(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2007 (15.02.2007)

PCT

(10) International Publication Number
WO 2007/018496 A1

(51) International Patent Classification:
*A61K 31/325* (2006.01)

(21) International Application Number:
PCT/US2005/026439

(22) International Filing Date: 26 July 2005 (26.07.2005)

(25) Filing Language: English

(26) Publication Language: English

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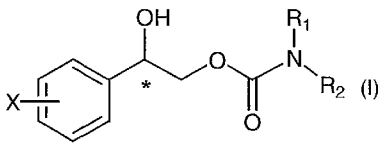
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

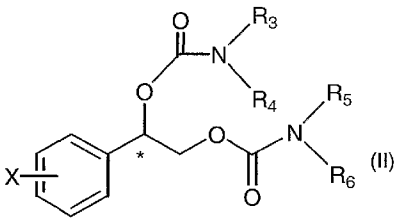
**Published:**
— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) **Title:** METHODS FOR TREATING SUBSTANCE-RELATED DISORDERS



(I)



(II)

(57) **Abstract:** This invention is directed to a method for preventing, treating or ameliorating substance-related disorders, in a subject in need thereof comprising administering to the subject an effective amount of a compound selected from: Formula (I), or Formula (II) or pharmaceutically acceptable forms thereof, wherein phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and $C_1$-$C_4$ alkyl; wherein $C_1$-$C_4$ alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, $C_1$-$C_4$ alkyl, $C_1$ $C_4$ alkoxy, amino, nitro and cyano). In addition, methods are included involving co-administration of compounds of the invention with one or more compounds known to treat substance-induced disorders.

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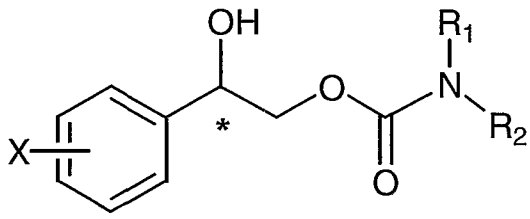
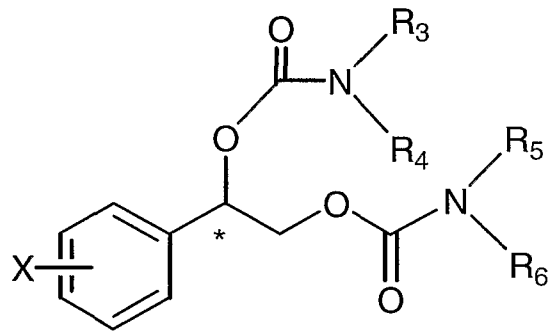
Abstract of the Invention

This invention is directed to a method for preventing, treating or ameliorating substance-related disorders, in a subject in need thereof comprising administering to the subject an effective amount of a compound selected from:




Formula (I), or




Formula (II)

or pharmaceutically acceptable forms thereof, wherein phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and $C_1$-$C_4$ alkyl; wherein $C_1$-$C_4$ alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, amino, nitro and cyano). In addition, methods are included involving co-administration of compounds of the invention with one or more compounds known to treat substance-induced disorders.

# METHODS FOR TREATING SUBSTANCE-RELATED DISORDERS

## FIELD OF THE INVENTION

This invention is directed to methods for preventing, treating or ameliorating Substance-Related Disorders. More particularly, this invention is directed to the use of certain halogenated 2-phenyl-1, 2-ethanediol monocarbamate or dicarbamate compounds, either alone or in combination with other medications, for preventing, treating or ameliorating Substance-Related Disorders, including Substance Dependence, Abuse and Substance – Induced Disorders.

## BACKGROUND OF THE INVENTION

Substance-Related Disorders include disorders related to the taking of a drug of abuse and include Substance Use Disorders such as Substance Dependence and Abuse and Substance-Induced Disorders such as Substance Withdrawal syndromes and Substance Induced Psychosis and Mood Disorders. Substance Dependence is a cluster of cognitive, behavioral and physiological symptoms the essential feature of which is that the individual affected continues the use of the substance despite significant substance-related problems.

Many drugs can cause dependence or physical and/or psychological addiction. Opiates (such as heroin, opium, morphine and the like), sympathomimetics (such as cocaine, amphetamines, methamphetamines and the like), sedative-hypnotics (such as ethanol, benzodiazepines, barbiturates, inhalants, phencyclidines and the like) and those with a combination of opioid and sympathomimetic effects (such as nicotine and the like) are considered to be drugs that cause dependence or physical and/or psychological addiction.

Substance Dependence or addiction is characterized by a craving or compulsion for taking the substance and an inability to limit its intake. Additionally, drug dependence is associated with drug tolerance, the loss of effect of the drug following repeated administration, and withdrawal, the

appearance of physical and behavioral symptoms when the drug is not consumed. Sensitization occurs if repeated administration of a drug leads to an increased response to each dose. Tolerance, sensitization and withdrawal are phenomena evidencing a change in the central nervous system resulting from continued use of drugs that cause addiction. Such changes motivate the addicted individual to continue consuming the drug despite serious social, legal, physical and/or professional consequences.

Direct, indirect or trans-synaptic changes to dopamine release and/or reuptake have been implicated in disorders resulting from addictive behaviors and in rewarding and/or reinforcing drug use, as in a "Reward Deficiency Syndrome." Dopamine is a monoamine neurotransmitter that physiologically functions in the forebrain's integration of information in sensory, limbic and motor systems. Since reduced dopaminergic functions have been found in individuals with a minor allele of the dopamine receptor, the dopamine receptor appears to be a reinforcement or reward gene. Variants of the dopamine receptor gene have been associated with alcoholism, obesity, pathological gambling, attention deficit hyperactivity disorder, Tourette syndrome, cocaine dependence, nicotine dependence, polysubstance abuse and other drug dependencies.

Attempts to treat Substance Dependence have included pharmaceutical and behavioral intervention. Treatment has included administering pharmacologic agents (e.g. bupropion, naltrexone, acamprosate and the like) either alone or with other agents to variously block dopamine reuptake or enhance dopamine release. Drug treatment has also been optionally coextensive with behavior modification therapies to treat addiction. (See, Hoffman et al., Front. Neuroendocrinol., 1998, 19(3):187-231; Hitri et al., Clin. Pharmacol., 1994, 17:1-22; Noble, Alcohol Supp., 1994, 2:35-43; Blum et al., Pharmacogenetics, 1995, 5:121-141; US Pat. 5, 039,680, US Pat. 5,075,341, US Pat. 5,232,934, US Pat. 5,556,837, US Pat. 5,556,838, US Pat. 5,574,052, US Pat. 5,762,925, US Pat. 6,593,367, US Pat. 6,109,269, US Pat. 6,716,868, US Pat. App. 20030144271, PCT App. WO0141763)(All incorporated herein by reference).

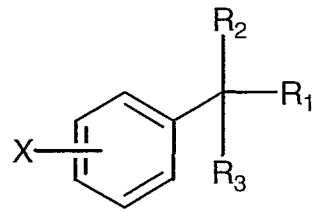
Substance Abuse is a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of the substance. These problems occur repeatedly for at least a 12 month period.

Substance–Induced Disorders refers to a wide variety of temporary or more chronic syndromes due to the physiological effects of the substance on the central nervous system. Such disorders may develop during or shortly after use of the substance. These include; acute intoxication and withdrawal, and a variety of substance-induced mental disorders such as; delirium, persisting dementia, persisting amnestic disorder, psychotic disorder, mood disorder, anxiety disorder, sexual dysfunction and sleep disorder.

See, Diagnostic And Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) Pages 175-272, Published by The American Psychiatric Association, Washington, DC (1994) (incorporated herein by reference).

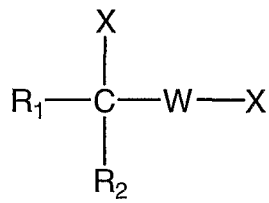
There remains a need for effective pharmacologic therapies to prevent, treat or ameliorate Substance-Related Disorders resulting from the different classes of abusable drugs. In particular, there is a need for small molecule compounds that may be readily synthesized, that are potent and stabilizing mediators and restorative agents for neurotransmitter pathways and are useful for preventing, treating or ameliorating Substance-Related Disorders including Substance Use Disorders such as Substance Dependence (drug addiction) and Substance Abuse and Substance-Induced Disorders, including but not limited to; acute intoxication and withdrawal, and substance-induced mental disorders such as; delirium, persisting dementia, persisting amnestic disorder, psychotic disorder, mood disorder, anxiety disorder, sexual dysfunction and sleep disorder.

Substituted phenyl alkyl carbamate compounds have been described in US Pat. 3,265,728 to Bossinger, et al (incorporated herein by reference) as useful in treating the central nervous system, having tranquilization, sedation and muscle relaxation properties of the formula:

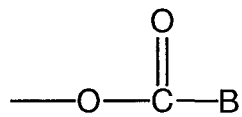



wherein $R_1$ is either carbamate or alkyl carbamate containing from 1 to 3 carbon atoms in the alkyl group; $R_2$ is either hydrogen, hydroxy, alkyl or hydroxy alkyl containing from 1 to 2 carbons; $R_3$ is either hydrogen or alkyl containing from 1 to 2 carbons; and X can be halogen, methyl, methoxy, phenyl, nitro or amino.

A method for inducing calming and muscle relaxation with carbamates has been described in US Pat. 3,313,692 to Bossinger, et al (incorporated herein by reference) by administering a compound of the formula:



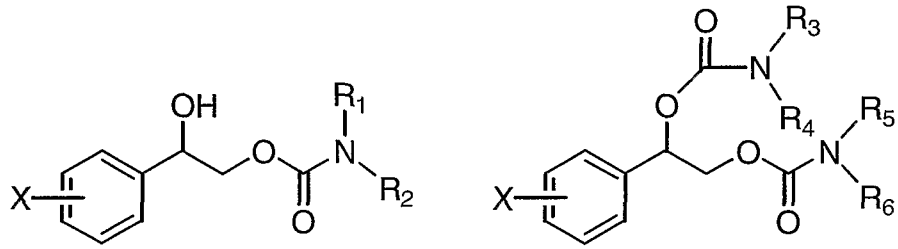

in which W represents an aliphatic radical containing less than 4 carbon atoms, wherein $R_1$ represents an aromatic radical, $R_2$ represents hydrogen or an alkyl radical containing less than 4 carbon atoms, and X represents a hydrogen, hydroxy, alkoxy or alkyl radical containing less than 4 carbon atoms or a radical of the formula:




in which B represents an organic heterocyclic, ureido or hydrazino amine radical or the radical $-N(R_3)_2$, wherein $R_3$ represents hydrogen or an alkyl radical containing less than 4 carbon atoms.

Optically pure forms of substituted phenyl alkyl carbamate compounds have been described in US Pat. 6,103,759 to Choi, et al (incorporated herein

by reference) as effective for treating and preventing central nervous system disorders including convulsions, epilepsy, stroke and muscle spasm and as useful in the treatment of central nervous system diseases, particularly as anticonvulsants, antiepileptics, neuroprotective agents and centrally acting muscle relaxants and, in particular, as halogen substituted 2-phenyl-1,2-ethanediol monocarbamate and dicarbamate compounds of the formulae:

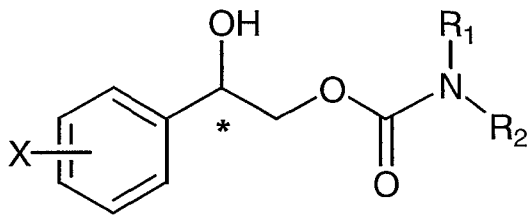



wherein one enantiomer predominates and wherein the phenyl ring is substituted at X with one to five halogen atoms selected from fluorine, chlorine, bromine or iodine atoms and $R_1$, $R_2$ , $R_3$, $R_4$, $R_5$ and $R_6$ are each selected from hydrogen and straight or branched alkyl groups with one to four carbons optionally substituted with a phenyl group with substituents selected from the group consisting of hydrogen, halogen, alkyl, alkyloxy, amino, nitro and cyano. Pure enantiomeric forms and enantiomeric mixtures are described wherein one of the enantiomers predominates in the mixture for the compounds represented by the formulae above; preferably, one of the enantiomers predominates to the extent of about 90% or greater; and, most preferably, about 98% or greater.

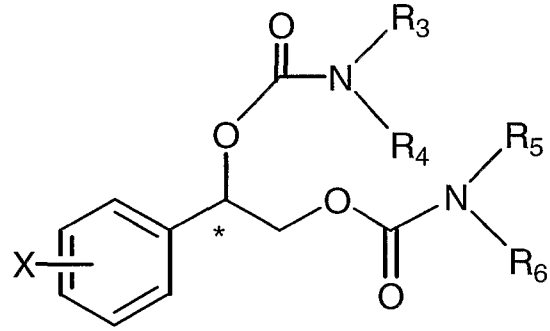
Recent preclinical studies have revealed previously unrecognized pharmacological properties which suggest that a form of a substituted phenyl alkyl carbamate compound is useful in preventing, treating or ameliorating a wide variety of substance-related disorders . Such monocarbamate and dicarbamate compounds thereof have not been previously described as useful for preventing, treating or ameliorating substance-related disorders such as substance dependence and the many Substance-Induced Disorders

## SUMMARY OF THE INVENTION

The present invention is directed to a method for preventing, treating or ameliorating substance-related disorders including substance dependence or drug addiction in a subject in need thereof comprising administering to the subject an effective amount of a carbamate compound of




Formula (I), or




Formula (II)

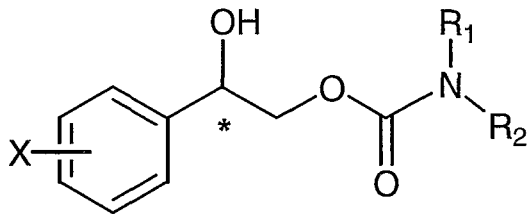
or pharmaceutically acceptable forms thereof, wherein all variables are as described herein.

The present invention is also directed to a method for use of a compound of Formula (I) or Formula (II) for preventing, treating or ameliorating substance-induced disorders or diseases and disorders resulting from the use of dependence inducing or addictive drugs.

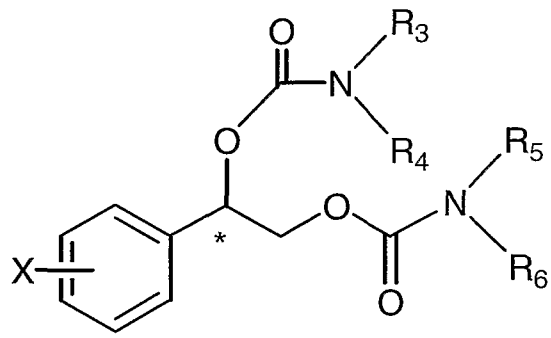
The method of the present invention includes the use of a compound of Formula (I) or Formula (II) for modulating the effect of substance dependence or addiction associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders, i.e., substance-induced disorders.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method for preventing, treating or ameliorating Substance-Related Disorders in a subject in need thereof comprising administering to the subject an effective amount of a compound selected from Formula (I) or Formula (II):




Formula (I)




Formula (II)

or pharmaceutically acceptable forms thereof, wherein

phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine, and

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and $C_1$-$C_4$ alkyl, wherein $C_1$-$C_4$ alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, amino, nitro and cyano).

The present invention is also directed to a method for preventing, treating or ameliorating substance-related disorders including substance dependence or drug addiction in a subject in need thereof comprising administering to the subject an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound selected from Formula (I) or Formula (II).

The present invention also includes methods for preventing, treating or ameliorating substance-induced disorders or diseases and disorders resulting from the use of addictive drugs and for modulating the effect of addiction associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders in a subject in need thereof comprising administering to the subject an effective amount of a compound selected from Formula (I) or Formula (II) or administering to the subject an effective amount of a pharmaceutical composition comprising a

pharmaceutically acceptable carrier and a compound selected from Formula (I) or Formula (II).

The present invention also includes methods for the preventing, treating or ameliorating substance-induced disorders including substance dependence comprising administering to a subject, in need of such treatment, an effective amount of a combination product having a compound selected from Formula (I) or Formula (II) or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound selected from Formula (I) or Formula (II) in combination with an effective amount of one or more compounds known to treat substance-related disorders. Compounds known to treat substance-related disorders include, but are not limited to; naltrexone, naloxone or other opioid receptor antagonists, fluoxetine or other SSRI antidepressants, thyrotropin-releasing hormone analogues, venlafaxine or other SNRI *antidepressants*, MAO *Inhibitors antidepressants*, *tricyclic antidepressants*, bupropion, lithium carbonate, anticonvulsants, acamprosate, disulfiram (antabuse), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, an N-methyl-D-aspartic acid (NMDA) glutamate receptor modulator and the like.

The methods of the present invention further include preventing, treating or ameliorating substance-induced disorders in a subject in need thereof comprising administering an effective amount of a compound of the present invention and a pharmaceutical composition or combination product thereof in a therapy regimen coextensive with behavior modification.

This invention includes the use of a compound selected from Formula (I) or Formula (II) or pharmaceutical composition thereof for the preparation of a medicament for preventing, treating or ameliorating substance-related disorders such as substance dependence and abuse and substance induced disorders.

Examples of a compound selected from Formula (I) for use in the present method include an enantiomer of Formula (I) or an enantiomer of Formula (I) in an enantiomeric mixture wherein one enantiomer predominates.

Examples of a compound selected from Formula (II) for use in the present method include an enantiomer of Formula (II) or an enantiomer of Formula (II) in an enantiomeric mixture wherein one enantiomer predominates.

For an enantiomeric mixture of Formula (I) or Formula (II) wherein one enantiomer predominates, the enantiomer predominates to the extent of about 90% or greater. Examples of the present invention also include enantiomeric mixtures wherein said enantiomer predominates to the extent of about 98% or greater.

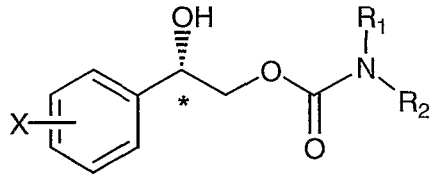
Other examples of said compound of Formula (I) or Formula (II) include compounds wherein X is chlorine, wherein X is substituted at the ortho position of the phenyl ring of Formula (I) or Formula (II) and, wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are hydrogen.

An example of the present method includes the use of an enantiomer selected from Formula (I) or Formula (II) or an enantiomeric mixture thereof wherein one enantiomer predominates, wherein X is chlorine and, wherein X is substituted at the ortho position of the phenyl ring.

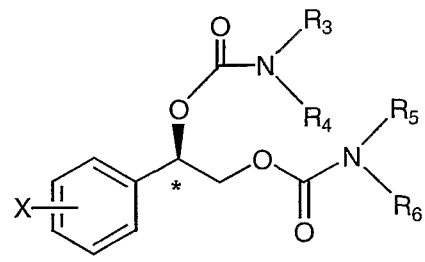
The present method also includes the use of an enantiomer selected from Formula (I) or Formula (II) or an enantiomeric mixture thereof wherein one enantiomer predominates and, wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are hydrogen.

For enantiomeric mixtures wherein one enantiomer selected from Formula (I) or Formula (II) predominates, said enantiomer predominates to the extent of about 90% or greater. Enantiomeric mixtures within the scope of the present invention also include those wherein said enantiomer predominates to the extent of about 98% or greater.

The present invention is directed to a method for preventing, treating or ameliorating substance related disorders in a subject in need thereof comprising administering to the subject an effective amount of an enantiomer selected from Formula (Ia) or Formula (IIa) or an enantiomeric mixture of Formula (Ia) or Formula (IIa) wherein one enantiomer predominates:



Formula (Ia)



Formula (IIa)

or pharmaceutically acceptable forms thereof, wherein

phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine, and

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and $C_1$-$C_4$ alkyl, wherein $C_1$-$C_4$ alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, amino, nitro and cyano).

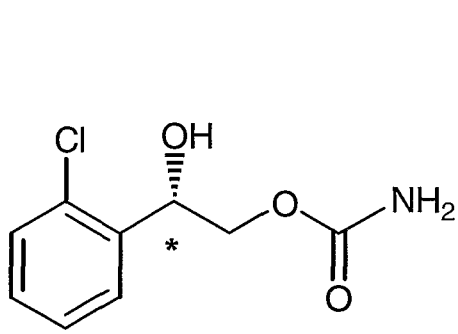
Examples of the present method include the use of an enantiomer selected from Formula (Ia) or Formula (IIa) or an enantiomeric mixture thereof wherein one enantiomer predominates, wherein X is chlorine and, wherein X is substituted at the ortho position of the phenyl ring.

The present method also includes the use of an enantiomer selected from Formula (Ia) or Formula (IIa) or enantiomeric mixture thereof wherein one enantiomer predominates and, wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are hydrogen.

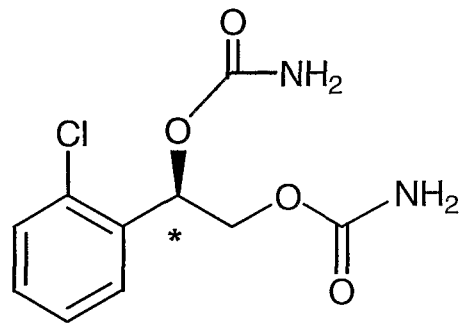
For enantiomeric mixtures wherein one enantiomer selected from Formula (Ia) or Formula (IIa) predominates, said enantiomer predominates to the extent of about 90% or greater. Enantiomeric mixtures within the scope of the present invention include those wherein said enantiomer predominates to the extent of about 98% or greater.

The present invention is directed to a method for preventing, treating or ameliorating substance related disorders in a subject in need thereof comprising administering to the subject an effective amount of an enantiomer

selected from Formula (Ib) or Formula (IIb) or an enantiomeric mixture of Formula (Ib) or Formula (IIb) wherein one enantiomer predominates:




Formula (Ib)




Formula (IIb)

For enantiomeric mixtures wherein one enantiomer selected from Formula (Ib) or Formula (IIb) predominates, said enantiomer predominates to the extent of about 90% or greater. Enantiomeric mixtures within the scope of the present invention include those wherein said enantiomer predominates to the extent of about 98% or greater.

The present invention is directed to compounds of Formula (I) or Formula (II) or pharmaceutically acceptable forms thereof. Where other crystalline or polymorphic forms of the instant compounds may exist, as such they are also intended to be included within the scope of the present invention.

The term "forms" refers to various isomers and mixtures thereof for a compound of Formula (I) or Formula (II). The term "isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. Such substances have the same number and kind of atoms but differ in structure. The structural difference may be in constitution (geometric isomers) or in an ability to rotate the plane of polarized light (stereoisomers). The term "stereoisomer" refers to isomers of identical constitution that differ in the arrangement of their atoms in space. Enantiomers and diastereomers are stereoisomers wherein an asymmetrically substituted carbon atom acts as a chiral center. The term "chiral" refers to a molecule that is not superposable on its mirror image, implying the absence of an axis and a plane or center of symmetry.

It is apparent to those skilled in the art that the compounds of the invention are present as racemates, enantiomers and enantiomeric mixtures thereof. A carbamate enantiomer selected from Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb) contains an asymmetric chiral carbon atom at the benzylic position, which is the aliphatic carbon adjacent to the phenyl ring (represented by the asterisk in the structural formulae).

The term "racemate" or "racemic mixture" refers to a compound of equimolar quantities of two enantiomeric species, wherein the compound is devoid of optical activity. The term "optical activity" refers to the degree to which a chiral molecule or nonracemic mixture of chiral molecules rotates the plane of polarized light.

The term "enantiomer" refers to one of a pair of molecular species that are mirror images of each other and are not superposable. The term "diastereomer" refers to stereoisomers that are not related as mirror images. The symbols "R" and "S" represent the configuration of substituents around a chiral carbon atom(s). The symbols "R*" and "S*" denote the relative configurations of of substituents around a chiral carbon atom(s). .

The isomeric descriptors "R," "S," "S*" or "R*" are used as described herein for indicating atom configuration(s) relative to a core molecule and are intended to be used as defined in the literature (IUPAC Recommendations for Fundamental Stereochemistry (Section E), Pure Appl. Chem., 1976, 45:13-30)(incorporated by reference herein).

Compounds of the present invention may be prepared as described in Bossinger '728 (incorporated herein by reference), Bossinger '692 (incorporated herein by reference) and Choi '759 (incorporated herein by reference). It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The present invention provides a method for preventing, treating or ameliorating substance dependence in a subject in need thereof comprising administering to the subject an effective amount of a compound selected from Formula (I) or Formula (II).

The present invention also provides a method for use of a compound of Formula (I) or Formula (II) in preventing, treating or ameliorating substance induced disorders.

The method of the present invention includes the use of said compound for modulating the effect of substance dependence associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders.

The methods of the present invention further include the use of said compound, wherein said compound is an enantiomer of a compound selected from Formula (I) or Formula (II); or, wherein said compound is an enantiomer selected from Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb); or, wherein said compound is an enantiomer of a compound selected from Formula (I) or Formula (II) in an enantiomeric mixture wherein said enantiomer predominates; or, wherein said compound is an enantiomer selected from Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb) in an enantiomeric mixture wherein said enantiomer predominates.

The present methods also include the use of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound selected from Formula (I) or Formula (II) for preventing, treating or ameliorating substance related disorders including diseases and disorders resulting from the use of addictive drugs or for modulating the effect of addiction associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders in a subject in need thereof in a subject in need thereof.

These methods include the use of a compound selected from Formula (I) or Formula (II) for the preparation of a medicament for preventing, treating

or ameliorating substance related disorders including diseases and disorders resulting from the use of addictive drugs or for modulating the effect of addiction associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders in a subject in need thereof.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, alpha-ketoglutarate and alpha-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate bicarbonate and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal, for example; sodium, potassium or lithium, or alkaline earth metals, for example calcium salts of carboxylic acids can also be made.

The method of the present invention is also directed to a method for preventing, treating or ameliorating substance related disorders including drug addiction, diseases and disorders resulting from the use of addictive drugs or for modulating the effect of addiction associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or Formula (II), a pharmaceutical composition thereof, a pharmaceutical composition containing one or more of said compounds or a pharmaceutical composition containing one or more of said compounds and a safe and effective amount of one or more additional agents.

The term “substance dependence” also referred to as "drug addiction"

refers to physical and/or psychological addiction to opiates (such as heroin, opium, morphine and the like), sympathomimetics (such as cocaine, amphetamines, methamphetamines and the like), sedative-hypnotics (such as ethanol, benzodiazepines, barbiturates, phencyclidines and the like), those with a combination of effects (such as nicotine and the like) and the like or mixtures thereof.

The phrases "substance related disorders" also referred to as "diseases and disorders resulting from the use of addictive drugs" and "addiction associated diseases and disorders and symptoms thereof" and "physiologic events associated with such diseases and disorders" refer to drug withdrawal disorders such as alcohol withdrawal (with or without perceptual disturbances and/or delirium), amphetamine withdrawal, cocaine withdrawal, nicotine withdrawal, opioid withdrawal, sedative withdrawal, hypnotic withdrawal, anxiolytic withdrawal (with or without perceptual disturbances and/or delirium), nicotine withdrawal (with or without disturbances associated with smoking cessation) and withdrawal symptoms due to other substances, substance-induced anxiety disorder with onset during withdrawal; vulnerability even after long periods of absence to environmental trigger induced craving; substance-induced mood disorder with onset during withdrawal; and substance-induced sleep disorder with onset during withdrawal and other substance-induced disorders, including but not limited to; acute intoxication and withdrawal, and substance-induced mental disorders such as; delirium, persisting dementia, persisting amnestic disorder, psychotic disorder, mood disorder, anxiety disorder, sexual dysfunction and sleep disorder.

The term "preventing, treating or ameliorating" refers to (i) preventing a disease, disorder or condition from occurring in an animal which may be predisposed to the disease or disorder and/or effects thereof but has not yet been diagnosed as having it; (ii) inhibiting or arresting the development of the disease, disorder or condition and (iii) relieving or causing regression of the disease, disorder or condition.

In relation to substance-related disorders , the term "preventing, treating

or ameliorating" also refers to suppressing the psychological addiction or physical tolerance to the drug of abuse, and relieving or preventing a withdrawal syndrome resulting from the drug dependence.

The term "administering" refers to a means for preventing, treating or ameliorating substance dependence, preventing, treating or ameliorating diseases and disorders resulting from the use of addictive drugs or modulating the effect of addiction associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders with an instant compound. Such means include therapeutically or prophylactically administering an effective amount of a compound, composition or medicament of the present invention at different times during the course of a therapy or concurrently in a combination form. Prophylactic administration can occur prior to the manifestation of symptoms characteristic of drug addiction such that diseases and disorders resulting from the use of addictive drugs or the effect of addiction associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders is prevented, treated, ameliorated or, alternatively, delayed in its progression. The methods of the present invention are further to be understood as embracing all possible therapeutic or prophylatic treatment regimens to be imagined by those skilled in the art.

The term "subject" refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" refers to that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes therapeutic alleviation of the symptoms of the disease or disorder being treated and prophylactic.

The effective amount of a compound selected from Formula (I) or Formula (II) or pharmaceutical composition thereof may be from about 0.01

μg/Kg/dose to about 300 mg/Kg/dose. Effective amounts may also be from about 0.01 μg/Kg/dose to about 100 mg/Kg/dose. An effective amount also contemplated may be from about 0.05 μg/Kg/dose to about 10 mg/Kg/dose. Another effective amount includes from about 0.1 μg/Kg/dose to about 5 mg/Kg/dose. Therefore, the effective amount of the active ingredient contained per dosage unit (e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like) as described herein may be in a range of from about 700 ng/dose to about 21 g/dose for a subject having a weight of about 70 Kg.

The term "composition" refers to a product containing a compound of the present invention (such as a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from such combinations of the specified ingredients in the specified amounts).

The term "medicament" refers to a product for use in preventing, treating or ameliorating substance related disorders such as substance dependence, substance abuse or substance induced disorders in a subject in need thereof.

The term "pharmaceutically acceptable" refers to molecular entities and compositions that are of sufficient purity and quality for use in the formulation of a composition or medicament of the present invention. Since both human use (clinical and over-the-counter) and veterinary use are equally included within the scope of the present invention, a formulation would include a composition or medicament for either human or veterinary use.

The term "pharmaceutically acceptable salt thereof" refers to an acid or basic salt of the compounds of the invention that are of sufficient purity and quality for use in the formulation of a composition or medicament of the present invention and are tolerated and sufficiently non toxic to be used in a pharmaceutical preparation.

A compound selected from Formula (I) or Formula (II) or pharmaceutical composition thereof or a pharmaceutically acceptable salt thereof may be administered by any conventional route of administration including, but not

limited to oral, pulmonary, intraperitoneal, intravenous, intramuscular, subcutaneous, transdermal, buccal, nasal, sublingual, ocular, rectal and vaginal. In addition, administration directly to the nervous system includes, and is not limited by present technology to, intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal or peri-spinal delivery or by delivery via intracranial or intravertebral needles or catheters with or without pump devices.

It will be readily apparent to those skilled in the art that any dose or frequency of administration that provides the therapeutic or prophylactic effect described herein is suitable for use in the present invention.

Dosage regimens may be varied depending upon the requirement of the subjects (including factors associated with the particular subject being treated, including subject age, weight and diet, strength of the preparation, the advancement of the disease condition and the mode and time of administration) and the use of a particular compound of Formula (I) or Formula (II) or pharmaceutical composition thereof or a pharmaceutically acceptable salt thereof. Optimal dosages to be administered may be readily determined by those skilled in the art and will result in the need to adjust the dose to an appropriate therapeutic or prophylactic level. The use of either daily administration or post-periodic dosing may be employed.

Preferably, a compound of Formula (I) or Formula (II) or pharmaceutical composition thereof or a pharmaceutically acceptable salt thereof for preventing, treating or ameliorating substance related disorders such as substance dependence, substance abuse or substance induced disorders in a subject in need thereof is administered orally or parenterally.

In accordance with the methods of the present invention, a compound of Formula (I) or Formula (II) or pharmaceutical composition thereof described herein or a pharmaceutically acceptable salt thereof may be administered separately, at different times during the course of therapy or concurrently in divided combination or single combination forms. Advantageously, a compound selected from Formula (I) or Formula (II) or pharmaceutical

compositions thereof may be administered in a single daily dose or the total daily dosage may be administered via continuous delivery or in divided doses of two, three or four times daily. The instant invention is therefore to be understood as embracing all such methods and regimes of continuous, simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

To prepare a pharmaceutical composition of the present invention, a compound of Formula (I) or Formula (II) as the active ingredient or a pharmaceutically acceptable salt thereof is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral).

Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of various pharmaceutically acceptable carriers may be found in The Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

Methods of formulating pharmaceutical compositions have been described in numerous publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1-3, edited by Lieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications, Volumes 1-2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

Preferably, a pharmaceutical composition is in a unit dosage form such as a tablet, pill, capsule, caplet, gelcap, lozenge, granule, powder, sterile parenteral solution or suspension, metered aerosol or liquid spray, drop, ampoule, autoinjector device or suppository for administration by oral, intranasal, sublingual, intraocular, transdermal, parenteral, rectal, vaginal, inhalation or insufflation means. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration or may be adapted to provide a preparation for intramuscular injection.

In preparing a pharmaceutical composition having a solid dosage form for oral administration, such as a tablet, pill, capsule, caplet, gelcap, lozenge, granule or powder (each including immediate release, timed release and sustained release formulations), suitable carriers and additives include but are not limited to diluents, granulating agents, lubricants, binders, glidants, disintegrating agents and the like. If desired, tablets may be sugar coated, gelatin coated, film coated or enteric coated by standard techniques.

For preparing a solid dosage form, the principal active ingredient is mixed with a pharmaceutical carrier (e.g. conventional tableting ingredients such as diluents, binders, adhesives, disintegrants, lubricants, antiadherents and glidants). Sweeteners and flavorants may be added to chewable solid dosage forms to improve the palatability of the oral dosage form. Additionally, colorants and coatings may be added or applied to the solid dosage form for ease of identification of the drug or for aesthetic purposes. These carriers are formulated with the pharmaceutical active to provide an accurate, appropriate dose of the pharmaceutical active with a therapeutic release profile.

In preparing a pharmaceutical composition having a liquid dosage form for oral, topical and parenteral administration, any of the usual pharmaceutical media or excipients may be employed. Thus, for liquid unit dosage forms, such as *suspensions* (*i.e. colloids, emulsions and dispersions*) *and solutions*, suitable carriers and additives include but are not limited to pharmaceutically acceptable wetting agents, dispersants, flocculation agents, thickeners, pH control agents (i.e. buffers), osmotic agents, coloring agents, flavors, fragrances, preservatives (i.e. to control microbial growth, etc.) and a liquid vehicle may be employed. Not all of the components listed above will be required for each liquid dosage form. The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, but are not limited to aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Biological Experimental Example

The activities of a compound of the present invention for use in preventing, treating or ameliorating substance related disorders, diseases and disorders resulting from the use of addictive drugs or for modulating the effect of addiction associated diseases and disorders and symptoms thereof or the effect of physiologic events associated with such diseases and disorders were evaluated in the following experimental example which is intended to be a way of illustrating but not limiting the invention.

A compound of the present invention was tested in ethanol preferring rats, a model for acute and chronic drug addiction in humans using an adaptation of a published method (See, Rezvani, AH et al. *Alcohol & Alcoholism*, Vol. 25, No. 5, pp. 573-575, 1990, Rezvani AH, et al., *Alcohol and Alcoholism* (Oxford), 2000, 35(1), 76-83).

*Materials and Methods*

An enantiomer of Formula (Ib) was orally administered in a dose range of from about 10 to about 90 mg/kg in test and control treatment groups of 10 rats per group over a period of 14 days. Test conditions reflected approaches for evaluating patterns of drinking (e.g., single or multiple events).

*Animals:*

Adult male selectively-bred alcohol preferring (P) rats were used. The selectively-bred alcohol-preferring (P) rats have been characterized and have been widely used to study the effects of different compounds on voluntary alcohol intake (Rezvani et al, 1990, 1991, 1992a, 1992b, 1999, 2000, 2002; 2003; Murphy et al, 1988; Overstreet et al., 1992, 1999; Li and McBride, 1995).

Rats were housed individually in wire mesh cages under a constant room temperature of 22 +1 oC and 12:12 light-dark cycle (8:00-20:00, dark). Animal were fed Agway Prolab Rat/Mouse/ Hamster 3000 formula and water ad libitum.

*Protocol:*

Establishment of baseline alcohol intake: Alcohol intake was determined using a standard two-bottle choice method (as described in Murphy et al. 1988; McBride et al. 1990; Rezvani et al. 1990, 1991, 1993, 1995, 1997, Rezvani and Grady, 1994).

Animals were first given free access to water in a graduated Richter tube for 1 day. After the first day, the animals were given access to only a solution of 10% (v/v) ethanol for 3 consecutive days. During this period animals became accustomed to drinking from Richter tubes and to the taste and pharmacological effects of alcohol. Thereafter, they were given free access to both water and a solution of 10% alcohol for at least 3 consecutive weeks and throughout of the period of study. The rats had free access to food. Water and alcohol intake was recorded at 6 and 24 hour after the treatment, food intake was measured at 24 hour. Animal body weight was measured every day.

*Phase I. Acute Administration:*

After establishment of a stable baseline for alcohol, food, and water intake, rats were daily administered (via gavage tube) at the same time each day with either vehicle or one of the three doses (10, 30 and 90 mg/kg) of the compound using a random treatment order. The interval between treatment administration was at least 3 days. Alcohol and water intake was recorded 6 and 24 h after treatment administration and food intake was recorded at 24 hr. A total of 8-10 animals per group were used. All animals completed the acute administration study phase.

*Phase II. Chronic Administration:*

The effect of chronic administration of a test compound on alcohol intake and tolerance to the anti-craving effects of the test compound was tested in naïve rats treated (via gavage tube) once a day either vehicle or test compound. A test compound dose of 45 mg/Kg was selected as an effective dose for chronic administration based on the results of the acute administration study phase. Themost effective dose was then used for the chronic adminstiration phase and administered for 14 consecutive days. Alcohol and

water intake was recorded 6 and 24 h after each treatment administration and food intake was recorded at 24 hr.

*Statistical analysis of data:*

The results were presented as means ±SEM (Standard Error of the Means). Alcohol intake (g/kg) was calculated by multiplying the volume of alcohol consumed in mL by 10% and 0.7893 (a factor representing ethanol density)/body weight in kg. Alcohol preference, expressed as percentage, was calculated as follows (volume of alcohol consumed (mL) /total fluid intake (mL)) x 100 (as described in Rezvani and Grady, 1994; Rezvani et al., 1997). Statistical differences between treatment and control groups were determined by using ANOVA and Turkey Student's t test for multiple comparisons.

*Results*

Table 1 provides data for the treatment groups demonstrating the effect of the test compound on acute ethanol and water intake. At a dose of about 45 mg/kg and up, the test compound had a significant effect on alcohol intake without developing a tolerance for the test compound's affect on ethanol intake.

Table 1

| Day | Alcohol Intake (g/Kg) | | Water Intake (g/Kg) | | Alcohol Pref (%) | | Total Fluid Intake (mL/Kg) | | Body Weight (g) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Veh | Drug | Veh | Drug | Veh | Drug | Veh | Drug | Veh | Drug |
| BL | 5.30 | 5.30 | 30 | 30 | 71 | 71 | 97 | 97 | 384 | 384 |
| 1 | 3.70 | 1.61 | 36 | 62 | 58 | 28 | 82 | 82 | 412 | 418 |
| 2 | 4.00 | 1.31 | 31 | 60 | 64 | 24 | 82 | 76 | 414 | 415 |
| 3 | 4.70 | 1.37 | 19 | 60 | 76 | 24 | 78 | 77 | 417 | 413 |
| 4 | 4.80 | 1.03 | 27 | 68 | 71 | 16 | 88 | 81 | 418 | 415 |
| 5 | 5.20 | 1.24 | 27 | 68 | 72 | 21 | 94 | 83 | 421 | 419 |
| 6 | 5.30 | 1.10 | 20 | 61 | 78 | 21 | 87 | 75 | 425 | 421 |
| 7 | 5.30 | 1.85 | 21 | 48 | 77 | 34 | 89 | 71 | 428 | 424 |
| 8 | 5.60 | 2.21 | 20 | 52 | 79 | 35 | 91 | 80 | 432 | 426 |
| 9 | 5.40 | 2.19 | 18 | 40 | 81 | 45 | 86 | 67 | 436 | 429 |
| 10 | 6.00 | 3.06 | 17 | 44 | 83 | 52 | 93 | 83 | 437 | 431 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 11 | 5.40 | 2.93 | 16 | 30 | 82 | 57 | 86 | 67 | 440 | 435 |
| 12 | 4.20 | 2.67 | 20 | 27 | 73 | 58 | 73 | 60 | 442 | 436 |
| 13 | 4.40 | 2.37 | 31 | 48 | 65 | 42 | 87 | 78 | 439 | 431 |
| 14 | 4.40 | 2.32 | 46 | 54 | 59 | 40 | 102 | 83 | 448 | 437 |

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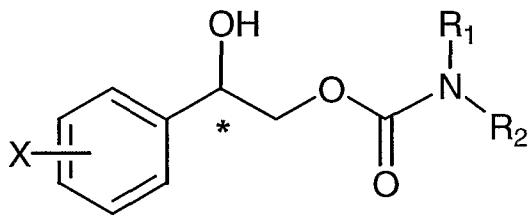
All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. The discussion of references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinence of the cited references.

The present invention is not to be limited in terms of the particular embodiments described in this application, which are intended as single illustrations of individual aspects of the invention. Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods within the scope of the invention, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing description. Such modifications and variations are intended to fall within the scope of the appended claims. The present invention is to be limited only by

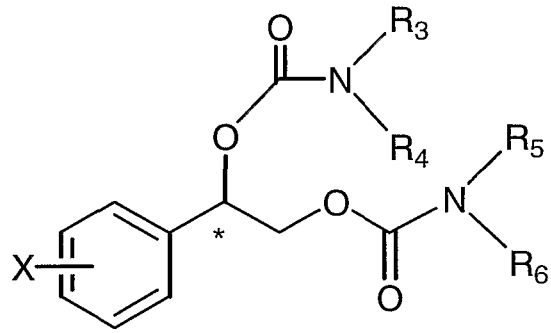
the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A method for preventing, treating or ameliorating substance-related disorders in a subject in need thereof comprising administering to the subject an effective amount of a carbamate compound selected from



Formula (I), or



Formula (II);

or pharmaceutically acceptable forms thereof or a pharmaceutically acceptable salts thereof, wherein

phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and,

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and $C_1$-$C_4$ alkyl; wherein $C_1$-$C_4$ alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, amino, nitro and cyano).

2. The method of claim 1, wherein X is chlorine.

3. The method of claim 1, wherein X is substituted at the ortho position of the phenyl ring.

4. The method of claim 1, wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are hydrogen.

5. The method of claim 1, wherein the compound of Formula (I) is selected from an enantiomer of Formula (I) or an enantiomer of Formula (I) in an enantiomeric mixture wherein one enantiomer predominates.

6. The method of claim 5, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 90% or greater.

7. The method of claim 6, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 98% or greater.

8. The method of claim 1, wherein the compound of Formula (II) is selected from an enantiomer of Formula (II) or an enantiomer of Formula (II) in an enantiomeric mixture wherein one enantiomer predominates.

9. The method of claim 8, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 90% or greater.

10. The method of claim 9, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 98% or greater.

11. The method of claim 1, wherein the method further comprises preventing, treating or ameliorating a substance-induced disorder resulting from the use of an addictive drug.

12. The method of claim 11, wherein the addictive drug is selected from heroin, opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants, barbiturates, phencyclidines or nicotine.

13. The method of claim 11, wherein the substance-induced disorder is selected from alcohol withdrawal (with or without perceptual disturbances and/or delirium), seizures, psychosis, amphetamine withdrawal, cocaine withdrawal, nicotine withdrawal, opioid withdrawal, sedative withdrawal, hypnotic withdrawal, anxiolytic withdrawal (with or without perceptual disturbances and/or delirium), nicotine withdrawal

(with or without disturbances associated with smoking cessation), withdrawal symptoms due to other substances, substance-induced anxiety disorder with onset during withdrawal, vulnerability to environmental trigger induced craving, substance-induced mood disorder with onset during withdrawal or substance-induced sleep disorder with onset during withdrawal.

14. The method of claim 1, wherein the method further comprises co-administrating to the subject an effective amount of a combination product, wherein the combination product is selected from a compound of claim 1 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 1 and an effective amount of one or more compounds known to treat substance-induced disorders.

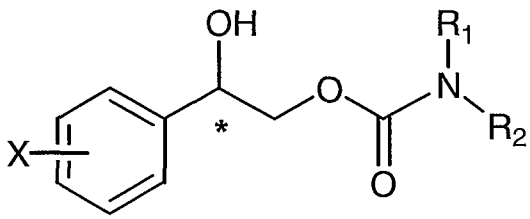
15. The method of claim 14, wherein the compound known to treat substance-induced disorders is one or more compounds selected form the group consisting of; naltrexone, naloxone or other opioid receptor antagonists, fluoxetine or other SSRI antidepressants, thyrotropin-releasing hormone analogues, venlafaxine or other SNRI antidepressants, MAO Inhibitor antidepressants, tricyclic antidepressants, bupropion, lithium carbonate, anticonvulsants, acamprosate, disulfiram (antabuse), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

16. The method of claim 14, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of acamprosate, naltrexone, naloxone and disulfiram.

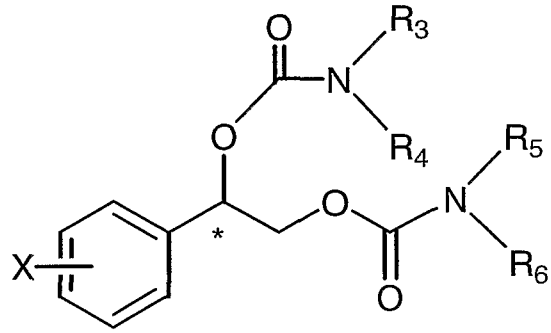
17. The method of claim 1, wherein the effective amount is from about 0.01 μg/Kg/dose to about 300 mg/Kg/dose.

18. A method for preventing, treating or ameliorating substance-related

disorders in a subject in need thereof comprising administering to the subject an effective amount of an enantiomer selected from Formula (I) or Formula (II) or an enantiomer selected from Formula (I) or Formula (II) in an enantiomeric mixture wherein one enantiomer predominates:




Formula (I)




Formula (II)

or pharmaceutically acceptable forms thereof or a pharmaceutically acceptable salt thereof, wherein

phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and,

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and $C_1$-$C_4$ alkyl; wherein $C_1$-$C_4$ alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, amino, nitro and cyano).

19. The method of claim 18, wherein X is chlorine.

20. The method of claim 18, wherein X is substituted at the ortho position of the phenyl ring.

21. The method of claim 18, wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are hydrogen.

23. The method of claim 18, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 90% or greater.

24. The method of claim 23, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 98% or greater.

25. The method of claim 18, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 90% or greater.

26. The method of claim 25, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 98% or greater.

27. The method of claim 18, wherein the method further comprises preventing, treating or ameliorating a substance-induced disorder resulting from the use of an addictive drug.

28. The method of claim 27, wherein the addictive drug is selected from heroin, opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants, barbiturates, phencyclidines or nicotine.

29. The method of claim 27, wherein the substance induced disorder is selected from alcohol withdrawal (with or without perceptual disturbances and/or delirium), seizures, psychosis, amphetamine withdrawal, cocaine withdrawal, nicotine withdrawal, opioid withdrawal, sedative withdrawal, hypnotic withdrawal, anxiolytic withdrawal (with or without perceptual disturbances and/or delirium), nicotine withdrawal (with or without disturbances associated with smoking cessation), withdrawal symptoms due to other substances, substance-induced anxiety disorder with onset during withdrawal, vulnerability to environmental trigger induced craving, substance-induced mood disorder with onset during withdrawal or substance-induced sleep disorder with onset during withdrawal.

30. The method of claim 18, wherein the method further comprises co-

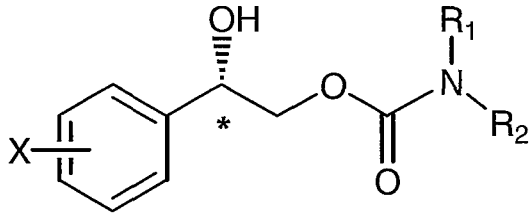
administrating to the subject an effective amount of a combination product, wherein the combination product is selected from an enantiomer of claim 18 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer of claim 18 and an effective amount of one or more compounds known to treat substance-induced disorders.

31. The method of claim 30, wherein the compound known to treat substance-induced disorders is one or more compounds selected form the group consisting of naltrexone, naloxone or other opioid receptor antagonists, fluoxetine or other SSRI antidepressants, thyrotropin-releasing hormone analogues, venlafaxine or other SNRI antidepressants, MAO Inhibitor antidepressants, tricyclic antidepressants, bupropion, lithium carbonate, anticonvulsants, acamprosate, disulfiram (antabuse), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

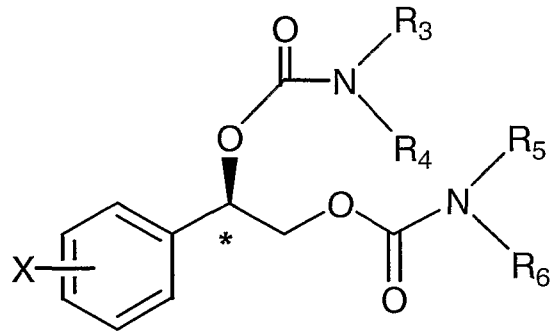
32. The method of claim 30, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of acamprosate, naltrexone, naloxone and disulfiram.

33. The method of claim 18, wherein the effective amount is from about 0.01 μg/Kg/dose to about 300 mg/Kg/dose.

34. The method of claim 18, wherein the enantiomer selected from Formula (I) or Formula (II) is an enantiomer selected from Formula (Ia) or Formula (IIa) or an enantiomer selected from Formula (Ia) or Formula (IIa) in an enantiomeric mixture wherein one enantiomer predominates:



Formula (Ia)



Formula (IIa)

or pharmaceutically acceptable forms thereof or a pharmaceutically acceptable salt thereof, wherein

phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and,

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and $C_1$-$C_4$ alkyl; wherein $C_1$-$C_4$ alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, amino, nitro and cyano).

35. The method of claim 34, wherein X is chlorine.

36. The method of claim 34, wherein X is substituted at the ortho position of the phenyl ring.

37. The method of claim 34, wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are hydrogen.

38. The method of claim 34, wherein the enantiomer of Formula (Ia) in an enantiomeric mixture predominates to the extent of about 90% or greater.

39. The method of claim 38, wherein the enantiomer of Formula (Ia) in an enantiomeric mixture predominates to the extent of about 98% or greater.

40. The method of claim 34, wherein the enantiomer of Formula (IIa) in an enantiomeric mixture predominates to the extent of about 90% or greater.

41. The method of claim 40, wherein the enantiomer of Formula (IIa) in an enantiomeric mixture predominates to the extent of about 98% or greater.

42. The method of claim 34, wherein the method further comprises preventing, treating or ameliorating a substance-induced disorder resulting from the use of an addictive drug.

43. The method of claim 42, wherein the addictive drug is selected from heroin, opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants, barbiturates, phencyclidines or nicotine.

44. The method of claim 42, wherein the substance induced disorder is selected from alcohol withdrawal (with or without perceptual disturbances and/or delirium), seizures, psychosis, amphetamine withdrawal, cocaine withdrawal, nicotine withdrawal, opioid withdrawal, sedative withdrawal, hypnotic withdrawal, anxiolytic withdrawal (with or without perceptual disturbances and/or delirium), nicotine withdrawal (with or without disturbances associated with smoking cessation), withdrawal symptoms due to other substances, substance-induced anxiety disorder with onset during withdrawal, vulnerability to environmental trigger induced craving, substance-induced mood disorder with onset during withdrawal or substance-induced sleep disorder with onset during withdrawal.

45. The method of claim 34, wherein the method further comprises co-administrating to the subject an effective amount of a combination product, wherein the combination product is selected from an enantiomer of claim 34 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer of claim 34 and

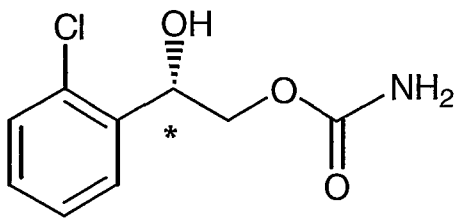
an effective amount of one or more compounds known to treat substance-induced disorders.

46. The method of claim 45, wherein the compound known to treat substance-induced disorders is one or more compounds selected form the group consisting of naltrexone, naloxone or other opioid receptor antagonists, fluoxetine or other SSRI antidepressants, thyrotropin-releasing hormone analogues, venlafaxine or other SNRI antidepressants, MAO Inhibitor antidepressants, tricyclic antidepressants, bupropion, lithium carbonate, anticonvulsants, acamprosate, disulfiram (antabuse), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

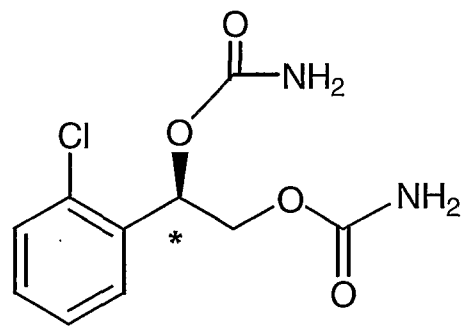
47. The method of claim 45, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of; acamprosate, naltrexone, naloxone and disulfiram.

48. The method of claim 34, wherein the effective amount is from about 0.01 µg/Kg/dose to about 300 mg/Kg/dose.

49. The method of claim 18, wherein the enantiomer selected from Formula (I) or Formula (II) is an enantiomer selected from Formula (Ib) or Formula (IIb) or an enantiomer selected from Formula (Ib) or Formula (IIb) in an enantiomeric mixture wherein one enantiomer predominates:




Formula (Ib)




Formula (IIb)

or pharmaceutically acceptable forms thereof or a pharmaceutically acceptable salt thereof wherein

phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and,

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen and $C_1$-$C_4$ alkyl; wherein $C_1$-$C_4$ alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, amino, nitro and cyano).

50. The method of claim 49, wherein X is chlorine.

51. The method of claim 49, wherein X is substituted at the ortho position of the phenyl ring.

52. The method of claim 49, wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are hydrogen.

53. The method of claim 49, wherein the enantiomer of Formula (Ib) in an enantiomeric mixture predominates to the extent of about 90% or greater.

54. The method of claim 53, wherein the enantiomer of Formula (Ib) in an enantiomeric mixture predominates to the extent of about 98% or greater.

55. The method of claim 49, wherein the enantiomer of Formula (IIb) in an enantiomeric mixture predominates to the extent of about 90% or greater.

56. The method of claim 53, wherein the enantiomer of Formula (IIb) in an enantiomeric mixture predominates to the extent of about 98% or greater.

57. The method of claim 49, wherein the method further comprises

preventing, treating or ameliorating a substance-induced disorder resulting from the use of an addictive drug.

58. The method of claim 57, wherein the addictive drug is selected from heroin, opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants barbiturates, phencyclidines or nicotine.

59. The method of claim 57, wherein the substance induced disorder is selected from alcohol withdrawal (with or without perceptual disturbances and/or delirium), seizures, psychosis, amphetamine withdrawal, cocaine withdrawal, nicotine withdrawal, opioid withdrawal, sedative withdrawal, hypnotic withdrawal, anxiolytic withdrawal (with or without perceptual disturbances and/or delirium), nicotine withdrawal (with or without disturbances associated with smoking cessation), withdrawal symptoms due to other substances, substance-induced anxiety disorder with onset during withdrawal, vulnerability to environmental trigger induced craving, substance-induced mood disorder with onset during withdrawal or substance-induced sleep disorder with onset during withdrawal.

.60. The method of claim 49, wherein the method further comprises co-administrating to the subject an effective amount of a combination product, wherein the combination product is selected from an enantiomer of claim 49 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer of claim 49 and an effective amount of one or more compounds known to treat substance-induced disorders.

61. The method of claim 60, wherein the compound known to treat substance-induced related disorders is one or more compounds selected form the group consisting of; naltrexone, naloxone or other opioid receptor antagonists, fluoxetine or other SSRI antidepressants, thyrotropin-releasing hormone analogues, venlafaxine or other SNRI antidepressants, MAO Inhibitor antidepressants, tricyclic

antidepressants, bupropion, lithium carbonate, anticonvulsants, acamprosate, disulfiram (antabuse), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

.62. The method of claim 60, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of; acamprosate, naltrexone, naloxone and disulfiram.

63. The method of claim 49, wherein the effective amount is from about 0.01 μg/Kg/dose to about 300 mg/Kg/dose.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/026439

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/325

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

EPO-Internal, CHEM ABS Data, WPI Data, PAJ, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/067927 A (ORTHO-MCNEIL PHARMACEUTICAL, INC) 6 September 2002 (2002-09-06) page 1, line 11 - line 15 page 7, line 18 - page 8, line 5 page 2, line 7 page 13, paragraph 2; example 1 | 1-63 |
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| X | US 3 313 692 A (BOSSINGER CHARLES D ET AL) 11 April 1967 (1967-04-11) column 1, line 25 - line 26 page 3, line 62 - line 63 column 9 | 1-63 |

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in 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 document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 October 2005 | 28/10/2005 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Bendl, E |

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/026439

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/067926 A (ORTHO-MCNEIL PHARMACEUTICAL, INC)<br>6 September 2002 (2002-09-06)<br>page 7<br>page 1, line 14 - line 15<br>page 12, line 32 | 1-63 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/026439

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

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

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

Although claims 1-63 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

**Remark on Protest**

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

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

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/026439

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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