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(54) **Title**: METHODS OF TREATING PSYCHOLOGICAL CONDITIONS

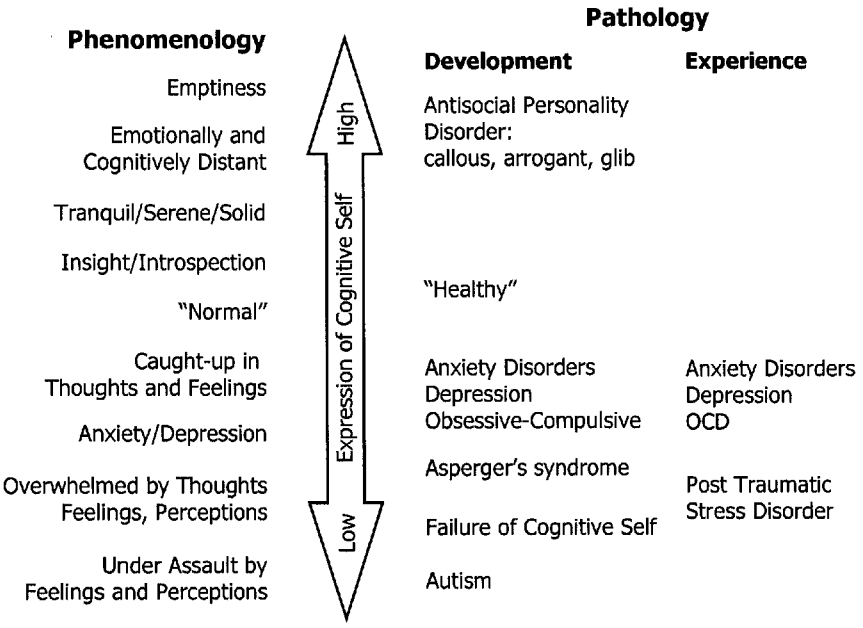


Figure 1

(57) **Abstract**: A method and composition for inducing in a subject a tolerance to a psychoactive substance or for treating an abnormal mental condition in a subject. The composition used in the method comprises in one embodiment a 5-HT_{2B} receptor agonist disposed within a pharmaceutically-acceptable vehicle or carrier.

METHODS OF TREATING PSYCHOLOGICAL CONDITIONS

Background

[0001] Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system (CNS) and enterochromaffin cells in the gastrointestinal tract of animals including humans. In the central nervous system, serotonin plays an important role as a neurotransmitter in the modulation of anger, aggression, body temperature, mood, sleep, human sexuality, appetite, and metabolism, as well as stimulating vomiting. The 5-HT receptors are the receptors for serotonin.

[0002] The serotonin 2B receptor ($5\text{-}HT_{2B}$ receptor) is known to be involved in brain development, being one of the first serotonin receptors to appear in embryonic neural tissue. Furthermore, a study of genetic variations in the serotonin-2B receptor gene concluded that serotonin-2B contributes to brain architecture and pathways that are involved in illegal drug reward.

[0003] There is a major division in the architecture of the mind, between the cognitive systems mediated by the serotonin receptors, and affective systems mediated by other receptors. The cognitive domain understands the world in terms of ideas and concepts, while the affective domain understands the world in terms of feelings.

[0004] It appears that the cognitive and affective domains each include a center of the "self." The cognitive self is mediated by the three serotonin-2 ($5\text{-}HT_2$) receptors ($5\text{-}HT_{2A}$, $5\text{-}HT_{2B}$, $5\text{-}HT_{2C}$), while the affective self is mediated by the two sigma receptors. The receptor that thirty-five known psychoactive drugs most strongly interact with is the serotonin-2B receptor ($5\text{-}HT_{2B}$). The serotonin-2A ($5\text{-}HT_{2A}$) receptor ranks fifth, and serotonin-2C ($5\text{-}HT_{2C}$) ranks sixth (see Table 1). Current thinking attributes most of the effects of “hallucinogens” to their action at the serotonin-2A (and perhaps serotonin-2C) receptor.

[0005] Table 1:

Receptor	Bsq
serotonin-2B	19.48
serotonin-1A	16.63
serotonin-7	14.93
serotonin-1D	14.57
serotonin-2A	13.81
serotonin-2C	13.35
alpha-2C	12.99
serotonin-6	12.43
serotonin-1B	11.95
serotonin-1E	11.51
alpha-2A	11.30
alpha-2B	11.14

*Bsq is the square root of the sum of squares, of the affinity of each of thirty-five psychoactive drugs at the named receptor.

[0006] Thus, the three serotonin-2 receptors are a useful point of departure for a discussion of how the mind reacts to agents affecting psychology.

[0007] The cognitive self plays two fundamental roles, including integration of cognitive information and filtering or inhibition of thought, sensation and feeling.

[0008] Modulation of the strength of these functions has a dramatic effect on the psyche. Drugs which strengthen the cognitive self strengthen both the integration and the filtering/inhibition functions. Normally, we tend to be caught up in our thoughts and feelings. When the cognitive self is strengthened by a low to moderate dose of certain psychoactive drugs, we gain a little distance from our thoughts and feelings, while at the same time strengthening our ability to integrate cognitive information (ideas, concepts, etc.). This facilitates reflection and introspection which can lead to insight.

[0009] If the cognitive self is strengthened further, these concerns can drop away leading to a very solid and relaxed state which may be tranquil or serene. These effects of low to moderate doses are enjoyable and can be rewarding. However, higher doses take the subject beyond this moderate state into realms in which the filtering/inhibitory functions are so strong that one becomes emotionally and cognitively distant. If one goes further still, the experience becomes empty.

[0010] Users of the psychoactive drugs that are truly selective for the serotonin-2 receptors (e.g., MEM and DOB are pure serotonin-2 drugs; 2C-T-2, 2C-B-fly and DOET are almost

pure serotonin-2 drugs) find the experience of the "sweet spot" enjoyable, but relatively subtle and simple compared to what drugs such as LSD, psilocybin and mescaline are capable of. Thus there is a tendency for users to increase the dose hoping for a stronger reaction. This dose abuse is counter-productive, and leads into the distant or empty psychological domain.

[0011] While most of the psychoactive drugs contemplated in the present work strengthen the cognitive self, a few weaken it, either absolutely or relatively. When the cognitive self is weakened, the effect is powerful, in the sense of being overwhelming. This needs to be distinguished from potent, in the sense of a drug being fully active at a low dose.

[0012] LSD is a drug which weakens the cognitive self absolutely, by acting as an antagonist (or weak partial agonist) at the serotonin-2 receptors. It appears that the cognitive self is similar to what has been called the "ego," thus LSD is famous for producing "ego loss," a state which can appear to be equivalent to the satori or kensho of Buddhism.

[0013] However, it is not this simple. Reducing the cognitive self may have a "heaven" or "hell" quality. Whether the subject experiences "heaven" or "hell" depends on the set and setting, and a subject may experience both in the course of a single drug experiment.

[0014] The serotonin-2 spectrum, as noted, appears to be an axis of central importance to the structure of the mind. Due to its inhibitory/filtering/integrative functions, it interacts richly with many other components of the mind. As indicated in Fig. 1, it appears that quite a few disorders lie along this spectrum. At some times, the serotonin-2 receptor system seems to play the role of a kind of immune system of the mind, whose function is to maintain mental evenness and stability, suppressing the excesses of sensation that characterize drug induced states and possibly a wide range of mental disorders. There is evidence that the mental immune system is relatively dormant in adults, so it may have played its principal role in establishing mental evenness and stability during development and maturation.

[0015] Consider the special role that the mental immune system might play during development. While each individual receptor-mediated mental module may have a genetically determined level of expression, the mental immune system may act to modulate over-expression during development, so as to lead to a more even mental landscape at maturity. If the mental immune system does not operate efficiently, then heterogeneity in the proportioning of the various mental components, which appear early in development, can become amplified through development, leading to a very uneven or rugged mental landscape at maturity.

[0016] In summary, the cognitive self integrates ideas and concepts into an understanding of things and the world. It plays an important role in the filtering or inhibition of sensation, thoughts and feelings. It appears to play a protective role and act as a coping mechanism, which may relate to its possible ego function. It also functions as a kind of mental immune

system, responding dynamically, adaptively, and selectively to intense mental states, building a protection against their reoccurrence, which lasts for years. It may be the seat of intention or volition. Its role is purely cognitive; it generates no feelings or emotions. It appears to be dynamic, in the sense that our self-confidence or self-respect can be strengthened or shattered by experience.

[0017] It is the object of the present invention to enhance the effectiveness of this mental immune system to protect against mental disorders and adverse and/or intense mental conditions.

Description of the Drawings

[0018] Figure 1 is a schematic drawing of the range of mental phenomonology in relation to the spectrum of levels of expression of the serotonin-2 system, which modulates the cognitive self.

[0019] Figure 2 is a generalized chemical structure which represents examples of the 5-HT_{2B} receptor agonists of the present invention.

[0020] Figure 3 shows the chemical structure of MEM.

[0021] Figure 4 shows the chemical structure of MEM-fly, an MEM derivative.

[0022] Figure 5 shows the receptor affinity profile of MEM.

Detailed Description of the Invention

[0023] The present invention is based on the discovery that selective serotonin-2B receptor (5-HT_{2B}) agonistic drugs (e.g., MEM and other phenylethylamine derivatives as represented in Figure 2) are able to produce a lasting tolerance to many psychoactive drugs, and can be used in the treatment of abnormal mental conditions that operate via a wide variety of receptors. The serotonin 2B receptor appears to have the general property of responding to intense mental sensations or experiences by building a defense against their reoccurrence. This mental immune system appears to be built in the days immediately following the experience, is substantially effective within one week, and tends to last at least two years. The present invention contemplates that this protective function applies to the effects of drugs, and to mental conditions or sensations of similar intensity, as might occur in schizophrenia, bipolar disorder, depression, obsessive compulsive disorder, disorders of rage, anxiety/panic disorders, and autism.

[0024] The present invention contemplates that activation (agonism) of the serotonin-2B (5-HT_{2B}) receptor via a 5-HT_{2B} receptor agonist is the key to activating this mental immune system.

[0025] In accordance with the present invention, the drug 2,5-dimethoxy-4-ethoxy-phenylisopropylamine (MEM) (and other serotonin 2B receptor-specific compounds, such as

contemplated herein and as specifically represented in Figure 2) activates the protective function in situations where the serotonin 2B receptor is normally dormant. For example, the psychoactive drug 5-MeO-MIPT activates the serotonin-7 system, expanding consciousness and potentially crossing the mental event horizon to place the subject in an alternate reality. This effect is reliable, and is repeatable many times over without building tolerance to the drug. However, if 5-MeO-MIPT is taken together with MEM, the mental immune system is invoked to build a lasting tolerance to the drug 5-MeO-MIPT. Within a few days the subject will have completely lost the ability to experience the effects of 5-MeO-MIPT, and the immunity will last for years. This suggests that the mental immune system tends to be dormant, but can be activated by MEM or other serotonin 2B receptor agonists. The chemical structure of MEM is shown in Fig. 3. Mem-fly, a MEM derivative is shown in Fig. 4.

[0026] Without wishing to be bound by theory, it is asserted herein that schizophrenia is due to an over-expression of the serotonin-7 system, the same receptor responsible in large part for the dramatic effects of 5-MeO-MIPT. By creating a lasting immunity to the effects of over-expression of the serotonin-7 system through drug activation of the serotonin 2B receptor, it is contemplated that the same protection can be provided as a treatment for schizophrenia. The effectiveness of specific serotonin 2B receptor agonists in invoking the mental immune system is directly proportional to the intensity of the mental effect that it is desired to be protected against. In one method of the invention therefore, the treatment is to administer a dose of MEM (e.g., 10-50 mg) to the subject while the subject is experiencing full-blown psychosis (or during other strong psychological or intense mental state). The therapeutic effects become evident within one week typically.

[0027] However, the mental immune mechanism is not specific to behaviors involving the serotonin-7 system. It also protects against other intense mental states. Thus the invention contemplates activating the serotonin 2B receptor system to provide lasting protection against the mania and depression of bipolar disorder, or the panic attacks of anxiety disorders as well as autism (and other conditions contemplated herein), all of which are quite intense states. Although the mental immune system does not spontaneously protect against these states, it is considered that this may be because it is in a latent or dormant state until activation. By activating the mental immune system with MEM or other serotonin 2B agonists, we are able to use the mind's natural immune mechanisms to treat mental disorders that currently are managed only through daily medications which produce a wide range of serious side effects. Ideally, treatment with MEM or other serotonin 2B receptor agonists would be needed only once every few years.

[0028] MEM was assayed at fifty-one receptors, transporters, and ion channels, but showed measurable affinity at only four sites: 5-HT_{2B} 64.5 nm, 5-HT_{2A} 3948 nm, $sigma_1$ 5077 nm, 5-HT_7 7156 nm (Fig. 5). Thus MEM shows 61-fold selectivity for the 5-HT_{2B} receptor. Its

effects at the other three receptors are either imperceptible, or barely perceptible. MEM is an exceptionally selective drug (Fig. 5). MEM-fly (Fig. 4) is one example of a derivative of MEM which might be used alternatively (others are described in Fig. 2 and the related description).

[0029] When activated, for example by using the methods contemplated herein, the mental immune system responds adaptively and selectively to threats as they arise, and retains a memory that protects for years against the reappearance of those threats. When this mental immune system fails, a wide range of mental disorders can manifest, just as when the body's immune system fails, there may appear maladies ranging from opportunistic infections to cancers. Autism, for example, is contemplated to be a result of the complete failure of the mental immune system starting at the earliest ages. The present invention contemplates, without wishing to be bound by theory, that autism is a result of a profound under-expression of the cognitive-self mediated by under-expression of serotonin-2 receptors. The complexity of the interaction between the cognitive-self and the remainder of the modulatory personality (the suite of mental functions mediated by receptor systems, and their proportioning in individuals) can generate the observed diversity of manifestations of autism.

[0030] If the serotonin-2 system is uniformly under-expressed over its normal spatial distribution, then diversity can emerge from variation in the configuration of the remainder of the modulatory personality, which becomes starkly revealed when the inhibitory/filtering/integration function of the serotonin-2 system fails. In this case the manifestations of autism will be as diverse as the underlying personalities. If the serotonin-2 system is more dramatically under-expressed in some regions of its normal spatial distribution, then through heterogeneous disinhibition, this will tend to alter the revealed pattern of the underlying modulatory personality, either exaggerating or tempering its inherent strengths and weaknesses.

[0031] If the serotonin-2 system plays a special role during development, assuring an even mental landscape at maturity, then absence of the homogenizing influence of serotonin-2 would cause mental inhomogeneities that appear early in development to become exaggerated through the remainder of development toward maturity. The final results of such a process will vary widely from individual to individual. Such dramatic variation among individuals is characteristic of autism.

[0032] The approach of the present invention which is applicable to autism is the use of selective serotonin-2B receptor agonists, such as MEM, thereby providing a lasting protection (over a period of years) against the intense and overwhelming sensations which manifest in the psychological condition of autism.

[0033] Similarly, it has been found that MEM is able to produce a tolerance lasting years, to the serotonin-7 receptor agonist 5-MeO-MIPT. It is further contemplated herein that MEM

(and other serotonin 2B receptor agonists) can also be used as a treatment to produce lasting protection against the excess serotonin-7 activity associated with schizophrenia and therefore to diminish the negative effects of schizophrenia. The best time to apply this treatment would be at the initial onset of schizophrenia in a subject.

[0034] Hallucinogens are considered to be non-addictive. None-the-less, they are capable of producing such pleasure that some users will attempt to use them repeatedly and frequently, even daily. With such aggressive use, many hallucinogens quickly lose their effectiveness, and users eventually desist. This is an interesting phenomena when we note that hallucinogens interact with a wide variety of receptors, including dopamine, which are considered to be involved in the addiction process. What sets "classical hallucinogens" apart, by definition, is their action at the serotonin-2 receptors.

[0035] Among the many receptors that classical hallucinogens interact with, a variety of classes or patterns of tolerance or habituation can been observed, including:

(1) No tolerance – It appears that tolerance does not develop to the effects through the serotonin-7 receptor in drugs such as DMT, 5-MeO-DMT, and 5-MeO-MIPT.

(2) Short-lived tolerance – Tolerance at the serotonin-2 receptor develops quickly with daily use. The effects will be substantially diminished the second day, and nearly extinguished within a few days. Normal response can be restored with one week of abstinence.

(3) Long-lived tolerance – Tolerance to some other receptors, such as imidazoline (MDMA) and beta (DOM), can develop even with infrequent use (e.g., monthly). The effects mediated through these receptors may be noticeably greater with first use, and diminish to zero after several uses, even if these uses are at irregular, widely spaced intervals. The lack of effect can not be overcome by using larger doses. This loss of effectiveness has been shown to endure through at least two years of abstinence, but apparently can be reversed by much longer periods of abstinence. Long-lived tolerance does not occur in the serotonin-2 receptors, which are the greatest common denominator of classical hallucinogens. Therefore, when long-lived tolerance occurs, the drug does not lose all effect, but eventually retains primarily the serotonin-2 effect, and thus converges qualitatively with the pure serotonin-2 drugs, MEM and DOB.

[0036] It appears that long-lived tolerance can develop rapidly. The speed at which long-term tolerance develops seems to be proportional to the drama of the drug effects. Thus it is typical to hear that the first time a drug's full effects were experienced was one of the most

memorable experiences in one's life, but it was never to be repeated. Near complete tolerance often follows a single "magical" experience. Or, the "magic" of the initial experience may diminish rapidly and taper to zero over the course of the next several experiences.

[0037] Further, serotonin-2B may cause long-lived tolerance. As is evidenced by the present invention, activation of the serotonin-2B receptors dramatically activates the mental immune system. The strongest evidence to support this assertion that serotonin-2B underlies long-lived tolerance is that while 5-MeO-MIPT by itself does not produce tolerance, if it is taken together with MEM, the user can develop complete long-term tolerance to the 5-MeO-MIPT after a single experience. Because MEM is highly selective for the serotonin-2B receptor, this implies that activation of the serotonin-2B receptor alone is able to produce long-term tolerance to the effects of other receptors.

[0038] Interestingly, 5-MeO-MIPT does not produce tolerance when combined with DOI. DOI is unique among the drugs assessed in the present work in having serotonin-2C as its best hit (and the serotonin-2B receptor as the lowest of the three serotonin-2 receptor affinities). This implies that the relative affinities of serotonin-2B receptor and the other serotonin-2 receptors are important in producing tolerance. It appears that long-term tolerance develops most effectively when affinity to serotonin-2B receptor exceeds affinity to serotonin-2A receptor and serotonin-2C receptor.

[0039] Data on long-lived tolerance to drugs is very scarce. However, drugs which appear to produce long-lived tolerance include Mescaline, MDMA, DIPT, DOM, and drugs which appear not to produce long-lived tolerance include 5-MeO-MIPT, DMT, 2C-B, Salvinorin A, LSD, 5-MeO-DMT.

[0040] In Table 2, drugs which apparently produce long-lived tolerance are listed in bold, while drugs which apparently do not produce long-lived tolerance are listed in italics. The drugs are ranked by the difference between the affinity for the serotonin-2B receptor, and the affinity at either of the serotonin-2A receptor or serotonin-2C receptor (whichever is the highest). This ranking clearly separates the long-lived tolerance producing drugs from the drugs which do not produce long-lived tolerance. The rule of thumb is that long-lived tolerance develops when the affinity for serotonin-2B receptor is at least an order of magnitude greater than affinity for serotonin-2A receptor or serotonin-2C receptor. (* For DIPT, MDMA, and mescaline, the serotonin-2A and serotonin-2C affinities were measured as >10,000 nm, thus for these drugs we can only say that the parameter is greater than some value).

[0041] Table 2:

Drug	2B-2ACmax	5ht2b	5ht2[ac]max
DOM	1.64	4.00	2.36
DIPT	>1.40	3.48	<2.08
MDMA	>1.30	3.64	<2.34
Mescaline	>1.10*	3.97	<2.87
5-MeO-MIPT	0.88	3.32	2.44
DMT	0.49	3.91	3.42
2C-B	0.31	4.00	3.69
Salvinorin A	0.00	0.00	0.00
LSD	-0.42	3.11	3.54
5-MeO-DMT	-0.86	0.69	1.55

[0042] In one embodiment of the present invention, if a selective serotonin-2B receptor agonist such as MEM is administered weekly, together with an addictive drug such as heroin, cocaine (including "crack" cocaine), or methamphetamine (including "crystal methamphetamine", a.k.a. "ice"), it will quickly (within a few doses of MEM) extinguish the ability of the addictive drug to produce reward, and this extinction would last for years. If a subject experiences the full rush of an addictive drug, three hours after taking a dosage of MEM (e.g., 20 mg), a near extinction of pleasurable effects may be produced after a single co-administration.

[0043] For example, in one case exemplary of the present invention, a middle aged male subject, roughly 70 kg, took 14 mg of 5-MeO-MIPT three hours after ingesting 20 mg of MEM. The subject experienced the full and dramatic effects of the 5-MeO-MIPT. Eight days later, the same subject took 16 mg of 5-MeO-MIPT three hours after 20 mg of MEM. Two months after the initial experiment, the same subject took 14 mg of 5-MeO-MIPT three hours after 20 mg of MEM. In both experiments, the effects of the 5-MeO-MIPT did not develop at all. Over the few months following the initial experiment, the same subject took several doses of 5-MeO-MIPT alone: 12 mg, 14 mg, 15 mg, 16 mg, 14 mg. The effects of the 5-MeO-MIPT failed to develop in any of these experiments.

[0044] Long-lived tolerance, evidently caused by serotonin-2B, has developed to a wide variety of receptors: alpha-2, beta-2, imidazoline-1, serotonin-7. It would appear possible then for the same mechanism to extinguish the response to the receptors invoked by addictive drugs (e.g., heroin at mu opioid).

[0045] It is important to recognize that while the effects of MEM or another serotonin 2B receptor agonist will extinguish the rewarding property of addictive drugs, it does not necessarily eliminate the cravings of individuals already addicted to the drug, or withdrawal when the drug is suddenly terminated. Thus, if MEM or another serotonin 2B receptor

agonist is used to extinguish the rewarding effects of addictive drugs, the drug user would effectively be thrust into an irreversible "cold turkey" withdrawal, and may need medical assistance to get through the difficult withdrawal process. It is also important to recognize that MEM or another serotonin 2B receptor agonist would not protect against the toxic properties of drugs, thus, there would be a danger from users attempting to escalate the dose to obtain the effect that is no longer available.

[0046] Human Pharmacology of MEM

[0047] The human pharmacology of MEM is described by Shulgin (1978).

> "The para-ethoxy homolog of TMA-2 is 4-ethoxy-2,5-dimethoxyphenylisopropylamine (60, MEM, 4-ethoxy-2,5-dimethoxyamphetamine). The threshold and effective levels of MEM are quantitatively similar to those reported for TMA-2, i.e., 12 and 20 mg, respectively. In a study employing nine subjects with dosages ranging from 15 to 40 mg, there were consistent reports of color intensification, wavering and flickering in the visual field, and a relatively long-lasting euphoria. There were indications of extrapyramidal tremors, paresthesia, and a slight mydriasis. The effects are quite slow to be apparent (up to 2 hr) and the overall experience is quite lengthy. Qualitatively, the subjective reports likened MEM as being more like MDA than the homolog TMA-2 (p. 300)."

[0048] Shulgin & Shulgin (1991) describe in detail, an experiment with 25 mg of MEM in which the subject experienced repressed grief, and the MEM experience seemed to have a therapeutic effect (p. 50-52). Some additional observations by Shulgin & Shulgin (1991) follow:

> "The qualitative effects ... were along the psychedelic line (color, visual intensity, wavering of the visual field, emotional euphoria)
>
> "I explored MEM quite thoroughly in the 20 to 30 milligram area, in these early years, and found it to be a most impressive psychedelic. In 1977, I went up to 60 milligrams and found it not to be the profound self-analysis drug I had hoped it would be... I learned to recommend dosages in the 20-30 milligrams area...
>
> "... frequent reports of color enrichment and eyes-closed fantasy. The material insists on being complex, but seems nonetheless to leave you in charge." p. 50.

"(with 20 mg) I experienced some physical discomfort, but doesn't that tell us about the work to be done, rather than the property of the material? The breakthrough I had was the following day (and this seems to be the way MEM operates, i.e., first the energy and expansion, next day insight) was of the highest value and importance for me. I was given a methodology for dealing with my shadow parts. No small gift. And I did it all alone and the results were immediate. I am so grateful." (p. 767.)

[0049] Synthesis of MEM

[0050] Below is a process for the synthesis of MEM (Fig. 3), as described in Shulgin & Shulgin (1991, pp. 764-766).

[0051] A solution of 83 g bourbonal (also called ethyl vanillin, or vanillal, or simply 3-ethoxy-4-hydroxybenzaldehyde) in 500 mL MeOH was treated with a solution of 31.5 g KOH pellets (85% material) dissolved in 250 mL H_2O. There was then added 71 g methyl iodide, and the mixture was held under reflux conditions for 3 h. All was added to 3 volumes of H_2O, and this was made basic with the addition of 25% NaOH. The aqueous phase was extracted with 5x200 mL CH_2Cl_2. The pooling of these extracts and removal of the solvent under vacuum gave a residue of 85.5 g of the product 3-ethoxy-4-methoxybenzaldehyde, with a mp of 52-53 °C. When this product was recrystallized from hexane, its mp was 49-50 °C. When the reaction was run with the same reactants in a reasonably anhydrous environment, with methanolic KOH, the major product was the acetal, 3-ethoxy-a,a,4-trimethoxytoluene. This was a white glistening product which crystallized readily from hexane, and had a mp of 44-45 °C. Acid hydrolysis converted it to the correct aldehyde above. The addition of sufficient H_2O in the methylation completely circumvents this by-product. A solution of 1.0 g of this aldehyde and 0.7 g malononitrile in 20 mL warm absolute EtOH, when treated with a few drops of triethylamine, gave immediate yellow color followed, in a few min by the formation of crystals. Filtration, and washing with EtOH, gave bright yellow crystals of 3-ethoxy-4-methoxybenzalmalononitrile with a mp of 141-142 °C.

[0052] A well stirred solution of 125.4 g 3-ethoxy-4-methoxybenzaldehyde in 445 mL acetic acid was treated with 158 g 40% peracetic acid (in acetic acid) at a rate at which, with ice cooling, the internal temperature did not exceed 27 °C. The addition required about 45 min. The reaction mixture was then quenched in some 3 L H_2O. There was the generation of some crystals which were removed by filtration. The mother liquor was saved. The solid material weighed, while still wet, 70 g and was crude formate ester. A small quantity was recrystallized from cyclohexane twice, to provide a reference sample of 3-ethoxy-4-methoxyphenyl formate with a mp of 63-64 °C. The bulk of this crude formate ester was

dissolved in 200 mL concentrated HCl which gave a deep purple solution. This was quenched with water which precipitated a fluffy tan solid, which was hydrated phenolic product that weighed about 35 g, and melted in the 80-90 °C. range. The mother liquors of the above filtration were neutralized with Na_2CO_3, then extracted with 3x100 ml Et2O. Removal of the solvent gave a residue of about 80 g that was impure formate (containing some unoxidized aldehyde). To this there was added 500 mL 10% NaOH, and the dark mixture heated on the steam bath for several h. After cooling, the strongly basic solution was washed with CH_2Cl_2, and then treated with 200 mL Et2O, which knocked out a heavy semi-solid mass that was substantially insoluble in either phase. This was, again, the crude hydrated phenol. The Et2O phase, on evaporation, gave a third crop of solids. These could actually be recrystallized from MeOH/H_2O, but the mp always remained broad. When subjected to distillation conditions, the H_2O was finally driven out of the hydrate, and the product 3-ethoxy-4-methoxyphenol distilled as a clear oil at 180-190 °C at 0.8 mm/Hg. This product, 45.1 g, gave a fine NMR spectrum, and in dilute CCl_4 showed a single OH band at 3620 cm-1, supporting the freedom of the OH group on the aromatic ring from adjacent oxygen. Efforts to obtain an NMR spectrum in D_2O immediately formed an insoluble hydrate. This phenol can serve as the starting material for either MEM (see below) or EEM (see separate recipe).

[0053] To a solution of 12.3 g 3-ethoxy-4-methoxyphenol in 20 mL MeOH, there was added a solution of 4.8 g flaked KOH in 100 mL heated MeOH. To this clear solution there was then added 10.7 g methyl iodide, and the mixture held at reflux on the steam bath for 2 h. This was then quenched in 3 volumes H_2O, made strongly basic with 10% NaOH, and extracted with 3x100 mL CH_2Cl_2. Removal of the solvent from the pooled extracts under vacuum gave 9.4 g of an amber oil which spontaneously crystallized. The mp of 1,4-dimethoxy-2-ethoxybenzene was 42-43.5 °C, and was used, with no further purification, in the following step.

[0054] A mixture of 17.3 g N-methylformanilide and 19.6 g $POCl_3$ was allowed to stand for 0.5 h, producing a deep claret color. To this there was added 9.2 g 1,4-dimethoxy-2-ethoxybenzene, and the mixture was held on the steam bath for 2 h. It was then poured into chipped ice and, with mechanical stirring, the dark oily phase slowly became increasingly crystalline. This was finally removed by filtration, providing a brown solid mat which showed a mp of 103.5-106.5 °C. All was dissolved in 75 mL boiling MeOH which, on cooling, deposited fine crystals of 2,5-dimethoxy-4-ethoxybenzaldehyde that were colored a light tan and which, after air drying to constant weight, weighed 8.5 g and had a mp of 108-109.5 °C. Search was made by gas chromatography for evidence of the other two theoretically possible positional isomers, but none could be found. The NMR spectrum showed the two para-protons as clean singlets, with no noise suggesting other isomers. There was a single

peak by GC (for the recrystallized product) but the mother liquors showed a contamination that proved to be N-methylformanilide. A 0.3 g sample, along with 0.3 g malononitrile, was dissolved in 10 mL warm absolute EtOH, and treated with a drop of triethylamine. There was the immediate formation of a yellow color followed, in 1 min, by the deposition of fine yellow needles. Filtering and air drying gave 0.25 g of 2,5-dimethoxy-4-ethoxybenzalmalononitrile, with a mp of 171-172 °C.

[0055] A solution of 7.3 g 2,5-dimethoxy-4-ethoxybenzaldehyde in 25 g glacial acetic acid was treated with 3.6 g nitroethane and 2.25 g anhydrous ammonium acetate, and heated on the steam bath. After two h, the clear solution was diluted with an equal volume of H_2O, and cooled in an ice bucket. There was the formation of a heavy crop of orange crystals which were removed by filtration. The dry weight of 1-(2,5-dimethoxy-4-ethoxyphenyl)-2-nitropropene was 4.8 g and the mp was 120-124 °C. Recrystallization of an analytical sample from MeOH gave a mp of 128-129 °C. Anal. ($C_{13}H_{17}NO_5$) C,H.

[0056] To a gently refluxing suspension of 3.3 g LAH in 400 mL anhydrous Et2O under a He atmosphere, there was added 4.3 g 1-(2,5-dimethoxy-4-ethoxy)-2-nitropropene by allowing the condensing Et2O to drip into a shunted Soxhlet thimble apparatus containing the nitrostyrene, thus effectively adding a warm saturated ether solution of it to the hydride mixture. The addition took 2 h. Refluxing was maintained for 5 h, and then the reaction mixture was cooled to 0 °C with an external ice bath. The excess hydride was destroyed by the cautious addition of 300 mL of 1.5 N H_2SO_4. When the aqueous and Et2O layers were finally clear, they were separated, and 100 g of potassium sodium tartrate was dissolved in the aqueous fraction. Aqueous NaOH was then added until the pH was >9, and this was then extracted with 3x100 mL CH_2Cl_2. Evaporation of the solvent from the pooled extracts produced an almost white oil that was dissolved in 100 mL anhydrous Et2O and saturated with anhydrous HCl gas. There was deposited a white crystalline solid of 2,5-dimethoxy-4-ethoxyamphetamine hydrochloride (MEM) which weighed 3.1 g and had a mp of 171-172.5 °C. Anal. ($C_{13}H_{22}ClNO_3$) C,H,N.

Utility

[0057] Treatment of Mental Disorders

[0058] Method 1 – In order for serotonin 2B receptor agonists (referred to herein as "the agonist") such as MEM (or other substances represented in Fig. 2) to activate the mental immune system for long-term protection against mental disorders, the subject needs to be in the full experience of the mental disorder at the time of treatment with the agonist. The effectiveness of the agonist in activating the mental immune system will be directly

proportional to the intensity of the mental effects of the disorder at the time of treatment with the agonist.

[0059] Thus for schizophrenia, the subject is preferably completely psychotic, and not under treatment by antipsychotic medication such as zyprexa. For mania (or the manic phase of bipolar disorder) the subject should be fully manic, in the absence of stabilizing medication such as lithium. For depression (or the depressed phase of bipolar disorder), the subject should be fully depressed, in the absence of antidepressants such as Prozac or stabilizers such as lithium. For severe anxiety or panic disorder, the subject should be completely anxious or in a state of complete panic, in the absence of antianxiety drugs such as xanax. For obsessive compulsive disorder, the subject should be in the full throes of obsession and compulsion, in the absence of treatment such as Prozac. For chronic pain, the subject should be fully experiencing severe pain, in the absence of painkillers such as morphine. For autism, the subject should be fully autistic, but this is not an issue because there is no current treatment for autism.

[0060] It is likely that treatment of mental disorders by activation of the mental immune system in the manner described herein is maximally effective when it is applied at the initial onset of the disorder. Thus for example, when a patient is first admitted to a hospital at the first onset of schizophrenia, rather than treating the patient with antipsychotic medication, the patient would instead be treated with the agonist of the present invention to activate the mental immune system.

[0061] The agonist, for example MEM, would be administered as a single weekly dose of 10-50 mg, preferably 20 mg, until the aggravating condition subsides. Immunity does not manifest during the actual agonist treatment experience, which may last ten to fourteen hours. Immunity develops in the days following the agonist treatment, and is likely fully developed within one week. If the mental disorder was producing very intense mental effects at the time of treatment with the agonist, a single dose provokes significant protection by the mental immune system. If the agonist treatment does not show clear signs of provoking mental immunity after two or three applications, the subject should be treated by conventional means (e.g., antipsychotic medication).

[0062] Method 2 – In Method 1 described above, it was emphasized that the patient should not be receiving conventional pharmaceutical treatment at the time that the agonist is administered. This is not due to a concern with drug interaction (since the agonist is selective for the serotonin-2B receptor). Thus it is likely that the only relevant drug interactions would arise from: 1) treatments that are antagonists of the serotonin-2B receptor, which could block the effectiveness of the agonist; 2) selective serotonin reuptake inhibitors (SSRIs), which could make the patient dangerously sensitive to serotonin agonists.

Rather, it is because the agonist will be more effective if the patient is experiencing the full intensity of the mental disorder. To the extent that conventional pharmaceutical treatments reduce the intensity of the mental disorder, they will reduce the effectiveness of treatment by the agonist.

[0063] While the method of choice involves treatment by the agonist alone, without other medications that might reduce the intensity of the disorder during the agonist treatment, there are situations where the agonist treatment could be used together with conventional treatments.

[0064] It is often the case that finding the right treatment for a patient involves some trial-and-error by the attending physician, with a variety of medications before an effective medication is found. In this situation, a patient will receive a medication, but it will not relieve the symptoms of the mental disorder. This would represent an opportunity to administer the agonist together with the ineffective medication. This is not an ideal approach, because it is often the case that unsatisfactory treatments provide partial relief, and this partial relief would reduce the effectiveness of the agonist.

[0065] As in the primary method, the agonist could be administered as a single weekly dose (e.g., 10-50 mg), until the aggravating condition subsides.

[0066] Treatment of Drug Addiction

[0067] In order for the agonist to eliminate the pleasurable reward provided by addictive and/or psychoactive drugs such as, but not limited to, heroin, cocaine (including "crack" cocaine), and methamphetamine (including "crystal methamphetamine, a.k.a., "ice"), the agonist treatment or experience derived therefrom must be in full effect at the time that the subject experiences the full rush of the addictive drug. As noted above, the full effects of the agonist take a few hours to develop. Thus, the agonist should be administered about three hours before administration of the addictive drug (e.g., heroin, cocaine, methamphetamine). The same principles discussed above apply for the treatment of addiction.

[0068] The agonist is preferably administered as a single weekly dose (e.g., 10-50 mg, for example 20 mg) followed three hours later by a full dose of the addictive drug (e.g., heroin, cocaine, methamphetamine), until the reward from the addictive drug is extinguished. Immunity does not manifest during the actual agonist experience, which may last ten to fourteen hours. Immunity develops in the days following the agonist treatment, and is likely fully developed within one week. If the addictive drug was producing very intense mental effects at the time of treatment with the agonist, a single dose provokes significant protection by the mental immune system. If agonist treatment does not show clear signs of provoking mental immunity after two or three applications, the subject should be treated by conventional means (e.g., twelve step program, methadone maintenance).

[0069] It is important to keep in mind that the agonist may extinguish reward, but may not extinguish craving or withdrawal effects. This may put the addict in a very difficult situation. They will likely need medical treatment to help them through the withdrawal process.

[0070] Initial Activation of the Mental Immune System

[0071] Drugs that act agonistically at the serotonin-2 receptors, such as MEM and other 5-HT_{2B} receptor agonists as described herein, are known to quickly develop short-lived tolerance. However, the subject can recover from such tolerance within one week of abstinence. Thus, in order to initially activate the mental immune system, the agonist could be administered at weekly intervals, until full immunity develops.

[0072] The duration of the long-lived tolerance stimulated by activation of the mental immune system will generally last between two and seven years. Thus, one might expect to need to repeat the agonist treatment to reactivate the mental immune system, several years after the previous treatment. The preferred dose range for MEM (or other 5-HT_{2B} receptor agonists described herein) is 10-50 mg, and more preferably 20 mg.

[0073] The Chemical Family

[0074] The 5-HT_{2B} receptor agonists contemplated for use in the methods of the present invention comprise, for example, substances having the chemical structure as shown in Fig. 2. The structure comprises a phenylethylamine backbone consisting of 8 carbon atoms as represented by numerals 1-8, and having up to seven R groups comprising R_2 to R_8, linked to carbons 2-8, respectively, of the phenylethylamine backbone.

[0075] The R groups R_2, R_3, R_5, R_6, R_7 and R_8 are each defined herein in one embodiment as one of H, CH_3, or OCH_3.

[0076] Alternatively, R_2 and R_3 may comprise together a single bridging moiety "R_2-R_3" forming a cyclizing linkage between carbons 2 and 3 (for example as shown in Fig. 4), wherein the R_2-R_3 group comprises:

-CH_2CH_2O- or –OCH_2CH_2- or –$CH_2CH_2CH_2O$- or –$OCH_2CH_2CH_2$- or –CHCHO- or –OCHCH- or –CH_2CHCHO- or –$OCHCHCH_2$- or –$CHCHCH_2O$- or –OCH_2CHCH-.

[0077] Further, alternatively, R_5 and R_6 may comprise together a single bridging moiety "R_5-R_6" forming a cyclizing linkage between carbons 5 and 6 (for example as shown in Fig. 4), wherein the R_5-R_6 group comprises:

-CH_2CH_2O- or –OCH_2CH_2- or –$CH_2CH_2CH_2O$- or –$OCH_2CH_2CH_2$- or –CHCHO- or –OCHCH- or –CH_2CHCHO- or –$OCHCHCH_2$- or –$CHCHCH_2O$- or –OCH_2CHCH-.

[0078] The R group R_4 is defined herein as one of H; F; Cl; Br; I; or NO_2; or as

$ZC_aH_pX_q$: wherein Z is a sulfur atom, or an oxygen atom, or is absent, C_a is a carbon atom; H_p is "p" number of hydrogen atoms, X_q is "q" number of atoms of a halide (where a halide is defined as F, Cl, Br, or I), and wherein (p,q) is one of (3,0), (2,1), (1,2), or (0,3); or as

$ZC_bH_mX_nC_aH_pX_q$: wherein Z and $C_aH_pX_q$ are as described above, C_b is a carbon atom, H_m is "m" number of hydrogen atoms, X_n is "n" number of atoms of a halide, and wherein (m,n) is one of (2,0), (1,1), (0,2); or (1,0), wherein when (m,n) is (1,0), C_b is double bonded to C_a; or as

$ZC_cH_jX_kC_bH_mX_nC_aH_pX_q$: wherein Z, $C_bH_mX_n$ and $C_aH_pX_q$ are as defined above, C_c is a carbon atom, H_j is "j" number of hydrogen atoms, X_k is "k" number of atoms or a halide, and wherein (j,k) is one of (2,0), (1,1), (0,2); or (1,0), wherein when (j,k) is (1,0), C_c is double bonded to C_b.

[0079] An example of a preferred 5-HT_{2B} receptor agonist of the invention is "MEM" shown in Fig. 3, wherein, following the generalized chemical structure of Fig. 2, R_2=OCH_3, R_3=H, R_4=OCH_2CH_3, R_5=OCH_3, R_6=H, R_7=H, and R_8=CH_3. Another example of a 5-HT_{2B} receptor agonist which can be used in the present invention is "MEM-fly" shown in Fig. 4, wherein R_2-R_3= -CH_2CH_2O-, R_4=OCH_2CH_3, R_5-R_6= -OCH_2CH_2-, R_7=H, and R_8=CH_3.

[0080] Therapeutic Composition

[0081] A therapeutically effective amount of a composition of the present invention refers to an amount of the agonist which is effective in controlling, treating or moderating any of the mental or physiological conditions described herein. The terms "controlling", "treating" or "moderating" are intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the progression of the disease or condition and does not necessarily indicate a total elimination of all symptoms of the disease or condition.

[0082] A therapeutically effective amount of the compound used in the treatment described herein can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species size, age, and general health; the specific disease or condition involved; the degree of or involvement or the severity of the disease or condition; the response of the individual subject; the particular compound administered; the mode of administration; the bioavailability

characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

[0083] Practice of the method of the present invention comprises administering to a subject a therapeutically effective amount of the composition described herein, in any suitable systemic or local formulation, in an amount effective to deliver an appropriate dosage. The dosage for example can be administered on a one-time basis, or (for example) from one to five times per day or once or twice per week (for example) or other protocol as described elsewhere herein.

[0084] The 5-HT_{2B} receptor agonists of the invention may be provided as disposed in a pharmaceutically-acceptable vehicle or carrier such as are well known in the art. Pharmaceutical compositions of the invention can be manufactured utilizing techniques known in the art.

[0085] The compounds or compositions of the present invention may be administered by a variety of routes, for example, orally, intranasally, intrarectally or parenterally (i.e., subcutaneously, intravenously, intramuscularly, intraperitoneally, or intratracheally).

[0086] For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions, or emulsions. Solid unit dosage forms can be capsules of the ordinary gelatin type containing, for example, surfactants, lubricants and inert fillers such as lactose, sucrose, and cornstarch or they can be sustained release preparations.

[0087] In another embodiment, the compounds of this invention can be tabletted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders, such as acacia, cornstarch, or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate. Liquid preparations are prepared by dissolving the active ingredient in an aqueous or non-aqueous pharmaceutically acceptable solvent which may also contain suspending agents, sweetening agents, flavoring agents, and preservative agents as are known in the art.

[0088] For parenteral administration, the compounds may be dissolved in a physiologically acceptable pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable pharmaceutical carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative, or synthetic origin. The pharmaceutical carrier may also contain preservatives, and buffers as are known in the art.

[0089] The compounds of this invention can also be administered topically. This can be accomplished by simply preparing a solution of the compound to be administered, preferably using a solvent known to promote transdermal absorption such as ethanol or dimethyl sulfoxide (DMSO) with or without other excipients. Preferably topical administration will be

accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety.

[0090] As noted above, the compositions can also include an appropriate carrier. For topical use, any of the conventional excipients may be added to formulate the active ingredients into a lotion, ointment, powder, cream, spray, or aerosol. For surgical implantation, the active ingredients may be combined with any of the well-known biodegradable and bioerodible carriers, such as polylactic acid and collagen formulations. Such materials may be in the form of solid implants, sutures, sponges, wound dressings, and the like. In any event, for local use of the materials, the active ingredients usually be present in the carrier or excipient in a weight ratio of from about 1:1000 to 1:20,000, but are not limited to ratios within this range. Preparation of compositions for local use are detailed in Remington's Pharmaceutical Sciences, latest edition, (Mack Publishing).

[0091] Additional pharmaceutical methods may be employed, as explained elsewhere herein, to control the duration of action. Increased half-life and controlled release preparations may be achieved through the use of polymers to conjugate, complex with, or absorb the composition described herein. The controlled delivery and/or increased half-life may be achieved by selecting appropriate macromolecules (for example, polysaccharides, polyesters, polyamino acids, homopolymers polyvinyl pyrrolidone, ethylenevinylacetate, methylcellulose, or carboxymethylcellulose, and acrylamides such as N-(2-hydroxypropyl) methacrylamide, and the appropriate concentration of macromolecules as well as the methods of incorporation, in order to control release.

[0092] Another possible method useful in controlling the duration of action by controlled release preparations and half-life is incorporation of the molecule or its functional derivatives into particles of a polymeric material such as polyesters, polyamides, polyamino acids, hydrogels, poly(lactic acid), ethylene vinylacetate copolymers, copolymer micelles of, for example, PEG and poly(1-aspartamide).

[0093] Alternatively, it is possible to entrap the compositions in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules), or in macroemulsions. Such techniques are disclosed in the latest edition of Remington's Pharmaceutical Sciences for example.

[0094] U.S. Pat. No. 4,789,734 describe methods for encapsulating compositions in liposomes which may be used in the present invention. Essentially, the material is dissolved in an aqueous solution, the appropriate phospholipids and lipids added, along with surfactants if required, and the material dialyzed or sonicated, as necessary. Microspheres

formed of polymers or proteins are well known to those skilled in the art, and can be tailored for passage through the gastrointestinal tract directly into the blood stream. Alternatively, the agents can be incorporated and the microspheres, or composite of microspheres, implanted for slow release over a period of time, ranging from days to months. See, for example, U.S. Pat. Nos. 4,906,474; 4,925,673; and 3,625,214.

[0095] It may be desired to use oral dosage forms intended for intraluminal application of the compounds (e.g., application of the compounds directly to the small intestine) are preferably formulated to have "enteric" coatings wherein the orally taken dosage form passes through the stomach before dissolving. Some formulations are designed to begin dissolving or releasing the active compound within the small intestine (proximal or distal), and may continue releasing the compound in the colon. Such formulations are well known to persons of ordinary skill in the art and it is not deemed necessary that they be described in detail therein, however, some descriptions will be provided in any event below.

[0096] Examples of formulations which are designed to dissolve, or release the compounds of the present invention only in the small intestine and/or the colon are shown for example in U.S. Pat. No. 6,773,720 (Col. 2, line 47-Col. 5, line 29), U.S. Pat. No. 6,551,620 (Col. 3, line 1-Col. 9, line 29), U.S. Pat. No. 6,004,581 (Col. 3, line 66-Col. 18, line 43), U.S. Pat. No. 5,409,711 (Col. 1, line 43-Col. 5, line 41), U.S. Pat. No. 4,496,553 (Col. 5, line 12-Col. 7, line 37). In another embodiment, the compound may be delivered in a dosage form designed to dissolve substantially entirely in the ileum (e.g., U.S. Pat. No. 5,948,818-Col. 3, line 50-60).

[0100] When the composition is to be used as an injectable material, it can be formulated into a conventional injectable carrier. Suitable carriers include biocompatible and pharmaceutically acceptable phosphate buffered saline solutions, which are preferably isotonic.

[0101] For reconstitution of a lyophilized product in accordance with this invention, one may employ a sterile diluent, which may contain materials generally recognized for approximating physiological conditions and/or as required by governmental regulation. In this respect, the sterile diluent may contain a buffering agent to obtain a physiologically acceptable pH, such as sodium chloride, saline, phosphate-buffered saline, and/or other substances which are physiologically acceptable and/or safe for use. In general, the material for intravenous injection in humans should conform to regulations established by the Food and Drug Administration, which are available to those in the field.

[0102] The pharmaceutical composition may also be in the form of an aqueous solution containing many of the same substances as described above for the reconstitution of a lyophilized product.

[0103] The compounds can also be administered as a pharmaceutically acceptable acid- or base-addition salt, formed by reaction with inorganic acids such as hydrochloric acid,

hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, and phosphoric acid, and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, and fumaric acid, or by reaction with an inorganic base such as sodium hydroxide, ammonium hydroxide, potassium hydroxide, and organic bases such as mono-, di-, trialkyl and aryl amines and substituted ethanolamines.

[0104] Although the present invention and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the invention as defined by the appended claims. Moreover, the scope of the present application is not intended to be limited to the particular embodiments of the process, compositions of matter, means, methods and steps described in the specification. As one of ordinary skill in the art will readily appreciate from the disclosure of the present invention, processes, compositions of matter, means, methods, or steps, presently existing or later to be developed that perform substantially the same function or achieve substantially the same result as the corresponding embodiments described herein may be utilized according to the present invention. Accordingly, the appended claims are intended to include within their scope such processes, compositions of matter, means, methods, or steps.

[0105] References cited:

[0106] Shulgin, Psychotomimetic drugs: structure-activity relationships. In L. L. Iversen, S. D. Iversen & S. H. Snyder (Eds) (pp. 243-333). New York: Plenum Press, 1978.

[0107] Shulgin and Shulgin, PIHKAL: A chemical love story. Transform Press), 1991.

[0108] Abbreviations:

DOB, (±)-2,5-Dimethoxy-4-bromoamphetamine

MDA, (±)-3,4-Methylenedioxyamphetamine

MDMA, (±)-3,4-Methylenedioxymethamphetamine

Mescaline, 3,4,5-Trimethoxyphenethylamine

2C-B, 4-Bromo-2,5-dimethoxyphenethylamine

DMT, N,N-Dimethyltryptamine

Psilocin, 4-Hydroxy-N,N-dimethyltryptamine

5-MeO-DMT, 5-Methoxy-N,N-Dimethyltryptamine

2C-E, 4-Ethyl-2,5-dimethoxyphenethylamine

2C-T-2, 4-Ethylthio-2,5-dimethoxyphenethylamine

ALEPH-2, (±)-4-Ethylthio-2,5-dimethoxyamphetamine

MEM, (±)-2,5-Dimethoxy-4-ethoxyamphetamine

5-MeO-MIPT, N-Isopropyl-5-methoxy-N-methyltryptamine
DIPT, N,N-Diisopropyltryptamine
5-MeO-DIPT, N,N-Diisopropyl-5-methoxytryptamine
DPT, N,N-Dipropyltryptamine
4C-T-2, (±)-4-ethylthio-2,5-dimethoxyphenylbutylamine
6-fluoro-DMT, 6-fluoro-N,N-Dimethyltryptamine lisuride
DOI, (±)-2,5-Dimethoxy-4-iodoamphetamine
2C-B-fly, 1-(8-Bromo-2,3,6,7-tetrahydrobenzo[1,2-b;4,5-b']difuran-4-yl)2-aminoethane
DOM, (±)-2,5-Dimethoxy-4-methylamphetamine
DOET, (±)-2,5-Dimethoxy-4-ethylamphetamine
TMA, (±)-3,4,5-Trimethoxamphetamine
TMA-2, (±)-2,4,5-Trimethoxamphetamine

[0109] All references, patents and patent applications cited herein are hereby expressly incorporated herein in their entirety by reference.

What is claimed is:

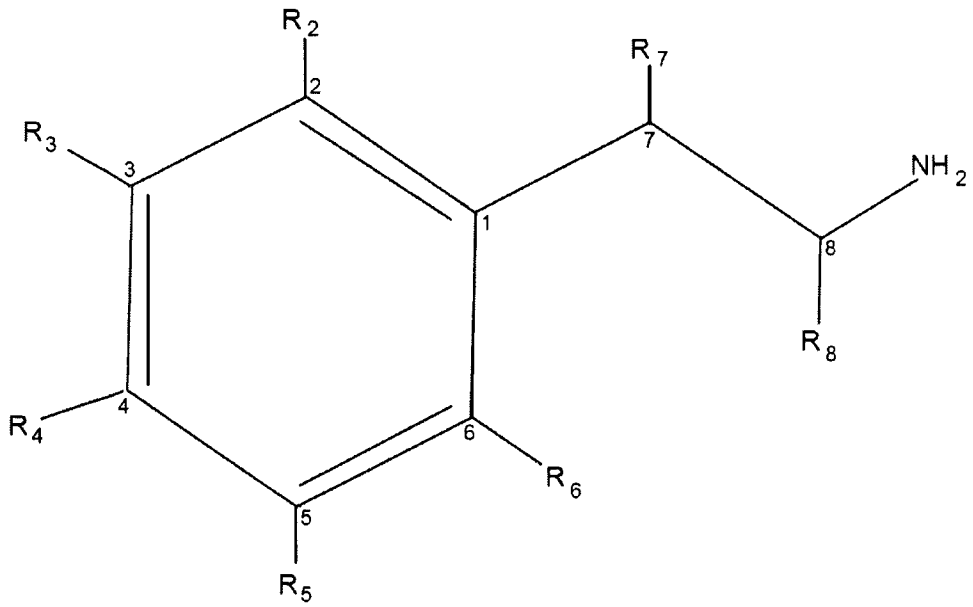
1. A method of inducing in a subject a tolerance to a psychoactive substance administered to the subject, comprising:

administering to the subject a 5-HT_{2B} receptor agonist which binds with high specificity to the 5-HT_{2B} receptor; and

administering to the subject a quantity of the psychoactive substance sufficient to induce a psychoactive response in the subject, wherein the psychoactive substance is administered shortly after the 5-HT_{2B} receptor agonist is administered to the subject, and wherein a tolerance to the psychoactive substance is induced in the subject such that when the psychoactive substance is subsequently administered to the subject, the psychoactive response induced in the subject by the psychoactive substance is diminished or eliminated.

2. The method of claim 1 wherein the 5-HT_{2B} receptor agonist comprises a substance having a chemical structure as shown in Formula I,

(I)



wherein:

R_2 is H, CH_3, or OCH_3 and R_3 is H, CH_3, or OCH_3; or

R_2 and R_3 together comprise $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2CH_2CH_2O-$, $-OCH_2CH_2CH_2-$, $-CHCHO-$, $-OCHCH-$, $-CH_2CHCHO-$, $-OCHCHCH_2-$, $-CHCHCH_2O-$, or $-OCH_2CHCH-$;

R_4 is one of H; F; Cl; Br; I; or NO_2; or

$ZC_aH_pX_q$: wherein Z is a sulfur atom, or an oxygen atom, or is absent, C_a is a carbon atom; H_p is "p" number of hydrogen atoms, X_q is "q" number of atoms of a halide (where a halide is defined as F, Cl, Br, or I), and wherein (p,q) is one of (3,0), (2,1), (1,2), or (0,3); or

$ZC_bH_mX_nC_aH_pX_q$: wherein Z and $C_aH_pX_q$ are as described above, C_b is a carbon atom, H_m is "m" number of hydrogen atoms, X_n is "n" number of atoms of a halide, and wherein (m,n) is one of (2,0), (1,1), (0,2); or (1,0), wherein when (m,n) is (1,0), C_b is double bonded to C_a; or

$ZC_cH_jX_kC_bH_mX_nC_aH_pX_q$: wherein Z, $C_bH_mX_n$ and $C_aH_pX_q$ are as defined above, C_c is a carbon atom, H_j is "j" number of hydrogen atoms, X_k is "k" number of atoms or a halide, and wherein (j,k) is one of (2,0), (1,1), (0,2); or (1,0), wherein when (j,k) is (1,0), C_c is double bonded to C_b;

R_5 is H, CH_3 or OCH_3 and R_6 is H, CH_3 or OCH_3; or

R_5 and R_6 together comprise $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2CH_2CH_2O-$, $-OCH_2CH_2CH_2-$, $-CHCHO-$, $-OCHCH-$, $-CH_2CHCHO-$, $-OCHCHCH_2-$, $-CHCHCH_2O-$, or $-OCH_2CHCH-$;

R_7 is H, CH_3, or OCH_3; and

R_8 is H, or CH_3.

3. The method of claim 1 wherein the psychoactive substance is addictive.

4. A pharmaceutical composition comprising the 5-HT_{2B} receptor agonist of claim 2 and a pharmaceutically-acceptable vehicle or carrier, the pharmaceutical composition for use in a treatment for inducing a tolerance to a psychoactive substance in the subject.

5. A method of treating an abnormal mental condition in a subject having the abnormal mental condition, comprising:

providing a 5-HT_{2B} receptor agonist which binds with high specificity to the 5-HT_{2B} receptor ; and

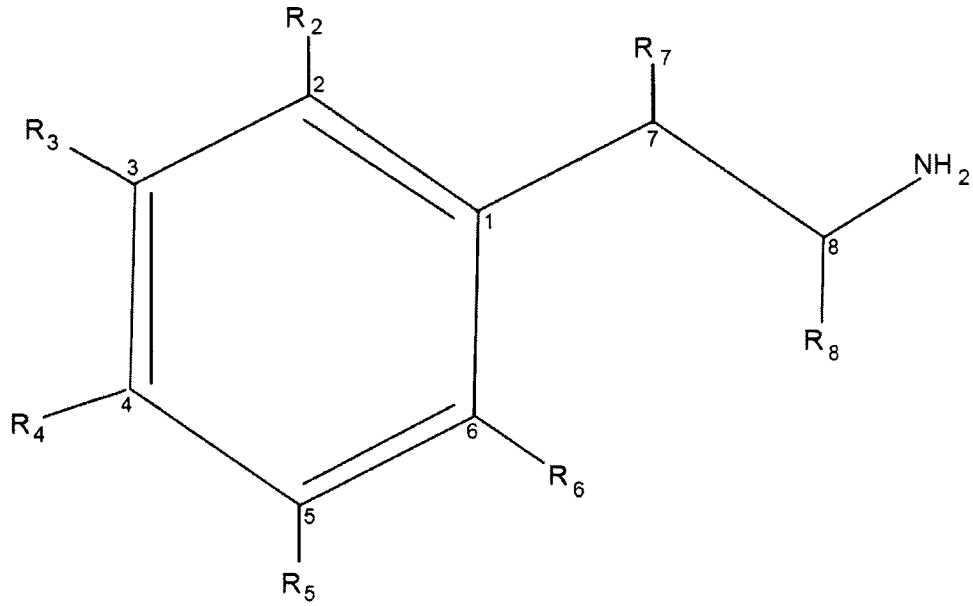
administering to the subject a quantity of the 5-HT_{2B} receptor agonist to the subject when the subject is experiencing an intense mental state characteristic of the

mental condition, wherein the treatment of the subject with the 5-HT_{2B} receptor agonist diminishes the intensity of future intense mental states characteristic of the mental condition in the subject.

6. The method of claim 5 wherein the abnormal mental condition is autism, schizophrenia, bipolar disorder, depression, an anxiety/panic disorder, severe pain, disorders of rage, or obsessive compulsive disorder.

7. The method of claim 5 wherein the 5-HT_{2B} receptor agonist comprises a substance having a chemical structure as shown in Formula I,

(I)



wherein:

R_2 is H, CH_3, or OCH_3 and R_3 is H, CH_3, or OCH_3; or

R_2 and R_3 together comprise $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2CH_2CH_2O-$, $-OCH_2CH_2CH_2-$, $-CHCHO-$, $-OCHCH-$, $-CH_2CHCHO-$, $-OCHCHCH_2-$, $-CHCHCH_2O-$, or $-OCH_2CHCH-$;

R_4 is one of H; F; Cl; Br; I; or NO_2; or

$ZC_aH_pX_q$: wherein Z is a sulfur atom, or an oxygen atom, or is absent, C_a is a carbon atom; H_p is "p" number of hydrogen atoms, X_q is "q" number of atoms of a halide (where a halide is defined as F, Cl, Br, or I), and wherein (p,q) is one of (3,0), (2,1), (1,2), or (0,3); or

$ZC_bH_mX_nC_aH_pX_q$: wherein Z and $C_aH_pX_q$ are as described above, C_b is a carbon atom, H_m is "m" number of hydrogen atoms, X_n is "n" number of atoms of a halide, and wherein (m,n) is one of (2,0), (1,1), (0,2); or (1,0), wherein when (m,n) is (1,0), C_b is double bonded to C_a; or

$ZC_cH_jX_kC_bH_mX_nC_aH_pX_q$: wherein Z, $C_bH_mX_n$ and $C_aH_pX_q$ are as defined above, C_c is a carbon atom, H_j is "j" number of hydrogen atoms, X_k is "k" number of atoms or a halide, and wherein (j,k) is one of (2,0), (1,1), (0,2); or (1,0), wherein when (j,k) is (1,0), C_c is double bonded to C_b;

R_5 is H, CH_3 or OCH_3 and R_6 is H, CH_3 or OCH_3; or

R_5 and R_6 together comprise $-CH_2CH_2O-$, $-OCH_2CH_2-$, $-CH_2CH_2CH_2O-$, $-OCH_2CH_2CH_2-$, $-CHCHO-$, $-OCHCH-$, $-CH_2CHCHO-$, $-OCHCHCH_2-$, $-CHCHCH_2O-$, or $-OCH_2CHCH-$;

R_7 is H, CH_3, or OCH_3; and

R_8 is H, or CH_3.

8. A pharmaceutical composition comprising the 5-HT_{2B} receptor agonist of claim 7 and a pharmaceutically-acceptable vehicle or carrier, the pharmaceutical composition for use in treating a subject having an abnormal mental condition.

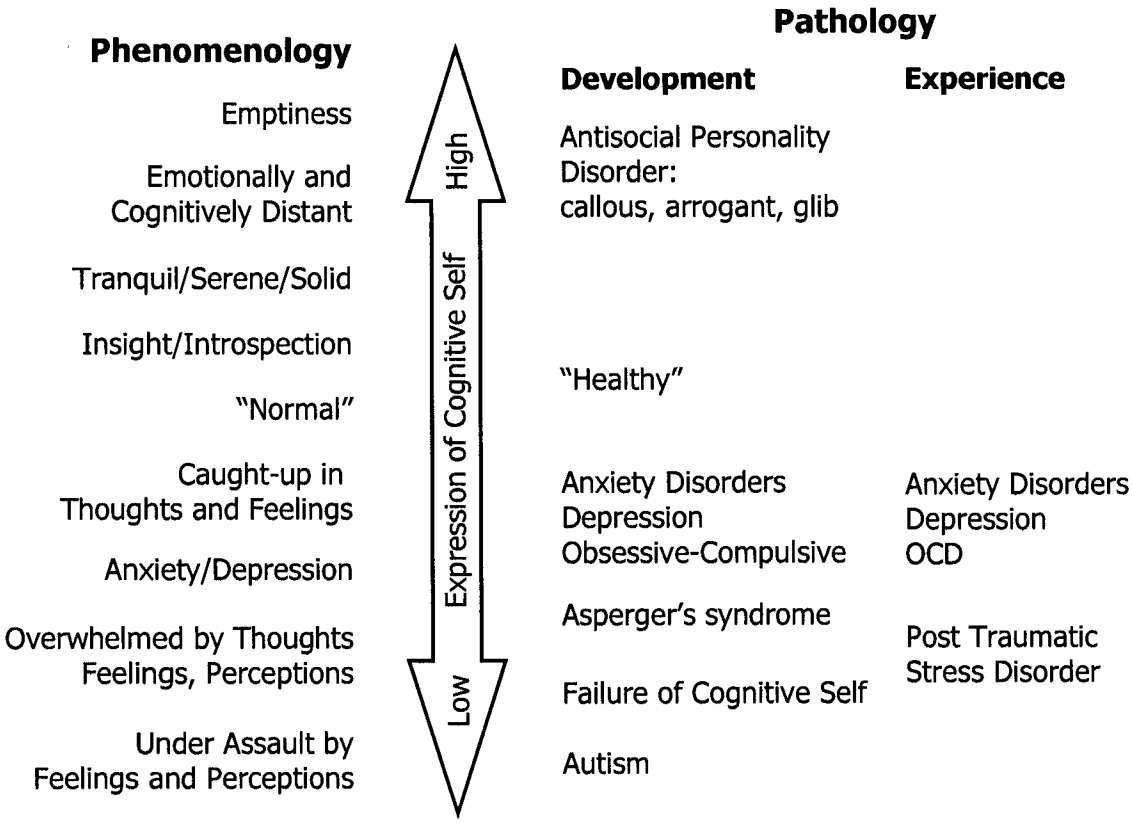


Figure 1

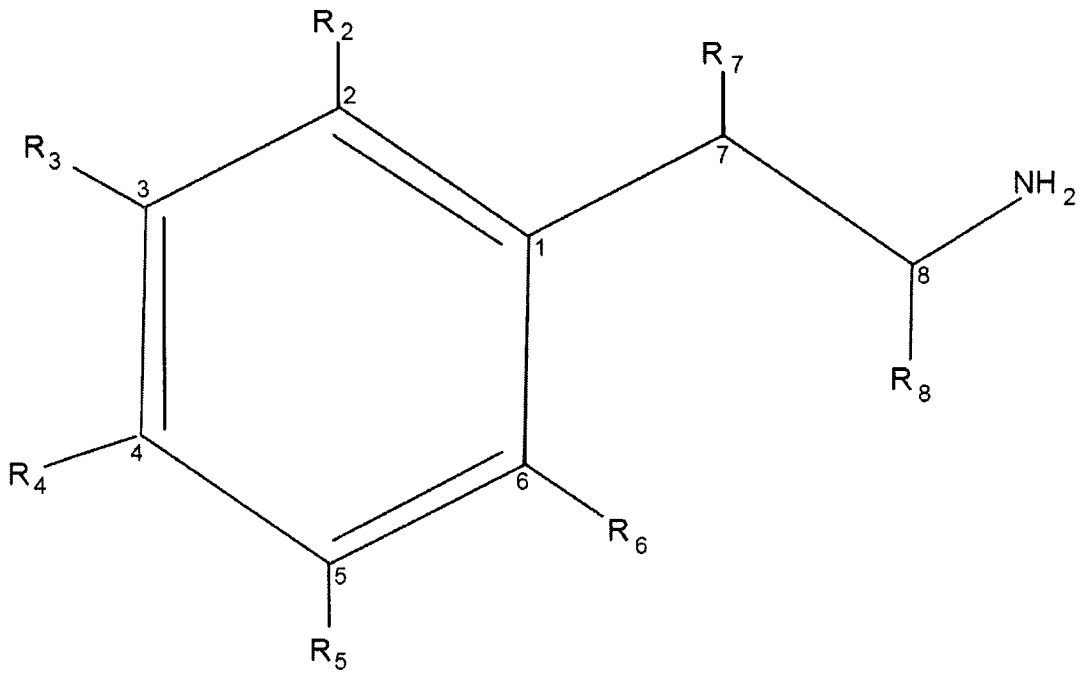


Figure 2

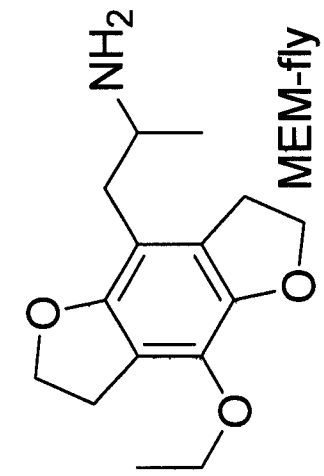


Figure 4

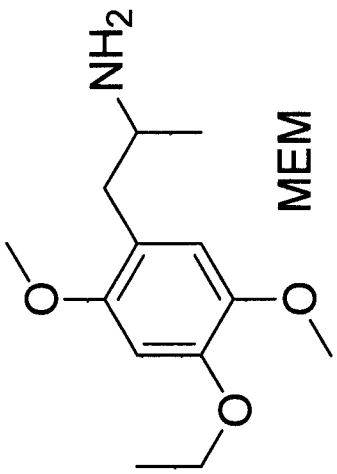


Figure 3

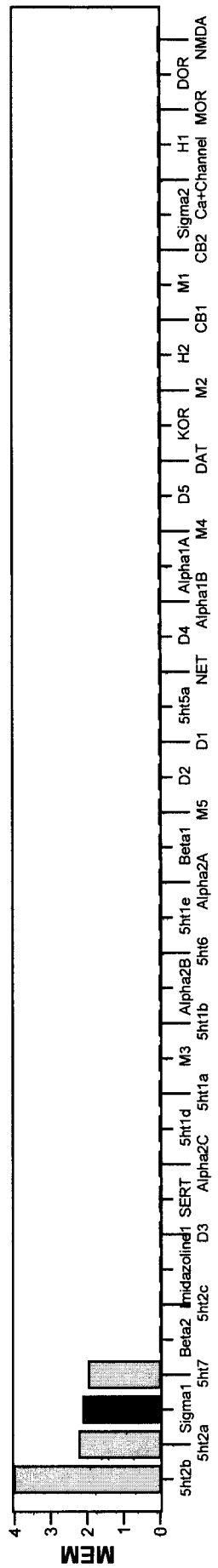


Figure 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/48494

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 33/02 (2009.01)
USPC - 514/646
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)
PC (8): A01N 33/02 (2009.01)
USPC: 514/646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
PC (8): A01N 33/02 (2009.01) (See keywords below)
USPC: 514/646 ;424/94.1 (see keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: DB=PGPB,USPT,USOC,EPAB,JPAB: Google: Scholar/patents: mescaline phenylethylamine serotonin agonist long lived tolerance 5HT2b agonist

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0027208 A1 (CARON et al) 01 February 2007 (01.02.2007) para [0024];[0028];[0046];[0048];[0050];[0052];[0065]-[0070];[0327]	1-8
Y	Porter et al. 'Functional characterization of agonists at recombinant human 5-HT2A, 5-HT2B and 5-HT2C receptors in CHO-K1 cells', British Journal of Pharmacology, 1999, Vol 128, p 13-20. pg 14, Figure 1; pg 16, Table 1; pg 17, Col 2, para 3	1-8

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2009 (25.07.2009)	10 SEP 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)