TREATMENT FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER

A method is provided for treating Attention Deficit Hyperactivity Disorder (ADHD) by use of a 5-HT1A agonist, more particularly selected from the group consisting of flesinoxan, losipitron, BAX x 3702, F11440, LY228729, LY293284, NAEB086, S14506, S14671, S16924 and gepirone.
TREATMENT FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER

FIELD OF THE INVENTION

[0001] The present invention is directed to a novel method of treating Attention-Deficit/Hyperactivity Disorder ("ADHD").

BACKGROUND OF THE INVENTION

[0002] Attention-Deficit/Hyperactivity Disorder (ADHD) is a behavior disorder characterized by problems with control of attention and hyperactivity-impulsivity. The attentional difficulties and impulsivity associated with ADHD have been persuasively documented in laboratory investigations using cognitive tasks. Although these problems typically present together, one may be present without the other to qualify for a diagnosis (Am. Psychiatric Assoc. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision, 2000) (DSM-IV-TR). Generally, attention deficit or inattention becomes apparent when a child enters elementary school. A modified form of the disorder can persist into adulthood (Am. Psychiatric Assoc. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed., 1987). With respect to the attention component, the child is easily distracted by outside stimuli, neglects finishing tasks, and has difficulty maintaining attention. Regarding the activity component, the child is often fidgety, impulsive, and overactive. The symptoms of ADHD may be apparent as young as preschoolers and are virtually always present prior to the age of 7 (Halperin et al., J. Am. Acad. Child Adolescent Psychiatry, 32:1038–1043, 1993).

[0003] According to the DSM-IV-TR, diagnostic criteria for Attention-Deficit/Hyperactivity Disorder relate to symptoms associated with inattention and/or hyperactivity-impulsivity. Three subtypes of ADHD are diagnosed based on the predominant symptoms presented.

[0004] Many of the symptoms that are characteristic of ADHD occur occasionally in normal children. Children with ADHD, however, exhibit these symptoms frequently, which tends to interfere with the child’s day to day
functioning. Such children are often challenged by academic underachievement because of excitability and impaired interpersonal relationships.

[0005] ADHD affects 2-6% of grade school children. Pediatricians report that approximately 4% of their patients have ADHD; however, in practice the diagnosis is made in children who meet several, but not all of the diagnostic criteria that is recommended in DMS-IV-TR (Wolraich et al., Pediatrics, 86(1):95-101, 1990). Boys are four times more likely to have the disorder than girls and the disorder is found in all cultures (Ross & Ross, Hyperactivity, New York, 1982).

[0006] Psychomotor stimulants are the most common treatment for ADHD. Safer & Krager (1988) reported that 99% of the children with ADHD were treated with stimulants, of which 93% were given methylphenidate hydrochloride (Ritalin), and the remainder were given dextroamphetamine sulfate (d-amphetamine) or pemoline (Safer & Krager, J.A.M.A., 260:2256-2258, 1988). Four separate psychostimulant medications consistently reduce the central features of ADHD, particularly the symptoms of inattention and ADHD associated hyperactivity-impulsivity: methylphenidate, d-amphetamine, pemoline, and a mixture of amphetamine salts (Spender et al., Arch. Gen. Psychiatry, 52:434-443, 1995). These drugs block uptake sites for catecholamines on presynaptic neurons or stimulate the release of granular stores of catecholamines. They are metabolized and leave the body fairly rapidly, and have a therapeutic duration of action of 1 to 4 hours. The psychostimulants do not appear, however, to effect long-term changes in social or academic skills (Pelham et al., J. Clin. Child Psychology, 27:190-205, 1998). Stimulants are generally started at a low dose and adjusted weekly. Common stimulant side effects include insomnia, decreased appetite, stomachaches, headaches, and jitteriness. Psychostimulants also have the potential for abuse, because they are addictive. Thus, current methods of treating ADHD provide inadequate treatment for some patients and/or have side effects that limit their usefulness.

[0007] Children who cannot tolerate psychostimulants often use the atypical antidepressant bupropion (Buck, Pediatr. Pharmacother. Vol. 8, No. 4, April, 2002).
While bupropion is not as effective as stimulants, it may be used as an adjunct to augment stimulant treatment.

Effective pharmacotherapy for ADHD is complicated by the presence of comorbid behavioral disorders, including aggression, impulse control disorders, and depression, which may be relieved by compounds that do not address the core behavioral symptoms of inattentiveness and impulsivity/hyperactivity.

Castellanos et al. concluded that ADHD is a genetically programmed disorder of brain development resulting from altered function of the frontal-striatal-pallidal-thalamocortical loops which regulate cognitive processes, attention, and motor output behaviors (Castellanos et al., Arch. Gen. Psychiatry, 53: 607-616, 1996). Although the precise etiology of ADHD is unknown, neurotransmitter deficits, genetics, and perinatal complications have been implicated.

Individuals with ADHD have been reported to have impairments in their ability to perceive intervals of time (Conners & Levin, Psychopharmacol. Bulletin, 32(1):67-73, 1996). Time perception is a useful measure of cognitive function, sensitive to dopaminergic and cholinergic manipulations in animals and humans. As in all behavioral tasks, several processes underlie good steady state performance in a temporal task. These behavioral tasks include: attention, motivation, short and long term memory, motor coordination, and instrumental learning. Scaling, discrimination, and reproduction are the three main types of temporal tasks that have been identified. In scaling, subjects must, for example, categorize a stimulus into a given set of categories ("that was a long duration") or verbally estimate the duration ("that was a 4 s duration"). In discrimination, a comparison is made between two durations ("the second stimulus was longer than the first"). Finally, in reproduction, a response is made that bears some relation with the stimulus (e.g. only responses that are as long or longer than the stimulus are correct).

Time perception is a particularly effective measure for testing cognitive deficits in ADHD individuals. For example, Conners & Levin (1996) showed that ADHD adults improve in measures of attention and timing with the administration of nicotine. Nicotine, like the psychostimulants methylphenidate and
d-amphetamine, acts as an indirect dopamine agonist and improves attention and arousal. Studies indicate that adults and adolescents with ADHD smoke much more frequently than normal individuals or those with other psychiatric conditions, perhaps as a form of self-medication for ADHD symptoms. The results indicate that there was a significant clinician-rated global improvement, self-rated vigor and concentration, and improved performance on chronometric measures of attention and timing accuracy, and side effects were minimal (Conners & Levin, supra).

At present, seven main 5-HT receptor classes have been identified: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7. Radioligand binding studies have revealed at least five subtypes of the 5-HT_1 receptor (1A, 1B, 1D, 1E and 1F). 5-HT_1A receptors are located primarily in hippocampus, entorhinal cortex, septal nuclei and raphé nuclei. 5-HT_1A receptors are present presynaptically on 5-HT neurons in the raphé nuclei, where they function as autoreceptors, decreasing the firing rate of 5-HT neurons and decreasing 5-HT turnover (Sprouse and Aghajanian, Eur. J. Pharmacol. 128:295-98, 1986; Sprouse and Aghajanian, Synapse, 1:3-9, 1987; Hamon et al., J. Pharmacol. Exp. Ther., 246:745-52, 1988). In 5-HT terminal fields, 5-HT_1A receptors are reported to mediate firing rate of target neurons and the release of neurotransmitters. For example, 5-HT_1A receptors have been reported to mediate a decrease in the firing rate of CA1 pyramidal neurons in CA1 of dorsal hippocampus has been reported (see Tada et al., J. Pharmacol. Exp. Ther. 288:843-848, 1999), as well as enhancement of norepinephrine (NE) release in the hippocampus. 5-HT_1A receptors are believed to mediate inhibitory signaling through pertussin toxin-sensitive G proteins, which results in inhibition of cAMP accumulation, activation of potassium channels, or inactivation of calcium channels (Peroutka, J. Neurochem., 60:408-416, 1993; Hoyer et al., Pharmacol. Rev., 46:157-203, 1994).

Compounds having 5-HT_1A activity in the central nervous system may be categorized, according to well recognized pharmacological principles, as full agonists, partial agonists, and antagonists (see Fletcher et al., Trends Pharmacol. Sci. 14(12):41-8, 1993). 5-HT_1A agonists are numerous and include a range of chemical structures, but many possess a piperazine or aryl piperazine core. 5-HT_1A
full agonists and partial agonists are reported to be useful as antianxiety agents or antidepressants.

[0014] The prototypical 5-HT₁ₐ full agonist is 8-hydroxy-2(di-n-propylamino)tetralin (8-OH-DPAT), which is reported to have an affinity \((K_i)\) of 2.5 nM for 5-HT₁ₐ receptors, well above its affinity for α₁ adrenergic receptors \((K_i=380\, \text{nM})\) or 5-HT₁₉ receptors \((K_i=930\, \text{nM})\) (Schipper, J. et al., 1991, Hum. Psychopharmacol. 6:S53-61, 1991). The affinity of 8-OH-DPAT for other neurotransmitter receptors \((K_i>1000\, \text{nM};\) Schipper et al., 1991, *supra*) is functionally inconsequential. In addition to having a selective affinity for 5-HT₁ₐ receptors, 8-OH-DPAT produces biochemical, electrophysiological and behavioral effects that are employed as a standard by which 5-HT₁ₐ ligands are functionally characterized as agonists. For example, 8-OH-DPAT inhibits 5-HT dorsal raphé neuron firing (Sprouse and Aghajanian, 1986; 1987, *supra*), induces hypothermia (Hjorth, J. Neural Transm. 61: 131-35, 1985) and spontaneous tail flicks (Millan et al. J. Pharmacol. Exp. Ther. 256:973-82, 1991), inhibits forskolin-induced cAMP production (Pauwels et al., Biochem. Pharmacol., 45(2):375-83, 1993) and stimulates corticosterone secretion (Przegalinski et al., Pharmacol. Biochem. Behav., 33:329-43, 1989). The clinical usefulness of 8-OH-DPAT is limited, however, by its extremely short half-life and poor oral availability.

[0015] Flesinoxan, a phenylpiperazine derivative \([(+)\,4-fluoro-N-[2-[4-[2-(hydroxymethyl)-1, 4-benzodioxane-5-yl] 1-piperazinyl]ethyl]benzamide] HCl\), is a potent and selective 5-HT₁ₐ full agonist (Van Wijngaarden et al., Eur. J. Pharmacol. 188:301-312, 1990). The selectivity of flesinoxan for 5-HT₁ₐ receptors is well-documented. Flesinoxan is reported to have \(K_i\) of 1.7 nM for 5-HT₁ₐ receptors, compared to the functionally lower affinity for 5-HT₁ᵦ \((K_i=160\, \text{nM})\) and dopamine D₂ \((K_i=140\, \text{nM})\) receptors, and an even lower affinity for α₁ adrenergic receptors \((K_i=380\, \text{nM})\), where it acts as an antagonist, and 5-HT₁ᵦ receptors \((K_i=810\, \text{nM})\) (Schipper, J. et al., 1991, *supra*; Boddeke et al. Naunyn-Schmied. Arch. Pharmacol., 345:257-263, 1992). In a two-lever operant drug discrimination procedure, in which rats were trained to discriminate flesinoxan (0.5 mg/kg i.p.) from saline, flesinoxan

[0016] Flesinoxan was developed as an antihypertensive agent (EP0138280). Flesinoxan, like other 5-HT₁A agonists, has been described as useful in the treatment of anxiety and depression (EP0307061; Grof et al., Int. Clin. Psychopharmacol 83:167-72, 1993; Bradford and Stevens, Am Coll Neuropsychopharmacol. (Abstr. 167), 1994). Flesinoxan also has been shown to enhance word and picture recall, word recognition, and reaction times. These improvements were apparent only after a few days of dosing, however, and were most pronounced in elderly subjects, 75 years of age and older (EP710481A1). Therefore, these “cognitive enhancement” effects are likely related to improved memory rather than to effects on inattention or impulsivity. Moreover, the tests used are not relevant to DSM-IV-TR ADHD diagnostics. Note that impulsivity in ADHD is characterized by impatience and difficulty delaying response (DSM-IV-TR at 86). Another 5-HT₁A agonist, lesopitron, has been suggested to be useful as a “cognitive enhancer” for treatment of dementia, memory dysfunction, and Alzheimer’s disease (U.S. Patent No. 5,182,281).

[0017] The azapirone derivative buspirone is a partial 5-HT₁A agonist that also has significant affinity for dopamine D₂ receptors, where it acts as an antagonist. Thus, unlike flesinoxan, buspirone will functionally bind to both 5-HT₁A and D₂ receptors at the same concentration. In addition, the major metabolite of buspirone is active as an antagonist at adrenergic α₂ receptors. 5-HT₁A partial agonists have been suggest to have therapeutic potential in the treatment of impulse control disorders, depression and alcohol abuse (van Hest, Psychopharmacol., 107:

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474, 1992; Schipper et al., 1991, supra, 1991; Cervo et al., Eur. J. Pharmacol., 158:53, 1988; Glitz and Pohl, Drugs, 41:11, 1991). Because these drugs have effects at numerous receptors, however, especially including NE and DA receptors, the mechanism of such effects is unclear, and likely complex.

Buspirone has been suggested as effective for the treatment of ADHD, however its beneficial effects are thought to be mediated through its unique ability to increase NE and DA output (Malhotra et al., J. Am. Acad. Child Adolesc. Psychiatr. 37(4):364-371, 1998). Buspirone’s actions on 5-HT system were suggested to be useful in controlling behavioral disruptions, such as aggression and mood disruptions, which symptoms are related to conduct disorders sometimes comorbid with ADHD (Malhotra et al., 1998, supra). Buspirone also has been asserted to be useful in the treatment of ADHD because it shares some of the electrophysiological properties of stimulants d-amphetamine and methylphenidate, without concomitant motor stimulation (EP0497314; Balon, J. Clin. Pharmacol., 10: 77, 1990). Stimulants effective in the treatment of ADHD, d-amphetamine and methylphenidate, also are active on NE and DA systems. This suggests that the effects of the non-specific, partial agonist buspirone is through catecholaminergic mechanisms. Therefore, 5-HT$_{1A}$ full agonists would not be predicted to alleviate inattention or hyperactivity.

**SUMMARY OF INVENTION**

This invention relates to methods and compositions useful for treating ADHD in humans. The compounds for use in the invention are believed to be effective in the treatment of ADHD and to exhibit reduced side effects and are not expected to have abuse potential, as compared to other available therapeutics.

In one embodiment of this invention, a method of treating ADHD in humans is provided, which method comprises administering to an individual in need of treatment a therapeutically effective amount of one or more 5-HT$_{1A}$ agonists, or pharmaceutically acceptable salts thereof.
[0021] Another embodiment of this invention is to provide the use of 5-HT$_{1A}$ agonists, or pharmaceutically acceptable salts thereof, for the manufacture of a medicament for the treatment of ADHD.

[0001] The 5-HT$_{1A}$ agonists of this invention may be full agonists or partial agonists, provided that they are effective in models of ADHD and/or the treatment of ADHD. Preferably, the 5-HT$_{1A}$ agonists of this invention are selective for 5-HT$_{1A}$ receptors over 5-HT$_{1B/1D}$, 5-HT$_2$, D$_2$, D$_4$, $\alpha_1$, and $\alpha_2$ receptors, and serotonin, dopamine and norepinephrine transporters, especially over D$_2$ and $\alpha_1$ receptors.

[0023] The 5-HT$_{1A}$ agonists of this invention have intrinsic activity, as measured by maximal inhibition of forskolin-stimulated cAMP production as a proportion of the maximal effect produced by natural agonist 5-HT, that is 0.5-1.0. Preferably the intrinsic activity of the 5-HT$_{1A}$ agonists of this invention is at least about 0.6-1.0. More preferably the intrinsic activity of the 5-HT$_{1A}$ agonists of this invention is at least about 0.7-1.0. Most preferably the intrinsic activity of the 5-HT$_{1A}$ agonists of this invention is at least about 0.8-1.0.

[0024] 5-HT$_{1A}$ receptor agonists that are useful in this invention include, but are not limited to, any one of, or any combination of the following compounds: flusesinoxan [(+)4-fluoro-N-[2-(4-[2-(hydroxymethyl)-1, 4-benzodioxane-5-yl] 1-piperazinyl)ethyl][benzamide] HCl], BAY x 3702 (R-(-)-2-[4-[(chroman-2-ylmethyl)-amino]-butyl]-1,1-dioxo-benzo[d]isothiazolone hydrochloride), F11440 [4-methyl-2-(4-[4-(pyrimidin-2-yl)-piperazino]-butyl)-2H,4H-1,2,4-triazin-3,5-dione], lesopitron (2-[4-[4-(4—chloro-1H-pyrazol-1-yl)]-butyl]-1-piperazinyl] pyrimidine), LY228729 [(+)4(diisopropylamino)-1,3,4,5-tetrahydrobenz-[c,d][indole-6-carboxamide]], (-) LY293284 [(+)4R-6-acetyl-4-[di-n-propylamino]1,2,4,5-tetrahydrobenz-[c,d]indole], NAE-086 [(R)-3,4-dihydro-N-isopropyl-3-(N-isopropyl-N-propylamino)-2H-1-benzopyran-5-carboxamide], S14506 (1[2-[4-fluorobenzoyl]amino]ethyl)-4-(7-methoxynaphthyl)piperazine], S14671 [(4-[thienoyl-2]aminoethyl)-1-(7-methoxynaphthy]piperazine], S16924 [(R)-2-[(1-(2-[3-dihydrobenzo(1,4) dioxin-5-yl]-ethoxy]-pyrroldin-3yl)]-1-(4-fluro-phenyl)-ethanone], gepirone, and ipsapirone.
In an embodiment of this invention, the 5-HT1A agonist is a compound of formula I:

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\begin{align*}
\text{I} & \quad \text{wherein:} \\
-R_1 \text{ and } R_2 & \text{ independently of each other represent hydrogen or an alkyl having 1-3 carbon atoms,} \\
-R_3 & \text{ is hydrogen or straight or branched chain alkyl having 1-3 carbon atoms,} \\
-R_4 & \text{ is hydrogen, halogen, alkyl having 1-3 carbon atoms, methylene, ethydiene or vinyl, a straight or branched hydroxyalkyl group having 1-3 carbon atoms, which may be etherified or esterified, or an alkyl branched hydroxyalkyl group having 1-3 carbon atoms in the straight or branched alkyl group, an oxo group or a phenyl group,} \\
-R_5 & \text{ is a hydrogen or fluoro atom,} \\
-n & \text{ has the value 0 or 1,} \\
-A & \text{ is the group } -\text{CH}_2-\text{CH}_2- \text{ or } -\text{CH(CH}_3)-\text{CH}_2-; \\
-B & \text{ is an aryl group or heteroaryl group which may be substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, nitrile, nitro, alkoxy having 1-3 carbon atoms, hydroxy, esterified hydroxy, and alkyl having 1 or 2 carbon atoms; and} \\
\text{wherein} \\
& \text{the compound may be a racemate or a single diastereomer or enantiomer;} \\
& \text{or a pharmaceutically acceptable acid addition salt thereof.}
\end{align*}
\]
[0026] In another embodiment of this invention, the 5-HT\textsubscript{1A} agonist is compound of formula II:

![Chemical Structure](image)

II

wherein:

- \( n \) can have the value 1 to 6;
- \( R \) is a hydrogen, a halogen, a lower alkyl radical having 1-4 carbon atoms, a heteroaryl radical, a sulpho radical, an N-substituted or N,N-disubstituted sulphamoyl radical, a nitro radical, a hydroxyl radical, an oxo radical, a lower alkoxy radical having 1-4 carbon atoms, a cyano radical, a lower alkylcarboxylate radical having 1-4 carbon atoms, an aryl or substituted aryl radical, or an amino or substituted amino radical of formula

![Chemical Structure](image)

in which \( R_1 \) and \( R_2 \), independently are a hydrogen, an alkyl radical, an aryl radical, an alkylcarbonyl radical, an arylcarbonyl radical, an alkylsulphonyl radical or an arylsulphonyl radical, the alkyl fragments of these radicals containing from 1-4 carbon atoms; and

wherein
the compound may be a racemate or a single diastereomer or enantiomer; or a pharmaceutically acceptable acid addition salt thereof.

[0027] Another object of the invention is to provide pharmaceutical compositions for the treatment of ADHD that have reduced side effects as compared to other available treatments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

[0029] FIGS. 1 A-C – Graphs depict the relative response rate of C57BL/6J mice in the Peak Procedure (PIP 30 second reinforcement interval) after administration of 1, 2, or 4 mg/kg of d-amphetamine (triangles) compared to vehicle (circles). * p < 0.05; ** p < 0.01; *** p < 0.001.

[0030] FIGS. 2 A-B – Graphs depict the relative response rate of C3H mice in the Peak Procedure after administration of 0.03 mg/kg of fleisinoxan (triangles) or vehicle (circles); 2A: PIP 30 second reinforcement interval; 2B: PIP 45 second reinforcement interval.

[0031] FIGS. 3 A-B – Graphs depict the relative response rate of C3H mice in the Peak Procedure after administration of 0.1 mg/kg, of fleisinoxan (triangles) or vehicle (circles); 3A: PIP 30 second reinforcement interval; 3B: PIP 45 second reinforcement interval.

[0032] FIGS. 4 A-B – Graphs depict the relative response rate of C3H mice in the Peak Procedure after administration of 0.01 mg/kg (open circles) or 0.001 mg/kg (triangles) of 8-OH-DPAT or vehicle (circles); 4A: 30 second reinforcement interval; 4B: 45 second reinforcement interval.

[0033] FIG. 5 – Graph depicts the effect of 4 mg/kg amphetamine on locomotor activity in coloboma mutant and wild-type mice (compared to vehicle), as measured by total distance traveled in a fixed time period. * p < 0.05; ** p < 0.01.
[0034] FIGS. 6 A-F—Graphs depict the effect of 0.3 mg/kg flesinoxan (compared to vehicle) on locomotor activity in coloboma mutant (Cm) and wild-type (WT) mice; 6A,D total distance traveled in centimeters; 6B,E total distance traveled in centimeters per 5 minute block of the behavioral session; 6C,F: frequency of zone crossings per 5 minute block of the behavioral session.

[0035] FIGS. 7 A-C—Graphs depict the effect of 0.1 mg/kg of 8-OH-DPAT on locomotor activity in coloboma mutant (Cm) and wild-type (WT) mice compared to saline vehicle; 7A: total distance traveled in centimeters; 7B: total distance traveled in centimeters per 5 minute block of the behavioral session; 7C: frequency of zone crossings per 5 minute block of the behavioral session.

DETAILED DESCRIPTION OF THE INVENTION

[0036] This invention provides a method of treating ADHD in humans. As used herein, ADHD comprises the distinct sets of symptoms associated with the three subtypes defined in DSM-IV-TR, inattention, hyperactivity/impulsivity, or combined, which present in an individual as ADHD.

[0037] ADHD of the predominantly inattentive type is diagnosed if six (or more) of the following symptoms of inattention (and fewer than six of the hyperactivity-impulsivity symptoms below) have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level. The inattention component of ADHD may include one or more of the following symptoms: (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities, (b) often has difficulty sustaining attention in tasks or play activities, (c) often does not seem to listen when spoken to directly, (d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions), (e) often has difficulty organizing tasks and activities, (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework), (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools), (h) is
often easily distracted by extraneous stimuli, and (i) is often forgetful in daily activities (DSM-IV-TR, supra).

[0038] ADHD of the predominantly hyperactive/impulsive type is diagnosed if six (or more) of the following symptoms of hyperactivity-impulsivity (and fewer than six of the inattention symptoms above) have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level. The hyperactivity component of ADHD may include one or more of the following symptoms: (a) often fidgets with hands or feet or squirms in seat, (b) often leaves seat in classroom or in other situations in which remaining seated is expected, (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness), (d) often has difficulty playing or engaging in leisure activities quietly, (e) is often “on the go” or often acts as if “driven by a motor,” and (f) often talks excessively. The impulsivity component of ADHD may include one or more of the following symptoms: (g) often blurts out answers before questions have been completed, (h) often has difficulty awaiting turn, and (i) often interrupts or intrudes on others (e.g., butts into conversations or games) (DSM-IV-TR, supra).

[0039] The most common subtype of ADHD is the combined type, which comprises all three sets of symptoms, inattention, hyperactivity and impulsivity. Combined-type ADHD is diagnosed if six (or more) symptoms of attention and six (or more) symptoms of hyperactivity/impulsivity have persisted for at least 6 months (DSM-IV-TR, supra).

[0040] ADHD of the combined type, as well as the inattentive and hyperactive/impulsive subtypes, may be treated according to this invention. Other forms of ADHD, to the extent that they are clinically distinct from that described in DSM-IV-TR, are also within the scope of this invention.

[0041] Unlike traditional therapeutics, which have the potential to be abused and/or have undesirable side effects, the present invention is not expected to have the abuse potential of psychostimulants, the most widely prescribed current pharmacological treatment, and may have a side effect profile distinct from other types of pharmacologic therapeutics. Therefore, an advantage of the method of
ADHD treatment provided by this invention is that certain of the undesirable side effects may be reduced or avoided.

[0042] As discussed above, ADHD is diagnosed based on an individual possessing symptoms in the symptom clusters inattentiveness, hyperactivity and impulsiveness, those terms are clinically recognized in the art, as for example, DSM-IV-TR.

[0043] Preferably, ADHD is treated according to this invention by administering therapeutic amounts of compounds that are selective 5-HT_{1A} agonists. “Selective,” as used herein, means having a greater affinity for 5-HT_{1A} receptors than for 5-HT_{1B/1D}, 5-HT_{2}, D_{2}, D_{4}, α_{1} or α_{2} receptors and for serotonin transporter (SERT), dopamine transporter (DAT), and norepinephrine transporter (NET). Selectivity may be based on relative K_{i} values or on relative affinity constants determined using saturation binding studies coupled with Scatchard analysis to determine K_{d} values.

[0044] Preferably, the 5-HT_{1A} agonists of this invention have an affinity for 5-HT_{1A} receptors that differs from 5-HT_{1B/1D}, 5-HT_{2}, D_{2}, D_{4}, α_{1} or α_{2} receptors or SERT, DAT, or NET, by at least 1 pK_{i} (e.g., 1 order of magnitude). More preferably, the 5-HT_{1A} agonists of this invention have an affinity for 5-HT_{1A} receptors that differs from that for D_{2} receptors by at least about 2 pK_{i} (e.g., 2 order of magnitude). Most preferably, the 5-HT_{1A} agonists of this invention have an affinity for 5-HT_{1A} receptors that differs from their affinities for 5-HT_{1B/1D}, 5-HT_{2}, D_{2}, D_{4}, α_{1} or α_{2} receptors or SERT, DAT, or NET by at least about 2 pK_{i} (e.g., 2 order of magnitude).

[0045] As used herein, pK_{i} means the negative log of the affinity constant (K_{i}) expressed in M. For example, flesinoxan has an affinity for 5-HT_{1A} of K_{i} = 1.7 nM (1.7x10^{-9} M) which equals 8.77 pK_{i}, and an affinity for D_{2} receptors of K_{i} = 140 nM (1.4x10^{-7} M), which equals 6.85 pK_{i} (see Schipper et al., 1991, supra). Accordingly, for flesinoxan, the difference in affinity for 5-HT_{1A} and D_{2} receptors (ΔpK_{i}) is about 1.92. Based on the K_{i} values reported by Schipper et al., 1991, supra, the ΔpK_{i} for 5-HT_{1A} and D_{2} receptors is 2.94 for 8-OH-DPAT and is 0.44 for
buspirone. Koek et al., J. Pharmacol. Exp. Ther., 287:266-283, 1998, have reported comparable pKᵢ values for 5-HT₁A and D₂ receptors for flesinoxan: 8.91 and 7.05, respectively (ΔpKᵢ = 1.86), and for buspirone: 7.5 and 7.43, respectively (ΔpKᵢ = 0.07). For another selective 5-HT₁A agonist F11440, Koek et al., 1998, supra, report a pKᵢ of 8.33 and 5.75 for 5-HT₁A and D₂ receptors, respectively (ΔpKᵢ = 2.58). Thus, a 5-HT₁A agonist that is reported to have significant (or equal) agonist activity at D₂ receptors, such as sunipetron (U.S. Pat. No. 6,300,329), or affinity for D₂ receptors that is functionally equivalent to 5-HT₁A receptors, such as buspirone (ΔpKᵢ<1), is not within the scope of this invention.

Flesinoxan (+)-(4-fluoro-N-[2-[4-[2-(hydroxymethyl)-1, 4-benzodioxane-5-yl]-1-piperazinyl]ethyl]benzamide hydrochloride), then, is a selective 5-HT₁A agonist. Other examples of selective 5-HT₁A agonists include BAY x 3702 (R-(-)-2-[4-[(chroman-2-ylmethyl)-amino]-butyl]-1,1-dioxo-benzo[di]thiazolone hydrochloride), F11440 [4-methyl-2-(4-[4-(pyrimidin-2-yl)-piperazino]-butyl)-2H,4H-1,2,4-triazin-3,5-dione], and ipsapirone.

Preferably, the 5-HT₁A agonists for use in this invention have an intrinsic activity at 5-HT₁A receptors greater than 0.5. “Intrinsic activity,” is the proportion of maximal inhibition of forskolin-stimulated cAMP achieved by a test compound relative to the maximal inhibition of forskolin-stimulated cAMP achieved by the natural agonist 5-HT (see Koek et al., 1998, supra). Inhibition of forskolin-stimulated cAMP production may be measured in stably transfected cell lines (for example, HeLa or CHO cells) that express 5-HT₁A receptors (Pauwels, et al., 1993, supra; Koek et al., 1998, supra; Evans et al., J. Pharmacol. Exp. Ther., 297(3):1025-35, 2001). For use in this invention, 5-HT₁A agonists display intrinsic activity at 5-HT₁A receptors of at least 0.5-1.0. Preferably, the 5-HT₁A agonists of this invention have an intrinsic activity of at least about 0.6-1.0. Even more preferably, the 5-HT₁A agonists of this invention have an intrinsic activity of at least about 0.7-1.0. Most preferably, the 5-HT₁A agonists of this invention have an intrinsic activity of at least about 0.8-1.0 (see Koek et al., 1998, supra).

The azapirone derivatives gepirone and ipsapirone are 5-HT₁A partial agonists chemically related to buspirone that have significant affinity for D₂
-16-

receptors as well as 5-HT\textsubscript{1A} receptors. Nevertheless, gepirone has sufficient intrinsic activity at the 5-HT\textsubscript{1A} receptor (0.77, Koek et al., 1998, supra), that it also is expected to be a useful 5-HT\textsubscript{1A} agonist in this invention.

[0049] The following compounds have the preferred intrinsic activity: flesinoxan (0.93), F11440 (1.0), LY228729 (0.88), S14506 (0.95), lesopitron (0.70), and gepirone (0.77).

[0050] The compounds having formulas I or II below are preferred for use with this invention.

[0051] Treatment of ADHD according to this invention is provided by administering to an individual in need of treatment a therapeutically effective amount of a compound of formula I:

\[
\begin{array}{c}
\text{\textbf{I}} \\
\end{array}
\]

wherein:

- \(R_1\) and \(R_2\) independently of each other represent hydrogen or an alkyl having 1-3 carbon atoms;
- \(R_3\) is an aryl group or heteroaryl group which may be substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, nitrile, nitro, alkoxy having 1-3 carbon atoms, hydroxy, esterified hydroxy, and alkyl having 1 or 2 carbon atoms;
- \(X\) is O, S, or NH;
- B is the group –CH₂–CH₂– or –CH(CH₃)–CH₂–;
- n has the value 0 or 1;
- p has the value 0 or 1;
  --where p has the value 1,
A is O-CH₃, or forms, with the two carbon atoms of the phenyl group, an optionally substituted, entirely or partly unsaturated, cyclic group having 5-7 atoms in the ring, which comprises 1-3 hetero atoms from the group O, S, and N, with the proviso that the sum of the number of oxygen and sulfur atoms is at most two, --- and where A is not O-CH₃,
  R₄ is hydrogen or straight or branched chain alkyl having 1-3 carbon atoms, and
  R₅ is hydrogen, halogen, alkyl having 1-3 carbon atoms, methylene, ethyldiene or vinyl, a straight or branched hydroxyalkyl group having 1-3 carbon atoms, which may be etherified or esterified, or an alkyl branched hydroxyalkyl group having 1-3 carbon atoms in the straight or branched alkyl group, an oxo group or a phenyl group; and
- R₆ is a hydrogen or fluoro atom.

wherein
- the compound may be a racemate or a single diastereomer or enantiomer;
- or a pharmaceutically acceptable acid salt thereof.

[0052] In a preferred embodiment of this invention, the 5-HT₄ agonist is a compound of formula I, wherein

- R₁, R₂, and R₆ are hydrogen;
- R₃ is a lipophilic aromatic alkyl, selected from the group consisting of benzene, halogenated benzene, cyclohexane, and 2-thiophene;
- X is O, S, or NH;
- B is the group –CH₂–CH₂–;
- n has the value 1;
-p has the value 0 or 1;
   -- where p is 1,
   A is O-CH₃, or forms, with the two carbon atoms of the phenyl
   group, an optionally substituted benzodioxane, a hydroxyalkyl
   having 1-2 carbon atoms, or a furan,
   --- and where A is not O-CH₃,
   R₄ is H, and R₅ is H, or chiral –CH₂OH – at the 2 position of
   the benzodioxane ring;

or pharmaceutically acceptable salts thereof, which is administered to individuals to
provide treatment of ADHD.

[0053] In a more preferred embodiment of this invention, the 5-HT₁₅ agonist
if formula I is flesinoxan [(+)9-fluoro-N-[2-[4-[2-(hydroxymethyl)-1, 4-
benzodioxane-5-y]l] 1-piperazinyl]ethyl]benzamide], or pharmaceutically
acceptable salts thereof, preferably hydrochloride, wherein R₁, R₂, and R₅ are
hydrogen; R₃ is a halogenated benzene group, having a fluoro in the para position;
X is O; n has the value 1; p has the value 1; A is benzodioxane; R₄ is hydrogen; R₅
is chiral –CH₂OH – at the 2 position of the benzodioxane ring; and B is the group –
CH₂–CH₂--; and which is administered to individuals to provide treatment of
ADHD.

[0054] The compounds of formula I described above, and the preferred and
more preferred embodiments, and their method of synthesis are described in U.S.
Patent No. 4,833,142; U.S. Patent No. 5,914,263; and European Patent No. 138,280;
and Kuipers et al., J. Med. Chem. 40:300-312, 1997; which are incorporated herein
by reference in their entireties. The affinity of phenyl piperazines for 5-HT₁₅
receptors is described by Schipper et al., 1991, supra; and Kuipers et al., 1997,
supra; which are incorporated herein by reference in their entireties.

[0055] In still another aspect of this invention, the 5-HT₁₅ agonist is a
compound of the formula II:
wherein:
- n can have the value 1 to 6;
- R is a hydrogen, a halogen, a lower alkyl radical having 1-4 carbon atoms, a heteroaryl radical, a sulpho radical, an N-substituted or N,N-di-substituted sulhamoyl radical, a nitro radical, a hydroxyl radical, an oxo radical, a lower alkoxyradical having 1-4 carbon atoms, a cyano radical, a lower alkylcarboxylate radical having 1-4 carbon atoms, an aryl or substituted aryl radical, or an amino or substituted amino radical of formula

\[
\begin{array}{c}
\text{N} \\
\text{R}_1 \\
\text{N} \\
\text{R}_2
\end{array}
\]

in which \( R_1 \) and \( R_2 \), independently are a hydrogen, an alkyl radical, an aryl radical, an alkylcarbonyl radical, an arylcarbonyl radical, an alkylsulphonyl radical or an arylsulphonyl radical, the alkyl fragments of these radicals containing from 1-4 carbon atoms; and

wherein
- the compound may be a racemate or a single diastereomer or enantiomer;
- or a pharmaceutically acceptable acid addition salt thereof.
A preferred compound of formula II of this invention is lesopitron (2-[4-(4-(4-chloro-1H-pyrazol-1-yl)-butyl]-1-piperazinyl] pyrimidine), or a pharmaceutically acceptable salt thereof, preferably dihydrochloride, wherein n has the value 4; and R is chloro; which is administered to individuals to provide treatment of ADHD.

The compounds of formula II, described above, including lesopitron, and their method of synthesis are described in U.S. Patent Nos. 5,128,343; 5,182,281; 5,162,323; 5,536,836; and 5,872,125; and EP 382,637 B1; which are incorporated herein by reference in their entireties. The affinity of lesopitron for 5-HT1A receptors is described by Costall et al., J. Pharmacol. Exp. Ther., 262:90-98, 1992; and Farré, Behav. Pharmacol., 3(Suppl.1):23, 1992. Lesopitron is reported to have virtually no affinity for other 5-HT receptor subtypes or other neurotransmitter receptors.

ADHD is treated according to this invention by administering therapeutic amounts of compounds according to formulas I or II, or combinations thereof.

This invention also includes the use of prodrugs of the compounds of formulas I and II, specifically derivatives of the compounds of formulas I and II that are inactive but are converted to an active form in the body following administration.

ADHD is also treated according to this invention by administering therapeutic amounts of other 5-HT1A agonists. A non-exhaustive list of other 5-HT1A agonists that would be useful in this invention includes, but is not limited to, the following: BAY x 3702 (R-(R)-2-[4-[(chroman-2-ylmethyl)-amino]-butyl]-1,1-dioxo-benzo[d]isothiazolone hydrochloride), F11440 [4-methyl-2-(4-[4-(pyrimidin-2-yl)-piperazino]-butyl)-2H,4H-1,2,4-triazin-3,5-dione], LY228729 [(+)-4(dipropylamino)-1,3,4,5-tetrahydrobenz-[c,d]inden-6-carboxamide], (-) LY293284 [(+)-4R-6-acetyl-4-[di-n-propylamino]1,2,4,5-tetrahydrobenz-[c,d]indole], NAE-086 [(R)-3,4-dihydro-N-isopropyl-3-(N-isopropyl-N-propylamino)-2H-1-benzopyran-5-carboxamide], S14506 [1(2-[4-fluorobenzoylamino]ethyl)-4-(7-methoxynaphthyl)piperazine], S14671 [(4-[(thenoyl-

5-HT\textsubscript{1A} agonists for use in this invention may be identified by a number of assays, known in the art that measure receptor affinity or functional parameters (including intrinsic activity) described above. These assays include, but are not limited to (1) in vitro affinity binding assays, for example in tissue or cell preparations, and (2) functional assays.

Affinity of a particular compound of the invention at 5-HT\textsubscript{1A} receptors can be determined, for example, using a single saturating concentration according to any of the procedures well known in the art, using \textsuperscript{3}H]-8-OH-DPAT as ligand for displacement, in membrane preparations from brain tissue or transfected cells stably expressing 5-HT\textsubscript{1A} receptors. Determination of a lesser affinity of the compounds of this invention for other receptors may be determined by methods known in the art. An exemplary protocol for a 5-HT\textsubscript{1A} binding assay is described briefly below. To provide means to assess the neurotransmitter receptor selectivity of a target 5-HT\textsubscript{1A} agonist, exemplary ligand binding assay protocols for key neurotransmitter receptors, 5-HT\textsubscript{1B/1D}, 5-HT\textsubscript{2}, D\textsubscript{2}, D\textsubscript{4}, \textalpha\textsubscript{1}, and \textalpha\textsubscript{2}, are described briefly below, as are binding assay protocols for serotonin transporter (SERT), dopamine transporter (DAT) and norepinephrine transporter (NET). Alternative ligand binding assay protocols for these receptors, as well as ligand binding assay protocols for other neurotransmitter receptors, may be found in the art.
[0063] 5-HT\textsubscript{1A} receptor binding assays may be carried out, for example, in HEK-293 cells expressing human recombinant 5-HT\textsubscript{1A} receptors, using a final concentration of \[^{3}H\]8-OH-DPAT (221 Ci/mmol) of 0.5 nM. The reference compound also is 8-OH-DPAT; \(K_i\) of reference compound 8-OH-DPAT in this assay is approximately 1.6 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM MgCl\(_2\), 0.5 mM EDTA and 0.1% ascorbic acid for 60 minutes at 25° C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to 5-HT\textsubscript{1A} binding sites. The sensitivity of the assay is approximately \(K_D=0.8\) nM and \(B_{\text{max}}=622\) pmol/mg protein. For reference, see Hoyer et al., Eur. J. Pharmacol., 118:13-23, 1985; Schoeffter and Hoyer, Naunyn-Schmiedeberg’s Arch. Pharmacol., 340:135-38, 1989, which are incorporated herein by reference, in their entireties.

[0064] 5-HT\textsubscript{1B/1D} receptor binding assays may be carried out, for example, in membrane preparations from rat or bovine striatum or human cerebral cortex, using a final concentration of \[^{3}H\]5-carboxyamidotryptamine (5-CT) (20-70 Ci/mmol) of 0.75 nM or 2 nM in cortex. The reference compound is 5-CT; \(K_i\) of reference compound 5-CT in this assay is approximately 0.7-1.1 nM. Alternatively, one may use a final concentration of \(^{125}\text{I}\)iodocyanopindolol (ICP) (2200 Ci/mmol) of 0.15 nM in striatum, and 5-HT as the reference compound; \(K_i\) of reference compound in this assay 5-HT is approximately 13.8 nM. For the assay using 5-CT (primarily 5-HT\textsubscript{1B}), reactions are carried out in 50 mM TRIS-HCl (pH 7.7) containing 4 mM CaCl\(_2\), 100 nM 8-OH-DPAT, 100 nM mesulergine, 10 µM pargyline, and 0.1% ascorbic acid for 60 minutes at 25° C. For the assay using ICP (primarily 5 HT\textsubscript{1D}), reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 60 µM (-)isoproterenol for 60 minutes at 37° C. Reactions are terminated by rapid vacuum filtration onto glass fiber filters, and radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to 5-HT\textsubscript{1B/1D} binding sites. The sensitivity of the assay is approximately \(K_D=0.12-1.0\) nM and \(B_{\text{max}}=2.1-60\) fmol/mg tissue. For reference, see Hoyer et al., 1985, supra; Schoeffter and Hoyer, 1989,
supra; Waebaer et al., Naunyn-Schmiedeberg's Arch. Pharmacol., 337:595-601, 1988, which are incorporated herein by reference, in their entireties.

[0065] 5-HT$_2$ (5-HT$_2A$) receptor binding assays may be carried out, for example, in membrane preparations from rat or human cerebral cortex, using a final concentration of [³H]ketanserin (60-90 Ci/mmol) of 1.0-2.0 nM. The reference compound may be methysergide or ketanserin. K$_i$ of reference compound methysergide in this assay is approximately 1.6 nM; K$_i$ of reference compound ketanserin in this assay is approximately 4.0 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.6) for 60 minutes at 37° C or for 90 minutes at 25° C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to 5-HT$_2$ binding sites. The sensitivity of the assay is approximately K$_D$=0.43-2.0 nM and B$_{max}$=10.0-30.9 fmol/mg protein. For reference, see Leysen et al. Mol. Pharmacol., 21:301-14, 1982; Martin and Humphrey, Neuropharmacol., 33(3/4):261-73, which are incorporated herein by reference, in their entireties.

[0066] D$_2$ receptor binding assays may be carried out, for example, in CHO cells expressing human recombinant D$_2$ receptors, using a final concentration of [³H]spiperone (20-60 Ci/mmol) of 0.2 nM. The reference compound is haloperidol; K$_i$ of reference compound haloperidol in this assay is approximately 2.8 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 5 mM MgCl$_2$, 1 mM EDTA for 60 minutes at 25° C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to D$_2$ binding sites. The sensitivity of the assay is approximately K$_D$=0.1 nM and B$_{max}$=1.5 pmol/mg protein. For reference, see Jarvis et al. J. Receptor Res. 13(10-4):573-590, 1993; Gundlach et al., Life Sciences, 35:1981-88, 1984, which are incorporated herein by reference, in their entireties.

[0067] D$_4$ receptor binding assays may be carried out, for example, in CHO cells expressing human recombinant D$_4$ receptors, using a final concentration of
\([^{3}\text{H}]\text{YM-09151-2 (70-87 Ci/mmol) of 0.3 nM. The reference compound is haloperidol; } K_i \text{ of reference compound haloperidol is approximately 0.8 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 5 mM KCl, 5 mM MgCl}_2, 5 mM EDTA, and 1.5 mM CaCl}_2, \text{ for 60 minutes at 22}^\circ \text{ C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to D}_4 \text{ binding sites. The sensitivity of the assay is approximately } K_D=0.26 \text{ nM and } B_{\text{max}}=43 \text{ pmol/mg protein. For reference, see Van Tol, et al., Nature, 350:610, 1991; Van Tol, et al., Nature, 358:149, 1992; Seeman et al., Eur. J. Pharmacol., 233:173, 1993, which are incorporated herein by reference, in their entirety.}

\[0068\] \( \alpha_1 \) receptor binding assays may be carried out, for example, in rat forebrain membranes, using a final concentration of \([^{3}\text{H}]\text{7-MeOxy-prazosin (70-87 Ci/mmol) of 0.3 nM. The reference compound is phentolamine mesylate; } K_i \text{ of reference compound phentolamine mesylate in this assay is approximately 5.4 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.7) for 60 minutes at 25^\circ \text{ C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to } \alpha_1 \text{ binding sites. The sensitivity of the assay is approximately } K_D=0.2 \text{ nM and } B_{\text{max}}=95 \text{ fmol/mg protein. For reference, see Timmermans, et al. Mol. Pharmacol. 20: 295-301, 1981, with modifications; and Reader, et al. J. Neural Transmission. 68: 79-95, 1987, which are incorporated herein by reference, in their entirety.}

\[0069\] \( \alpha_2 \) receptor binding assays may be carried out, for example, in rat cortical membranes, using a final concentration of \([^{3}\text{H}]\text{RX 821002 (40-60 Ci/mmol) of 1.0 nM. The reference compound is phentolamine mesylate; } K_i \text{ of reference compound phentolamine mesylate in this assay is approximately 3.2 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) for 75 minutes at 25^\circ \text{ C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to } \alpha_2 \text{ binding sites. The}
sensitivity of the assay is approximately $K_D = 1.5 \text{ nM}$ and $B_{\text{max}} = 60 \text{ fmol/mg protein}$. For reference, see O'Rourke, et al. *J. Pharmacol. Exp. Ther.* 268(3): 1362, 1993; and Reader, et al. *J. Neural Transmission.* 68: 79-95, 1987, which are incorporated herein by reference, in their entireties.

[0070] SERT binding assays may be carried out, for example, in human platelet membranes, using a final concentration of $[^3\text{H}]$citalopram, N-Methyl (70-87 Ci/mol) of 0.7 nM. The reference compound is imipramine; $K_i$ of reference compound imipramine in this assay is approximately 4.0 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.4), containing 120 mM NaCl and 5 mM KCl for 60 minutes at 25° C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to SERT binding sites. The sensitivity of the assay is approximately $K_D = 2.5 \text{ nM}$ and $B_{\text{max}} = 425 \text{ fmol/mg protein}$. For reference, see D'Amato, et al. *J. Pharmacol. & Exp. Ther.* 242: 364-371, 1987; and Brown, et al. *Eur. J. Pharmac.* 123: 161-165, 1986, which are incorporated herein by reference, in their entireties.

[0071] DAT binding assays may be carried out, for example, in guinea pig striatal membranes, using a final concentration of $[^3\text{H}]$WIN,35,428 (60-87 Ci/mmol) of 2.0 nM. The reference compound is GBR-12909; $K_i$ of reference compound GBR-12909 in this assay is approximately 7.1 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 120 mM NaCl for 2 hours at 0-4° C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to DAT binding sites. The sensitivity of the assay is approximately $K_D = 28.0 \text{ nM}$ and $B_{\text{max}} = 113 \text{ fmol/mg protein}$. For reference, see Madras, et al. *Mol. Pharmacol.* 36: 518-524, 1989; and Javitch, et al. *Mol. Pharmacol.* 26: 35-44, 1984, which are incorporated herein by reference, in their entireties.

[0072] NET binding assays may be carried out, for example, in rat forebrain membranes, using a final concentration of $[^3\text{H}]$nisoxetine (60-85 Ci/mmol) of 1.0 nM. The reference compound is desipramine; $K_i$ of reference compound
desipramine in this assay is approximately 0.7 nM. Reactions are carried out in 50 mM TRIS-HCl (pH 7.4), containing 300 mM NaCl and 5 mM KCl for 4 hours at 0°-4° C. After termination of the reaction by rapid vacuum filtration onto glass fiber filters, radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any binding of test compound(s) to NET binding sites. The sensitivity of the assay is approximately K_D=0.8 nM and B_max=10.5 fmol/mg protein. For reference, see Raisman, et al. *Eur. J. Pharmacol.* 78: 345-351, 1982; and Langer, et al. *Eur. J. Pharmac.* 72: 423, 1981, which are incorporated herein by reference, in their entireties.

Functionally, 5-HT₁A agonists and partial agonists have been shown to inhibit forskolin-induced cAMP production in HeLa or CHO cells that are stably transfected to express 5-HT₁A receptors, as described by Pauwels et al., *Biochem. Pharmacol.* 45:375-383, 1993; Koek et al., 1998 *supra*; and Evans et al., 2001, *supra*; which are incorporated by reference herein, in their entireties. 5-HT₁A agonists also induce hypothermia and spontaneous tail flicks in rodents, as described by Hjorth et al., 1985, *supra*; Millan et al., *Eur. J. Pharmacol.* 203:319-22, 1991; Millan et al., *J. Pharmacol. Exp. Ther.* 256:973-82, 1991, which are incorporated by reference herein, in their entireties.

5-HT₁A agonists for use in this invention are expected to display positive results in models of ADHD, such as improved performance in the peak procedure and reduced locomotor activity in spontaneously hyperactive animals, as described herein, as well as in clinical studies of ADHD patients.

The utility of the compounds of this invention for treating ADHD is based on the surprising discovery disclosed herein that fleinoxan and 8-OH-DPAT share certain activity profiles with other compounds known to be useful for treating such conditions. Amphetamines enhance monoaminergic transmission; however, their mechanism of action in ADHD is still the subject of much speculation. Without being bound by theory, one possible mechanism is the enhancement of dopamine release in those areas of the brain that are involved in attentional mechanisms, such as the frontal cortex, however, such a model seems to be overly simplistic and incomplete (Nestler, Hyman, & Malenka, “Sleep, Arousal and
Attention,” Ch. 18, In: Molecular Neuropharmacology: A Foundation for Clinical Neuroscience, McGraw Hill, 2001). Psychoactive substances such as amphetamines typically show a U-shape curve, with low doses being effective, and high doses being disruptive.

The mechanism underlying these U-shape curves is poorly understood, with one possibility being the differential action on pre- and postsynaptic dopamine D2 receptors. It is possible that low doses preferentially affect the post- (or pre-) synaptic receptors, and that only higher doses affect both types. The differential action could be the result of different binding characteristics (due to subtle changes in the receptors), or to differences in the amount of receptor reserve (where high receptor reserve results in a stronger effect). This dual pre- and postsynaptic action of dopamine (and of dopamine agonists) is mimicked in the serotonergic system, in which the 5-HT₁₆ and 5-HT₁₇ receptors exist as both autoreceptors (presynaptic) and heteroreceptors (postsynaptic) and have opposite effects. Presynaptic action typically results in a reduction of neurotransmitter release (and less activation of target receptors), whereas postsynaptic action results in enhanced activation of target receptors.

Although the main target of amphetamine-like drugs (and of bupropion, one antidepressant used for ADHD when adverse reactions prevent the use of psychostimulants) is the dopaminergic system, strong interactions between dopamine and serotonin are known. As a result, drugs that affect the serotonin system will very likely have secondary effects in the dopaminergic system. Moreover, serotonergic drugs that have a dual pre- and postsynaptic action would be expected to show U-shaped responses. Thus, a drug that has positive effects on performance at low doses, and disrupts performance at high doses, may be a drug that mimics amphetamine-like effects, and therefore may be of value in the treatment of ADHD.

The dose of the compound used in treating ADHD in accordance with this invention will vary in the usual way with the seriousness of the disorder, the weight, and metabolic health of the individual in need of treatment. The preferred initial dose for the general patient population will be determined by
routine dose-ranging studies, as are conducted, for example, during clinical trials. Therapeutically effective doses for individual patients may be determined, by titrating the amount of drug given to the individual to arrive at the desired therapeutic or prophylactic effect, while minimizing side effects. A preferred initial dose for flesinoxan is between about 0.04 mg/day and 4 mg/day, in single or multiple daily doses. A more preferred initial dose for flesinoxan is between about 0.1 mg/day and 1 mg/day. A most preferred initial dose for flesinoxan between about 0.1 mg/day and 0.5 mg/day. For the other 5-HT_{1A} agonists of this invention, a preferred initial dose is between about 0.01 mg/day and 100 mg/day, in single or multiple daily doses. A more preferred initial dose for the other 5-HT_{1A} agonists of this invention is between about 0.1 mg/day and 10 mg/day. A most preferred initial dose for the other 5-HT_{1A} agonists of this invention is between about 0.1 mg/day and 2 mg/day.

Administration of the compounds of this invention may be by any method used for administering therapeutics, such as for example oral, parenteral, intravenous, intramuscular, subcutaneous, or rectal administration.

In addition to comprising the therapeutic compounds for use in this invention, the pharmaceutical compositions for use with this invention may also comprise a pharmaceutically acceptable carrier. Such carriers may comprise additives, such as preservatives, excipients, fillers, wetting agents, binders, disintegrants, buffers may also be present in the compositions of the invention. Suitable additives may be, for example magnesium and calcium carbonates, carboxymethylcellulose, starches, sugars, gums, magnesium or calcium stearate, coloring or flavoring agents, and the like. There exists a wide variety of pharmaceutically acceptable additives for pharmaceutical dosage forms, and selection of appropriate acceptable additives is a routine matter for those skilled in art of pharmaceutical formulation.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, transdermal delivery devices, aerosols, pumps, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions.
In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Unit dose forms for oral administration may be tablets, capsules, and the like, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; and carriers or fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine. Additives may include disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycolate or microcrystalline cellulose; preservatives, and pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

In addition to unit dose forms, multi-dosage forms are also contemplated to be within the scope of the invention. Delayed-release compositions, for example those prepared by employing slow-release coatings, micro-encapsulation, and/or slowly-dissolving polymer carriers, will also be apparent to those skilled in the art, and are contemplated to be within the scope of the invention. Delayed release compositions are especially desirable for transdermal delivery devices.

The solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, for example with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, and hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil or fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for
example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired
c conventional flavoring or coloring agents.

[0086] For transdermal administration, the compound may be dispersed
within a physiologically compatible matrix or carrier, which is then provided in the
form of an ointment, gel, cream, lotion, or other components of topical compositions
that are known to the art. Preferably transdermal administration is via a skin patch
or other known transdermal delivery device which contains a saturated or
unsaturated formulation. The formulation may optionally include permeation
enhancers, and an anti-irritant, where indicated. The matrix or carrier may also
contain excipients, inert fillers, dyes, pigments, and other conventional components
of pharmaceutical products or transdermal devices known to the art, for example,
hydrophilic water absorbing polymers such as polyvinyl alcohol and polyvinyl
pyrrolidone individually or in combination.

[0087] For parenteral administration, fluid unit dosage forms are prepared
utilizing the compound and a sterile vehicle, and, depending on the concentration
used, can be either suspended or dissolved in the vehicle. In preparing solutions the
compound can be dissolved in water or saline for injection and filter sterilized
before filling into a suitable vial or ampoule and sealing. Advantageously, additives
such as a local anaesthetic, preservative and buffering agent can be dissolved in the
vehicle. Suitable buffering agents are, for example, phosphate and citrate salts. To
enhance the stability, the composition can be frozen after filling into the vial and the
water removed under vacuum. Parenteral suspensions are prepared in substantially
the same manner, except that the compound is suspended in the vehicle instead of
being dissolved, and sterilization cannot be accomplished by filtration. The
compound can be sterilized by conventional means, for example by exposure to
radiation or ethylene oxide, before being suspended in the sterile vehicle.
Advantageously, a surfactant or wetting agent is included in the composition to
facilitate uniform distribution of the compound.

[0088] The invention will be explained in more detail below by way of
examples, which illustrate the effectiveness of prototypical compounds fleinoxan
and 8-OH-DPAT in treating ADHD.
EXAMPLE 1

[0089] The peak procedure is a behavioral model designed to assess an animal’s ability to learn an appropriate time period in which to perform a task and a time period in which the animal will be rewarded if the task is performed. The model provides information concerning excitatory and inhibitory components of behavior, as subjects must respond to perform a task when appropriate and stop responding in an “empty trial” when time for reward has elapsed and the reward has not been delivered. The task is sensitive to conditions where there is a failure in inhibitory mechanisms, such as seems to be the case for ADHD (Pliszka et al., Biol. Psychiatry, 48:238-46, 2000).

[0090] In the peak procedure, mice are trained to work for food that is delivered at the same time in each trial, but withdrawn in some unreinforced trials. Typically, the response rate increases up to a maximum around the reinforcement time, and then decreases to a low toward the end of the trial. The shape of the response rate indicates whether the animal is sensitive to the time of reinforcement. To be able to perform well in this model, the animals need to be able to learn several tasks. First, the animal must make an association between a response (lever pressing, nose poking or key pecking) and the delivery of reward. Second, the animal must be able to perceive and remember time. Third, the animal must act on its remembered time by starting and then stopping or inhibiting the response. Fourth, the animal must be able to compare the elapsed time in the trials with its remembered time to reinforcement. In each trial the time clock is reset, and the animal must reset its internal “counter,” i.e., at the beginning of each trial animals should start “timing” the trial time from zero. The ability to perform this task depends on the animal’s working memory. Starting the internal clock at the beginning of the trial requires that the animal pays attention to the trial start time, which could be in the form of a visual signal, or as reported herein, the introduction of a lever into the experimental chamber. Failure to attend resulted in higher variability and a loss of accuracy during trial performance. Accuracy is measured by looking at the shape of the response function; therefore, if the response function
is sharper and centered on the reinforcement time it supports a conclusion that attentional processes have been heightened.

[0091] All mice were food deprived to a target weight of 85 – 90% of their free-feeding weight before training began. Mice were fed approximately 10% of their body weight until they reached their target weight. On average, 1 week of food deprivation was sufficient to reach the target weight. During this time, all subjects were fed Bioserve 500 mg precision dustless pellets as their daily ration. They were exposed to Carnation™ evaporated milk in the home cage to avoid a possible neophobic reaction to the reinforcement. Subjects were given 1-week “vacations” every 4 to 6 weeks at which time they were allowed free access to food and a new free-feeding body weight baseline was recorded. Water was continuously available in the cage. For the amphetamine dose response curve, C57BL/6J mice were used; for the flesinoxan and 8-OH-DPAT studies, C3H mice were used.

[0092] Once deprived, animals were trained to lever-press in an operant chamber using ultrasensitive levers. Sixteen mouse operant chambers (Med Associates, Georgia, VT) were configured identically with two retractable ultrasensitive levers, stimulus lights, and a dipper for delivery of condensed milk. A house light was placed on the opposite wall from the levers. Each chamber was placed in isolation cubicle. A fan provided white masking noise and adequate air.

[0093] Training and testing consisted of 1-h daily sessions. Subjects started on a concurrent fixed ratio 1-fixed time 1 min (FR 1- FT 1) schedule of reinforcement in which the house light served as the discriminative stimulus. Food was delivered every 1 min but the delivery was immediate if the animal made a response. Most animals acquired the lever-press response quickly, and those that did not were manually shaped by reinforcing successively closer approximations to the dipper using pinhole video cameras mounted in the attenuating cubicles. After no more than 1 week on this schedule, mice began training with a fixed-interval (FI) 10 s schedule in which all trials were separated by a 20 s, intertrial interval. The house light was on during the trials. Levers were introduced into the chamber at the beginning of the trial. All premature responses had no programmed consequences.
Once a scalloped response curve was achieved, all subjects were placed on an FI 30 s schedule for approximately 1 week before moving to the peak interval procedure 30 second schedule (PIP 30 s).

[0094] Peak trials were programmed to occur at random with the restriction that no more than two unreinforced trials be presented consecutively. In peak trials, the house light was presented for 120 s. There was an average of eight peak trials per session. Responding was recorded in bins of 5 s each and monitored graphically. When the response rate showed a clear peak centered at 30 s, subjects were considered well trained. On average, it took 12 days for the mice to reach a clear peak. After about 3 weeks, mice were switched to a PIP 45 s, simply by changing reinforcement time and lever side. All other parameters were kept constant (intertrial interval, bin size, etc). As with the 30 s schedule, for the PIP 45 s mice were trained until stable performance was obtained. After 3 weeks in this condition, mice were switched to a double 30 s/45 s PIP procedure PIP 30 s – 45 s. In this condition mice were tested with two different fixed interval values. The first half of the session consisted of either a PIP 30 s or a PIP 45 s, chosen at random. The second part of the session consisted of the other value. Therefore some mice started a session with a PIP 30 s and finished with a PIP 45 s, and some with the opposite order, but all experienced both orders across different days.

[0095] Once the performance during peak trials was stable, pharmacologic studies were commenced. During washout periods, all responses were unreinforced. Responses during these peak trials were recorded and transformed into a relative responding measure by dividing the number of responses in each 5 minute bin by the maximum response rate at any time interval in that trial. After relative responses had been calculated for each trial, an Analysis of Variance (ANOVA) with trial time and dose as within factors was performed. Significant interactions were followed up by planned pair-wise comparisons between the saline response and the corresponding drug dose response.

[0096] In subjects with problems of inhibition and response control, it will be beneficial to find a drug that improves performance by sharpening the response curve and providing the subject with greater control over the start and stop time for
response. The experiments with mice and the timing procedure were designed to maximize the chance of finding drugs that improve performance. Amphetamine was tested in low to moderately high doses for comparison. Amphetamine, a drug of abuse, is used by humans to enhance attention or vigilance at low doses, and as a recreational drug (that results in a "high" state) at much higher doses (more than five times the attention enhancing dose).

[0097] Figure 1 shows the response pattern obtained with d-amphetamine. At the lower doses, 1 and 2 mg/kg, the amphetamine curve demonstrates a higher peak in the curve followed by a rapid decrease, relative to saline (Figures 1A, 1B). Conversely, at the higher 4 mg/kg dose, the amphetamine curve does not peak as high as the lower dose and the curve is flatter (Figure 1C). Times at which pairwise comparisons between saline and amphetamine reached significance are indicated on the graphs. ANOVA revealed a significant dose x trial time interaction, p < 0.001.

[0098] Improved performance is demonstrated by a sharp peak in the curve followed by a rapid decrease. A sharpened curve is indicative of heightened attentional processes. A less marked peak in the curve followed by a flattening is indicative of deteriorated performance. The lowest two doses of amphetamine (1 mg/kg, 2 mg/kg) had positive effects on the PIP 30s task, as they sharpened the curve as depicted in Figures 1A and 1B. The highest dose of amphetamine (4 mg/kg) disrupted performance on the PIP 30s task, flattening the curve as depicted in Figure 1C. These results indicate that at low doses, amphetamine, a known therapeutic drug for ADHD, can improve performance in a task that measures attentive behavior.

EXAMPLE 2

[0099] The following results were obtained using the methods described in Example 1, but with two different doses of the 5-HT1\textsubscript{A} agonist flesinoxan (+)-(4-fluoro-N-[2-[4-[2-(hydroxymethyl)-1, 4-benzodioxane-5-yl] 1-piperazinyl]ethyl]benzamide). After 4 weeks of training in the double PIP procedure, mice were tested with flesinoxan. Flesinoxan was dissolved in distilled
H₂O and injected to half the mice in a low dose (0.1 mg/kg) or a lower dose (0.03 mg/kg), whereas the other subjects were injected with vehicle.

[00100] Figure 2 demonstrates increased attentive behavior at the “lower” dose of flesinoxan. In the PIP 30 s, 0.03 mg/kg flesinoxan, the peaks of the response curve is higher and the curves are sharper than vehicle. This effect is evident but less robust in the PIP 45s schedule, indicating that the more robust effect observed at the PIP 30 s could be attributable to a positive effect on attentional processes in contrast to a more central enhancing effect on information processing, which should result in better performance at all intervals tested. ANOVA revealed a significant dose x trial time interaction in the PIP 30 s (Fig. 2A; p < 0.0023; F(1,23) = 2.169), but not in the PIP 45 s (Fig. 2B; p = 0.9128; F(1,23) = 0.619).

[00101] At a higher, but still relatively low, dose, however, flesinoxan was less effective. At 0.1 mg/kg flesinoxan, the performance curves were more comparable to saline curve both in the PIP 30 s and PIP 45 s (Figures 3A, and 3B, respectively), but were not disruptive (compare to Figure 1C). ANOVA revealed no main dose effect or dose x trial time interaction. In conclusion, flesinoxan at low doses improves attentive behavior, and is expected to be useful in the treatment of ADHD.

EXAMPLE 3

[00102] The following results were obtained using the methods described in Example 1. After 4 weeks of training in the double PIP procedure, mice were tested with the 5-HT₁A agonist 8-OH-DPAT. 8-OH-DPAT was dissolved in distilled H₂O and injected to half the mice in a low dose (0.1 mg/kg), whereas the other subjects were injected with vehicle. After 3 days of washout, the treatments were reversed and a Latin Square design was completed except that the mice previously treated with drug were treated with vehicle and those mice treated previously with vehicle were administered a lower dose of 8-OH-DPAT (0.01 mg/kg). After 2 days of washout, the Latin Square design was completed at the 0.01 mg/kg dose.

[00103] Figure 4 demonstrates that at both 0.1 mg/kg and 0.01 mg/kg 8-OH-DPAT, the performance curves were not significantly different from the saline curve both in the PIP 30 s and PIP 45 s (Figures 4A and 4B, respectively). ANOVA
revealed no dose main effect or dose x trial time interaction. The 0.01 mg/kg dose of 8-OH-DPAT was slightly disruptive.

[00104] In conclusion, 8-OH-DPAT was not shown to improve attentive behavior in the peak procedure. This result is most likely due to the short half-life of the compound.

EXAMPLE 4

[00105] The coloboma (Cm) mutant mouse has been proposed as a rodent model for ADHD (for review, see Wilson, Neurosci. Biobehav. Rev., 24:51-57, 2000). The rationale for this proposal is three fold: first, Cm mutants (heterozygote) exhibit elevated spontaneous locomotor hyperactivity which averages three to four times the activity of wild-type littermates (Hess et al., J. Neurosci., 12:2865-2874, 1992; Hess et al., J. Neurosci., 16:3104-3111, 1996); second, this Cm mutation-associated hyperactivity can be ameliorated by low and moderate doses (2 – 16 mg/kg) of D-amphetamine (Hess et al., 1996, supra), a psychostimulant commonly prescribed to treat ADHD; and lastly, Cm mutant mice exhibit delays in achieving complex neurodevelopmental milestones in behavior (Heyser et al., Brain Res. Dev. Brain Res., 89:264-269, 1995) and deficits in hippocampal physiology and learning performance (Steffensen et al., Synapse, 22:281-289, 1996; Raber et al., J. Neurochem., 68:176-186, 1997) which may correspond to impairments seen in ADHD.

[00106] The genetic defects associated with Cm mutant mice include a deletion of the gene Snap (Hess et al., 1992, supra; Hess et al., Genomics, 21:257-261, 1994). Snap encodes SNAP-25, which is a key component of the synaptic vesicle docking and fusion complex required for regulated synaptic transmission. As a result, Cm mutant animals show marked deficits in Ca\(^{2+}\)-dependent dopamine release (Raber et al., supra). This hypofunctioning DA system, which may involve meso-cortical, meso-limbic, as well as nigro-striatal circuitries has been suggested as a possible mechanism underlying hyperactivity associated with Cm mutation (Sagvolden, et al., Behav. Brain Res., 94:61-71, 1998; Sagvolden and Sergeant, Behav. Brain Res., 94:1-10, 1998). Preliminary linkage studies suggest that polymorphs of SNAP-25 maybe associated with ADHD (Brophy et al., Mol.
Psychiatr., 7:913-17, 2002; Barr et al., Mol. Psychiatr., 5:405-09, 2000). Cm mutant mice therefore may provide a useful animal model of ADHD.

Amphetamine, but not methylphenidate, normalizes the hyperactivity in Cm mutant mice; in both control and Cm mutants, methylphenidate increases locomotor activity in a dose-dependent manner (Hess et al., 1996, supra). The differential effect of these two ADHD medicaments, which both act at the presynaptic terminal, has been attributed to the differing mechanisms of action of increasing synaptic DA concentrations (Hess et al., 1996, supra).

It has now been surprisingly found that flesinoxan, a specific 5-HT1A receptor agonist produces an amphetamine-like effect on hyperactivity in coloboma mice.

Animals

Heterozygote coloboma mice were originally purchased from The Jackson Laboratory (Bar Harbor, ME) and were bred and maintained in our colony. In the current study, mutant mice and wild-type littermates, all aged 8 to 10 weeks, were used. Animals were divided into 4 groups: mutant/drug-treatment, mutant/vehicle-control, wild-type/drug-treatment, wild-type/vehicle-control (n=4-13 per group). Age and gender were balanced among groups. All animals were housed as littermates (2-4 mice per cage) and were maintained on ad libitum food and water with a 12 hr light/dark cycle.

Behavioral Testing

The Open-field (OF) test was performed under normal lighting conditions (400 lux). Mice (Cm/+, WT) were brought into the experimental room and allowed at least 1 hr of acclimation. Thirty min prior to testing, animals received an i.p. injection of either either d-amphetamine (4 mg/kg), saline vehicle, flesinoxan (0.3 mg/kg), or distilled H2O vehicle. Each mouse was then placed into an OF arena (27 x 27 x 20 cm) with an infrared beam array system (Med Associates, St. Albans, VT) that automatically monitored the animal's activity. Four animals of matching genotype and treatment were tested at one time. The test session lasted 40 min and animals were returned to the home cage at the end of the session. Test
measures included locomotion (distance traveled in cm) and number of center entries (zone crossings).

Results

[00111] The data reveal a significant genotypic effect on parameters of hyperactivity that is reduced by amphetamine or flesinoxan treatment. Coloboma mutant mice are hyperactive relative to wild-type mice, as measured by increased locomotor activity. A genotypic effect on total ambulatory distance is depicted in Figures 5 and 6A, which illustrate that vehicle-treated mutant Cm mice traveled roughly three-six times further in distance than did their saline-treated wild-type littermates (18,386 ± 6387 vs. 3116 ± 338 centimeters, Fig. 5; 6112 ± 1621 vs. 2385 ± 692 centimeters, Fig. 6A, the scale of which is consistent with previously reported findings (Hess et. al., 1992, 1996, supra). And Figure 6C, for example, illustrates that saline-treated mutant mice crossed zones more frequently than did their saline-treated wild-type littermates.

[00112] The genotype-related difference in locomotion was diminished in flesinoxan-treated animals and reversed in amphetamine-treated animals.

[00113] Administration of amphetamine, 4 mg/kg, to wild-type mice had a stimulatory effect, significantly increasing total distance traveled, as illustrated in Figure 5 (3116 ± 338 vs. 11657 ± 2370 centimeters; ANOVA F_{(1,15)} = 11.276, p = 0.0043). By contrast, the same dose of amphetamine administered to Cm mutant mice significantly decreased total distance traveled relative to saline-treated Cm mutants (18386 ± 6387 vs. 5966 ± 1938 cm; ANOVA F_{(1,11)} = 5.355, p = 0.0459) to within the range of saline-treated wild-type mice. Amphetamine effectively normalized the hyperactive locomotor behavior of the coloboma mutant mice, significantly decreasing locomotion in the Cm mutant mice. ANOVA revealed a significant treatment x genotype interaction (F_{(1,25)} = 11.038, p = 0.0027).

[00114] Flesinoxan surprisingly had an amphetamine-like effect on total ambulatory distance of Cm mutant mice. Administration of 0.3 mg/kg flesinoxan reduced the total ambulatory distance of the Cm mutants from 6112 ± 1621 to 1462 ± 411, as illustrated in Figure 6A. This represents a reduction in locomotor
activity of more than 75% compared to that of saline-treated Cm mutants
\( F_{(1,20)} = 5.138, p = 0.034 \). ANOVA revealed a significant treatment \( \times \) genotype effect
\( F_{(1,20)} = 6.669, p = 0.0178 \). Analyzed across 5 minute time bins, the effect of
0.3 mg/kg flesinoxan on Cm hyperactivity, as depicted in Figure 6B, is equally
impressive. ANOVA revealed a significant time \( \times \) treatment interaction effect
\( F_{(1,140)} = 3.901, p = 0.006 \) time \( \times \) genotype \( \times \) treatment interaction effect
\( F_{(1,140)} = 3.932, p = 0.0006 \).

[00115] As Figure 6C shows, flesinoxan decreased the frequency of zone
crossings in Cm mutants to within the range of saline-treated wild-type mice, but the
overall effect did not reach statistical significance \( F_{(1,20)} = 3.773, p = 0.0683 \). When
analyzed across 5 minute time bins, however, significant time \( \times \) treatment
\( F_{(1,140)} = 2.303, p = 0.030 \) and time \( \times \) treatment \( \times \) genotype \( F_{(1,140)} = 3.626, p = 0.0013 \)
effects were observed.

[00116] Notably, flesinoxan only marginally affected locomotion in wild-type
animals, as measured by distance traveled (Figures 6A and 6B) or zones crossed
(Figure 6C). This differential drug effect made the locomotor activity of flesinoxan-
treated mutant and wild-type animals indistinguishable from that of saline-treated
wild-type animals. In other words, flesinoxan effectively normalized the
hyperactivity associated with the Cm mutation. Figures 6D-F represent the results
of another trial conducted as described above, with the conclusions as indicated
above.

[00117] It has previously been shown that the psychostimulant anti-ADHD
agents d-amphetamine, but not methylphenidate, reinstated normal locomotor
activity of the Cm mutants, suggesting an inconsistent effect of psychostimulants on
this model of hyperactivity (Hess et. al., 1996, supra). However, the findings of this
invention suggest that 5-HT\(_{1A}\) agonists, like flesinoxan have a specific regulatory
role over hyperactivity. In summary, flesinoxan is acting like the anti-ADHD agent
amphetamine in the Cm animal model of ADHD, but lacks the adverse stimulant
properties of amphetamine observed in wild-type mice, demonstrating the
therapeutic potential and advantages of 5-HT\(_{1A}\) agonist flesinoxan as anti-ADHD
agents.
EXAMPLE 5

[00118] The following results were obtained using the methods described in Example 4. The Coloboma mutant (Cm) mice in this study exhibited hyperactivity that was surprisingly reduced by the 5-HT$_{1A}$ agonist 8-OH-DPAT. Administration to Cm mice of 0.1 mg/kg of 8-OH-DPAT attenuated total ambulatory distance by almost 50% compared to vehicle: from 14702 ± 2611 to 7813 ± 2606 centimeters (Figure 7A). This effect did not reach statistical significance, however, perhaps in part because of the high variability in the activity of the animals combined with the more limited hyperactivity of this group of Cm mutants ($F_{(1,38)}$=3.914, $p=0.552$). When analyzed by 5 minute activity bins. (see Figure 7B), the 8-OH-DPAT-induced reduction in hyperactivity also is evident, but the effect did not reach statistical significance. 8-OH-DPAT (0.1 mg/kg) significantly decreased the total frequency of zone crossings in Cm mice (Figure 7C; $F_{(1,38)}$ = 5.098, $p = 0.030$). ANOVA revealed no time treatment interaction effect, however. Lower doses of 8-OH-DPAT (0.001 or 0.01 mg/kg) produced no significant attenuation of Cm hyperactivity (data not shown), due in part to variability in activity among subjects.

[00119] In wild-type mice, 8-OH-DPAT decreased total ambulatory distance slightly, but non-significantly, from 7720 ± 2726 to 4517 ± 1599, as depicted in Figure 7A; see also Figure 7B. This differential drug effect made the overall locomotor activity of 8-OH-DPAT-treated mutant and wild-type animals indistinguishable from that of saline-treated wild-type animals. In other words, 8-OH-DPAT effectively normalized the hyperactivity associated with the Cm mutation. The findings of this invention suggest that 5-HT$_{1A}$ agonists, like 8-OH-DPAT have a specific regulatory role over hyperactivity. In summary, 8-OH-DPAT is acting like the anti-ADHD agent amphetamine in the Cm animal model of ADHD, demonstrating the therapeutic potential of 5-HT$_{1A}$ agonists as anti-ADHD agents.

[00120] The above Examples are for illustrative purposes only and are not intended to limit the scope of the invention.
WE CLAIM:

1. A method of treating Attention-Deficit/Hyperactivity Disorder ("ADHD") in humans by administering a pharmaceutical formulation containing a therapeutically effective amount of a compound or compounds having full agonist or partial agonist activity at 5-HT$_{1A}$ receptors, wherein any non-5-HT$_{1A}$ agonist that is included in said formulation as an active ingredient, no such active ingredient is nicotine or a nicotinic agonist with the proviso that said formulation does not comprise nicotine or a nicotine agonist or buspirone or sunipetron.

2. A method according to claim 1 wherein 5-HT$_{1A}$ agonist is a compound according to the formula I:

![Chemical Structure](image)

wherein

- $R_1$ and $R_2$ independently of each other represent hydrogen or an alkyl having 1-3 carbon atoms;
- $R_3$ is an aryl group or heteroaryl group which may be substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, nitrite, nitro, alkoxy, having 1-3 carbon atoms, hydroxy, esterified hydroxy, and alkyl having 1 or 2 carbon atoms;
- $X$ is O, S, or NH;
- $B$ is the group $-CH_2-CH_2-$ or $-CH(CH_3)-CH_2-$;
- n has the value 0 or 1;
- p has the value 0 or 1;

-- where p has the value 1,

A is O-CH₃, or forms, with the two carbon atoms of the phenyl
group, an optionally substituted, entirely or partly unsaturated,
cyclic group having 5-7 atoms in the ring, which comprises 1-3
hetero atoms from the group O, S, and N, with the proviso that
the sum of the number of oxygen and sulfur atoms is at most two,

--- and where A is not O-CH₃,

R₄ is hydrogen or straight or branched chain alkyl having 1-3
carbon atoms and R₅ is hydrogen, halogen, alkyl having
1-3 carbon atoms, methylene, ethyldiene or vinyl, a
straight or branched hydroxyalkyl group having 1-3
carbon atoms, which may be etherified or esterified, or an
alkyl branched hydroxyalkyl group having 1-3 carbon
atoms in the straight or branched alkyl group, an oxo
group or a phenyl group; and

- R₆ is a hydrogen or fluoro atom;

wherein

- the compound may be a racemate or a single diastereomer or enantiomer;
- or a pharmaceutically acceptable acid addition salt thereof.

3. The method of claim 2,

wherein

- R₁, R₂, and R₆ are hydrogen;
- R₃, is a lipophilic aromatic alkyl, selected from the group consisting of
  benzene, halogenated benzene, cyclohexane, and 2-thiophene;
- X is O, S, or NH;
- B is the group --CH₂-CH₂--
- n has the value 1; and
- p has the value 0 or 1,

-- and where p has the value 1.
A is O-CH₃, or forms, with the two carbon atoms of the phenyl group, an optionally substituted benzodioxane, a hydroxyalkyl having 1-2 carbon atoms, or a furan, R₃,

and where A is not O-CH₃,

R₄ is hydrogen, and

R₅ is hydrogen, or chiral –CH₂OH– at the 2 position of the benzodioxane ring.

4. The method according to claim 3, wherein the compound is flesinoxan, wherein

-R₁, R₂, and R₆ are hydrogen;

-R₃ is halogenated benzene group, having a fluoro in the para position;

-X is O;

-B is the group –CH₂–CH₂–;

-n has the value 1;

-p has the value 1;

-A is benzodioxane;

-R₄ is hydrogen

-R₅ is chiral –CH₂OH– at the 2 position of the benzodioxane ring; and

-the salt is hydrochloride.

5. The method according to claim 4, wherein the compound is administered at a dose of approximately 0.04 mg/day to 4 mg/day.

6. The method according to claim 5, wherein the compound is administered at a dose of approximately 0.1 mg/day and 1 mg/day.

7. The method according to claim 6, wherein the compound is administered at a dose of approximately 0.1 mg/day and 0.5 mg/day.
8. The method according to claim 1, wherein the 5-HT<sub>1A</sub> agonist is a compound having the formula II:

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\[ \text{II} \]
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wherein

- n can have the value 1 to 6;
- R is a hydrogen, a halogen, a lower alkyl radical having 1-4 carbon atoms, a heteroaryl radical, a sulpho radical, an N-substituted or N,N-disubstituted sulphamoyl radical, a nitro radical, a hydroxyl radical, an oxo radical, a lower alkoxyradical having 1-4 carbon atoms, a cyano radical, a lower alkylcarboxylate radical having 1-4 carbon atoms, an aryl or substituted aryl radical, or an amino or substituted amino radical of formula

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\[ R_1 \]
\[ R_2 \]
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in which R<sub>1</sub> and R<sub>2</sub>, independently are a hydrogen, an alkyl radical, an aryl radical, an alkylcarbonyl radical, an arylcarbonyl radical, an alkylsulphonyl radical or an arylsulphonyl radical, the alkyl fragments of these radicals containing from 1-4 carbon atoms; and

wherein

- the compound may be a racemate or a single diastereomer or enantiomer;
-or a pharmaceutically acceptable acid addition salt thereof.

9. The method according to claim 8, wherein the compound is lesopitron, wherein
- n is 4,
- R is chloro; and
- the salt is dihydrochloride.

10. The method according to claim 1, wherein the 5-HT$_{1A}$ agonist is selected from the group consisting of flesinoxan, lesopitron, BAY x 3702, F11440, LY228729, LY293284, NAE-086, S14506, S14671, S16924, or geprine.

11. The method according to claim 1, wherein the 5-HT$_{1A}$ agonist(s) is the sole ADHD active component(s) of the formulation.

12. The method according to claim 10, wherein the 5-HT$_{1A}$ agonist is administered at a dose of approximately 0.01 mg/day to 100 mg/day.

13. The method according to claim 10, wherein the 5-HT$_{1A}$ agonist is administered at a dose of approximately 0.1 mg/day and 10 mg/day.

14. The method according to claim 10, wherein the 5-HT$_{1A}$ agonist is administered at a dose of approximately 0.1 mg/day and 2 mg/day.

15. The method according to claim 1, wherein the intrinsic activity of the 5-HT$_{1A}$ agonist is at least 0.5-1.0.

16. The method according to claim 15, wherein the intrinsic activity of the 5-HT$_{1A}$ agonist is at least about 0.6-1.0.

17. The method according to claim 16, wherein the intrinsic activity of the 5-HT$_{1A}$ agonist is at least about 0.7-1.0.

18. The method according to claim 17, wherein the intrinsic activity of the 5-HT$_{1A}$ agonist is at least about 0.8-1.0.
19. The method according to claim 2, wherein the difference in affinity of the 5-HT\textsubscript{1A} agonist for 5-HT\textsubscript{1A} receptors compared to any of 5-HT\textsubscript{1B/1D}, 5-HT\textsubscript{2}, D\textsubscript{2}, D\textsubscript{4}, \alpha\textsubscript{1} or \alpha\textsubscript{2} receptors or SERT, DAT, or NET (\textDelta pK\textsubscript{i}) is at least 1.

20. The method according to claim 2, wherein the difference in affinity of the 5-HT\textsubscript{1A} agonist for 5-HT\textsubscript{1A} compared to D\textsubscript{2} receptors (\textDelta pK\textsubscript{i}) is at least about 2.

21. The method according to claim 2, wherein the difference in affinity of the 5-HT\textsubscript{1A} agonist for 5-HT\textsubscript{1A} receptors compared to any of 5-HT\textsubscript{1B/1D}, 5-HT\textsubscript{2}, D\textsubscript{2}, D\textsubscript{4}, \alpha\textsubscript{1} or \alpha\textsubscript{2} receptors or SERT, DAT, or NET (\textDelta pK\textsubscript{i}) is at least about 2.
**FIGURE 6**

6A

![Bar chart showing total distance traveled (cm) with groups labeled as Flesinoxan (0.3 mg/kg) and Vehicle.](image)

6B

![Line chart showing total distance traveled (cm) with groups labeled as Cm, Flesinoxan (0.3 mg/kg), Cm, Vehicle, WT, Flesinoxan (0.3 mg/kg), and WT, Vehicle.](image)
Figure 6D

Total Distance Traveled (cm)

- Flesinoxan (0.3 mg/kg)
- Vehicle

Cm

WT
### ANOVA Table for Total Distance

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Figure 6E

Total Distance Travelled (cm)

Time Bin

Cm, Flesinoxan (0.3 mg/kg)
Cm, Vehicle
WT, Flesinoxan (0.3 mg/kg)
WT, Vehicle
ANOVA Table for Total Distance (cm)

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FIGURE 7

7A

Total Distance Traveled (cm)

- DPAT 0.1 mg/kg
- Vehicle

Cm
WT

7B

Total Distance Traveled (cm)

- Cm, DPAT 0.1 mg/kg
- Cm, Vehicle
- WT, DPAT 0.1 mg/kg
- WT, Vehicle

5 10 15 20 25 30 35 40
## INTERNATIONAL SEARCH REPORT

### International Application No

PCT/US2004/002793

### A. CLASSIFICATION OF SUBJECT MATTER

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

| IPC 7 | A61K A61P |

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

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, CHEMABS Data, EMBASE, BIOSIS, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

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

"E" earlier document 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 declaration, 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 or in combination with one or more other documents, such combination being obvious to a person skilled in the art.

**S** document member of the same patent family

Date of the actual completion of the international search

10 June 2004

Date of mailing of the international search report

29. 06. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5018 Patentlaan 2 NL, - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 851 apo nl, Fax: (+31-70) 340-8016

Authorized officer

A. Jakobs
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INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 1-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:  
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.
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