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

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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

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Prior Publication Data

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

![Chemical Structure](image)

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

Related U.S. Application Data
Division of application No. 09/628,557, filed on Jul. 28, 2000, now Pat. No. 6,455,543.

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Primary Examiner—Zinna Northington Davis
Attorney, Agent, or Firm—McDermott Will & Emery LLP

ABSTRACT
Cis-2,6-disubstituted piperidine analogs, or lobeline analogs, having the general formula:
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 nonpyridine, 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; Broussolle 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 dihydrotetabenazine (DTBZ) site on vesicular monoamine transporter-2 (VMAT2), thus increasing the cytosolic DA available for reverse transport by the plasma membrane transporter (DAT) (Teng 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 piperidine 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.
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 R² are the same or are independently different from one another and represent hydrogen or a lower straight chain or branched alkyl or R¹ and R² together form a ring including a —CH—, —CH₂—, —CH₂—CH—, —cis-CH=CH—, —cis-CH₂—CH=CH— or —cis-CH=CH— CH₂— 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 and sulfur; and an ortho, para 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, CHO or C=O, and Y² cannot be CH₂, CHO or C=O.

It is prefered that when R² and/or R³ is a saturated hydrocarbon ring, the ring includes, but is not limited to, cyclobutane, cyclopentane, cyclohexane, cycloheptene or cyclooctene, 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 saturated 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 further preferred that when R² and/or R³ is a nitrogen containing heterocyclic moiety, the moiety includes, but is not limited to, azetine, piperdine, piperazine, pyrazine, pyrazole, pyrazolidino, imidazolino, pyrimidine, pyridazine or phenyl groups are methyl and ethyl.

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, piperazine, pyrazine, pyrazole, pyrazolidino, imidazolino, pyrimidine, pyridazine or phenyl groups are methyl and ethyl.

It is preferred that when R² and/or R³ is a nitrogen containing heterocyclic moiety, the moiety includes, but is not limited to, azetine, piperdine, piperazine, pyrazine, pyrazole, pyrazolidino, imidazolino, pyrimidine, pyridazine or phenyl groups are methyl and ethyl.
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 1x10^{-5} 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 nicotinic receptor generally do not interact with the DAT; and those that interact with the DAT show only modest nicotinic receptor activity.

The nine cis-2,6-disubstituted piperidino derivatives listed in Table 1 have the chemical structure of formula (H). They were assayed for nicotinic receptor interaction and affinity [3H]nicotine binding assay and afforded inhibition constants (Ki values) ranging from 0.0043 uM to >100 uM. 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 uM. 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 evaluated and afforded inhibition constants (Ki values) ranging from 0.08 uM to 54 uM.

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 ketolactone 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 hydroxyalkene 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 hydroxyalkene 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-styrylpiperidine**

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-styrylpiperidine. Percent yield=78.6% Mp=139-141°C. 1H NMR (300 MHz, CDCl₃) δ: 1.40-1.80 (m, 1H), 2.23 (s, 3H), 2.50-2.64 (t, 2H), 6.04-6.20 (t, 2H), 6.39-6.50 (d, 2H) and 7.10-7.38 (m, 10H). 13C NMR (CDCl₃) δ: 23.75, 33.56, 42.32, 68.36, 126.26, 127.38, 128.61, 133.89 and 137.13 ppm.

### EXAMPLE 2

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

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 over anhydrous Na₂SO₄. The salts were removed by filtration and the solvent was removed by rotary evaporation affording 450 mg of a pink-colored compound. The product was recrystallized from acetone yielding 300 mg of the product. Percent yield=21.6%. 

H NMR (300 MHz, CDCl₃) δ: 1.30–1.98 (m, 6H), 2.20 (s, 3H), 2.63–2.74 (d, 3H), 2.95–3.20 (m, 2H), 3.61–3.78 (d, 1H), 3.83–4.12 (m, 2H), 4.50–4.72 (m, 1H), 4.80–4.90 (d, 1H), 6.90–7.00 (d, 2H), 7.10–7.70 (m, 8H), 7.50–7.60 (d, 2H), 7.80–7.90 (d, 2H) and 9.85 (s, 1H); 13 C NMR (CDCl₃) 23.52, 32.56, 33.17, 33.95, 40.18, 40.07, 60.79, 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 hemisulphate was dissolved in 15 ml of 85% H₃PO₄ 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 salts. The aqueous solution was extracted with acetone (20 ml x 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%. 

H NMR (300 MHz, CDCl₃) 1.15–1.60 (m, 6H), 2.02 (s, 3H), 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); 13 C NMR (CDCl₃) 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,25S,6R- and Cis-10S,25S,6R-N-methyl-6-[(2-hydroxy-2-phenyl)-ethyl]-2-trans-styrylpiperidine

In a 250 ml round bottom flask was added 0.80 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 acetone was added in small portions to quench the reaction. The solvents were evaporated to dryness and water was added precipitating 0.75 g of an off-white crystalline solid (1:1 mixture of diastereomers, which was purified on silicagel eluting with 75:25 (CHCl₃/EtOH). The yield of the product (a mixture of diastereomers) was 93.4%. 

H 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, 4H); 13 C NMR (CDCl₃) δ: 23.69, 24.15, 26.74, 29.68, 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-[(2-hydroxy-2-phenyl)ethyl]-2-phenacylpyridine 

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 50.0%. 

H NMR (300 MHz, CDCl₃) δ: 0.70–0.90 (m, 6H), 1.18 (s, 3H), 1.40–1.90 (m, 6H), 2.44–2.56 (m, 2H), 4.56–4.60 (dd, 1H) and 7.04–7.30 (m, 10H); 13 C NMR (CDCl₃) δ: 25.77, 29.24, 29.38, 29.42, 29.46, 29.68, 31.44, 35.93, 39.07, 74.64, 125.50, 125.85, 127.42, 128.17, 128.35, 128.37, 142.85 and 144.91 ppm. 

EXAMPLE 6

High Affinity [3H]Nicotine Binding Assay

The ability to displace S-(-)[3H]nicotine binding from rat striatal membranes to assess interaction with the c4δ2 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 in 10 ml of ice-cold modified Krebs-HEPES buffer (in mM: 20 HEPES, 118 NaCl, 4.8 KCl, 2.5 CaCl₂, 1.2 MgSO₄, adjusted to pH to 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 ml 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 ml of fresh ice-cold 10% 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 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]nicotine (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 3 ml of ice-cold buffer followed immediately by filtration through a Whatman GF/B glass fiber filters (presoaked in 0.5% polyethylenimine (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 nicotine. For competition curves, the IC₅₀ values were corrected for ligand concentration (Cheng et al., 1973).
sucre solution (0.32 M sucrose and 5 mM sodium bicarbonate, pH 7.4) with 12 passes of a teflon-pestle homogenizer (clearance approximately 0.003 in). The homogenate was centrifuged at 2,000 g, 4°C for 10 min. The supernatant was centrifuged at 12,000 g, 4°C for 20 minutes. The resulting pellet was resuspended in 1.5 ml ice-cold assay buffer (in mM; 125 NaCl, 5 KCl, 1.5 KH2PO4, 1.5 MgSO4, 1.25 CaCl2, 10 glucose, 0.1 L-ascorbate, 25 HEPES, 0.1 EDTA and 0.1 pargyline; pH 7.4). The final protein concentration was 400 μg/ml. Assays were performed in duplicate in a total vol of 500 μl. Aliquots (50 μl synapticosomal suspension containing 20 μg of protein) were added to assay tubes containing 350 μl buffer and 50 μl of 1 of 9 concentrations (final concentration, 1 nM-1 mM) of analog or vehicle. Synaptosomes were incubated at 34°C for 10 min before the addition of 50 μl of [3H]DA (30.1 Ci/mole, final concentration 10 nM) and incubation proceeded for 10 min at 34°C. High affinity uptake was defined as the difference between accumulation in the absence and presence of 10 μM GBR 12935. Preliminary studies demonstrated that at 10 minutes [3H]DA uptake is within the linear range of the time-response curve when experiments are performed at 34°C. Accumulation was terminated by addition of 3 ml ice-cold assay buffer containing 1 mM pyrocatechol and rapid filtration through a Whatman GF/B glass fiber filter paper (presoaked with buffer containing 1 mM pyrocatechol) using a Brandel Cell Harvester. The filters were washed 3 times with 3 ml of 10 ml ice-cold buffer containing 2 mM pyrocatechol, and then transferred to scintillation vials and radioactivity determined (Packard Model B1600TR scintillation counter, Meriden, Conn.). Protein concentration was determined using bovine serum albumin as the standard (Bradford, 1976). Competition curves for analog inhibition of [3H]DA uptake were generated. Nonlinear regression analysis was used to fit curves either in the absence or presence of 9 concentrations of analog. IC50 values were corrected for concentration of free [3H]DA (Cheng-Prusoff, 1973) to yield true inhibition constants (Ki=IC50/[1+c/Km]), where c is the concentration of free [3H]DA and Km is the concentration of analog at which half maximal [3H]DA uptake is achieved. These values (Ki) were converted to pKi by statistical analysis.

In the examples listed in the Table, a series of cis-2,6-disubstituted piperidines, structurally related to lobeline, were synthesized and tested for activity in the high affinity nicotinic receptor binding assay and the dopamine uptake assay to assess the interaction of these piperidines with these specific proteins on the presynaptic terminal of dopaminergic neurons in the CNS. Some of these compounds have greater selectivity for interaction with DAT than for interaction with nicotinic receptors, whereas other compounds interact with both nicotinic receptors and DAT, more similar to lobeline. Other compounds were more selective for the nicotinic receptor than 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.


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):

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[Chemical Structure Image]
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wherein:

\[ X^1-Y^1 \] 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 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;

\[ R^1 \] and \[ R^4 \] are the same or are independently different from one another and represent a saturated or unsaturated hydrocarbon group; 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 and sulfur; and an ortho, meta or para-substituted benzene.

with the proviso that when \[ R^2 \] and \[ R^3 \] are unsubstituted phenyl groups and \[ X^1-Y^1 \] and \[ X^2-Y^2 \] are saturated carbon-carbon bonds, \[ Y^1 \] and \[ Y^2 \] cannot be \( \text{CH}=\text{CH} \) or \( \text{CH}==\text{CH} \); and with the further proviso that when \[ R^2 \] and \[ R^3 \] are unsubstituted phenyl or substituted phenyl groups having an alkyl, alicyclic or cyclic group as substituents and \[ X^1-Y^1 \] and \[ X^2-Y^2 \] are saturated nitrogen-carbon bonds, \[ X^1 \] and \[ X^2 \] cannot be \( \text{C}=\text{O} \); and with the further proviso that when \[ X^1-Y^1 \] and \[ X^2-Y^2 \] are saturated carbon-carbon bonds, \[ X^1 \] and \[ X^2 \] cannot be \( \text{CH}=\text{CH} \) or \( \text{CH}==\text{CH} \); and \[ Y^1 \] and \[ Y^2 \] cannot be \( \text{CH}=\text{OH} \) or \( \text{CH}==\text{OH} \); and with the further proviso that when \[ X^1-Y^1 \] and \[ X^2-Y^2 \] are carbon-carbon double bonds, \[ R^2 \] and \[ R^3 \] cannot be a saturated or unsaturated hydrocarbon ring with an ortho-, meta- or para substituted moiety selected from the group consisting of hydrogen, methyl, ethyl, \( \text{C}_3-\text{C}_7 \) straight chain or branched alkyl, \( \text{C}_3-\text{C}_9 \) cycloalkyl, vinyl, allyl, \( \text{C}_4-\text{C}_9 \) alkenyl, benzyl, phenylethyl, N-methylamino, N,N-dimethylamino, carboxylate, methylecarboxylate, ethylecarboxylate, propylcarboxylate, isopropylcarboxylate, carboxaldehyde, acetoxy, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N-methylecarboxamide, N,N-dimethylecarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, thiol, methythio, 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, phencyclidine, opiates, barbiturates, benzodiazepines, canabinoids, hallucinogens, and alcohol.

3. The method of claim 1, wherein said administering of the compounds is performed subcutaneously, intramuscularly, intravenously, transdermally, 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 neurotransmitter 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, cycloenpentene, cyclohexene, cyclooctene or cyclocapentaene.

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, triazine, 1,2,3-triazole, 1,2,4-triazole, pyridine or pyridazine.

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-oxathin.

10. The method of claim 1, wherein the unsaturated sulfur containing heterocyclic moiety includes thiocane, thiophene, thiothene, 2,5-dihydrothiophene, 1,3-dithiolium, 1,3-dithioline, 1,2-dithiolium, 1,2-dithiolen, thiane, 1,2-dithiane, 1,3-dithiane, 1,4-dithiyl, or thiopyranium.

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, methylecarboxylate, ethylecarboxylate, propylcarboxylate, isopropylcarboxylate, carboxaldehyde, acetoxy, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N-methylecarboxamide, N,N-dimethylecarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl,
methoxy, ethoxy, propoxy, isopropoxy, thiol, methylthio, ethylthio, propionylthio, fluoro, chloro, bromo, iodo, trifluoromethyl, vinyl, allyl, propargyl, nitro, carbamoyl, ureido, azido, isocyanate, thioisocyanate, hydroxylamino, and nitroso.

14. The method of claim 1, 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, piperidine, piperezine, pyrazine, pyrazolide, imidazoline, pyrimidine, oxadiazine, pyrazoline, imidazole, imidazoline, pyrimidine, hexahydropyrimidine, pyrrole, pyridylidine, 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, thiophene, 2,5-dihydrothiophene, 1,3-dithiolium, 1,3- dithiolane, 1,2-dithiolium, 1,2-dithiolane, thiane, 1,2-dithiane, 1,3-dithiane, or thiopyran; the selenium containing heterocyclic moiety includes selene naphene; the mixed heterocyclic moiety includes thiadiazole, thiazole or oxazine; and the substituent for the substituted benzene includes at least one member selected from the group consisting of methyl, ethyl, isopropyl, tert-butyl, sec-butyl, isobutyl, amino, N-methylamino, N,N-dimethylamino, carboxylate, methacryloxyacrylate, ethylcarboxylate, propynylcarboxylate, isopropylcarboxylate, carboxaldehyde, aceytoxy, propionyloxy, isopropionyloxy, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxanide, N,N-dimethylcarboxamide, N-N dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, propionyl, methoxy, ethoxy, propoxy, isopropoxy, thiol, methylthio, ethylthio, propionylthio, 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, seleniumenyl, oxazolyl, 1,2,3-triazole, 1,2,4-triazole, imidazoline, pyrimidine, pyrazidine or triazine.

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

17. The method of claim 15, wherein the pharmaceutical salts are hydrochloride, hydrobromide, sulfate, hydrosulfate, 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-β-(para-toluenesulfonyl)oxyphenethyl]-1-methyl-2-piperidyl]-acetophenone.

23. The method of claim 1, wherein said compound is cis-2S,6R-N-methyl-6-[1-(2-hydroxy-2-phenylethyl)-2-phenylethylpiperidin-4-yl]-acetophenone.

24. A cis-2,6-substituted piperidino compound or pharmaceutically effective salt thereof comprising formula (I):

\[
\begin{align*}
R_1 \quad R_2 \quad R_3 \quad R_4
\end{align*}
\]

wherein:

- \(X^1\) and \(X^2\) are the same or are independently different from one another and represent a saturated carbon-carbon bond, a cis-carbon-carbon double bond, a 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;

- \(R_1\) and \(R_2\) are the same or are independently different from one another and represent hydrogen or a lower straight chain or branched alkyl or \(R_1\) and \(R_2\) together form a ring including a \(-CH_2-\), \(-CH_2-\), \(-CH_2-\), \(-CH_2-\), \(-CH_2-\), \(-CH_2-\), \(-CH_2-\) or \(-CH_2-\) moiety; and

- \(R_3\) and \(R_4\) 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 and sulfur; and an ortho, meta or para-substituted benzene;

- with the proviso that when \(R_2\) and \(R_4\) are unsubstituted phenyl groups and \(X^1\) and \(X^2\) are saturated...
carbon-carbon bonds, Y^1 and Y^2 cannot be CHOR or C=O, wherein R is lower alkyl, lower alkenyl, lower alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, lower alkoxycarbonyl, lower alkyaminocarbonyl, higher alkylcarbonyl or poly(alkyleneoxide)-carbonyl; with the further proviso that when R^2 and R^3 are unsubstituted phenyl groups or substituted phenyl groups having an alkyl, alkoxy, chlorine or CF_3 as substituents and X^1—Y^1 and X^2—Y^2 are saturated nitrogen-carbon bonds, X^1 and X^2 cannot be C=O; and with the further proviso that when X^1—Y^1 and X^2—Y^2 are saturated carbon-carbon bonds, X^1 and X^2 cannot be CH_3 or CH=CH, or CH=CH, C=O or CH=CH; with the further proviso that when X^1—Y^1 and X^2—Y^2 are carbon-carbon double bonds, R^2 and R^3 cannot be a saturated or unsaturated hydrocarbon ring with an ortho-, meta- or para substituted moiety selected from the group consisting of hydrogen, methyl, ethyl, C_3-C_7 straight chain or branched alkyl, C_6-C_7 cycloalkyl, vinyl, allyl, C_6-C_7, alkyl, benzyl, phenylethyl, N-methylamino, N,N-dimethylamino, carboxylate, methylcarboxylate, ethylcarboxylate, propylcarboxylate, isopropylcarboxylate, carboxaldehyde, acetoxo, propionyloxo, isopropionyloxo, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isoproxy, thiol, methythio, ethythio, propi thiol, fluoro, chloro, bromo, iodo, trifluoromethyl, propargyl, nitro, carbamoyl, ureido, azido, isocyanate, thiocyanate, hydroxyamin and nitroso.

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 or cyclooctene; the nitrogen containing heterocyclic moiety includes azetine, piperazine, pyrazine, pyrazoline, imidazoline, pyrimidine, hexa-hydropyrimidine, pyrrole, pyrrolidine, triazine, 1,2,3-triazole, 1,2,4-triazole, pyridine or pyridazidine; the oxygen containing heterocyclic moiety includes furan, tetrahydrofuran, 2,5-dihydrofuran, pyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane or 1,4-oxathionin; the sulfur containing heterocyclic moiety includes thiophene, thiophene, 2,5-dihydrothiophene, 1,3-dithioline, 1,2-dithiolane, 1,2-dithiane, thiene, 1,2-dithiane, 1,3-dithiane, 1,4-dithiane, or thiopyran; the selenium containing heterocyclic moiety includes thiazolidine, 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, carboxaldehyde, acetoxo, propionyloxo, isopropionyloxo, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzyl, sulfate, methylsulfate, hydroxyl, methoxy, ethoxy, propoxy, isoproxy, thiol, methythio, ethythio, propi thiol, fluoro, chloro, bromo, iodo, trifluoromethyl, propargyl, nitro, carbamoyl, ureido, azido, isocyanate, thiocyanate, hydroxyamin and nitroso.

The compound of claim 24, wherein when either X^1—Y^1 or X^2—Y^2 is a saturated carbon-carbon bond, Y^1 or Y^2 represents CH_3, CH—OH, CHO-alkyl where said alkyl is a lower straight chain or branched alkyl, CH—OSO_2—C_3H_5, CH—OSO_2—p-C_6H_4CH_3, CH—SH, C_6H_5—SH, CH—S-alkyl where said alkyl is a lower straight chain or branched alkyl, CH—NO_2, CH—CF_3, CH—NHOH, CH—OCHO, CH—F, CH—Cl, CH—Br, CH—I, CH—NH_2, CH—NH-alkyl where said alkyl is a lower straight chain or branched alkyl, CH—N(NH)alkyl, alkyl where said alkyl is a lower straight chain or branched alkyl, CH—OPENH_2, CH—OPENH-alkyl where said alkyl is a lower straight chain or branched alkyl, CH—OCONH(alkyl)_2 where said alkyl is a lower straight chain or branched alkyl, CH—N=C=O or 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, acetoxyl, propionyloxyl, isopropionyloxyl, cyano, aminomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, carboxamide, N,N-methylcarboxamide, N,N-dimethylcarboxamide, acetyl, propionyl, formyl, benzoyl, sulfate, methylsulfate, hydroxyl, 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-phenylethyl)]-2-phenylethylpiperidine.

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