

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 June 2006 (08.06.2006)

PCT

(10) International Publication Number
WO 2006/060202 A2

(51) International Patent Classification:
A61K 31/4172 (2006.01)

(21) International Application Number:
PCT/US2005/042007

(22) International Filing Date:
18 November 2005 (18.11.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/632,028 30 November 2004 (30.11.2004) US

(71) Applicant (for all designated States except US): **BAYER PHARMACEUTICALS CORPORATION** [US/US];
400 Morgan Lane, West Haven, Connecticut 06516 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **ORTIZ, Astrid** [US/US]; 14 Augusta Drive, Unit 4, Vernon, New Jersey 07462 (US).

(74) Agents: **GREENMAN, Jeffrey, M.** et al.; Bayer Pharmaceuticals Corporation, 400 Morgan Lane, West Haven, Connecticut 06516 (US).

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

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

Published:

— without international search report and to be republished upon receipt of that report

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

(54) Title: IMIDAZOLE DERIVATIVES FOR THE TREATMENT OF PSYCHIATRIC DISORDERS

(57) Abstract: This invention relates to imidazole derivatives which are useful in treating psychiatric disorders.



WO 2006/060202 A2

IMIDAZOLE DERIVATIVES FOR THE TREATMENT OF PSYCHIATRIC DISORDERS

[001] This application claims benefit of U.S. Provisional Application Serial No. 60/632,028; filed on November 30, 2004, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[002] This invention relates to imidazole derivatives which are useful in treating psychiatric disorders including schizophrenia, depression, and anxiety disorders.

BACKGROUND OF THE INVENTION

[003] Psychiatric disorders, including schizophrenia, depression, and anxiety disorders, are one of the leading causes of disability in the U.S. and other developed countries (Murray CJL, Lopez AD, eds. Global Burden of Disease, 1996). Approximately 44.3 million people in the United States (Narrow, NIMH ECA prospective data, 1998) and 450 million people worldwide (World Health Organization) suffer from a diagnosable mental disorder. Mental illness accounts for over 15% of the burden of disease in established market economies, such as the United States, more than the disease burden caused by all cancers (Murray CJL, Lopez AD, eds. Global Burden of Disease, 1996).

[004] Schizophrenia ranks among the top ten causes of disability in developed countries worldwide countries (Murray CJL, Lopez AD, eds. Global Burden of Disease, 1996). Approximately 1.1 percent of the population (2.2 million American adults (Narrow, NIMH ECA prospective data, 1998) or 51 million people worldwide (World Health Organization) suffer from schizophrenia. Schizophrenia, long considered the most chronic, debilitating and costly mental illness, consumes a total of about \$65 billion a year for direct treatment, societal and family costs (Murray CJL, Lopez AD, eds. Global Burden of Disease, 1996). Schizophrenia is characterized by profound disruption in cognition and emotion, affecting the most fundamental human attributes: language, thought, perception, affect, and sense of self. Positive symptoms include psychotic manifestations, such as hearing internal voices or experiencing other sensations not connected to an obvious source (hallucinations) and assigning unusual significance or meaning to normal events or holding fixed false personal beliefs (delusions). Negative symptoms are characterized by affective flattening and lack of initiative or goals (avolition), loss of usual interests or pleasures (anhedonia), disturbances of sleep and eating, dysphoric mood (depressed, anxious, irritable, or angry mood) and difficulty concentrating or focusing attention (American Psychiatric Association.

Diagnostic and Statistical Manual on Mental Disorders, fourth edition (DSM-IV). Washington, DC: American Psychiatric Press, 1994).

[005] The standard treatment for schizophrenia is neuroleptics drugs. Typical neuroleptics such as haloperidol or chlorpromazine treat positive (hallucinations and delusions), but not negative (reduced motivation and emotional expressiveness) symptoms of schizophrenia. Long term treatment with these drugs produce unacceptable side effects such as tardive dyskinesia (TD). Advantages of the newer “atypical” antipsychotics such as clozapine, olanzapine, and risperidone including reducing some negative symptoms and a lowering risk of TD. The atypical antipsychotics, however, can produce unacceptable side effects such as agranulocytosis (lowering of white blood cells) (clozapine) and serious weight gain (olanzapine). If given at too high of a dose, the newer medications may lead to problems such as social withdrawal and symptoms resembling Parkinson’s disease.

[006] Major depression is the leading cause of disability worldwide, ranked second only to ischemic heart disease in magnitude of disease burden in established market economies countries. The annual cost for treatment and lost wages is estimated at \$43.7 - \$52.9 billion (Murray CJL, Lopez AD, eds. Global Burden of Disease, 1996). Depression is common, affecting approximately 9.9 million Americans (Narrow, NIMH ECA prospective data, 1998) and 121 million people worldwide (World Health Organization). Major depression is a multifaceted disorder characterized by primarily by dysphoric mood and loss of interest or pleasure in activities that were once enjoyable. Other physical and psychological symptoms include inability to concentrate, motor disturbances (psychomotor retardation or agitation), feelings of worthlessness, inappropriate guilt, thoughts of suicide, and disturbances in appetite and sleep (American Psychiatric Association. Diagnostic and Statistical Manual on Mental Disorders, fourth edition (DSM-IV). Washington, DC: American Psychiatric Press, 1994).

[007] Pharmacological treatments for depression including the older tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) and newer the selective serotonin reuptake inhibitors (SSRIs) appear equally efficacious. There are several limitation for current pharmacotherapies. Current antidepressants can cause serious side effects that may limit compliance. Antidepressant medications must be taken regularly for 3 to 4 weeks (in some cases, as many as 8 weeks) before the full therapeutic effect occurs. Overall, the proportion of patients estimated to be true drug responders is low; on average, about 20 to 25% of patients who present with major depression. Furthermore, 35 to 45% of patients have depression that is resistant to all drug treatment modalities.

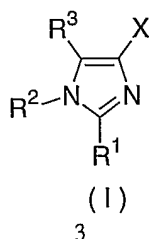
[008] Anxiety disorders are the most common mental disorder, affecting 19.1 million (13.3%) of the adult U.S. population (Narrow, NIMH ECA prospective data, 1998) and 490 million people worldwide (World Health Organization). Anxiety disorders cost the U.S. more than \$42 billion a year, almost one third of the \$148 billion total mental health bill for the U.S (Greenberg et al., *J Clin. Psychiatry*, 60:427-35). More than \$22.84 billion of those costs are associated with the repeated use of healthcare services, as those with anxiety disorders seek relief for symptoms that mimic physical illnesses. Anxiety disorders are a group of syndromes that include generalized anxiety disorder, panic disorder, phobias, obsessive-compulsive disorder, and post traumatic stress disorder. Although each disorder has its own distinct features, all share common symptoms of excessive worrying, intense fears and dread, hypervigilance and/or somatic symptoms, in the absence of a dangerous situation (American Psychiatric Association. Diagnostic and Statistical Manual on Mental Disorders, fourth edition (DSM-IV). Washington, DC: American Psychiatric Press, 1994). Benzodiazepines (BZDs) offer relief from the debilitation caused by the acute symptoms of anxiety disorders. Adverse effects associated with BZDs including daytime sedation, cognitive impairment, tolerance, and a high risk of physical dependency, limit their usefulness. Antidepressants (including TCAs, MAOIs, SSRIs, and atypicals) also effective in treating anxiety, but are limited by their side effects and safety profiles. The azopyrine compound buspirone has a good safety and tolerability profile, but limited efficacy. Beta-blockers diminish the physical symptoms of anxiety and therefore may be useful only in patients with pronounced cardiac symptoms or tremor.

[009] Despite the presents of some pharmaceuticals to treat psychiatric disorders, there remains a need for new pharmaceuticals that are both safe and effects agents treatment of disease and for useful methods to prepare them.

[010] The present invention relates to compounds which are useful in the treatment of psychiatric disorders such as schizophrenia, depression, and anxiety disorders.

DETAILED DESCRIPTION OF THE INVENTION

[011] The invention relates to substituted imidazole derivatives that have utility in the treatment of psychiatric disorders, said derivatives of the Formula (I), prodrugs thereof, tautomers thereof and salts thereof



wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁–C₆)alkyl sulfonyl, (C₁–C₆)alkyl sulfonyl-amino, (C₁–C₆)alkyl carbonyl-amino, (C₁–C₆)alkyl amino-carbonyl-amino, or phenyl,

(C₂–C₆)alkyl,

cyclohexyl optionally substituted with (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

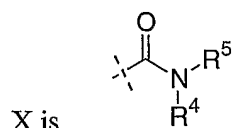
1-naphthyl or 2-naphthyl optionally substituted with halogen, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, or phenyl;

R³ is hydrogen, (C₁–C₆)alkyl, benzyl, chloro, or bromo;



where R⁴ is hydrogen or (C₁–C₆)alkyl;

R⁵ is selected from

(C₂–C₉)alkyl or (C₇–C₁₁)bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, (C₁–C₆)alkoxy, (C₁–C₆)alkyl-amino, bis[(C₁–C₃)alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted (C₁–C₆)alkyl, or fluorine,

benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C₁–C₆)alkyl, and optionally substituted on the phenyl ring with one or more halogen, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C₁–C₆)alkyl, hydroxy-substituted (C₁–C₆)alkyl, (C₁–C₃)alkoxy-substituted (C₁–C₃)alkyl, benzyl, or phenyl optionally substituted with one or more of (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen,

–NR⁶R⁷

where R⁶ is hydrogen or (C₁–C₆)alkyl;

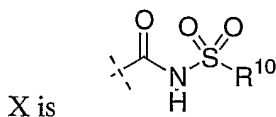
R⁷ is (C₁–C₉)alkyl; or phenyl optionally substituted with one or more of (C₁–C₆)alkyl, hydroxy-substituted (C₁–C₆)alkyl, (C₁–C₃)alkoxy-substituted (C₁–C₃)alkyl, phenyl, hydroxy, benzyloxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom, or

R⁶ and R⁷, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more (C₁–C₆)alkyl, (C₁–C₆)alkoxy, hydroxy-substituted (C₁–C₃)alkyl, (C₁–C₃)alkoxy-substituted (C₁–C₃)alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

or

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, (C₁–C₆)alkyl-amino, bis[(C₁–C₃)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C₁–C₆)alkyl, phenyl-substituted (C₁–C₆)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C₁–C₆)alkyl, hydroxy, benzyloxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

or



where R¹⁰ is (C₁-C₉)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or a fluorine atom, or

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

[012] Methods of synthesizing compounds of Formula (I) are described in WO 03/040107 (PCT/EP01/03247), which is incorporated herein in its entirety.

[013] Examples of compounds of Formula (I) include, but are not limited to:

- 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(4-fluorophenyl)-4-piperidinol;
- 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(4-chlorophenyl)-4-piperidinol;
- 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-[3-(trifluoromethyl)phenyl]-4-piperidinol;
- 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(4-trifluoromethoxyphenyl)-4-piperidinol;
- 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(3-fluorophenyl)-4-piperidinol;
- 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl}carbonyl}-4-(3-chlorophenyl)-4-piperidinol;
- 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(3-fluoro-4-chlorophenyl)-4-piperidinol;
- 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-[3-(trifluoromethoxy)phenyl]-4-piperidinol;
- 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[1-(2-pyridinyl)-4-piperidinyl]-1H-imidazole-4-carboxamide;
- [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-

yl](cyclohexyl)methanone;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-pyridinyl)-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
N'-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-chloro-2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
N'-(4-chloro-2-methylphenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-(2,4-dichlorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-[2,4-bis(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-(2-chloro-4-cyanophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carbohydrazide;
1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-methyl-1H-imidazole-4-carboxamide;
1-(4-isopropylphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;

2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-
 2(1H)-yl-1H-imidazole-4-carboxamide;
 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-
 imidazole-4-carbohydrazide;
 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-
 1H-imidazole-4-carboxamide;
 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclopentyl]-
 1H-imidazole-4-carboxamide;
 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-
 hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-N-[(1S,2S)-2-
 hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
 1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-
 hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
 1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1R,2R)-2-
 hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
 1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(cis)-2-
 hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
 4-(4-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-
 yl]carbonyl}-1-piperazinyl)benzonitrile; and
 4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-
 piperazinyl)benzonitrile.

[014] When any moiety is described as being substituted, it can have one or more of the indicated substituents that can be located at any available position on the moiety. When there are two or more substituents on any moiety, each term shall be defined independently of any other in each occurrence.

[015] Representative salts of the compounds of the present invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate,

nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, and undecanoate.

[016] Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine salts and *N*-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

[017] It will be appreciated that diastereomers and enantiomers of the exemplified structures will often be possible, and that pure isomers represent preferred embodiments. It is intended that pure stereoisomers, and mixtures thereof, are within the scope of the invention.

[018] The compounds of this invention may, either by nature of asymmetric centers or by restricted rotation, be present in the form of isomers. Any isomer may be present in the (*R*)-, (*S*)-, or (*R,S*) configuration, preferably in the (*R*)- or (*S*)- configuration, whichever is most active.

[019] All isomers, whether separated, pure, partially pure, or in racemic mixture, of the compounds of this invention are encompassed within the scope of this invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art.

[020] Geometric isomers by nature of substituents about a double bond or a ring may be present in *cis* (= *Z*-) or *trans* (= *E*-) form, and both isomeric forms are encompassed within the scope of this invention.

[021] The particular process to be utilized in the preparation of the compounds of this invention depends upon the specific compound desired. Such factors as the selection of the specific moieties and the specific substituents on the various moieties, all play a role in the path to be followed in the preparation of the specific compounds of this invention. These factors are readily recognized by one of ordinary skill in the art.

[022] For synthesis of any particular compound, one skilled in the art will recognize that the use of protecting groups may be required for the synthesis of compounds containing certain substituents. A description of suitable protecting groups and appropriate methods of adding and removing such groups may be found in: *Protective Groups in Organic Synthesis*, Second Edition, T. W. Greene, John Wiley and Sons, New York, 1991.

[023] It is anticipated that prodrug forms of the compounds of this invention will prove useful in

certain circumstances, and such compounds are also intended to fall within the scope of the invention. Prodrug forms may have advantages over the parent compounds exemplified herein, in that they are better absorbed, better distributed, more readily penetrate the central nervous system, are more slowly metabolized or cleared, etc. Prodrug forms may also have formulation advantages in terms of crystallinity or water solubility. For example, compounds of the invention having one or more hydroxyl groups may be converted to esters or carbonates bearing one or more carboxyl, hydroxyl or amino groups, which are hydrolyzed at physiological pH values or are cleaved by endogenous esterases or lipases *in vivo*. See for example U.S. Patent Nos. 4,942,184; 4,960,790; 5,817,840; and 5,824,701 (all of which are incorporated herein by reference in their entirety), and references therein.

Methods of Use

[024] As used herein, various terms are defined below.

[025] When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles “a,” “an,” “the,” and “said” are intended to mean that there are one or more of the elements. The terms “comprising,” “including,” and “having” are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[026] The term “subject” as used herein includes mammals (e.g., humans and animals).

[027] The term “treatment” includes any process, action, application, therapy, or the like, wherein a subject, including a human being, is provided medical aid with the object of improving the subject’s condition, directly or indirectly, or slowing the progression of a condition or disorder in the subject.

[028] The term “combination therapy” or “co-therapy” means the administration of two or more therapeutic agents to treat a disease condition and/or disorder. Such administration encompasses co-administration of two or more therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each inhibitor agent. In addition, such administration encompasses use of each type of therapeutic agent in a sequential manner.

[029] The phrase “therapeutically effective” means the amount of each agent administered that will achieve the goal of improvement in a disease condition or disorder severity, while avoiding or minimizing adverse side effects associated with the given therapeutic treatment.

[030] The term “pharmaceutically acceptable” means that the subject item is appropriate for use in a pharmaceutical product.

[031] The compounds of the present invention are useful in treating psychiatric disorders including schizophrenia, depression, and anxiety disorders.

[032] The compounds of the present invention may be used alone or in combination with additional therapies and/or compounds known to those skilled in the art in the treatment of psychiatric disorders. Alternatively, the methods and compounds described herein may be used, partially or completely, in combination therapy.

[033] Such co-therapies may be administered in any combination of two or more drugs (*e.g.*, a compound of the invention in combination with an antipsychotic drug). Such co-therapies may be administered in the form of pharmaceutical compositions, as described above.

[034] Based on well known assays used to determine the efficacy for treatment of conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient (*e.g.*, compounds) to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

[035] The total amount of the active ingredient to be administered may generally range from about 0.0001 mg/kg to about 200 mg/kg, and preferably from about 0.01 mg/kg to about 200 mg/kg body weight per day. A unit dosage may contain from about 0.05 mg to about 1500 mg of active ingredient, and may be administered one or more times per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous, and parenteral injections, and use of infusion techniques may be from about 0.01 to about 200 mg/kg. The daily rectal dosage regimen may be from 0.01 to 200 mg/kg of total body weight. The transdermal concentration may be that required to maintain a daily dose of from 0.01 to 200 mg/kg.

[036] Of course, the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age of the patient, the diet of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention may be ascertained by those skilled in the art using conventional treatment tests.

[037] The compounds of this invention may be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need

of treatment for a particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound. A pharmaceutically acceptable carrier is any carrier which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A therapeutically effective amount of a compound is that amount which produces a result or exerts an influence on the particular condition being treated. The compounds described herein may be administered with a pharmaceutically-acceptable carrier using any effective conventional dosage unit forms, including, for example, immediate and timed release preparations, orally, parenterally, topically, or the like.

[038] For oral administration, the compounds may be formulated into solid or liquid preparations such as, for example, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms may be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers.

[039] In another embodiment, the compounds of this invention may be tableted with conventional tablet bases in combination with binders, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, dyes, coloring agents, and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include diluents either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

[040] Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above, may also be present.

[041] The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The emulsions may also contain sweetening and flavoring agents.

[042] Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, and preservative, flavoring and coloring agents.

[043] The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which may be a sterile liquid or mixture of liquids with or without the addition of a pharmaceutically acceptable surfactant or emulsifying agent and other pharmaceutical adjuvants.

[044] The parenteral compositions of this invention may typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant.

[045] The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents.

[046] The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables.

[047] A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug (e.g., compound) with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug.

[048] Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (*see*, e.g., U.S. Patent No. 5,023,252, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[049] Another formulation employs the use of biodegradable microspheres that allow controlled, sustained release. Such formulations can be comprised of synthetic polymers or copolymers. Such formulations allow for injection, inhalation, nasal or oral administration. The construction and use of biodegradable microspheres for the delivery of pharmaceutical agents is well known in the art (e.g., U.S. Patent No. 6, 706,289, incorporated herein by reference).

[050] It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. For example, direct techniques for administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in U.S. Patent No. 5,011,472, incorporated herein by reference.

[051] The compositions of the invention may also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Any of the compositions of this invention may be preserved by the addition of an antioxidant such as ascorbic acid or by other suitable preservatives. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

[052] Formulations suitable for subcutaneous, intravenous, intramuscular, and the like; suitable pharmaceutical carriers; and techniques for formulation and administration may be prepared by any of the methods well known in the art (*see, e.g.*, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 20th edition, 2000).

[053] It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

Evaluation of Biological Activity

[054] In order that this invention may be better understood, the following examples are set forth. These examples are for the purpose of illustration only, and are not to be construed as limiting the scope of the invention in any manner. All publications mentioned herein are incorporated by reference in their entirety.

[055] Demonstration of the activity of the compounds of the present invention may be accomplished through *in vitro*, *ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent for the treatment of a psychiatric disorder, the following assays may be used.

Depression Model

[056] A forced swim or tail suspension model may be used to assess the efficacy of antidepressant compounds (see, e.g., Porsolt, et al., *Nature* 266:730-732, 1977; Steru, et al., *Psychopharmacology* 85:367-370, 1985).

Forced Swim Test

Rats or mice are placed in a cylinder filled with water (23-25°C) from which no escape is possible. Initially, animals struggle and try to escape, but eventually adopt a characteristic immobile posture and make no further attempts to escape except for small movements needed their head above water. Animals are dosed with a compound and the activity (swimming or climbing) or immobility is measured by an observer. The immobility is considered by some to reflect a 'behavioral despair' in which animals cease to struggle to escape the aversive situation. A wide variety of clinically used antidepressants (TCAs, MAOIs, SSRIs, atypicals) decrease immobility in this test and has a good predictive validity in that it detects antidepressants with different mechanisms of action but its construct validity is weak. At least two distinct active behavioral patterns are produced by pharmacologically selective antidepressant drugs. Serotonin-selective reuptake inhibitors increase swimming behavior, whereas drugs acting primarily to increase extracellular levels of norepinephrine or dopamine increase climbing behavior. There are false positives (psychostimulants) but relatively few false negatives (β -adrenergic agonists). The test is sensitive to muscle-relaxant (benzodiazepines) and sedative (neuroleptics) effects, leading to enhanced immobility. False positives and false negatives can often be screened by measuring if the compound produces locomotor stimulation or sedation.

Tail Suspension Test

[057] When suspended by the tail, mice will initially struggle and try to escape and then alternate between active escape attempts and immobility. In this test, animals are dosed with a

compound and the immobility is measured by an observer for 6 min. Porsolt describes the immobile behavior as 'behavioral despair' which animals cease to struggle to escape the aversive situation. A large variety of clinically antidepressants (tricyclics, MAOIs, SSRIs, and atypicals) reduce immobility in this model. The test has a good predictive validity for antidepressant activity and works for most antidepressant classes including but has some false positives (psychostimulants). The test is sensitive to muscle-relaxant (benzodiazepines) and sedative (neuroleptics) effects, which lead to enhanced immobility. False positives and false negatives can often be screened by measuring if the compound produces locomotor stimulation or sedation. Strain differences in the tail suspension test have been found in mice. The tail suspension test has some face validity but its construct validity is rather weak.

Schizophrenia Model

[058] A prepulse inhibition model may be used to assess the efficacy of antipsychotic compounds (see Swerdlow and Geyer, *Schizophrenia Bulletin* 24: 285-301, 1998).

Prepulse Inhibition

[059] Prepulse inhibition is the process whereby a relatively mild stimulus, the prepulse, suppresses the response to a strong, startle-eliciting stimulus when the prepulse precedes the startle stimulus by a brief duration (about 10 to 500 milliseconds). Prepulse inhibition is a cross-species phenomenon (ie, it is present in mammals ranging from mice to humans), yet it is relatively absent among schizophrenic patients. The deficit in PPI in schizophrenic patients is thought to reflect the loss of sensorimotor gating that may lead to sensory flooding and cognitive fragmentation. In this test, mice or rats are administered compounds and individually placed into a holder on a transducer platform to measure whole body startle. The holder is housed in a startle chamber with background white noise. Following a brief habituation period, animals are given multiple trials of a weak auditory prepulse stimulus, followed by a strong auditory startle stimulus. Four types of trials are given: prepulse plus startle, prepulse alone, startle alone, and no stimulation. PPI is measured as the amount of inhibition of startle following the prepulse and is expressed as the percentage of basic startle. As a control, measurements are taken in the no stimulation and prepulse alone trials. PPI is considered a test with good predictive, face and construct validity for schizophrenia. Putative antipsychotics can be tested alone to determine if they enhance PPI. Alternately, antipsychotics can be screened to determine if they block various agents that disrupt PPI (apomorphine, d- amphetamine, PCP, ketamine, DOI). Finally, mutant mice with or without drugs can be screened using the PPI procedure.

Anxiety Model

[060] An elevated plus maze model may be used to assess the efficacy of anxiolytic compounds (see Pellow and File, *Pharm. Biochem. Behav.* 24, 525-529, 1986).

Elevated Plus Maze

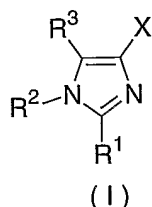
[061] The elevated plus maze is widely used as an anxiety paradigm that examines the conflict between the drive to explore and the aversiveness of heights and open spaces of rats or mice. The maze is a cross made up of two open and two closed arms that is raised above the ground. The combination of light, the open arms, and the height is thought to produce unconditioned fear or anxiety responses in mice or rats. The test apparatus is an open top maze constructed of opaque plastic with alternating open and enclosed arms. For rats, each arm is 45-55 cm long and 8-12 cm wide, with the sides of the enclosed arms 35-45 cm high, the juncture approximately 10 x 10 cm, and the maze is elevated 45-55 cm above the floor. The mouse elevated plus maze consists of two closed arms (15 x 6 x 30 cm) and two open arms (1 x 6 x 30 cm) forming a cross, with a quadrangular center (6 x 6cm). The maze is placed 50 cm above the floor. Testing is performed in a room free of noise and distraction. On test days animals are administered drug or vehicle. If a pretreatment period is necessary, the animals are returned to the home cage for the duration of the pretreatment time; otherwise, the animals are placed in a clear plastic holding chamber singly or with cage mates for 1-10 minutes prior to test time. Rats are then placed in the center of the maze always oriented in the same direction, either consistently facing an open arm or an enclosed arm. For 5-10 minutes, entries into each arm and the time spent in each arm are recorded by the observer(s) or by videotape or a computer receiving input from a video camera mounted above the maze. To count as an entry, all four paws must be inside the arm. If necessary, additional measures of anxiety-related behaviors will be recorded, i.e., time spent motionless, time spent in the center, time spent grooming, and the number of rears, stretching postures or feces produced. Following testing the animals are returned to the home cages. When animals are placed in the center of the maze, they spend most of their time in the closed arms, avoiding the open arms. Anxiolytic drugs, such as benzodiazepines, will increase the amount of time animals spend in the open arms. The test is also sensitive to anxiogenic drugs, which lends strong support for its predictive validity.

[062] The structures, materials, compositions, and methods described herein are intended to be representative examples of the invention, and it will be understood that the scope of the invention is not limited by the scope of the examples. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the invention.

Claims

What is claimed:

1. A method for treating psychiatric disorders comprising administering to a subject in need thereof an effective amount of a compound of Formula (I)



wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, (C_1-C_6) alkyl sulfonyl, (C_1-C_6) alkyl sulfonyl-amino, (C_1-C_6) alkyl carbonyl-amino, (C_1-C_6) alkyl amino-carbonyl-amino, or phenyl,

(C_2-C_6) alkyl,

cyclohexyl optionally substituted with (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

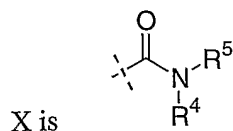
1-naphthyl or 2-naphthyl optionally substituted with halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or phenyl;

R^3 is hydrogen, (C_1-C_6) alkyl, benzyl, chloro, or bromo;



where R^4 is hydrogen or (C_1-C_6) alkyl;

R^5 is selected from

(C_2-C_9) alkyl or (C_7-C_{11}) bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, (C_1-C_6) alkyl-amino, bis[(C_1-C_3) alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted (C_1-C_6) alkyl, or fluorine,

benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C_1-C_6) alkyl, and optionally substituted on the phenyl ring with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C_1-C_6) alkyl, hydroxy-substituted (C_1-C_6) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, benzyl, or phenyl optionally substituted with one or more of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen,

$-NR^6R^7$

where R^6 is hydrogen or (C_1-C_6) alkyl;

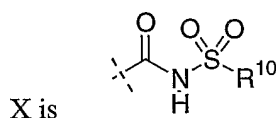
R^7 is (C_1-C_9) alkyl; or phenyl optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy-substituted (C_1-C_6) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom, or

R^6 and R^7 , taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more (C_1-C_6) alkyl, (C_1-C_6) alkoxy, hydroxy-substituted (C_1-C_3) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

or

R^4 and R^5 , taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkyl-amino, bis $[(C_1-C_3)$ alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C_1-C_6) alkyl, phenyl-substituted (C_1-C_6) alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C_1-C_6) alkyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or halogen;

or



where R^{10} is (C_1-C_9) alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, or a fluorine atom, or

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

2. The method of claim 1, wherein said compound of Formula (I) is selected from

1- $\{[2-(2\text{-chlorophenyl})-1-(4\text{-chlorophenyl})-1H\text{-imidazol-4-yl}]carbonyl\}$ -4-(4-fluorophenyl)-4-piperidinol;

1- $\{[2-(2\text{-chlorophenyl})-1-(4\text{-chlorophenyl})-1H\text{-imidazol-4-yl}]carbonyl\}$ -4-(4-chlorophenyl)-4-piperidinol;

1- $\{[2-(2\text{-chlorophenyl})-1-(4\text{-chlorophenyl})-1H\text{-imidazol-4-yl}]carbonyl\}$ -4-[3-(trifluoromethyl)phenyl]-4-piperidinol;

1- $\{[2-(2\text{-chlorophenyl})-1-(4\text{-chlorophenyl})-1H\text{-imidazol-4-yl}]carbonyl\}$ -4-(4-trifluoromethoxyphenyl)-4-piperidinol;

1- $\{[2-(2\text{-chlorophenyl})-1-(4\text{-chlorophenyl})-1H\text{-imidazol-4-yl}]carbonyl\}$ -4-(3-

fluorophenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(3-chlorophenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-fluoro-4-chlorophenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethoxy)phenyl]-4-piperidinol;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[1-(2-pyridinyl)-4-piperidinyl]-1H-imidazole-4-carboxamide;
[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](cyclohexyl)methanone;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-pyridinyl)-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
N'-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-chloro-2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
N'-(4-chloro-2-methylphenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-(2,4-dichlorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-[2,4-bis(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-(2-chloro-4-cyanophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carbohydrazide;
1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide;

1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-methyl-1H-imidazole-4-carboxamide;
1-(4-isopropylphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(cis)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
4-(4-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile; and
4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile.

3. The method of claim 1 or 2, wherein said psychiatric disorder is schizophrenia, depression, or anxiety disorders.
4. The method of claim 3, further comprising administering a pharmaceutical agent for psychiatric disorders in combination with said compound of Formula (I).
5. The method of claim 4, wherein said psychiatric disorder is schizophrenia.
6. The method of claim 5, wherein said pharmaceutical agent is selected from haloperidol, chlorpromazine, clozapine, olanzapine, and risperidone.
7. The method of claim 4, wherein said psychiatric disorder is depression.
8. The method of claim 7, wherein said pharmaceutical agent is selected from tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors.
9. The method of claim 4, wherein said psychiatric disorder is anxiety disorders.
10. The method of claim 9, wherein said pharmaceutical agent is selected from benzodiazepines, buspirone, tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors, and beta-blockers.
11. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) as defined in claim 1 or 2, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier and one or more pharmaceutical agents for psychiatric disorders.
12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) as defined in claim 1 or 2, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier and one or more pharmaceutical agents for schizophrenia.
13. The pharmaceutical composition of claim 12, wherein said pharmaceutical agent is selected from haloperidol, chlorpromazine, clozapine, olanzapine, and risperidone.
14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) as defined in claim 1 or 2, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier and one or more pharmaceutical agents for depression.

15. The pharmaceutical composition of claim 14, wherein said pharmaceutical agent is selected from tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors.
16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) as defined in claim 1 or 2, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier and one or more pharmaceutical agents for anxiety disorders.
17. The pharmaceutical composition of claim 16, wherein said pharmaceutical agent is selected from benzodiazepines, buspirone, tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors, and beta-blockers.