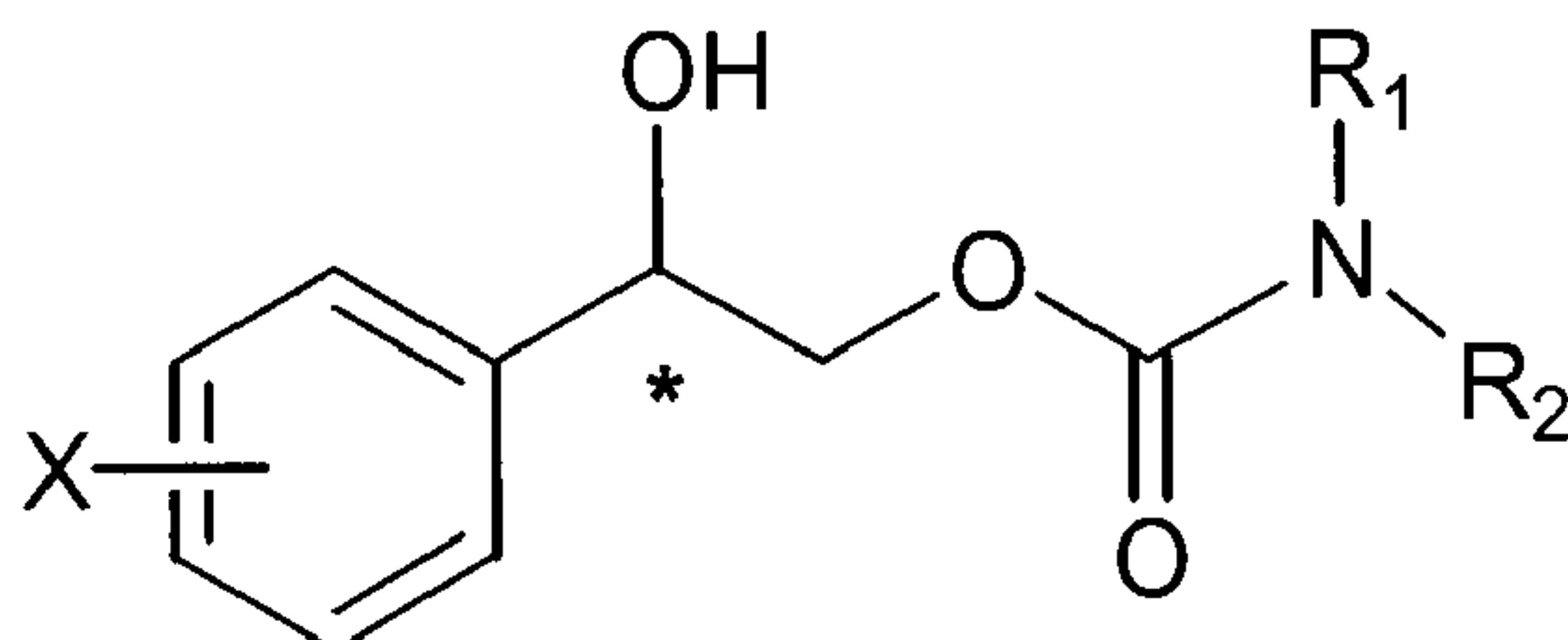




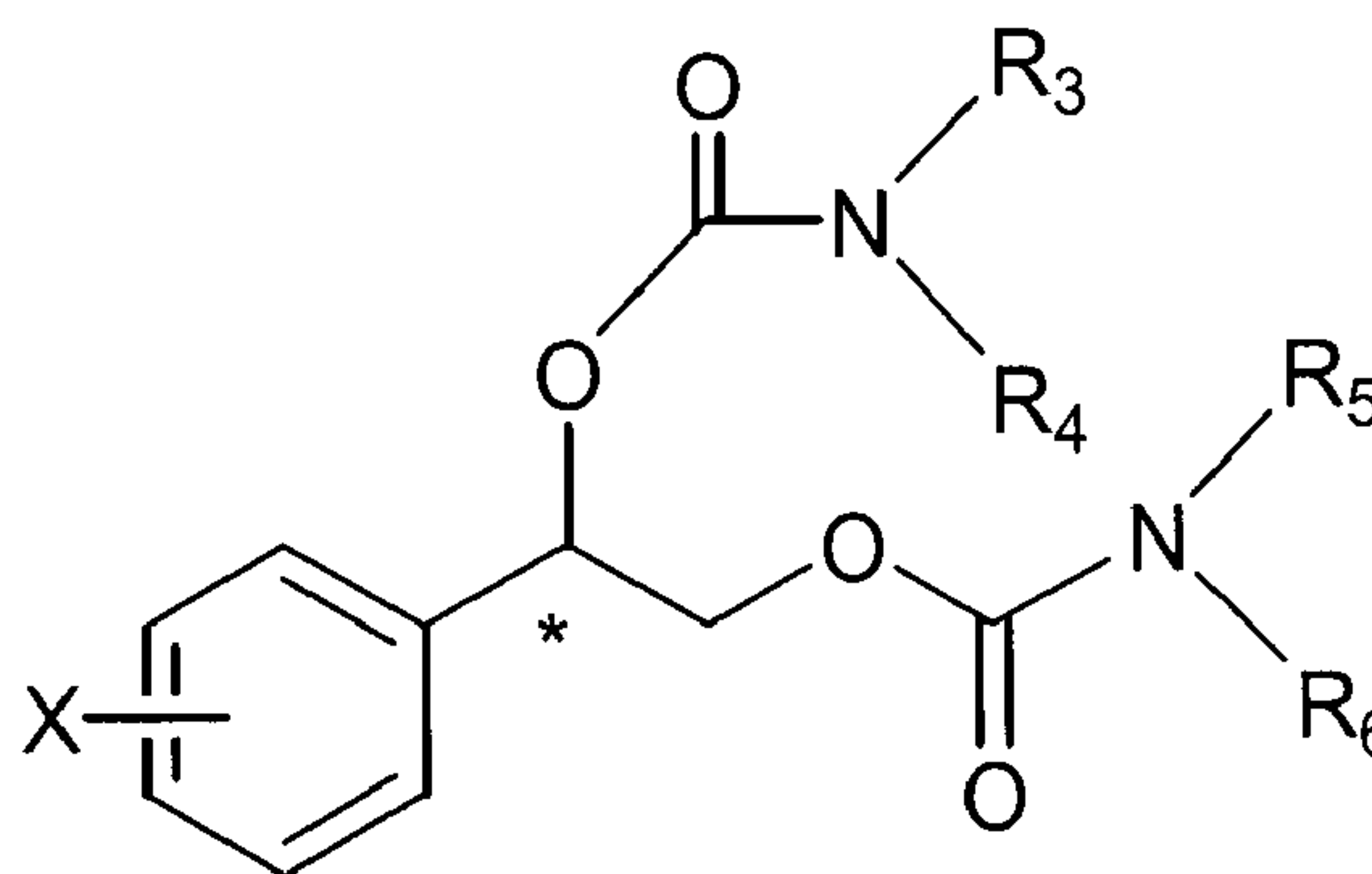
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(54) **Titre : PROCÉDES POUR TRAITER DES TROUBLES LIÉS À DES SUBSTANCES**  
(54) **Title: METHODS FOR TREATING SUBSTANCE-RELATED DISORDERS**



Formula (I)



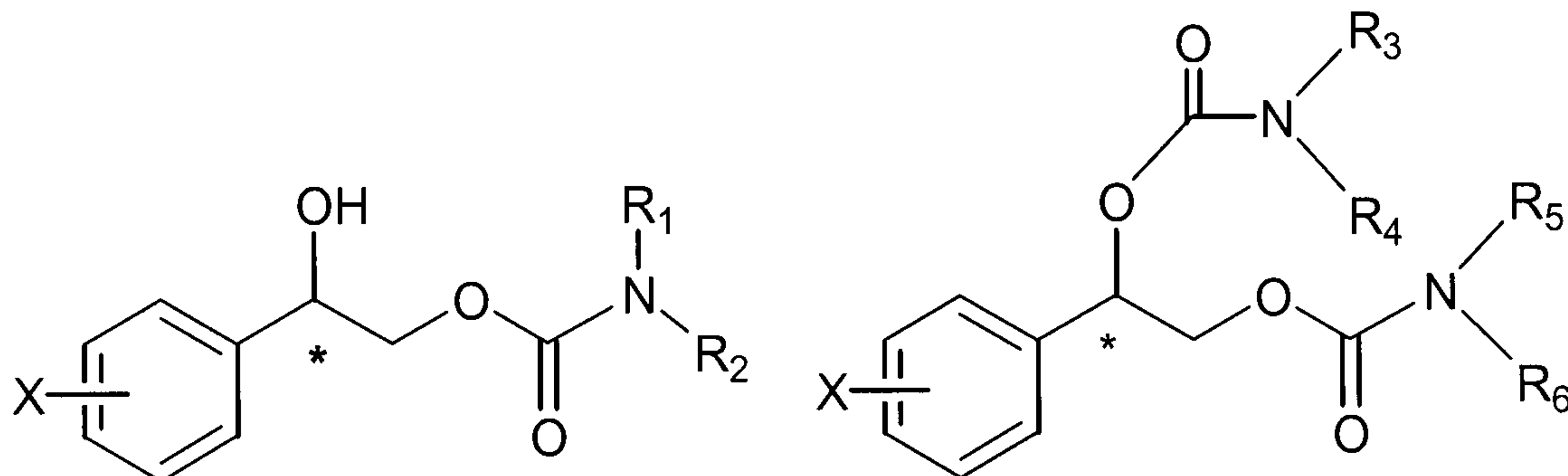
Formula (II)

(57) **Abrégé/Abstract:**

This invention is directed to the use of an effective amount of a compound selected from: (see 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<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl; wherein C<sub>1</sub>-C<sub>4</sub> alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano) for preventing, treating or ameliorating substance-related disorders, in a subject in need thereof. In addition, uses are included involving co-administration of compounds of the invention with one or more compounds known to treat substance-induced disorders.

## Abstract of the Invention

This invention is directed to the use of 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<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl; wherein C<sub>1</sub>-C<sub>4</sub> alkyl is optionally substituted with phenyl (and, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano) for preventing, treating or ameliorating substance-related disorders, in a subject in need thereof. In addition, uses 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  
5 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.

### 10 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  
15 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  
20 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  
25 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).

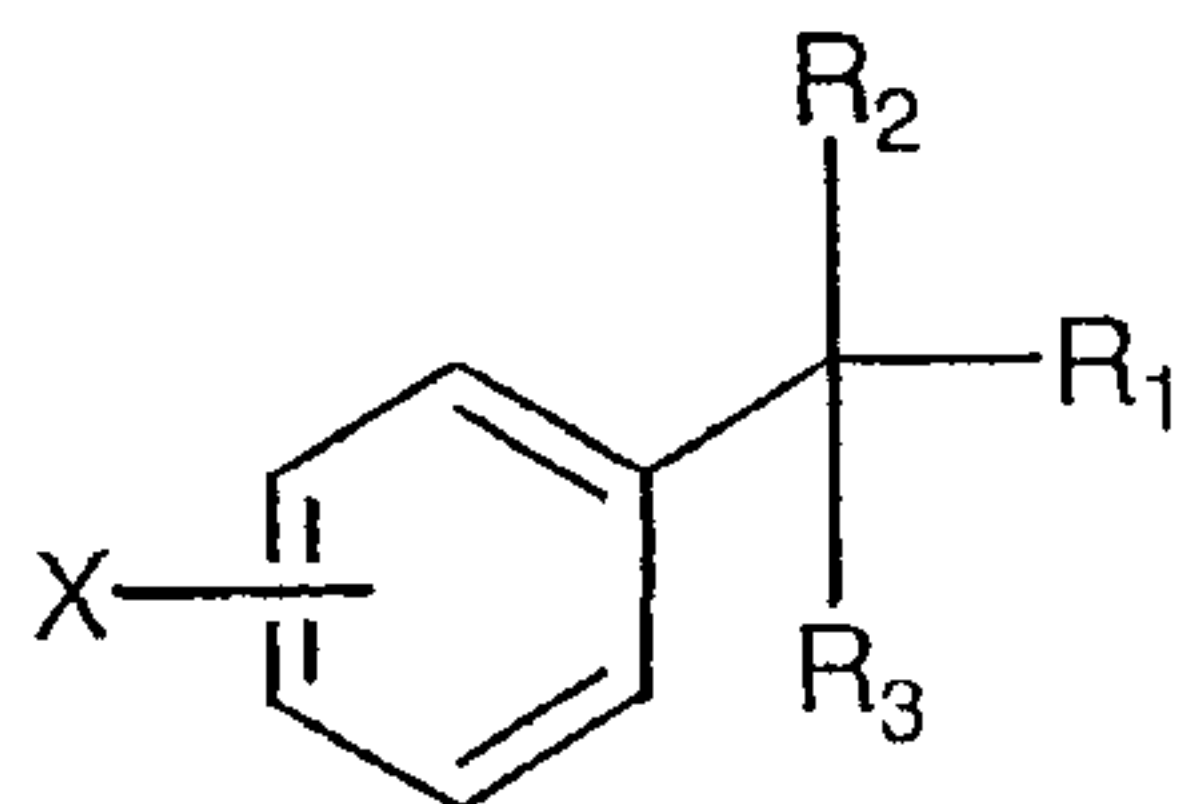
Substance Abuse is a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of the substance. These problems occur repeatedly for at least a 12 month period.

5            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,  
10   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).

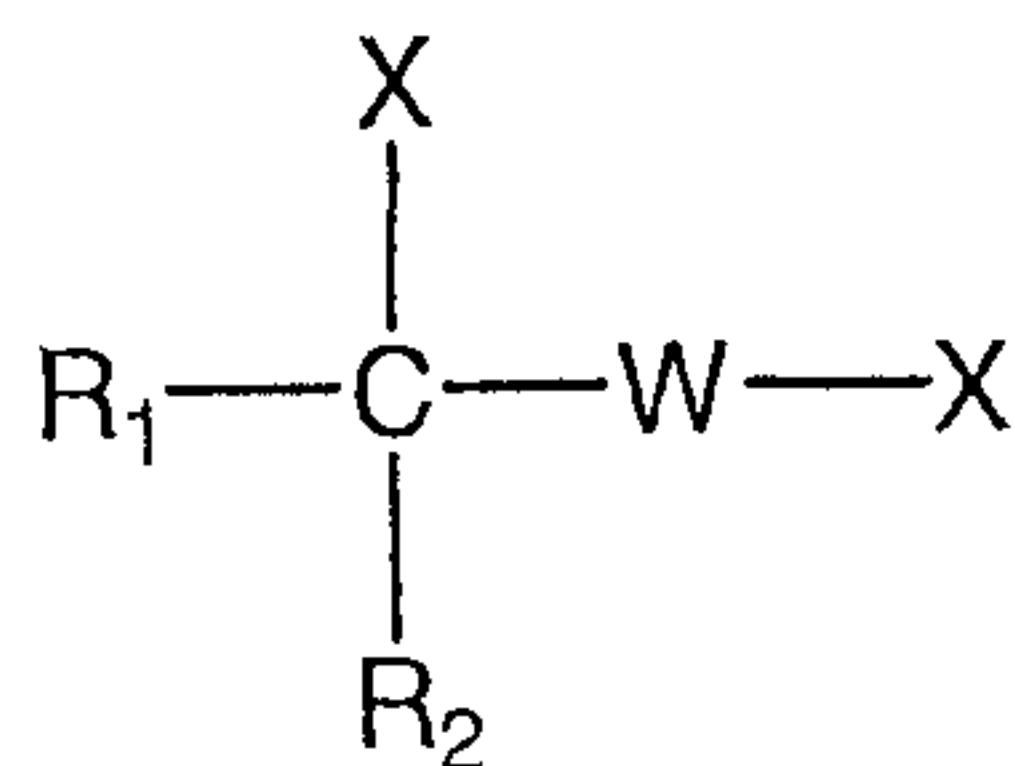
15            There remains a need for effective pharmacologic therapies to prevent, treat or ameliorate Substance-Related Disorders resulting from the different classes of abusable drugs. In particular, there is a need for small molecule compounds that may be readily synthesized, that are potent and stabilizing mediators and restorative agents for neurotransmitter pathways and are useful  
20   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,  
25   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 as  
useful in treating the central nervous system, having tranquilization, sedation  
30   and muscle relaxation properties of the formula:



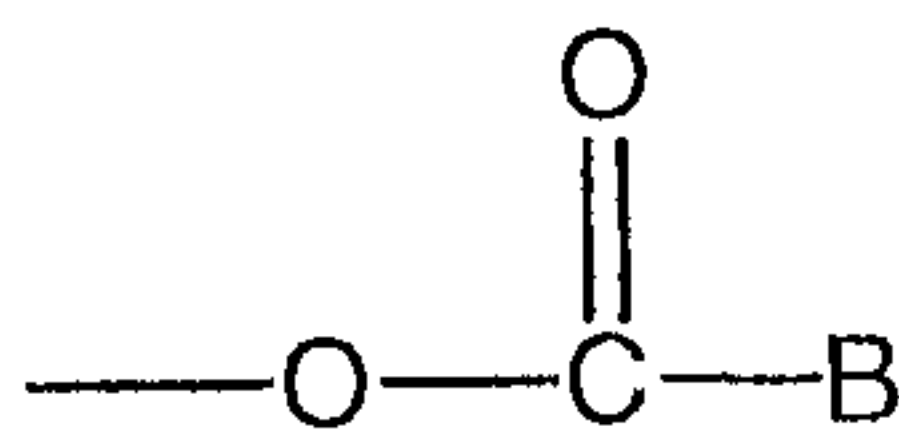
wherein  $R_1$  is either carbamate or alkyl carbamate containing from 1 to 3 carbon atoms in the alkyl group;  $R_2$  is either hydrogen, hydroxy, alkyl or hydroxy alkyl containing from 1 to 2 carbons;  $R_3$  is either hydrogen or alkyl  
 5 containing from 1 to 2 carbons; and X can be halogen, methyl, 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  
 by administering a compound of the formula:



10

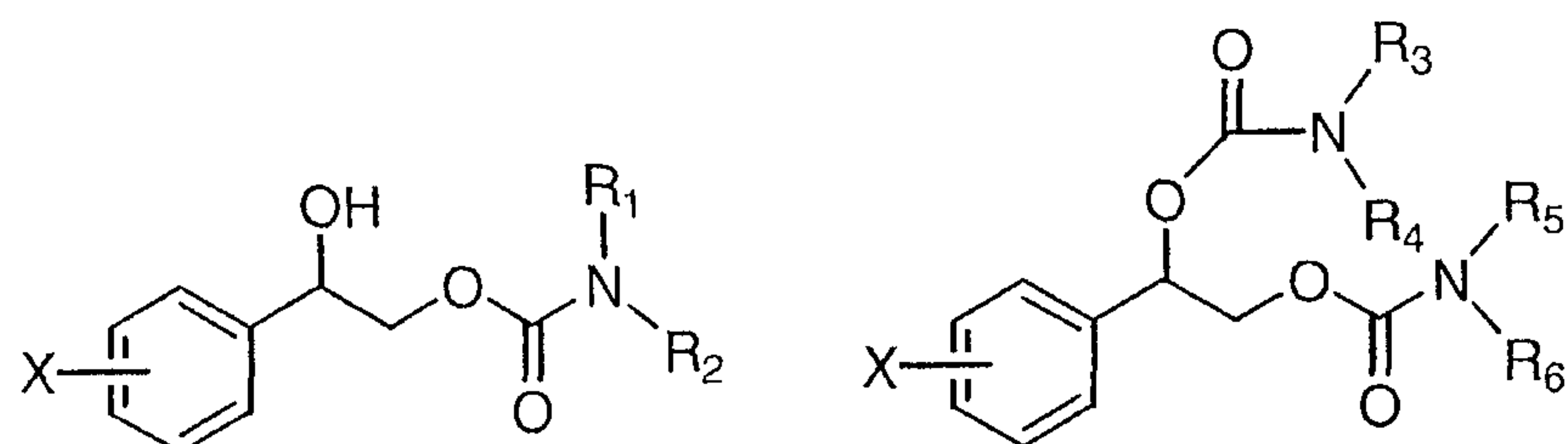
in which W represents an aliphatic radical containing less than 4 carbon atoms, wherein  $R_1$  represents an aromatic radical,  $R_2$  represents hydrogen or an alkyl radical containing less than 4 carbon atoms, and X represents a hydrogen, hydroxy, alkoxy or alkyl radical containing less than 4 carbon atoms or a radical  
 15 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.

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

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:

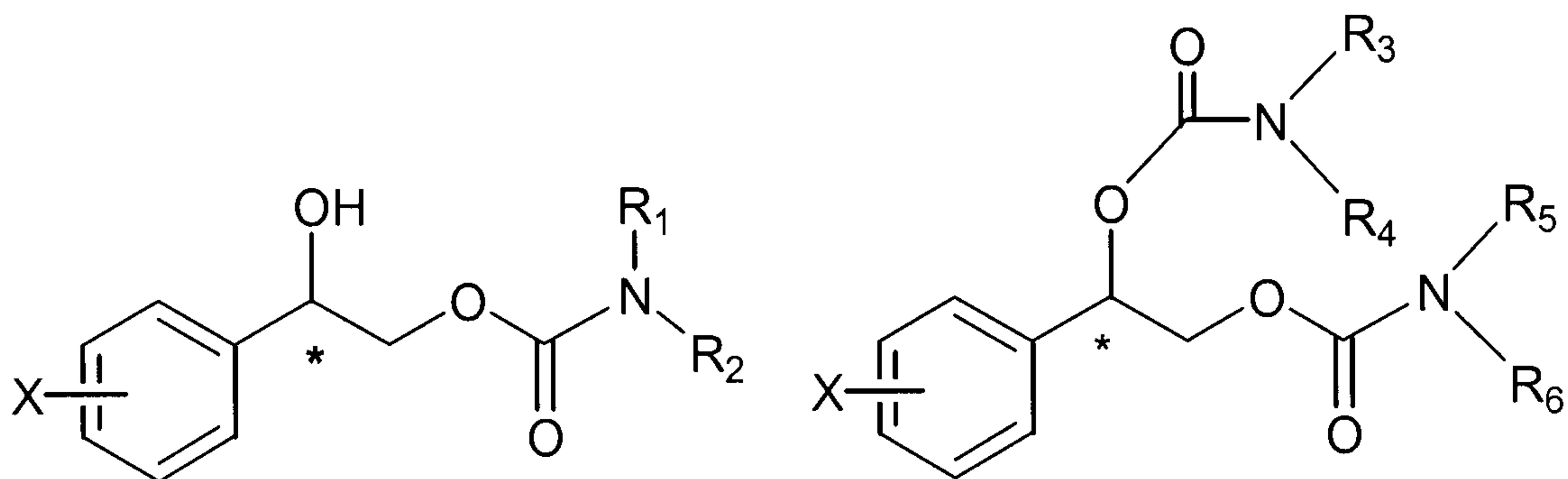


wherein one enantiomer predominates and wherein the phenyl ring is substituted at X with one to five halogen atoms selected from fluorine, chlorine, bromine or iodine atoms and  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are each selected from hydrogen and straight or branched alkyl groups 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  
 5 subject an effective amount of a carbamate compound of



Formula (I), or

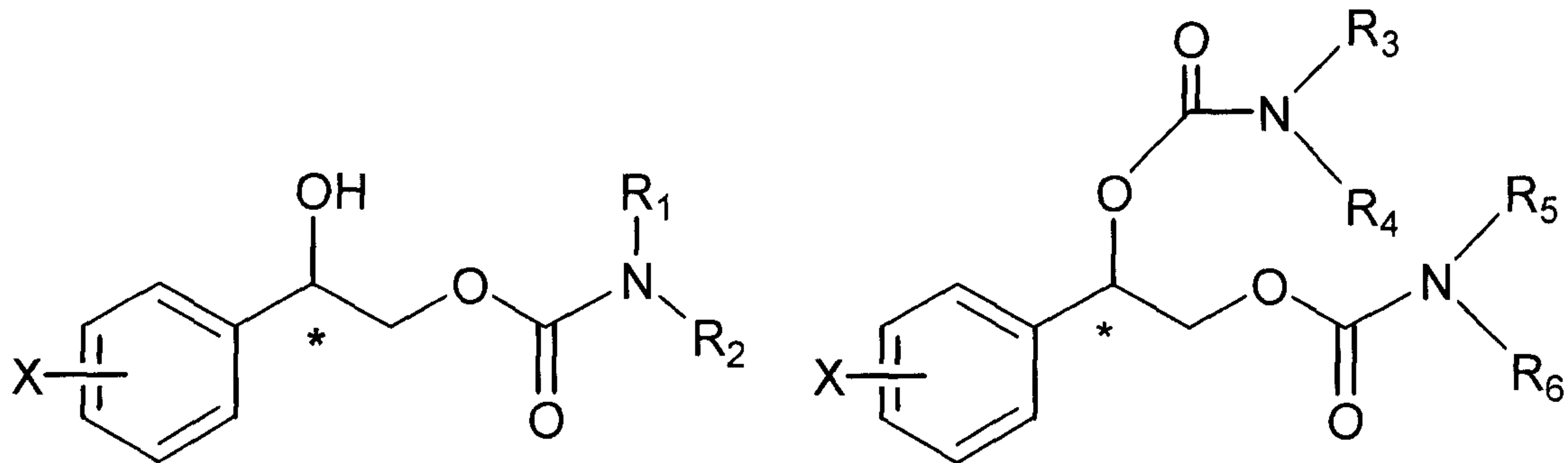
Formula (II)

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  
 10 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  
 15 effect of physiologic events associated with such diseases and disorders, i.e., substance-induced disorders.

In one aspect, the present invention provides for the use of an effective amount of a carbamate compound selected from



Formula (I), or

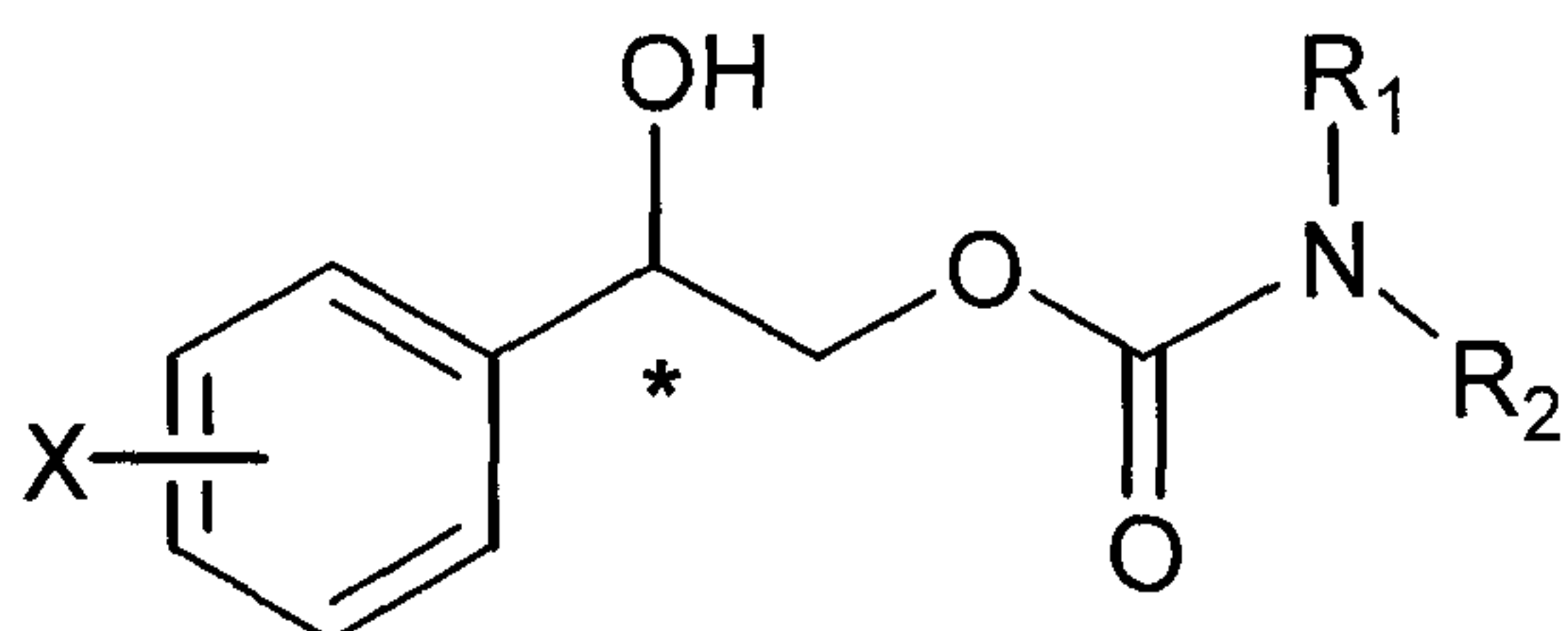
Formula (II);

or a pharmaceutically acceptable salt thereof, wherein

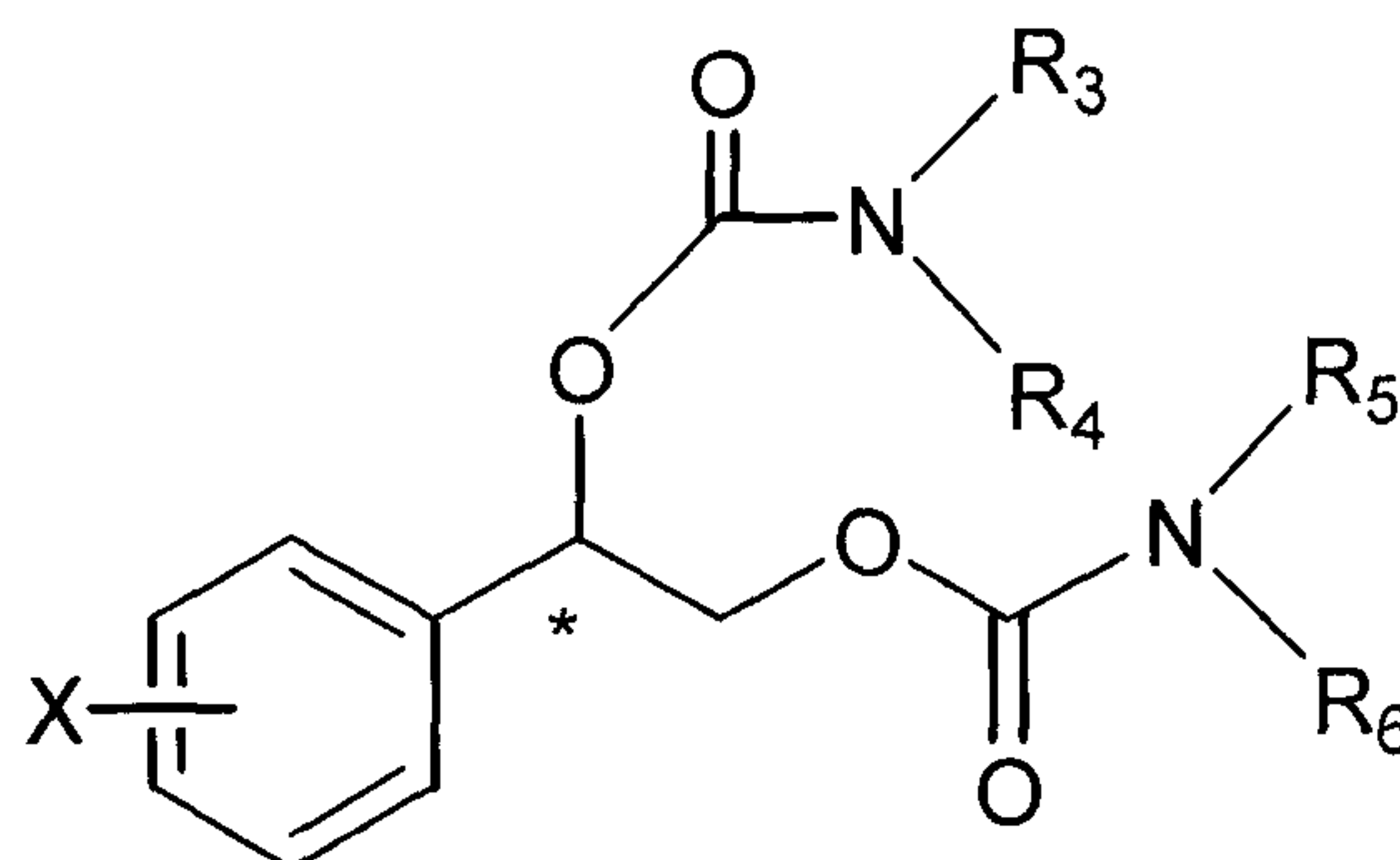
phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and,

$R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  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), in the manufacture of a medicament for preventing, treating or ameliorating one or more substance-related disorders selected from the group consisting of substance dependence, substance abuse, substance withdrawal syndrome, substance induced psychosis and substance induced mood disorder.

In another aspect, the present invention provides for the use of 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)



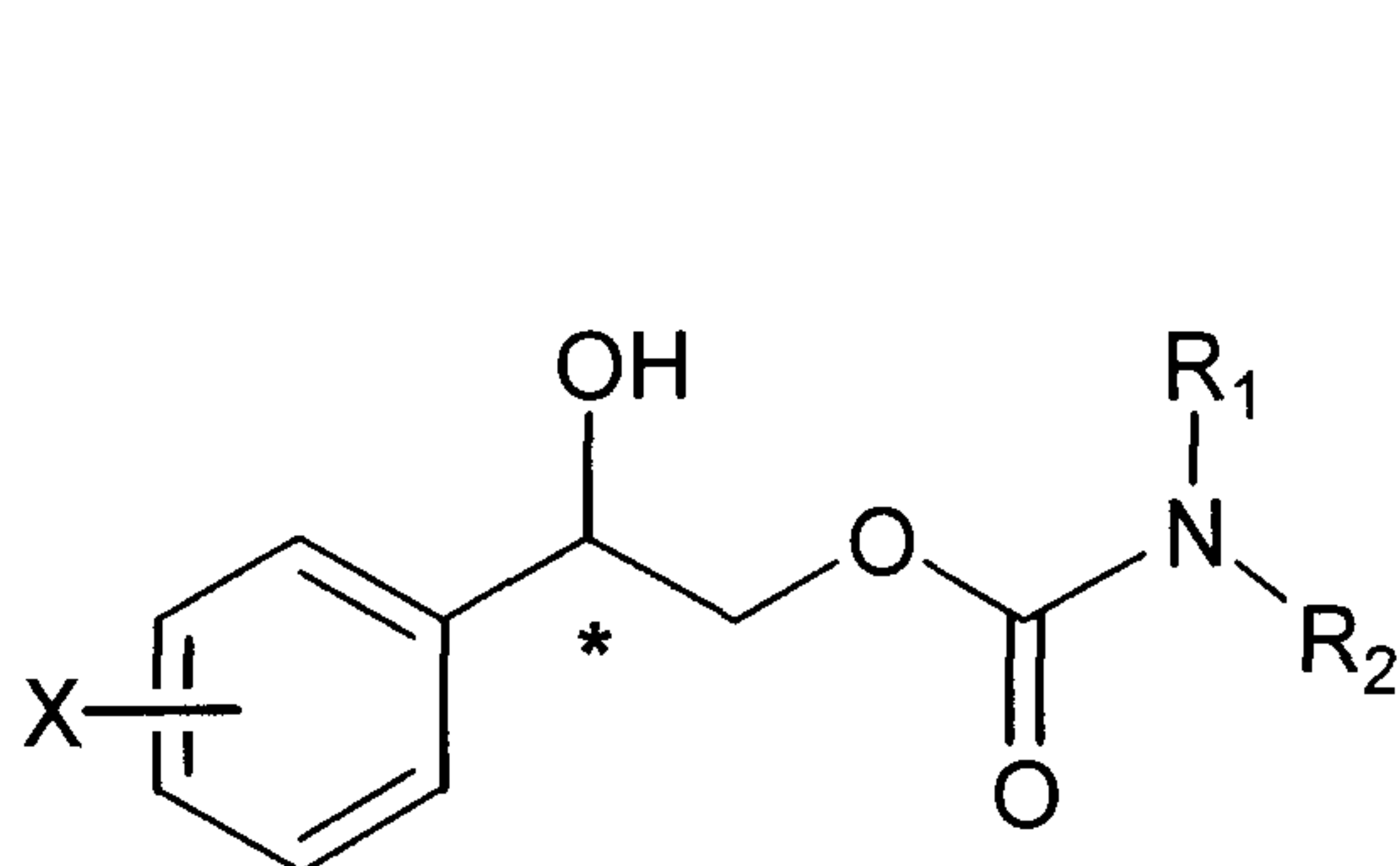
Formula (II)

or a pharmaceutically acceptable salt thereof, wherein

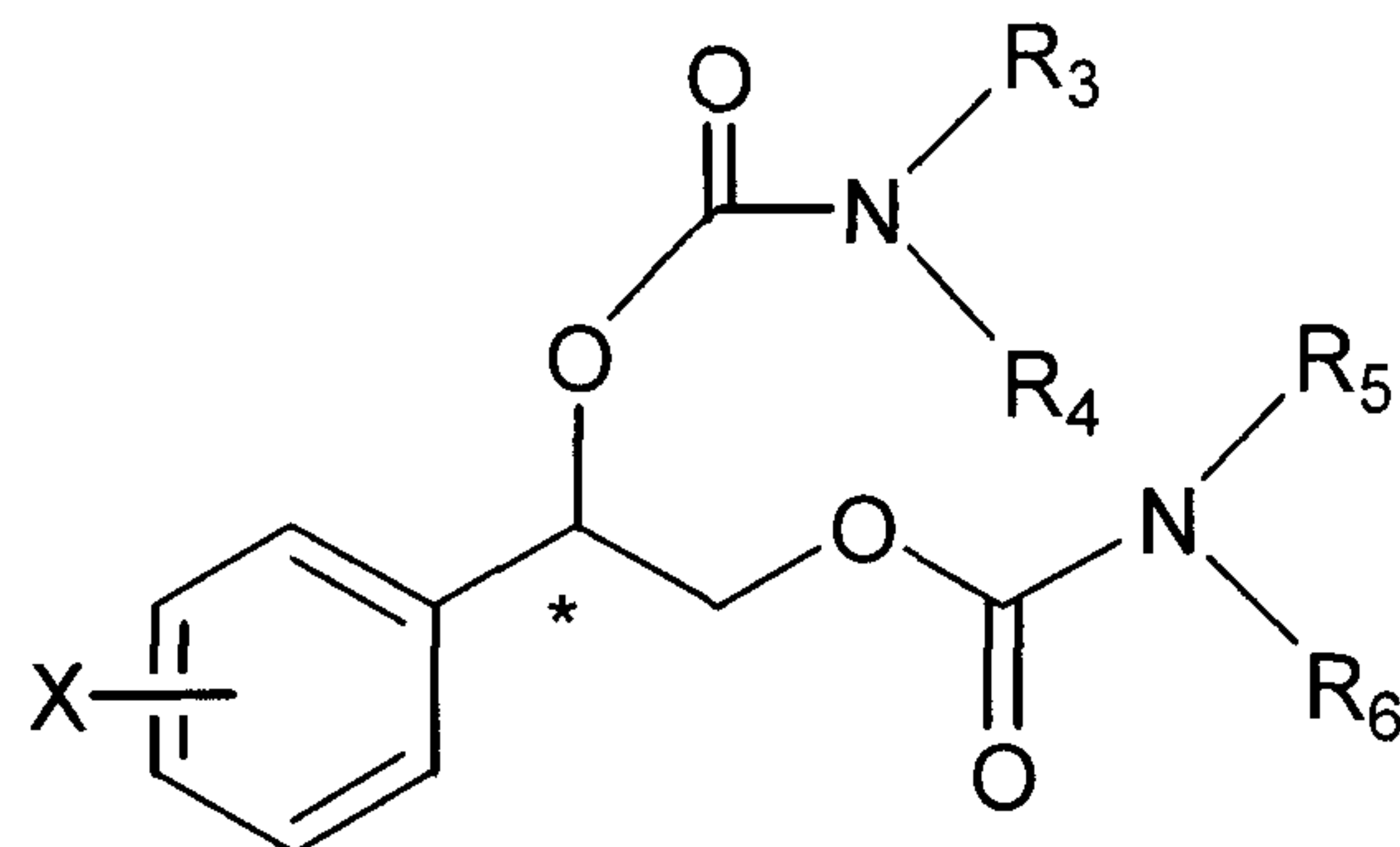
phenyl is substituted at X with one to five halogen atoms selected from the  
 5 group consisting of fluorine, chlorine, bromine and iodine; and,

$R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  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,  $C_1$ - $C_4$   
 10 alkyl,  $C_1$ - $C_4$  alkoxy, amino, nitro and cyano),  
 in the manufacture of a medicament for preventing, treating or ameliorating one  
 or more substance-related disorders selected from the group consisting of  
 substance dependence, substance abuse, substance withdrawal syndrome,  
 substance induced psychosis and substance induced mood disorder.

15 In another aspect, there is provided use of an effective amount of a  
 carbamate compound selected from



Formula (I)



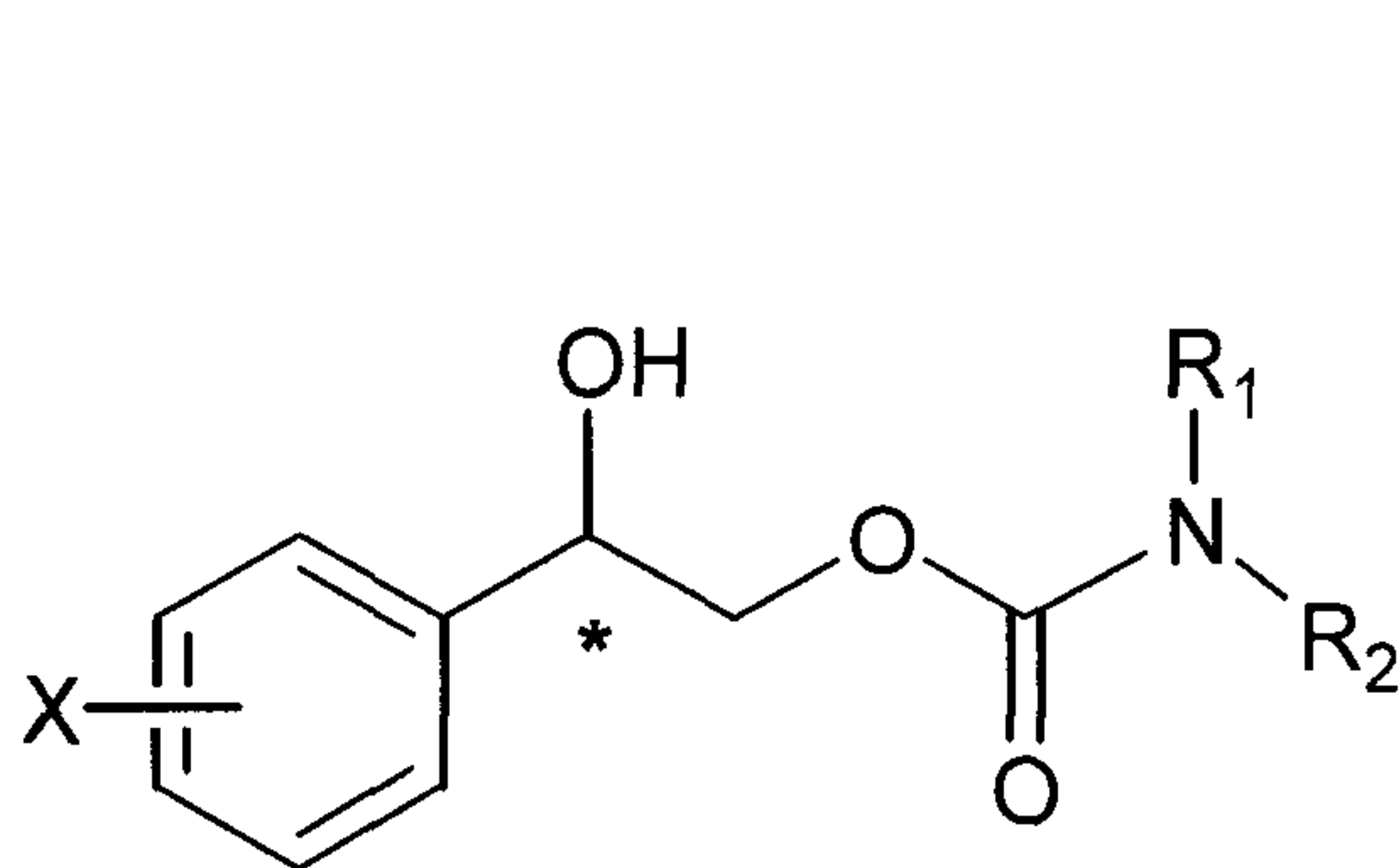
Formula (II)

or a pharmaceutically acceptable salt thereof, wherein

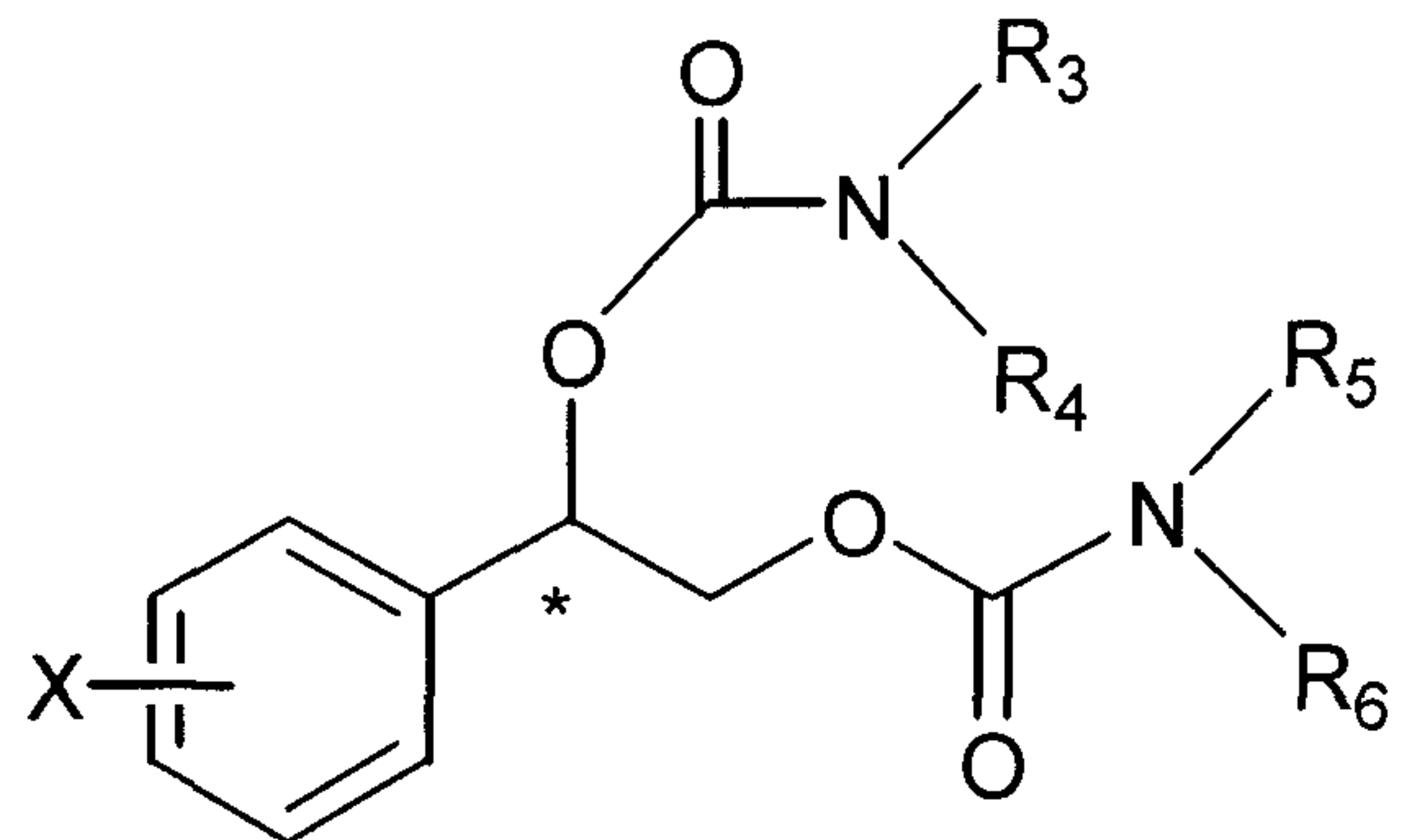
phenyl is substituted at X with one to five halogen atoms selected from the group consisting of fluorine, chlorine, bromine and iodine; and,

5  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  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, 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, for preventing, treating or  
10 ameliorating one or more substance-related disorders selected from the group consisting of substance dependence, substance abuse, substance withdrawal syndrome, substance induced psychosis and substance induced mood disorder in a subject in need thereof.

In another aspect, there is provided the use of an effective amount of an enantiomer selected from Formula (I) or Formula (II) or an enantiomer selected  
15 from Formula (I) or Formula (II) in an enantiomeric mixture wherein one enantiomer predominates:



Formula (I)



Formula (II)

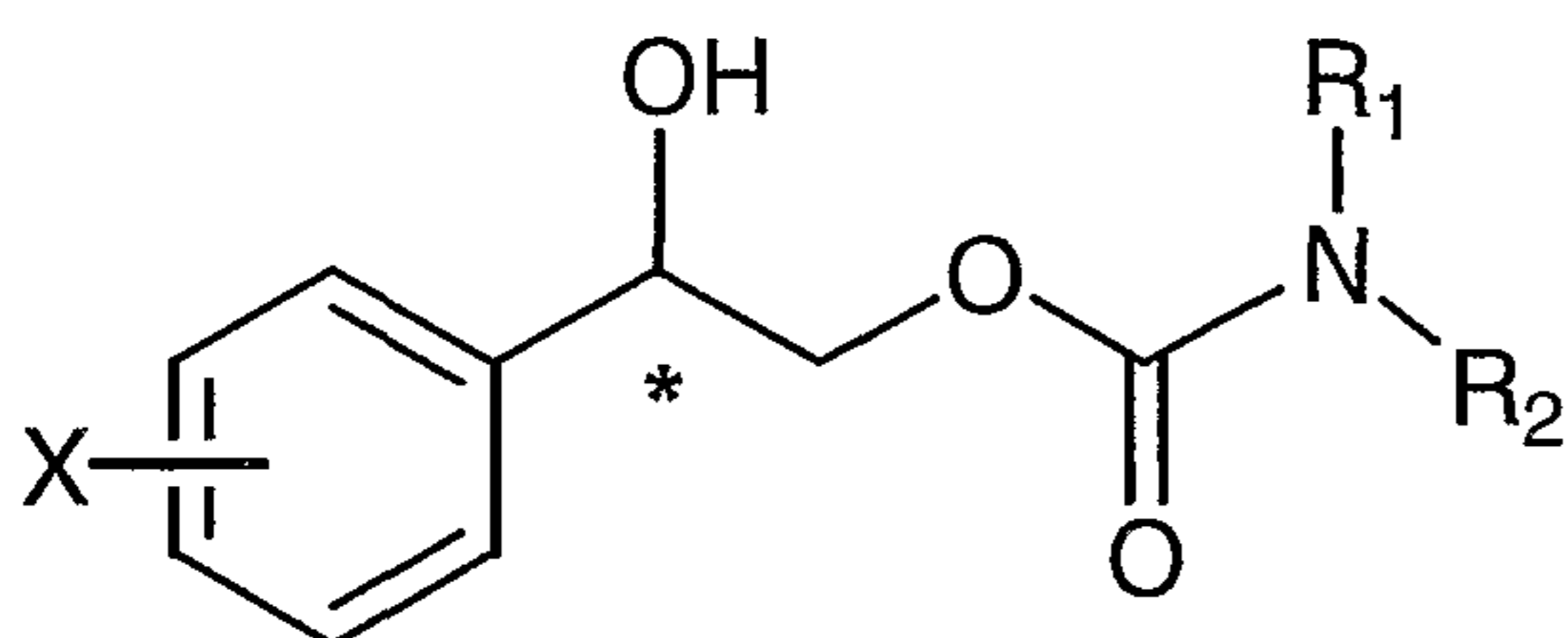
or a pharmaceutically acceptable salt thereof, wherein

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

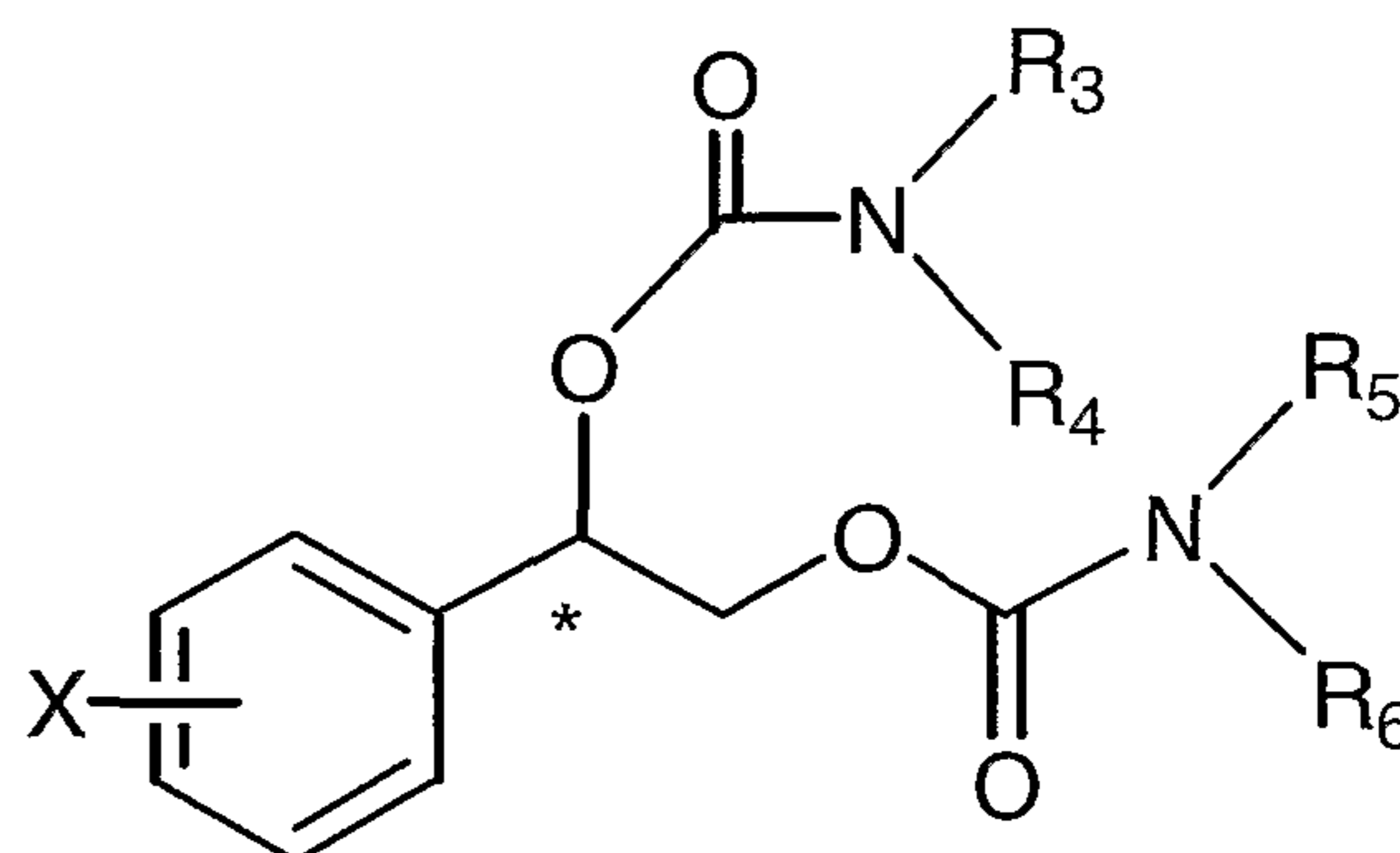
5  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are independently selected from the group consisting of hydrogen and  $C_1$ - $C_4$  alkyl; wherein  $C_1$ - $C_4$  alkyl is optionally substituted with phenyl, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, amino, nitro and cyano, for preventing, treating or ameliorating one or more substance-related disorders selected from the group consisting of substance dependence, substance abuse, substance withdrawal syndrome, substance induced psychosis and substance induced mood disorder in a subject in need thereof.

## DETAILED DESCRIPTION OF THE INVENTION

15 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

5  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  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).

10 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).

15 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  
20 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)<sup>TM</sup>, 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  
5 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.

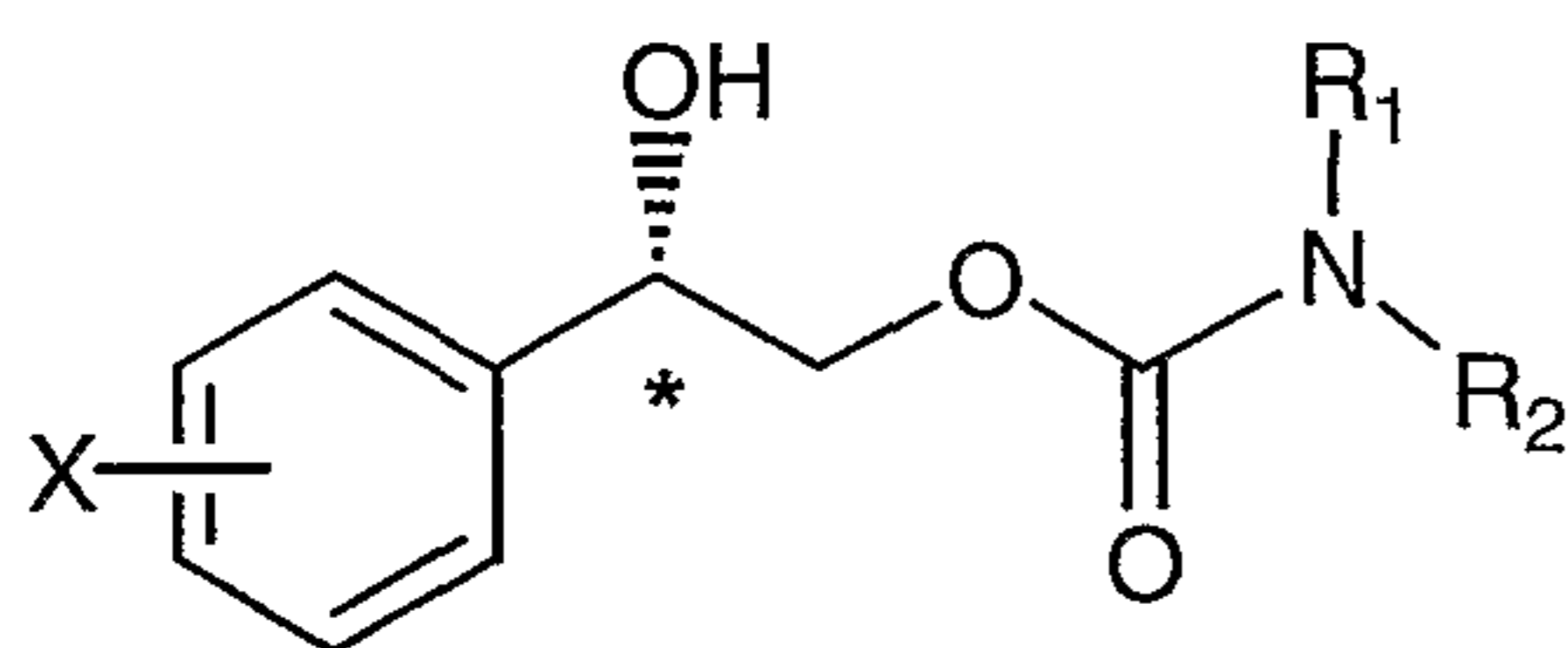
Other examples of said compound of Formula (I) or Formula (II) include  
10 compounds wherein X is chlorine, wherein X is substituted at the ortho position of the phenyl ring of Formula (I) or Formula (II) and, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> 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  
15 wherein one enantiomer predominates, wherein X is chlorine and, wherein X is substituted at the ortho position of the phenyl ring.

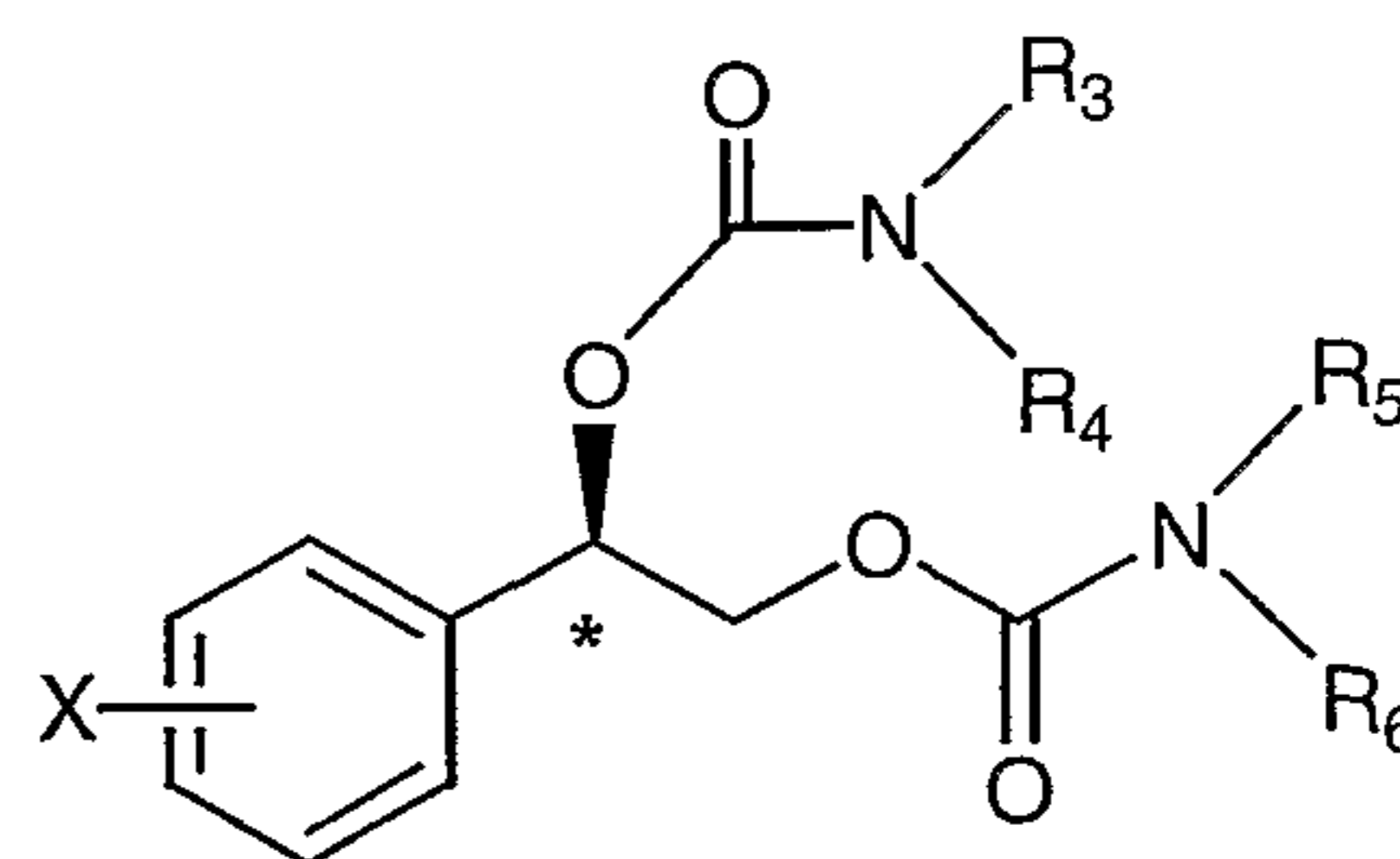
The present method also includes the use of an enantiomer selected from Formula (I) or Formula (II) or an enantiomeric mixture thereof wherein one enantiomer predominates and, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.

20 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.

25 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

5  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  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).

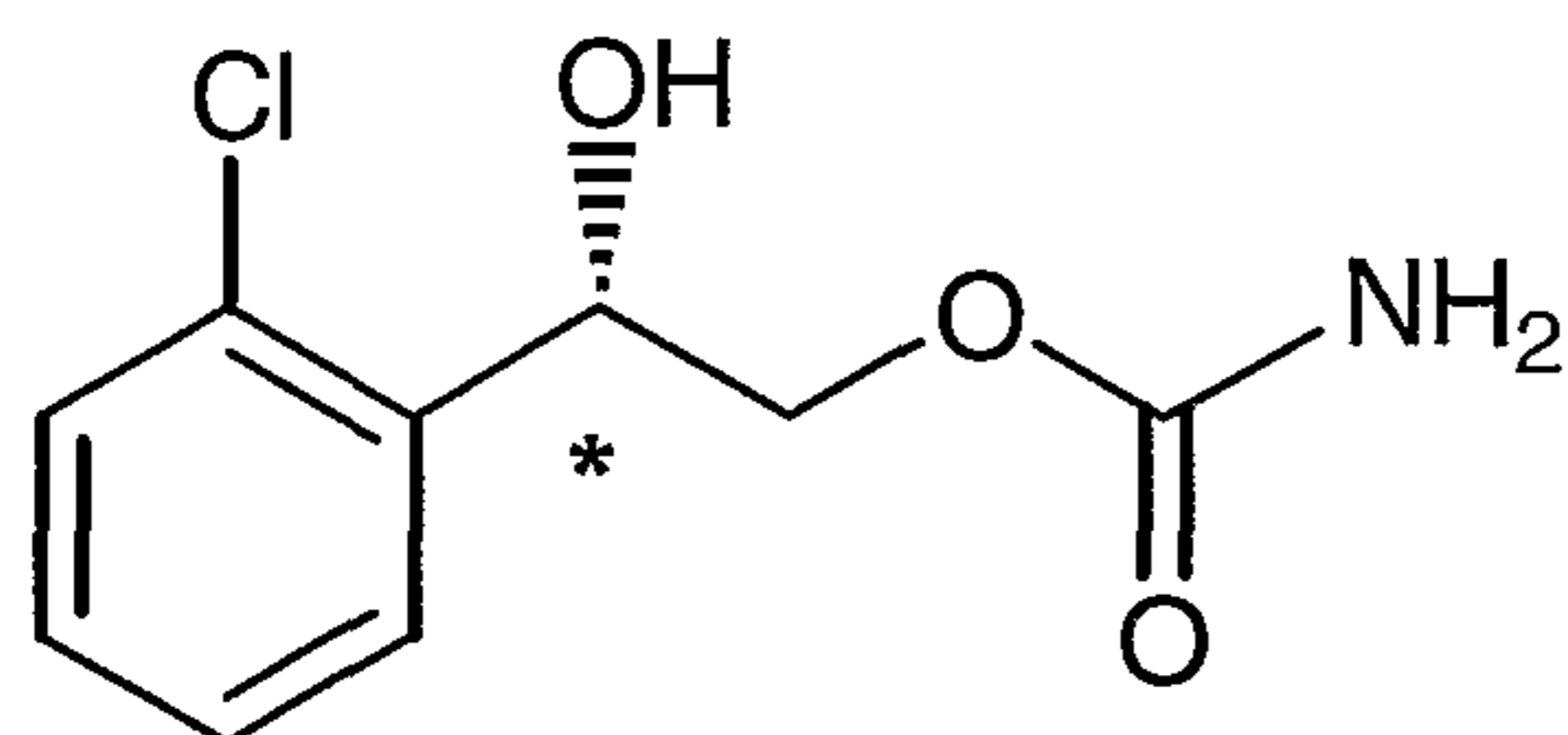
10 Examples of the present method include the use of an enantiomer selected from Formula (Ia) or Formula (IIa) or an enantiomeric mixture thereof wherein one enantiomer predominates, wherein X is chlorine and, wherein X is substituted at the ortho position of the phenyl ring.

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

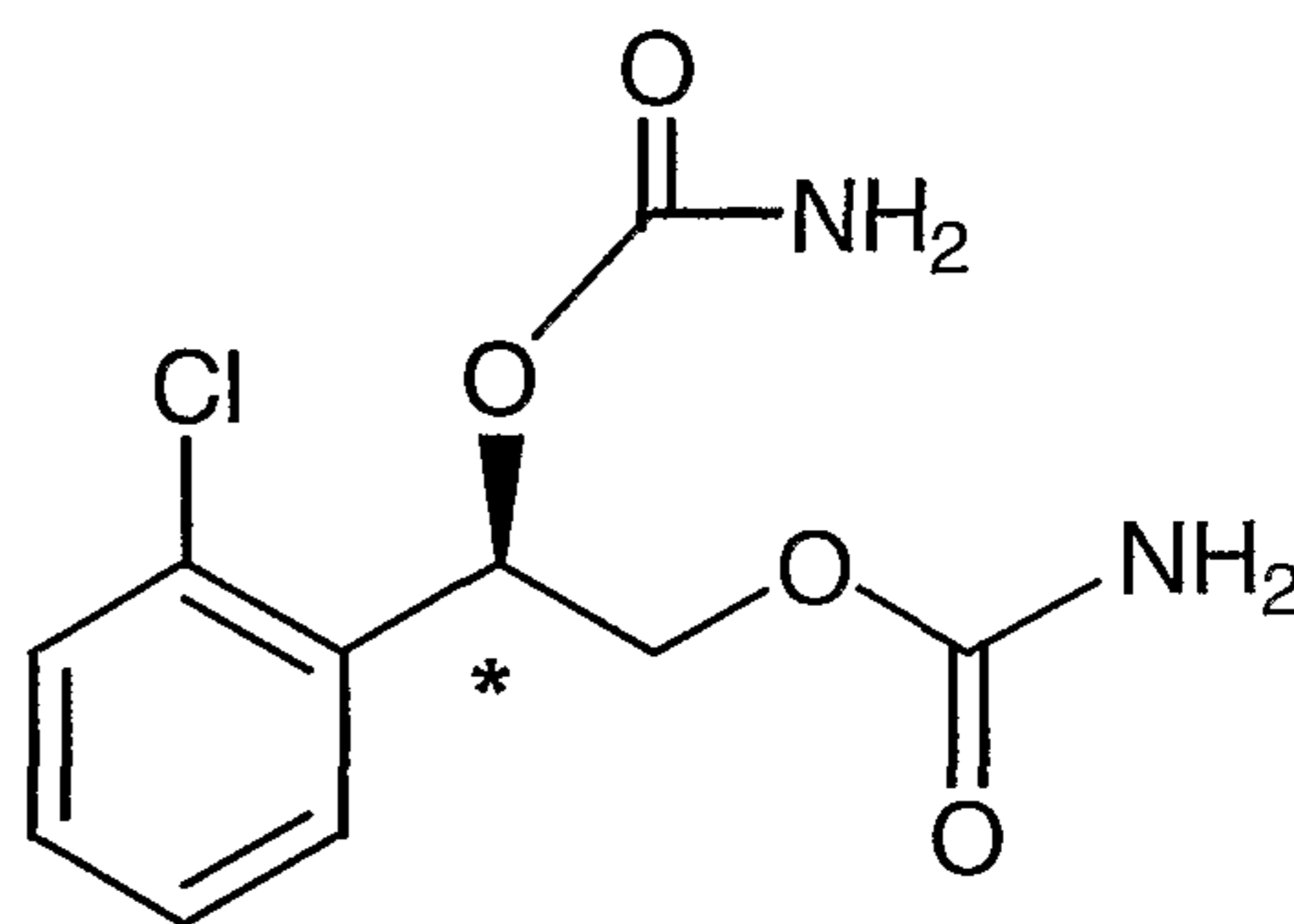
For enantiomeric mixtures wherein one enantiomer selected from Formula (Ia) or Formula (IIa) predominates, said enantiomer predominates to the extent of about 90% or greater. Enantiomeric mixtures within the scope of the present invention include those wherein said enantiomer predominates to  
20 the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

Compounds of the present invention may be prepared as described in Bossinger '728, Bossinger '692 and Choi '759. 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).

5       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.

10       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.

15       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.

25       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.

30       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  
5 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,  
10 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  
15 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.

20 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  
25 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  
30 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  
5 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  
10 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),  
15 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  
20 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 amnesic disorder, psychotic disorder, mood disorder, anxiety disorder, sexual dysfunction and sleep disorder.

25 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  
30 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.

5 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  
10 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  
15 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 prophylactic treatment  
20 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.

25 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.

30 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  
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  
10 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  
15 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  
20 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  
25 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  
30 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, 5 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 10 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 15 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 20 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 25 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 30 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,  
5 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  
10 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  
15 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  
20 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  
25 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  
30 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  
5 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  
10 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  
15 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  
20 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  
25 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  
30 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  
5 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  
10 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*

15 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:*

20 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).

25 Rats were housed individually in wire mesh cages under a constant room temperature of 22 +1 °C and 12:12 light-dark cycle (8:00-20:00, dark). Animals 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).

5           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  
10 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.

15    *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  
20 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:*

25           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  
30 study phase. The most effective dose was then used for the chronic administration 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  $\pm$ 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

*References for Example Above*

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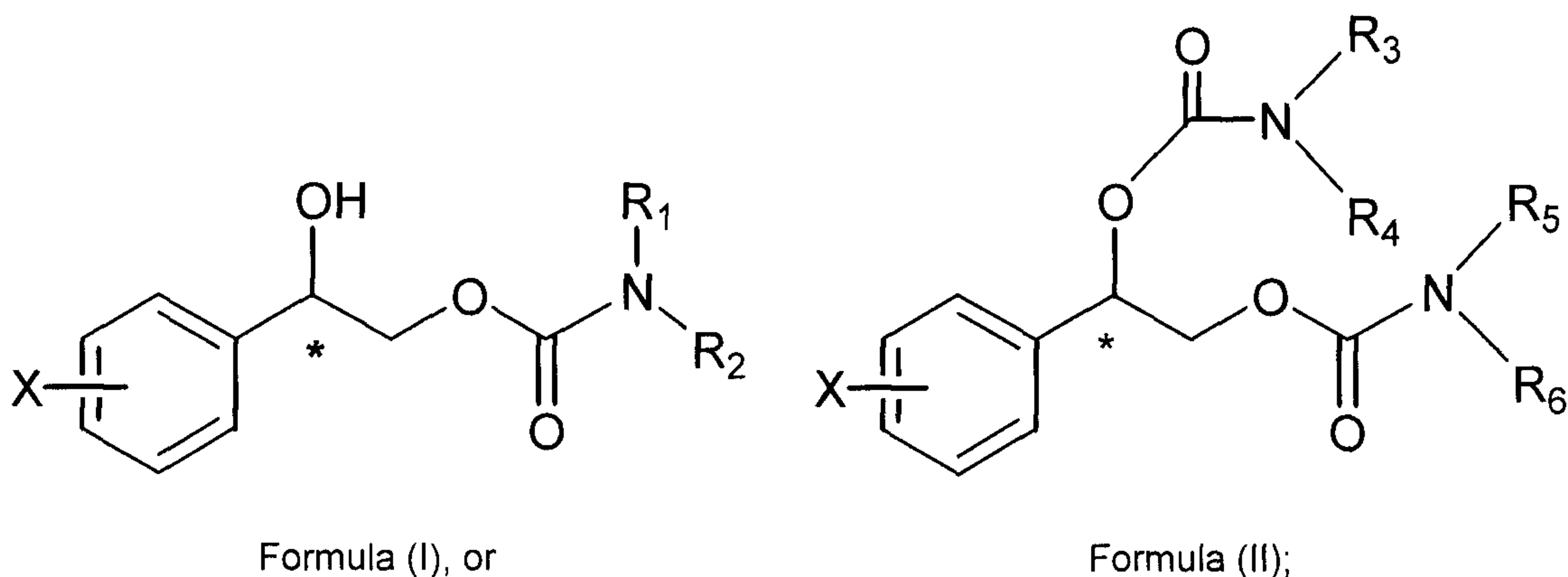
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The discussion of references herein is intended merely to summarize the  
 15 assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinence of the cited references.

The scope of the claims should be given the broadest interpretation consistent with the description as a whole.

What is claimed is:

1. Use of a carbamate compound selected from



or a pharmaceutically acceptable salt thereof, wherein

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

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from the group consisting of  
 hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl; wherein C<sub>1</sub>-C<sub>4</sub> alkyl is optionally substituted with  
 phenyl, wherein phenyl is optionally substituted with substituents  
 independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl,  
 10 C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano,

in the manufacture of a medicament for preventing, treating or ameliorating one or  
 more substance-related disorders selected from the group consisting of  
 substance dependence, substance abuse, substance withdrawal syndrome,  
 substance induced psychosis and substance induced mood disorder.

- 15 2. The use of claim 1, wherein X is chlorine.
3. The use of claim 1, wherein X is substituted at the ortho position of the phenyl ring.
4. The use of claim 1, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.
5. The use 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 use of claim 5, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 90% or greater.
- 5 7. The use of claim 6, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 98% or greater.
8. The use 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.
- 10 9. The use of claim 8, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 90% or greater.
10. The use of claim 9, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 98% or greater.
11. The use of claim 1, wherein the substance-related disorder is a disorder  
15 resulting from the use of an addictive drug.
12. The use 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.
- 20 13. The use of claim 11, wherein the substance-related 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,  
25 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.

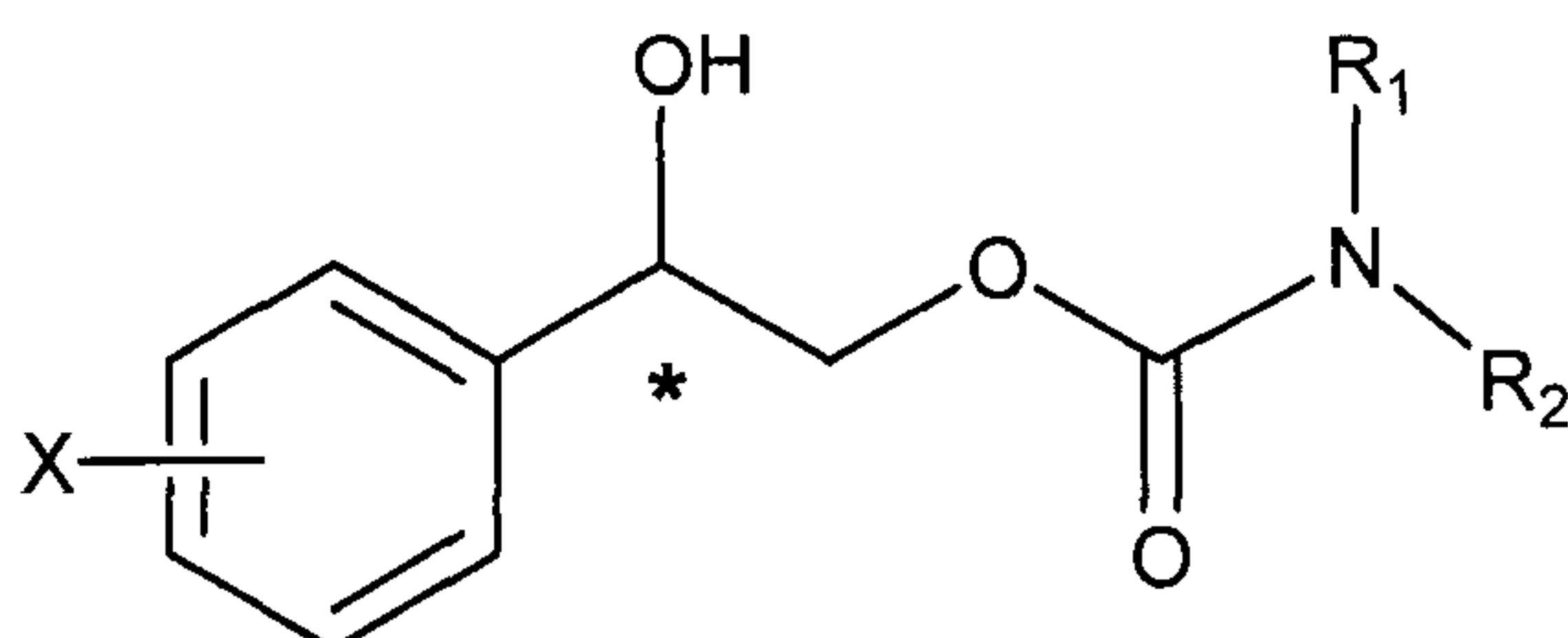
14. The use of claim 1, wherein the medicament is a combination product, wherein the combination product is selected from a compound as defined in claim 1 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as defined in claim 1 and one or more compounds known to treat substance-induced disorders.

15. The use of claim 14, wherein the compound known to treat substance-induced disorders is one or more compounds selected from 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<sup>TM</sup>), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

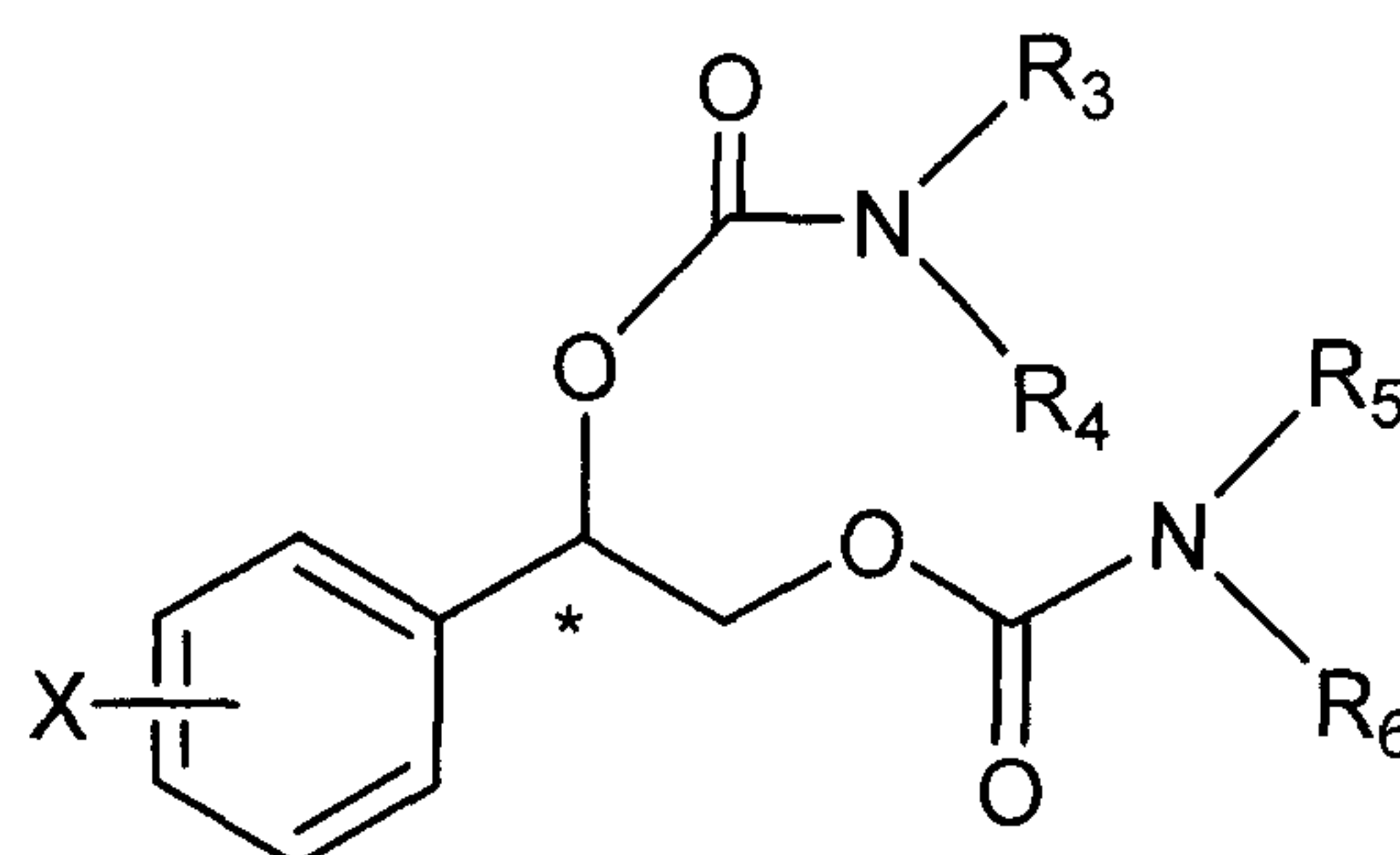
16. The use of claim 14, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of acamprosate, naltrexone, naloxone and disulfiram.

17. The use of claim 1, wherein an effective amount of said compound is from about 0.01 µg/Kg/dose to about 300 mg/Kg/dose.

18. The use 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 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<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl; wherein C<sub>1</sub>-C<sub>4</sub> alkyl is optionally substituted with phenyl, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano,

in the manufacture of a medicament for preventing, treating or ameliorating one or more substance-related disorders selected from the group consisting of substance dependence, substance abuse, substance withdrawal syndrome, substance induced psychosis and substance induced mood disorder.

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

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

21. The use of claim 18, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.

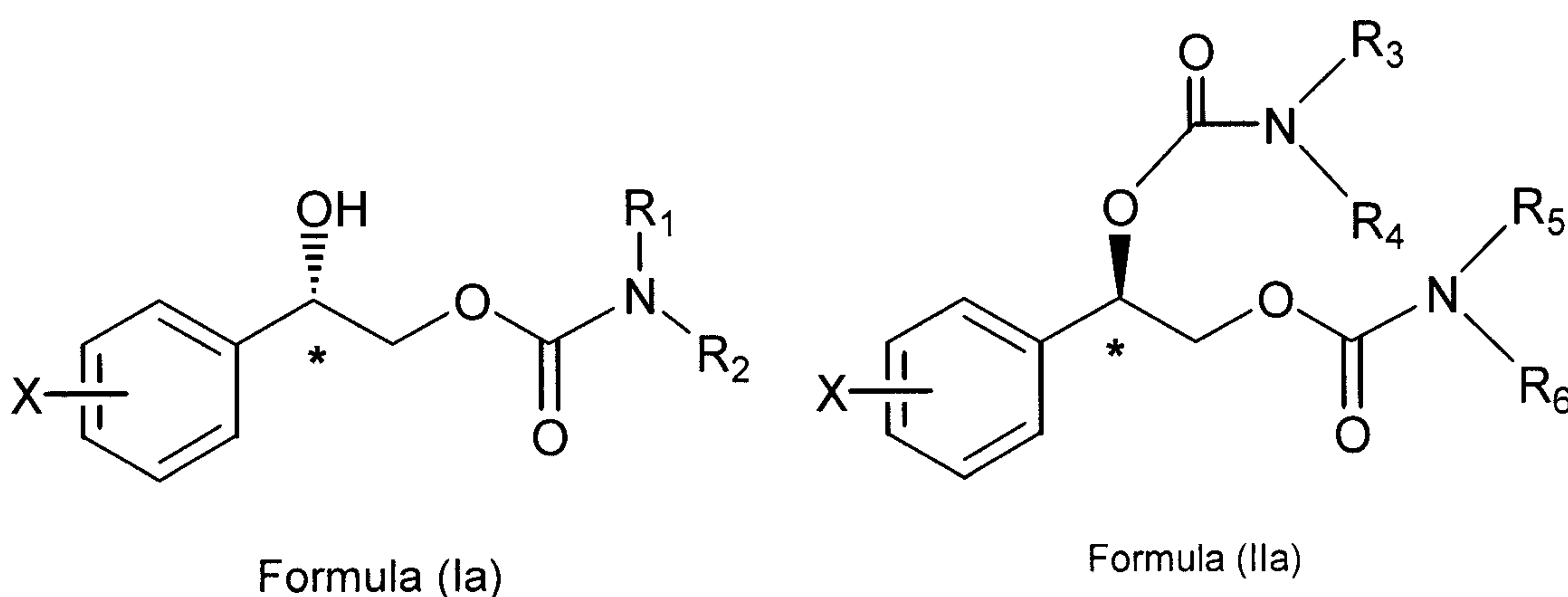
23. The use of claim 18, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 90% or greater.

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

25. The use of claim 18, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 90% or greater.
26. The use of claim 25, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 98% or greater.
- 5 27. The use of claim 18, wherein the substance-related disorder is a disorder resulting from the use of an addictive drug.
28. The use of claim 27, wherein the addictive drug is selected from heroin, opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants, barbiturates,  
10 phencyclidines or nicotine.
29. The use of claim 27, wherein the substance-related 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,  
15 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  
20 withdrawal or substance-induced sleep disorder with onset during withdrawal.
30. The use of claim 18, wherein the medicament is a combination product, wherein the combination product is selected from an enantiomer as defined in claim 18 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer as defined in claim 18 and one or more  
25 compounds known to treat substance-induced disorders.
31. The use of claim 30, wherein the compound known to treat substance-induced disorders is one or more compounds selected from 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<sup>TM</sup>), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

32. The use 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 use of claim 18, wherein an effective amount of said enantiomer is from about 0.01  $\mu\text{g/Kg/dose}$  to about 300 mg/Kg/dose.
34. The use 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:



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, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen,  $C_1$ - $C_4$  alkyl,

C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano.

35. The use of claim 34, wherein X is chlorine.
36. The use of claim 34, wherein X is substituted at the ortho position of the phenyl ring.
- 5 37. The use of claim 34, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.
38. The use of claim 34, wherein the enantiomer of Formula (Ia) in an enantiomeric mixture predominates to the extent of about 90% or greater.
39. The use of claim 38, wherein the enantiomer of Formula (Ia) in an enantiomeric mixture predominates to the extent of about 98% or greater.
- 10 40. The use of claim 34, wherein the enantiomer of Formula (IIa) in an enantiomeric mixture predominates to the extent of about 90% or greater.
41. The use of claim 40, wherein the enantiomer of Formula (IIa) in an enantiomeric mixture predominates to the extent of about 98% or greater.
42. The use of claim 34, wherein the substance-related disorder is a disorder  
15 resulting from the use of an addictive drug.
43. The use 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.
- 20 44. The use of claim 42, wherein the substance-related 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,  
25 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.

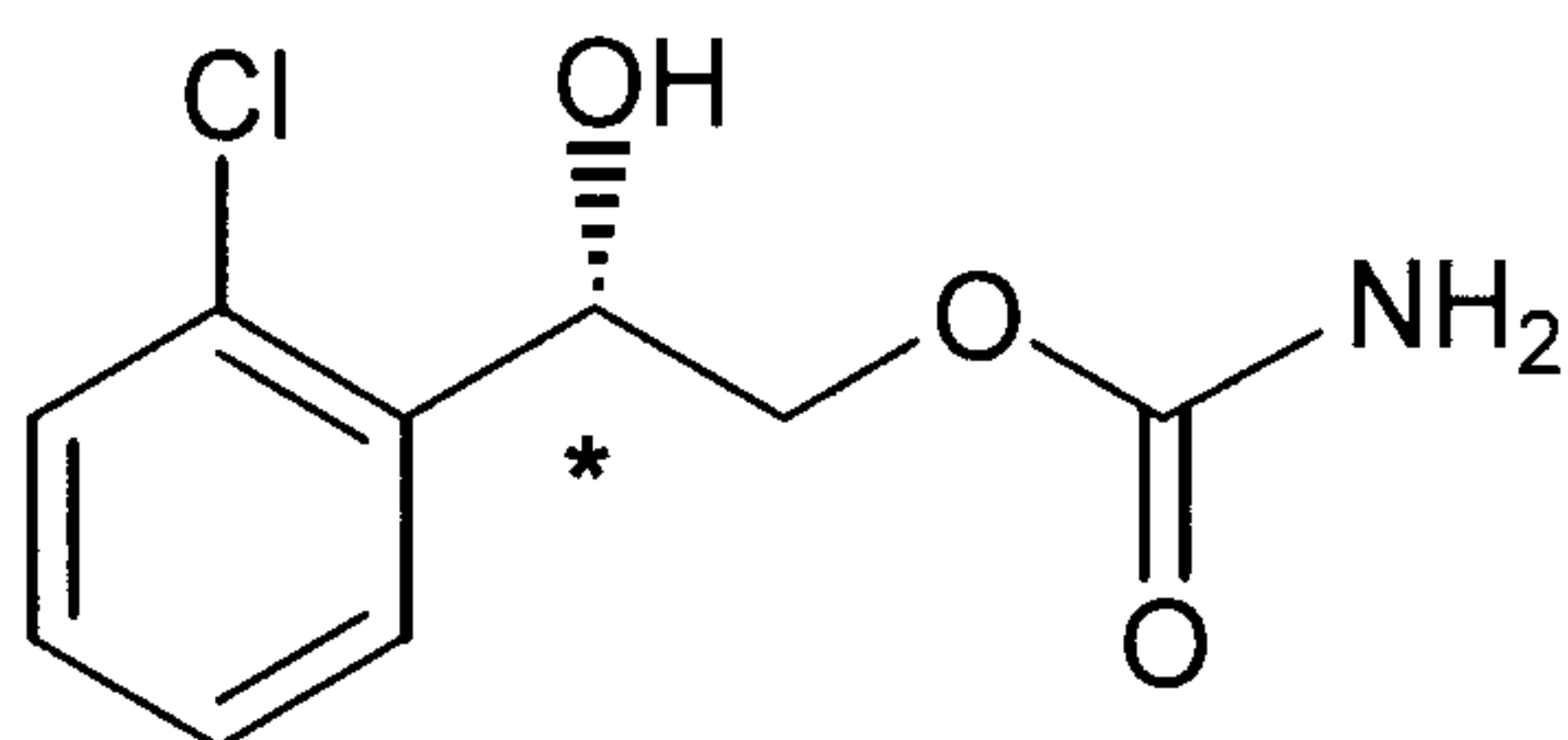
45. The use of claim 34, wherein the medicament is a combination product, wherein the combination product is selected from an enantiomer as defined in claim 34 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer as defined in claim 34 and one or more compounds known to treat substance-induced disorders.

46. The use of claim 45, wherein the compound known to treat substance-induced disorders is one or more compounds selected from 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.

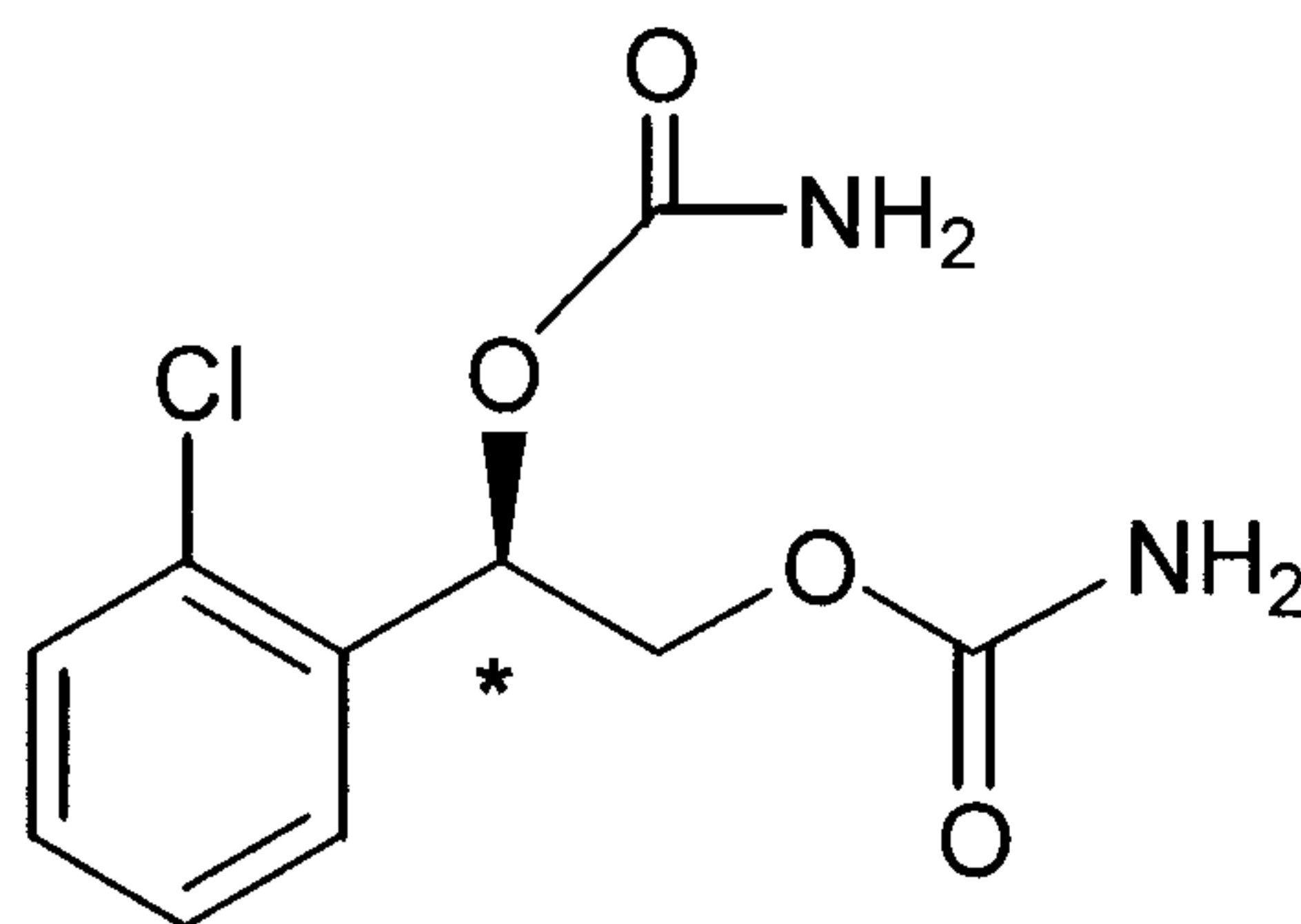
47. The use of claim 45, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of acamprosate, naltrexone, naloxone and disulfiram.

48. The use of claim 34, wherein an effective amount of said enantiomer is from about 0.01 µg/Kg/dose to about 300 mg/Kg/dose.

49. The use 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 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<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl; wherein C<sub>1</sub>-C<sub>4</sub> alkyl is optionally substituted with phenyl, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano.

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

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

52. The use of claim 49, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.

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

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

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

56. The use of claim 53, wherein the enantiomer of Formula (IIb) in an

enantiomeric mixture predominates to the extent of about 98% or greater.

57. The use of claim 49, wherein the substance-related disorder is a disorder resulting from the use of an addictive drug.

58. The use 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 use of claim 57, wherein the substance-related 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 use of claim 49, wherein the medicament is a combination product, wherein the combination product is selected from an enantiomer as defined in claim 49 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer as defined in claim 49 and one or more compounds known to treat substance-induced disorders.

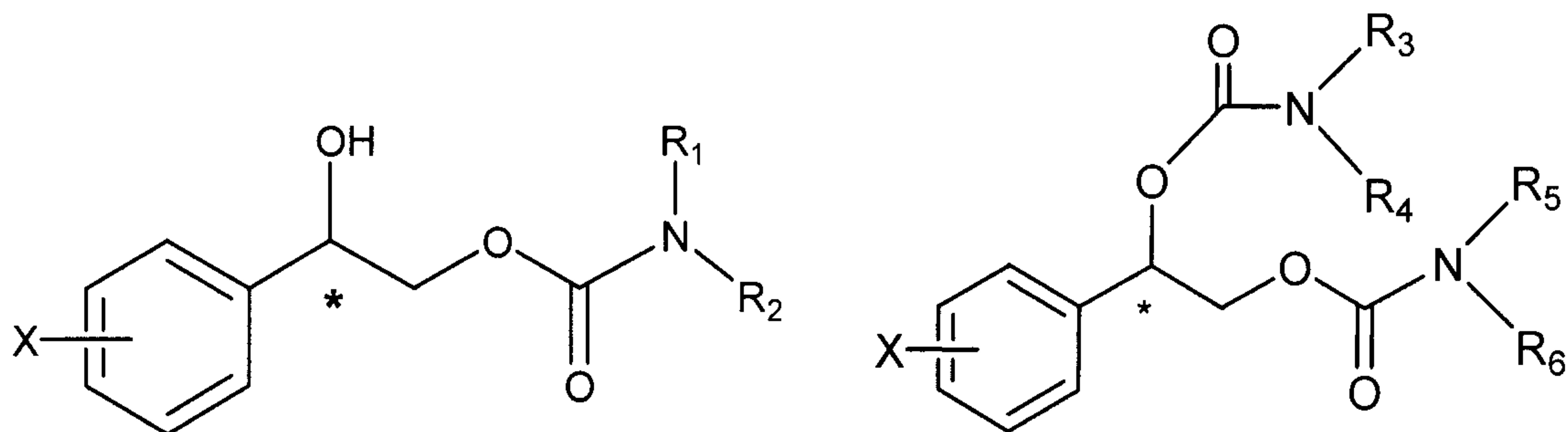
61. The use of claim 60, wherein the compound known to treat substance-induced related disorders is one or more compounds selected from the group consisting of naltrexone, naloxone or other opioid receptor antagonists, fluoxetine or other SSRI antidepressants, thyrotropin-releasing hormone analogues, venlafaxine or other SNRI antidepressants, MAO Inhibitor antidepressants, tricyclic antidepressants, bupropion, lithium carbonate, anticonvulsants, acamprosate, disulfiram (antabuse<sup>TM</sup>), calcium channel

blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

62. The use 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 use of claim 49, wherein an effective amount of said enantiomer is from about 0.01  $\mu\text{g/Kg/dose}$  to about 300 mg/Kg/dose.

64. The use of an effective amount of a carbamate compound selected from



Formula (I), or

Formula (II);

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, 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, for preventing, treating or ameliorating one or more substance-related disorders selected from the group consisting of substance dependence, substance abuse, substance withdrawal syndrome, substance induced psychosis and substance induced mood disorder in a subject in need thereof.

65. The use of claim 64, wherein X is chlorine.

66. The use of claim 64, wherein X is substituted at the ortho position of the phenyl ring.
67. The use of claim 64, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.
- 5 68. The use of claim 64, 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.
69. The use of claim 68, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 90% or greater.
- 10 70. The use of claim 69, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 98% or greater.
71. The use of claim 64, 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.
- 15 72. The use of claim 71, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 90% or greater.
73. The use of claim 72, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 98% or greater.
74. The use of claim 64, wherein the substance-related disorder results from the use of an addictive drug.
- 20 75. The use of claim 74, wherein the addictive drug is selected from heroin, opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants, barbiturates, phencyclidines or nicotine.
- 25 76. The use of claim 74, wherein the substance-related 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.

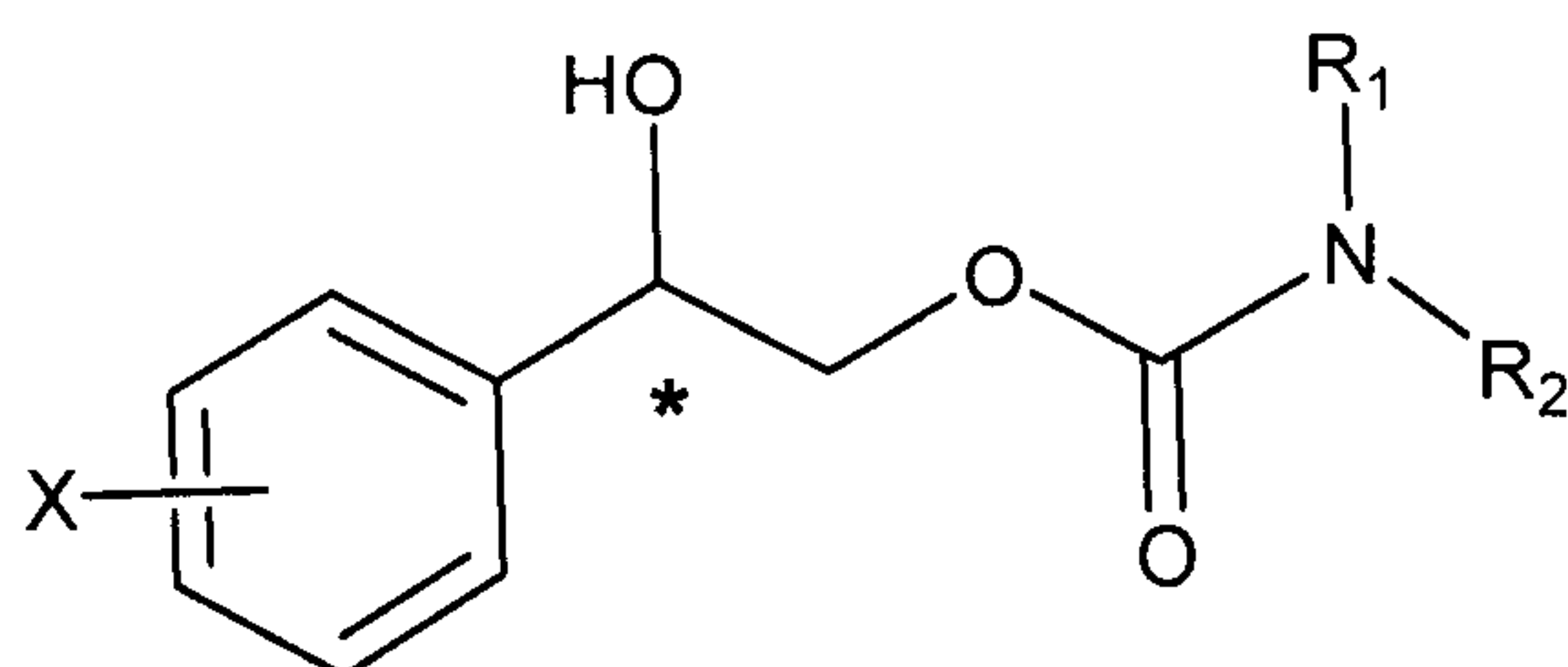
77. The use of claim 64, wherein the use further comprises using an effective amount of a combination product, wherein the combination product is selected from a compound of claim 64 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 64 and an effective amount of one or more compounds known to treat substance-induced disorders.

78. The use of claim 77, wherein the compound known to treat substance-induced disorders is one or more compounds selected from 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<sup>TM</sup>), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

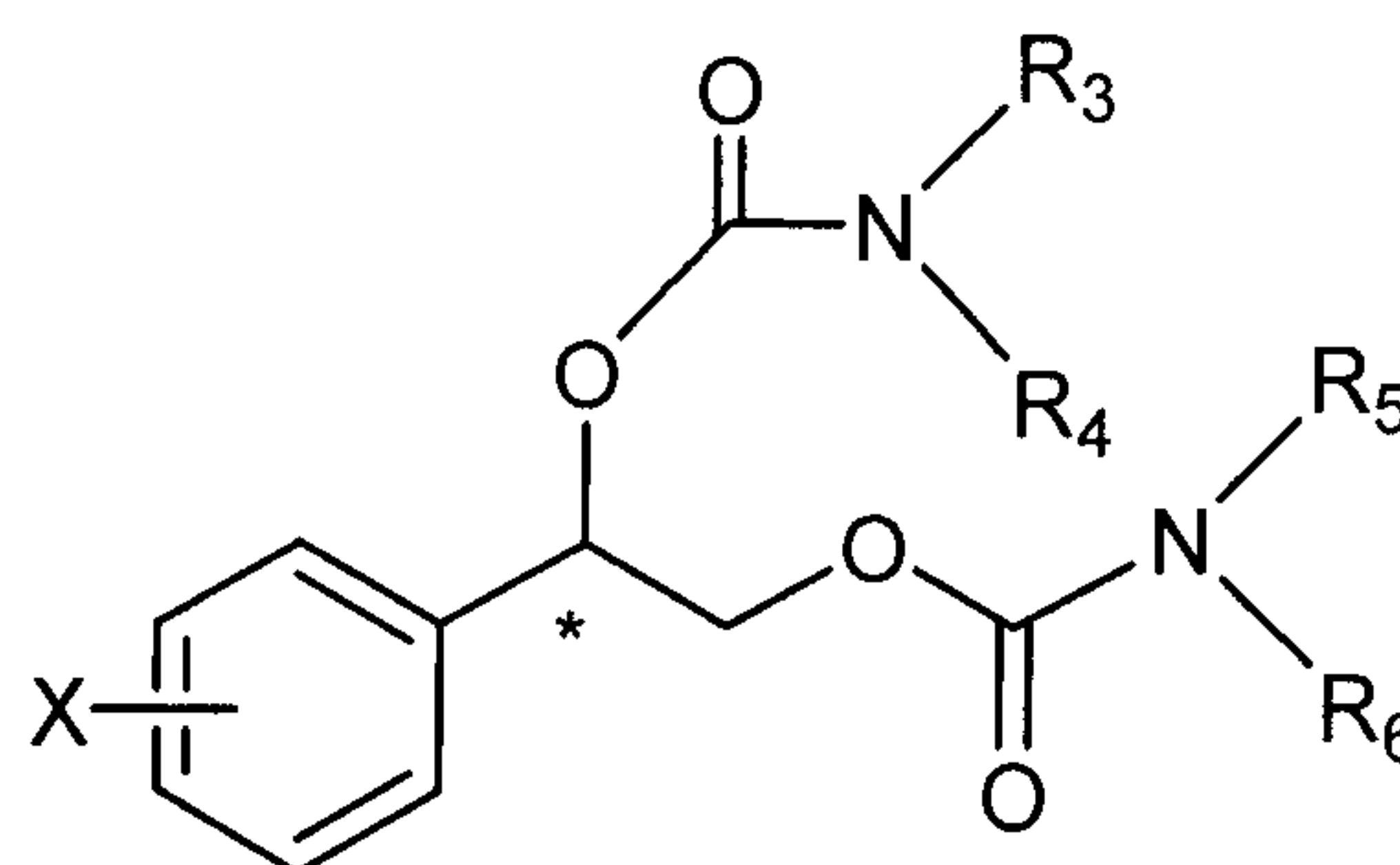
79. The use of claim 77, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of acamprosate, naltrexone, naloxone and disulfiram.

80. The use of claim 64, wherein the effective amount is from about 0.01  $\mu\text{g/Kg/dose}$  to about 300 mg/Kg/dose.

81. The use of 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 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<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from the group consisting of  
 5 hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl; wherein C<sub>1</sub>-C<sub>4</sub> alkyl is optionally substituted with phenyl, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano,

for preventing, treating or ameliorating one or more substance-related  
 10 disorders selected from the group consisting of substance dependence, substance abuse, substance withdrawal syndrome, substance induced psychosis and substance induced mood disorder in a subject in need thereof.

82. The use of claim 81, wherein X is chlorine.

83. The use of claim 81, wherein X is substituted at the ortho position of the  
 15 phenyl ring.

84. The use of claim 81, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.

85. The use of claim 81, wherein the enantiomer of Formula (I) in an enantiomeric mixture predominates to the extent of about 90% or greater.

86. The use of claim 85, wherein the enantiomer of Formula (I) in an enantiomeric  
 20 mixture predominates to the extent of about 98% or greater.

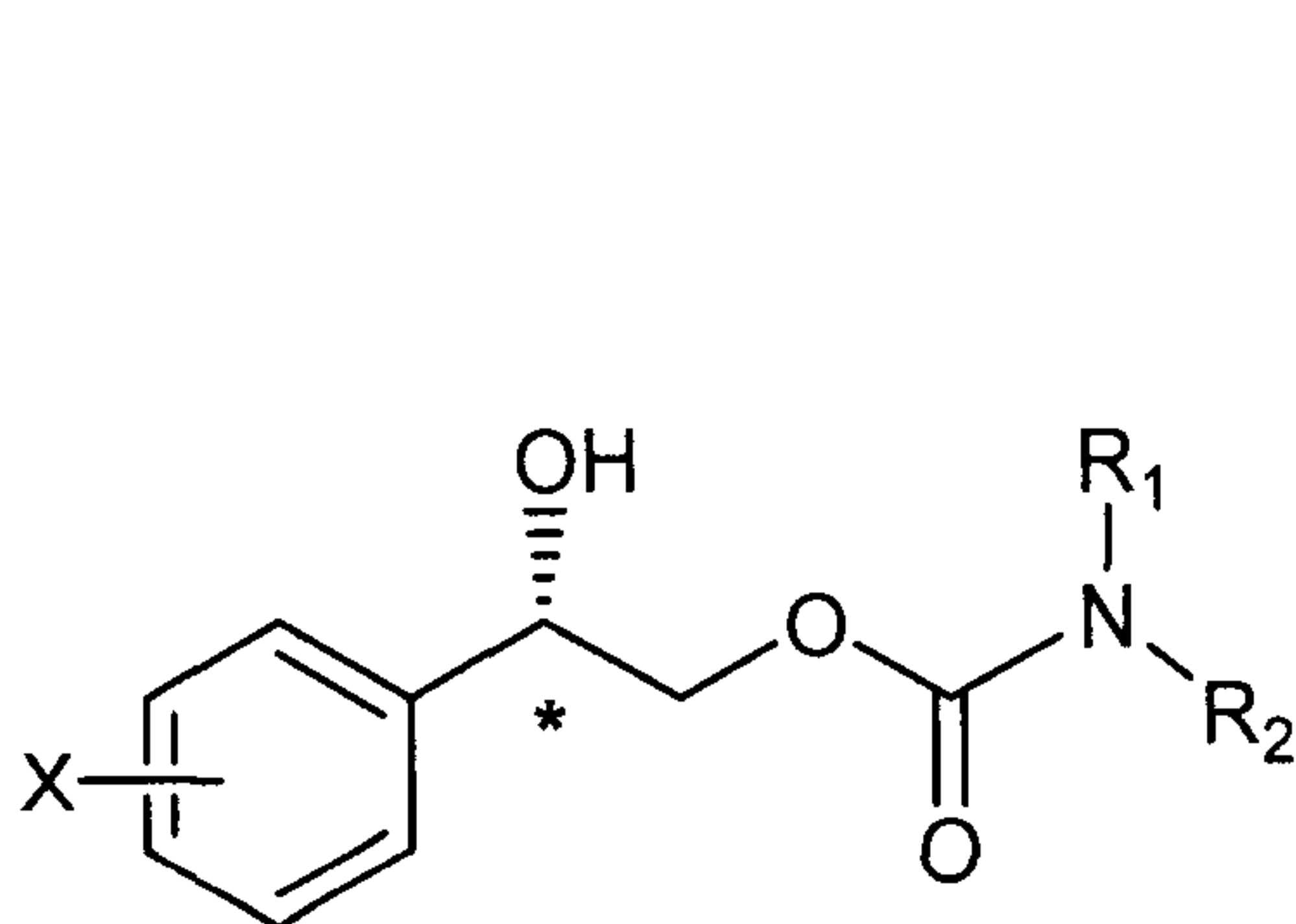
87. The use of claim 81, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 90% or greater.
88. The use of claim 87, wherein the enantiomer of Formula (II) in an enantiomeric mixture predominates to the extent of about 98% or greater.
- 5 89. The use of claim 81, wherein the substance-related disorder results from the use of an addictive drug.
90. The use of claim 89, wherein the addictive drug is selected from heroin, opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants, barbiturates, phencyclidines or nicotine.
- 10 91. The use of claim 89, wherein the substance-related 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.
- 15 20 92. The use of claim 81, wherein the use further comprises using an effective amount of a combination product, wherein the combination product is selected from an enantiomer of claim 81 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer of claim 81 and an effective amount of one or more compounds known to treat substance-induced disorders.
- 25 93. The use of claim 92, wherein the compound known to treat substance-induced disorders is one or more compounds selected from 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  
 5 blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

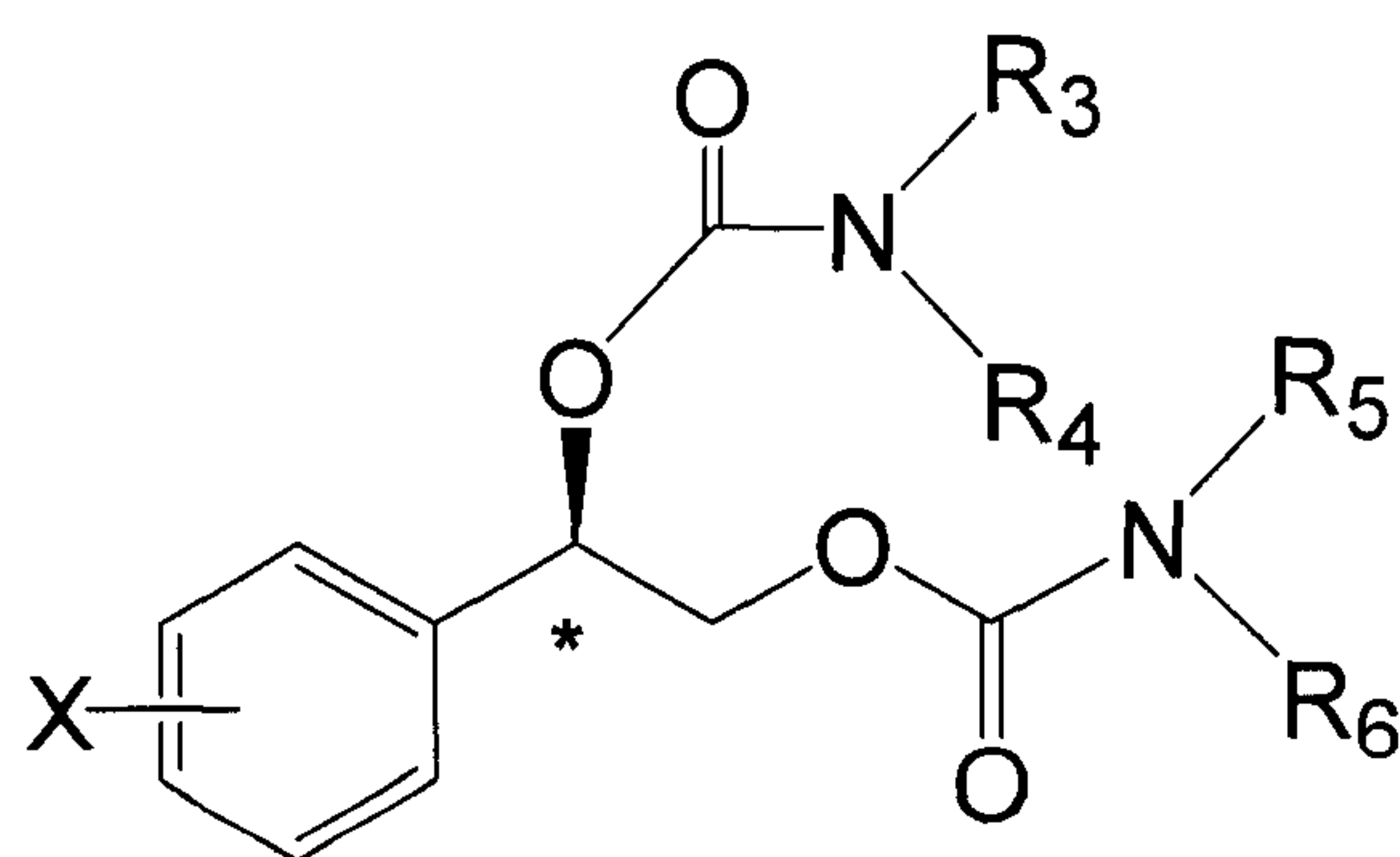
94. The use of claim 92, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of acamprosate, naltrexone, naloxone and disulfiram.

10 95. The use of claim 81, wherein the effective amount is from about 0.01 µg/Kg/dose to about 300 mg/Kg/dose.

96. The use of claim 81, 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  
 15 mixture wherein one enantiomer predominates:



Formula (Ia)



Formula (IIa)

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,

20 R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl; wherein C<sub>1</sub>-C<sub>4</sub> alkyl is optionally substituted with phenyl, wherein phenyl is optionally substituted with substituents

independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano.

97. The use of claim 96, wherein X is chlorine.

98. The use of claim 96, wherein X is substituted at the ortho position of the phenyl ring.

99. The use of claim 96, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.

100. The use of claim 96, wherein the enantiomer of Formula (Ia) in an enantiomeric mixture predominates to the extent of about 90% or greater.

101. The use of claim 100, wherein the enantiomer of Formula (Ia) in an enantiomeric mixture predominates to the extent of about 98% or greater.

102. The use of claim 96, wherein the enantiomer of Formula (IIa) in an enantiomeric mixture predominates to the extent of about 90% or greater.

103. The use of claim 102, wherein the enantiomer of Formula (IIa) in an enantiomeric mixture predominates to the extent of about 98% or greater.

104. The use of claim 96, wherein the substance-related disorder results from the use of an addictive drug.

105. The use of claim 104, wherein the addictive drug is selected from heroin, opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants, barbiturates, phencyclidines or nicotine.

106. The use of claim 104, wherein the substance-related 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.

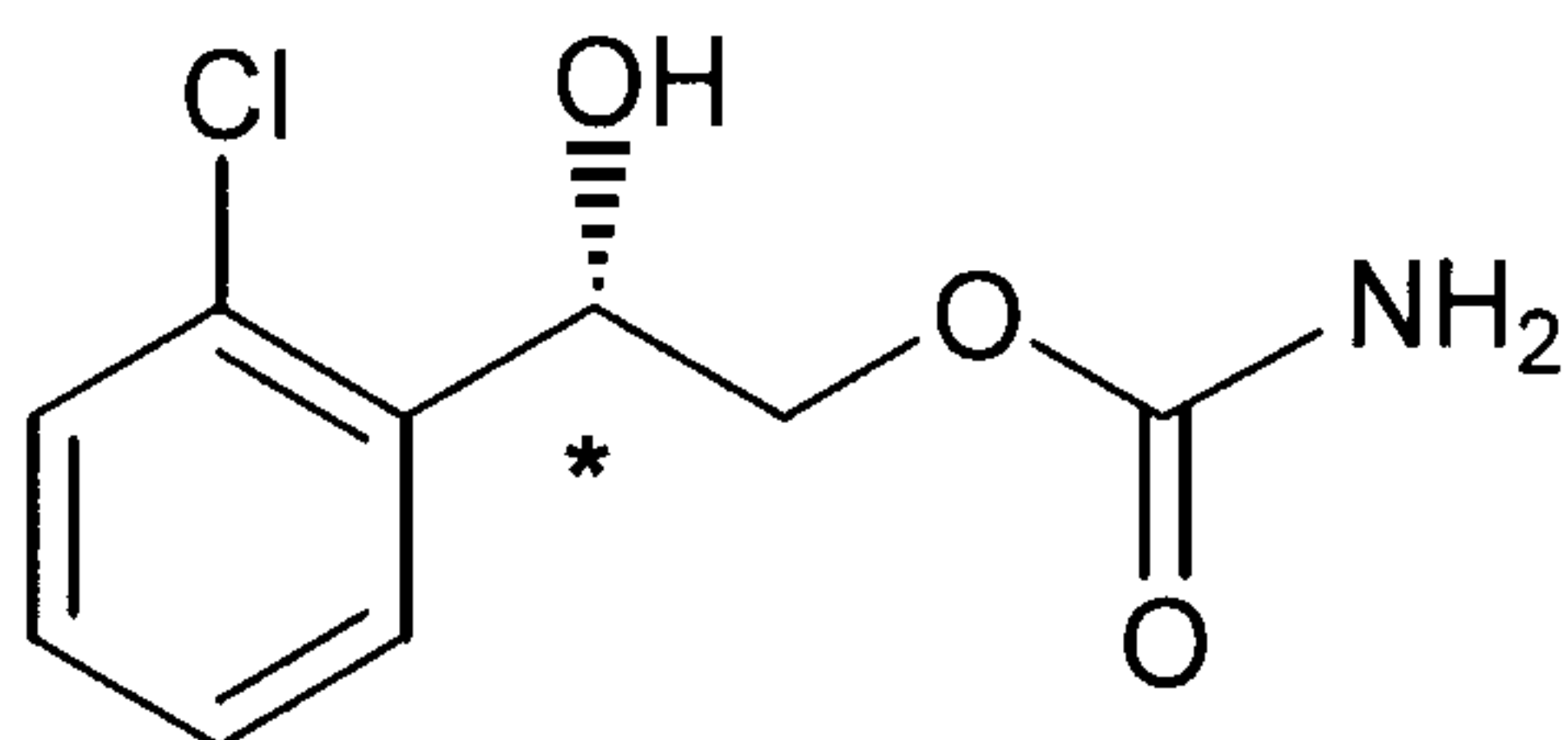
107. The use of claim 96, wherein the use further comprises using an effective  
5 amount of a combination product, wherein the combination product is selected from an enantiomer of claim 96 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer of claim 96 and an effective amount of one or more compounds known to treat substance-induced disorders.

10 108. The use of claim 107, wherein the compound known to treat substance-induced disorders is one or more compounds selected from 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  
15 antidepressants, tricyclic antidepressants, bupropion, lithium carbonate, anticonvulsants, acamprosate, disulfiram (antabuse<sup>TM</sup>), calcium channel blockers, serotonin antagonists, GABA-altering drugs, dopaminergic drugs, and N-methyl-D-aspartic acid (NMDA) glutamate receptor modulators.

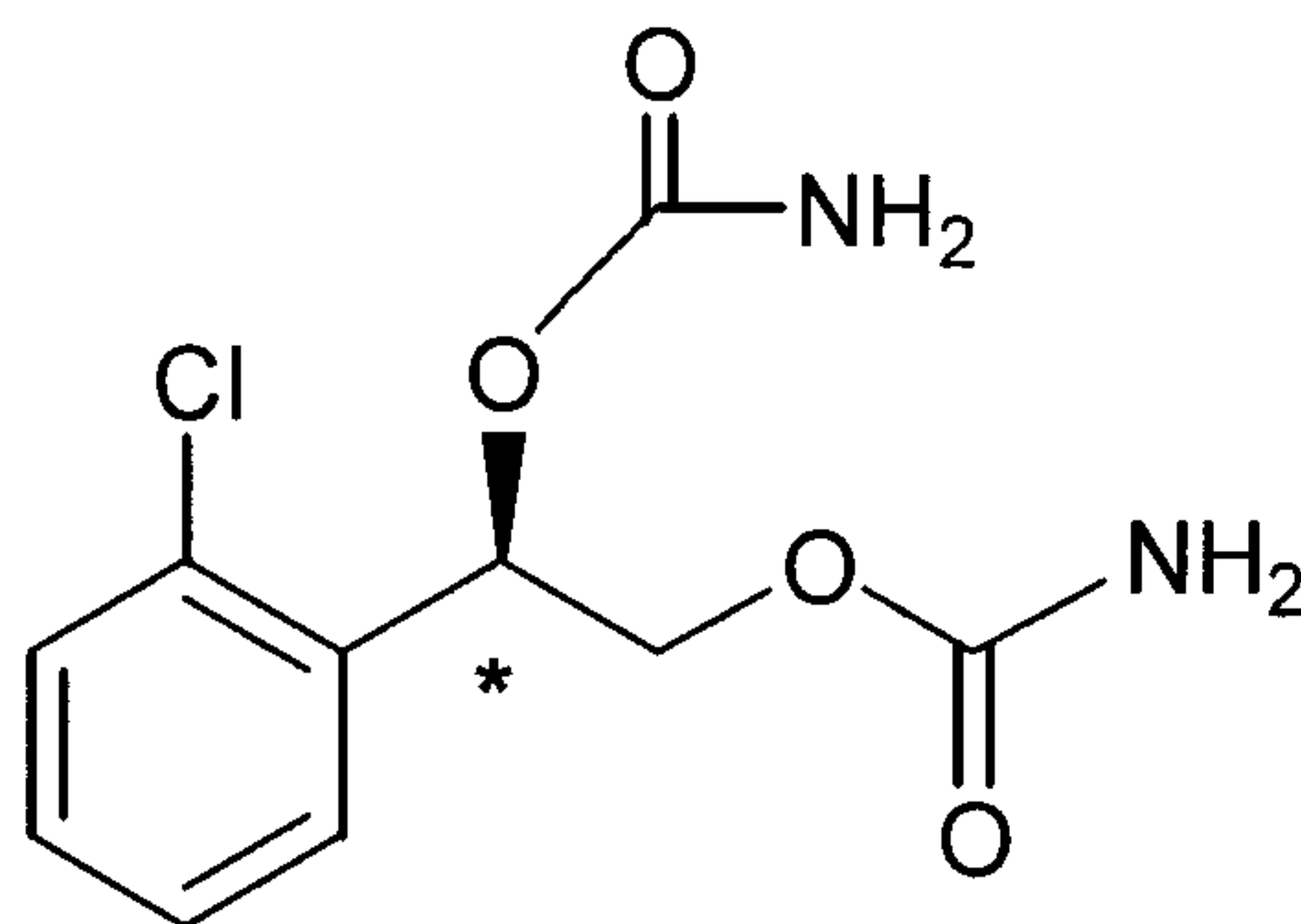
109. The use of claim 107, wherein the compound known to treat substance-  
20 induced disorders is one or more compounds selected from the group consisting of acamprosate, naltrexone, naloxone and disulfiram.

110. The use of claim 96, wherein the effective amount is from about 0.01  $\mu\text{g/Kg/dose}$  to about 300 mg/Kg/dose.

111. The use of claim 81, wherein the enantiomer selected from Formula (I) or  
25 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 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<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl; wherein C<sub>1</sub>-C<sub>4</sub> alkyl is optionally substituted with phenyl, wherein phenyl is optionally substituted with substituents independently selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, amino, nitro and cyano.

112. The use of claim 111, wherein X is chlorine.

113. The use of claim 111, wherein X is substituted at the ortho position of the phenyl ring.

114. The use of claim 111, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen.

115. The use of claim 111, wherein the enantiomer of Formula (Ib) in an enantiomeric mixture predominates to the extent of about 90% or greater.

116. The use of claim 115, wherein the enantiomer of Formula (Ib) in an enantiomeric mixture predominates to the extent of about 98% or greater.

117. The use of claim 111, wherein the enantiomer of Formula (IIb) in an enantiomeric mixture predominates to the extent of about 90% or greater.

118. The use of claim 115, wherein the enantiomer of Formula (IIb) in an

enantiomeric mixture predominates to the extent of about 98% or greater.

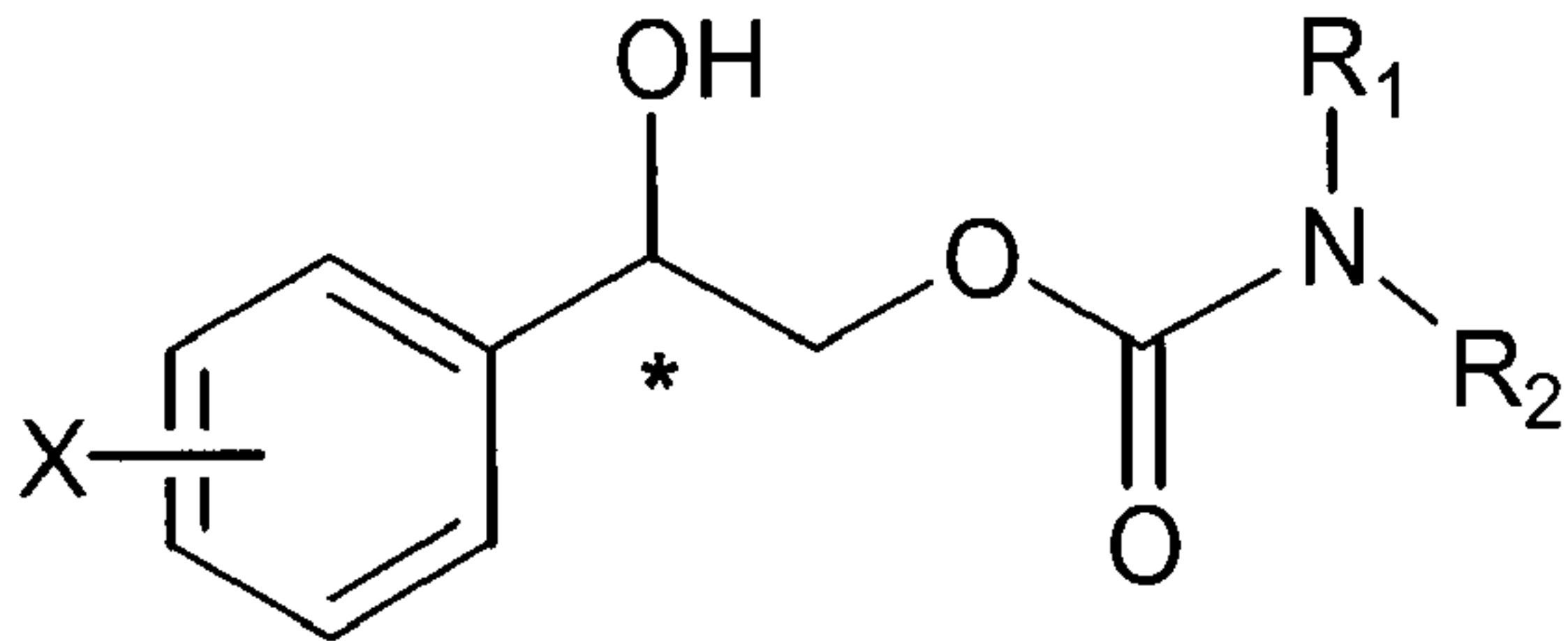
119. The use of claim 111, wherein the substance-related disorder results from the use of an addictive drug.
120. The use of claim 119, wherein the addictive drug is selected from heroin,  
5 opium, morphine, cocaine, amphetamines, methamphetamines, ethanol, benzodiazepines, methadone, oxycodone, codeine, inhalants barbiturates, phencyclidines or nicotine.
121. The use of claim 119, wherein the substance-related is selected from alcohol  
10 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  
15 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.
122. The use of claim 111, wherein the use further comprises using an effective  
20 amount of a combination product, wherein the combination product is selected from an enantiomer of claim 111 or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an enantiomer of claim 111 and an effective amount of one or more compounds known to treat substance-induced disorders.
123. The use of claim 122, wherein the compound known to treat substance-  
25 induced related disorders is one or more compounds selected from 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.

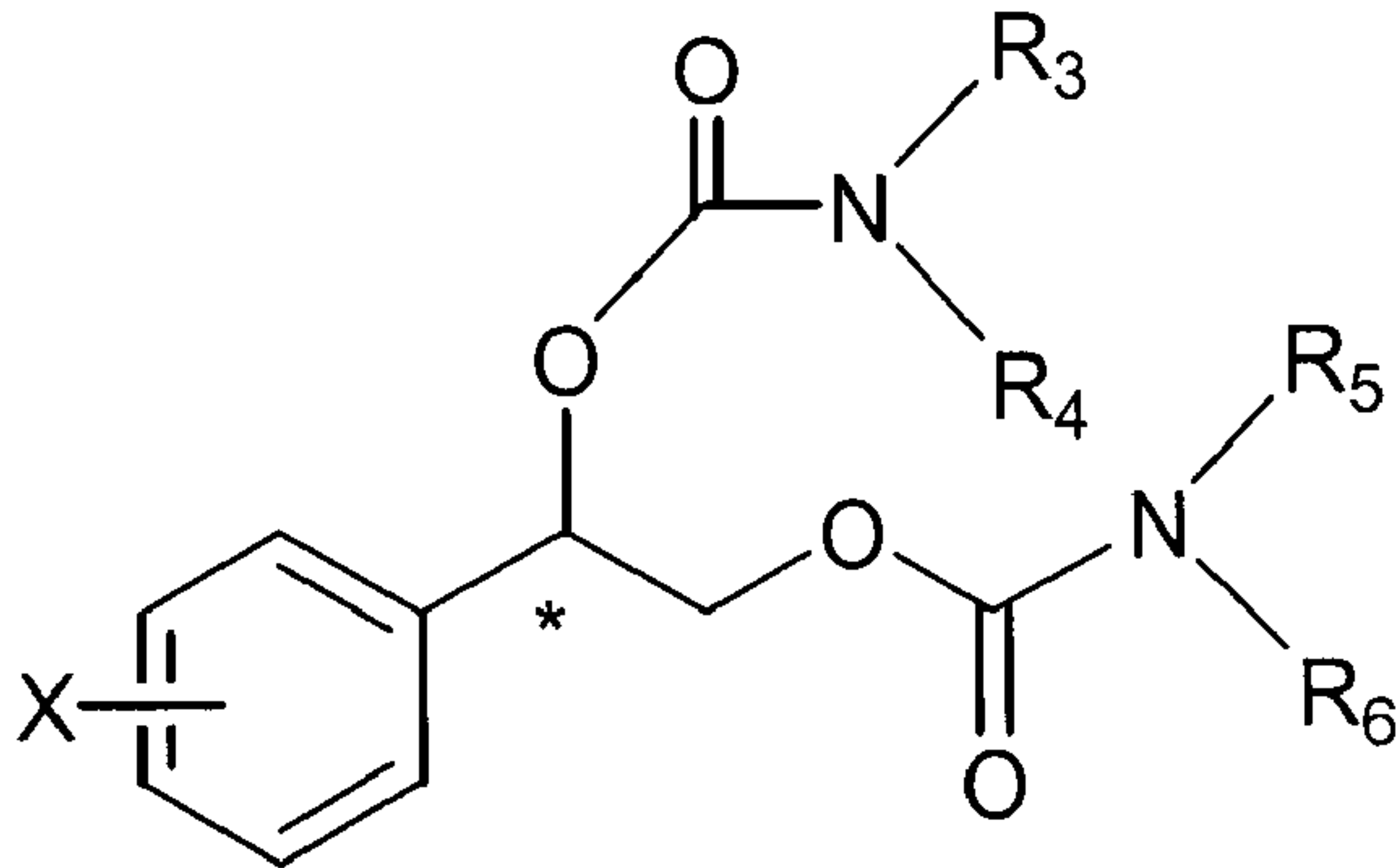
124. The use of claim 122, wherein the compound known to treat substance-induced disorders is one or more compounds selected from the group consisting of acamprosate, naltrexone, naloxone and disulfiram.

125. The use of claim 111, wherein the effective amount is from about 0.01 µg/Kg/dose to about 300 mg/Kg/dose.

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Formula (I)



Formula (II)