsive to, or cannot be treated with ketamine (e.g., S-ketamine), e.g., because it is contraindicated in said patient;
- 3.73. Any foregoing method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is administered to the patient concurrently with a PDE1 (cyclic nucleoside phosphodiesterase 1) inhibitor (e.g., administered simultaneously, separately, or sequentially), in free base or pharmaceutically acceptable salt form;
- 3.74. Method 3.73, wherein the PDE1 inhibitor is a compound according to Formula II:



wherein R₂ is H and R₃ and R₄ together form a tri- or tetra-methylene bridge [pref. with the carbons carrying R₃ and R₄ having the R and S configuration respectively]; or R₂ and R₃ are each methyl and R₄ is H; or R₂ and R₄ are H and R₃ is isopropyl [pref. the carbon carrying R₃ having the R configuration];

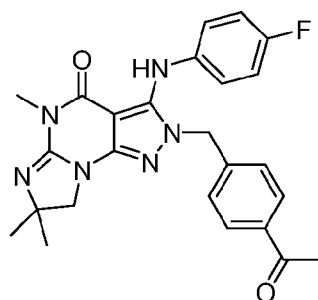
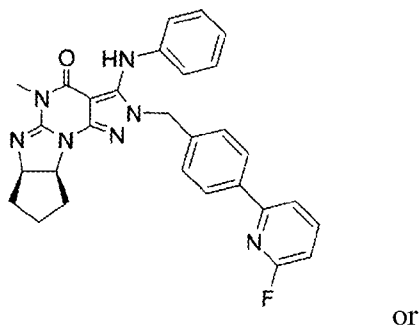
R₆ is (optionally halo-substituted) phenylamino or (optionally halo-substituted) benzylamino;

R₁₀ is (optionally halo-substituted) phenyl, (optionally halo-substituted) pyridyl (for example 3-fluoropyrid-2-yl), thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl), or C₁-alkylcarbonyl (e.g., methylcarbonyl);

in free base or pharmaceutically acceptable salt form;

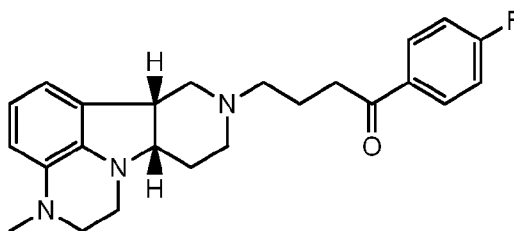
- 3.75. Method 3.74, wherein, in the Compound of Formula II, R₆ is phenylamino or 4-fluorophenylamino;

- 3.76. Method 3.74, wherein, in the Compound of Formula II, R₁₀ is 3-fluoropyrid-2-yl or methylcarbonyl;
- 3.77. Method 3.74, wherein, in the Compound of Formula II, R₆ is phenylamino or 4-fluorophenylamino and R₁₀ is 3-fluoropyrid-2-yl or methylcarbonyl;
- 3.78. Any Methods 3.74-3.77, wherein the Compound of Formula II is

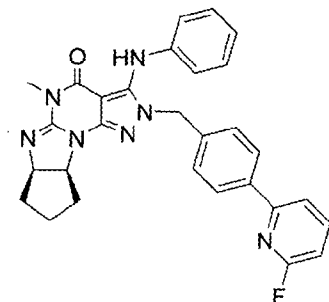


in free base or pharmaceutically acceptable salt form;

- 3.79. Method 3.77, wherein the Compound of Formula II is in the form of the monophosphate salt;
- 3.80. Any of Methods 3.74-3.79, wherein the Compound of Formula I is:



in free base or pharmaceutically acceptable salt form, e.g., tosylate salt form,
optionally in a deuterated form; and the Compound of Formula II is:



in free base or pharmaceutically acceptable salt form, e.g., monophosphate salt form;

- 3.81 Any of Methods 3.74-3.80, comprising administration of a pharmaceutical composition comprising therapeutically effective amounts of both a Compound of Formula I and a Compound of Formula II;
- 3.82 Any preceding method, wherein the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is a compound of Formula I, in free base or pharmaceutically acceptable salt form, optionally in deuterated form, and wherein the compound is administered in the form of a long-acting injectable (LAI) composition comprising the compound of Formula I dissolved or dispersed or in a pharmaceutically acceptable carrier and a polymeric matrix comprising polymers selected from polyortho esters (POE), polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, or a poly(lactic acid-glycolic acid) copolymer;
- 3.83 Method 3.82, wherein the pharmaceutically acceptable carrier comprises water (e.g., an aqueous buffer) and/or an organic solvent (e.g., a water-miscible organic solvent);
- 3.84 Method 3.82 or 3.83, wherein the polymers comprise a polylactic acid and/or a polyglycolic acid polymer;
- 3.85 Method 3.82 or 3.83, wherein the polymers comprise a poly(lactic acid-glycolic acid) copolymer, e.g., poly-d,l-lactide-co-glycolide (PLGA), for example, a PLGA copolymer with a lactide-to-glycolide molar ratio of about 50:50 to 90:10, or 50:50 to 85:15, or 50:50 to 75:25, and/or a molecular weight of 5,000 to 500,000 Daltons, or 5,000 to 150,000 Daltons, or 20,000 to 200,000 Daltons, or 24,000 to 38,000 Daltons;
- 3.86 Any of Methods 3.82-3.85, wherein the LAI composition is administered by, or formulated for administration by, intramuscular or subcutaneous injection;
- 3.87 Method 3, or any of 3.1-3.86, wherein the patient has no prior history of depression;

- 3.88 Method 3, or any of 3.1-3.87, wherein the patient shows evidence of cerebral damage or cerebral disease on magnetic resonance imaging (MRI) prior to administration of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 3.89 Method 3, or any of 3.1-3.88, wherein the patient has a positive serum antibody or antigen test for one or more of Herpes simplex Virus 1, Herpes Simplex Virus 2, West Nile Virus, Nipah Virus, human immunodeficiency virus, rabies virus, Epstein-Barr Virus, cytomegalovirus, coronavirus (e.g., MERS-CoV, SARS-CoV, SARS-CoV2, or influenza virus (e.g., influenza A, such as H1N1, H2N2, H3N2, H5N1, H7N7), prior to administration of the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand;
- 3.90 Method 3, or any of 3.1-3.89, wherein the patient has a positive serum antibody test for autoantibodies against the NMDA receptor, the AMPA receptor, the voltage-gated potassium channel (VGKC), the LGL1 protein, the GABA receptor, the glycine receptor, the glutamate receptor, or the CASPR2 receptor;
- 3.91 Any foregoing method, wherein the patient has elevated levels of one or more biomarkers indicative of CNS inflammation, e.g., selected from TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, ICAM-1, VCAM-1, YKL-40, Nlrp3, and Flt-1, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF);
- 3.92 Any foregoing method, wherein the patient has changes in levels of one or more biomarkers indicative of CNS inflammation and/or loss of BBB integrity, e.g., increased levels of ICAM-1, VCAM-1, E-selectin, P-selectin, or soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), or reduced levels of Cldn5, Occludin, and ZO-1, in the serum or CSF;
- 3.93 Any foregoing method, wherein the patient has depressed levels of one or more anti-inflammatory biomarkers indicative of CNS inflammatory dysfunction, e.g., TNF- β , IFN- α , IL-4, and IL-10, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF);
- 3.94 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has a

- reduced level of one or more biomarkers indicative of CNS inflammation, e.g., TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, ICAM-1, VCAM-1, YKL-40, Nlrp3, and Flt-1, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;
- 3.95 Method 3.94, wherein the patient has at least a 5%, 10%, 15%, 20%, or 25%, 30%, 35%, 40%, 45%, or 50%, reduction in the level of the one or more biomarkers indicative of CNS inflammation, e.g., within 28 days of the initiation of treatment;
- 3.96 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has favorable changes in levels of one or more biomarkers indicative of CNS inflammation and/or loss of BBB integrity, e.g., increased levels of ICAM-1, VCAM-1, E-selectin, P-selectin, or soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), or reduced levels of Cldn5, Occludin, and ZO-1, in the serum or CSF, compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;
- 3.97 Method 3.96, wherein the patient has at least a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, reduction or increase in the level of the one or more biomarkers indicative of CNS inflammation, e.g., within 28 days of the initiation of treatment;
- 3.98 Any foregoing method, wherein after treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), the patient has an increased level of one or more anti-inflammatory biomarkers indicative of CNS inflammatory dysfunction, e.g., TNF- β , IFN- α , IL-4, and IL-10, in the blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), compared to a pre-treatment baseline, e.g., within 28 days of the initiation of treatment;
- 3.99 Method 3.98, wherein the patient has an increase of at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, in the levels of the one or more anti-inflammatory biomarkers indicative CNS inflammatory dysfunction, e.g., within 28 days of the initiation of treatment, e.g., within 28 days of the initiation of treatment;

- 3.100 Any foregoing method, wherein the method further comprises the step of testing one or more body fluids or tissues from the patient for the presence and/or concentration of one or more biomarkers indicative of CNS inflammation or CNS inflammatory dysfunction prior to the initiation of treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), and/or subsequent to the initiation of said treatment, and optionally comparing the pre-treatment and one or more post-treatment results thereof to quantify the effectiveness of the treatment in the patient and/or to adjust the treatment regimen;
- 3.101 Method 3.100, wherein the biomarkers are selected from one or more of TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, YKL-40, Nlrp3, Flt-1, ICAM-1, VCAM-1, E-selectin, P-selectin, Cldn5, Occludin, and ZO-1, soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), TNF- β , IFN- α , IL-4, and IL-10;
- 3.102 Method 3.100 or 3.101, wherein the one or more body fluids or tissues are selected from blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, CSF, and/or CNS microglial cells (e.g., isolated from CSF), or brain biopsy tissue samples;
- 3.103 Any foregoing method, wherein the method further comprises the step of non-invasively testing the central nervous system of the patient for the presence and/or concentration of one or more biomarkers indicative of CNS inflammation or CNS inflammatory dysfunction prior to the initiation of treatment with the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., Compound of Formula, optionally in deuterated form), and/or subsequent to the initiation of said treatment, and optionally comparing the pre-treatment and one or more post-treatment results thereof to quantify the effectiveness of the treatment in the patient and/or to adjust the treatment regimen;
- 3.104 Method 3.103, wherein the biomarkers are selected from one or more of TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, YKL-40, Nlrp3, Flt-1, ICAM-1, VCAM-1, E-selectin, P-selectin, Cldn5, Occludin, and ZO-1, soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), TNF- β , IFN- α , IL-4, and IL-10;

- 3.105 Method 3.103 or 3.104, wherein the step comprises an imaging method, such as magnetic resonance imaging (MRI), positron emission tomography (PET), functional MRI (fMRI), to evaluate the presence and/or concentration of said biomarkers;
- 3.106 Any of Methods 3.100-3.105, wherein the method comprises the step of initiating, altering, or terminating, the treatment regimen (e.g., the selected 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, the dose thereof, the route of administration thereof, the frequency of administration thereof, the form of administration thereof, and/or the combination of the selected 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand with any another therapeutic agent), based on the observed changes in the levels of one or more of said biomarkers.

[0041] In another aspect, the disclosure provides a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g., a compound of Formula I, as hereinbefore described, for example lumateperone, in free base or salt form, optionally in deuterated form, for use in the treatment of psychiatric disorders in a patient in need thereof, wherein the patient has elevated levels of pro-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, or elevated levels of C-reactive protein (CRP), or Csf1, and/or depressed levels of anti-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- β , IFN- α , IL-4, and IL-10, e.g., for use in any of Methods 3, et seq.

[0042] In another aspect, the disclosure provides the use of a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, e.g. a compound of Formula I, as hereinbefore described, for example lumateperone, in free base or salt form, optionally in deuterated form, in the manufacture of a medicament for treatment of psychiatric disorders in a patient in need thereof, wherein the patient has elevated levels of pro-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, or elevated levels of C-reactive protein (CRP), or Csf1, and/or depressed levels of anti-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- β , IFN- α , IL-4, and IL-10, e.g., for any of Methods 3, et seq.

[0043] In some embodiments described herein, particularly suitable patients for carrying out the disclosed methods may be identified by measuring the levels of certain biomarkers in body fluids or tissues from said patients. These biomarkers may indicate the presence of CNS inflammation, or the presence of CNS inflammatory dysfunction, either due to infection, autoimmunity, or other causes. Thus, psychological symptoms in said patients may be

particularly attributed to such inflammatory changes, and may particularly benefit from the unique properties and activities of the compounds described herein. Biomarkers indicative of CNS inflammation include TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, CRP, SAA, Csf1, ICAM-1, VCAM-1, YKL-40, Nlrp3, and Flt-1, which may be identified or quantified in samples taken from blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, cerebrospinal fluid (CSF), and/or microglial cells isolated from CSF). In particular, changes in certain biomarkers are indicative of a breakdown of the integrity of the blood-brain barrier, such as ICAM-1, VCAM-1, E-selectin, P-selectin, Cldn5, Occludin, and ZO-1, or soluble isoforms thereof (e.g., sICAM-1, sVCAM1, sP-selectin, sE-selectin), which may be identified or quantified in the serum or CSF. Disruption of the BBB can lead to cellular damage and cell lysis, leading to the presence of tight junction proteins that are normally membrane-bound in the CSF and plasma. Alternatively, CNS inflammation induced by inflammatory cytokines can upregulate proteins that loosen the BBB or downregulate proteins that tighten the BBB, in order to allow infiltration of immune cells into the CSF. Changes in levels of any or all of these biomarkers may be indicative of CNS inflammation and/or BBB damage or loss of BBB integrity. Similarly, another class of biomarkers are those associated with anti-inflammatory properties, such as the anti-inflammatory cytokines. Decreases in the levels of such biomarkers may be indicative of CNS inflammatory dysfunction, i.e., dysfunction of the normal bodily controls on cellular inflammation. Examples of such biomarkers include TNF- β , IFN- α , IL-4, and IL-10, which likewise may be identified or quantified in samples taken from blood, plasma, serum, peripheral blood mononuclear cells (PBMC) (e.g., isolated from blood), urine, cerebrospinal fluid (CSF), and/or microglial cells isolated from CSF. In addition to detecting these biomarkers in body fluids and tissues, much work has been accomplished on non-invasive imaging technologies (e.g., MRI, PET) to obtain the same information, especially in hard-to-access body compartments such as the CNS. Additional information on methods of measuring such biomarkers and for interpreting changes in these biomarker's levels may be found in: Zhu et al., "Circulating tight junction proteins mirror blood-brain barrier integrity in leukaemia central nervous system metastasis," *Hematol Oncol*, 35(3):365-373 (2017); Abe, et al. "Soluble cell adhesion molecules in hypertriglyceridemia and potential significance on monocyte adhesion," *Arterioscler. Thromb. Vasc. Biol.*, 18(5): 723-31 (1998); Janelidze et al., "CSF Biomarkers of neuroinflammation and cerebrovascular dysfunction

in early Alzheimer disease,” *Neurology*, 91(9):e867-e877 (2018); Beanio et al., “Towards PET imaging of the dynamic phenotypes of microglia.” *Clinical and Experimental Immunology*, 206(3): 282-300 (2021).

[0044] The term “5-HT_{2A} receptor ligand” refers to a compound which displays, at least, pharmacological activity at the serotonin 5-HT_{2A} receptor, for example, compounds having an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at said receptor. In some embodiments, this term refers to a compound having an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at said receptor (agonism or antagonism).

[0045] The term “5-HT_{2A} /D2 receptor ligand” refers to a compound which displays, at least, pharmacological activity at both the serotonin 5-HT_{2A} receptor and at the D2 receptor, for example, compounds having an IC₅₀ of less than 250 nM or an EC₅₀ of less than 250 nM for activity (agonism and/or antagonism) at each of said receptors. In some embodiments, this term refers to a compound having an IC₅₀ or EC₅₀ of less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 75 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, for activity at one or both of these receptors (agonism or antagonism).

[0046] The words “treatment” and “treating” are to be understood accordingly as embracing prophylaxis and treatment or amelioration of symptoms of disease and/or treatment of the cause of the disease. In particular embodiments, the words “treatment” and “treating” refer to prophylaxis or amelioration of symptoms of the disease.

[0047] The term “patient” may include a human or non-human patient.

[0048] If not otherwise specified or clear from context, the following terms herein have the following meanings:

[0049] “Alkyl” as used herein is a saturated or unsaturated hydrocarbon moiety, e.g., one to twenty-one carbon atoms in length, which may be linear or branched (e.g., n-butyl or tert-butyl), preferably linear, unless otherwise specified. For example, “C₁₋₂₁ alkyl” denotes an alkyl group having 1 to 21 carbon atoms. In one embodiment, alkyl is optionally substituted with one or more hydroxy or C₁₋₂₂alkoxy (e.g., ethoxy) groups. In another embodiment, alkyl contains 1 to 21 carbon atoms, preferably straight chain and optionally saturated or unsaturated, for example

R₁ may be an alkyl chain containing 1 to 21 carbon atoms, preferably 6-15 carbon atoms, 16-21 carbon atoms, e.g., so that together with the -C(O)- to which it attaches, e.g., when cleaved from the compound of Formula I, forms the residue of a natural or unnatural, saturated or unsaturated fatty acid.

[0050] The 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand, for example a substituted heterocycle fused gamma-carboline as described herein, may be in free base, pharmaceutically acceptable salt, or prodrug form. Pharmaceutically acceptable salts include, for example, the tosylate salts in the case of Compounds of Formula I. Where dosages or amounts of a salt are given by weight, e.g., milligrams per day or milligrams per unit dose, the dosage amount of the salt is given as the weight of the corresponding free base, unless otherwise indicated.

[0051] In any and all embodiments described herein, the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand may also be a SERT ligand, i.e., said compounds may be a 5-HT_{2A}/SERT or a 5-HT_{2A}/D2/SERT receptor ligand.

[0052] In any and all embodiments described herein, the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand may be free or substantially free of any opioid receptor activity (e.g., free or substantially free of mu-opioid receptor activity, e.g., having an IC₅₀ greater than 50 nM or greater than 100 nM or greater than 150 nM).

[0053] The 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand may in some cases also exist in prodrug form. A prodrug form is compound which converts in the body to the active compound. For example, compounds which contain hydroxy or carboxy substituents may form physiologically hydrolysable and acceptable esters. As used herein, "physiologically hydrolysable and acceptable ester" means esters which are hydrolysable under physiological conditions to yield acids (in the case of compounds which have hydroxy substituents) or alcohols (in the case of compounds which have carboxy substituents) which are themselves physiologically tolerable at doses to be administered. For example, wherein Y of the compound of Formula I is -C(H)(OR₁), and R₁ is -C(O)-C₁₋₂₁alkyl, e.g., -C(O)-C₃alkyl or -C(O)-C₉alkyl, these compounds may hydrolyze under physiological condition to yield a compound of Formula I wherein Y is -C(H)(OH) on the one hand and C₁₋₂₁alkyl-C(O)OH, e.g., C₃alkyl-C(O)OH or C₉alkyl-C(O)OH on the other hand. As will be appreciated the term thus embraces conventional pharmaceutical prodrug forms. When a prodrug (e.g., the compound of formula (I) wherein R₁ is -C(O)-C₁-

₂₁alkyl) is used, the dosage amount is calculated based on the amount of the compound of formula (I) wherein Y is -C(=O)- or -CH(OH)-, in free base form.

[0054] The term “concurrently” when referring to a therapeutic use means administration of two or more active ingredients to a patient as part of a regimen for the treatment of a disease or disorder, whether the two or more active agents are given at the same or different times or whether given by the same or different routes of administrations. Concurrent administration of the two or more active ingredients may be at different times on the same day, or on different dates or at different frequencies.

[0055] The term “simultaneously” when referring to a therapeutic use means administration of two or more active ingredients at or about the same time by the same route of administration.

[0056] The term “separately” when referring to a therapeutic use means administration of two or more active ingredients at or about the same time by different route of administration.

[0057] With respect to concurrent treatment using a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand (e.g., a compound of Formula I) and an NMDA receptor antagonist (e.g., ketamine), without being bound by theory, it is believed that the combination of these agents would permit lower doses of both agents to be used to treat depression, or other neuropsychiatric disorders described herein, such that the dissociative effects produced by the NMDA receptor antagonist would be minimized while the synergistic antidepressants effects would be maximized.

[0058] Dosages employed in practicing the present disclosure will of course vary depending, e.g. on the particular disease or condition to be treated, the particular active compounds used, the mode of administration, and the therapy desired. Unless otherwise indicated, an amount of an active compound for administration (whether administered as a free base or as a salt form) refers to or is based on the amount of the compound in free base form (i.e., the calculation of the amount is based on the amount of active moiety in free base form, not taking into account the weight of the counter ion in the case of a salt).

[0059] The 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand may be administered by any suitable route, including orally, intra-muscularly, subcutaneously, parenterally, transmucosally, or transdermally, but are preferably administered orally or transmucosally. The 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand may be administered, for example, in the form of a tablet, a capsule, a wafer, an injection (e.g., intravenous, intramuscular, or subcutaneous injection), or an oral, rapidly disintegrating tablet, wafer, or film for sublingual or buccal administration.

[0060] For the avoidance of doubt, any disclosure of a numerical range, e.g., “up to X” amount is intended to include the upper numerical limit X. Therefore, a disclosure of “up to 60 mg” is intended to include 60 mg.

[0061] Pharmaceutical compositions comprising compounds of the Disclosure may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus, oral dosage forms may include tablets, capsules, solutions, suspensions and the like.

[0062] Compounds of the present disclosure may be included as a long-acting injectable formation (i.e., depot formulation), e.g., by dispersing, dissolving, suspending, or encapsulating the Compounds of the Invention in a polymeric matrix as described in herein, such that the Compound is continually released as the polymer degrades over time. The release of the Compounds of the Invention from the polymeric matrix provides for the controlled- and/or delayed- and/or sustained-release of the Compounds, e.g., from the pharmaceutical depot composition, into a subject, for example a warm-blooded animal such as man, to which the pharmaceutical depot is administered. Thus, the pharmaceutical depot delivers the Compounds of the Invention to the subject at concentrations effective for treatment of the particular disease or medical condition over a sustained period of time, e.g., 1 week to 3 months.

[0063] Polymers useful for the polymeric matrix in the Composition of the Invention (e.g., Depot composition of the Invention) may include a polyester of a hydroxyfatty acid and derivatives thereof or other agents such as polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly-beta.-hydroxybutyric acid, epsilon.-capro-lactone ring opening polymer, lactic acid-glycolic acid copolymer, 2-hydroxybutyric acid-glycolic acid copolymer, polylactic acid-polyethylene glycol copolymer or polyglycolic acid-polyethylene glycol copolymer), PEG-PLGA copolymer or block copolymer, a polymer of an alkyl alpha-cyanoacrylate (for example poly(butyl 2-cyanoacrylate)), a polyalkylene oxalate (for example polytrimethylene oxalate or polytetramethylene oxalate), a polyortho ester, a polycarbonate (for example polyethylene carbonate or polyethylenepropylene carbonate), a polyortho-carbonate, a polyamino acid (for example poly-gamma.-L-alanine, poly-.gamma.-benzyl-L-glutamic acid or poly-y-methyl-L-glutamic acid), a hyaluronic acid ester, and the like, and one or more of these polymers can be used.

[0064] If the polymers are copolymers, they may be any of random, block and/or graft copolymers. When the above alpha-hydroxycarboxylic acids, hydroxydicarboxylic acids and

hydroxytricarboxylic acids have optical activity in their molecules, any one of D-isomers, L-isomers and/or DL-isomers may be used. Among others, alpha-hydroxycarboxylic acid polymer (preferably lactic acid-glycolic acid polymer), its ester, poly-alpha-cyanoacrylic acid esters, etc. may be used, and lactic acid-glycolic acid copolymer (also referred to as poly(lactide-alpha-glycolide) or poly(lactic-co-glycolic acid), and hereinafter referred to as PLGA) are preferred. Thus, in one aspect the polymer useful for the polymeric matrix is PLGA. As used herein, the term PLGA includes polymers of lactic acid (also referred to as polylactide, poly(lactic acid), or PLA). Most preferably, the polymer is the biodegradable poly(d,l-lactide-co-glycolide) polymer, such as PLGA 50:50, PLGA 85:15 and PLGA 90:10

[0065] In a preferred embodiment, the polymeric matrix of the invention is a biocompatible and biodegradable polymeric material. The term “biocompatible” is defined as a polymeric material that is not toxic, is not carcinogenic, and does not significantly induce inflammation in body tissues. The matrix material should be biodegradable wherein the polymeric material should degrade by bodily processes to products readily disposable by the body and should not accumulate in the body. The products of the biodegradation should also be biocompatible with the body in that the polymeric matrix is biocompatible with the body. Particular useful examples of polymeric matrix materials include poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxanone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mono- and distearate, and the like. The preferred polymers for use in the practice of this aspect of the disclosure are polylactide, polyglycolide, and poly(d,l-lactide-co-glycolide). It is preferred that the molar ratio of lactide to glycolide in such a copolymer be in the range of from about 75:25 to 50:50.

[0066] In the case of polyester polymers, including polylactide, polyglycolide, and poly(d,l-lactide-co-glycolide), it is understood that the polymers can have either carboxylic acid end groups or carboxylic ester end groups. Particularly useful are poly(d,l-lactide-co-glycolide) copolymers (PLGA copolymers) with a lactide-to-glycolide molar ratio of about 50:50 to 90:10, or 50:50 to 85:15, or 50:50 to 75:25, and/or a molecular weight of 5,000 to 500,000 Daltons, or 5,000 to 150,000 Daltons, or 20,000 to 200,000 Daltons, or 24,000 to 38,000 Daltons.

[0067] Useful PLGA polymers may have a weight-average molecular weight of from about 5,000 to 500,000 Daltons, preferably about 150,000 Daltons. Dependent on the rate of degradation to be achieved, different molecular weight of polymers may be used. For a diffusional mechanism of drug release, the polymer should remain intact until all of the drug is released from the polymeric matrix and then degrade. The drug can also be released from the polymeric matrix as the polymeric excipient bioerodes.

[0068] The PLGA may be prepared by any conventional method, or may be commercially available. For example, PLGA can be produced by ring-opening polymerization with a suitable catalyst from cyclic lactide, glycolide, etc. (see EP-0058481B2; Effects of polymerization variables on PLGA properties: molecular weight, composition and chain structure).

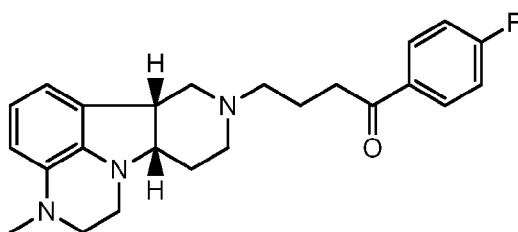
[0069] It is believed that PLGA is biodegradable by means of the degradation of the entire solid polymer composition, due to the break-down of hydrolysable and enzymatically cleavable ester linkages under biological conditions (for example in the presence of water and biological enzymes found in tissues of warm-blooded animals such as humans) to form lactic acid and glycolic acid. Both lactic acid and glycolic acid are water-soluble, non-toxic products of normal metabolism, which may further biodegrade to form carbon dioxide and water. In other words, PLGA is believed to degrade by means of hydrolysis of its ester groups in the presence of water, for example in the body of a warm-blooded animal such as man, to produce lactic acid and glycolic acid and create the acidic microclimate. Lactic and glycolic acid are by-products of various metabolic pathways in the body of a warm-blooded animal such as man under normal physiological conditions and therefore are well tolerated and produce minimal systemic toxicity.

[0070] For long-acting injectable compositions, the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand may be dissolved, dispersed, or suspended in the polymeric matrix, and/or further admixed with a pharmaceutically acceptable diluent or carrier. Such carrier may be aqueous, such as water suitable for injection (e.g., an aqueous buffer), or non-aqueous, such as an organic solvent, or a mixture of a water and an organic solvent (e.g., a water-miscible organic solvent). In some embodiments, the 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand is encapsulated in microspheres or microparticles which are suspended or dispersed in the pharmaceutically acceptable diluent or carrier, as described in U.S. 9,708,322, and U.S. 9,956,227, the contents of each of which are hereby incorporated by reference in their entireties. Further information for the preparation of

microparticles can be found in U.S. 2008/0069885, the contents of which are incorporated herein by reference in its entirety.

EXAMPLES

[0071] **Drugs and Experimental Design.** Lumateperone, also known as ITI-007 or IC200056 tosylate salt, is the Compound of Formula I, wherein X is N(CH₃), and Y is C=O:



in the form of its tosylate salt. It is approved by the U.S. Food & Drug Administration (FDA) for the treatment for schizophrenia, and bipolar depression in adults. Lumateperone provides selective and simultaneous modulation of serotonin, dopamine and glutamate neurotransmission and is particularly of interest in the context of psychiatric disorders.

[0072] All other reagents are obtained in the highest purity available from Sigma-Aldrich (St. Louis, MO) unless otherwise noted. For most experiments, mice or rats at least 8 weeks of age are given an intraperitoneal (IP) injection of lumateperone (0.3, 1, 3, or 8 mg/kg) or its vehicle (v/v: 5% DMSO, 5% Tween 20, 15% polyethylene glycol [PEG] 400, and 75% pure HPLC water). Some rodents are given a cotreatment with a subcutaneous (SC) injection of lipopolysaccharide (LPS, 500 µg/kg; Sigma-Aldrich, ref# 0127:B8) diluted in 0.9% injectable saline while control group animals receive injections of all vehicles matching the experimental conditions. In experiments in which delayed administration of lumateperone is studied, mice (n = 4-9 per group) first receive a subcutaneous injection of LPS or saline followed by an IP injection of lumateperone (3 mg/kg) or its vehicle 30 minutes later. In experiments using restraint stress, mice assigned to the restraint stress group receive a single injection of lumateperone (3 mg/kg) or its vehicle and are immediately placed in a rodent restraint bag. In behavioral experiments, rats receive a pretreatment of lumateperone (1 mg/kg) or its vehicle on day 1. On day 2, either no injection for naïve rats, or saline or LPS is injected (1 mg/kg, SC). On day 3, rats receive another injection of either lumateperone or saline and are tested the following day (day 4).

[0073] **Animals.** Adult, male C57BL/6 mice weighing 28-30 grams at the time of the experiment are housed in groups of 4 or 5 in small cages. Adult, male Sprague-Dawley rats weighing 175-200 grams at the time of arrival after shipping are housed in pairs. All animals are housed under standard laboratory housing conditions with a 12-hour light/dark cycle and *ad libitum* access to food and water.

[0074] **Tissue Collection.** Mice are euthanized 2 hours after lumateperone injection (for cotreatment studies with LPS) or application of restraint stress for sample collection. Rats are euthanized 18 hours after LPS injection for sample collection. Hippocampi from mice and rats are rapidly dissected under RNase-free conditions and placed in 1.5 mL Eppendorf tubes. When appropriate, samples are snap frozen in liquid nitrogen prior to storage at -80°C until further analysis. Trunk blood is collected from mice into serum collection tubes, allowed to clot at room temperature for 1 hour, then centrifuged at 1,500g for 10 minutes at 4°C .

[0075] **Multiplex Assays.** In mouse serum, protein levels of IL-1b, IL-6, IL-10 and TNF-alpha are measured using a V-Plex Meso Scale Discovery (MSD) Multiplex spot assay Mouse Neuroinflammation 1 panel (Meso Scale Diagnostics, Rockville, MD). All samples are run in duplicates or triplicates according to manufacturer instructions and analyzed with MSD Discovery Workbench software (Meso Scale Diagnostics).

[0076] **Quantitative Real-Time PCR.** Mouse hippocampal tissue is homogenized with glass beads in 1 mL of TRIzol reagent using a BeadBeater (Biospec Products, Bartlesville, OK). Heavy phase-lock gel tubes enabled separation of phases following the addition of 400 μL chloroform to the sample and centrifugation at 12,000 rpm for 10 minutes at room temperature. RNA is extracted using Qiagen Rneasy kit (Qiagen, Hilden, Germany). For cDNA synthesis, 2 μg of total RNA is used (SuperScript IV Reverse Transcriptase; ThermoFisher Scientific, Waltham, MA). The purity and concentration of RNA is measured with a Nanodrop spectrophotometer; the optical density (OD) 260/280 and OD 260/230 are within 1.8-2.3. In the hippocampus, 4 key markers of pro- and anti-inflammatory cytokines and chemokines (*Il1b*: ID Mm00434228_m1, *Tnfa*: ID Mm00443258_m1, *Il6*: ID Mm00446190_m1, and *Il10*: ID Mm01288386_m1; ThermoFisher Scientific) are initially chosen for analysis (n = 5-12 per group). In subsequent experiments, the transcripts for other markers of inflammation are chosen for analysis including *Icam1* (ID Mm00516023_m1; a cell adhesion molecule involved in immune cell migration), *Cldn5* (ID Mm00727012_s1; a tight junctions protein), colony stimulating factor 1 (*Csf1*: ID

Mm00432686_m1; a factor that regulates microglia function) and its receptor *Csf1r* (ID Mm01266652_m1), and the nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3 inflammasome complex (*Nlrp3*: Mm00840904_m1). *Gapdh* (ID Mm99999915_g1) is chosen as a housekeeping gene. QuantStudio 7 (ThermoFisher Scientific) is used for analyzing the plates (MicroAmp Optical 384-well plates; Applied Biosystems, Waltham, MA, and ThermoFisher Scientific) that are loaded with TaqMan Universal Master Mix II without uracil-DNA glycosylate in a 20 μ l reaction volume using 100 ng cDNA per well. All mRNAs are measured by qRT-PCR on ABI Prism 7900HT system using TaqMan Gene Expression Assays. Ct values of genes of interest are normalized to that of the reference gene (*Gapdh*).

[0077] **NanoString.** The mouse neuropathology panel includes 770 genes associated with themes of neurotransmission, neuron-glia interaction, neuroplasticity, cell structure integrity, neuroinflammation and metabolism. A total of 13 housekeeping genes are used for expression normalization (*Aars*: NM_146217.4, *Asb10*: NM_080444.4, *Ccdc127*: NM_024201.3, *Cnot10*: NM_153585.5, *Csnk2a2*: NM_009974.3, *Fam104a*: NM_138598.5, *Gusb*: NM_010368.1, *Lars*: NM_134137.2, *Mtol*: NM_026658.2, *Supt7l*: NM_028150.1, *Tada2b*: NM_001170454.1:3224, *Tbp*: NM_013684.3:70, and *Xpnpep1*: NM_133216.3:1826, see Figure 1-1). Hippocampal RNA is extracted using the Qiagen microkit (Qiagen) and is evaluated by the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA) to assess RNA concentration, quality, and integrity. Sample preparation, hybridization, and detection (100 ng per sample, n = 5-6 per group) are carried out according to NanoString manufacturer's instructions (NanoString Technologies, Seattle, WA). The normalized data are transformed to log2 score to express the fold change. NanoString results (raw and normalized counts) are derived from RCC files using the nSolver software (version 2.6; NanoString Technologies). A complementary gene software analysis tool, ROSALIND[®] Advanced Analysis Software (NanoString Technologies), is also used, which provides comprehensive free cloud-based data analysis for nCounter data by directly analyzing raw RCC files generated from NanoString. Data are imported into ROSALIND[®] Advanced Analysis Software for normalization, calculation of fold-changes, *P* values, identification of enriched pathways, and heatmaps.

[0078] **Microglia Enrichment.** In male adult rats (8-9 weeks old, n = 8-12 per group) that are previously treated with either LPS and lumateperone or vehicle 1 day prior (18 hours), hippocampi are dissected and placed in 1 mL of medium A solution containing 0.6% glucose and 15 mM

HEPES. Brain tissue is then processed through a dounce homogenizer followed by passages through 16- and 20-gauge needles. One mL of medium A is added to wash cell suspension, which is passed through a 70 mm cell strainer and kept on ice. Next, 6 mL of 100% Percoll solution (9 parts of Percoll [GE Healthcare, Chicago, IL] and 1 part of HBSS) is added to obtain a 75% Percoll solution. The 75% Percoll cell suspension is then underlaid a layer of 25% Percoll solution containing Phenol red, which has a layer of PBS on top. The discontinuous Percoll density gradient is layered as followed: 75%, 25%, and 0% isotonic Percoll (PBS) to isolate hippocampal microglia. The gradients are then centrifuged at 4 °C for 25 minutes at 3,000 rpm in swinging buckets with minimal acceleration and deceleration and no brake. After centrifugation, the top layer containing myelin and debris (interface PBS/25% Percoll) is removed and the cellular layer at the 25%/75% interphase is collected and washed. Pilot experiments compare the gene expression of the different fractions and validated the presence of microglia in the interphase layer. The final pellet is resuspended in 350 µL of Buffer RLT from Qiagen microkit (Qiagen) to perform RNA extraction according to the manufacturer's instructions.

[0079] **Restraint Stress Protocol.** Acute restraint stress is performed using special rodent “decapicone” restraint bags in the traditional triangle shape (Braintree Scientific, Braintree, MA; ref# MDC-200). Mice (n = 11-13 per group) are maintained in their restraint bag while placed on a secure surface at room temperature for 2 hours. Mice are euthanized at the end of the 2 hour stress session and whole hippocampal samples are collected. Control, non-stressed mice remain in their home cages in an adjoining room and are euthanized for sample collection at the same time point as stressed mice.

[0080] **BBB Permeability Assay.** Sodium fluorescein (NaFl) permeability assay is performed as previously described (Olsen et al., “Correlation between breakdown of the blood–brain barrier and disease outcome of viral encephalitis in mice,” *Antiviral Res.* 75:104-112 (2007)) with minor adjustments. Mice (n = 4-8 per group) are administered lumateperone and either dosed with LPS or restrained as described above. At 45 minutes prior to tissue collection, mice receive 200 µl of 10% NaFl (Cat# F6377, MilliporeSigma), IP. Mice are then euthanized via isoflurane overdose, and blood is collected via cardiac stick and allowed to clot while protected from light. Mice are perfused with 15 ml 1 x PBS solution. Brains are then excised and flash frozen, protected from light. Serum is collected from blood samples via centrifugation at 1,500g at 4 °C for 10 minutes. Brains are homogenized in 1 x PBS and centrifuged at 10,000g at 4 °C for 10 minutes, and the

supernatant is collected for both protein concentration via Peirce BCA Protein Assay and further analysis. Proteins from both serum and tissue homogenate are extracted via trichloroacetic acid precipitation (Cat# T6399, MilliporeSigma) on ice, and centrifuged at 10,000g at 4 °C for 10 minutes. Samples are run in duplicate on a FITC Filter spectrophotometer (EnVision 2105, PerkinElmer, Waltham, MA; excitation: 485 nm, emission: 535 nm). The average fluorescence of sham mice is subtracted from each value prior to calculation. Tissue homogenate fluorescent readings are first normalized to total protein concentration, and the cerebrum / serum ratio of arbitrary fluorescence units is calculated.

[0081] **Behavioral Evaluation.** All behavioral tests are performed in the morning with adult male Sprague-Dawley rats (n = 9-11 per group for the experiments with LPS, and n = 13-14 per group for the naïve rats).

[0082] **Novelty Suppressed Feeding Test (NSFT).** This test measures consumption of a familiar food in a novel environment, relying on rodents' aversion to eating in a novel environment after a period of food deprivation (Ramaker and Dulawa, "Identifying fast-onset antidepressants using rodent models," *Mol. Psychiatry* 22:656-665 (2017)). Rats are food-deprived overnight and placed in an open field ($76.5 \times 76.5 \times 40$ cm³) with a small amount of food pellets (6 pellets total). At the time of the test, rats are exposed to the open field for the first time (novelty) and allowed to explore it for a maximum of 15 minutes under red light. The latency for the animal to approach the food pellets and take its first bite is manually scored. A home cage feeding test (HCFT) is performed afterwards to ensure latency measured in NSFT is not a matter of difference in hunger. A home cage food intake analysis evaluated the amount of food eaten (in grams) over a period of 10 minutes following the end of the entire test session.

[0083] **Novelty Induced Hypophagia (NIH).** This conflict-based behavioral task assesses the impact of environmental stressors on conditioned approach response for a palatable food reward (Ramaker and Dulawa, 2017). Rats are habituated with diluted (1:3 milk/water) sweetened condensed milk which is accessible in their home cage for 1 hour each day for 3 consecutive days. Initially, animals are tested in their home cage under normal lighting. For testing after drug treatment, the latency to drink is recorded after rats are placed in a novel clean cage of the same dimensions with no bedding and under dim lighting (~50 lux) with white paper under the cages to enhance aversion.

[0084] **Open Field Test (OFT).** Rats are placed in an open field box ($76.5 \times 76.5 \times 40 \text{ cm}^3$) under dim lighting and locomotor activity over a 10 minute period is measured using ANY-Maze Software (Stoelting Co., Wood Dale, IL).

[0085] **Reward Sniffing Test** (also known also as female urine sniffing test (FUST)): In this anhedonia-based assay, rats are brought to a well-ventilated testing room under dim lighting. A sterile cotton-tipped applicator is attached to one wall in the home cage for 1 hour to habituate rats to this new object. For the 2 phases of the 5 minute test, rats are first exposed to a new cotton tip dipped in sterile water as a control that is removed at the end of the 5 minutes; 45 minutes later, another cotton tip previously dipped into fresh rat urine collected from females of the same strain is attached to the cage wall. Male behavior is video recorded and latency to first sniff of the cotton tip and total time spent sniffing the cotton-tipped applicator are determined.

[0086] **Statistical Analysis.** Data are expressed as mean $\pm$ SEM. All statistical analyses are performed using GraphPad version 9 or earlier (GraphPad Software, San Diego, CA). Sample sizes for the experiments are calculated using expected effect size and variance based on previous data. The Kolmogorov–Smirnov test is used as a test of normality. Unpaired t-tests 2-sided are used for comparison between 2 groups. When the normal distribution is not confirmed, the Mann–Whitney U test is used to compare the mean ranks of 2 groups. Multiple group comparisons are made using 1-way ANOVA followed by a Bonferroni post hoc test or Tukey’s multiple comparison test. NanoString nCounter analysis is based on multivariate linear regression with Benjamini-Yekutieli adjustment. Probability value is noted in each figure and details on specific tests used are stated in the figure legends. Outliers are removed using the median absolute deviation (MAD) equation (median plus or minus 2.5 times the MAD method for outlier detection).

Example 1: Lumateperone dose-dependently normalizes the pro-inflammatory state.

[0087] Specific cytokines are elevated in serum or plasma of patients with MDD and other psychiatric disorders. Here, the gene and protein expression of a subset of pro- and anti-inflammatory cytokines is measured in mouse brain in response to an inflammatory challenge using a single dose of LPS ($500 \mu\text{g/kg}$) to induce acute brain inflammation. Samples are collected 2 hours after coinjections of LPS and lumateperone or vehicle. mRNA is isolated and analyzed by qRT-PCR or NanoString Neuropath panel. The ability of lumateperone to ameliorate LPS-induced changes in hippocampal mRNA levels of these cytokines is studied using 3 doses of lumateperone (0.3, 3, and 8 mg/kg , IP). These doses span lumateperone’s effective dose range for modulation of

antipsychotic-like and antidepressant-like activity in rodents (*see* Snyder et al., “Functional profile of a novel modulator of serotonin, dopamine, and glutamate neurotransmission,” *Psychopharmacology* 232:605-621 (2015)). The results are shown in Table 1A as relative change in mRNA levels for each cytokine gene (*Il1b*, *Il6*, *Tnfa*, *Il10*) normalized to the control group using the Dct method (n=5-12 per group):

Table 1A: Hippocampal cytokine mRNA expression				
	IL-1b	IL-6	TNF-alpha	IL-10
Control	0	0	0	0
LPS	2.88	1.03	1.75	0.43
Luma, 0.3 mg/kg	2.26	0.52	0.43	– 0.28
Luma, 3 mg/kg	0.85	0.15	– 0.09	2.53
Luma, 8 mg/kg	0.43	0.16	– 0.24	3.73

[0088] As expected, LPS treatment significantly increases gene expression for pro-inflammatory cytokines in hippocampus but did not significantly alter that of the anti-inflammatory cytokine *Il10* relative to control mice, as determined by 1-way ANOVA analyses (effect of LPS treatment on levels of *Il1b*: $F_{(4,40)} = 16.48$, $P < .01$; *Il6*: $F_{(4,43)} = 11.57$, $P < .001$; *Tnfa*: $F_{(4,43)} = 24.51$, $P < .001$; *Il10*: $F_{(4,41)} = 13.15$, $P > .99$).

[0089] The results show that when administered at the same time as LPS, lumateperone dose-dependently lowers LPS-induced elevations of hippocampal mRNA levels of the pro-inflammatory genes *Il1b*, *Tnfa* and *Il6* (*Il1b*: doses of 3 and 8 mg/kg, $P < .001$; *Il6*: dose of 3 mg/kg, $P < .001$, 8 mg/kg, $P < .01$; *Tnfa*: all doses, $P < .001$). In addition, lumateperone significantly increases hippocampal mRNA levels of the anti-inflammatory cytokine *Il10* at doses of 3 and 8 mg/kg when compared with levels seen in animals receiving LPS alone (post hoc comparison of means: $P = .004$ and $P < .001$ compared with LPS at lumateperone doses of 3 and 8 mg/kg, respectively).

[0090] To determine if lumateperone also reduces LPS-induced increases in pro-inflammatory cytokine protein levels in peripheral blood, a dose of 3 mg/kg lumateperone is selected for further analysis based on data from the above dose-response study in hippocampal tissue. An additional experimental group receiving an injection with lumateperone alone is included as an additional

control. Protein concentration is measured using the Multiplex MSD assay V-Plex technology. Results are expressed in pg/mL, except for IL-6, which is measured in ng/mL.

Table 1B: Serum cytokine concentration				
	IL-1b	IL-6	TNF-alpha	IL-10
Saline only	1.32	0.51	14.08	24.80
LPS	6.27	14.52	335.3	980.4
Luma	1.47	0.09	9.38	48.93
Luma + LPS	2.69	1.49	56.33	1014.3

[0091] A pattern of results similar to that seen for gene expression changes in hippocampal tissue is obtained when examining protein levels of inflammatory biomarkers in serum. Two-way ANOVA revealed a significant effect of LPS, which elevated the protein levels of all biomarkers studied (Tukey multiple comparison vs control; IL-1b: $F_{(1,17)} = 15.21$, $P < .0012$; IL-6: $F_{(1, 19)} = 27.77$, $P < .0001$; TNF-a: $F_{(1, 20)} = 69.12$, $P < .0001$; IL-10: $F_{(1, 16)} = 38.24$, $P < .001$).

[0092] It is found that lumateperone treatment reduces circulating protein levels in serum of the pro-inflammatory cytokines IL-1b, TNF-a, and IL-6 compared with mice treated with LPS alone (IL-1b: LPS v. LPS+Luma, $P = .0081$; IL-6: LPS v. LPS+Luma, $P < .0001$; TNF-a: LPS v. LPS+Luma, $P < .0001$). Previous work has shown that LPS, which is a cell wall component of gram-negative bacteria, binds to Toll-like receptor 4 (TLR4) and activates nuclear factor kappa B (NFkB) signaling (Hoshino et al., "Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product," *J. Immunol.* 162:3749-3752 (1999)) as well as a mixed gene profile that is not strictly pro-inflammatory, as it is known to also upregulate IL-10 signaling molecules in primary rodent microglia.

[0093] In contrast to brain tissue, it is found that LPS challenge increases IL-10 protein levels in serum. Two-way ANOVA did not reveal any drug effect ($F_{(1, 16)} = 0.03489$, $P = .8542$) for IL-10 protein levels in serum, although lumateperone treatment by itself, without LPS, induces a significant IL-10 increase if compared with control only. These data demonstrate that, compared with vehicle, lumateperone increases the protein levels of the anti-inflammatory cytokine IL-10 while normalizing certain pro-inflammatory cytokines elevated by LPS in serum and brain.

[0094] To gain a deeper understanding of the transcriptional pathways and regulatory mechanisms altered by lumateperone in the context of elevated inflammation, NanoString nCounter-based

analysis is performed following coinjection of LPS (500 µg/kg) and lumateperone (3 mg/kg) with sample collection 2 hours after injection. The NanoString platform has been effectively used to quantitatively measure in vivo gene expression of target genes in several neuropathological mouse models. When coinjected with LPS, NanoString software analyses confirmed that lumateperone significantly decreased the expression of genes involved in inflammatory processes, as shown in the following table:

Table 1C: Differential expression versus baseline of control group			
Gene set (NanoString)	LPS	LPS+Luma	Luma
Adaptive immune response	0.571	0.938	0.344
Angiogenesis	– 0.144	0.891	0.616
Apoptosis	0.915	– 0.453	– 0.442
Astrocyte function	1.391	– 0.308	– 0.837
Autophagy	0.588	0.548	– 0.731
Carbohydrate metabolism	0.507	0.668	– 0.837
Cell cycle	– 0.148	0.385	– 0.75
Cellular stress	0.499	0.813	– 0.432
Cytokine signaling	0.993	– 0.599	– 0.543
DNA damage	0.578	0.042	– 0.614
Epigenetic regulation	0.312	0.892	0.729
Growth factor signaling	0.76	0.698	0.226
Inflammatory signaling	1.086	– 0.93	– 1.032
Innate immune response	0.939	– 0.655	– 0.611
Insulin signaling	0.28	0.809	0.858
Lipid metabolism	– 0.192	0.89	– 0.818
Matrix remodeling	– 0.583	0.447	– 0.4
Microglia function	0.377	0.915	0.466
Neurons and neurotransmission	– 0.422	0.979	0.435
NF-κB	1.215	– 0.689	– 0.499
Notch	0.876	1.05	0.834
Oligodendrocyte function	0.181	0.48	– 1.176

Wnt	- 0.476	1.186	0.9
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[0095] Generally, directed global significance scores measure the extent to which a given gene is up-regulated or down-regulated relative to a given covariate. It is calculated similarly to a unidirected global significance score, but it takes into account the sign of the t-statistic. Scores were calculated by nSolver software, using the control group as a reference.

[0096] Thus here, the directed global significance scores measure the extent to which a given gene set is up- or downregulated relative to the control group. The result show that LPS+Lumateperone treatment downregulates gene expression sets involved in cytokine signaling, inflammatory signaling , innate immune response, and the NF-kB pathway. Pathway analysis also documents an increase in genes associated with angiogenesis, epigenetic regulation, and Notch and Wnt pathways in groups injected with lumateperone.

[0097] Surprisingly, it is found that lumateperone alone alters gene expression in some of these pathways to a comparable extent (i.e., scored similarly) as did combined treatment with LPS+Lumateperone.

[0098] The following table shows the top genes involved in microglial function, neuroprotection, and inflammation which are found to be altered in the LPS + lumateperone group, compared to the LPS group.

Table 1D: LPS+Luma vs LPS					
	Gene name	Log2	P value	Lower	Upper
Neuroprotect	Fos	2.27	5.6×10^{-7}	1.68	2.86
	Egr1	0.87	0.0031	0.37	1.37
	Cldn5	0.812	1.4×10^{-5}	0.541	1.08
	Vegfa	0.227	0.0202	0.0524	0.402
	Ngf	0.126	0.43	- 0.18	0.432
Inflammation	Ikbkb	- 0.132	0.0313	- 0.242	- 0.021
	Tnfrsf1b	- 0.31	0.313	- 0.896	0.275
	Il1r1	- 0.309	0.0664	- 0.619	0.001
	Myd88	- 0.433	0.00442	- 0.695	- 0.172
	Tnfrsf1a	- 0.434	0.0124	- 0.74	- 0.128

	Nfkb2	− 0.972	0.0012	− 1.47	− 0.476
	Ly6a	− 0.925	6.9×10^{-7}	− 1.17	− 0.681
	Osmr	− 1.21	8.6×10^{-8}	− 1.49	− 0.937
	Il1b	− 1.42	0.0258	− 2.56	− 0.274
	Lrg1	− 1.67	0.00584	− 2.72	− 0.624
	Socs3	− 1.57	1.1×10^{-5}	− 2.08	− 1.06
	Ccr2	− 1.71	0.00737	− 2.82	− 0.599
	Casp4	− 2.24	7.0×10^{-5}	− 3.09	− 1.38
Microglia	Maff	1.21	0.00453	0.476	1.93
	Cd36	0.332	0.518	− 0.656	1.32
	Cx3cr1	0.231	0.00202	0.105	0.356
	Tmem144	0.227	0.0373	0.0292	0.425
	Tmem100	0.186	0.0444	0.0173	0.355
	P2ry12	0.14	0.0467	0.0115	0.269
	Ptgs2	− 0.358	0.00803	− 0.593	− 0.122

[0099] As shown in the table above, NanoString software analyses also show that compared with LPS alone, the LPS+Lumateperone combination increased expression of markers of neuroprotection such as *Fos*, *Egr1*, *Cldn5*, *Vegfa*, and *Ngf* while robustly decreasing expression of genes involved in inflammation such as *Casp4*, *Ccr2*, *Socs3*, *Lrg1*, *Il1b*, *Osmr*, *Ly6a*, *Myd88*, *Il1r1*, *Nfkb2*, *Tnfrsf1*, and *Ikbkb*.

[00100] Microglia markers of homeostasis including *Maff*, *Cx3cr1*, *Cd36*, *Trem100*, *Trem144*, and *P2ry12* are found to be upregulated by lumateperone, further supporting the potential protective properties of lumateperone in acute inflammatory conditions.

[00101] Next, using ROSALIND® Advanced Analysis Software and a filter set to $P < .04999$, a heatmap of cytokine-specific gene expression comparing LPS+Luma versus LPS alone is obtained. The data analysis with ROSALIND® confirms that lumateperone significantly downregulates genes that promote inflammation (e.g., *Osmr*, *Tnfrsf1a*, *Tnfrsf11b*, *Prl*, and *Il1r1*). Venn diagrams based on this analysis reveal some overlap of significantly altered gene expression changes ($P \leq .04999$) when group comparisons are performed. The results show that: the receptor for advanced glycation end products (RAGE) pathway is significantly altered when comparing

LPS versus control; brain-derived neurotrophic factor (BDNF) signaling pathway is among the most significant pathways altered in the group LPS+Lumateperone versus LPS; and IL-6 regulation is also one of the top pathways altered when comparing Lumateperone versus LPS. In summary, it is discovered that lumateperone reverses acute inflammatory conditions by normalizing key pathways involved in inflammation in parallel with enhancing a gene signature indicative of tissue protection and repair.

Example 2: Lumateperone reduces pre-established LPS-induced proinflammatory cytokine mRNA levels in the hippocampus.

[00102] Based on these findings, it was desired to study whether a delayed administration of lumateperone would alter an established state of elevated inflammation and thereby reestablish immune system homeostasis. Adult mice first receive a subcutaneous injection of either LPS injection (500 µg/kg) or vehicle (0.9% saline), and 30 minutes later the mice are injected IP with either lumateperone (3 mg/kg) or vehicle (5% DMSO, 5% Tween-20, 15% PEG-400, 75% water). Samples are collected 1.5 hours later (i.e., 2 hours after LPS injection). The results are shown in Table 2A as relative change in hippocampal mRNA levels for each cytokine gene (*Il1b*, *Il6*, *Tnfa*, *Il10*) normalized to the control group using the Dct method (n=4-9 per group) as in Example 1:

Table 2A: Hippocampal cytokine mRNA expression (delayed injection)				
	IL-1b	IL-6	TNF-alpha	IL-10
Saline/Vehicle	0	0	0	0
Saline/LPS	2.89	1.10	2.33	1.88
Luma/Vehicle	0.90	- 0.46	- 0.31	2.98
Luma/LPS	2.07	- 0.10	0.34	3.87

[00103] LPS is found to significantly increase hippocampal mRNA levels of *Il1b*, *Il6*, and *Tnfa* (2-way ANOVA, LPS effect: *Il1b*: $F_{(1, 19)} = 94.51$, $P < .0001$; *Il6*: $F_{(1, 20)} = 8.008$, $P = .0104$; *Tnfa*: $F_{(1, 20)} = 63.35$, $P < .0001$), and the delayed injection of lumateperone is found to reduce mRNA levels (*Il1b*: LPS v. LPS+Luma, $P = .0433$; *Il6*: LPS v. LPS+Luma, $P = .0078$; *Tnfa*: LPS v. LPS+Luma, $P < .0001$). These results indicate that lumateperone exhibits similar effects when given as a co-injection with LPS or 30 minutes after the LPS injection. It also shows that the mRNA levels of *Il10* are elevated by lumateperone in the presence or absence of LPS. Two-way ANOVA analyses of *Il10* show an effect of LPS ($F_{(1, 20)} = 21.31$, $P = .0002$) and lumateperone ($F_{(1,$

$_{20} = 69.02$, $P < .0001$) which confirms that lumateperone modulates hippocampal mRNA levels of this anti-inflammatory cytokine.

[00104] Supplementary key markers revealed by NanoString analyses are also examined, using the same procedure as described above.

Table 2B: Hippocampal cytokine mRNA expression (delayed injection)			
	<i>Icam1</i>	<i>Cldn5</i>	<i>Csf1</i>
Saline/Vehicle	0	0	0
Saline/LPS	4.33	− 0.63	0.41
Luma/Vehicle	0.28	0.33	0.05
Luma/LPS	1.26	0.20	− 0.11

[00105] It is found that there is a significant interaction, treatment (LPS) effect by drug effect (lumateperone) for *Cldn5* and *Icam1*. Lumateperone decreases levels of *Icam1* (LPS v. LPS+Luma, $P < .0001$) and coadministration of LPS with lumateperone increases *Cldn5* (LPS v. LPS+Luma, $P < .0001$). Analyses of the levels of *Csf1* mRNA show an interaction between drug and treatment and drug effect where lumateperone decreases *Csf1* relative to the LPS group (LPS v. LPS+Luma, $P = .0009$). Collectively, these results indicate that transcriptional modulation of genes related to inflammation and tissue repair is initiated when lumateperone is administered at a delay following LPS-induced inflammation.

Example 3: Lumateperone reinforces BBB integrity in the hippocampus.

[00106] Systemic inflammation is associated with increased permeability of the BBB, and this has been discussed as a potential factor underlying depression pathophysiology. In this experiment, mice receive a single injection of lumateperone (3 mg/kg, IP) at the same time (coinjection) or 30 minutes after (delayed) LPS injection. Forty-five minutes before sample collection, mice receive NaFl injections (200 μ l of 10% solution, IP) (Table 3).

Condition (2 h)	Control	Experimental group	Experimental + Luma	Experimental + Luma (delayed)
LPS paradigm	*1.000 $\pm$ 0.0957	1.406 $\pm$ 0.0873	**0.8632 $\pm$ 0.1273	***0.6515 $\pm$ 0.04580

Restraint Stress paradigm	1.000 ± 0.0311	1.132 ± 0.07244	\$0.7278 ± 0.1699	
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[00107] Mice treated with LPS demonstrate significantly increased NaFl brain penetration, and this is significantly dampened in both the lumateperone coinjection group and in the lumateperone delayed injection group (control = normalized to 1, LPS = 1.406, control vs LPS: Tukey's multiple comparison test $P < .05$; LPS+Luma = 0.863, LPS vs LPS+Luma: $P < .01$; LPS+Luma (delayed) = 0.652, LPS vs LPS+Luma (delayed): $P < .001$ – all units in arbitrary units normalized to control. $F_{(3, 21)} = 11.49$, $P = .0001$. Table 1). These data demonstrate that lumateperone administered in combination with LPS rescued the integrity of the BBB.

Example 4: Lumateperone attenuates stress-induced inflammation and BBB permeability.

[00108] To determine if lumateperone could normalize brain pathological inflammation induced by an acute stressor, restraint stress is used, which is a stressor known to evoke increases in inflammation. Mice receive a single injection of lumateperone (3 mg/kg, IP) or vehicle (5% DMSO, 5% Tween-20, 15% PEG-400, 75% water) immediately before being placed in a rodent restraint bag for 2 hours. Control mice receive vehicle treatment and are returned to their home cage before sample collection. Protein concentration is measured using the Multiplex MSD assay V-Plex technology, normalized to the control group. Results are expressed in pg/mL.

Table 4A: Serum cytokine concentration				
	IL-1b	IL-6	TNF-alpha	IL-10
Control	0.7	141.3	6.75	17.18
Stressed	1.65	627.4	10.28	86.78
Stressed + Luma	0.81	137.7	7.67	70.03

[00109] It is found that acute restraint stress results in significant elevations in serum IL-1b, IL-6, and TNF-a levels while each of these proteins are significantly reduced to control levels in mice receiving lumateperone (IL-1b: Stress v. Stress+Luma, Bonferroni's multiple comparisons test $P < .001$; IL-6: Stress v. Stress+Luma, $P < .001$; TNF-a: Stress v. Stress+Luma, $P = .007$, compared with controls). Corresponding data is collected for hippocampal mRNA expression according to the procedure of Example 1. The results are shown in Table 4B as relative change in mRNA levels for each cytokine gene (*Il1b*, *Il6*, *Tnfa*, *Il10*) normalized to the control group using the Dct method:

Table 4B: Hippocampal cytokine mRNA expression				
	IL-1b	IL-6	TNF-alpha	IL-10
Control	0	0	0	0
Stressed	1.05	0.037	- 0.076	2.29
Stressed + Luma	0.39	- 0.051	- 0.407	2.87

[00110] In the hippocampus of the same mice, acute restraint stress leads to an increase in mRNA levels for *Il1b* (control = normalized to zero, $P = .007$) which are not significantly decreased after lumateperone treatment. At this time point, *Tnfa* and *Il6* mRNA levels are not altered by acute restraint stress. Interestingly, IL-10 serum protein and hippocampal mRNA levels are both increased by lumateperone compared with controls (IL-10 protein levels: control v. Stress+Luma, Bonferroni's multiple comparisons test $P = .001$; *Il10* mRNA levels: control normalized to zero, Stress+Luma, $P < .001$).

[00111] Using similar procedures as described above, serum corticosterone levels and hippocampal *Cldn5* mRNA expression are measured as well (corticosterone is measured using a commercial ELISA kit).

Table 4C: Hippocampal mRNA expression	
	Cldn5
Control	0
Stressed	- 0.138
Stressed + Luma	0.330

Table 4D: Serum concentration	
	Corticosterone (ng/mL)
Control	22.65
Stressed	238.5
Stressed + Luma	167.3

[00112] The data shows that corticosterone levels are increased in blood serum of stressed mice and the elevated levels are significantly dampened by lumateperone (Stress vs Stress+Luma: $P < .001$; $F_{(2, 27)} = 124.2$, $P < .001$). It is also confirmed that *Cldn5* transcripts are significantly

elevated by lumateperone in stressed animals (Stress vs Stress+Luma: $P < .001$; $F_{(2, 36)} = 11.44$, $P < .001$).

[00113] In a separate cohort, it is found that acute restraint stress does not significantly increase NaFl brain penetration (Control = normalized to 1, Stress = 1.132). However, lumateperone alone does significantly decrease NaFl brain penetration in the stress + lumateperone cohort compared with the stress cohort (Stress+Luma = 0.7278; Stress vs Stress+Luma: unpaired t-test $P < .05$; $t_{(7)} = 2.373$; See Table 3, above).

Example 5: Lumateperone decreases anxiety and normalizes LPS-induced anhedonia.

[00114] LPS is administered to induce a transient anhedonic state in rats and behaviors that rely on the reward system are measured by using female urine as a rewarding stimulus to study whether lumateperone could rescue transient LPS-induced deficits.

[00115] In a pilot study, a dose response curve is conducted with varying doses of LPS to select an optimal dose for inducing an anhedonic response in rats. Based on these studies, a SC dose of 1 mg/kg LPS is selected. Rats are first injected with pre-treatment lumateperone (1 mg/kg; IP) or vehicle. This is followed 24 hours later by an injection of LPS (1 mg/kg; SC). Then, 24 hours later the rats are injected with posttreatment lumateperone (1 mg/kg; IP) or vehicle. Control rats are administered saline instead of LPS and vehicle instead of lumateperone. Anhedonia is assessed using FUST (female urine sniffing test) and measuring latency to sniff the reward combined with time spent sniffing the reward. Latency sniffing water is used as a control. The results are shown in the table below (time in seconds) with outliers removed using the MAD Method:

Table 5A: FUST			
	Latency sniffing reward	Time sniffing reward	Latency sniffing water
Control	28.00	16.99	190.56
LPS + Vehicle	164.2	11.11	274.27
LPS + Luma	68.13	17.38	207.60

[00116] The results show that when exposed to the reward cue (female urine), the LPS-treated male rats who had been administered lumateperone exhibit a decreased latency to sniff the urine-soaked cotton tip, compared with the LPS group. Overall, it is found that lumateperone-treated rats spend as long as control rats sniffing the reward cue during the 5-minute test period.

Importantly, rats did not significantly differ with respect to the time spent exploring the water-dipped cotton tip that served as a control test. Locomotion in an open field (track length in meters) is also measured as a control. As shown in the following table, locomotor activity is also affected regardless of the group:

Table 5B: Locomotion	
	Latency sniffing water
Control	13.29
LPS + Vehicle	12.81
LPS + Luma	12.27

[00117] Basal levels of anxiety are also tested using 2 commonly used tests, NSFT and novelty induced hypophagia (NIH), in the absence of LPS. It is well documented that rodents experience increased stress levels when placed in a novel environment (Ramaker and Dulawa, 2017). These two tests exploit this feature by measuring latency to feed in food-deprived rats (NSFT), or latency to receive a reward to which they have been habituated prior to the test (NIH).

[00118] Similar to the previous study, rats are injected with lumateperone (1 mg/kg; IP) on days 1 and 3. It is found that lumateperone reduces the latency to feed in the NSFT (control: 657.8 s, Luma: 507.9 s, Mann–Whitney U test $P = .0009$, Table 6).

	Control	Luma	Statistical Test	P value
NSFT (s)	657.8 $\pm$ 60.4	507.9 $\pm$ 55.7	Mann-Whitney U	***.0009
Control HCFT (g)	6.0 $\pm$ 0.5	6.0 $\pm$ 0.3	Unpaired t-test	ns .9897
NIH – novel cage (s)	65.4 $\pm$ 16.4	30.5 $\pm$ 13.8	Mann-Whitney U	*.0257
OFT (m)	17.2 $\pm$ 3.4	32.8 $\pm$ 10.2	Unpaired t-test	ns .8879

[00119] In contrast, it is found that there is no effect on feeding itself, as shown in the HCFT (which is a control used for NSFT). Likewise in the NIH test, which measures anxiety in a slightly different setting and does not require food deprivation, lumateperone is found to reduce latency to drink the reward (i.e., diluted condensed milk; control: 65.4 s, Luma: 30.5 s, Mann–Whitney U

test $P = .0257$, Table 2) when rats are placed in a stress-inducing novel, empty, and brightly lit cage. Here again, locomotion assessed in an open field did not reveal a significant effect for lumateperone between treatment groups (Table 6).

[00120] In summary, these results confirm that lumateperone has the potential to reduce anhedonia and to decrease basal levels of anxiety in a stressful situation.

Example 6: Lumateperone acts on rat microglia isolated from hippocampus after LPS-induced inflammation.

[00121] Based on the associations revealed by gene ontology analyses above, it was desired to study the potential involvement of microglia in the reduction of LPS-induced inflammation mediated by lumateperone administration. Microglia, the resident immune cells of the brain, have emerged as a likely effector for initiating and resolving neuroinflammation in a wide range of conditions and disorders. Therefore, the impact of lumateperone on *in vivo* inflammatory activity in hippocampal microglia is specifically monitored, interrogating a time window in which inflammation would be detected in enriched preparations of rat brain microglia.

[00122] Exploratory experiments reveal that in microglia-enriched fractions from rat hippocampi, inflammation is returned closer to background levels at +26 hours after a dose of LPS. Thus, an earlier time point of +18 h after the LPS injection is selected to assess potential changes indicative of inflammation. Rats are pretreated with the same dose of LPS used for biochemical and RNA-based experiments (500 µg/kg diluted in 0.9% saline) and receive either lumateperone (3 mg/kg in vehicle) or vehicle (5% DMSO, 5% Tween-20, 15% PEG-400, 75% water) injection 16 hours later.

[00123] Hippocampi on both sides of the brain are collected 2 hours later (+18 hour from LPS injection) and microglia are rapidly isolated in an enriched fraction by Percoll gradient. RNA is extracted from the resulting, reconstituted cell pellet and RT-qPCR is performed. The results are shown in Table 7 as relative change in mRNA levels for each cytokine gene (*Il1b*, *Il6*, *Tnfa*, *Nlrp3*, *Csf1r*) normalized to the control group using the Dct method (n= 8-12 per group):

Table 7: Hippocampal microglial cytokine mRNA expression					
	IL-1b	IL-6	TNF-alpha	NLRP3	Csf1R
Control	0	0	0	0	0
LPS	2.82	0.89	- 0.28	0.71	0.50
LPS + Luma	0.38	- 0.22	- 1.00	- 0.48	- 0.05

[00124] The results show that LPS treatment leads to significant increases in *Il1b* and *Il6* gene expression in isolated hippocampal microglia; these increases are significantly suppressed by lumateperone administration (*Il1b*: 1-way ANOVA $F_{(2,17)} = 15.05$, $P < .001$; *Il6*: 1-way ANOVA $F_{(2,20)} = 6.622$, $P = .006$). For *Nlrp3*, lumateperone significantly decreases the gene expression level compared with LPS alone (1-way ANOVA, $F_{(2,26)} = 4.302$, $P = .02$). At this time point, however, *Tnfa* gene expression did not differ from controls, most likely reflecting a different response time course in isolated microglia compared with that observed in whole tissue.

[00125] Nevertheless, lumateperone administration is found to lead to decreased *Tnfa* mRNA levels when compared with microglia isolated from either control rats or LPS-treated rats (*Tnfa*: 1-way ANOVA $F_{(2,20)} = 3.868$, $P = .04$). LPS shows a trend toward increasing *Csf1r* mRNA levels in microglia while lumateperone tends to reduce this response (1-way ANOVA $F_{(2,29)} = 0.9725$, $P = .39$). This trend parallels the observed effects of lumateperone treatment in whole tissue. In summary, this data suggests that lumateperone suppresses LPS-induction of a subset of proinflammatory genes expressed in hippocampal microglia.

[00126] **Example 7: Post-hoc analysis of Phase 3 clinical trial of lumateperone in schizophrenic patients.**

[00127] A randomized, double-blind, placebo-controlled, phase 3 clinical trial was conducted with 450 patients with schizophrenia, aged 18 to 60 years, who were experiencing an acute exacerbation of psychosis. Patients were included if they were experiencing an acute exacerbation of psychosis, defined as a total score on the Brief Psychiatric Rating Scale of 15 out of 40 or higher, with a score of 4 or higher on 2 or more positive symptoms, and onset of the acute episode within 4 weeks of screening. Patients were required to have a score of 4 or higher, indicating moderate to severe disease severity, on the Clinical Global Impression–Severity of Illness (CGI-S) at screening and baseline. Severity of illness was confirmed at baseline by a Positive and Negative Syndrome Scale (PANSS) total score of 70 or higher, indicating moderate to extreme symptoms of schizophrenia. A subgroup of these patients experienced co-morbid depression symptoms at baseline (defined as having a Calgary Depression Scale for Schizophrenia (CDSS) score greater than 6 at baseline). Full details of the clinical study were reported in Correll et al., *JAMA Psychiatry*, 77(4): 349–358 (2020).

[00128] Patients were randomized 1:1:1 (150 patients in each arm) to receive, once daily for 28 days, either 60 mg lumateperone tosylate (42 mg free base), 40 mg lumateperone tosylate (28 mg free base), or placebo.

[00129] The primary efficacy end point was mean change from baseline to day 28 in the Positive and Negative Syndrome Scale (PANSS) total score versus placebo. The key secondary efficacy measure was the Clinical Global Impression–Severity of Illness (CGI-S) score. The PANSS subscale scores, social function, safety, and tolerability were also assessed. Primary and key secondary efficacy measures were assessed weekly. Safety was assessed by treatment-emergent adverse events (TEAEs), modified physical examinations, 12-lead electrocardiograms (ECGs), vital signs, and clinical laboratory tests (blood and urine samples for clinical laboratory analysis were collected from all subjects upon screening and on Days 1, 8, 28, and 33, following overnight fast).

[00130] The results from the trial demonstrated that lumateperone is effective for improving the symptoms of schizophrenia and has a favorable safety profile.

[00131] Using blood samples stored from the study, a post-hoc analysis of inflammatory biomarkers in PBMCs from the patients with schizophrenia and co-morbid depression is conducted. Analysis is performed on samples from day 0 and day 28 for the patients treated with 60 mg lumateperone. Day 0 samples are available for 20 patients, while day 28 samples are available only for 18 patients. Mean baseline CDSS is 10.0, and mean baseline PANSS total score is 88.7 in the selected patients.

[00132] Samples were processed to isolate PBMC according to standard procedures using the Ficoll-Paque method. Statistical analysis was performed using the paired t-test, two-tailed. Samples were tested for C-reactive protein (CRP), serum amyloid A (SAA), soluble ICAM-1, soluble VCAM-1, IL-1 β , TNF- α , IL-6, IL-10, IL-2, IL-8, IL-13, and IFN- γ . ICAM-1 and VCAM-1 are expressed by the vascular endothelium, macrophages, and lymphocytes. Upon cytokine stimulation, their concentrations greatly increase. ICAM-1 can be induced by IL-1 β and TNF. ICAM and VCAM proteins may also be involved in pathogen transit into CNS.

[00133] The results are shown in the table below (biomarker levels expressed in ng/mL; some values of N are less than the patient totals due to samples with levels of biomarker below the minimum for quantification):

Biomarker	CRP		SAA		sICAM-1		sVCAM-1	
Day	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28
Average	78.8	50.5	286.9	157.9	184.8	119.6	78.9	49.1
Median	61.3	38.0	233.6	147.3	136.9	83.6	60.1	42.0
STDV	61.8	33.9	241.6	144.5	147.2	87.5	56.2	41.5
95% CI upper	105.8	58.3	392.8	221.2	249.3	116.0	103.6	67.2
95% CI lower	51.7	28.6	181.0	94.6	120.3	133.4	54.3	30.9
N =	20	19	20	20	20	18	20	20

Biomarker	IL-1 β		TNF- α		IL-6		IL-10	
Day	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28
Average	1.76	1.01	0.27	0.83	0.20	0.55	0.09	2.14
Median	1.65	0.74	0.27	0.43	0.18	0.32	0.07	0.21
STDV	0.60	0.87	0.12	0.98	0.09	0.48	0.04	4.43
95% CI upper	2.03	1.53	0.34	1.34	0.24	0.78	0.09	4.30
95% CI lower	1.48	0.50	0.21	0.32	0.16	0.33	0.07	0.00
N =	17	11	15	14	17	17	17	18

Biomarker	IL-2		IL-8		IL-13		IFN- γ	
Day	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28
Average	0.18	0.37	74.5	105.3	1.31	2.38	1.11	0.86
Median	0.17	0.25	36.3	44.0	1.11	1.56	1.01	0.71
STDV	0.05	0.44	34.0	131.2	0.75	2.82	0.67	0.51
95% CI upper	0.20	0.57	91.2	169.6	1.67	3.68	1.43	1.30
95% CI lower	0.15	0.17	57.8	41.0	0.95	1.07	0.77	0.41
N =	18	18	16	16	17	18	16	5

[00134] These data indicate that patients with schizophrenia and co-morbid depression have elevated levels of inflammatory biomarkers in their blood cells (PBMCs) at baseline, and that after 28 days of treatment with lumateperone treatment, these levels are significantly reduced. These

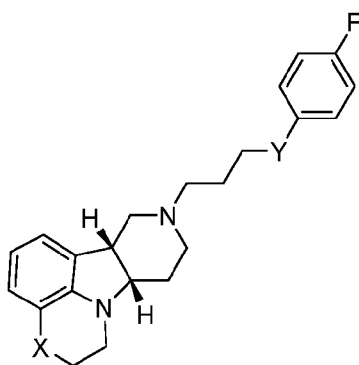
results also demonstrate that patients with a schizophrenia accompanied by depressive symptoms can be identified a priori by measuring inflammatory biomarkers in the blood.

[00135] Interestingly, unlike the measurement of depressive symptoms (CDSS), the placebo group did not show significant changes in biomarker levels (data not shown).

CLAIMS

We claim:

1. A method for the treatment of psychiatric disorders caused by viral, bacterial, or autoimmune encephalitis, and for treatment of psychiatric symptoms of viral, bacterial, and autoimmune encephalitis comprising administering to a patient in need thereof, a therapeutically effective amount of a 5-HT_{2A} or 5-HT_{2A}/D2 receptor ligand.
2. The method according to claim 1, wherein the ligand is a Compound of Formula I:



Formula I

wherein:

X is –N(H)–, –N(CH₃)– or –O–;

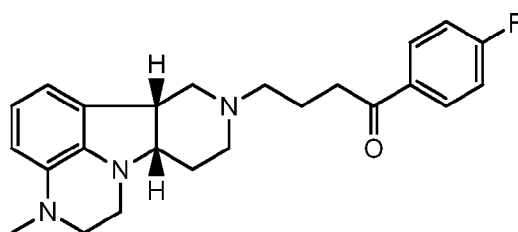
Y is –C(=O)–, –C(H)(OH)– or –C(H)(OR₁)–;

R₁ is –C(O)–C₁₋₂₁alkyl (e.g., –C(O)–C₁₋₅alkyl, –C(O)–C₆₋₁₅alkyl or –C(O)–C₁₆₋₂₁alkyl), preferably said alkyl is a straight chain, optionally saturated or unsaturated and optionally substituted with one or more hydroxy or C₁₋₂₂alkoxy (e.g., ethoxy) groups, for example R₁ is –C(O)–C₆alkyl, –C(O)–C₇alkyl, –C(O)–C₉alkyl, –C(O)–C₁₁alkyl, –C(O)–C₁₃alkyl or –C(O)–C₁₅alkyl, wherein such compound hydrolyzes to form the residue of a natural or unnatural, saturated or unsaturated fatty acid, e.g., the compound hydrolyzes to form the hydroxy compound on the one hand and octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid or hexadecanoic acid on the other hand,

optionally in deuterated form,

in free base, pharmaceutically acceptable salt, or prodrug form.

3. The method according to claim 2, wherein X in the compound of Formula I is $-\text{N}(\text{H})-$, $-\text{N}(\text{CH}_3)-$ or $-\text{O}-$.
4. The method according to claim 3, wherein X in the compound of Formula I is $-\text{N}(\text{CH}_3)-$.
5. The method according to claim 3 or 4, wherein Y in the compound of Formula I is $-\text{C}(=\text{O})-$.
6. The method according to claim 2, wherein the Compound of Formula I is lumateperone:



7. The method according to claim 6, wherein the Compound of Formula I is in the form of a free base or a pharmaceutically acceptable salt, e.g., a tosylate salt.
8. The method according to any one of claims 2-7, wherein the method comprises once daily administration of a unit dosage for oral administration, for example a tablet or capsule, comprising the compound of Formula I in free base or pharmaceutically acceptable salt form, e.g., in tosylate salt form, in an amount equivalent 1 to 100 mg of free base, e.g., in an amount equivalent to 1 to 75 mg, or 1 to 60 mg, or 1 to 40 mg, or 1 to 30 mg, or 1 to 20 mg, or 1 to 10 mg, or 1 to 5 mg, or 40 to 60 mg, or 20 to 40 mg, or 10 to 20 mg, or about 60 mg, or about 40 mg, or about 30 mg, or about 20 mg, or about 10 mg, or about 5 mg, of free base, and a pharmaceutically acceptable diluent or carrier.
9. The method according to any one of claims 2-7, wherein the method comprises once daily administration of a unit dosage for oral transmucosal administration, e.g., a sublingual or buccal orally disintegrating tablet, wafer, or film, comprising the compound of Formula I in free base or pharmaceutically acceptable salt form, e.g., in tosylate salt form, in an amount equivalent to 0.5 to 30 mg of free base, e.g., in an amount equivalent to 1 to 30 mg, or 1 to 20 mg, or 1 to 15 mg, or 1 to 10 mg, or 20 to 30 mg, or 10 to 20

mg, or about 5 mg, or about 10 mg, or about 15 mg, or about 20 mg, of free base, and a pharmaceutically acceptable diluent or carrier.

10. The method according to any one of claims 1-7, wherein the 5-HT_{2A} or 5-HT_{2A}/D₂ receptor ligand is administered in the form of a long-acting injectable (LAI) composition, e.g., for intramuscular or subcutaneous injection.
11. The method according to any one of claims 1-10, wherein the encephalitis is viral encephalitis.
12. The method according to claim 11, wherein the encephalitis is caused by, or suspected to be caused by, Herpes simplex Virus 1, Herpes Simplex Virus 2, West Nile Virus, Nipah Virus, human immunodeficiency virus, rabies virus, Epstein-Barr Virus, cytomegalovirus, coronavirus (e.g., MERS-CoV, SARS-CoV, SARS-Cov2), or influenza virus (e.g., influenza A, such as H1N1, H2N2, H3N2, H5N1, H7N7).
13. The method according to any one of claims 1-10, wherein the encephalitis is bacterial encephalitis.
14. The method according to claim 13, wherein the encephalitis is caused by, or believed to be caused by, toxoplasmosis, rickettsia, mycoplasma, Borrelia (e.g., Lyme disease), or malaria.
15. The method according to any one of claims 1-10, wherein the encephalitis is autoimmune encephalitis.
16. The method according to claim 15, wherein the encephalitis is caused by, or believed to be caused by, autoantibodies against the NMDA receptor, the AMPA receptor, the voltage-gated potassium, channel (VGKC), the LGL1 protein, the GABA receptor, the glycine receptor, the glutamate receptor, or the CASPR2 receptor.
17. The method according to any one of claims 1-16, wherein the psychiatric disorder and/or the psychiatric symptom is depression (e.g., acute depression, depression of MDD, depression of bipolar disorder), anxiety, (e.g., acute anxiety), psychosis (e.g., schizophrenia), post-traumatic stress-disorder, anhedonia, memory loss, impairment of executive functioning, difficulty concentrating, seizures, difficulty sleeping, hallucination, change in personality, or any combination thereof.
18. The method according to any one of claims 1-17, wherein the method protects or reinforces the blood-brain barrier.

19. The method according to any one of claims 1-18, wherein the patient has elevated levels of pro-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, or elevated levels of C-reactive protein (CRP) or Csf1, and/or depressed levels of anti-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- β , IFN- α , IL-4, and IL-10.
20. The method according to any one of claims 1-19, wherein the 5-HT_{2A} or 5-HT_{2A/D2} receptor ligand or the compound of Formula I is administered intra-nasally, subcutaneously, intramuscularly, intravenously, orally, sub-lingually, intra-peritoneally, or buccally, such as an oral rapidly dissolving tablet, wafer, or film, which dissolves in the oral cavity for transmucosal absorption.
21. The method according to any one of claims 1-20, wherein the patient has not responded to, or has not responded adequately to, or who suffers undesirable side effects from, treatment with another antidepressant agent, for example, any one or more of a selective serotonin reuptake inhibitor (SSRI), a serotonin reuptake inhibitor (SRI), a tricyclic antidepressant, a monoamine oxidase inhibitor, a norepinephrine reuptake inhibitor (NRI), a dopamine reuptake inhibitor (DRI), an SRI/NRI, an SRI/DRI, an NRI/DRI, an SRI/NRI/DRI (triple reuptake inhibitor, or a serotonin receptor antagonist.
22. A method for protecting or reinforcing the blood-brain barrier, comprising administering to a patient in need thereof, a therapeutically effective amount of a 5-HT_{2A} or 5-HT_{2A/D2} receptor ligand.
23. A method for the treatment of psychiatric disorders in a patient in need thereof, wherein the patient has elevated levels of pro-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- α , IFN- γ , IL-1 (IL-1 α and/or IL-1 β), IL-6, IL-8, IL-12, IL-15, IL-17, IL-18, or elevated levels of C-reactive protein (CRP), or Csf1, and/or depressed levels of anti-inflammatory cytokines in the CNS (e.g., in the cerebrospinal fluid), such as TNF- β , IFN- α , IL-4, and IL-10, the method comprising administering a therapeutically effective amount of a 5-HT_{2A} or 5-HT_{2A/D2} receptor ligand to the patient.

International application No
PCT/US2023/067204

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/4985 A61P25/18 A61P25/24 ADD.		
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) A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI 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 2021/060009 A1 (SNYDER GRETCHEN [US] ET AL) 4 March 2021 (2021-03-04) paragraphs [0316] - [0333]; claim 15; example all Methods 1.30; 2.29 and 3.30; meningococcal meningitis; pages 6,10,15	1-23
X	WO 2019/178484 A1 (INTRA CELLULAR THERAPIES INC [US]) 19 September 2019 (2019-09-19) paragraphs [0076] - [0093]; claim 15; example all Methods 1.30; 2.28 and 3.30; meningococcal meningitis; pages 14,27,39	1-23
☒ 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 "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 24 August 2023		Date of mailing of the international search report 01/09/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Megido, Benigno

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2023/067204

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	OLSEN ET AL: "Correlation between breakdown of the blood-brain barrier and disease outcome of viral encephalitis in mice", ANTIVIRAL RESEARCH, ELSEVIER BV, NL, vol. 75, no. 2, 3 May 2007 (2007-05-03), pages 104-112, XP022058883, ISSN: 0166-3542, DOI: 10.1016/J.ANTIVIRAL.2006.11.013 the whole document -----	
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