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(54) **Composition for the treatment and prevention of nicotine addiction containing a nicotine receptor agonist and an anti-depressant or anti-anxiety drug**

(57) Pharmaceutical compositions are disclosed for the treatment of nicotine dependence or addiction, tobacco dependence or addiction, reduction of nicotine withdrawal symptoms or aiding in the cessation or lessening of tobacco use or substance abuse. The pharma-

ceutical compositions are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an anti-depressant or anxiolytic agent and a pharmaceutically acceptable carrier. The method of using these compounds is also disclosed.

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Description

Background of the Invention

[0001] The present invention relates to pharmaceutical compositions for the treatment of nicotine dependence or addiction in a mammal (e.g. human) comprising a nicotine receptor partial agonist (NRPA) and an anti-depressant or anxiolytic agent. The term NRPA refers to all chemical compounds which bind at neuronal nicotinic acetylcholine specific receptor sites in mammalian tissue and elicit a partial agonist response. A partial agonist response is defined here to mean a partial, or incomplete functional effect in a given functional assay. Additionally, a partial agonist will also exhibit some degree of antagonist activity by its ability to block the action of a full agonist (Feldman, R.S., Meyer, J.S. & Quenzer, L.F. Principles of Neuropsychopharmacology, 1997; Sinauer Assoc. Inc.). The present invention may be used to treat mammals (e.g. humans) for tobacco dependence or addiction and nicotine dependence or addiction; to palliate the effects of nicotine withdrawal and to enhance the outcomes of other smoking cessation therapies.

[0002] The invention also relates to aryl fused azapolycyclic compounds that bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function and are referred to in WO 9818798-A1, WO 9935131-A1 and WO 9955680-A1. The foregoing applications are owned in common with the present application and are incorporated herein by reference in their entireties.

[0003] The NRPA compounds that bind to neuronal nicotinic receptor sites can be used in combination with an anti-depressant such as for example, a tricyclic anti-depressant (e.g. amitriptyline, imipramine), a serotonin reuptake inhibitor anti-depressant (SRI) (e.g. sertraline, paroxetine, or fluoxetine), an atypical anti-depressant (bupropion, nefazodone), or a monoamine oxidase inhibitor (e.g., phenelzine, tranylcypromine) in order to treat the depression associated with addiction such as to nicotine or tobacco, alcohol dependence, cocaine addiction or tobacco or nicotine dependence independently of other psychiatric illness. The compounds that bind to neuronal nicotinic receptor sites can be used in combination with anxiolytic agents, such as for example, a benzodiazepine (e.g. diazepam, alprazolam, chlordiazepoxide) or non-benzodiazepine anxiolytics (e.g. buspirone, hydroxyzine, doxepin) in order to treat the anxiety associated with addiction such as to nicotine or tobacco, alcohol dependence, cocaine addiction or tobacco or nicotine dependence independently of other psychiatric illness.

[0004] Tobacco dependence represents the most important preventable cause of illness and death in our society, responsible for more than 400,000 deaths each year. Half of all smokers will die of diseases directly related to tobacco use, and many smokers will suffer sig-

nificant morbidity.

[0005] People smoke because of the reinforcing effects of nicotine. Nicotine is a powerful psychoactive agent that activates the same brain pathways as cocaine and other psychostimulants, producing agent-associated tolerance and withdrawal effects.

[0006] Nicotine replacement therapies (NRTs) have been used for smoking cessation. These are available in the form of gum, the transdermal patch, and nasal inhaler. The gum Nicorette® (nicotine polacrilex) delivers nicotine through buccal absorption following chewing. There are also non-nicotine pharmacologic therapies for treating nicotine addiction.

Summary of Invention

[0007] The invention provides a pharmaceutical composition for treating nicotine dependence or addiction, tobacco dependence or addiction, reducing nicotine withdrawal symptoms or aiding in the cessation or lessening of tobacco use or substance abuse. The therapeutically effective pharmaceutical combination is comprised of a nicotine receptor partial agonist and an anti-depressant or anxiolytic agent and a pharmaceutically acceptable carrier.

[0008] In a more specific embodiment of the invention, the anti-depressant is selected from a tricyclic anti-depressant, a serotonin reuptake inhibitor anti-depressant (SRI), an atypical anti-depressant or a monoamine oxidase inhibitor, their pharmaceutically active salts and their optical isomers. In another more specific embodiment of the invention, the anti-depressant is selected from amitriptyline, imipramine, sertraline, paroxetine, fluoxetine, bupropion, nefazodone, phenelzine, tranylcypromine, moclobemide, venlafaxine or a pharmaceutically acceptable salt or their optical isomers thereof. A preferred antidepressant is bupropion hydrochloride or one of its optical isomers.

[0009] In another more specific embodiment of this invention, the nicotine receptor partial agonist is selected from:

- 9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

- 3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
- 9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
- 6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;
- 5-oxo-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;
- 6-oxo-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;
- 4,5-difluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 5-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene-4-carbonitrile;
- 4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 5-ethynyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene-4-carbonitrile;
- 6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;
- 10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 4-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 4-methyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 4-trifluoromethyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 4-nitro-10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 7-methyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,5,8-tetraene;
- 6-methyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,5,8-tetraene;
- 6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,5,8-tetraene;
- 6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,5,8-tetraene;
- 6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-pentaene;
- 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-pentaene;
- 14-methyl-5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-pentaene;
- 5-oxa-7,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,6,8-tetraene;
- 6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,6,8-tetraene;
- 4-chloro-10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-4-yl cyanide;
- 1-(10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
- 10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-4-ol;
- 7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2,4(8),6,9-tetraene;
- 4,5-dichloro-10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;
- 11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-5-carbonitrile;
- 1-[11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
- 1-[11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-5-yl]-1-propanone;
- 4-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-5-carbonitrile;
- 5-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-4-carbonitrile;
- 6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 6-methyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 5,6-dimethyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;
- 5-methyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;
- 6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;
- 5,8,15-triazatetracyclo[11.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]heptadeca-2(7),3,5-triene;

ca-2(11),3,5,7,9-pentaene;  
 7-methyl-5,8,15-triazatetracyclo[11.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]  
 heptadeca-2(11),3,5,7,9-pentaene;  
 6-methyl-5,8,15-triazatetracyclo[11.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]  
 heptadeca-2(11),3,5,7,9-pentaene;  
 6,7-dimethyl-5,8,15-triazatetracyclo[11.3.1.0<sup>2,11</sup>.  
 0<sup>4,9</sup>]heptadeca-2(11),3,5,7,9-pentaene;  
 7-oxa-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]hexa-  
 deca-2(10),3,5,8-tetraene;  
 6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.  
 0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;  
 5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.  
 0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;  
 6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.  
 0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;  
 7-methyl-5-oxa-6,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.  
 0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;  
 4,5-difluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene;  
 4-chloro-5-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-  
 2(7),3,5-triene;  
 5-chloro-4-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-  
 2(7),3,5-triene;  
 4-(1-ethynyl)-5-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]tri-  
 deca-2(7),3,5-triene;  
 5-(1-ethynyl)-4-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]tri-  
 deca-2(7),3,5-triene;  
 5,6-difluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-  
 2,4,6-triene;  
 6-trifluoromethyl-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-  
 2,4,6-triene;  
 6-methoxy-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene;  
 11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-  
 6-ol;  
 6-fluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene;  
 11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-  
 5-ol;  
 4-nitro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene;  
 5-nitro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene;  
 5-fluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene; and  
 6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]tri-  
 deca-2(7),3,5-triene and

their pharmaceutically acceptable salts and their  
 optical isomers.

**[0010]** Preferably, the nicotine receptor partial agonist  
 is selected from

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyri-  
 do[1,2-a][1,5]diazocin-8-one;  
 9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyri-  
 do[1,2-a][1,5]diazocin-8-one;  
 9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyri-

do[1,2-a][1,5]diazocin-8-one;  
 9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyri-  
 do[1,2-a][1,5]diazocin-8-one;  
 9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyri-  
 do[1,2-a][1,5]diazocin-8-one;  
 9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyri-  
 do[1,2-a][1,5]diazocin-8-one;  
 9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-meth-  
 ano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-  
 1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-  
 1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyri-  
 do[1,2-a][1,5]diazocin-8-one;  
 9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-  
 1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 6-methyl-5-thia-5-dioxo-6,13-diazatetracyclo  
 [9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;  
 4-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),  
 3,5-triene;  
 4-trifluoromethyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]do-  
 deca-2(7),3,5-triene;  
 4-nitro-10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),  
 3,5-triene;  
 6-methyl-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]  
 pentadeca-2(10),3,5,8-tetraene;  
 6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.  
 0<sup>4,9</sup>]hexadeca-2(11),3,5,7,9-pentaene;  
 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]hexadeca-  
 2(11),3,5,7,9-pentaene;  
 5-oxa-7,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]penta-  
 deca-2(10),3,6,8-tetraene;  
 6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.  
 0<sup>4,8</sup>]pentadeca-2(10),3,6,8-tetraene;  
 10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-  
 4-yl cyanide;  
 1-(10-azatricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-trien-  
 4-yl)-1-ethanone;  
 11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-triene-  
 5-carbonitrile;  
 1-[11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-  
 5-yl]-1-ethanone;  
 1-[11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-  
 5-yl]-1-propanone;  
 4-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene-5-carbonitrile;  
 5-fluoro-11-azatricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene-4-carbonitrile;  
 6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.  
 0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;  
 6-methyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]  
 hexadeca-2(10),3,5,8-tetraene;  
 6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.0<sup>2,10</sup>.  
 0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;  
 6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.  
 0<sup>4,8</sup>]hexadeca-2(10),3,5,8-tetraene;  
 6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.0<sup>2,10</sup>.

0<sup>4,8</sup>]hexadeca-2(10),3,6,8-tetraene;  
 5,6-difluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-  
 2,4,6-triene;  
 6-trifluoromethyl-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-  
 2,4,6-triene;  
 6-methoxy-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene;  
 6-fluoro-11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),  
 3,5-triene; and  
 11-aza-tricyclo[7.3.1.0<sup>2,7</sup>]trideca-2(7),3,5-trien-  
 5-ol and

their pharmaceutically acceptable salts and their optical isomers.

**[0011]** The invention also provides a method of treating a mammal having a condition which presents with tobacco or nicotine addiction, nicotine withdrawal symptoms, alcohol dependence or cocaine or other substance addiction. The mammal is administered a nicotine receptor partial agonist or a pharmaceutically acceptable salt thereof, and an antidepressant or anxiolytic agent or a pharmaceutically acceptable salt thereof. The nicotine receptor partial agonist and the anti-depressant or anxiolytic agent are present in amounts that render the composition effective in the treatment of tobacco or nicotine addiction, nicotine withdrawal symptoms, alcohol dependence or cocaine or other substance addiction. In a more specific embodiment of the invention, the anti-depressant is selected from a tricyclic anti-depressant, a serotonin reuptake inhibitor anti-depressant, (SRI), an atypical anti-depressant, and a monoamine oxidase inhibitor. In another more specific embodiment of this invention anxiolytic agent is selected from a benzodiazepine or a non-benzodiazepine anxiolytic. In another more specific embodiment of this invention, the anxiolytic agent is a benzodiazepine or a non-benzodiazepine anxiolytic. In a more specific embodiment of the invention, the anxiolytic agent is selected from diazepam, alprazolam, chlordiazepoxide, buspirone, hydroxyzine and doxepin or a pharmaceutically acceptable salt thereof. A preferable anxiolytic is doxepin or a pharmaceutically acceptable salt or optical isomers thereof.

**[0012]** In another more specific embodiment of this invention the nicotine receptor partial agonist is selected from

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyri-

do[1,2-a][1,5]diazocin-8-one;  
 9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;  
 9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(2-propyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;  
 6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;  
 5-oxo-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;  
 6-oxo-5,7,13-triazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;  
 4,5-difluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;  
 5-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene-4-carbonitrile;  
 4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;  
 5-ethynyl-10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene-4-carbonitrile;  
 6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,8</sup>]pentadeca-2(10),3,8-triene;  
 10-aza-tricyclo[6.3.1.0<sup>2,7</sup>]dodeca-2(7),3,5-triene;



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