Title: METHODS FOR TREATING DISORDERS ASSOCIATED WITH UNDESIRED ACTIVITY OF NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS

Abstract: This invention is directed to a method of treating one or more disorders associated with an undesired downstream activity of at least one subtype of neuronal nicotinic acetylcholine receptor, comprising treating a patient with noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof so as to attenuate said undesired effect.
before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
METHODS FOR TREATING DISORDERS ASSOCIATED WITH UNDESIRED ACTIVITY OF NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application Serial No. 62/118397 filed February 19, 2015 of which is hereby incorporated by reference into this application in its entirety.

FIELD OF THE INVENTION

[0002] This invention is directed to a method of treating one or more diseases or disorders associated with undesired downstream response(s) of neuronal nicotinic acetylcholine receptor activity, comprising treating a patient with noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof so as to attenuate said undesired effect. This invention is further directed a method of attenuating undesired downstream response(s) of neuronal nicotinic acetylcholine receptor activity in a cell that expresses at least one subtype of neuronal nicotinic acetylcholine receptor.

STATE OF THE ART

[0003] A number of functions and disorders are associated with downstream effect(s) of neuronal nicotinic acetylcholine receptor (nAChR) activity. These include substance abuse and withdrawal; depression; schizophrenia; anxiety-related disorders; regulation of the mood-enhancing effects of antidepressant drugs; baseline affective state; memory and attention (including Alzheimer's disease and attention deficit disorder).

[0004] Substance addiction is a serious public health problem throughout the world. Heroin and other drugs, including prescription painkillers, are widely abused. Opioid use is also linked to approximately 50% of violent crimes in the United States and costs the U.S. economy billions of dollars per year.

[0005] Smoking and other forms of nicotine use pose a serious threat to global health. In the United States alone, annual mortality from smoking (including environmental exposure, i.e. "second-hand smoke") is greater than 440,000. Costs associated with smoking-related illness in the United States total $96 billion in medical costs and $97 billion in lost productivity each year. Furthermore, smoking significantly increases the risk
of a number of diseases, including coronary artery disease, stroke, lung cancer and other cancers, and chronic obstructive pulmonary disease. An estimated 46 million people in the United States are smokers, 20.6 percent of the U.S. population.

[0006] The CDC estimates that about 1 in 10 adults in the United States suffer from depression. High levels of depression correlate with high rates of other diseases, including obesity, heart disease, and stroke. Likewise, psychotic disorders (e.g., schizophrenia and bipolar disorder); anxiety-related disorders (e.g., obsessive-compulsive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder); as well as impulse-control disorders like attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD); and memory disorders (e.g., Alzheimer's disease, dementia) affect a large number of Americans and have high societal costs.

[0007] Given the immense harm of the diseases associated with undesired result(s) of nAChR activity, there remains a need for effective and safe drugs that are capable of binding to nAChRs and modulating their downstream activity.

SUMMARY OF THE INVENTION

[0008] This invention is predicated, at least in part, on the surprising discovery that at low concentrations, noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof attenuates the undesired activity of at least a subset of nAChRs. Without being bound by theory, it is believed that the nAChRs can be activated by a number of ligands, including acetylcholine, nicotine, epibatidine, and choline, and undesired binding of such ligands leads to diseases or mediates the manifestations of diseases including (but not limited to) substance abuse and withdrawal; depression; schizophrenia: anxiety-related disorders; and memory and attention disorders (including Alzheimer's disease and attention deficit disorder). Without being bound by theory, it is believed that low doses of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof attenuate undesirable nAChR activity without itself causing undesirable nAChR activity at these doses.

[0009] Noribogaine is a well-known member of the ibogaine family of alkaloids and is sometimes referred to as 12-hydroxyibogaine. Noribogaine has been disclosed for treatment of substance addiction, including nicotine, opioids, cocaine and alcohol. See
U.S. Patent Application Pub. Nos. 2014/0288056; 2015/023147; 2015/0238503; 2015/0258105; and 2015/0258106; each of which is incorporated herein by reference in its entirety. The structure of noribogaine combines the features of tryptamine, tetrahydrohavaine and indolazepines. Noribogaine can be depicted by the following formula:

![Noribogaine structure]

[0010] A prolonged QT interval is a marker of potential Torsades de Pointes, a serious arrhythmia that can result in death. It has been shown that treatment with noribogaine imparts a dose-dependent prolongation of the treated patient's QT interval, rendering higher dosing of noribogaine unacceptable. Therefore, it is important to administer noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof at a level that is both efficacious and safe. Administration of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof at a dose between about 1 mg/kg body weight and about 4 mg/kg body weight provides a therapeutic reduction in withdrawal symptoms and/or an increase in time to resumption of opioid use in opioid-addicted patients, while also maintaining a QT interval prolongation below about 50 ms.

[0011] Without being bound by theory, it is contemplated that a lower dose of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof is effective at treating or attenuating the diseases and conditions described herein which are mediated by LIACHR activity because noribogaine's direct action to the receptor modulates the downstream effects of this receptor in response to endogenous and exogenous ligand binding. Such lower dosing minimizes the risk of dangerous QT interval prolongation.

[0012] Nicotinic acetylcholine receptors are ligand-gated ion channels made up of five transmembrane subunits arranged so as to form a central pore. There are two subtypes: muscle-type nAChRs and neuronal-type nAChRs. Neuronal-type nAChRs may be homomeric or heteromeric combinations of α (i.e., α2-α10) and β (i.e., β2-β4) subunits. The endogenous agonist for nAChRs is acetylcholine; nicotine, epibatidine, and choline are also known nAChR agonists.
[0013] In one aspect, this invention relates to a method for attenuating an undesired downstream response as a result of nAChR activity in a cell, the method comprising administering to a cell comprising at least one nAChR an effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof to attenuate the downstream response. In one embodiment, the nAChR comprises at least one subunit selected from the group consisting of α3, α5, α7, β4, and β2. In an especially preferred embodiment, the cell is a neuron.

[0014] In one aspect, this invention relates to a method for attenuating an undesired downstream response as a result of nAChR activity in a subject having a disorder associated with nAChR activity, the method comprising administering to the subject an effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof to attenuate the undesired response, thereby treating or attenuating the disorder. In one embodiment, the disorder is an anxiety-related disorder. In one embodiment, the disorder is a depression-related disorder. In one embodiment, the disorder is schizophrenia. In one embodiment, the disorder is addiction to an addictive substance. In one embodiment, the substance is selected from the group consisting of an opioid, cocaine, nicotine, and alcohol. In one embodiment, the disorder is a memory or attention disorder. In one embodiment, the memory or attention disorder is selected from the group consisting of Alzheimer's disease, dementia, attention deficit hyperactivity disorder, and attention deficit disorder.

[0015] In one aspect of this invention, activity of the nAChR is inhibited by noribogaine, noribogaine derivative, or salt or solvate thereof. In one aspect of this invention, desensitization of the nAChR is attenuated. In one embodiment, the nAChR is expressed by a neuron of a subject.

**BRIEF DESCRIPTION OF THE FIGURES**

[0016] **FIG. 1** shows the dose-dependent inhibition of epibatidine-evoked Ca$^{2+}$ responses in cx3-(α5, β4, β2) nAChRbs by noribogaine, ibogaine, 18-MC and mecamylamine.

[0017] **FIG. 2** shows the modulation of epibatidine-evoked Ca$^{2+}$ dose-responses in α3-(α5, β4, β2) nAChRs by noribogaine and mecamylamine.
FIG. 3 illustrates the alignment of the second transmembrane region T2 of the human α3, α4, α5, α7, β2, and β4 nAChR subunits.

FIG. 4 illustrates the subunit composition of nAChRs occurring in the habenula of mice.

FIG. 5 represents mean noribogaine concentration-time profiles in healthy patients after single oral dosing with 3, 10, 30 or 60 mg doses. Inset: Individual concentration-time profiles from 0-12 h after a 10 mg dose.

FIG. 6 represents mean plasma noribogaine glucuronide concentration-time profiles in healthy patients after single oral 30 or 60 mg doses.

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of this invention will be limited only by the appended claims.

The detailed description of the invention is divided into various sections only for the reader's convenience and disclosure found in any section may be combined with that in another section. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a plurality of compounds.
I. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein the following terms have the following meanings.

The term "about" when used before a numerical designation, e.g., temperature, time, amount, concentration, and such other, including a range, indicates approximations which may vary by (±) or (−) 20%, 10%, 5%, 1%, or any subrange or subvalue there between. Preferably, the term "about" when used with regard to a dose amount means that the dose may vary by ±10%.

"Administration" refers to introducing an agent, such as noribogaine, into a patient. Typically, an effective amount is administered, which amount can be determined by the treating physician or the like. Any route of administration, such as oral, topical, subcutaneous, peritoneal, intra-arterial, inhalation, vaginal, rectal, nasal, introduction into the cerebrospinal fluid, or instillation into body compartments can be used. The agent, such as noribogaine, may be administered by direct blood stream delivery, e.g. sublingual, buccal, intranasal, or intrapulmonary administration.

The related terms and phrases "administering" and "administration of," when used in connection with a compound or pharmaceutical composition (and grammatical equivalents), refer both to direct administration, which may be administration to a patient by a medical professional or by self-administration by the patient, and/or to indirect administration, which may be the act of prescribing a drug. For example, a physician who instructs a patient to self-administer a drag and/or provides a patient with a prescription for a drag is administering the drug to the patient.

The term "activity", with respect to a nAChR, refers to any activity of the receptor, including (without limitation) activation, inhibition, down-regulation, or desensitization of the receptor. In a preferred embodiment, the nAChR activity attenuated by the compound described herein is an activity that is mediated by a ligand (e.g., an
endogenous or exogenous ligand of the receptor). In an especially preferred embodiment, the noribogaine, noribogaine derivative, salt or solvate thereof attenuates activation and/or desensitization of the receptor.

[0030] "Periodic administration" or "periodically administering" refers to multiple treatments that occur on a daily, weekly, or monthly basis. Periodic administration may also refer to administration of noribogaine, noribogaine derivative, or salt or solvate thereof one, two, three, or more times per day. Administration may be via transdermal patch, gum, lozenge, sublingual tablet, intranasal, intrapulmonary, oral administration, or other administration.

[0031] "Comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. "Consisting of shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0032] As used herein, the terms "addiction" and "dependence" are used interchangeably to refer to the patient's inability to stop using a drug, even when it would be in his/her best interest to stop. U.S. Patent Application Pub. Nos. 2015/0238503; 2015/0258106; and 2015/0258106 relate to treatment of substance abuse, and each is incorporated by reference herein in its entirety. Treatment of addiction includes amelioration of at least one symptom of acute withdrawal or post-acute withdrawal, and/or preventing or reducing the risk of relapse to substance abuse. Any substance of addiction is contemplated, including, without limitation, nicotine, caffeine, alcohol, opioids, cocaine, barbituates, and other narcotics or prescription drugs.

[0033] As used herein, the term "alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 12 carbon atoms, 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, and more preferably 1 to 3 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH₃⁺), ethyl
(CH₃CH₂⁻), "-propyl (CH₃CH₂CH₂⁻), isopropyl ((CH₃)₂CH⁻), n-butyl (CH₃CH₂CH₂CH₂⁻), isobutyl ((CH₃)₂CHC₃⁻), sec-butyl ((CH₃)(CH₂CH₂CH₂)⁻), tert-butyl ((CH₃)₃C⁻), n-pentyl (CH₃CH₂CH₂CH₂CH₂⁻), and neopentyl ((CH₃)₃C⁻). The term "Cₙ alkyl" refers to an alkyl group having x carbon atoms, wherein x is an integer, for example, C₃ refers to an alkyl group having 3 carbon atoms.

[0034] "Alkenyl" refers to straight or branched hydrocarbyl groups having from 2 to 6 carbon atoms and preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1 to 2 sites of vinyl (\(>\text{C}==\text{C}<\)) unsaturation. Such groups are exemplified, for example, by vinyl, allyl, and but-3-en-1-yl. Included within this term are the cis and trans isomers or mixtures of these isomers.

[0035] "Alkynyl" refers to straight or branched monovalent hydrocarbyl groups having from 2 to 6 carbon atoms and preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of acetylenic (\(-\text{C}==\text{C}-\)) unsaturation. Examples of such alkynyl groups include acetylenyl (\(-\text{C}==\text{CH}\)), and propargyl (\(-\text{CH}_2\text{C}==\text{CH}\)).

[0036] "Substituted alkyl" refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarboxylamino, aminothiocarbonylamino, ammocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonlamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenylxoy, substituted cycloalkenylxoy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO₂H, substituted sulfonyl, sulfenylxoy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

[0037] "Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy,
substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyle, aminosulfonamido, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocycloxy, substituted heterocycloxy, heterocyclithio, substituted heterocyclithio, nitro, SO3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein and with the proviso that any hydroxy or thiol substitution is not attached to a vinyl (unsaturated) carbon atom.

[0038] "Substituted alkynyl" refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyle, aminosulfonamido, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocycloxy, substituted heterocycloxy, heterocyclithio, substituted heterocyclithio, nitro, SO3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein and with the proviso that any hydroxy or thiol substitution is not attached to an acetylenic carbon atom.
"Alkoxy" refers to the group -O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, w-butoxy, r-butoxy, sec-butoxy, and w-pentoxy.

"Substituted alkoxy" refers to the group -0-(substituted alkyl) wherein substituted alkyl is defined herein.

"Acyl" refers to the groups H-C(0)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Acyl includes the "acetyl" group C\(^\text{\text{3\text{4\text{}}\text{1\text{}}}\text{}}\)C(0)-.

"Acylamino" refers to the groups -NR\(^3\text{C(0)}\)alkyl, -NR\(^3\text{C(0)}\)substituted alkyl, -NR\(^3\text{C(0)}\)cycloalkyl, -NR\(^3\text{C(0)}\)cycloalkenyl, -NR\(^3\text{C(0)}\)substituted cycloalkenyl, -NR\(^3\text{C(0)}\)alkenyl, -NR\(^3\text{C(0)}\)alkynyl, -NR\(^3\text{C(0)}\)substituted alkynyl, -NR\(^3\text{C(0)}\)aryl, -NR\(^3\text{C(0)}\)heteroaryl, -NR\(^3\text{C(0)}\)substituted heteroaryl, -NR\(^3\text{C(0)}\)heterocyclic, and -NR\(^3\text{C(0)}\)substituted heterocyclic wherein R\(^3\) is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(0)O, substituted alkyl-C(0)O-, alkenyl-C(0)O-, substituted alkenyl-C(0)O-, alkynyl-C(0)O-, substituted alkynyl-C(0)O-, aryl-C(0)O-, substituted aryl-C(0)O-, cycloalkyl-C(0)O-, substituted cycloalkyl-C(0)O-, cycloalkenyl-C(0)O-, substituted cycloalkenyl-C(0)O-, heteroaryl-C(0)O-, substituted heteroaryl-C(0)O-, heterocyclic-C(0)O-, and substituted
heterocyclic-C(0)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0044] "Amino" refers to the group -NH₂.

[0045] "Substituted amino" refers to the group -NR³⁹R⁴⁰ where R³⁹ and R⁴⁰ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, -SO₂alkyl, -SOi-substituted alkyl, -SCValkenyl, -SOi-substituted alkenyl, -SO ²-cycloalkyl, -SO₂-substituted cycloalkenyl, -SO2-cycloalkenyl, -SC^ substituted cycloalkenyl, -S02-aryl, -S02-substituted aryl, -S02-heteroaryl, -SCb-substituted heteroaryl, -SCb-heterocyclic, and -SO ²-substituted heterocyclic and wherein R³⁵ and R⁴⁰ are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R³⁹ and R⁴⁰ are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. When R³⁹ is hydrogen and R⁴⁰ is alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When R³⁹ and R⁴⁰ are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R³⁹ or R⁴⁰ is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R³⁹ nor R⁴⁰ are hydrogen.

[0046] "Aminocarbonyl" refers to the group -C(0)NR⁴¹R⁴² where R⁴¹ and R⁴² are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R⁴¹ and R⁴² are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl,
alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0047] "Aminothiocarbonyl" refers to the group -C(S)NR^{41}R^{42} where R^{41} and R^{42} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{41} and R^{42} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0048] "Aminocarbonylamino" refers to the group -NR^{38}C(0)NR^{41}R^{42} where R^{38} is hydrogen or alkyl and R^{41} and R^{42} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{41} and R^{42} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0049] "Aminothiocarbonylamino" refers to the group -NR^{38}C(S)NR^{41}R^{42} where R^{38} is hydrogen or alkyl and R^{41} and R^{42} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{41} and R^{42} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.
cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0050] "Aminocarbonyloxy" refers to the group -O-C(=O)NR^4R^42 where R^41 and R^42 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^41 and R^42 are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alicenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0051] "Aminosulfonyloxy" refers to the group -O-SO_2NR^4R^42 where R^41 and R^42 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^41 and R^42 are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alicenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0052] "Aminosulfonyloxy" refers to the group -O-SO_2NR_4R^42 where R^41 and R^42 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^41 and R^42 are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alicenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.
cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0053] "Aminosulfonlamino" refers to the group -NR^3\_S\_O\_NR^4\_R^2 where R^3 is hydrogen or alkyl and R^4 and R^2 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aikenyl, substituted aikenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^4 and R^2 are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, aikenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0054] "Amidino" refers to the group -C(=NR^4\_3)NR^4\_R^2 where R^4, R^2, and R^13 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aikenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^4 and R^2 are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, aikenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0055] "Aryl" or "Ar" refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benoxazolinone, 2H-1,4-benoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom. Preferred aryl groups include phenyl and naphthyl.

[0056] "Substituted aryl" refers to aryl groups which are substituted with 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkyl, substituted alkyl, aikenyl, substituted aikenyl, alkynyl, substituted alkynyl,
alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarboxamino, aminocarbonylamino, aminocarbonyloxy, aminosulfonoyl, aminosulfonylamino, amidino, aiyl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocycloxy, substituted heterocycloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

[0057] "Aryloxy" refers to the group -0-aryl, where aryl is as defined herein, that includes, by way of example, phenoxy and naphthoxy.

[0058] "Substituted aryloxy" refers to the group -0-(substituted aryl) where substituted aryl is as defined herein.

[0059] "Arylthio" refers to the group -S-aryl, where aryl is as defined herein.

[0060] "Substituted arylthio" refers to the group -S-(substituted aryl), where substituted aryl is as defined herein.

[0061] "Carbonyl" refers to the divalent group -C(O)- which is equivalent to -C(=0)-.

[0062] "Carboxy" or "carboxyl" refers to -COOH or salts thereof.

[0063] "Carboxyl ester" or "carboxy ester" refers to the groups -C(0)0-alkyl, -C(0)0-substituted alkyl, -C(0)0-alkenyl, -C(0)0-substituted alkenyl, -C(0)0-alkynyl, -C(0)0-substituted alkynyl, -C(0)0-aryl, -C(0)0-substituted aryl, -C(0)0-cycloalkyl, -C(0)0-substituted cycloalkyl, -C(0)0-cycloalkenyl, -C(0)0-substituted cycloalkenyl, -C(0)0-heteroaryl, -C(0)0-substituted heteroaryl, -C(0)0-heterocyclic, and -C(0)0-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, substituted alkynyl, substituted alkynyl, substituted aryl, substituted arylthio, substituted arylthio, substituted aryloxy, substituted aryloxy, substituted arylthio, substituted arylthio, substituted cycloalkyl, substituted cycloalkylthio, substituted cycloalkylthio, substituted cycloalkenyl, substituted cycloalkenylthio, substituted cycloalkenylthio, substituted cycloalkenyloxy, substituted cycloalkenyloxy, substituted cycloalkenylthio, substituted cycloalkenylthio, substituted heteroaryl, substituted heteroarylthio, substituted heteroarylthio, substituted heterocyclic, substituted heterocycloxy, substituted heterocycloxy, substituted heterocyclylthio, substituted heterocyclylthio, nitro, SO3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.
alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryi, substituted heteroaryi, heterocyclic, and substituted heterocyclic are as defined herein.

[0064] "(Carboxyl ester)amino" refers to the group -NR<sub>3</sub>-C(0)0-alkyl, -NR<sub>3</sub>-C(0)0-substituted alkyl, -NR<sub>3</sub>-C(0)0-alkenyl, -NR<sub>3</sub>-C(0)0-substituted alkenyl, -NR<sub>3</sub>-C(0)0-alkynyl, -NR<sub>3</sub>-C(0)0-substituted alkynyl, -NR<sub>3</sub>-C(0)0-aryl, -NR<sub>3</sub>-C(0)0-substituted aryl, -NR<sub>3</sub>-C(0)0-cycloalkyl, -NR<sub>3</sub>-C(0)0-substituted cycloalkyl, -NR<sub>3</sub>-C(0)0-cycloalkenyl, -NR<sub>3</sub>-C(0)0-substituted cycloalkenyl, -NR<sub>3</sub>-C(0)0-heteroaryl, -NR<sub>3</sub>-C(0)0-substituted heteroaryl, -NR<sub>3</sub>-C(0)0-heterocyclic, and -NR<sub>3</sub>-C(0)0-substituted heterocyclic wherein R<sup>3</sup> is alkyl or hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryi, substituted heteroaryi, heterocyclic, and substituted heterocyclic are as defined herein.

[0065] "(Carboxyl ester)oxy" refers to the group -0-C(0)0-alkyl, substituted -0-C(0)0-alkyl, -0-C(0)0-alkenyl, -0-C(0)0-substituted alkenyl, -0-C(0)0-alkynyl, -0-C(0)0-substituted alkynyl, -0-C(0)0-aryl, -0-C(0)0-substituted aryl, -0-C(0)0-cycloalkyl, -0-C(0)0-substituted cycloalkyl, -0-C(0)0-cycloalkenyl, -0-C(0)0-substituted cycloalkenyl, -0-C(0)0-heteroaryl, -0-C(0)0-substituted heteroaryl, -0-C(0)0-heterocyclic, and -0-C(0)0-substituted heterocyclic wherein R<sup>3</sup> is alkyl or hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryi, substituted heteroaryi, heterocyclic, and substituted heterocyclic are as defined herein.

[0066] "Cyano" refers to the group -CN.

[0067] "Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. One or
more of the rings can be aryl, heteroaryl, or heterocyclic provided that the point of
attachment is through the non-aromatic, non-heterocyclic ring carbocyclic ring. Examples
of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl,
cyclopentyl, and cyclooctyl. Other examples of cycloalkyl groups include
bicycle[2,2,2]octanyl, norbornyl, and spirobicyclo groups such as spiro[4.5]dec-8-yl.

[0068] "Cycloalkenyl" refers to non-aromatic cyclic alkyl groups of from 3 to 10 carbon
atoms having single or multiple cyclic rings and having at least one >C=C< ring
unsaturation and preferably from 1 to 2 sites of >C=C< ring unsaturation.

[0069] "Substituted cycloalkyl" and "substituted cycloalkenyl" refers to a cycloalkyl or
cycloalkenyl group having from 1 to 5 or preferably 1 to 3 substituents selected from the
group consisting of oxo, thione, alkyl, substituted alkyl, alkenyl, substituted alkenyl,
alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino,
substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino,
aminothiocarbonylamino, aminocarbonyloxy, aminocarbonylamino,
aminocarbonyloxy, aminosulfonylamino, aminosulfonyloxyl, aminosulfonylamine,
aminosulfonylamino, amidino, aryl, substituted aryl, arvinox, substituted aryloxy, arythio,
substituted arythio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy,
cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy,
cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl,
cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted
cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted
heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted
heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted
heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO3H, substituted
sulfonyl, sulfonyleoxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said
substituents are defined herein.

[0070] "Cycloalkyloxy" refers to -O-cycloalkyl.

[0071] "Substituted cycloalkyloxy" refers to -O-(substituted cycloalkyl).

[0072] "Cycloalkylthio" refers to -S-cycloalkyl.

[0073] "Substituted cycloalkylthio" refers to -S-(substituted cycloalkyl).
"Cycloalkenyloxy" refers to -O-cycloalkenyl.

"Substituted cycloalkenyloxy" refers to -0-(substituted cycloalkenyl).

"Cycloalkenylthio" refers to -S-cycloalkenyl.

"Substituted cycloalkenylthio" refers to -S-(substituted cycloalkenyl).

"Guanidino" refers to the group -NHC(=NH)NH₂.

"Substituted guanidino" refers to -NR₄C(=NR₄)N(R₄)₂, where each R₄ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and two R₄ groups attached to a common guanidino nitrogen atom are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that at least one R₄ is not hydrogen, and wherein said substituents are as defined herein.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is fluoro or chloro.

"Haloalkyl" refers to alkyl groups substituted with 1 to 5, 1 to 3, or 1 to 2 halo groups, wherein alkyl and halo are as defined herein.

"Haloalkoxy" refers to alkoxy groups substituted with 1 to 5, 1 to 3, or 1 to 2 halo groups, wherein alkoxy and halo are as defined herein.

"Haloalkylthio" refers to alkylthio groups substituted with 1 to 5, 1 to 3, or 1 to 2 halo groups, wherein alkylthio and halo are as defined herein.

"Hydroxy" or "hydroxyl" refers to the group -OH.

"Heteroaaryl" refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaaryl groups can have a single ring (e.g., pyridyl, pyridinyl or fuyl) or multiple condensed rings (e.g., indolizinyln or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaaryl group are optionally oxidized to
provide for the N-oxide (N→0), sulfinyl, and/or sulfonyl moieties. Preferred heteroaryls include pyridinyl, pyrrolyl, indolyl, thiophenyl, and furanyl.

[0086] "Substituted heteroaryl" refers to heteroaryl groups that are substituted with from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.

[0087] "Heteroaryloxy" refers to -0-heteroaryl.

[0088] "Substituted heteroaryloxy" refers to the group -0-(substituted heteroaryl).

[0089] "Heteroarylthio" refers to the group -S-heteroaryl.

[0090] "Substituted heteroarylthio" refers to the group -S-(substituted heteroaryl).

[0091] "Heterocycle" or "heterocyclic" or "heterocycloalkyl" or "heterocyclyl" refers to a saturated or partially saturated, but not aromatic, group having from 1 to 10 ring carbon atoms and from 1 to 4 ring heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen. Heterocycle encompasses single ring or multiple condensed rings, including fused bridged and spiro ring systems. In fused ring systems, one or more the rings can be cycloalkyl, aryl, or heteroaryl provided that the point of attachment is through the non-aromatic heterocyclic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfinyl, and/or sulfonyl moieties.

[0092] "Substituted heterocyclic" or "substituted heterocycloalkyl" or "substituted heterocyclyl" refers to heterocyclyl groups that are substituted with from 1 to 5 or preferably 1 to 3 of the same substituents as defined for substituted cycloalkyl.

[0093] "Heterocyclyloxy" refers to the group -O-heterocycyl.

[0094] "Substituted heterocyclyloxy" refers to the group -O-(substituted heterocycyl).

[0095] "Heterocyclylthio" refers to the group -S-heterocycyl.

[0096] "Substituted heterocyclylthio" refers to the group -S-(substituted heterocycyl).

[0097] Examples of heterocycle and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine,
isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthopyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, caroline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazole, piperidine, piperazine, indole, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), 1,1-dioxothiomorpholinyl, piperidinyl, pyrrolidine, and tetrahydrofuranyl.

[0098] "Nitro" refers to the group -N0₂.

[0099] "Oxo" refers to the atom (=0) or (-0\).}

[0100] "Spiro ring systems" refers to bicyclic ring systems that have a single ring carbon atom common to both rings.

[0101] "Sulfonyl" refers to the divalent group -S(0)₂.

[0102] "Substituted sulfonyl" refers to the group -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SC₇H₇-substituted alkenyl, -SC₇H₇-cycloalkyl, -SO₂-alkyl, -SO₂-cycloalkenyl, -SO₂-alkenyl, -SO₂-substituted cycoalkenyl, -SO₂-substituted alkyl, -SO₂-aromatic, -SO₂-aryl, -SO₂-substituted aromatic, -SO₂-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, are, substituted are, heterocyclic, substituted heterocyclic, and substituted heterocyclic are as defined herein. Substituted sulfonyl includes groups such as methyl-SO₂-, phenyl-SO₂-, and 4-methylphenyl-SC₇H₇. The term "alkylsulfonyl" refers to -SO₂-alkyl. The term "haloalkylsulfonyl" refers to -SO₂-alkyl where haloalkyl is defined herein. The term "(substituted sulfonyl)amino" refers to -NH(substituted sulfonyl), and the term "(substituted sulfonyl)aminocarbonyl" refers to -C(0)NH(substituted sulfonyl), wherein substituted sulfonyl is as defined herein.

[0103] "Sulfonyloxy" refers to the group -OSO₂-alkyl, -OSO₂-substituted alkyl, -OSO₂-alkenyl, -OSO₂-substituted alkenyl, -OSO₂-cycloalkyl, -OSO₂-cycloalkenyl, -OSO₂-aryl, -OSO₂-substituted are, -OSO₂-aromatic, -OSO₂-substituted aromatic, -OSO₂-substituted heterocyclic, wherein substituted sulfonyl is as defined herein.
heteroaryl, -OSO\textsubscript{2}-heterocyclic, -OSO\textsubscript{2}-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0104] "Thioacyl" refers to the groups H-C(S)-, alkyl-C(S)-, alkenyl-C(S)-, substituted alkenyl-C(S)-, alkynyl-C(S)-, substituted alkynyl-C(S)-, cycloalkyl-C(S)-, substituted cycloalkyl-C(S)-, cycloalkenyl-C(S)-, substituted cycloalkenyl-C(S)-, aryl-C(S)-, substituted aryl-C(S)-, heteroaryl-C(S)-, substituted heteroaryl-C(S)-, heterocyclic-C(S)-, and substituted heterocyclic-C(S)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0105] "Thiol" refers to the group -SH.

[0106] "Thiocarbonyl" refers to the divalent group -C(S)- which is equivalent to -C(=S)-.

[0107] "Thione" refers to the atom (\(=S\)).

[0108] "Alkylthio" refers to the group -S-alkyl wherein alkyl is as defined herein.

[0109] "Substituted alkylthio" refers to the group -S-(substituted alkyl) wherein substituted alkyl is as defined herein.

[0110] "Compound" or "compounds" as used herein is meant to include the stereoisomers and tautomers of the indicated formulas.

[0111] "Stereoisomer" or "stereoisomers" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers.

[0112] "Tautomer" refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring \(=N\)- moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.
As used herein, the term "phosphate ester" refers to any one of the mono-, di- or triphosphate esters of noribogaine, wherein the mono-, di- or triphosphate ester moiety is bonded to the 12-hydroxy group and/or the indole nitrogen of noribogaine.

As used herein, the term "phosphate ester" refers to any one of the mono-, di- or triphosphate esters of noribogaine, wherein the mono-, di- or triphosphate ester moiety is bonded to the 12-hydroxy group and/or the indole nitrogen of noribogaine.

As used herein, the term "monophosphate" refers to the group -P(0)(OH) 2.

As used herein, the term "diphosphate" refers to the group -P(0)(OH)-OP(O)(OH) 2.

As used herein, the term "triphosphate" refers to the group -P(0)(OH)- (OP(0)(OH)) 2OH.

As used herein, the term "ester" as it refers to esters of the mono-, di- or triphosphate group means esters of the monophosphate can be represented by the formula -P(0)(OR 4) 2, where each R 4 is independently hydrogen, Ci-Ci? alkyl, C 3-C 10 cycloalkyl, C 6-C 14 aryl, heteroaryl of 1 to 10 carbon atoms and 1 to 4 optionally oxidized heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur and the like, provided that at least one R 45 is not hydrogen. Likewise, exemplary esters of the di- or triphosphate can be represented by the formulas -P(0)(OR 45)-OP(0)(OR 45) 2 and -P(0)(OR 45)-(OP(0)(OR 45)) 2OR 45, where R 45 is as defined above.

As used herein, the term "hydrolyzable group" refers to a group that can be hydrolyzed to release the free hydroxy group under hydrolysis conditions. Examples of hydrolyzable group include, but are not limited to those defined for R above. Preferred hydrolysable groups include carboxyl esters, phosphates and phosphate esters. The hydrolysis may be done by chemical reactions conditions such as base hydrolysis or acid hydrolysis or may be done in vivo by biological processes, such as those catalyzed by a phosphate hydrolysis enzyme. Nonlimiting examples of hydrolysable group include groups linked with an ester-based linker (-C(O)O- or -OC(O)-), an amide-based linker (-C(O)NR 46- or -NR 46C(O)-), or a phosphate-linker (-P(0)(OR 46)-O-, -O-P(0)(OR 46)-O-, -0-P(S)(OR 46)-O-, -0-P(S)(SR 46)-O-, -S-P(0)(OR 46)-O-, -0-P(0)(OR 46)-S-, -S-P(0)(OR 46)-S-, -0-P(S)(OR 46)-S-, -S-P(S)(OR 46)-S-, -0-P(0)(R 46)-O-, -0-P(S)(R 46)-O-.
Substituted groups of this invention, as set forth above, do not include polymers obtained by an infinite chain of substituted groups. At most, any substituted group can be substituted up to five times.

"Noribogaine" refers to the compound:

![Noribogaine structure]

as well as noribogaine derivatives or pharmaceutically acceptable salts and pharmaceutically acceptable solvates thereof. It should be understood that where "noribogaine" is mentioned herein, one more polymorphs of noribogaine can be utilized and are contemplated. In some embodiments, noribogaine is noribogaine glucuronide.

Noribogaine can be prepared by demethylation of naturally occurring ibogaine:

![Demethylated ibogaine structure]

which is isolated from *Tahernanth iboga*, a shrub of West Africa. Demethylation may be accomplished by conventional techniques such as by reaction with boron tribromide/methylene chloride at room temperature followed by conventional purification. See, for example, Huffman, et al., J. Org. Chem. 50:1460 (1985), which incorporated herein by reference in its entirety. Noribogaine can be synthesized as described, for example in U.S. Patent Pub. Nos. 2013/0165647, 2013/0303756, and 2012/0253037, PCT Patent Publication No. WO 2013/040471 (includes description of making noribogaine polymorphs), and U.S. Patent App. No. 13/593,454, each of which is incorporated herein by reference in its entirety.

"Noribogaine derivatives" refer to esters or O-carbamates of noribogaine, or pharmaceutically acceptable salts and/or solvates of each thereof. Also encompassed
within this invention are derivatives of noribogaine that act as prodrug forms of noribogaine. A prodrug is a pharmacological substance administered in an inactive (or significantly less active) form. Once administered, the prodrug is metabolized in vivo into an active metabolite. Noribogaine derivatives include, without limitation, those compounds set forth in US Patent Nos. 6,348,456 and 8,362,007; as well as in US Patent Application Serial No. 13/165,626; and US Patent Application Publication Nos. US2013/0165414; US2013/0165647; US2013/0165425; and US2013/0165414; all of which are incorporated herein by reference. Non-limiting examples of noribogaine derivatives encompassed by this invention are given in more detail in the "Compositions of the Invention" section below.

[0124] In some embodiments, the methods of the present disclosure entail the administration of a prodrug of noribogaine that provides the desired maximum serum concentrations and efficacious average noribogaine serum levels. A prodrug of noribogaine refers to a compound that metabolizes, in vivo, to noribogaine. In some embodiments, the prodrug is selected to be readily cleavable either by a cleavable linking arm or by cleavage of the prodrug entity that binds to noribogaine such that noribogaine is generated in vivo. Examples of prodrugs of noribogaine are provided in United States Patent Application Serial No. 13/165626, the entire content of which is incorporated herein by reference.

[0125] This invention is not limited to any particular chemical form of noribogaine or noribogaine derivative, and the drug may be given to patients either as a free base, solvate, or as a pharmaceutically acceptable acid addition salt. In the latter case, the hydrochloride salt is generally preferred, but other salts derived from organic or inorganic acids may also be used. Examples of such acids include, without limitation, those described below as "pharmaceutically acceptable salts" and the like.

[0126] "Pharmaceutically acceptable composition" refers to a composition that is suitable for administration to a mammal, preferably a human. Such compositions include various excipients, diluents, carriers, and such other inactive agents well known to the skilled artisan.

[0127] “Pharmaceutically acceptable salt” refers to pharmaceutically acceptable salts, including pharmaceutically acceptable partial salts, of a compound, which salts are derived
from a variety of organic and inorganic counter ions well known in the art and include, by
way of example only, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid,
methane sulfonic acid, phosphorous acid, nitric acid, perchloric acid, acetic acid, tartaric
acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, aconitic acid, salicylic
acid, thalic acid, embonic acid, enanthic acid, oxalic acid and the like, and when the
molecule contains an acidic functionality, include, by way of example only, sodium,
potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like.

[0128] "Therapeutically effective amount" or "therapeutic amount" refers to an amount
of a drug or an agent that, when administered to a patient suffering from a condition, will
have the intended therapeutic effect, e.g., alleviation, amelioration, palliation or
elimination of one or more manifestations of the condition in the patient. The
therapeutically effective amount will vary depending upon the patient and the condition
being treated, the weight and age of the subject, the severity of the condition, the salt,
solvate, or derivative of the active drug portion chosen, the particular composition or
excipient chosen, the dosing regimen to be followed, timing of administration, the manner
of administration and the like, all of which can be determined readily by one of ordinary-
skill in the art. The full therapeutic effect does not necessarily occur by administration of
one dose, and may occur only after administration of a series of doses. Thus, a
therapeutically effective amount may be administered in one or more administrations. For
example, and without limitation, a therapeutically effective amount of noribogaine, in the
context of drag dependency, refers to an amount of noribogaine that attenuates the
dependency and/or symptoms of acute withdrawal for at least about 2 hours beyond
control (placebo), at least about 5 hours beyond control, and preferably at least about 10
hours beyond control.

[0129] A "therapeutic level" of a drug is an amount of noribogaine, noribogaine
derivative, or pharmaceutical salt or solvate thereof that is sufficient to treat the disease or
symptoms thereof, but not high enough to pose any significant risk to the patient.
Therapeutic levels of drugs can be determined by tests that measure the actual
concentration of the compound in the blood of the patient. This concentration is referred
to as the "serum concentration." Where the serum concentration of noribogaine is
mentioned, it is to be understood that the term "noribogaine" encompasses any form of
noribogaine, including derivatives thereof.
The term "dose" refers to a range of noribogaine, noribogaine derivative, or pharmaceutical salt or solvate thereof that provides a therapeutic serum level of noribogaine when given to a patient in need thereof. The dose is recited in a range, for example from about 20 mg to about 120 mg, and can be expressed either as milligrams or as mg/kg body weight. The attending clinician will select an appropriate dose from the range based on the patient's weight, age, degree of addiction, health, and other relevant factors, all of which are well within the skill of the art.

The term "unit dose" refers to a dose of drug that is given to the patient to provide therapeutic results, independent of the weight of the patient. In such an instance, the unit dose is sold in a standard form (e.g., 20 mg tablet). The unit dose may be administered as a single dose or a series of subdoses. In some embodiments, the unit dose provides a standardized level of drug to the patient, independent of weight of patient. Many medications are sold based on a dose that is therapeutic to all patients based on a therapeutic window. In such cases, it is not necessary to titrate the dosage amount based on the weight of the patient.

"Treatment," "treating," and "treat" are defined as acting upon a disease, disorder, or condition with an agent to reduce or ameliorate harmful or any other undesired effects of the disease, disorder, or condition and/or its symptoms. "Treatment," as used herein, covers the treatment of a human patient, and includes: (a) reducing the risk of occurrence of the condition in a patient determined to be predisposed to the condition but not yet diagnosed as having the condition, (b) impeding the development of the condition, and/or (c) relieving the condition, i.e., causing regression of the condition and/or relieving one or more symptoms of the condition. "Treating" or "treatment of a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results such as the reduction of symptoms.

As used herein, the term "patient" refers to mammals and includes humans and non-human mammals.

As used herein, the term "opiate" refers to naturally-occurring alkaloids found in the opium poppy. As used herein, the term "opioid" refers to naturally-occurring opiates and synthetic or semi-synthetic opioids that have psychoactive effects. A non-limiting list
of opioids can be found in U.S. Application Pub. No. 2015/0231147, which is incorporated herein by reference in its entirety.

[0135] As used herein, the term "QT interval" refers to the measure of the time between the start of the Q wave and the end of the T wave in the electrical cycle of the heart. Prolongation of the QT interval refers to an increase in the QT interval.

[0136] The term "solvate" as used herein refers to complexes with solvents in which noribogaine is reacted or from which noribogaine is precipitated or crystallized. For example, a complex with water is known as a "hydrate". Solvates of noribogaine are within the scope of the invention. It will be appreciated by those skilled in organic chemistry that many organic compounds can exist in more than one crystalline form. For example, crystalline form may vary based on the solvate used. Thus, all crystalline forms of noribogaine or the pharmaceutically acceptable solvates thereof are within the scope of the present invention.

[0137] A "pharmaceutically acceptable solvate" or "hydrate" of a compound of the invention means a solvate or hydrate complex that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound, and includes, but is not limited to, complexes of a compound of the invention with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

[0138] The therapeutically effective amount of the compound may be higher or lower, depending on the route of administration used. For example, when direct blood administration (e.g., sublingual, pulmonary and intranasal delivery) is used, a lower dose of the compound may be administered. In one aspect, a therapeutically effective amount of noribogaine or derivative is from about 50 ng to less than 100 μg per kg of body weight. Where other routes of administration are used, a higher dose of the compound may be administered.

[0139] A "sub-therapeutic level" of noribogaine or pharmaceutical salt and/or solvate thereof that is less than the therapeutic level described above. For example, the sub-therapeutic level of noribogaine may be e.g., 80%, 70%, 60%, 50%, 40%, 30%, 20%, or
10% less than a therapeutically effective amount (e.g., 120 mg) of noribogaine, or any subvalue or subrange there between.

[0140] As defined herein, a "prophylactically effective amount" of a drug is an amount, typically less than the therapeutically effective amount, that provides attenuation and/or prevention of a disease or disorder or symptoms of a disease or disorder in a patient. For example, the prophylactically effective amount of the compound is expected to be less than the therapeutically effective amount because the level of inhibition does not need to be as high in a patient who no longer has a disease or disorder or symptoms of a disease or disorder (e.g., no longer physically addicted to nicotine). For example, a prophylactically effective amount is preferably 90%, 80%, 70%, 60%, 50%, 40%, 30%, or 10% less than a therapeutically effective amount. However, a prophylactically effective amount may be the same as the therapeutically effective amount. The prophylactically effective amount may vary for different a diseases or disorders or symptoms of different diseases or disorders.

[0141] As defined herein, a "maintenance amount" of a drug or an agent is an amount, typically less than the therapeutically effective amount that provides attenuation and/or prevention of syndrome disease or disorder or symptoms of a disease or disorder in a patient. The maintenance amount of the compound is expected to be less than the therapeutically effective amount because the level of inhibition does not need to be as high in a patient who is no longer physically manifests a disease or disorder or symptoms of a disease or disorder. For example, a maintenance amount is preferably 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% less than a therapeutically effective amount, or any subvalue or subrange there between.

II. Compositions of the Invention

[0142] As will be apparent to the skilled artisan upon reading this disclosure, this invention provides compositions for treating diseases associated with undesired downstream effect(s) of nAChR activity in a subject, comprising noribogaine, noribogaine derivatives, prodrugs of noribogaine, pharmaceutically acceptable salts and/or solvates of each thereof. This invention further provides compositions for treating a cell expressing at
least one nAChR, comprising noribogaine, noribogaine derivatives, prodrugs of noribogaine, pharmaceutically acceptable salts and/or solvates of each thereof.

[0143] In some embodiments, the composition is formulated for oral, transdermal, internal, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intraarterial, intramuscular, intraperitoneal, intracutaneous or subcutaneous delivery.

[0144] In one embodiment, the noribogaine derivative is represented by Formula I:

![Formula I]

or a pharmaceutically acceptable salt and/or solvate thereof,

wherein R is hydrogen or a hydrolyzable group such as hydrolyzable esters of from about 1 to 12 carbons.

[0145] Generally, in the above formula, R is hydrogen or a group of the formula:

![Group X]

wherein X is a C1-C12 group, which is unsubstituted or substituted. For example, X may be a linear alkyl group such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl or n-dodecyl, or a branched alkyl group, such as i-propyl or sec-butyl. Also, X may be a phenyl group or benzyl group, either of which may be substituted with lower alkyl groups or lower alkoxy groups. Generally, the lower alkyl and/or alkoxy groups have from 1 to about 6 carbons. For example, the group R may be acetyl, propionyl or benzoyl. However, these groups are only exemplary.

[0146] Generally, for all groups X, they may either be unsubstituted or substituted with lower alkyl or lower alkoxy groups. For example, substituted X may be 0-, m- or p-methyl or methoxy benzyl groups.
[0147] Ci-Ci₂ groups include C₁-C₁₂ alkyl, C₃-C₁₂ cycloalkyl, C₂-C₁₂ aryl, C₇-C₁₂ arylalkyl, wherein Cᵢ indicates that the group contains i carbon atoms. Lower alkyl refers to C₁-C₄ alkyl and lower alkoxy refers to C₁-C₄ alkoxy.

[0148] In one embodiment, the noribogaine derivative is represented by Formula II:

![Formula II](image)

or a pharmaceutically acceptable salt and/or solvate thereof,

wherein

[---] is a single or double bond;

R¹ is halo, OR², or C₁-C₁₂ alkyl optionally substituted with 1 to 5 R¹₀;

R² is hydrogen or a hydrolysable group selected from the group consisting of -C(0)R⁵, -C(0)OR⁵ and -C(0)N(R⁷)₂ where each R⁵ is selected from the group consisting of C₁-C₆ alkyl optionally substituted with 1 to 5 R¹₀, and each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ alkyl optionally substituted with 1 to 5 R¹₀, C₅-C₁₄ aryl optionally substituted with 1 to 5 R¹₀, C₃-C₁₀ cycloalkyl optionally substituted with 1 to 5 R¹₀, C₁-C₁₀ heteroaryl having 1 to 4 heteroatoms and which is optionally substituted with 1 to 5 R¹₀, C₁-C₆ heterocyclic having 1 to 4 heteroatoms and which is optionally substituted with 1 to 5 R¹₀, and where each R⁵, together with the nitrogen atom bound thereto form a Ci-Ce heterocyclic having 1 to 4 heteroatoms and which is optionally substituted with 1 to 5 R¹₀;

R³ is selected from the group consisting of hydrogen, C₁-C₁₂ alkyl optionally substituted with 1 to 5 R¹₀, aryl optionally substituted with 1 to 5 R¹₀, -C(0)R⁶, -C(0)NR⁶R⁶ and -C(0)OR⁶;

R⁴ is selected from the group consisting of hydrogen, -(CH₂)ₘ OR⁸, -(CH₂)ₘ CN, -(CH₂)ₘ COR⁸, -(CH₂)ₘ CO₂R⁸, -(CH₂)ₘ C(0)NR⁷
R^8, -(CH_2)_mC(0)NR^7NR^8R^9, -(CH_2)_mC(0)NR^7NR^8C(0)R^9,
and -(CH_2)_mNR^8R^9;
m is 0, 1, or 2;
L is a bond or C_1-C_12 alkylene;
R^5 is selected from the group consisting of hydrogen, C_1-C_12 alkyl substituted with
1 to 5 R^10, C_1-C_12 alkenyl substituted with 1 to 5 R^10, -X-YVX^1-,
R^7, -SO_2NR^7R^8, -O-C(0)R^9, -C(0)OR^8, -C(0)NR^7R^8, -NR^7R^8, -
NHC(0)R^9, and -NR^7C(0)R^9;
each R^6 is independently selected from the group consisting of hydrogen, C_1-C_12 alkyl, C_2-C_12 alkenyl, C_2-C_12 alkynyl, C_6-C_10 aryloaryl, C_1-C_6 heteroaryl having 1 to
4 heteroatoms, and C_i-C_g heterocycle having 1 to 4 heteroatoms, and
wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle are
optionally substituted with 1 to 5 R^10;
X^1 is selected from the group consisting of O and S;
Y is C_1-C_4 alkylene or C_5-C_10 arylylene, or a combination thereof;
n is 1, 2, or 3;
R^7 and R^8 are each independently selected from the group consisting of hydrogen,
C_1-C_12 alkyl optionally substituted with 1 to 5 R^10, C_1-C_6 heterocycle
having 1 to 4 heteroatoms and which is optionally substituted with 1 to 5
R^10, C_3-Cycloalkyl optionally substituted with 1 to 5 R^10, C_6-C_10 aryloaryl optionally substituted with 1 to 5 R^10 and C_1-C_6 heteroaryl having 1 to 4
heteroatoms optionally substituted with 1 to 5 R^10;
R^9 is selected from the group consisting of C_1-C_12 alkyl optionally substituted with
1 to 5 R^10, C_i-C_g heterocycle having 1 to 4 heteroatoms optionally
substituted with 1 to 5 R^10, Cs-Cycloalkyl optionally substituted with 1 to 5 R^10, C_6-C_10 aryloaryl optionally substituted with 1 to 5 R^10 and C_1-C_6 heteroaryl having 1 to 4 heteroatoms optionally substituted with 1 to 5 R^10;
R^10 is selected from the group consisting of C_1-C_4 alkyl, phenyl, halo, -OR^11, -
CN, -COR^1, -C_0_2R^11, -C(0)NHR^11, -NR^11R^11, -C(0)NR^11R^11, -C(0)NHR^11, -C(0)NHR^11R^11, -C(0)NHNC(0)R^11, -S02NR^11R^11, -C(0)NR^11R^11C(0)R^11,
and -C(0)NR^11NHC(0)R^11; and
R^11 is independently hydrogen or C_1-C_12 alkyl;
provided that:
when L is a bond, then R^5 is not hydrogen;
when \( \text{-----} \) is a double bond, R^1 is an ester hydrolyzable group, R^3 and R^4 are both hydrogen, then -L-R^5 is not ethyl;
when \( \text{-----} \) is a double bond, R^1 is -OH, halo or C_1-C_12 alkyl optionally substituted with 1 to 5 R^6, or a aryl optionally substituted with 1 to 5 R^6;
when \( \text{-----} \) is a double bond, R^1 is OR^2, R^4 is hydrogen, -L-R^5 is ethyl, then R^2 is not a hydrolyzable group selected from the group consisting of an ester, amide, carbonate and carbamate.

[0149] In one embodiment, the noribogaine derivative is represented by Formula III:

![Formula III](image)

or a pharmaceutically acceptable salt and/or solvate thereof,

wherein

\( \text{-----} \) is a single or double bond;
R^{12} is halo, -OH, -SH, -NH_2, -S(0)=N(R^1)^2, -R^1-L-R^3, -R^2-L'-R^19, -R^2-L'-R^20 or -R^2-L^1-CHR=R^6, where R^2 is O, S or NR^17;
L^1 is alkylene, arylene, -C(0)-alkylene, -C(0)-arylene, -C(0)=0-alkylene, -C(0)=0-arylene, -C(0)NR^20-alkylene, -C(0)NR^20-arylene, -C(NR^20)NR^20-alkylene or -C(NR^20)NR^20-arylene, wherein L^1 is configured such that -O-L^1-R^18 is -OC(0)-alkylene-R^8, -OC(0)-0-arylene-R^18, -OC(0)-0-alkylene-R^18, -OC(O)-0-alkylene-R^18, -OC(O)-0-arylene-R^18, -OC(O)-NR^20-alkylene-R^18, -OC(O)-NR^20-0-arylene-R^18, -OC(O)-NR^20-0-alkylene-R^18, -OC(O)-NR^20-0-arylene-R^18, and wherein the alkylene and arylene are optionally substituted with 1 to 2 R^16;
R^{13} is hydrogen, -S(0), S(0), S(0)-R^20, -C(0)R^20, -C(0)NR^15, -C(0)OR^15, C,-C_12 alkyl optionally substituted with 1 to 5 R^6, C_1-C_12 alkenyl optionally substituted with 1 to 5 R^6, or aryl optionally substituted with 1 to 5 R^6;
$R^{14}$ is hydrogen, halo, -OR, -CN, C$_{12}$-alkyl, C$_{12}$-alkoxy, aryl or aryloxy,
where the alkyl, alkoxy, aryl, and aryloxy are optionally substituted with 1 to 5 $R^{16}$;

each $R^{15}$ is independently selected from the group consisting of hydrogen, C$_{1}$-C$_{12}$
alkyl, C$_{2}$-C$_{12}$-alkenyl, C$_{2}$-C$_{12}$-alkynyl, aryl, heteroaryl, and heterocycle, and
wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle are
optionally substituted with 1 to 5 $R^{16}$;

$R^{16}$ is selected from the group consisting of phenyl, halo, -OR, -
CN, -COR, -CO$_2$R, -NR$_2$R, -NR$_2$C(0)R, -NR$_2$SO$_2$R, -C(0)NR$_2$
$R^{17}$, -C(0)NR$_2$-C(0)R, -SO$_2$NR$_2$R, -C(0)NR$_2$C(0)R

each $R^{17}$ is independently hydrogen or C$_{1}$-C$_{12}$ alkyl optionally substituted with
from 1 to 3 halo;

$R^{18}$ is hydrogen, -C(0)R$_2$, -C(0)OR$_2$, -C(0)N(R$_2$)$_2$ or -N(R$_2$)C(0)R;

$R^{19}$ is hydrogen, -
N(R$_2$)$_2$, -C(0)N(R$_2$)$_2$, -C(NR$_2$)$_2$, -C(NSO$_2$R$_2$)$_2$, -C(0)NR$_2$C(0)R
N(R$_2$)$_2$, -NR$_2$C(S)N(R$_2$)$_2$, -NR$_2$C(NR$_2$)$_2$, -NR$_2$C(NSO$_2$R$_2$)$_2$, -NR$_2$C(0)R
$_2$ or tetrazole; and

each $R^{20}$ is independently selected from the group consisting of hydrogen, C$_{1}$-C$_{12}$
alkyl and aryl;

provided that:

when \( \leftrightarrow \) is a double bond and $R^{13}$ and $R^{14}$ are hydrogen, then $R^{12}$ is not
hydroxy;

when \( \leftrightarrow \) is a double bond, $R^{14}$ is hydrogen, $R^{12}$ is -O-\( \cdot \)-R, -O-L-\( ^{18} \)-R, -O-L-\( ^{19} \)-R,
-\( ^{18} \)-L-R, and $L^{1}$ is alkylene, then -O-L-\( ^{18} \)-R, -O-L-\( ^{19} \)-R, -O-L-\( ^{20} \)-R are not
methoxy;

when \( \leftrightarrow \) is a double bond, $R^{14}$ is hydrogen, $R^{5}$ is O, $L^{1}$ is -C(O)-
alkylene, -C(0)-arylene, -C(0)-arylene, -C(0)-alkylene, -C(0)NR$_2$, alkylene, or -C(0)NR$_2$-arylene, then none of $R^{18}$, $R^{19}$ or $R^{20}$ are hydrogen.

In one embodiment, the noribogaine derivative is represented by Formula IV:
or a pharmaceutically acceptable salt and/or solvate thereof,

wherein

\( R_2 \) is selected from the group consisting of hydrogen, a hydrolysable group
selected from the group consisting of \(-\text{C}(0)R_3\), \(-\text{C}(0)\text{NR}_4R_5\) and \(-\text{C}(0)\text{OR}_6\), where \( R_3 \) is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl, \( R_4 \) and \( R_5 \) are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkynyl, substituted alkenyl, alkynyl, substituted alkenyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryls, heterocyclic and substituted heterocyclic, \( R_6 \) is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkenyl, alkynyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, provided that \( R_1 \) is not a saccharide or an oligosaccharide;

\( L_2 \) is selected from the group consisting of a covalent bond and a cleavable linker group:

\( R_2 \) is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic, provided that \( R \) is not a saccharide or an oligosaccharide;

provided that when \( L_2 \) is a covalent bond and \( R_2 \) is hydrogen, then \( R_2 \) is selected from the group consisting of \(-\text{C}(0)\text{NR}_4R_5\) and \(-\text{C}(0)\text{OR}_6\); and

further provided that when \( R_1 \) is hydrogen or \(-\text{C}(0)R_3\) and \( V \) is a covalent bond, then \( R_2 \) is not hydrogen.

[0151] In one embodiment, the noribogaine derivative is represented by Formula V:
or a pharmaceutically acceptable salt and/or solvate thereof,
wherein:

\[ \text{refers to a single or a double bond provided that when } \text{ is a single bond,} \]

Formula V refers to the corresponding dihydro compound;

\[ \text{R}^27 \text{ is hydrogen or S0}_2\text{OR}^{29}; \]
\[ \text{R}^28 \text{ is hydrogen or S0}_2\text{OR}^{29}; \]
\[ \text{R}^29 \text{ is hydrogen or C}_1 \text{- C}_6 \text{ alkyl;} \]

provided that at least one of \( R^{27} \) and \( R^{28} \) is not hydrogen.

[0152] In one embodiment, the noribogaine derivative is represented by Formula VI:

\[ \text{VI} \]

or a pharmaceutically acceptable salt and/or solvate thereof,
wherein:

\[ \text{refers to a single or a double bond provided that when } \text{ is a single bond,} \]

Formula VI refers to the corresponding vicinal dihydro compound;

\[ \text{R}^{30} \text{ is hydrogen, a monophosphate, a diphosphate or a triphosphate; and} \]
\[ \text{R}^{31} \text{ is hydrogen, a monophosphate, a diphosphate or a triphosphate;} \]

provided that both \( R^{30} \) and \( R^{31} \) are not hydrogen;

wherein one or more of the monophosphate, diphosphate and triphosphate groups of \( R^{30} \)
and \( R^{31} \) are optionally esterified with one or more C1-Ce alkyl esters.

III. Methods of the Invention

[0153] As will be apparent to the skilled artisan upon reading this disclosure, the present invention provides a method for treating a disease associated with an undesired downstream effect of nAChR activity in a patient in need thereof, the method comprising administering to the patient a dosage of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof. The present invention further provides a method for treating a cell expressing at least one nAChR, the method comprising
administering to the cell noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof.

[0154] In one aspect, this invention relates to treatment or attenuation of a disease associated with an undesired downstream effect of nAChR activity, or a symptom of said disease. In one embodiment, the disease is associated with activation of one or more nAChR subtypes. In one embodiment, the disease is associated with desensitization of one or more nAChR subtypes. In one embodiment, the treatment comprises administration of a therapeutically effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof to a patient having or suspected of having a disease associated with an undesired downstream effect of nAChR activity.

[0155] In one aspect, this invention relates to a method for treating a disease associated with an undesired downstream effect of nAChR activity, comprising administering to the patient an effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof to treat said disease.

[0156] In one aspect, this invention relates to attenuating at least one symptom of a disease associated with an undesired downstream effect of nAChR activity in a subject, the method comprising administering to the subject an effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof to attenuate said symptom.

Low Dose Noribogaine

[0157] In one aspect, this invention is based on the surprising and unexpected discovery that low doses of noribogaine, noribogaine derivative, salt or solvate thereof are effective for attenuating diseases or disorders (or symptoms thereof) that are associated with an undesired downstream response as a result of nicotinic acetylcholine receptor (nAChR) activity. Without being bound by theory, it is contemplated that such low doses of noribogaine, noribogaine derivative, salt or solvate thereof result in a decreased risk of unacceptable QT interval prolongation while also providing a therapeutic effect.

[0158] In one aspect, this invention is directed to treatment of a disease or disorder (or symptom thereof) that is associated with an undesired downstream response as a result of
nicotinic acetylcholine receptor (nAChR) activity in a patient in need thereof, the method comprising administering to the patient an effective, low dose of noribogaine, noribogaine derivative, salt or solvate thereof. In one embodiment, the disease or disorder is a depressive disorder, an anxiety disorder, a memory disorder, or an attention disorder. In one embodiment, the disease or disorder is addiction to an addictive substance and/or withdrawal from the addictive substance. In one embodiment, the addictive substance is nicotine or caffeine.

[0159] "Depressive disorders" or "depression-related disorders" include major depressive disorder and dysthymic disorder (American Psychiatric Association, 1994a; American Psychiatric Association, 1994b). Major depressive disorder is characterized by the occurrence of one or more major depressive episodes without manic or hypomanic episodes. A major depressive episode is defined as a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it can include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation. Dysthymic disorder involves a type of depression that is not severe enough to be called a major depressive episode, but that lasts much longer than major depressive disorder, without high phases. U.S. Patent Application Pub. No. 2015/0258107 relates to treatment of depressive disorders and is incorporated by reference herein in its entirety.

[0160] "Anxiety disorders" include panic disorder, agoraphobia with or without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder and generalized anxiety disorder. It is contemplated that the compounds of this invention will be effective in treating these disorders in patients who have been diagnosed as having such disorders.

[0161] It is contemplated that the compounds utilized herein can be effective in treating ADHD or ADD in patients who have the disorder, based upon the diagnostic criteria described in DSM-IV or DSM-5. It is further contemplated that the compounds utilized herein will be effective in reducing symptoms of this disorder, including impulsivity or
lack of self-control. It is also contemplated that the compounds described herein will be effective in preventing relapse of ADD or ADHD.


[0163] It is contemplated that the compounds utilized herein can be effective in treating memory and attention disorders, including dementia and Alzheimer's disease, in patients who have the disorder, based upon standard diagnosis protocols.

[0164] In one embodiment, the effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides an average serum concentration of less than about 60 ng/mL. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides an average serum concentration of less than about 50 ng/mL. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides an average serum concentration of less than about 40 ng/mL. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides an average serum concentration of less than about 30 ng/mL. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides an average serum concentration of less than about 20 ng/mL.

[0165] In one embodiment, the QT interval is not prolonged more than about 20 ms. In one embodiment, the QT interval is not prolonged more than about 10 ms.

[0166] In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 70 mg and about 150 mg. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 75 mg and about 150 mg. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 80 mg and about 140 mg. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 90 mg and about 140 mg. In one embodiment, the dosage or aggregate
dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 90 mg and about 130 mg. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 100 mg and about 130 mg. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 110 mg and about 130 mg.

[0167] In some embodiments, the therapeutically effective amount of the compound is from about 50 ng to less than 10 µg per kilogram body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 50 ng to about 5 µg per kilogram body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 50 ng to about 1 µg per kilogram body weight per day. In another embodiment, the therapeutically effective amount of the compound is from about 50 ng to about 1 µg per kilogram body weight per day. In yet another embodiment, the therapeutically effective amount of the compound is from about 500 ng to less than 10 µg per kilogram body weight per day. In yet another embodiment, the therapeutically effective amount of the compound is from about 1 µg to less than 10 µg per kilogram body weight per day. In yet another embodiment, the therapeutically effective amount of the compound is about 50 ng, about 100 ng, about 150 ng, about 200 ng, about 250 ng, about 300 ng, about 350 ng, about 400 ng, about 450 ng, about 500 ng, about 550 ng, about 600 ng, about 650 ng, about 700 ng, about 750 ng, about 800 ng, about 850 ng, about 900 ng, about 950 ng, about 1 µg, about 2 µg, about 3 µg, about 3 µg, about 4 µg, about 5 µg, about 6 µg, about 7 µg, about 8 µg, about 9 µg, about 10 µg per kilogram body weight per day. The therapeutically effective amount of the compound may be any amount within any of these ranges, including endpoints.

Noribogaine Dosing

[0168] In one aspect, this invention is directed to a method for treatment of a disorder or disease (and/or symptom thereof) that is associated with an undesired downstream response as a result of nicotinic acetylcholine receptor (nAChR) activity in a patient in need thereof comprising administering to the patient an effective amount of noribogaine, noribogaine derivative, salt or solvate thereof so as to treat the disease or disorder, or to ameliorate a symptom thereof. In one embodiment, the effective amount of noribogaine,
noribogaine derivative, salt or solvate thereof is a low dose as described above. In one embodiment, the effective amount is a higher dose.

[0169] Without being bound by theory, it is contemplated that a higher dose of noribogaine, noribogaine derivative, salt or solvate thereof will be acceptable in the treatment of some disorders/symptoms, e.g. addiction to addictive substances, schizophrenia, or suicidal depression. Such disorders are associated with a high risk of immediately life-threatening symptoms (e.g., suicide, homicide, overdose, etc.). Moreover, the symptoms associated with such disorders may be severe and/or life-altering. Therefore, an increased risk of QT interval prolongation may be appropriate for patients suffering from these disorders.

[0170] "Suicidal depression" refers to severe depression that is accompanied by suicidal ideation and/or an increased risk of suicide.

[0171] In one embodiment, the disease or disorder is schizophrenia. In one embodiment, the disease or disorder is addiction to an addictive substance and/or withdrawal from the addictive substance. In one embodiment, the addictive substance is alcohol, an opioid, cocaine, a barbituate, or another narcotic or prescription drug.

[0172] It is contemplated that the compounds utilized herein can be effective in treating schizophrenia in patients who have the disorder, based upon the diagnostic criteria described in DSM-IV or DSM-5. Schizophrenia is characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction. It is further contemplated that the compounds utilized herein will be effective in reducing symptoms of this disorder. It is also contemplated that the compounds described herein will be effective in preventing relapse of schizophrenia.

[0173] In one embodiment, the effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides an average serum concentration of less than about 180 ng/mL. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides an average serum concentration of between about 50 ng/mL and about 180 ng/mL.
In some embodiments, the serum concentration is sufficient to attenuate said symptoms or treat said disease while maintaining a QT interval of less than about 500 ms during treatment. In some embodiments, a QT interval of less than about 470 ms is maintained during treatment. Preferably, a QT interval of less than about 450 ms is maintained during treatment. In one embodiment, a QT interval of less than about 420 ms is maintained during treatment.

In one embodiment, the QT interval is not prolonged more than about 50 ms. In one embodiment, the QT interval is not prolonged more than about 40 ms. In one embodiment, the QT interval is not prolonged more than about 30 ms. In one embodiment, the QT interval is not prolonged more than about 20 ms.

In one embodiment, the average serum concentration of noribogaine after treatment is less than about 180 ng/mL. In one embodiment, the average serum concentration of noribogaine is less than about 150 ng/mL. In one embodiment, the average serum concentration of noribogaine is less than about 130 ng/mL. In one embodiment, the average serum concentration of noribogaine is less than about 120 ng/mL. In one embodiment, the average serum concentration of noribogaine is less than about 110 ng/mL. In one embodiment, the average serum concentration of noribogaine is less than about 100 ng/mL.

In one embodiment, the dosage of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a maximum serum concentration (Cmax) of less than about 250 ng/mL. In one embodiment, the dosage of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a maximum serum concentration (Cmax) of less than about 150 ng/mL. In one embodiment, the dosage of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a Cmax between about 40 ng/mL and about 250 ng/mL. In one embodiment, the dosage of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a Cmax between about 60 ng/mL and about 200 ng/mL. In one embodiment, the dosage of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof provides a Cmax between about 100 ng/mL and about 180 ng/mL.
In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 1 mg/kg to about 4 mg/kg body weight per day. The aggregate dosage is the combined dosage, for example the total amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof administered over a 24-hour period where smaller amounts are administered more than once per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 1.8 mg/kg to about 4 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 1.3 mg/kg to about 3 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 1.5 mg/kg to about 3 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 1.7 mg/kg to about 3 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 2 mg/kg to about 4 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 2 mg/kg to about 3 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 2 mg/kg body weight. The ranges include both extremes as well as any subranges there between.

In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 4 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 3 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 2 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1.9 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1.8 mg/kg body-weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine,
noribogaine derivative, or salt or solvate thereof is about 1.7 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1.6 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1.5 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1.4 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1.3 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1.2 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1.1 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1 mg/kg body weight per day.

[0180] In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 0.1 mg/kg to about 1 mg/kg body weight per day. The aggregate dosage is the combined dosage, for example the total amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof administered over a 24-hour period where smaller amounts are administered more than once per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 0.3 mg/kg to about 1 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 0.3 mg/kg to about 0.8 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 0.5 mg/kg to about 0.8 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 0.6 mg/kg to about 0.8 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is from about 0.7 mg/kg to about 1 mg/kg body weight.
noribogaine derivative, or salt or solvate thereof is from about 0.7 mg/kg to about 0.8 mg/kg body weight. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.5 mg/kg body weight. The ranges include both extremes as well as any subranges there between.

[0181] In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 1 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.9 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.8 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.6 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.5 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.4 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.3 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.2 mg/kg body weight per day. In one embodiment, the dosage or aggregate dosage of noribogaine, noribogaine derivative, or salt or solvate thereof is about 0.1 mg/kg body weight per day.

[0182] In another embodiment, there is provided a unit dose of noribogaine, noribogaine derivative, or salt or solvate thereof. The unit dose may be any dose provided herein. In one embodiment, the unit dose is about 120 mg. In one embodiment, the unit dose is between about 5 mg and about 120 mg. It being understood that the term "unit dose" means a dose sufficient to provide therapeutic results whether given all at once or serially over a period of time.

[0183] In some embodiments, the patient is administered an initial dose of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof, followed by
one or more additional doses. In one embodiment, such a dosing regimen provides an average serum concentration of noribogaine of less than about 180 ng/mL. In one embodiment, the one or more additional doses maintain an average serum concentration of less than about 180 ng/mL over a period of time.

[0184] In some embodiments, the patient is administered periodically, such as once, twice, three time, four times or five time daily with noribogaine, noribogaine derivative, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the administration is once daily, or once every second day, once every third day, three times a week, twice a week, or once a week. The dosage and frequency of the administration depends on the route of administration, dosage, age and body weight of the patient, condition of the patient, without limitation. Determination of dosage and frequency suitable for the present technology can be readily made a qualified clinician.

[0185] Noribogaine, noribogaine derivative, or a pharmaceutically acceptable solvate or salt thereof, suitable for administration in accordance with the methods provide herein, can be suitable for a variety of delivery modes including, without limitation, oral and transdermal delivery. Compositions suitable for internal, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intra-arterial, intramuscular, intraperitoneal, intracutaneous and subcutaneous routes may also be used. Possible dosage forms include tablets, capsules, pills, powders, aerosols, suppositories, parenterals, and oral liquids, including suspensions, solutions and emulsions. Sustained release dosage forms may also be used. All dosage forms may be prepared using methods that are standard in the art (see e.g., Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton Pa. 1980).

[0186] In a preferred embodiment, noribogaine, noribogaine derivative, or a pharmaceutically acceptable salt or solvate thereof is administered orally, which may conveniently be provided in tablet, caplet, sublingual, liquid or capsule form. In certain embodiments, the noribogaine is provided as noribogaine HC1, with dosages reported as the amount of free base noribogaine. In some embodiments, the noribogaine HC1 is provided in hard gelatin capsules containing only noribogaine HC1 with no excipients.

Treatment of a Cell
In one aspect, described herein is a method for attenuating an unwanted downstream effect of nAChR activity in a cell comprising at least one nAChR, the method comprising treating the cell with an effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof. In one embodiment, the cell is a neuron.

In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 0.3 µM and about 50 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 1 µM and about 50 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 5 µM and about 50 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 10 µM and about 50 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 20 µM and about 50 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 25 µM and about 50 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 30 µM and about 50 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 40 µM and about 50 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 0.3 µM and about 40 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 0.3 µM and about 30 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 0.3 µM and about 20 µM. In one embodiment, the effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof is between about 0.3 µM and about 10 µM.
Patient Pre-screening and Monitoring

[0189] Pre-screening of patients before treatment with noribogaine and/or monitoring of patients during noribogaine treatment may be required to ensure that QT interval is not prolonged beyond a certain value. For example, QT interval greater than about 500 ms can be considered dangerous for individual patients. Pre-screening and/or monitoring may be necessary at high levels of noribogaine treatment.

[0190] In one embodiment, a patient receiving a therapeutic dose of noribogaine is monitored in a clinical setting. Monitoring may be necessary to ensure the QT interval is not prolonged to an unacceptable degree. A "clinical setting" refers to an inpatient setting (e.g., inpatient clinic, hospital, rehabilitation facility) or an outpatient setting with frequent, regular monitoring (e.g., outpatient clinic that is visited daily to receive dose and monitoring). Monitoring includes monitoring of QT interval. Methods for monitoring of QT interval are well-known in the art, for example by ECG.

[0191] In one embodiment, a patient receiving a therapeutic dose of noribogaine is not monitored in a clinical setting. In one embodiment, a patient receiving a maintenance dose of noribogaine is monitored periodically, for example daily, weekly, monthly, or occasionally. This is particularly relevant where the therapeutic dose of noribogaine administered to the patient is below that known to cause a problematic QT interval prolongation, e.g., when the aggregate dose is below about 120 mg per day.

[0192] As it relates to pre-screening or pre-selection of patients, patients may be selected based on any criteria as determined by the skilled clinician. Such criteria may include, by way of non-limiting example, pre-treatment QT interval, pre-existing cardiac conditions, risk of cardiac conditions, age, sex, general health, and the like. The following are examples of selection criteria for disallowing noribogaine treatment or restricting dose of noribogaine administered to the patient: high QT interval before treatment (e.g., such that there is a risk of the patient's QT interval exceeding about 500 ms during treatment); congenital long QT syndrome; bradycardia; hypokalemia or hypomagnesemia; recent acute myocardial infarction; uncompensated heart failure; and taking other drugs that increase QT interval. In some embodiments, the methods can include selecting and/or administering/providing noribogaine to a patient that lacks one more of such criteria.
In one embodiment, this invention relates to pre-screening a patient to determine if the patient is at risk for prolongation of the QT interval beyond a safe level. In one embodiment, a patient at risk for prolongation of the QT interval beyond a safe level is not administered noribogaine. In one embodiment, a patient at risk for prolongation of the QT interval beyond a safe level is administered noribogaine at a limited dosage.

In one embodiment, this invention relates to monitoring a patient who is administered a therapeutic dose of noribogaine. In one embodiment, the dose of noribogaine is reduced if the patient has serious adverse side effects. In one embodiment, the noribogaine treatment is discontinued if the patient has serious adverse side effects. In one embodiment, the adverse side effect is a QT interval that is prolonged beyond a safe level. The determination of a safe level of prolongation is within the skill of a qualified clinician.

Formulations

This invention further relates to pharmaceutically acceptable formulations comprising a unit dose of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof, wherein the amount of noribogaine is sufficient to provide an average serum concentration of less than about 180 ng/mL when administered to a patient. In a preferred embodiment, the amount of noribogaine is sufficient to provide an average serum concentration of less than about 100 ng/mL when administered to a patient. The formulation may comprise any amount of noribogaine, noribogaine derivative, or pharmaceutically acceptable salt or solvate thereof as described herein.

In some embodiments, the unit dose of noribogaine is administered in one or more dosings.

In some embodiments, the formulation designed for administration in accordance with the methods provide herein can be suitable for a variety of delivery modes including, without limitation, oral and transdermal delivery. Formulations suitable for internal, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intra-arterial, intramuscular, intraperitoneal, intracutaneous and subcutaneous routes may also be used. Possible formulations include tablets, capsules, pills, powders, aerosols, suppositories, parenterals, and oral liquids, including suspensions, solutions and emulsions. Sustained release dosage
forms may also be used. All formulations may be prepared using methods that are
standard in the art (see e.g., Remington's Pharmaceutical Sciences, 16th ed., A. Oslo
editor, Easton Pa. 1980).

[0198] In a preferred embodiment, the formulation is designed for oral administration,
which may conveniently be provided in tablet, caplet, sublingual, liquid or capsule form.
In certain embodiments, the noribogaine is provided as noribogaine HCl, with dosages
reported as the amount of free base noribogaine. In some embodiments, the noribogaine
HCl is provided in hard gelatin capsules containing only noribogaine HCl with no
excipients.

EXAMPLES

[0199] The following Examples are intended to further illustrate certain embodiments of
the disclosure and are not intended to limit its scope.

Example 1. Pharmacokinetics and pharmacodynamics of noribogaine in humans

[0200] Thirty-six healthy, drug-free male volunteers, aged between 18-55 years, were
enrolled in and completed the study. This was an ascending single-dose, placebo-
controlled, randomized double blind, parallel group study. Mean (SD) age was 22.0 (3.3)
years, mean (SD) height was 1.82 (0.08) m, and mean (SD) weight was 78.0 (9.2) kg.
Twenty-six subjects were Caucasian, 3 were Asian, 1 Maori, 1 Pacific Islander, and 5
Other. The protocol for this study was approved by the Lower South Regional Ethics
Committee (LRS/12/06/015), and the study was registered with the Australian New
Zealand Clinical Trial Registry (ACTRN126 12000821897). All subjects provided signed
informed consent prior to enrolment, and were assessed as suitable to participate based on
review of medical history, physical examination, safety laboratory tests, vital signs and
ECG.

[0201] Within each dose level, 6 participants were randomized to receive noribogaine
and 3 to receive placebo, based on a computer-generated random code. Dosing began with
the lowest noribogaine dose, and subsequent cohorts received the next highest dose after
the safety, tolerability, and blinded pharmacokinetics of the completed cohort were
reviewed and dose-escalation approved by an independent Data Safety Monitoring Board.
Blinded study drug was administered as a capsule with 240 ml of water after an overnight
fast of at least 10 hours. Participants did not receive any food until at least 5 hours post-dose. Participants were confined to the study site from 12 hours prior to drug administration, until 72 hours post-dose, and there were subsequent outpatient assessments until 216 hours post-dose.

[0202] Blood was obtained for pharmacokinetic assessments pre-dose and then at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 18, 24, 30, 36, 48, 60, 72, 96, 120, 168 and 216 hours post-dose. Samples were centrifuged and plasma stored at -70 °C until analyzed. Block 24 hour urine collections were obtained following study drug administration for the 30 and 60 mg cohorts. Aliquots were frozen at -20 °C until analyzed.

[0203] Pulse oximetry and capnography data were collected continuously using a GE Carescape B650 monitoring system from 2 hours prior to dosing and until six hours after dosing, and thereafter at 12, 24, 48 and 72 hours post-dosing. Additional oximetry data were collected at 120, 168 and 216 hours. Pupillary miosis was assessed by pupillometry. Dark-adapted pupil diameter was measured in triplicate using a Neuroptics PLR-200 pupillometer under standardized light intensity (<5 lux) pre-dose, and at 2, 4, 6, 12, 24, 48, 72, 96, 120, 168 and 216 hours post-dosing.

[0204] Plasma noribogaine concentrations were determined in the 3 mg and 10 mg dose groups using a validated, sensitive LCMSMS method. Sample preparation involved double extraction of basified plasma samples with tert-butyl methyl ether, drying the samples under a stream of nitrogen and reconstitution of sample with acetonitrile:B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5μm C18 column and detected with a triple - quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d₄ was used as the internal standard. The precursor-product ion transition values for noribogaine were m/z 297.6 → 122.3, and for the internal standard noribogaine-d₄ m/z 301.1 → 122.2. Analyst® software was used for data acquisition and processing. The ratio of the peak area of noribogaine to the internal standard noribogaine^\dagger was used for calibration and measurement of the unknown concentration of noribogaine. The lower limit of quantification (LLOQ) was 0.025 ng/ml noribogaine. The calibration curve was between 0.025 and 25.600 ng/ml noribogaine. Mobile phase A was acetonitrile:B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid,
and mobile phase B was acetonitrile B.P. water (95:5, v/v) containing 0.1% (v/v) formic acid. Total run time was 6 minutes. Binary flow: Initial concentration was 8% mobile phase B; hold at 8% mobile phase B for 0.5 minutes and linear rise to 90% mobile phase B over 1.5 minutes; hold at 90% mobile phase B for 1 minute and then drop back to 8% mobile phase B over 0.01 minute. Equilibrate system for 3 minutes. Total run time was 6 minutes. Within- and between-day assay precision was < 9%, and within- and between-day assay accuracy was < 9%.

[0205] Plasma noribogaine concentrations were determined in the 30 mg and 60 mg dose groups using a validated, sensitive LCMSMS method. Sample preparation involved deproteinization of plasma samples with acetonitrile and dilution of sample with 0.1% (v/v) formic acid. The compounds were separated by a 150 x 2.0 mm Luna 5μm C18 column and detected with a triple - quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d4 was used as the internal standard. The precursor-product ion transition values for noribogaine were m/z 297.6 -> 122.3, and for the internal standard noribogaine-d4 m/z 301.1 -> 122.2. Analyst* software was used for data acquisition and processing. The ratio of the peak area of noribogaine to the internal standard noribogaine-d4 was used for calibration and measurement of the unknown concentration of noribogaine. The LLOQ was 0.50 ng/ml noribogaine. The calibration curve was between 0.50 and 256.00 ng/ml noribogaine. Mobile phase was the same as method A, and binary flow was also the same as method A. The within- and between-day assay precision was < 9%, and the within- and between-day assay accuracy was < 9%.

[0206] Plasma noribogaine glucuronide concentrations were determined in the 30 mg and 60 mg dose groups using a validated sensitive LCMSMS method. Sample preparation involved deproteinization of plasma samples with acetonitrile, drying the samples under a stream of nitrogen and reconstitution of sample with acetonitrile: B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid. The compounds were separated by a 150 x 2.0 mm Luna 5μm C18 column and detected with a triple - quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogame-d.4 was used as the internal standard. The precursor-product ion transition values for noribogaine glucuronide were m/z 472.8 -> 297.3, and for the internal standard noribogaine-d4 m/z 301.1 -> 122.2. Analyst* software was used for data...
acquisition and processing. The ratio of the peak area of noribogaine glucuronide to the internal standard noribogaine-d4 was used for calibration and measurement of the unknown concentration of noribogaine glucuronide. The LLOQ was 0.050 ng/ml noribogaine glucuronide. The calibration curve was between 0.050 and 6.400 ng/ml noribogaine glucuronide. Mobile phases was the same as method A. Binary flow: Initial concentration was 6% mobile phase B; hold at 6% mobile phase B for 0.5 minutes and linear rise to 90% mobile phase B over 2 minutes; hold at 90% mobile phase B for 1 minute and then drop back to 6% mobile phase B over 0.01 minute. Equilibrate system for 3.5 minutes. Total run time was 7 minutes. The within- and between-day assay precision was < 11%, and the within- and between-day assay accuracy was < 10%.

Urine noribogaine and noribogaine glucuronide concentrations were determined in the 30 mg and 60 mg dose groups using a validated sensitive LCMSMS method. Sample preparation involved deproteinization of urine samples with acetonitrile and dilution of the sample with 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5µm C18 column and detected with a triple - quadrupole API 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogame-d4 was used as the internal standard. The precursor-product ion transition values for noribogaine were m/z 297.6 -> 122.3, noribogaine glucuronide m/z 472.8 -> 297.3, and for the internal standard noribogaine-oU m/z 301.1 -> 122.2. Analyst® software was used for data acquisition and processing. The ratios of the peak area of noribogaine and noribogaine glucuronide to the internal standard noribogaine-d4 were used for calibration and measurement of the unknown concentration of noribogaine and its glucuronide. Assay LLOQ was 20.0 ng/ml for noribogaine and 2.0 ng/ml for noribogaine glucuronide. The calibration curve was between 20.0 and 5120.0 ng/ml noribogaine, and 2.0 and 512.0 ng/ml noribogaine glucuronide. Mobile phases were as described in method A, and binary flow as in method C. The within- and between-day assay precision was < 13%, and within- and between-day assay accuracy was < 12%.

Noribogaine and noribogaine glucuronide concentrations above the limit of quantification were used to calculate pharmacokinetic parameters using model-independent methods. The maximum plasma concentration (Cmax) and time to maximum plasma concentration (Tmax) were the observed values. Plasma concentration data in the post-distribution phase of the plasma concentration-time plot were fitted using linear
regression to the formula \( \ln C = \ln C_0 - t \cdot K_{el} \), where \( C_0 \) was the zero-time intercept of the extrapolated terminal phase and \( K_{el} \) was the terminal elimination rate constant. The half-life (t1/2) was determined using the formula \( t_{1/2} = 0.693/K_{el} \). The area under the concentration-time curve (AUC) from time zero to the last determined concentration-time point (\( t_f \)) in the post-distribution phase was calculated using the trapezoidal rule. The area under the curve from the last concentration-time point in the post-distribution phase (\( C_{tf} \)) to time infinity was calculated from \( AUC_{t_f} = C_{tf}/K_{el} \). The concentration used for \( C_{tf} \) was the last determined value above the LLOQ at the time point. The total AUC was obtained by adding AUC0-\( t_f \) and AUC0-\( C_{tf} \). Noribogaine apparent clearance (\( CL/F \)) was determined using the formula \( CL/F = Dose/AUC_0-t \cdot 1000 \), and apparent volume of distribution (\( Vd/F \)) was determined using the formula \( Vd/F = (CL/F)/K_{el} \). Total urine noribogaine was the sum of both analytes.

Summary statistics (means, standard deviations, and coefficients of variation) were determined for each dose group for safety laboratory test data, ECG and pharmacokinetic parameters, and pharmacodynamic variables. Categorical variables were analysed using counts and percentages. Dose-proportionality of AUC and Cmax was assessed using linear regression. The effect of dose on pharmacodynamic parameter values over time was assessed using two-factor analysis of variance (ANOVA). Pairwise comparisons (with Tukey-Kramer adjustment) between each dose group to the placebo were conducted at each time point using the least squares estimates obtained from the ANOVA, using SAS Proc Mixed (SAS ver 6.0).

Results

Pharmacokinetics: Mean plasma concentration-time plots of noribogaine are shown in Figure 5, and mean pharmacokinetic parameters are shown in Table 1.

<table>
<thead>
<tr>
<th>Noribogaine</th>
<th>3 mg (n=6) (mean (SD))</th>
<th>10 mg (n=6) (mean (SD))</th>
<th>30 mg (n=6) (mean (SD))</th>
<th>60 mg (n=6) (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (ng hr/ml)</td>
<td>74.2 (13.1)</td>
<td>254.5 (78.9)</td>
<td>700.4 (223.3)</td>
<td>1962.2 (726.5)</td>
</tr>
<tr>
<td>AUC0-216 (ng hr/ml)</td>
<td>72.2 (13.2)</td>
<td>251.4 (78.5)</td>
<td>677.6 (221.1)</td>
<td>1935.4 (725.4)</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>5.2 (1.4)</td>
<td>14.5 (2.1)</td>
<td>55.9 (14.8)</td>
<td>116.0 (22.5)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.9 (0.6)</td>
<td>2.9 (1.8)</td>
<td>1.8 (0.6)</td>
<td>2.4 (0.6)</td>
</tr>
</tbody>
</table>
Noribogaine was rapidly absorbed, with peak concentrations occurring 2-3 hours after oral dosing. Fluctuations in individual distribution-phase concentration-time profiles may suggest the possibility of enterohepatic recirculation (see highlighted individual 4-8 hour profiles in Figure 5, insert). Both Cmax and AUC increased linearly with dose (Table 1, upper panel). Mean half-life estimates of 28-50 hours were observed across dose groups for noribogaine. Volume of distribution was extensive (1417-3086 L across dose groups).

Mean plasma noribogaine glucuronide concentration-time plots for the 30 mg and 60 mg dose group are shown in Figure 6, and mean pharmacokinetic parameters are shown in Table 1, lower panel. Noribogaine glucuronide was detected in all subjects by 0.75 hours, with peak concentrations occurring 3-4 hours after noribogaine dosing. Mean half-life of 21-23 hours was estimated for plasma noribogaine glucuronide. The proportion of noribogaine glucuronide Cmax and AUC relative to noribogaine was 3-4% for both dose groups. Total urine noribogaine elimination was 1.16 mg and 0.82 mg for the 30 mg and 60 mg dose groups respectively, representing 3.9% and 1.4% of the doses administered.

Pharmacodynamics: There was no evidence of pupillary constriction in subjects dosed with noribogaine. No between-dose group differences in pupil diameter were detected over time. After adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences (p>0.9).

Noribogaine treatment showed no analgesic effect in the cold pressor test. Analgesic effect was assessed based on duration of hand immersion in ice water and on

<table>
<thead>
<tr>
<th>Parameter</th>
<th>30 mg (upper panel)</th>
<th>60 mg (upper panel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>1.8 (0.6)</td>
<td>4.1 (1.2)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>3.0 (0.6)</td>
<td>3.8 (1.2)</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>20.6 (4.9)</td>
<td>23.1 (3.0)</td>
</tr>
<tr>
<td>AUC0-24 (ng.hr/ml)</td>
<td>-</td>
<td>25.8 (9.3)</td>
</tr>
<tr>
<td>AUC0-216 (ng.hr/ml)</td>
<td>-</td>
<td>25.7 (9.1)</td>
</tr>
<tr>
<td>Vd/F (L)</td>
<td>2485.1 (801.5)</td>
<td>3085.8 (1197.0)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>41.4 (7.0)</td>
<td>42.3 (12.0)</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>40.9 (8.7)</td>
<td>49.2 (11.5)</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>27.6 (7.0)</td>
<td>29.1 (9.3)</td>
</tr>
</tbody>
</table>

![Table 1: Pharmacokinetic parameters for noribogaine and noribogaine glucuronide](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAIoAAADcCAYAAAAFlDp+AAAgAElEQVR42mOvAf0RQ7wZAAAAAElFTkSuQmCC)
visual analog scale (VAS) pain scores upon hand removal from the water bath. For duration of hand immersion, after adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences (p>0.9). Similarly, for VAS pain scores, after adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences (p=0.17).

Example 2. Safety and tolerability of noribogaine in healthy humans

[0215] Safety and tolerability of noribogaine were tested in the group of volunteers from Example 1. Cold pressor testing was conducted in 1 °C water according to the method of Mitchell et al. (J Pain 5:233-237, 2004) pre-dose, 6, 24, 48, 72 and 216 hours post-dosing. Safety evaluations included clinical monitoring, recording of adverse events (AEs), safety laboratory tests, vital signs, ECG telemetry from -2h to 6h after dosing, and 12-lead electrocardiograms (ECGs) up to 216 hours post-dosing.

Results

[0216] A total of thirteen adverse events were reported by seven participants (Table 2). Six adverse events were reported by three participants in the placebo group, five adverse events were reported by two subjects in the 3 mg dose group, and one adverse event was reported by single subjects in the 10 mg and 30 mg dose groups, respectively. The most common adverse events were headache (four reports) and epistaxis (two reports). All adverse events were of mild-moderate intensity, and all resolved prior to study completion. There were no changes in vital signs or safety laboratory tests of note. In particular, there were no changes in oximetry or capnography, or changes in respiratory rate. There were no QTcF values >500 msec at any time. One subject dosed with 10 mg noribogaine had a single increase in QTcF of >60 msec at 24 hours post-dosing.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Blepharitis</td>
<td>Epistaxis</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Bruising</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eye pain, nonspecific Infection at cannula site</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 3. Effect of noribogaine on nACliR receptor activity in vitro

MATERIAL & METHODS

[0217] Materials and reagents. Fluo-2HA (high affinity) was purchased from TEFLabs, Inc. (Austin, TX). G418 sulfate, and Minimal Essential Medium was purchased from InVitrogen, (Carlsbad, CA). Mecamylamine, epibatidine, PNU-120596 and all buffer constituents were purchased from Sigma-Aldrich Corp. (St. Louis, MO). Ibogaine was provided by Dr. Deborah Mash at the University of Miami (Miami, FL). 18-MC was purchased at Orbiter Pharmaceutical. Noribogaine hydrochloride was purchased at Sigma Aldrich Chemie GmbH (Buchs Switzerland). SH-SY5Y human neuroblastoma cells which express endogenous nAChR a3, a5, a7, β2, and β4 subunit genes were purchased from ATCC (Manassas, VA.).

[0218] Cell Culture. SH-SY5Y cells were cultured in 50% Minimal Essential Medium (MEM) and 50% F12 + Glutamax containing 10% (v/v) fetal bovine serum at 37 °C in a 5% CO₂ incubator. SH-SY5Y cells were passaged every 4-6 days at 70-80% confluency using standard cell culture methods.

[0219] Ca²⁺ flux assays of Ca²⁺ channels expressed in SH-SY5Y cells. SH-SY5Y cells were plated in 96 well, black-walled, clear-bottom, poly-D-lysine coated plates at a density of approximately 100,000 cells/well in Minimal Essential Medium containing 10% (v/v) fetal bovine serum and grown for 2 days at 37 °C in a 5% CO₂ incubator. Cells were replenished with fresh media 16 to 20 hours before experiment. The cells were washed once with Hank's balanced salt solution (HBSS), loaded with 3 μM Fluo-2A diluted in 50 μl HBSS buffer, incubated for 1.5 h at room temperature, and then washed with HBSS and maintained in HBSS at 25 °C for 15 minutes. The plates of dye-loaded transfected cells were placed into a temperature-controlled (25 °C) FlexStation III apparatus (Molecular
Devices) to monitor fluorescence (excitation, 488 nm; emission, 525 nm; cutoff, 515 nm). For evaluation of the effects of test compounds using the Ca\(^{2+}\) flux assay, compounds were prepared in 96-well plates at X2 concentration in HBSS and the assay was initiated by the addition of 50 µl/well containing test compounds and the agonist epibatidine. For all assays, fluorescence values were collected at 0.5 Hz for 20 seconds (baseline), at which time stimulus buffers were added, and were further collected for 3 min.

**[0220] Data Analysis.** After obtaining a calcium mobilization trace for each sample, the calcium response to each condition was quantified as the change in signal from baseline (peak fluorescence) (denoted as \(AF/F\)) and noted by arbitrary fluorescent units. Peak fluorescence intensity occurred about 20-30 s after the addition of the agonist ligand. The raw fluorescence units data files generated on the Flexstation plate reader are automatically exported and processed by in-house data analysis tools. GraphPad Prism 5.04 was used to generate dose response curves. The data analysis, dose-response curve-fitting routines were carried out using GraphPad Prism 5.04 (GraphPad Software, Inc.). The data were expressed as the mean ± standard error of replicates.

**[0221] Sequence Alignments.** An *in silico* model of the binding site location of ibogaine proposes that ibogaine partially overlaps with the PCP binding site and interacts with the middle portion of the M2 transmembrane helices that form the wall of the channel pore. In this model, ibogaine in the neutral state interacts via hydrogen bonding with a serine (SER) (position 6'), leucine (LEU) (position 9'), and valine/phenylalanine (VAL/PHE) (position 12/13') rings. Van der Waals interactions between the aliphatic ring of ibogaine and the VAL/PHE and LEU rings were described for the outer region, whereas its methoxy moiety was proposed to form hydrogen bonds with several hydroxy! groups at the lower, deeper, serine ring. This is in contrast with the proposed binding of mecamylamine, which was shown to interact with the outer ring portion of the pore. Sequences of various nicotinic subunits were acquired from the Universal Protein Resource (UniProt) and sequence alignments were carried out using ClustalW.
RESULTS

Binding of [3H]epibatidine to nAChR subtypes stably expressed in SH-SY5Y cells.

Functional inhibitory potencies of noribogaine at heteromeric neuronal nicotinic receptors cc3-(α5, β4, β2) nAChRs subtypes epibatidine-evoked calcium flux.

The potency of noribogaine, and the control compounds ibogaine, 18-MC, and mecamylamine, in modulating the activation of endogenous human α3-(α5, β4, β2) nAChR subtypes was examined. Fluorescent Ca$^{2+}$ flux assays of Ca$^{2+}$ channels expressed in cell lines, including SH-SY5Y, is well documented. Fluorescent calcium traces and calculated maximal calcium peak values following the addition of the agonist epibatidine were collected. The EC50 of epibatidine dose-response curves in this assay was 3.4 ± 2.1 nM (Table 3) and matched the range of values reported in the literature. None of the test compounds influenced the basal calcium concentration, indicating that none were promoting partial nAChR agonism or artifactual stimulations under these conditions. Epibatidine concentration for inhibition dose-response assays were chosen at ~5 times its EC50 to allow sub-maximal stimulation without a large excess of agonist applied (50 nM).

Table 3

<table>
<thead>
<tr>
<th>nAChR Subtype</th>
<th>Noribogaine IC50 (μM)</th>
<th>n</th>
<th>Epibatidine EC50 (nM)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>α3-(α5, β4, β2)</td>
<td>0.488±0.109</td>
<td>5</td>
<td>3.4±2.1</td>
<td>2</td>
</tr>
</tbody>
</table>

Noribogaine inhibited epibatidine-evoked calcium flux at α3-(α5, β4, β2) nAChRs with an IC50 of 488 ± 109 nM (Figure 1, Table 4). Ibogaine inhibited epibatidine-evoked calcium flux at α3-(α5, β4, β2) with an IC50 of 38 ± 20 nM (Figure 1, Table 4). Mecamylamine inhibited epibatidine-evoked calcium flux at α3-(α5, β4, β2) nAChRs with an IC50 of 88 ± 8 nM (Figure 1, Table 4). The values for mecamylamine matched previously reported values for this type of assay (data not shown). 18-MC inhibited epibatidine-evoked calcium flux at α3-(α5, β4, β2) with an IC50 of 2.05 ± 0.26 μM (Figure 1, Table 4). 18-MC was marginally soluble at concentrations >100 μM.

Table 4
[0224] Ibogaine has been proposed to bind in the pore area of the nicotinic receptors, partially overlapping the PCP binding, deeper than the binding site of the channel blocker mecamylamine. Noribogaine at 0.3 and 1.5 µM decreased by 30 and 70% the maximal response of epibatidine-evoked calcium flux at α3-(α5, β4, β2) without affecting the EC₅₀ for epibatidine (from 9 nM to 11, and 22 nM) (Figure 2). This phenomenon is prototypical of non-competitive inhibitory mode of noribogaine at the α3-containing nAChRs.

Sequence alignment of the M2 transmembrane helices of alpha and beta nAChRs subunits with prototypical torpedo M2 subunit

[0225] It has been shown that the 2nd transmembrane (T2) region lines the pore of nAChRs and is involved in interactions with pore blocking antagonists, such as 18-MC and ibogaine (Arias et al. 2010; Arias et al. 2011). The model proposed by Arias et al was used for the basis of our analysis. M2 segments of human α3, α4, a5, β2, β4, and α7 nAChRs subunit proteins were aligned using ClustalW (Figure 3). Differences and similarities in the sequences were annotated for amino acids of interest; namely SER 6', LEU 9', VAL13', PHE14'. SER 6' was conserved in all subunits except a7', where the residue was THR. LEU 9' was conserved in all subunits except a5 where the residue was VAL. VAL13' was conserved in all subunits except β4 where the residue was PHE14'. PHE14' was conserved in all subunits. For each subunit, there were no differences noted in between human and rat species for these key amino acids (not shown).

DISCUSSION

[0226] In this work, we focused on the mechanics of noribogaine pharmacology on the ionotropic cholinergic receptors and discuss their potential contributions to noribogaine physiological outputs. We show that noribogaine is a non-competitive inhibitor of several neuronal ionotropic cholinergic receptors species, including heteromeric α3-containing nAChRs, at mid-nanomolar potencies. Ibogaine also displayed low and mid-nanomolar potencies at these targets (Table 1). This is in contrast to reported apparent affinities and
potencies of ibogaine (from 100 to 1000 times less potent/affine) at other targets commonly thought to be primordial (e.g. NMDA, SERT) for its effects at impeding addiction-related behaviors.

Both noribogaine and ibogaine had high specificity for the receptor populations expressed in the SH-SY5Y cell-line, and this specificity was higher than that observed for rat nAChRs. Recent work demonstrated that ibogaine allosterically inhibits (+/-)-epibatidine-induced Ca\(^{2+}\) influx in \(\alpha3\beta4\) nAChR via a site overlapping with the PCP binding site (Arias et al. 2010). Amino acids presumed to govern ibogaine and noribogaine’s binding are highly conserved between human and rats, with no differences in either subunit investigated (\(\alpha3, 4, a5, \beta2, \beta4, a7\)). Thus, the striking difference of sensitivity to noribogaine (and ibogaine) observed between rat and human nAChRs in cellular models is not readily explained by a species difference in the presumed binding site itself. On the other hand, we observed variations in some of these key amino acids within subunits \(\beta2/\beta4\) and \(\alpha3/\alpha5\). A PHE was present in \(\beta4\) in place of the conserved VAL in all other subunits, rendering this ring more bulky and hydrophobic where ibogaine and noribogaine, as well as other drugs with an aromatic structure (e.g. coronaridine, 18-MC), could possibly better interact and stabilize in this otherwise relatively large open area in the pore. Interestingly, the a5 subunit has a VAL in position 5’ instead of a LEU as for the \(\alpha3, \beta4, \beta2\) subunits, which constitutes an aliphatic-conserved substitution of smaller size. Such substitution, even if subtle, could result in significant changes in the sensitivity of the a5-containing channels to particular ligands.

The macroscopic activation and deactivation kinetics of the a3-containing channels in response to epibatidine stimulation were peculiar in the presence of noribogaine. Noribogaine increased the \(t_{1/2}\) of the macroscopic activation kinetics of the calcium transient with more subtle modulation of the deactivation kinetics. The slopes of the activation traces were similar to control, indicating that the increase in \(t_{1/2}\) resulted mostly in a delay at opening of the channels rather than a net decrease of activate-able channels to start with (as seen with lower concentration of the agonist epibatidine). In contrast, 18-MC and mecamylamine had no effect on the macroscopic activation of the channel and both sharply accelerated the macroscopic deactivation. These results underlie a distinctive mechanism of noribogaine in modulating the gating and transition rates.
properties of these nicotinic receptor channels that is not shared by 18-MC or mecamylamine. Overall, noribogaine appeared to impede gating properties (closed to open, and open to deactivated/desensitized channels) possibly reflecting an increase of the free energy necessary for these conformational transitions. Interestingly, similar mechanisms were recently described and studied in depth for ibogaine at the hERG channels (Thurner et al. 2014) and it was proposed that ibogaine only blocks open channels, and must be released for the channel to deactivate. In this study, steady state of activation and deactivation was shifted to more negative membrane potentials.

[0229] Knockout mice studies have shown that α4 and β2 are critically involved in the rewarding effects of nicotine while α5, αl, and β4 may contribute to the somatic aspects of nicotine withdrawal (Fowler et al. 2008). The habenula-interpeduncular system and β4 nAChR subunits in this pathway play an important role in nicotine withdrawal. Decreased signs of nicotine withdrawal have been observed not only in mice lacking α5 but also in β4 knockout (KO) animals (Salas et al. 2004, 2009; De Biasi and Salas 2008). Bupropion, an anti-depressant also prescribed for smoking cessation, blocked norepinephrine and dopamine reuptake, and was later discovered to preferentially antagonized α3β4 nAChRs as well (Slemmer et al. 2000; Arias 2009). 18-MC was an antagonist at α3β4 nAChR receptors mXenopus oocytes (Maisonneuve and Glick 2003), with supplemental activities at opioids receptor sites and batrachotoxin-sensitive sodium channels sites (Glick and Maisonneuve 2000). It is unclear if 18-MC mediates all of its in vivo behavioral effects through blockade of α3β4 nAChR uniquely. Nonetheless, intra-cranial injections of 18-MC in rats suggested that α3β4 nACliRs-rich region habenula-interpeduncular system are implicated in nicotine self-administration (Glick et al. 2011). Taken together, noribogaine, displaying, which displays a targeted dual activity at oc3(a5, β4, β2)- habenula type and a 7 nAChRs, is a suitable drug for nicotine cessation drug-based therapy.

[0230] The habenula receives input from the limbic system and basal ganglia while the fasciculus retroflexus is the primary habenular output to the midbrain. The habenula is a critical crossroad that influences the brain’s response to pain, stress, anxiety, sleep, reward and disappointment. Dysfunction of the habenula has been linked to depression, schizophrenia, and the effects of drugs of abuse, a7 nAChRs are predominantly expressed in the CNS, including the hippocampus, cortex, and ventral tegmental area, and are
involved with long term potentiation (LTP), memory, and attention deficits. These receptors may play an important role in anxiety-related disorders, may regulate the mood-enhancing effects of antidepressant drugs, the baseline affective state, and the expression of various symptoms of schizophrenia (Fowler et al. 2008). Of note, mecamylamine was shown to have antidepressant effect in mice mediated by the a.2 and e.7 subunit (Rabenstein et al. 2006). Thus, given its pharmacological profile at the nAChRs targets, noribogaine is expected to have beneficial effects in a variety of neuropsychiatric disorders. Of interest, the combination of potential anxiolytic properties via a.7 and anti-addictive properties via b.4, appears suitable for the known comorbidity of substance-abuse related disorders (e.g. alcohol and nicotine) complicated with anxiety related disorders (notably PTSD), a co-occurrence particularly prevalent in returning veterans (Saxon 2011).

Activities at these targets were equivalent or even more potent than some drugs currently used in therapeutics to modulate nicotinic receptor function (e.g. varenicline, bupropion, mecamylamine, Table 1). In these assays, noribogaine and ibogaine did not show any partial agonist activity, in contrast to many agonist-desensitizer drugs developed thus far to treat diseases associated with nAChRs dysregulation.

Figure 4 represents the subunit composition of nAChRs occurring in the habenula of P18 wild-type mice as originally described in (Scholze et al. 2012). The diagram illustrates a proposed subunit composition and relative expression levels of heterooligomeric receptors in this brain region. The SH-SY5Y cell line has been shown to express a.3, a.5, b.2 and b.4 subunits, resulting in a heterogeneous population of nicotinic receptors composed of a.3b.4, a.3a.5b.4, a.3b.4b.2, a.3a.5b.4b.2 nAChRs (Wang et al. 1996) that represents a useful cellular model of the nAChR population expressed in certain neurons of the habenula.
What is claimed is:

1. A method for attenuating an undesired downstream response as a result of nicotinic acetylcholine receptor (nAChR) activity in a cell comprising at least one nAChR, the method comprising administering to the cell an effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof attenuate the undesired downstream effect of nAChR activity.

2. The method of claim 1, wherein the cell is a neuronal cell.

3. The method of claim 1 or 2, wherein the amount of noribogaine, noribogaine derivative, or salt or solvate thereof administered is between about 1 x 10^{-8} M and about 1 x 10^{-4} M.

4. The method of claim 1 or 2, wherein the amount of noribogaine, noribogaine derivative, or salt or solvate thereof administered is between about 0.3 µM and about 50 µM.

5. A method for attenuating an undesired downstream response as a result of nicotinic acetylcholine receptor (nAChR) activity in a subject having a disorder associated with the downstream effect of nAChR activity, the method comprising administering to the subject an effective amount of noribogaine, noribogaine derivative, or salt or solvate thereof to attenuate the downstream effect, thereby treating or attenuating the disorder.

6. The method of claim 5, wherein the disorder is selected from the group consisting of an anxiety-related disorder, a depression-related disorder, schizophrenia, addiction to an addictive substance, a memory disorder, and an attention disorder.

7. The method of claim 6, wherein the disorder is addiction to an addictive substance.

8. The method of claim 7, wherein the substance is selected from the group consisting of an opioid, cocaine, nicotine, and alcohol.

9. The method of claim 6, wherein the disorder is a memory disorder or an attention disorder.
10. The method of claim 9, wherein the memory disorder or attention disorder is selected from the group consisting of Alzheimer's disease, dementia, attention deficit hyperactivity disorder, and attention deficit disorder.

11. The method of any one of claims 1-10, wherein the nAChR comprises at least one subunit selected from the group consisting of α3, α4, α7, β4, and β2.

12. The method of any one of claims 1-11, wherein activity of the nAChR is inhibited by noribogaine, noribogaine derivative, or salt or solvate thereof.

13. The method of any one of claims 5-10, wherein the amount of noribogaine, noribogaine derivative, or salt or solvate thereof administered to the subject is sufficient to provide an average serum concentration of noribogaine or noribogaine derivative of less than about 180 ng/mL.

14. The method of claim 13, wherein the amount of noribogaine, noribogaine derivative, or salt or solvate thereof administered to the subject is sufficient to provide an average serum concentration of noribogaine or noribogaine derivative less than about 60 ng/mL.

15. The method of any one of claims 5-10, wherein administration of noribogaine, noribogaine derivative, or salt or solvate thereof results in a QT interval prolongation of less than about 20 ms in the subject.
FIGURE 1

![Graph showing stimulated Ca\(^{2+}\) influx (% of control) versus log [inhibitor] (M). The graph includes data points for NORI, IBO, 18MC, and MECA.]

FIGURE 2

![Graph showing stimulated Ca\(^{2+}\) influx (% of control) versus log [Epibatidine] (M). The graph includes data points for CTR, + NORI (0.3), and + NORI (1.5).]
Helix-Z

Human a3 -LVYLPSCGEKTVLCISVLISLTLFVLVTETIPSTSLVIP-
Human a4 -LVYLPSCGEKTVLCISVLISLTLFVLVTETIPSTSLVIP-
Human a5 -LVYLPSCGEKTVLCISVLISLTLFVLVTETIPSTSLVIP-
Human a7 -LVYLPSCGEKTVLCISVLISLTLFVLVTETIPSTSLVIP-
Human b2 -LVYLPSCGEKVLCISVLISLTLFVLVTETIPSTSLVIP-
Human b4 -LVYLPSCGEKVLCISVLISLTLFVLVTETIPSTSLVIP-

FIG. 3
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC(8)** - A61K 31/00; A61K 31/33; A61K 31/395; A61K 31/55 (2016.01)

**CPC** - A61K 31/00; A61K 31/33; A61K 31/395; A61K 31/55 (2016.05)

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(8)** - A61K 31/00; A61K 31/33; A61K 31/395; A61K 31/55 (2016.01)

**CPC** - A61K 31/00; A61K 31/33; A61K 31/395; A61K 31/55 (2016.05)

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

U.S. Classes - 514/1 ; 514/183; 514/212.01; 514/213.01 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)


Search terms used: attenuate undesired downstream response of nicotinic acetylcholine receptor activity noribogaine

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
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<td>document</td>
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<td></td>
<td>of Psychopharmacology, 20 May 2015 (20.05.2015). Vol. 29, No. 6, Pgs. 704-71 1,</td>
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<td>entire document</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  * "A" document defining the general state of the art which is not considered to be of particular relevance
  * "E" earlier application or patent but published on or after the international filing date
  * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  * "O" document referring to an oral disclosure, use, exhibition or other means
  * "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is considered to combine one or more other documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

**Date of the actual completion of the international search** 17 May 2016

**Date of mailing of the international search report** 10 JUN 2016

**Name and mailing address of the ISA/ Authorized officer**

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, VA 22313-1450

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Authorized officer

Blaine R. Copenhaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

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.: 11, 12 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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 additional fees, this Authority did not invite payment of additional fees.

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 and, where applicable, the payment of a protest fee.

□ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

□ No protest accompanied the payment of additional search fees.