Cis-2,6-Disubstituted Piperidines for the Treatment of Psychostimulant Abuse and Withdrawal, Eating Disorders, and Central Nervous System Diseases and Pathologies

Linda P. Dwoskin
University of Kentucky, ldwoskin@email.uky.edu

Peter A. Crooks
University of Kentucky, pcrooks@uky.edu

Marlon D. Jones
University of Kentucky, mdjones310@comcast.net

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CIS-2,6-DISUBSTITUTED PIPERIDINES FOR THE TREATMENT OF PSYCHOSTIMULANT ABUSE AND WITHDRAWAL, EATING DISORDERS, AND CENTRAL NERVOUS SYSTEM DISEASES AND PATHOLOGIES

Inventors: Linda P. Dwoskin, Lexington, KY (US); Peter A. Crooks, Lexington, KY (US); Marion D. Jones, Lexington, KY (US)

Assignee: University of Kentucky Research Foundation, Lexington, KY (US)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154 (b) by 238 days.

Primary Examiner—Zinna Northington Davis

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ABSTRACT

Cis-2,6-disubstituted piperidine analogs, or lobeline analogs, having the general formula:

are used to treat diseases of the central nervous system, drug abuse and withdrawal therefrom as well as to treating eating disorders.

42 Claims, No Drawings
OTHER PUBLICATIONS


M. Marks et al. “Nicotinic Binding Sites in Rat and Mouse Brain: Comparison of Acetylcholine, Nicotine, and α-Bungarotoxin” Molecular Pharmacology. 30:427–436.


CIS-2,6-DISUBSTITUTED PIPERIDINES FOR THE TREATMENT OF PSYCHOSTIMULANT ABUSE AND WITHDRAWAL, EATING DISORDERS, AND CENTRAL NERVOUS SYSTEM DISEASES AND PATHOLOGIES

CROSS-REFERENCED TO RELATED APPLICATIONS

This application is a Divisional of application Ser. No. 09/628,557 filed Jul. 28, 2000, now U.S. Pat. No. 6,455,543 issued Sep. 24, 2002, which claims the benefit of Provisional Application No. 60/146,144 filed Jul. 30, 1999.

FIELD OF THE INVENTION

The present invention relates to lobeline analogs, specifically cis-2,6-disubstituted piperidines, and their method of use in the treatment of diseases and pathologies of the central nervous system (CNS), the treatment of drug abuse and withdrawal therefrom as well as to the treatment of eating disorders such as obesity.

BACKGROUND OF THE INVENTION

Alpha-Lobeline (lobeline), a lipophilic nonpyridino, alkaloid constituent of Indian tobacco, is a major alkaloid in a family of structurally-related compounds found in Lobelia inflata. Lobeline has been reported to have many nicotine like effects, including tachycardia and hypertension (Olin et al., 1995), hyperalgesia (Hamann et al., 1994) and improvement of learning and memory (Decker et al., 1993). Lobeline has high affinity for nicotinic receptors (Lippiello et al., 1986; Broursolle et al., 1989). However, no obvious structural resemblance of lobeline to nicotine is apparent and structure function relationships between $S(-)$-nicotine and lobeline do not suggest a common pharmacophore (Barlow et al., 1989). Also, differential effects of lobeline and nicotine suggest that these drugs may not be active through a common CNS mechanism, even though lobeline has been considered a mixed nicotinic agonist/antagonist.

Lobeline evokes dopamine (DA) release from rat striatal slices. However, lobeline evoked DA release is neither dependent upon extracellular calcium nor is it sensitive to mecamylamine, a noncompetitive nicotinic receptor antagonist. Thus, lobeline evoked DA release occurs via a different mechanism than does nicotine to evoke DA release (Teng et al., 1997, 1998; Clarke et al., 1996). In this respect, lobeline also inhibits DA uptake into rat striatal synaptic vesicles via an interaction with the dihydro tropabenazine (DTBZ) site on vesicular monoamine transporter-2 (VMAT2), thus increasing the cytosolic DA available for reverse transport by the plasma membrane transporter (DAT) (Tong et al., 1997, 1998). Thus, lobeline interacts with nicotinic receptors and blocks nicotine-evoked DA release, but also interacts with DA transporter proteins to modify the concentration of DA in the cytosolic and vesicular storage pools, thereby altering subsequent dopaminergic neurotransmission.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating an individual who suffers from a disease or pathology of the central nervous system (CNS) or for treating an individual for drug dependence or withdrawal for drug dependence. The method comprises of administering to the individual an effective amount of a cis-2,6-substituted piperidino compound, i.e., a lobeline analog, including pharmaceutically acceptable salts of such compounds thereof. As used herein, an “effective amount” refers to an amount of a drug effective to reduce an individual’s desire for a drug of abuse or for food, or for alleviating at least one of the symptoms of the disease or pathological symptom of a CNS pathology.

The compound can be administered alone, combined with an excipient, co-administered with a second drug having a similar or synergistic effect. The compound is administered subcutaneously, intramuscularly, intravenously, transdermally, orally, intranasally, intrapulmonary or rectally. The use of cis-2,6-disubstituted piperidines and derivatives thereof in treating diseases or pathologies of the CNS is implicated. In particular, the treatment of dependencies of such drugs as cocaine, amphetamine, caffeine, nicotine, phencyclidine, opiates, barbiturates, benzodiazepines, cannabinoids, hallucinogens, and alcohol is implicated. Also, the treatment of eating disorders such as obesity is implicated.

In a preferred aspect of the invention, the method of treatment reduces an individual’s desire for the drug of abuse or for food by at least one day, but it is also preferred that the treatment method further comprise administering behavior modification counseling to the individual. Although the compound of the present invention is contemplated primarily for the treatment of drug abuse and withdrawal and for eating disorders, other uses are also suggested by the studies discussed herein. Thus, cognitive disorders, brain trauma, memory loss, psychosis, sleep disorders, obsessive compulsive disorders, panic disorders, myasathenia gravis, Parkinson’s disease, Alzheimer’s disease, schizophrenia, Tourette’s syndrome, Huntington’s disease, attention deficit disorder, hyperkinetic syndrome, chronic nervous exhaustion, narcolepsy, motion sickness and depression, and related conditions are considered to be susceptible to treatment with a compound of the present invention.

As shown by the results of the studies described herein, lobeline analogs are found to be effective in inhibiting uptake of extracellular DA by cells of the CNS. Some of these analogs are also nicotinic receptor antagonists. Either or both mechanisms can thereby work to alter the distribution of the intracellular DA pools and as a result alter extracellular DA concentration.

As used herein the term “lobeline” refers to a compound having the general chemical formula 2-[6-(β-hydroxyphenethyl)-1-methyl-2-piperidyl]-acetophenone. The term “lobeline analogs” and equivalents thereof as used herein, refers to chemical derivatives of lobeline obtained by oxidation or reduction of lobeline, others obtained by esterification of lobeline and redox derivatives, as well as various substitutions at the N-position of the piperidinyl moiety.

DETAILED DESCRIPTION OF THE INVENTION

The 2,6-disubstituted piperidine lobeline analogs of the present invention include those contemplated by the following formula (I), without regard to chirality:

wherein:

- n is zero or an integer in the range from 1 to 3;
- $X^1$—$Y^1$ and $X^2$—$Y^2$ are the same or are independently different from one another and represent a saturated carbon-carbon bond, a cis-carbon-carbon double bond, a transcarbon-carbon double bond, a carbon-carbon triple bond; a
saturated sulfur-carbon bond, a saturated selenium-carbon bond, an oxygen-carbon bond, a saturated nitrogen-carbon bond, a N-alkyl substituted saturated nitrogen-carbon bond where said alkyl is a lower straight chain or branched alkyl, a nitrogen-carbon double bond, or a nitrogen-nitrogen double bond; R1 and R4 are the same or are independently different from one another and represent hydrogen or a lower straight chain or branched alkyl or R2 and R3 together form a ring including a \(-\text{CH} = \text{CH}, -\text{CH} = \text{CH}-\), or \(-\text{cis-CH} = \text{CH}, -\text{cis-CH} = \text{CH}-\) or \(-\text{cis-CH} = \text{CH}, -\text{cis-CH} = \text{CH}-\) moiety;

R2 and R3 are the same or are independently different from one another and represent a saturated or unsaturated hydrocarbon ring; a nitrogen containing heterocyclic moiety; an oxygen containing heterocyclic moiety; a sulfur containing heterocyclic moiety; a selenium containing heterocyclic moiety; a mixed heterocyclic moiety containing at least two atoms selected from the group consisting of nitrogen, oxygen, sulfur, and an ortho, meta or para-substituted benzene;

with the proviso that when \( n = 0 \), R2 and R3 are unsubstituted phenyl groups, and X1-Y1 and X2-Y2 are saturated carbon-carbon bonds, Y1 cannot be CH2, CHOH or C=O, and Y2 cannot be CH2, CHOH or C=O.

It is preferred that when R2 and/or R3 is a saturated hydrocarbon ring, the ring includes, but is not limited to, cyclobutane, cyclopentane, cyclohexane, cycloheptane or cyclooctane, including all possible substitution patterns, geometric and stereoisomers, racemic, diastereomeric and enantiomeric forms thereof.

It is further preferred that when R2 and/or R3 is an unsaturated hydrocarbon ring, the ring includes, but is not limited to, benzene, cyclopentene, cyclohexene, cycloheptene, cyclooctene or cyclopentadiene, including all possible substitution patterns, geometric and stereoisomers, racemic, diastereomeric and enantiomeric forms thereof.

It is also preferred that when R2 and/or R3 is a nitrogen containing heterocyclic moiety, the moiety includes, but is not limited to, azetine, piperdine, pyrazine, pyrazole, pyrazolidine, imidazolidine, pyrimidine, hexahydropyrimidine, pyrrole, pyridine, triazine, 1,2,3-triazole, 1,2,4-triazole, pyridine or pyrazidine, including all possible substitution patterns, geometric and stereoisomers, racemic, diastereomeric and enantiomeric forms thereof.

It is further preferred that R2 and/or R3 is an oxygen containing heterocyclic moiety, the moiety includes, but is not limited to, furan, tetrahydrofuran, 2,5-dihydrofuran, pyran, tetrahydropryan, 1,4-dioxane, 1,3-dioxane or 1,4-oxathin, including all possible substitution patterns, geometric and stereoisomers, racemic, diastereomeric and enantiomeric forms thereof.

It is further preferred that when R2 and/or R3 is a sulfur containing heterocyclic moiety, the moiety includes, but is not limited to, thietane, thiophene, thionaphene, 2,5-dihydrothiophene, 1,3-dithiolium, 1,3-dithiolane, 1,2-dithiolium, thiame, 1,2-dithiane, 1,3-dithiane, 1,4-dithiane, or thiopyranylium, including all possible substitution patterns, geometric and stereoisomers, racemic, diastereomeric and enantiomeric forms thereof.

It is further preferred that when R2 and/or R3 is a selenium containing heterocyclic moiety, the moiety includes, but is not limited to, thiazolidine, thiazole and oxazine, including all possible substitution patterns, geometric and stereoisomers, racemic, diastereomeric and enantiomeric forms thereof.

The substituted benzene includes at least one substituent, where the substituent is selected from, but is not limited to, the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, amino, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carboxaldehyde, acetoxyl, propionyloxyl, isopropionyloxyl, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N-methylcarboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, thiol, thiolithio, ethylithio, propiothiol, fluoro, chloro, bromo, iodo, trifluoromethyl, vinyl, alkyl, propargyl, nitro, carbamoyl, ureido, azido, isocyante, thioisocyanate, hydroxlylamo and nitroso.

It is further preferred that when either X1-Y1 or X2-Y2 is a saturated carbon-carbon bond, Y1 or Y2 represents CH2, CH-CH2, CHOH or CH-OH, CH-CN, CH-Br, CH-I, CH-NH2, CH-CH=CH, or CH-CH=C(CH3)-.

The above 2,6-substituted piperidino analogs are preferred in their cis-geometrical isomeric forms, or in their trans isomeric forms, including all possible geometric, racemic, diastereomeric, and enantiomeric forms thereof.

The above cis-2,6-substituted piperidines as well as analogs thereof can be administered in their free base form or as a soluble salt. When it is desired to employ a salt of a cis-2,6-substituted piperidine or its analog, it is preferred that a soluble salt be employed. Some preferred salts include hydrochloride, hydrobromide, nitrate, sulfate, phosphate, tartrate, galactarate, fumarate, citrate, maleate, glycolate, malate, ascorbate, lactate, aspartate, glutamate, methanesulfonate, p-toluenesulfonate, benzenesulfonate, salicylate, propionate, and succinate salts. The above salt forms may be in some cases hydrates or solvates with alcohols and other solvents.

A pharmaceutical composition containing a compound of the invention is also contemplated, which may include a conventional additive, such as a stabilizer, buffer, salt, preservative, filler, flavor enhancer and the like, as known to those skilled in the art. Representative buffers include phosphates, carbonates, citrates and the like. Exemplary preservatives include EDTA, EGTA, BHA, BHT and the like. A composition of the invention may be administered by
inhalation, i.e., intranasally as an aerosol or nasal formulation; topically, i.e., in the form of an ointment, cream or lotion; orally, i.e., in solid or liquid form (tablet, gel cap, time release capsule, powder, solution, or suspension in aqueous or non aqueous liquid; intravenously as an infusion or injection, i.e., as a solution, suspension or emulsion in a pharmaceutically acceptable carrier; transdermally, e.g., via a transdermal patch; rectally as a suppository and the like.

Generally, the pharmacologically effective dose of a present compound is in the amount ranging from about 1×10⁻⁶ to about 1 mg/kg body weight/day. The amount to be administered depends to some extent on the lipophilicity of the specific compound selected, since it is expected that this property of the compound will cause it to partition into fat deposits of the subject. The precise amount to be administered can be determined by the skilled practitioner in view of desired dosages, side effects and medical history of the patient and the like.

The cis-2,6-disubstituted piperidino analogs of the present invention exhibit selectivity for either neuronal nicotinic acetylcholine receptors and/or the dopamine transporter protein (DAT). The derivatives that are active towards the DAT, and those that interact with the DAT show only modest nicotinic receptor activity.

### TABLE 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ki (µM) [³H]Nicotine Binding Assay</th>
<th>Ki (µM) [³H]Dopamine Uptake Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. X₁ = X₂ = CH₂</td>
<td>0.0043</td>
<td>45</td>
</tr>
<tr>
<td>Y₁ = C—O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y₂ = (S)—CHOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. X₁ = X₂ = Y₁ = Y₂ = CH₂</td>
<td>14.3</td>
<td>3.0</td>
</tr>
<tr>
<td>3. X₁ = X₂ = Y₁ = CH₂</td>
<td>0.0041</td>
<td>39</td>
</tr>
<tr>
<td>Y₁ = C—O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y₂ = (S)—CHOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. X₁ = X₂ = CH₂</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Y₁ = Y₂ = C—O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. X₁, Y₁ = X₂, Y₂ = trans CH—CH</td>
<td>&gt;100</td>
<td>0.8</td>
</tr>
<tr>
<td>6. X₁ = CH₂</td>
<td>0.13</td>
<td>3.0</td>
</tr>
<tr>
<td>Y₁ = C—O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X₁, Y₂ = trans CH—CH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. X₁ = X₂ = CH₂</td>
<td>0.93</td>
<td>54</td>
</tr>
<tr>
<td>Y₁ = (S)—CHOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y₂ = (R)—CHOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. X₁ = X₂ = Y₁ = CH₂</td>
<td>0.16</td>
<td>8.9</td>
</tr>
<tr>
<td>Y₁ = (S)—CHOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. X₁ = CH₂</td>
<td>4.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Y₁ = (S)—CHOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X₁, Y₂ = trans CH—CH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The nine cis-2,6-disubstituted piperidino derivatives listed in Table 1 have the chemical structure of formula (II).

The nine cis-2,6-disubstituted piperidino analogs of the present invention exhibit selectivity for either neuronal nicotinic acetylcholine receptors and/or the dopamine transporter protein (DAT). The derivatives that are active towards the nicotinic receptor generally do not interact with the DAT, and those that interact with the DAT show only modest nicotinic receptor activity.

The nine compounds in Table 1 were evaluated in the high affinity [³H]nicotine binding assay and afforded inhibition constants (Ki values) ranging from 0.0043 µM to >100 µM. Five of these compounds were in the range of 4–160 nM. Three of these compounds were in the range of 0.93–14 nM. One compound was >100 µM. The cis-2,6-disubstituted piperidino derivatives listed in Table 1 were also assayed for inhibition of DAT activity, i.e., inhibition of [³H]DA uptake into the dopaminergic presynaptic terminal. Nine compounds were assayed and afforded inhibition constants (Ki values) ranging from 0.08 µM to 54 µM.

Removal of both functionalities of the lobeline molecule resulted in loss of affinity for the nicotinic receptor and a 100-fold more potent inhibition of the dopamine transporter compared with lobeline. Removal of either the hydroxyl group or the keto group of lobeline resulted in a 50-fold loss of affinity for the nicotinic receptor. Interestingly, the ketolobeline analog inhibited DAT 10-fold more potently than lobeline, whereas lobelanidine inhibited DAT equipotently compared to lobeline. Conversion of the hydroxy group of lobeline to a bulky tosloxy group reduced the affinity of the nicotinic receptor by only 3-fold, but did not alter the interaction with the DA transporter. The hydroxylobeline had a similar potency with the meso-transdiene (the most potent compound) in the DA uptake assay, but had 1000-fold lower affinity for the nicotinic receptor. Also, the completely defunctionalized lobeline molecule and the hydroxylalkene analog were both less potent than the meso-transdiene in inhibiting DA uptake into striatal synaptosomes. This data indicates that appropriate structural modification of the lobeline molecule affords compounds in which the interaction with DAT is enhanced. Furthermore, in one compound, i.e., the meso-transdiene, the nicotinic receptor interaction has been eliminated and the compound is thus selective for inhibition of DAT.

The invention will now be discussed by certain examples that illustrate but do not limit the invention.

### EXAMPLE 1

**Cis-2,6-di-trans-styryl piperidine**

1.00 g (2.95 mmol) of lobelanidine was dissolved in 15 ml of 85% H₃PO₄ and allowed to stir overnight at 60° C. The reaction mixture was taken up in H₂O and made basic with solid K₂CO₃ (pH–8). The pH was adjusted by the addition of solid NaOH (pH–10). The aqueous solution was extracted three times with 15 ml of EtOAc. The organic layers were combined and dried over anhydrous MgSO₄. The salts were removed via filtration and solvent removed by rotary evaporation affording 0.70 g of crude product. This compound was recrystallized from MeOH affording 0.60 g of pure cis-2,6-di-trans-styryl piperidine. Percent yield = 78.6%.

### EXAMPLE 2

**Cis-28,6R,8S-2-[6-β-paramethoxyphenethyl]-1-methyl-2-piperidyl]-acetophenone**

1.00 g (2.58 mmol) of lobeline hemisulfate was dissolved in 25 ml of pyridine and was added dropwise to a solution (cooled to 0° C) containing 0.60 g (3.14 mmol) of p-toluenesulfonyl chloride dissolved in 15 ml of pyridine. After addition, the reaction was allowed to stir for 2 hours and then poured into 50 ml of ice-cold water and the mixture...
was stirred for an additional two hours. The aqueous solution was extracted three times with 25 ml of EtOAc. The organic layers were combined and dried with anhydrous MgSO₄. The salt was removed by filtration and the organic layers were combined and dried with anhydrous MgSO₄. The aqueous solution was extracted with ethyl acetate, and the solvent was removed by rotary evaporation affording 0.75-0.80 g of a yellow oil. The compound was purified by silica gel chromatography eluting with EtOAc to afford 0.25 g of the product. The yield was 50.6%. ¹³C NMR (CDCl₃): δ: 7.50-7.50 (d, 1H), 7.50-7.60 (d, 2H), 6.85-6.90 (d, 2H) and 8.95 (s, 1H). ¹³C NMR (CDCl₃): δ: 21.16, 22.25, 23.32, 23.55, 27.35, 38.29, 40.18, 40.07, 60.79, 63.69, 71.05, 125.56, 125.76, 127.39, 128.28, 128.44, 128.69, 128.77, 133.67, 133.96, 135.87, 140.03, 141.98, 144.47 and 195.21 ppm.

EXAMPLE 3

Cis-2S,6R-N-methyl-6-phenacyl-2-trans-styrylpiperidine

1.00 g (2.58 mmol) of lobeline hemisulfate was dissolved in 15 ml of 85% H₂PO₄ and the solution was allowed to stir for 24 hrs at 50°C. Phosphoric acid was then neutralized with K₂CO₃ and a little ice cold H₂O was added to dissolve the solid. The aqueous solution was extracted with ethyl acetate (20 ml×3). The organic layers were combined and dried with anhydrous MgSO₄. The salts were removed by filtration and the solvent was removed via rotary evaporation affording 0.60 g of a gummy solid, which contained mainly the trans isomer. Percent yield=84.6%. ¹³N NMR (300 MHz, CDCl₃): δ: 1.15-1.60 (m, 6H), 2.47-2.71 (m, 3H), 3.16-3.34 (dd, 1H), 5.80-6.00 (dd, 1H), 6.18-6.28 (d, 1H), and 6.90-7.38 (m, 8H) and 7.64-7.80 (d, 2H). ¹³C NMR (CDCl₃): δ: 23.52, 32.56, 33.17, 40.52, 44.02, 59.62, 68.08, 126.00, 127.15, 127.92, 128.36, 128.44, 130.29, 132.91, 133.91, 136.95, 136.99 and 198.83 ppm.

EXAMPLE 4

Cis-10S,2S,6R-N-methyl-6-[1-(2-hydroxy-2-phenyl)-ethyl]-2-trans-styrylpiperidine

In a 250 ml round bottom flask was added 0.8 g of cis-2S,6R-N-methyl-6-phenacyl-2-trans-styrylpiperidine, and 50 ml of ethanol. Sodium borohydride was added until all of the starting material was consumed (determined by TLC). The solution was cooled to 0°C and ace tone was added in small portions to quench the reaction. The solvents were evaporated to dryness and water was added by precipitation of 0.75 g of an off-white crystalline solid (1:1 mixture of diastereomers, which was purified on silica eluting with 75:25 (CHCl₃/ethyl alcohol). The yield of the product (a mixture of diastereomers) was 93.4%. ¹³N NMR (300 MHz, CDCl₃): δ: 1.17-2.06 (m, 12H), 2.12 (s, 3H), 2.35 (s, 3H), 2.50-6.20 (m, 4H), 2.70-3.20 (m, 4H), 4.78-4.80 (dd, 1H), 5.04-5.14 (dd, 1H), 5.96-6.20 (m, 2H), 6.32-6.42 (dd, 2H) and 7.04-7.34 (m, 20H). ¹³C NMR (CDCl₃): δ: 23.69, 24.15, 26.74, 29.08, 33.26, 39.94, 41.10, 41.41, 62.93, 63.00, 65.62, 68.32, 71.76, 73.90, 125.46, 126.15, 126.19, 126.83, 127.01, 127.37, 128.16, 128.23, 128.50, 130.58, 132.61, 133.85, 136.83, 136.95, 145.32 and 145.45 ppm.

EXAMPLE 5

Cis-2S,6R-N-methyl-6-[1-(2-hydroxy-2-phenyl)ethyl]-2-phenylethylpiperidine

0.50 g (1.55 mmol) of cis-2S,6R-N-methyl-6-phenacyl-2-trans-styrylpiperidine was dissolved in 50 ml of ethanol and placed into a Parr hydrogenation apparatus with 0.10 g of 10% Pd-on-Carbon. After removal of air, hydrogen gas was introduced until a pressure of 40 psig was reached. The reaction was allowed to proceed for 48 hrs. The Pd catalyst was removed through filtration with Celite, and ethanol was removed by rotary evaporation to afford 0.30 g of a yellow oil. The compound was purified by silica gel chromatography eluting with EtOAc to afford 0.25 g of the product. The yield was 50.6%. ¹³C NMR (300 MHz, CDCl₃): δ: 7.50-7.60 (m, 6H), 3.16-3.34 (dd, 1H), 5.80-6.00 (dd, 1H), 6.18-6.28 (d, 1H), and 6.90-7.38 (m, 8H) and 7.64-7.80 (d, 2H). The yield of the product (a mixture of diastereomers, which was purified on silica eluting with EtOAc to afford 0.30 g of a yellow oil. The compound was purified by silica gel chromatography eluting with EtOAc to afford 0.25 g of the product. The yield was 50.6%. ¹³C NMR (CDCl₃): δ: 23.52, 32.56, 33.17, 40.52, 44.02, 59.62, 68.08, 126.00, 127.15, 127.92, 128.36, 128.44, 130.29, 132.91, 133.91, 136.95, 136.99 and 198.83 ppm.

EXAMPLE 6

High Affinity [³H]Nicotine Binding Assay

The ability to displace S(-)-[³H]NIC binding from rat striatal membranes to assess interaction with the α4β2 subtype was determined. The [³H]NIC binding assay was performed according to previously published methods (Romano et al., 1980; Marks et al., 1986; Crooks et al., 1995). Striata from two rats were dissected, pooled and homogenized with a Tekmar polytron mixer in 250 mM Tris buffer (pH 7.5). The homogenate was incubated at 37°C for 5 minutes to promote hydrolysis of endogenous acetylcholine, and centrifuged at 15,000 g for 20 minutes and the pellet was resuspended in 10 vol of ice-cold distilled water and incubated at 37°C for 5 minutes, followed by centrifugation at 15,000 g for 20 min. The pellet containing the striatal membranes was resuspended in 10 vol of fresh ice-cold 1% Krebs-HEPES buffer and incubated at 37°C for 10 min after which it was centrifuged at 15,000 g for 20 minutes. The latter sequence of resuspension, incubation and centrifugation was repeated. The pellet was frozen under fresh Krebs-HEPES buffer and stored at -40°C until assay. Upon assay, the pellet was resuspended in Krebs-HEPES buffer, incubated at 37°C for 5 minutes and centrifuged at 15,000 g for 20 min. The final pellet was resuspended in 3.6 ml of ice-cold water which provides for approximately 200 μg protein/100 μl aliquot. Competition assays were performed in duplicate in a final volume of 200 μl Krebs-HEPES buffer containing 250 mM Tris buffer (pH 7.5 at 4°C). Reactions were initiated by addition of 100 μl of membrane suspension to 3 nM [³H]NIC (50 μl) and 1 of at least 9 concentrations of analog (50 μl). After 90 minutes incubation at 4°C, reactions were terminated by dilution of the samples with 5 ml of ice-cold buffer followed immediately by filtration through a Whatman GF/B glass fiber filters (presoaked in 0.5% polyethyleneimine (PEI) using a Brandel Cell Harvester. Filters were rinsed 3x with 3 ml of ice-cold buffer, transferred to scintillation vials and 5 ml scintillation cocktail added. Nonspecific binding was defined as binding in the presence of 10 μM NIC. For competition curves, the IC₅₀ values were corrected for ligand concentration (Cheng et al., 1973).

EXAMPLE 7

[³H]Dopamine ([³H]DA) Uptake Assay, Striatal Synaptosomal Preparation

[³H]DA uptake was performed according to a modification of the previously reported methods (Dwoskin et al., 1999). Striata were homogenized in 20 ml of ice-cold
Cotinine, the major brain metabolite of nicotine, stimulates nicotinic receptors to interact with both nicotinic receptors and DAT. These combinations of pharmacological activity are considered to be beneficial for the treatment of psychostimulant abuse and withdrawal, eating disorders, and central nervous system diseases and pathologies.

The foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalence thereof may be resorted to, falling within the scope of the invention claimed.

REFERENCES

The pertinent disclosures of the references listed below and as discussed above herein are incorporated herein by reference.


Cheng Y. C. et al., “Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 percent inhibition (I_{50}) of an enzymatic reaction,” Biochem. Pharmacol., 1973; 22: 3099–3108.


What is claimed is:

1. A method of treating an individual for dependence on a drug of abuse or withdrawal from a drug of abuse comprising administering to the individual an effective amount of a cis-2,6-substituted piperidino compound or pharmaceutically effective salt thereof comprising formula (I):

\[ R_1 \text{ and } R_4 \text{ are the same or are independently different from one another and represent a saturated carbon-carbon bond, a cis-carbon-carbon double bond, a trans-carbon-carbon double bond, a carbon-carbon triple bond; a saturated sulfur-carbon bond, a saturated selenium-carbon bond, an oxygen-carbon bond, a saturated nitrogen-carbon bond, a N-alkyl substituted saturated nitrogen-carbon bond where said alkyl is a lower straight chain or branched alkyl, a nitrogen-carbon double bond, or a nitrogen-nitrogen double bond; } \]

R1 and R4 are the same or are independently different from one another and represent a saturated or unsaturated hydrocarbon ring with an ortho-, meta- or para-substituted moiety selected from the group consisting of hydrogen, methyl, ethyl, C3-C7 alkyl, vinyl, allyl, C4-C6 alkenyl, benzyl, phenylethyl, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carboxaldehyde, acetoxy, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-methylaminoethyl, N,N-dimethylaminomethyl, N,N-dimethylaminomethylcarboxamide, N,N-dimethylcarboxamide, N,N-dimethylcarboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, thiol, methylthio, ethylthio, propiophiol, fluoro, chloro, bromo, iodo, trifluoromethyl, propargyl, nitro, carbamoyl, ureido, azido, isocyanate, thioisocyanate, hydroxylamino, and nitroso.

2. The method of claim 1, wherein said drug of abuse is selected from the group consisting of cocaine, amphetamine, caffeine, nicotine, pentylcyclidine, opiates, barbiturates, benzodiazepines, canabinoids, hallucinogens, and alcohol.

3. The method of claim 1, wherein said administering of the compounds is perfromed subcutaneously, intramuscularly, intravenously, orally, intranasally, intrapulmonary or rectally.

4. The method of claim 1, wherein said administering of the compound inhibits uptake of dopamine by cells of the central nervous system of the individual.

5. The method of claim 1, wherein said administering of the compound inhibits binding of neurotransmitters or drugs to nicotinic receptors on cells of the central nervous system of the individual.

6. The method of claim 1, wherein the saturated hydrocarbon ring includes cyclobutane, cyclopentane, cyclohexane, cycloheptane or cyclooctane.

7. The method of claim 1, wherein the unsaturated hydrocarbon ring includes benzene, cyclopentene, cyclohexene, cycloheptene, cyclooctene or cyclocapandiene.

8. The method of claim 1, wherein the nitrogen containing heterocyclic moiety includes azetine, piperidine, piperazine, pyrazine, pyrazole, pyrazolidine, imidazole imidazoline, pyrimidine, hexa-hydropyrimidine, pyrrole, pyrrolidine, fumaric acid, acetoxy, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethylcarboxamide, N,N-dimethylcarboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, thiol, methylthio, ethylthio, propiophiol, fluoro, chloro, bromo, iodo, trifluoromethyl, propargyl, nitro, carboxamide, ureido, azido, isocyanate, thioisocyanate, hydroxylamino, and nitroso.

9. The method of claim 1, wherein the oxygen containing heterocyclic moiety includes furan, tetrahydrofuran, 2,5-dihydrofuran, pyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane or 1,4-oxathianin.

10. The method of claim 1, wherein the saturated sulfur containing heterocyclic moiety includes thietane, thiophene, 2,5-dihydrothiophene, 1,3-dithiane, 1,2-dithiolium, 1,2-dithiolium, thiane, 1,2-dithiane, 1,3-dithiane, 1,4-thiopyran.

11. The method of claim 1, wherein the selenium containing heterocyclic moiety is selenophene.

12. The method of claim 1, wherein the mixed heterocyclic moiety is thiazolidine, thiazole or oxazin.

13. The method of claim 1, wherein the substituted benzene includes at least one substituent selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, amino, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carboxaldehyde, acetoxy, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, N,N-dimethylcarboxamide, N,N-dimethylcarboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl,
chloro, bromo, iodo, trifluoromethyl, vinyl, allyl, propargyl, nitro, carbamoyl, ureido, azido, isocyanate, thioisocyanate, hydroxylamino, and nitroso; or a hydrocarbon or heterocyclic ring comprising pyridyl, furanyl, naphthyl, thiazole, selenothienyl, oxazolyl, 1,2,3-triazole, 1,2,4-triazole, imidazoline, pyrimidine, pyridazine or triazine.

16. The method of claim 1, wherein the pharmaceutical salts are hydrochloride, hydrobromide, sulfate, hydrogensulfate, citrate, fumarate and tartrate salts of said compound.

17. The method of claim 15, wherein the pharmaceutical salts are hydrochloride, hydrobromide, sulfate, hydrogensulfate, citrate, fumarate and tartrate salts of said compound.

18. The method of claim 1, wherein said lower straight chain or branched alkyl contains one to seven carbon atoms.

19. The method of claim 18, wherein said alkyl is methyl or ethyl.

20. The method of claim 15, wherein said lower straight chain or branched alkyl contains one to seven carbon atoms.

21. The method of claim 20, wherein said alkyl is methyl or ethyl.

22. The method of claim 1, wherein said compound is cis-2S,0R,8S-2-[6-[p-para-toluenesulfonyloxyphenethyl]-1-methyl-2-piperidyl]-acetophenone.

23. The method of claim 1, wherein said compound is cis-2S,6R-N-methyl-0-[1-(2-hydroxy-2-phenylethyl)-2-phenylethylpiperidine.

24. A cis-2,6-substituted piperidino compound or pharmaceutically effective salt thereof comprising formula (I):
carbon-carbon bonds, \( Y^1 \) and \( Y^2 \) cannot be CHOR or C=O, wherein \( R \) is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, amino, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carbalkaldehyde, acetoxyl, propionyloxyl, isopropionyloxyl, cyano, aminothiol, N-methylaminothiol, N,N-dimethylaminothiol, carbainide, N-methylcarbainide, N,N-dimethylcarbainide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isoproxy, thiol, methylthio, ethylthio, propiothiol, fluoro, chloro, bromo, iodo, trifluoroethyl, propargyl, nitro, carbamoyle, ureido, azido, isocyanate, thiocyanate, hydroxylamino, and nitroso.

24. The compound of claim 23, wherein the unsaturated hydrocarbon ring includes benzene, cyclopentene, cyclohexene, cycloheptene, cyclooctene or cyclopentadiene; the nitrogen containing heterocyclic moiety includes azetine, piperidine, pyrroline, pyrazoline, pyrimidine, oxazine, triazine, 1,2,4-triazine, 1,2,3-triazole, 1,2,4-triazole, pyridine or pyridazine; the oxygen containing heterocyclic moiety includes furan, tetrahydrofuran, 2,5-dihydrofuran, pyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane or 1,4-oxathin; the sulfur containing heterocyclic moiety includes thiophene, thiophene, 2,5-dihydirothiophene, 1,3-dithiolane, 1,2-dithiolane, 1,2-dithiane, 1,2-dithiane, 1,3-dithiane, 1,4-dithiane, or tripyranylum; the selenium containing heterocyclic moiety includes selenazole, thiazole or oxazin; and the substituent for the substituted benzene includes at least one member selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, amino, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carbalkaldehyde, acetoxyl, propionyloxyl, isopropionyloxyl, cyano, aminothiol, N-methylaminothiol, N,N-dimethylaminothiol, carbainide, N-methylcarbainide, N,N-dimethylcarbainide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isoproxy, thiol, methylthio, ethylthio, propiothiol, fluoro, chloro, bromo, iodo, trifluoroethyl, propargyl, nitro, carbamoyle, ureido, azido, isocyanate, thiocyanate, hydroxylamino, and nitroso.

25. The compound of claim 24, wherein the saturated hydrocarbon ring includes cyclobutane, cyclopentane, cyclohexane, cycloheptane or cyclooctane.

26. The compound of claim 24, wherein the unsaturated hydrocarbon ring includes benzene, cyclopentene, cyclohexane, cycloheptene, cyclooctene or cyclopentadiene.

27. The compound of claim 24, wherein the nitrogen containing heterocyclic moiety includes azetine, piperidine, pyrroline, pyrazoline, pyrimidine, oxazine, triazine, 1,2,4-triazine, 1,2,3-triazole, 1,2,4-triazole, pyridine or pyridazine.

28. The compound of claim 24, wherein the oxygen containing heterocyclic moiety includes furan, tetrahydrofuran, 2,5-dihydrofuran, pyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane or 1,4-oxathin.

29. The compound of claim 24, wherein the unsaturated sulfur containing heterocyclic moiety includes thiophene, thiophene, 2,5-dihydrothiophene, 1,3-dithiolane, 1,2-dithiolane, 1,2-dithiane, 1,2-dithiane, 1,3-dithiane, 1,4-dithiane, 1,2-thiaprylamyl, or thiopyranylum.

30. The compound of claim 24, wherein the selenium containing heterocyclic moiety is selenophene.

31. The compound of claim 24, wherein the mixed heterocyclic moiety is thiazolidine, thiazole or oxazin.

32. The compound of claim 24, wherein the substituted benzene includes at least one substituent selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, amino, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carbalkaldehyde, acetoxyl, propionyloxyl, isopropionyloxyl, cyano, aminothiol, N-methylaminothiol, N,N-dimethylaminothiol, carbainide, N-methylcarbainide, N,N-dimethylcarbainide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isoproxy, thiol, methylthio, ethylthio, propiothiol, fluoro, chloro, bromo, iodo, trifluoroethyl, propargyl, nitro, carbamoyle, ureido, azido, isocyanate, thiocyanate, hydroxylamino, and nitroso.

33. The compound of claim 24, wherein the saturated hydrocarbon ring includes cyclobutane, cyclopentane, cyclohexane, cycloheptane or cyclooctane; the unsaturated hydrocarbon ring includes benzene, cyclopentene, cyclohexene, cycloheptene, cyclooctene or cyclopentadiene; the nitrogen containing heterocyclic moiety includes azetine, piperazine, pyrazine, pyrazole, pyrazolidine, imidazole imidazoline, pyrimidine, hexahydroprymidine, pyrrole, pyrrolidine, triazine, 1,2,3-triazole, 1,2,4-triazole, pyridine or pyridazine; the oxygen containing heterocyclic moiety includes furan, tetrahydrofuran, 2,5-dihydrofuran, pyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane or 1,4-oxathin; the sulfur containing heterocyclic moiety includes thiophene, thiophene, 2,5-dihydrothiophene, 1,3-dithiolane, 1,2-dithiolane, 1,2-dithiane, 1,2-dithiane, 1,3-dithiane, 1,4-dithiane, or tripyranylum; the selenium containing heterocyclic moiety includes selenazole, thiazole or oxazin; and the substituent for the substituted benzene includes at least one member selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, amino, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carbalkaldehyde, acetoxyl, propionyloxyl, isopropionyloxyl, cyano, aminothiol, N-methylaminothiol, N,N-dimethylaminothiol, carbainide, N-methylcarbainide, N,N-dimethylcarbainide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isoproxy, thiol, methylthio, ethylthio, propiothiol, fluoro, chloro, bromo, iodo, trifluoroethyl, propargyl, nitro, carbamoyle, ureido, azido, isocyanate, thiocyanate, hydroxylamino, and nitroso.

34. The compound of claim 24, wherein when either \( X^1 \) or \( X^2 \) is a saturated carbon-carbon bond, \( Y^1 \) or \( Y^2 \) represents CH2, CH—OH, CHO-alkyl where said alkyl is a lower straight chain or branched alkyl, CH—OSO2—C6H5, CH—OSO2—p-C6H4CH3, CH—SH, CH—S—alkyl where said alkyl is a lower straight chain or branched alkyl, CH—NO2, CH—CF3, CH—NHOH, CH—OCHO, CH—F, CH—Cl, CH—Br, CH—I, CH—NH2, CH—NH—alkyl where said alkyl is a lower straight chain or branched alkyl, CH—N(alkyl) where said alkyl is a lower straight chain or branched alkyl, CH—N—alkyl where said alkyl is a lower straight chain or branched alkyl, CH—N—O or C=O, C=S, CH—O—phenyl, substituted CH—O— phenyl where the substituent is at least one
member selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, amino, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carboxaldehyde, acetoxo, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N-methylcarboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxy, methoxy, ethoxy, propoxy, isoproxy, thiol, methylthio, ethylthio, propiothiol, fluoro, chloro, bromo, iodo, trifluoromethyl, vinyl, allyl, propargyl, nitro, carbamoyl, ureido, azido, isocyanate, thioisocyanate, hydroxylamino, and nitroso; or a hydrocarbon or heterocyclic ring comprising pyridyl, furanyl, naphthyl, thiazole, selenothienyl, oxazolyl, 1,2,3-triazole, 1,2,4-triazole, imidazoline, pyrimidine, pyridazine or triazine.

35. The compound of claim 24, wherein the pharmaceutical salts are hydrochloride, hydrobromide, sulfate, hydrosulfate, citrate, fumarate and tartrate salts of said compound.

36. The method of claim 34, wherein the pharmaceutical salts are hydrochloride, hydrobromide, sulfate, hydrosulfate, citrate, fumarate and tartrate salts of said compound.

37. The compound of claim 24, wherein said lower straight chain or branched alkyl contains one to seven carbon atoms.

38. The method of claim 37, wherein said alkyl is methyl or ethyl.

39. The method of claim 34, wherein said lower straight chain or branched alkyl contains one to seven carbon atoms.

40. The method of claim 39, wherein said alkyl is methyl or ethyl.

41. The compound of claim 24, wherein said compound is cis-2S,6R,8S-2-[6-para-toluenesulfonyloxyphenethyl]-1-methyl-2-piperidyl-acetophenone.

42. The compound of claim 24, wherein said compound is cis-2S,6R-N-methyl-6-[1-(2-hydroxy-2-phenyl)ethyl]-2-phenylethylpiperidine.