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Use Of GAL3 Receptor Antagonists For The Treatment Of Depression And/Or Anxiety And Compounds Useful in Such Methods

G00002

Background of the Invention

Throughout this application, various publications are referenced in parentheses by author and year. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application to describe more fully the art to which this invention pertains.

Depression is the most common of mental disorders and yet is often underdiagnosed and undertreated, inflicting substantial morbidity and psychosocial impairment on its sufferers. Depression is mainly characterized by sadness, flatness, loss of feeling, anhedonia (lack of pleasure), tearfulness, agitation or retardation, thoughts of guilt, and worthlessness; in severe cases, suicide, hallucinations and delusions.

Depression can be mainly categorized into bipolar disorders, identifying wide swings of mood; major depressive illness, marked by severe depressive symptoms but without manic swings; and less defined milder forms of bipolar and major depression that fall short of the specific diagnostic criteria e.g. dysthymic disorder (formerly called depressive neurosis). The symptomatology and diagnostic criteria for depression are

set out in the DSMIV guidelines (American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders). Although many patients have single episodes of major depressive illness, the condition also can be repetitive, and this recurrent condition is frequently called unipolar depressive illness.

The key features of depressive illness are a markedly gloomy mood in which there is a loss of interest in life, and general feelings of hopelessness and worthlessness. Depressive symptoms range in severity from mild mood swings to severe delusions about self-worth, accomplishments, and the future.

The "blackness" of the presentation in the depressed patient is most often accompanied by severe motor retardation with profound sleep and appetite disturbance and suicidal ideation. Furthermore, depressive illness can also present in a highly anxious or agitated state.

The degree to which the underlying brain mechanisms in anxiety and depression differ or overlap remains unknown. The fact, however, that to some extent the same neurotransmitter systems are involved in depression and anxiety does not mean that the mechanisms are identical. However, the majority of people in an episode of either depression or anxiety also meet criteria for at least one other psychiatric disorder. But by far the strongest comorbidities in both cases are between depression and anxiety disorders. Therefore, it is now becoming common clinical practice to treat both indications with antidepressants such as SSRIs.

The key clinical features of anxiety disorders relate to various combinations of psychological and physical manifestations of anxiety, not attributable to real danger and occurring either in attacks (panic disorder - PD) or as a persisting state (generalized anxiety disorder -GAD). Other neurotic features may be present (obsessional or hysterical symptoms) but do not dominate the clinical picture.

The Pathophysiology of Depression

Theories underlying the pathophysiology of depression have developed from several lines of evidence including: 1) changes in neurotransmitter monoamine levels; 2)endocrine imbalance; and 3) electrophysiological studies on sleep functions.

Evidence implicating the role of neurotransmitters in depression, in particular the monoamines serotonin, noradrenaline and dopamine, include the success of pharmacological agents in treating depressive disorders. Many of the tricylic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) effective in the treatment of depression increase the availability of the catecholamines (noradrenaline and dopamine) and indolamines (serotonin) in the central nervous system (CNS). The clinical efficacy of these agents has given rise to the catecholamine-indolamine hypothesis of depression. This theory postulates that a certain level of amines and/or receptor sensitivity to catecholamines functions to generate a normal mood. A receptor

insensitivity, a depletion of monoamines, or a decrease in their release, synthesis or storage have been postulated to lead to depression.

Current Treatments for Depression

A variety of pharmacological agents have been employed to treat depression based on the catecholamine-indolamine hypothesis of depression. Drugs used to treat depression include MAOIs, atypical antipsychotics, lithium, TCAs, and SSRIs. In addition, a number of off-label agents such as antiepileptics are used to treat depression in treatment-resistant patients.

Tricyclic antidepressants are about equal to SSRIs in effectiveness against depression thus providing supporting evidence for the catecholamine-indolamine hypothesis of depression. However, SSRIs have largely displaced TCAs because of side effects associated with TCAs and the need to monitor EKG and plasma drug concentration. Although the SSRIs are viewed as an improvement over other antidepressants, they are not without their clinical problems. Adverse effects on sexual function, primarily anorgasmia and delayed ejaculation, have been consistently reported. Other, common side-effects include sleep disorders, yawning, weight changes, suicidal ideation and extrapyramidal-like side-effects such as dystonic reactions. Thus, there clearly remains a medical need for new treatments of depression, without the adverse side-effect profile of existing agents and with improved efficacy.

Current treatments for anxiety

There is now considerable direct evidence for the efficacy of the SSRIs both in depression and in anxiety disorders.

Of the current SSRIs approved for marketing in the USA all have shown sufficient efficacy to be further approved for the treatment of at least one anxiety disorder, for example; obsessive compulsive disorder (OCD) and generalized anxiety disorder (GAD). Compounds such as paroxetine and sertraline are also indicated for the treatment of panic disorder (PD).

However, it is clear from the issues raised earlier relating to the efficacy and side- effect profile of SSRIs and for that matter the more widely prescribed benzodiazapines, there still exists a real medical need for novel approaches for the treatment of anxiety and depression.

Discovery Of GAL3 Receptor Subtype And Its Role In Depression and Anxiety

The investigations leading to the present invention arose from the discovery that mRNA for the GAL3 receptor is localized to areas of the rat brain associated with mood and emotion (see PCT International Publication No. WO 98/15570, published April 16, 1998), thus supporting the expression of GAL3 in those regions. Protein for the GAL3 receptor is also shown to localize to areas of the rat brain associated with mood and emotion (see Table 11 and discussion herein).

This discovery led to the hypothesis that the GAL3 receptor may play a role in controlling the activity of catecholamine and indolamine neurons in the CNS. Galanin is known to hyperpolarize neurons, including monoaminergic neurons (Seutin, et al., 1989) and to have inhibitory effects on 5-HT neurons (Xu, et al., 1998), and dopamine neurons (Gopalan, et al., 1993; De Weille, et al., 1989; Jansson, et al., 1989; Nordstrom, et al., 1987; Weiss, et al., 1998). In light of these reports, a series of in vivo behavioral experiments were carried out to evaluate the antidepressant properties of a selective GAL3 receptor antagonist. The rat Forced Swim Test and the rat Social Interaction Test were employed to evaluate the use of selective GAL3 receptor antagonists to treat depression and anxiety. These models are considered by experts in the field to reflect the potential of agents to treat depression and anxiety.

Rat Forced Swim Test (FST)

The rat Forced Swim Test (FST) is a behavioral test that is used to screen compounds for antidepressant efficacy (Porsolt et al., 1977, 1978; Porsolt, 1981). This test is widely used as it is reliable across laboratories, relatively easy to perform and is sensitive to the effects of some of the major classes of antidepressant drugs, including TCAs and MAOIs, and various atypical antidepressants. Furthermore, this test is relatively selective for antidepressant drugs, as few psychoactive drugs produce similar behavioral actions in the FST.

In the rat FST, animals are placed in a cylinder of

water, from which there is no escape, for an extended period of time. Typically, animals will display a range of behaviors such as immobility, climbing, swimming, and diving, with immobility being predominant after several minutes of immersion in the water. Consequently, many past studies have only measured or scored immobility after the administration of the test agent. Unfortunately, this method does not score any other active behaviors that may be produced by potential antidepressants. Thus, if a particular class of antidepressant were to have very little effect on immobility, yet produce characteristic behaviors during the FST, these behaviors would not be scored and the conclusion would be that the compound in question does not possess antidepressant action.

Recently, however, a sampling technique was developed to score active behaviors in the FST, such as swimming, climbing and diving, in addition to immobility (Detke, et al., 1995; Lucki, 1997; Page, et al., 1999; Reneric and Lucki, 1998). This modified sampling technique has indicated that SSRIs, such as fluoxetine, paroxetine and sertraline, significantly decrease immobility and increase swimming time (Detke, et al., 1995; Page, et al., 1999). In contrast, selective reuptake inhibitors of norepinephrine (NE) increase climbing behavior but do not alter swimming time (Detke, et al., 1995; Page, et al., 1999).

Rat Social Interaction Test (SIT)

There are a number of paradigms that have been used to determine whether a compound possesses anxiolytic action.

A number of these tests involve food or water deprivation, punishment or measurement of consummatory behavior (see File, et al., 1980; File, 1985; Rodgers, et al., 1997; and Treit, 1985, for review). In addition, in these models, prior conditioning reduces the uncertainty or anxiety. In general, these tests lack ethological validity.

One model that is based upon an unconditioned response that does not involve punishment or deprivation is the Social Interaction Test (SIT) (File and Hyde, 1978, 1979). In this model, rats previously housed singly are placed in a familiar, dimly lit, test arena with weight-matched, novel partners. The principal anxiogenic stimulus under these conditions is the partner novelty, which involves an unconditioned response to a potential threat. After pharmacological treatments, the following behaviors are scored as active social interaction: grooming, sniffing, biting, boxing, wrestling, following, crawling over and crawling under. A wide range of psychoactive drugs have been examined in this paradigm and it has been shown that the social interaction test can distinguish anxiolytics from antidepressants, antipsychotics, analeptics and sedative agents (File, 1985; Guy and Gardner, 1985). This test can detect anxiolytic agents such as the benzodiazepines (File and Hyde, 1978; File and Hyde, 1979; File, 1980), in addition to non-benzodiazepines, including paroxetine and other SSRIs (Lightowler, et al., 1994). Finally, the social interaction test can detect anxiogenic agents, including the inverse benzodiazepine receptor agonists (File, et al., 1982; File and Pellow, 1983; File and Pellow, 1984;

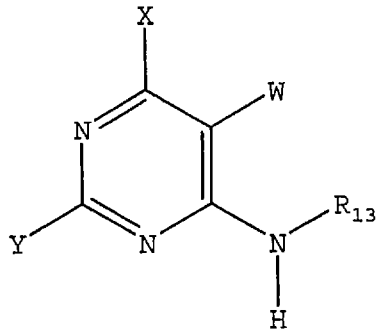
File, 1985).

In an embodiment of the present invention the synthesis of novel pyrimidines which bind selectively to the cloned human GAL3 receptor, compared to other cloned human G-protein coupled receptors, as measured in *in vitro* assays, is disclosed. In a further embodiment of the present invention the synthesis of indolones which bind selectively to the cloned human GAL3 receptor, compared to other cloned human G-protein coupled receptors, as measured in *in vitro* assays, is disclosed. The *in vitro* receptor assays described hereinafter were performed using various cultured cell lines, each transfected with and expressing only a single galanin-type receptor.

From the binding information described hereinafter, it has unexpectedly been discovered that compounds which are specific for the human GAL3 receptor with a binding affinity greater than ten-fold higher than the binding affinity with which the compounds bind to a human GAL1 receptor are effective in animal models of depression and anxiety which are predictive of efficacy in humans. Thus, we demonstrate that the GAL3 receptor antagonists, which may be classified as neutral antagonists, inverse agonists or allosteric modulators, provide a novel method to treat depressive disorders and/or anxiety.

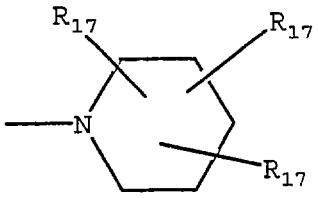
Summary of the Invention

The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is; $NR_{11}R_{12}$;



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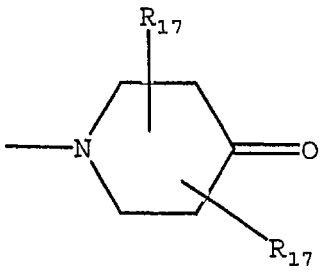

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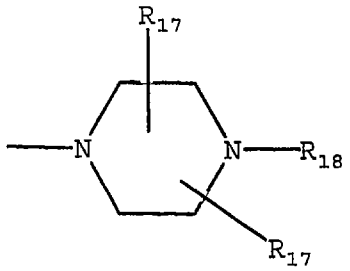

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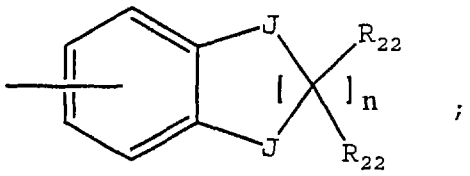
wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-C_6)alkyl, Q_1 or Q_2;

wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



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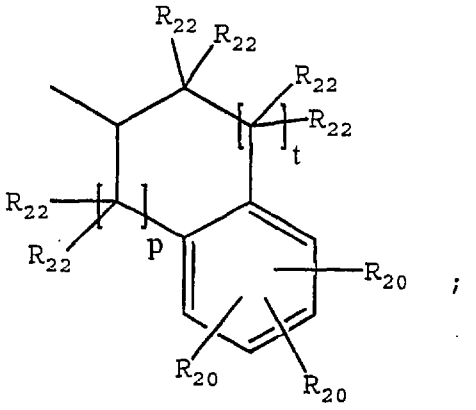
wherein Q_2 is



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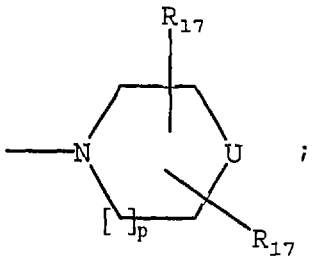
wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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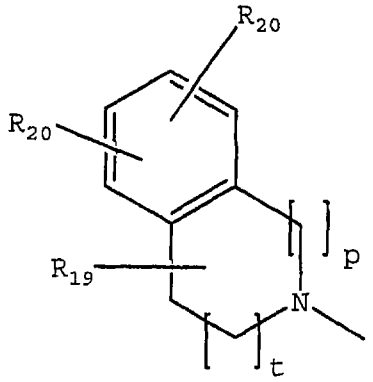

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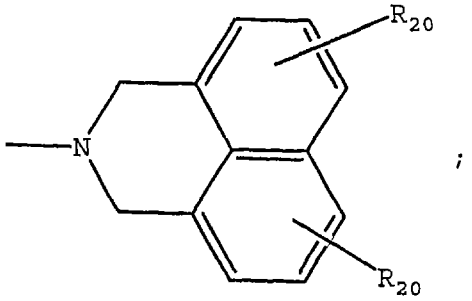

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wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl,

straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-

C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

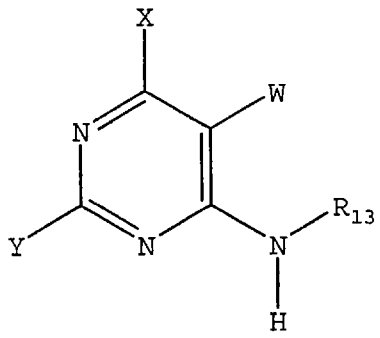
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

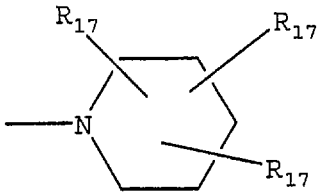
a pharmaceutically acceptable salt thereof.

The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



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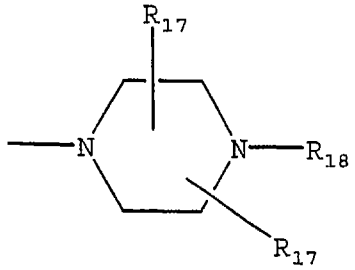


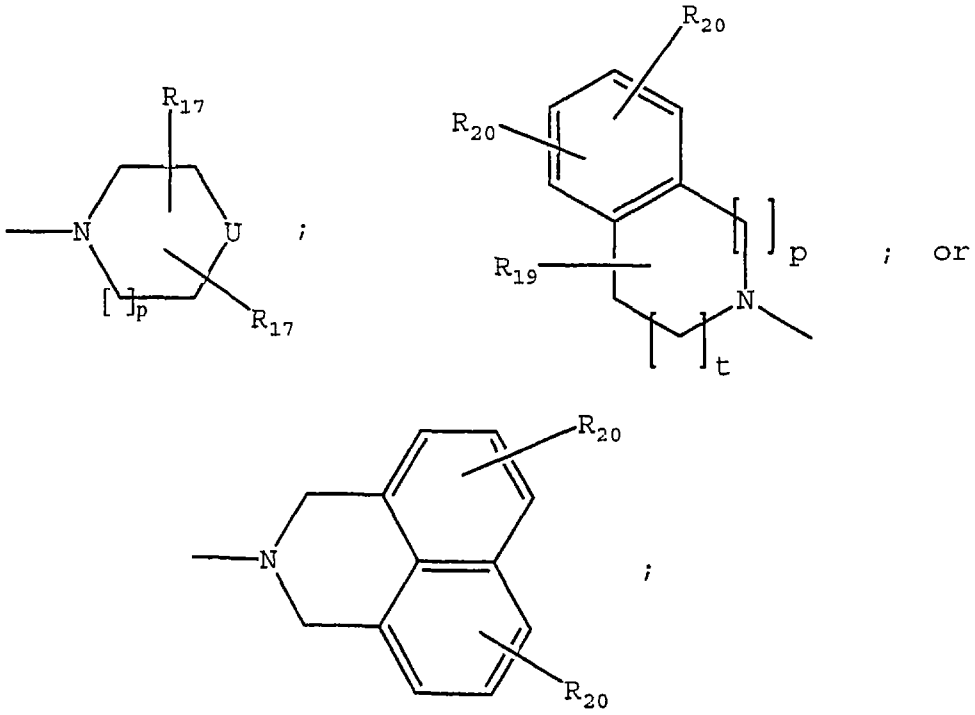
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;



wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

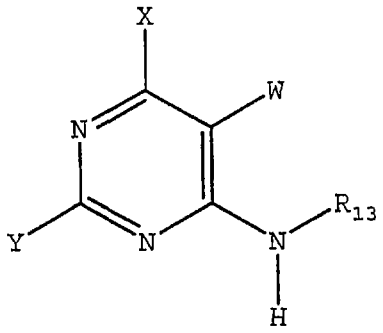
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

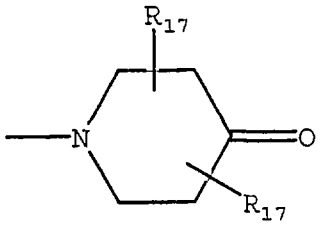
a pharmaceutically acceptable salt thereof.

The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or

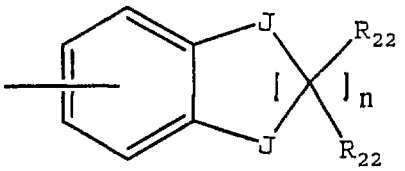


;

wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



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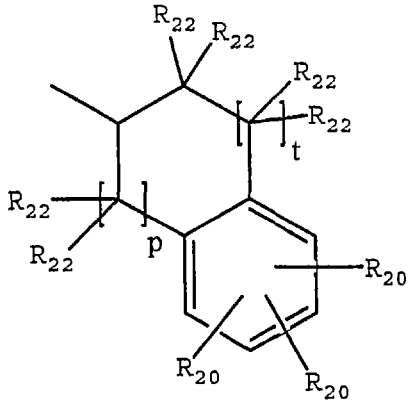
wherein Q_2 is

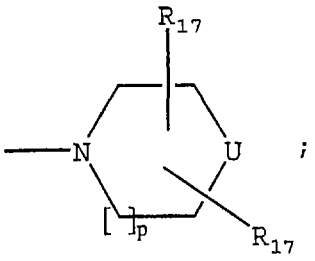


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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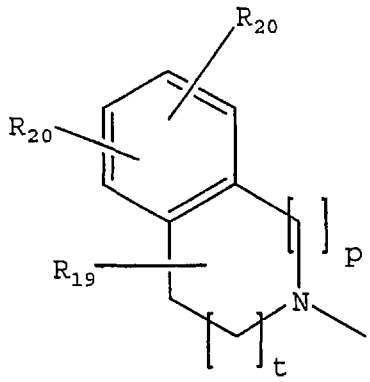

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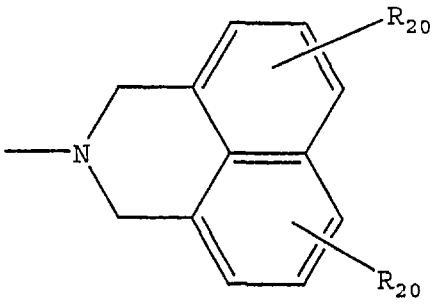


;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or

branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

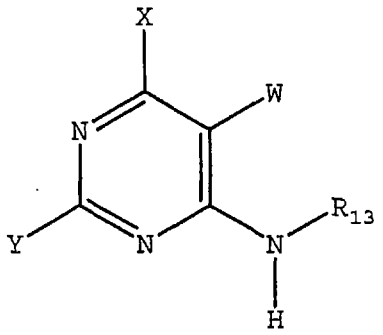
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

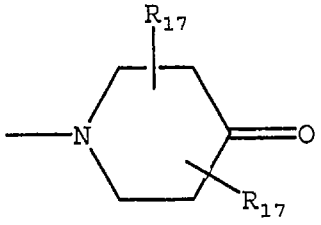
a pharmaceutically acceptable salt thereof.

The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21},

$-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

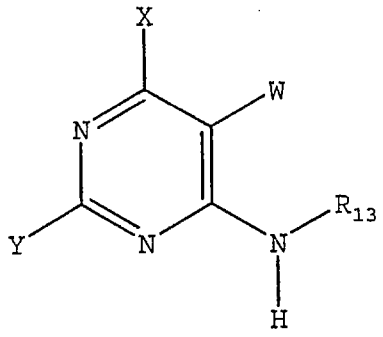
wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

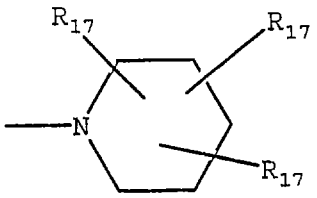
a pharmaceutically acceptable salt thereof.

The present invention also provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is; $NR_{11}R_{12}$;



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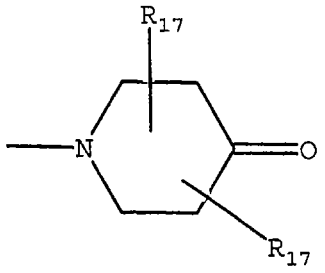
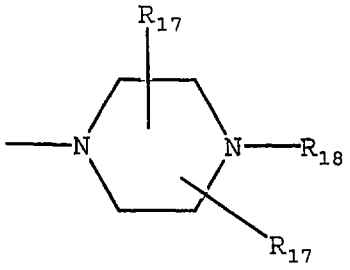


; or



;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl (C_1-C_6)alkyl;

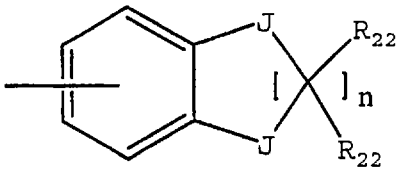
wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-

C_6)alkyl, Q_1 or Q_2;

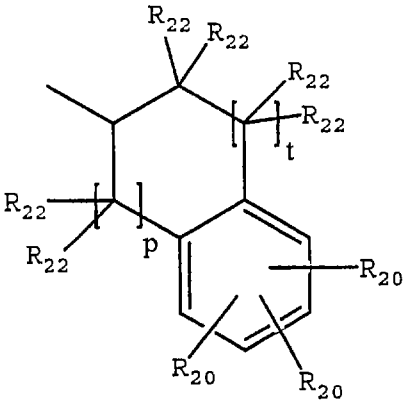
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

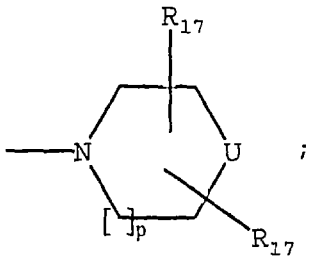


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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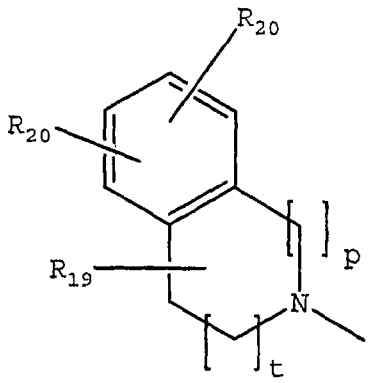
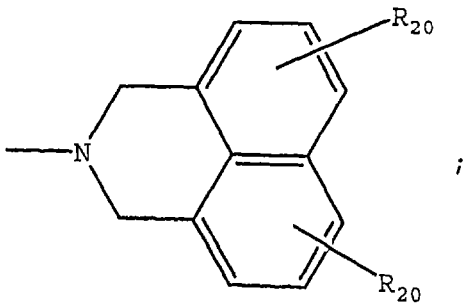


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$,

$-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

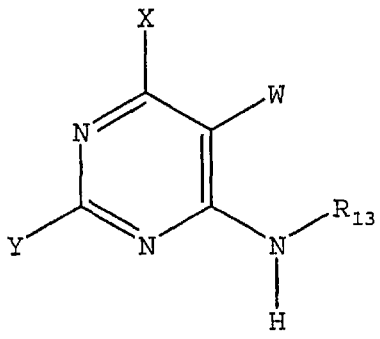
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

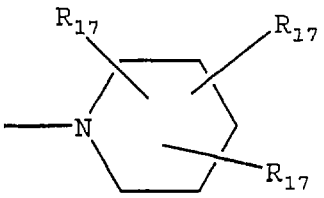
a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



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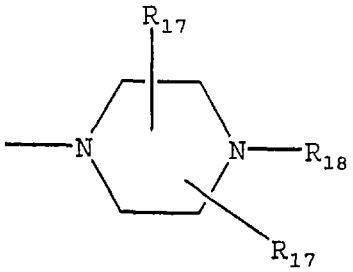


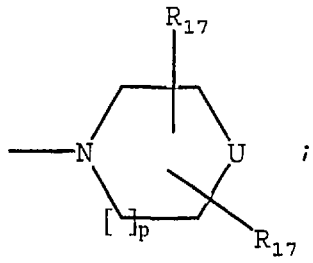
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl(C_1-C_6)alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;



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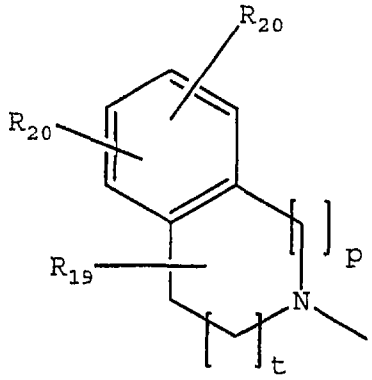

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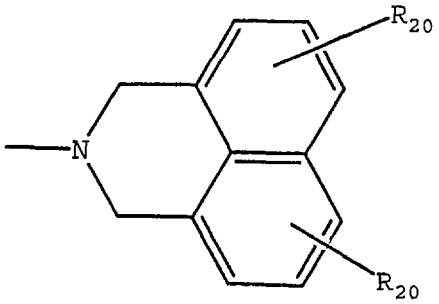


;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

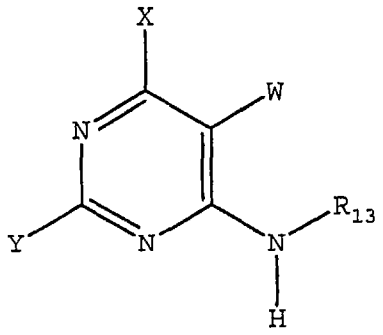
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

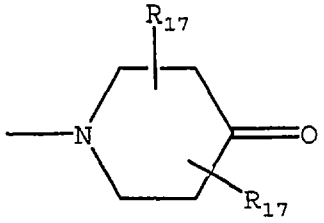
a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or

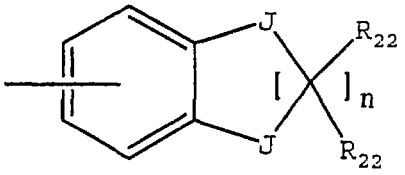


;

wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

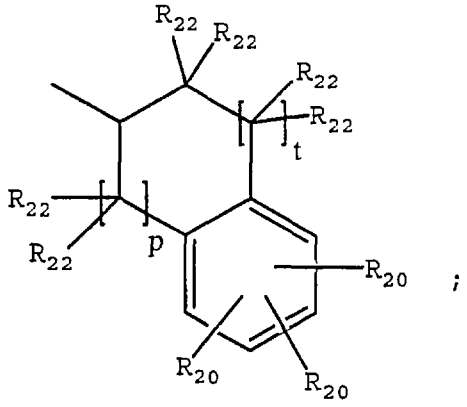
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

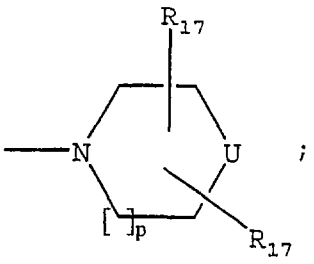


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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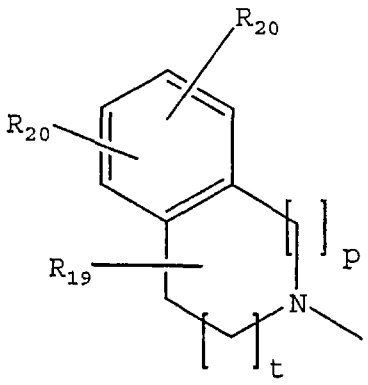

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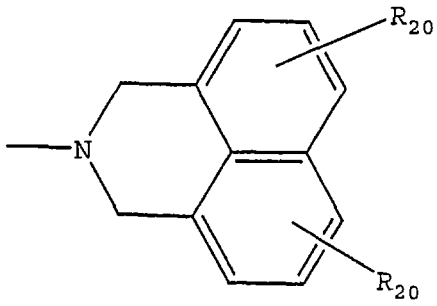


;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl,

straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

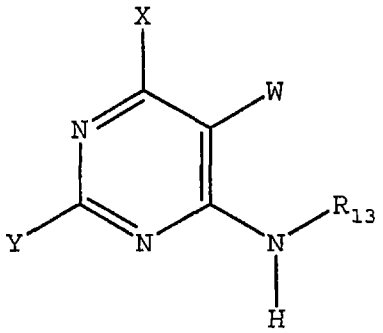
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

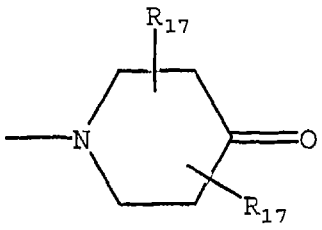
a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

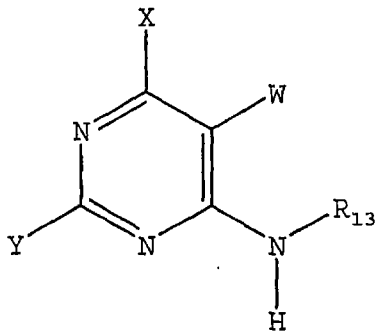
wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

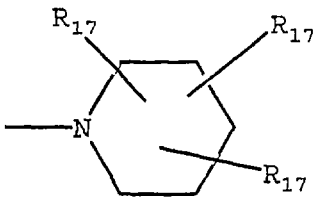
a pharmaceutically acceptable salt thereof.

The invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is; $NR_{11}R_{12}$;



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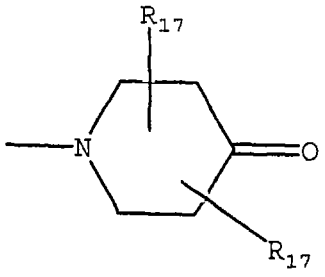
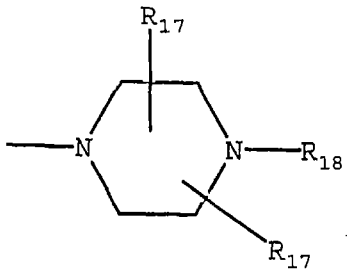


; or



;

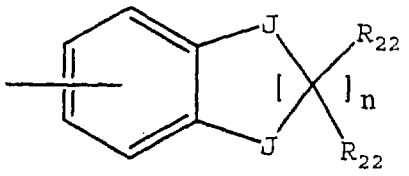
wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl$(C_1$-$C_6)$alkyl, Q_1 or Q_2;

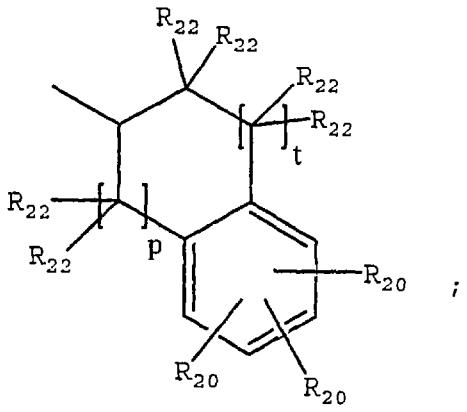
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

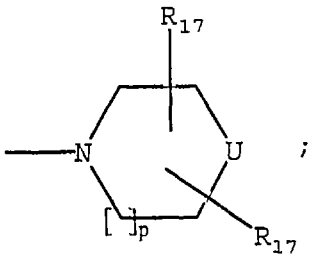


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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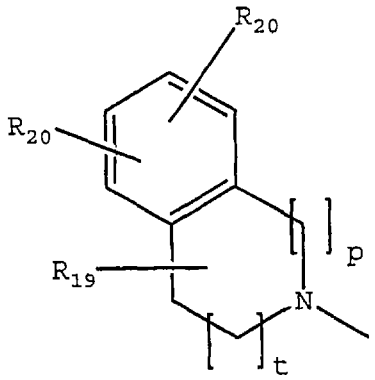

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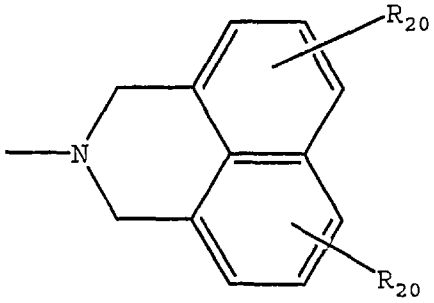


;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21},

$-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, -$CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

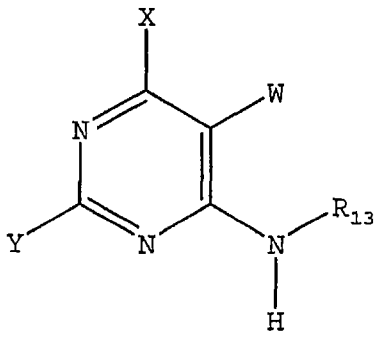
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

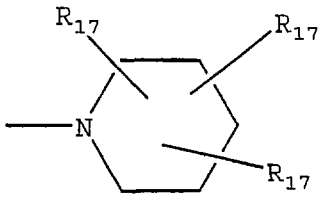
a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



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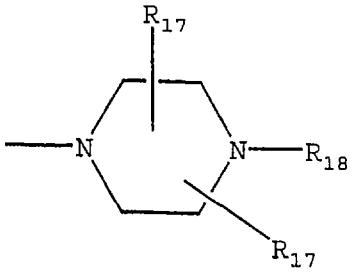


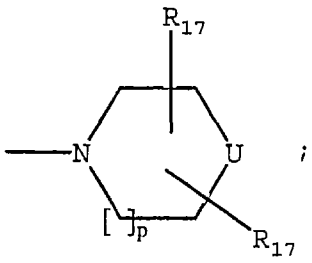
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;



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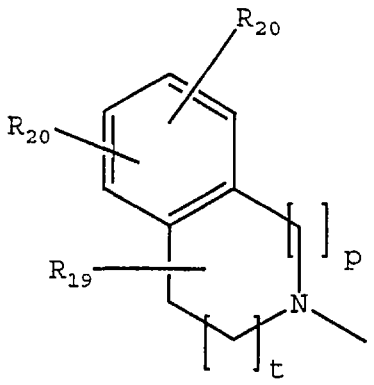

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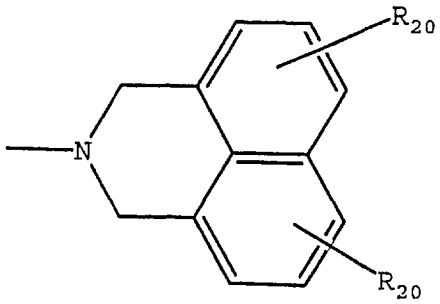


;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, -NR_{16}, S, $C(R_{17})_2$, or -NSO_2R_{16};

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

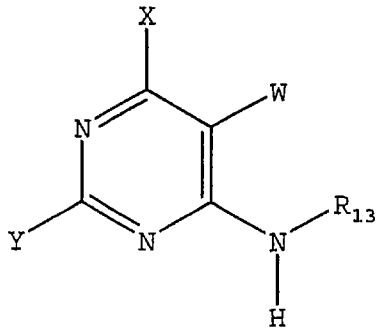
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

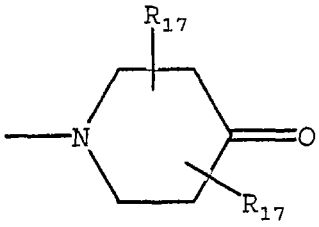
a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

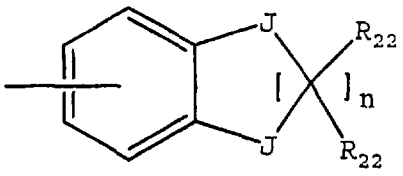
wherein X is $N(CH_3)_2$ or



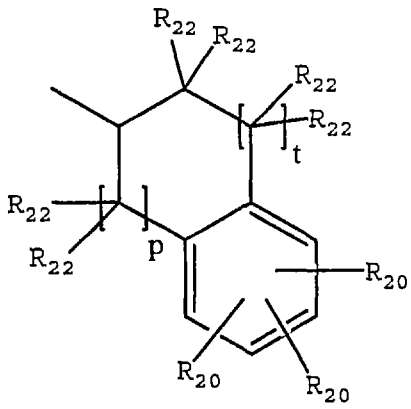
wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



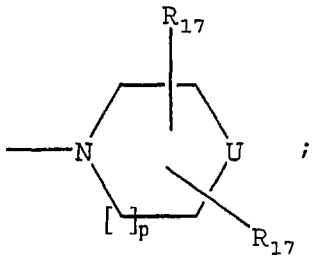
wherein Q_2 is



wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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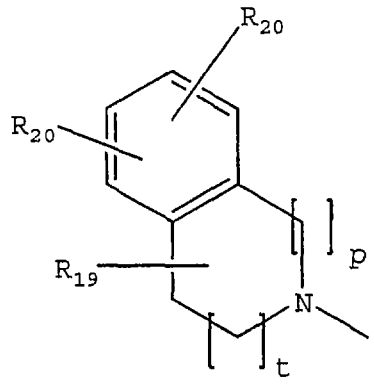
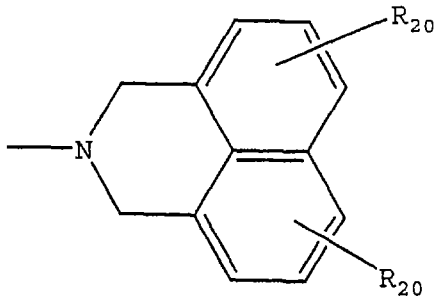


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or

branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

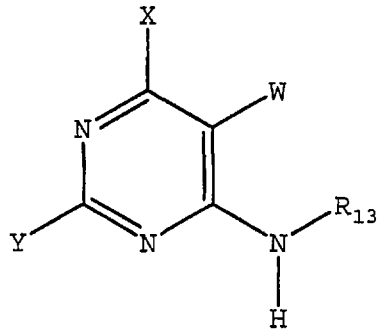
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

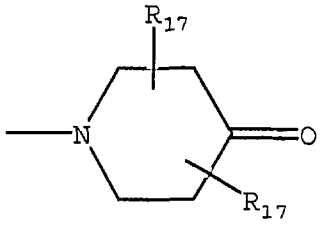
a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -

$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

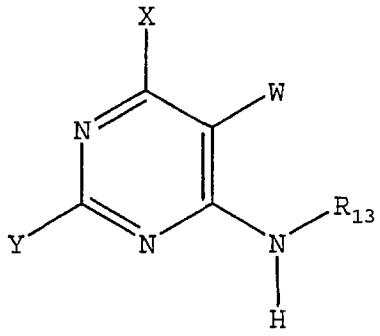
wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

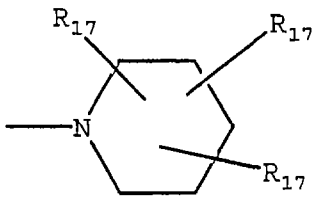
a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is; $NR_{11}R_{12}$;



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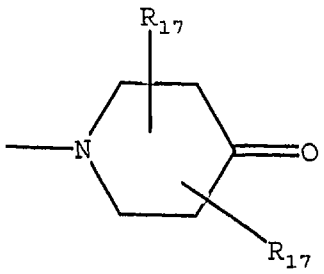
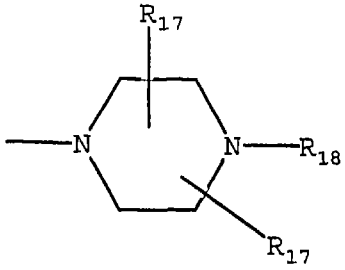


; or



;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

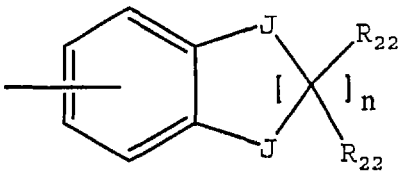
wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl$(C_1$-

C_6)alkyl, Q_1 or Q_2;

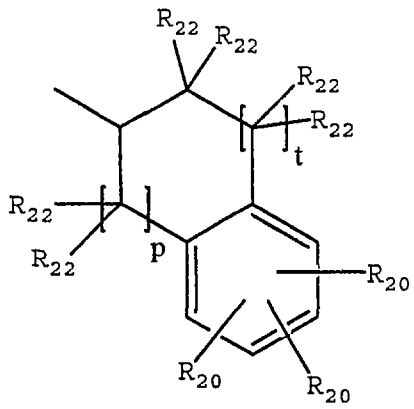
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

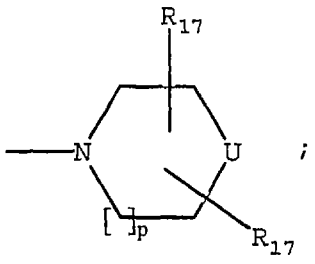


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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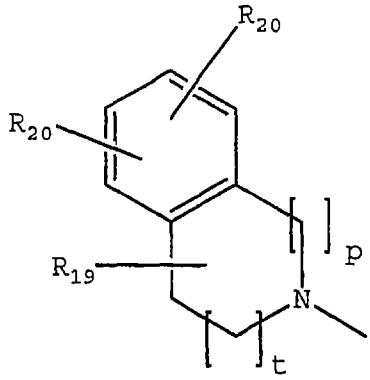
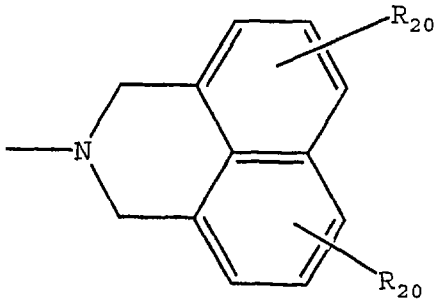


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21},

$-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

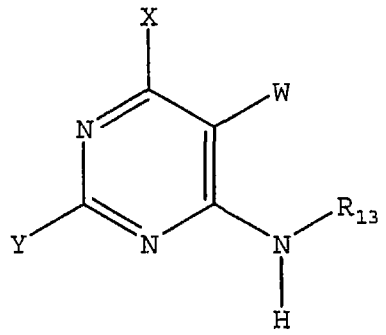
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

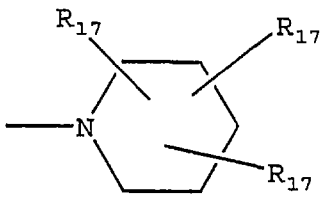
a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



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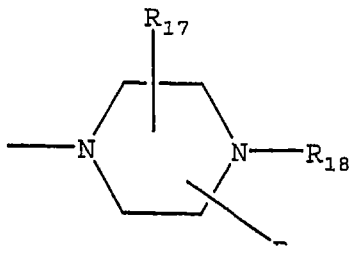


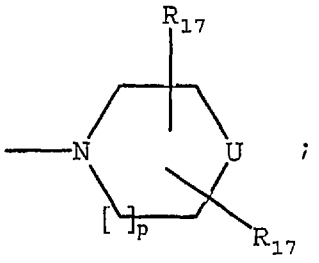
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;



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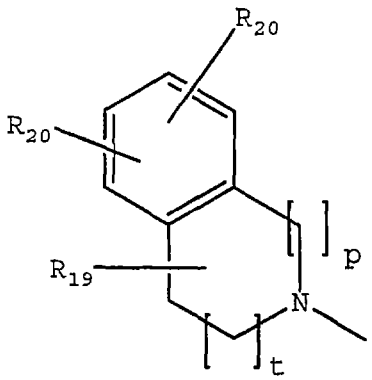
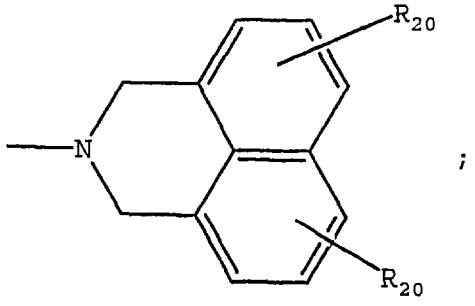


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl,

$(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, -

$CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

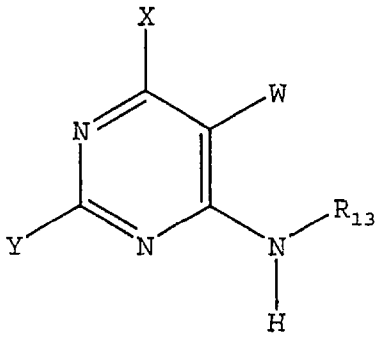
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

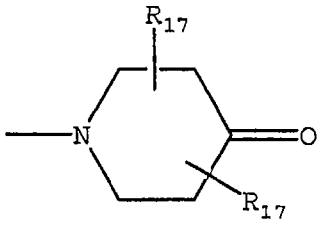
a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or

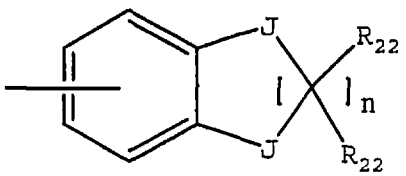


;

wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

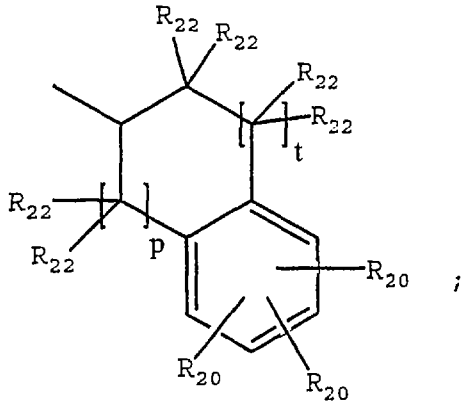
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

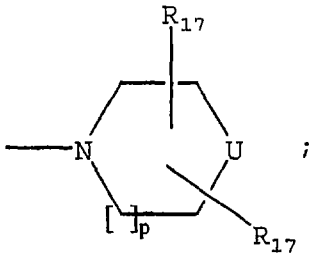
wherein Q_2 is

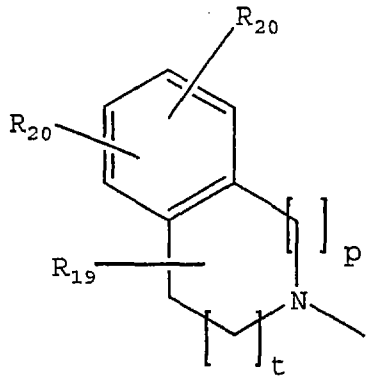


wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

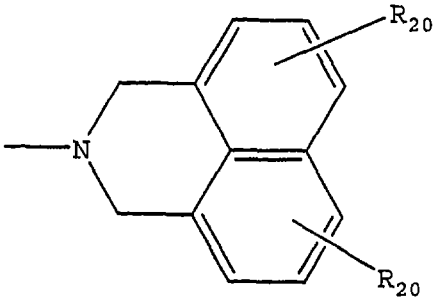
wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;





or



wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

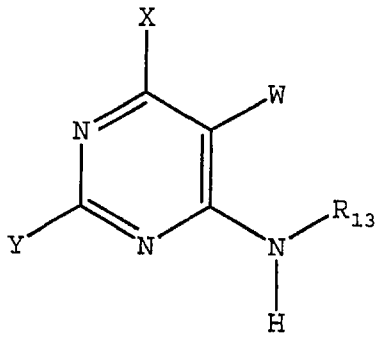
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

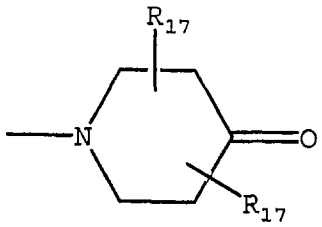
a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

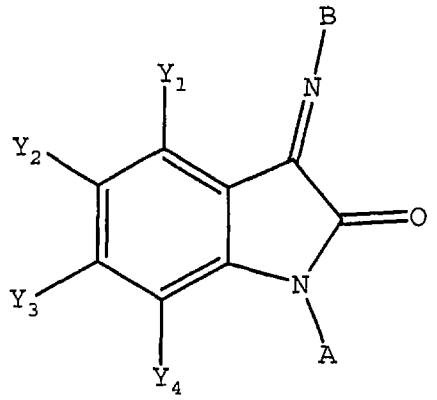
wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

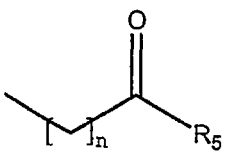


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



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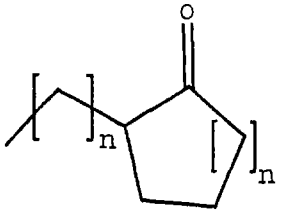

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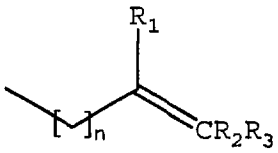
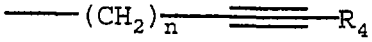
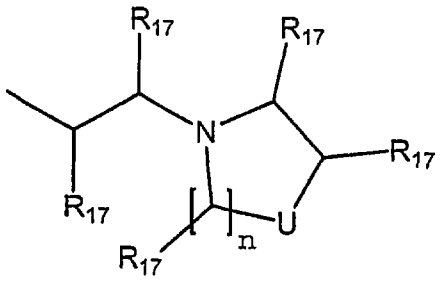


; or



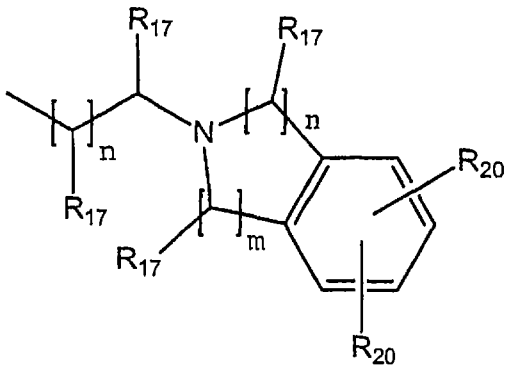
;

wherein Q_3 is



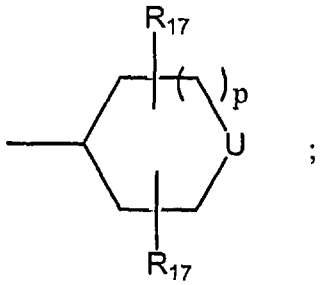
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

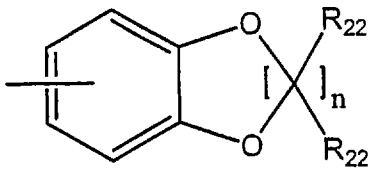
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

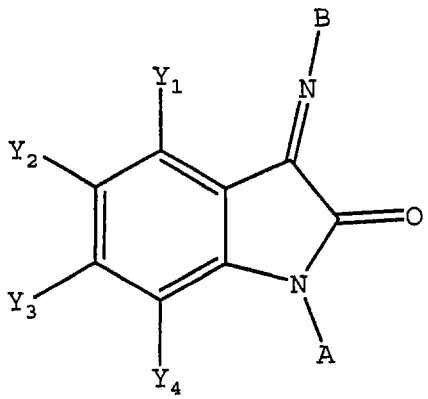


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

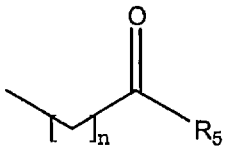
The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;



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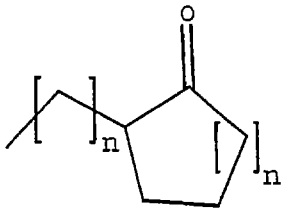
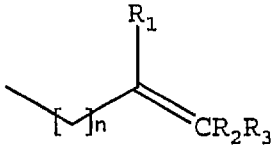
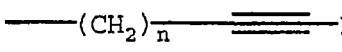


;

wherein A' is



; or



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

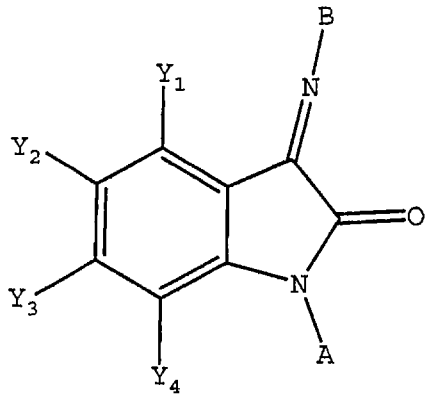
wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat

the subject's depression wherein the compound has the structure:

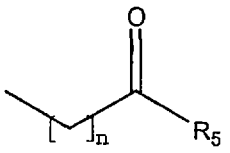


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A′ is



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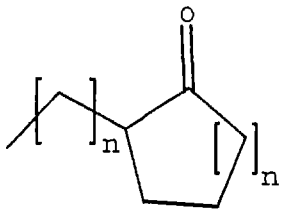

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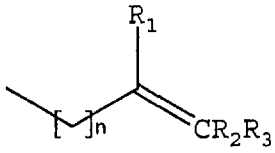
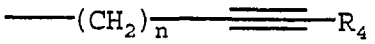


; or

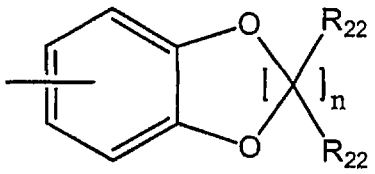


;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



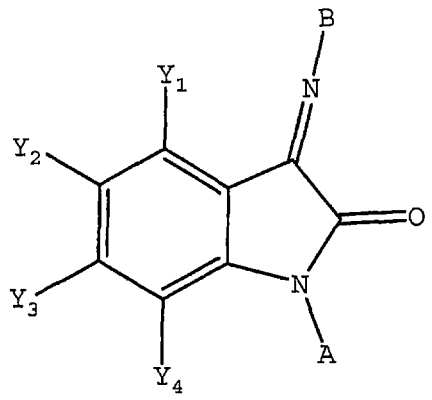
;

wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

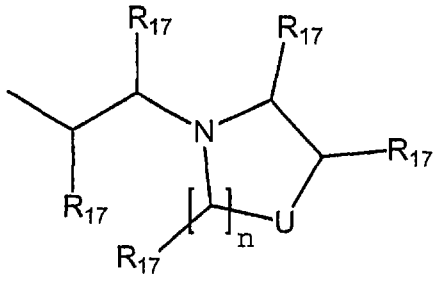


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

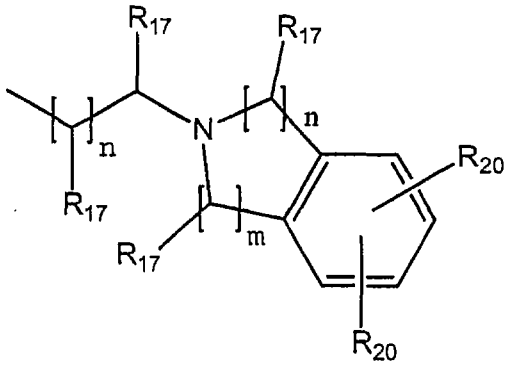
wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



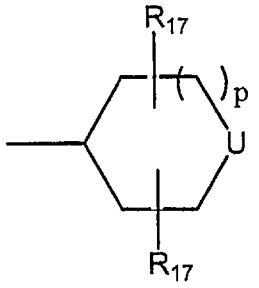
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

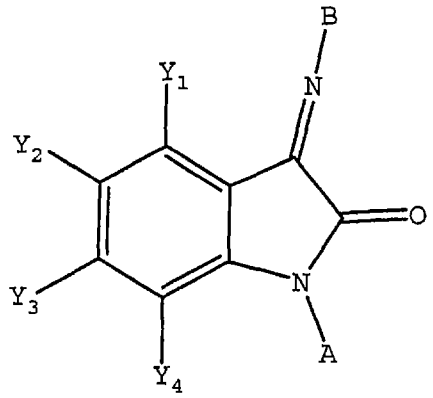
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



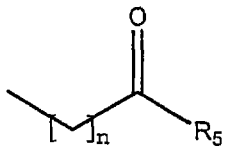
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or

branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



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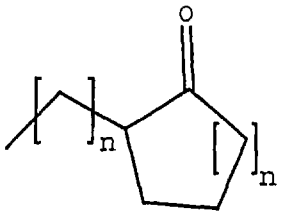
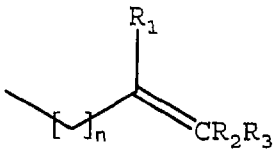
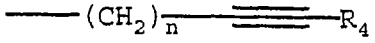


;

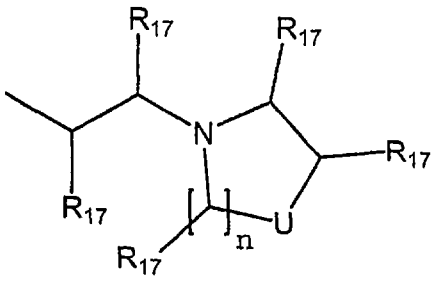


; or



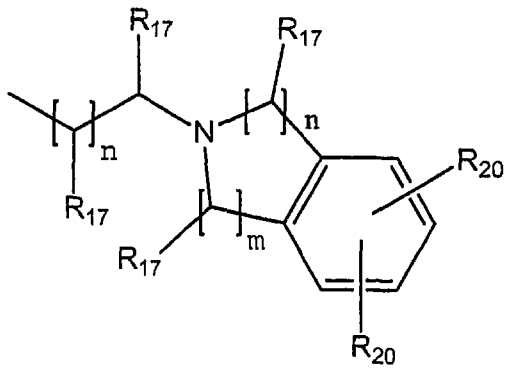
;

wherein Q_3 is



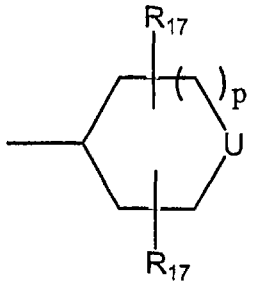
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

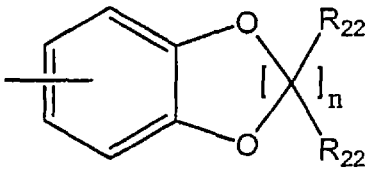
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

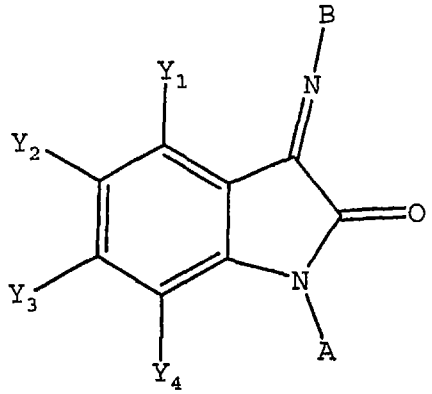


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

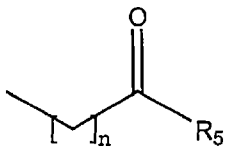


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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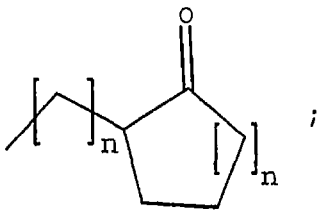

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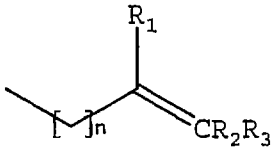
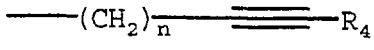


; or  ;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

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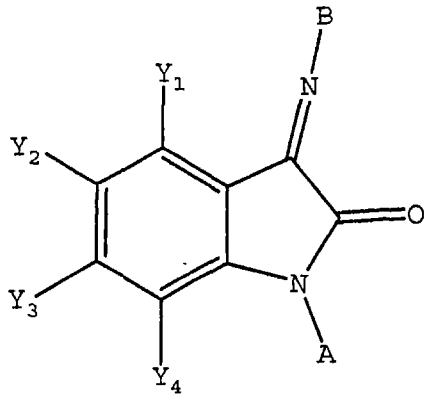
The invention provides a method of treating a subject suffering from anxiety which comprises administering to

the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

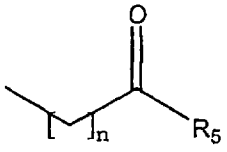


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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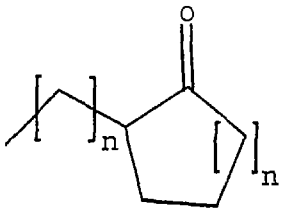

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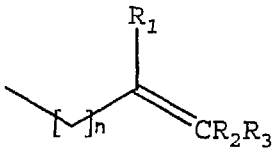
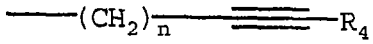


; or

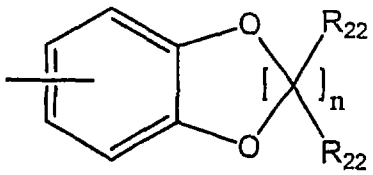


;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



;

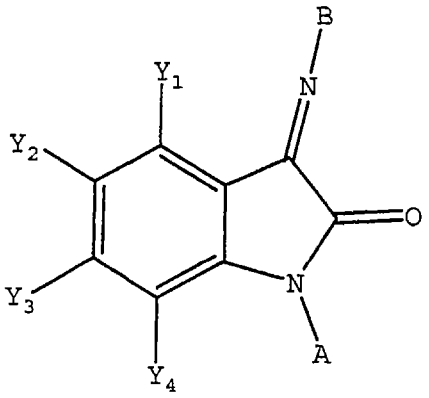
wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F,

Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



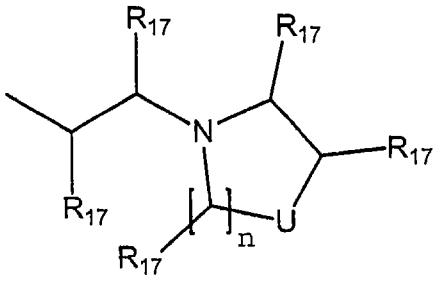
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7

alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

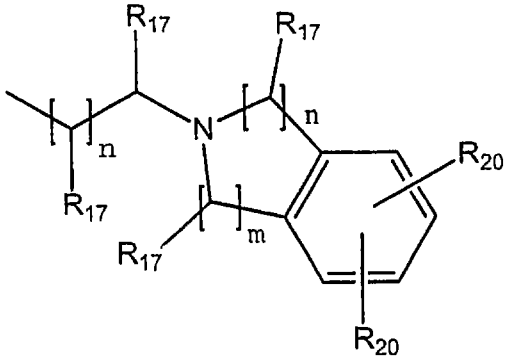
wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



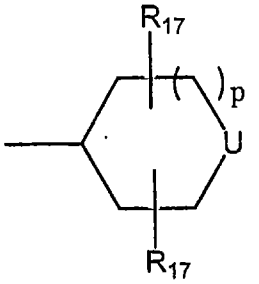
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained

or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

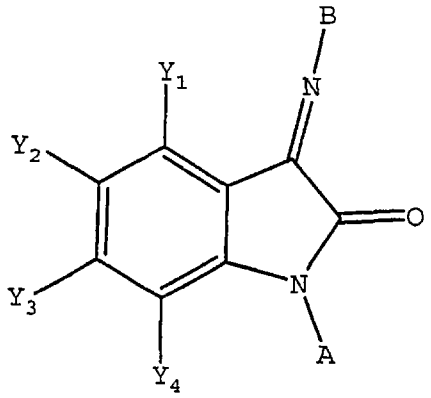
wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

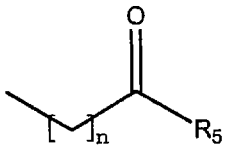


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



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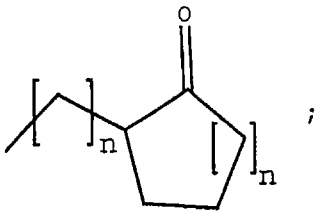

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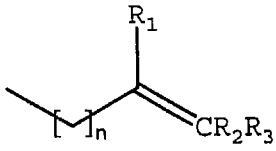
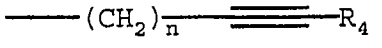
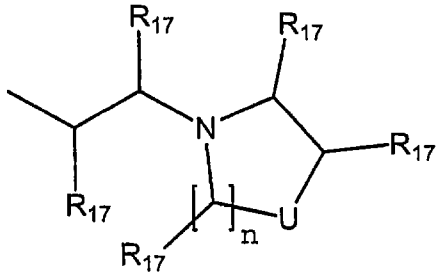


; or



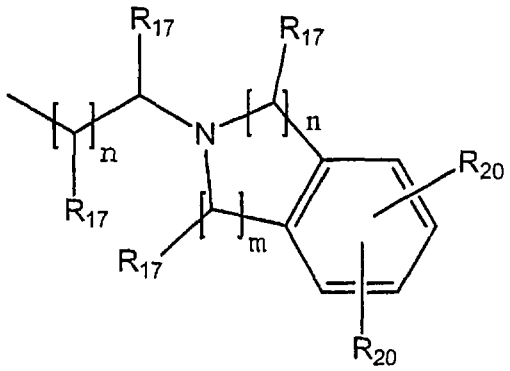
;

wherein Q_3 is



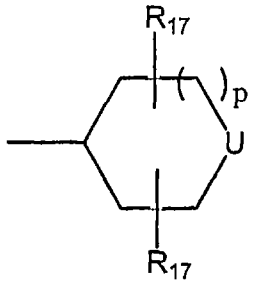
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

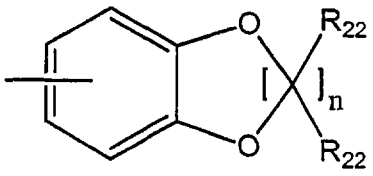
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

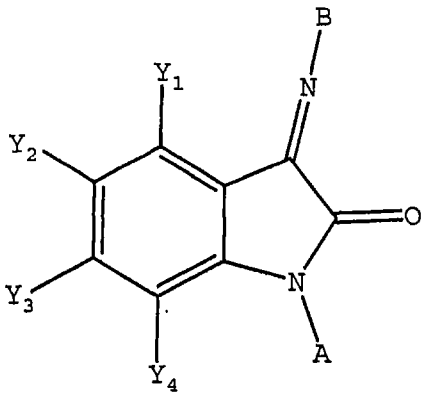


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



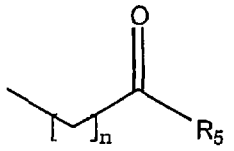
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -

H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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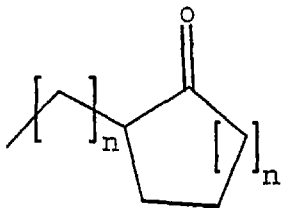

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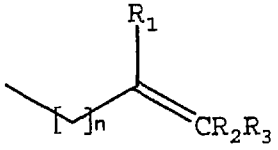
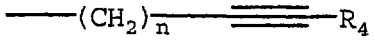


; or



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

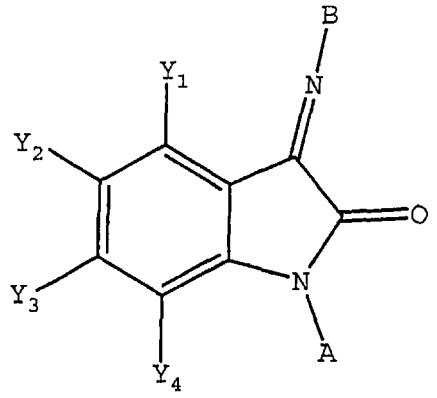
wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

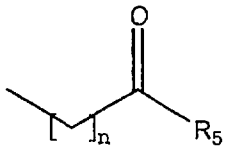
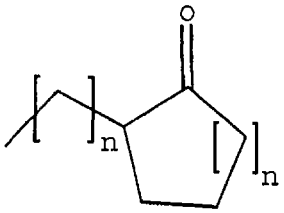


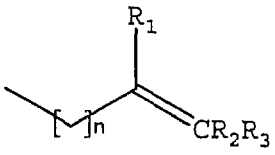
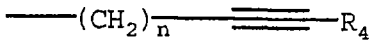
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl$(C_1$-$C_6)$alkyl or heteroaryl$(C_1$-$C_6)$alkyl;

wherein A' is

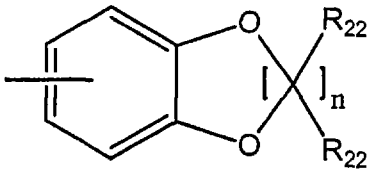
 ;  ;

 ; or  ;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

 ;

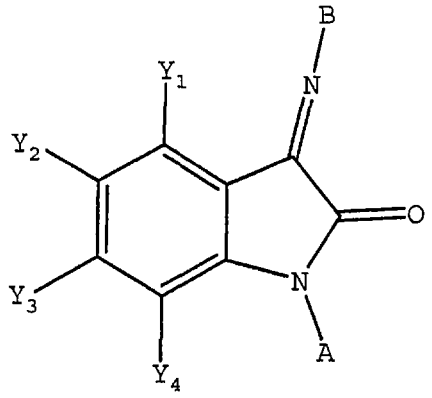
wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F,

Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



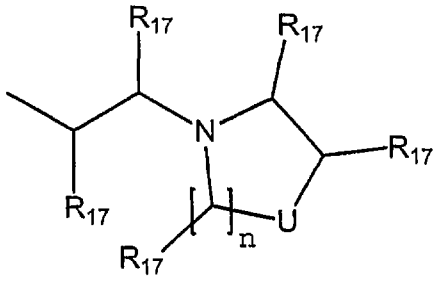
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7

cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

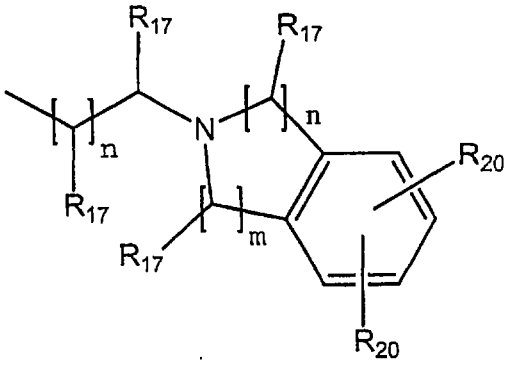
wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



;

wherein Q_4 is



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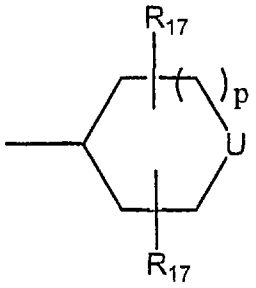
wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

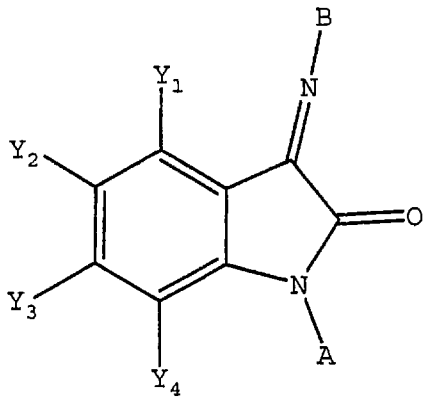
wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



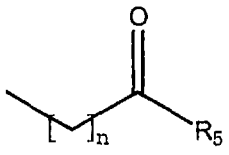
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7

cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is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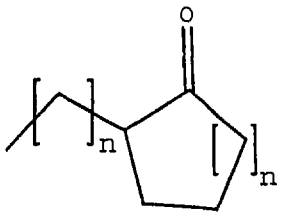
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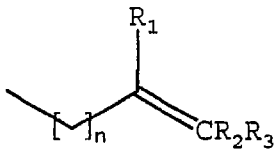
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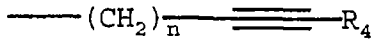
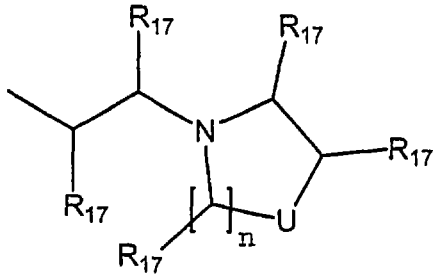

;

wherein Q_3 is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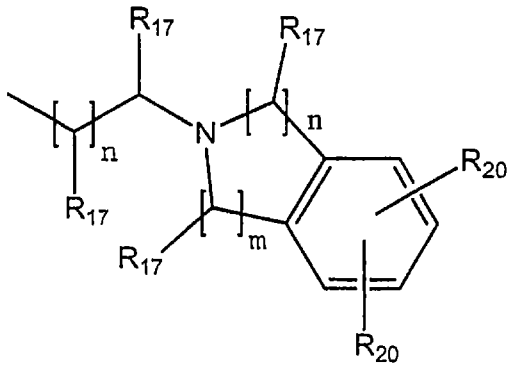
wherein Q_4 is



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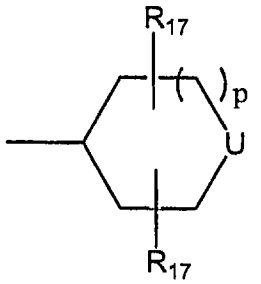
wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_6$ or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

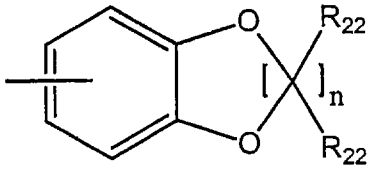
wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with

one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

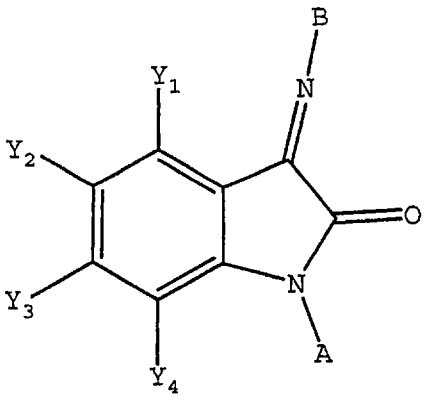


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



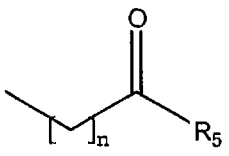
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently - H; straight chained or branched C_1-C_7 alkyl,

monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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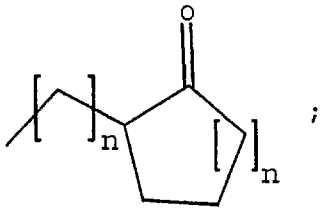

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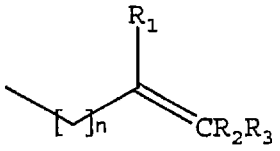

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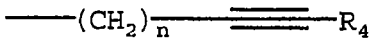


;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

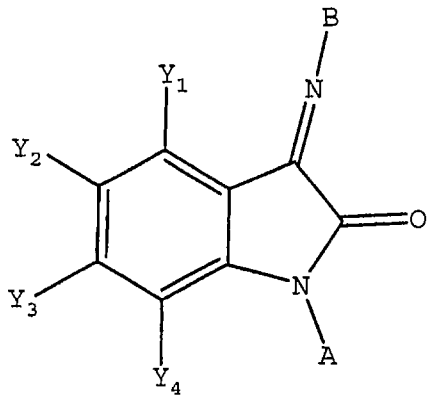
wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:

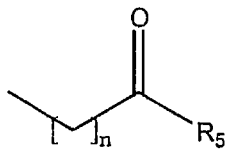


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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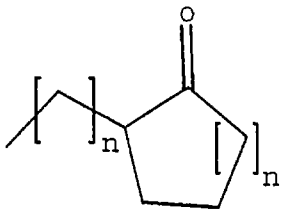

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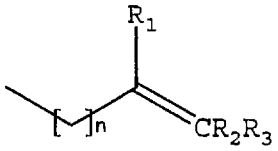

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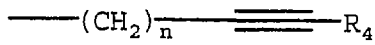
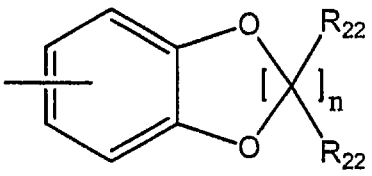


;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



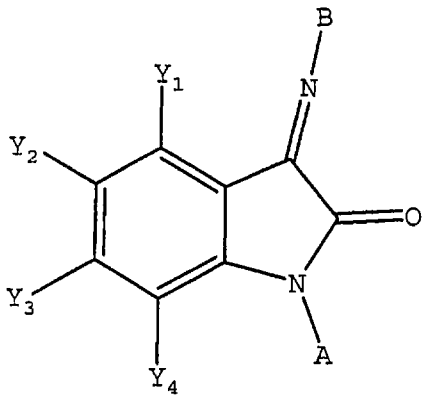
;

wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



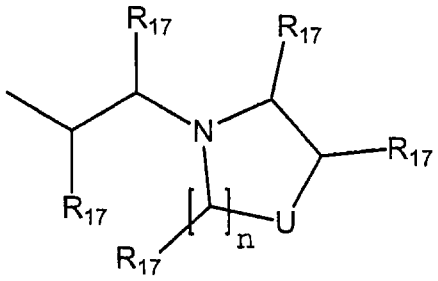
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7

alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

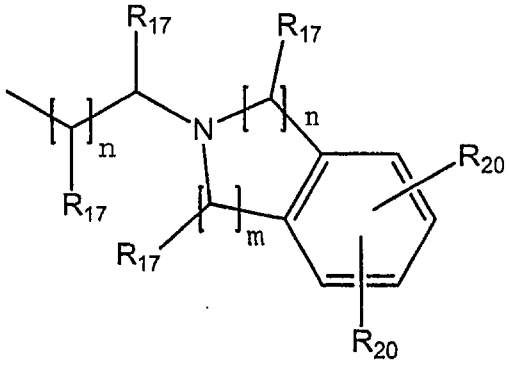
wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



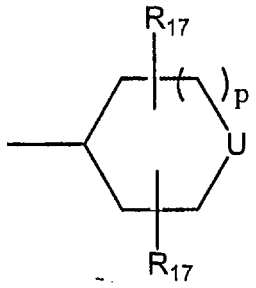
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating depression in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor;

(b) (1) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 50 percent, at a concentration of 10μM; and

(2) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 50 percent, at a concentration of 10μM; and

(c) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

The invention provides a method of treating anxiety in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3

receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor; and

(b) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

Brief Description of the Figures

Figure 1: Rat Forced Swim Test Results (Immobility: Normal Rats)

Vehicle (V) and test compounds (F10 = fluoxetine at 10 mg/kg ip; C1, C3, C10 or C30 = Example 92 at 1, 3, 10 or 30 mg/kg ip) were injected into normal rats by intraperitonal administration (n = 5 for each treatment condition). One hour later, rats were examined in a 5 minute forced swim test. For each treatment condition, the number of 5-sec intervals culminating with a display of immobility was derived and plotted as the average +/- S.E.M. A significant decrease in immobility was observed for rats injected with fluoxetine at 10 mg/kg, or with Example 92 at 3 and 10 mg/kg, relative to vehicle injected controls ($p < 0.01$, ANOVA and Student-Nerman-Keuls).

Figure 2: Rat Forced Swim Test Results (Climbing: Normal Rats)

Vehicle (V) and test compounds (F10 = fluoxetine at 10 mg/kg ip; C1, C3, C10 or C30 = Example 92 at 1, 3, 10 or 30 mg/kg ip) were injected into normal rats by intraperitonal administration (n = 5 for each treatment condition). One hour later, rats were examined in a 5 minute forced swim test. For each treatment condition, the number of 5-sec intervals culminating with a display of climbing was derived and plotted as the average +/- S.E.M. A significant increase in climbing was observed for rats injected with Example 92 at 10 mg/kg, relative to vehicle injected controls ($p < 0.01$, ANOVA and

Student-Nerman-Keuls), but not in rats dosed with Example 92 at 30 mg/kg ip.

Figure 3: Rat Forced Swim Test Results (Swimming: Normal Rats)

Vehicle (V) and test compounds (F10 = fluoxetine at 10 mg/kg ip; C1, C3, C10 or C30 = Example 92 at 1, 3, 10 or 30 mg/kg ip) were injected into normal rats by intraperitonal administration (n = 5 for each treatment condition). One hour later, rats were examined in a 5 minute forced swim test. For each treatment condition, the number of 5-sec intervals culminating with a display of swimming was derived and plotted as the average +/- S.E.M. A significant increase in swimming was observed for rats injected with fluoxetine at 10 mg/kg ip or with Example 92 at 30 mg/kg, relative to vehicle injected controls ($p < 0.01$, ANOVA and Student-Nerman-Keuls).

Figure 4: Social Interaction Test Results (Social Interaction: Unfamiliar Rats)

Vehicle (V) and test compounds (CLD 5 = chlordiazepoxide at 5 mg/kg ip; C10, C30 or C100 = Example 92 at 10, 30 or 100 mg/kg ip) were injected into normal rats by intraperitonal administration (n = 5 for each treatment condition). One hour later, unfamiliar rats were examined in a 15 minute social interaction test. For each treatment condition, the amount of time spent in social interaction was derived and plotted as the average +/- S.E.M. A significant increase in social interaction was observed for rats injected with chlordiazepoxide at 5 mg/kg i.p. or with Example 92 at 10 mg/kg ip ($p < 0.05$) as well as 30 mg/kg ($p < 0.01$). When the dose of Example

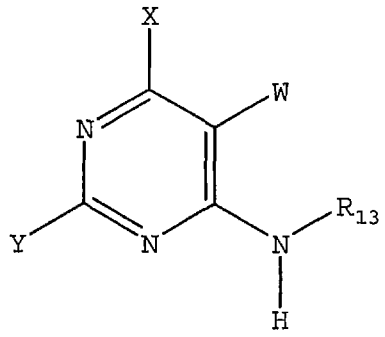
92 was increased to 100 mg/kg, the amount of social interaction time was significantly less than measured after chlordiazepoxide at 5 mg/kg ip or Example 92 at 30 mg/kg ip ($p < 0.01$). Significance in all cases was determined by ANOVA and Student-Nerman-Keuls.

Figure 5: Western Blot Results

In order to establish the specificity of the anti-GAL3 antiserum, membranes prepared from COS-7 cells transiently transfected with the rat recombinant GAL3 (Borowsky et al., 1999) (Lane 2) or mock-transfected (vector only) (Lane 3) were applied to an SDS-PAGE gel and blotted using the GAL3 receptor polyclonal antibody. Lane 1 corresponds to molecular weight marker. The anti-GAL3 antiserum labeled proteins in membranes only from rat GAL3-transfected cells (Lane 2); a predominant band was evident with an apparent molecular weight of approximately 56 kDa, (somewhat higher than the amino acid-derived value of 40.4 kDa). The apparently high molecular weight observed for rat GAL3 very likely reflects post-translational processing such as glycosylation; note that rat GAL3 contains multiple N-terminal glycosylation sites (Smith et al., 1998). Relative to the predominant band, additional species of higher molecular weight as well as lower molecular weight were labeled by the GAL3 antiserum. These are interpreted as protein aggregates of C-terminal fragments, as they are absent in mock-transfected cells.

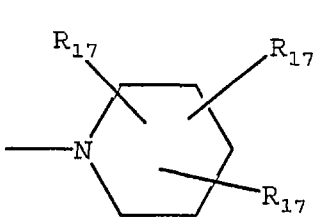
Detailed Description of the Invention

The present invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is; $NR_{11}R_{12}$;



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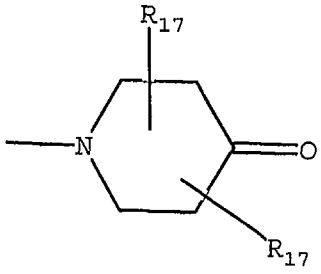
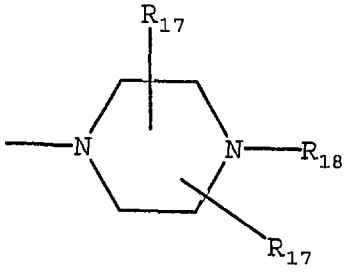


; or



;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl,

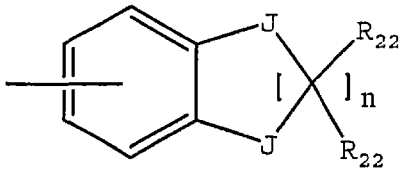
$(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl$(C_1$-$C_6)$alkyl, Q_1 or Q_2;

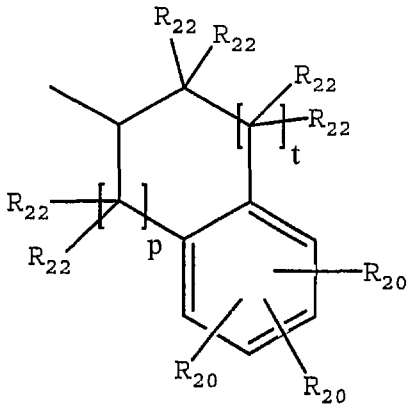
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

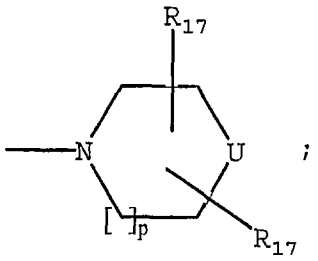


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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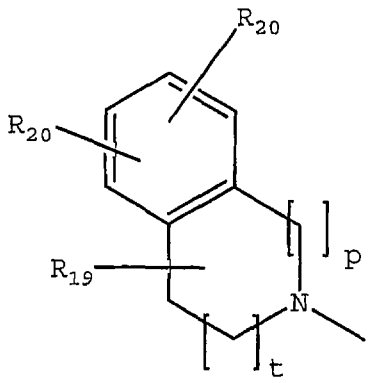
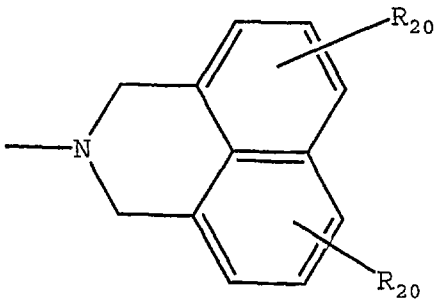


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl,

straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-

C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

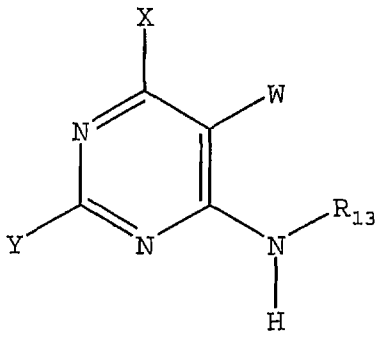
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

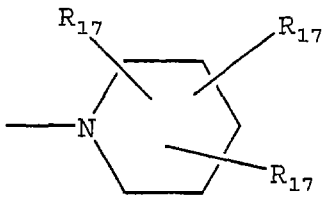
a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

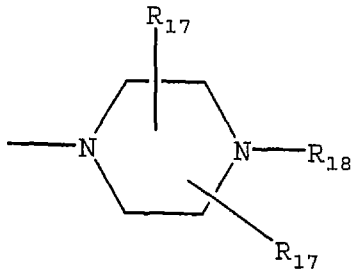


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



; or



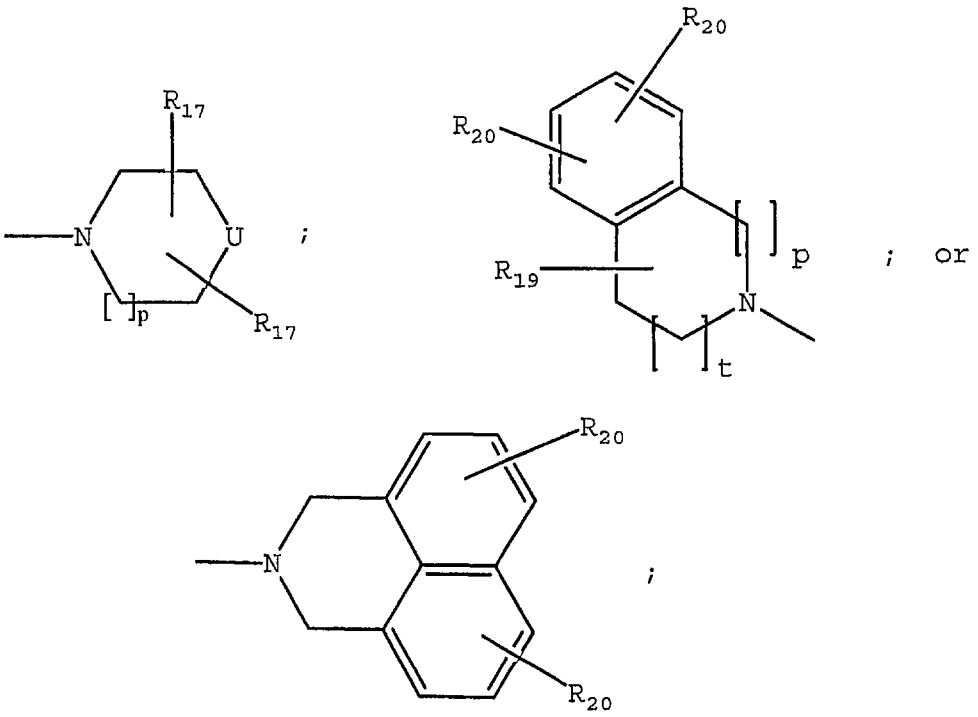
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein Y is $NR_{14}R_{15}$;



wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

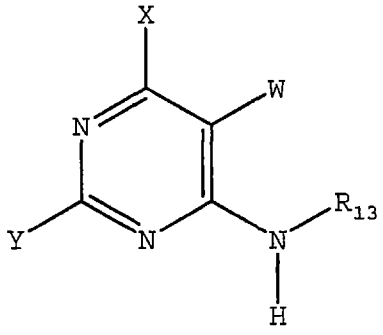
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

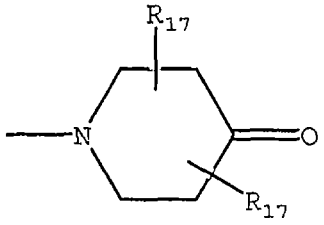
a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

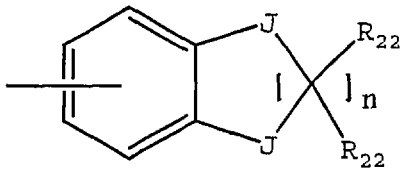
wherein X is $N(CH_3)_2$ or



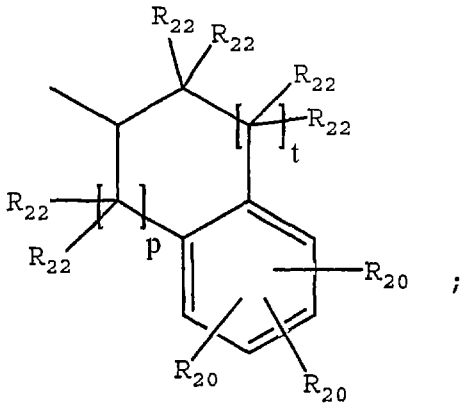
wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



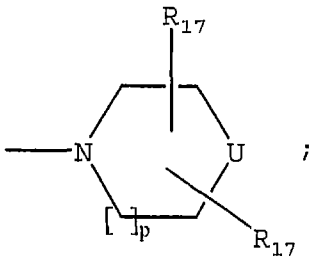
wherein Q_2 is



wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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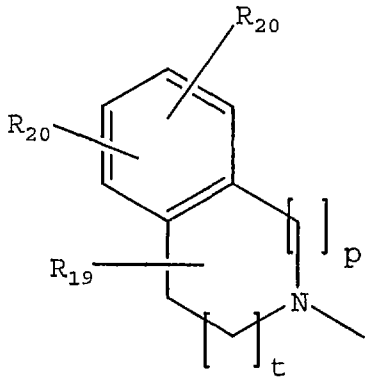
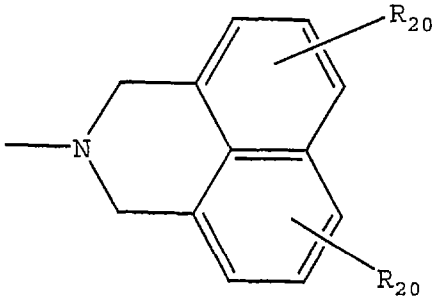


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or

branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

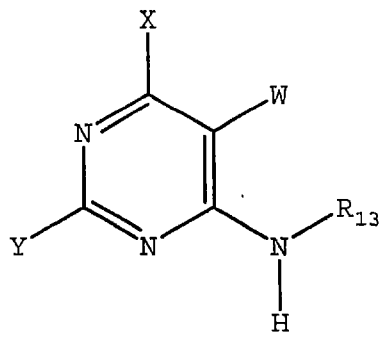
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

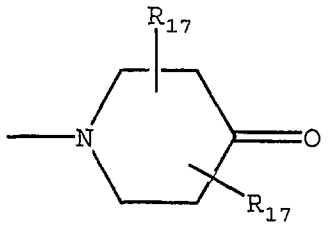
The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl,

propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q-O-(CH_2)_m-CH_3$, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m-Z$;

wherein R_{15} is $(C(R_{19})_2)_m-N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7

polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "bicyclic alkyl ring systems" includes, but is not limited to, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane and bicyclo[2.2.2]octane. In addition, the bicyclic alkyl ring systems may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_{21})_2$, $-OR_{21}$, $-COR_{21}$, -

CO_2R_{21}, $-CON(R_{21})_2$ or $(CH_2)_n-O-(CH_2)_m-CH_3$.

As used in the present invention, the term "cycloalkyl" includes, C_3-C_7 cycloalkyl moieties which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n-O-(CH_2)_m-CH_3$.

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n-O-(CH_2)_m-CH_3$.

As used in the present invention, the term "cycloalkenyl" includes, C_5-C_7 cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight

chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or

branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

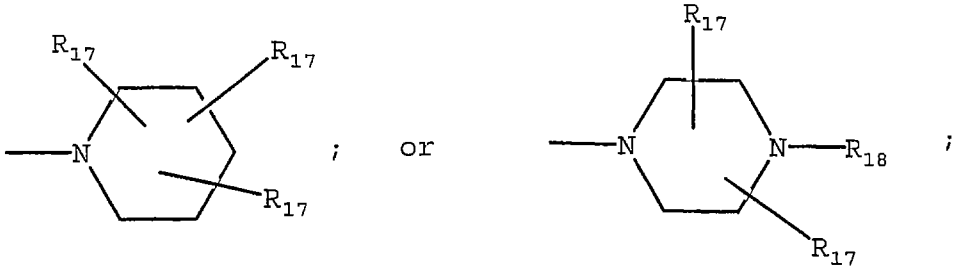
The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In one embodiment of any of the methods described herein, the compound is enantiomerically and diasteriomerically pure. In one embodiment, the compound is enantiomerically or diasteriomerically pure.

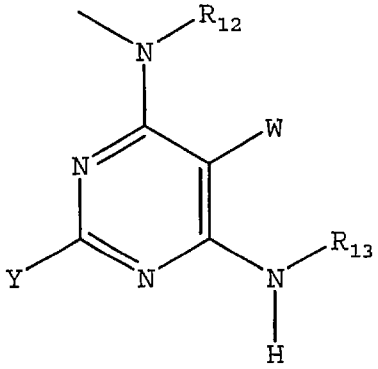
In one embodiment of any of the methods described herein, the compound can be administered orally.

In one embodiment, X is:



In one embodiment, X is $NR_{11}R_{12}$ and R_{11} is H or straight chained or branched C_1-C_7 alkyl.

In one embodiment, the compound has the structure:

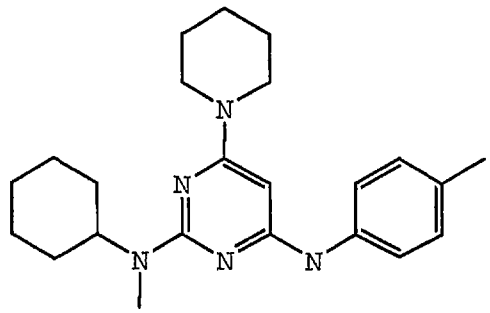


In one embodiment, R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

In one embodiment, R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

In one embodiment, R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

In one embodiment, the compound is selected from the group consisting of: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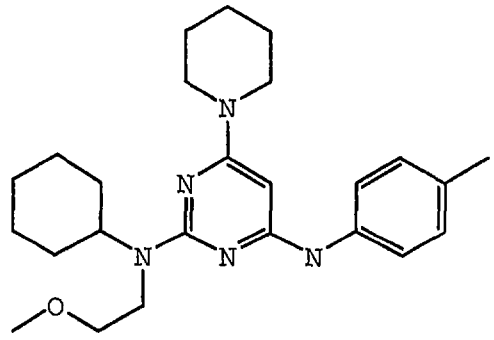
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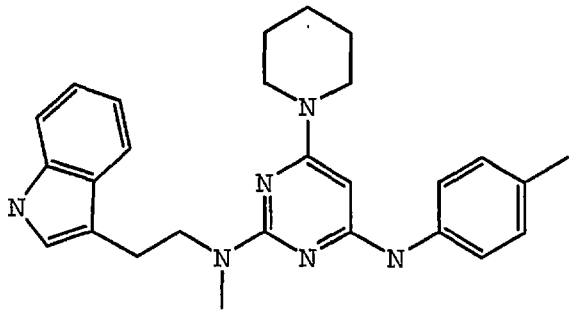
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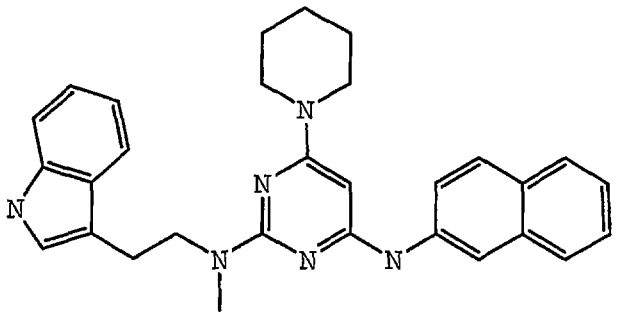
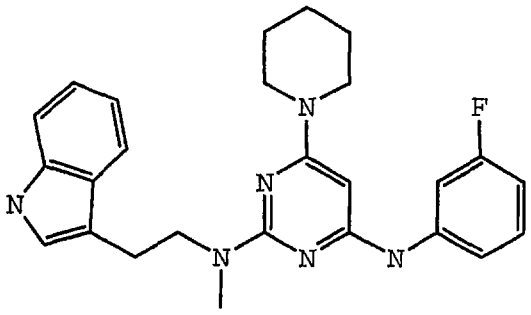


;



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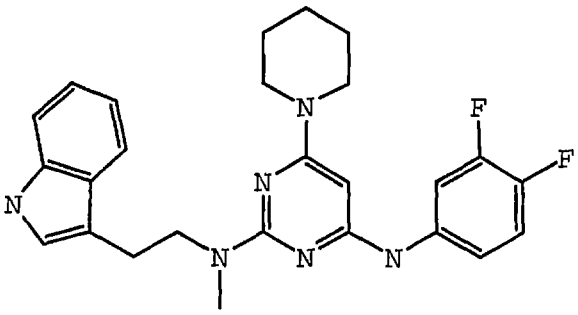

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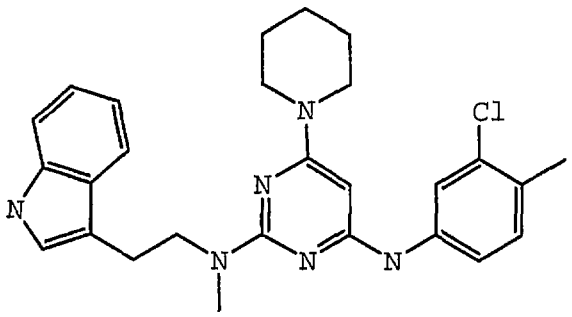
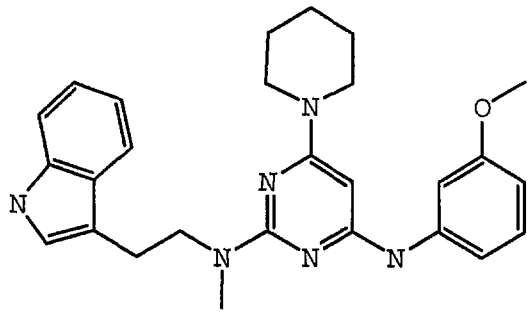
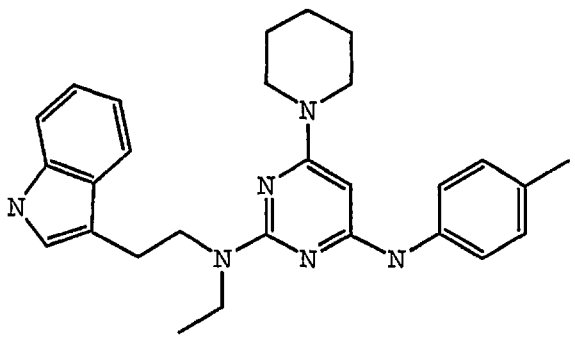

N
Cl
N
N
N
N
N

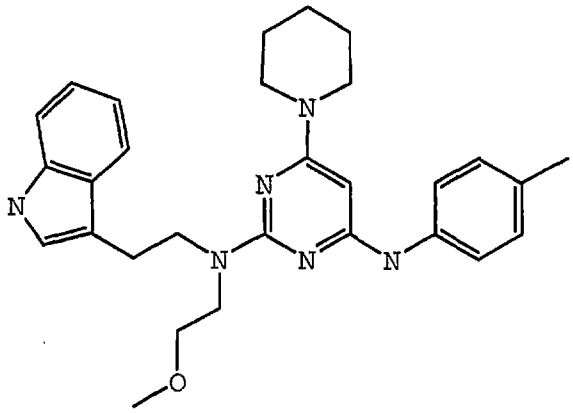
;


N
O
N
N
N
N
N

;


N
N
N
N
N
N

;



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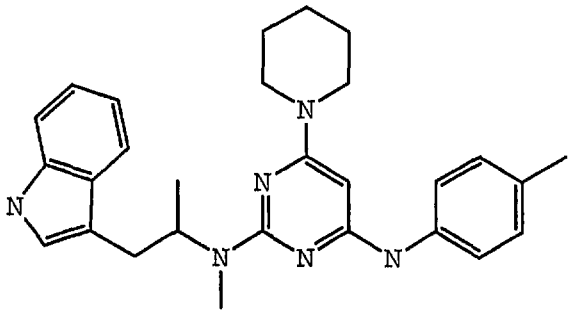

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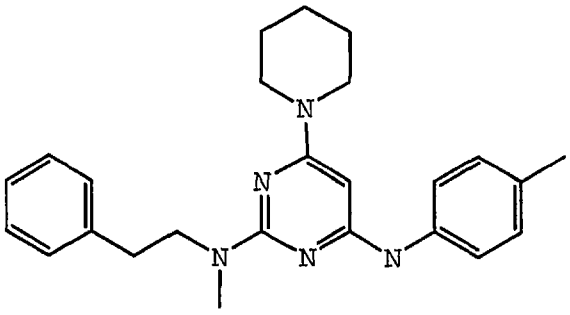
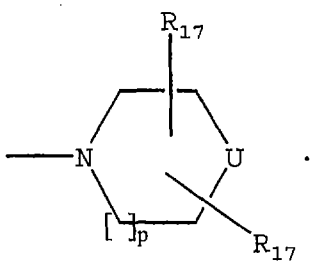


.

In one embodiment, Y is

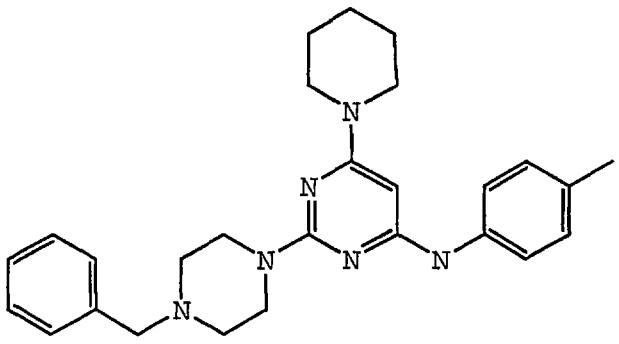


In one embodiment, U is NR_{16}.

In one embodiment, R_{16} is $(CH_2)_m$-Z.

In one embodiment, Z is aryl or heteroaryl.

In one embodiment, the compound is selected from the group consisting of:



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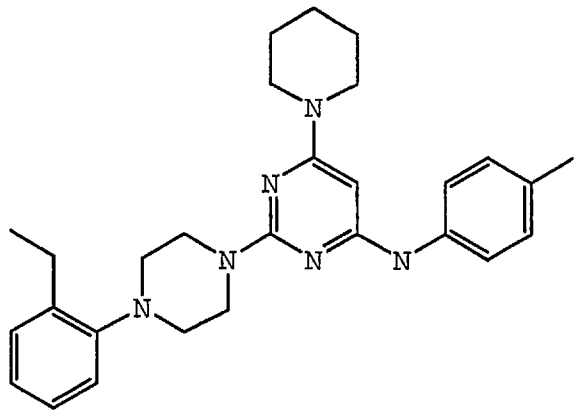

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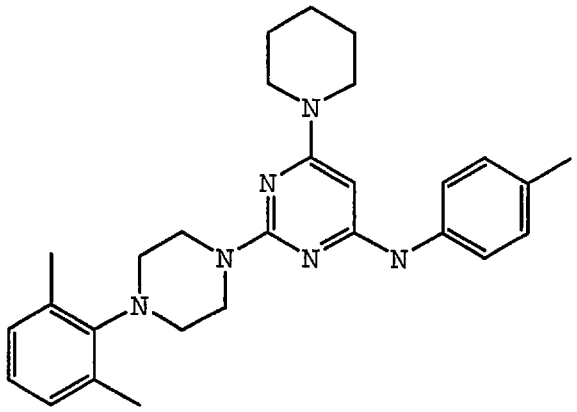

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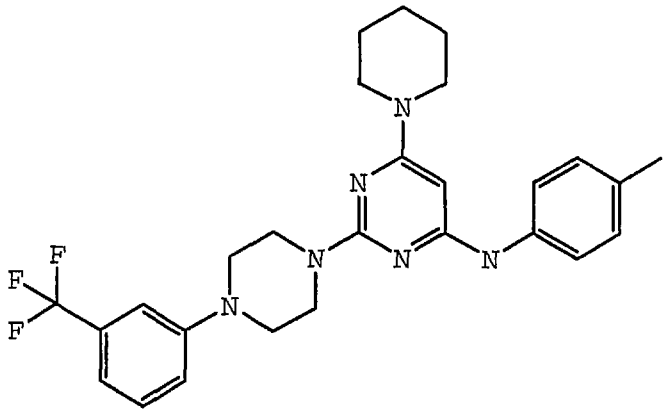

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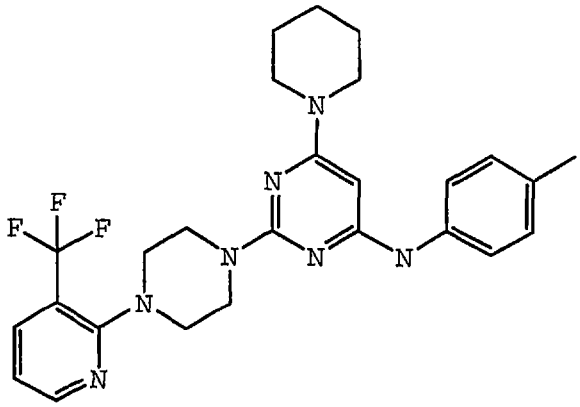
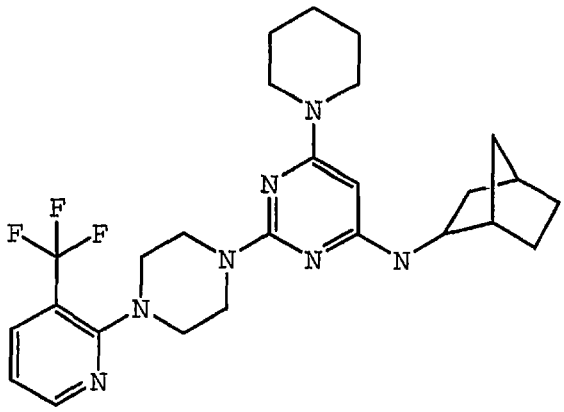
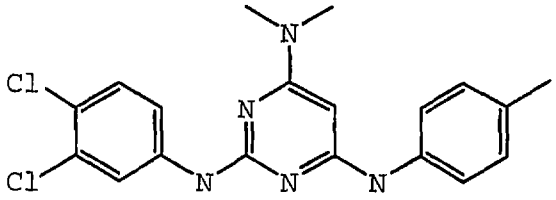


; and



.

In one embodiment, the compound is selected from the group consisting of:



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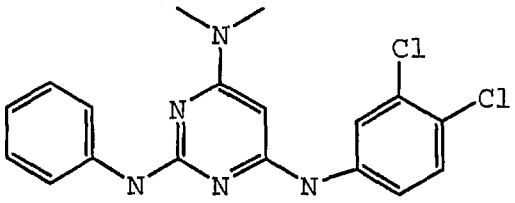

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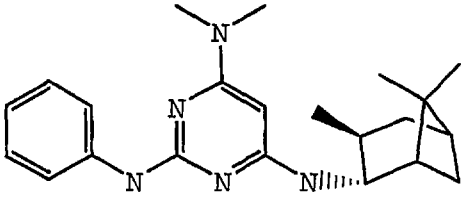

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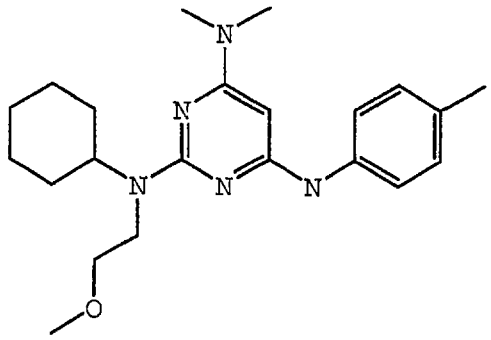

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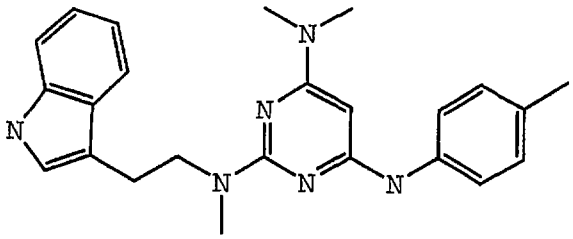
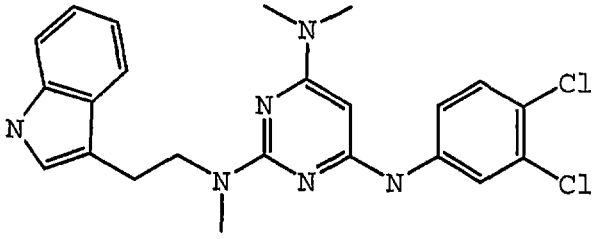
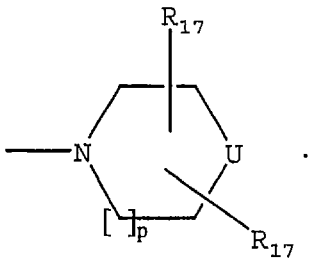


; and

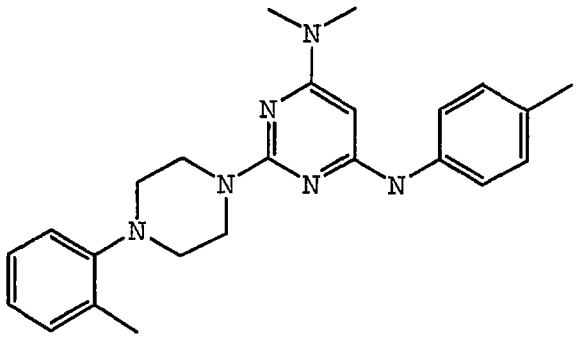


In one embodiment, Y is

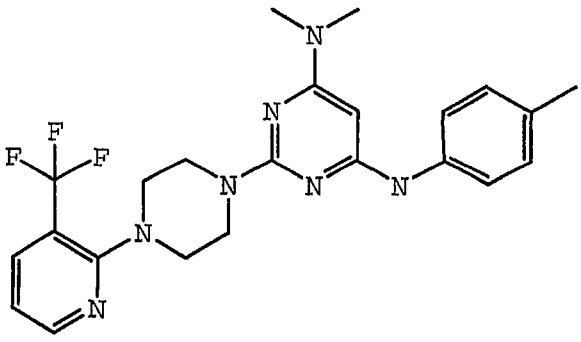


In one embodiment, U is NR_{16}.

In one embodiment, the compound is

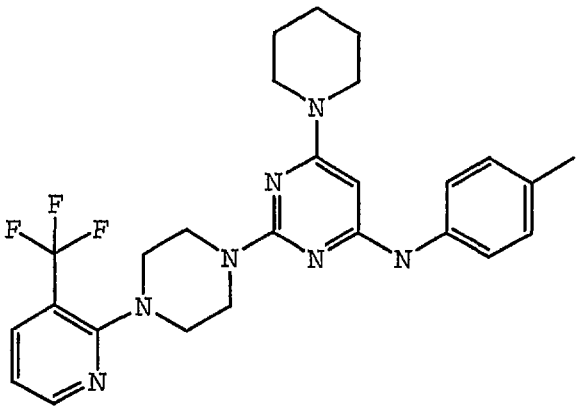


; or

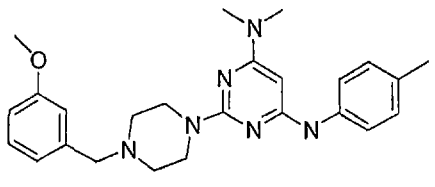


.

In one embodiment, the compound is



In one embodiment, the compound is selected from the group consisting of: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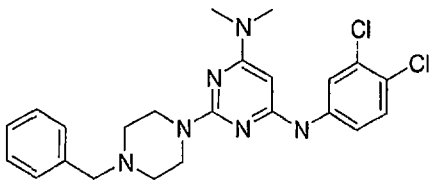
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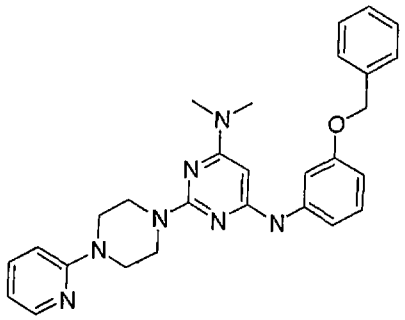
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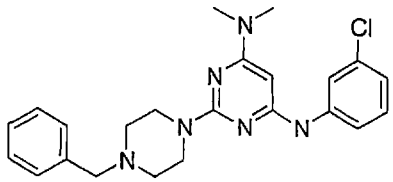
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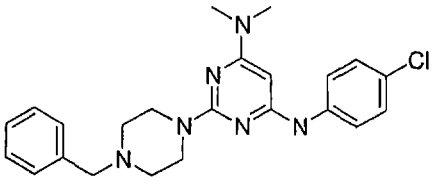
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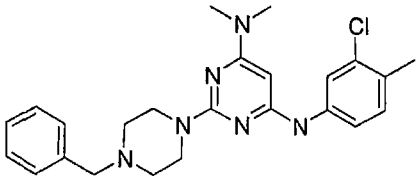
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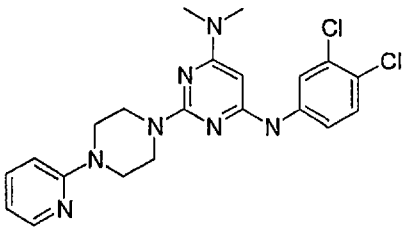
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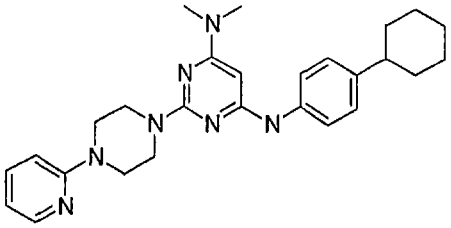
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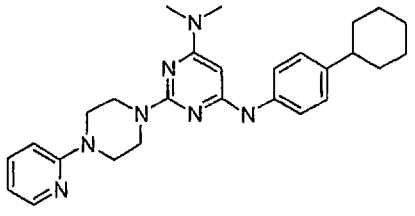
In one embodiment, the compound is selected from the group consisting of: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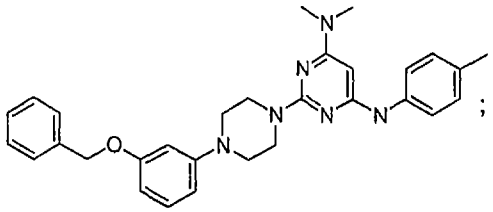
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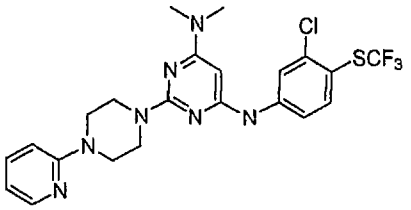
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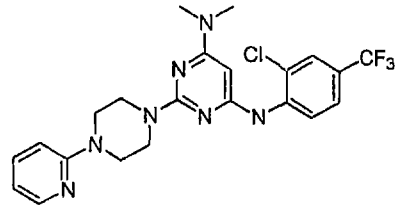
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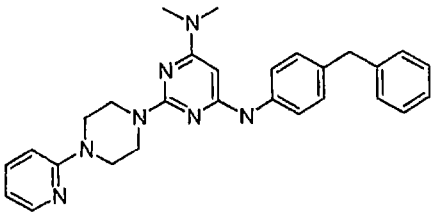
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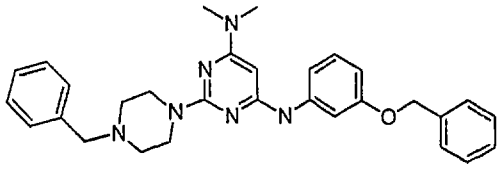
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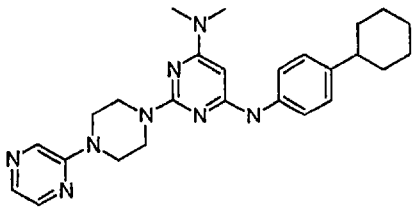
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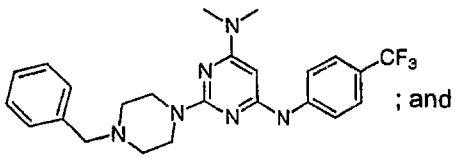
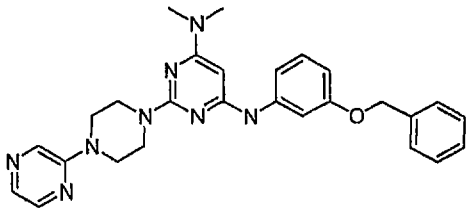
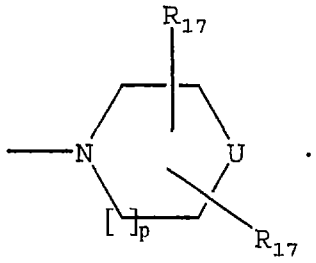

; and


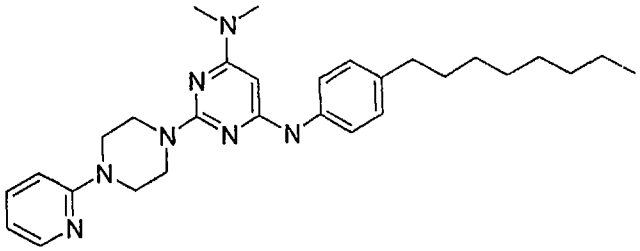
In one embodiment, X is $N(CH_3)_2$.

In one embodiment, Y is

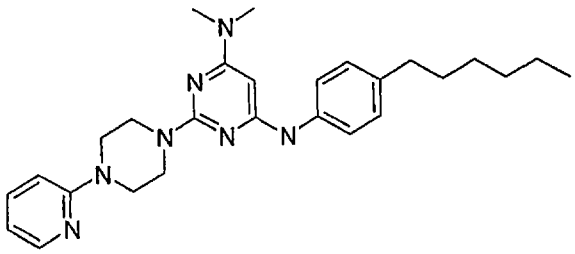


In one embodiment, R_{13} is an aryl substituted with a C_1-C_{10} straight chained alkyl.

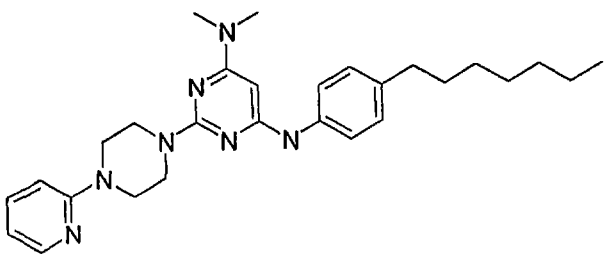
In one embodiment, the compound is selected from a group consisting of:



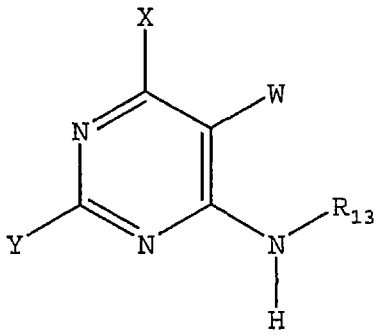
;



; and

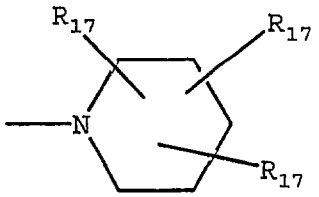


The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

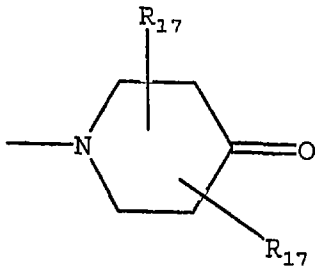


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

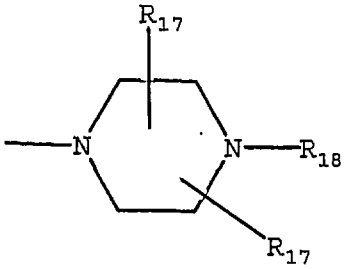
wherein X is; $NR_{11}R_{12}$;



;



; or



;

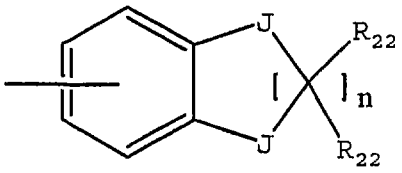
wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-C_6)alkyl, Q_1 or Q_2;

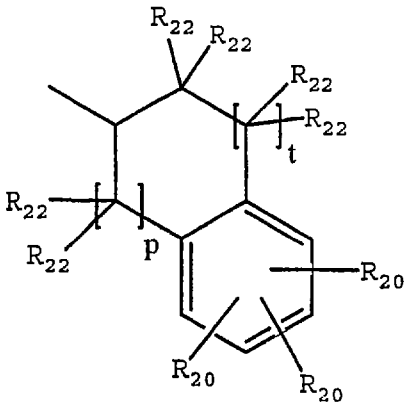
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is



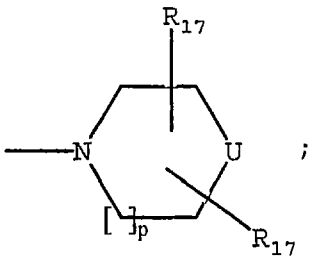
;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl,

monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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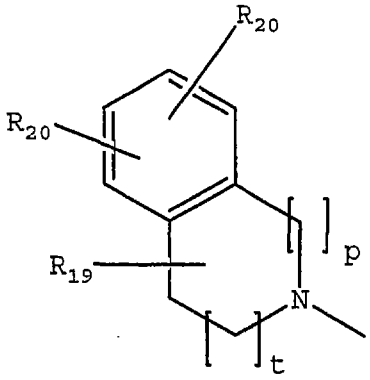
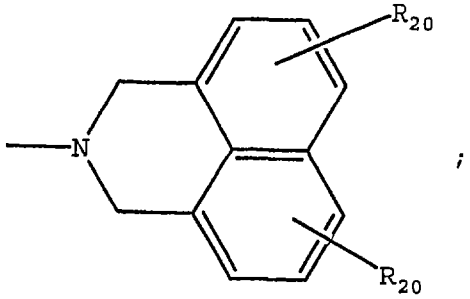


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl,

straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

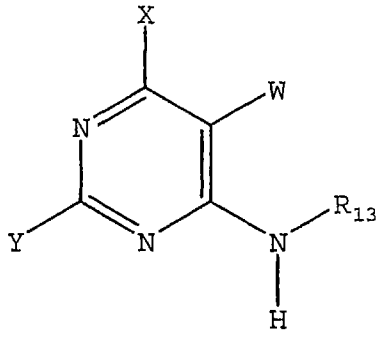
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

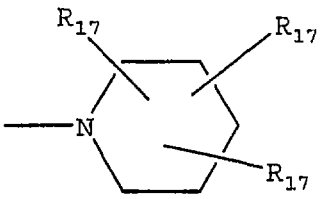
a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

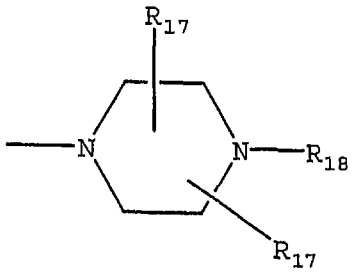


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



; or



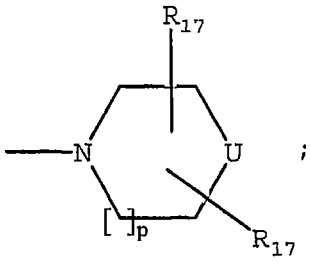
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl(C_1-C_6)alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;



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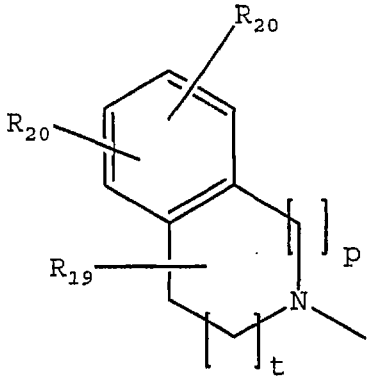
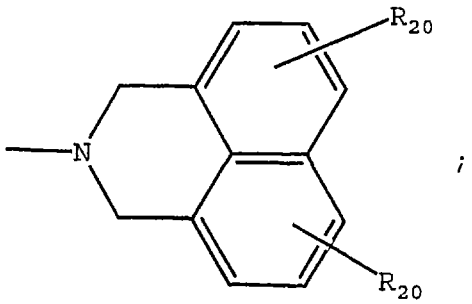


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

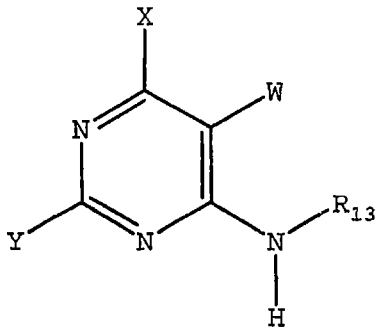
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

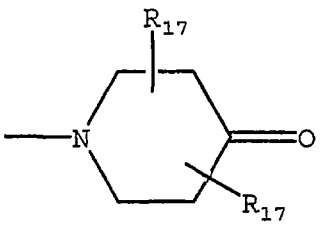
a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or

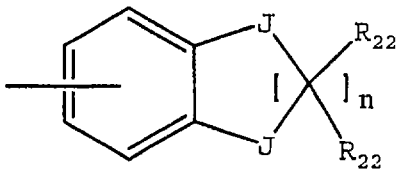


;

wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

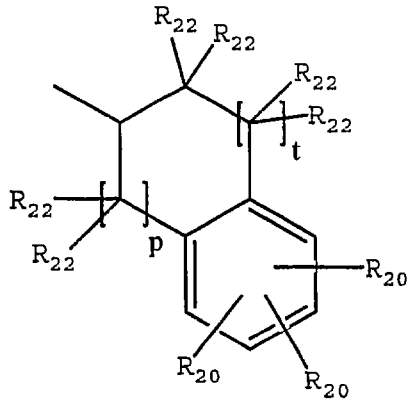
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

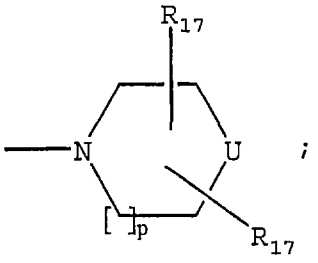


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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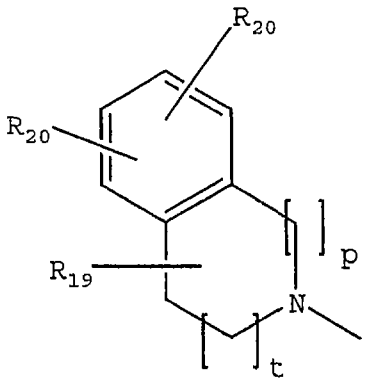
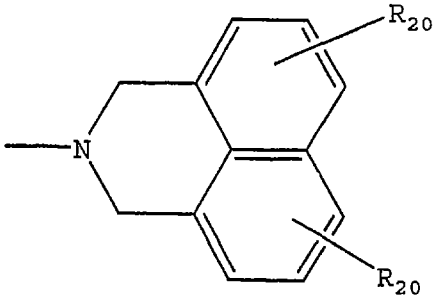


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl,

straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

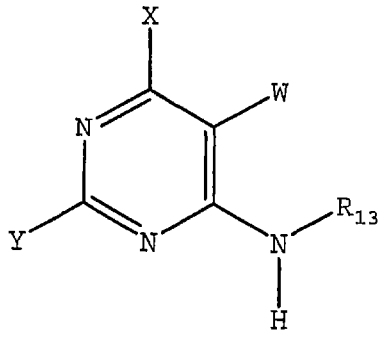
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

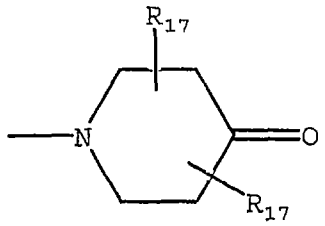
a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "bicyclic alkyl ring systems" includes, but is not limited to, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane and bicyclo[2.2.2]octane. In addition, the bicyclic alkyl ring systems may be substituted with one or more of the following: -F, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_{21})_2$, -OR_{21}, -COR_{21}, -CO_2R_{21}, -$CON(R_{21})_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkyl" includes, C_3-C_7 cycloalkyl moieties which may be

substituted with one or more of the following: -F, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with one or more of the following: -F, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkenyl" includes, C_5-C_7 cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

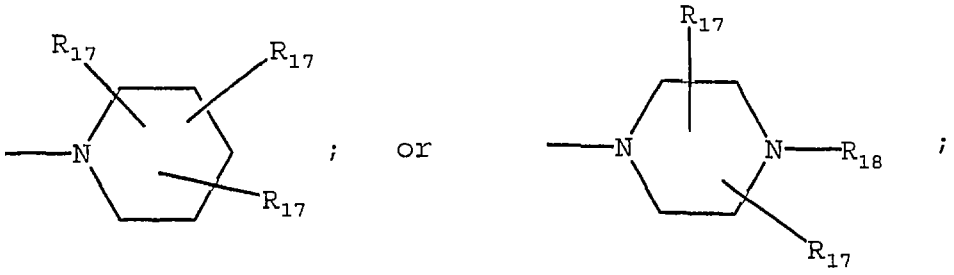
The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In one embodiment of any of the methods described herein, the compound is enantiomerically and diasteriomerically pure. In one embodiment, the compound is enantiomerically or diasteriomerically pure.

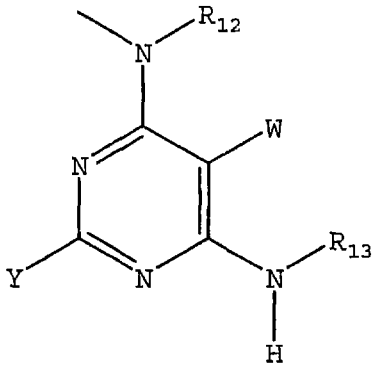
In one embodiment, the compound can be administered orally.

In one embodiment, X is:



In one embodiment, X is $NR_{11}R_{12}$ and R_{11} is H or straight chained or branched C_1-C_7 alkyl.

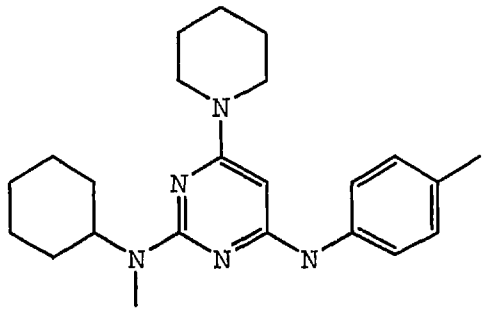
In one embodiment, the compound has the structure:



In one embodiment, R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

In one embodiment, R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

In one embodiment, the compound is selected from the group consisting of: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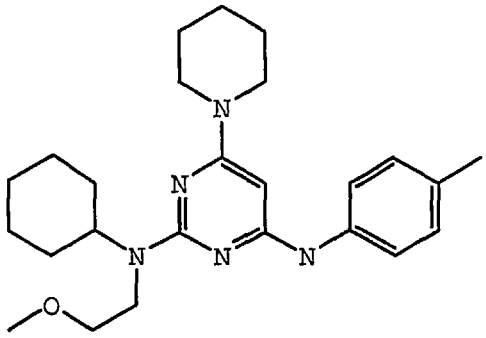
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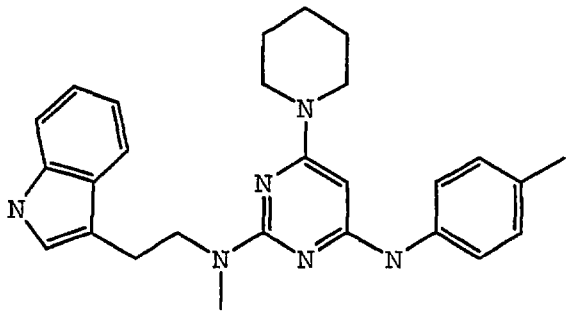
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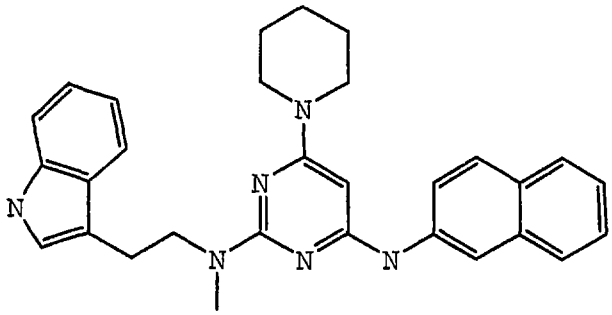

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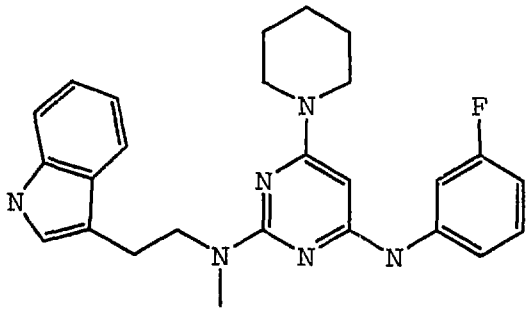

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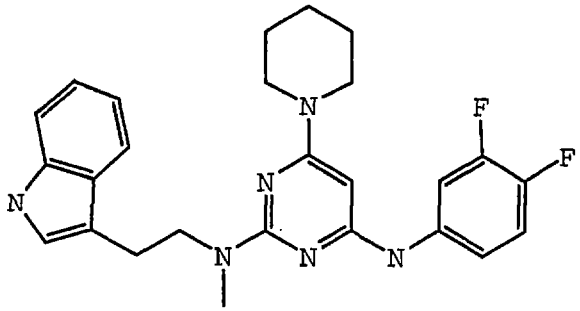

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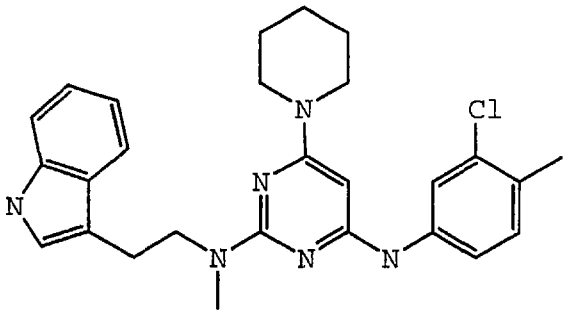

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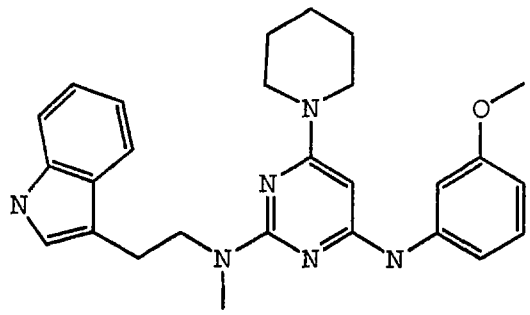

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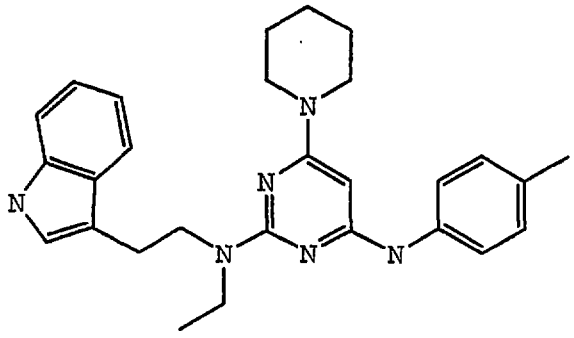

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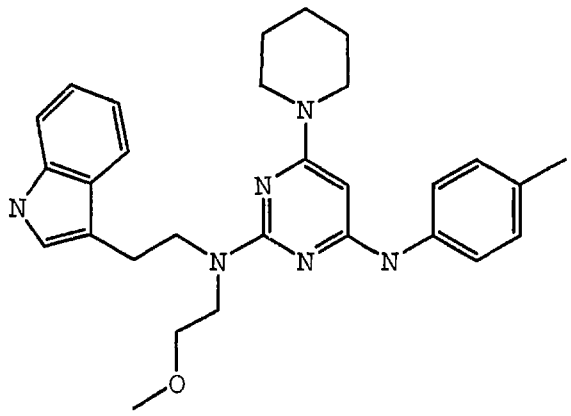
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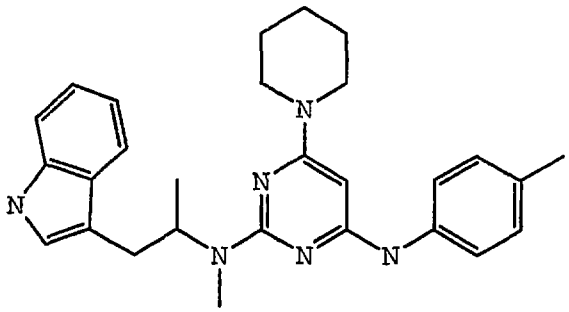
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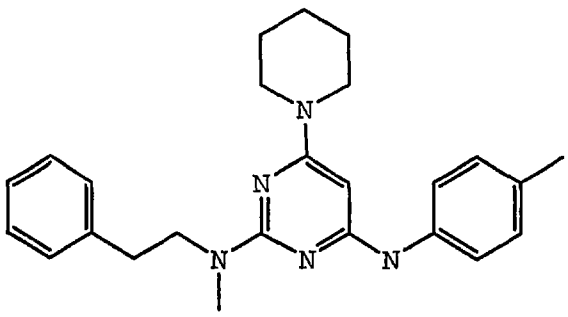
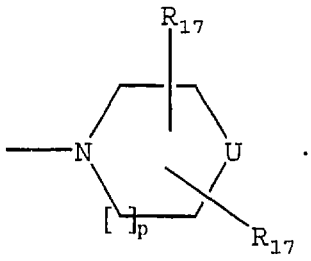

.

In one embodiment, Y is

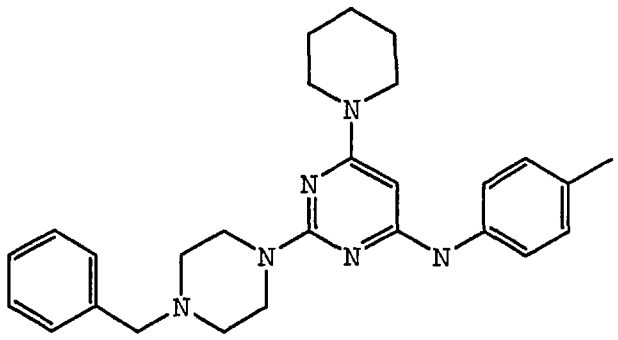


In one embodiment, U is NR_{16}.

In one embodiment, R_{16} is $(CH_2)_m$-Z.

In one embodiment, Z is aryl or heteroaryl.

In one embodiment, the compound is selected from the group consisting of:



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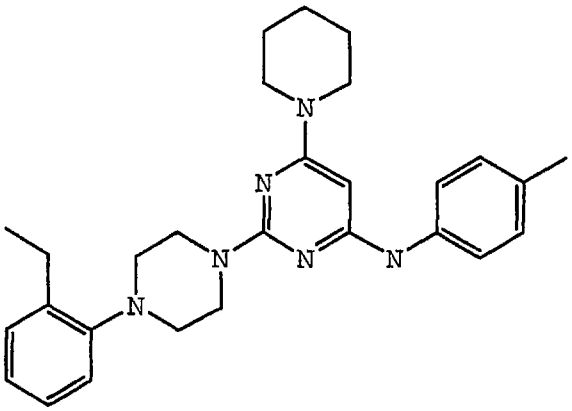

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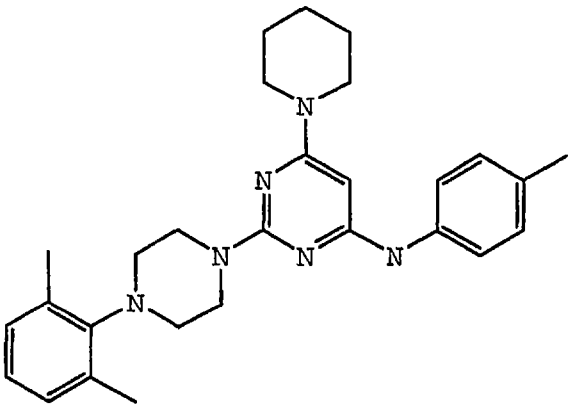

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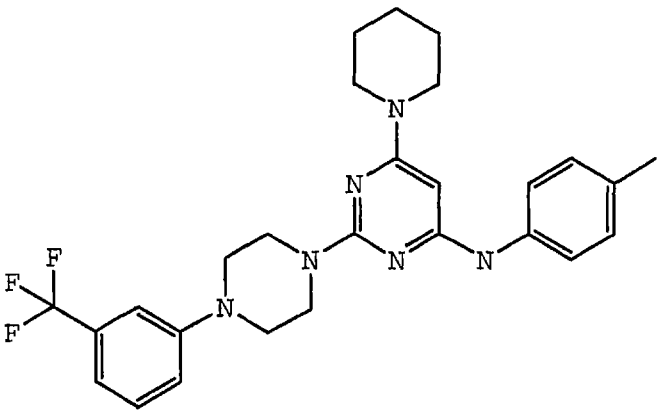

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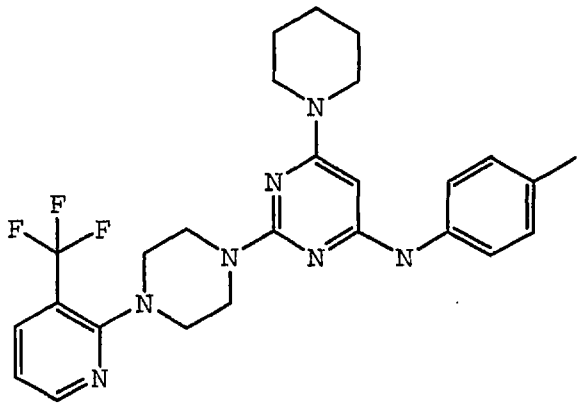
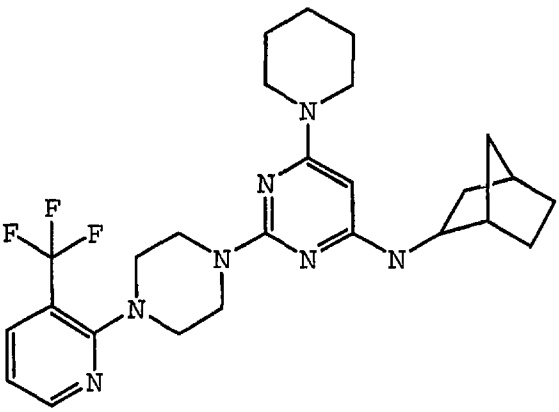
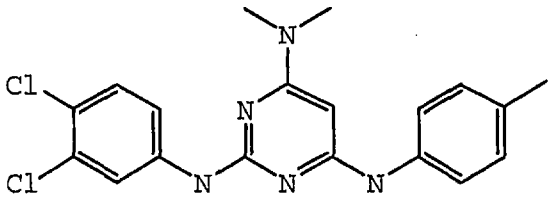


; and



.

In one embodiment, the compound is selected from the group consisting of:



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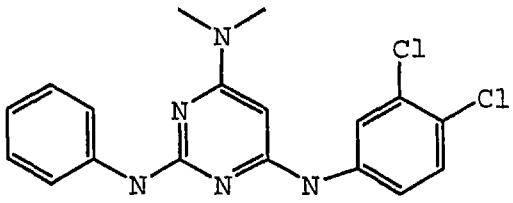

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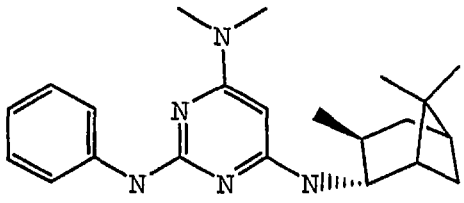

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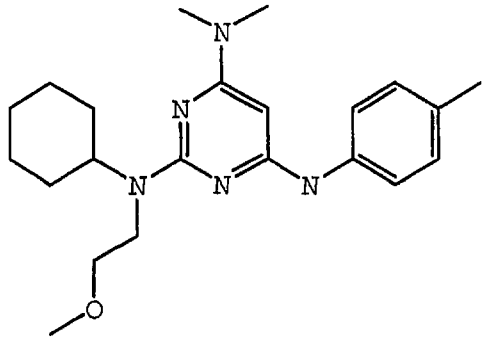

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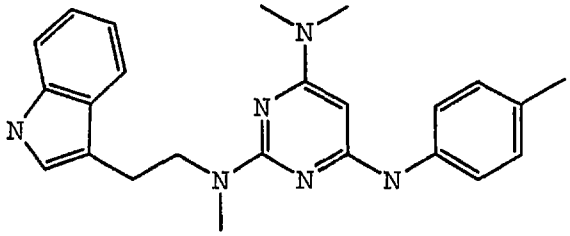
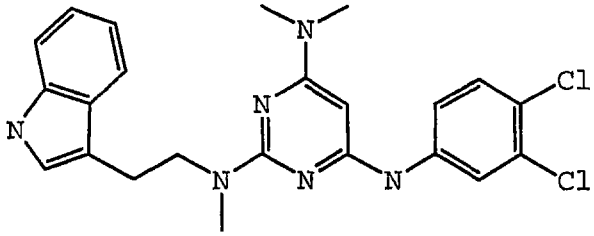
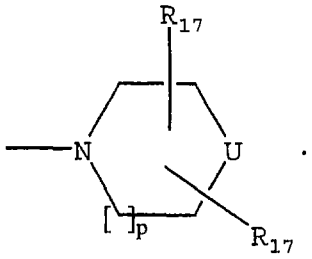


; and



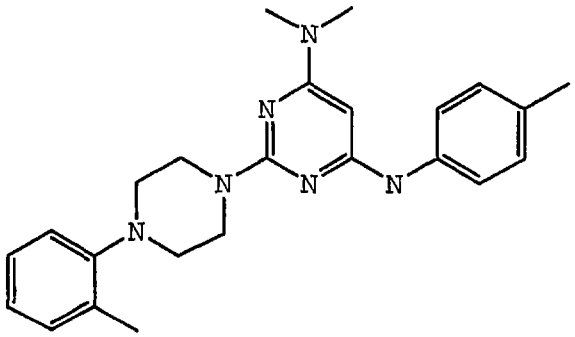
.

In one embodiment, Y is

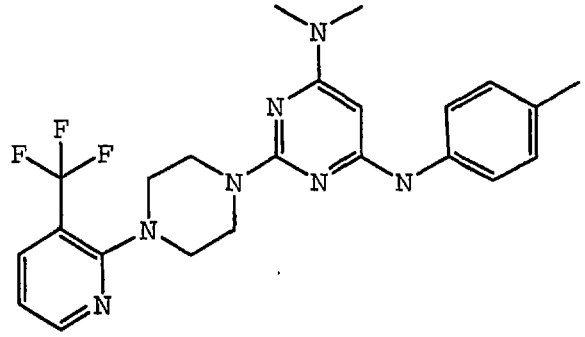


In one embodiment, U is NR_{16}.

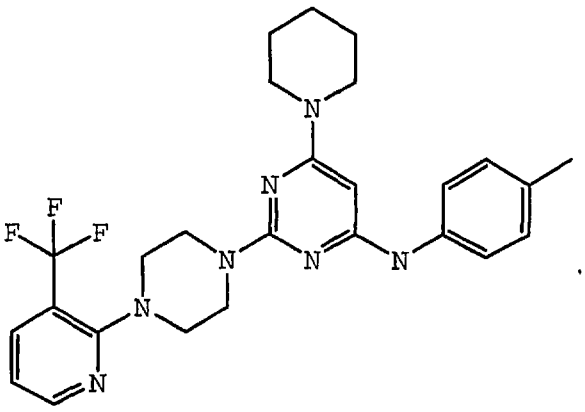
In one embodiment, the compound is



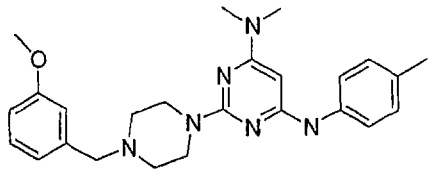
; or



In one embodiment, the compound is



In one embodiment, the compound is selected from the group consisting of: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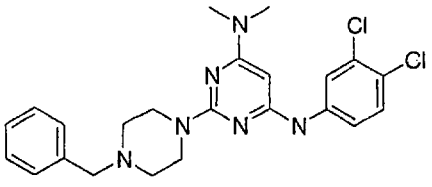
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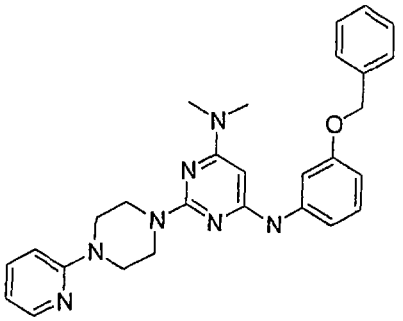
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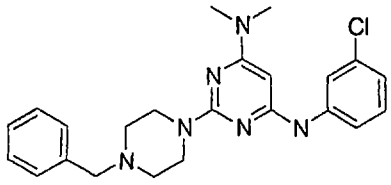
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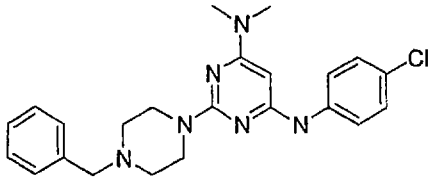
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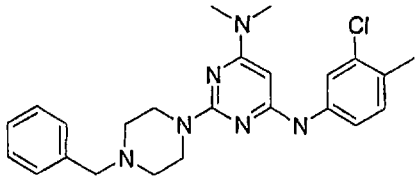
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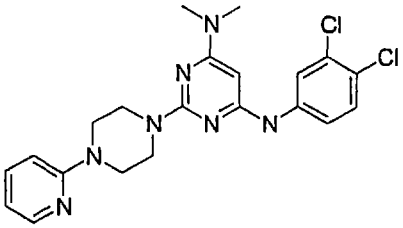
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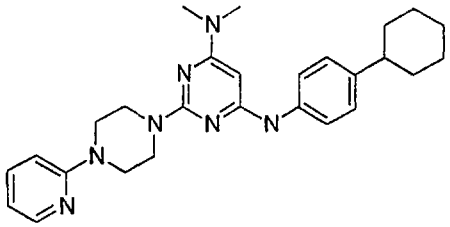
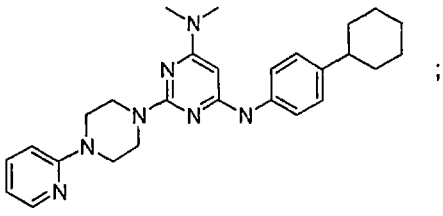

.

In one embodiment, the compound is selected from the group consisting of: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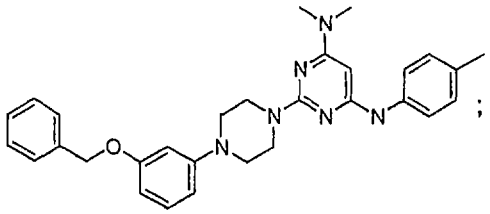
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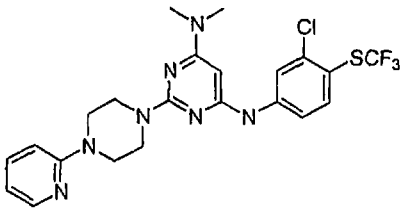
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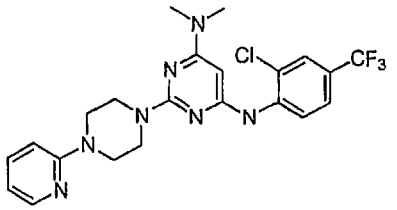
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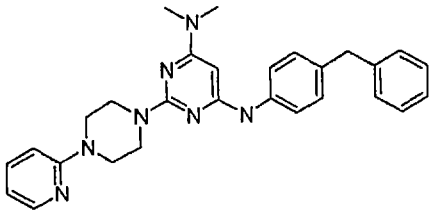
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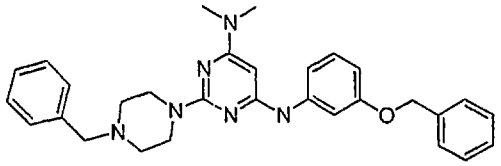
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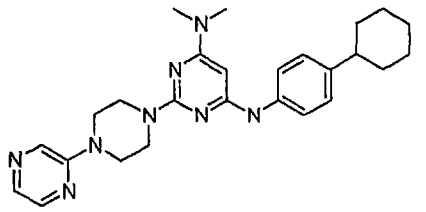
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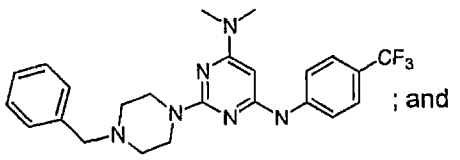
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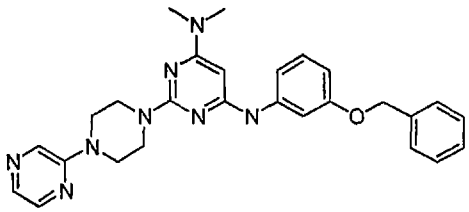
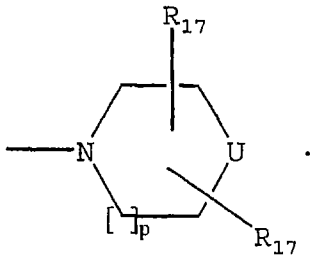


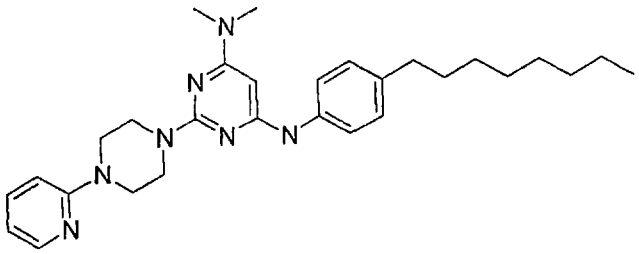
In one embodiment, X is $N(CH_3)_2$.

In one embodiment, Y is



In one embodiment, R_{13} is an aryl substituted with a C_1-C_{10} straight chained alkyl.

In one embodiment, the compound is selected from a group consisting of:



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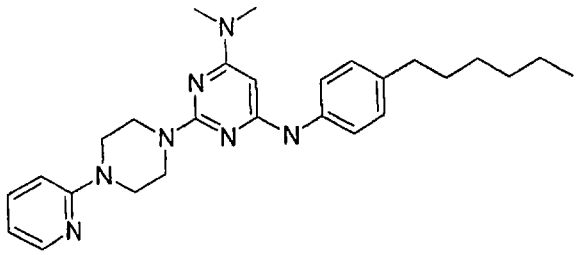
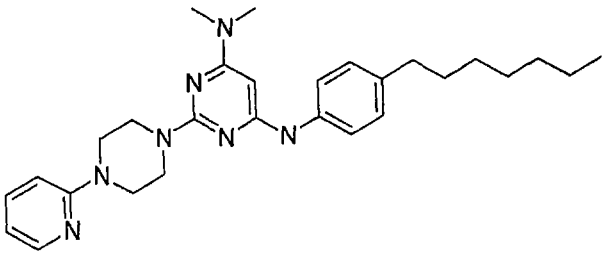
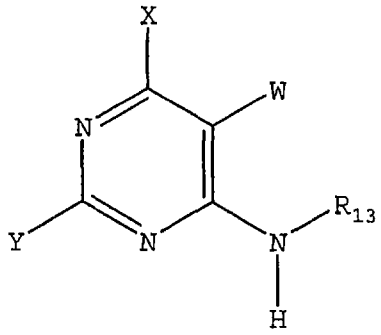


; and

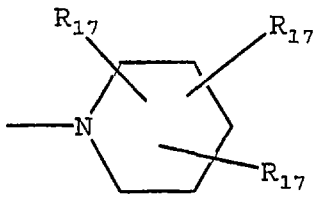


The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

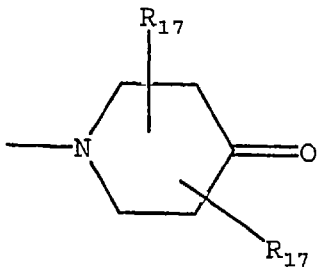


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

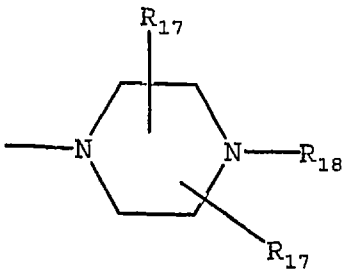
wherein X is; $NR_{11}R_{12}$;



;



; or



;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

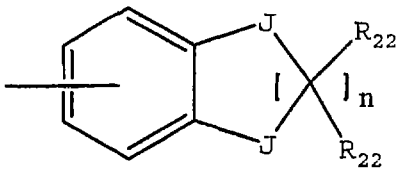
wherein R_{12} is straight chained or branched C_1-C_7 alkyl,

$(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-C_6)alkyl, Q_1 or Q_2;

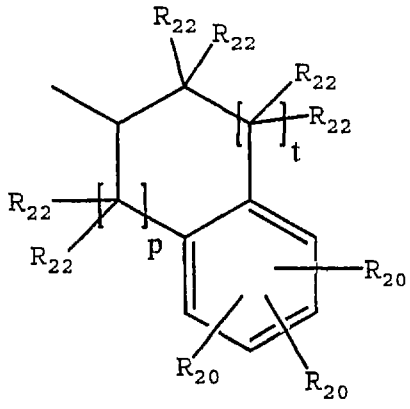
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is



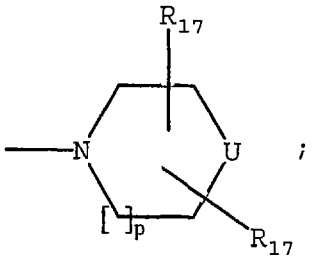
;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or

branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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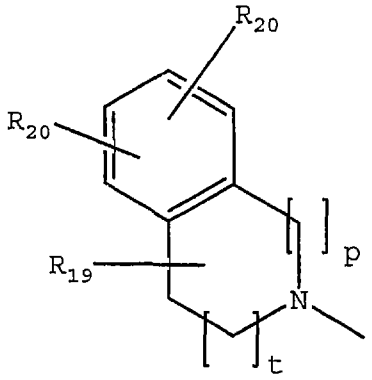
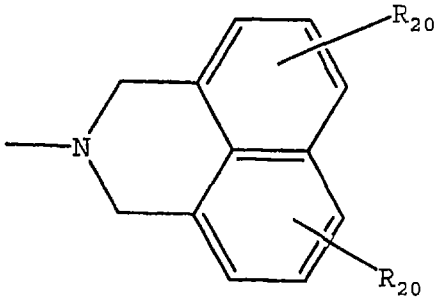


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight

chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

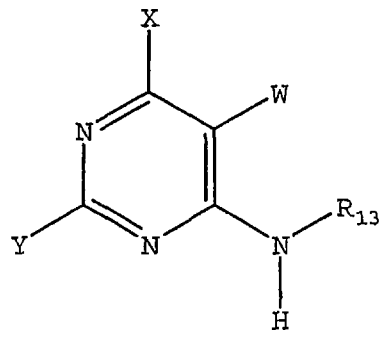
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

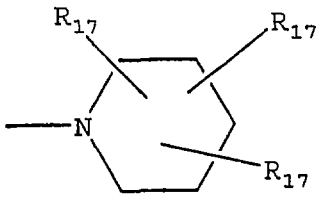
a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

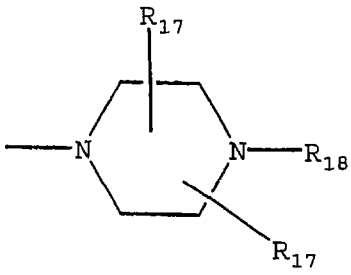


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



; or



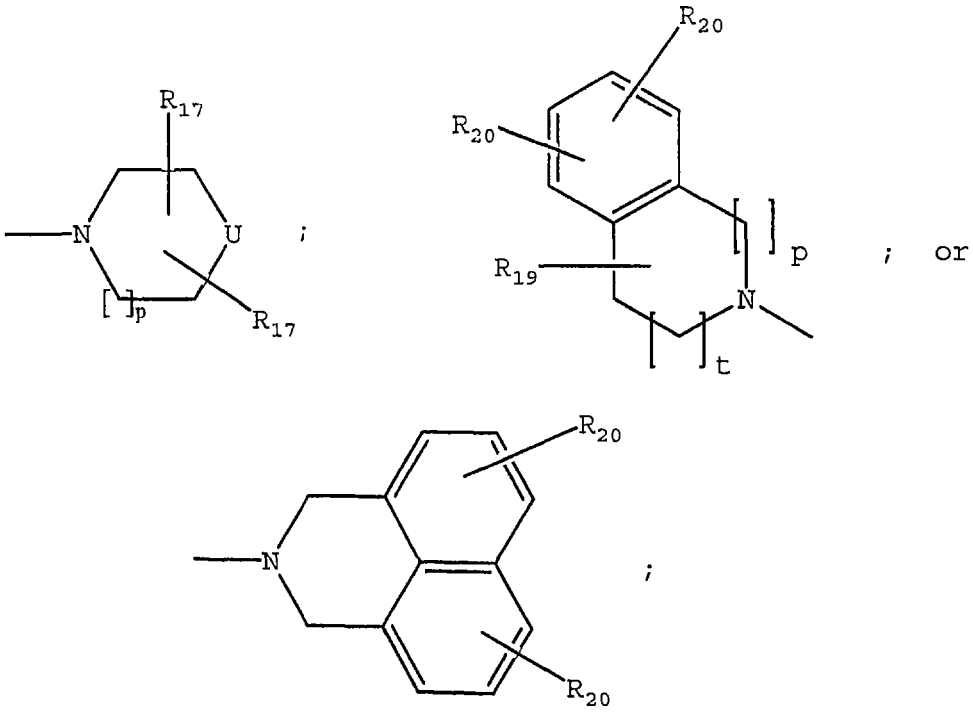
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl(C_1-C_6)alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;



wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

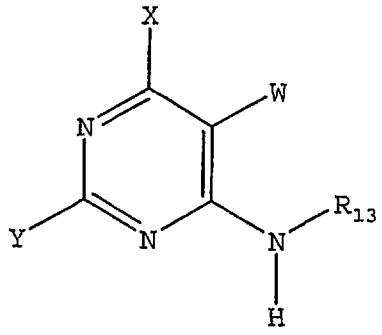
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

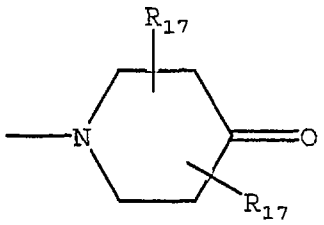
a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

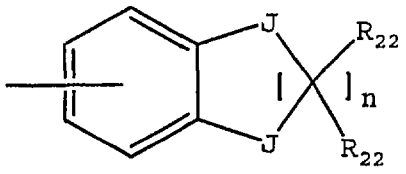
wherein X is $N(CH_3)_2$ or



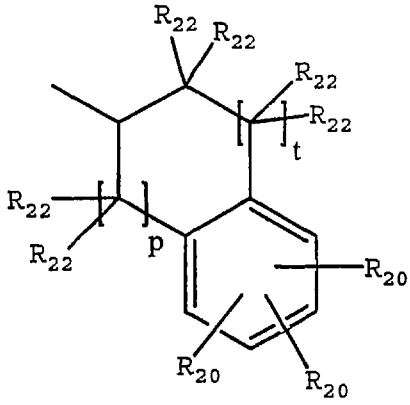
wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



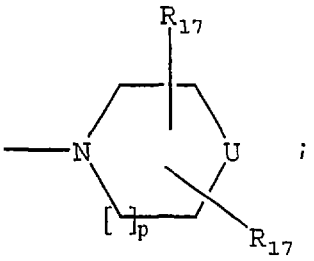
wherein Q_2 is



wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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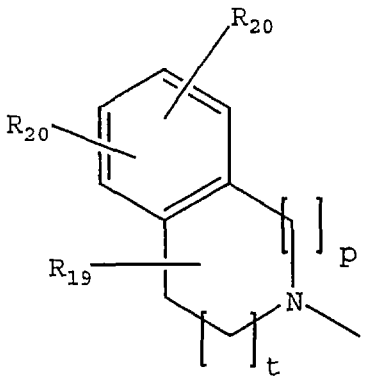
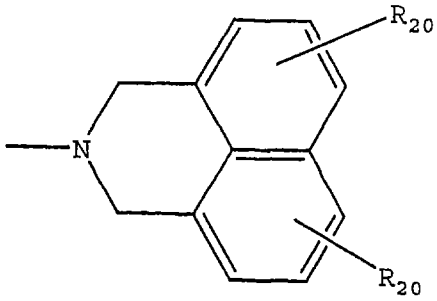


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or

branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

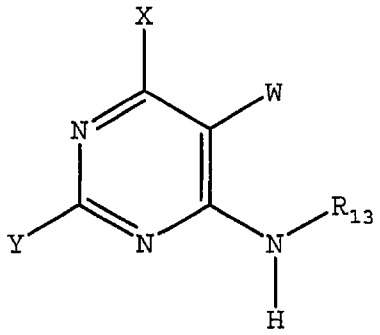
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

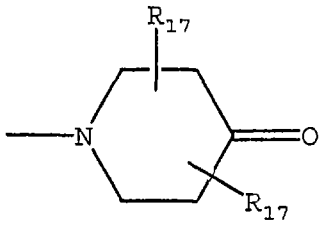
a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21},

$-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "bicyclic alkyl ring systems" includes, but is not limited to, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane and bicyclo[2.2.2]octane. In addition, the bicyclic alkyl ring systems may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7

polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_{21})_2$, $-OR_{21}$, $-COR_{21}$, $-CO_2R_{21}$, $-CON(R_{21})_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkyl" includes, C_3-C_7 cycloalkyl moieties which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkenyl" includes, C_5-C_7 cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7

alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN,

straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

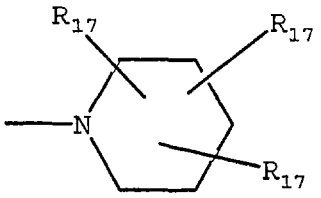
The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

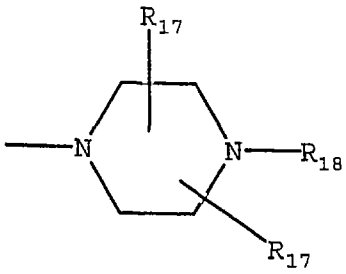
In one embodiment of any of the pharmaceutical compositions described herein, the compound is enantiomerically and diasteriomerically pure. In one embodiment the compound is enantiomerically or diasteriomerically pure.

In one embodiment of any of the pharmaceutical compositions described herein, the compound can be administered orally.

In one embodiment, X is:



; or



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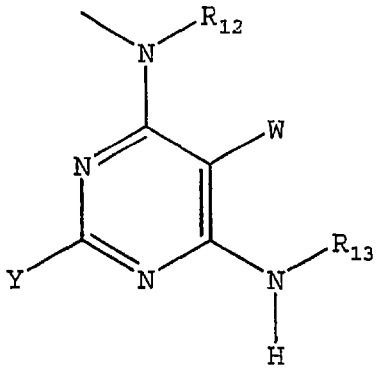
In one embodiment, X is $NR_{11}R_{12}$ and R_{11} is H or straight chained or branched C_1-C_7 alkyl.

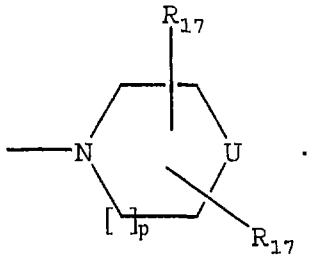
In one embodiment, the compound has the structure:



In one embodiment, R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

In one embodiment, R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

In one embodiment, Y is

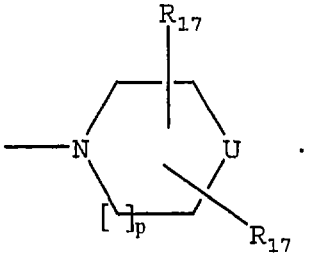


In one embodiment, U is NR_{16}.

In one embodiment, R_{16} is $(CH_2)_m$-Z.

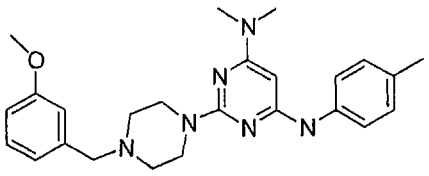
In one embodiment, Z is aryl or heteroaryl.

In one embodiment, Y is



In one embodiment, U is NR_{16}.

In one embodiment, the compound is selected from the group consisting of: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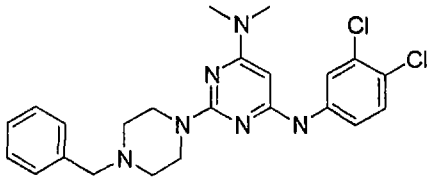
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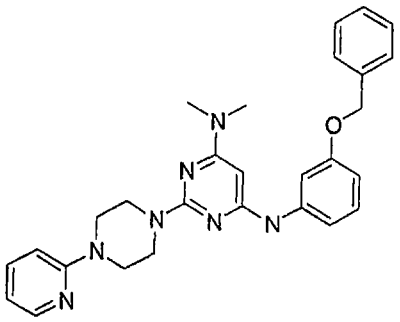
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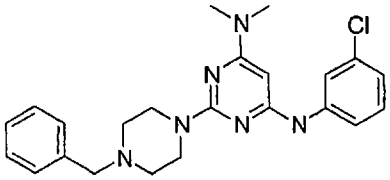
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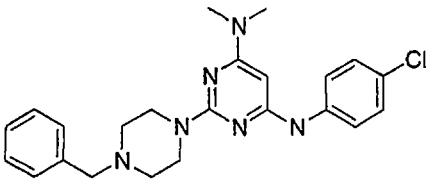
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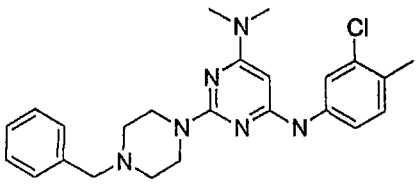
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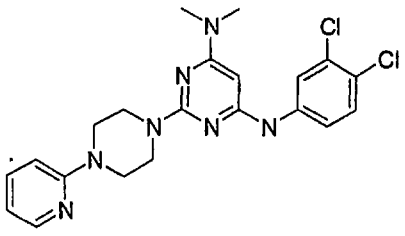
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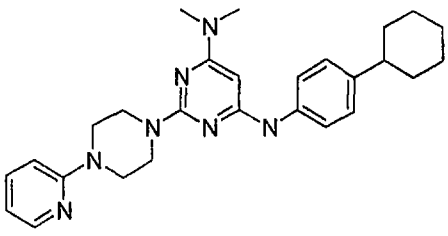
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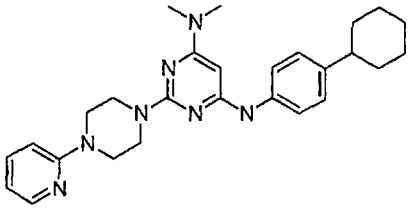
In one embodiment, compound is selected from the group consisting of: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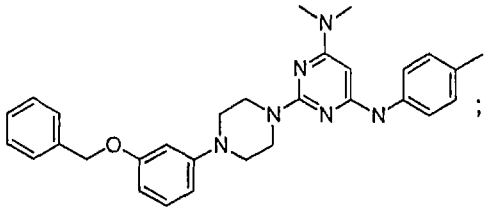
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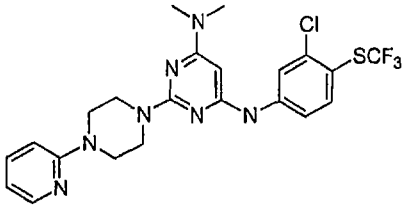
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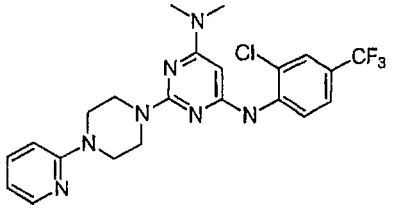
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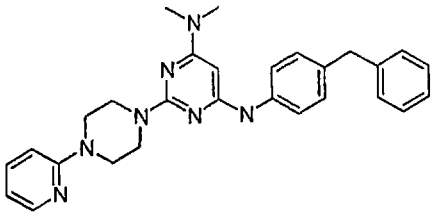
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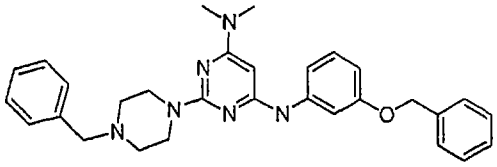

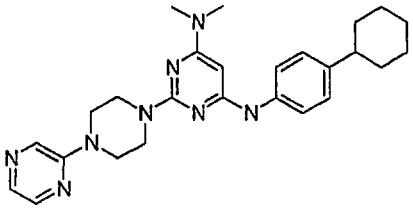
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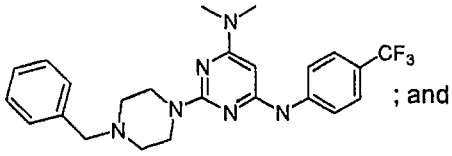
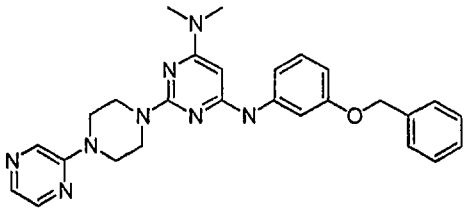

; and



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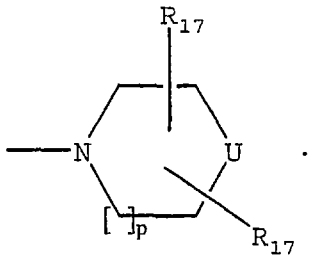
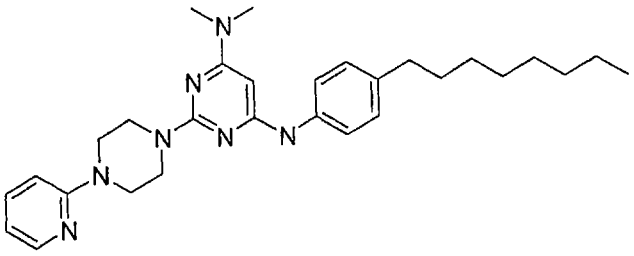
In one embodiment, X is $N(CH_3)_2$.

In one embodiment, Y is



In one embodiment, R_{13} is an aryl substituted with a C_1-C_{10} straight chained alkyl.

In one embodiment, the compound is selected from a group consisting of: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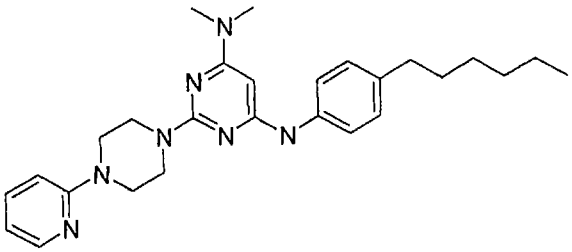
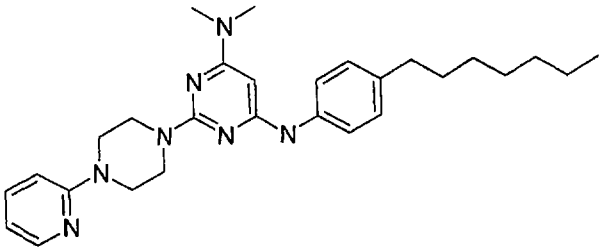

; and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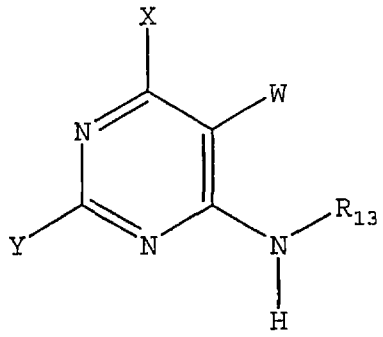
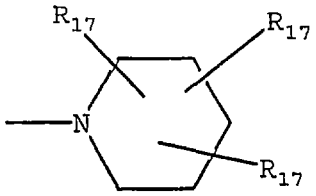
The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is; $NR_{11}R_{12}$;



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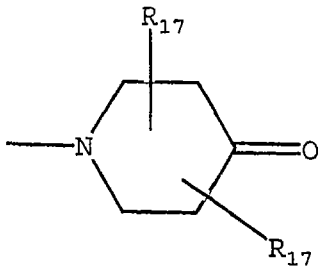
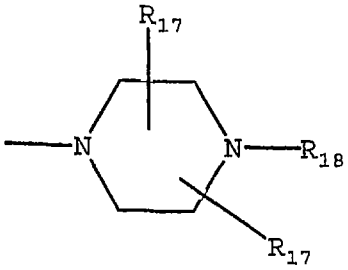


; or



;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl, or aryl $(C_1$-$C_6)$alkyl;

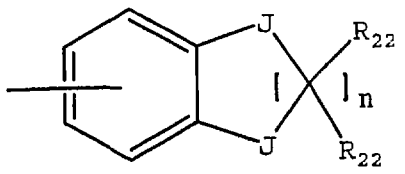
wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl,

noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1-C_6)alkyl, Q_1 or Q_2;

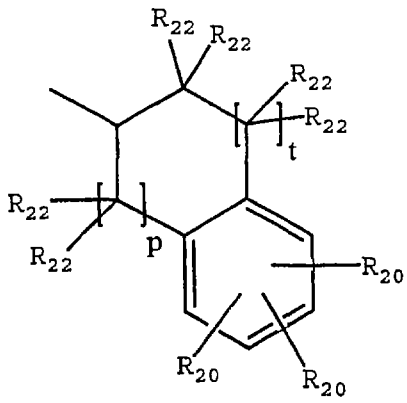
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

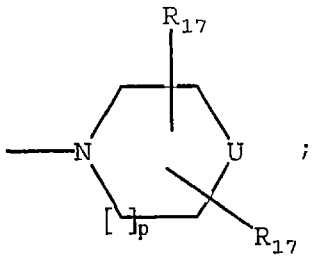


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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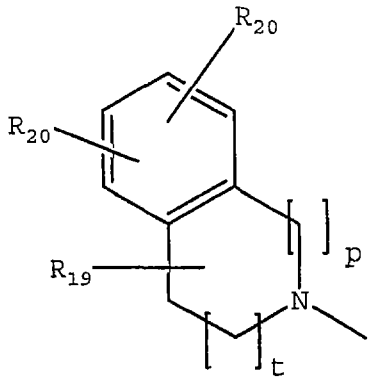
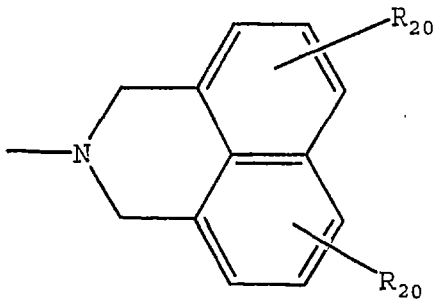


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, $(C(R_{19})_2)_mN(R_{16})_2$ or $(C(R_{19})_2)_m$-Z;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl, or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

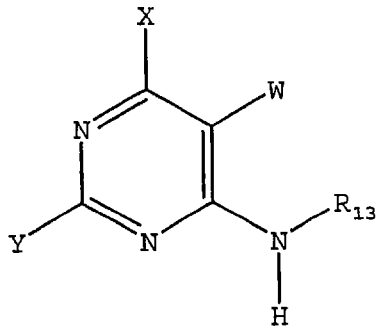
wherein t is 1 or 2;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

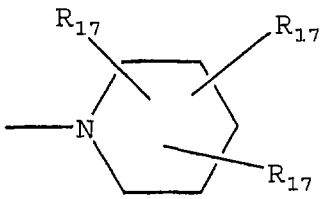
a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:

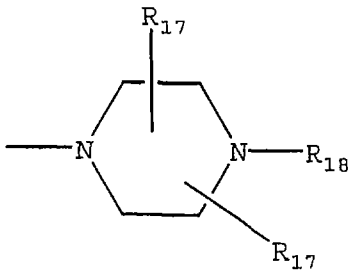


wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $NR_{11}R_{12}$;



; or



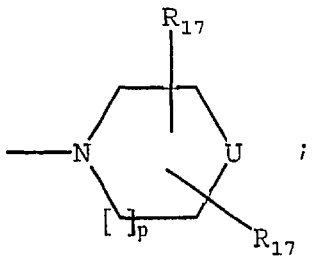
;

wherein R_{11} is H, straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, aryl or aryl(C_1-C_6)alkyl;

wherein R_{12} is straight chained or branched C_1-C_7 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, or -$(CH_2)_m$-Z;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;



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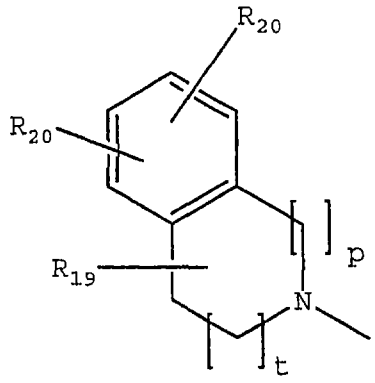
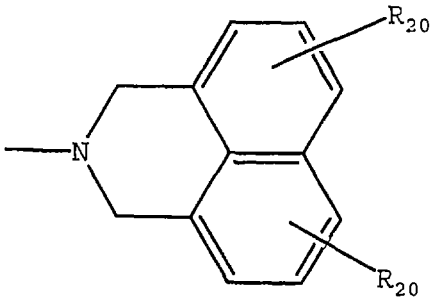


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

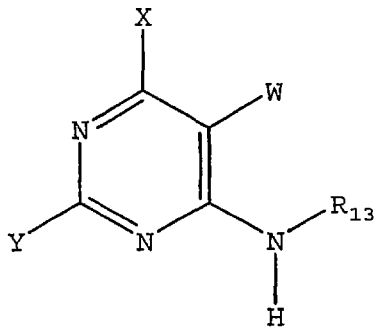
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

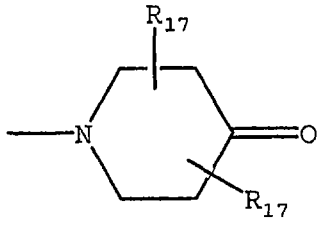
a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or

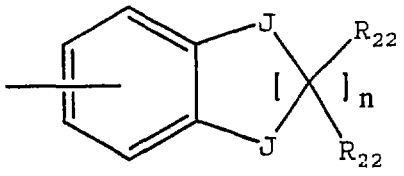


;

wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2;

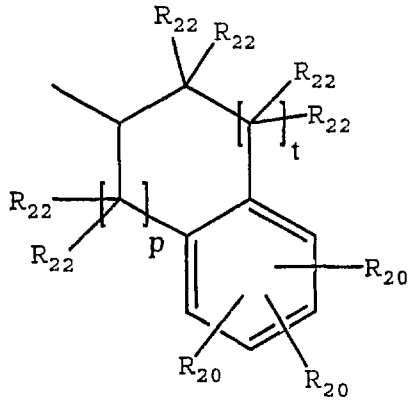
wherein aryl may be substituted with one or more C_1-C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})$-Z;

wherein Q_1 is



;

wherein Q_2 is

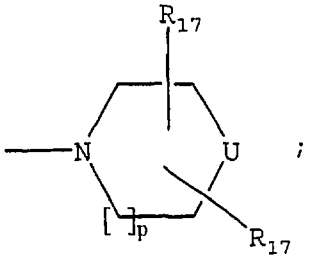


;

wherein each J is independently O, S, $C(R_{22})_2$ or NR_4;

wherein R_4 is -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein Y is $NR_{14}R_{15}$;



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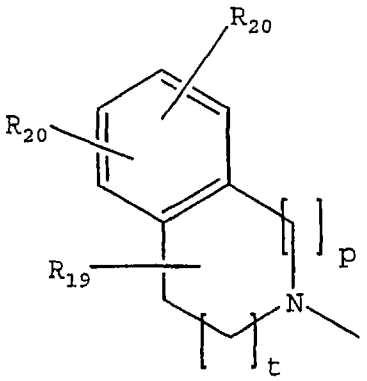
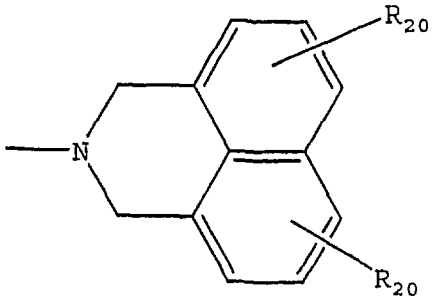


; or



;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is straight chained or branched C_3-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight

chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein R_{18} is straight chained or branched C_1-C_6 alkyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each R_{22} is independently H, F, Cl or C_1-C_4 straight chained or branched alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

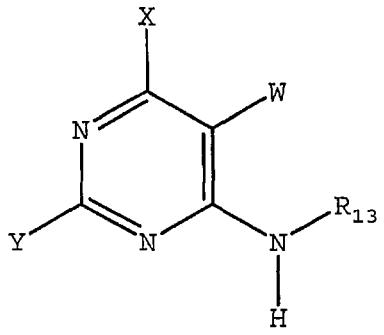
wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

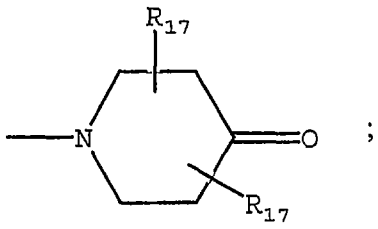
a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

wherein X is $N(CH_3)_2$ or



;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl(C_1-C_6)alkyl;

wherein Y is $NR_{14}R_{15}$;

wherein R_{14} is H, straight chained or branched C_1-C_6 alkyl, $(CH_2)_q$-O-$(CH_2)_m$-CH_3, C_3-C_6 cycloalkyl, or $(C(R_{19})_2)_m$-Z;

wherein R_{15} is $(C(R_{19})_2)_m$-$N(R_{16})_2$;

wherein Z is C_3-C_{10} cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein each R_{17} is independently H; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, -$COOR_{21}$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{19} is independently H, or straight chained or branched C_1-C_6 alkyl;

wherein each R_{21} is independently -H; straight chained or

branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein q is an integer from 2 to 4 inclusive; or

a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "bicyclic alkyl ring systems" includes, but is not limited to, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane and bicyclo[2.2.2]octane. In addition, the bicyclic alkyl ring systems may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_{21})_2$, $-OR_{21}$, $-COR_{21}$, $-CO_2R_{21}$, $-CON(R_{21})_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkyl" includes, C_3-C_7 cycloalkyl moieties which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight

chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkenyl" includes, C_5-C_7 cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen

atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

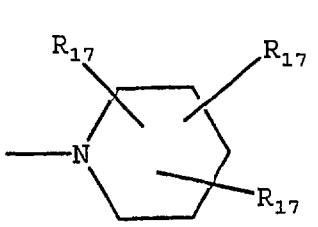
The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

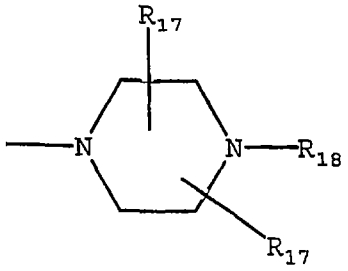
In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In one embodiment of any of the compounds described herein, the compound is enantiomerically or diasteriomerically pure. In one embodiment of any of the compounds described herein, the compound is enantiomerically and diasteriomerically pure.

In one embodiment, X is:



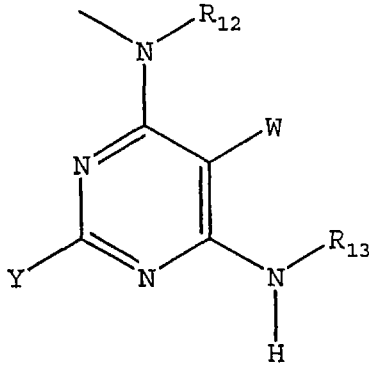
; or



;

In one embodiment, X is $NR_{11}R_{12}$ and R_{11} is H or straight chained or branched C_1-C_7 alkyl.

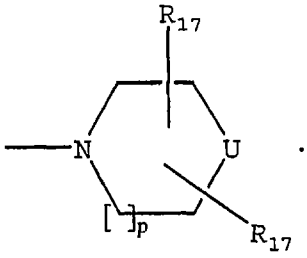
In one embodiment, the compound has the structure:



In one embodiment, R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

In one embodiment, R_{14} is H, straight chained or branched C_1-C_6 alkyl or $(CH_2)_q$-O-$(CH_2)_m$-CH_3.

In one embodiment, Y is

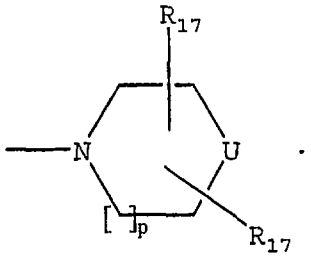


In one embodiment, U is NR_{16}.

In one embodiment, R_{16} is $(CH_2)_m$-Z.

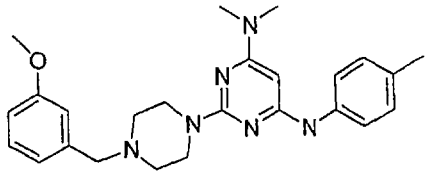
In one embodiment Z is aryl or heteroaryl.

In one embodiment, Y is



In one embodiment, U is NR_{16}.

In one embodiment, the compound is selected from the group consisting of: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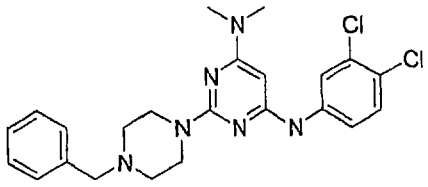
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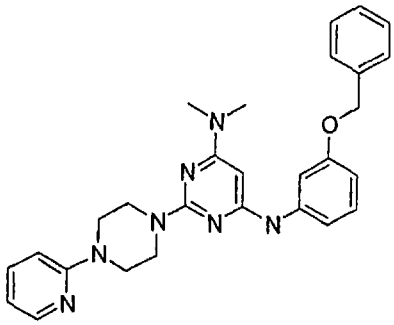
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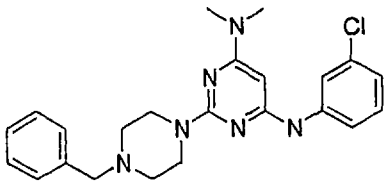
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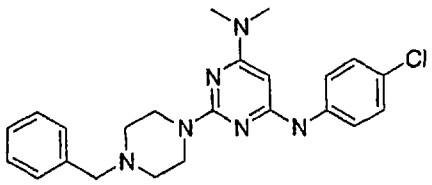
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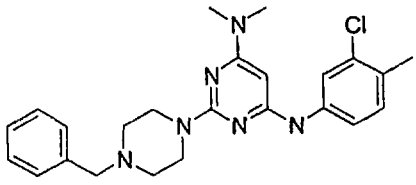
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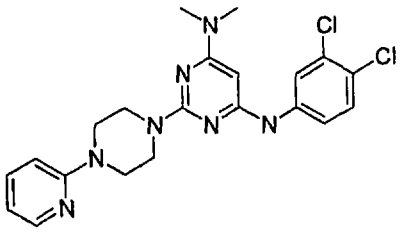
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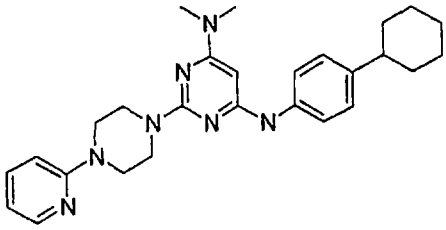
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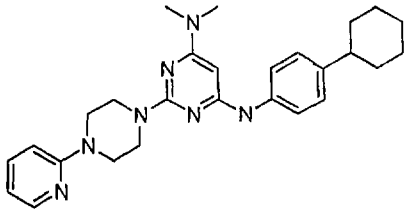
In one embodiment, the compound is selected from the group consisting of: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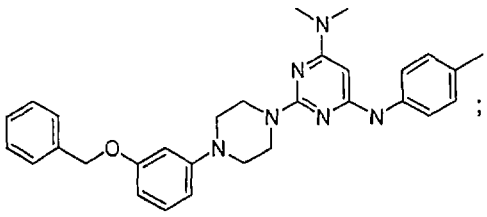
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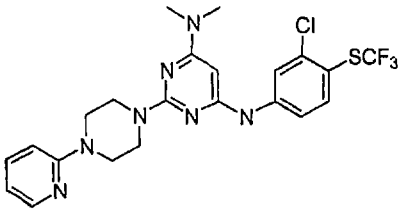
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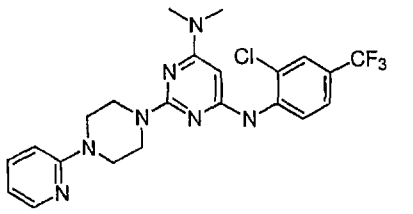
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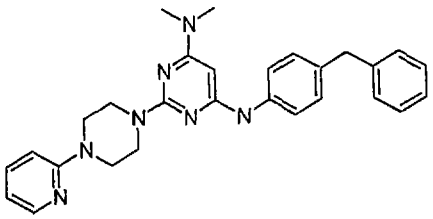
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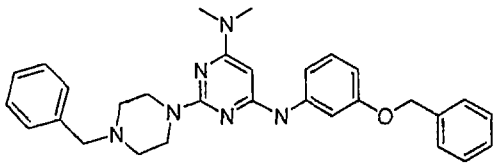
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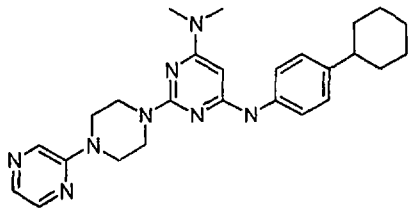
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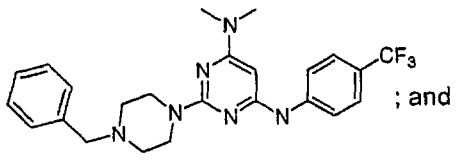
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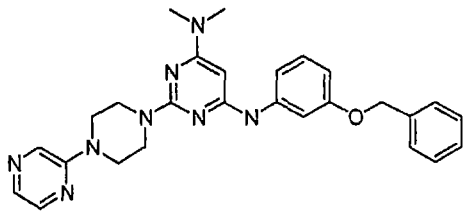

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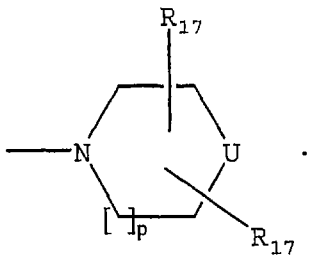
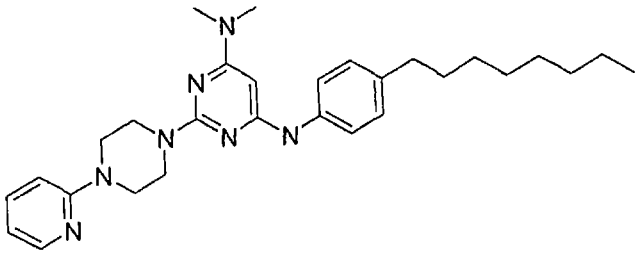
In one embodiment, X is $N(CH_3)_2$.

In one embodiment, Y is



In one embodiment, R_{13} is an aryl substituted with a C_1-C_{10} straight chained alkyl.

In one embodiment, the compound is selected from a group consisting of: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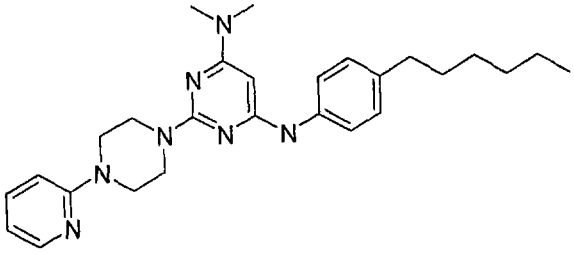
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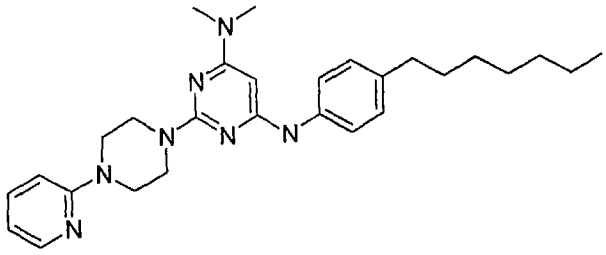

.

The invention provides a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

The invention provides a pharmaceutical composition made by combining a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

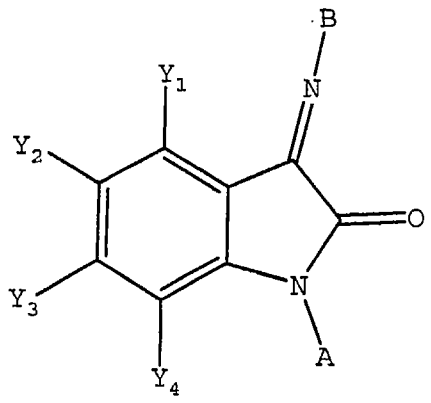
The invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's depression.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's anxiety.

The invention provides a method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's depression and anxiety.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

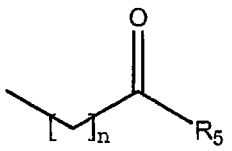


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



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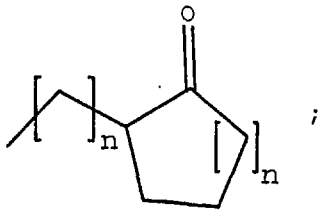

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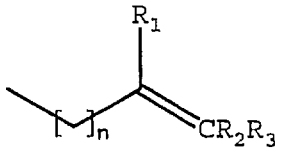
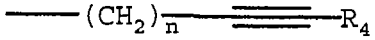
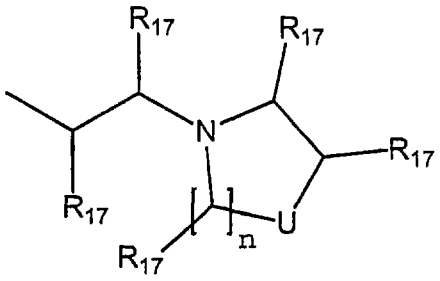


; or



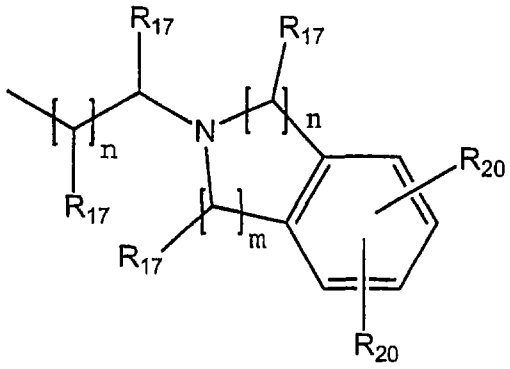
;

wherein Q_3 is



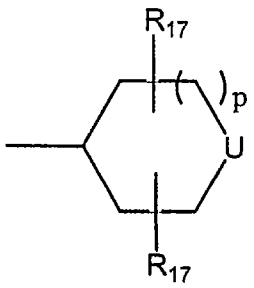
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

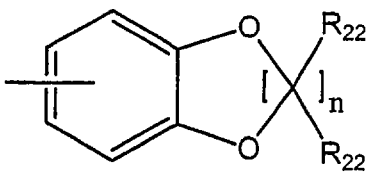
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

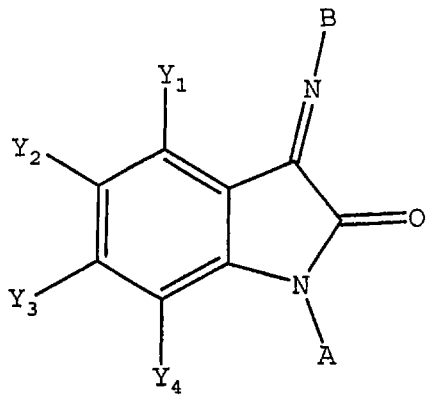


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

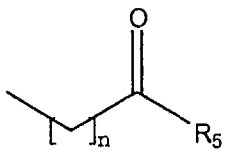


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or

polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;



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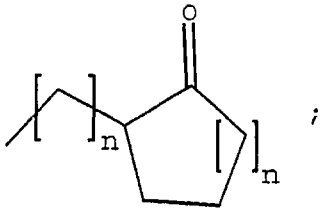
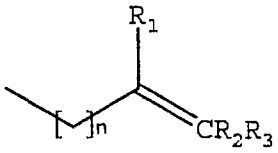
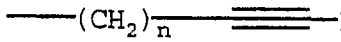


;

wherein A' is



; or 

;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7

alkyl, $-N(R_4)_2$, $-OR_6$ or aryl;

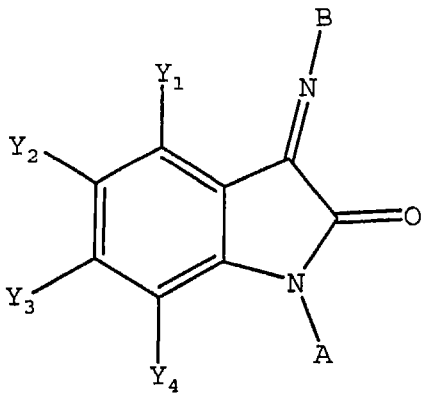
wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:



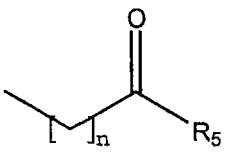
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl,

monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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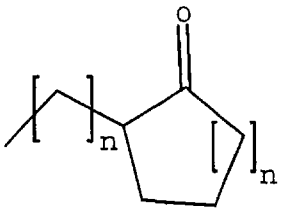

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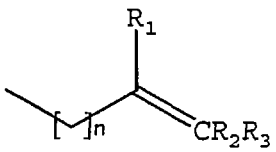
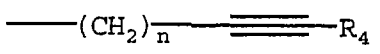


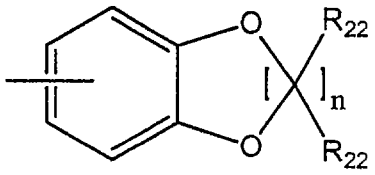
; or


;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



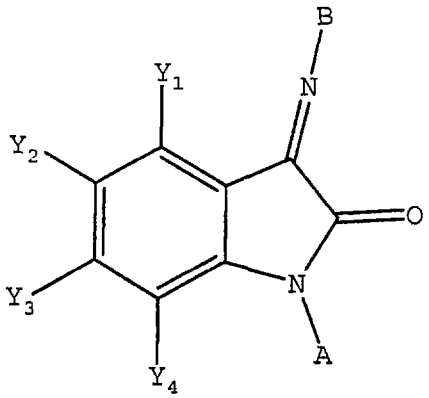
;

wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of compound effective to treat the subject's depression wherein the compound has the structure:

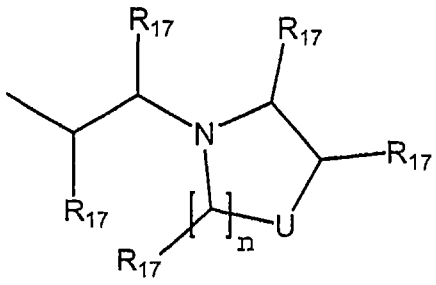


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

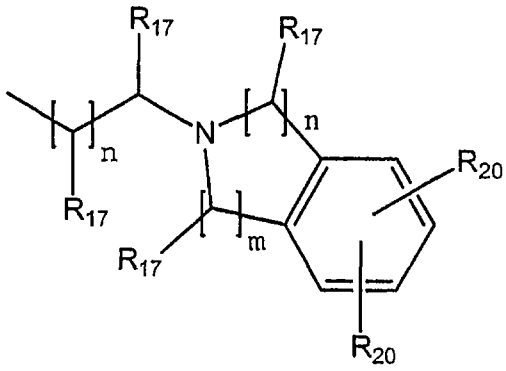
wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

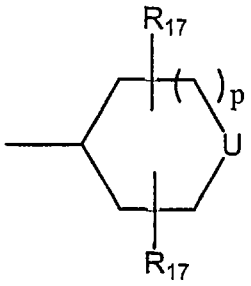
wherein Q_3 is



wherein Q_4 is



wherein Q_5 is



wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_q-O-(CH_2)_m-CH_3$;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "cycloalkyl" includes C_3-C_7 cycloalkyl moieties which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n-O-(CH_2)_m-CH_3$.

As used in the present invention, the term "cycloalkenyl" includes C_5-C_7 cycloalkenyl moieties which may be substituted with one or more of the

following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-

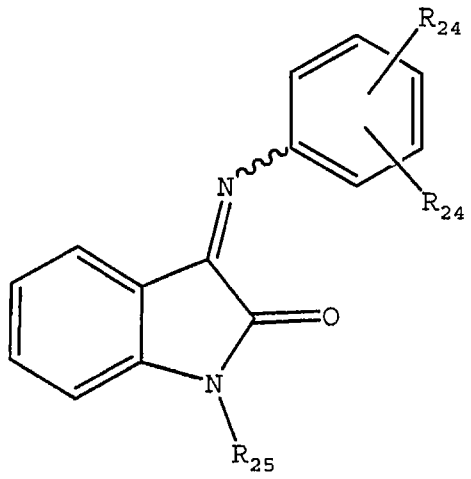
benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -SR_4, -$OCOR_4$, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

The present invention also provides a method of treating a subject suffering from depression which compromises administering to the subject an amount of compound effective to treat the subject's depression, wherein the compound has the structure:



;

wherein each R_{24} is independently one or more of the following: H, F, Cl, Br, I, CF_3, OCH_3 or NO_2;

wherein R_{25} is methyl, ethyl, allyl, phenyl and the phenyl is optionally substituted with a F, Cl, Br, CF_3, NO_2.

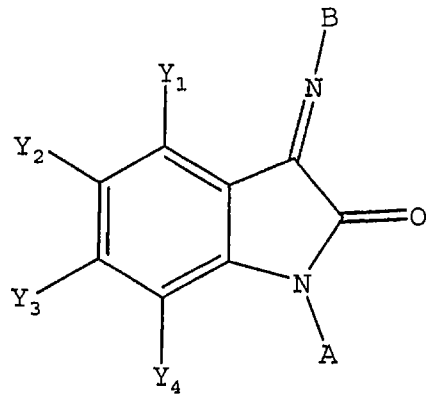
In one embodiment of any one of the methods described herein, the compound is enantiomerically or diastereomerically pure. In one embodiment of any of the methods described herein, the compound is enantiomerically and diastereomerically pure.

In one embodiment, the compound is a pure Z imine isomer

or a pure Z alkene isomer. In one embodiment, the compound is a pure E imine isomer or a pure E alkene isomer.

In one embodiment, the compound is administered orally.

In one embodiment, the compound has the structure:

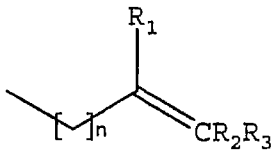


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, -F, -Cl, -Br, -I, $-OR_4$, $-N(R_4)_2$, or $-CON(R_4)_2$;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, or phenyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl$(C_1$-$C_6)$alkyl or heteroaryl$(C_1$-$C_6)$alkyl; and

wherein A' is

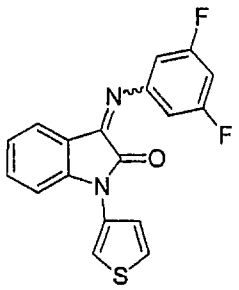


In one embodiment, B is heteroaryl. In one embodiment, B is aryl.

In one embodiment, B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, $-CF_3$, straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, or $-CON(R_4)_2$.

In one embodiment, A is aryl. In one embodiment, A is heteroaryl.

In one embodiment, the compound is selected from the group consisting of:



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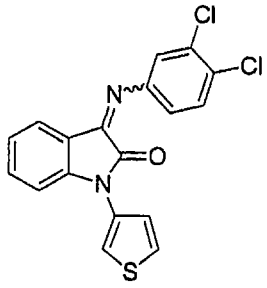
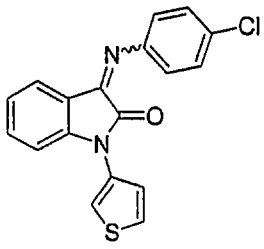
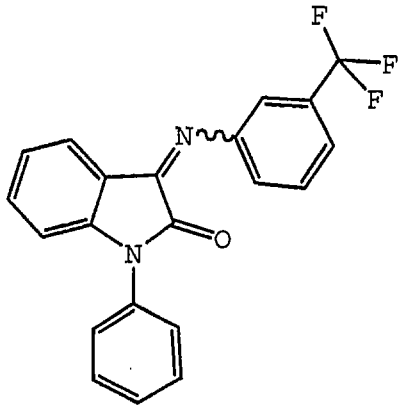


; and



In one embodiment, the compound is selected from the group consisting of:



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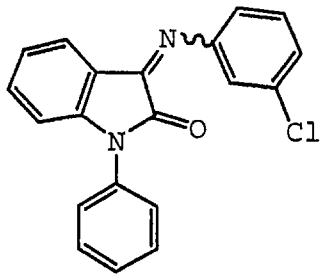

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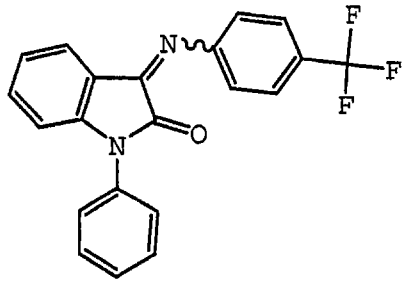

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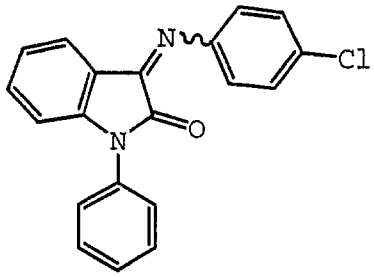
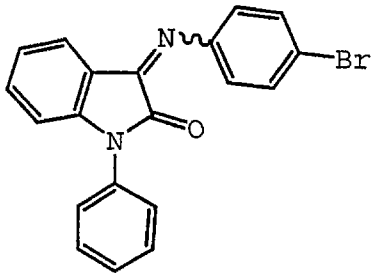


;



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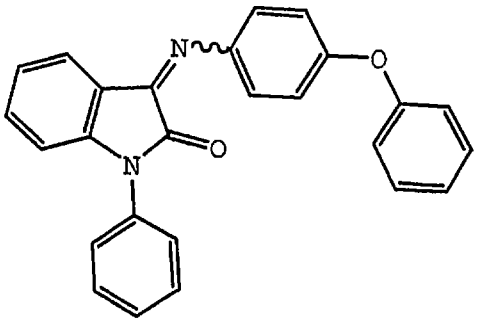
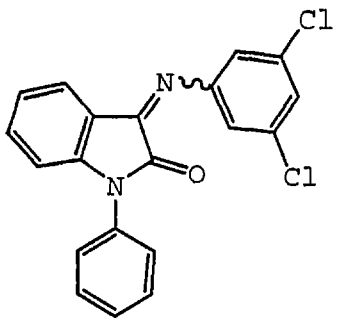
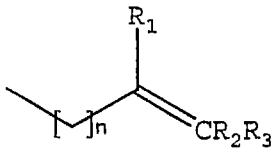


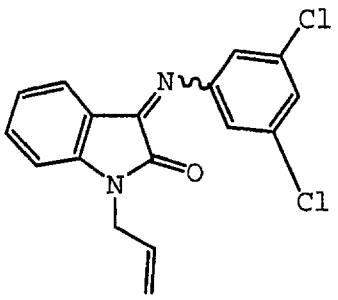
; and



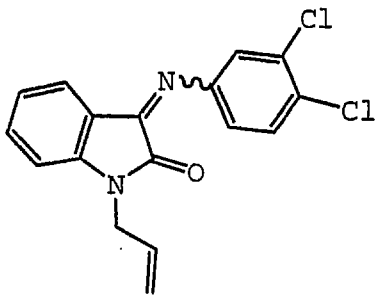
In one embodiment, A is A' and A' is



In one embodiment, the compound is:



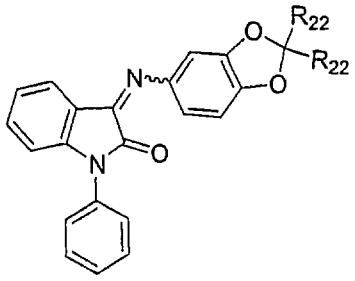
; or



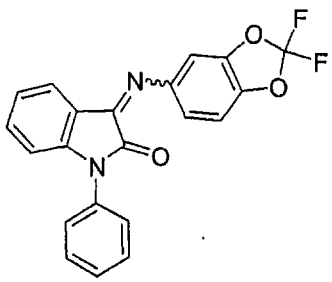
In one embodiment, B is Q_6.

In one embodiment, A is aryl.

In one embodiment, the compound has the structure:



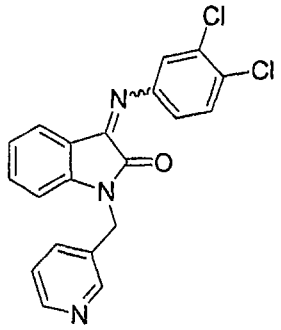
In one embodiment, the compound is:



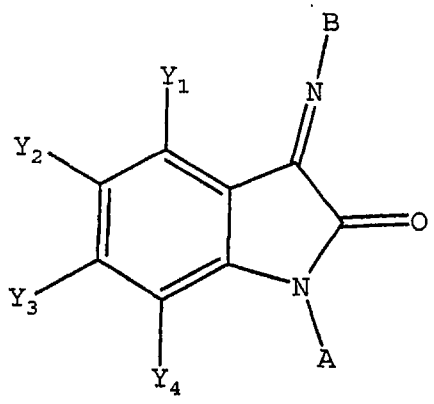
In one embodiment, B is aryl.

In one embodiment, A is $(CHR_{17})-(CHR_{17})_n-Z$.

In one embodiment, the compound is:



The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:



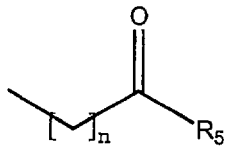
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -

H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is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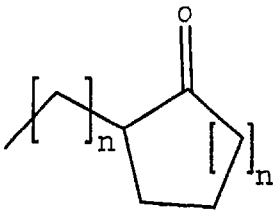
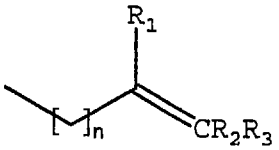
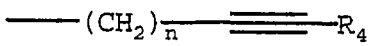
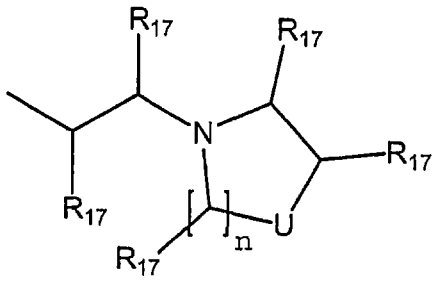
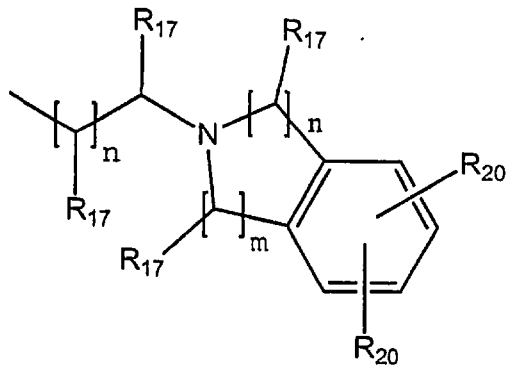

;

; or

;

wherein Q_3 is



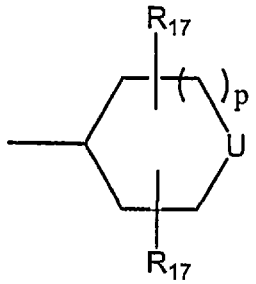
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

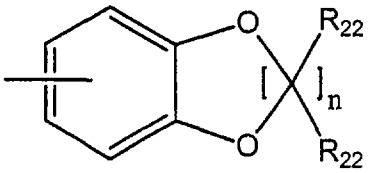
wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen

atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

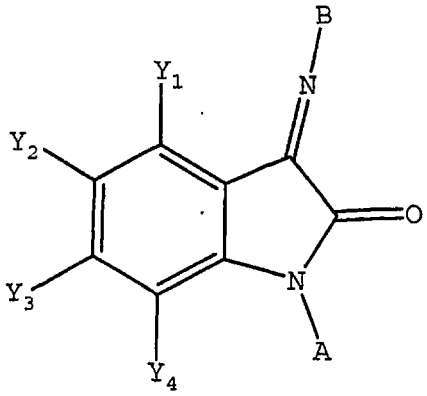


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

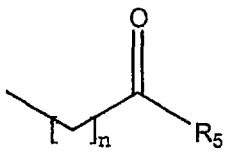


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

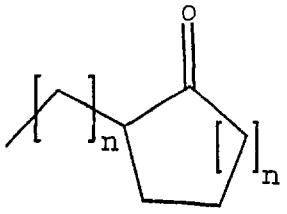
wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



;



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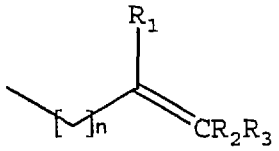
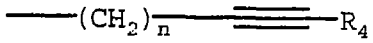


; or 

;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

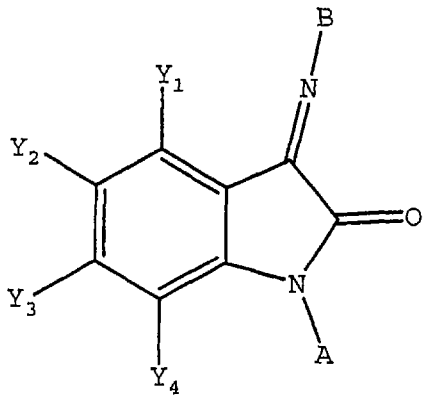
wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to

the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

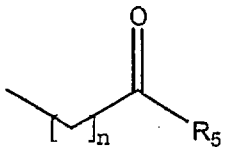


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

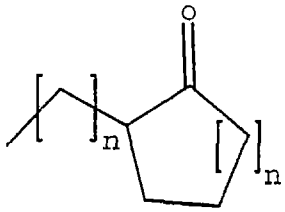
wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



;



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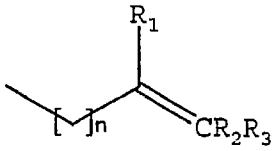
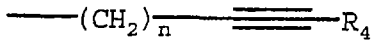


; or

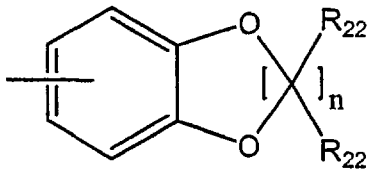


;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



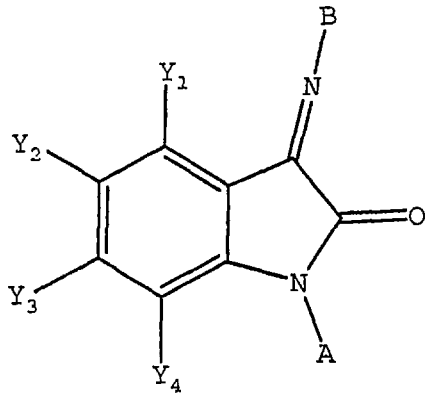
;

wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of compound effective to treat the subject's anxiety wherein the compound has the structure:

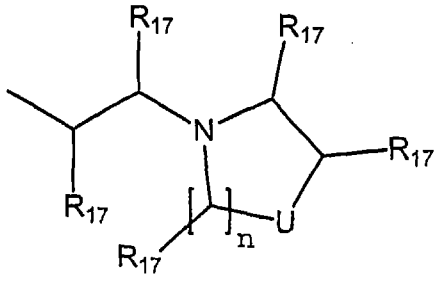


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

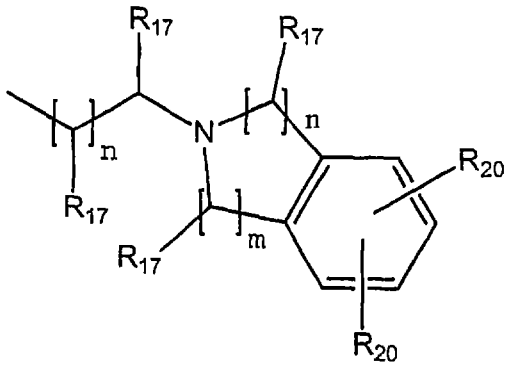
wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



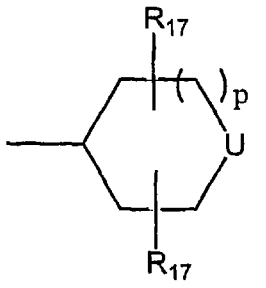
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched

C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "cycloalkyl" includes C_3-C_7 cycloalkyl moieties which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or

$(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkenyl" includes C_5-C_7 cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl,

purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

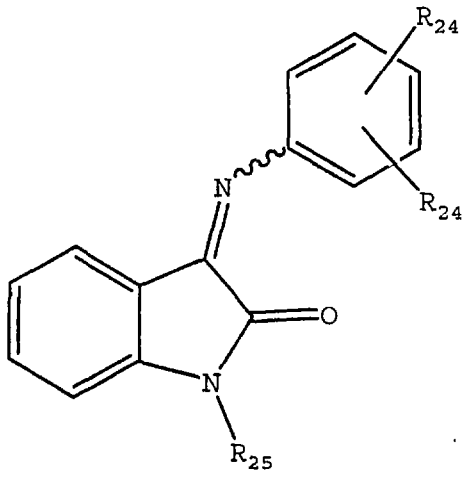
The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained

or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

The present invention also provides a method of treating a subject suffering from anxiety which compromises administering to the subject an amount of compound effective to treat the subject's anxiety where in the compound has the structure:



;

wherein each R_{24} is independently one or more of the following: H, F, Cl, Br, I, CF_3, OCH_3 or NO_2;

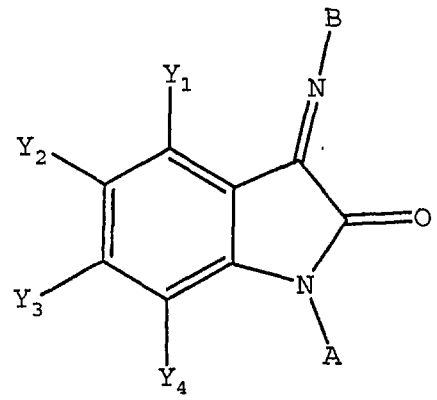
wherein R_{25} is methyl, ethyl, allyl, phenyl and the phenyl is optionally substituted with a F, Cl, Br, CF_3, NO_2.

In one embodiment of any of the methods described herein, the compound is enantiomerically and diastereomerically pure. In one embodiment of any of the methods described herein, the compound is enantiomerically or

diastereomerically pure.

In one embodiment of any of the methods described herein, the compound is a pure Z imine isomer or a pure Z alkene isomer. In one embodiment, the compound is a pure E imine isomer or a pure E alkene isomer.

In one embodiment, the compound has the structure:

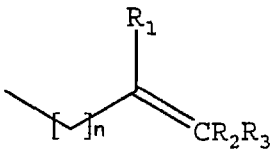


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, -F, -Cl, -Br, -I, $-OR_4$, $-N(R_4)_2$, or $-CON(R_4)_2$;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, or phenyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl; and

wherein A' is

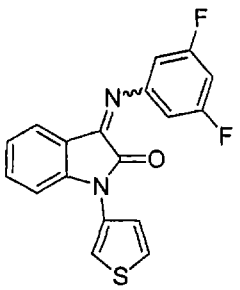


In one embodiment, B is heteroaryl. In one embodiment, B is aryl.

In one embodiment, B is phenyl and the phenyl is optionally substituted with one or more of the following: -F, -Cl, -Br, $-CF_3$, straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, or $-CON(R_4)_2$.

In one embodiment, A is aryl. In one embodiment, A is heteroaryl.

In one embodiment, the compound is selected from the group consisting of:



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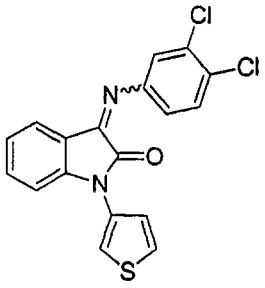
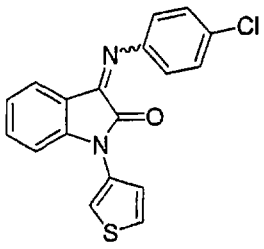
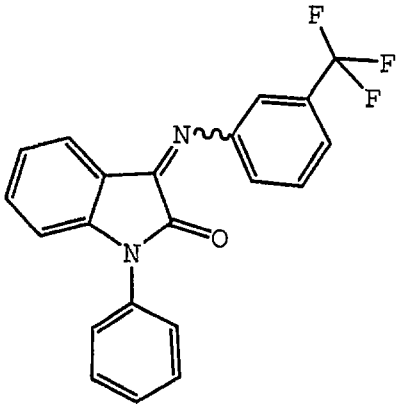


; and



In one embodiment, the compound is selected from the group consisting of:



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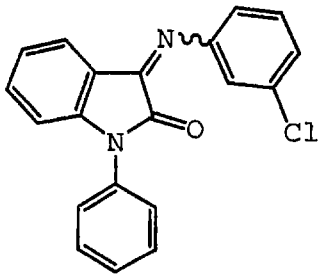

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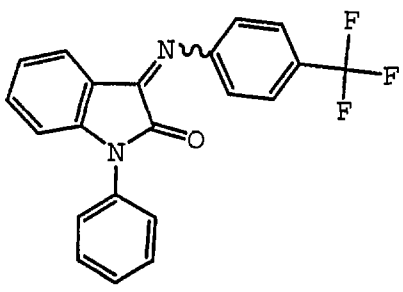

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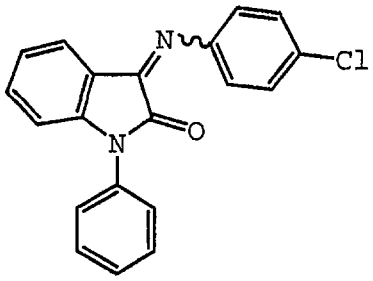

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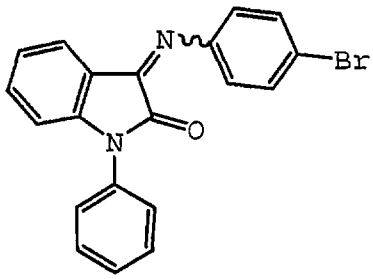

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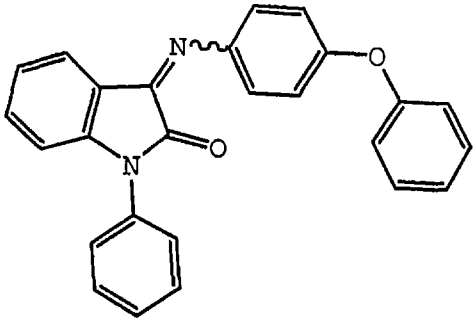
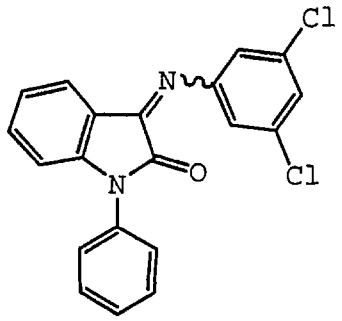
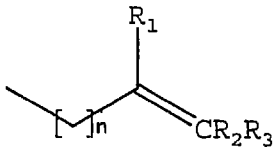


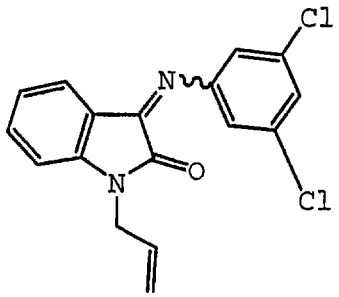
; and



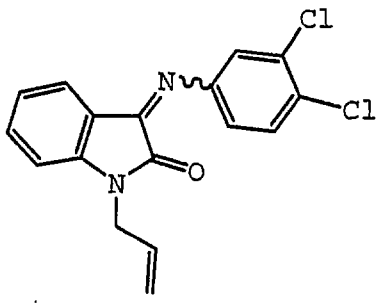
In one embodiment, A is A' and A' is



In one embodiment, the compound is:



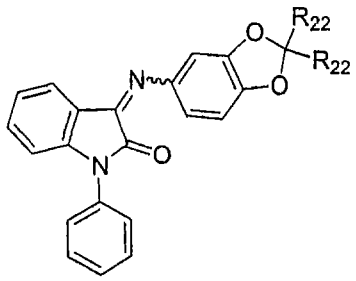
; or



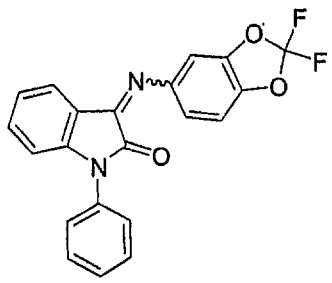
In one embodiment, B is Q_6.

In one embodiment, A is aryl.

In one embodiment, the compound has the structure:



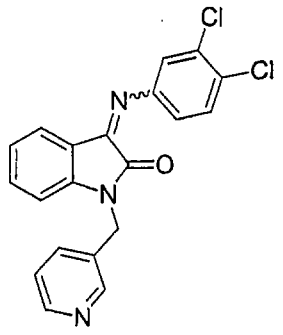
In one embodiment, the compound is:



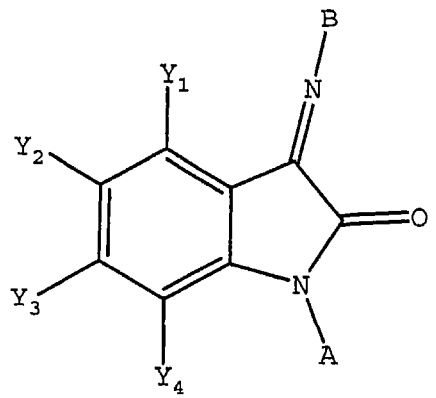
In one embodiment, B is aryl.

In one embodiment, A is $(CHR_{17})-(CHR_{17})_n-Z$.

In one embodiment, the compound is:



The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



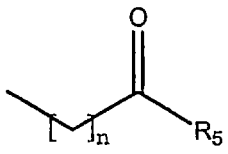
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained

or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



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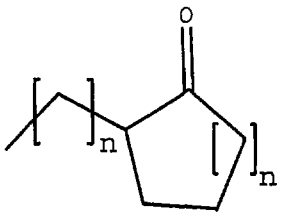

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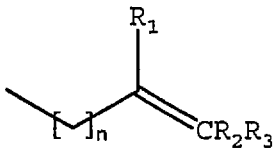
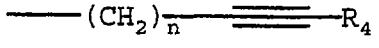
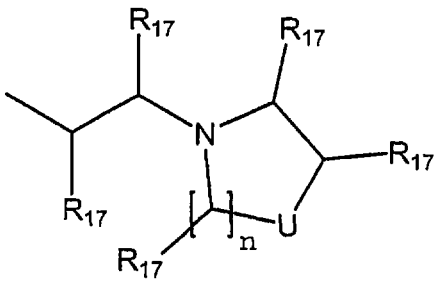


; or


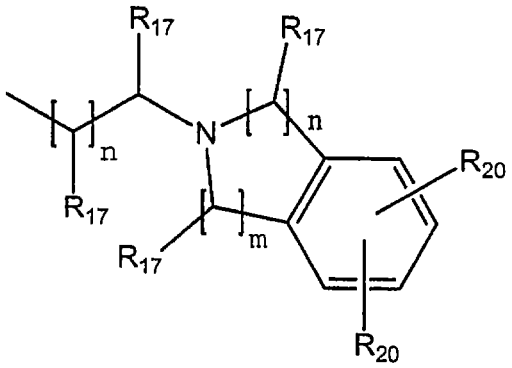
;

wherein Q_3 is



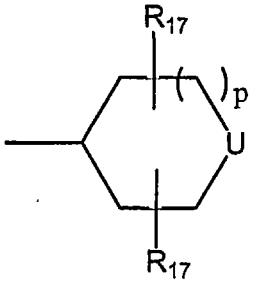
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; -NO_2; -N_3; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, -$N(R_{21})_2$, -$CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

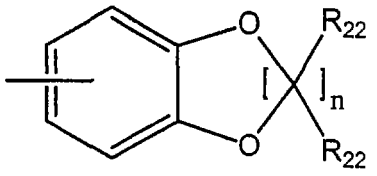
wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen

atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

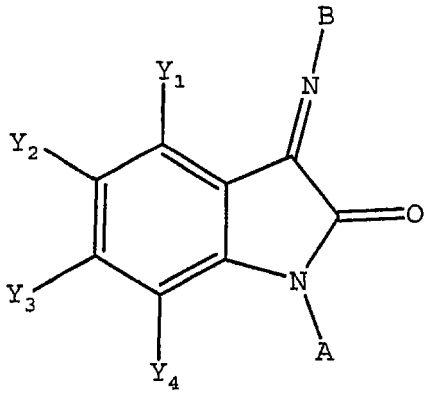


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

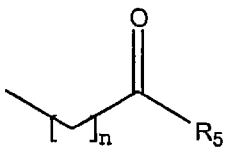


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



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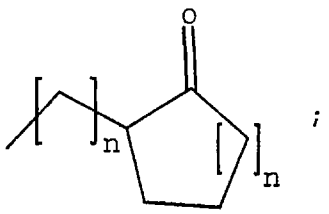

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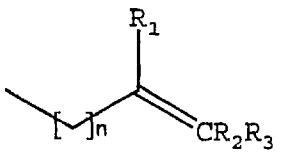
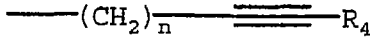


; or



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

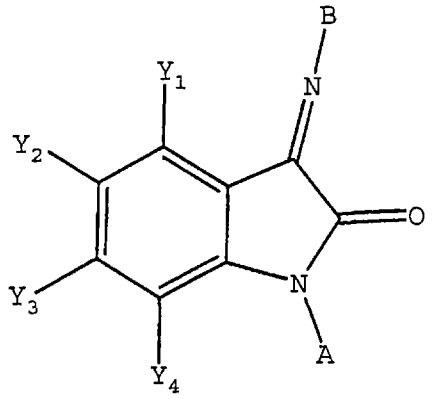
wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

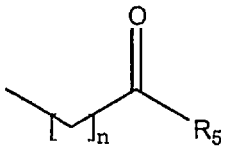
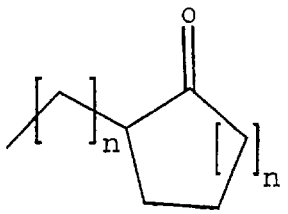


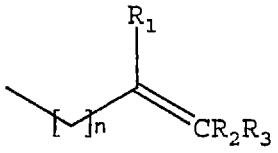
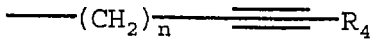
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is

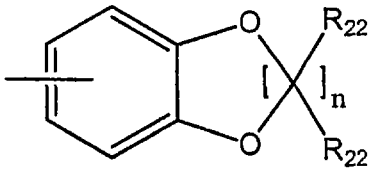
 ;  ;

 ; or  ;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

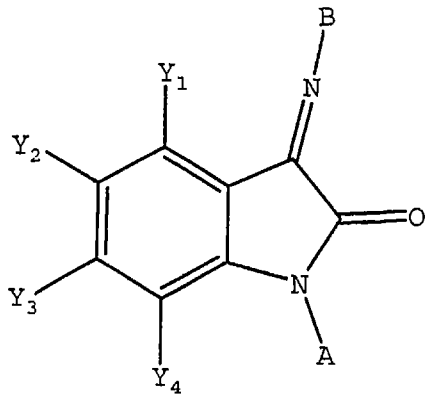
 ;

wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:

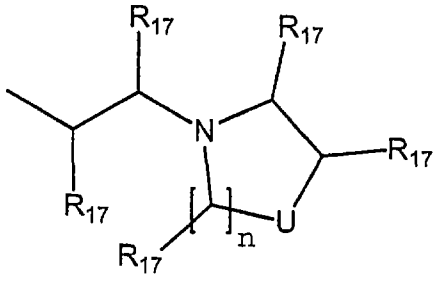


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

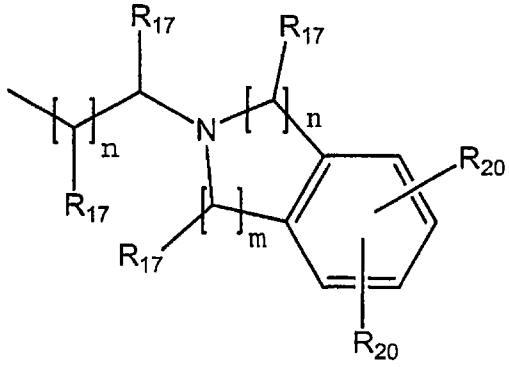
wherein A is Q_3, Q_4, Q_5, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



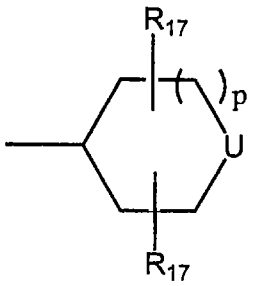
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; -OR_{21}, -$OCOR_{21}$, -COR_{21}, -$NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or -$COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "cycloalkyl" includes C_3-C_7 cycloalkyl moieties which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched

C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkenyl" includes C_5-C_7 cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and

nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN,

straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

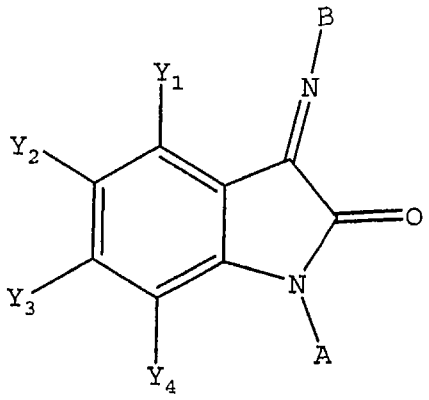
In one embodiment of any of the pharmaceutical compositions described herein, the compound is enantiomerically and diastereomerically pure. In one embodiment, the compound is enantiomerically or diastereomerically pure.

In one embodiment, the compound is a pure Z imine isomer or a pure Z alkene isomer.

In one embodiment, the compound is a pure E imine isomer or a pure E alkene isomer.

In one embodiment, the composition can be administered orally.

In one embodiment of the pharmaceutical composition, the compound has the structure:

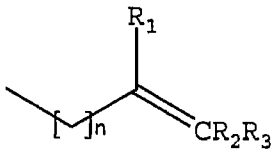


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, -F, -Cl, -Br, -I, $-OR_4$, $-N(R_4)_2$, or $-CON(R_4)_2$;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, or phenyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl; and

wherein A' is



In one embodiment, B is heteroaryl.

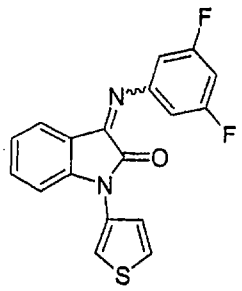
In one embodiment, B is aryl.

In one embodiment, B is phenyl and the phenyl is

optionally substituted with one or more of the following: -F, -Cl, -Br, $-CF_3$, straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, or $-CON(R_4)_2$.

In one embodiment, A is aryl. In one embodiment, A is heteroaryl.

In one embodiment, the compound is selected from the group consisting of:



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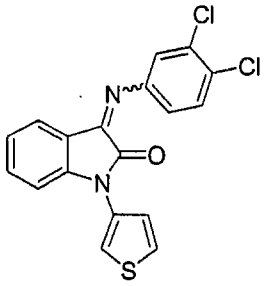
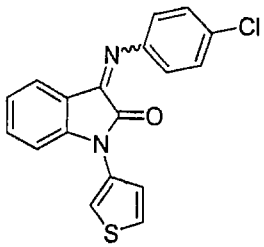


; and



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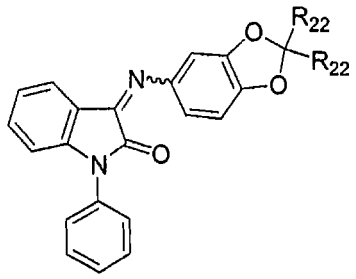
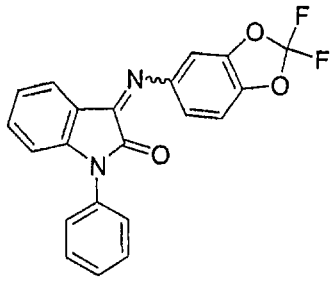
In one embodiment, B is Q_6.

In one embodiment, A is aryl.

In one embodiment, the compound has the structure:



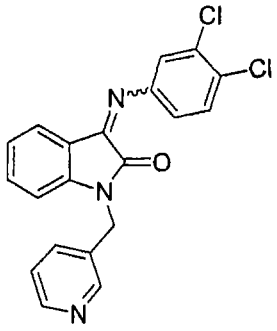
In one embodiment, the compound is:



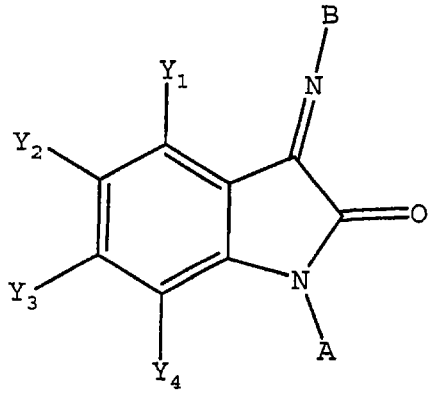
In one embodiment, B is aryl.

In one embodiment, A is $(CHR_{17})-(CHR_{17})_n-Z$.

In one embodiment, the compound is:



The invention provides a compound having the structure:

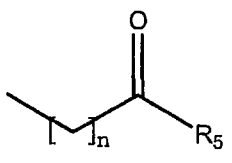


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', Q_3, Q_4, Q_5, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl; or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein A' is



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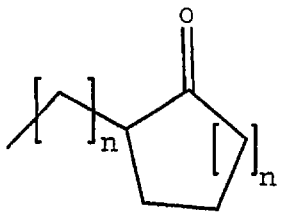

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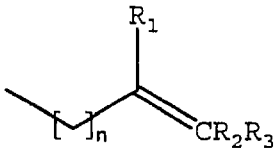
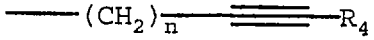
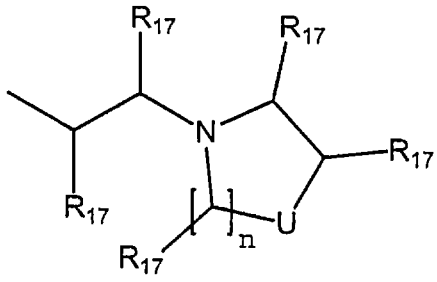


; or 

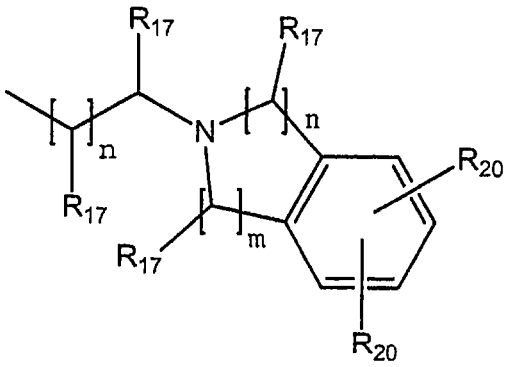
;

wherein Q_3 is



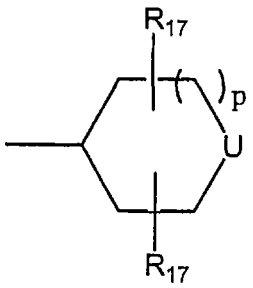
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6, aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, -$(CH_2)_m$-Z, or $(CH_2)_n$-O-$(CH_2)_m$-CH_3;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or

polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

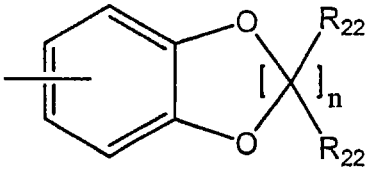
wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein q is an integer from 2 to 4 inclusive;

wherein B is aryl, heteroaryl, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein a tricyclic heteroaryl is a fused three member aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is

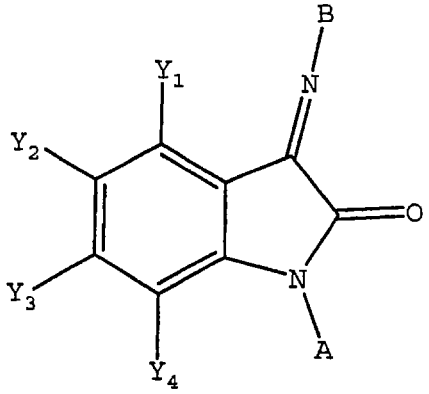


;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:

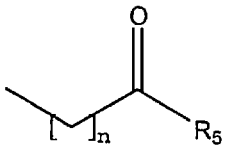


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl$(C_1$-$C_6)$alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl$(C_1$-$C_6)$alkyl or heteroaryl$(C_1$-$C_6)$alkyl;

wherein A' is



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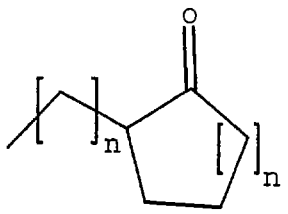

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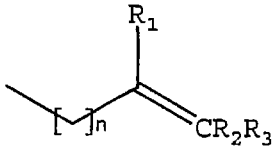
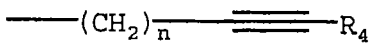


; or



;

wherein R_1 and R_2 are each independently H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, or -CN;

wherein R_3 is H, straight chained or branched C_1-C_7 alkyl, -F, -Cl, -Br, -I, -NO_2, -CN, -OR_6 aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1-C_7 alkyl, -$N(R_4)_2$, -OR_6 or aryl;

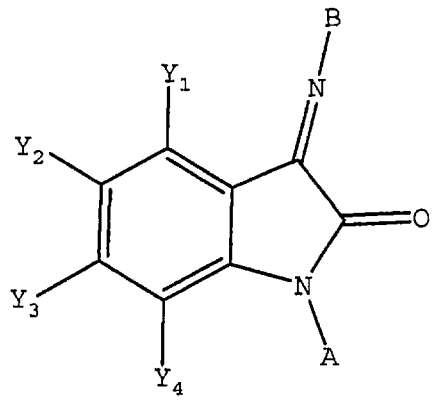
wherein R_6 is straight chained or branched C_1-C_7 alkyl or aryl;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

wherein n is an integer from 1 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:

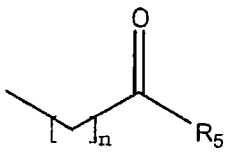


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

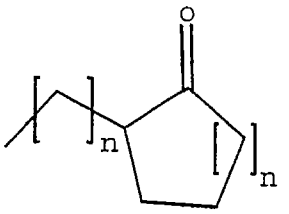
wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl or heteroaryl(C_1-C_6)alkyl;

wherein A' is



;



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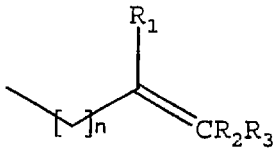
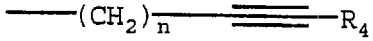


; or

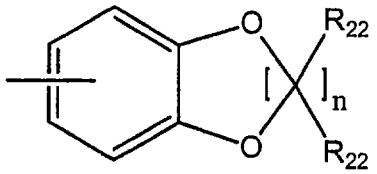


;

wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6;

wherein a tricyclic heteroaryl is a fused three ring aromatic system in which one or more of the rings is heteroaryl; carbazole; or acridine;

wherein Q_6 is



;

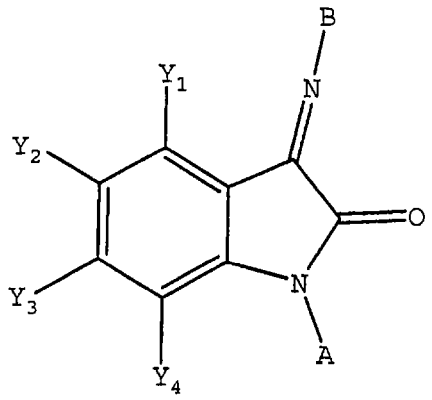
wherein n is an integer from 1 to 4 inclusive;

wherein each R_{22} is independently H, F,

Cl, or straight chained or branched C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



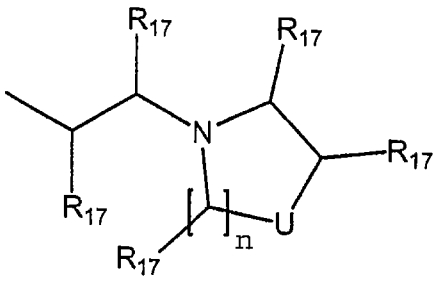
wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-N(R_4)_2$, $-CON(R_4)_2$, or $-COOR_4$; aryl or heteroaryl; or any two of Y_1, Y_2, Y_3 and Y_4 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl, aryl or aryl(C_1-C_6)alkyl;

wherein A is Q_3, Q_4, Q_5, aryl substituted with an

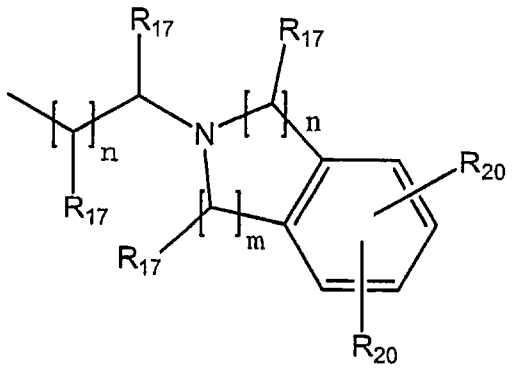
aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR_{17})-$(CHR_{17})_n$-Z;

wherein Q_3 is



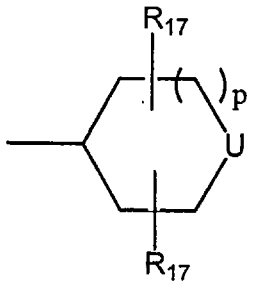
;

wherein Q_4 is



;

wherein Q_5 is



;

wherein each R_{17} is independently H; straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m-Z$, or $(CH_2)_n-O-(CH_2)_m-CH_3$;

wherein each R_{20} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl; -F, -Cl, -Br, or -I; $-NO_2$; $-N_3$; -CN; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, or $-COOR_{21}$; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R_{21} is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, C_5-C_7 cycloalkenyl or aryl;

wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1-C_4 alkyl;

wherein q is an integer from 2 to 4 inclusive;

wherein each m is an integer from 0 to 4 inclusive;

wherein each n is an integer from 1 to 4 inclusive;

wherein each p is an integer from 0 to 2 inclusive;

wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_5-C_7 cycloalkenyl, $-(CH_2)_m$-Z, or $(CH_2)_q$-O-$(CH_2)_m$-CH_3;

wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

or a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "cycloalkyl" includes C_3-C_7 cycloalkyl moieties which may be substituted with one or more of the following: -F, $-NO_2$, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7

alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

As used in the present invention, the term "cycloalkenyl" includes C_5-C_7 cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

In the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups

include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, -$N(R_4)_2$, -OR_4, -COR_4, -$NCOR_4$, -CO_2R_4, -$CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO_2, -CN, straight chained or branched C_1-C_7 alkyl, straight

chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl, $-N(R_4)_2$, $-OR_4$, $-SR_4$, $-OCOR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, $-CON(R_4)_2$ or $(CH_2)_n$-O-$(CH_2)_m$-CH_3.

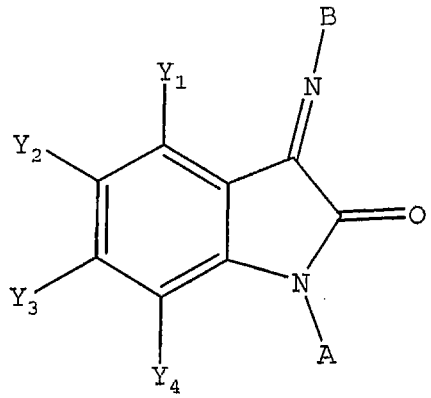
In one embodiment of any of the compounds described herein, the compound is enantiomerically and diastereomerically pure. In one embodiment, the compound is enantiomerically or diastereomerically pure.

In one embodiment, the compound is a pure Z imine isomer or a pure Z alkene isomer.

In one embodiment, the compound is a pure E imine isomer or a pure E alkene isomer.

In one embodiment, the compound can be administered orally.

In one embodiment, the compound has the structure:

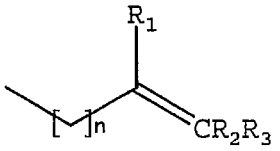


wherein each of Y_1, Y_2, Y_3, and Y_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, -F, -Cl, -Br, -I, $-OR_4$, $-N(R_4)_2$, or $-CON(R_4)_2$;

wherein each R_4 is independently -H; straight chained or branched C_1-C_7 alkyl, $-CF_3$, or phenyl;

wherein A is A', straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, aryl$(C_1$-$C_6)$alkyl or heteroaryl$(C_1$-$C_6)$alkyl; and

wherein A' is



In one embodiment, B is heteroaryl.

In one embodiment, B is aryl.

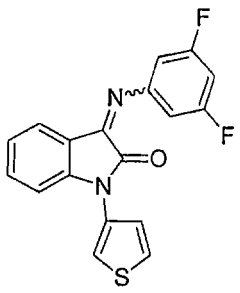
In one embodiment, B is phenyl and the phenyl is

optionally substituted with one or more of the following: -F, -Cl, -Br, $-CF_3$, straight chained or branched C_1-C_7 alkyl, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, or $-CON(R_4)_2$.

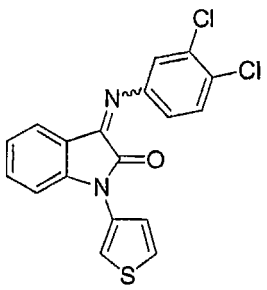
In one embodiment, A is aryl.

In one embodiment, A is heteroaryl.

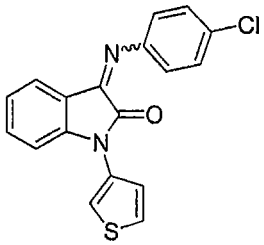
In one embodiment, the compound is selected from the group consisting of:



;



; and

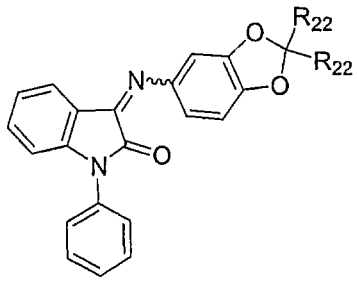


.

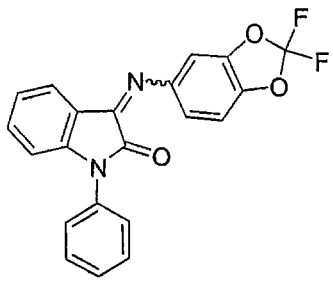
In one embodiment, B is Q_6.

In one embodiment, A is aryl.

In one embodiment, the compound has the structure:



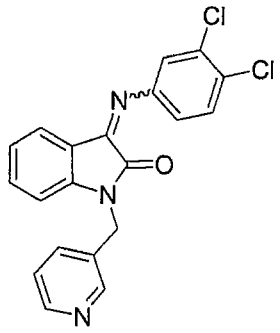
In one embodiment, the compound is:



In one embodiment, B is aryl.

In one embodiment, A is $(CHR_{17})-(CHR_{17})_n-Z$.

In one embodiment, the compound is:



In one embodiment, the compound is a pure Z imine isomer.

In one embodiment, the compound is a pure E imine isomer.

The invention provides a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

The invention provides a pharmaceutical composition made by combining a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

The invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of any of the compounds described herein and a pharmaceutically acceptable carrier.

The invention provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's

depression.

The invention provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's anxiety.

The invention provides a method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of any of the compounds described herein effective to treat the subject's depression and anxiety.

The invention provides for each pure stereoisomer of any of the compounds described herein. Such stereoisomers may include enantiomers, diastereomers, or E or Z alkene or imine isomers. The invention also provides for stereoisomeric mixtures, including racemic mixtures, diastereomeric mixtures, or E/Z isomeric mixtures. Stereoisomers can be synthesized in pure form (Nógrádi, M.; Stereoselective Synthesis, (1987) VCH Editor Ebel, H. and Asymmetric Synthesis, Volumes 3 - 5, (1983) Academic Press, Editor Morrison, J.) or they can be resolved by a variety of methods such as crystallization and chromatographic techniques (Jaques, J.; Collet, A.; Wilen, S.; Enantiomer, Racemates, and Resolutions, 1981, John Wiley and Sons and Asymmetric Synthesis, Vol. 2, 1983, Academic Press, Editor Morrison, J).

In addition the compounds of the present invention may be present as enantiomers, diasteriomers, isomers or two or more of the compounds may be present to form a racemic or diastereomeric mixture.

The compounds of the present invention are preferably 80% pure, more preferably 90% pure, and most preferably 95% pure.

Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The acids and bases from which these salts are prepared include but are not limited to the acids and bases listed herein. The acids include, but are not limited to, the following inorganic acids: hydrochloric acid, hydrobromic acid, hydroiodic acid,

sulfuric acid and boric acid. The acids include, but are not limited to, the following organic acids: acetic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The bases include, but are not limited to ammonia, methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of the compounds described herein.

The present invention includes within its scope prodrugs of the compounds of the invention. In general, such prodrugs will be functional derivatives of the compounds of the invention which are readily convertible in vivo into the required compound. Thus, in the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

The present invention further includes metabolites of the compounds of the present invention. Metabolites include active species produced upon introduction of compounds of this invention into the biological milieu.

Throughout the invention, the term "binding affinity" describes the concentration of a compound required to occupy one-half of the binding sites in a receptor population, as detectable by radioligand binding. Binding affinity concentration can be represented as K_i, inhibition constant, or K_D, dissociation constant.

The term "selectivity of binding affinity" refers to the ability of a chemical compound to discriminate one receptor from another. For example, a compound showing selectivity for receptor A versus receptor B will bind receptor A at lower concentrations than those required to bind receptor B.

Therefore, the statements of the form "binds to the GAL3 receptor with a binding affinity at least ten-fold higher than" a named receptor, indicates that the binding affinity at the GAL3 receptor is at least ten-fold greater than that for a named receptor, and binding affinity measurements (i.e. K_i or K_D) for the compound are at least ten-fold lower in numerical value.

The present invention provides a method of treating depression in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor;

(b) (1) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 50 percent, at a concentration of 10μM; and

(2) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 50 percent, at a concentration of 10μM; and

(c) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

The present invention provides a method of treating anxiety in a subject which comprises administering to the subject a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor; and

(b) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

In some embodiments of this invention, the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 30-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

In further embodiments of the invention, the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 50-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

In other embodiments of the invention, the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 100-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

In still other embodiments of the invention, the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least 200-fold higher than the binding affinity with which it binds to the human GAL1 receptor.

For the purposes of this invention the term "pharmaceutically acceptable carrier" has been defined herein.

The term "antagonist" refers to a compound which binds to, and decreases the activity of, a receptor in the presence of an agonist. In the case of a G-protein coupled receptor, activation may be measured using an appropriate second messenger system which is coupled to

the receptor in a cell or tissue in which the receptor is expressed. Some specific but by no means limiting examples of well-known second messenger systems are adenylate cyclase, intracellular calcium mobilization, ion channel activation, guanylate cyclase, inositol phospholipid hydrolysis, and MAP kinase activation. Conversely, the term "agonist" refers to a compound which binds to, and increases the activity of, a receptor as compared with the activity of the receptor in the absence of any agonist. Methods to perform second messenger assays are described in PCT International Publication No. 97/46250 and in PCT International Publication No. 98/15570, the contents of which are hereby incorporated by reference.

In the case that a receptor has activity in the absence of an agonist (constitutive receptor activity) the antagonist may act as an inverse agonist or an allosteric modulator, as opposed to a neutral antagonist, and suppress receptor signaling independent of the agonist (Lutz and Kenakin, 1999). The categories of "antagonist compounds" are therefore seen to include 1) neutral antagonists (which block agonist actions but do not affect constitutive activity); 2) inverse agonists (which block agonist actions as well as constitutive activity by stabilizing an inactive receptor conformation); 3) and allosteric modulators (which block agonist actions to a limited extent and which may also block constitutive activity through allosteric regulation). The probability that an antagonist is neutral and therefore of "zero efficacy" is relatively low, given that this would require identical affinities for different tertiary

conformations of the receptor. Thus, Kenakin proposed in 1996 that, "with the development of sensitive test systems for the detection of inverse agonism will come a reclassification of many drugs. It might be observed that numerous previously classified neutral antagonists may be inverse agonists" (Kenakin, 1996). Indeed, there is now evidence from studies with known pharmacological agents to support the existence of inverse agonists for numerous receptors, including histamine, $5HT_{1A}$, $5HT_{2C}$, cannabinoid, dopamine, calcitonin and human formyl peptide receptors, among others (de Ligt, et al, 2000; Herrick-Davis, et al, 2000; Bakker, et al, 2000). In the case of the $5HT_{2C}$ receptor, clinically effective atypical antipsychotics drugs such as sertindole, clozapine, olanzapine, ziprasidone, risperidone, zotepine, tiospirone, fluperlapine and tenilapine displayed potent inverse activity whereas typical antipsychotic drugs such as chlorpromazine, thioridazine, spiperone and thiothixene were classified as neutral antagonists (Herrick-Davis et al, 2000). In the case of the histamine H_1 receptor, the therapeutically used anti-allergics cetirizine, loratadine and epinastine were found to be inverse agonists. These findings further extend the idea that many compounds previously thought of as neutral antagonists will be reclassified as inverse agonists when tested in a constitutively active receptor system (de Ligt et al, 2000).

For the purpose of the claimed invention, a GAL3 antagonist useful in the treatment of depression is one which a) selectively binds to the GAL3 receptor, and b) displays antidepressant activity in the rat Forced Swim

Test. Furthermore, a GAL3 antagonist useful in the treatment of anxiety is one which a) selectively binds to the GAL3 receptor, and b) displays anxiolytic activity in the rat Social Interaction. Also for the purpose in the present invention, a GAL3 antagonist useful in the treatment of depression and anxiety, is one which a) selectively binds to the GAL3 receptor, b) displays antidepressant activity in the rat Forced Swim Test, and c) displays anxiolytic activity in the rat Social Interaction Test.

In order to test compounds for selective binding to the human GAL3 receptor the cloned cDNAs encoding both the human and rat GAL1 and GAL2 receptors have been used. The cloning and assay methods for the human and rat GAL1 receptors may be found in PCT International Publication No. WO 95/22608, the contents of which are hereby incorporated by reference. The cloning and assay methods for the human and rat GAL2 receptors may be found in PCT International Publication No. WO 97/26853, the contents of which are hereby incorporated by reference.

The present invention provides for a method of determining the binding affinity of a GAL3 antagonist, wherein the GAL3 antagonist is dissolved in a "suitable solvent". A "suitable solvent" means one which permits the measurement of binding affinity of the GAL3 antagonist to the human GAL3 receptor at concentrations less than 1 μM, preferably less than 100 nM. Examples of solvents include, but are not limited to, DMSO, ethanol, N,N-dimethylacetamide, or water. For indolones, the

preferred solvent is 3% DMSO (final concentration in the assay). For pyrimidines, the preferred solvent is 1% ethanol/0.09% polypuronic acid F-127 (final concentration in the assay). For any other type of compounds, the preferred solvent is the solvent which permits the measurement of binding affinity of a GAL3 antagonist at the lowest concentration. Once a suitable solvent is ascertained for the binding assay of the human GAL3 receptor, the same solvent is used in assays to determine the binding affinity at the GAL1 receptor, the serotonin transporter, the norepinephrine transporter, and the dopamine transporter. A solvent of 0.4% DMSO is used in the central monoamine oxidase enzyme assay.

In certain embodiments, the aforementioned GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

In other embodiments, the GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least 30-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

In still other embodiments, the GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least 50-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

In some embodiments, the GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least 100-fold higher than the

binding affinity with which it binds to the human GAL2 receptor.

In further embodiments, the GAL3 receptor antagonist additionally binds to the human GAL3 receptor with a binding affinity at least 200-fold higher than the binding affinity with which it binds to the human GAL2 receptor.

In other embodiments, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the human $5HT_{1B}$, human $5HT_{1D}$, human $5HT_{1E}$, human $5HT_{1F}$, human $5HT_{2A}$, rat $5HT_{2C}$, human $5HT_6$ and human $5HT_7$ receptors.

In still another embodiment, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human histamine H_1 receptor.

In still another embodiment, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human dopamine D_1, D_2, D_3, D_4 and D_5 receptors.

In a further embodiment, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human α_{1A} adrenoceptor, the human α_{1B} adrenoceptor and the human α_{1D} adrenoceptor.

In another embodiment, the receptor antagonist also binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human α_{2A} adrenoceptor, the human α_{2B} adrenoceptor and the human α_{2C} adrenoceptor.

In certain embodiments, the GAL3 receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human $5HT_4$ receptor.

In further embodiments, the GAL3 receptor antagonist also binds to the human GAL3 receptor with a binding affinity less than ten-fold higher than the binding affinity with which it binds to the human $5HT_{1A}$ receptor.

In some embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 30 percent. In further embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 30 percent. In other embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 15 percent. In still other embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 15 percent. In still other embodiments the receptor antagonist does not inhibit the activity of central monoamine oxidase A and/or central monoamine oxidase B greater than 10 percent.

The binding properties of compounds at different receptors were determined using cultured cell lines that selectively express the receptor of interest. Cell lines were prepared by transfecting the cloned cDNA or cloned genomic DNA or constructs containing both genomic DNA and cDNA encoding the receptors as further described in the Experimental Details herein below. Furthermore, the binding interactions of compounds at different transporters and enzymes were determined using tissue preparations and specific assays as further described in the Experimental Details herein below.

In connection with this invention, a number of cloned receptors discussed herein, as stably transfected cell lines, have been made pursuant to, and in satisfaction of, the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure, and are made with the American Type Culture Collection, 10801 University Blvd., Manassas, Virginia 20110-2209. Specifically, these deposits have been accorded ATCC Accession Numbers as follows:

ATCC Deposits:			
Designation	Receptor	ATCC Accession No.	Date of Deposit
	human GAL1	CRL-1650	
(CHO)hGalR2-264	human GAL2	CRL 12379	07/22/1997
L-hGalR3-228	human GAL3	CRL-12373	07/01/1997
5HT1A-3	human 5-HT_{1A}	CRL 11889	05/11/1995
Ltk-11	human 5-HT_{1B} (formerly human 5-HT1D2)	CRL 10422	04/17/1990
Ltk-8-30-84	human 5-HT_{1D} (formerly human 5-HT1D1)	CRL 10421	04/17/1990
$5HT_{1E}$-7	human 5-HT_{1E}	CRL 10913	11/06/1991
L-5-HT_{1F}	human 5-HT_{1F}	CRL 10957	12/27/1991
L-NGC-$5HT_2$	human 5-HT_{2A} (formerly human 5-HT2)	CRL 10287	10/31/1989
pSr-1c	rat 5-HT_{2C} (formerly rat 5HT1C)	67636	
pBluescript-hS10	human 5-HT_4	75392	12/22/1992
L-5HT-4B	human 5-HT_7 (formerly human 5-HT4B)	CRL 11166	10/20/1992
L-α_{1C}	human α_{1A} (formerly human α1C)	CRL11140	09/25/1992
L-α_{1B}	human α_{1B}	CRL11139	09/25/1992
L-α_{1A}	human α_{1D} (formerly hum α1A)	CRL11138	09/25/1992
L-α_{2A}	human α_{2A}	CRL11180	11/06/1992
L-NGC-α_{2B}	human α_{2B}	CRL10275	10/25/1989
L-α_{2C}	human α_{2C}	CRL11181	11/06/1992
pDopD$_1$-GL-30	human D_5 (formerly hum D1β)	40839	07/10/1990
pCEXV-H_1	human H_1	75346	11/06/1992

- The "5-HT_{1C}", "5-HT_{1D1}", "5-HT_{1D2}", "5-HT_{4B}", and "5-HT_2" receptors were renamed the "5-HT_{2C}", "5-HT_{1D}", "5-HT_{1B}", "5-HT_7", and "5-HT_{2A}" receptors, respectively, by the Serotonin Receptor Nomenclature Committee of the IUPHAR.

- The "human α_{1C}", "human α_{1A}", and "human $D_{1\beta}$" were renamed the "human α_{1A}", "human α_{1D}", and "human D_5" respectively.

The following receptor sequences have been deposited with the GenBank DNA database, which is managed by the National Center for Biotechnology (Bethesda, MD).

GENBANK DEPOSITS		
DESIGNATION	RECEPTOR	GENBANK No.
human mRNA for D-1 receptor	human D_1 (formerly human $D_{1\alpha}$)	X58987
human dopamine D2 receptor (DRD2) mRNA complete cds	human D_2	M29066
Rat mRNA for dopamine D3 receptor	rat D_3	X53944
Homo sapiens dopamine D4 receptor (DRD4) gene (D4.4) sequence	human D_4	L12397

* The "human $D_{1\alpha}$" receptor was renamed the "human D_1" receptor.

This invention further provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. In one embodiment, the amount of the compound is an amount from about 0.01 mg to about 800 mg. In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 500 mg. In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 250 mg. In another embodiment, the amount of the compound is an amount from about 0.1 mg to about 60 mg. In another embodiment, the amount of the compound is an amount from about 1 mg to about 20 mg. In a further embodiment, the carrier is a liquid and the composition is a solution. In another embodiment, the carrier is a solid and the composition is a powder or tablet. In a further embodiment, the carrier is a gel and the composition is a capsule or suppository.

This invention provides a pharmaceutical composition made by combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier.

This invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier.

In the subject invention a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes

reduction, remission, or regression of the disease. In the subject application, a "subject" is a vertebrate, a mammal, or a human.

The present invention provides for a method of treating a subject suffering from depression which comprises administering to the subject an amount of a compound provided in the present invention effective to treat the subject's depression. The present invention also provides for a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of a compound provided in the present invention effective to treat the subject's anxiety. The present invention further provides for a method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of a compound described in the present invention effective to treat the subject's depression and anxiety.

The present invention provides for the use of any of the chemical compounds disclosed herein for the preparation of a pharmaceutical composition for treating an abnormality. The invention also provides for the use of a chemical compound for the preparation of a pharmaceutical composition for treating an abnormality, wherein the abnormality is alleviated by decreasing the activity of a human GAL3 receptor. In one embodiment, the abnormality is depression. In one embodiment, the abnormality is anxiety. In one embodiment, the abnormality is depression and anxiety.

In one embodiment, the chemical compound is a GAL3

receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor;

(b) (1) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 50 percent, at a concentration of 10μM; and

(2) the GAL3 receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 50 percent, at a concentration of 10μM; and

(c) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine transporter.

In one embodiment, the chemical compound is a GAL3 receptor antagonist, wherein:

(a) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to the human GAL1 receptor; and

(b) the GAL3 receptor antagonist binds to the human GAL3 receptor with a binding affinity at least ten-fold higher than the binding affinity with which it binds to each of the following transporters: serotonin transporter, norepinephrine transporter, and dopamine

transporter.

In the present invention the term "pharmaceutically acceptable carrier" is any pharmaceutical carrier known to those of ordinary skill in the art as useful in formulating pharmaceutical compositions. On December 24, 1997 the Food and Drug Administration of the United States Department of Health and Human Services published a guidance entitled "Q3C Impurities: Residual Solvent". The guidance recommends acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient, and recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms. Table 1 of the guidance lists "Class 1 Solvents". The guidance then states that the use of Class 1 Solvents should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. The guidance further states that Class 2 Solvents should be limited in order to protect patients from potentially adverse effects. The guidance characterized the following solvents as Class 1 Solvents: benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, and 1,1,1-trichloroethane. The guidance characterized the following solvents as Class 2 Solvents: acetonitrile, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethene, dichloromethane, 1,2-dimethoxyethane, N,N-dimethylacetamide, N,N-dimethylformamide, 1,4-dioxane, 2-ethoxyethanol, ethyleneglycol, formamide, hexane, methanol, 2-methoxyethanol, methylbutyl ketone, methylcyclohexane, N-methylpyrrolidone, nitromethane, pyridine, sulfolane, tetralin, toluene, 1,1,2-

trichloroethene and xylene. As used in this invention the term "pharmaceutically acceptable carrier" shall not include Class 1 or Class 2 Solvents.

In an embodiment of the present invention, the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch. In yet a further embodiment, the compound may be delivered to the subject by means of a spray or inhalant.

A solid carrier can include one or more substances which may also act as endogenous carriers (e.g. nutrient or micronutrient carriers), flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose,

polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmoregulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate or isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellent.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or

subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.

The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will

result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

Experimental Details

I. Synthesis of Chemical Compounds

The following examples are for the purpose of illustrating methods useful for making compounds of this invention.

General Methods: All reactions were performed under an Argon atmosphere and the reagents, neat or in appropriate solvents, were transferred to the reaction vessel via syringe and cannula techniques. Anhydrous solvents were purchased from the Aldrich Chemical Company and used as received. The examples described in the patent were named using the ACD/Name Program (version 4.01, Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada). The ^{1}H NMR and ^{13}C NMR spectra were recorded at either 300 MHz (GEQE Plus) or 400 MHz (Bruker Avance) in $CDCl_3$ as solvent and tetramethylsilane as the internal standard unless otherwise noted. Chemical shifts (δ) are expressed in ppm, coupling constants (J) are expressed in Hz, and splitting patterns are described as follows: s = singlet; d = doublet; t = triplet; q = quartet; quintet; sextet; septet; br = broad; m = mutiplet; dd = doublet of doublets; dt = doublet of triplets. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Unless otherwise, mass spectra were obtained using electrospray ionization (ESI, Micromass Platform II) and MH^+ is reported. Thin-layer Chromatography (TLC) was carried out on glass plates pre-coated with silica gel 60 F_{254} (0.25 mm, EM Separations Tech.). Preparative TLC was carried out on glass sheets pre-coated with silica gel GF (2 mm, Analtech). Flash column chromatography was

performed on Merck silica gel 60 (230 -400 mesh). Melting points (mp) were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected.

The following additional abbreviations are used: HOAc, acetic acid; DIPEA, diisopropylethylamine; DMF, *N,N*-dimethylformamide; EtOAc, ethyl acetate; MeOH, methanol; TEA, triethylamine; THF, tetrahydrofuran; All solvent ratios are volume/volume unless stated otherwise.

A. General Procedures for Preparing Pyrimidines

The compounds of this invention were prepared by sucessively displacing the three chlorine atoms of a 2,4,6-trichloropyrimidine with amines. It was found that some amines (i.e. anilines) selectively displace the 2-position chlorine of 2,4,6-trichloropyrimidine, whereas other amines (e.g. piperidine) selectively displace the 4- or 6-position chlorine first (note that the 4- and 6-positions are chemically equivalent). Some amines react non-selectively at both the 2- and 4- positions of 2,4,6-trichloropyrimidine. It was also found that if the pyrimidine is substituted at the 4- or 6-position with an amine (mono- or di-substituted, or unsubstituted), then the next amine (mono- or di-substituted) undergoes substitution at the 2-position of the pyrimidine. Thus, several different Procedures were used to obtain the compounds described by this invention. The following Procedures are representative of the methods that are useful for making compounds of this invention.

Procedure A:

4,6-DICHLORO-*N*-PHENYL-2-PYRIMIDINAMINE: A solution of 2,4,6-trichloropyrimidine (5.5 g, 30 mmol) in tetrahydrofuran (15 mL) was added dropwise to a solution of aniline (2.8 mL, 1 equivalent) in tetrahydrofuran (25 mL). *N*,*N*-diisopropylethylamine (5.2 mL) was added and the solution was stirred at room temperature overnight. The solvent was removed and the crude material was purified by flash chromatography on silica gel. The column was eluted with 3% ethyl acetate in hexane, followed by 15% ethyl acetate in hexane. The eluent was removed, giving 4,6-dichloro-*N*-phenyl-2-pyrimidinamine (1.11 g, 4.6 mmol, 15%, R_f = 0.4 in 3% ethyl acetate in hexane).

Procedure B:

4,6-DICHLORO-*N*-(3,4-DICHLOROPHENYL)-2-PYRIMIDINAMINE: A solution of 2,4,6-trichloropyrimidine (5.00 g), 3,4-dichloroaniline (4.45 g, 1 equivalent) in 1,4-dioxane (20 mL) and *N*,*N*-diisopropylethylamine (10 mL) was heated at reflux with stirring for 3 hours. The solvent was removed and the crude material was purified by flash chromatography on silica gel. The column was eluted with a gradient of cyclohexane to ethyl acetate/cyclohexane (1:9). The eluent was removed, giving 4,6-dichloro-*N*-(3,4-dichlorophenyl)-2-pyrimidinamine (1.83 g, 58%, R_f = 0.39 in ethyl acetate/cyclohexane, 2:3).

Procedure C:

6-CHLORO-N^4,N^4-DIMETHYL-N^2-PHENYL-2,4-PYRIMIDINEDIAMINE:

Dimethylamine in tetrahydrofuran (2*M*, 15 mL) was added to a solution of 4,6-dichloro-*N*-phenyl-2-pyrimidinamine (0.715 g, 2.97 mmol) in tetrahydrofuran (30 mL) and *N*,*N*-diisopropylethylamine (0.52 mL). The resulting mixture was stirred at room temperature overnight. The solvent was removed and the crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (1:9). The eluent was removed, giving 6-chloro-N^4,N^4-dimethyl-N^2-phenyl-2,4-pyrimidinediamine (0.592 g, 2.39 mmol, 80%, R_f = 0.3).

Procedure D:

2,4-DICHLORO-6-(1-PIPERIDINYL)PYRIMIDINE: A mixture of 2,4,6-trichloropyrimidine (5.0 g, 27 mmol) and piperidine (2.3 g, 27 mmol) in tetrahydrofuran (50 mL) and *N*,*N*-diisopropylethylamine (3.5 g, 27 mmol) was stirred at room temperature for 24 hours. The solvent was removed and the crude material was purified by flash chromatography on silica gel. The column was eluted with a gradient of hexane to yield ethyl acetate/hexane (1:4). The eluent was removed, giving 2,4-dichloro-6-(1-piperidinyl)pyrimidine (3.67 g, 15.8 mmol, 59%, R_f = 0.58 in ethyl acetate/hexane, 1:4).

Procedure E:

4-CHLORO-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}PYRIMIDINE: A mixture of 2,4-dichloro-6-(1-piperidinyl)pyrimidine (100 mg, 0.43 mmol) and 1-[3-(trifluoromethyl)pyrid-2-yl]piperazine (119 mg, 0.52 mmol) in chlorobenzene(1 mL) was heated at 140°C in a sealed tube for 24 hours. The solvent was removed and

the crude material was purified by preparative TLC, eluting with hexane/ethyl acetate (9:1). 4-chloro-6-(1-piperidinyl)-2-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}pyrimidine was obtained as a solid (79 mg, 0.19 mmol, 44%).

Procedure F:

N-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: A mixture of 4-chloro-6-(1-piperidinyl)-2-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}pyrimidine (75.0 mg, 0.176 mmol), *p*-toluidine (23.1 mg, 0.216 mmol), 1,1'-(bisdiphenylphosphino)-1,1'-binaphthol (8.4 mg), tris(dibenzylidene acetone)dipalladium(0) (8.2 mg), and sodium *tert*-butoxide (86.4 mg) in dry toluene (1 mL) was heated at 90°C in a sealed tube for 90 minutes. The solvent was removed and the crude material was purified by preparative TLC, eluting with hexane/ethyl acetate (4:1). N-(4-Methylphenyl)-6-(1-piperidinyl)-2-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}-4-pyrimidinamine was obtained, from the band at R_f = 0.4, as a solid (59.5 mg, 0.119 mmol, 68%).

Procedure G:

N^2-ETHYL-N^2-[2-(1H-3-INDOLYL)ETHYL]-N^4-(4-METHYLPHENYL)-6-PIPERIDINO-2,4-PYRIMIDINEDIAMINE: A mixture of *N*-[4-chloro-6-(1-piperidinyl)-2-pyrimidinyl]-*N*-ethyl-*N*-[2-(1*H*-indol-3-yl)ethyl]amine (33.4 mg, 0.087 mmol) and *p*-toluidine (47 mg, 0.43 mmol) was heated neat under argon at 160°C in a sealed tube for 12 hours. The crude material was purified by preparative TLC, eluting with

hexane/ethyl acetate (4:1). N^2-Ethyl-N^2-[2-(1*H*-3-indolyl)ethyl]-N^4-(4-methylphenyl)-6-piperidino-2,4-pyrimidinediamine was obtained, from a band at R_f = 0.37, as a solid (15 mg, 0.033 mmol, 38%).

Procedure H:

2,6-DICHLORO-*N*,*N*-DIMETHYL-4-PYRIMIDINAMINE: Sodium hydride (0.13 g, 0.79 mmol) was added to a solution of 2,6-dichloro-4-pyrimidinamine (0.40 g, 0.95 mmol) in dry tetrahydrofuran (5 mL) and stirred for 10 minutes, at which point gas evolution had ceased. Methyl iodide (0.06 mL, 0.95 mmol) was added and the resulting solution was stirred for 3 hours at room temperature. The solution was quenched with aqueous ammonium chloride/ammonium carbonate. The solution was extracted with ethyl acetate and the extracts were dried over sodium sulfate. The solvent was removed and the resulting crude product was purified by flash chromatography over silica gel, eluting with hexane/ethyl acetate (2:1). The desired product (R_f = 0.55) was obtained as a white powder (70 mg, 0.36 mmol, 46%).

Procedure I:

N-ETHYL-2-(1*H*-INDOL-3-YL)ETHANAMINE: Step 1. Acetic anhydride (1.02 g) was added dropwise to a stirring solution of tryptamine (1.60 g) in tetrahydrofuran (5 mL) at 0°C and then brought to room temperature. After 2 hours, the solvent was removed and the residue was taken up into ethyl acetate. The solution was filtered through a plug of silica gel and the solvent removed, giving *N*-[2-(1H-indol-3-yl)ethylacetyltryptamineacetamide (1.65 g, 100%).

Step 2. Lithium aluminum hydride in tetrahydrofuran (1*M*, 30 mL) was added dropwise to a stirring solution of *N*-[2-(1H-indol-3-yl)ethylacetyltryptamineacetamide (2.02 g) in tetrahydrofuran (10 mL) at 0°C. The solution was then heated at reflux overnight. The solution was cooled to 0°C and water was very carefully added dropwise. The white solid was filtered and rinsed with ether/methanol (9:1, 2 X 25 mL). The solvent was removed from the filtrate, giving *N*-ethyl-2-(1*H*-indol-3-yl)ethanamine as a viscous pale yellow oil (1.75 g, 93%).

Procedure J:

4-CHLORO-*N*-[2-(1*H*-INDOL-3-YL)-1-METHYLETHYL]-6-(1-PIPERIDINYL)-2-PYRIMIDINAMINE: A mixture of 2,4-dichloro-6-(1-piperidinyl)pyrimidine (80 mg, 0.34 mmol), α-methyltryptamine (59 mg, 0.34 mmol), and potassium carbonate (47 mg, 0.34 mmol) in chlorobenzene(1 mL) was heated at 150°C in a sealed tube for 16 hours. The solvent was removed and the crude material was purified by preparative TLC, eluting with cyclohexane/ethyl acetate (4:1). 4-Chloro-*N*-[2-(1*H*-indol-3-yl)-1-methylethyl]-6-(1-piperidinyl)-2-pyrimidinamine (R_f = 0.19) was obtained as a solid (64.5 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.68 (br d, 1H, *J* = 7.5), 7.32 (d, 1H, *J* = 7.8), 7.16 (t, 1H, *J* = 7.8), 7.12 (t, 1H, *J* = 7.8), 6.95 (d, 1H, *J* = 2.1), 5.87 (s, 1H), 4.89 (br d, 1H, *J* = 8.1), 4.36 (sextet, 1H, *J* = 6.6), 3.58 - 3.50 (m, 4H), 3.07 (dd, 1H, *J* = 14.4, 5.1), 2.83 (dd, 1H, *J* = 14.1, 7.2), 1.70 - 1.55 (m, 6H), 1.16 (d, 3H, *J* = 6.6).

Procedure K:

N-(4-METHYLPHENYL)-2-(1-PIPERAZINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: A solution of 2-(4-benzyl-1-piperazinyl)-*N*-(4-methylphenyl)-6-(1-piperidinyl)-4-pyrimidinamine (0.40 g, 0.90 mmol) and ammonium formate (0.28 g, 4.5 mmol) in methanol over 10% palladium/charcoal was stirred at 70°C for 3 hours. The solution was cooled and passed through celite. The solvent was removed, giving the desired product as a solid (0.21 g, 0.60 mmol, 66%).

Procedure L:

N-(4-METHYLPHENYL)-2-[4-(3-METHYL-2-PYRIDINYL)-1-PIPERAZINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: A mixture of *N*-(4-methylphenyl)-2-(1-piperazinyl)-6-(1-piperidinyl)-4-pyrimidinamine (100 mg, 0.284 mmol), 2-bromo-3-methylpyridine (54 mg, 0.312 mmol), 1,1'-(bisdiphenylphosphino)-1,1'-binaphthol (13 mg), tris(dibenzylidene acetone)dipalladium(0) (13 mg), and sodium tert-butoxide (136 mg) in dry toluene (4 mL) was heated at 90°C in a sealed tube for 2 hours. The reaction was quenched with water and the solution was extracted three times with ethyl acetate. The solvent was dried and removed. The crude material was purified by preparative TLC, eluting with hexane/ethyl acetate (2:1). *N*-(4-methylphenyl)-2-[4-(3-methyl-2-pyridinyl)-1-piperazinyl]-6-(1-piperidinyl)-4-pyrimidinamine was obtained, from the band at R_f = 0.46, as a solid (17.1 mg, 0.0385 mmol, 14%).

Procedure M:

4,6-DICHLORO-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-

PIPERAZINYL}PYRIMIDINE and 2,4-DICHLORO-6-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}PYRIMIDINE: A solution of 4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazine (127 mg, 0.66 mmol), 2,4,6-trichloropyrimidine (100 mg, 0.55 mmol) and *N,N*-diisopropylethylamine (95 μL) in tetrahydrofuran (1 mL) was stirred at 0°C for 15 minutes. At this time, the starting material could no longer be detected by TLC. The solvent was removed and the crude material was purified by preparative TLC, eluting with ethyl acetate/hexane (1:4). Two bands were removed giving 4,6-dichloro-2-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}pyrimidine (41.7 mg, 0.110 mmol, 17%, R_f = 0.41), and 2,4-dichloro-6-{4-[3-(trifluoromethyl)-2-pyridinyl]-1-piperazinyl}pyrimidine (162 mg, 0.429 mmol, 65%, R_f = 0.10).

Procedure N:

4-{4-[4-CHLORO-6-(DIMETHYLAMINO)-2-PYRIMIDINYL]-1-PIPERAZINYL}PHENOL: DIPEA (4.535 g, 0.0260 mol) was added to a stirred solution of 4-N,N-dimethylamino-2,6-dichloropyrimidine (2.00 g, 0.0104 mol) and 4-(1-piperazinyl)phenol (2.23 g, 0.0125 mol) in THF (50 mL) at room temperature under argon. The resulting mixture was refluxed for 48 h, cooled to room temperature, quenched with water (100 mL), concentrated under reduced pressure and the crude product was redissolved in EtOAc. The organic layer was separated and washed with water (2 X 100 mL), brine (2 X 100 mL) and purified by column

chromatography on silica using EtOAc/Hexane (1:9), giving the desired product (2.77 g, 80%).

Procedure O:

A solution of p-toludine (0.2 g, 1.87 mmol) in THF (2 mL) was added to a stirred suspension of NaH (0.11 g, 2.79 mmol) in anhydrous THF (2 mL) at room temperature. The resulting mixture was heated at 40 °C for 15 minutes under argon and cooled to room temperature. 6-Chloropyrimidine (0.34 g, 1.03 mmol) in THF (25 mL) was added to the above mixture and the resulting mixture was heated at refluxed for 15 h. The reaction mixture was then cooled to room temperature and quenched with saturated. NH_4Cl(2 drops). The crude product was concentrated under reduced pressure and redissolved in EtOAc. The organic layer was separated and washed with aqueous citric acid (2 X 100 mL), water (2 X 100 mL) and brine (2 X 100 mL). The crude product was purified by column chromatography on silica using EtOAc/hexanes (1:4), giving the desired product (0.23 g, 55%).

Procedure P:

2-(4-BENZYL-1-PIPERAZINYL)-N^4-(3,4-DICHLOROPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Potassium tert-butoxide (1.6 mmol, 1 M in 2-methyl 2-propanol) was added to a

solution of *N*-[2-(4-benzyl-1-piperazinyl)-6-chloro-4-pyrimidinyl]-*N*,*N*-dimethylamine (0.331 g, 0.997 mmol) and 3,4 dichloroaniline (0.178 g, 1.10 mmol) in dioxane (2 mL). Subsequently, tris(dibenzylidineacetone)dipalladium (40 mg, 0.04 mmol) and 2,2'-Bis(diphenylphosphino)-1,1'binapthyl (44 mg, 0.070 mmol) were added and the mixture was stirred for 7 h at 110 °C. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was treated with saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by preparative TLC using hexane/EtOAc to give the desired product (300 mg, 65 %).

Procedure Q:

N-[2-(4-BENZYL-1-PIPERAZINYL)-6-CHLORO-4-PYRIMIDINYL]-*N*,*N*-: DIPEA (5.00 g, 40.0 mmol) was added dropwise to a solution of the *N*-(2,6-dichloro-4-pyrimidinyl)-*N*,*N*-dimethylamine (5.70 g, 29.6 mmol) and benzyl piperazine (6.00 g, 34.0 mmol) in m-xylene (15 mL). The mixture was stirred overnight at 130 °C, cooled to room temperature, treated with saturated $NaHCO_3$ (50 mL) and then extracted with CH_2Cl_2 (3 X 50 mL). The organic layer

was washed with brine (2 X 100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using EtOAc/hexane (1:3), giving the desired product (6.8 g, 20 mmol, 67%).

Procedure R:

*N*⁴,*N*⁴-DIMETHYL-*N*⁶-(4-METHYLPHENYL)-*N*²-(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: A mixture of *N*-[4-(dimethylamino)-6-(4-toluidino)-2-pyrimidinyl]-2-phenylacetamide (60 mg, 0.166 mmol), and LAH (1mL, 1M in THF) in THF (10 mL) was refluxed for 3h.

The crude product was concentrated *in vacuo* and treated with saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by preparative TLC using hexane/EtOAc (1:3), giving the desired product (30 mg, 52 %).

Procedure S:

N-[4-(DIMETHYLAMINO)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-2-PHENYLACETAMIDE: A mixture of *N*⁴,*N*⁴-dimethyl-*N*⁶-(4-methylphenyl)-2,4,6-pyrimidinetriamine (122 mg, 0.50 mmol), phenylacetyl chloride (84 mg, 0.55 mmol), and

triethylamine (100 mg, 1.00 mmol) in CH_2Cl_2 was stirred at room temperature for 16h. The crude product was concentrated *in vacuo* and treated with saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by preparative TLC using hexane/EtOAc (1:3), giving the desired product (60 mg, 33 %).

Procedure T:

A mixture of N^4-(3-methoxyphenyl)-N^6,N^6-dimethyl-2-[4-(2-thienylcarbonyl)-1-piperazinyl]-4,6-pyrimidinediamine (28 mg, 0.06 mmol) and LAH (300 uL 1M, 0.3 mmol) in THF (10 mL) was refluxed for 16 h. The crude product was concentrated *in vacuo* and treated with saturated $NaHCO_3$ (50 mL) and extracted with EtOAc (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by preparative TLC using hexane/EtOAc (1:3), giving the desired product (20 mg, 39 %).

Procedure U:

2-[4-(3-METHOXYBENZYL)-1-PIPERAZINYL]-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: A solution of N^4-(3-methoxyphenyl)-N^6,N^6-dimethyl-2-(1-piperazinyl)-4,6-pyrimidinediamine (36 mg, 0.1 mmol), DIPEA (52 mg, 0.4 mmol), and 1-(chloromethyl)-3-methoxybenzene (20 mg, 0.13 mmol) in 5 mL of dioxane was stirred at 100 °C for 16 h. The crude product was concentrated *in vacuo* and treated with saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (32 mg, 70 %).

Procedure V:

6-CHLORO-N^4-(4-METHYLPHENYL)-2,4-PYRIMIDINEDIAMINE: A mixture of 4,6-dichloro-2-pyrimidinamine (1.64 g, 0.01 mol), *p*-toluidine (1.07 g, 0.01 mol) in dioxane (2 mL) was heated in a sealed tube for 30 minutes at 140 °C. The crude product was treated with NaOH (50 ml, 2M) and extracted with CH_2Cl_2 (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product

was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (2 g, 78 %).

Procedure W:

N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-THIENYLCARBONYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: A mixture of 2-thiophenecarboxylic acid (15 mg, 0.12 mmol), DIPEA (129 mg, 1.00 mmol) and O-(7-azabenzotriazol-1-yl)N,N,N',N'-tetramethyluronium hexafluorophosphate (44 mg, 0.12 mmol) in DMF (5 mL) was stirred at room temperature for 30 minutes. N^4-(3-methoxyphenyl)-N^6,N^6-dimethyl-2-(1-piperazinyl)-4,6-pyrimidinediamine (36 mg, 0.10 mmol) was added to the above mixture and stirred at room temperature for 16 h. The crude product was treated with saturated $NaHCO_3$ (50 mL) and extracted with EtOAC (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (25 mg, 57 %).

Procedure X:

2-(4-BENZYL-1-PIPERAZINYL)-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: A mixture of N^4-(3-methoxyphenyl)-N^6,N^6-dimethyl-2-(1-piperazinyl)-4,6-pyrimidinediamine (36 mg, 0.10 mmol) and benzaldehyde (11 mg, 0.1 mmol) in a solution of methanol (5 mL) and acetic acid (0.5 mL) was stirred at room temperature for 1 h. Sodium cyanoborohydride (7 mg, 0.1 mmol) was added to the above solution and stirred at room temperature for 16 h. The crude product was treated with saturated $NaHCO_3$ (50 mL) and extracted with EtOAC (3 X 50 mL). The organic layer was washed with brine (2 X 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (8 mg, 40 %).

Procedure Y:

2-[4-(4-BROMOPHENYL)-1-PIPERAZINYL]-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: A mixture of N^4-(3-methoxyphenyl)-N^6,N^6-dimethyl-2-(1-piperazinyl)-4,6-pyrimidinediamine (36 mg, 0.1 mmol), 1-bromo-4-fluorobenzene (20 mg, 0.13 mmol) was heated at 100 °C for 1 h. The crude product was dissolved in CH_2Cl_2 (0.5 mL)

and purified by preparative TLC using 5 % methanol in EtOAc, giving the desired product (20 mg, 40 %).

Procedure Z:

2-[4-(2-METHOXYBENZYL)-1-PIPERAZINYL]-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: A mixture of N^4,N^4-dimethyl-N^6-(4-methylphenyl)-2-(1-piperazinyl)-4,6-pyrimidinediamine (30 mg, 0.086 mmol), 1-(chloromethyl)-2-methoxybenzene (17 mg, 0.1 mmol) and triethylaminie (200 mg, 2 mmol) in 1 DMF (1 mL) heated by microwave at 200 °C for 12 minutes. The crude product was treated with saturated $NaHCO_3$ (50 mL) and extracted with EtOAC (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (10 mg, 27 %).

Procedure AA:

N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-THIENYLCARBONYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

A solution of N^4-(3-methoxyphenyl)-N^6,N^6-dimethyl-2-(1-piperazinyl)-4,6-pyrimidinediamine (33 mg, 0.1 mmol), 2-thiophenecarbonyl chloride (20 mg, 0.14 mmol), and

triethylamine (40 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 16 h. The crude product was concentrated *in vacuo* and treated with saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product as a pale red oil (35 mg, 80 %).

Procedure BB:

N^4,*N*^{4}-DIMETHYL-*N*^{6}-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: A mixture of 6-chloro-*N*^{4}-(4-methylphenyl)-2,4-pyrimidinediamine (1.5 g, 6.4 mmol), and *N*,*N*-dimethylamine hydrochloride (0.56 g, 7 mmol) and triethylamine (1.4 g, 14 mmol) in DMF (2 mL), was heated at 170 °C for 16 h. The product was filtered out and the organic layer was treated with saturated $NaHCO_3$ (50 mL) and extracted with EtOAC (3 X 50 mL). The organic layer was washed with brine (2 X 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica using hexane/EtOAc (1:3), giving the desired product (0.6 g, 40 %).

Procedure CC:

N-(4-METHYLPHENYL)-2-[4-(1-OXIDO-2-PYRIDINYL)-1-PIPERAZINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: A solution of 3- cholorperbenzoic acid (450 mg, 2.6 mmol), and 30 % H_2O_2 (0.1 mL) in CH_2Cl_2 (2 mL) was added to a solution of N-(4-methylphenyl)-6-(1-piperidinyl)-2-[4-(2-pyridinyl)-1-piperazinyl]-4-pyrimidinamine (150 mg, 0.300 mmol) in CH_2Cl_2 at 0 °C. The resulting mixture was gradually warmed to room temperature and stirred for 24 h, crude product was treated with saturated $NaHCO_3$ (50 mL) and extracted with EtOAC (3 X 50 mL). Combined organic layers were washed with brine (2 X 50 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by chromatography on silica using hexane/EtOAc (1:3) to give the desired product.

Piperazines that were not commercially available were synthesized according to the method previously described (Ennis and Ghazal, 1992).

The following are examples to illustrate the compounds of this invention. Procedures A - BB as described above, were used and any modifications are noted in parentheses.

Example 1: N^2-CYCLOHEXYL-N^2-METHYL-N^4-(4-METHYLPHENYL)-6-

(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G (for substitution with cyclohexylamine), and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, 2H, J = 7.8), 7.12 (d, 2H, J = 7.8), 5.29 (s, 1H), 4.43 (br s, 1H), 3.55 - 3.44 (m, 5H), 3.01 (s, 3H), 2.33 (s, 3H), 2.00 - 1.05 (m, 16H).

Example 2: N^2-CYCLOHEXYL-N^2-(2-METHOXYETHYL)-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, J (130°C), and F (2 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 2H, J = 8.1), 7.10 (d, 2H, J = 8.1), 6.17 (br s, 1H), 5.31 (s, 1H), 4.58 - 4.43 (m, 1H), 3.61 - 3.57 (m, 4H), 3.52 - 3.48 (m, 4H), 3.39 (s, 3H), 2.31 (s, 3H), 1.83 - 1.75 (m, 4H), 1.70 - 1.50 (m, 7H), 1.43 - 1.37 (m, 4H), 1.19 - 1.05 (m, 1H); ESI-MS m/z 424 (MH^+).

Example 3: N^4-(4-METHYLPHENYL)-N^2-PHENYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures A, B (for substitution with aniline), and E (100°C, for substitution with piperidine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, 2H, J = 8.7), 7.26 (t, 2H, J = 7.8), 7.19 (d, 2H, J = 8.7), 7.15 (d, 2H, J = 7.8), 6.95 (t, 1H, J = 7.8), 6.82 (br s, 1H), 6.48 (br s, 1H), 5.49 (s, 1H), 3.56 - 3.46 (m, 4H), 2.34 (s, 3H), 1.67 - 1.52 (m, 6H); ESI-MS m/z 360 (MH^+).

Example 4: N^2,N^4-DI(4-METHYLPHENYL)-6-PIPERIDINO-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D and G (100°C, 12 hours, for substitution of p-toludine at C2 and C4 of the pyrimidine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 2H, J = 8.3), 7.20 (d, 2H, J = 7.8), 7.15 (d, 2H, J = 8.3),

7.10 (d, 2H, J = 8.3), 6.79 (br s, 1H), 6.46 (br s, 1H), 5.52 (s, 1H), 3.51 (t, 4H, J = 4.6), 2.36 (s, 3H), 2.31 (s, 3H), 1.69 - 1.53 (m, 6H); ESI-MS m/z 374 (MH^+).

Example 5: N^2-(4-CHLOROPHENYL)-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G (for substitution with 4-chloroaniline), and G (3.5 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 7.72 (br s, 1H), 7.54 (d, 2H, J = 8.3), 7.28 - 7.17 (m, 6H), 5.36 (s, 1H), 3.61 - 3.46 (m, 4H), 2.36 (s, 3H), 1.76 - 1.53 (m, 6H); ESI-MS m/z 393 (MH^+ with ^{35}Cl), 395 (MH^+ with ^{37}Cl).

Example 6: N^2-METHYL-N^4-(4-METHYLPHENYL)-N^2-PHENYL-6-(1-PIPERIDINyl)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G (140°C, 90 minutes, for substitution with aniline), and G (3.5 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 - 7.33 (m, 4H), 7.18 - 7.14 (overlapping t at 7.16 & d at 7.15, 3H), 7.07 (d, 2H, J = 7.8), 6.25 (br s, 1H), 5.41 (s, 1H), 3.54 (s, 3H), 3.50 - 3.42 (m, 4H), 2.33 (s, 3H), 1.68 - 1.50 (m, 6H); ESI-MS m/z 374 (MH^+).

Example 7: N^2-METHYL-N^2,N^4-DI(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G (180°C, 10 hours, for substitution with N-methyl-p-toluidine), and G (140°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 - 7.04 (m, 8H), 6.19 (br s, 1H), 5.38 (s, 1H), 3.52 (s, 3H), 3.48 - 3.41 (m, 4H), 2.38 (s, 3H), 2.31 (s, 3H), 1.67 - 1.49 (m, 6H); ESI-MS m/z 388 (MH^+).

Example 8: N^2-[2-(5-METHYL-1H-3-INDOLYL)ETHYL]-N^4-(4-

METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:
Prepared by Procedures D, J, and G (160°C, 12 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.43 (s, 1H), 7.23 (d, 1H, *J* = 8.4), 7.15 (d, 2H, *J* = 8.4), 7.10 (d, 2H, *J* = 8.4), 7.00 (d, 1H, *J* = 8.4), 6.98 (s, 1H), 6.43 (br s, 1H), 5.37 (s, 1H), 4.86 (br t, 1H, *J* = 7.1), 3.70 (q, 2H, *J* = 7.1), 3.52 - 3.43 (m, 4H), 3.02 (t, 2H, *J* = 7.1), 2.46 (s, 3H), 2.32 (s, 3H), 1.67 - 1.49 (m, 6H); ESI-MS *m/z* 441 (MH^+).

Example 9: N^2-[2-(5-METHOXY-1*H*-3-INDOLYL)ETHYL]-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:
Prepared by Procedures D, E (160°C, 36 hours), and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.15 (d, 2H, *J* = 8.4), 7.12 (d, 2H, *J* = 8.4), 7.08 - 7.04 (m, 3H), 6.85 (dd, 1H, *J* = 8.8, 2.6), 6.48 (br s, 1H), 5.36 (s, 1H), 4.96 (br s, 1H), 3.85 (s, 3), 3.72 - 3.67 (m, 2H), 3.55 - 3.45 (m, 4H), 3.02 (t, 2H, *J* = 6.9), 2.32 (s, 3H), 1.68 - 1.49 (m, 6H); ESI-MS *m/z* 457 (MH^+).

Example 10: N^2-[2-(1*H*-3-INDOLYL)ETHYL]-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:
Prepared by Procedures D, E (100°C), and G (150°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 7.63 (d, 1H, *J* = 7.8), 7.31 (d, 1H, *J* = 7.8), 7.23 - 7.09 (m, 6H), 6.94 (s, 1H), 6.60 (br s, 1H), 5.36 (s, 1H), 4.95 (t, 1H, *J* = 6.3), 3.68 (dt, 2H, *J* = 6.3, 6.9), 3.48 - 3.44 (m, 4H), 3.01 (t, 2H, *J* = 6.9), 2.31 (s, 3H), 1.65 - 1.48 (m, 6H); ESI-MS *m/z* 427 (MH^+).

Example 11: N^2-[2-(1H-3-INDOLYL)ETHYL]-N^2-METHYL-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 4 hours), and F (12 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.71 (d, 1H, *J* = 7.8), 7.36 (d, 1H, *J* = 7.8), 7.22 (d, 2H, *J* = 7.8), 7.20 (t, 1H, *J* = 7.8), 7.17 - 7.09 (m, 3H), 7.03 (s, 1H), 6.40 (br s, 1H), 5.35 (s, 1H), 3.91 (t, 2H, *J* = 7.8), 3.56 - 3.46 (m, 4H), 3.16 (s, 3H), 3.09 (t, 2H, *J* = 7.8), 2.33 (S, 3H), 1.70 - 1.52 (m, 6H); ESI-MS *m/z* 441 (MH^+).

Example 12: N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^2-METHYL-N^4-PHENETHYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 12 hours), and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.71 (d, 1H, *J* = 7.8), 7.34 (t, 2H, *J* = 7.8), 7.24 - 7.15 (m, 5H), 7.08 (t, 1H, *J* = 7.8), 6.98 (s, 1H), 4.95 (s, 1H), 4.39 (br s, 1H), 3.88 (t, 2H, *J* = 7.8), 3.57 - 3.48 (m, 6H), 3.12 (s, 3H), 3.05 (t, 2H, *J* = 7.8), 2.89 (t, 2H, *J* = 7.8), 1.68 - 1.53 (m, 6H); ESI-MS *m/z* 455 (MH^+).

Example 13: N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^2-METHYL-N^4-(2-NAPHTHYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE:

Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and E (160°C, 12 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.92 (s, 1H), 7.78 - 7.75 (m, 3H), 7.72 (d, 1H, *J* = 8.1), 7.46 - 7.41 (m, 2H), 7.37 (d, 2H, *J* = 8.4), 7.20 (t, 1H, *J* = 7.8), 7.11 (t, 1H, *J* = 7.8), 7.01 (s, 1H), 6.42 (br s, 1H), 5.45 (s, 1H), 3.95 (t, 2H, *J* = 7.8), 3.56 - 3.49 (m, 4H), 3.19 (s, 3H), 3.11 (t, 2H, *J* = 7.8), 1.62 - 1.59 (m, 6H); ESI-MS *m/z* 477 (MH^+).

Example 14: N^4-(3-FLUOROPHENYL)-N^2-[2-(1*H*-INDOL-3-

YL)ETHYL]-N^2-METHYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.71 (d, 1H, *J* = 7.8), 7.41 (dt, 1H, *J* = 9.5, 1.0), 7.34 (d, 1H, *J* = 7.8), 7.22 - 7.06 (m, 4H), 7.02 - 7.00 (s at 7.02 & d at 7.01 overlapping, 2H), 7.01 (s, 1H), 6.33 (br s, 1H), 5.34 (s, 1H), 3.90 (t, 2H, *J* = 7.8), 3.58 - 3.50 (m, 4H), 3.16 (s, 3H), 3.08 (t, 2H, *J* = 7.8), 1.70 - 1.54 (m, 6H); ESI-MS *m/z* 445 (MH^+).

Example 15: N^4-(3,4-DIFLUOROPHENYL)-N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^2-METHYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.68 (d, 1H, *J* = 7.8), 7.51 (ddd, 1H, *J* = 9.5, 7.8, 2.3), 7.35 (d, 1H, *J* = 7.8), 7.19 (t, 1H, *J* = 7.8), 7.11 (t, 1H, *J* = 7.8), 7.07 - 6.90 (m, 3H), 7.01 (s, 1H), 6.22 (br s, 1H), 5.23 (s, 1H), 3.89 (t, 2H, *J* = 7.8), 3.57 - 3.49 (m, 4H), 3.15 (s, 3H), 3.07 (t, 2H, *J* = 7.8), 1.68 - 1.53 (m, 6H); ESI-MS *m/z* 463 (MH^+).

Example 16: N^4-(3-CHLORO-4-METHYLPHENYL)-N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^2-METHYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.69 (d, 1H, *J* = 7.5), 7.51 (s, 1H), 7.36 (d, 1H, *J* = 7.8), 7.19 (t, 1H, *J* = 7.8), 7.14 - 7.06 (m, 3H), 7.01 (s, 1H), 6.18 (br s, 1H), 5.29 (s, 1H), 3.89 (t, 2H, *J* = 7.8), 3.53 - 3.48 (m, 4H), 3.13 (s, 3H), 3.07 (t, 2H, *J* = 7.8), 2.31 (s, 3H),

1.70 - 1.55 (m, 6H); ESI-MS *m/z* 475 (MH^+).

Example 17: N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^4-(3-METHOXYPHENYL)-N^2-METHYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methyltryptamine), and G. ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.71 (d, 1H, *J* = 7.8), 7.34 (d, 1H, *J* = 8.3), 7.25 - 7.04 (m, 4H), 7.01 (s, 1H), 6.89 (d, 1H, *J* = 7.8), 6.57 (dd, 1H, *J* = 8.3, 2.4), 6.30 (br s, 1H), 5.42 (s, 1H), 3.91 (t, 2H, *J* = 7.7), 3.76 (s, 3H), 3.57 - 3.49 (m, 4H), 3.16 (s, 3H), 3.08 (t, 2H, *J* = 7.7), 1.70 - 1.53 (m, 6H); ESI-MS *m/z* 457 (MH^+).

Example 18: N^2-ETHYL-N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-ethyltryptamine), and G. ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.71 (d, 1H, *J* = 7.8), 7.35 (d, 1H, *J* = 7.8), 7.25 - 7.16 (overlapping d at 7.23 & t at 7.22, 3H), 7.14 (t, 1H, *J* = 7.8), 7.08 (d, 2H, *J* = 7.8), 7.02 (s, 1H), 6.19 (br s, 1H), 5.34 (s, 1H), 3.82 (t, 2H, *J* = 7.9), 3.61 (q, 2H, *J* = 7.1), 3.55 - 3.45 (m, 4H), 3.08 (t, 2H, *J* = 7.9), 2.30 (s, 6H), 1.68 - 1.50 (m, 6H), 1.18 (t, 3H, *J* = 7.1); ESI-MS *m/z* 455 (MH^+).

Example 19: N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^2-(2-METHOXYETHYL)-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with *N*-methoxyethyltryptamine), and G. ^1H NMR (300 MHz, $CDCl_3$ δ 7.96 (br s, 1H), 7.72 (d, 1H, *J* = 7.5), 7.35 (d, 1H, *J* = 7.8), 7.27 - 7.07 (m, 6H),

7.02 (s, 1H), 6.19 (br s, 1H), 5.35 (s, 1H), 3.88 (dd, 2H, J = 9.9, 5.4), 3.74 (t, 2H, J = 6.0), 3.60 (dd, 2H, J = 10.5, 4.8), 3.57 - 3.46 (m, 4H), 3.34 (s, 3H), 3.12 - 3.07 (m, 2H), 2.32 (s, 6H), 1.70 - 1.58 (m, 6H); ESI-MS m/z 485 (MH^+).

Example 20: N^2-[2-(1*H*-3-INDOLYL)-1-METHYLETHYL]-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, J, and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H) 7.70 (d, 1H, J = 7.8), 7.36 (d, 1H, J = 8.1), 7.19 - 6.98 (m, 7H), 6.60 (br s, 1H), 5.35 (s, 1H), 4.89 (br s, 1H), 4.44 - 4.36 (m, 1H), 3.55 - 3.45 (m, 4H), 3.14 (dd 1H, J = 14.1, 5.1), 2.84 (dd, 1H, J = 14.1, 7.5), 2.33 (s, 3H), 1.62 - 1.50 (m, 6H), 1.18 (d, 3H, J = 6.6); ESI-MS m/z 441 (MH^+).

Example 21: N^2-[2-(1*H*-INDOL-3-YL)-1-METHYLETHYL]-N^2-METHYL-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution with N,α-dimethyltryptamine), and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (br s, 1H) 7.73 (d, 1H, J = 7.8), 7.34 (d, 1H, J = 7.8), 7.19 - 7.09 (m, 6H), 7.03 (s, 1H), 6.17 (br s, 1H), 5.34 (s, 1H), 3.51 - 3.44 (m, 5H), 3.11 - 3.05 (m, 1H), 3.02 (s, 2H), 2.90 (dd, 1H, J = 14.7, 7.5), 2.32 (s, 3H), 1.65 - 1.49 (m, 6H), 1.18 (d, 3H, J = 6.6); ESI-MS m/z 455 (MH^+).

Example 22: N^2-METHYL-N^4-(4-METHYLPHENYL)-N^2-PHENETHYL-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours, for substitution at C2 of the pyrimidine), and G. ESI-MS m/z 402 (MH^+).

Example 23: 2-(4-BENZYL-1-PIPERAZINYL)-*N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D, I (140°C, overnight, for substitution with *N*-benzylpiperazine), and F (2 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.26 (m, 5H) 7.18 (d, 1H, *J* = 7.8), 7.12 (d, 1H, *J* = 7.8), 6.18 (br s, 1H), 5.34 (s, 1H), 3.93 - 3.87 (m, 4H), 3.77 (t, 4H, *J* = 5.0), 3.55 (s, 2H), 3.48 - 3.42 (m, 4H), 2.49 (t, 4H, *J* = 5.0), 2.31 (s, 3H), 1.66 - 1.49 (m, 6H); ESI-MS *m/z* 443 (MH^+).

Example 24: *N*-(4-METHYLPHENYL)-2-(4-PHENYL-1-PIPERIDINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D, E (16 hours, for substitution with 4-phenylpiperidine), and F (1 hour). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 - 7.24 (m, 5H), 7.19 (d, 2H, *J* = 7.8), 7.12 (d, 2H, *J* = 7.8), 6.22 (br s, 1H), 5.36 (s, 1H), 4.89 (d with fine splitting, 2H, *J* = 13.0), 3.52 - 3.42 (m, 4H), 2.86 (dt, 2H, *J* = 1.0, 13.0), 2.73 (tt, 1H, *J* = 11.6, 1.5), 2.32 (s, 3H), 1.89 (d with fine splitting, 2H, *J* = 12.0), 1.74 (ddd, 2H, *J* = 13.0, 12.0, 1.5), 1.67 - 1.52 (m, 6H); ESI-MS *m/z* 428 (MH^+).

Example 25: *N*-(4-METHYLPHENYL)-2-(4-PHENYLPIPERAZINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D, G (180°C, 2.5 hours, for substitution with *N*-phenylpiperazine), and G (140°C, overnight). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, 2H, *J* = 7.8), 7.19 (d, 2H, *J* = 7.8), 7.13 (d, 2H, *J* = 7.8), 6.99 (d, 2H, *J* = 7.8), 6.89 (t, 1H, *J* = 7.8), 6.23 (br s, 1H), 5.38 (s, 1H), 3.91 (t, 2H, *J* = 4.6), 3.54 - 3.44 (m, 4H), 3.23 (t, 2H, *J* = 4.6), 2.34 (s, 3H), 1.71 - 1.51 (m, 6H); ESI-MS *m/z* 429 (MH^+).

Example 26: 2-[4-(2-ETHYLPHENYL)-1-PIPERAZINYL]-*N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

Prepared by Procedures D, E (120°C), and F. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 1H, *J* = 7.8), 7.24 - 7.08 (m, 7H), 6.37 (br s, 1H), 5.41 (s, 1H), 3.98 - 3.90 (m, 4H), 3.53 - 3.47 (m, 4H), 2.99 - 2.92 (m, 4H), 2.80 (q, 2H, *J* = 8.3), 2.35 (s, 3H), 1.69 - 1.54 (m, 6H), 1.31 (t, 3H, *J* = 8.3); ESI-MS *m/z* 457 (MH^+).

Example 27: 2-[4-(2,6-DIMETHYLPHENYL)-1-PIPERAZINYL]-*N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE:

Prepared by Procedures D, E (120°C), and F. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, 2H, *J* = 7.8), 7.15 (d, 2H, *J* = 7.8), 7.05 - 7.95 (m, 3H), 6.30 (br s, 1H), 5.39 (s, 1H), 3.88 (t, 4H, *J* = 4.6), 3.53 - 3.47 (m, 4H), 3.15 (t, 4H, *J* = 4.6), 2.37 (s, 6H), 2.34 (s, 3H), 1.68 - 1.53 (m, 6H); ESI-MS *m/z* 457 (MH^+).

Example 28: *N*-{2-[4-(2,4-DIMETHOXYPHENYL)PIPERAZINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINYL}-*N*-(4-METHYLPHENYL)AMINE:

Prepared by Procedures D, E (150°C, 16 hours), and F (5 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, 2H, *J* = 8.1), 7.12 (d, 2H, *J* = 8.1), 6.88 (d, 1H, *J* = 9.0), 6.50 (d, 1H, *J* = 2.4), 6.43 (dd, 1H, *J* = 8.7, 2.4), 6.23 (br s, 1H), 5.36 (s, 1H), 3.94 (t, 4H, *J* = 7.5), 3.87 (s, 3H), 3.79 (s, 3H), 3.52 - 3.44 (m, 4H), 3.03 (t, 4H, *J* = 7.5), 2.33 (s, 3H), 1.65 - 1.52 (m, 6H); ESI-MS *m/z* 488 (MH^+).

Example 29: *N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)PHENYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE:

Prepared by Procedures D, E (120°C, 16 hours), and F. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.36 (t, 1H, *J* = 7.8), 7.20 - 7.09 (m, 7H), 6.25 (br s, 1H), 5.37 (s, 1H), 4.93 (t, 4H, *J* = 4.6), 3.52 - 3.45 (m, 4H), 3.26 (t, 4H, *J* = 4.6), 2.34 (s, 3H), 1.66 - 1.52 (m, 6H); ESI-MS *m/z* 497 (MH^+).

Example 30: *N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-[4-(2-PYRIDYL)-1-PIPERAZINYL]-4-PYRIMIDINAMINE: Prepared by Procedures D, G (120°C, 12 hours, for substitution with *N*-pyrid-2-ylpiperazine), and G (140°C). ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (dd, 1H, *J* = 4.4, 1.5), 7.50 (dd, 1H, *J* = 7.8, 1.5), 7.20 (d, 2H, *J* = 8.1), 7.13 (d, 2H, *J* = 8.1), 6.69 (d, 1H, *J* = 7.8), 6.63 (t, 1H, *J* = 7.8), 6.26 (br s, 1H), 5.38 (s, 1H), 3.89 (t, 4H, *J* = 4.8), 3.62 (t, 4H, *J* = 4.8), 3.55 - 3.45 (m, 4H), 2.33 (s, 3H), 1.70 - 1.52 (m, 6H); ESI-MS *m/z* 430 (MH^+).

Example 31: *N*-(4-METHYLPHENYL)-2-[4-(3-METHYL-2-PYRIDINYL)-1-PIPERAZINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared from 2-(4-benzyl-1-piperazinyl)-*N*-(4-methylphenyl)-6-(1-piperidinyl)-4-pyrimidinamine by Procedures K and L. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, 1H, *J* = 4.4, 2.2), 7.42 (dd, 1H, *J* = 7.8, 2.2), 7.19 (d, 2H, *J* = 8.1), 7.12 (d, 2H, *J* = 8.1), 6.85 (dd, 1H, *J* = 7.8, 4.4), 6.20 (br s, 1H), 5.38 (s, 1H), 3.93 - 3.87 (m, 4H), 3.53 - 3.48 (m, 4H), 3.24 - 3.18 (m, 4H), 2.33 (s, 3H), 1.67 - 1.53 (m, 6H); ESI-MS *m/z* 444 (MH^+).

Example 32: *N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[4-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures D, E (16 hours), and F. ESI-MS *m/z* 498 (MH^+).

Example 33: *N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[6-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures D, E (16 hours), and F. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 8.1), 7.19 (d, 2H, *J* = 8.4), 7.14 (d, 2H, *J* = 8.4), 6.94 (d, 1H, *J* = 7.2), 6.80 (d, 1H, *J* = 8.7), 6.23 (br s, 1H), 5.37 (s, 1H), 3.90 - 3.87 (m, 4H), 3.69 - 3.66 (m, 4H), 3.50 - 4.46 (m, 4H), 2.34 (s, 3H), 1.67 - 1.53 (m, 6H); ESI-MS *m/z* 498 (MH^+).

Example 34: *N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures D, E (16 hours), and F. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, 1H, *J* = 4.4, 2.2), 7.87 (dd, 1H, *J* = 7.8, 2.2), 7.19 (d, 2H, *J* = 8.1), 7.13 (d, 2H, *J* = 8.1), 6.99 (dd, 1H, *J* = 7.8 4.4), 6.23 (br s, 1H), 5.37 (s, 1H), 3.89 (t, 4H, *J* = 4.8), 3.53 - 3.48 (m, 4H), 3.36 (t, 4H, *J* = 4.8), 2.33 (s, 3H), 1.67 - 1.53 (m, 6H); ESI-MS *m/z* 498 (MH^+).

Example 35: *N*-CYCLOHEXYL-6-(1-PIPERIDINYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures M, E (120°C, for addition of piperidine), and F (3 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, 1H, *J* = 5.6), 7.84 (d, 1H, *J* = 7.4), 6.95 (dd, 1H, *J* = 7.4, 5.6), 4.95 (s, 1H), 4.34 (br s, 1H), 3.84 (t, 4H, *J* = 5.1), 3.55 - 3.38 (m, 5H), 3.34 (t, 4H, *J* = 5.1), 2.02 (dd, 2H, *J* = 12.0, 1.4), 1.79 - 1.71 (m, 2H), 1.69 - 1.52 (m, 6H), 1.44 - 1.10 (m, 6H); ESI-MS *m/z* 490 (MH^+).

Example 36: *N*-BICYCLO[2.2.1]HEPT-2-YL-6-(1-PIPERIDINYL)-

2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures M, E (120°C, for addition of piperidine), and F (3 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, 1H, *J* = 5.6), 7.86 (d, 1H, *J* = 7.4), 6.95 (dd, 1H, *J* = 7.4, 5.6), 4.95 (s, 1H), 4.37 (br s, 1H), 3.84 (t, 4H, *J* = 5.1), 3.57 - 3.47 (m, 4H), 3.40 - 3.31 (m, 5H), 2.25 (br s, 2H), 1.78 (ddd, 2H, *J* = 13.0, 4.6, 1.4), 1.67 - 1.42 (m, 9H), 1.25 - 1.12 (m, 4H); ESI-MS *m/z* 502 (MH^+).

Example 37: *N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-[4-(2-PYRIMIDINYL)-1-PIPERAZINYL]-4-PYRIMIDINAMINE: Prepared by Procedures D, G (120°C, 12 hours, for substitution with *N*-pyrimid-2-ylpiperazine), and G (150°C, 24 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, 2H, *J* = 4.9), 7.19 (d, 2H, *J* = 7.8), 7.13 (d, 2H, *J* = 7.8), 6.50 (t, 1H, *J* = 7.8), 6.23 (br s, 1H), 5.37 (s, 1H), 3.97 - 3.82 (m, 8H), 3.56 - 3.44 (m, 4H), 2.34 (s, 3H), 1.70 - 1.53 (m, 6H); ESI-MS *m/z* 431 (MH^+).

Example 38: *N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2-(1-PYRROLIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D, G (120°C, 3 hours, for substitution with pyrrolidine), and G (140°C, 12 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 2H, *J* = 7.8), 7.11 (d, 2H, *J* = 7.8), 6.39 (br s, 1H), 5.34 (s, 1H), 3.56 (t, 4H, *J* = 5.6), 3.53 - 3.44 (m, 4H), 2.33 (s, 3H), 1.91 (quintet, 4H, *J* = 5.6), 1.67 - 1.50 (m, 6H); ESI-MS *m/z* 338 (MH^+).

Example 39: *N*-[2-(2,3-DIHYDRO-1*H*-INDOL-1-YL)-6-(1-PIPERIDINYL)-4-PYRIMIDINYL]-*N*-(4-METHYLPHENYL)AMINE: Prepared by Procedures D, E (16 hours), and F. ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.31 (d, 1H, *J* = 7.8), 7.28 - 7.15 (m, 6H), 6.86 (t, 1H, *J* = 7.8), 6.31 (br s, 1H), 5.49 (s, 1H), 4.22 (t, 4H, *J* = 8.3), 3.59 - 3.53 (m, 4H), 3.13 (t, 4H, *J* = 8.3), 2.35 (s, 3H), 1.70 - 1.55 (m, 6H); ESI-MS *m/z* 386 (MH^+).

Example 40: *N*-(4-METHYLPHENYL)-*N*-[6-(1-PIPERIDINYL)-2-(1,2,3,4-TETRAHYDRO-1-QUINOLINYL)-4-PYRIMIDINYL]AMINE: Prepared by Procedures D, G (180°C, 3 hours, for substitution with 1,2,3,4-tetrahydroquinoline), and G (140°C, 12 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 1H, *J* = 7.8), 7.19 (d, 2H, *J* = 7.8), 7.15 - 7.07 (m, 4H), 6.93 (t, 1H, *J* = 7.8), 6.33 (br s, 1H), 5.49 (s, 1H), 4.04 (t, 2H, *J* = 6.0), 3.54 - 3.44 (m, 4H), 2.79 (t, 2H, *J* = 6.0), 2.34 (s, 3H), 1.98 (pentet, 2H, *J* = 6.0), 1.69 - 1.52 (m, 6H); ESI-MS *m/z* 400 (MH^+).

Example 41: *N*-(4-METHYLPHENYL)-*N*-[6-(1-PIPERIDINYL)-2-(1,2,3,4-TETRAHYDRO-2-ISOQUINOLINYL)-4-PYRIMIDINYL]AMINE: Prepared by Procedures D, G (180°C, 3 hours, for substitution with 1,2,3,4-tetrahydroisoquinoline), and G (140°C, 12 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 7.8), 7.26 - 7.06 (m, 7H), 6.37 (br s, 1H), 5.35 (s, 1H), 4.89 (s, 2H), 4.00 (t, 2H, *J* = 6.0), 3.58 - 3.44 (m, 4H), 2.91 (t, 2H, *J* = 6.0), 2.32 (s, 3H), 1.68 - 1.47 (m, 6H); ESI-MS *m/z* 400 (MH^+).

Example 42: *N*-[2-(6,7-DIMETHOXY-3,4-DIHYDRO-2(1*H*)-ISOQUINOLINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINYL]-*N*-(4-METHYLPHENYL)AMINE: Prepared by Procedures D, E (160°C, 12 hours), and F (5 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, 2H, *J* = 7.8), 7.13 (d, 2H, *J* = 7.8), 6.70 (s,

1H), 6.64 (s, 1H), 6.25 (br s, 1H), 5.36 (s, 1H), 4.82 (s, 2H), 4.01 (t, 2H, *J* = 5.9), 3.89 (s, 3H), 3.87 (s, 3H), 3.58 - 3.44 (m, 4H), 2.84 (t, 2H, *J* = 5.9), 2.33 (s, 3H), 1.68 - 1.52 (m, 6H); ESI-MS *m/z* 460 (MH^+).

Example 43: *N*-[2-(2,3-DIHYDRO-1*H*-BENZO[DE]ISOQUINOLIN-2-YL)-6-(1-PIPERIDINYL)-4-PYRIMIDINYL]-*N*-(4-METHYLPHENYL)AMINE: Prepared by Procedures D, E (160°C, 12 hours), and G. ESI-MS *m/z* 436 (MH^+).

Example 44: 4-PHENYL-1-[4-(1-PIPERIDINYL)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-4-PIPERIDINOL: Prepared by Procedures D, E (23 hours), and F. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, 2H, *J* = 7.5), 7.36 (t, 2H, *J* = 7.8), 7.26 (t, 1H + $CHCl_3$, *J* = 7.8), 7.19 (d, 2H, *J* = 8.4), 7.12 (d, 2H, *J* = 8.4), 6.20 (br s, 1H), 5.36 (s, 1H), 4.67 (br d, 2H, *J* = 13.5), 3.50 - 3.45 (m, 4H), 4.67 (br t, 2H, *J* = 13.1), 2.33 (s, 3H), 2.10 (dt, 2H, *J* = 4.2, 12.6), 1.78 (br d, 2H, *J* = 13.5), 1.65 - 1.53 (m, 6H); ESI-MS *m/z* 444 (MH^+).

Example 45: N^2,N^2-BIS(2-METHOXYETHYL)-N^4-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-2,4-PYRIMIDINEDIAMINE: Prepared by Procedures D, G [140°C, 2 hours, for substitution with bis(methoxyethyl)amine], and G (140 °C, 1.5 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 2H, *J* = 7.8), 7.10 (d, 2H, *J* = 7.8), 6.20 (br s, 1H), 5.33 (s, 1H), 3.77 (t, 4H, *J* = 6.2), 3.59 (t, 4H, *J* = 6.3), 3.47 - 3.40 (m, 4H), 3.36 (s, 6H), 1.64 - 1.49 (m, 6H); ESI-MS *m/z* 400 (MH^+).

Example 46: *N*-(4-METHYLPHENYL)-2-(3-PHENYL-4-MORPHOLINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared

by Procedures D, E (16 hours), and F (1 hour). ^{1}H NMR (300 MHz, $CDCl_3$)
δ 7.51 (d, 2H, *J* = 7.8), 7.31 (t, 2H, *J* = 7.8), 7.23 (t, 1H, *J* = 7.8), 7.15 (d, 2H, *J* = 7.8), 7.10 (d, 2H, *J* = 7.8), 6.22 (br s, 1H), 5.84 (d, 1H, *J* = 1.0), 5.36 (s, 1H), 4.51 - 4.42 (m, 2H), 3.94 (m, 2H), 3.66 (dt, 1H, *J* = 1.0, 11.5), 3.49 - 3.43 (m, 4H), 3.24 (dt, 1H, *J* = 1.5, 11.5), 2.32 (s, 3H), 1.64 - 1.47 (m, 6H); ESI-MS *m/z* 430 (MH^+).

Example 47: *N*-(4-METHYLPHENYL)-2-(2-PHENYL-4-MORPHOLINYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D, E (14 hours), and F (100°C, 2 hours). ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 2H, *J* = 7.8), 7.38 (t, 2H, *J* = 7.8), 7.34 (t, 1H, *J* = 7.8), 7.18 (d, 2H, *J* = 8.7), 7.13 (d, 2H, *J* = 8.4), 6.19 (br s, 1H), 5.38 (s, 1H), 4.70 (br d, 1H, *J* = 12.6), 4.58 - 4.51 (m, 1H), 4.11 (dd, 1H, *J* = 10.2, 2.4), 3.80 (dt, 1H, *J* = 2.7, 11.7), 3.50 - 3.43 (m, 4H), 3.10 (dt, 1H, *J* = 2.1, 12.8), 2.89 (dd, 1H, *J* = 13.2, 10.2), 2.33 (s, 3H), 1.66 - 1.50 (m, 6H); ESI-MS *m/z* 430 (MH^+).

Example 48: *N*-(4-METHYLPHENYL)-2-[(2*S*,3*R*)-3-METHYL-2-PHENYLMORPHOLINYL]-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D, E (120°C), and F (1 hour). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 2H, *J* = 7.8), 7.39 (t, 2H, *J* = 7.8), 7.27 (t, 1H, *J* = 7.8), 7.20 (d, 2H, *J* = 7.8), 7.14 (d, 2H, *J* = 7.8), 6.25 (br s, 1H), 5.39 (s, 1H), 4.99 - 4.90 (m, 1H), 4.77 (d, 1H, *J* = 1.5), 4.39 (dd, 1H, *J* = 13.0, 1.5), 4.15 (dd, 1H, *J* = 8.3, 1.5), 3.80 (dt, 1H, *J* = 3.7, 11.6), 3.53 - 3.45 (m, 4H), 3.26 (dt, 1H, *J* = 3.7, 13.0), 2.33 (s, 3H), 1.68 - 1.52 (m, 6H), 0.90 (d,

3H, J = 8.3); ESI-MS m/z 444 (MH^+).

Example 49: 2-[(2*R*,3*R*)-3-(METHOXYMETHYL)-2-PHENYLMORPHOLINYL]-*N*-(4-METHYLPHENYL)-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedures D, E, and F (3 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 2H, J = 7.8), 7.31 (t, 2H, J = 7.8), 7.27 - 7.20 (m, 3H), 7.13 (d, 2H, J = 7.8), 6.31 (br s, 1H), 5.84 (d, 1H, J = 1.0), 5.35 (dd, 1H, J = 9.3, 2.7), 5.11 (s, 1H), 4.28 (d with splitting, 1H, J = 13.0), 4.01 (t, 1H, J = 9.0), 3.58 - 3.46 (m, 6H), 3.40 (s, 3H), 3.27 - 3.15 (m, 1H), 2.31 (s, 3H), 1.69 - 1.50 (m, 6H); ESI-MS m/z 473 (MH^+).

Example 50: N^4,N^4-DIMETHYL-N^2,N^6-DIPHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight). ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 2H, J = 7.8), 7.38 - 7.27 (m, 6H), 7.11 - 7.04 (m, 1H), 6.95 (t, 1H, J = 7.8), 6.75 (br s, 1H), 6.38 (br s, 1H), 5.45 (s, 1H), 3.06 (s, 6H); ESI-MS m/z 306 (MH^+).

Example 51: N^4,N^4-DIMETHYL-N^6-(2-METHYLPHENYL)-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight). ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 2H, J = 7.5), 7.43 (d, 1H, J = 7.5), 7.31 - 7.24 (m, 3H), 7.21 (d, 1H, J = 7.8), 7.11 (t, 1H, J = 7.4), 6.96 (t, 1H, J = 7.7), 6.73 (br s, 1H), 6.12 (br s, 1H), 5.16 (s, 1H), 3.01 (s, 6H), 2.29 (s, 3H); ESI-MS m/z 320 (MH^+).

Example 52: N^4,N^4-DIMETHYL-N^6-(3-METHYLPHENYL)-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight). ^1H NMR (300 MHz, $CDCl_3$) δ 7.63

(d, 2H, J = 7.8), 7.29 (t, 2H, J = 7.8), 7.21 (d, 1H, J = 8.1), 7.16 - 7.11 (m, 2H), 6.97 (d, 1H, J = 8.1), 6.91 (d, 1H, J = 7.5), 6.78 (br s, 1H), 6.38 (br s, 1H), 5.44 (s, 1H), 3.05 (s, 6H), 2.35 (s, 3H); ESI-MS m/z 320 (MH^+).

Example 53: N^4,N^4-DIMETHYL-N^6-(3-METHYLPHENYL)-N^2-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (overnight). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, 2H, J = 7.8), 7.25 - 7.08 (m, 5H), 6.90 (d, 1H, J = 7.5), 6.86 (br s, 1H), 6.54 (br s, 1H), 5.44 (s, 1H), 3.05 (s, 6H), 2.34 (s, 3H), 2.31 (s, 3H); ESI-MS m/z 334 (MH^+).

Example 54: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight). ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 2H, J = 7.8), 7.28 (t, 2H, J = 7.5), 7.21 (d, 2H, J = 7.8), 7.15 (d, 2H, J = 8.1), 6.96 (t, 1H, J = 7.5), 6.71 (br s, 1H), 6.29 (br s, 1H), 5.39 (s, 1H), 3.04 (s, 6H), 2.34 (s, 3H); ESI-MS m/z 320 (MH^+).

Example 55: N^2-(3,4-DICHLOROPHENYL)-N^4, N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures B, C, and G (180°C, 3 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 1H, J = 2.1), 7.27 (d, 1H, J = 7.8), 7.24 (dd, 1H, J = 7.8, 2.1), 7.19 (d, 2H, J = 8.7), 7.15 (d, 2H, J = 8.7), 7.01 (br s, 1H), 6.59 (br s, 1H), 5.39 (s, 1H), 3.04 (s, 6H), 2.35 (s, 3H); ESI-MS m/z 388 (MH^+ with ^{35}Cl, ^{35}Cl), 390 (MH^+ with ^{35}Cl, ^{37}Cl),392 (MH^+ with ^{37}Cl, ^{37}Cl).

Example 56: N^4,N^4-DIMETHYL-N^2,N^6-BIS(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures B, C, and G (180°C, 3 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 2H, J = 8.7), 7.19 (d, 2H, J = 8.4), 7.14 (d, 2H, J = 8.4), 7.08 (d, 2H, J = 8.4), 6.73 (br s, 1H), 6.39 (br s, 1H), 5.37 (s, 1H), 3.02 (s, 6H); ESI-MS m/z 334 (MH^+).

Example 57: N^4-(3-FLUOROPHENYL)-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, overnight). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 2H, J = 7.8), 7.34 - 7.23 (m, 5H), 7.01 (t, 1H, J = 7.4), 6.77 (br s, 1H), 6.38 (br s, 1H), 5.43 (s, 1H), 3.07 (s, 6H); ESI-MS m/z 324 (MH^+).

Example 58: N^2-(4-CHLOROPHENYL)-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, overnight). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 2H, J = 7.5), 7.32 - 7.26 (m, 6H), 6.96 (t, 1H, J = 7.5), 6.77 (br s, 1H), 6.34 (br s, 1H), 5.34 (s, 1H), 3.04 (s, 6H); ESI-MS m/z 340 (MH^+ with ^{35}Cl), 342 (MH^+ with ^{37}Cl).

Example 59: N^4-(4-BROMOPHENYL)-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, overnight). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, 2H, J = 8.5), 7.42 (d, 2H, J = 8.5), 7.31 - 7.22 (m, 4H), 6.98 (t, 1H, J = 7.2), 6.92 (br s, 1H), 6.48 (br s, 1H), 5.35 (s, 1H), 3.05 (s, 6H), ESI-MS m/z 384 (MH^+ with ^{79}Br), 386 (MH^+ with ^{81}Br).

Example 60: N^4-(3,4-DICHLOROPHENYL)-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures

A, C, and G (0.5mL diisopropylethylamine added, 150°C, overnight). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d with s at the center, 3H, *J* = 7.8), 7.34 (d, 2H, *J* = 7.8), 7.29 (d, 1H, *J* = 8.7), 7.17 (dd, 1H, *J* = 8.7, 2.6), 6.98 (t, 1H, *J* = 7.8), 6.80 (br s, 1H), 6.33 (br s, 1H), 5.33 (s, 1H), 3.07 (s, 6H); ESI-MS *m/z* 373 (MH^+).

Example 61: N^4-(4-CHLORO-3-METHYLPHENYL)-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, 1 hour). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, 2H, *J* = 7.4, 0.9), 7.30 - 7.25 (m, 3H), 7.19 (d, 1H, *J* = 2.4), 7.12 (dd, 1H, *J* = 8.5, 2.4), 6.97 (t, 1H, *J* = 7.4), 6.88 (br s, 1H), 6.44 (br s, 1H), 5.35 (s, 1H), 3.05 (s, 6H), 2.35 (s, 3H); ESI-MS *m/z* 454(MH^+ with ^{35}Cl), 456 (MH^+ with ^{37}Cl).

Example 62: N^4-(3-CHLORO-4-METHYLPHENYL)-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and F (100°C, 3 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 2H, *J* = 7.8), 7.41 (d, 1H, *J* = 1.8), 7.30 (t, 2H, *J* = 7.8), 7.18 (d, 1H, *J* = 7.8), 7.09 (dd, 1H, *J* = 7.8, 1.8), 6.98 (t, 1H, *J* = 7.8), 6.67 (br s, 2H), 5.35 (s, 1H), 3.07 (s, 6H), 2.37 (s, 3H); ESI-MS *m/z* 454(MH^+ with ^{35}Cl), 456 (MH^+ with ^{37}Cl).

Example 63: N^4-(4-*tert*-BUTYLPHENYL)-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, 5 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 7.5), 7.36 (d, 2H, *J* = 8.7), 7.29 (d, 2H, *J* = 7.5), 7.25 (t, 2H, *J* = 8.7), 6.95 (t, 1H, *J* = 7.4), 6.69 (br s, 1H), 6.30 (br s, 1H), 5.44 (s, 1H), 3.05 (s, 6H), 1.33 (s, 9H); ESI-MS *m/z* 362 (MH^+).

Example 64: N^4,N^4-DIMETHYL-N^6-(4-PHENOXYPHENYL)-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, 2 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 2H, J = 7.8), 7.35 (t, 2H, J = 7.8), 7.31 - 7.24 (m, 3H), 7.12 (t, 2H, J = 7.8), 7.08 - 7.04 (m, 3H), 6.98 (t, 1H, J = 8.1), 6.74 (br s, 1H), 6.71 (dd, 1H, J = 7.8, 2.0), 6.43 (br s, 1H), 5.41 (s, 1H), 3.03 (s, 6H); ESI-MS m/z 398 (MH^+).

Example 65: N^4,N^4-DIMETHYL-N^6-(2-NAPHTHYL)-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, 2 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.80 (d, 1H, J = 7.5), 7.75 (d, 2H, J = 7.8), 7.65 (d, 2H, J = 7.5), 7.49 - 7.37 (m, 3H), 7.29 (t, 2H, J = 7.5), 6.98 (t, 1H, J = 8.1), 6.85 (br s, 1H), 6.59 (br s, 1H), 5.51 (s, 1H), 3.06 (s, 6H); ESI-MS m/z 356 (MH^+).

Example 66: N^4-CYCLOHEXYL-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C, 2 days). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 2H, J = 8.1), 7.26 (t, 2H, J = 8.1), 6.92 (t, 1H, J = 8.1), 6.64 (br s, 1H), 4.96 (s, 1H), 4.39 (br d, 1H, J = 8.1), 3.53 - 3.44 (m, 1H), 3.05 (s, 6H), 2.09 - 1.99 (m, 2H), 1.80 - 1.55 (m, 4H), 1.44 - 1.11 (m, 4H); ESI-MS m/z 312 (MH^+).

Example 67: N^4,N^4-DIMETHYL-N^6-(4-METHYLCYCLOHEXYL)-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, overnight). ESI-MS m/z 326 (MH^+).

Example 68: N^4-(4-*tert*-BUTYLCYCLOHEXYL)-N^6,N^6-DIMETHYL-N^2-

PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (150°C, overnight). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 8.4), 7.26 (t, 2H, *J* = 7.7), 6.92 (t, 1H, *J* = 7.1), 6.61 (br s, 1H), 4.96 (s, 1H), 4.32 (br d, 1H *J* = 8.4), 3.46 - 3.37 (m, 1H), 3.06 (s, 6H), 1.88 - 1.80 (m, 2H), 1.29 - 1.20 (m, 1H), 1.19 - 0,97 (m, 4H), 0.87 (s, 9H); ESI-MS *m/z* 368 (MH^+).

Example 69: N^4-BICYCLO[2.2.1]HEPT-2-YL-N^6,N^6-DIMETHYL-N^2-PHENYL-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (140°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 7.8), 7.26 (t, 2H, *J* = 8.0), 6.92 (t, 1H, *J* = 7.2), 6.62 (br s, 1H), 4.94 (s, 1H), 4.42 (br d, 1H, *J* = 5.4), 3.45 - 3.37 (m, 1H), 3.06 (S, 6H), 2.33 - 2.27 (m, 1H), 1.82 (dd, 1H, *J* = 12.3, 6.0), 1.56 - 1.42 (m, 2H), 1.30 - 1.14 (m, 5H), 0.91 - 0.85 (m, 1H); ESI-MS *m/z* 324 (MH^+).

Example 70: N^4,N^4-DIMETHYL-N^2-PHENYL-N^6-(1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (overnight). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 7.8), 7.26 (t, 2H, *J* = 7.8), 6.93 (t, 1H, *J* = 7.7), 6.87 (br s, 1H), 4.95 (s, 1H), 4.80 (br d, 1H, *J* = 6.9), 3.94 - 3.84 (m, 1H), 3.06 (s, 6H), 2.45 - 2.34 (m, 1H), 1.82 - 1.62 (m, 3H), 1.46 - 1.32 (m, 1H), 1.29 - 1.16 (m, 2H), 0.99 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H) ; ESI-MS *m/z* 366 (MH^+).

Example 71: N^4,N^4-DIMETHYL-N^2-PHENYL-N^6-[(2*R*,3*S*)-3,6,6-TRIMETHYLBICYCLO[3.1.1]HEPT-2-YL]-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, C, and G (5

hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 2H, J = 8.1), 7.26 (t, 2H, J = 8.1), 6.92 (t, 1H, J = 7.4), 6.72 (br s, 1H), 4.99 (s, 1H), 4.47 (br d, 1H, J = 8.4), 4.05 - 3.91 (m, 1H), 3.06 (s, 6H), 2.72 - 2.62 (m, 1H), 2.46 - 2.36 (m, 1H), 2.00 - 1.45 (m, 5H), 1.25 (s, 3H), 1.16 (d, 3H, J = 7.8), 1.10 (s, 3H); ESI-MS m/z 366 (MH^+).

Example 72: N^2,N^4,N^4-TRIMETHYL-N^2,N^6-BIS(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures D, E (150°C, 16 hours), and F (5 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2H, J = 8.1), 7.15 (br d, 4H, J ~ 8), 7.04 (d, 2H, J = 8.1), 6.19 (br s, 1H), 5.29 (s, 1H), 3.50 (s, 3H), 2.94 (s, 6H), 2.36 (s, 3H), 2.29 (s, 3H); ESI-MS m/z 348 (MH^+).

Example 73: N^2-CYCLOHEXYL-N^2,N^4,N^4-TRIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures D, E (150°C, 12 hours), and F (5 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 2H, J = 8.4), 7.10 (d, 2H, J = 8.1), 6.26 (br s, 1H), 5.22 (s, 1H), 4.66 - 4.52 (m, 1H), 3.01 (s, 3H), 2.99 (s, 6H), 2.32 (s, 3H), 1.87 - 1.64 (m, 5H), 1.52 - 1.35 (m, 4H), 1.22 - 1.06 (m, 1H); ESI-MS m/z 340 (MH^+).

Example 74: N^2-CYCLOHEXYL-N^2-(2-METHOXYETHYL)-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures H, J (overnight), and F (2 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 2H, J = 8.1), 7.11 (d, 2H, J = 8.1), 6.19 (br s, 1H), 5.22 (s, 1H), 4.60 - 4.50 (m, 1H), 3.64 - 3.55 (m, 4H), 3.39 (s, 3H), 2.99 (s, 6H), 2.31 (s, 3H), 1.83 - 1.75 (m, 4H), 1.73 - 1.63 (m, 1H), 1.52 - 1.38 (m, 4H), 1.19 - 1.05 (m, 1H); ESI-MS m/z 384

(MH^+).

Example 75: 2-(2,3-DIHYDRO-1*H*-INDOL-1-YL)-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, 16 hours), and F (2 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, 1H, *J* = 7.8), 7.26 (d, 2H, *J* = 7.8), 7.20 - 7.11 (m, 4H), 6.86 (t, 1H, *J* = 7.8), 6.31 (br s, 1H), 5.39 (s, 1H), 4.24 (t, 4H, *J* = 8.3), 3.13 (t, 4H, *J* = 8.3), 3.07 (s, 6H), 2.35 (s, 3H); ESI-MS *m/z* 346 (MH^+).

Example 76: N^2-[2-(1*H*-3-INDOLYL)ETHYL]-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures H, J, and G. ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.65 (d 1H, *J* = 7.8), 7.36 (d, 1H, *J* = 7.8), 7.21 - 7.09 (m, 6H), 7.04 (s, 1H), 6.52 (br s, 1H), 5.28 (s, 1H), 4.95 (br d, 1H, *J* = 7.2), 3.72 (q, 2H, *J* = 7.2), 3.06 (t, 2H, *J* = 7.8), 2.99(s, 6H), 2.32 (s, 3H); ESI-MS *m/z* 387 (MH^+).

Example 77: N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^2,N^4,N^4-TRIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures H, J, and G or F. ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.70 (d 1H, *J* = 7.8), 7.32 (d, 1H, *J* = 7.8), 7.22 (d, 2H, *J* = 7.8), 7.17 (t, 1H, *J* = 7.2), 7.12 (t, 1H, *J* = 7.2), 7.08 (d, 2H, *J* = 7.8), 6.98 (s, 1H), 6.36 (br s, 1H), 5.25 (s, 1H), 3.90 (t, 2H, *J* = 7.8), 3.14 (s, 3H), 3.07 (t, 2H, *J* = 7.8), 2.99(s, 6H), 2.30 (s, 3H); ESI-MS *m/z* 401 (MH^+).

Example 78: N^4-(3,4-DICHLOROPHENYL)-N^2-[2-(1*H*-3-INDOLYL)ETHYL]-N^2,N^6,N^6-TRIMETHYL-2,4,6-

PYRIMIDINETRIAMINE: Prepared by Procedures H, J, and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.75 (s, 1H), 7.68 (d 1H, *J* = 7.8), 7.35 (d, 1H, *J* = 7.8), 7.24 - 7.15 (m, 3H), 7.10 (t, 1H, *J* = 7.2), 7.00 (s, 1H) 6.23 (br s, 1H), 5.15 (s, 1H), 3.90 (t, 2H, *J* = 7.8), 3.14 (s, 3H), 3.08 (t, 2H, *J* = 7.8), 3.03 (s, 6H); ESI-MS *m/z* 455(MH^+ with ^{35}Cl), 457 (MH^+ with ^{37}Cl).

Example 79: N^2-[2-(1*H*-INDOL-3-YL)ETHYL]-N^2,N^4,N^4-TRIMETHYL-(2-NAPHTHYL)-6-(1-PIPERIDINYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures D, E (160°C, 28 hours), and G. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.92 (s, 1H), 7.90 - 7.03 (m, 10H), 6.95 (s, 1H) 6.84 (br s, 1H), 5.34 (s, 1H), 3.90 (t, 2H, *J* = 7.8), 3.17 (s, 3H), 3.07 (t, 2H, *J* = 7.8), 2.96 (s, 6H); ESI-MS *m/z* 437 (MH^+).

Example 80: 1-[4-(DIMETHYLAMINO)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-4-PHENYL-4-PIPERIDINOL: Prepared by Procedures H, E (150°C, 10 hours), and F (3 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 7.8), 7.35 (t, 2H, *J* = 7.8), 7.27 - 7.21 (m, 3H), 7.14 (d, 2H, *J* = 7.8), 6.24 (br s, 1H), 6.18 (br s, 1H), 5.28 (s, 1H), 4.43 - 4.37 (m, 2H), 4.03 (t, 2H, *J* = 5.6), 3.06 - 2.97 (m with s at 3.03, 8H), 2.66 - 2.58 (m, 2H), 2.34 (s, 3H).

Example 81: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-(4-PHENYL-1-PIPERIDINYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, 16 hours), and F (4 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 - 7.18 (m, 7H), 7.13 (d, 2H, *J* = 7.8), 6.25 (br s, 1H), 5.28 (s, 1H), 4.94 (d with fine splitting, 2H, *J* = 13.0), 3.01 (s, 6H), 2.87 (dt, 2H, *J* = 1.0, 13.0), 2.74 (tt, 1H, *J* = 11.6, 1.5), 2.32 (s, 3H),

1.90 (d with fine splitting, 2H, J = 12.0), 1.72 (ddd, 2H, J = 13.0, 12.0, 1.5); ESI-MS m/z 388 (MH^+).

Example 82: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-(3-PHENYL-4-MORPHOLINYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, 20 hours), and F (3 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, 2H, J = 7.8), 7.32 (t, 2H, J = 7.8), 7.23 (t, 1H, J = 7.8), 7.17 (d, 2H, J = 7.8), 7.09 (d, 2H, J = 7.8), 6.25 (br s, 1H), 5.88 (d, 1H, J = 1.0), 5.27 (s, 1H), 4.49 (t, 2H, J = 13.2), 3.94 (m, 2H), 3.66 (dt, 1H, J = 1.0, 11.5), 3.24 (dt, 1H, J = 1.5, 11.5), 2.97 (s, 6H), 2.32 (s, 3H); ESI-MS m/z 390 (MH^+).

Example 83: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-(2-PHENYL-4-MORPHOLINYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, 20 hours), and F (3 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 2H, J = 7.8), 7.38 (t, 2H, J = 7.8), 7.33 (t, 1H, J = 7.8), 7.19 (d, 2H, J = 7.8), 7.11 (d, 2H, J = 7.8), 6.22 (br s, 1H), 5.29 (s, 1H), 4.74 (dd, 1H, J = 13.2, 1.0), 4.59 - 4.51 (m, 2H), 4.16 - 4.08 (m, 1H), 3.80 (dt, 1H, J = 1.0, 11.9), 3.11 (dt, 1H, J = 1.5, 12.4), 2.98 (s, 6H), 2.90 (dd, 1H, J = 10.6, 11.9), 2.33 (s, 3H); ESI-MS m/z 390 (MH^+).

Example 84: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-{4-[(4-METHYLPHENYL)SULFONYL]-1-PIPERAZINYL}-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (150°C, overnight), and F (3 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 2H, J = 8.3), 7.31 (d, 2H, J = 8.3), 7.15 (d, 2H, J = 8.4), 7.11 (d, 2H, J = 7.2), 6.20 (br s, 1H), 5.22 (s, 1H), 3.87 (t, 4H, J = 4.2), 3.02 (t, 4H, J = 4.2), 2.95 (s, 6H), 2.43 (s, 3H), 2.33 (s, 3H); ESI-MS

m/z 467 (MH^+).

Example 85: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-[4-(2-METHYLPHENYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours), and F (12 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 - 7.10 (m, 6H), 7.02 - 6.96 (m, 2H), 6.28 (br s, 1H), 5.28 (s, 1H), 3.95 - 3.86 (m, 4H), 2.99 (s, 6H), 2.96 - 2.92 (m, 4H), 2.36 (s, 3H), 2.32 (s, 3H); ESI-MS *m/z* 403 (MH^+).

Example 86: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-[4-(3-METHYLPHENYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 12 hours), and F (12 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, 2H, J = 7.8), 7.17 (t, 1H, J = 7.8), 7.11 (d, 2H, J = 7.8), 6.91 (s, 1H), 6.89 (d, 1H, J = 7.8), 6.69 (d, 1H, J = 7.8), 6.33 (br s, 1H), 5.29 (s, 1H), 3.93 (t, 4H, J = 5.1), 3.22 (t, 4H, J = 5.1), 3.01 (s, 6H), 2.33 (s, 6H); ESI-MS *m/z* 403 (MH^+).

Example 87: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-[4-(4-METHYLPHENYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures D, E (160°C, 36 hours), and F (8 hours). ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, 2H, J = 9.0), 7.16 (d, 2H, J = 8.7), 7.10 (d, 2H, J = 9.0), 6.90 (d, 2H, J = 8.4), 6.24 (br s, 1H), 5.27 (s, 1H), 3.93 (t, 4H, J = 4.8), 3.18 (t, 4H, J = 5.1), 3.00 (s, 6H), 2.33 (s, 3H), 2.28 (s, 3H); ESI-MS *m/z* 403 (MH^+).

Example 88: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures H, E (16

hours), and F. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, 1H, *J* = 4.4, 2.2), 7.87 (dd, 1H, *J* = 7.8, 2.2), 7.20 (d, 2H, *J* = 8.1), 7.13 (d, 2H, *J* = 8.1), 6.98 (dd, 1H, *J* = 7.8, 4.4), 6.24 (br s, 1H), 5.28 (s, 1H), 3.90 (t, 4H, *J* = 4.8), 3.36 (t, 4H, *J* = 4.8), 3.00 (s, 6H), 2.32 (s, 3H); ESI-MS *m/z* 458 (MH^+).

Example 89: *N*-(4-METHYLPHENYL)-2-(1-PIPERIDINYL)-6-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures M, E (120°C, for addition of piperidine), and F. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, 1H, *J* = 4.4, 2.2), 7.87 (dd, 1H, *J* = 7.8, 2.2), 7.19 (d, 2H, *J* = 8.1), 7.12 (d, 2H, *J* = 8.1), 6.99 (dd, 1H, *J* = 7.8, 4.4), 6.28 (br s, 1H), 5.35 (s, 1H), 3.77 - 3.72 (m, 4H), 3.62 (t, 4H, *J* = 4.8), 3.33 (t, 4H, *J* = 4.8), 2.33 (s, 3H), 1.69 - 1.52 (m, 6H); ESI-MS *m/z* 498 (MH^+).

Example 90: 6-[2-(METHOXYMETHYL)-1-PIPERIDINYL]-*N*-(4-METHYLPHENYL)-2-{4-[3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-4-PYRIMIDINAMINE: Prepared by Procedures D, J (90°C, overnight), and F (2 hours). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, 1H, *J* = 4.4, 2.2), 7.88 (dd, 1H, *J* = 7.8, 2.2), 7.20 (d, 2H, *J* = 8.1), 7.12 (d, 2H, *J* = 8.1), 6.99 (dd, 1H, *J* = 7.8, 4.4), 6.23 (br s, 1H), 5.38 (s, 1H), 4.68 - 4.54 (m, 1H), 4.15 - 4.03 (m, 1H), 3.90 (t, 4H, *J* = 4.8), 3.57 (t, 1H, *J* = 9.7), 3.44 - 3.35 (m, 5H), 3.34 (s, 3H), 2.81 (t, 1H, *J* = 12.0), 2.33 (s, 3H), 1.93 - 1.86 (m, 1H), 1.72 - 1.41 (m, 3H), 1.29 - 1.25 (m, 1H), 0.91 - 0.86 (m, 1H); ESI-MS *m/z* 542 (MH^+).

Example 115: *N*-4-[3-(BENZYLOXY)PHENYL]-*N*-6-,*N*-6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 - 8.19 (m, 1H), 7.52 (dt, 1H, *J* = 1.9, 7.2), 7.43 - 7.20 (m, 7H), 6.96 (s, 1H), 6.88 (d, 1H, *J* = 8.0), 6.80 (d, 1H, *J* = 8.1), 6.69 - 6.63 (m, 2H), 5.34 (s, 1H), 5.03 (s, 2H), 4.03 - 3.97 (m, 4H), 3.66 (t, 4H, *J* = 5.2), 3.02 (s, 6H); ESI-MS *m/z* 482 (MH^+).

Example 116: 4-{4-[4-(DIMETHYLAMINO)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-1-PIPERAZINYL}PHENOL: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.19 - 7.14 (m, 4H), 6.85 - 6.79 (m, 4H), 5.31 (s, 1H), 5.22 (s, 1H), 3.96 (t, 4H, *J* = 5.1), 3.05 (t, 4H, *J* = 5.0), 3.03 (s, 6H), 2.34 (s, 3H); FIAMS *m/z* 405 (MH^+).

Example 117: N^4-[4-(BENZYLOXY)PHENYL]-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and

O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, 1H, *J* = 1.9, 5.6), 7.55 - 7.27 (m, 7H), 7.24 - 7.16 (m, 2H), 7.04 - 6.91 (m, 2H), 6.69 - 6.64 (m, 2H), 5.06 (s, 2H), 5.05 (s, 1H), 4.08 - 3.97 (m, 4H), 3.69 (t, 4H, *J* = 5.1), 3.03 (s, 6H); ESI-MS *m/z* 482 (MH^+).

Example 118: N^4-(1,3-BENZODIOXOL-5-YL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 - 8.18 (m, 1H), 7.48 (dt, 1H, *J* = 1.9, 8.1), 6.92 (d, 1H, *J* = 1.9), 6.75 (d, 1H, *J* = 8.2), 6.74 - 6.54 (m, 3H), 6.41 (br s, 1H), 5.95 (s, 2H), 5.16 (s, 1H), 3.89 (t, 4H, *J* = 5.1), 3.60 (t, 4H, *J* = 5.3), 2.99 (s, 6H); ESI-MS *m/z* 420 (MH^+).

Example 119: N^4-(2,3-DIHYDRO-1,4-BENZODIOXIN-6-YL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 - 8.18 (m, 1H), 7.49 (dt, 1H, *J* = 2.1, 7.1), 6.89 (d, 1H, *J* = 2.2), 6.81 (d, 1H, *J* = 8.6), 6.76 (d, 1H, *J* = 2.4), 6.68 (d, 1H, *J* = 8.5), 6.62 (dd, 1H, *J* = 4.6, 7.0), 6.18

(br s, 1H), 5.21 (s, 1H), 4.33 - 4.15 (m, 4H), 3.89 (t, 4H, J = 5.1), 3.61 (t, 4H, J = 5.1), 3.00 (s, 6H); ESI-MS m/z 434 (MH^+).

Example 120: N^4-(4-ISOQUINOLINYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, 1H, J = 1.5), 8.31 (d, 1H, J = 2.6), 8.27 - 8.19 (m, 1H), 8.01 (d, 1H, J = 8.2), 7.70 (d, 1H, J = 7.8), 7.59 - 7.52 (m, 1H), 7.51 - 7.45 (m, 2H), 6.78 (br s, 1H), 6.68 (d, 1H, J = 8.6), 6.63 (dd, 1H, J = 5.0, 7.1), 5.29 (s, 1H), 3.94 (t, 4H, J = 5.0), 3.63 (t, 4H, J = 5.3), 3.01 (s, 6H); ESI-MS m/z 427 (MH^+).

Example 121: N^4-(4-CYCLOHEXYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 - 8.19 (m, 1H), 7.49 (dt, 1H, J = 2.0, 6.9), 7.22 (d, 2H, J = 6.4), 7.16 (d, 2H, J = 8.2), 6.68 (d, 1H, J = 8.6), 6.66 - 6.60 (m, 1H), 6.21 (br s, 1H), 5.30 (s, 1H), 3.99 - 3.91 (m, 4H), 3.63 (t, 4H, J = 5.2), 3.02 (s, 6H), 2.53 - 2.42 (m, 1H), 1.92

- 1.79 (m, 4H), 1.48 - 1.32 (m, 4H), 1.31 - 1.19 (m, 2H); ESI-MS *m/z* 458 (MH^+).

Example 122: N^4,N^4-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-N^6-(5,6,7,8-TETRAHYDRO-1-NAPHTHALENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, 1H, *J* = 1.3, 4.9), 7.50 (dt, 1H, *J* = 2.2, 6.8), 7.17 (d, 1H, *J* = 7.5), 7.09 (t, 1H, *J* = 7.6), 6.94 (d, 1H, *J* = 7.7), 6.73 - 6.62 (m, 2H), 5.06 (s, 1H), 4.08 - 3.93 (m, 4H), 3.66 (t, 4H, *J* = 5.3), 3.00 (s, 6H), 2.79 (t, 2H, *J* = 6.0), 2.72 (t, 2H, *J* = 5.9), 1.88 - 1.67 (m, 4H), NH (1H, unobserved); ESI-MS *m/z* 430 (MH^+).

Example 123: N^4-(2,3-DIHYDRO-1*H*-INDEN-5-YL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 1H, *J* = 4.8), 7.51 (dt, 1H, *J* = 1.8, 6.9), 7.19 (d, 1H, *J* = 7.6), 7.14 (s, 1H), 7.04 (dd, 1H, *J* = 1.7, 7.7), 6.73 -

6.61 (m, 2H), 5.23 (s, 1H), 4.09 - 3.94 (m, 4H), 3.68 (t, 4H, J = 5.9), 3.04 (s, 6H), 2.89 (t, 4H, J = 7.8), 2.16 - 2.01 (m, 2H), NH (1H, unobserved); ESI-MS m/z 416 (MH^+).

Example 124: N^4-(3,4-DICHLOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 - 8.20 (m, 1H), 7.79 - 7.69 (m, 1H), 7.61 - 7.44 (m, 1H), 7.42 - 7.28 (m, 1H), 7.25 - 7.11 (m, 1H), 6.79 - 6.61 (m, 2H), 6.42 (br s, 1H), 5.22 (s, 1H), 3.98 - 3.82 (m, 4H), 3.65 - 3.56 (m, 4H), 3.02 (s, 6H); ESI-MS m/z 444 (MH^+ with ^{35}Cl, ^{35}Cl), 446 (MH^+ with ^{35}Cl, ^{37}Cl), 448 (MH^+ with ^{37}Cl, ^{37}Cl).

Example 125: N^4,N^4-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-N^6-[3-(TRIFLUOROMETHYL)PHENYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, stirred 3.5 h at -78 °C, warmed to 0 °C and stirred 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 8.24 - 8.18 (m, 1H), 7.86 (s, 1H), 7.78 - 7.22 (m, 4H), 6.65 (t, 2H, J = 5.0), 5.29 (s, 1H), 3.96 (t, 4H, J = 5.5), 3.64 (t, 4H, J = 5.2), 3.03 (s, 6H); ESI-MS m/z 444 (MH^+).

Example 126: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-[3-(DIMETHYLAMINO)PHENYL]-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 95 °C, 16 h), Q (dioxane, 120 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.37 (m, 7H), 7.25 (t, 1H, J = 2.0), 7.14 (dd, 1H, J = 1.5, 8.2), 7.05 (dd, 1H, J = 2.5, 8.2), 4.36 (s, 2H), 3.98 (br s, 4H), 3.36 (s, 4H), 3.11 (s, 6H), 3.05 (s, 6H), 2.60 (s, 1H); ESI-MS m/z 432 (MH^+).

Example 127: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-(2-METHYL-1,3-BENZOTHIAZOL-5-YL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (130 °C, 13 h), Q, and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.87 (d, 1H, J = 8.8), 7.52 - 7.38 (m, 6H), 5.58 (s, 1H), 4.58 (s, 1H), 4.30 (s, 2H), 3.79 - 3.42 (m, 4H), 3.22 - 2.91 (m, 4H), 3.09 (s, 6H), 2.98 (s, 3H); ESI-MS m/z 460 (MH^+).

Example 128: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-CYCLOHEPTYL-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (140 °C, toluene, 6 h), Q, and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 - 7.09 (m, 5H), 4.78 (s, 1H), 4.18 (br s, 1H), 3.74 (t, 4H, J = 5.2), 3.52 (s, 2H), 2.99 (s,

6H), 2.46 (t, 4H, J = 5.1), 2.03 - 1.92 (m, 2H), 1.87 - 1.68 (m, 11H); ESI-MS m/z 409 (MH^+).

Example 129: 4-{[2-(4-BENZYL-1-PIPERAZINYL)-6-(DIMETHYLAMINO)-4-PYRIMIDINYL]AMINO}-2-CHLOROBENZONITRILE: Prepared by Procedures P (toluene, 95 °C, 16 h), Q (dioxane, 120 °C), and A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, 1H, J = 3.1), 7.48 (d, 1H, J = 8.5), 7.42 - 7.22 (m, 6H), 6.45 (s, 1H), 5.20 (s, 1H), 3.79 (t, 4H, J = 5.2), 3.55 (s, 2H), 3.02 (s, 6H), 2.51 (t, 4H, J = 5.0); ESI-MS m/z 448 (MH^+ with ^{35}Cl), 450 (MH^+ with ^{37}Cl).

Example 130: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-(1,3,3-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL)-4,6-PYRIMIDINEDIAMINE: Prepared by procedures P (toluene, 95 °C, 16 h), Q (dioxane, 120 °C), and A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.21 (m, 6H), 4.87 (s, 1H), 3.79 - 3.69 (m, 4H), 3.53 (s, 2H), 3.46 (s, 1H), 2.98 (s, 6H), 2.46 (t, 4H, J = 5.1), 1.71 (s, 1H), 1.69 - 1.62 (m, 2H), 1.48 - 1.35 (m, 2H), 1.20 (d, 1H, J = 10.2), 1.19 - 1.02 (m, 1H), 1.14 (s, 3H), 1.07 (s, 3H), 0.79 (s, 3H); ESI-MS m/z 449 (MH^+).

Example 131: 2-{4-[3-(BENZYLOXY)PHENYL]-1-PIPERAZINYL}-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 2H, J = 7.1), 7.36 (t, 2H, J = 7.0), 7.29 (d, 1H, J = 7.1), 7.22 - 7.04 (m, 5H), 6.58 - 6.52 (m, 2H), 6.48 (d, 1H, J = 7.2), 5.29 (s, 1H), 5.21 (s, 1H), 5.03 (s, 2H), 3.89 - 3.80 (m, 4H), 3.28 - 3.15 (m, 4H), 3.00 (s, 6H), 2.30 (s, 3H); ESI-MS m/z 495 (MH^+).

Example 132: N^4,N^4-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-N^6-(3-QUINOLINYL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, 1H, J = 2.6), 8.31 (d, 1H, J = 2.5), 8.26 - 8.18 (m, 1H), 8.02 (d, 1H, J = 8.2), 7.71 (d, 1H, J = 7.7), 7.57 (dt, 1H, J = 1.5, 5.3), 7.53 - 7.46 (m, 2H), 6.68 (d, 1H, J = 8.6), 6.64 (dd, 1H, J = 4.9, 7.1), 5.30 (d, 2H, J = 3.7), 3.94 (t, 4H, J = 4.9), 3.64 (t, 4H, J = 5.4), 3.03 (s, 6H);

ESI-MS m/z 427 (MH^+).

Example 133: N^4-[4-BROMO-3-(TRIFLUOROMETHYL)PHENYL]-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 - 8.19 (m, 1H), 8.17 (d, 1H, *J* = 2.3), 7.57 (d, 1H, *J* = 8.7), 7.53 - 7.47 (m, 1H), 7.39 (d, 1H, *J* = 5.2), 6.69 (d, 1H, *J* = 8.7), 6.64 (t, 1H, *J* = 5.0), 6.27 (s, 1H), 5.19 (s, 1H), 3.94 - 3.87 (m, 4H), 3.65 - 3.59 (m, 4H), 3.04 (s, 6H); ESI-MS *m/z* 522 (MH^+ with ^{79}Br), 524 (MH^+ with ^{81}Br).

Example 134: *N*⁴-{3-CHLORO-4-[(TRIFLUOROMETHYL)SULFANYL]PHENYL}-*N*⁶,*N*⁶-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 - 8.19 (m, 1H), 7.91 (d, 1H, *J* = 2.3), 7.61 (d, 1H, *J* = 8.5), 7.50 (dt, 1H, *J* = 2.1, 8.5), 7.30 - 7.20 (m, 1H), 6.70 (d, 1H, *J* = 9.1), 6.64 (dd, 1H, *J* = 4.7, 7.1), 6.35 (br s, 1H), 5.26 (s, 1H), 3.92 (t, 4H, *J* = 5.6), 3.64 (t, 4H, *J* = 5.0), 3.06 (s, 6H); ESI-MS *m/z* 510 (MH^+ with ^{35}Cl), 512 (MH^+ with ^{37}Cl).

Example 135: *N*⁴-(3-ETHOXYPHENYL)-*N*⁶,*N*⁶-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 -

4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 - 8.19 (m, 1H), 7.50 (dt, 1H, *J* = 2.1, 6.9), 7.19 (t, 1H, *J* = 8.1), 6.96 (t, 1H, *J* = 2.1), 6.85 (d, 1H, *J* = 8.2), 6.68 (d, 1H, *J* = 8.6), 6.63 - 6.56 (m, 1H), 6.35 (br s, 1H), 5.36 (s, 1H), 4.09 - 3.98 (m, 2H), 3.91 (t, 4H, *J* = 5.3), 3.61 (t, 4H, *J* = 5.1), 3.02 (s, 6H), 1.39 (t, 3H, *J* = 5.7); ESI-MS *m/z* 420 (MH^+).

Example 136: *N*^{4}-[2-CHLORO-4-(TRIFLUOROMETHYL) PHENYL]-*N*^{6},*N*^{6}-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 - 8.15 (m, 1H), 8.15 (d, 1H, *J* = 2.1), 7.50 (dt, 1H, *J* = 2.0, 8.8), 7.42 - 7.33 (m, 2H), 6.69 (d, 1H, *J* = 8.6), 6.64 (dd, 1H, *J* = 4.8, 6.3), 6.28 (s, 1H), 5.18 (s, 1H), 3.91 (t, 4H, *J* = 5.0), 3.62 (t, 4H, *J* = 5.1), 3.04 (s, 6H); ESI-MS *m/z* 478 (MH^+ with ^{35}Cl), 480 (MH^+ with ^{37}Cl).

Example 137: *N*-4-(2-ADAMANTYL)-2-(4-BENZYL-1-PIPERAZINYL)-*N*-6-*N*-6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 90 °C), Q, and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.21 (m, 5H), 4.83 (s, 1H), 4.72 (br s, 1H), 3.74 (m, 3H), 3.52 (s, 2H), 2.98 (s,

6H), 2.46 (t, 4H, J = 5.3), 2.05 - 1.53 (m, 13H); ESI-MS m/z: 433 (MH^+).

Example 138: *N*-4-(1-NORADAMANTYL)-2-(4-BENZYL-1-PIPERAZINYL)-*N*-6-*N*-6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 90 °C), Q, and A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.20 (m, 5H), 4.97 (s, 1H), 4.67 (br s, 1H), 3.74 (s, 4H), 3.52 (s, 2H), 2.99 (s, 6H), 2.46 (t, 4H, J = 5.2), 2.32 - 1.51 (m, 15H); ESI-MS m/z: 447 (MH^+).

Example 139: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-[(1*S*,2*R*,3*R*,5*S*)-2,6,6-TRIMETHYLBICYCLO[3.1.1]HEPT-3-YL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 150 °C, 4 h), Q (neat, 130 °C), and A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.21 (m, 5H), 4.86 (s, 1H), 4.35 (br s, 1H), 3.75 (t, 4H, J = 4.6), 3.53 (s, 2H), 2.99 (s, 6H), 2.66 - 2.56 (m, 1H), 2.47 (t, 4H, J = 4.5), 2.41 - 2.33 (m, 1H), 1.98 - 1.92 (m, 1H), 1.83 (t, 1H, J = 5.8), 1.68 - 1.60 (m, 2H), 1.23 (s, 3H), 1.14 (d, 3H, J = 7.3), 1.05 (s, 3H), 0.92 (d, 2H); ESI-MS m/z: 449 (MH^+).

Example 140: 2-[4-(5-BROMO-2-PYRIDINYL)-1-PIPERAZINYL]-*N*⁴,*N*⁴-DIMETHYL-*N*⁶-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared using Procedure Y (DMF). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 1H, *J* = 2.6), 7.53 (dd, 1H, *J* = 2.6, 8.8), 7.19 (d, 2H, *J* = 8.5), 7.12 (d, 2H, *J* = 8.5), 6.21 (s, 1H), 5.28 (s, 1H), 3.88 (t, 4H, *J* = 5.0), 3.58 (t, 4H, *J* = 5.2), 3.00 (s, 6H), 2.33 (s, 3H); ESI-MS *m/z*: 468 (MH^+ with ^{79}Br), 470 (MH^+ with ^{81}Br).

Example 141: 6-{4-[4-(DIMETHYLAMINO)-6-(4-TOLUDINO)-2-PYRIMIDINYL]-1-PIPERAZINYL}NICOTINAMIDE: Prepared by Procedure Y (DMF). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.30 - 7.25 (m, 4H), 7.17 (d, 2H, *J* = 8.5), 7.13 (d, 2H, *J* = 8.6), 6.18 (br s, 1H), 5.28 (s, 1H), 3.82 (t, 2H, *J* = 5.1), 3.79 (t, 2H, *J* = 5.3), 3.60 (t, 2H, *J* = 5.1), 3.41 (t, 2H, *J* = 5.3), 2.99 (s, 6H), 2.33 (s, 3H); ESI-MS *m/z*: 433 (MH^+).

Example 142: 2-[4-(3-METHOXYBENZYL)-1-PIPERAZINYL]-*N*⁴,*N*⁴-DIMETHYL-*N*⁶-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedure Z (DIEA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 1H, *J* = 6.8), 7.17 (d, 2H, *J* = 8.3), 7.10 (d,

2H, J = 8.2), 6.93 (d, 1H, J = 2.3), 6.92 (d, 1H, J = 2.4), 6.80 (dd, 1H, J = 2.0, 7.6), 6.18 (br s, 1H), 5.25 (s, 1H), 3.82 (s, 3H), 3.78 (t, 4H, J = 5.1), 3.52 (s, 2H), 2.97 (s, 6H), 2.49 (t, 4H, J = 5.1), 2.31 (s, 3H); ESI-MS m/z: 433 (MH^+).

Example 143: 2-[4-(5-BROMO-2-PYRIDINYL)-1-PIPERAZINYL]-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure Y. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 1H, J = 2.4), 7.53 (dd, 1H, J = 2.5, 9.2), 7.20 (t, 1H, J = 8.1), 7.00 (t, 1H, J = 2.0), 6.85 (dd, 1H, J = 2.0, 8.0), 6.62 - 6.54 (m, 2H), 6.29 (s, 1H), 5.36 (s, 1H), 3.89 (t, 4H, J = 5.1), 3.80 (s, 3H), 3.58 (t, 4H, J = 4.9), 3.02 (s, 6H); ESI-MS m/z: 484 (MH^+ with ^{79}Br), 486 (MH^+ with ^{81}Br).

Example 144: N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure X. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 - 8.54 (m, 1H), 7.66 (dt, 1H, J = 1.8, 7.8), 7.45 (d, 1H, J = 7.8), 7.23 - 7.14 (m, 2H), 7.00 (t, 1H, J = 2.5), 6.87 - 6.78 (m, 1H), 6.61 - 6.54 (m, 1H), 6.26 (br s, 1H),

5.33 (s, 1H), 3.82 (t, 4H, J = 5.0), 3.78 (s, 3H), 3.70 (s, 2H), 2.99 (s, 6H), 2.56 (t, 4H, J = 5.0); ESI-MS m/z: 420 (MH^+).

Example 145: 2-[4-(CYCLOHEXYLMETHYL)-1-PIPERAZINYL]-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure T. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, 1H, J = 8.2), 7.00 - 6.95 (m, 1H), 6.85 (d, 1H, J = 8.2), 6.59 (d, 1H, J = 7.7), 6.32 (s, 1H), 5.36 (s, 1H), 3.82 - 3.71 (m, 4H), 3.79 (s, 3H), 3.69 - 3.62 (m, 2H), 3.58 - 3.50 (m, 2H), 3.01 (s, 6H), 2.54 - 2.45 (m, 1H), 1.87 - 1.48 (m, 8H), 1.45 - 1.29 (m, 4H); ESI-MS m/z: 425 (MH^+).

Example 146: N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(3-THIENYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures T (reduction 4 h) and W. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, 1H, J = 3.2, 5.1), 7.19 (t, 1H, J = 8.0), 7.16 - 7.11 (m, 1H), 7.08 (dd, 1H, J = 1.3, 4.9), 7.00 (t, 1H, J = 2.3), 6.82 (dd, 1H, J = 2.0, 8.3), 6.57 (dd, 1H, J = 2.5, 8.2), 6.25 (s, 1H), 5.33 (s, 1H),

3.79 (t, 4H, J = 5.5), 3.78 (s, 3H), 3.57 (s, 2H), 2.99 (s, 6H), 2.48 (t, 4H, J = 5.2)

ESI-MS m/z: 425 (MH^+).

Example 147: N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(4-PYRIDINYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure T (acylation with DIPEA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, 2H, J = 1.5, 5.8), 7.31 (d, 2H, J = 6.0), 7.19 (t, 1H, J = 8.3), 6.99 (t, 1H, J = 2.1), 6.83 (dd, 1H, J = 1.5, 7.8), 6.58 (dd, 1H, J = 2.0, 7.8), 6.28 (br s, 1H), 5.34 (s, 1H), 3.80 (t, 4H, J = 5.2), 3.78 (s, 3H), 3.54 (s, 2H), 3.00 (s, 6H), 2.49 (t, 4H, J = 5.3; ESI-MS m/z: 420 (MH^+).

Example 148: 2-[4-(3-METHOXYBENZYL)-1-PIPERAZINYL]-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure S. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 1H, J = 7.9), 7.17 (t, 1H, J = 8.2), 6.99 (t, 1H, J = 2.1), 6.95 - 6.84 (m, 2H), 6.86 - 6.78 (m, 2H), 6.59 - 6.55 (m, 1H), 6.29 (br s, 1H), 5.32 (s, 1H), 3.82 (s, 3H), 3.79 (t, 4H, J = 5.1), 3.77 (s, 3H), 3.52 (s, 2H),

2.99 (s, 6H), 2.49 (t, 4H, J = 5.1); ESI-MS m/z: 449 (MH^+).

Example 149: N^2-[2-(3-METHOXYPHENYL)ETHYL]-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE:

Prepared by Procedure F (dioxane, potassium *tert*-butoxide, 120 °C, 16 h), Q (toluene, TEA, 120 °C), A (CH_2Cl_2, Δ, TEA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, 1H, J = 7.9), 7.18 (d, 2H, J = 8.4), 7.12 (d, 2H, J = 8.3), 6.84 (d, 1H, J = 7.6), 6.82 - 6.74 (m, 2H), 6.28 (br s, 1H), 5.28 (s, 1H), 4.77 (s, 1H), 3.80 (s, 3H), 3.63 (q, 2H, J = 6.7), 2.99 (s, 6H), 2.89 (t, 2H, J = 7.4), 2.32 (s, 3H); ESI-MS m/z: 378 (MH^+).

Example 150: N^2-[2-(2-METHOXYPHENYL)ETHYL]-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE:

Prepared by Procedures F (dioxane, potassium *tert*-butoxide, 140 °C, 16 h), Q (toluene), and A (CH_2Cl_2, Δ, TEA). ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 - 7.12 (m, 4H), 7.12 (d, 2H, J = 8.1), 6.89 (d, 1H, J = 7.8), 6.86 (d, 1H, J = 7.6), 6.61 (d, 1H, J = 8.0), 6.50 (br s, 1H), 5.25 (s,

1H), 3.84 (s, 3H), 3.60 (q, 2H, J = 7.1), 3.00 (s, 6H), 2.93 (t, 2H, J = 7.6), 2.33 (s, 3H); ESI-MS m/z: 378 (MH^+).

Example 151: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(3,4-DICHLOROPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 140 °C, 6 h), Q (dioxane, 120 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 1H, J = 2.5), 7.35 - 7.30 (m, 4H), 7.29 - 7.22 (m, 2H), 7.13 (dd, 1H, J = 1.5, 8.5), 6.19 (br s, 1H), 5.21 (s, 1H), 3.78 (t, 4H, J = 5.0), 3.55 (s, 2H), 3.00 (s, 6H), 2.49 (t, 4H, J = 5.0); ESI-MS m/z: 457 (MH^+ with ^{35}Cl, ^{35}Cl), 459 (MH^+ with ^{35}Cl, ^{37}Cl), 461 (MH^+ with ^{37}Cl, ^{37}Cl).

Example 152: N^4-[4-(BENZYLOXY)CYCLOHEXYL]-2-(4-BENZYL-1-PIPERAZINYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (16 h), Q, and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.18 (m, 10H), 4.94 (s, 1H), 4.61 (d, 1H, J = 11.8), 4.51 (d, 1H, J = 11.8), 4.39 (br s, 1H), 3.75 (t, 4H, J = 5.0), 3.53 (s, 2H), 3.31 (dt, 1H, J = 5.3, 8.3), 2.95 (s, 6H), 2.46 (t, 4H, J = 5.0), 2.19 -

2.11 (m, 1H), 2.07 - 1.98 (m, 1H), 1.79 - 1.56 (m, 3H), 1.53 - 1.41 (m, 1H), 1.40 - 1.21 (m, 3H); ESI-MS *m/z*: 501 (MH^+).

Example 153: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-[(1*R*,2*R*,4*R*)-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (90 °C, 16 h), Q, and A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.22 (m, 6H), 4.81 (s, 1H), 4.36 (d, 1H, *J* = 7.0), 3.74 (s, 4H), 3.53 (s, 2H), 2.98 (s, 6H), 2.46 (t, 4H, *J* = 5.1), 1.84 (dd, 1H, *J* = 8.9, 12.9), 1.78 - 1.52 (m, 4H), 1.29 - 1.11 (m, 2H), 0.97 (s, 3H), 0.89 (s, 3H), 0.83 (s, 3H); ESI-MS *m/z*: 449 (MH^+).

Example 154: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-[4-(TETRAHYDRO-2-FURANYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A, P (16 h), and Q (dioxane, 120 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, 2H, *J* = 8.4), 7.11 (d, 2H, *J* = 8.0), 6.22 (br s, 1H), 5.29 (s, 1H), 4.12 - 4.03 (m, 1H), 3.91 (q, 1H, *J* = 6.7), 3.80 (t, 4H, *J* = 5.1), 3.76 (q, 1H, *J* = 7.5), 2.98 (s, 6H), 2.57 (t, 4H, *J* = 5.0), 2.56 - 2.40 (m, 2H), 2.32 (s,

3H), 2.05 - 1.96 (m, 1H), 1.94 - 1.80 (m, 2H), 1.57 - 1.45 (m, 1H); ESI-MS *m/z*: 397 (MH^+).

Example 155: 3-{[2-(4-BENZYL-1-PIPERAZINYL)-6-(DIMETHYLAMINO)-4-PYRIMIDINYL]AMINO}PHENOL: Prepared By Procedures P (Toluene, 120 °C, 40 H), Q (dioxane, 120 °C), AND A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.29 (m, 4H), 7.28 - 7.26 (m, 1H), 7.13 (t, 1H, *J* = 8.0), 6.84 (t, 1H, *J* = 2.8), 6.80 (ddd, 1H, *J* = 0.7, 2.0, 7.9), 6.48 (ddd, 1H, *J* = 0.7, 2.1, 8.0), 6.32 (br s, 1H), 5.32 (s, 1H), 3.79 (t, 4H, *J* = 5.0), 3.55 (s, 2H), 3.49 (s, 1H), 2.99 (s, 6H), 2.50 (t, 4H, *J* = 5.0); ESI-MS *m/z*: 405 (MH^+).

Example 156: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(4-FLUOROPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, sodium *tert*-butoxide, 120 °C, 16 h), Q (dioxane, 120 °C), and A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.30 (m, 4H), 7.29 - 7.21 (m, 3H), 6.99 (t, 2H, *J* = 8.6), 6.14 (br s, 1H), 5.13 (s, 1H), 3.77 (t, 4H, *J* = 4.9), 3.54 (s, 2H), 2.97 (s, 6H), 2.48 (t, 4H, *J* = 4.9); ESI-MS *m/z*: 407 (MH^+).

Example 157: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-(4-METHYLCYCLOHEXYL)-4,6-PYRIMIDINEDIAMINE: Prepared by

Procedures P (sodium *tert*-butoxide, toluene, 120 °C, 16 h), Q (dioxane, 120 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.10 (m, 6H), 4.82 (d, 1H, *J* = 4.9), 3.81 - 3.61 (m, 5H), 3.53 (s, 2H), 2.99 (s, 6H), 2.46 (t, 4H, *J* = 4.5), 1.79 - 1.46 (m, 7H), 1.29 - 0.98 (m, 2H), 0.90 (d, 3H, *J* = 6.6); ESI-MS *m/z*: 409 (MH^+).

Example 158: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-[4-(DIMETHYLAMINO)PHENYL]-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (sodium *tert*-butoxide, toluene, 120 °C, 16 h), Q (neat, 130 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.22 (m, 5H), 7.14 (d, 2H, *J* = 8.4), 6.71 (d, 2H, *J* = 8.8), 6.04 (br s, 1H), 5.08 (s, 1H), 3.85 - 3.74 (m, 4H), 3.54 (s, 2H), 2.94 (s, 6H), 2.93 (s, 6H), 2.48 (t, 4H, *J* = 5.1); ESI-MS *m/z*: 432 (MH^+).

Example 159: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-[4-(2-PHENYLETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedure S (toluene, 120 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.20 (m, 5H), 7.18 (d, 2H, *J* = 8.5), 7.12 (d, 2H, *J* = 8.5), 6.21 (br s, 1H), 5.26 (s, 1H),

3.88 - 3.79 (m, 4H), 2.99 (s, 6H), 2.90 - 2.83 (m, 2H), 2.68 - 2.63 (m, 2H), 2.60 (t, 4H, J = 4.4), 2.32 (s, 3H); ESI-MS m/z: 417 (MH^+).

Example 160: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(3-CHLOROPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, sodium tert-butoxide, 120 °C, 40 h), Q (dioxane, 120 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1H, J = 1.9), 7.38 - 7.23 (m, 5H), 7.20 - 7.11 (m, 2H), 6.95 (ddd, 1H, J = 1.2, 1.9, 7.6), 6.28 (br s, 1H), 5.24 (s, 1H), 3.79 (t, 4H, J = 5.0), 3.54 (s, 2H), 3.00 (s, 6H), 2.49 (t, 4H, J = 5.0); ESI-MS m/z: 423 (MH^+ with ^{35}Cl), 425 (MH^+ with ^{37}Cl).

Example 161: N^2,N^4,N^4-TRIMETHYL-N^6-(4-METHYLPHENYL)-N^2-[2-(2-PYRIDINYL)ETHYL]-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures F (dioxane, potassium tert-butoxide, 140 °C, 16 h), Q, and A (CH_2Cl_2, Δ, TEA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (ddd, 1H, J = 1.2, 2.1, 5.3), 7.57 (dt, 1H, J = 1.7, 7.6), 7.23 (d, 2H, J = 8.6), 7.18 (d, 1H, J = 7.7), 7.14 - 7.09 (m, 1H), 7.10 (d, 2H, J = 7.7), 6.29 (br s, 1H), 5.24 (s, 1H), 3.93 (dd, 2H, J = 5.9, 7.8), 3.11 (dd, 2H,

J = 6.0, 7.7), 3.08 (s, 3H), 3.00 (s, 6H), 2.32 (s, 3H); ESI-MS m/z: 363 (MH^+).

Example 162: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-N^2-(3-PHENYLPROPYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared using Procedures R, S, and V. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, J = 7.7), 7.22 - 7.14 (m, 5H), 7.11 (d, 2H, J = 8.1), 6.41 (br s, 1H), 5.27 (s, 1H), 4.76 (t, 1H, J = 5.7), 3.41 (dd, 2H, J = 7.0, 12.9), 2.96 (s, 6H), 2.70 (t, 2H, J = 7.7), 2.31 (s, 3H), 1.91 (t, 2H, J = 7.5); ESI-MS m/z: 362 (MH^+).

Example 163: 2-(4-CYCLOHEXYL-1-PIPERAZINYL)-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared using Procedures P (16 h), Q (dioxane, 120 °C), and A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, 1H, J = 8.3), 6.92 (t, 1H, J = 2.4), 6.78 - 6.73 (m, 1H), 6.53 - 6.48 (m, 1H), 6.39 (br s, 1H), 5.27 (s, 1H), 3.72 (t, 4H, J = 5.0), 3.71 (s, 3H), 2.92 (s, 6H), 2.55 (t, 4H, J = 5.1), 2.28 - 2.18 (m, 1H), 1.87 - 1.79 (m, 2H), 1.77 - 1.68 (m, 2H), 1.56 (d, 1H, J = 12.4), 1.24 - 1.08 (m, 4H), 1.08 - 0.97 (m, 1H); ESI-MS m/z: 411 (MH^+).

Example 164: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(3-FLUOROPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (140 °C, 4 h), Q (neat, 130 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.31 (m, 5H), 7.28 - 7.17 (m, 2H), 6.98 (ddd, 1H, *J* = 0.7, 2.0, 8.1), 6.67 (ddt, 1H, *J* = 0.9, 2.0, 8.3), 6.30 (br s, 1H), 5.27 (s, 1H), 3.79 (t, 4H, *J* = 5.1), 3.55 (s, 2H), 3.00 (s, 6H), 2.50 (t, 4H, *J* = 5.0); ESI-MS *m/z*: 407 (MH^+).

Example 165: N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-THIENYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure T. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, 1H, *J* = 1.2, 5.2), 7.19 (t, 1H, *J* = 8.1), 6.99 (t, 1H, *J* = 2.0), 6.96 - 6.91 (m, 2H), 6.83 (ddd, 1H, *J* = 0.8, 1.7, 7.9), 6.57 (dd, 1H, *J* = 2.0, 8.2), 6.25 (br s, 1H), 5.33 (s, 1H), 3.81 (t, 4H, *J* = 5.2), 3.78 (s, 3H), 3.76 (s, 2H), 2.99 (s, 6H), 2.53 (t, 4H, *J* = 5.1); ESI-MS *m/z*: 425 (MH^+).

Example 166: 2-[4-(2-METHOXYBENZYL)-1-PIPERAZINYL]-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure T (reduction 3 h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 1H, *J* = 1.6, 7.6), 7.23 (dd, 1H, *J* = 1.2, 7.6), 7.19 (t, 1H, *J* = 8.3), 7.01 (t, 1H, *J* = 1.9), 6.95 (dt, 1H, *J* = 1.0, 7.3), 6.87 (dd, 1H, *J* = 1.1, 8.3), 6.82 (ddd, 1H, *J* = 1.0, 2.0, 8.2), 6.57 (ddd, 1H, *J* = 0.7, 2.5, 8.2), 6.26 (br s, 1H), 5.32 (s, 1H), 3.82 (s, 3H), 3.81 (t, 4H, *J* = 5.1), 3.78 (s, 3H), 3.62 (s, 2H), 2.99 (s, 6H), 2.55 (t, 4H, *J* = 5.0); ESI-MS *m/z*: 449 (MH^+).

Example 167: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-[(1*R*,2*S*)-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene, 120 °C, 16 h), Q (neat, 130 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.22 (m, 5H), 4.82 (s, 1H), 4.51 (br s, 1H), 3.74 (m, 4H), 3.53 (s, 2H), 2.97 (s, 6H), 2.47 (t, 4H, *J* = 4.7), 2.39 - 2.30 (m, 1H), 1.76 - 1.68 (m, 4H), 1.66 (t, 1H, *J* = 4.7), 1.41 - 1.31 (m, 2H), 0.96 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H); ESI-MS *m/z*: 449 (MH^+).

Example 168: N^4-(2-ADAMANTYL)-2-(4-BENZYL-1-PIPERAZINYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: : Prepared by

Procedures P (90 °C, toluene), Q, and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.21 (m, 5H), 4.83 (s, 1H), 4.72 (br s, 1H), 3.74 (m, 5H), 3.52 (s, 2H), 2.98 (s, 6H), 2.46 (t, 4H, *J* = 5.3), 2.05 - 1.53 (m, 14H); ESI-MS *m/z*: 447 (MH^+).

Example 169: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(4-*TERT*-BUTYLCYCLOHEXYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 16 h), Q (neat, 130 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.22 (m, 5H), 4.82 (s, 1H), 3.74 (t, 4H, *J* = 4.7), 3.53 (s, 2H), 3.33 (s, 1H), 2.98 (s, 6H), 2.46 (t, 4H, *J* = 4.7), 1.15 - 0.91 (m, 9H), 0.86 (s, 9H); ESI-MS *m/z*: 451 (MH^+).

Example 170: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-CYCLOOCTYL-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (16 h), Q, and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.21 (m, 5H), 4.79 (s, 1H), 4.34 (s, 1H), 3.74 (t, 4H, *J* = 4.7), 3.53 (s, 2H), 2.99 (s, 6H), 2.40 (t, 4H, *J* = 4.6), 1.93 - 1.49 (m, 15H); ESI-MS *m/z*: 423 (MH^+).

Example 171: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(4-CHLOROPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (140 °C, Q (neat, 130 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.22 (m, 9H), 6.31 (br s, 1H), 5.21 (s, 1H), 3.78 (t, 4H, J = 5.1 Hz), 3.55 (s, 2H), 2.99 (s, 6H), 2.49 (t, 4H, J = 5.1); ESI-MS m/z: 423 (MH^+ with ^{35}Cl), 425 (MH^+ with ^{37}Cl).

Example 172: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(3-CHLORO-4-METHYLPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 120 °C, 16 h), Q (neat, 130 °C), and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - (d, 1H, J = 2.1), 7.38 - 7.09 (m, 5H), 7.07 (d, 1H, J = 2.1), 7.05 (d, 1H, J = 2.6), 6.02 (s, 1H), 5.21 (s, 1H), 3.78 (t, 4H, J = 5.6), 3.54 (s, 2H), 2.99 (s, 6H), 2.49 (t, 4H, J = 5.0), 2.31 (s, 3H); ESI-MS m/z: 437 (MH^+ with ^{35}Cl), 439 (MH^+ with ^{37}Cl).

Example 173: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-(1,2,3,4-TETRAHYDRO-2-NAPHTHALENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (16 h), Q, and A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.04 (m, 9H), 4.99

(s, 1H), 4.91 (s, 1H), 3.74 (m, 4H), 3.53 (s, 2H), 3.47 (m, 1H), 2. 99 (s, 6H), 2.90 - 2.69 (m, 2H), 2.49 (m, 4H), 2.09 - 1.71 (m, 4H); ESI-MS *m/z*: 443 (MH^+).

Example 174: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-[4-(2-THIENYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure X ($NaBH(OAc)_3$, CH_2Cl_2, molecular sieves). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, 2H, *J* = 8.3), 7.15 - 7.09 (m, 2H), 7.03 - 6.94 (m, 3H), 5.22 (br s, 1H), 4.85 (s, 1H), 3.86 - 3.79 (m, 4H), 3.77 (s, 2H), 2.98 (s, 6H), 2.62 - 2.53 (m, 4H), 2.32 (s, 3H); ESI-MS *m/z*: 409 (MH^+).

Example 175: 2-[4-(2-METHOXYBENZYL)-1-PIPERAZINYL]-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedure Z. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 1H, *J* = 1.6, 7.5), 7.23 (dt, 1H, *J* = 1.4, 7.6), 7.17 (d, 2H, *J* = 8.4), 7.10 (d, 2H, *J* = 8.3), 6.94 (t, 1H, *J* = 7.5), 6.87 (d, 1H, *J* = 7.6), 6.17 (br s, 1H), 5.24 (s, 1H), 3.82 (s, 3H), 3.79 (t, 4H, *J* = 5.0), 3.62 (s, 2H), 2.97 (s, 6H), 2.55 (t, 4H, *J* = 5.0), 2.31 (s, 3H); ESI-MS *m/z*: 433 (MH^+).

Example 176: N^2-(2-ANILINOETHYL)-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, Q (toluene, 100 °C), and F (potassium *tert*-butoxide, 110 °C, 16 h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 - 7.10 (m, 6H), 6.67 (dt, 1H, *J* = 0.8, 7.3), 6.59 (dd, 2H, *J* = 0.8, 8.4), 6.31 (br s, 1H), 5.28 (s, 1H), 4.99 (s, 1H), 3.66 (q, 2H, *J* = 6.0), 3.49 (s, 1H), 3.37 (t, 2H, *J* = 6.0), 3.00 (s, 6H), 2.33 (s, 3H); ESI-MS *m/z*: 363 (MH^+).

Example 177: N^4-(3-METHOXYPHENYL)-N^2,N^6,N^6-TRIMETHYL-N^2-[2-(2-PYRIDINYL)ETHYL]-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures F (dioxane, 140 °C, 15 h), A (CH_2Cl_2, Δ, TEA), and Q (toluene, TEA, Δ, 40 h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, 1H, *J* = 4.7), 7.58 (t, 1H, *J* = 7.4), 7.25 - 7.16 (m, 2H), 7.15 - 7.06 (m, 2H), 6.89 (d, 1H, *J* = 8.1), 6.57 (d, 1H, *J* = 6.7), 6.30 (br s, 1H), 5.31 (s, 1H), 3.95 (t, 2H, *J* = 6.4), 3.78 (s, 3H), 3.18 - 3.06 (m, 5H), 3.02 (s, 6H); ESI-MS *m/z*: 379 (MH^+).

Example 178: N^4-(4-CYCLOHEXYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, -78 °C for 3.5 h, warmed from -78 °C to 0 °C and stirred for 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.19-8.16 (m, 1H), 8.09-8.06 (m, 1H), 7.89-7.85 (m, 1H), 7.20-7.18 (m, 4H), 5.28 (s, 1H), 3.99 (t, 4H, *J* = 5.3), 3.73 (t, 4H, *J* = 5.3), 3.04 (s, 6H), 2.53-2.44 (m, 1H), 1.91- 1.71 (m, 4H), 1.46-1.71 (m, 6H); ESI-MS *m/z*: 459 (MH^+).

Example 179: *N*⁴-[3-(BENZYLOXY)PHENYL]-*N*⁶,*N*⁶-DIMETHYL-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, -78 °C for 3.5 h, warmed from -78 °C to 0 °C and stirred for 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (br s, 1H), 8.17-8.15 (m, 1H), 8.09-8.06 (m, 1H), 7.89 (d, 1H, *J* = 2.8), 7.45-7.29 (m, 9H), 5.32 (s, 1H), 5.05 (s, 2H), 4.03 (t, 4H, *J* = 5.6), 3.74 (t, 4H, *J* = 5.0), 3.05 (s, 6H); ESI-MS *m/z*: 483 (MH^+).

Example 180: *N*⁴-(2,3-DIHYDRO-1*H*-INDEN-5-YL)-*N*⁶,*N*⁶-DIMETHYL-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N,

Me_2NHHCl, -78 °C for 3.5 h, warmed from -78 °C to 0 °C and stirred for 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (br s, 1H), 8.16 (s, 1H), 8.10-8.97 (m, 1H), 7.91-7.87 (m, 1H), 7.19 (d, 1H, *J* = 6.3), 7.13 (s, 1H), 7.04 (d, 1H, *J* = 7.6), 5.23 (s, 1H), 4.03 (t, 4H, *J* = 5.2), 3.74 (t, 4H, *J* = 5.1), 3.05 (s, 6H), 2.89 (t, 2H, *J* = 6.9), 2.14-2.04 (m, 4H); ESI-MS *m/z*: 417 (MH^+).

Example 181: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, -78 °C for 3.5 h, warmed from -78 °C to 0 °C and stirred for 3 h), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.17 (s, 1H), 8.12 - 8.09 (m, 1H), 7.90 (d, 1H, *J* = 2.6), 7.18 (d, 2H, *J* = 8.6), 7.16 (d, 2H, *J* = 8.1), 5.19 (s, 1H), 4.18 - 4.02 (m, 4H), 3.77 (t, 4H, *J* = 5.1), 3.20 (br s, 3H), 2.99 (br s, 3H), 2.35 (s, 3H); ESI-MS *m/z*: 391 (MH^+).

Example 183: N^4-(3,4-DIMETHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRAZINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, Et_3N, Me_2NHHCl, -78 °C for 3.5 h, warmed from -78 °C to 0 °C and stirred for 3

h), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (br s, 1H), 8.16 (d, 1H, *J* = 1.3), 8.08 (dd, 1H, *J* = 1.5, 2.8), 7.88 (d, 1H, *J* = 2.5), 7.10 (d, 1H, *J* = 7.8), 7.08 - 7.00 (m, 2H), 5.26 (s, 1H), 4.00 (t, 4H, *J* = 5.1), 3.72 (t, 4H, *J* = 5.0), 3.03 (s, 6H), 2.24 (s, 6H); ESI-MS *m/z*: 405 (MH^+).

Example 184: 1-[2-(4-BENZYL-1-PIPERAZINYL)-6-(4-TOLUIDINO)-4-PYRIMIDINYL]-4-PIPERIDINONE: Prepared by Procedures a (Ch_2cl_2, -78 °C, 4 H), N (24 H), and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7. 38- 7.30 (m, 5H), 7,19-7,10 (m, 4H), 6.24 (s, 1H), 5.40 (s, 1H), 3.84-3.75 (m, 8H), 3.56 (s, 2H), 2.54-2.43 (m, 8H), 2.32 (s, 3H); ESI-MS *m/z*: 457 (MH^+).

Example 185: N^4,N^4-dimethyl-N^6-(2-propylphenyl)-2-[4-(2-pyridinyl)-1-piperazinyl]-4,6-pyrimidinediamine: Prepared by Procedures A (Ch_2cl_2, Tea, 3 - 4 H at -78 °C, then 3 - 4 H at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 - 8.18 (m, 1H), 7.56 - 7.40 (m, 2H), 7.25 - 7.07 (m, 3H), 6.75 - 6.60 (m, 2H), 6.04 (s, 1H), 5.04 (s, 1H), 3.91 (m, 4H), 3.62 (m, 4H), 2.96 (s, 6H), 2.60 (t, 2H, J = 7.5), 1.62 (m, 2H), 0.96 (t, 3H, J = 8.8); ESI-MS *M/Z*: 418 (MH^+).

Example 186: N^4-(2-BENZYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared

by Procedures A (CH_2CL_2, TEA, 3 - 4 H at -78 °C, then 3 - 4 H at 0 °C), N, AND O. ^1H NMR (400 MHZ, $CDCL_3$) δ 8.20 - 8.18 (M, 1H), 7.54 - 7.45 (M, 1H), 7.34 - 7.04 (M, 9H), 6.73 - 6.59 (M, 2H), 5.99 (BR S, 1H), 5.01 (S, 1H), 3.99 (S, 2H), 3.93 - 3.83 (M, 4H), 3.66 - 3.57 (M, 4H), 2.96 (S, 6H); ESI-MS *M/Z*: 466 (MH^+).

Example 187: *N*⁴-(4-HEXYLPHENYL)-*N*⁶,*N*⁶-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 460 (MH^+).

Example 188: *N*⁴-(4-BENZYLPHENYL)-*N*⁶,*N*⁶-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 - 8.18 (m, 1H), 7.52 - 7.45 (m, 1H), 7.32 - 7.09 (m, 9H), 6.78 (d, 1H, J = 9.2), 6.65 - 6.59 (m, 1H), 6.24 (br s, 1H), 5.29 (s, 1H), 3.96 (s, 2H), 3.91 - 3.83 (m, 4H), 3.63 - 3.55 (m, 4H), 3.00 (s, 6H); ESI-MS *m/z*: 466 (MH^+).

Example 189: *N*⁴-(4-HEPTYLPHENYL)-*N*⁶,*N*⁶-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 -

4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 - 8.18 (m, 1H), 7.57 - 7.44 (m, 1H), 7.38 - 7.08 (m, 4H), 6.75 - 6.57 (m, 2H), 6.26 (br s, 1H), 5.29 (s, 1H), 3.95 - 3.85 (m, 4H), 3.71 - 3.56 (m, 4H), 3.00 (s, 6H), 2.57 (t, 2H, J = 5.2), 1.84 - 1.51 (m, 4H), 1.40 - 1.16 (m, 6H), 0.93 - 0.82 (m, 3H); ESI-MS *m/z*: 474 (MH^+).

Example 190: N^4-(3,4-DIMETHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 - 8.19 (m, 1H), 7.55 - 7.44 (m, 1H), 7.31 - 7.23 (m, 1H), 7.14 - 7.02 (m, 2H), 6.73 - 6.59 (m, 2H), 6.18 (br s, 1H), 5.29 (s, 1H), 3.95 - 3.85 (m, 4H), 3.67 - 3.55 (m, 4H), 3.00 (s, 6H), 2.24 (s, 3H), 2.23 (s, 3H), ESI-MS *m/z*: 404 (MH^+).

Example 191: N^4-(3-ISOPROPYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 - 8.19 (m, 1H), 7.54 - 7.45 (m, 1H), 7.31 - 7.21 (m,

2H), 7.13 - 7.08 (m, 1H), 6.95 - 6.88 (m, 1H), 6.74 - 6.60 (m, 2H), 6.29 (br s, 1H), 5.37 - 5.34 (m, 1H), 3.96 - 3.87 (m, 4H), 3.68 - 3.57 (m, 4H), 3.00 (s, 6H), 2.95 - 2.85 (m, 1H), 1.36 - 1.19 (m, 6H); ESI-MS *m/z*: 418 (MH^+).

Example 192: N^4,N^4-DIMETHYL-N^6-(4-OCTYLPHENYL)-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.55 - 7.44 (m, 1H), 7.37 - 7.07 (m, 4H), 6.76 - 6.59 (m, 2H), 6.28 (br s, 1H), 5.29 (s, 1H), 3.96 - 3.86 (m, 4H), 3.69 - 3.56 (m, 4H), 3.00 (s, 6H), 2.57 (t, 2H, J = 5.1), 1.74 - 1.51 (m, 4H), 1.41 - 1.08 (m, 8H), 0.93 - 0.82 (m, 3H); ESI-MS *m/z*: 488 (MH^+).

Example 193: N^4-(3-IODOPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 - 8.18 (m, 1H), 8.01 - 7.93 (m, 1H), 7.56 - 7.45 (m, 1H), 7.39 - 7.29 (m, 1H), 7.11 - 6.95 (m, 2H), 6.78 - 6.56) (m, 2H), 6.42 - 6.25 (m, 1H), 5.34 (s, 1H), 3.95 - 3.85

(m, 4H), 3.65 - 3.56 (m, 4H), 3.00 (s, 6H); ESI-MS *m/z*: 502 (MH^+).

Example 194: N^4-(4-CHLOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.53 - 7.42 (m, 1H), 7.35 - 7.24 (m, 2H), 7.11 - 6.95 (m, 2H), 6.76 - 6.57 (m, 2H), 6.21 (s, 1H), 5.29 (s, 1H), 3.97 - 3.86 (m, 4H), 3.67 - 3.57 (m, 4H), 3.00 (s, 6H); ESI-MS *m/z*: 410 (MH^+).

Example 195: N^5-(2-CHLOROPHENYL)-N^4,N^4-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,5-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 - 8.10 (m, 2H), 7.55 - 7.12 (m, 4H), 7.05 - 6.90 (m, 2H), 6.61 (s, 1H), 5.31 (s, 1H), 3.95-3.85 (m, 4H), 3.65 - 3.54 (m, 4H), 3.00 (s, 6H); ESI-MS *m/z*: 410 (MH^+).

Example 196: N^4-(3,4-DIFLUOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.59 - 6.95 (m, 4H), 6.68 - 6.54 (m, 2H), 6.29 (s, 1H), 5.27 (s, 1H), 3.94 - 3.82 (m, 4H), 3.63 - 3.51 (m, 4H), 3.01 (s, 6H); ESI-MS *m/z*: 412 (MH^+).

Example 197: N^4-[3-METHOXY-5-(TRIFLUOROMETHYL)PHENYL]-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.18 (m, 1H), 7.58 - 7.11 (m, 3H), 6.77 - 6.38 (m, 3H), 6.34 (s, 1H), 5.25 (s, 1H), 3.96 - 3.88 (m, 4H), 3.85 (s, 3H), 3.69 - 3.55 (m, 4H), 3.00 (s, 6H); ESI-MS *m/z*: 474 (MH^+).

Example 198: N^4,N^4-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-N^6-(2,3,4-TRIFLUOROPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.18 (m, 1H), 7.58 - 7.11 (m,

3H), 6.77 - 6.38 (m, 2H), 6.34 (s, 1H), 5.25 (s, 1H), 3.96 - 3.88 (m, 4H), 3.85 (s, 3H), 3.69 - 3.55 (m, 4H), 3.00 (s, 6H); ESI-MS *m/z*: 430 (MH^+).

Example 199: N^4-(4-BROMO-2-FLUOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 - 8.17 (m, 1H), 7.61 - 7.01 (m, 4H), 6.75 - 6.57 (m, 2H), 6.34 (br s, 1H), 5.23 (s, 1H), 3.95 - 3.85 (m, 4H), 3.68 - 3.59 (m, 4H), 3.00 (s, 6H); ESI-MS *m/z*: 472 (MH^+).

Example 200: N^4-(4-FLUORO-3-METHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 - 8.17 (m, 1H), 7.56 - 7.47 (m, 1H), 7.21 - 6.89 (m, 3H), 6.75 - 6.58 (m, 2H), 6.24 (br s, 1H), 5.18 (s, 1H), 3.95 - 3.84 (m, 4H), 3.69 - 3.55 (m, 4H), 3.00 (s, 6H), 2.25 (s, 3H); ESI-MS *m/z*: 408 (MH^+).

Example 201: N^4-(2,5-DIMETHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 - 8.16 (m, 1H), 7.96 - 7.86 (m, 1H), 7.56 - 7.43 (m, 1H), 6.93 - 6.42 (m, 5H), 5.31 (s, 1H), 4.01 - 3.90 (m, 4H), 3.84 (s, 3H), 3.79 (s, 3H), 3.70 - 3.54 (m, 4H), 3.04(s, 6H); ESI-MS *m/z*: 436 (MH^+).

Example 202: N^4-(3,5-DIMETHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.17 (m, 1H), 7.55 - 7.44 (m, 1H), 6.73 - 6.58 (m, 2H), 6.59 - 6.53(m, 2H), 6.23 (br s, 1H) 5.37 (s, 1H), 3.98 - 3.88 (m, 4H), 3.77 (s, 6H), 3.62 - 3.58 (m, 4H), 3.01 (s, 6H); ESI-MS *m/z*: 436 (MH^+).

Example 203: N^4-[3-(BENZYLOXY)PHENYL]-2-[4-(3-BROMOPHENYL)-1-PIPERAZINYL]-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N (TEA), and O.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 6.26 (m, 14H), 5.29 (s, 1H), 5.06 (s, 2H), 3.97 - 3.82 (m, 4H), 3.21 - 3.14 (m, 4H), 3.01 (s, 6H); ESI-MS *m/z*: 560 (MH^+).

Example 204: N^4-(2-BROMO-4-METHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.16 (m, 1H), 7.81 (d, 1H, J = 8.8), 7.52 - 7.44 (m, 1H), 7.38 (d, 1H, J = 8.5), 7.08 (d, 1H, J = 8.5), 6.72 (m, 2H), 6.47 (br s, 1H), 5.24 (s, 1H), 3.90 (t, 4H, J = 6.3), 3.61 (t, 4H, J = 6.4), 3.01 (s, 6H), 2.28 (s, 3H); ESI-MS *m/z*: 468 (MH^+).

Example 205: N^4-(2,4-DICHLOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 - 8.17 (m, 1H), 8.21 (d, 1H, J = 9.2), 7.49 (t, 1H, J = 9.0), 7.38 - 7.16 (m, 2H), 6.71 - 6.59 (m, 2H), 6.57 (br s, 1H), 5.25 (s, 1H), 3.93 - 3.85 (m, 4H), 3.65 - 3.55 (m, 4H), 3.03 (s, 6H); ESI-MS *m/z*: 444 (MH^+).

Example 206: N^4-(3-FLUOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 - 6.39 (m, 9H), 5.30 (s, 1H), 3.97 - 3.85 (m, 4H), 3.74 - 3.58 (m, 4H), 3.01 (s, 6H); ESI-MS *m/z*: 394 (MH^+).

Example 207: N^4,N^4-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-N^6-[3-(TRIFLUOROMETHOXY)PHENYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 460 (MH^+).

Example 208: N^4-(2,5-DICHLOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 445 (MH^+).

Example 209: N^4,N^4-DIMETHYL-N^6-(4-PROPYLPHENYL)-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 418 (MH^+).

Example 210: N^4,N^4-DIMETHYL-N^6-(4-PENTYLPHENYL)-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 446 (MH^+).

Example 211: N^4-(4-*SEC*-BUTYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 432 (MH^+).

Example 212: N^4-(2-*TERT*-BUTYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 432 (MH^+).

Example 213: N^4-(2,5-DIMETHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 404 (MH^+).

Example 214: N^4-(3,5-DIMETHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 404 (MH^+).

Example 215: N^4-(2,3-DIMETHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 404 (MH^+).

Example 216: N^4-(3-BENZYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 466 (MH^+).

Example 217: N^4-(4-BROMO-2-CHLOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 489 (MH^+).

Example 218: N^4-(2,3-DICHLOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 445 (MH^+).

Example 219: N^4,N^4-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-N^6-(2,4,5-TRIFLUOROPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 430 (MH^+).

Example 220: N^4-(5-CHLORO-2-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 440 (MH^+).

Example 221: N^4,N^4-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-N^6-(3,4,5-TRIFLUOROPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 430 (MH^+).

Example 222: N^4-(2-CHLORO-5-FLUOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 428 (MH^+).

Example 223: N^4-(2-CHLORO-4-METHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 424 (MH^+).

Example 224: N^4-(3-CHLOROPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A (CH_2Cl_2, TEA, 3 - 4 h at -78 °C, then 3 - 4 h at 0 °C), N, and O. ESI-MS *m/z*: 410 (MH^+).

Example 225: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-[3-METHOXY-5-(TRIFLUOROMETHYL)PHENYL]-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures O (toluene, 75 °C), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 487 (MH^+).

Example 226: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-[2-METHOXY-5-(TRIFLUOROMETHYL)PHENYL]-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures O, Q (dioxane, 120 °C), and A. ESI-MS *m/z*: 487 (MH^+).

Example 227: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(2,5-DIMETHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures O, Q (dioxane, 120 °C), and A. ESI-MS *m/z*: 449 (MH^+).

Example 228: N^4-[3-(BENZYLOXY)PHENYL]-2-(4-BENZYL-1-PIPERAZINYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures O, Q (toluene, 120 °C), and A. ESI-MS *m/z*: 495 (MH^+).

Example 229: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-[4-(TRIFLUOROMETHYL)PHENYL]-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures P (toluene, 105 °C), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 457 (MH^+).

Example 230: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-(2,3,4-TRICHLOROPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures O (60 °C), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 492 (MH^+).

Example 231: 2-[4-(2-FURYLMETHYL)-1-PIPERAZINYL]-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE:

Prepared by Procedures R (16 h), P (sodium *tert*-butoxide, toluene, 120 °C), N (TEA, toluene reflux), and A. ESI-MS *m/z*: 393 (MH^+).

Example 232: N^2-[2-(4-METHOXYPHENYL)ETHYL]-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2,4,6-PYRIMIDINETRIAMINE:

Prepared by Procedures V, R, and S (DIEA, DMAP). ESI-MS *m/z*: 378 (MH^+).

Example 233: N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(TETRAHYDRO-2-FURANYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A, P (16 h), and Q (dioxane, 120 °C). ESI-MS *m/z*: 413 (MH^+).

Example 235: 2-[4-(4-METHOXYBENZYL)-1-PIPERAZINYL]-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedure Z. ESI-MS *m/z*: 433 (MH^+).

Example 237: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-N^2-[2-(2-THIENYL)ETHYL]-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures R, S, and V. ESI-MS *m/z*: 354 (MH^+).

Example 238: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-2-[4-(3-THIENYLMETHYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures AA, T (2 h), and W. ESI-MS *m/z*: 409 (MH^+).

Example 239: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-[4-CHLORO-2-(TRIFLUOROMETHYL)PHENYL]-N^6,N^6-DIMETHYL-4,6-

PYRIMIDINEDIAMINE: Prepared by Procedures O (100 °C, 40 h), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 491 (MH^+).

Example 240: N^4-(3-BROMO-4-METHYLPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures O (80 °C), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 469 (MH^+).

Example 241: 2-{4-[4-(DIMETHYLAMINO)-6-(4-TOLUIDINO)-2-PYRIMIDINYL]-1-PIPERAZINYL}NICOTINONITRILE: Prepared by Procedures O, Q (tyoluene, 120 °C), and A. ESI-MS *m/z*: 415 (MH^+).

Example 242: N^4,N^4-DIMETHYL-N^6-[4-METHYL-3-(2-PYRIDINYLAMINO)PHENYL]-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (toluene), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 482 (MH^+).

Example 243: N^4-(3-BROMOPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared

by Procedures O (85 °C), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 455 (MH^+).

Example 244: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-[2-CHLORO-4-(TRIFLUOROMETHYL)PHENYL]-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures P (16 h, toluene), Q (toluene, 120 °C), and A. ESI-MS *m/z*: 491 (MH^+).

Example 245: N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-[4-(2-PYRIDINYL)-1-PIPERAZINYL]-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A, N, and P. ESI-MS *m/z*: 406 (MH^+).

Example 246: N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-2-{4-[2-(TRIFLUOROMETHYL)PHENYL]-1-PIPERAZINYL}-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A, N, and P. ESI-MS *m/z*: 473 (MH^+).

Example 247: N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-N^2-(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, N, and P. ESI-MS *m/z*: 364 (MH^+).

Example 248: N^2,N^4,N^4-TRIMETHYL-N^6-(4-METHYLPHENYL)-N^2-(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures A, N, and P. ESI-MS *m/z*: 362 (MH^+).

Example 249: *N*-(4-METHYLPHENYL)-2-{4-[1-OXIDO-3-(TRIFLUOROMETHYL)-2-PYRIDINYL]-1-PIPERAZINYL}-6-(1-PIPERIDINYL)-4-PYRIMIDINAMINE: Prepared by Procedure CC. ESI-MS *m/z*: 514 (MH^+).

Example 250: N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-N^2-(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: Prepared by Procedures R and S. ESI-MS *m/z*: 348 (MH^+).

Example 251: N^4-(3-METHOXYPHENYL)-N^2,N^6,N^6-TRIMETHYL-N^2-(2-PHENYLETHYL)-2,4,6-PYRIMIDINETRIAMINE: : Prepared by Procedures A, N, and P. ESI-MS *m/z*: 378 (MH^+).

Example 252: 2-(4-BENZYL-1-PIPERAZINYL)-N^4-(3-METHOXYPHENYL)-N^6,N^6-DIMETHYL-4,6-PYRIMIDINEDIAMINE:

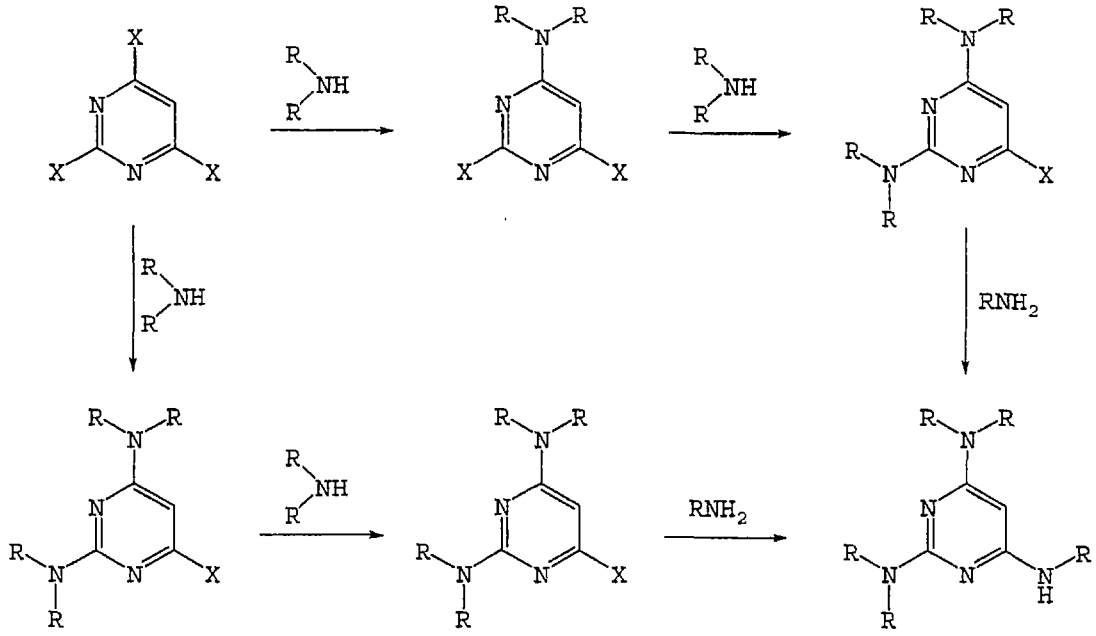
Prepared by Procedures A, N, and P. ESI-MS *m/z*: 419 (MH^+).

Example 253: 2-(4-BENZYL-1-PIPERAZINYL)-N^4,N^4-DIMETHYL-N^6-(4-METHYLPHENYL)-4,6-PYRIMIDINEDIAMINE: Prepared by Procedures A, N, and P. ESI-MS *m/z*: 403 (MH^+).

Examples 1-90 and 115-253 as described above are merely illustrative of the methods used to synthesize pyrimidine derivatives. Further derivatives may be obtained utilizing methods shown in Schemes 1-5b. The substituents in Schemes 1-5b are described in the Detailed Description.

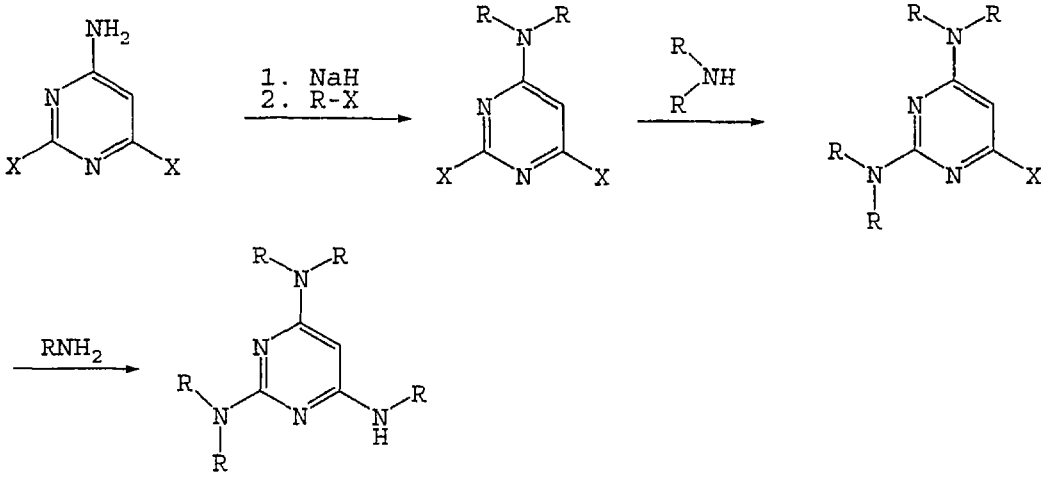
It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form pyrimidine derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T. W. and Wuts, P.G. M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

Scheme 1. Synthesis of Substituted Triaminopyrimidines



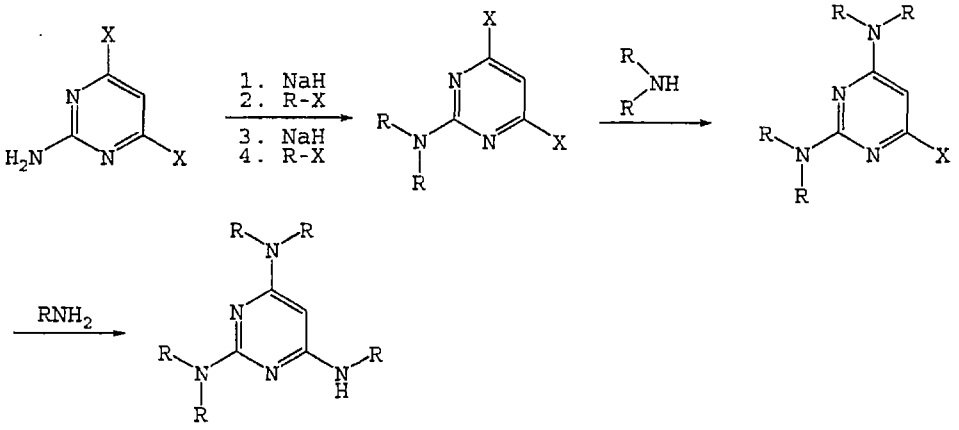
X =leaving group such halogen
OTf or OTs

Scheme 2. Alternate Synthesis of Substituted Triaminopyrimidines



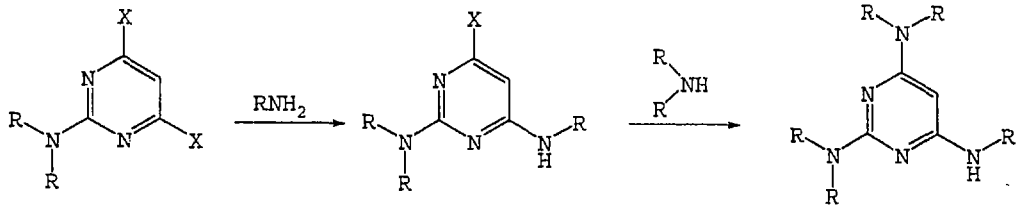
X =leaving group such halogen OTf or OTs

Scheme 3. Alternate Synthesis of Substituted Triaminopyrimidines

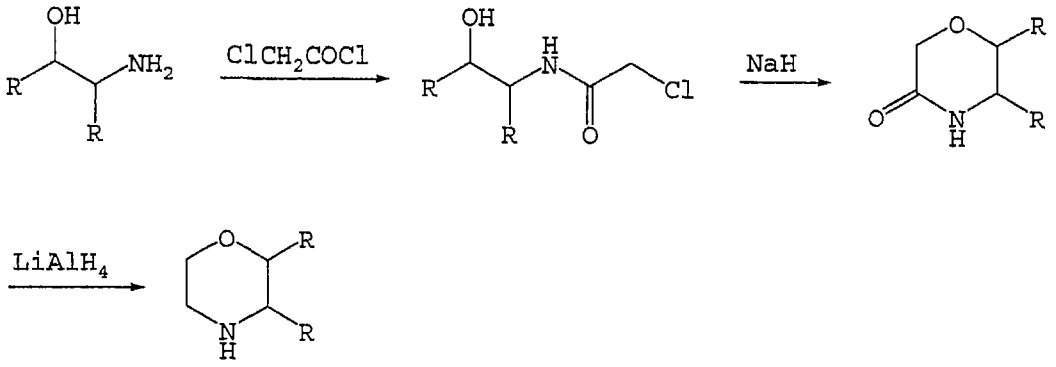


X =leaving group such halogen
OTf or OTs

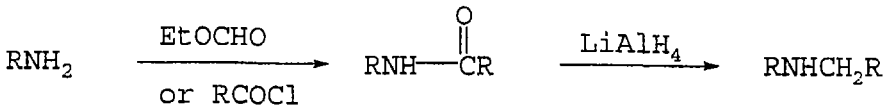
Alternatively,



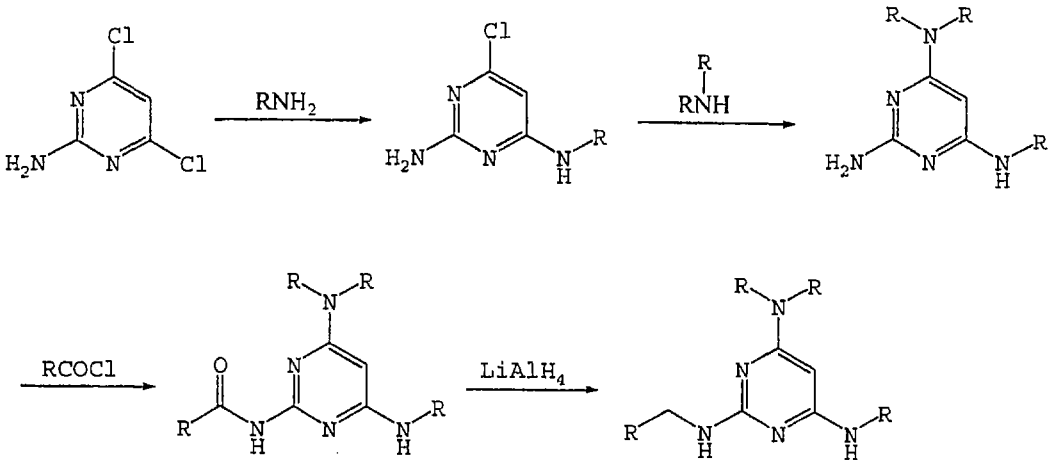
Scheme 4. Synthesis of Morpholine Intermediates



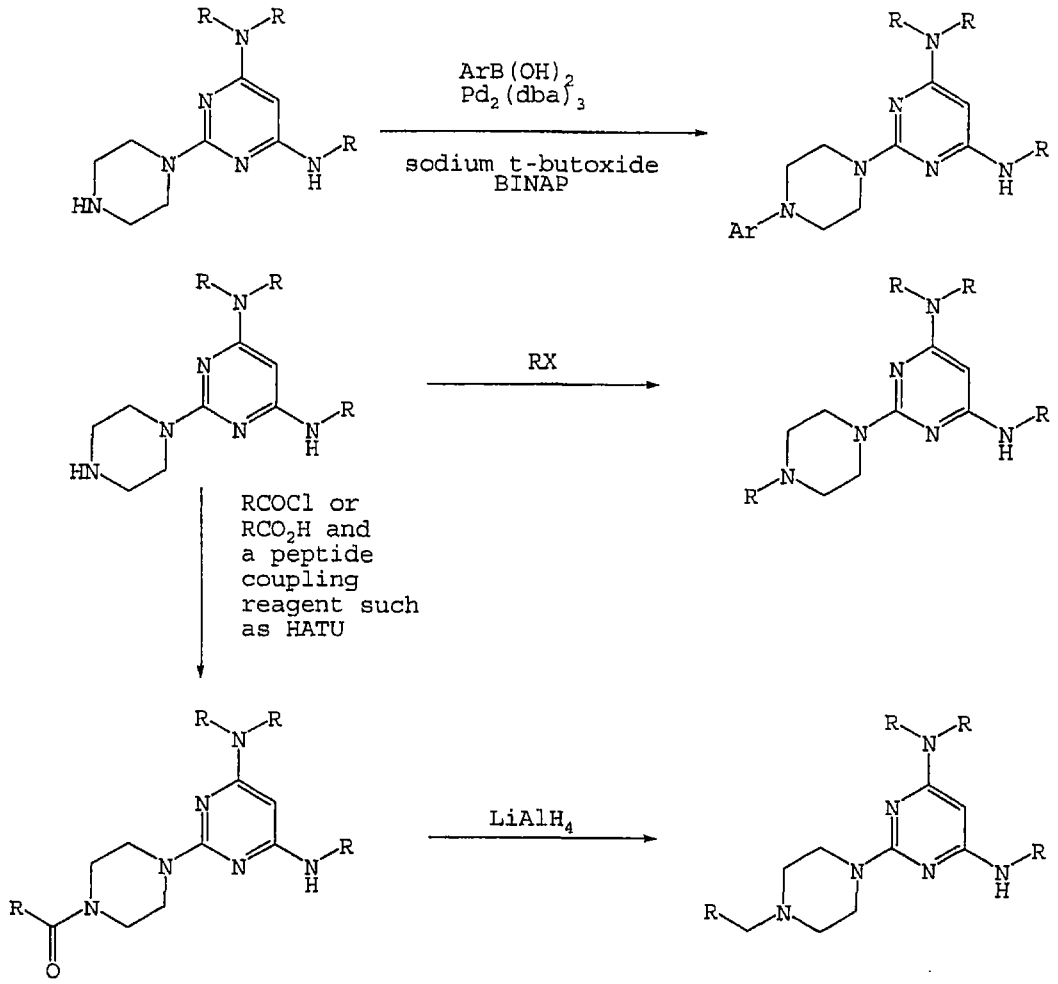
Scheme 5. Synthesis of N-Alkylamine Intermediates



Scheme 5a. Synthesis of Triaminopyrimidines from 2-Amidopyrimidines



Scheme 5b. Substitution on the Piperazine Moiety of 2-(Piperazin-1-yl)pyrimidines



X is a leaving group such as a halogen or tosylate; HATU is O-(7-azabenzenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; dba is dibenzylideneacetone; BINAP is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

Radioligand Binding of Pyrimidines at Cloned Galanin Receptors

The binding properties of the pyrimidines of the present invention were evaluated at the cloned human galanin receptors, GAL1, GAL2, and GAL3, using protocols described herein.

Radioligand Binding Assay Results

The pyrimidines described in Examples 1-90 and 115-253 were assayed using cloned human galanin receptors. The compounds were found to be selective for the GAL3 receptor. The binding affinities of the compounds of Examples 1-90 and 115-253 are illustrated in Tables 1-3a.

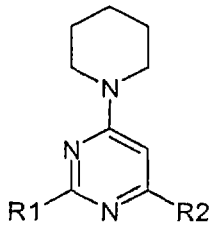
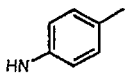
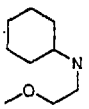
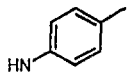
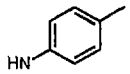
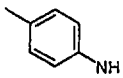
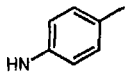
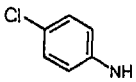
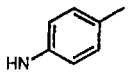
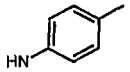
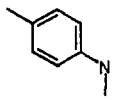
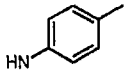
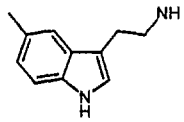
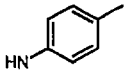
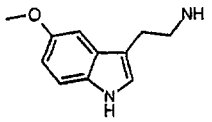
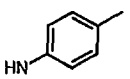


TABLE 1

	substitution		Ki (nM)		
Example	R1	R2	GalR1	GalR2	GalR3
1			668	188	35
2			2818	562	26
3			>5000	>5000	163
4			>5000	>5000	627
5			>5000	>5000	345
6			>5000	2157	248
7			1107	775	177
8			>5000	795	264
9			>5000	2110	568

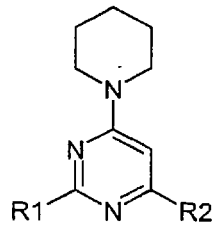
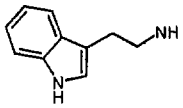
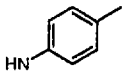
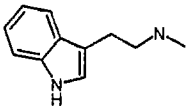
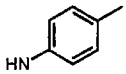
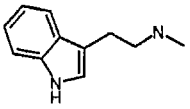
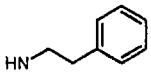
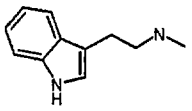
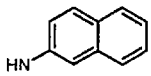
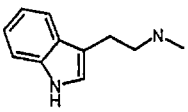
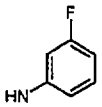
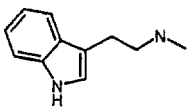
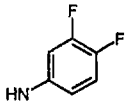
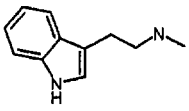
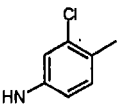
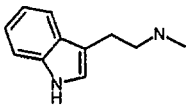
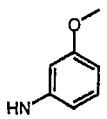


Table 1 continued

	substitution			Ki (nM)	
Example	R1	R2	GalR1	GalR2	GalR3
10			>5000	865	100
11			>5000	681	91
12			>5000	1995	322
13			2065	1413	81
14			>5000	1336	54
15			2427	624	73
16			>5000	>5000	33
17			>5000	2089	87

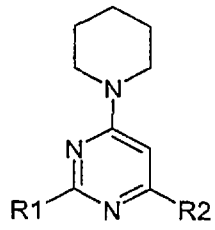
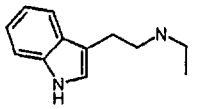
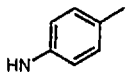
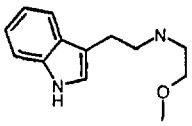
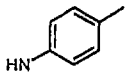
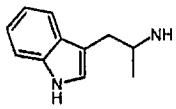
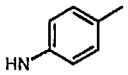
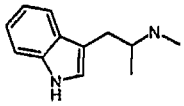
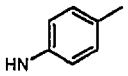
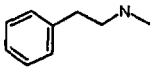
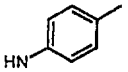
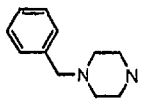
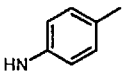
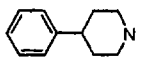
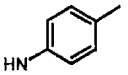
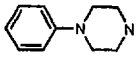
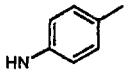
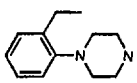
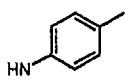


Table 1
continued

	substitution		Ki (nM)		
Example	R1	R2	GalR1	GalR2	GalR3
18			3589	543	40
19			>5000	1771	79
20			>5000	>5000	164
21			4786	1096	49
22			442	176	28
23			>5000	>5000	60
24			>5000	3961	210
25			>5000	1497	548
26			>5000	4049	85

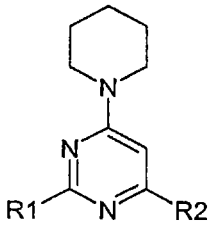
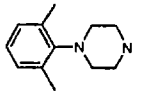
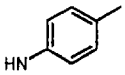
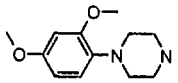
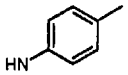
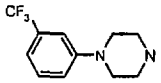
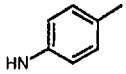
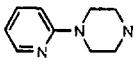
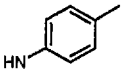
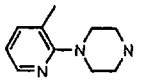
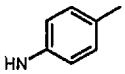
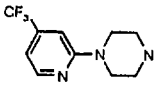
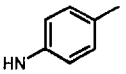
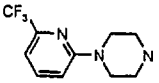
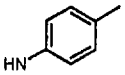
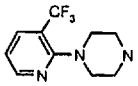
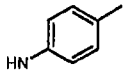
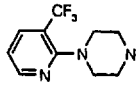
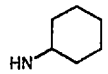
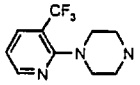


Table 1 continued

	substitution			Ki (nM)	
Example	R1	R2	GalR1	GalR2	GalR3
27			2692	272	63
28			>5000	>5000	270
29			716	359	46
30			>5000	2613	197
31			>5000	3402	174
32			>5000	1860	145
33			>5000	>5000	181
34			912	168	23
35					111
36			442	90	93

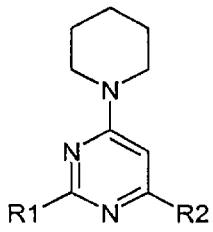
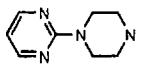
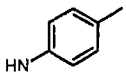
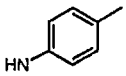
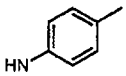
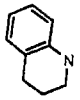
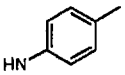
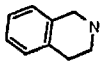
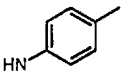
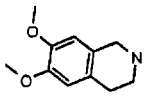
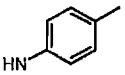
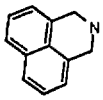
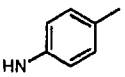
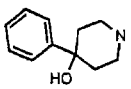
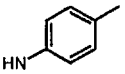
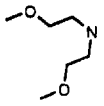
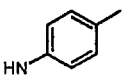


Table 1
continued

	substitution		Ki (nM)		
Example	R1	R2	GalR1	GalR2	GalR3
37			>5000	903	343
38			2901	516	320
39			>5000	>5000	128
40			>5000	2623	164
41			2131	840	151
42			>5000	1137	275
43			>5000	>5000	107
44			>5000	1023	133
45			>5000	>5000	505

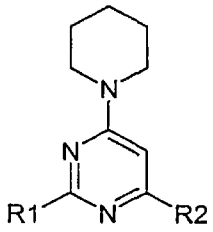


Table 1
continued

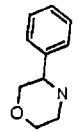
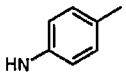
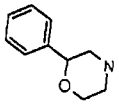
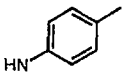
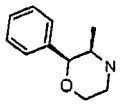
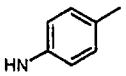
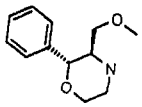
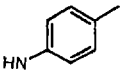
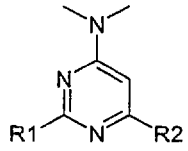
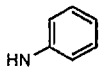
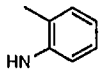
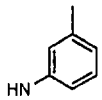
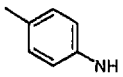
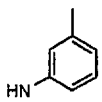
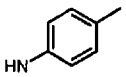
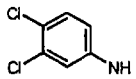
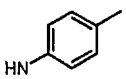
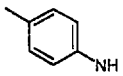
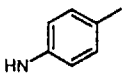
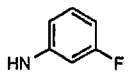
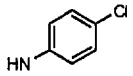
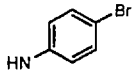
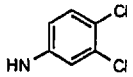
	substitution		Ki (nM)		
Example	R1	R2	GalR1	GalR2	GalR3
46			>5000	>5000	577
47			>5000	3012	115
48			>5000	4233	120
49			>5000	3273	211

TABLE 2



	substitution		Ki (nM)		
Example	R1	R2	GalR1	GalR2	GalR3
50			>5000	>5000	699
51			>5000	>5000	987
52			>5000	>5000	570
53			>5000	>5000	980
54			>5000	>5000	132
55			>5000	>5000	48
56			>5000	>5000	794
57			>5000	>5000	360
58			>5000	>5000	783
59			>5000	>5000	566
60			>5000	>5000	86

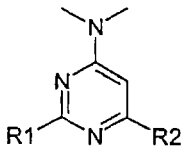
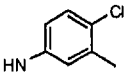
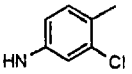
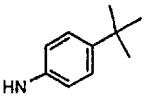
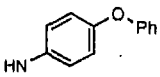
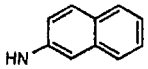
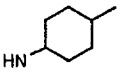
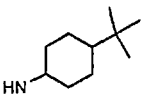
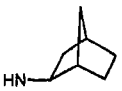
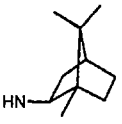


Table 2
continued

	substitution		Ki (nM)		
Example	R1	R2	GalR1	GalR2	GalR3
61			>5000	>5000	753
62			>5000	>5000	736
63			>5000	>5000	731
64			>5000	>5000	572
65			>5000	>5000	329
66			>5000	>5000	699
67			>5000	>5000	752
68			>5000	2155	164
69			>5000	>5000	417
70			>5000	944	476

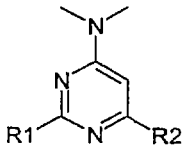
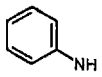
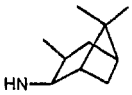
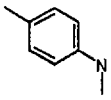
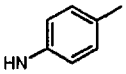
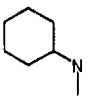
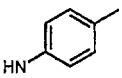
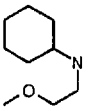
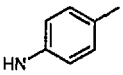
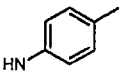
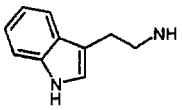
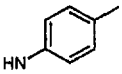
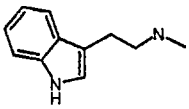
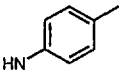
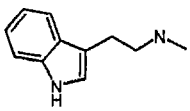
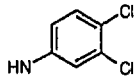


Table 2
continued

	substitution		Ki (nM)		
Example	R1	R2	GalR1	GalR2	GalR3
71			>5000	944	72
72			>5000	2083	132
73			>5000	1550	124
74			2291	468	47
75			1462	2458	144
76			3802	1657	392
77			3802	709	79
78			4942	1862	41

5

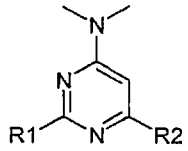
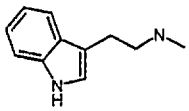
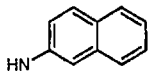
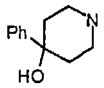
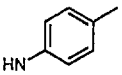
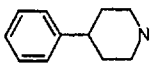
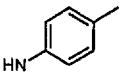
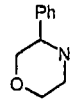
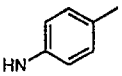
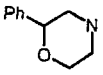
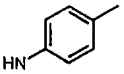
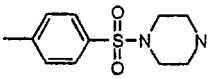
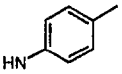
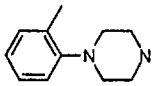
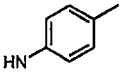
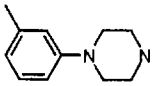
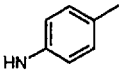
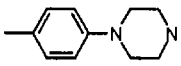
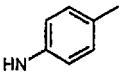
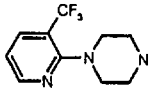
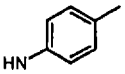
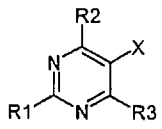


Table 2
continued

	substitution		Ki (nM)		
Example	R1	R2	GalR1	GalR2	GalR3
79			3802	1656	190
80			>5000	2478	615
81			>5000	4789	160
82			>5000	>5000	232
83			>5000	>5000	160
84			>5000	>5000	261
85			>5000	4228	72
86			>5000	>5000	227
87			>5000	4617	157
88			2188	355	39

Key: Ph = Phenyl

TABLE 3



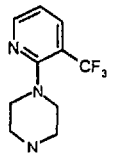
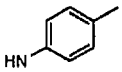
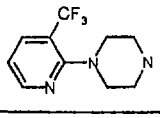
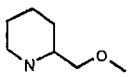
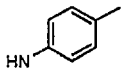
	substitution				Ki (nM)		
Example	X	R1	R2	R3	GalR1	GalR2	GalR3
89	H				1122	1274	105
90	H				>5000	2460	105

Table 3a.

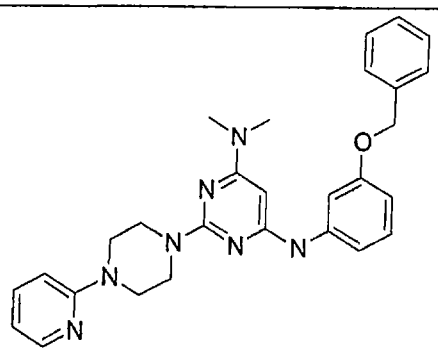
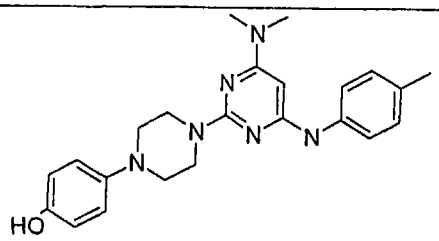
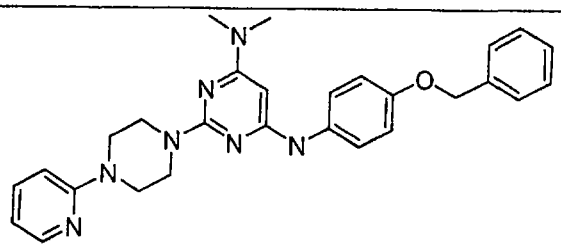
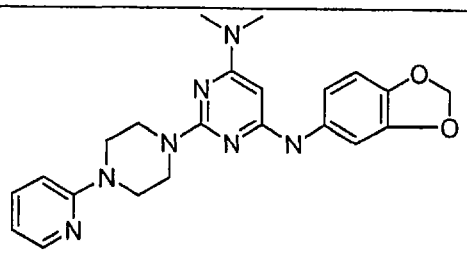
Example	Structure	Ki (nM) Gal3
115		13
116		479
117		61
118		508

Table 3a.

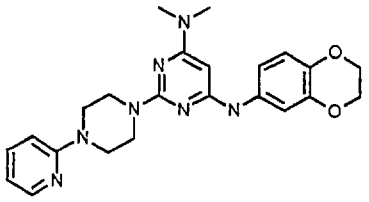
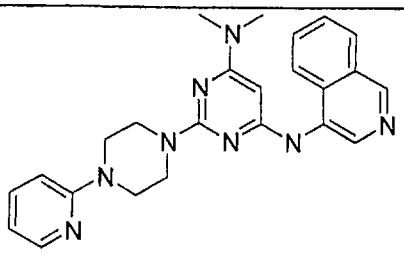
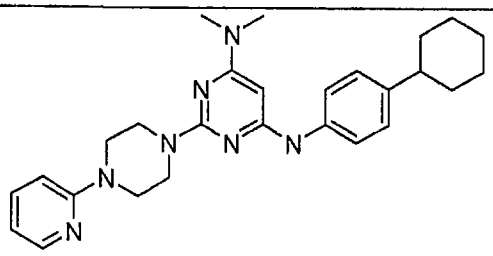
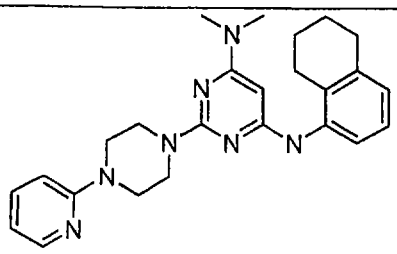
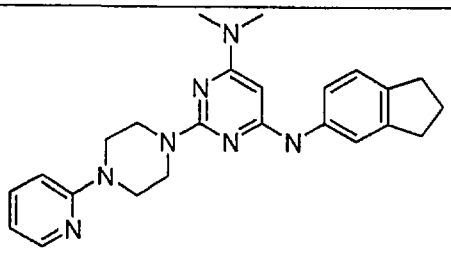
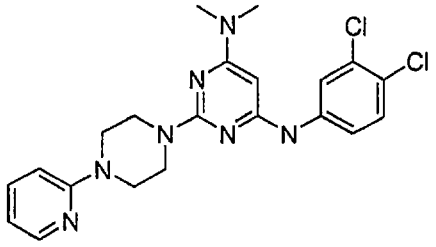
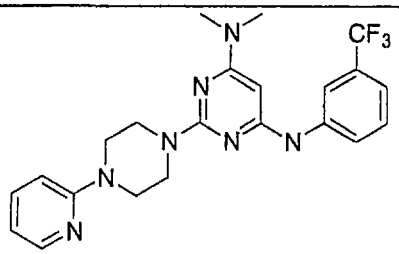
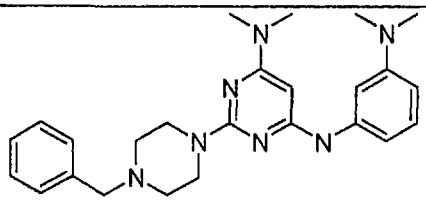
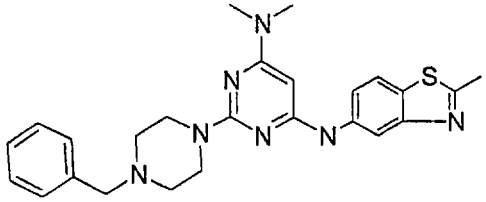
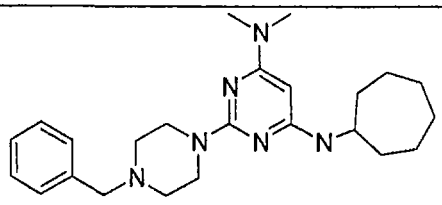
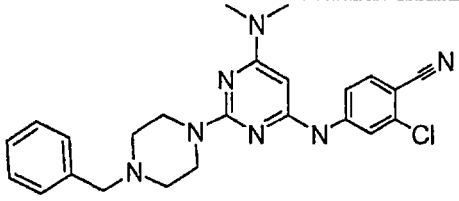
119		540
120		664
121		21
122		65
123		61

Table 3a.

124		36
125		75
126		99
127		255
128		249
129		405

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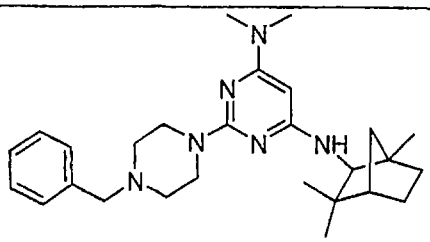
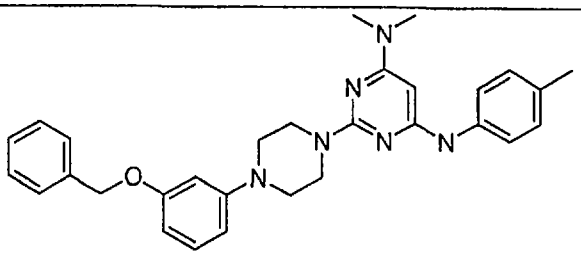
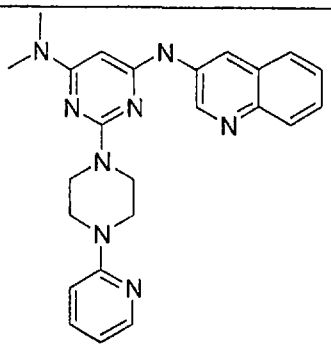
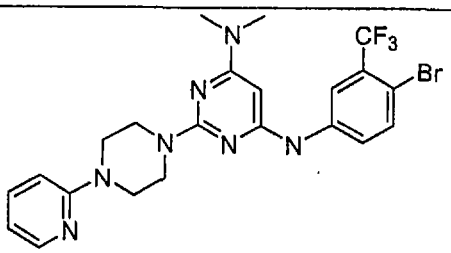
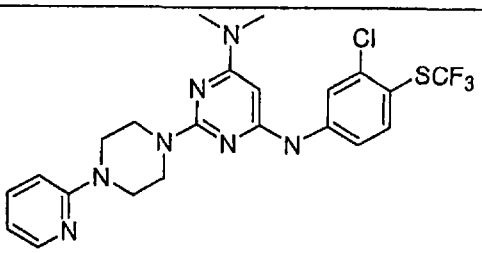
130		100
131		20
132		618
133		60
134		25

Table 3a.

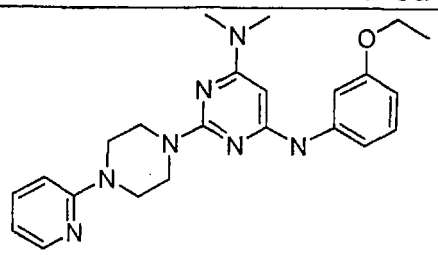
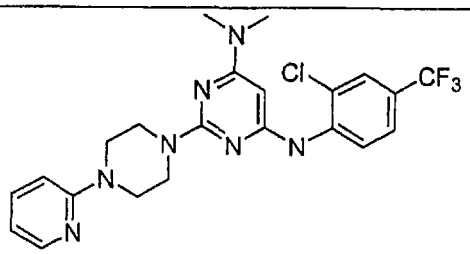
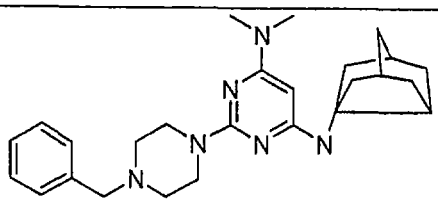
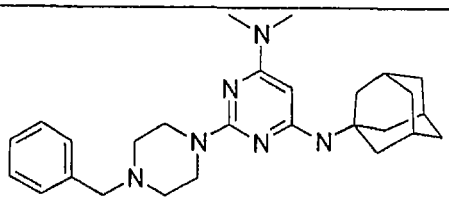
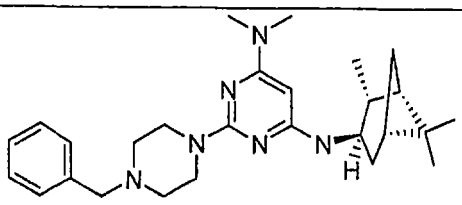
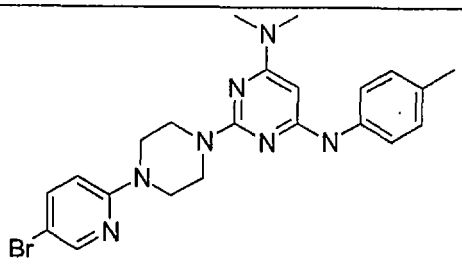
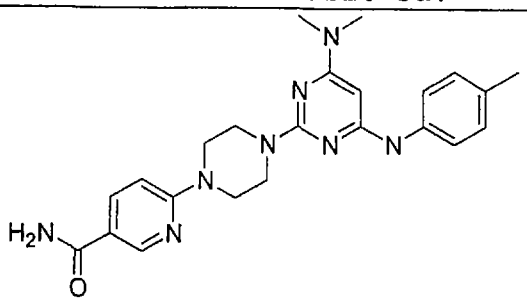
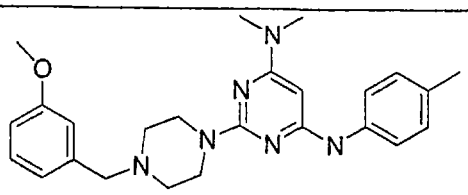
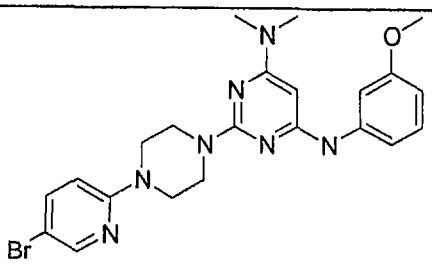
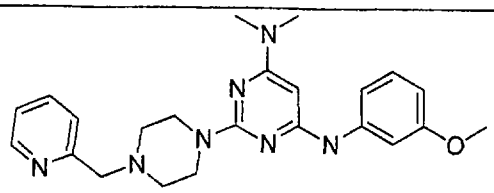
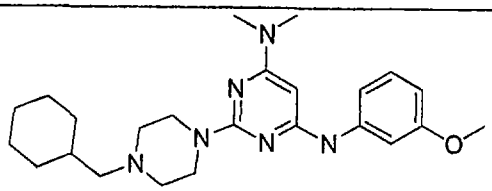
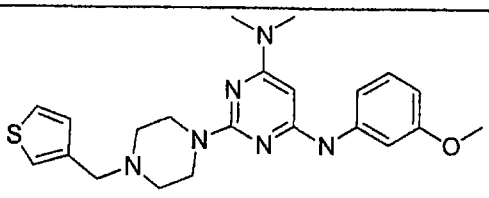
135		100
136		25
137		124
138		52
139		47
140		169

Table 3a.

141		509
142		28
143		144
144		529
145		155
146		72