



(22) Date de dépôt/Filing Date: 2002/01/31
(41) Mise à la disp. pub./Open to Public Insp.: 2002/08/08
(45) Date de délivrance/Issue Date: 2012/12/18
(62) Demande originale/Original Application: 2 438 582
(30) Priorité/Priority: 2001/01/31 (US09/775,341)

(51) Cl.Int./Int.Cl. *A61K 31/506* (2006.01),
A61K 45/00 (2006.01), *A61P 25/22* (2006.01),
A61P 25/24 (2006.01)

(72) Inventeurs/Inventors:
BLACKBURN, THOMAS P., US;
KONKEL, MICHAEL J., US;
BOTEJU, LAKMAL, US;
TALISMAN, IAN JAMIE, US;
WETZEL, JOHN M., US;
PACKIARAJAN, MATHIVANAN, US;
...

(73) Propriétaire/Owner:
H. LUNDBECK A/S, DK

(74) Agent: NORTON ROSE CANADA

(54) Titre : ANTAGONISTES DU RECEPTEUR GAL3 SERVANT A TRAITER UNE DEPRESSION
(54) Title: GAL3 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF DEPRESSION

(57) **Abrégé/Abstract:**

This invention is directed to pyrimidine and indolone derivatives which are selective antagonists for the GAL3 receptor. The invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This invention also provides a pharmaceutical composition made by combining a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This invention further provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This invention also provides a method of treating a subject suffering from depression and/or anxiety which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's depression and/or anxiety. This invention also provides a method of treating depression and/or 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.



(72) **Inventeurs(suite)/Inventors(continued)**: CHEN, HEIDI, US; JIMENEZ, HERMO, US; LAGU, BHARAT, US;
LIM, KITAE, US; NOBLE, STEWART, US

(74) **Agent(suite/continued)**: S.E.N.C.R.L.,S.R.L./LLP

ABSTRACT

This invention is directed to pyrimidine and indolone derivatives which are selective antagonists for the GAL3 receptor. The invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This invention also provides a pharmaceutical composition made by combining a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This invention further provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This invention also provides a method of treating a subject suffering from depression and/or anxiety which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's depression and/or anxiety. This invention also provides a method of treating depression and/or 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.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __3__

NOTE: For additional volumes please contact the Canadian Patent Office.

GAL3 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF DEPRESSION

This is a division of Canadian patent application no. 2,438,582 filed January 31, 2002.

5 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
10 the specification immediately preceding the claims.

15

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,
20 flatness, loss of feeling, anhedonia (lack of pleasure), tearfulness, agitation or retardation, thoughts of guilt, and worthlessness; in severe cases, suicide, hallucinations and delusions.

25 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
30 specific diagnostic criteria e.g. dysthymic disorder (formerly called depressive neurosis). The symptomatology and diagnostic criteria for depression are

WO 02/060392

PCT/US02/04608

2

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
5 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,
10 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.

15 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.

20

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
25 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
30 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
5 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.

10

The Pathophysiology of Depression

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

Evidence implicating the role of neurotransmitters in depression, in particular the monoamines serotonin,
20 noradrenaline and dopamine, include the success of pharmacological agents in treating depressive disorders. Many of the tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) effective in the treatment of
25 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
30 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.

5 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,
10 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
15 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
20 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,
25 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
30 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.

20 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
5 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
10 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
15 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
20 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
25 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).

30 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
5 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
10 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
15 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,
20 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,
25 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
30 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).

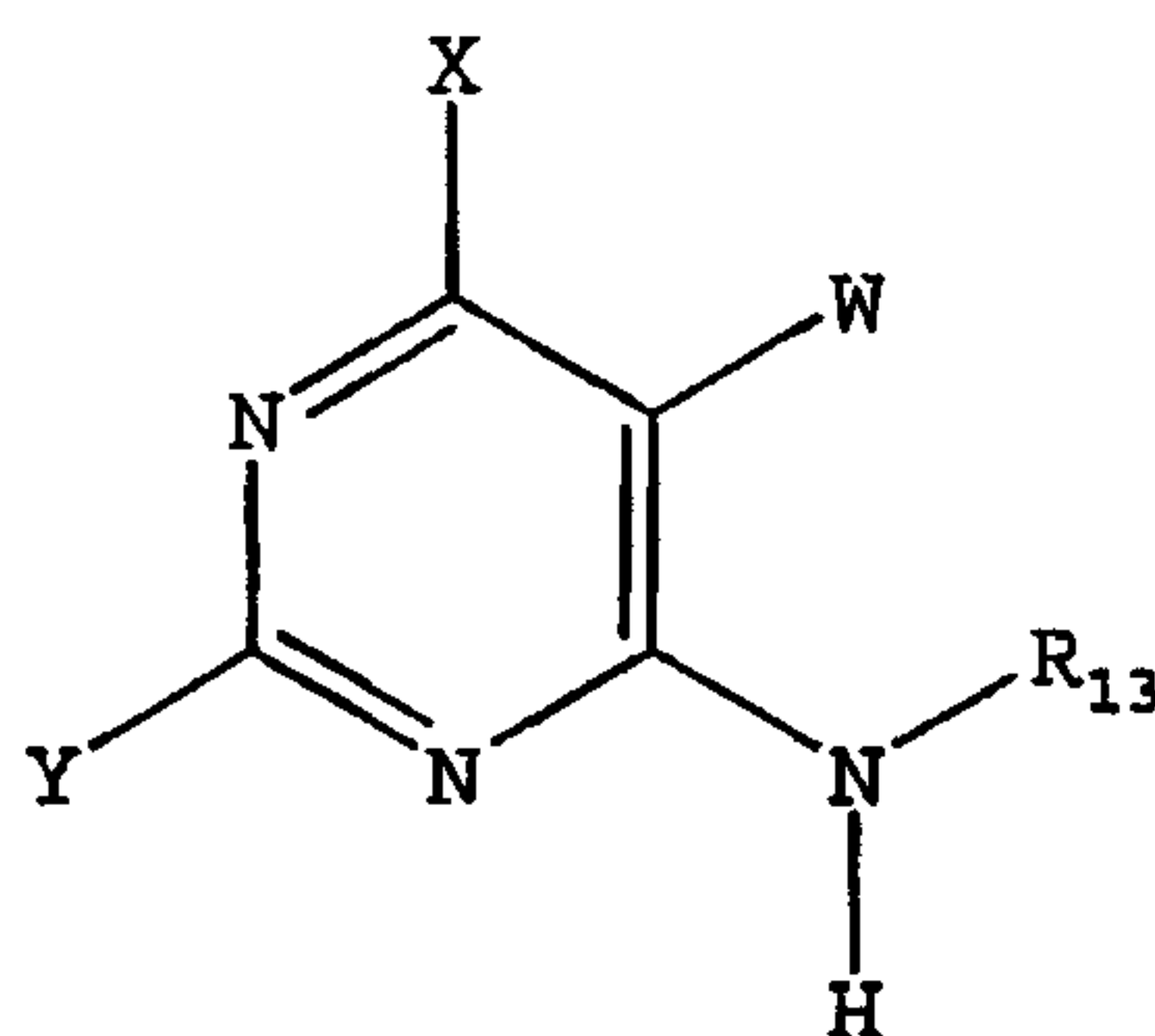
In an embodiment of the present invention the synthesis of novel pyrimidines which bind selectively to the cloned
5 human GAL3 receptor, compared to other cloned human G-protein coupled receptors, as measured in *in vitro* assays, is disclosed. In a further embodiment of the present invention the synthesis of indolones which bind selectively to the cloned human GAL3 receptor, compared
10 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.

15

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
20 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
25 agonists or allosteric modulators, provide a novel method to treat depressive disorders and/or anxiety.

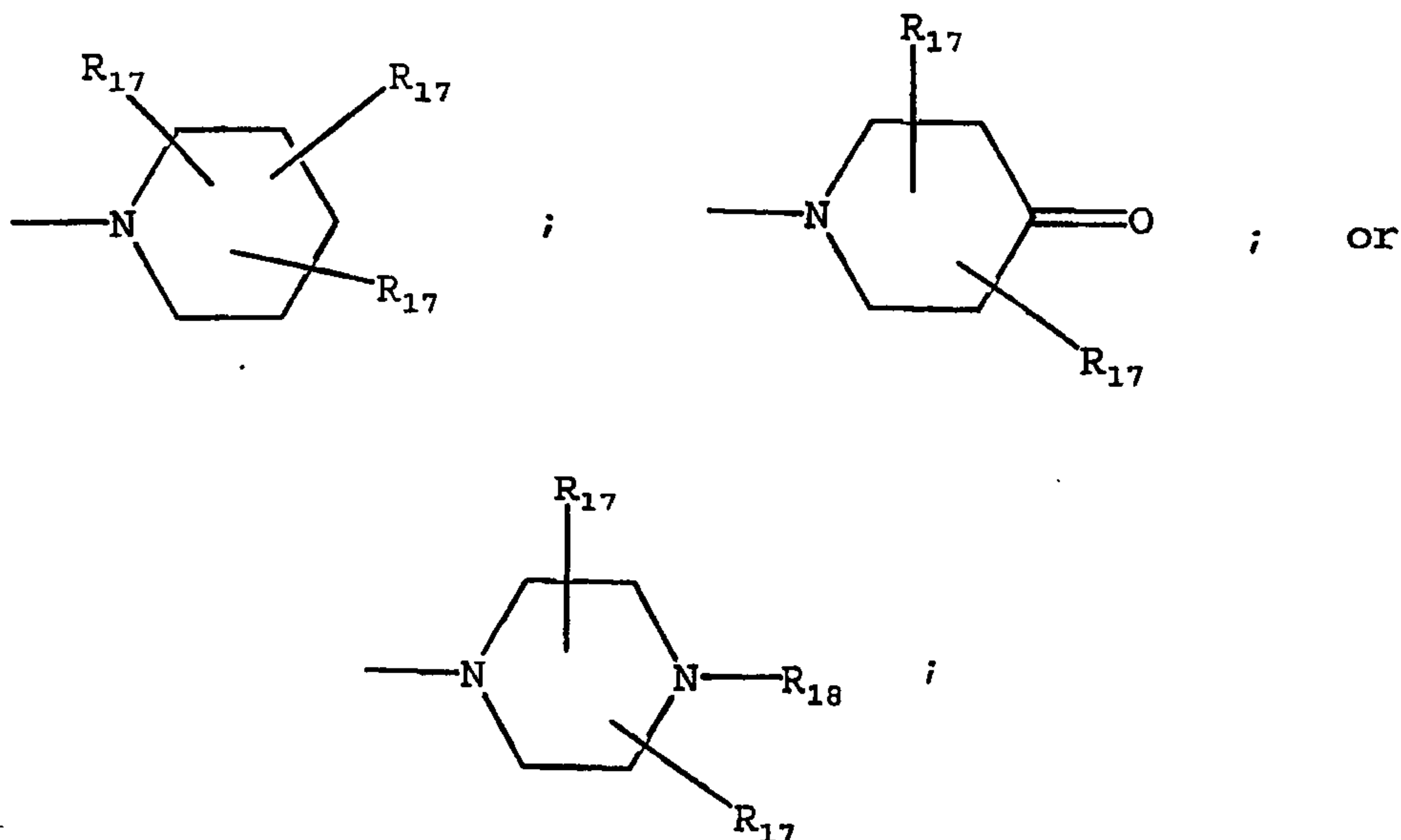
Summary of the Invention

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; $\text{NR}_{11}\text{R}_{12}$;



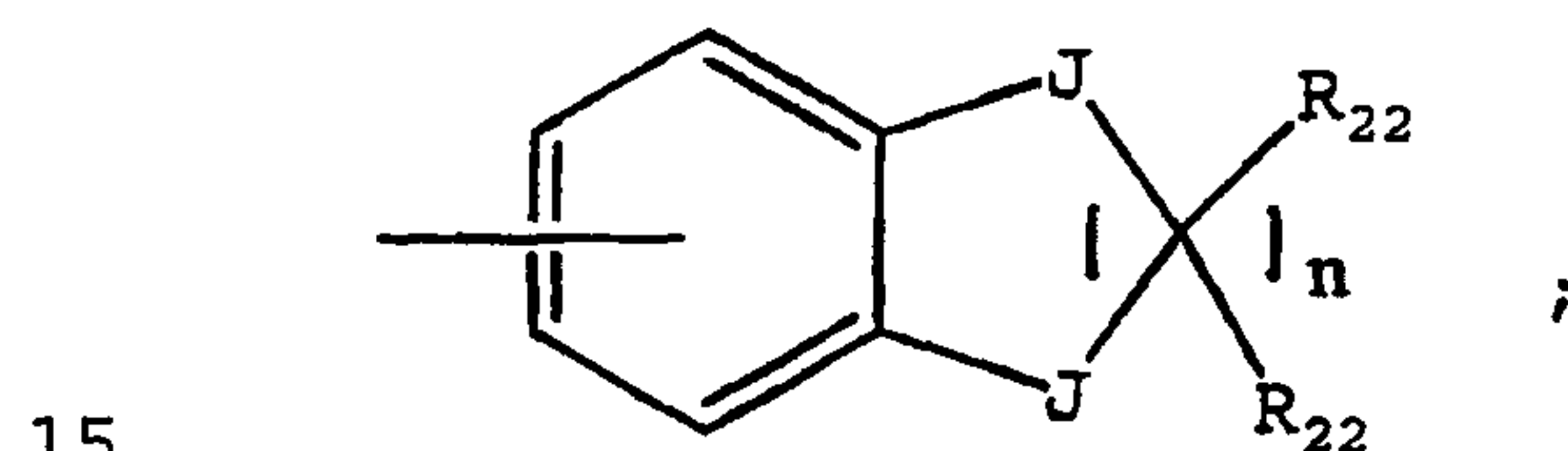
wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl, or aryl $(\text{C}_1\text{-C}_6)$ alkyl;

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

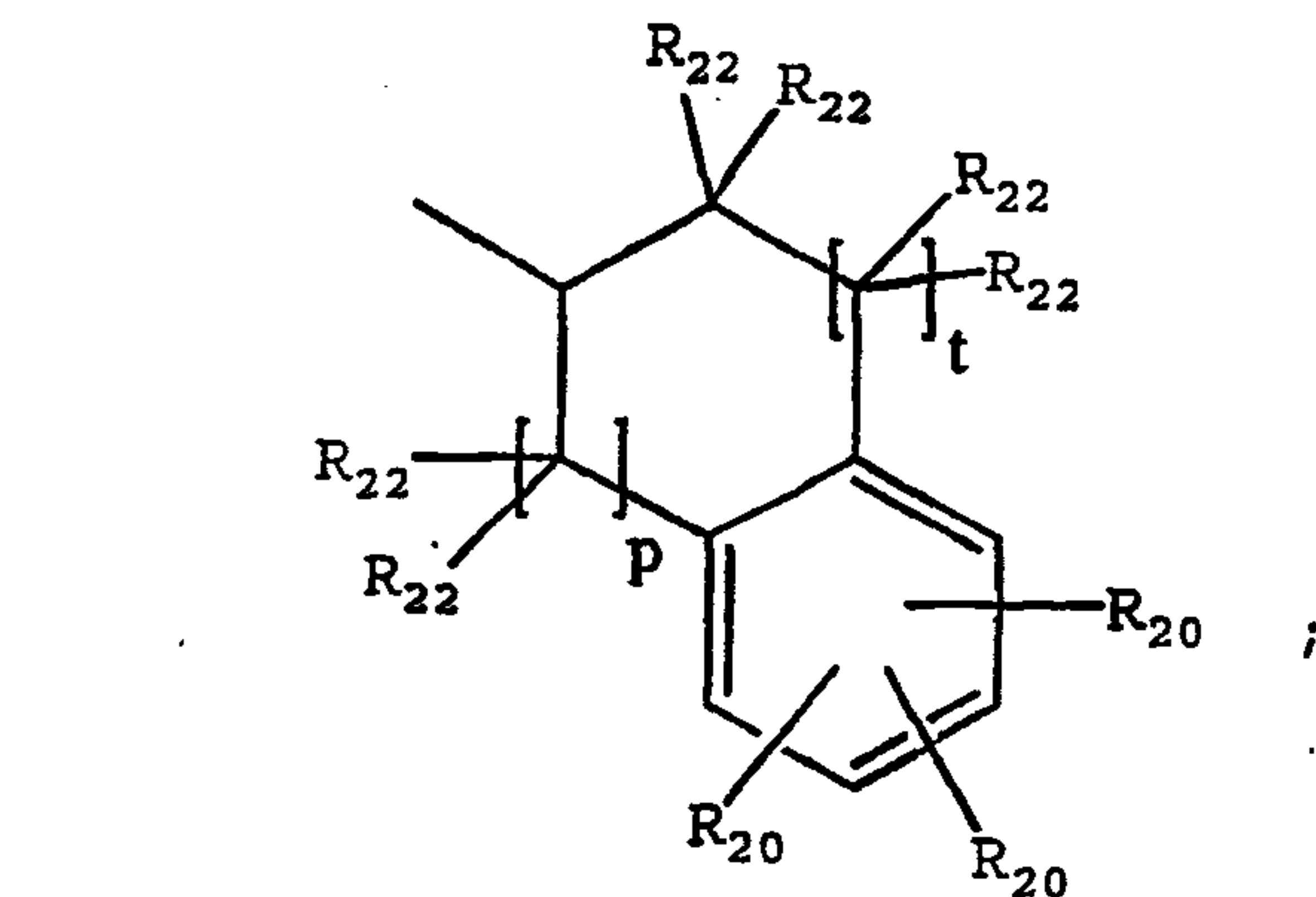
- 5 wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, C_3 - C_{10} cycloalkyl, heteroaryl, aryl, aryl(C_1 - C_6)alkyl, Q_1 or Q_2 ;

10 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 ;

WO 02/060392

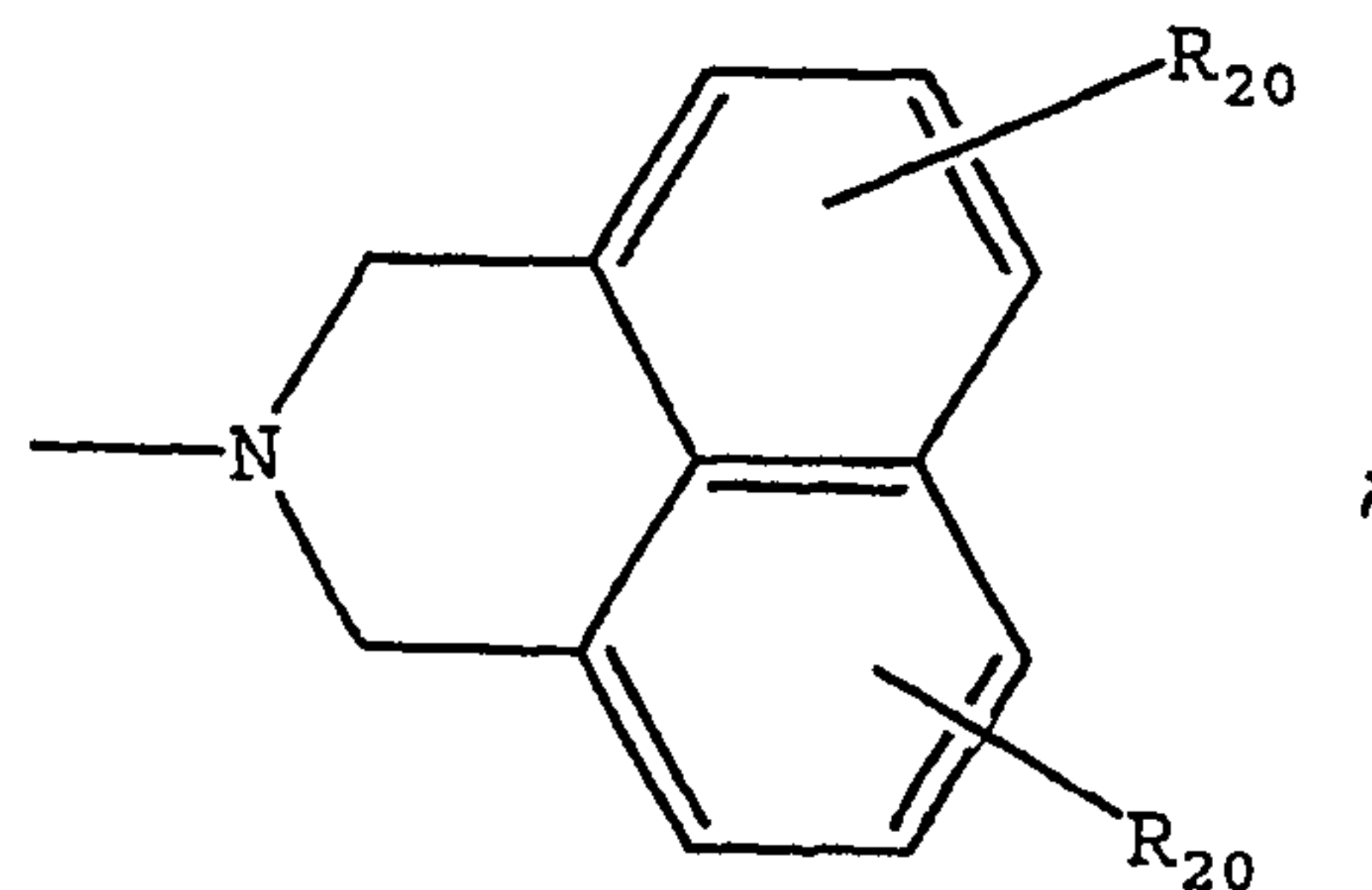
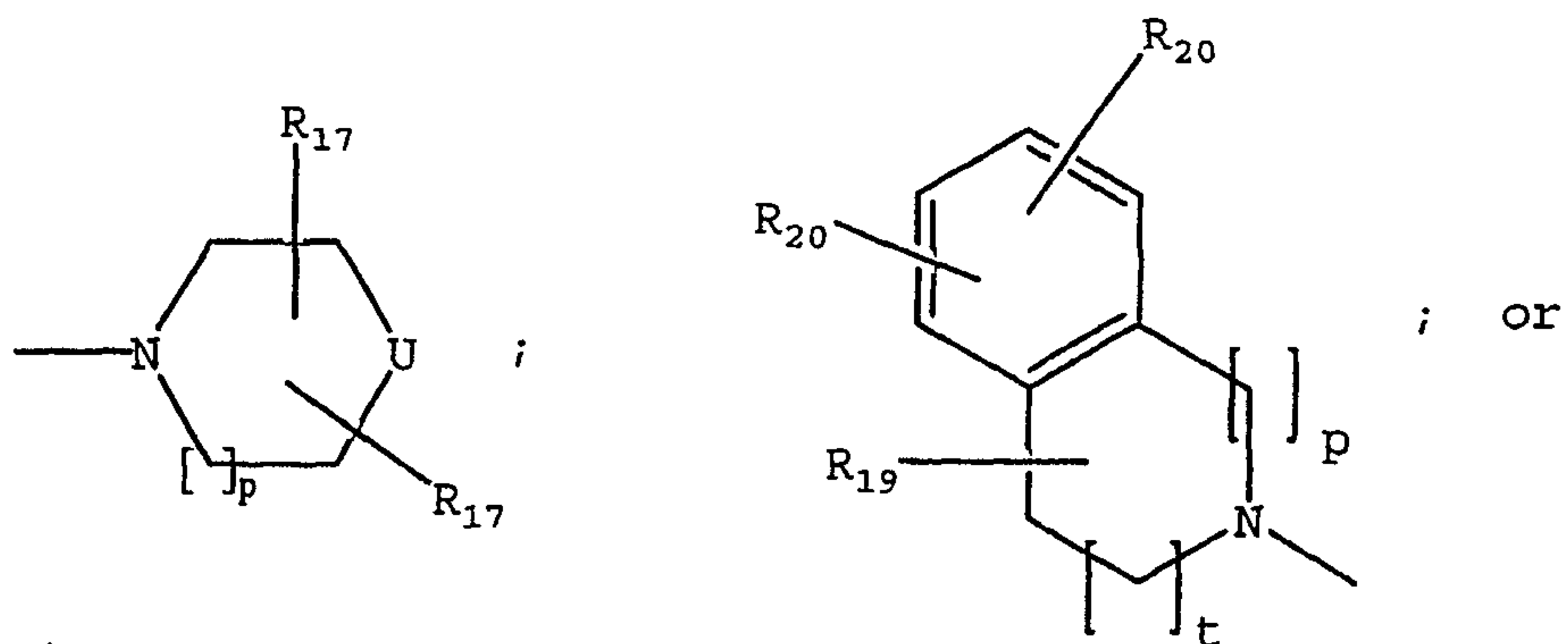
PCT/US02/04608

12

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;

5

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



10

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 $(C(R_{19})_2)_m-Z$;

15 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 $(C(R_{19})_2)_m-Z$;

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

WO 02/060392

PCT/US02/04608

13

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

5

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 $(CH_2)_n-O-(CH_2)_m-CH_3$;

10

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

15

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;

25

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-

30

WO 02/060392

PCT/US02/04608

14

C₆) alkyl;

wherein each R₂₂ is independently H, F, Cl or C₁-C₄ straight chained or branched alkyl;

5

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

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

10

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;

15

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

wherein Z is C₃-C₁₀ cycloalkyl, C₄-C₇ cyclic ether, C₄-C₇ cyclic thioether, aryl, or heteroaryl; or

20

a pharmaceutically acceptable salt thereof.

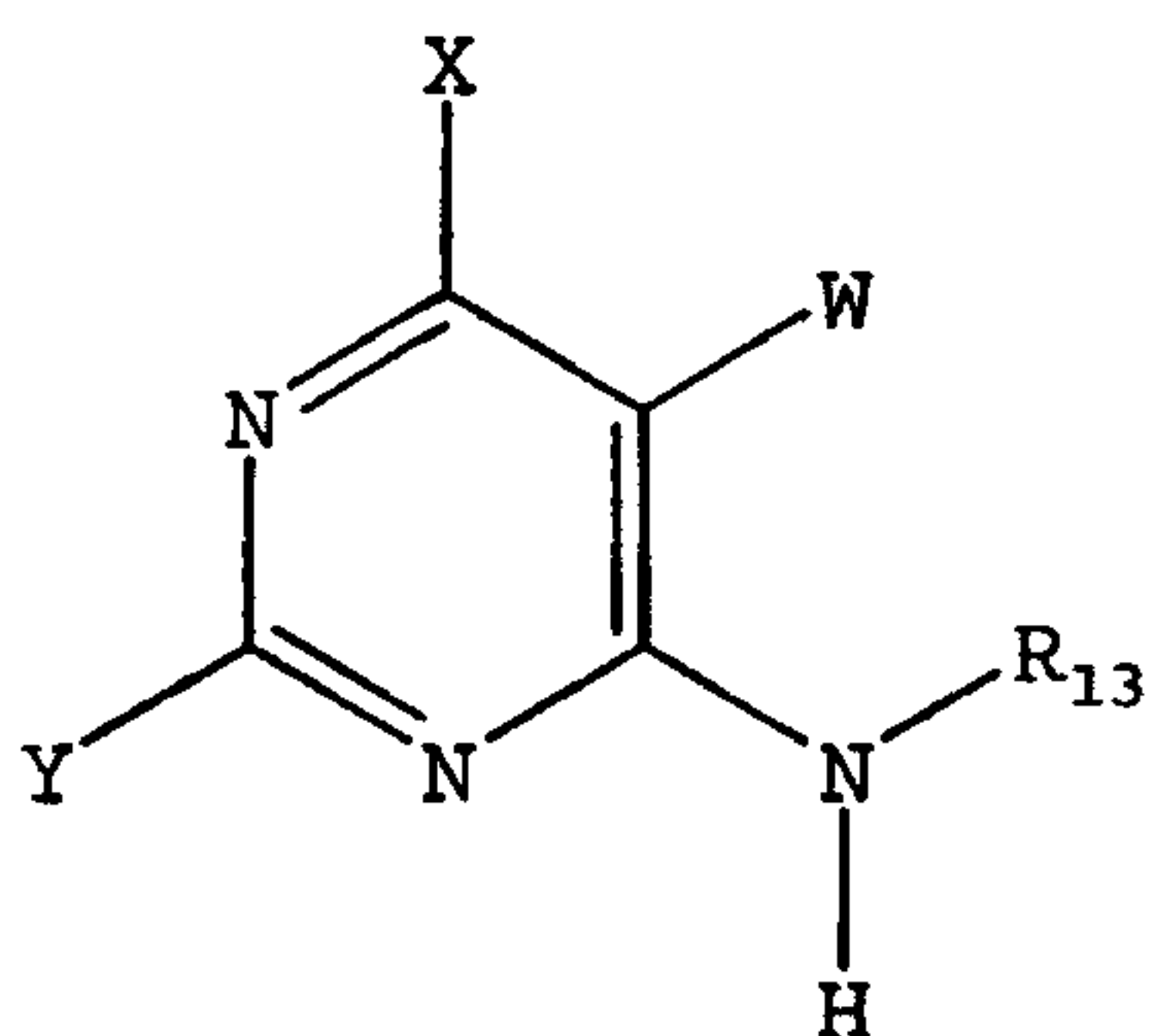
25

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:

WO 02/060392

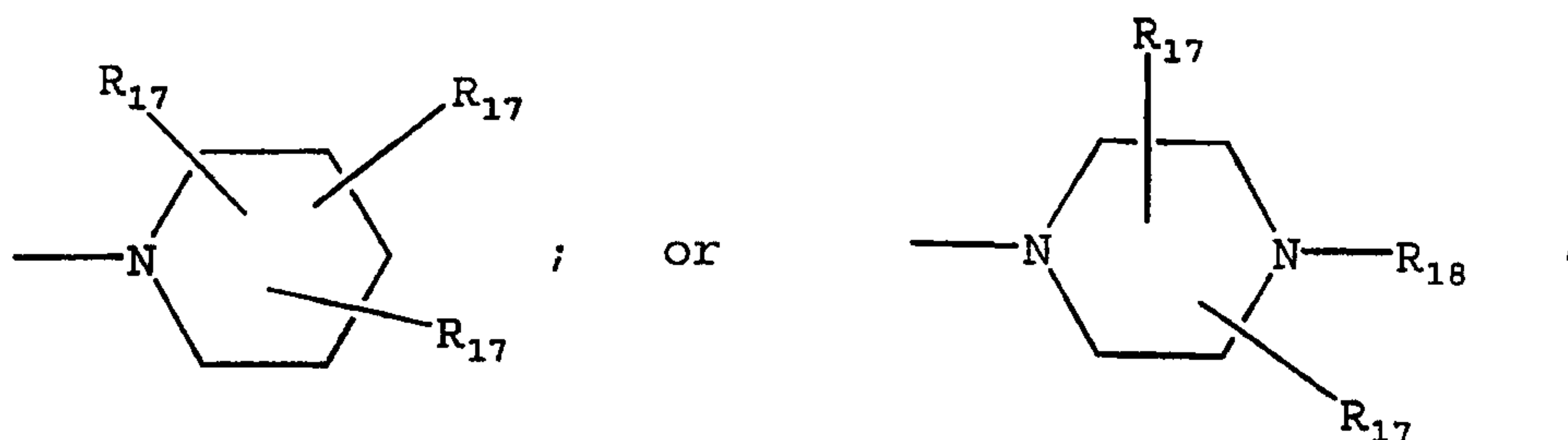
PCT/US02/04608

15



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

5 wherein X is $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

10 wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $\text{-(CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

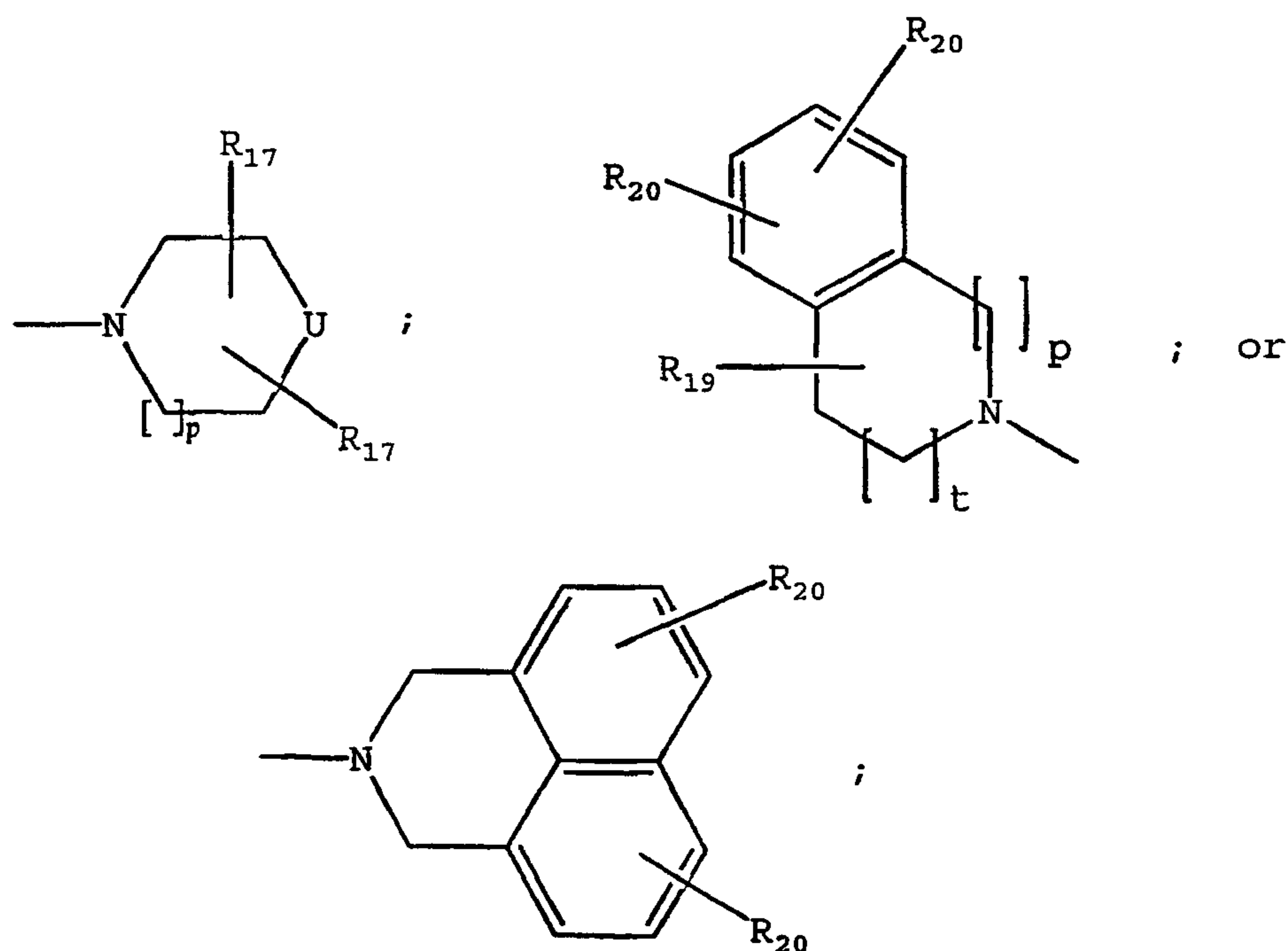
15

wherein Y is $\text{NR}_{14}\text{R}_{15}$;

WO 02/060392

PCT/US02/04608

16



wherein R₁₄ is H, straight chained or branched C₁-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

5

wherein R₁₅ is straight chained or branched C₃-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

10

wherein Z is C₃-C₁₀ cycloalkyl, aryl, or heteroaryl;

15

wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

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;

WO 02/060392

PCT/US02/04608

18

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

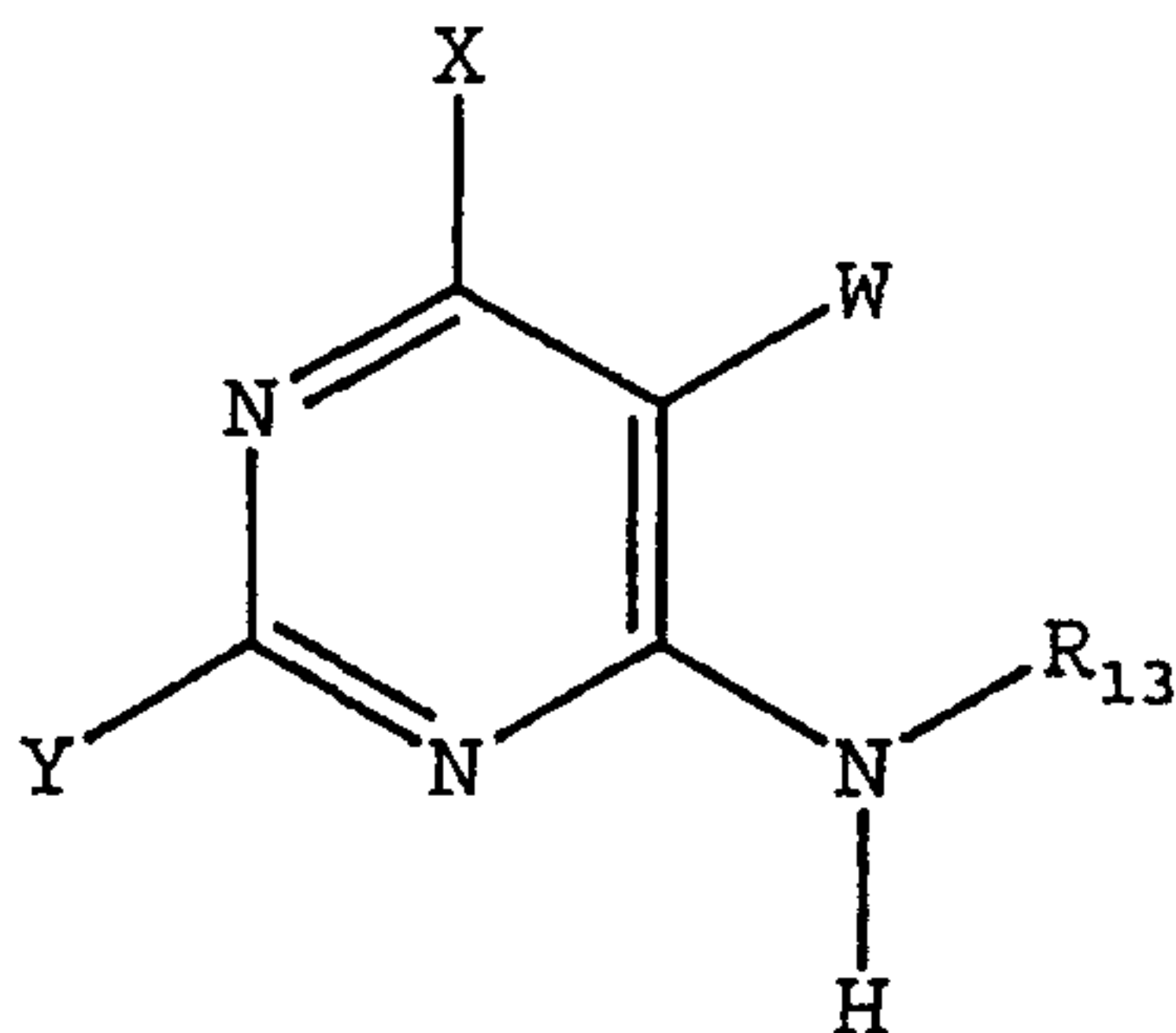
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

10

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:

15



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

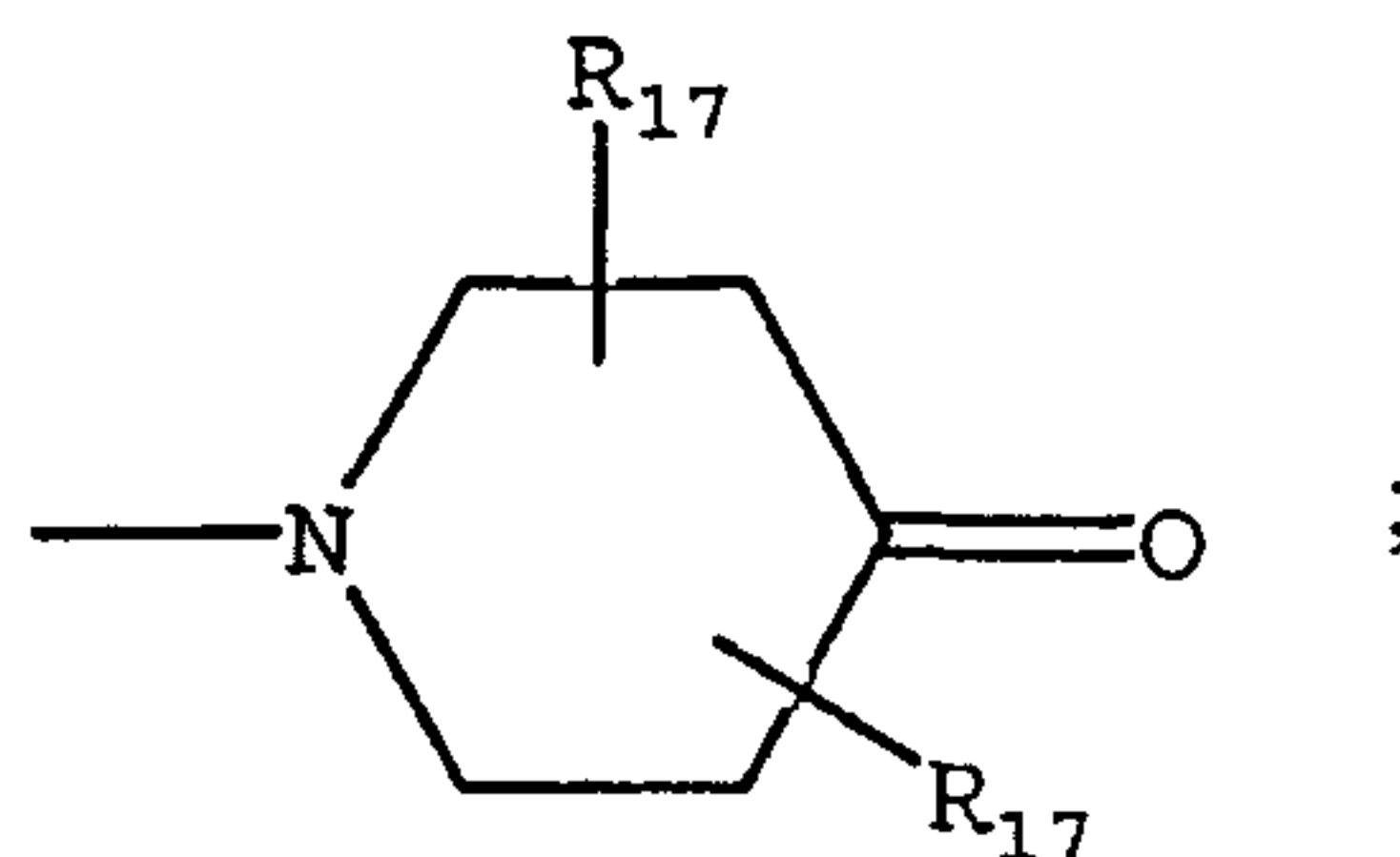
20

wherein X is $N(CH_3)_2$ or

WO 02/060392

PCT/US02/04608

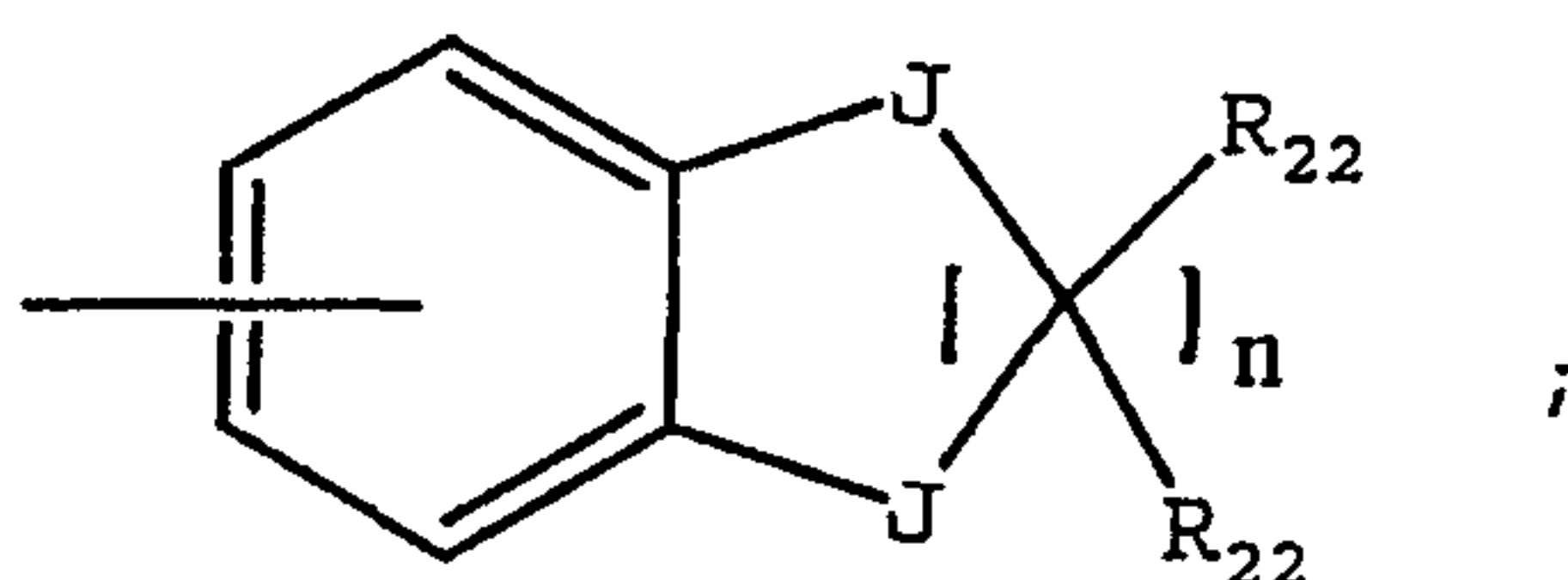
19



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

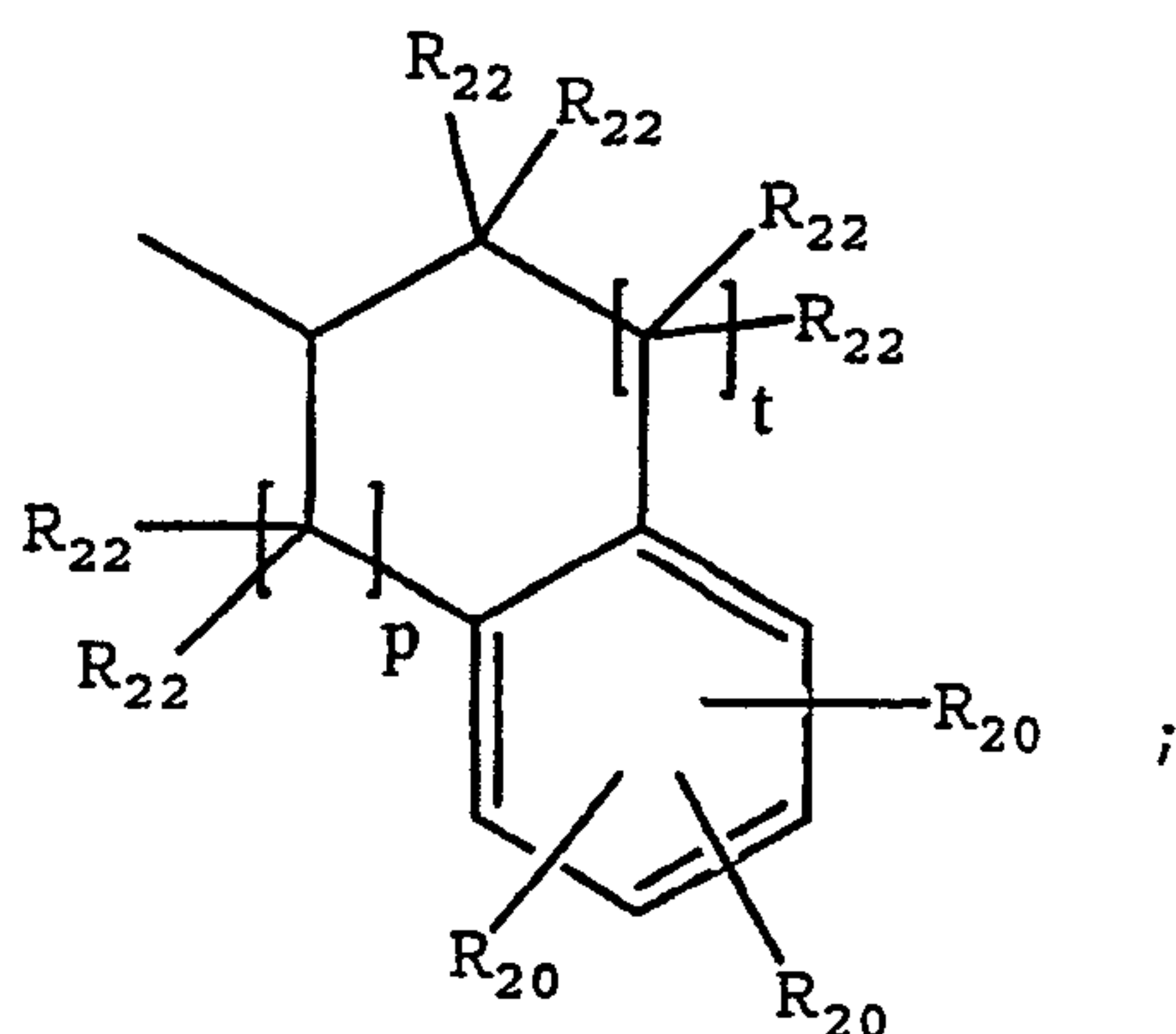
5

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

10 wherein Q_1 is

wherein Q_2 is

15



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

WO 02/060392

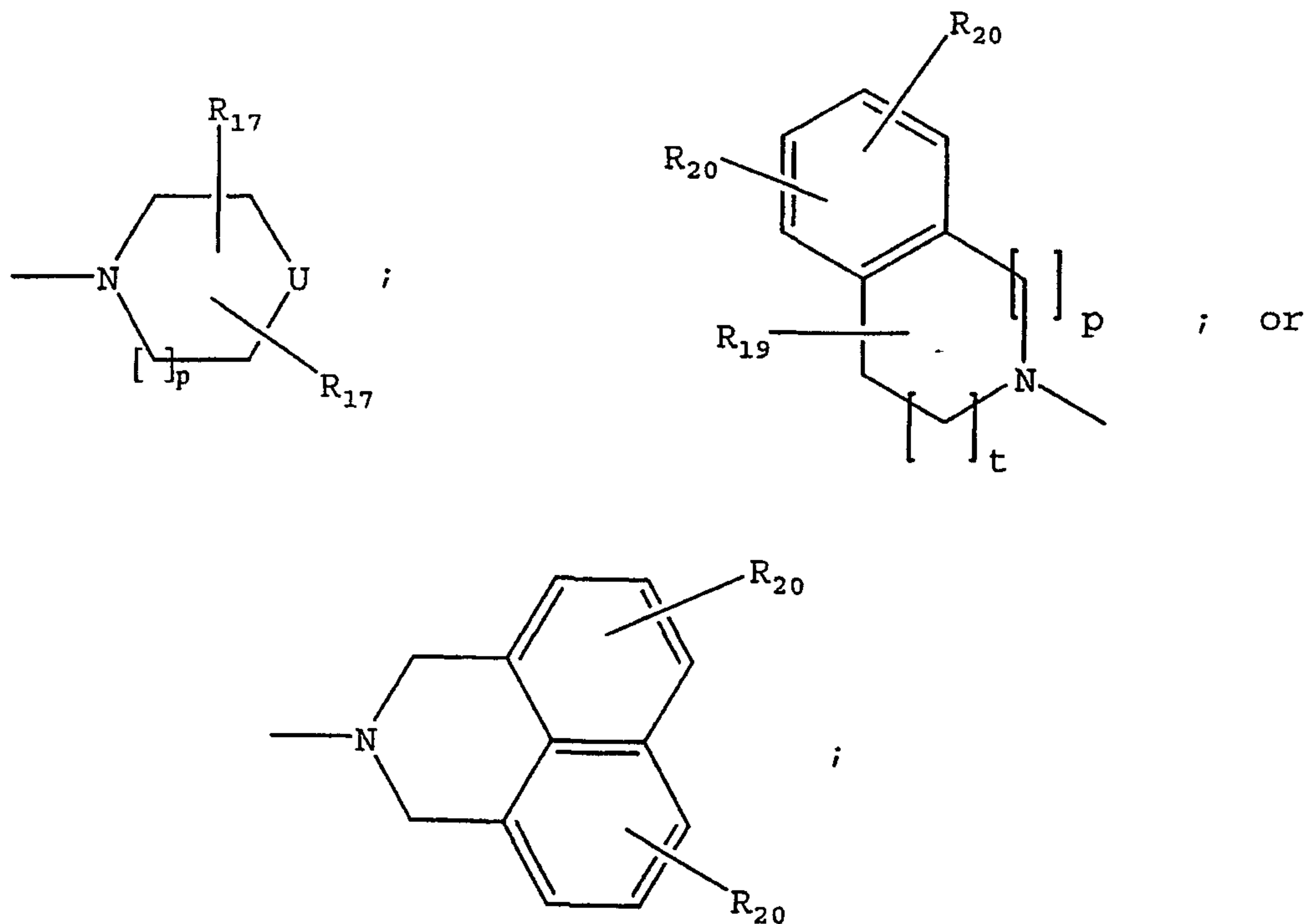
PCT/US02/04608

20

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;

5

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



10 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 $(C(R_{19})_2)_m-Z$;

15

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
 5 chained or branched C_2 - C_7 alkynyl, C_5 - C_7 cycloalkenyl, -
 $(CH_2)_m$ -Z, or $(CH_2)_q$ -O- $(CH_2)_m$ -CH₃;

wherein each R_{17} is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁,
 10 -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, 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
 15 cycloalkenyl, - $(CH_2)_m$ -Z, or $(CH_2)_n$ -O- $(CH_2)_m$ -CH₃;

wherein R_{18} is straight chained or branched C_1 - C_6 alkyl, -
 $(CH_2)_m$ -Z, or $(CH_2)_q$ -O- $(CH_2)_m$ -CH₃;

20 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;
 25 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;
 -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -
 CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R_{20} groups
 present on adjacent carbon atoms can join together to
 30 form a methylenedioxy group;

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

WO 02/060392

PCT/US02/04608

22

branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-
C₆)alkyl;

5

wherein each R₂₂ is independently H, F, Cl or C₁-C₄
straight chained or branched alkyl;

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

10

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

wherein p is an integer from 0 to 2 inclusive;

15

wherein q is an integer from 2 to 4 inclusive;

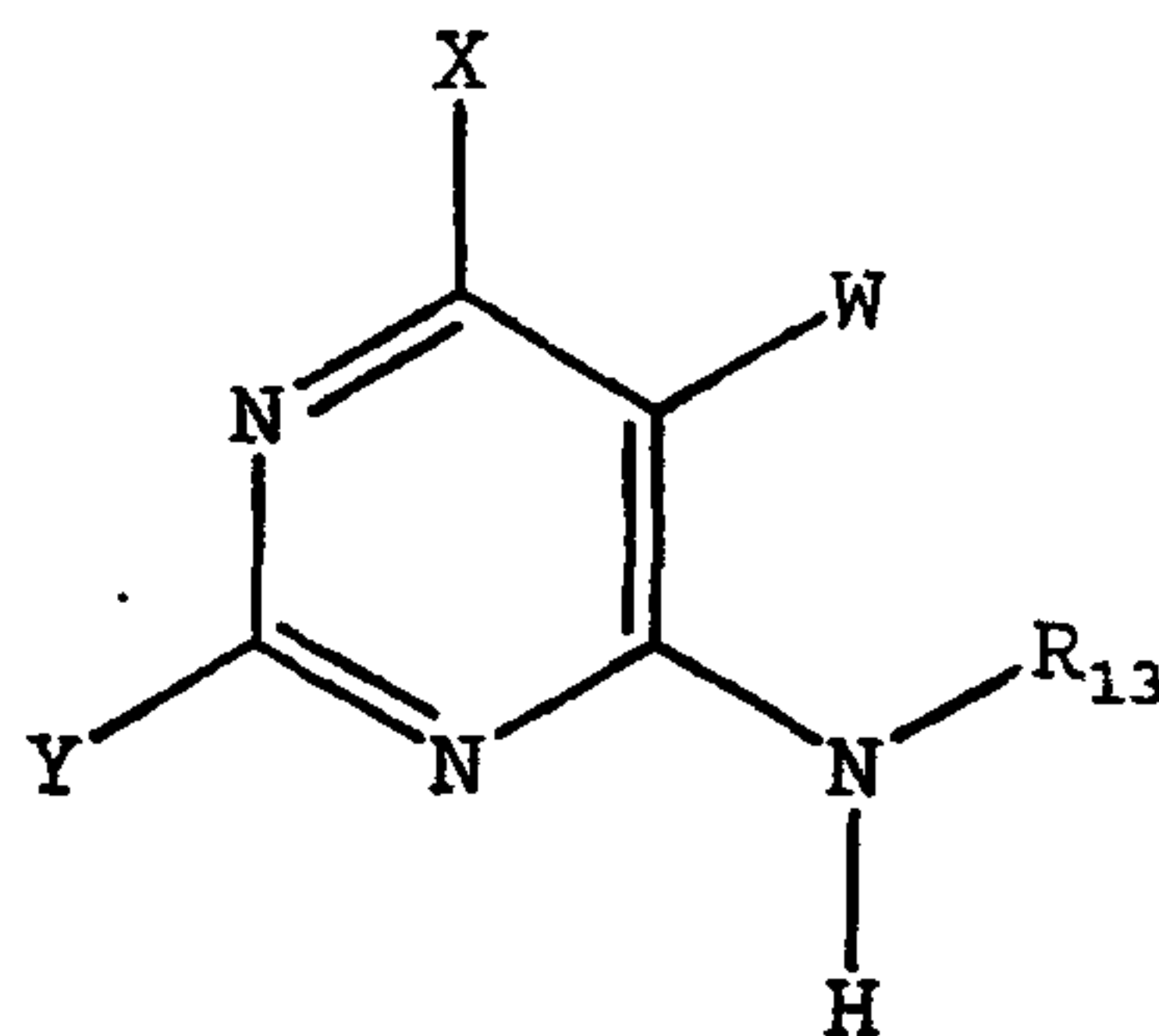
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

20

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:

25



WO 02/060392

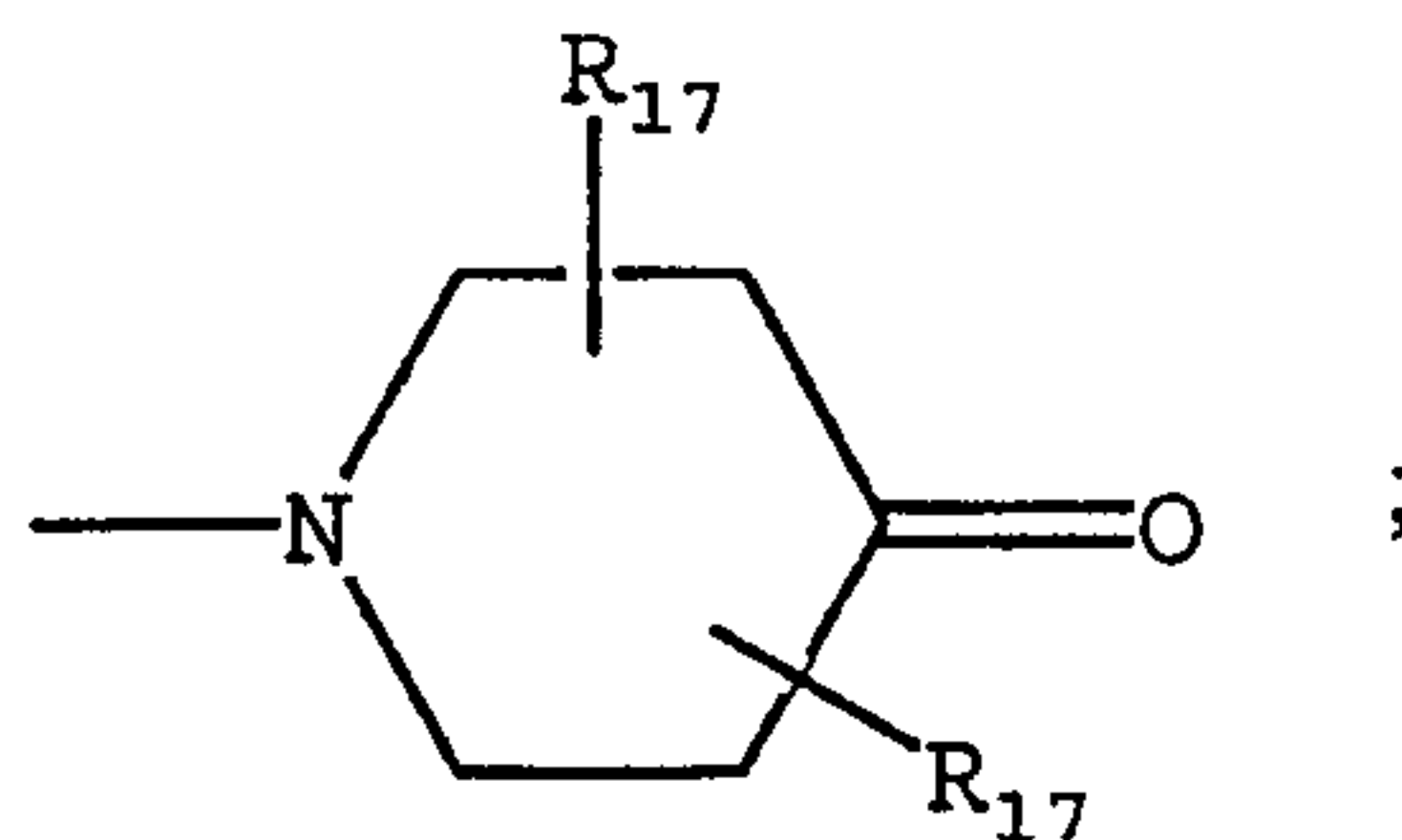
PCT/US02/04608

23

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

5

wherein X is $N(CH_3)_2$ or



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

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

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

20 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, 25 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; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$,

WO 02/060392

PCT/US02/04608

24

5 -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or
branched C₁-C₇ alkyl, straight chained or branched C₁-C₇
monofluoroalkyl, straight chained or branched C₁-C₇
polyfluoroalkyl, straight chained or branched C₂-C₇
alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇
cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

10 wherein each R₁₉ is independently H, or straight chained
or branched C₁-C₆ alkyl;

15 wherein each R₂₁ is independently -H; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-
C₆)alkyl;

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

20 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.

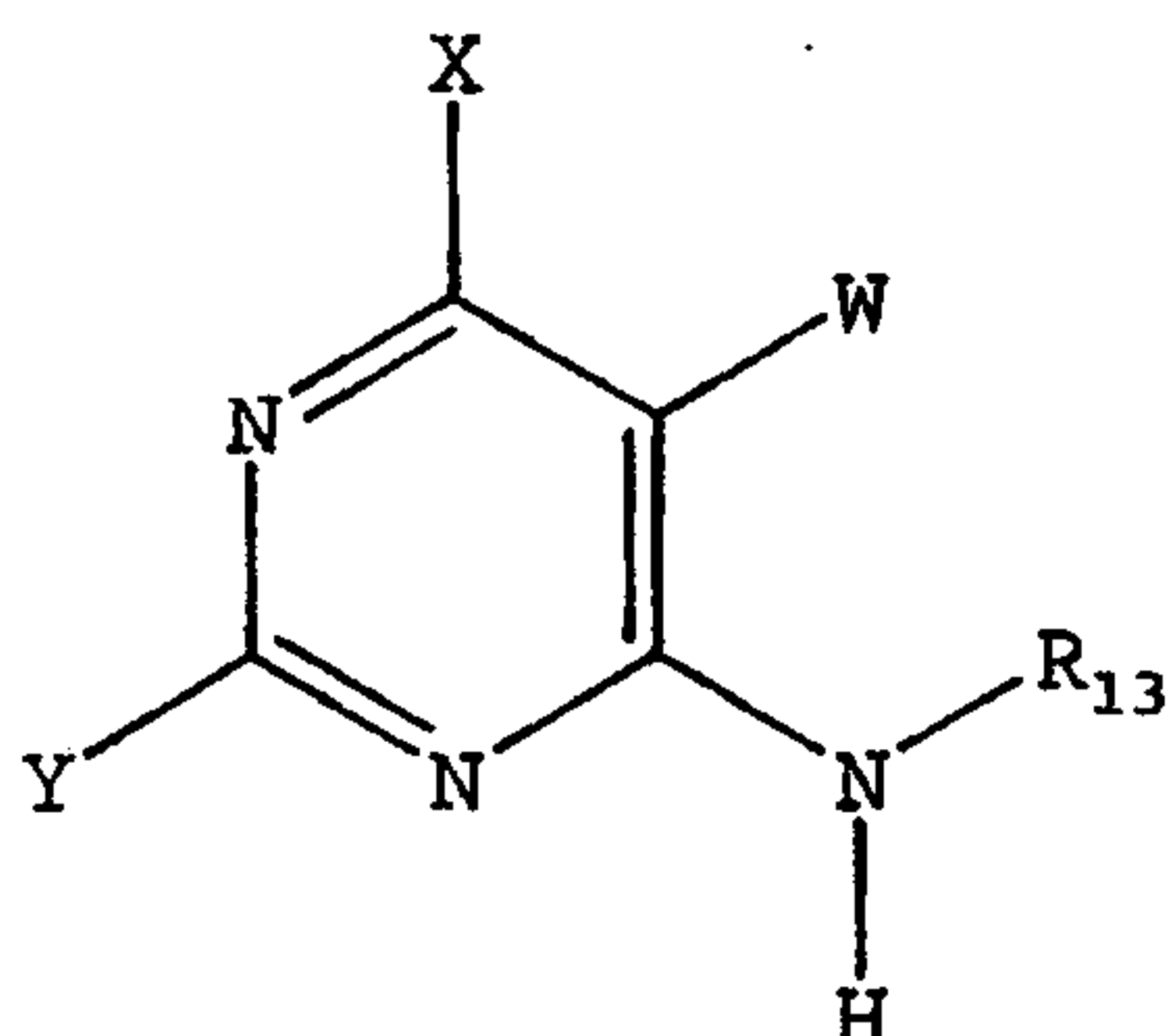
25

30 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:

WO 02/060392

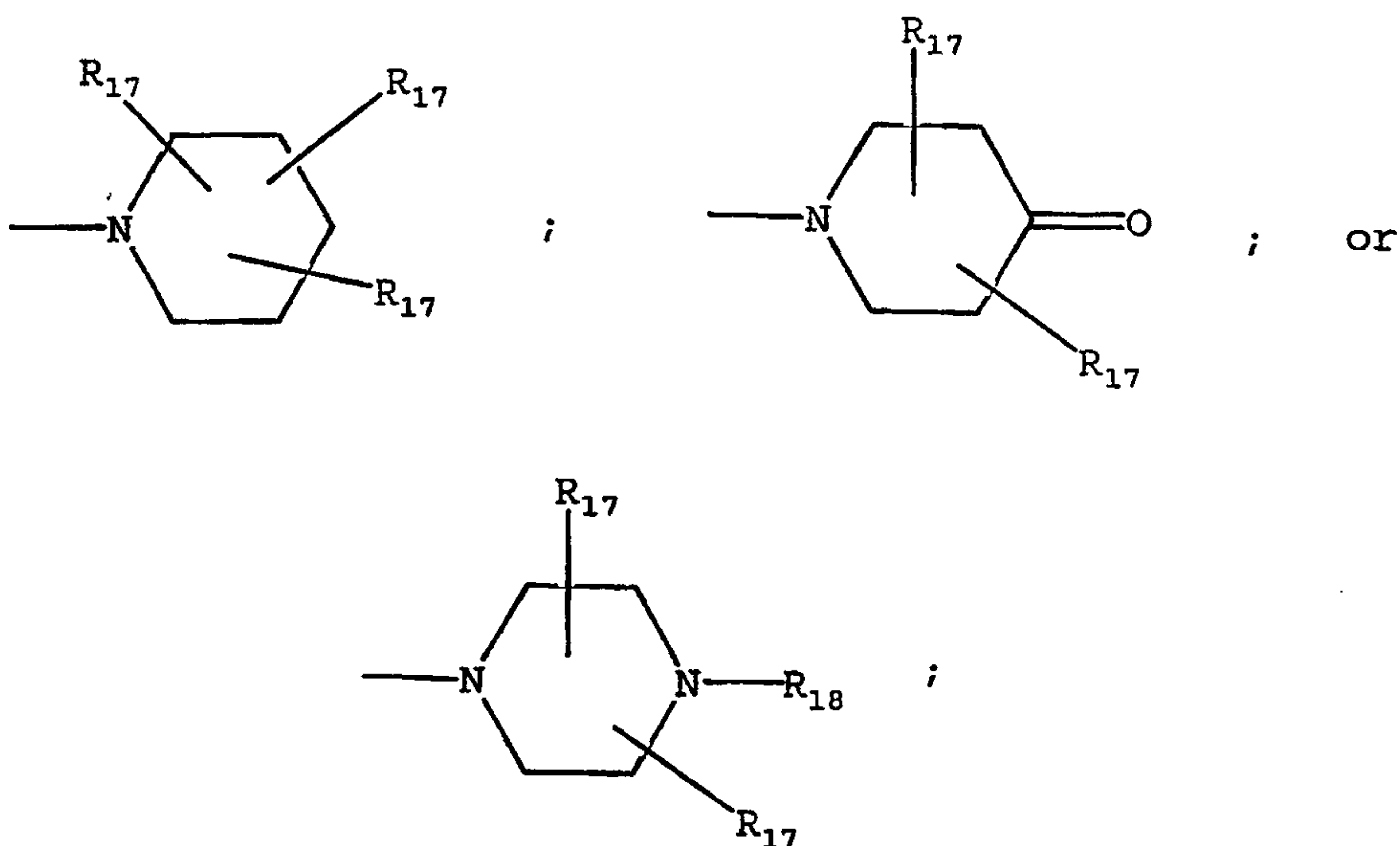
PCT/US02/04608

25



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

5 wherein X is; $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl, or aryl $(\text{C}_1\text{-C}_6)\text{alkyl}$;

10 wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $-(\text{CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, heteroaryl, aryl, aryl($\text{C}_1\text{-}$

WO 02/060392

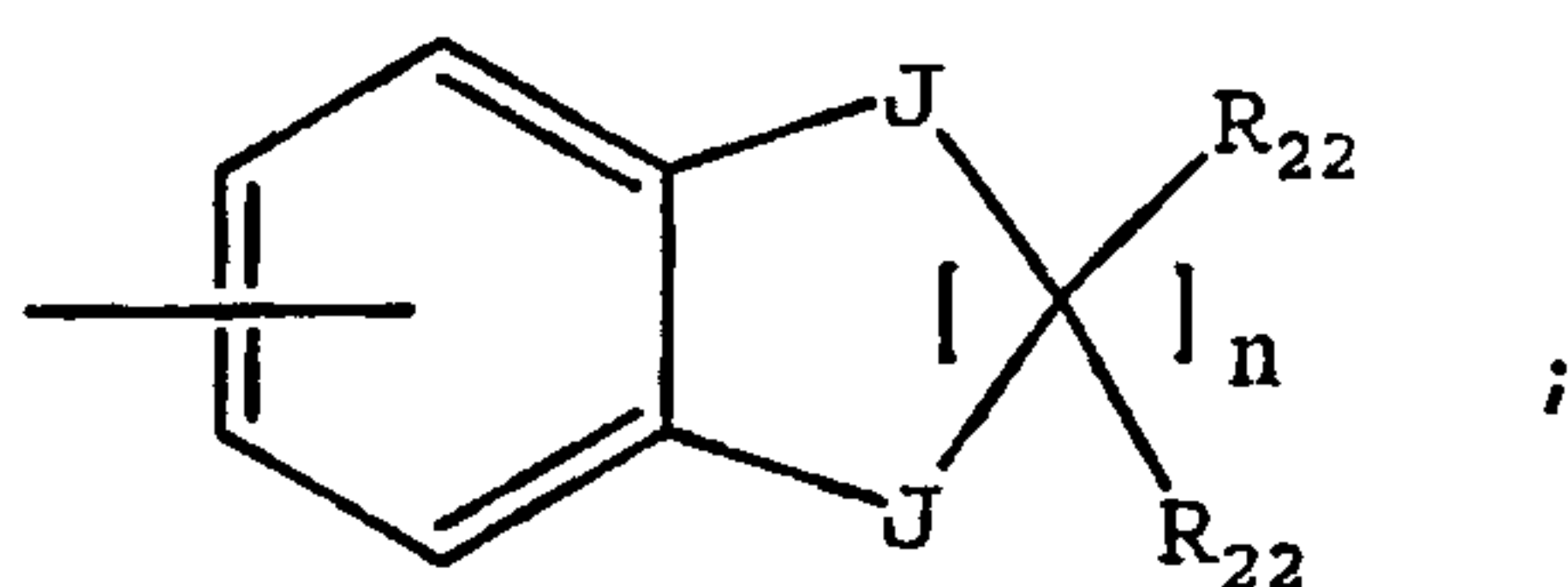
PCT/US02/04608

26

C_6)alkyl, Q_1 or Q_2 ;

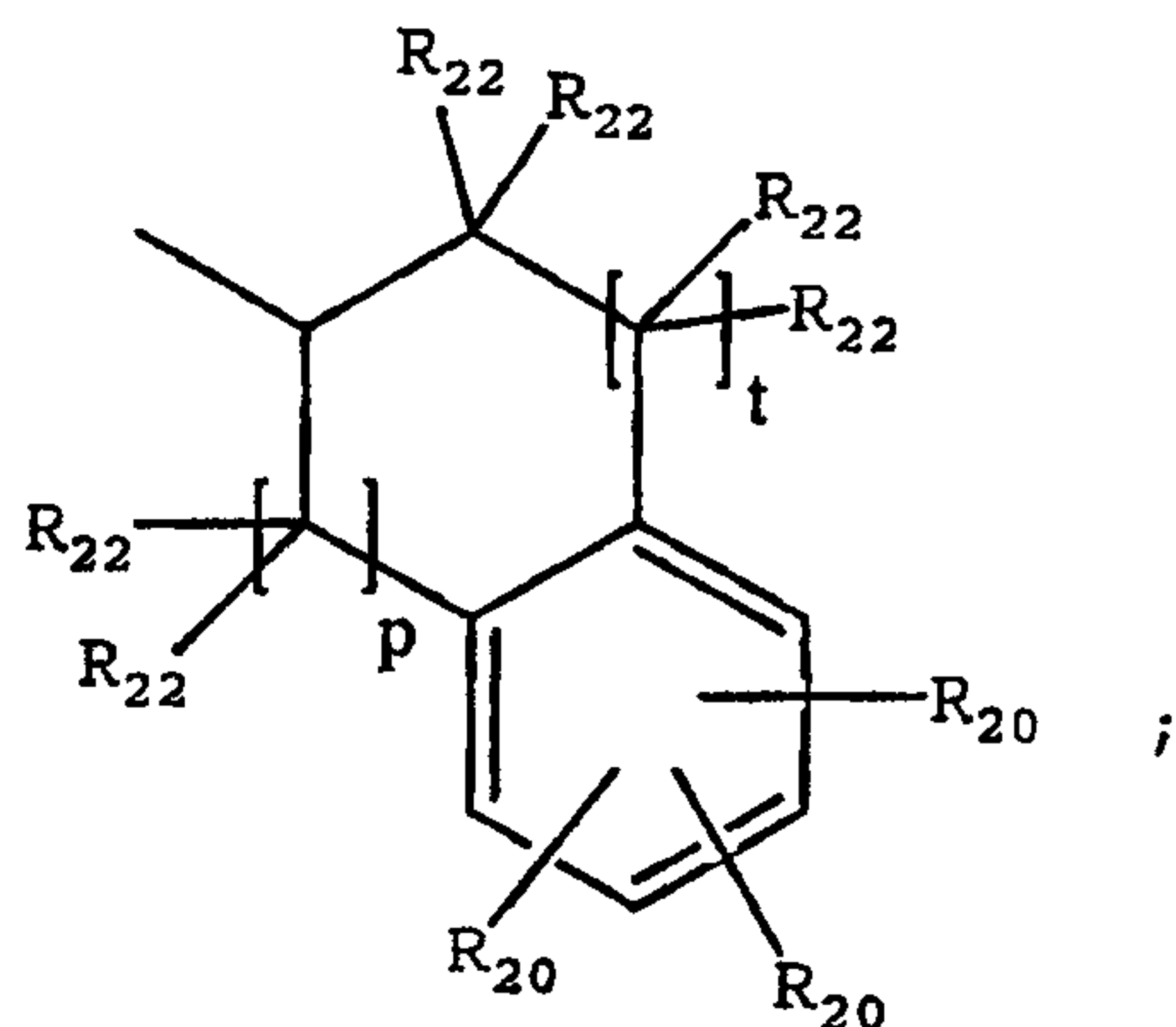
wherein aryl may be substituted with one or more C_1 - C_{10} straight chained or branched alkyl, aryl, heteroaryl, or
 5 $N(R_{19})-Z$;

wherein Q_1 is



10

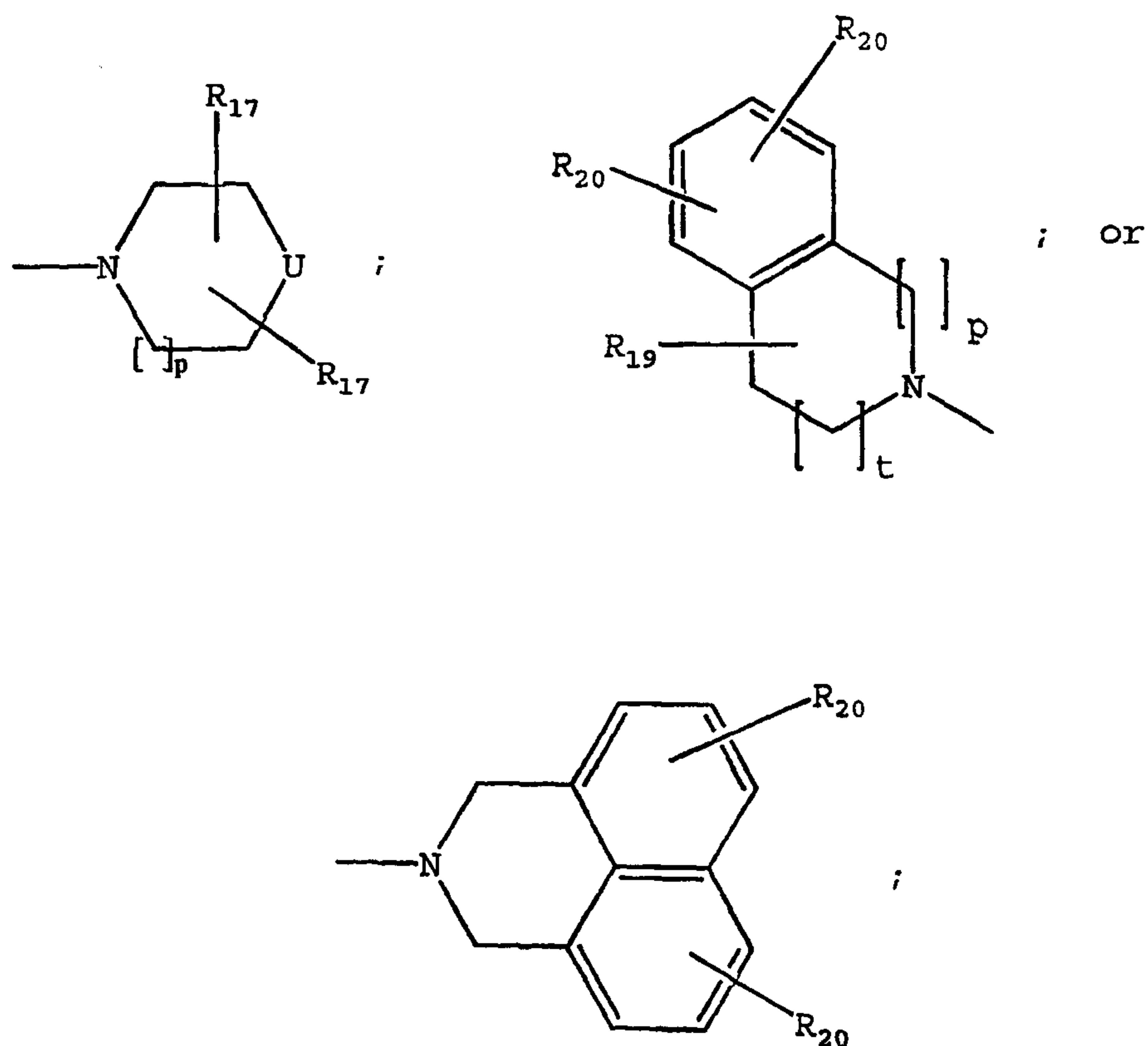
wherein Q_2 is



15 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
 20 cycloalkenyl or aryl;

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



5

wherein R₁₄ is H, straight chained or branched C₁-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

10

wherein R₁₅ is straight chained or branched C₃-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, (C(R₁₉)₂)_mN(R₁₆)₂ or (C(R₁₉)₂)_m-Z;

15

wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

20

wherein each R₁₇ is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁,

WO 02/060392

PCT/US02/04608

28

5 -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, -(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

10

wherein each R₁₉ is independently H, or straight chained or branched C₁-C₆ alkyl;

15 wherein each R₂₀ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups
20 present on adjacent carbon atoms can join together to form a methylenedioxy group;

25 wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, or aryl(C₁-C₆)alkyl;

30 wherein each R₂₂ is independently H, F, Cl or C₁-C₄ 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;

5

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

10

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

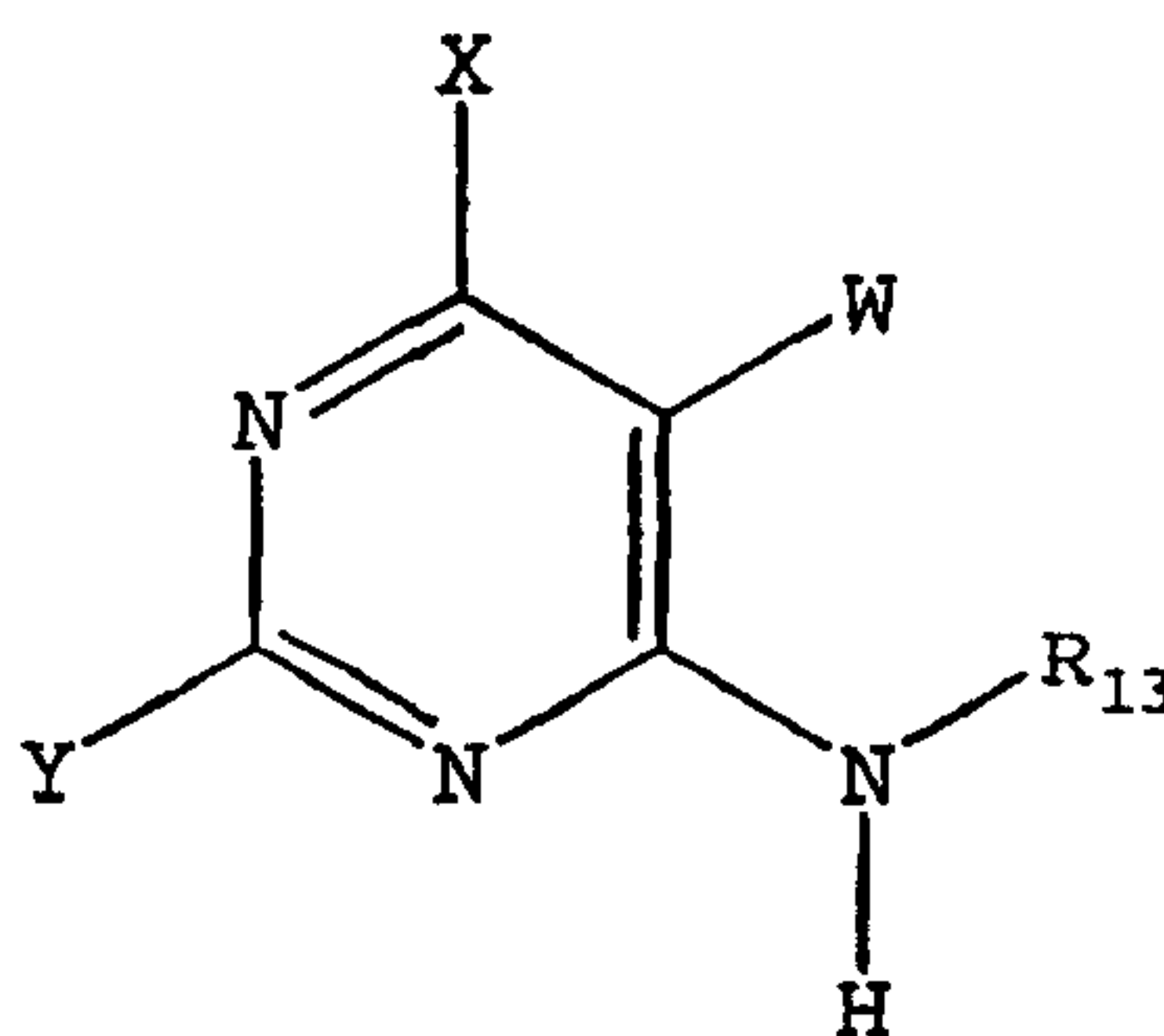
wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

15

a pharmaceutically acceptable salt thereof.

20

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;

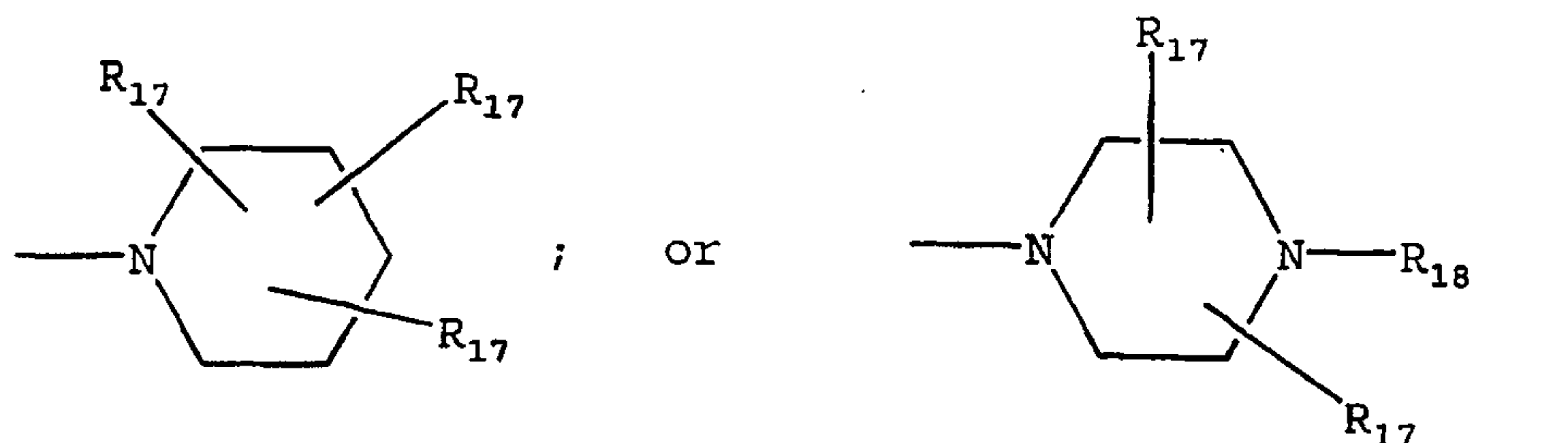
25

WO 02/060392

PCT/US02/04608

30

wherein X is $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

5

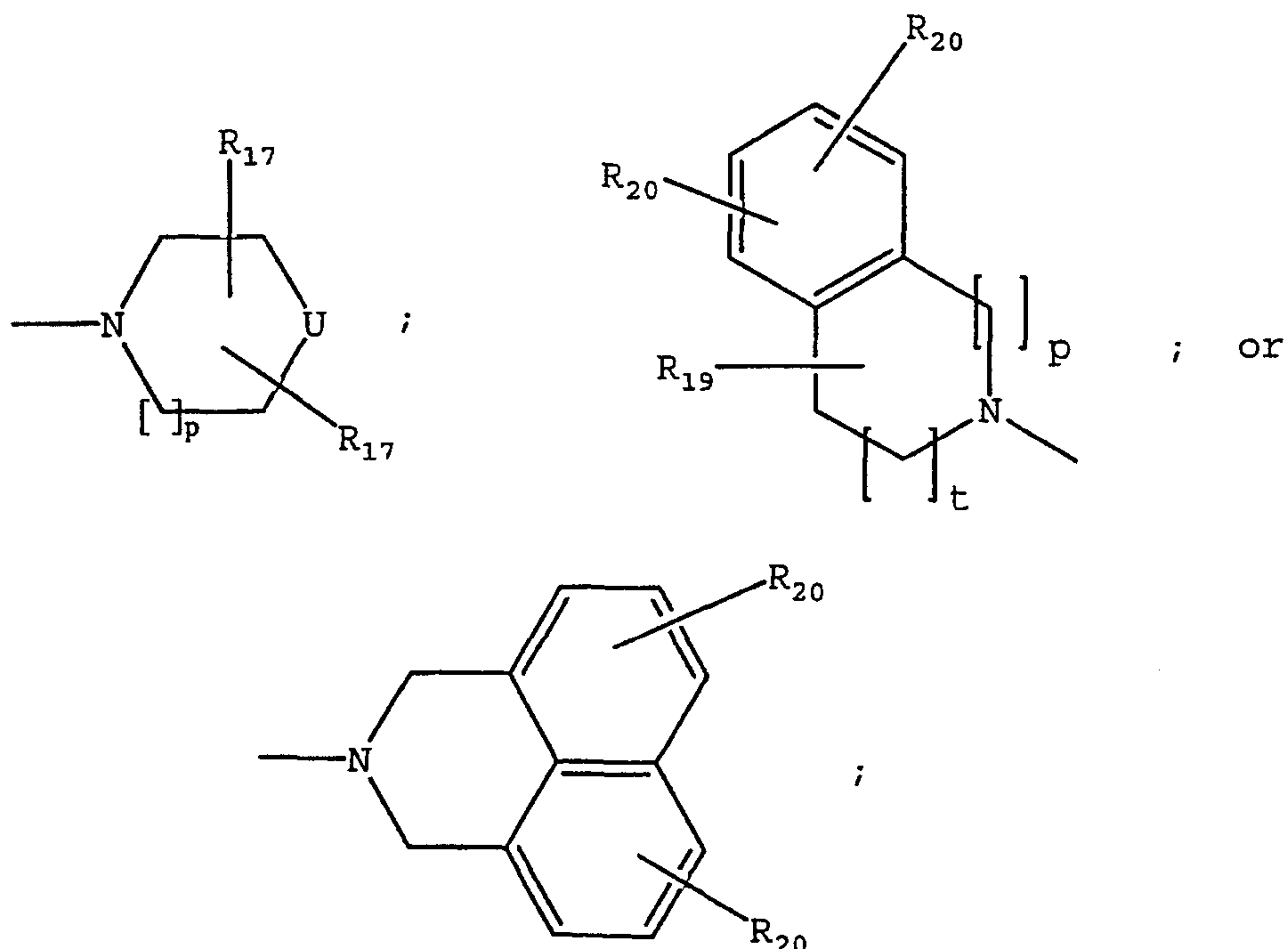
wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $\text{-(CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

10

wherein Y is $\text{NR}_{14}\text{R}_{15}$;

31



wherein R₁₄ is H, straight chained or branched C₁-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

5

wherein R₁₅ is straight chained or branched C₃-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

10

wherein Z is C₃-C₁₀ cycloalkyl, aryl, or heteroaryl;

wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15

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;

WO 02/060392

PCT/US02/04608

33

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

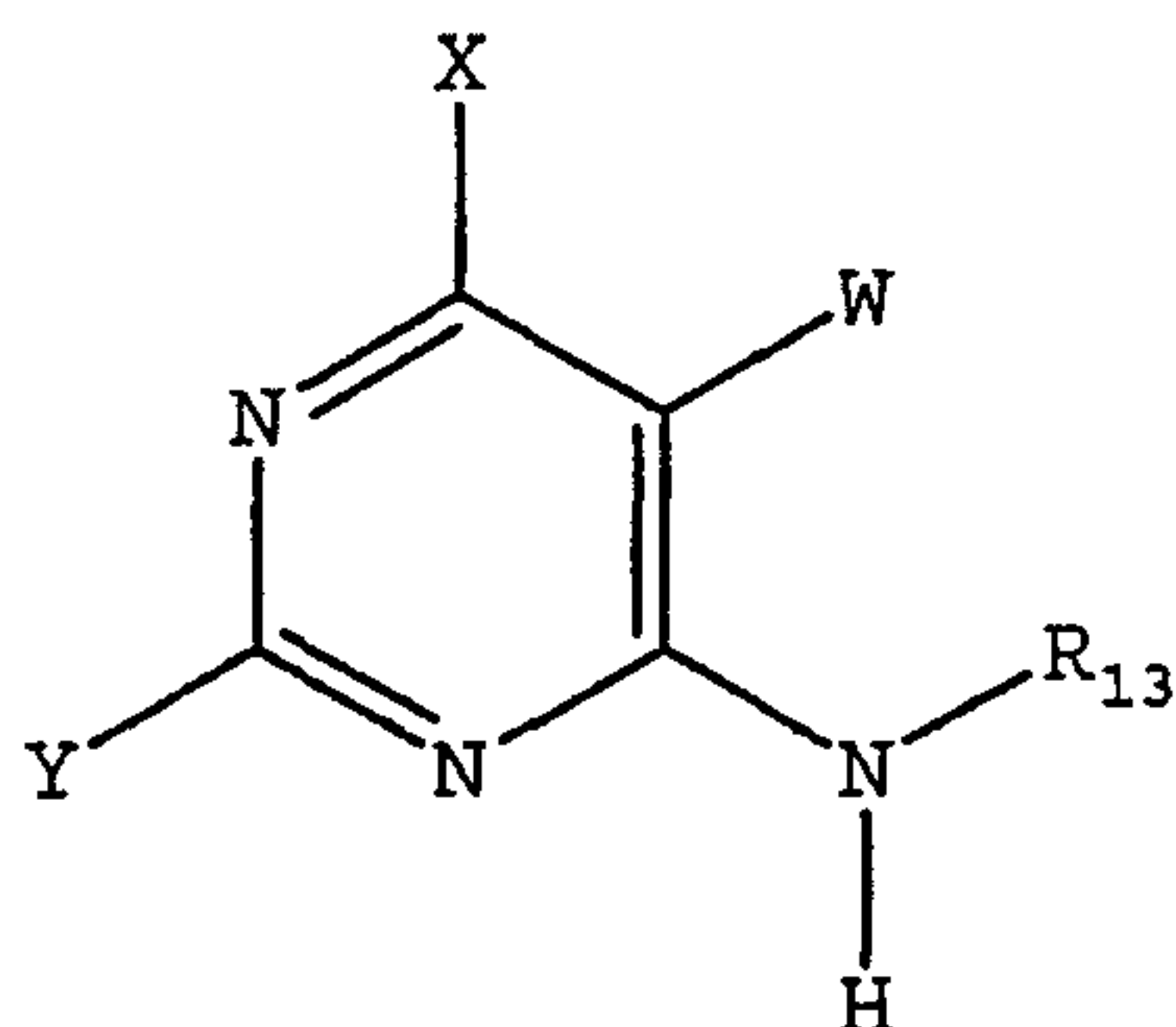
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

10

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:

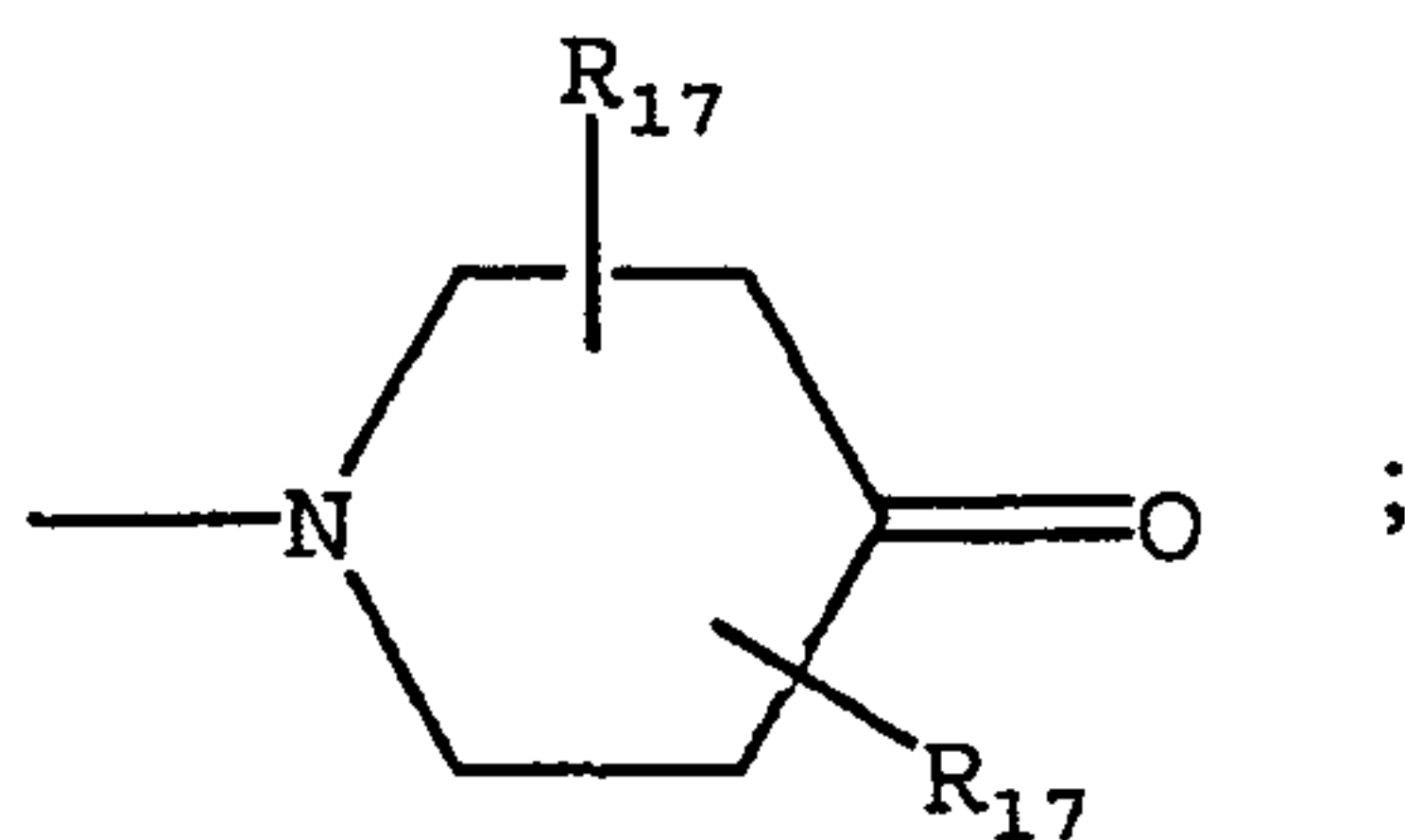
15



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

20

wherein X is N(CH₃)₂ or



WO 02/060392

PCT/US02/04608

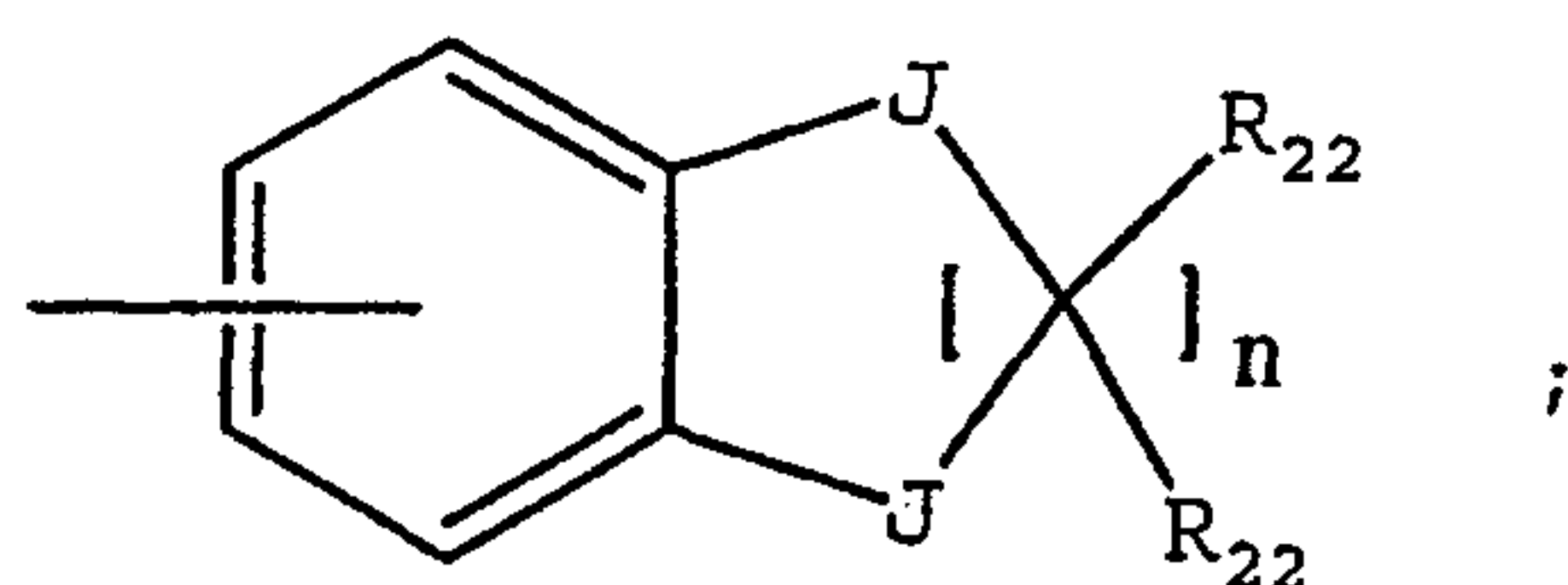
34

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

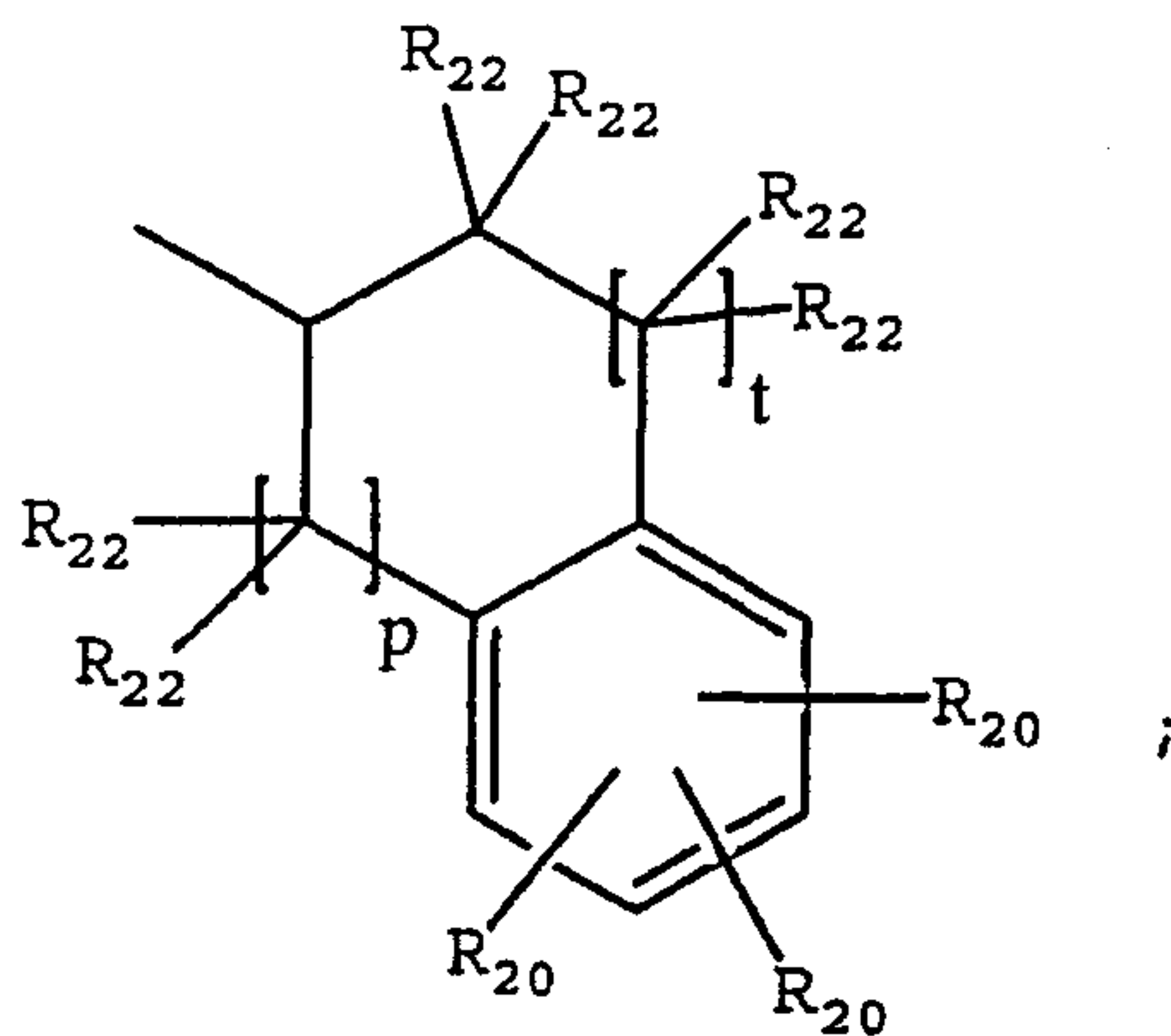
5 wherein aryl may be substituted with one or more C_1 - C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})-Z$;

wherein Q_1 is

10



wherein Q_2 is

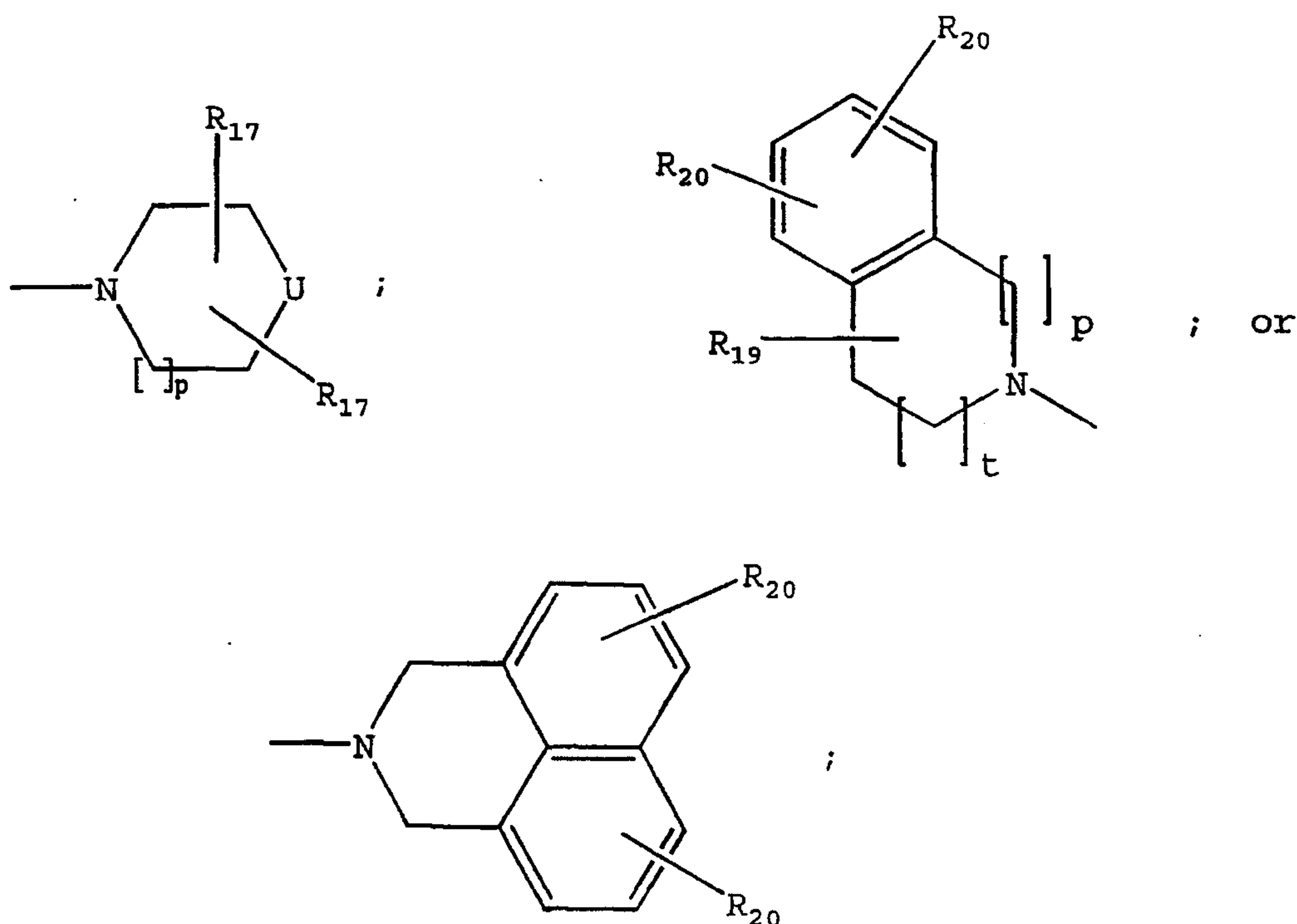


15

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

20 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 $\text{NR}_{14}\text{R}_{15}$;



5

wherein R_{14} is H, straight chained or branched $\text{C}_1\text{-C}_6$ alkyl, $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

10 wherein R_{15} is straight chained or branched $\text{C}_3\text{-C}_6$ alkyl, $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

wherein U is O, -NR_{16} , S, $\text{C}(\text{R}_{17})_2$, or $\text{-NSO}_2\text{R}_{16}$;

wherein Z is $\text{C}_3\text{-C}_{10}$ cycloalkyl, aryl, or heteroaryl;

15

wherein R_{16} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl,

straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

5 wherein each R₁₇ is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15

wherein each R₁₉ is independently H, or straight chained or branched C₁-C₆ alkyl;

20 wherein each R₂₀ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

30 wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

WO 02/060392

PCT/US02/04608

37

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;

5

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

wherein p is an integer from 0 to 2 inclusive;

10

wherein q is an integer from 2 to 4 inclusive;

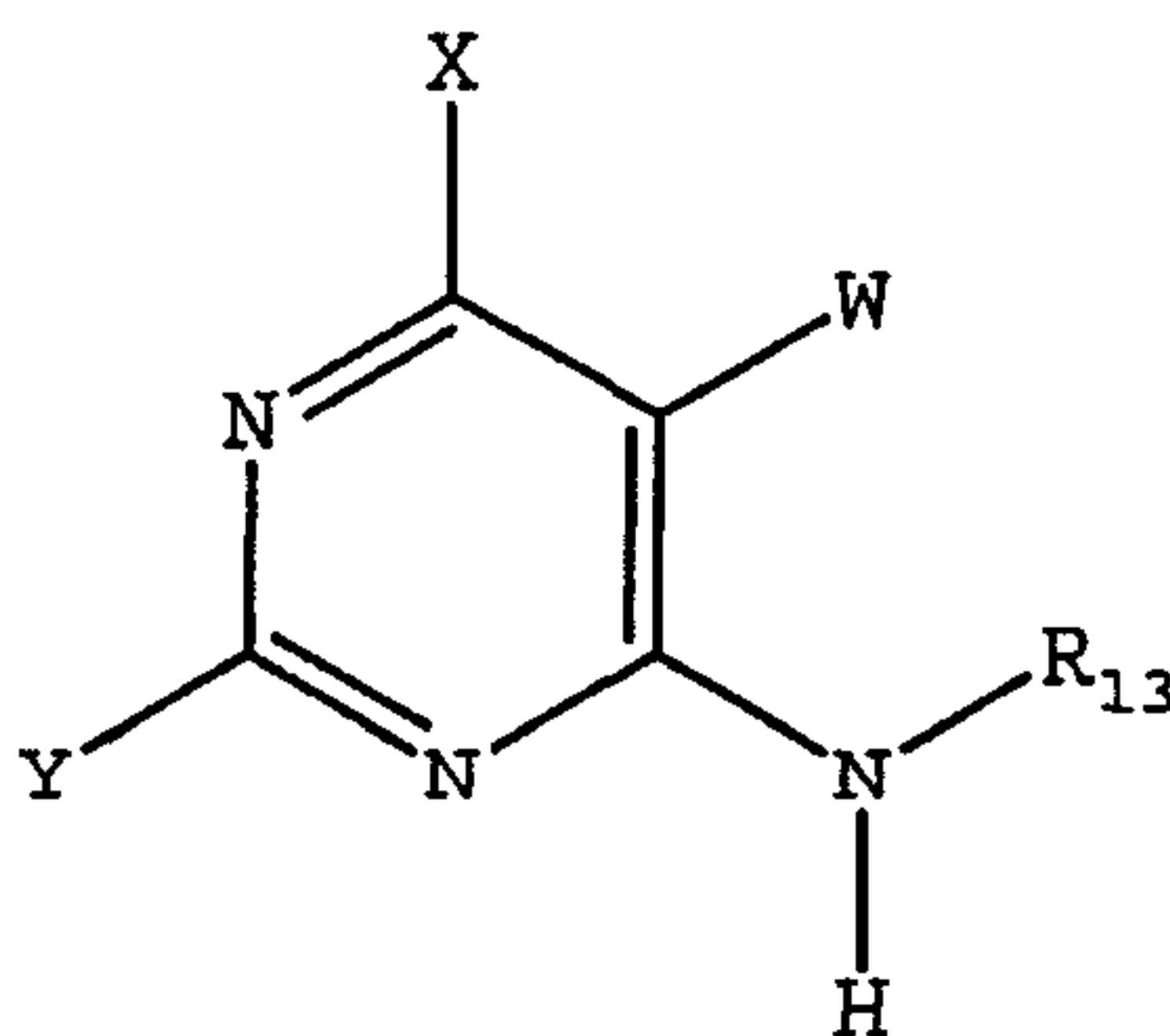
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

15

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:

20



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

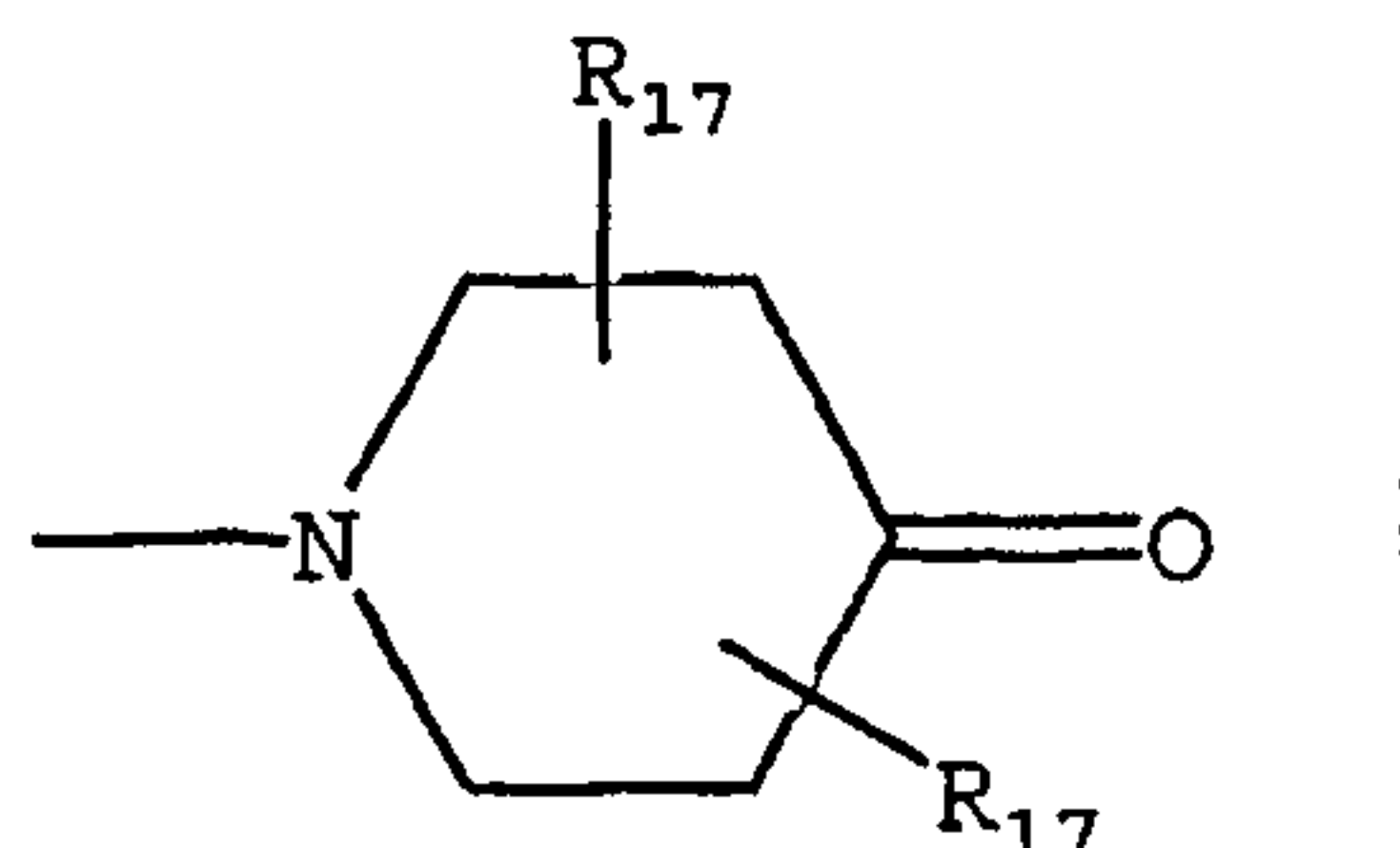
25

wherein X is $N(CH_3)_2$ or

WO 02/060392

PCT/US02/04608

38



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

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

10 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 $(C(R_{19})_2)_m$ - $N(R_{16})_2$;

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

20 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 ;

25 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;

- 5 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;

10

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

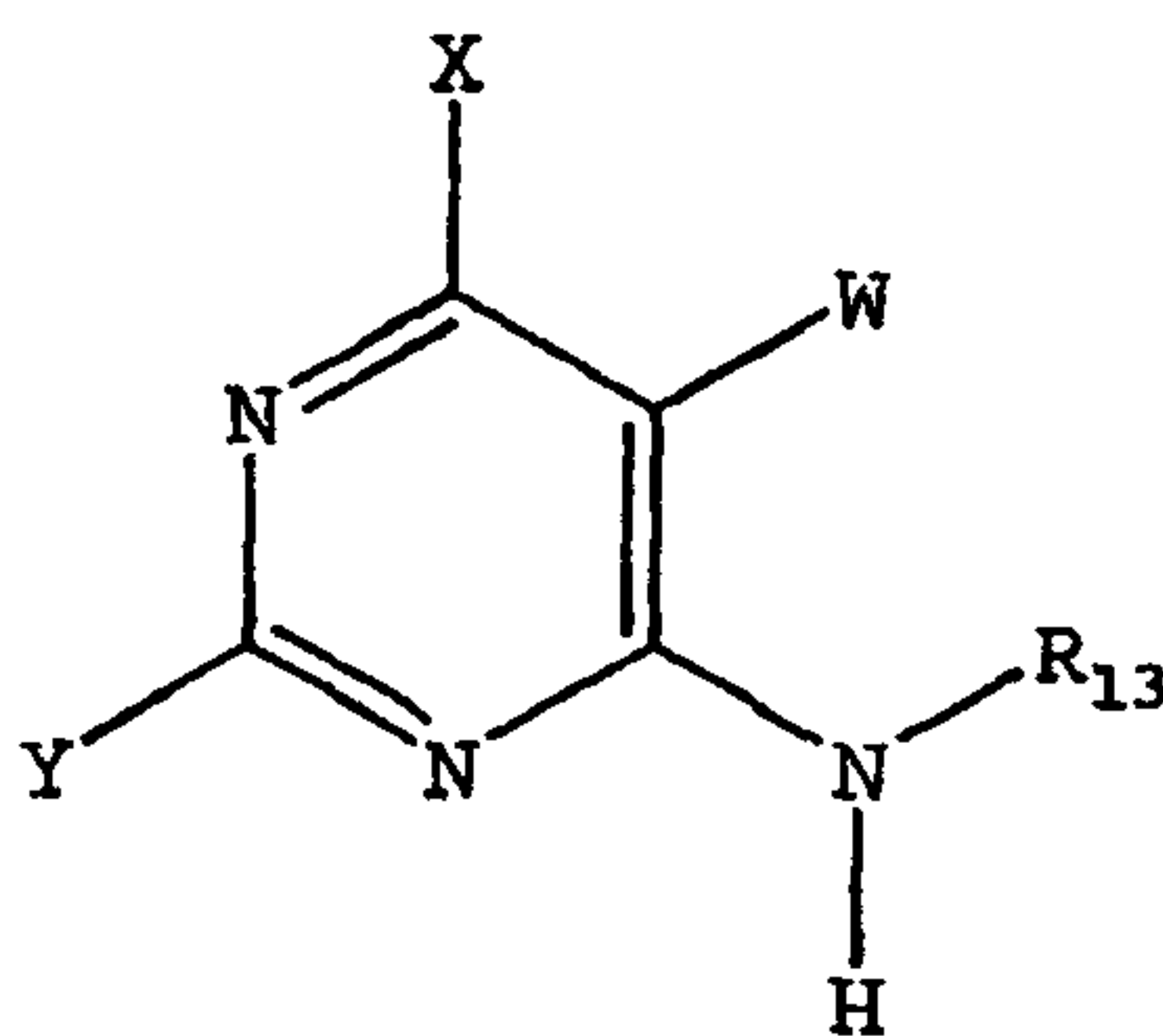
wherein each n is an integer from 1 to 4 inclusive;

15

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

a pharmaceutically acceptable salt thereof.

20 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;

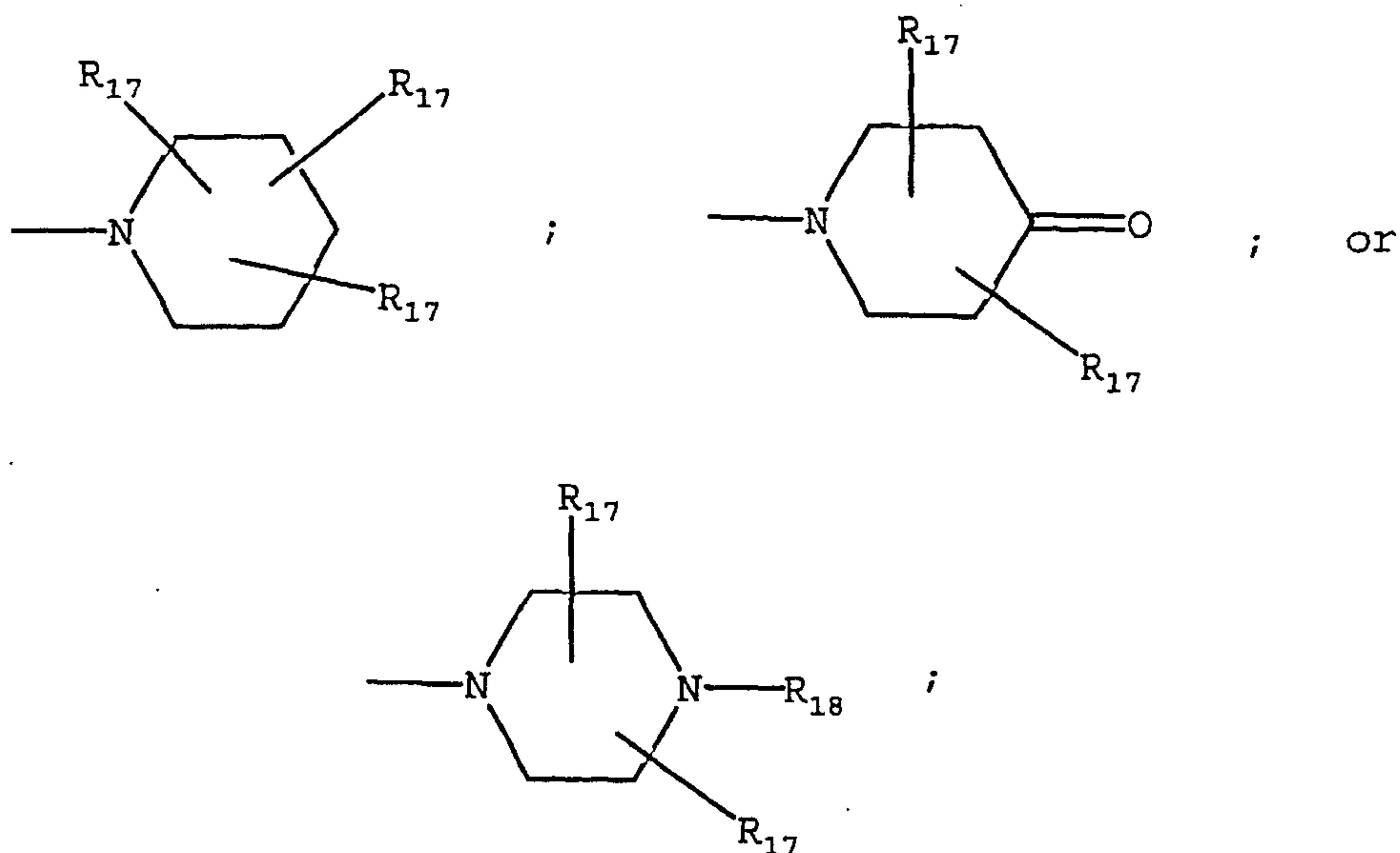
25

WO 02/060392

PCT/US02/04608

40

wherein X is; $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl, or aryl $(\text{C}_1\text{-C}_6)$ alkyl;

5

wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $\text{-(CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, heteroaryl, aryl, aryl $(\text{C}_1\text{-C}_6)$ alkyl, Q_1 or Q_2 ;

10

wherein aryl may be substituted with one or more $\text{C}_1\text{-C}_{10}$ straight chained or branched alkyl, aryl, heteroaryl, or $\text{N(R}_{19})\text{-Z}$;

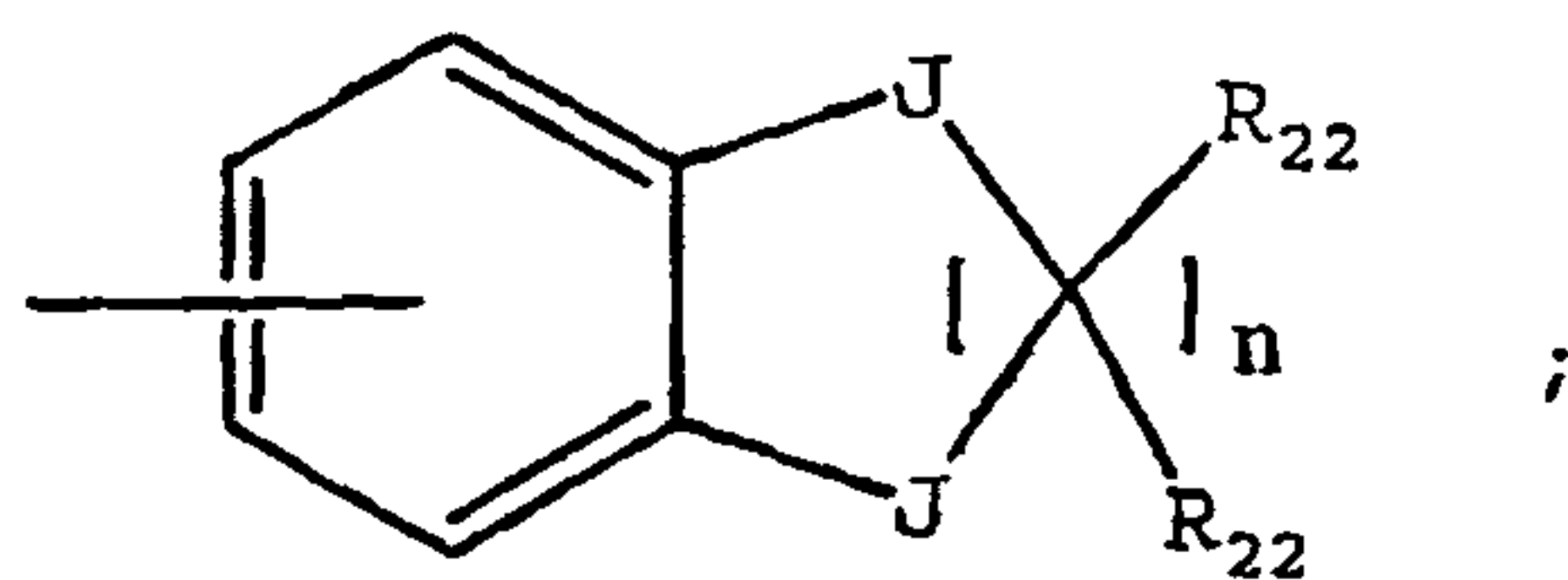
15

wherein Q_1 is

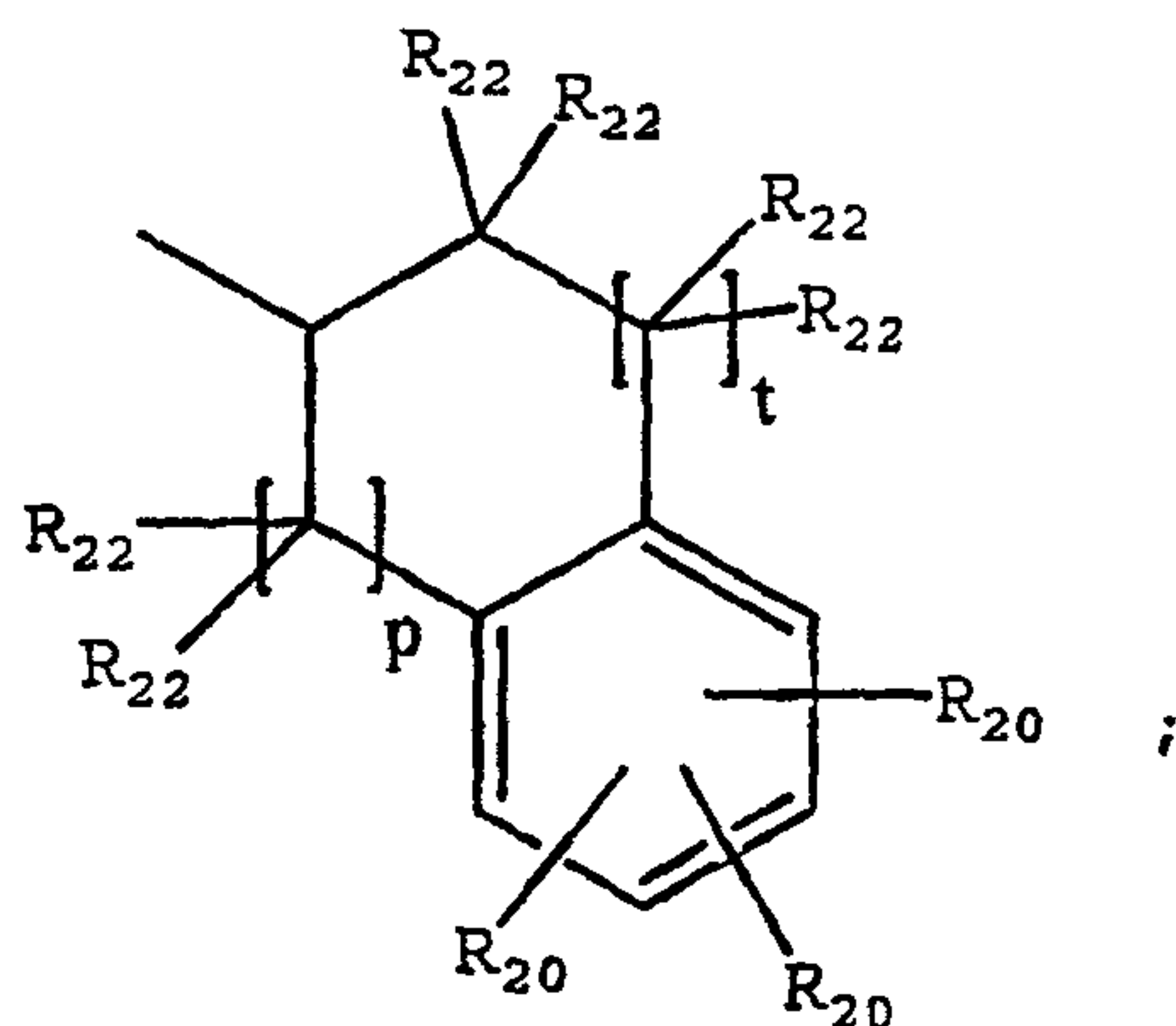
WO 02/060392

PCT/US02/04608

41



wherein Q₂ is



5

wherein each J is independently O, S, C(R₂₂)₂ or NR₄;

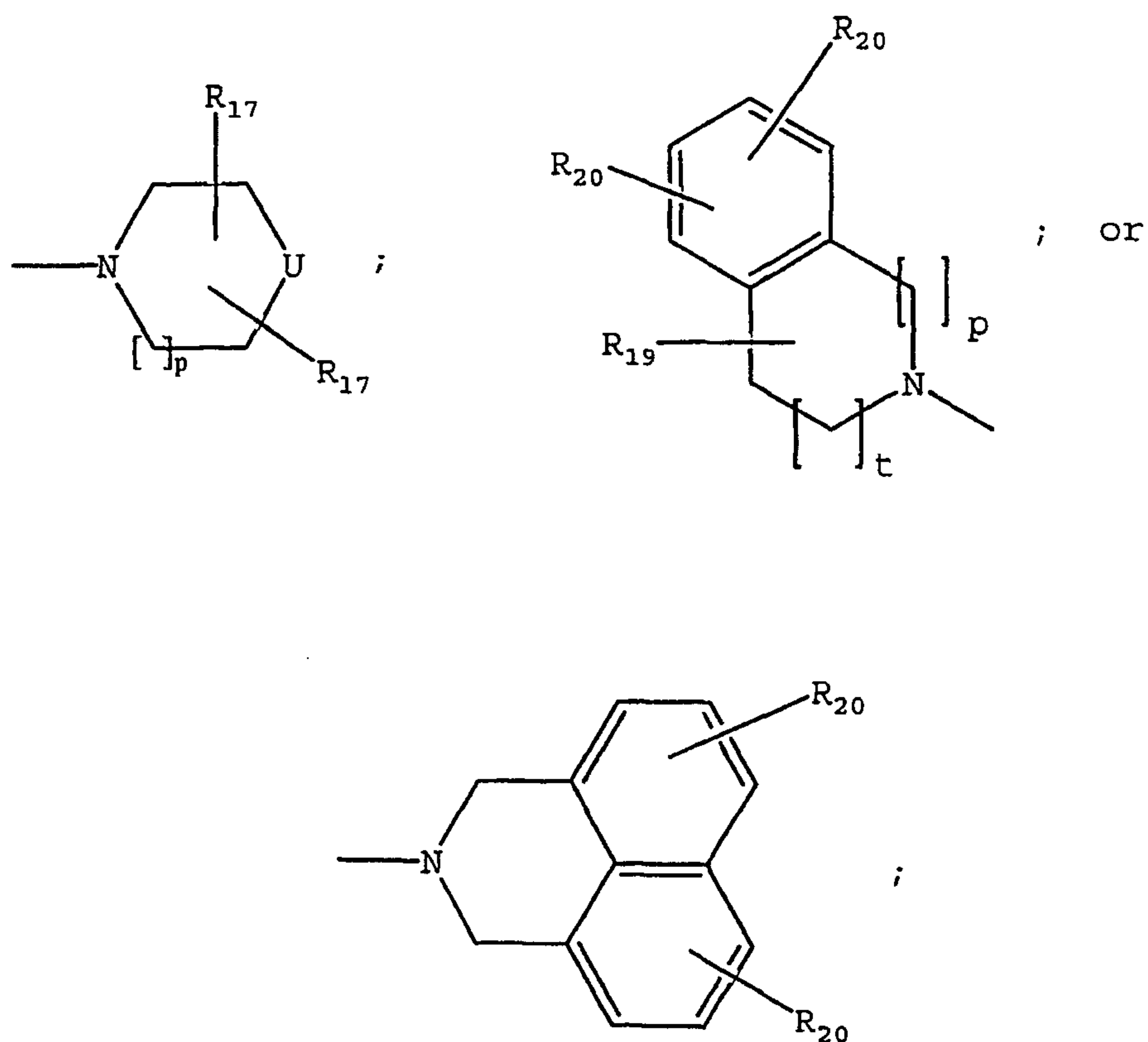
wherein R₄ is H; straight chained or branched C₁-C₇ alkyl,
 10 monofluoroalkyl or polyfluoroalkyl; straight chained or
 branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇
 cycloalkenyl or aryl;

wherein Y is NR₁₄R₁₅;

WO 02/060392

PCT/US02/04608

42



5

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 $(C(R_{19})_2)_m-Z$;

10

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 $(C(R_{19})_2)_m-Z$;

15

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

20

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

-NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, -(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

wherein each R₁₉ is independently H, or straight chained or branched C₁-C₆ alkyl;

wherein each R₂₀ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, or aryl(C₁-C₆)alkyl;

wherein each R₂₂ is independently H, F, Cl or C₁-C₄ straight chained or branched alkyl;

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

WO 02/060392

PCT/US02/04608

44

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

wherein p is an integer from 0 to 2 inclusive;

5

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

10

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

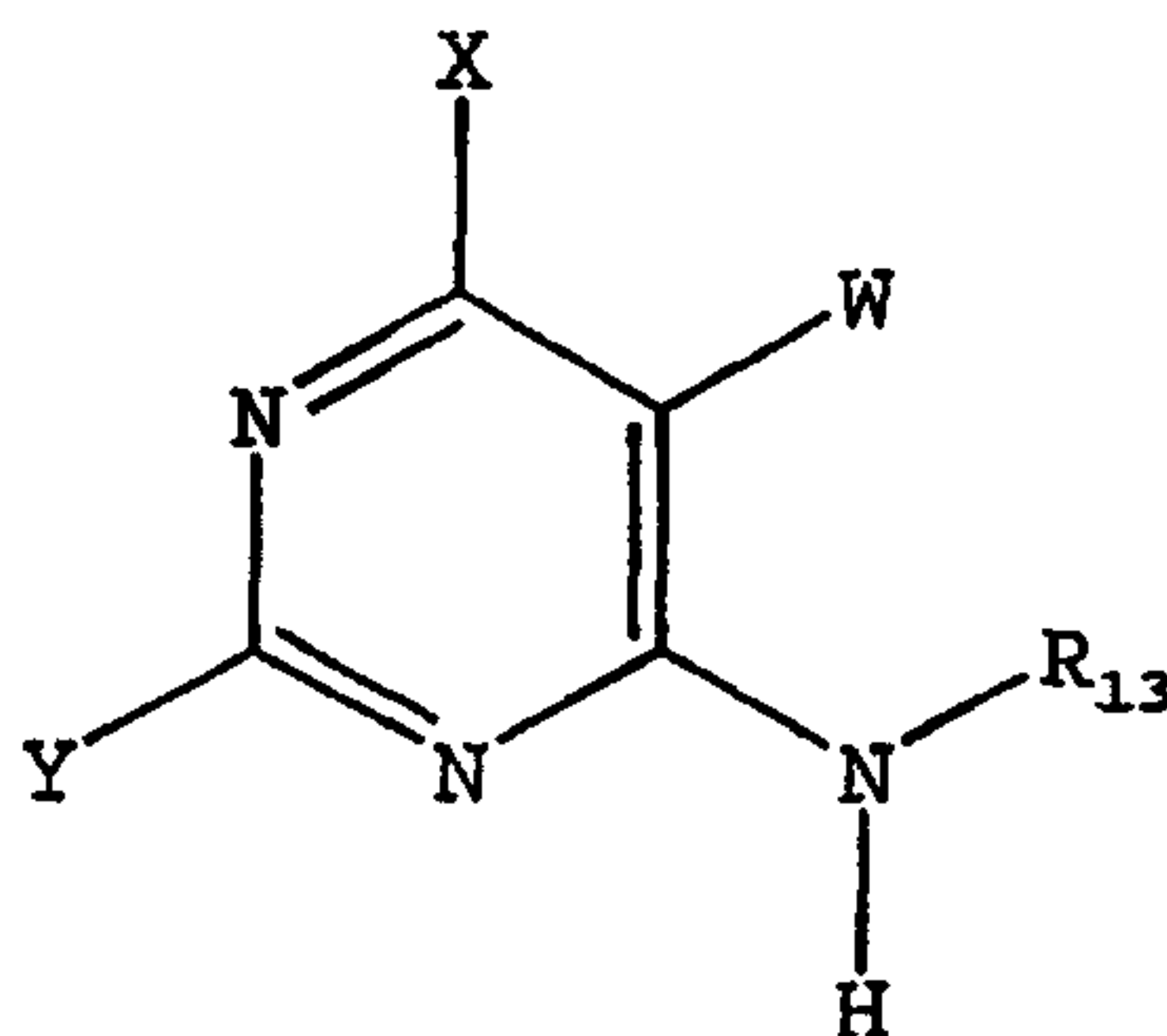
wherein Z is C₃-C₁₀ cycloalkyl, C₄-C₇ cyclic ether, C₄-C₇ cyclic thioether, aryl, or heteroaryl; or

15

a pharmaceutically acceptable salt thereof.

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

20



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

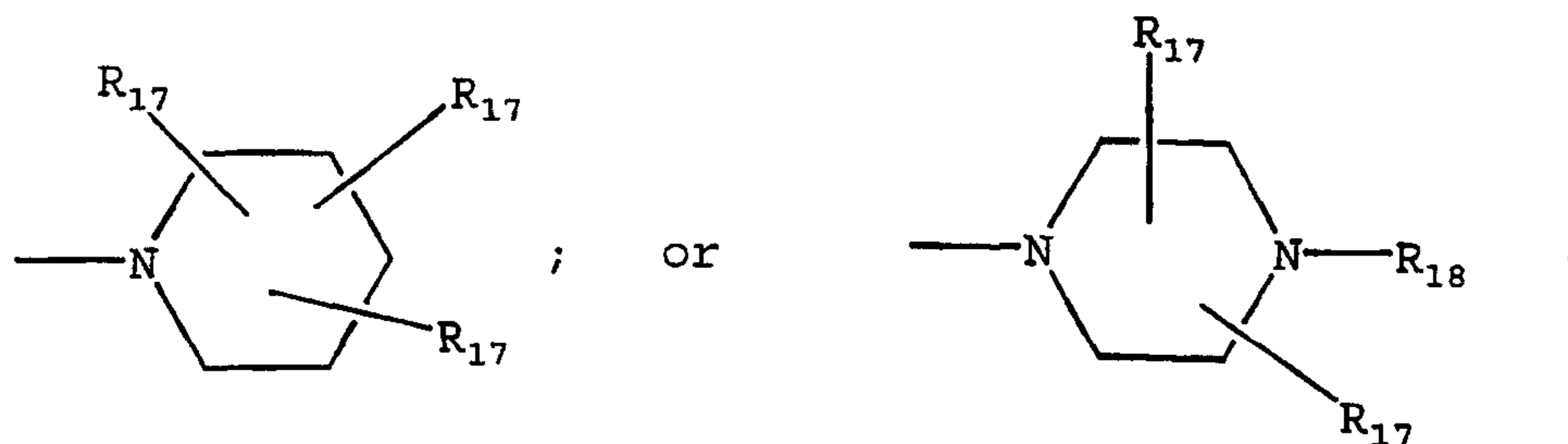
25

WO 02/060392

PCT/US02/04608

45

wherein X is $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

5

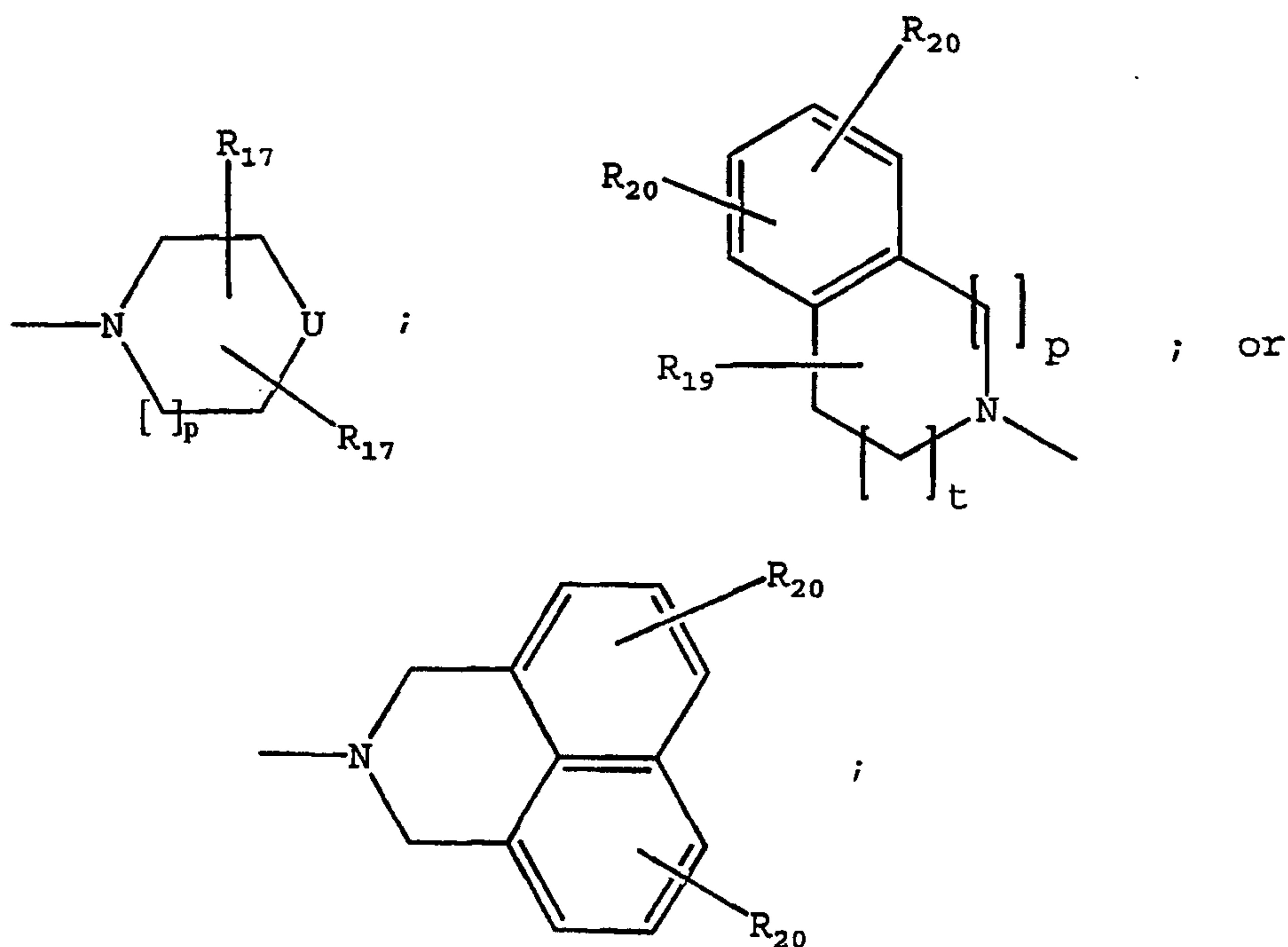
wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$, or $-(\text{CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

10

wherein Y is $\text{NR}_{14}\text{R}_{15}$;

46



wherein R₁₄ is H, straight chained or branched C₁-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

5

wherein R₁₅ is straight chained or branched C₃-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

10

wherein Z is C₃-C₁₀ cycloalkyl, aryl, or heteroaryl;

15

wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

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;

WO 02/060392

PCT/US02/04608

48

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

wherein p is an integer from 0 to 2 inclusive;

5

wherein q is an integer from 2 to 4 inclusive;

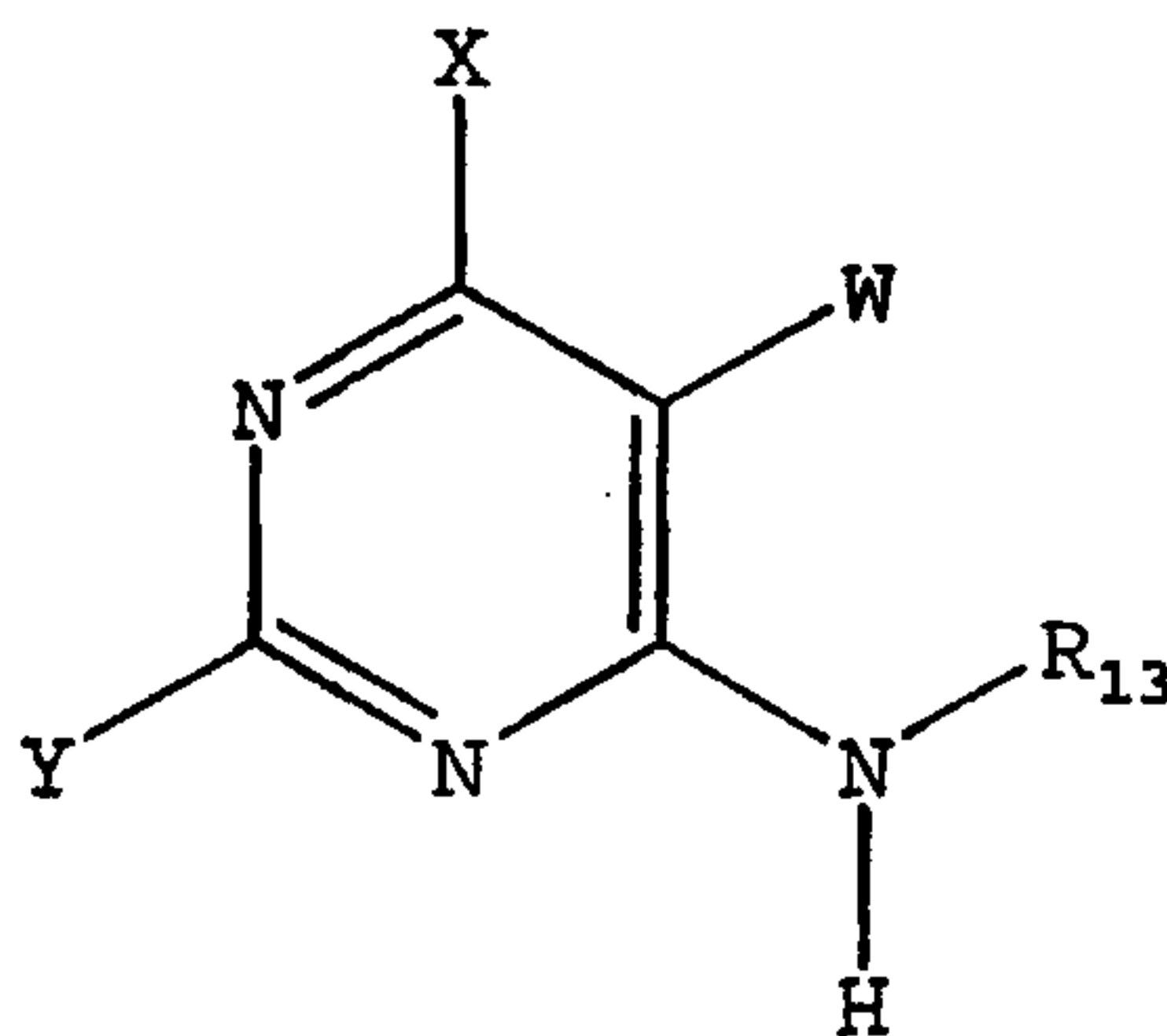
wherein t is 1 or 2; or

10

a pharmaceutically acceptable salt thereof.

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

15



20

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

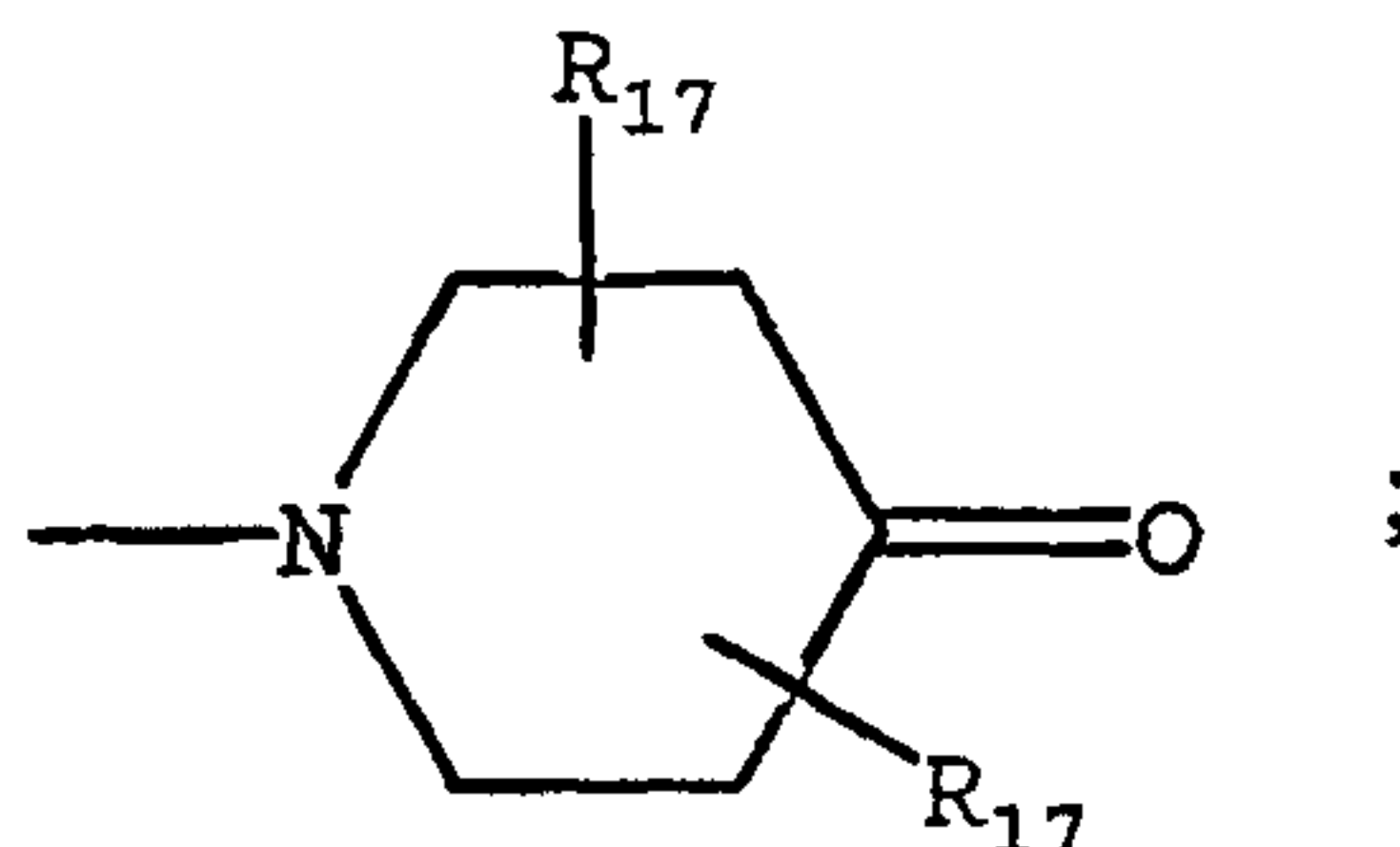
wherein X is N(CH₃)₂ or

25

WO 02/060392

PCT/US02/04608

49



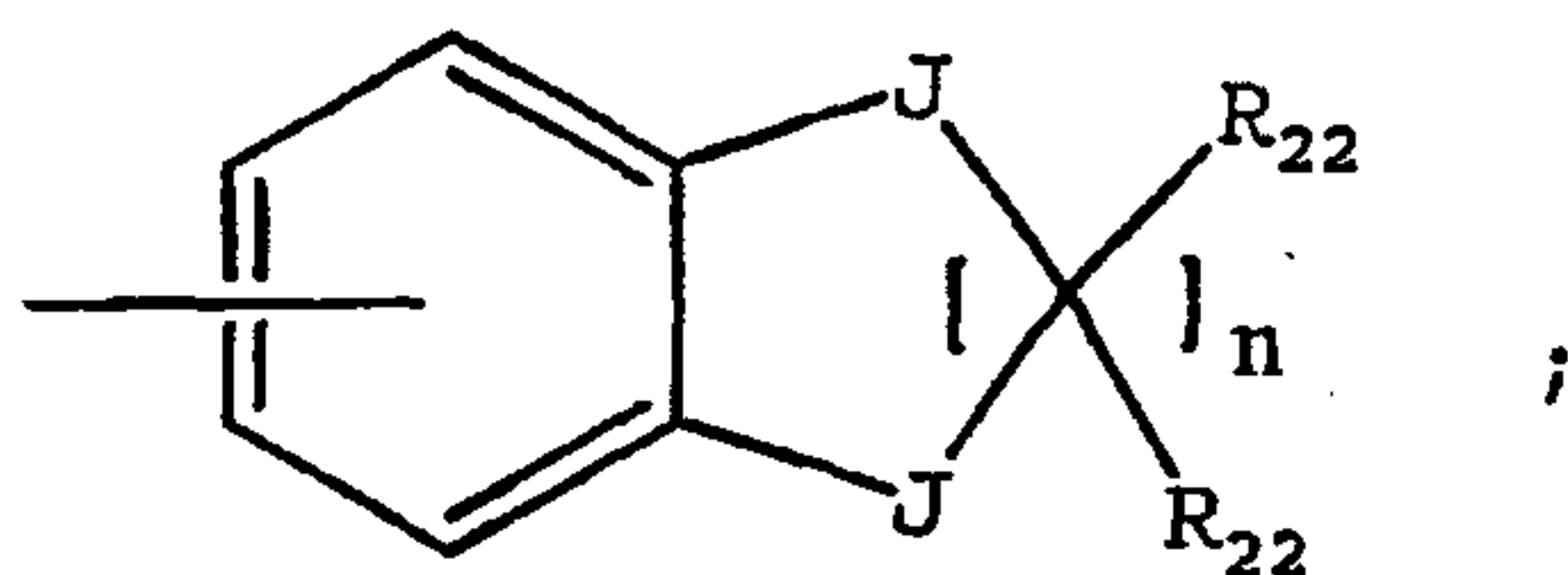
wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3 - C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2 ;

5

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

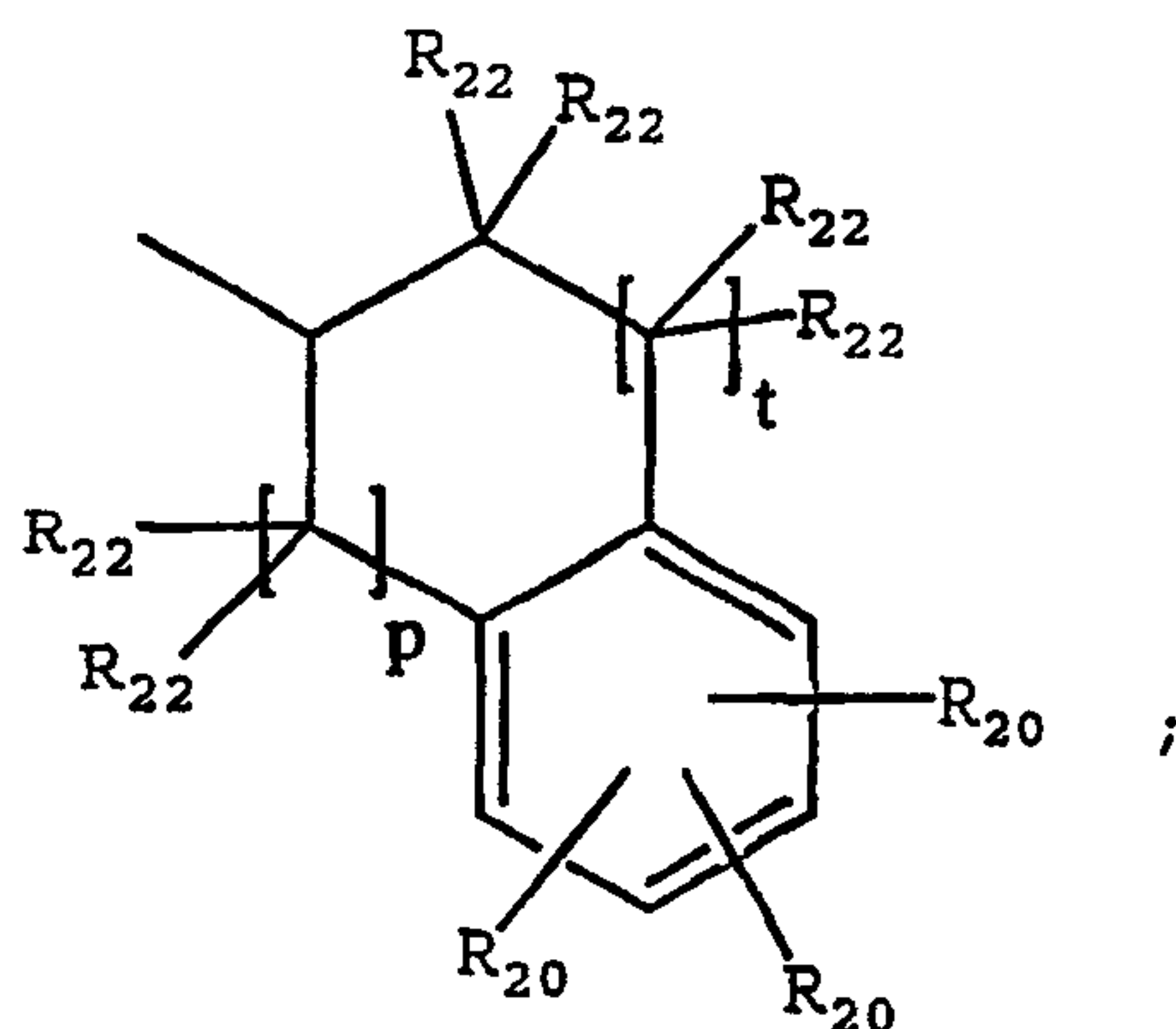
10

wherein Q_1 is



wherein Q_2 is

15



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

WO 02/060392

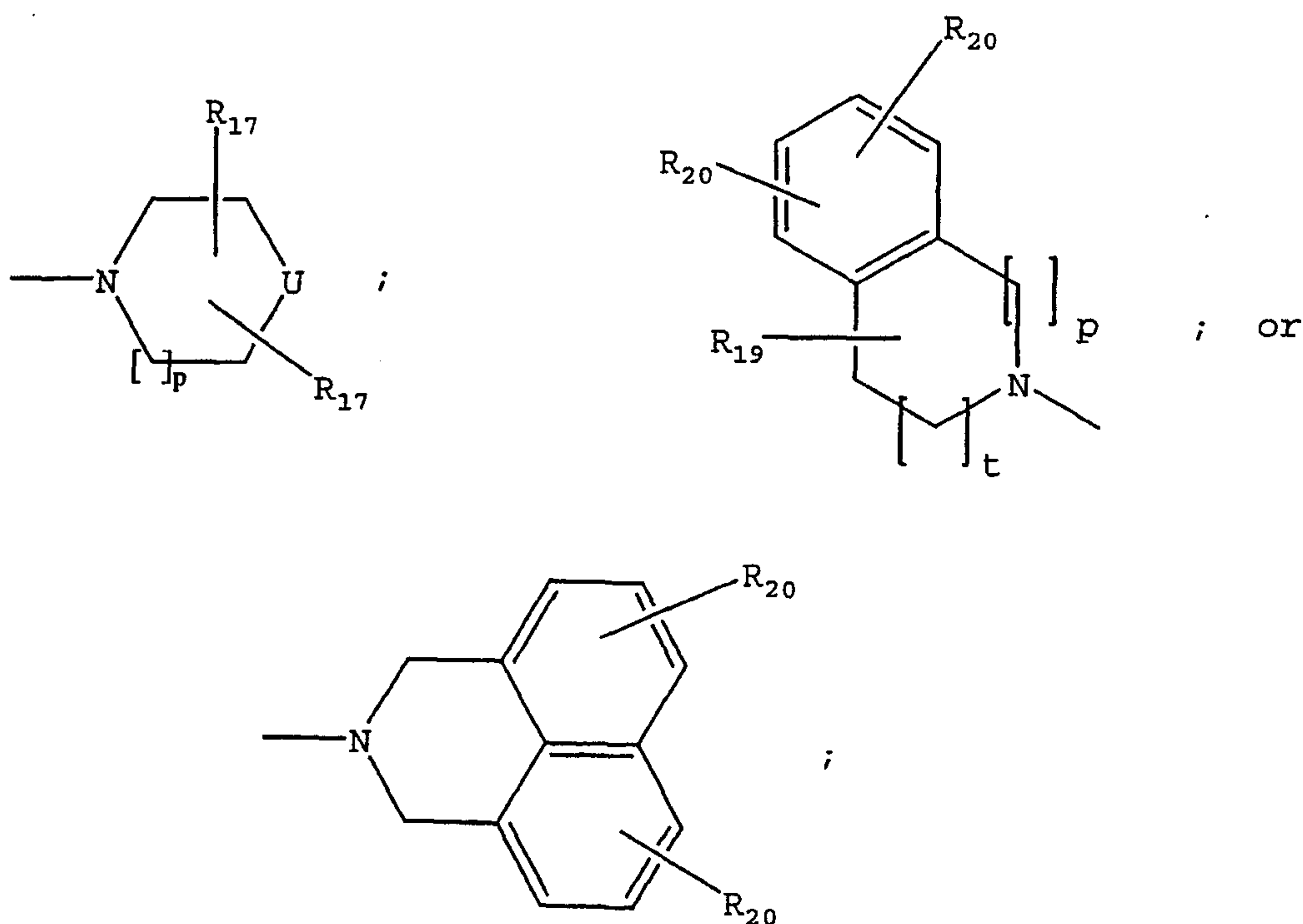
PCT/US02/04608

50

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;

5

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



10 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 $(C(R_{19})_2)_m-Z$;

15

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
 5 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; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$,
 10 $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, 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
 15 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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

20 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;
 25 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
 30 form a methylenedioxy group;

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

WO 02/060392

PCT/US02/04608

52

branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-
C₆)alkyl;

5

wherein each R₂₂ is independently H, F, Cl or C₁-C₄
straight chained or branched alkyl;

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

10

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

wherein p is an integer from 0 to 2 inclusive;

15

wherein q is an integer from 2 to 4 inclusive;

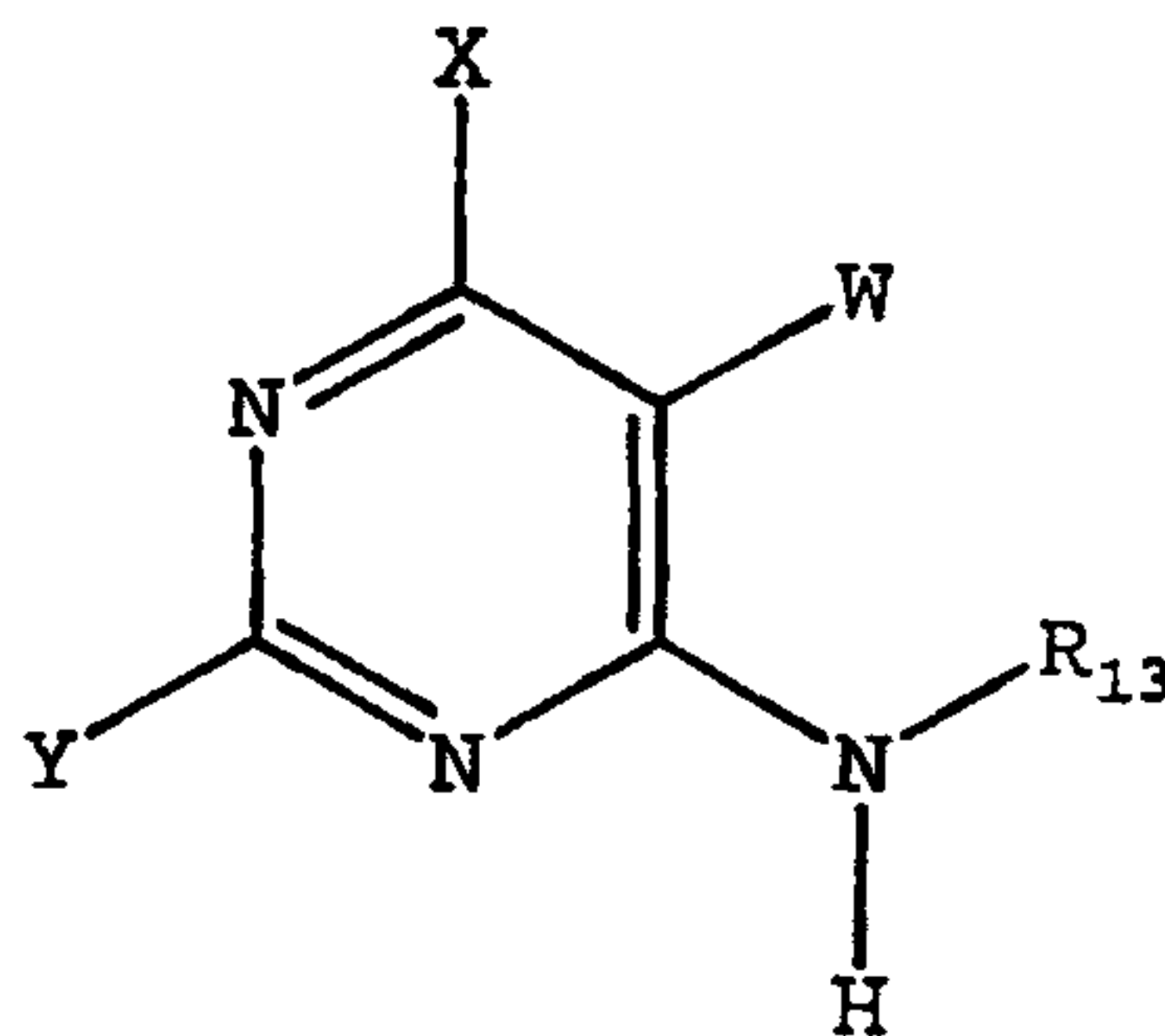
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

20

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

25



WO 02/060392

PCT/US02/04608

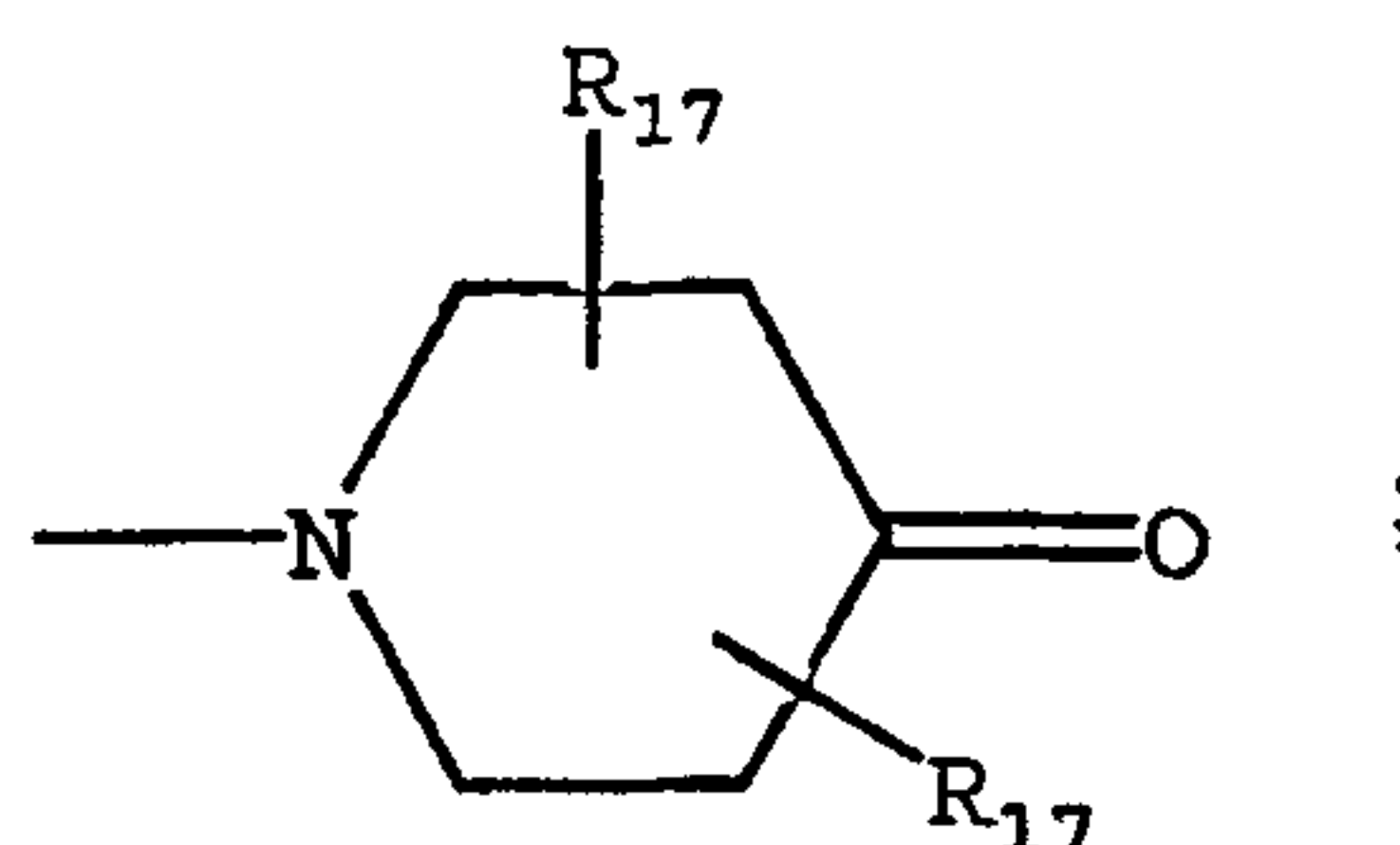
53

5

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

wherein X is $N(CH_3)_2$ or

10



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

15

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 $(C(R_{19})_2)_m-Z$;

20

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

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

25

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, -

$(\text{CH}_2)_m\text{-Z}$, or $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$;

5 wherein each R_{17} is independently H; $-\text{OR}_{21}$, $-\text{OCOR}_{21}$, $-\text{COR}_{21}$, $-\text{NCOR}_{21}$, $-\text{N}(\text{R}_{21})_2$, $-\text{CON}(\text{R}_{21})_2$, $-\text{COOR}_{21}$, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkynyl, $\text{C}_5\text{-C}_7$ cycloalkenyl, $-(\text{CH}_2)_m\text{-Z}$, or $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$;

10

wherein each R_{19} is independently H, or straight chained or branched $\text{C}_1\text{-C}_6$ alkyl;

15 wherein each R_{21} is independently -H; straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl or alkynyl; $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{C}_5\text{-C}_7$ cycloalkenyl, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

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

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

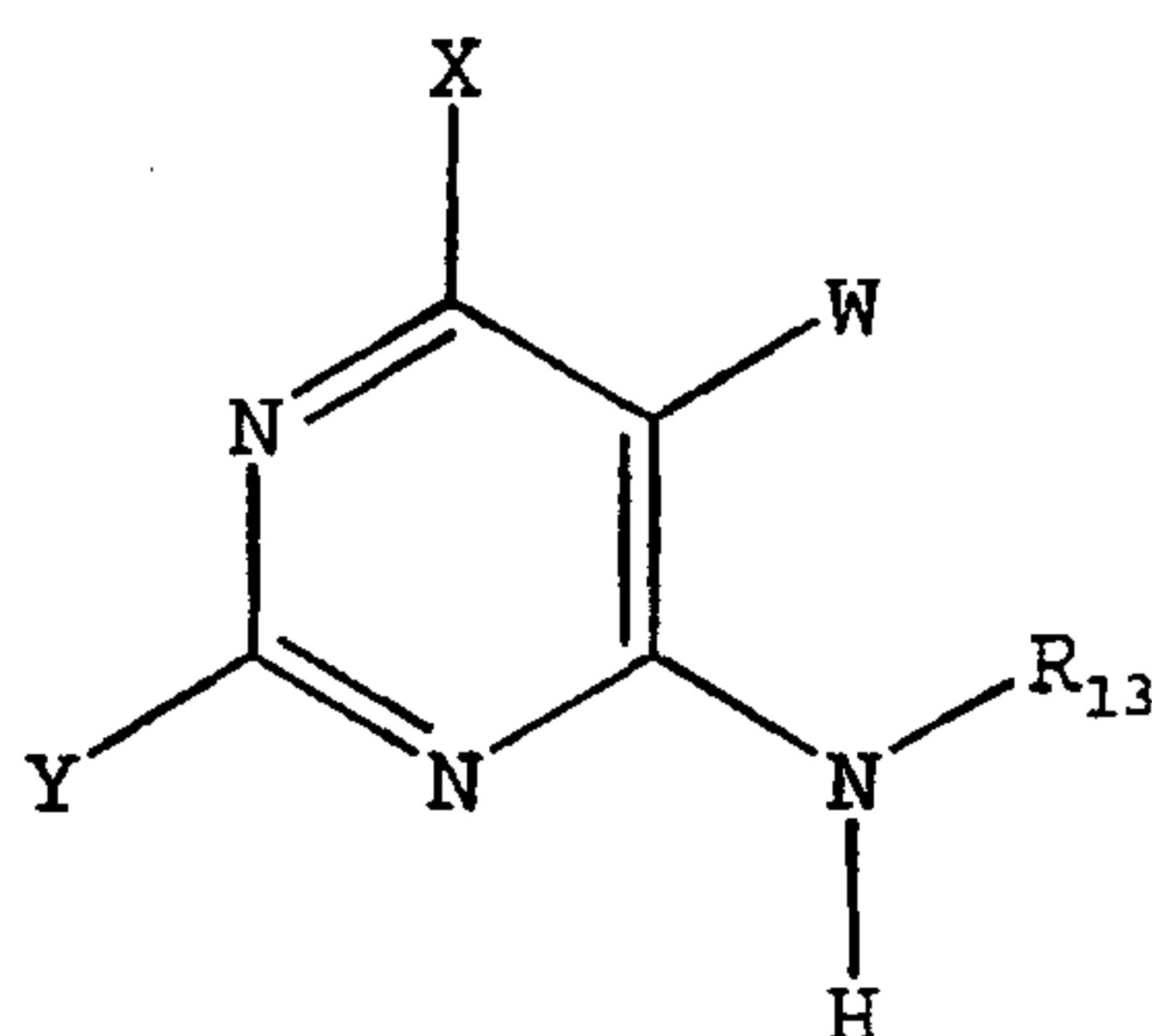
wherein q is an integer from 2 to 4 inclusive; or

25

a pharmaceutically acceptable salt thereof.

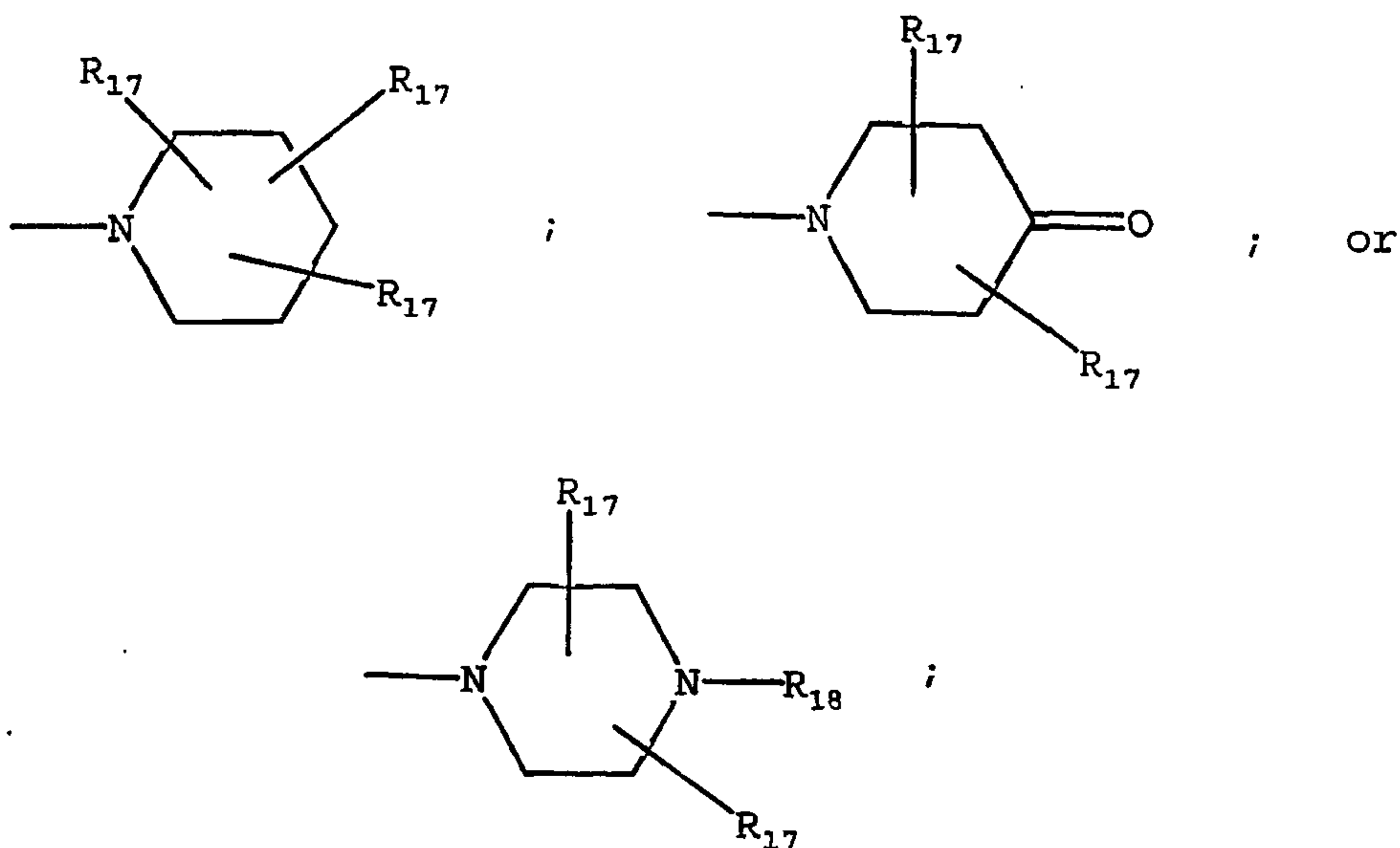
The invention provides a compound having the structure:

55



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

5 wherein X is; $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl, or aryl $(\text{C}_1\text{-C}_6)$ alkyl;

10 wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $-(\text{CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, heteroaryl, aryl, aryl($\text{C}_1\text{-}$

WO 02/060392

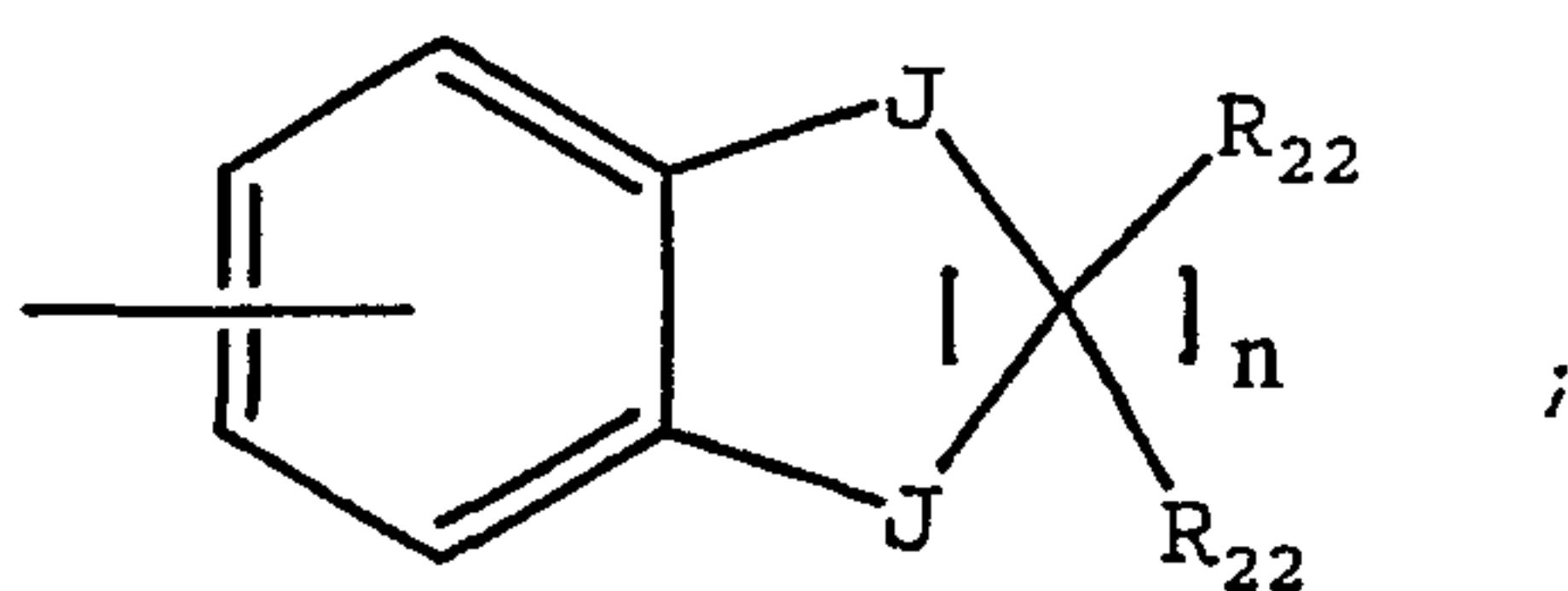
PCT/US02/04608

56

C₆)alkyl, Q₁ or Q₂;

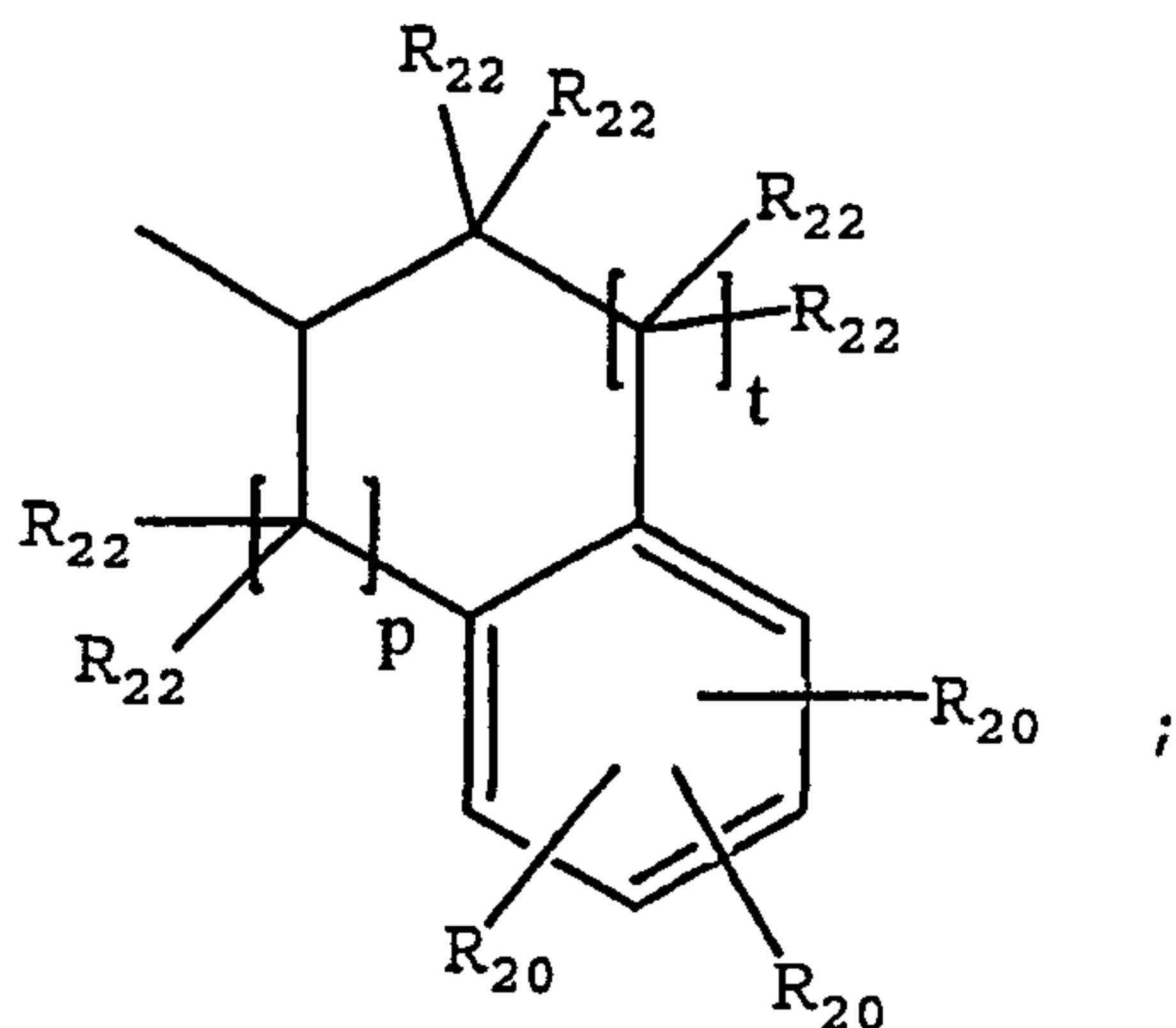
wherein aryl may be substituted with one or more C₁-C₁₀
straight chained or branched alkyl, aryl, heteroaryl, or
5 N(R₁₉)-Z;

wherein Q₁ is



10

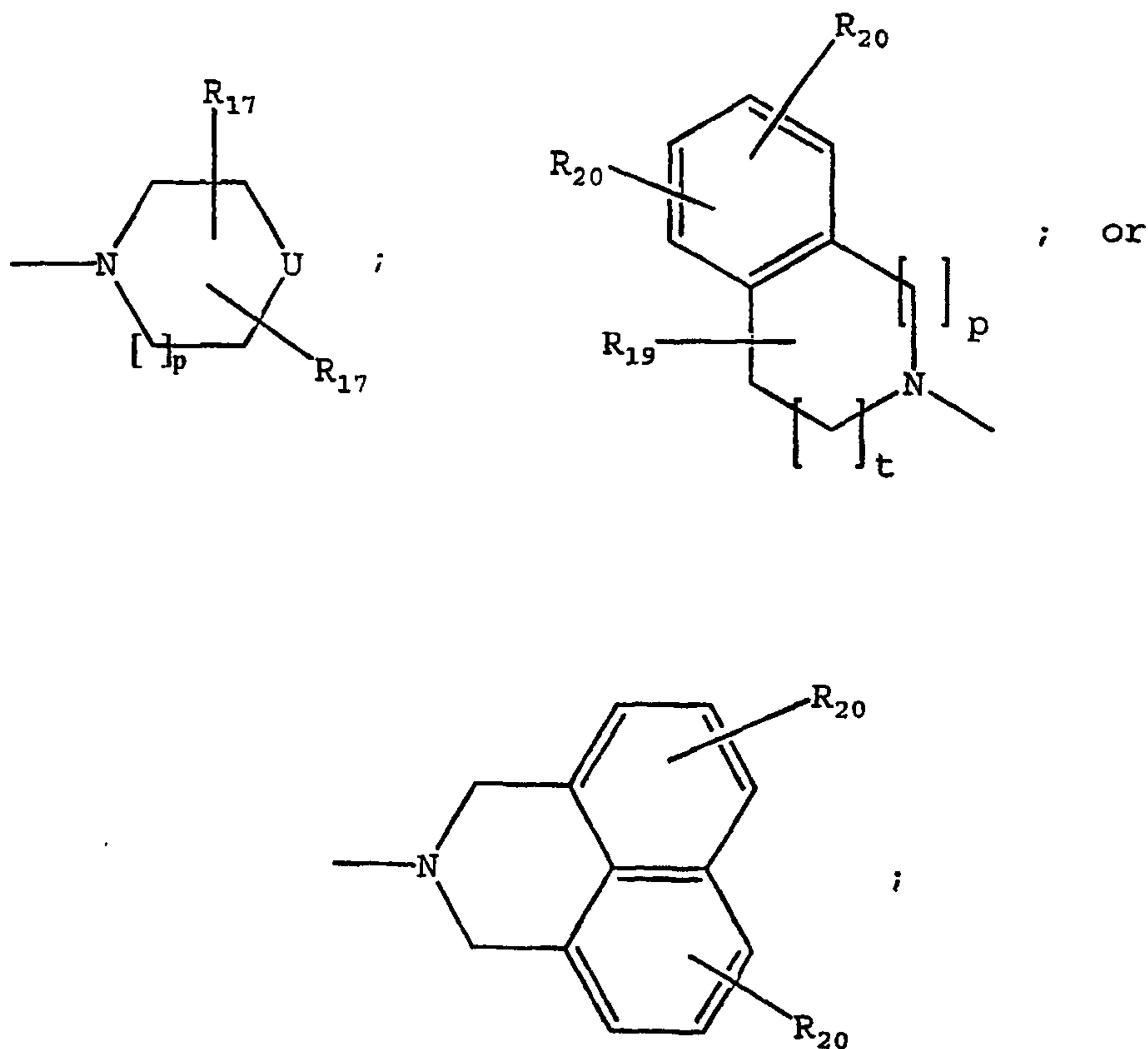
wherein Q₂ is



15 wherein each J is independently O, S, C(R₂₂)₂ or NR₄;

wherein R₄ is H; straight chained or branched C₁-C₇ alkyl,
monofluoroalkyl or polyfluoroalkyl; straight chained or
branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇
20 cycloalkenyl or aryl;

wherein Y is NR₁₄R₁₅;



5

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 $(C(R_{19})_2)_m-Z$;

10

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 $(C(R_{19})_2)_m-Z$;

15

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

20

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

5 -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

10 wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, -(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

wherein each R₁₉ is independently H, or straight chained or branched C₁-C₆ alkyl;

15 wherein each R₂₀ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

25 wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, or aryl(C₁-C₆)alkyl;

30 wherein each R₂₂ is independently H, F, Cl or C₁-C₄ straight chained or branched alkyl;

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

WO 02/060392

PCT/US02/04608

59

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

wherein p is an integer from 0 to 2 inclusive;

5

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

10

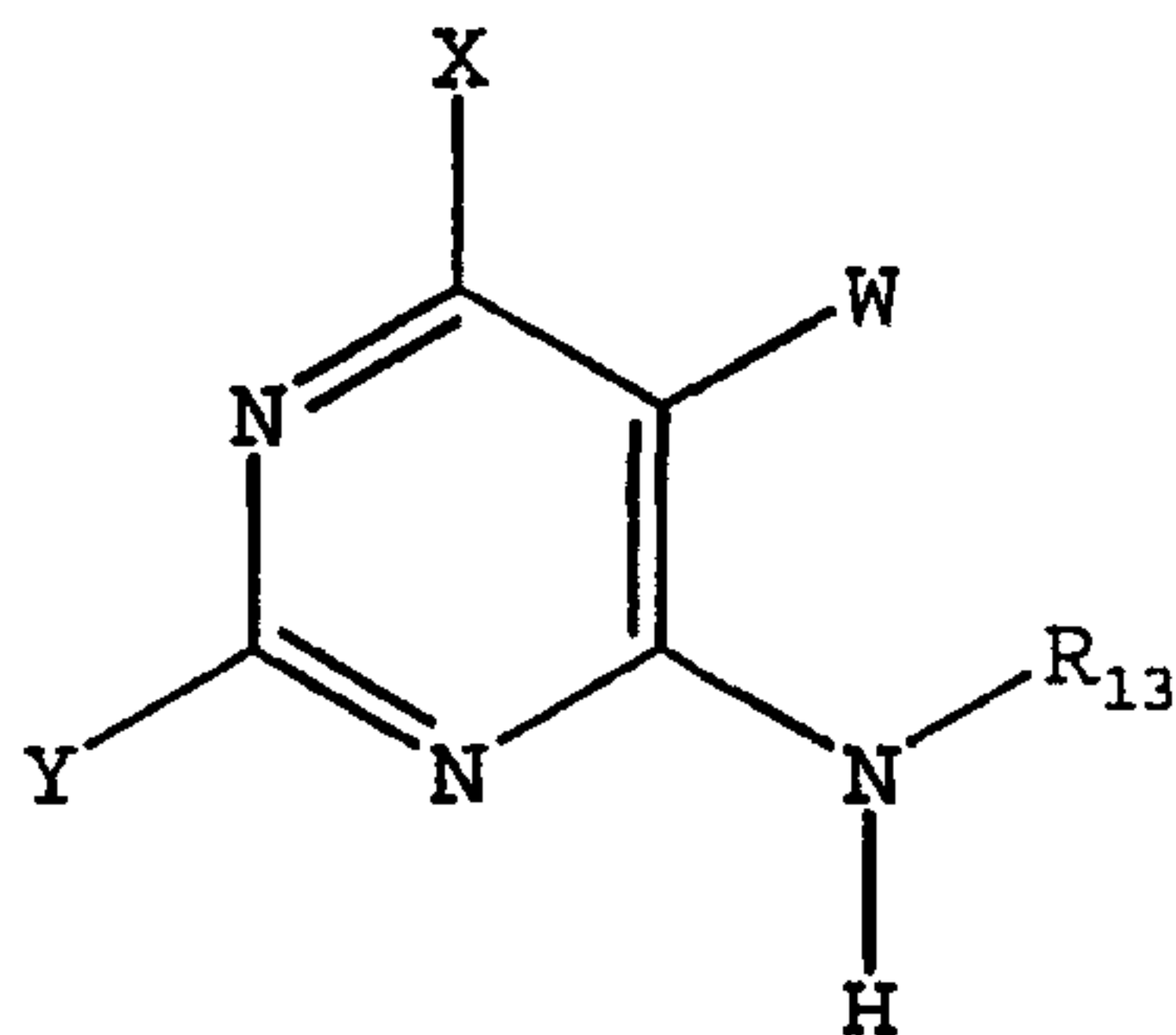
wherein U is O, $-NR_{16}$, S, $C(R_{17})_2$, or $-NSO_2R_{16}$;

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

15

a pharmaceutically acceptable salt thereof.

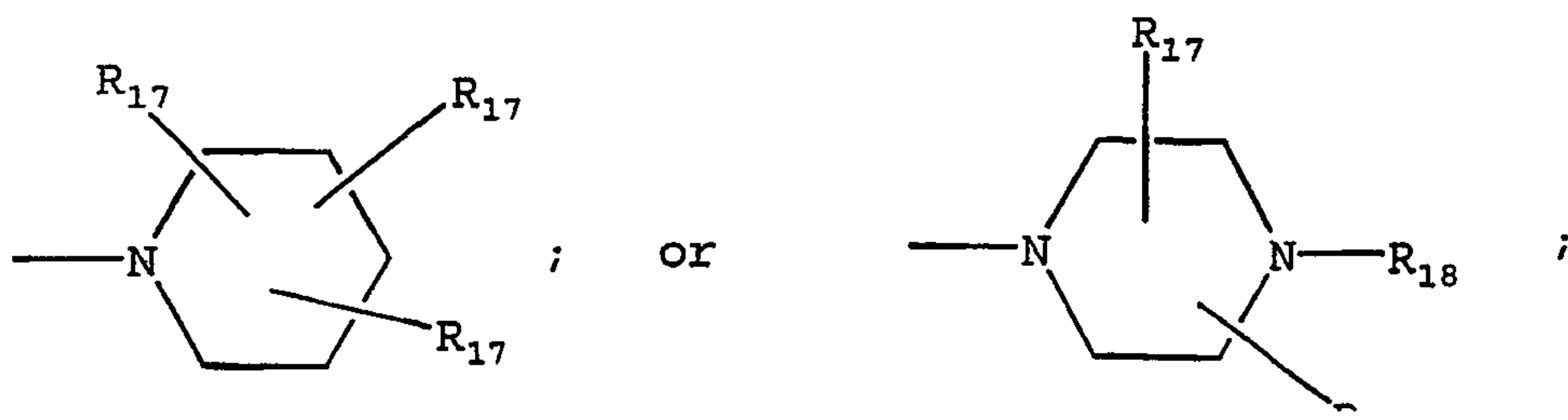
The invention provides a compound having the structure:



20

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

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



WO 02/060392

PCT/US02/04608

60

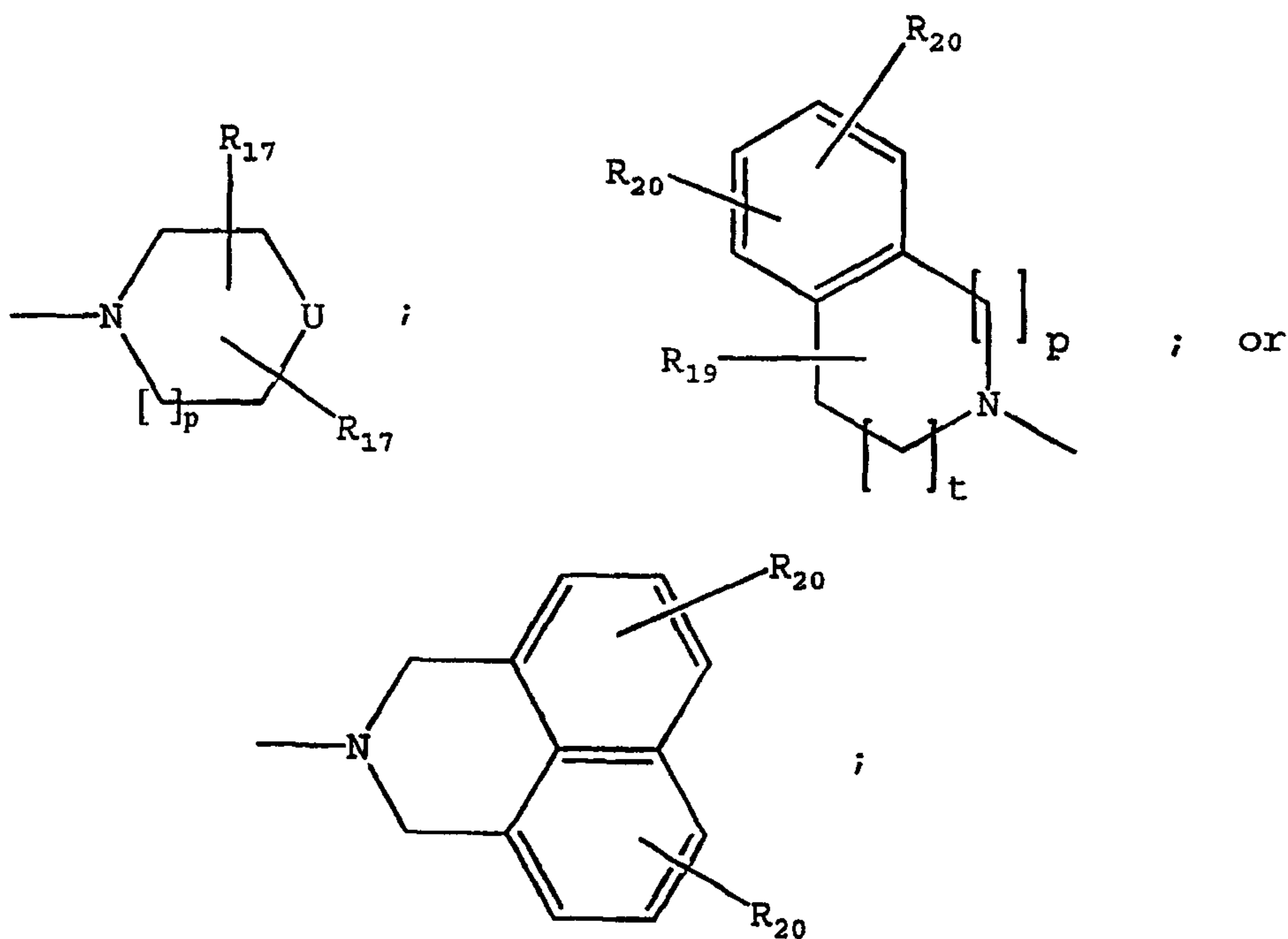
wherein R_{11} is H, straight chained or branched C_1 - C_7 alkyl, $(CH_2)_q-O-(CH_2)_m-CH_3$, aryl or aryl(C_1 - C_6)alkyl;

5 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;

10

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



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,

$(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

wherein U is O, -NR_{16} , S, $\text{C}(\text{R}_{17})_2$, or $\text{-NSO}_2\text{R}_{16}$;

5 wherein Z is $\text{C}_3\text{-C}_{10}$ cycloalkyl, aryl, or heteroaryl;

wherein R_{16} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl,
 straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl,
 straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl,
 10 straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl, straight
 chained or branched $\text{C}_2\text{-C}_7$ alkynyl, $\text{C}_5\text{-C}_7$ cycloalkenyl, -
 $(\text{CH}_2)_m\text{-Z}$, or $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$;

wherein each R_{17} is independently H; -OR_{21} , -OCOR_{21} , -COR_{21} ,
 15 -NCOR_{21} , $\text{-N}(\text{R}_{21})_2$, $\text{-CON}(\text{R}_{21})_2$, -COOR_{21} , straight chained or
 branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$
 monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$
 polyfluoroalkyl, straight chained or branched $\text{C}_2\text{-C}_7$
 alkenyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkynyl, $\text{C}_5\text{-C}_7$
 20 cycloalkenyl, $\text{-(CH}_2)_m\text{-Z}$, or $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$;

wherein R_{18} is straight chained or branched $\text{C}_1\text{-C}_6$ alkyl, -
 $(\text{CH}_2)_m\text{-Z}$, or $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$;

25 wherein each R_{19} is independently H, or straight chained
 or branched $\text{C}_1\text{-C}_6$ alkyl;

wherein each R_{20} is independently -H ; straight chained or
 branched $\text{C}_1\text{-C}_7$ alkyl, monofluoroalkyl or polyfluoroalkyl;
 30 straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl or alkynyl; $\text{C}_3\text{-}$
 C_7 cycloalkyl or $\text{C}_5\text{-C}_7$ cycloalkenyl; -F , -Cl , -Br , or -I ;
 -NO_2 ; -N_3 ; -CN ; -OR_{21} , -OCOR_{21} , -COR_{21} , -NCOR_{21} , $\text{-N}(\text{R}_{21})_2$, -

CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

5 wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

10

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

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

15

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

20

a pharmaceutically acceptable salt thereof.

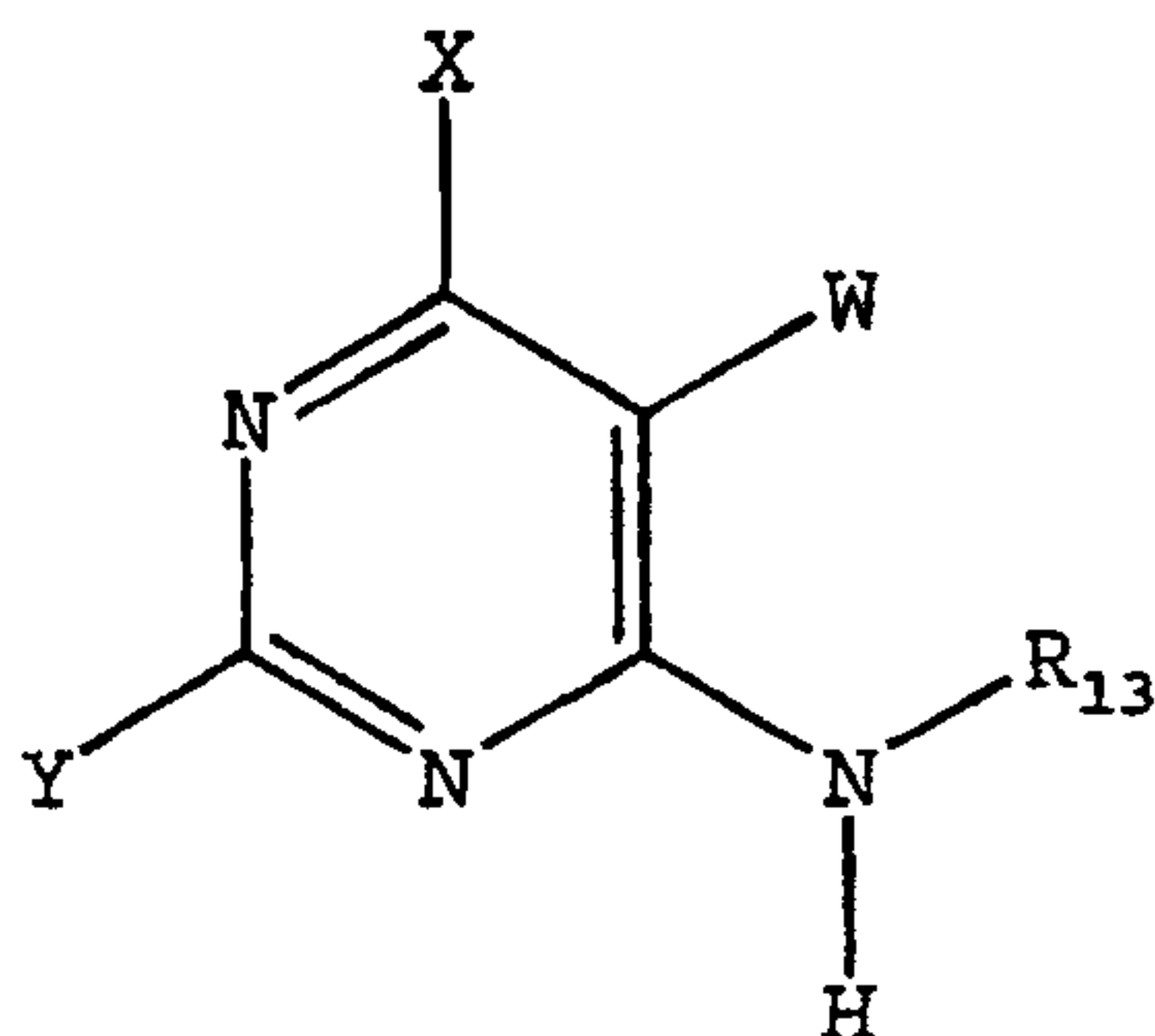
25

The invention provides a compound having the structure:

WO 02/060392

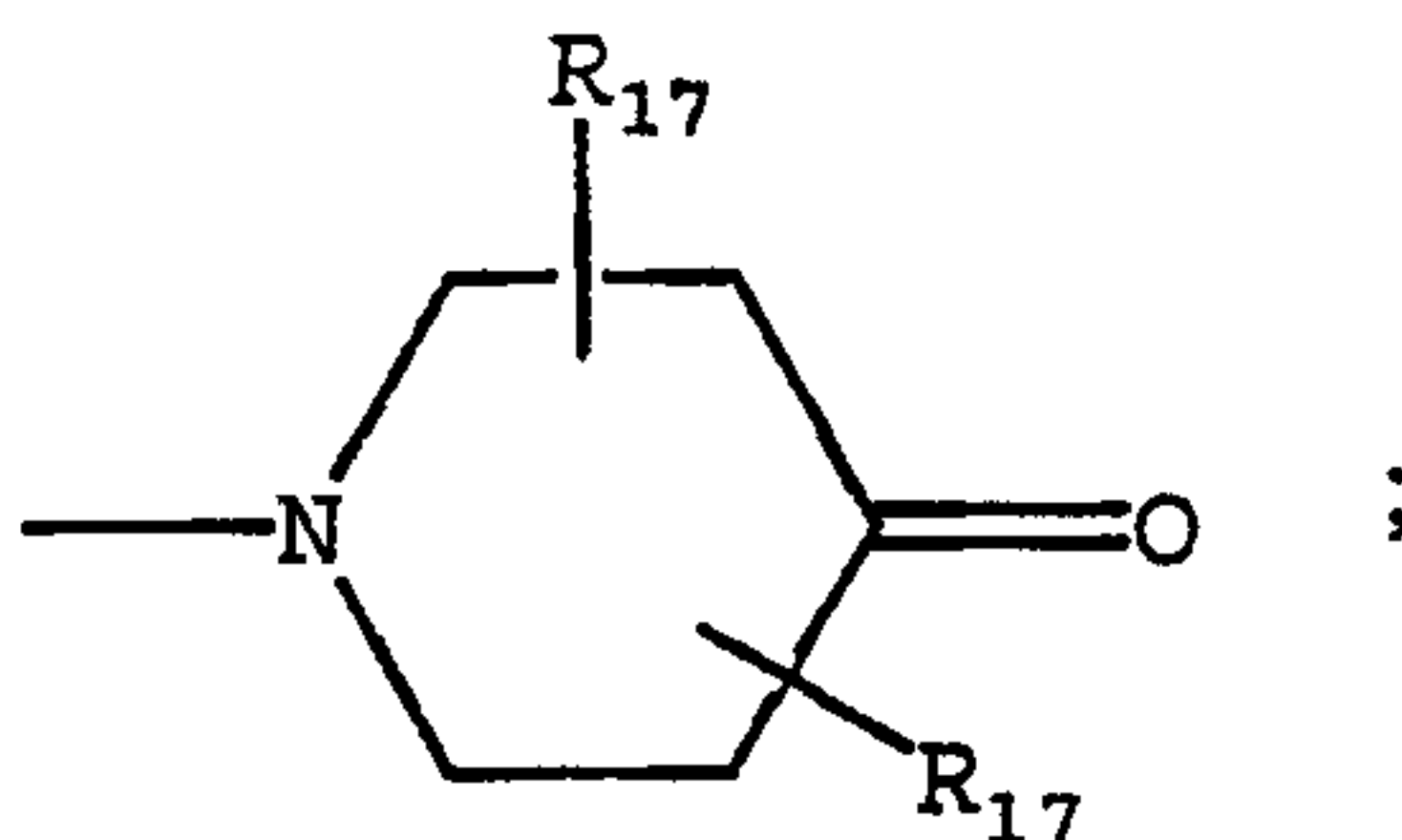
PCT/US02/04608

63



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

5 wherein X is $N(CH_3)_2$ or

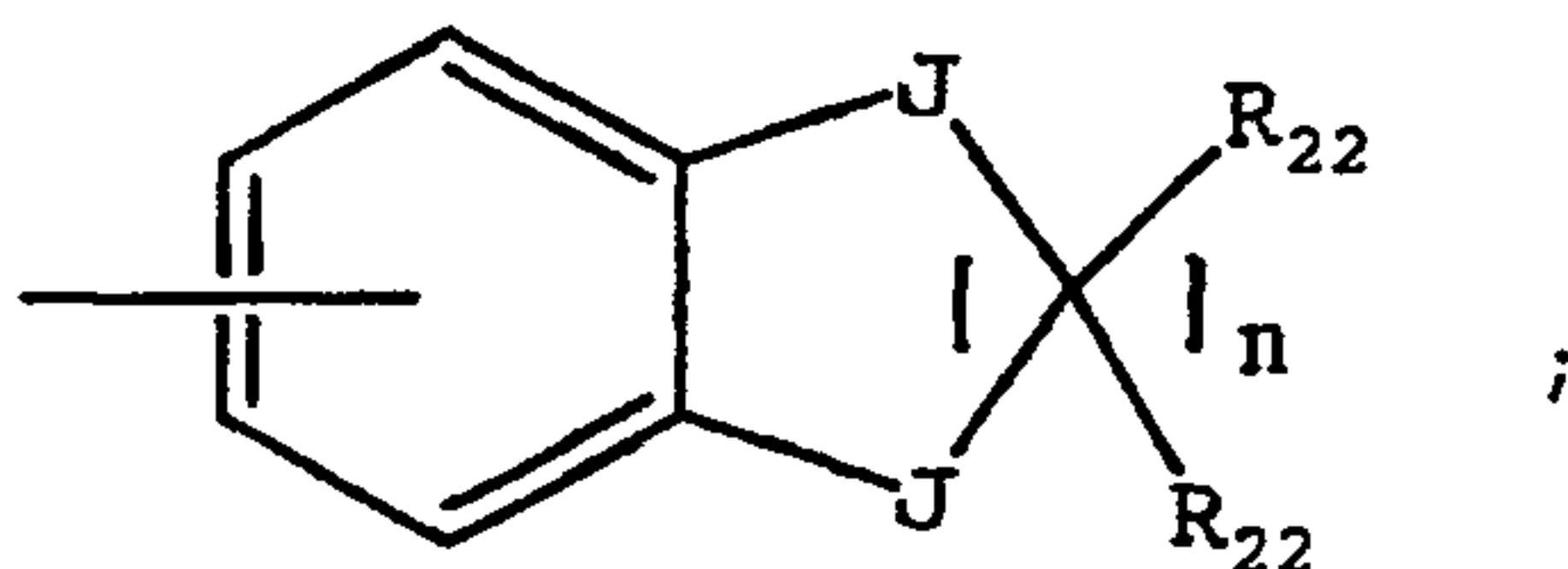


10 wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3-C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2 ;

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

15

wherein Q_1 is

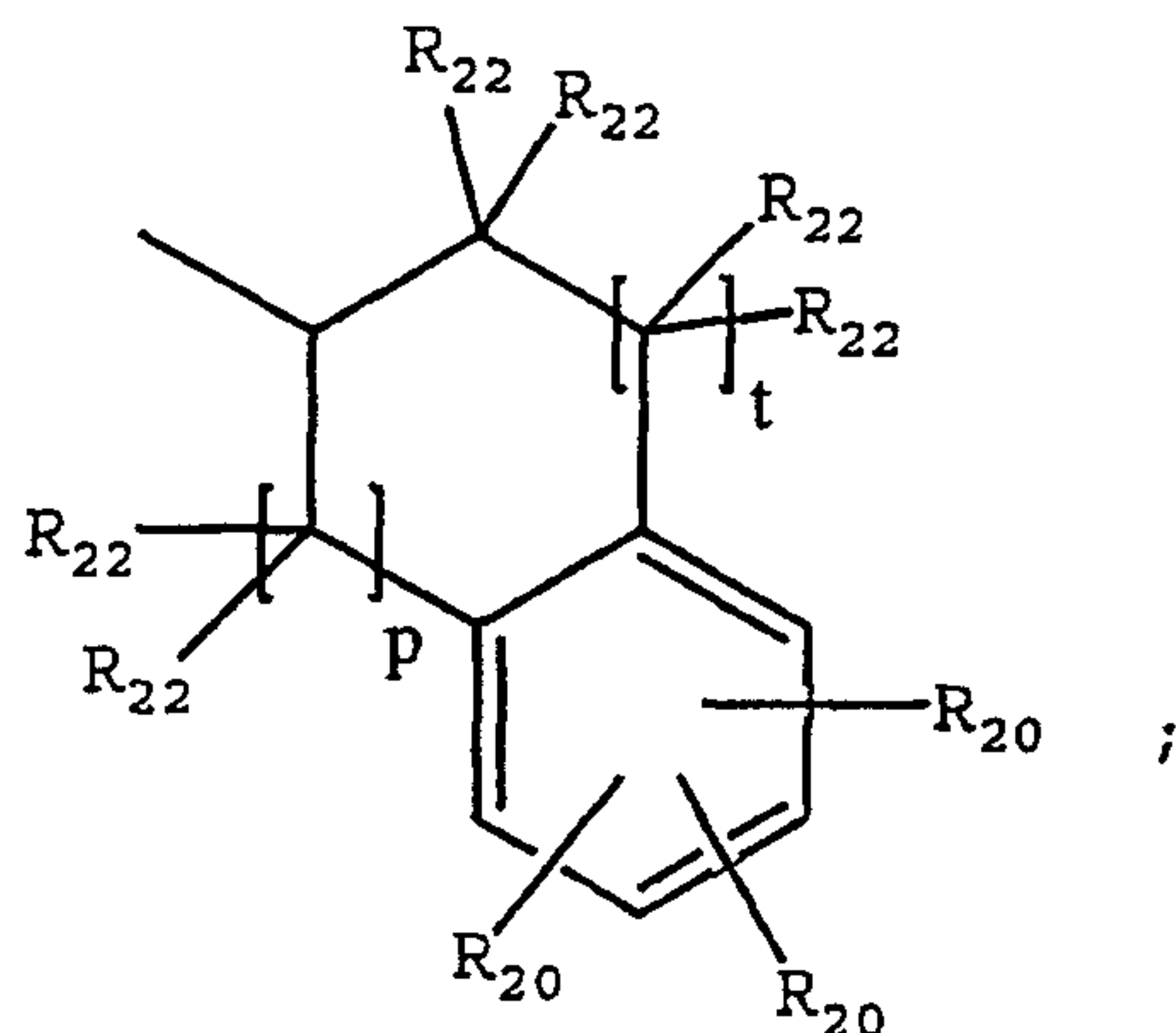


WO 02/060392

PCT/US02/04608

64

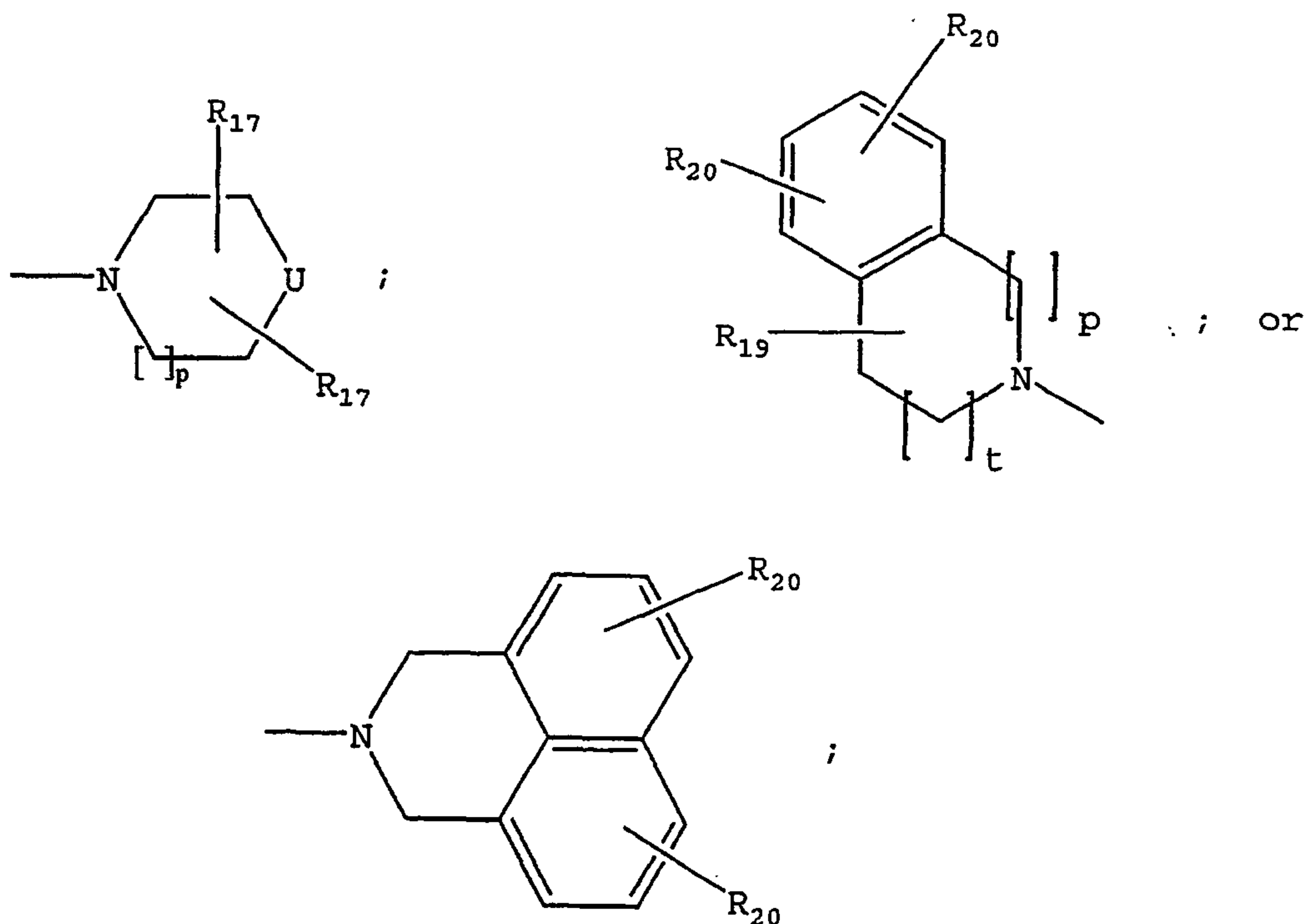
wherein Q_2 is



5 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
 10 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 $NR_{14}R_{15}$;



WO 02/060392

PCT/US02/04608

65

wherein R_{14} is H, straight chained or branched C_1 - C_6 alkyl, $(CH_2)_q$ -O- $(CH_2)_m$ -CH₃, C_3 - C_6 cycloalkyl, or $(C(R_{19})_2)_m$ -Z;

5

wherein R_{15} is straight chained or branched C_3 - C_6 alkyl, $(CH_2)_q$ -O- $(CH_2)_m$ -CH₃, C_3 - C_6 cycloalkyl, or $(C(R_{19})_2)_m$ -Z;

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

10

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- $(CH_2)_m$ -CH₃;

15

wherein each R_{17} is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, 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- $(CH_2)_m$ -CH₃;

25

wherein R_{18} is straight chained or branched C_1 - C_6 alkyl, - $(CH_2)_m$ -Z, or $(CH_2)_q$ -O- $(CH_2)_m$ -CH₃;

30

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 -
5 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;

10

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 -
15 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;

20 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;

25

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

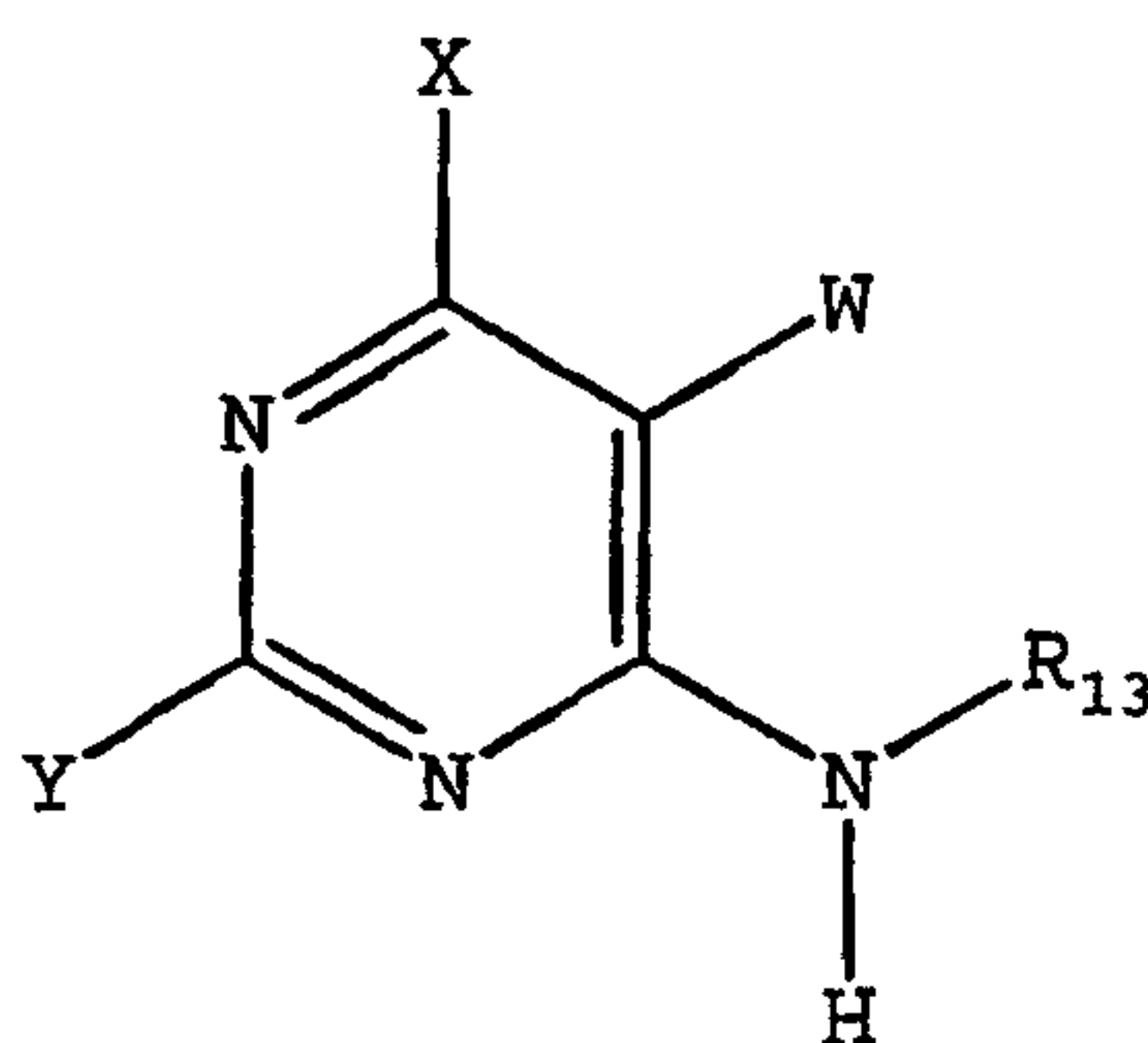
30 a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:

WO 02/060392

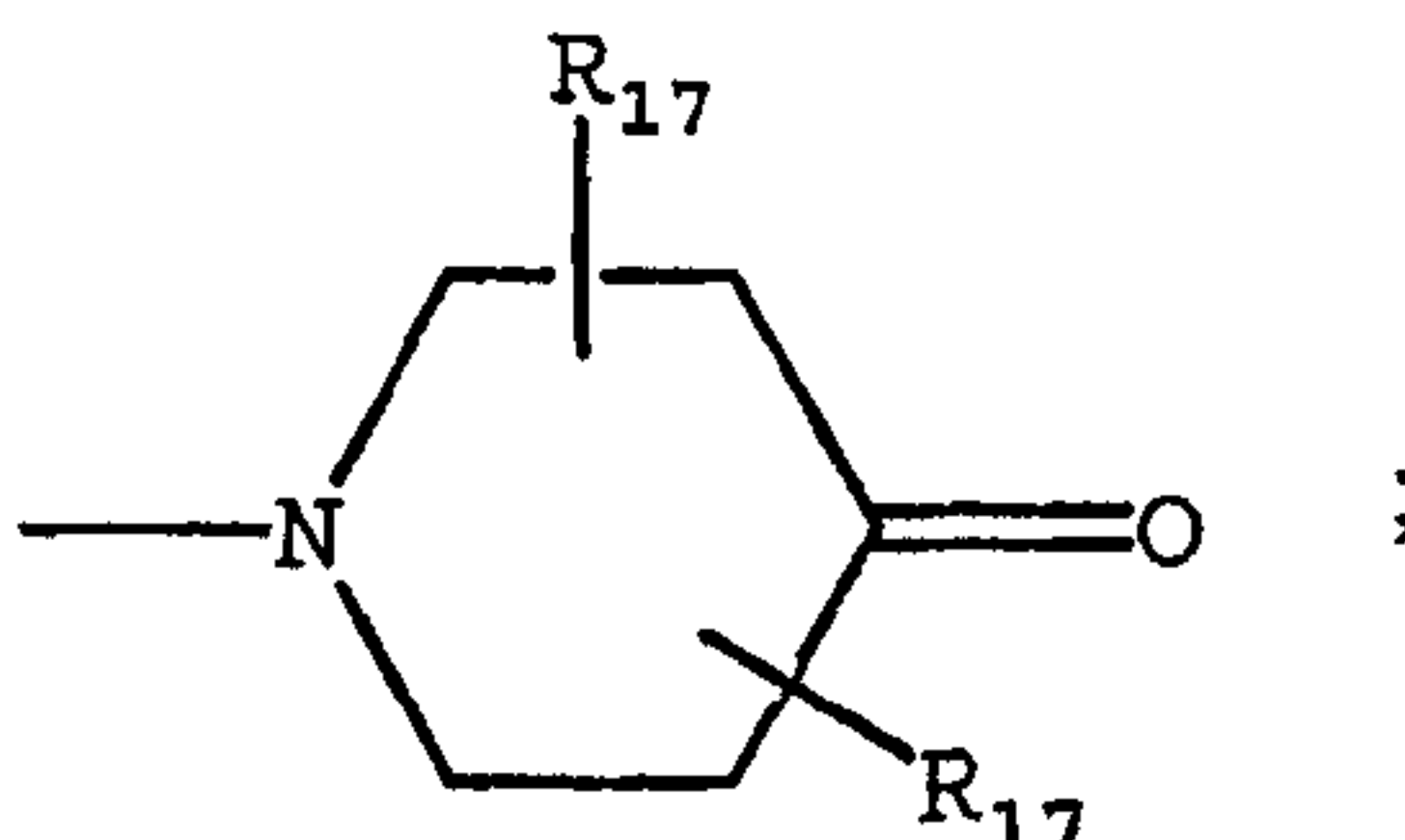
PCT/US02/04608

67



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

wherein X is $N(CH_3)_2$ or



10

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

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

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

20

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
 5 chained or branched C_2 - C_7 alkynyl, C_5 - C_7 cycloalkenyl, -
 $(CH_2)_m$ -Z, or $(CH_2)_q$ -O- $(CH_2)_m$ -CH₃;

wherein each R_{17} is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁,
 -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or
 10 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- $(CH_2)_m$ -CH₃;

15 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
 20 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;

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

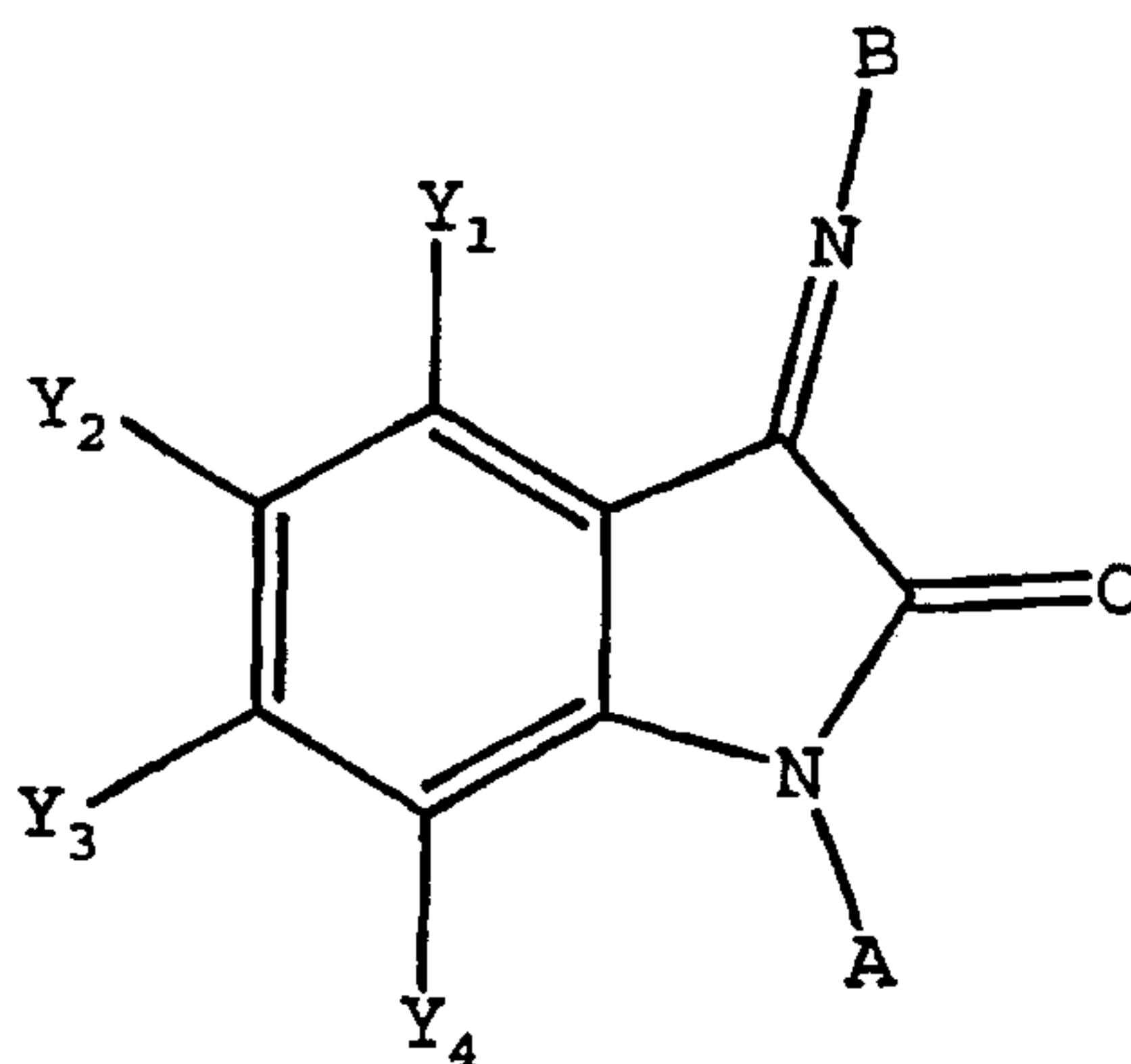
wherein each n is an integer from 1 to 4 inclusive;

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

30

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;

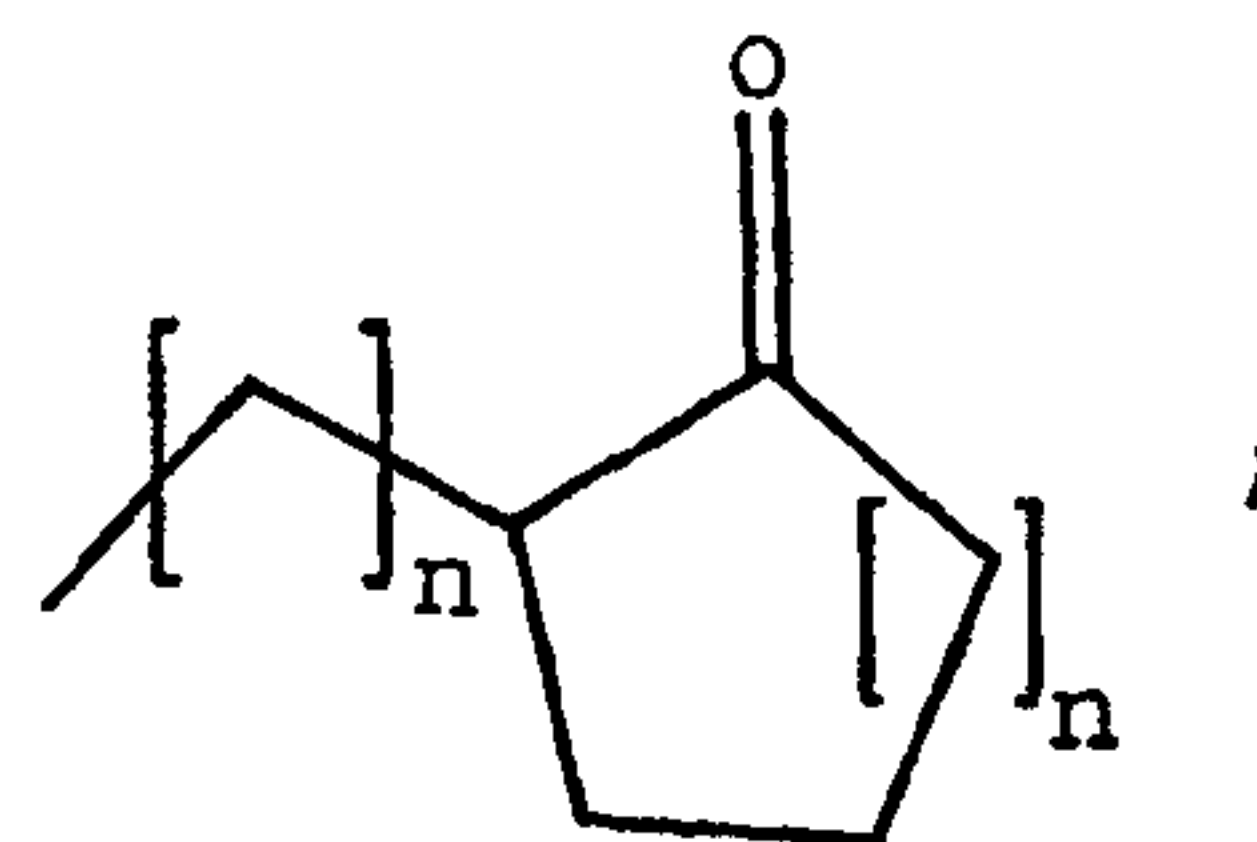
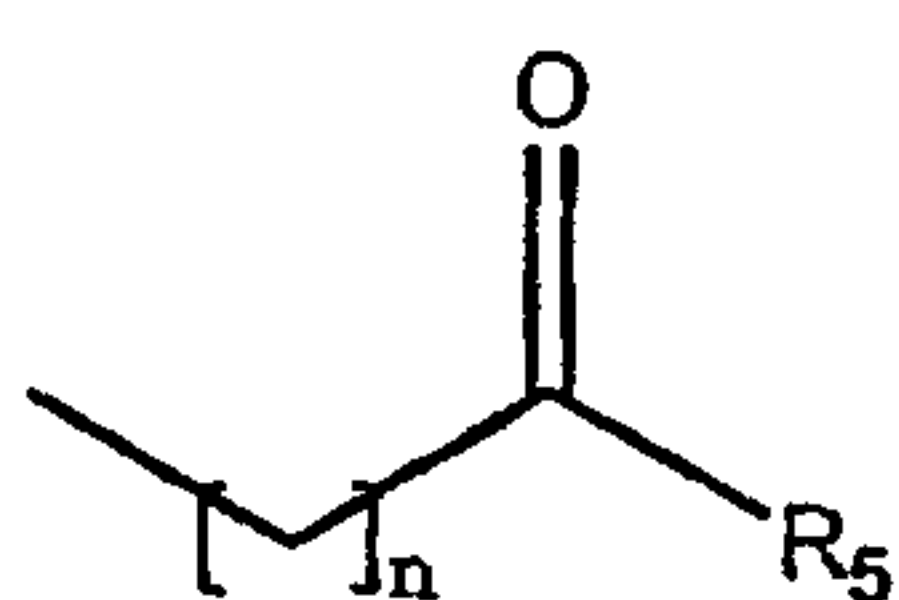
WO 02/060392

PCT/US02/04608

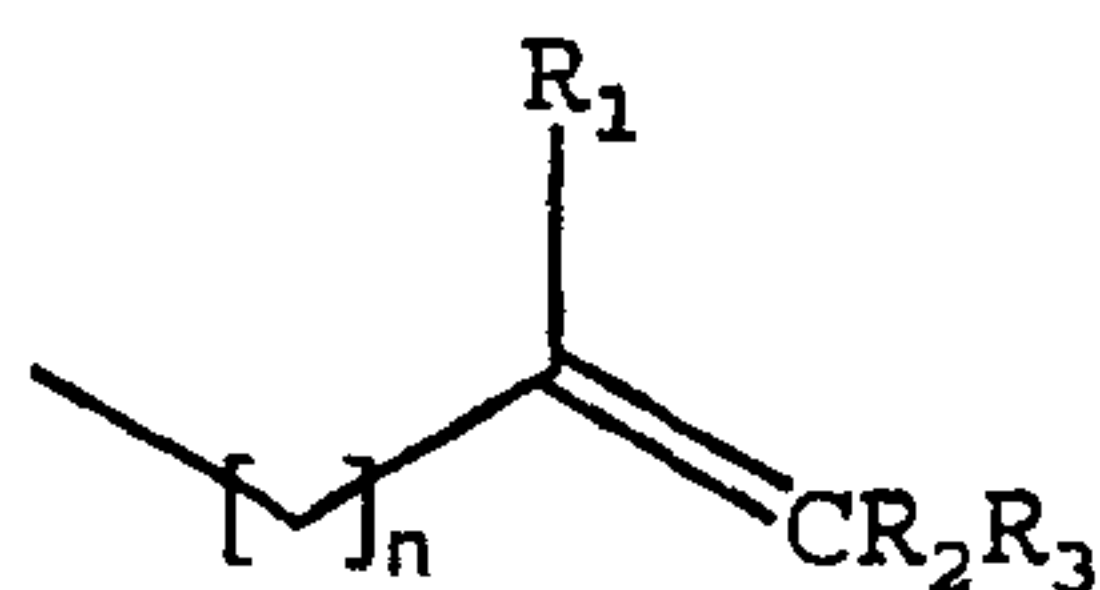
70

wherein A is A', Q₃, Q₄, Q₅, straight chained or
 branched C₁-C₇ alkyl, aryl, heteroaryl, aryl(C₁-
 C₆)alkyl, heteroaryl(C₁-C₆)alkyl, aryl substituted
 5 with an aryl or heteroaryl, heteroaryl substituted
 with an aryl or heteroaryl; or (CHR₁₇) - (CHR₁₇)_n-Z;

wherein A' is



10

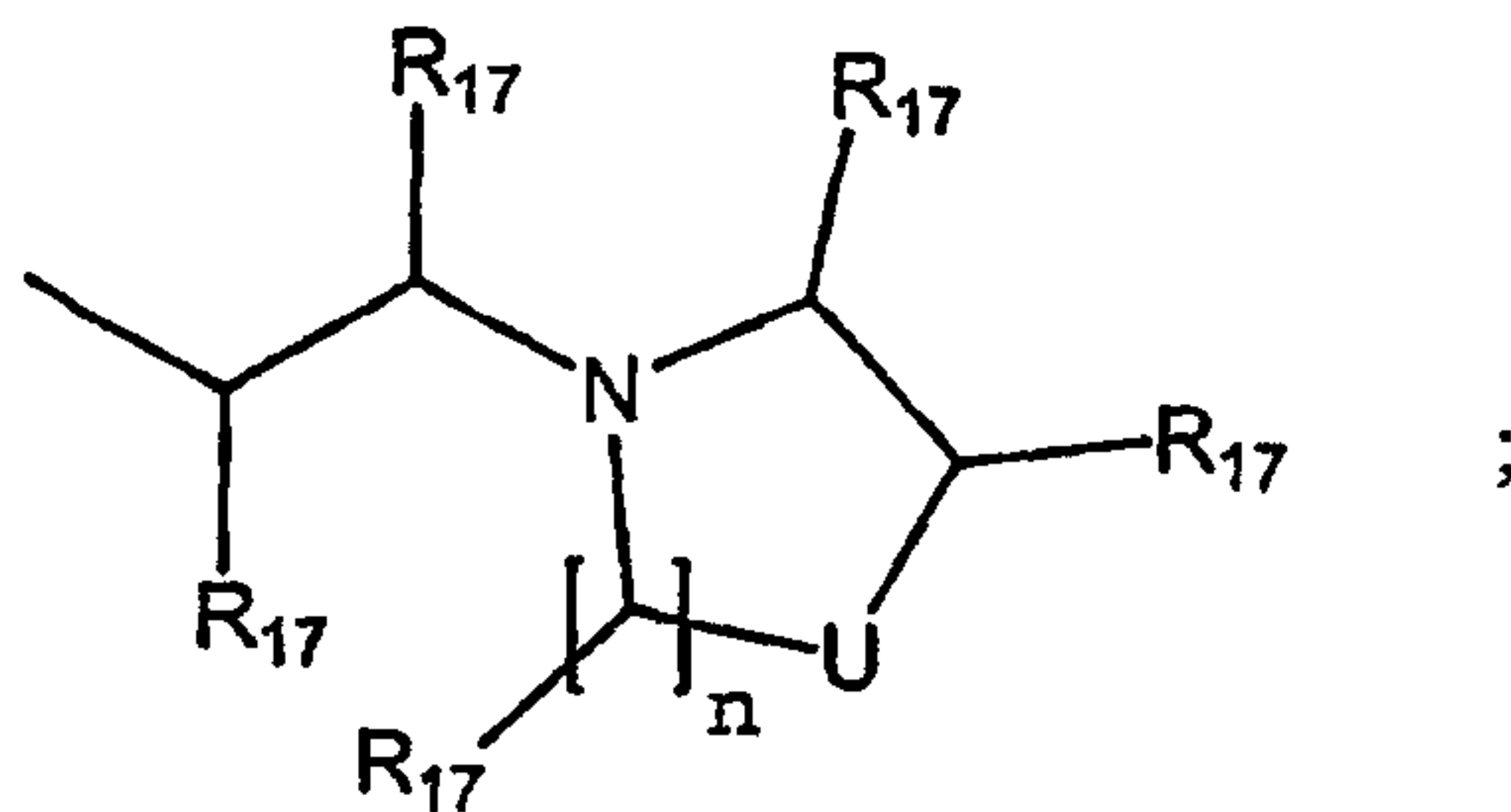


; or



wherein Q₃ is

15

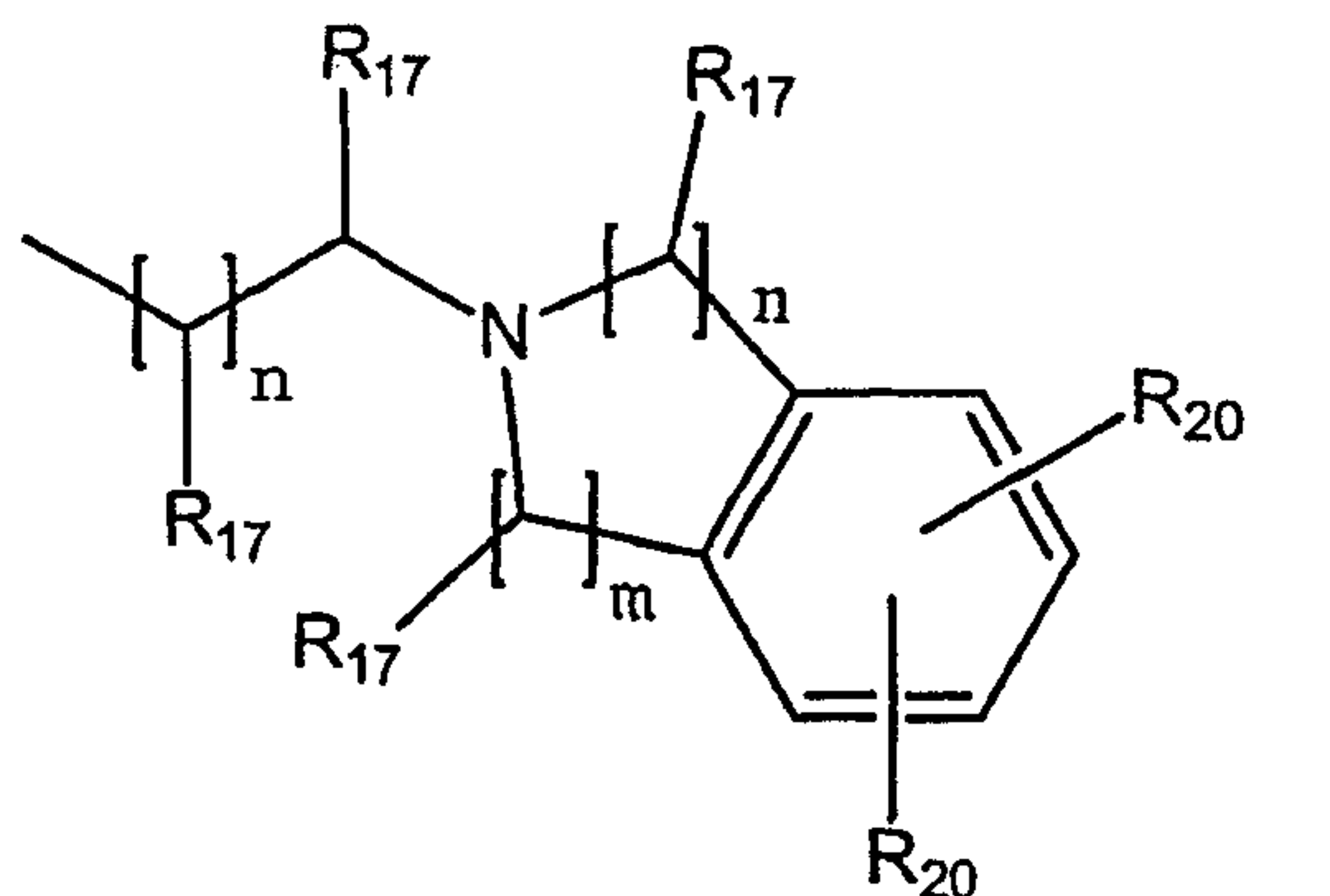


WO 02/060392

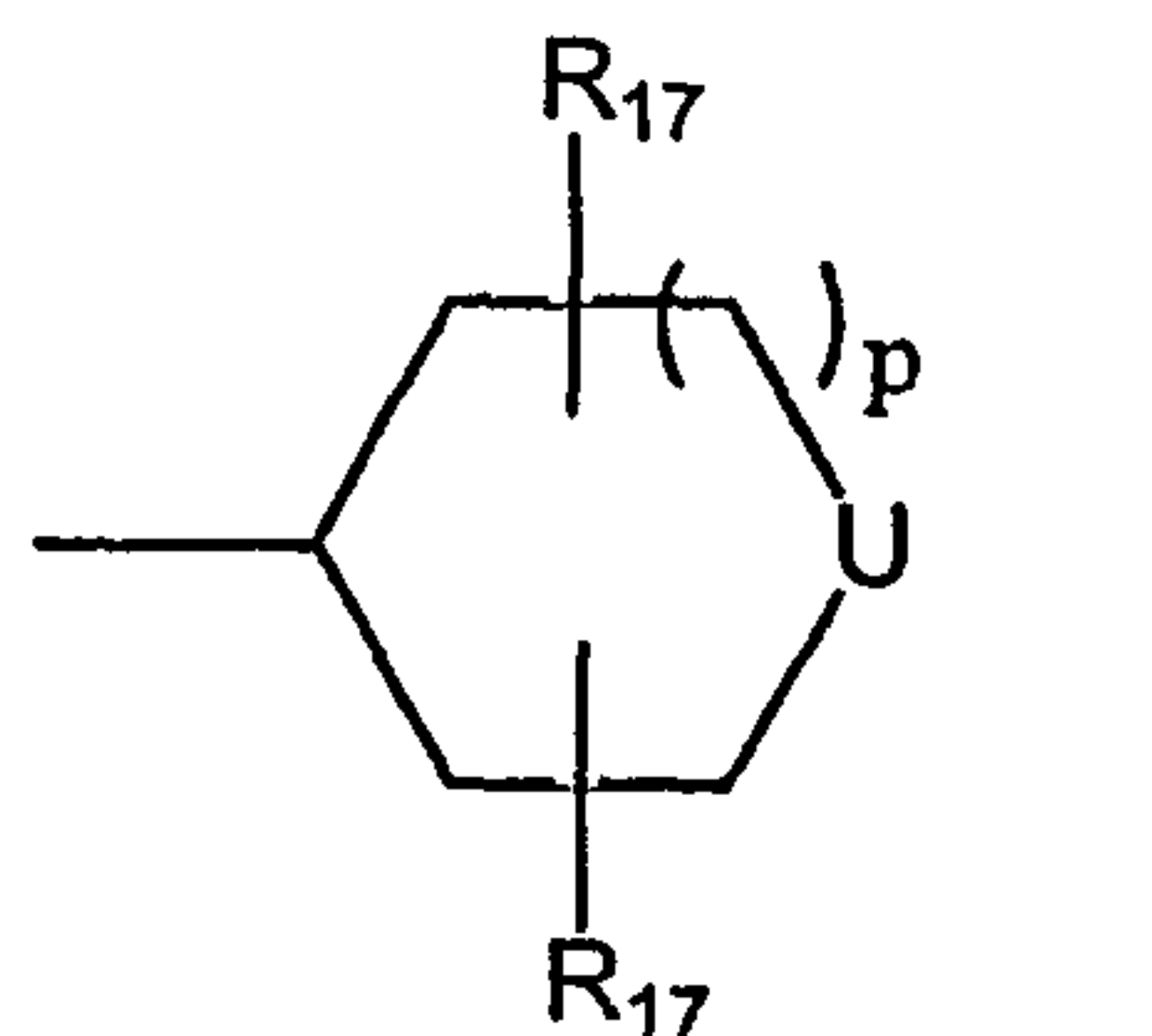
PCT/US02/04608

71

5 wherein Q_4 is



wherein Q_5 is



10

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;

15

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;

20

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;

5 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 $(CH_2)_n-O-(CH_2)_m-CH_3$;

15 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; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R_{20} groups present
20 on adjacent carbon atoms can join together to form a methylenedioxy group;

25 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;

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

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

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

15 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;

20

25 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;

WO 02/060392

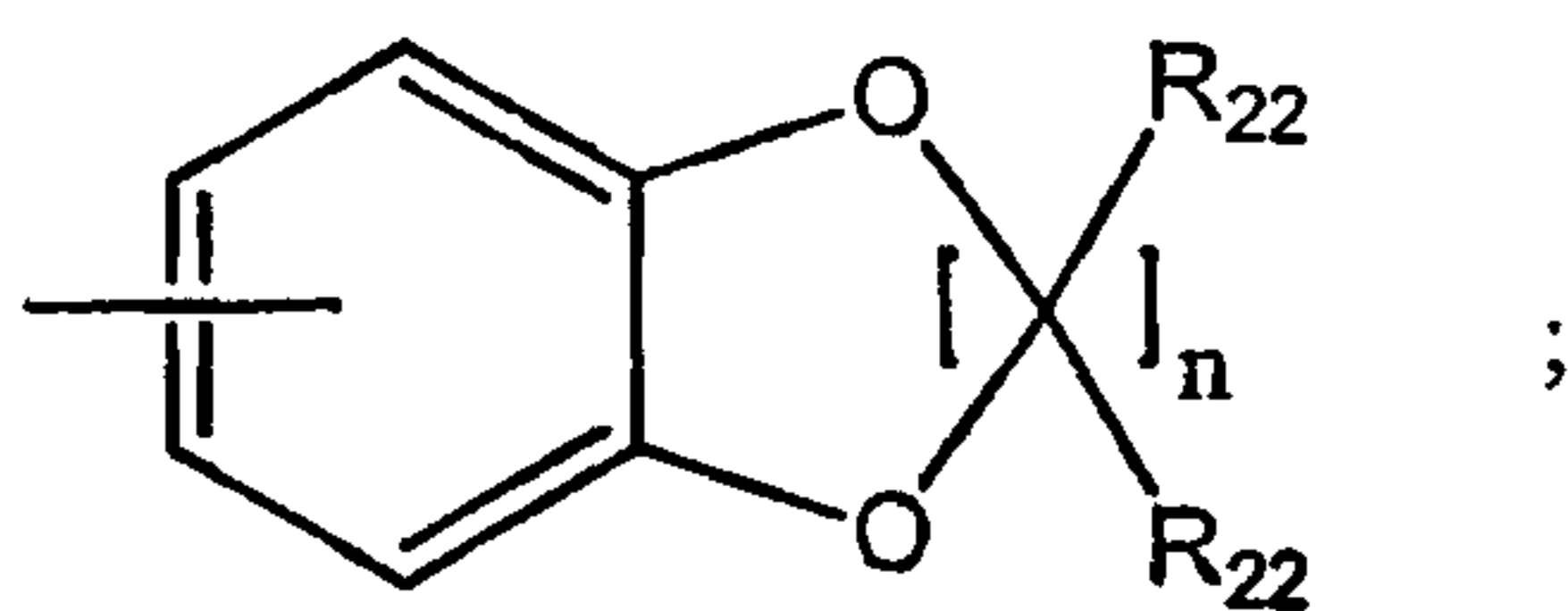
PCT/US02/04608

74

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

5

wherein Q_6 is



10

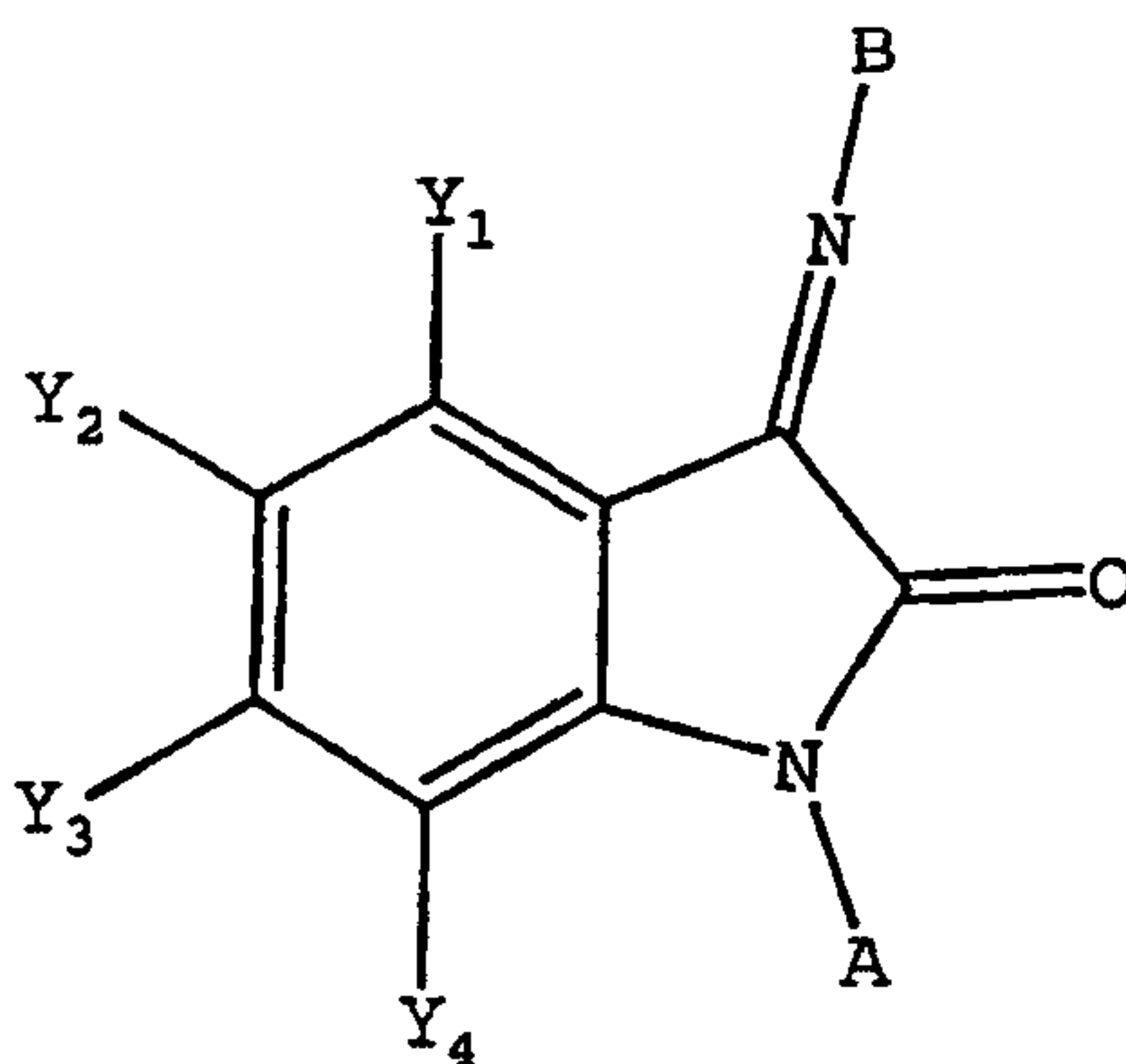
wherein each R_{22} is independently H, F, Cl, or straight chained or branched C_1 - C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

15

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:

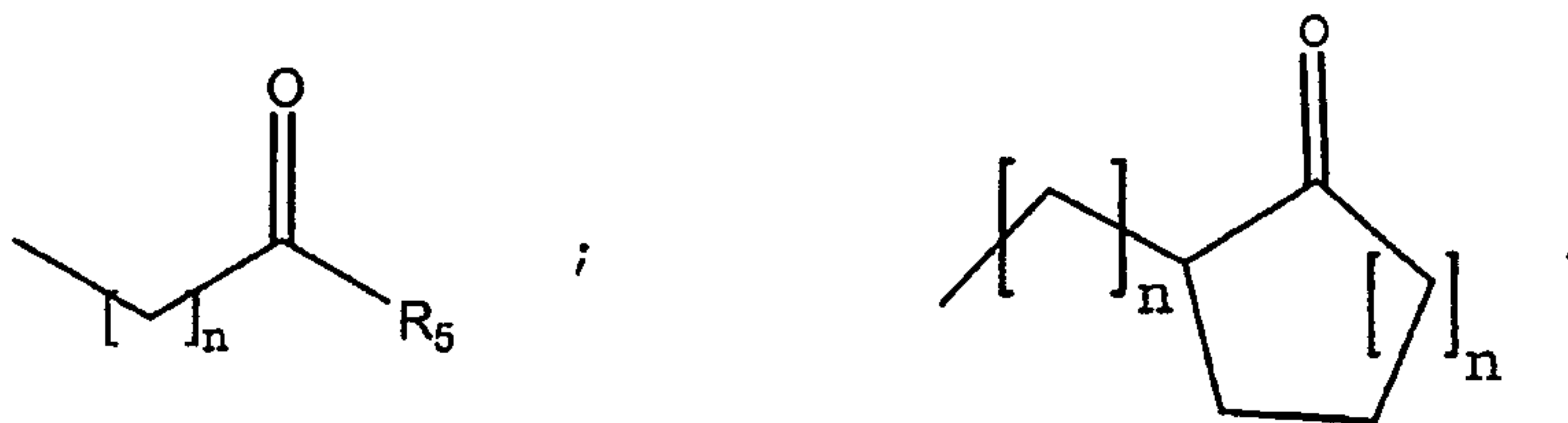
20



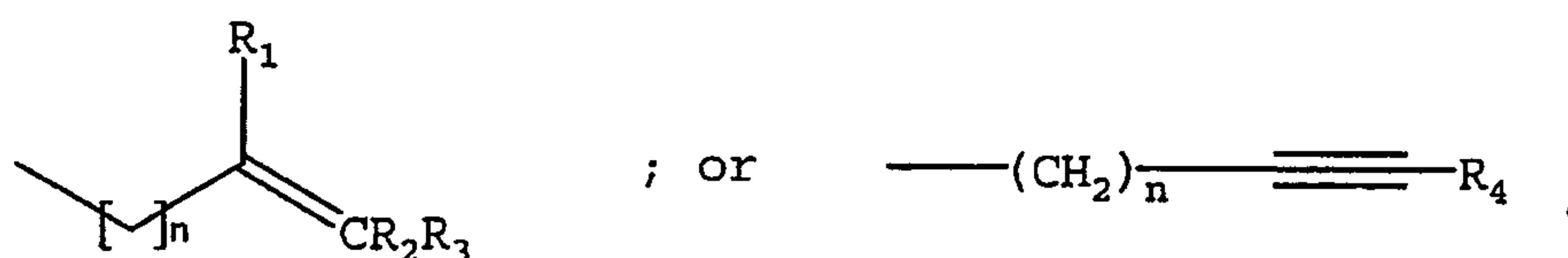
wherein each of Y_1 , Y_2 , Y_3 , and Y_4 is independently -
H; straight chained or branched C_1 - C_7 alkyl,
monofluoroalkyl or polyfluoroalkyl; straight chained
5 or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7
cycloalkyl, or C_5 - C_7 cycloalkenyl; -F, -Cl, -Br, or -
I; -NO₂; -N₃; -CN; -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -
N(R₄)₂, -CON(R₄)₂, or -COOR₄; aryl or heteroaryl; or
10 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
15 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
20 heteroaryl(C_1 - C_6)alkyl;



wherein A' is



5 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
10 alkyl, -F, -Cl, -Br, -I, - NO_2 , -CN, -OR₆ aryl or
 heteroaryl;

 wherein R_5 is straight chained or branched C_1 - C_7
 alkyl, -N(R_4)₂, -OR₆ or aryl;

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

 wherein B is aryl, or heteroaryl; provided however,
20 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;

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

 or a pharmaceutically acceptable salt thereof.

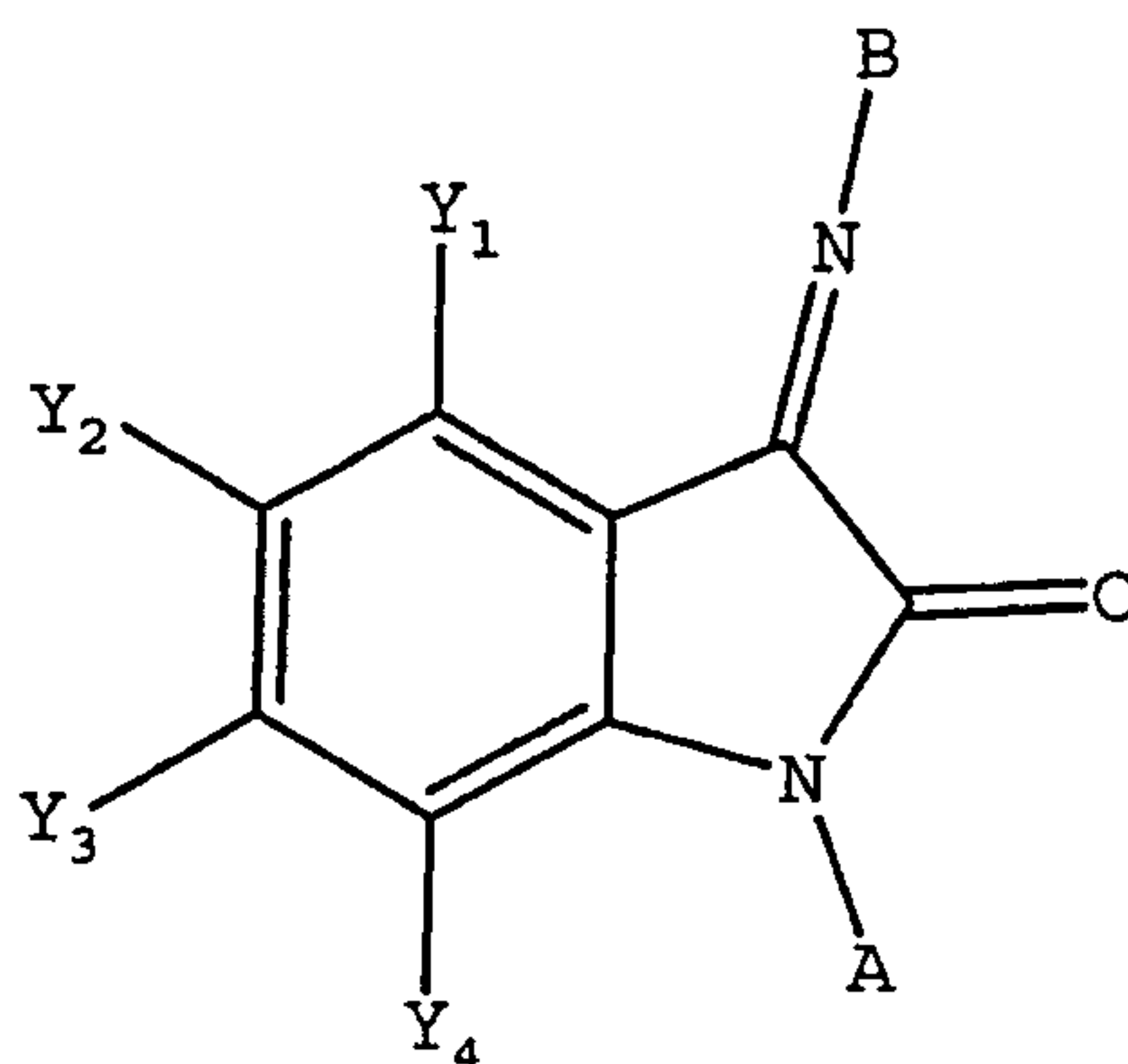
30 The invention provides a method of treating a subject
 suffering from depression which comprises administering
 to the subject an amount of compound effective to treat

WO 02/060392

PCT/US02/04608

77

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



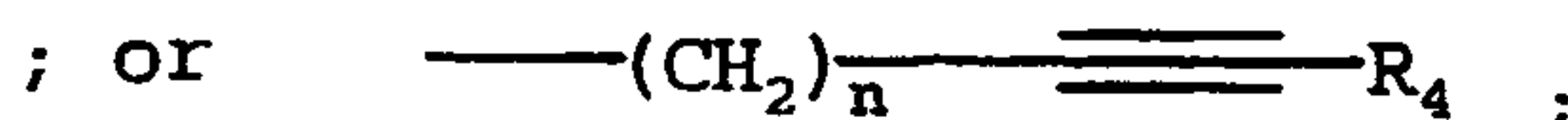
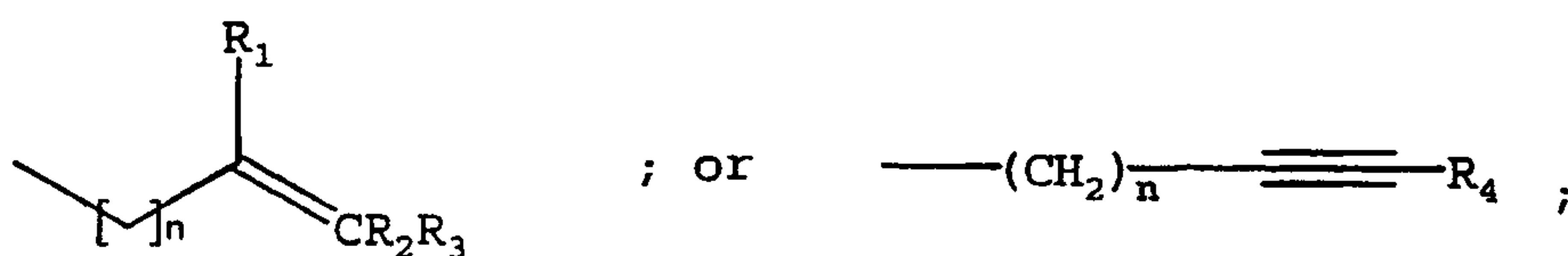
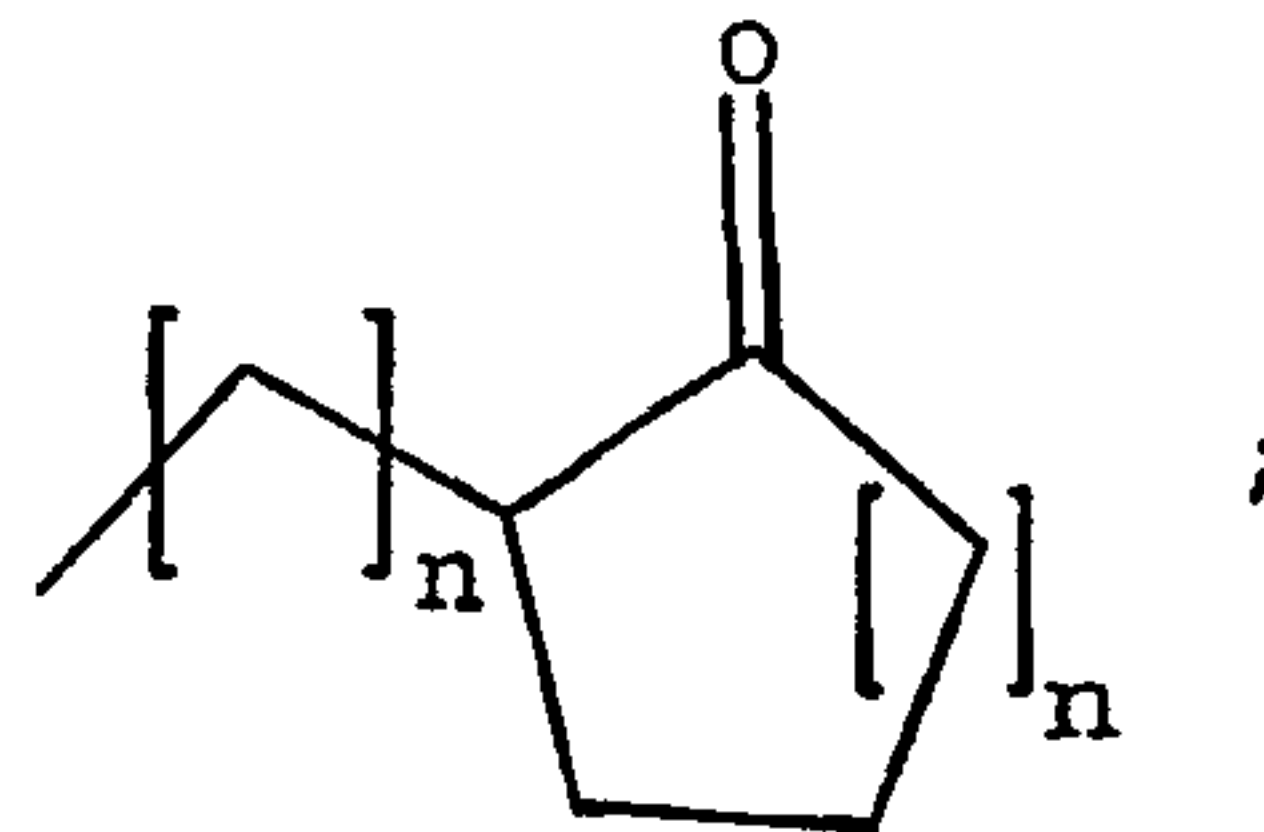
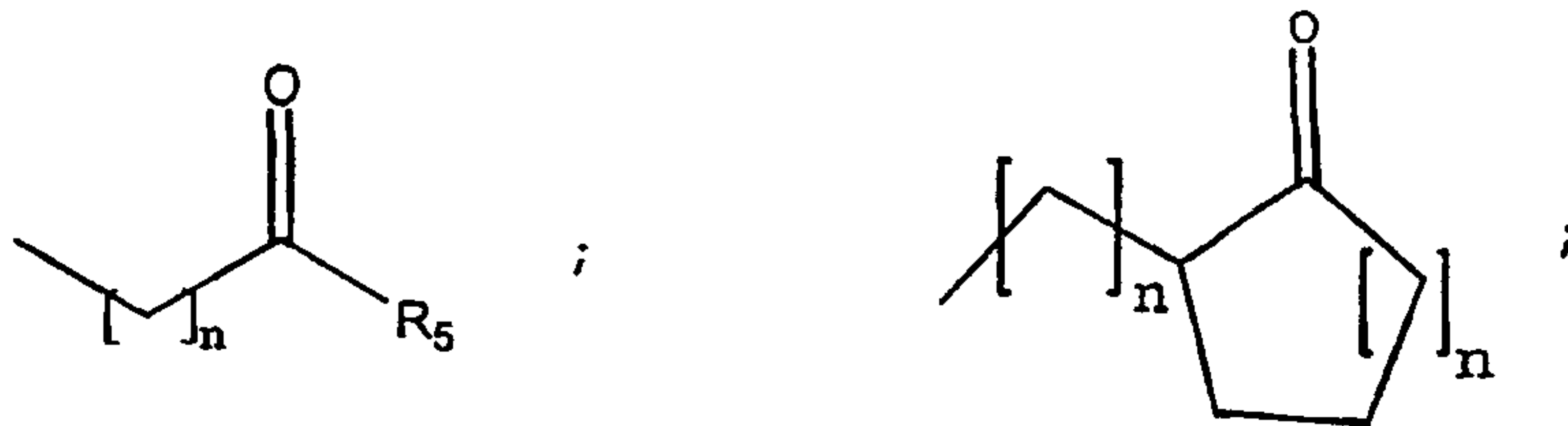
- 5 wherein each of Y_1 , Y_2 , Y_3 , and Y_4 is independently -
H; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained
or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7
10 cycloalkyl, or C_5 - C_7 cycloalkenyl; -F, -Cl, -Br, or -
I; - NO_2 ; - N_3 ; -CN; - 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;
- 15 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;
- 20 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;

WO 02/060392

PCT/US02/04608

78

wherein A' is



5

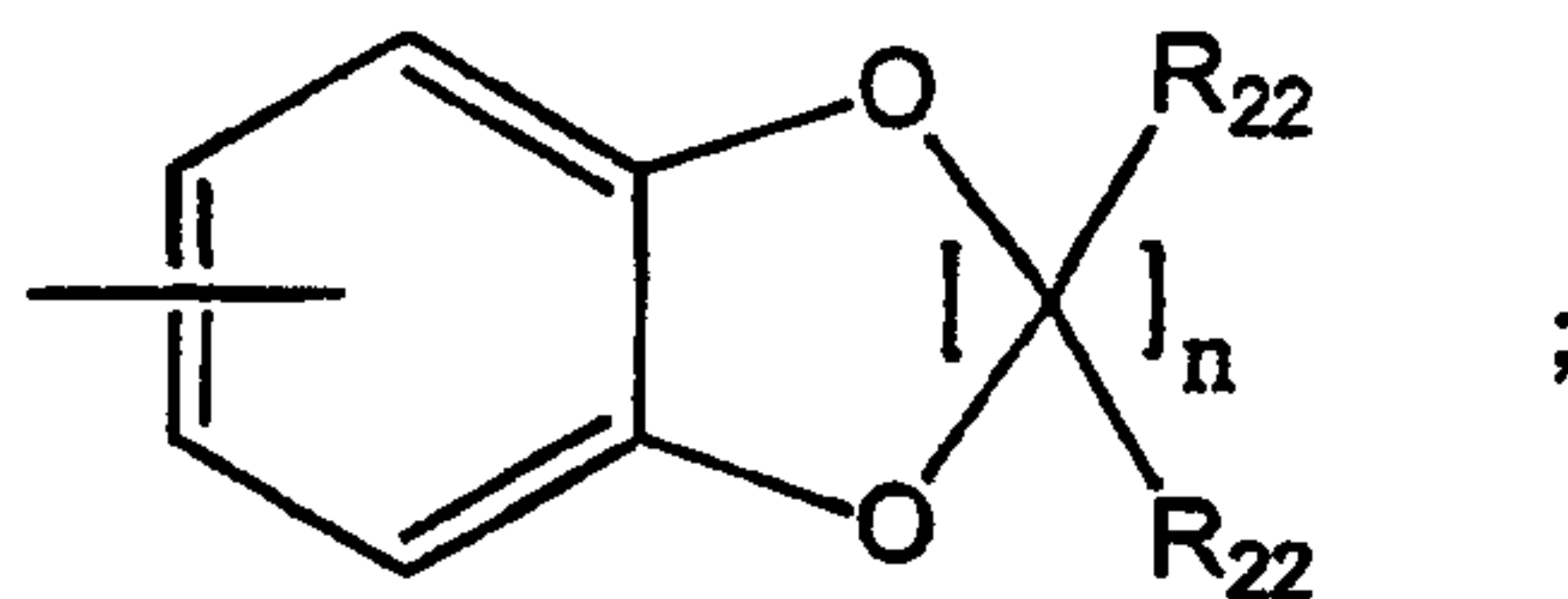
wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q₆;

10

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

15

wherein Q₆ is



20

wherein n is an integer from 1 to 4 inclusive;

WO 02/060392

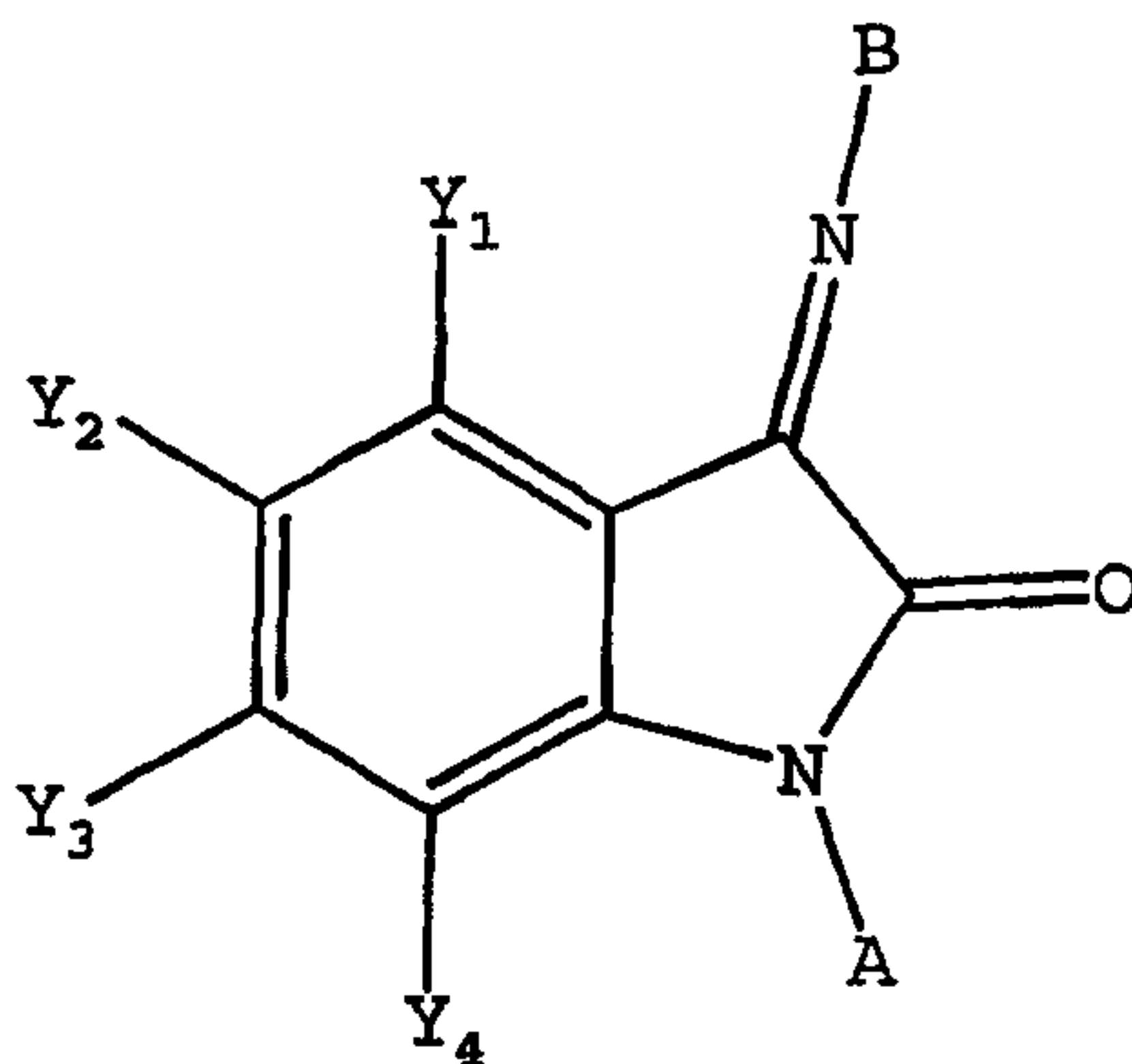
PCT/US02/04608

79

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

5 or a pharmaceutically acceptable salt thereof.

The invention provides a method of treating a subject
 10 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:



15

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
 20 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;

25

WO 02/060392

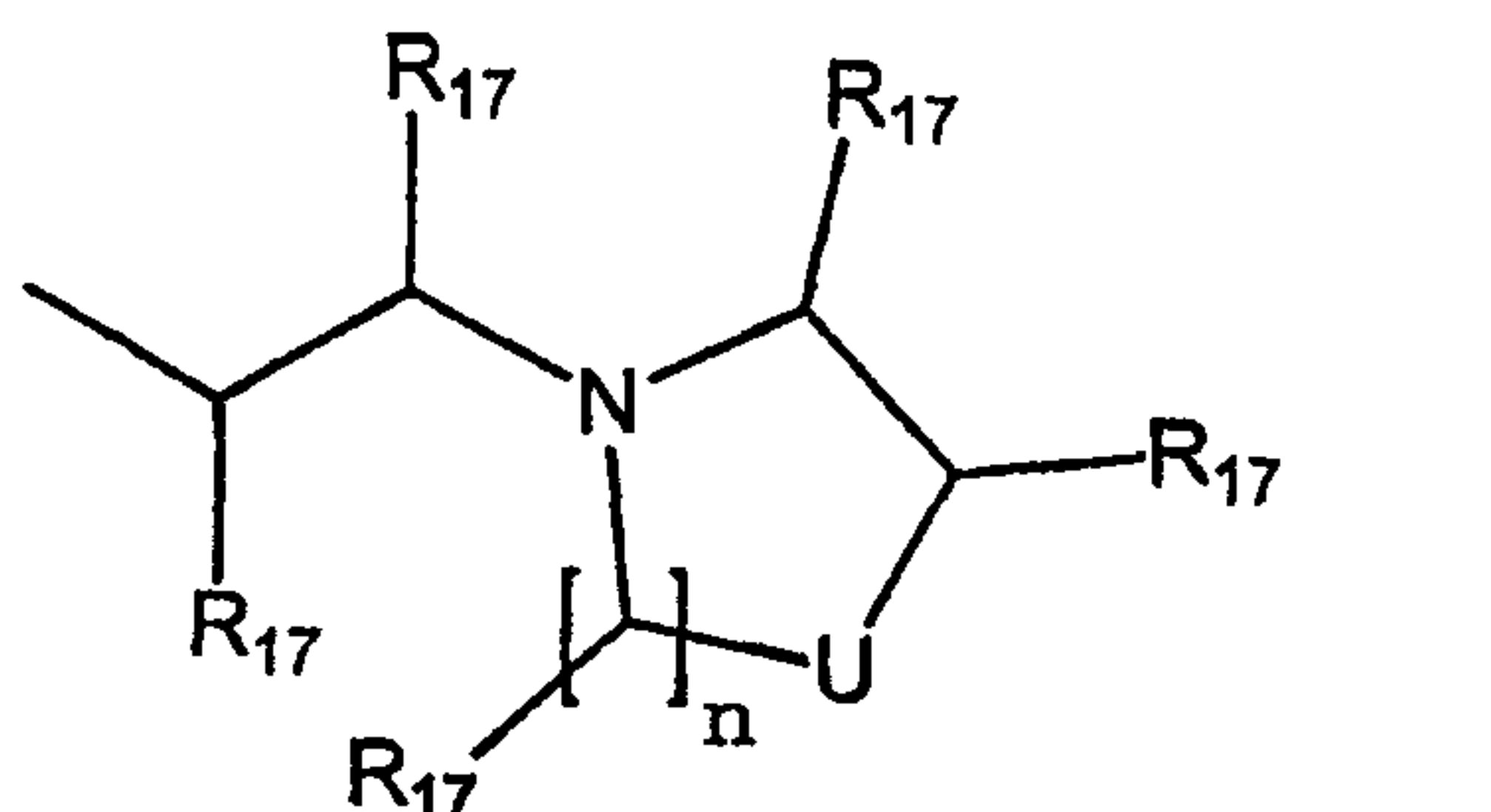
PCT/US02/04608

80

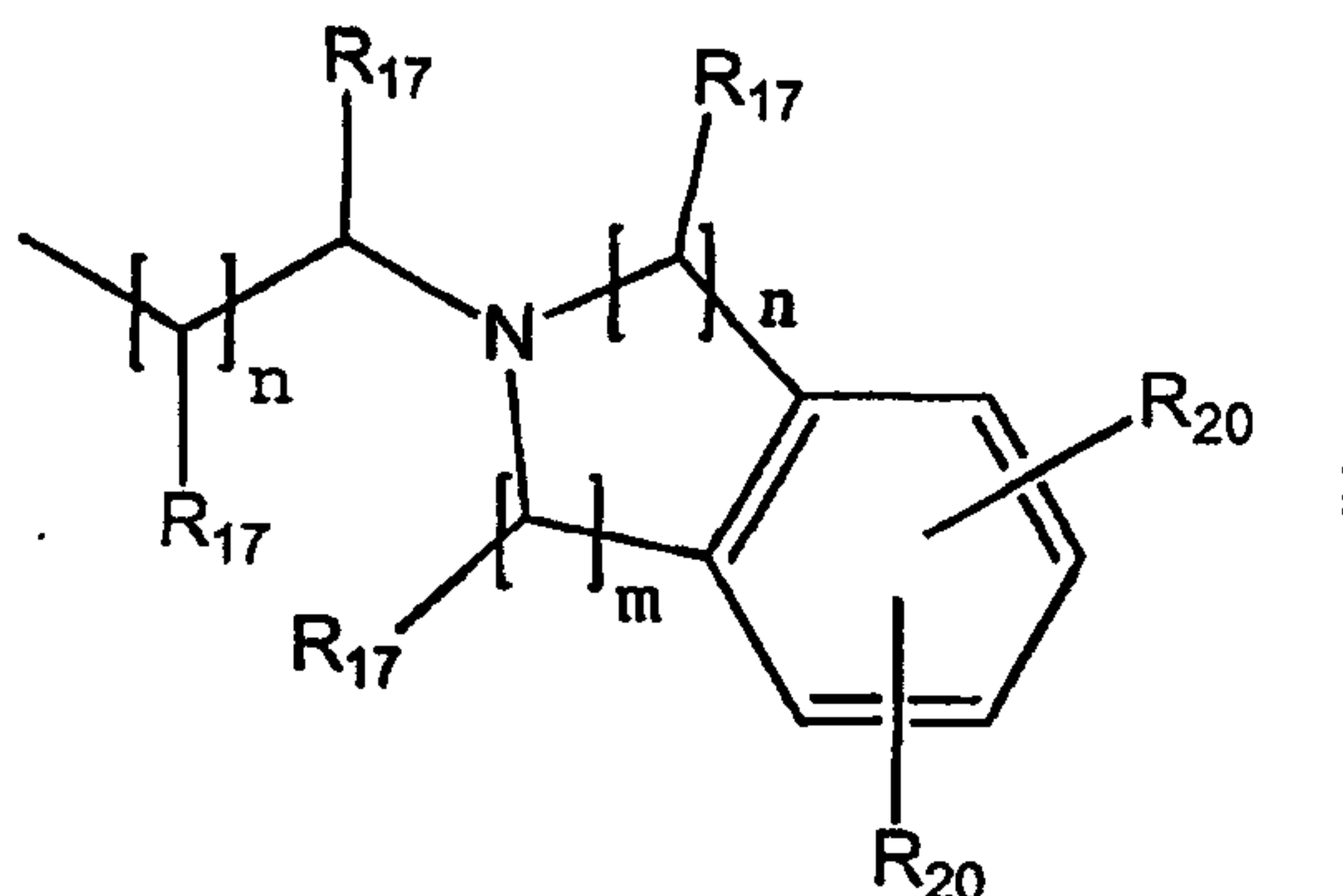
wherein each R_4 is independently -H; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, C_5 - C_7 cycloalkenyl, aryl or aryl(C_1 - C_6)alkyl;

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

wherein Q_3 is

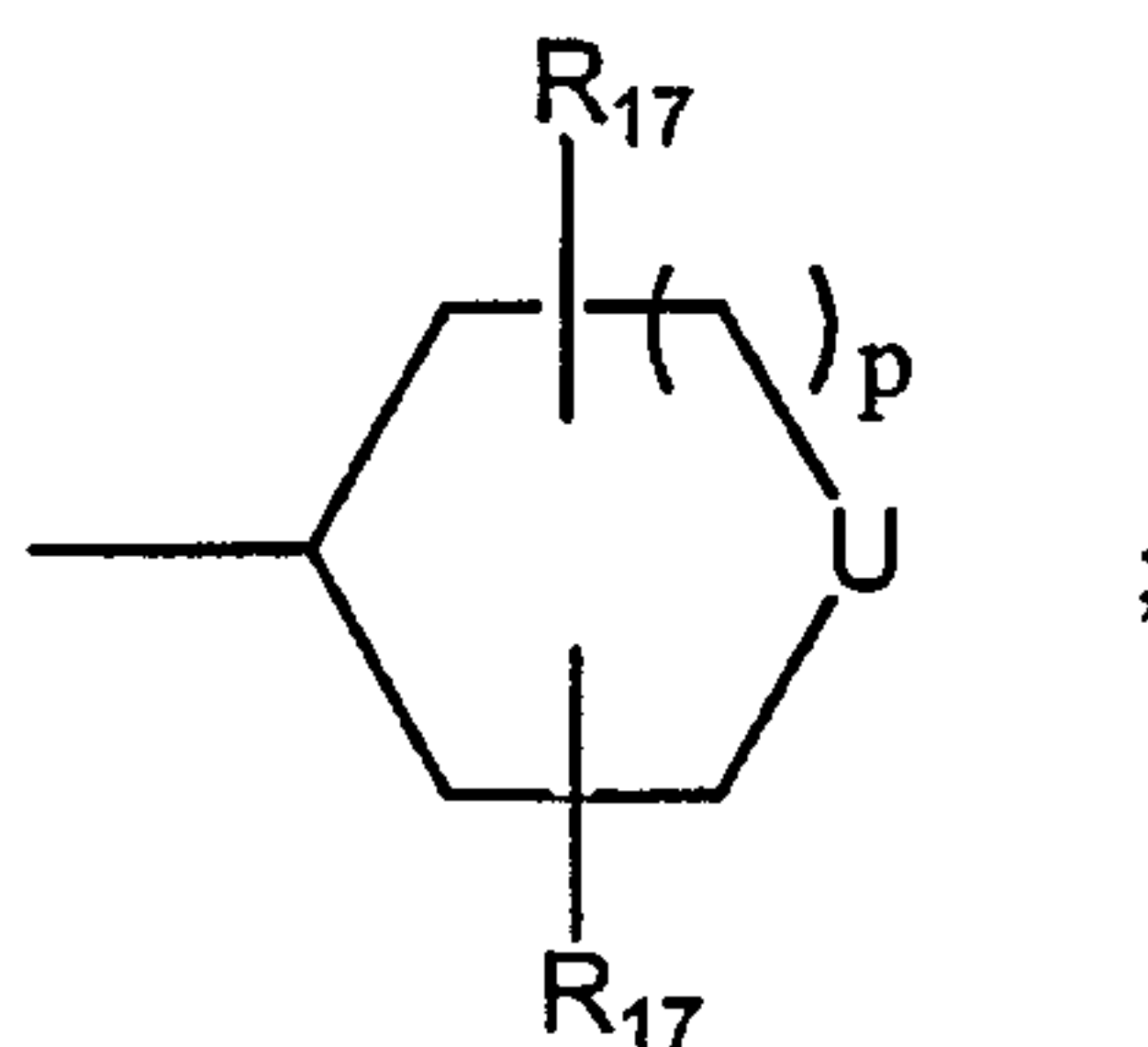


wherein Q_4 is



wherein Q_5 is

81



5 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 $(CH_2)_n-O-$
 10 $(CH_2)_m-CH_3$;

15 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; -NO₂; -N₃; -CN; -
 OR_{21} , -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R_{21})₂, -CON(R_{21})₂, or
 -COOR₂₁; aryl or heteroaryl; or two R_{20} groups present
 on adjacent carbon atoms can join together to form a
 20 methylenedioxy group;

25 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;

5

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

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

10

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;

15

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

20

wherein q is an integer from 2 to 4 inclusive;

25

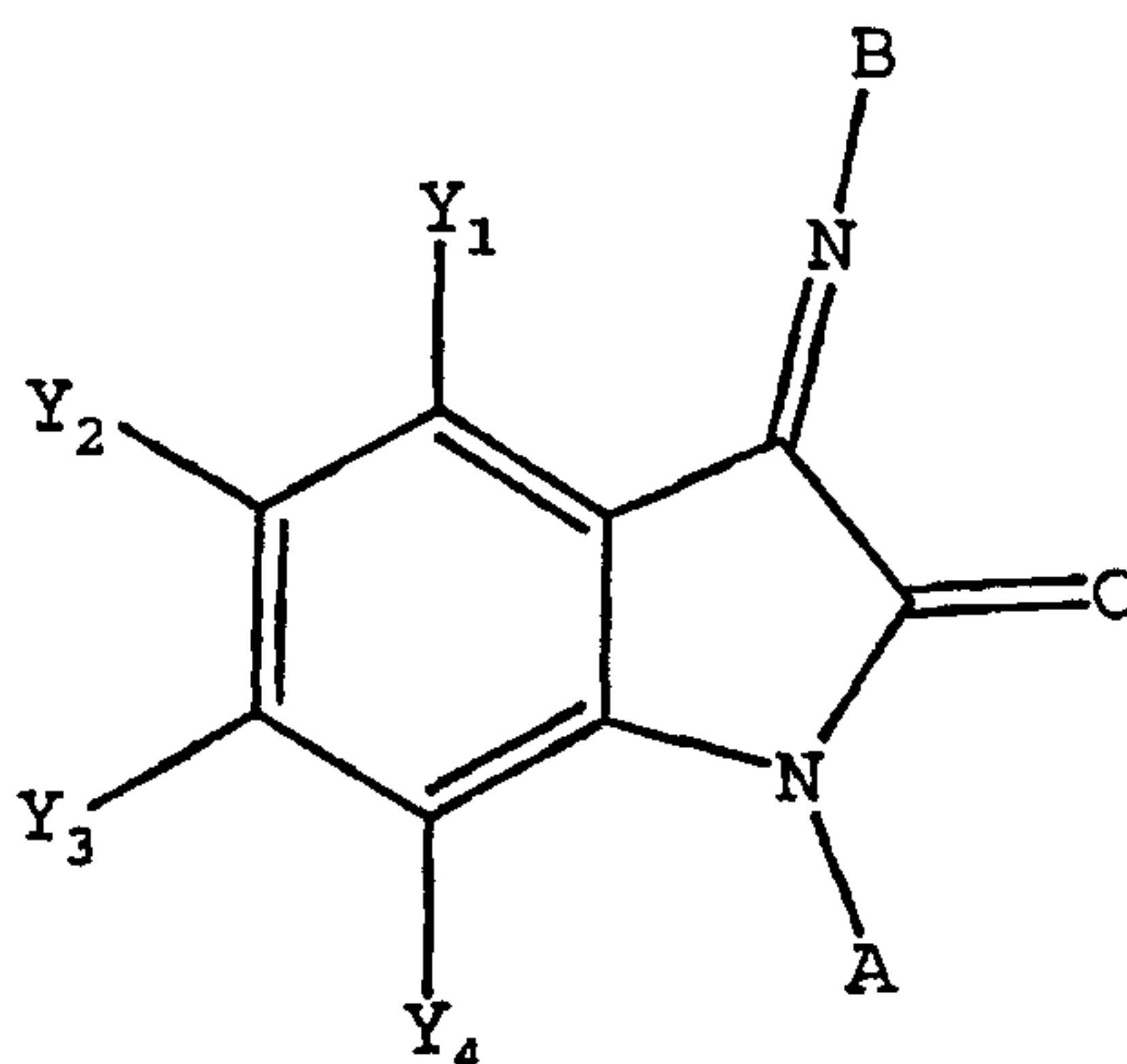
wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

30

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:

5



10

15

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;

20

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

WO 02/060392

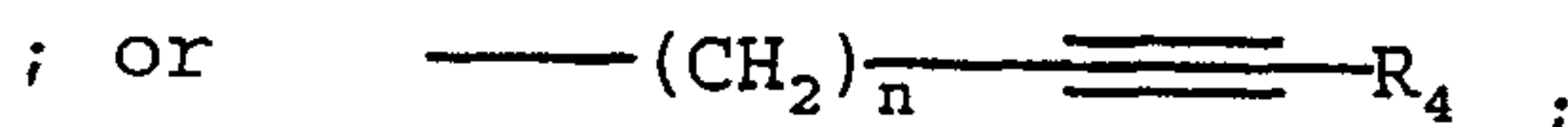
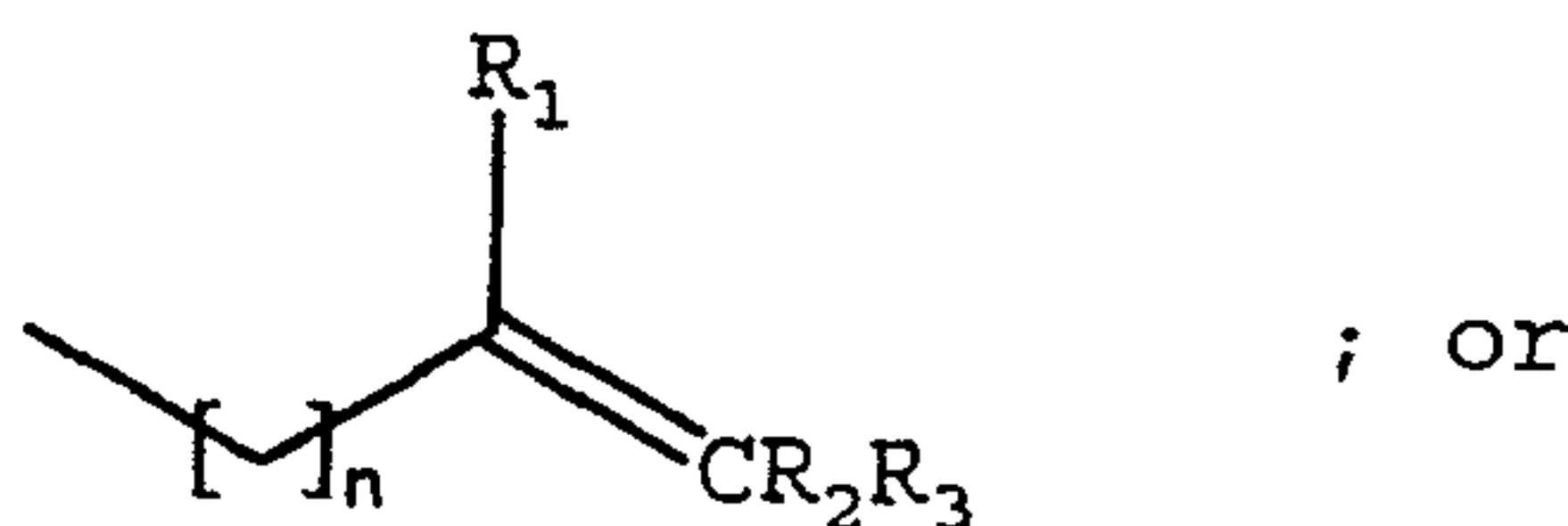
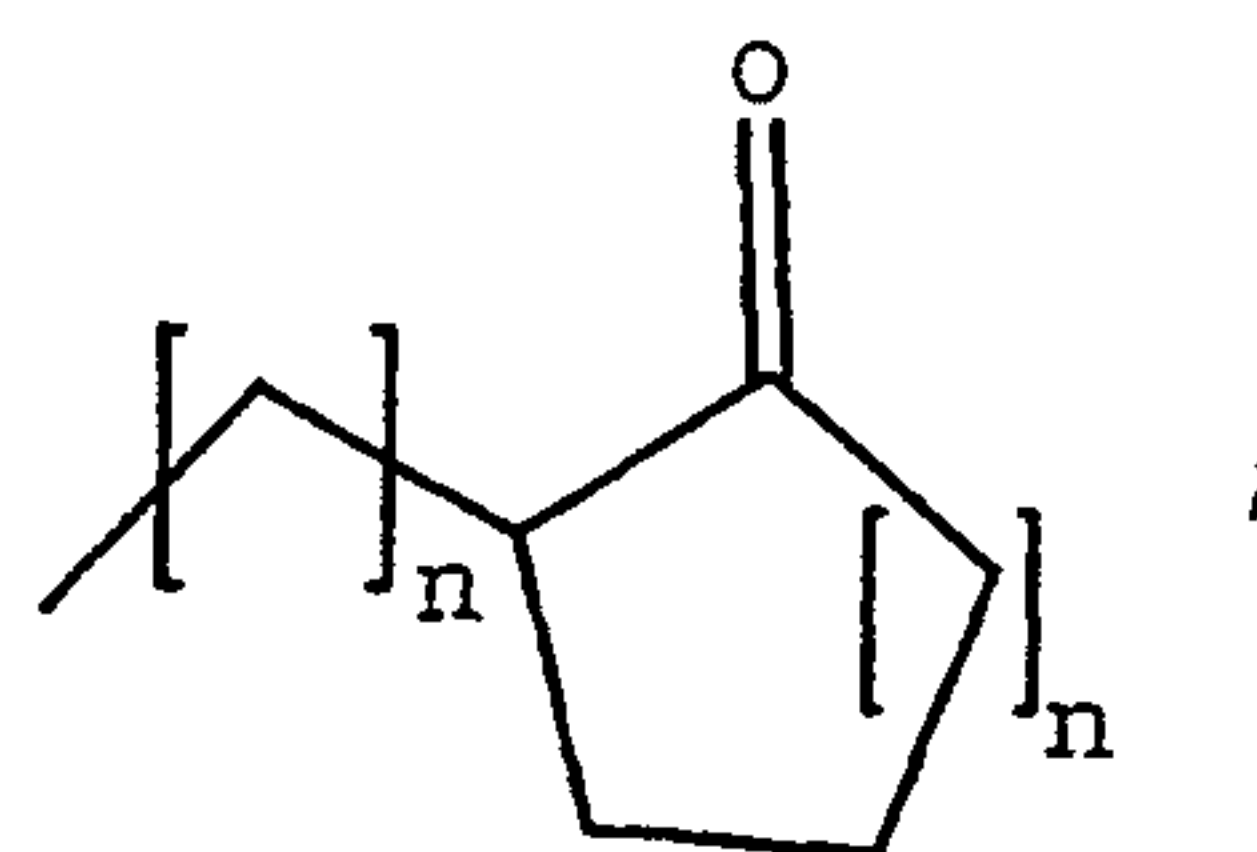
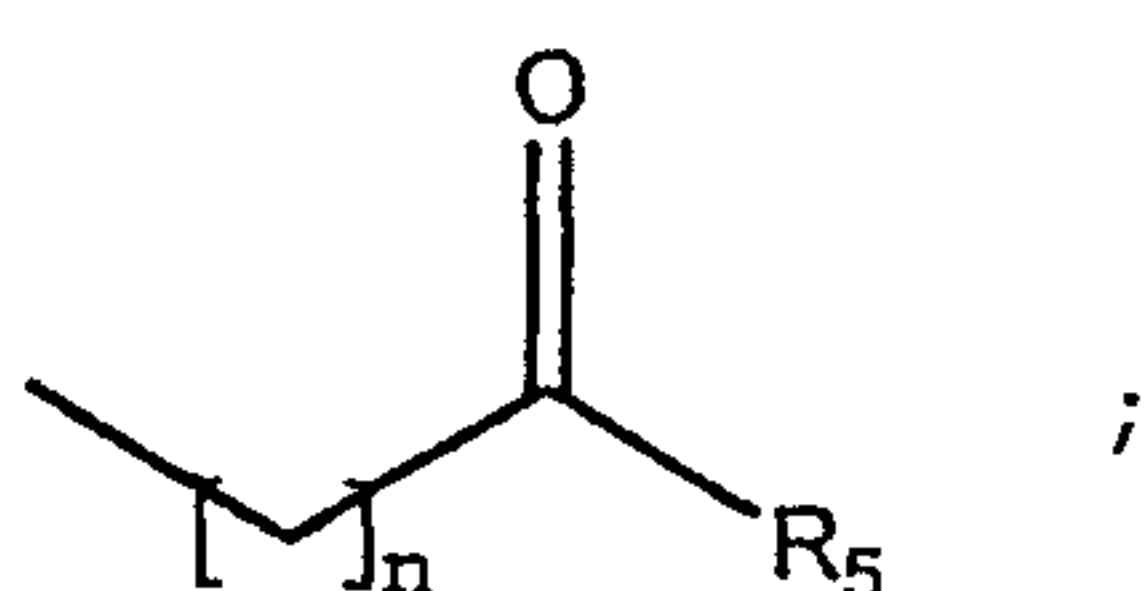
PCT/US02/04608

84

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 $(CHR_{17}) - (CHR_{17})_n - Z$;

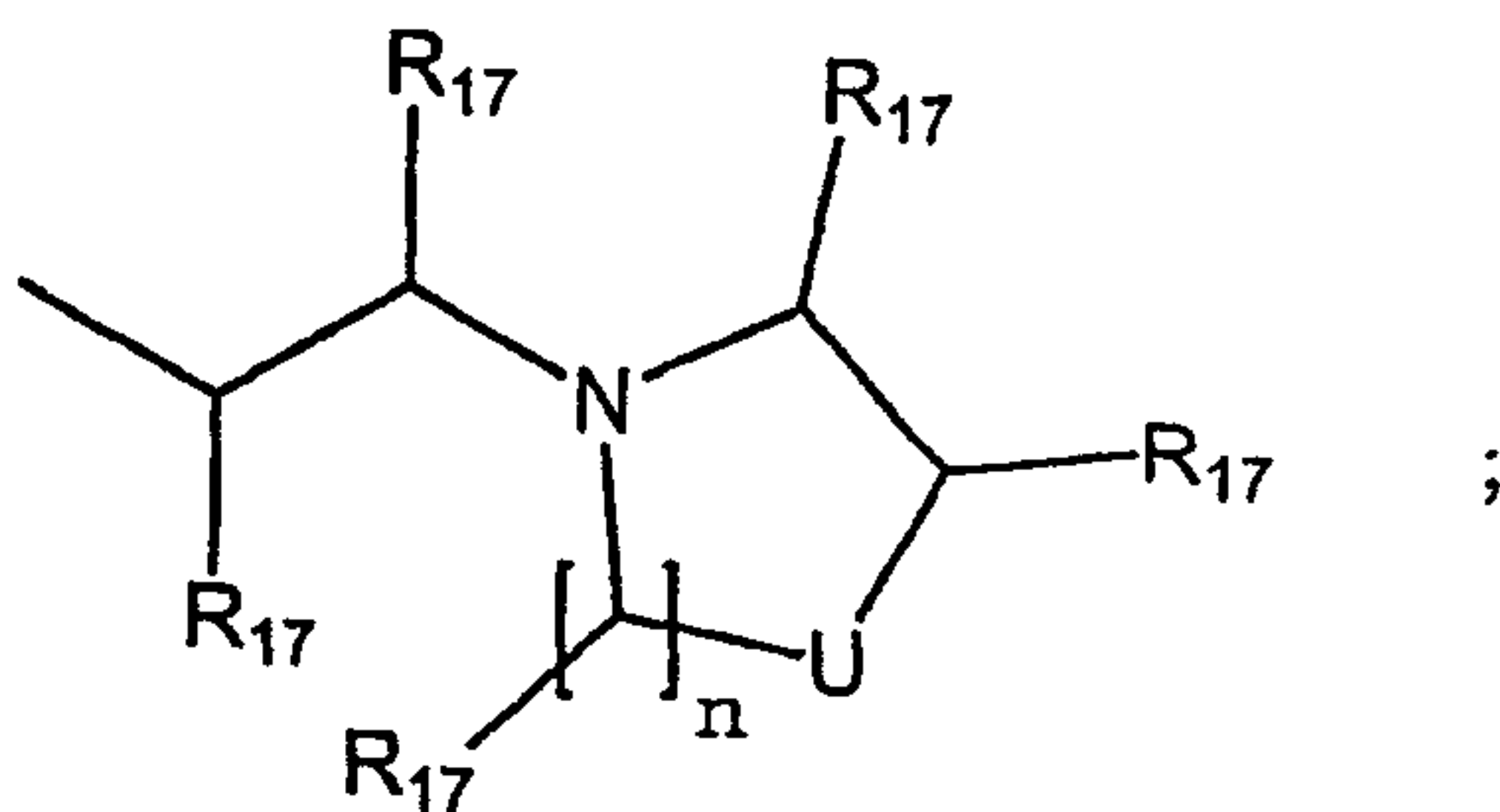
5

wherein A' is



10

wherein Q_3 is



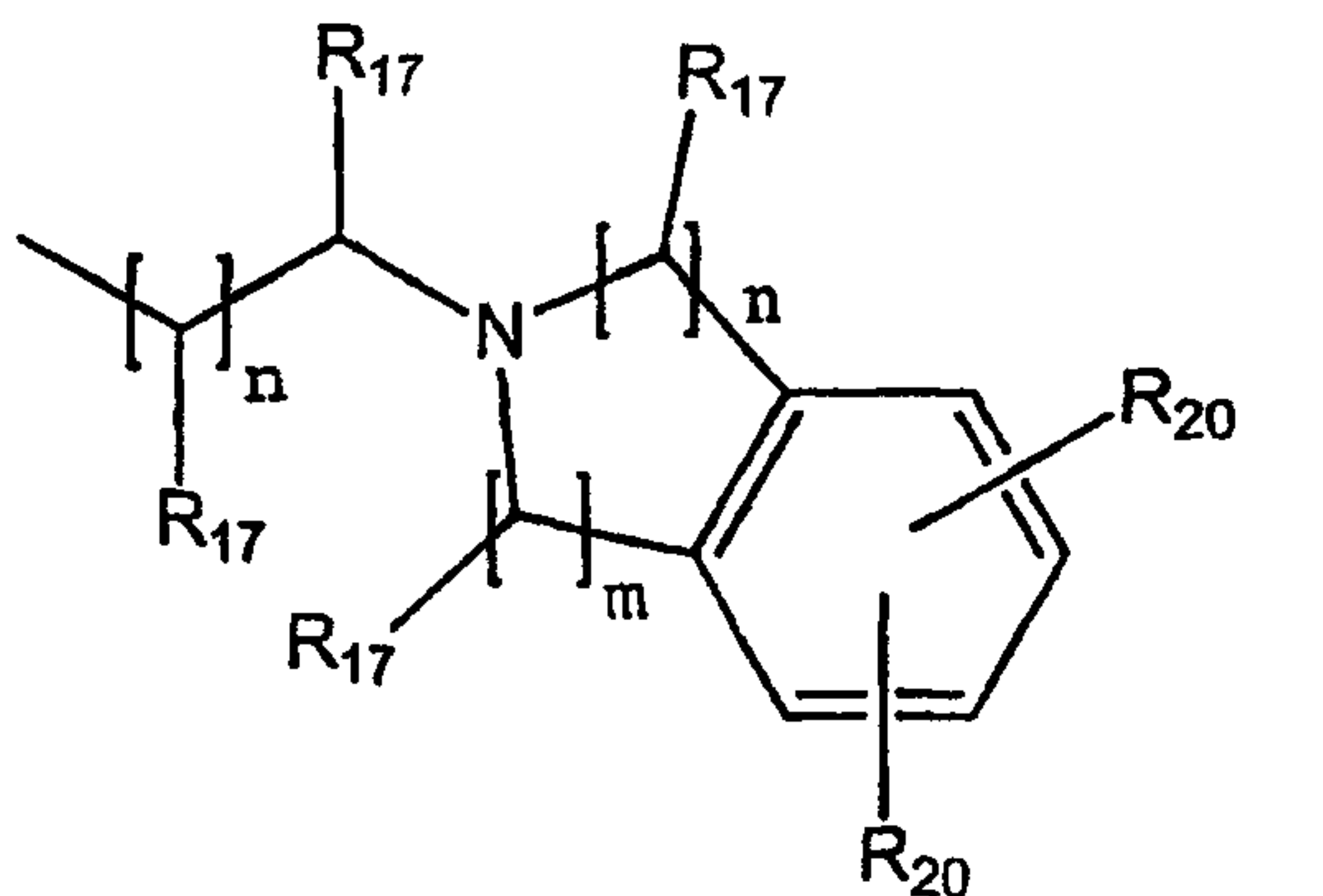
15

WO 02/060392

PCT/US02/04608

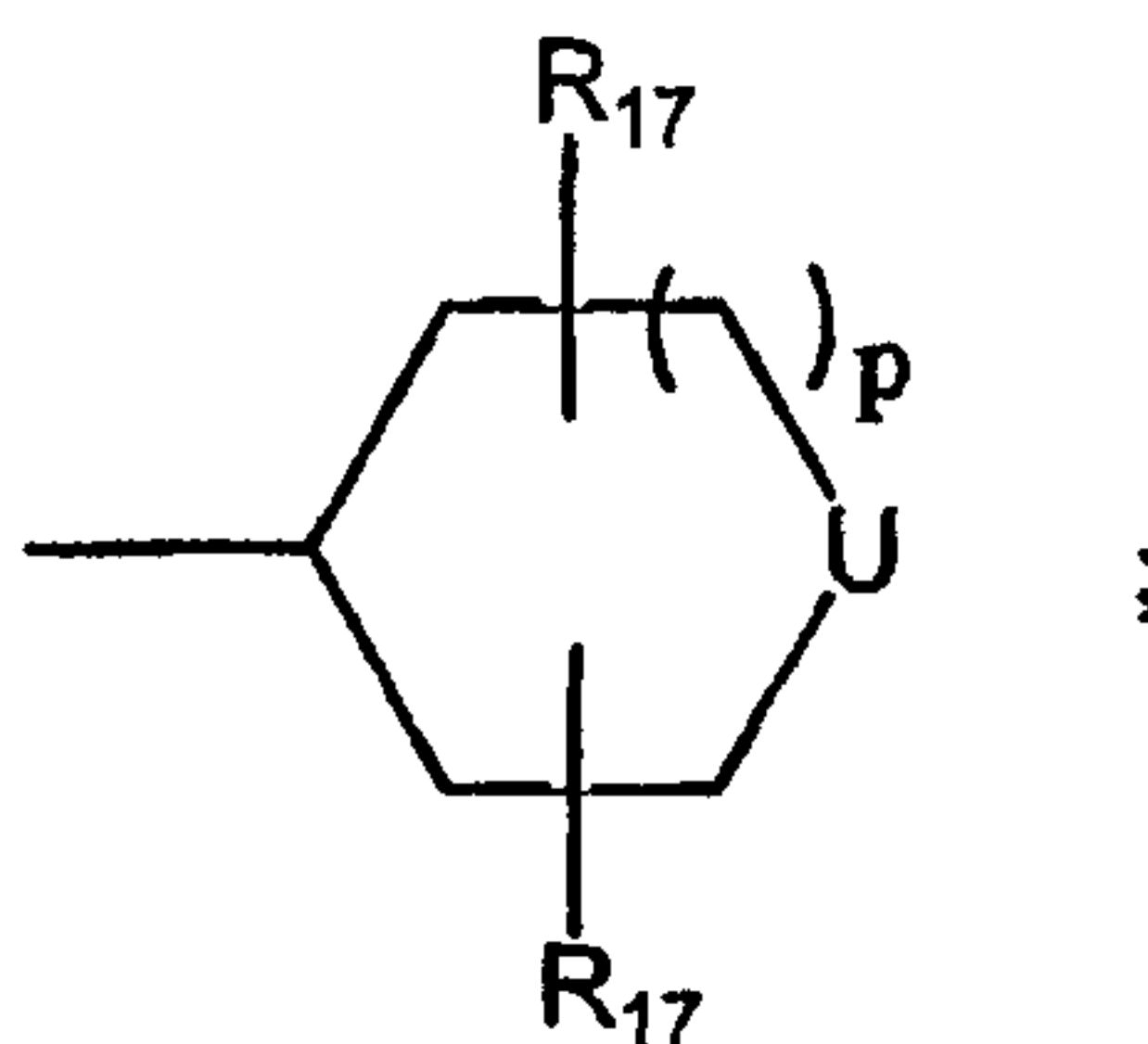
85

wherein Q_4 is



5

wherein Q_5 is



10

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;

15

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;

5 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 $(CH_2)_n-O-$
10 $(CH_2)_m-CH_3$;

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
15 alkenyl or alkynyl; C_3 - C_7 cycloalkyl or C_5 - C_7
cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -
OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or
-COOR₂₁; aryl or heteroaryl; or two R_{20} groups present
on adjacent carbon atoms can join together to form a
20 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
25 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;

WO 02/060392

PCT/US02/04608

87

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

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

5 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;

10 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,
15 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;

20 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
25 one or more of the following -F, -Cl, -Br, -I, -CN,
methyl, ethyl or methoxy;

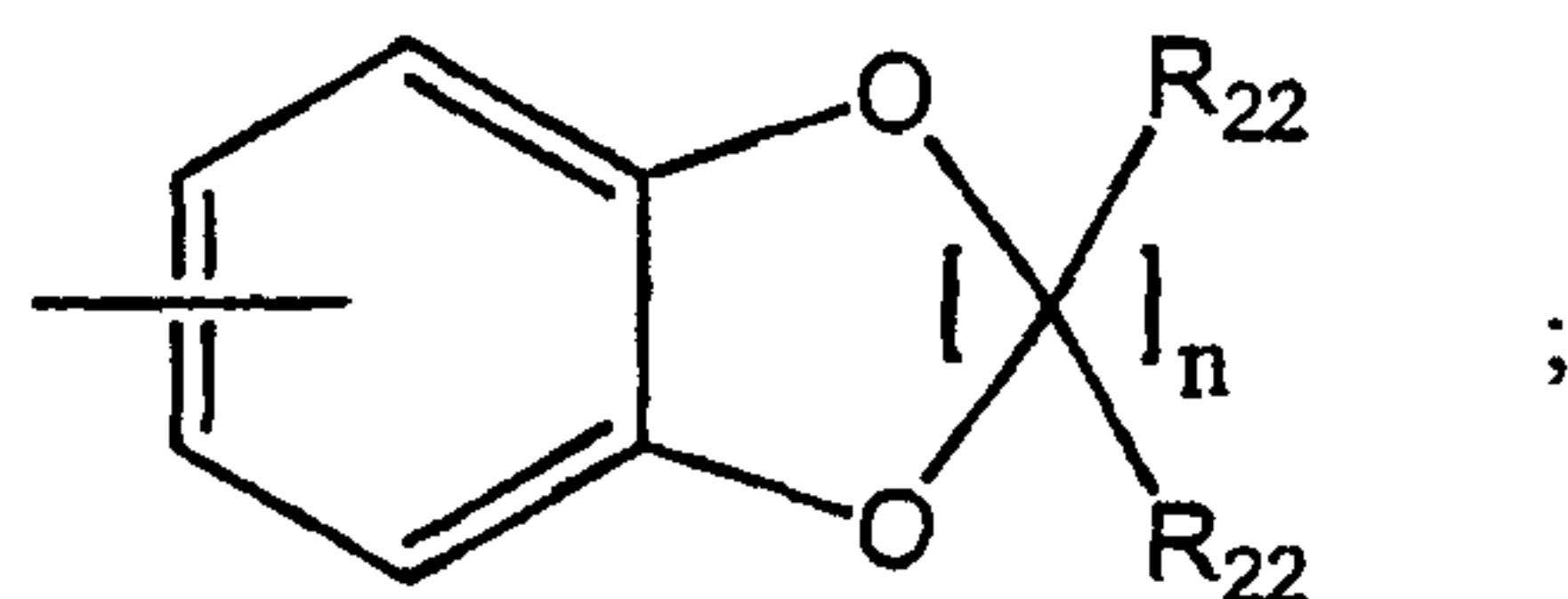
WO 02/060392

PCT/US02/04608

88

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

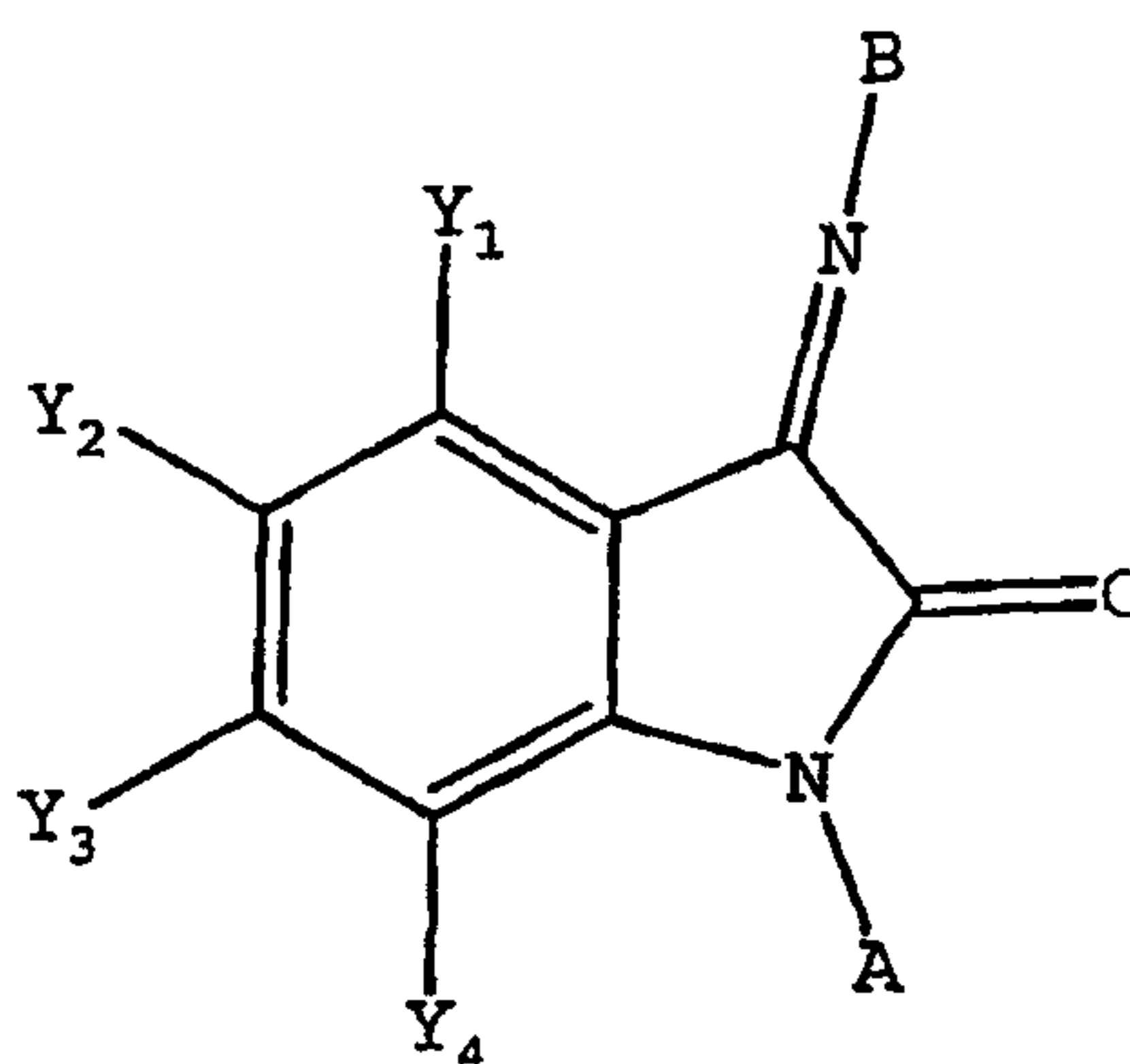
5 wherein Q_6 is



10 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.

15 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:



20

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
5 cycloalkyl, or C_5 - C_7 cycloalkenyl; -F, -Cl, -Br, or -
I; -NO₂; -N₃; -CN; -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -
N(R₄)₂, -CON(R₄)₂, or -COOR₄; 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;

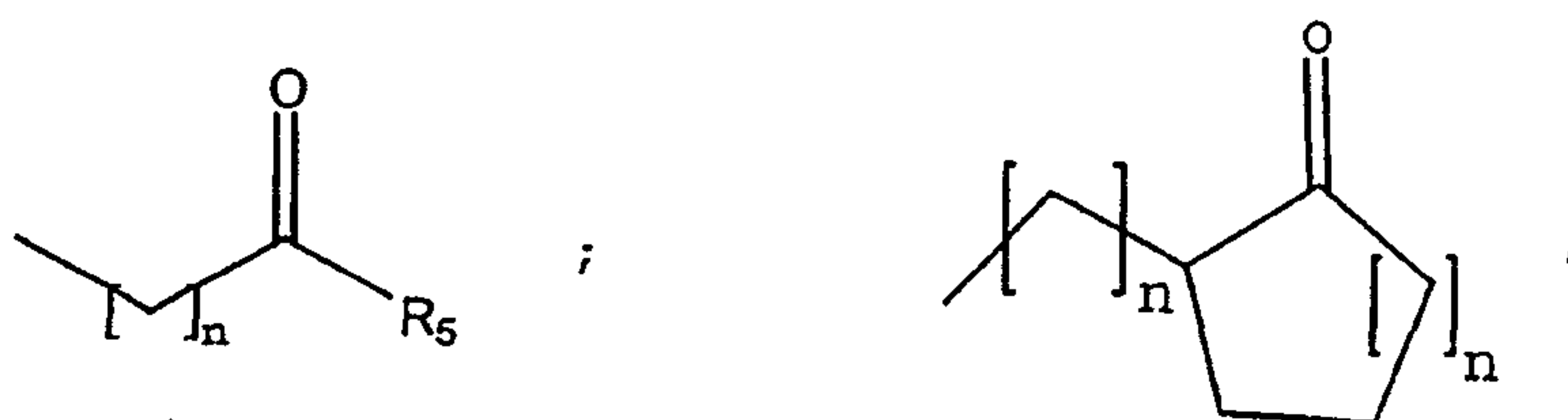
10

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
15 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;

20

wherein A' is

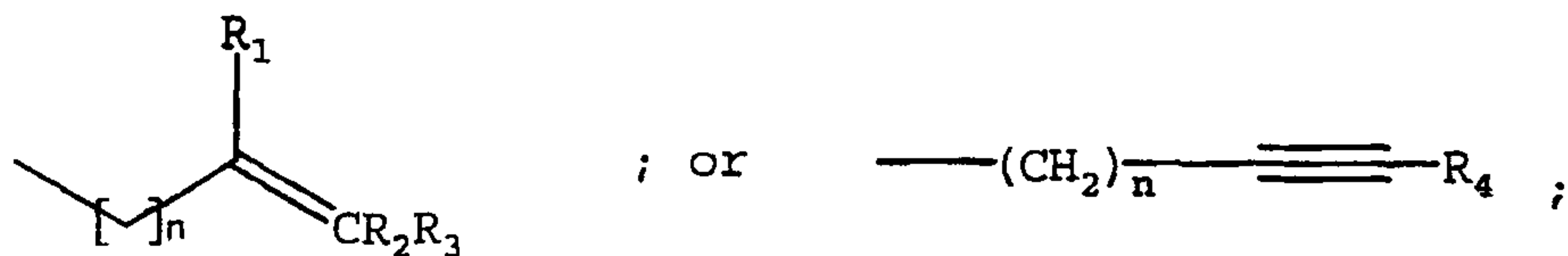


25

WO 02/060392

PCT/US02/04608

90



wherein R_1 and R_2 are each independently H, straight
 chained or branched C_1 - C_7 alkyl, -F, -Cl, -Br, -I, -
 5 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;

10

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

15

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

20

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;

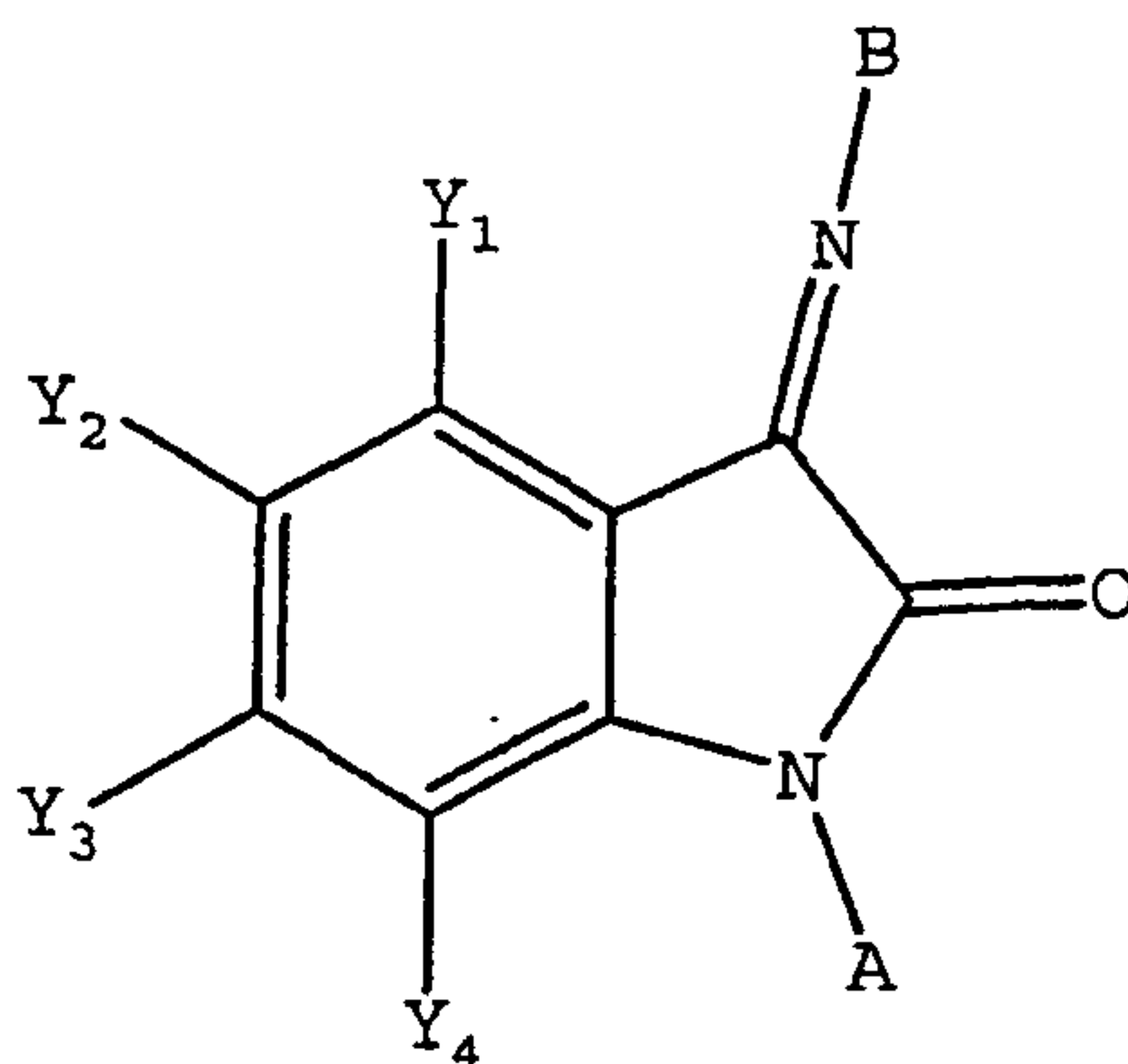
25

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:



5 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 -
10 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;

15 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;

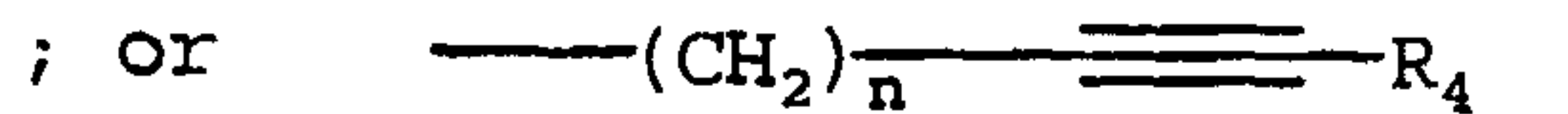
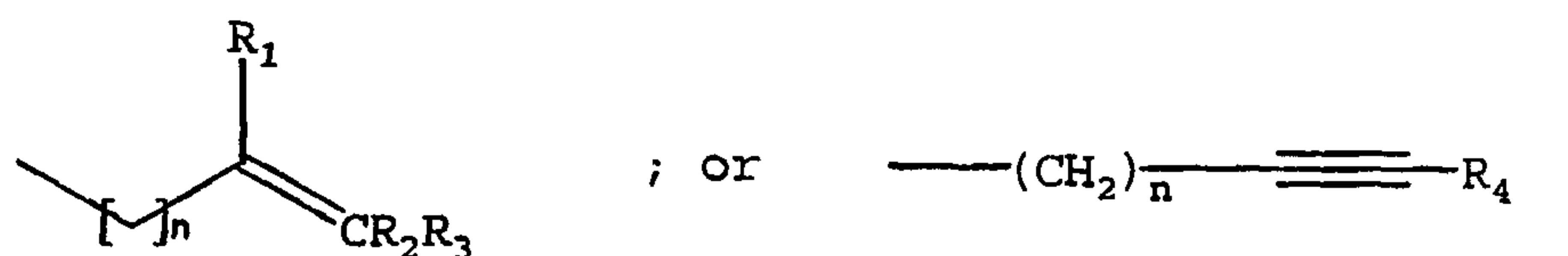
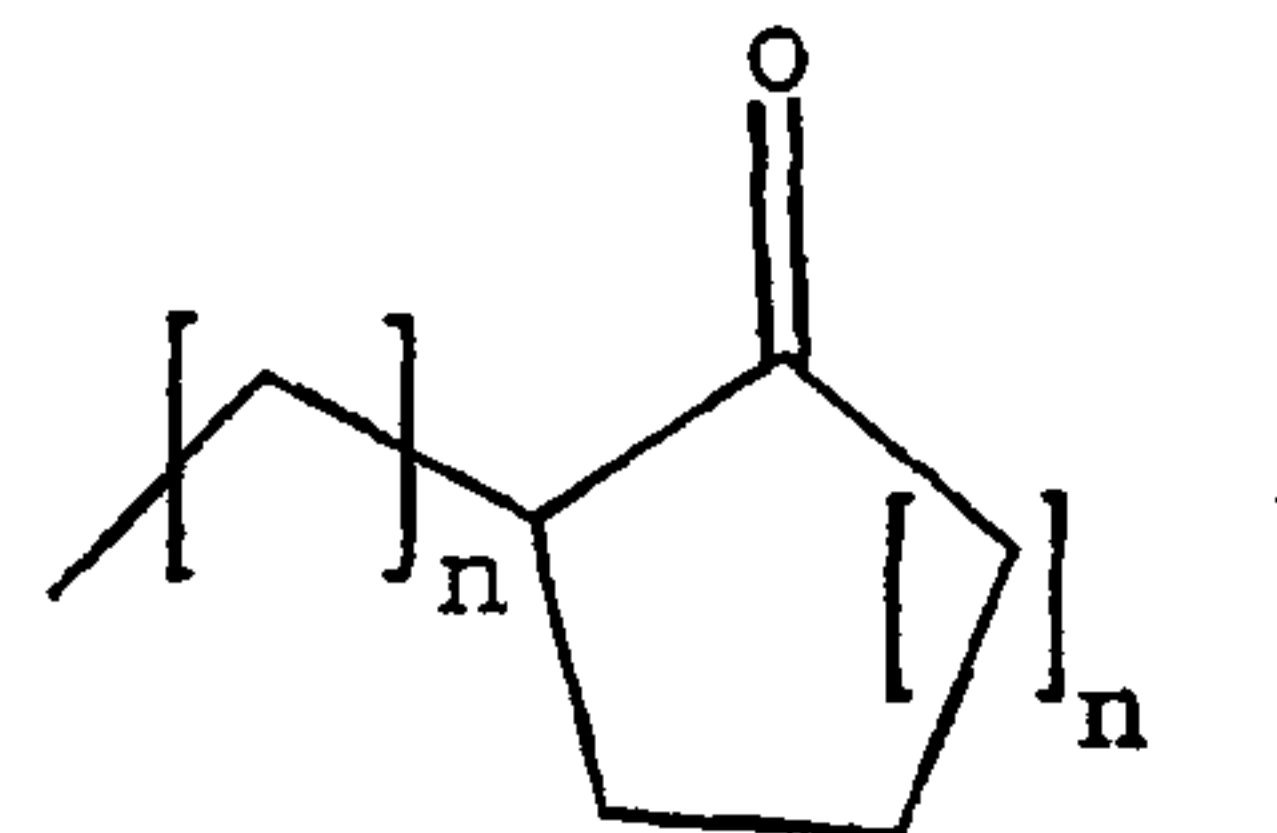
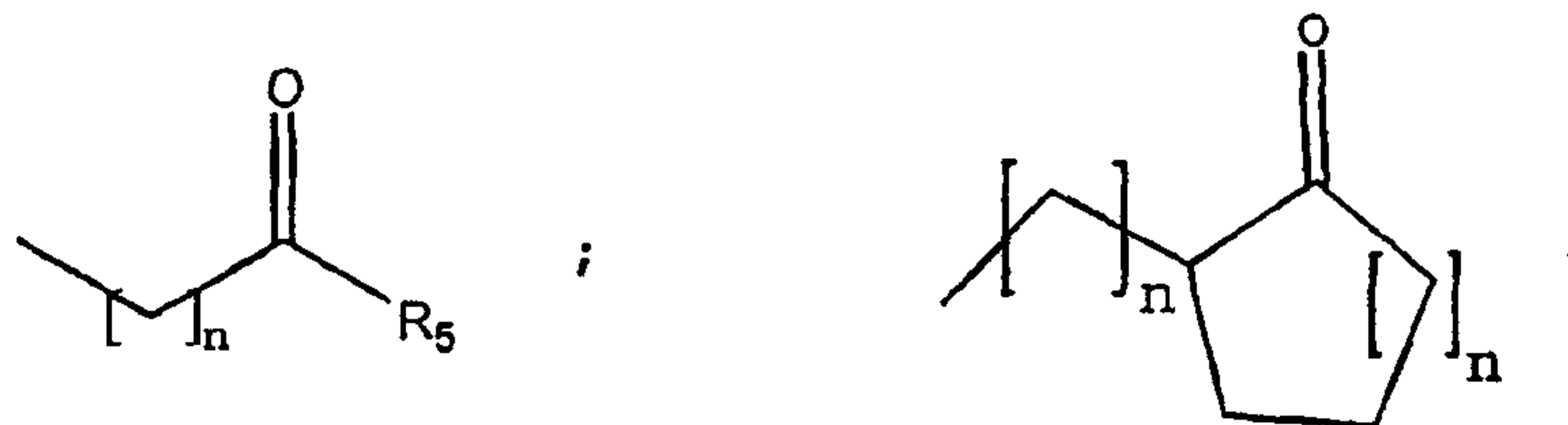
20 wherein A is A', straight chained or branched C_1 - C_7
alkyl, aryl, heteroaryl, aryl(C_1 - C_6)alkyl or
heteroaryl(C_1 - C_6)alkyl;

WO 02/060392

PCT/US02/04608

92

wherein A' is



5

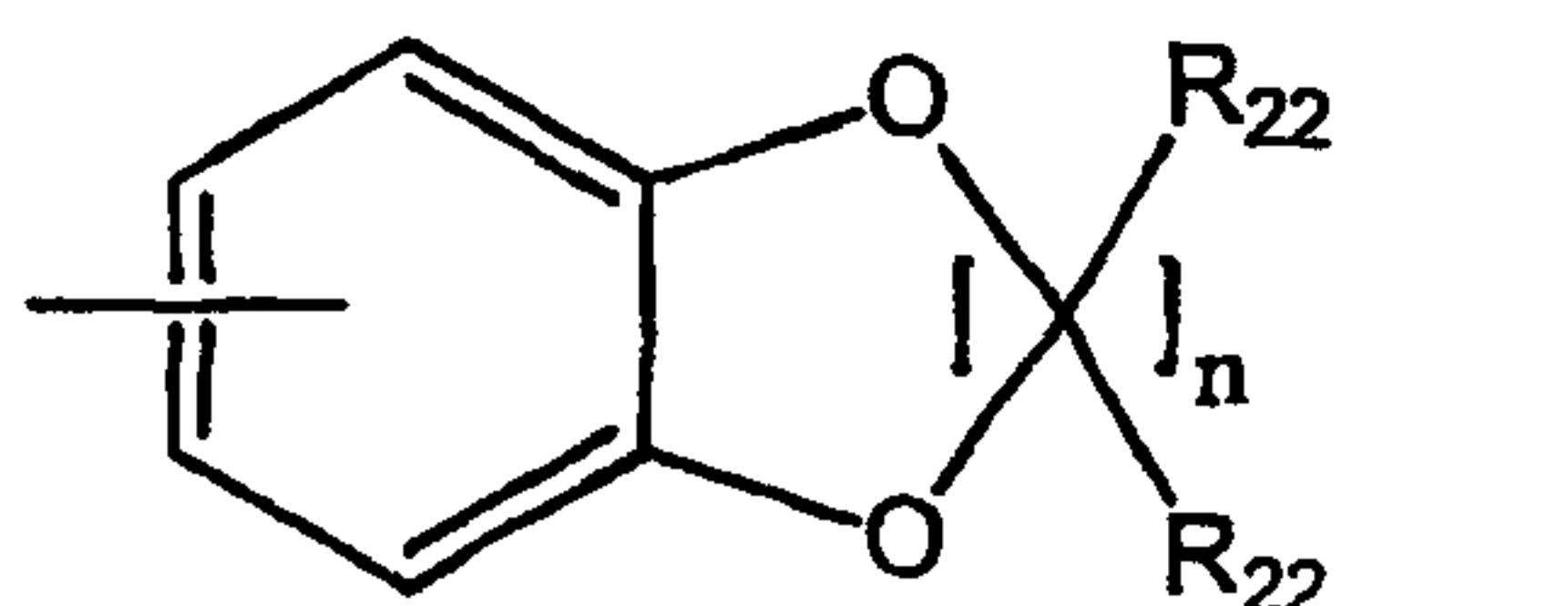
wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q₆;

10

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

15

wherein Q₆ is



wherein n is an integer from 1 to 4 inclusive;

20

wherein each R₂₂ is independently H, F,

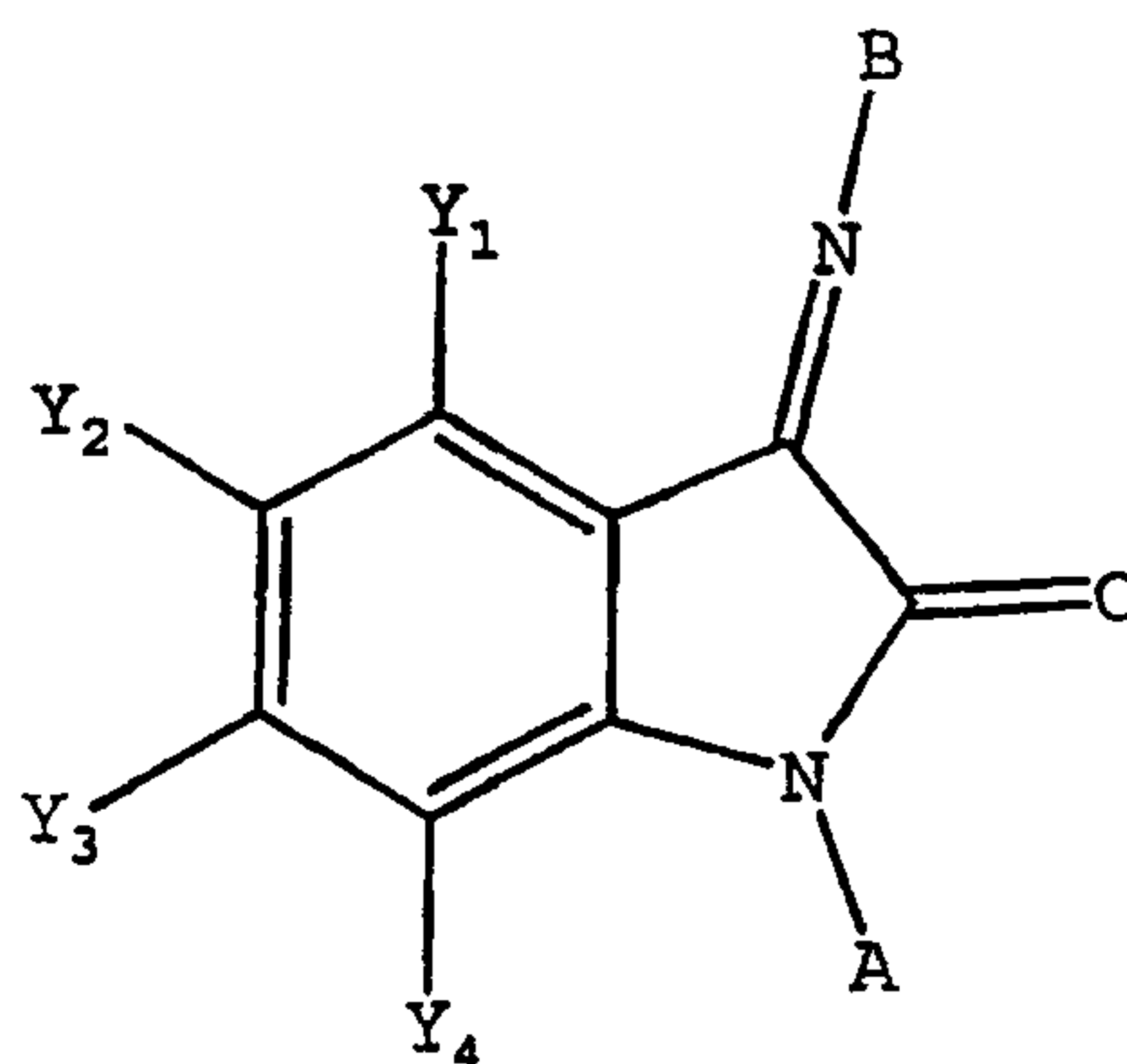
Cl, or straight chained or branched C₁-C₄ alkyl;

or a pharmaceutically acceptable salt thereof.

5

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:

10



wherein each of Y₁, Y₂, Y₃, and Y₄ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -N(R₄)₂, -CON(R₄)₂, or -COOR₄; aryl or heteroaryl; or any two of Y₁, Y₂, Y₃ and Y₄ present on adjacent carbon atoms can constitute a methylenedioxy group;

20

wherein each R₄ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇

25

WO 02/060392

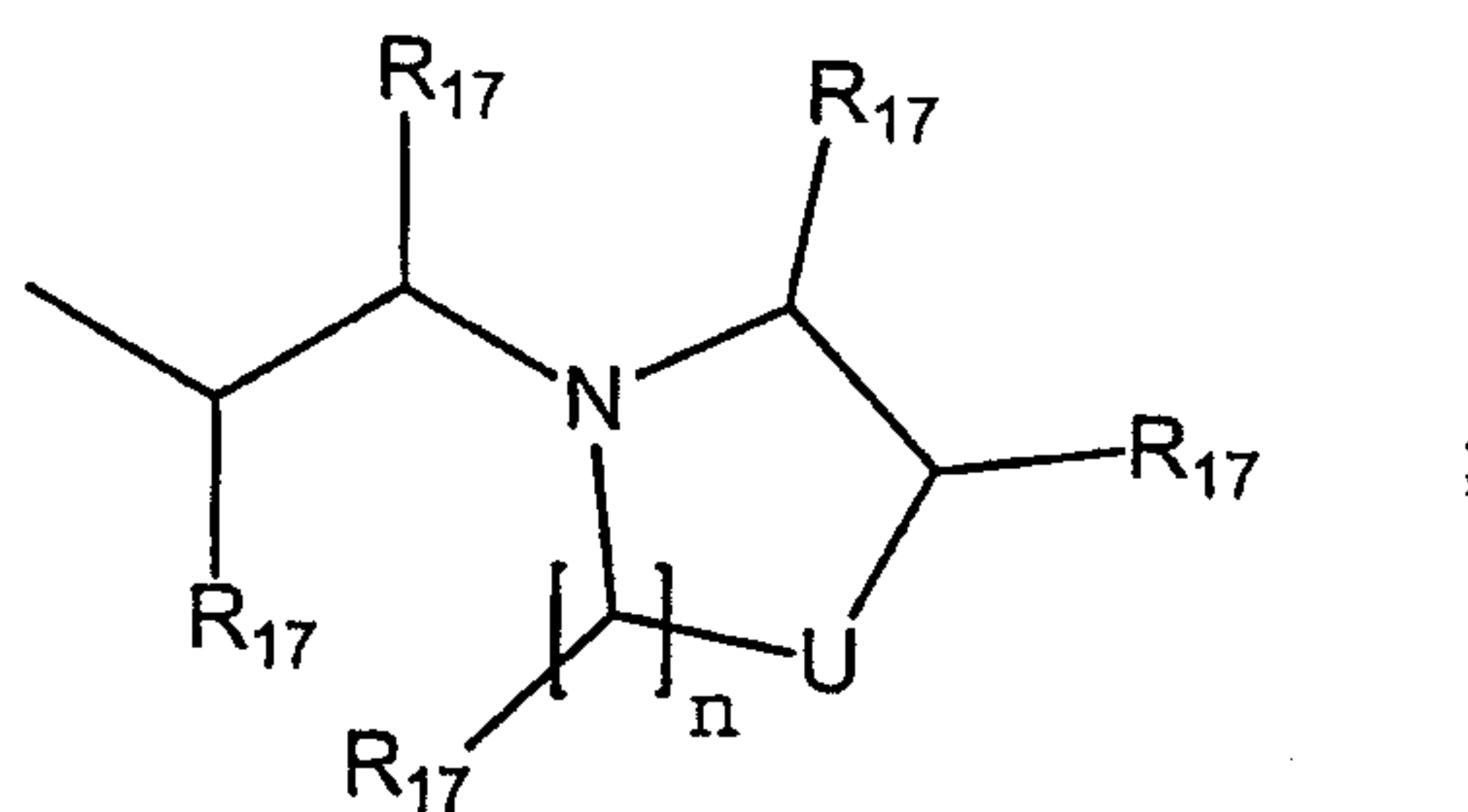
PCT/US02/04608

94

alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

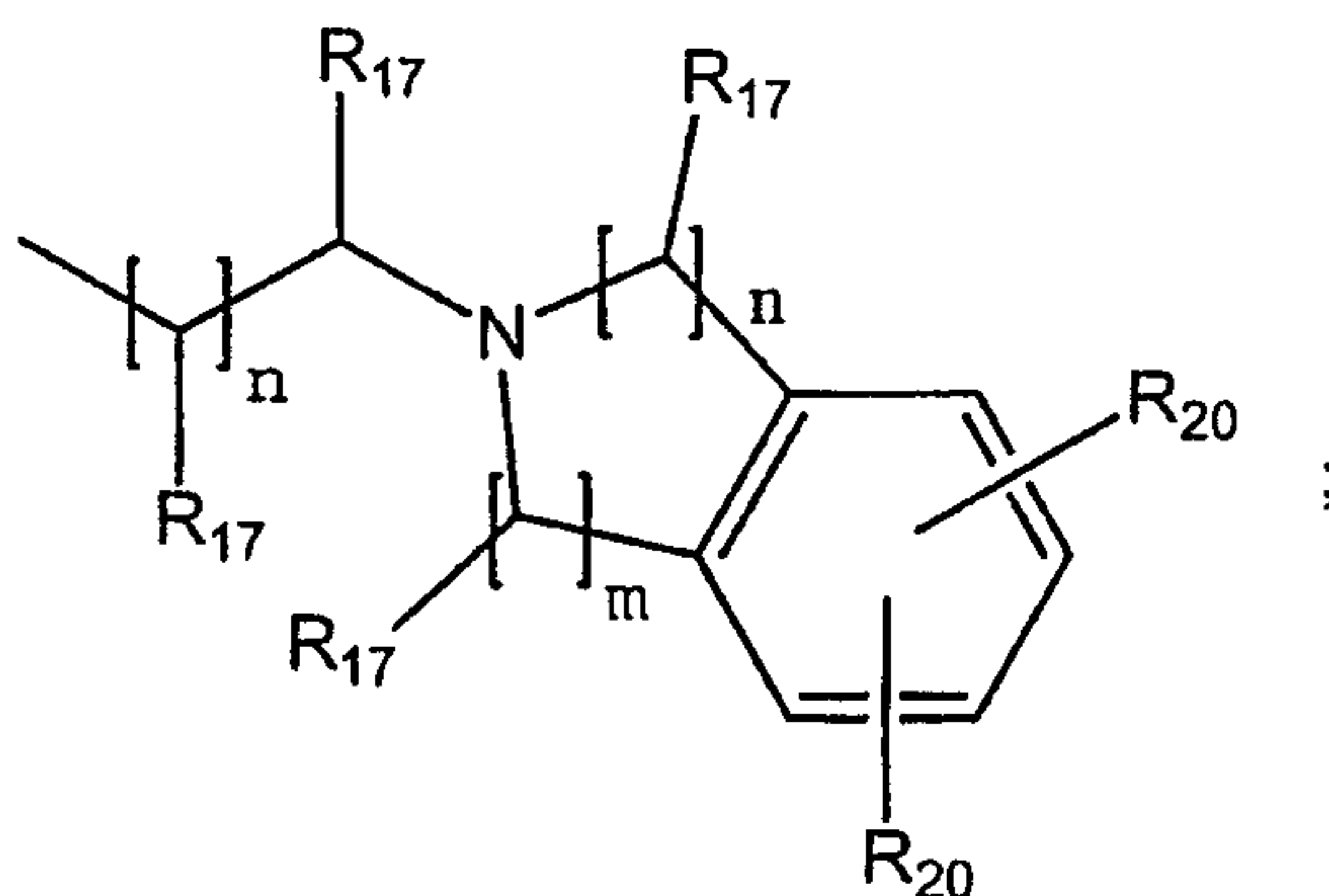
5 wherein A is Q₃, Q₄, Q₅, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR₁₇)_n-Z;

wherein Q₃ is

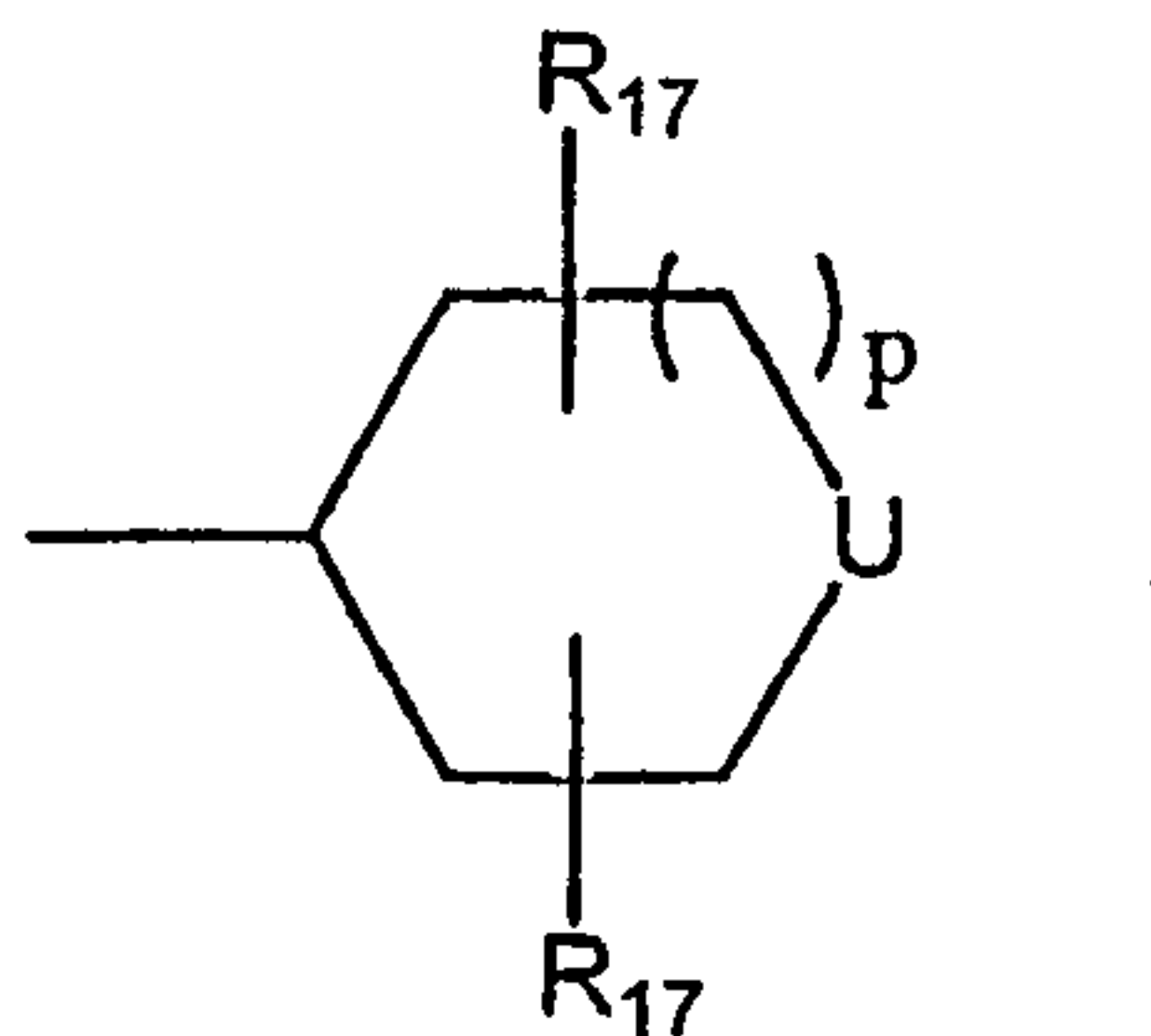


10

wherein Q₄ is



wherein Q₅ is



15

wherein each R₁₇ is independently H; straight chained

5 or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

10 wherein each R₂₀ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups present
15 on adjacent carbon atoms can join together to form a methylenedioxy group;

20 wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl or aryl;

25 wherein each R₂₂ is independently H, F, Cl, or straight chained or branched C₁-C₄ alkyl;

wherein q is an integer from 2 to 4 inclusive;

30 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, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

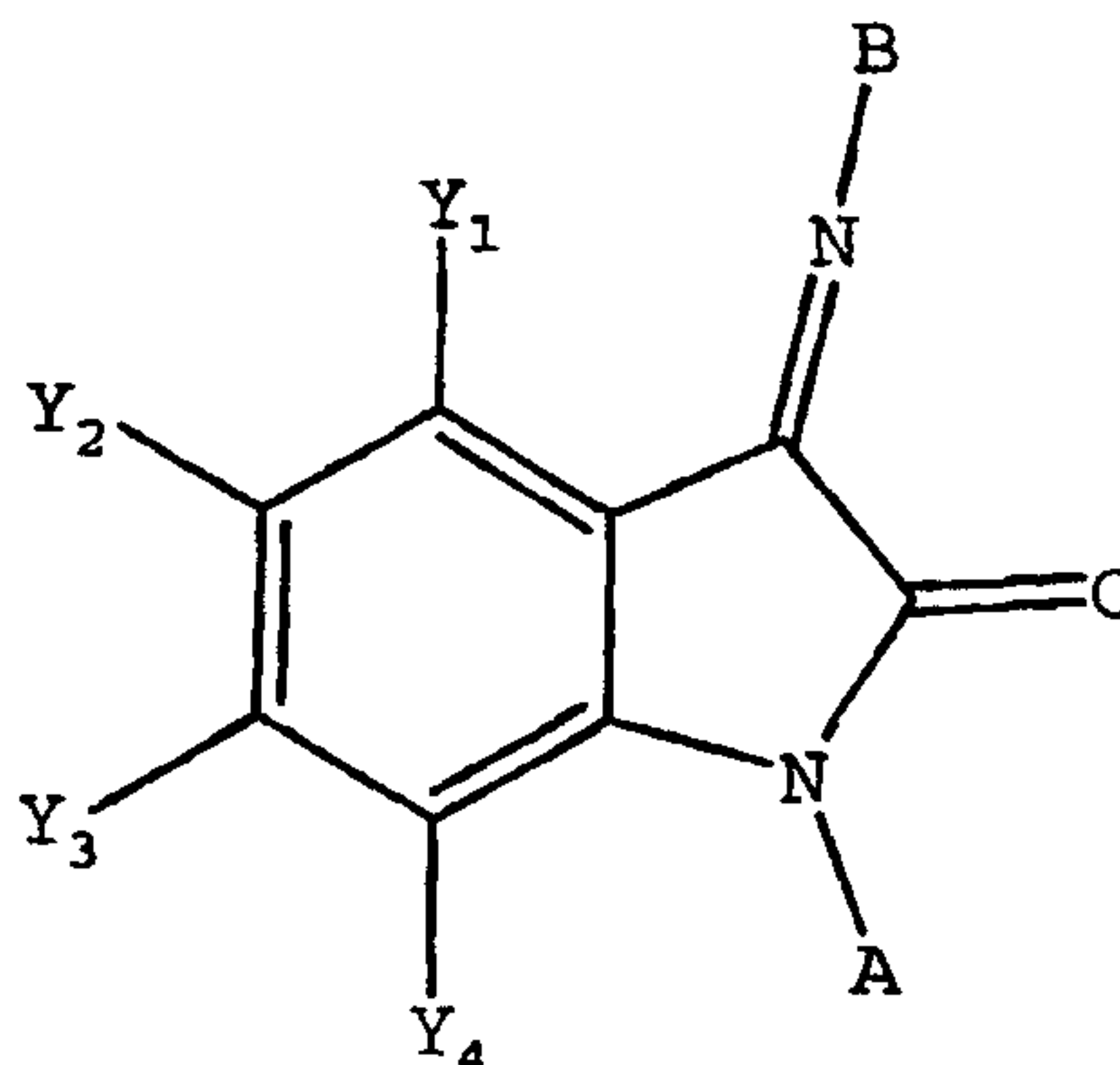
5 wherein Z is C₃-C₁₀ cycloalkyl, C₄-C₇ cyclic ether, C₄-C₇ cyclic thioether, aryl, or heteroaryl;

10 wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15 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
20 methoxy;

or a pharmaceutically acceptable salt thereof.

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



5 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 , - $NCOR_4$, -
 10 $N(R_4)_2$, - $CON(R_4)_2$, 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;

15 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;

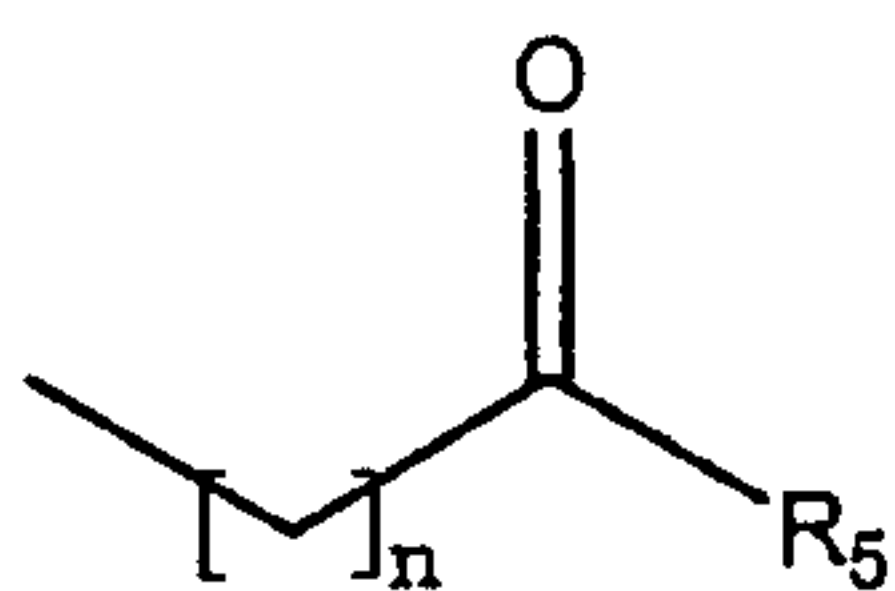
20 wherein A is A' , Q_3 , Q_4 , Q_5 , straight chained or
 branched C_1 - C_7 alkyl, aryl, heteroaryl, aryl(C_1 -
 C_6)alkyl, heteroaryl(C_1 - C_6)alkyl, aryl substituted
 with an aryl or heteroaryl, heteroaryl substituted
 with an aryl or heteroaryl; or $(CHR_{17})-(CHR_{17})_n-Z$;

WO 02/060392

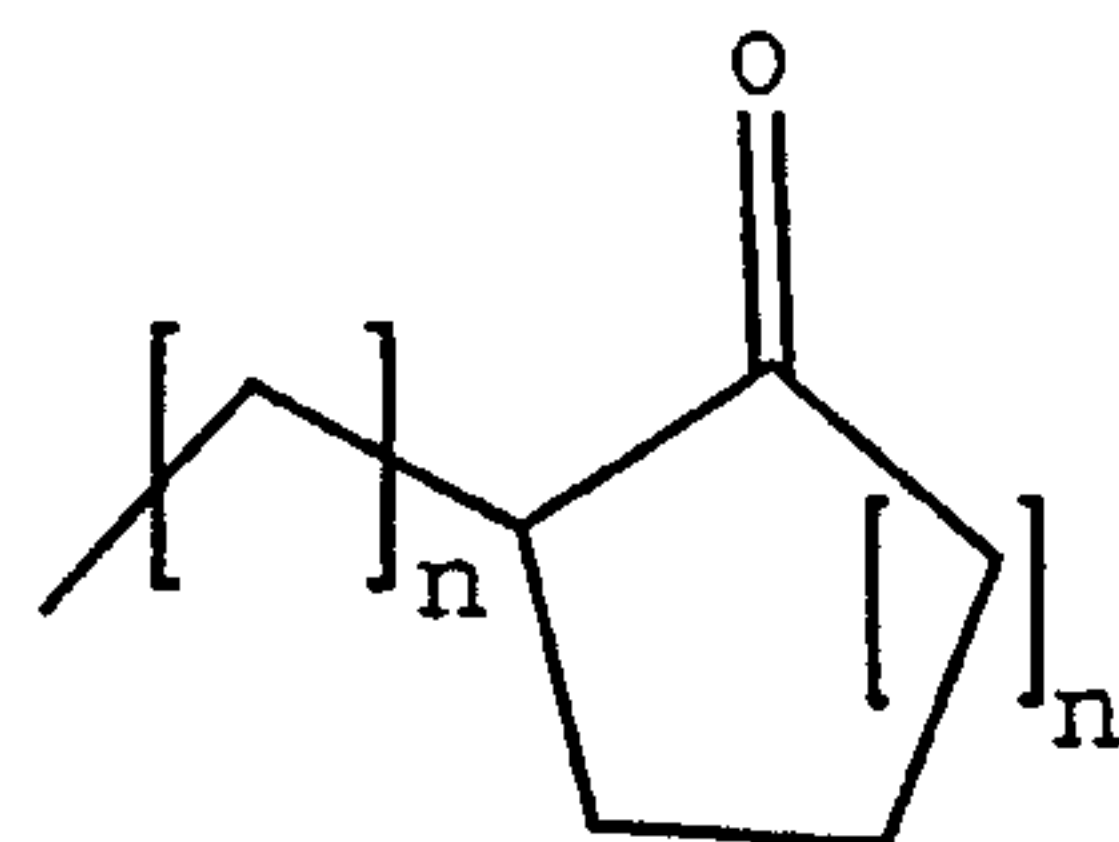
PCT/US02/04608

98

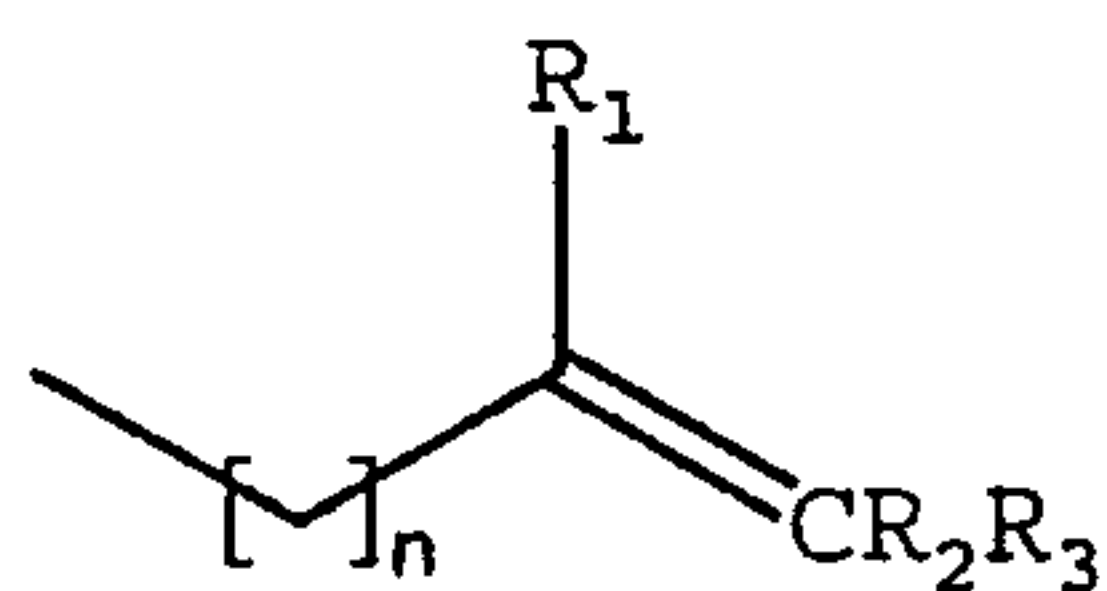
wherein A' is



;



;

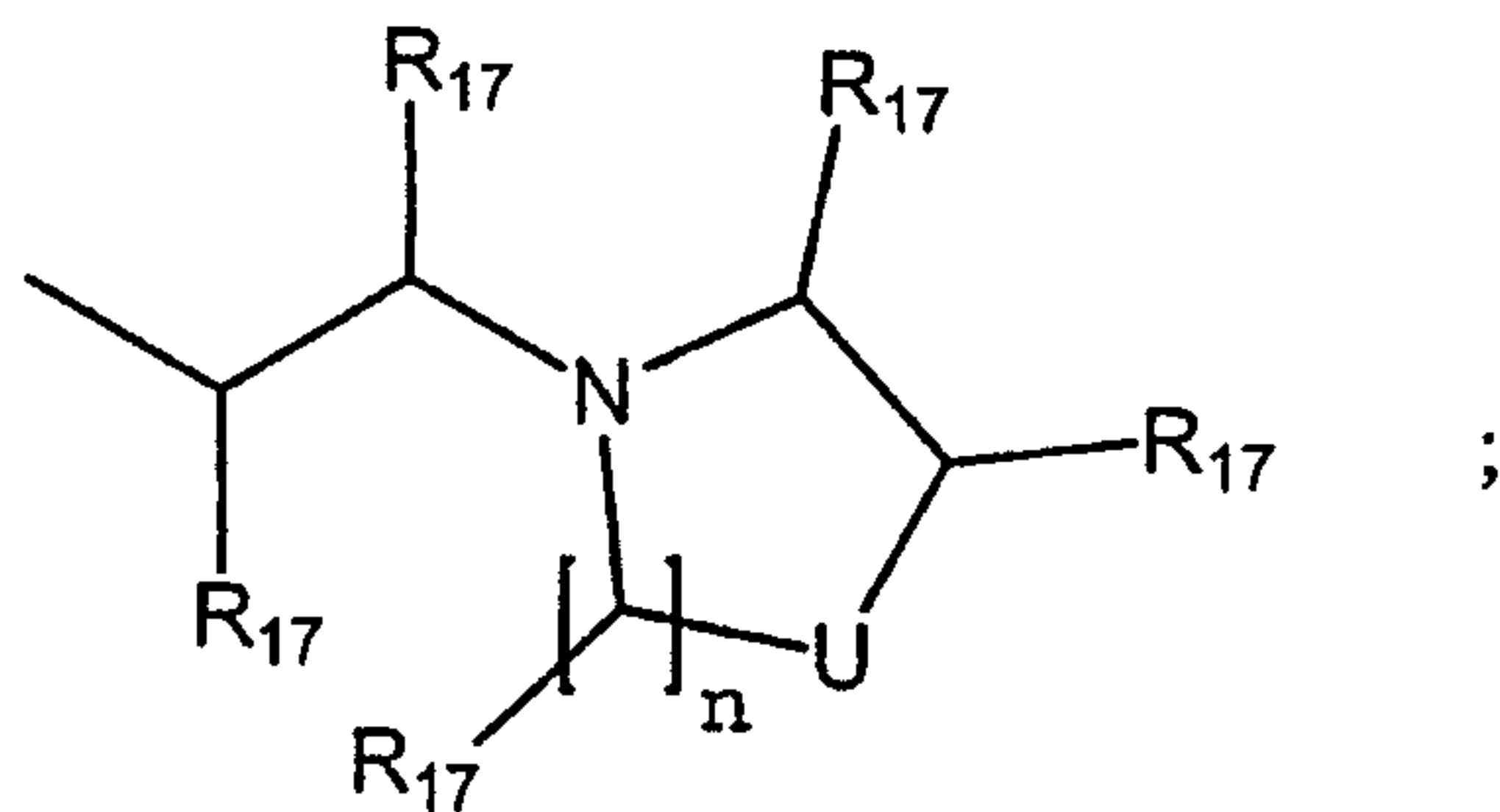


; or



;

5

wherein Q₃ is

;

10

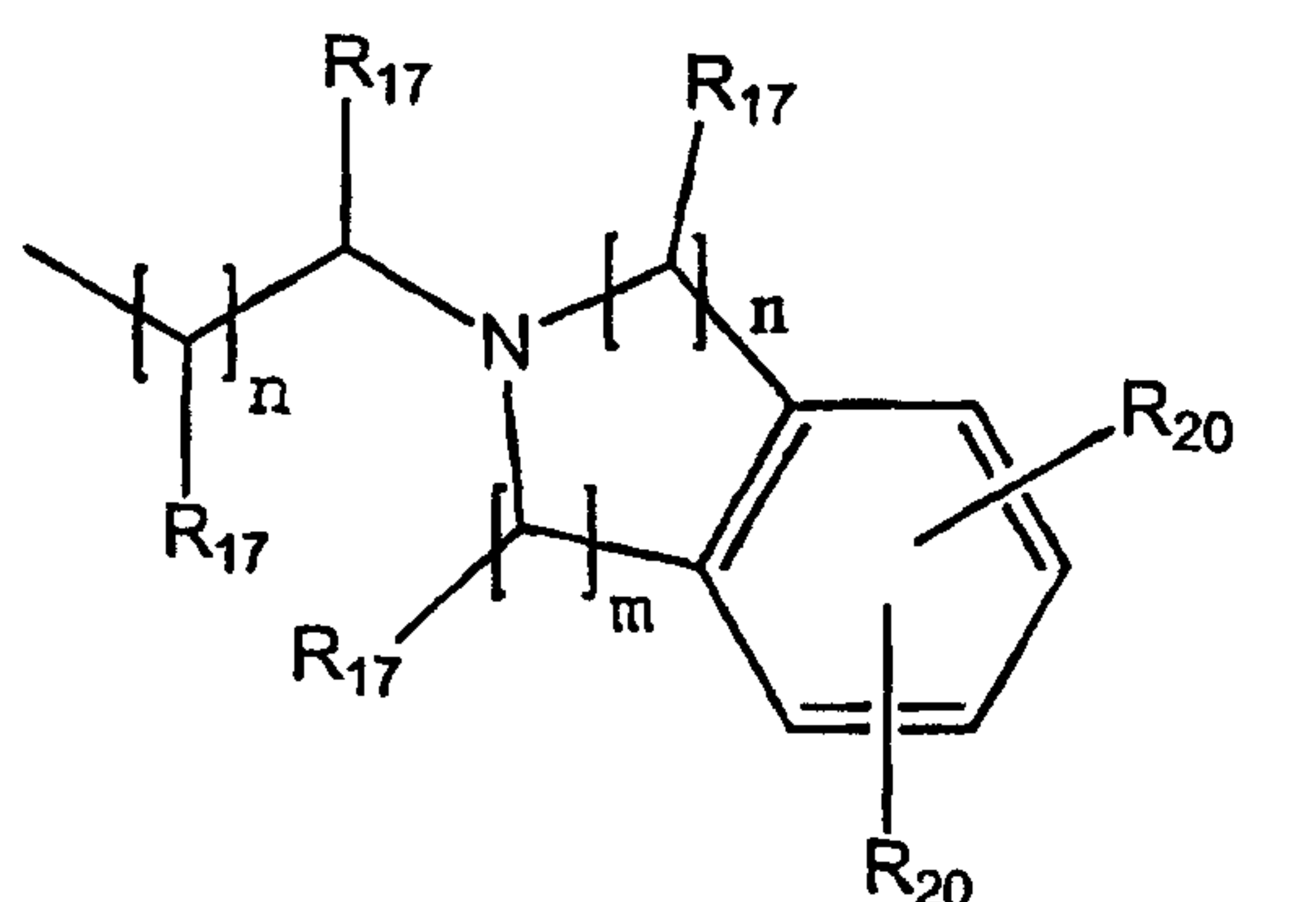
wherein Q₄ is

15

WO 02/060392

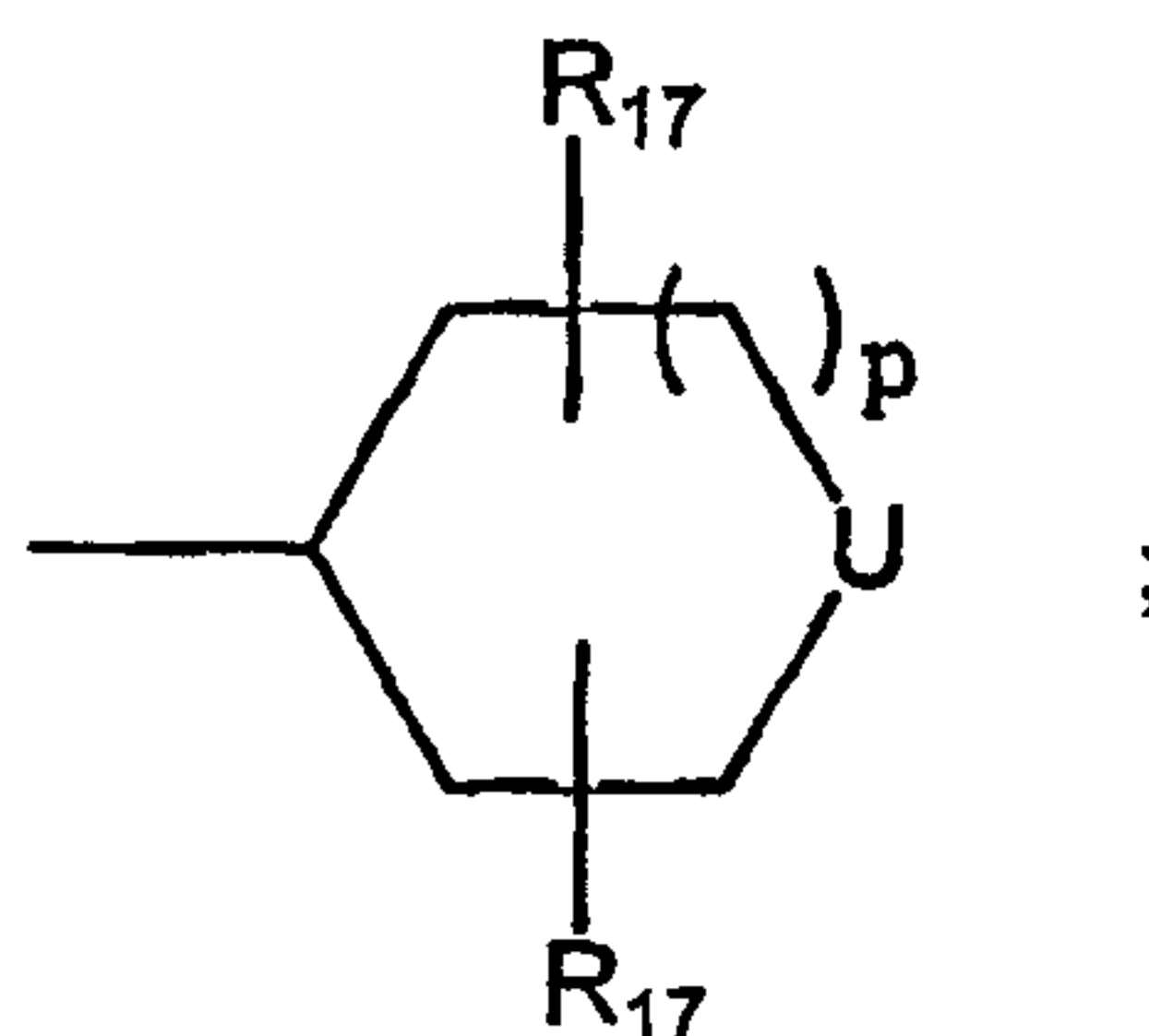
PCT/US02/04608

99



5

wherein Q_5 is



10

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;

15

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;

20

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;

- 5 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 $(CH_2)_n-O-$
 10 $(CH_2)_m-CH_3$;

- wherein each R_{20} is independently -H; straight
 chained or branched C_1 - C_7 alkyl, monofluoroalkyl or
 15 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; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R_{20} groups present
 20 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
 25 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;

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

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

10 wherein Z is C₃-C₁₀ cycloalkyl, C₄-C₇ cyclic ether,
C₄-C₇ cyclic thioether, aryl, or heteroaryl;

15 wherein R₁₆ is straight chained or branched C₁-C₇
alkyl, straight chained or branched C₁-C₇
monofluoroalkyl, straight chained or branched C₁-C₇
polyfluoroalkyl, straight chained or branched C₂-C₇
alkenyl, straight chained or branched C₂-C₇ alkynyl,
C₅-C₇ cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

wherein q is an integer from 2 to 4 inclusive;

20

25 wherein B is aryl, heteroaryl, aryl substituted with
an aryl or heteroaryl, heteroaryl substituted with
an aryl or heteroaryl, tricyclic heteroaryl or Q₆;
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;

WO 02/060392

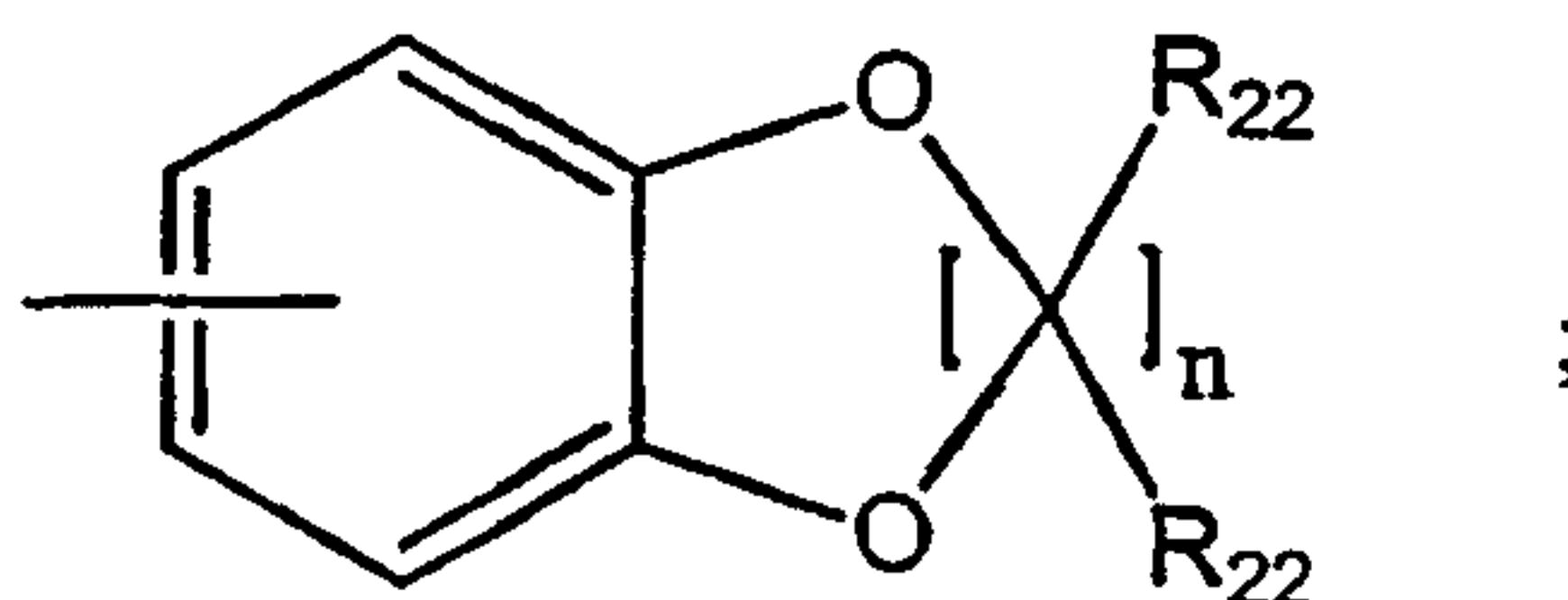
PCT/US02/04608

102

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

5

wherein Q_6 is



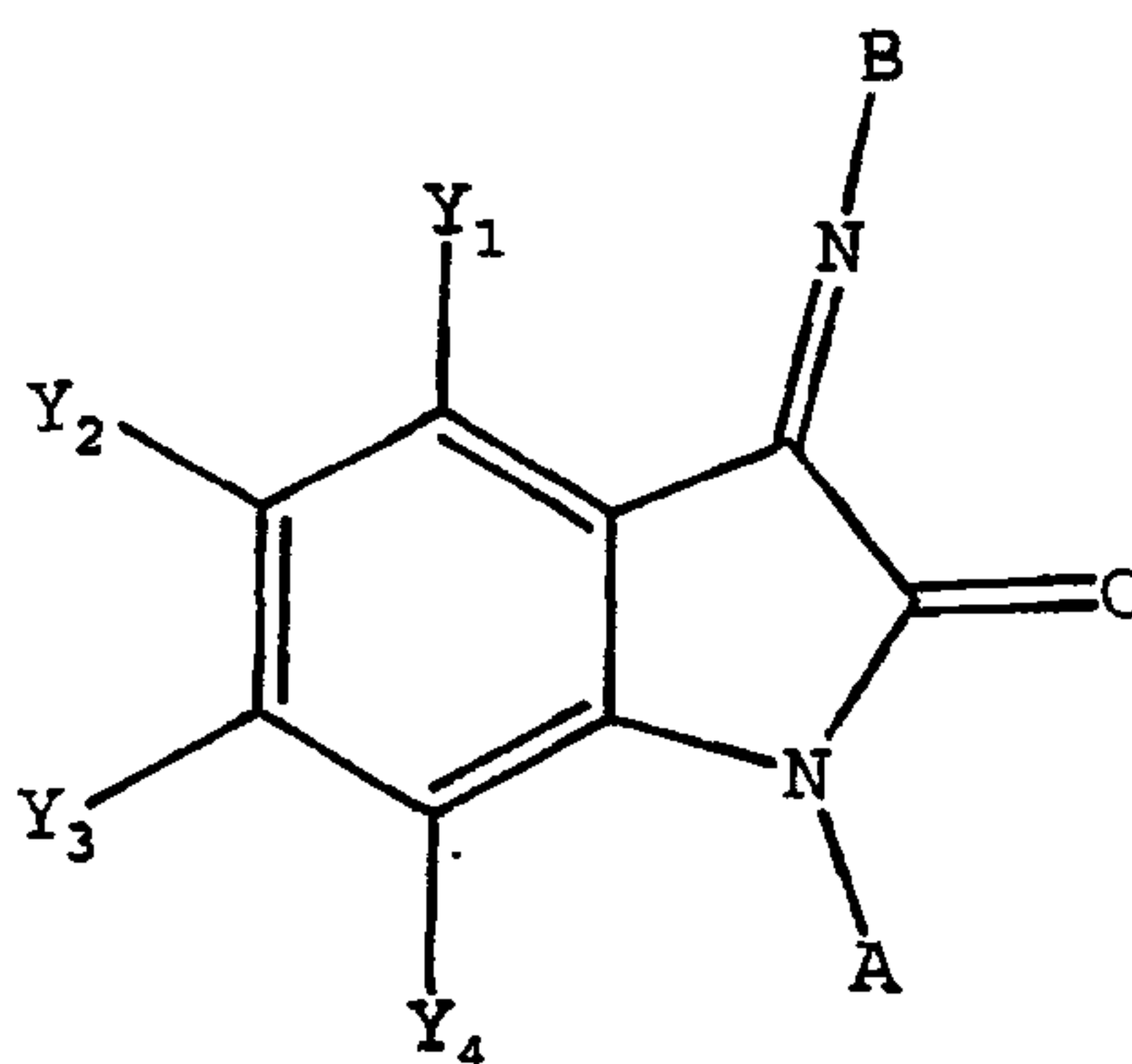
10

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.

15

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



20

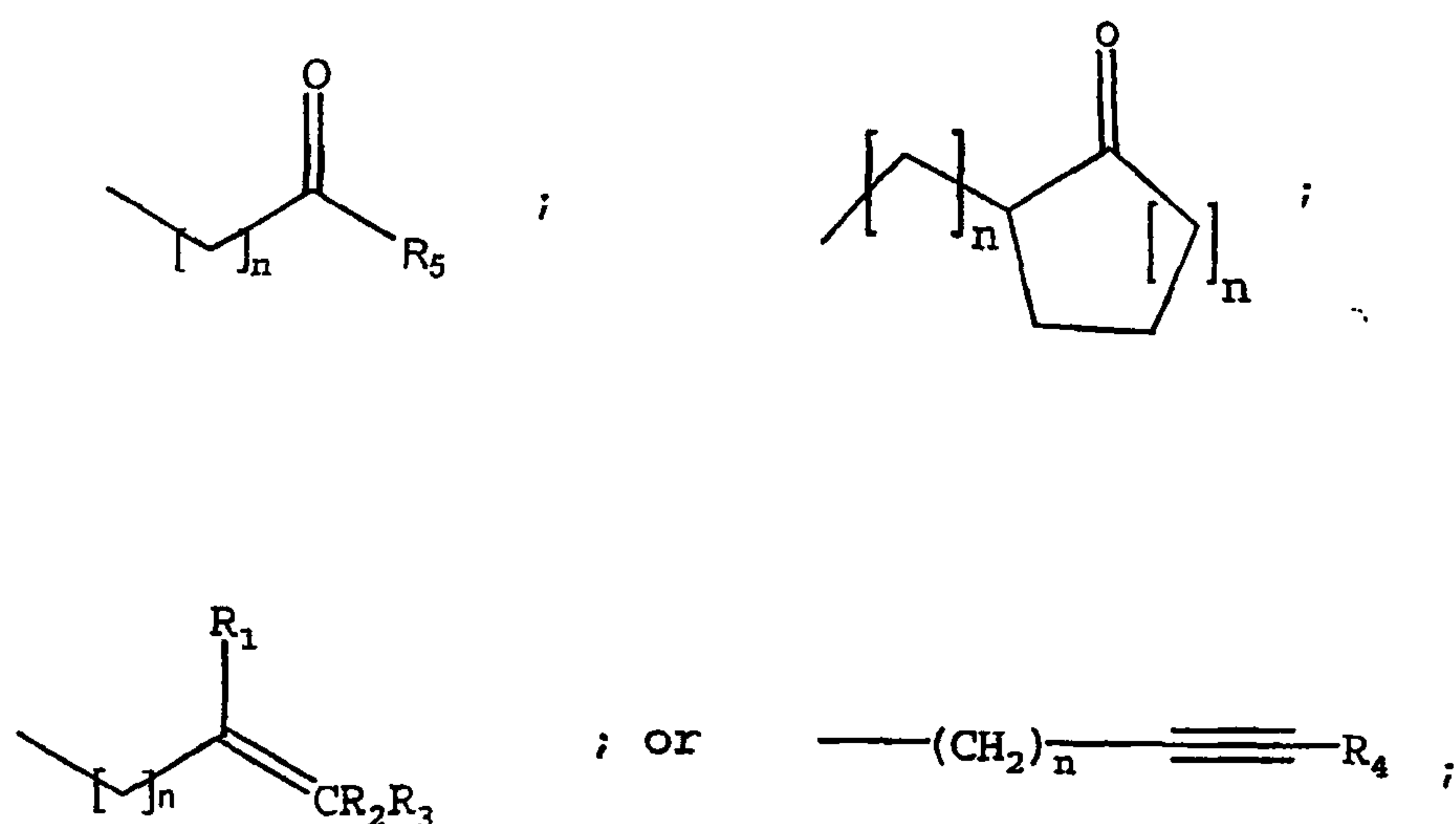
wherein each of Y_1 , Y_2 , Y_3 , and Y_4 is independently -

5 H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -N(R₄)₂, -CON(R₄)₂, or -COOR₄; aryl or heteroaryl; or any two of Y₁, Y₂, Y₃ and Y₄ present on adjacent carbon atoms can constitute a methylenedioxy group;

10 wherein each R₄ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

15 wherein A is A', straight chained or branched C₁-C₇ alkyl, aryl, heteroaryl, aryl(C₁-C₆)alkyl or heteroaryl(C₁-C₆)alkyl;

20 wherein A' is



5 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;

10 wherein R_3 is H, straight chained or branched C_1 - C_7 alkyl, -F, -Cl, -Br, -I, - NO_2 , -CN, -OR₆ aryl or heteroaryl;

wherein R_5 is straight chained or branched C_1 - C_7 alkyl, -N(R_4)₂, -OR₆ or aryl;

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

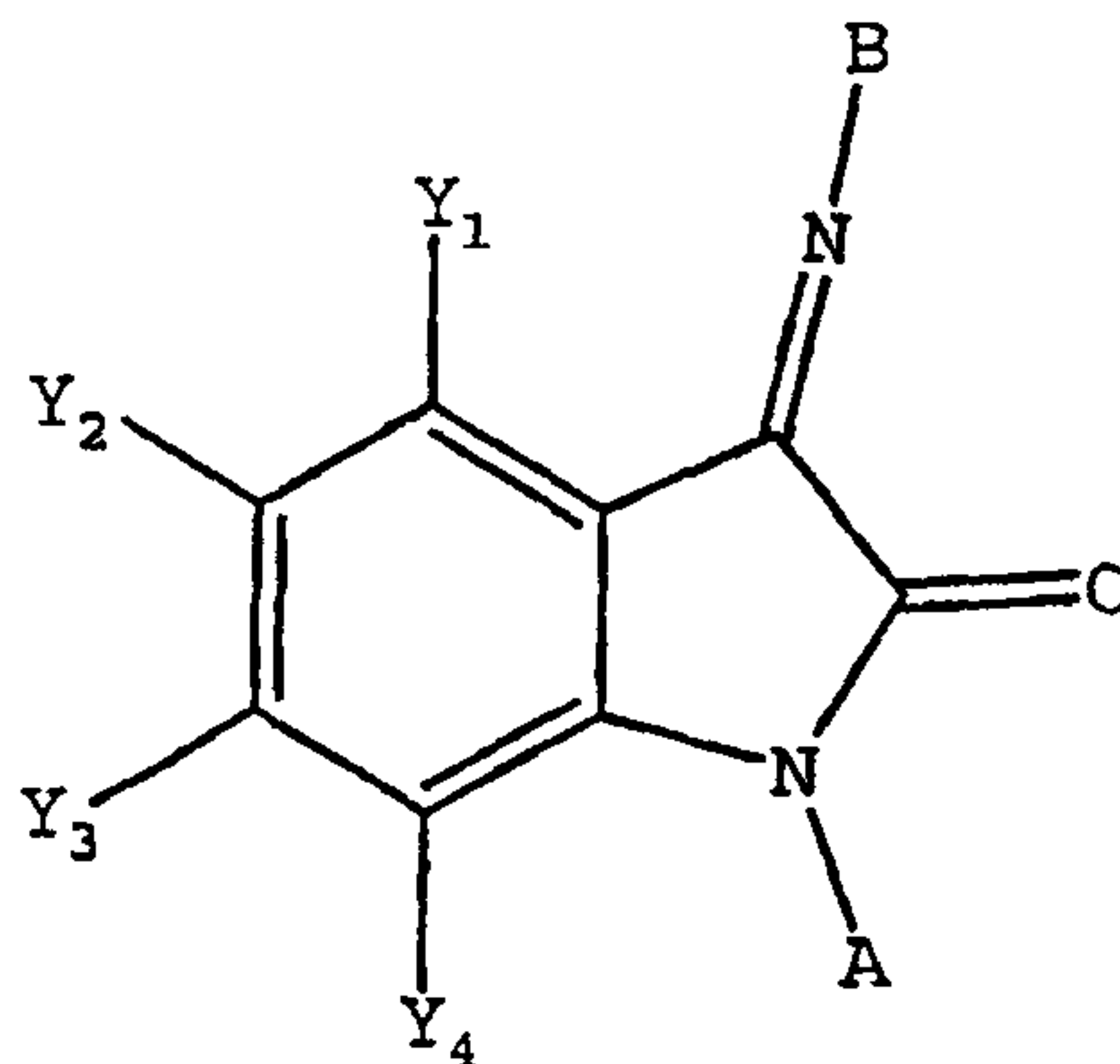
20 wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following -F, -Cl, -Br, -I, -CN, methyl, ethyl or methoxy;

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

or a pharmaceutically acceptable salt thereof.

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

105



wherein each of Y_1 , Y_2 , Y_3 , and Y_4 is independently -
 H; straight chained or branched C_1 - C_7 alkyl,
 5 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
 10 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
 15 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;

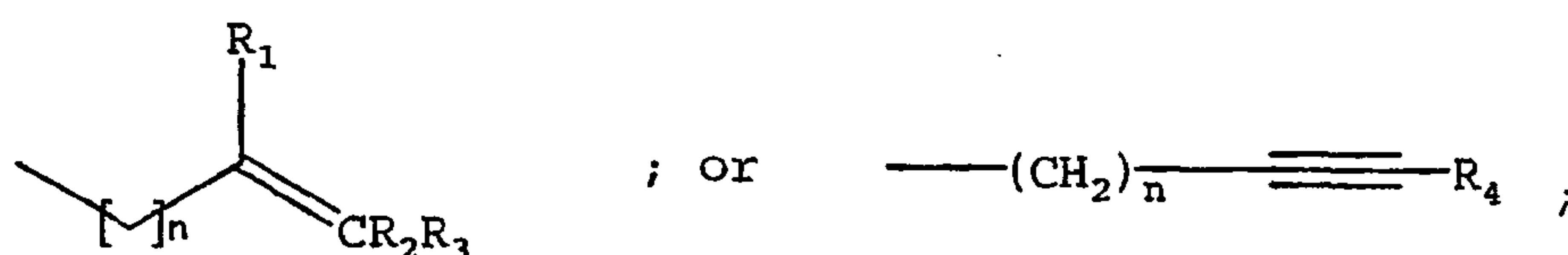
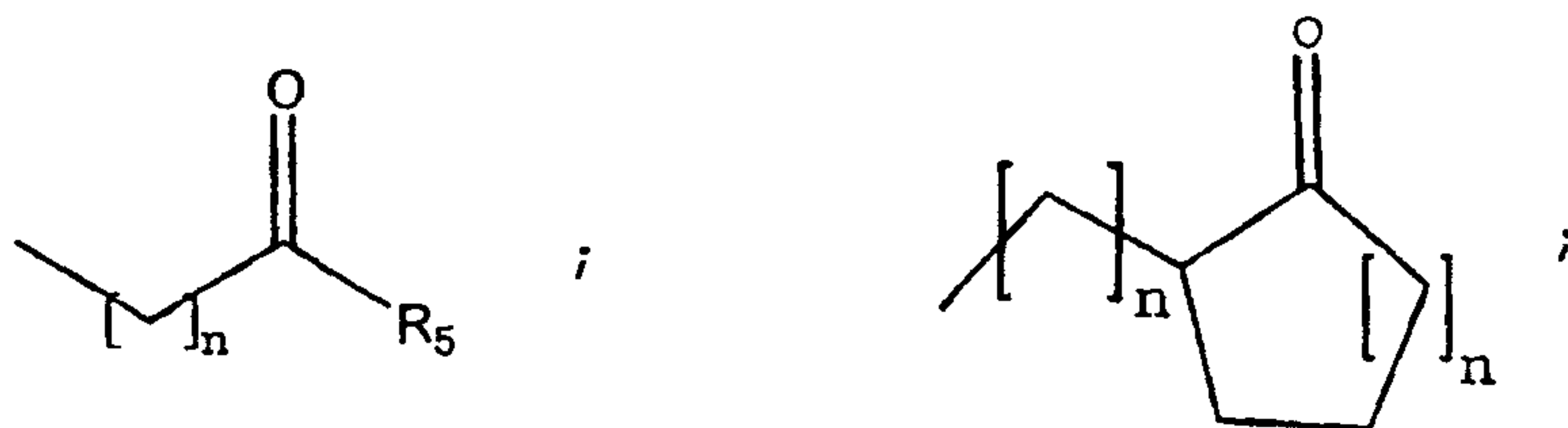
wherein A is A', straight chained or branched C_1 - C_7
 20 alkyl, aryl, heteroaryl, aryl(C_1 - C_6)alkyl or
 heteroaryl(C_1 - C_6)alkyl;

wherein A' is

WO 02/060392

PCT/US02/04608

106



5

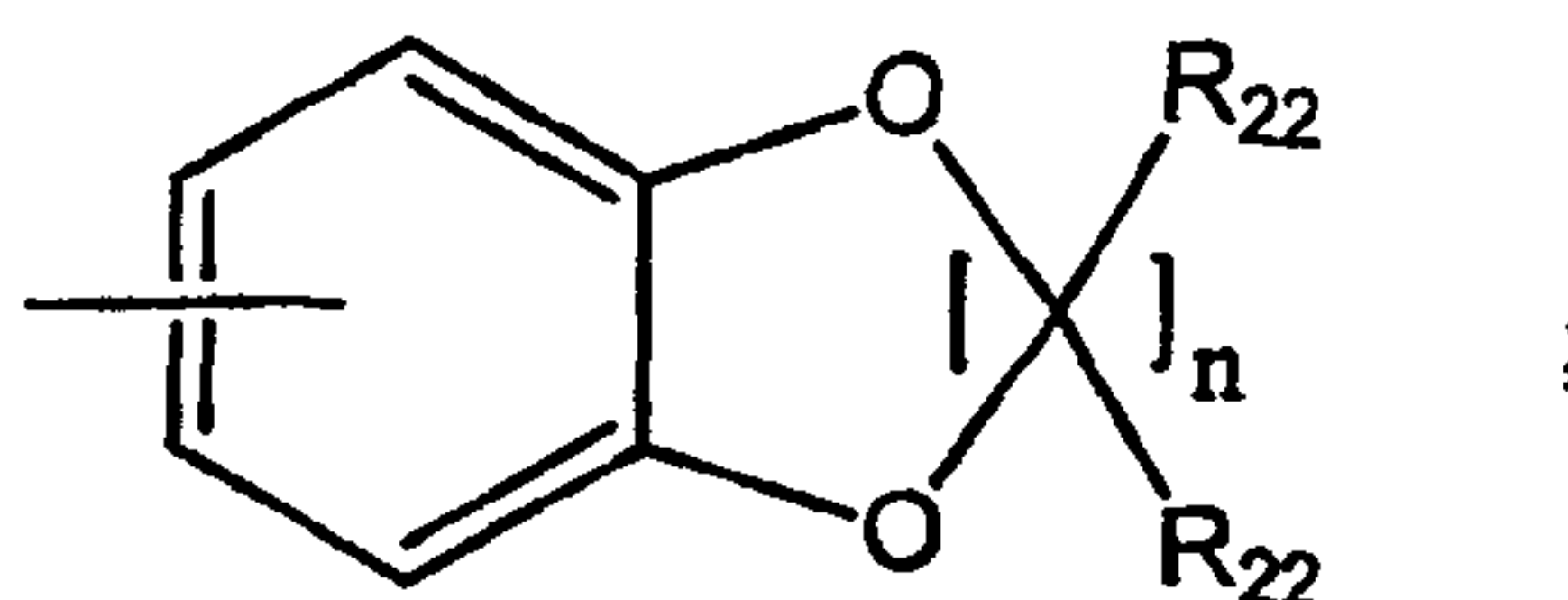
wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q₆;

10

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

15

wherein Q₆ is



wherein n is an integer from 1 to 4 inclusive;

20

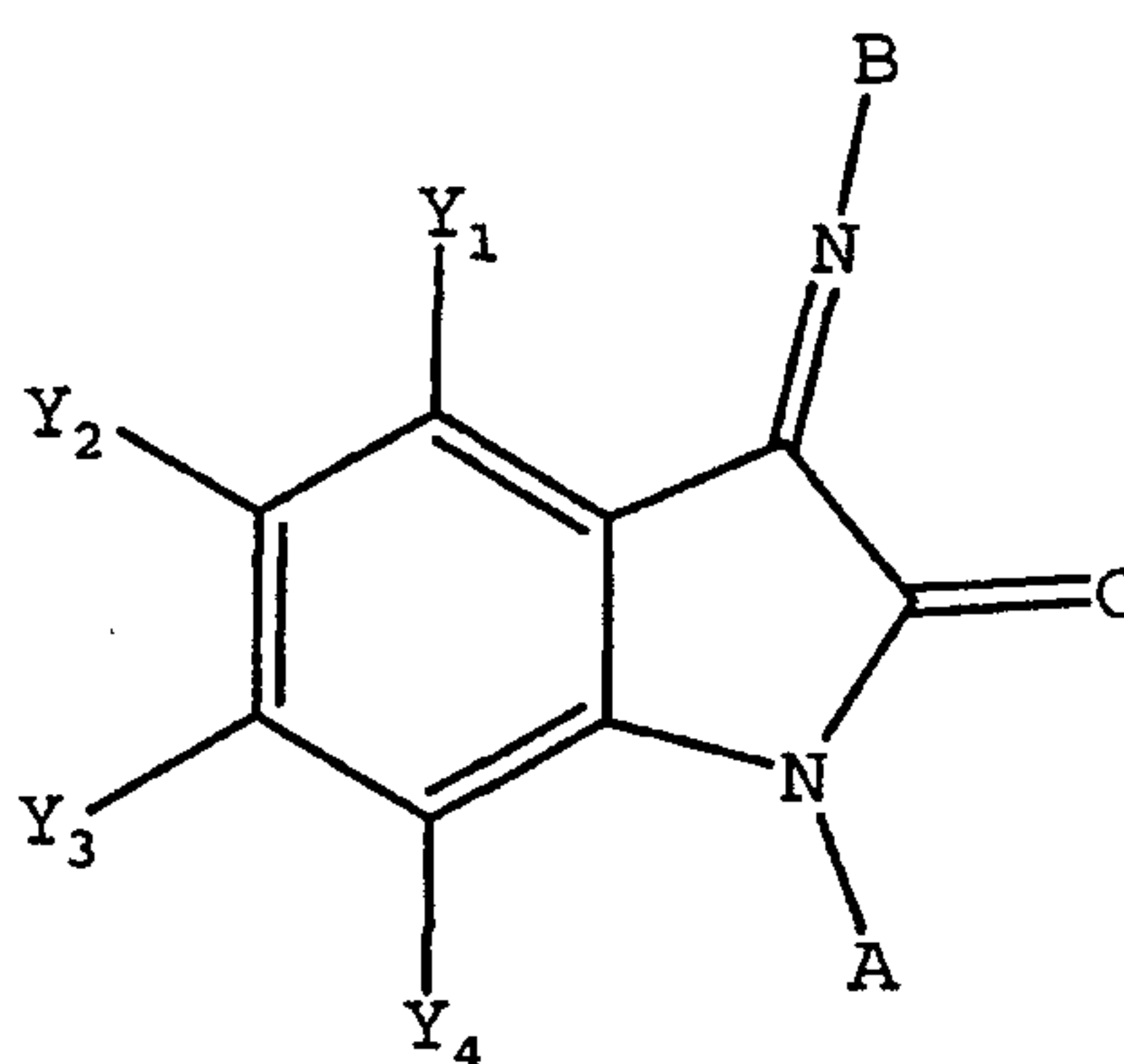
wherein each R₂₂ is independently H, F,

Cl, or straight chained or branched C₁-C₄ alkyl;

or a pharmaceutically acceptable salt thereof.

5

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



10

wherein each of Y₁, Y₂, Y₃, and Y₄ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -N(R₄)₂, -CON(R₄)₂, or -COOR₄; aryl or heteroaryl; or any two of Y₁, Y₂, Y₃ and Y₄ present on adjacent carbon atoms can constitute a methylenedioxy group;

15

20

wherein each R₄ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇

25

WO 02/060392

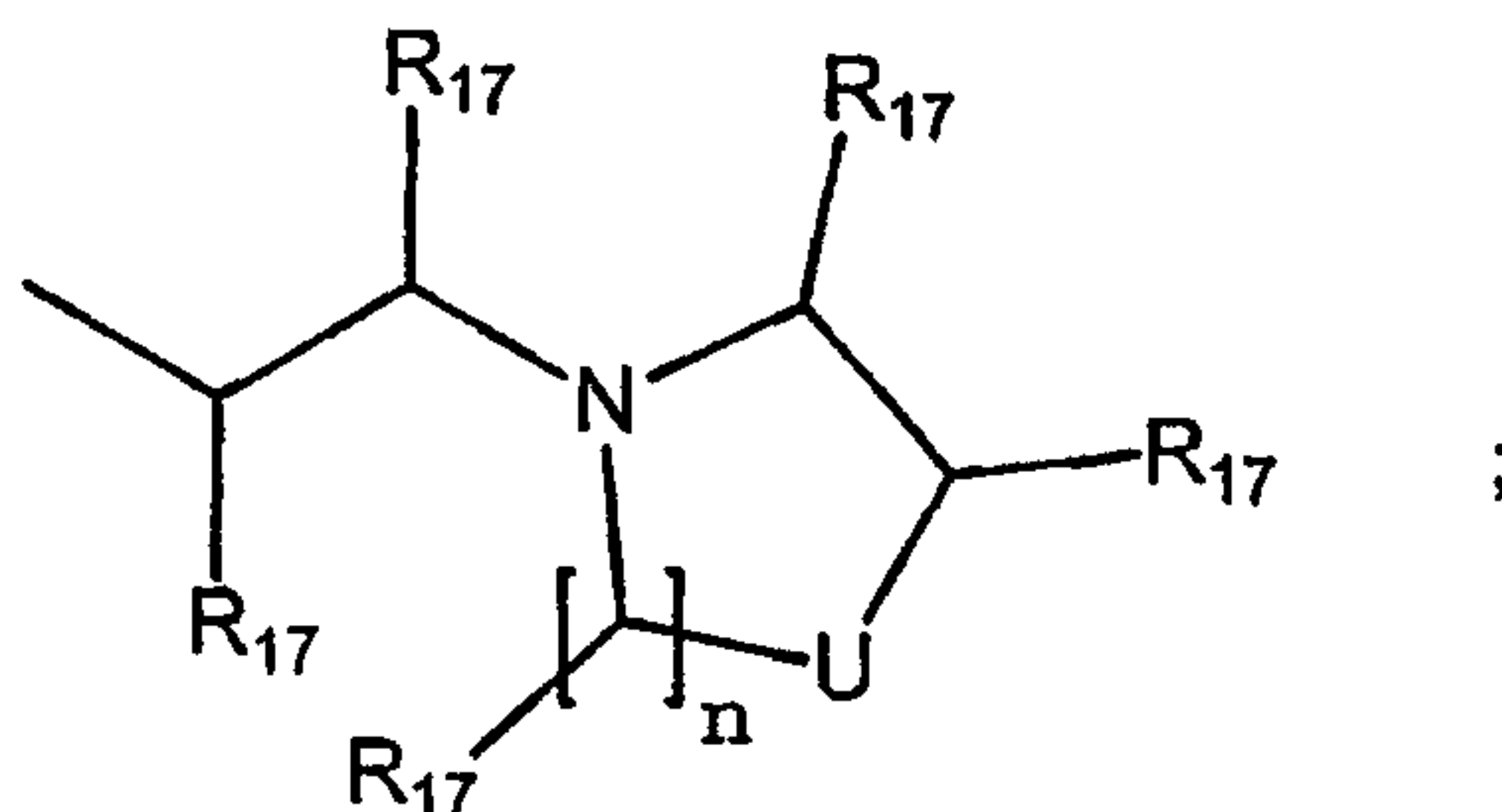
PCT/US02/04608

108

cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

wherein A is Q₃, Q₄, Q₅, aryl substituted with an
aryl or heteroaryl, heteroaryl substituted with an
5 aryl or heteroaryl, or (CHR₁₇) - (CHR₁₇)_n-Z;

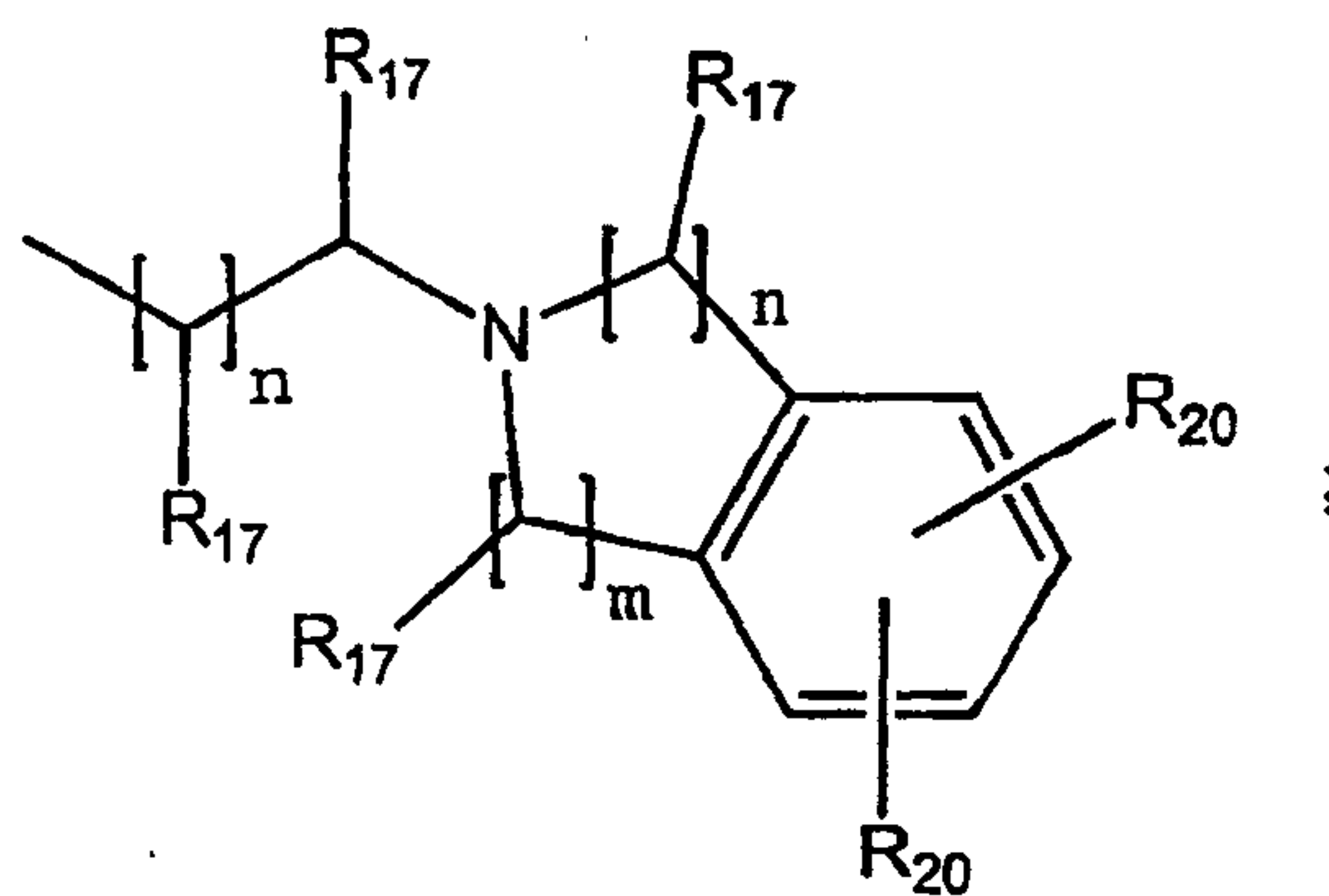
wherein Q₃ is



10

15

wherein Q₄ is



wherein Q₅ is

WO 02/060392

PCT/US02/04608

110

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;

5

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

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

10

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

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

15

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

20

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

25

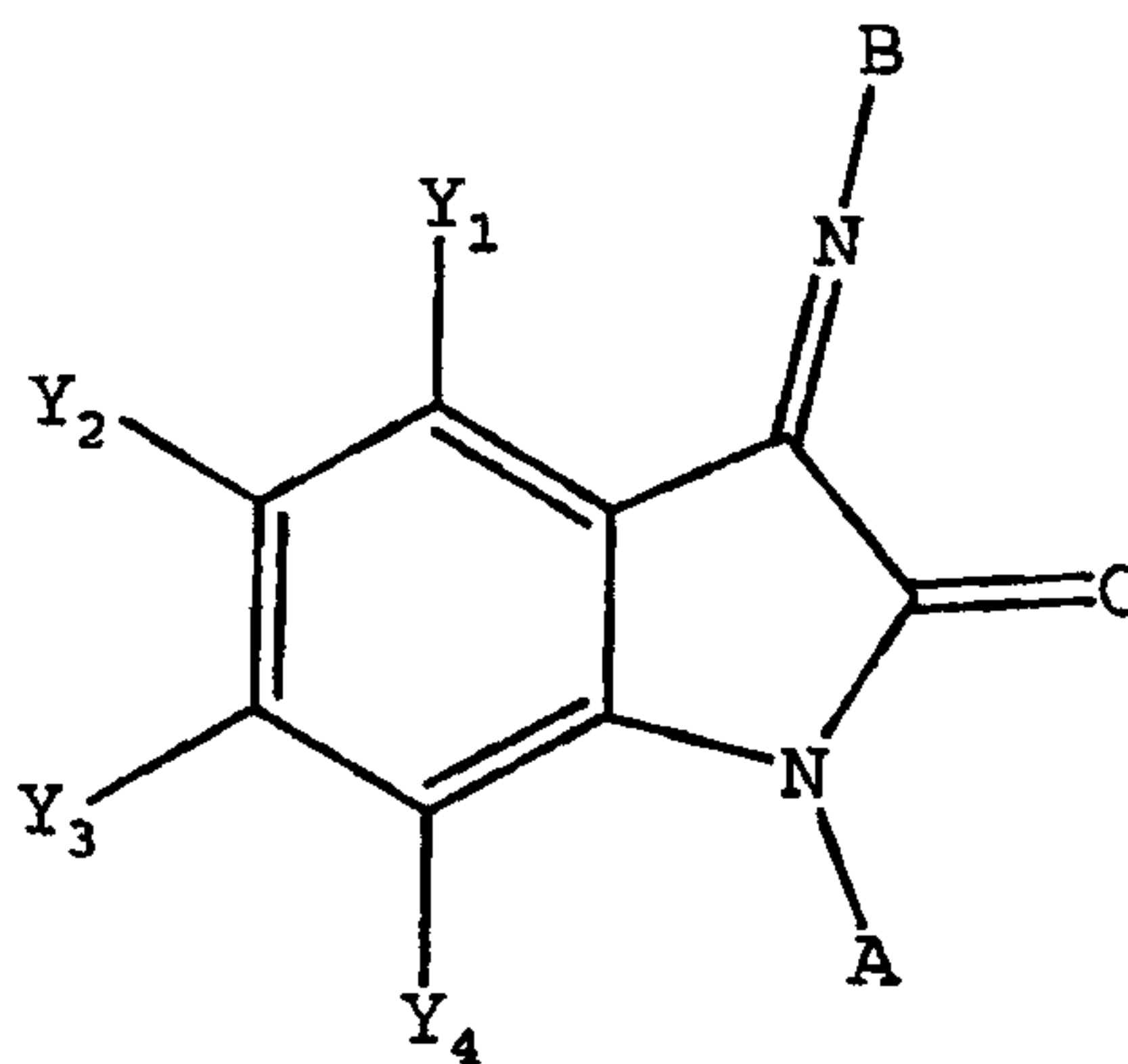
wherein B is aryl, or heteroaryl; provided however, if B is aryl or heteroaryl the carbon atom or carbon atoms ortho to the nitrogen atom of the imine bond may only be substituted with one or more of the following $-F$, $-Cl$, $-Br$, $-I$, $-CN$, methyl, ethyl or methoxy;

30

or a pharmaceutically acceptable salt thereof.

5

The invention provides a compound having the structure:



10

15

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;

20

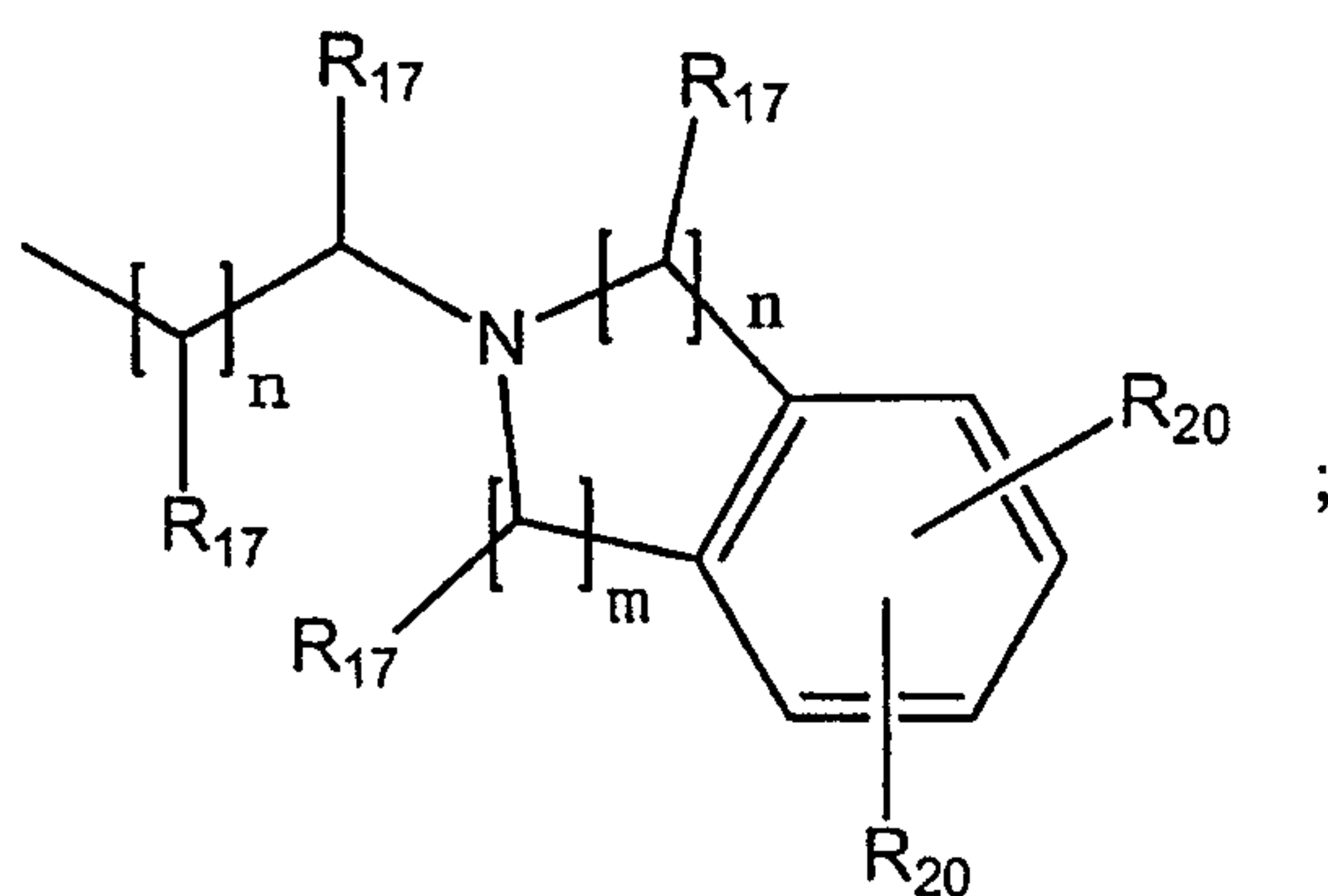
wherein each R_4 is independently -H; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, C_5 - C_7

WO 02/060392

PCT/US02/04608

113

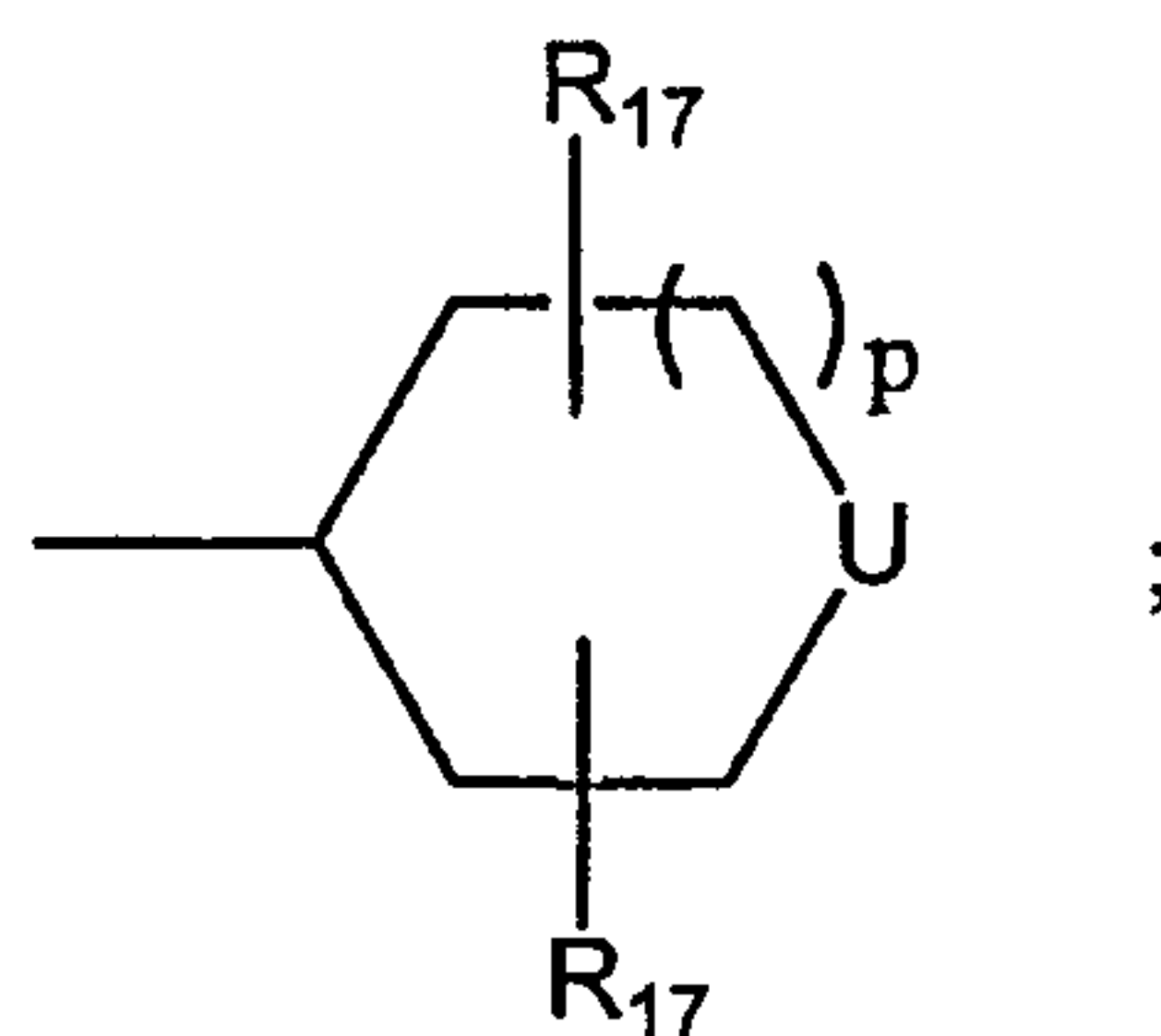
wherein Q₄ is



5

10

wherein Q₅ is



15

wherein R₁ and R₂ are each independently H, straight chained or branched C₁-C₇ alkyl, -F, -Cl, -Br, -I, -NO₂, or -CN;

20

wherein R₃ is H, straight chained or branched C₁-C₇ alkyl, -F, -Cl, -Br, -I, -NO₂, -CN, -OR₆, aryl or heteroaryl;

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

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

10 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 $(CH_2)_n-O-(CH_2)_m-CH_3$;

15

20 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;

25

30 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;

5

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

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

10

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

15

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

20

wherein q is an integer from 2 to 4 inclusive;

25

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

WO 02/060392

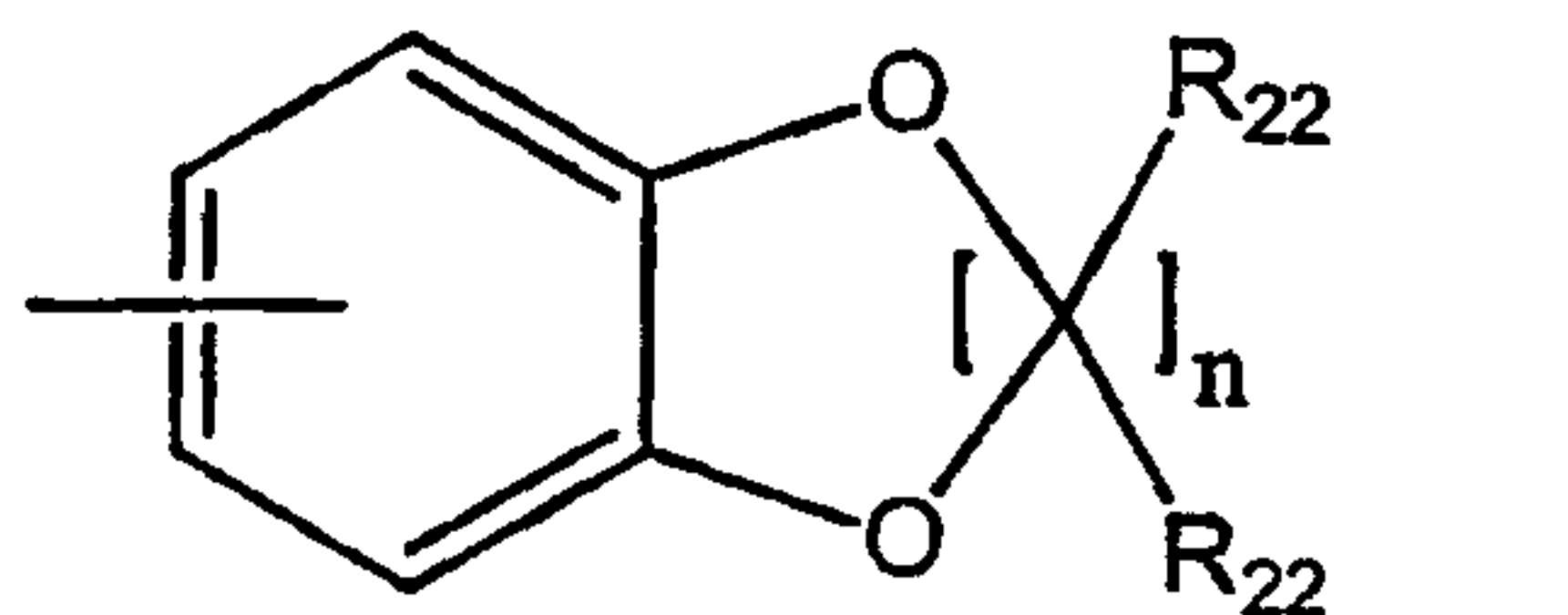
PCT/US02/04608

116

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

5 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 Q₆ is



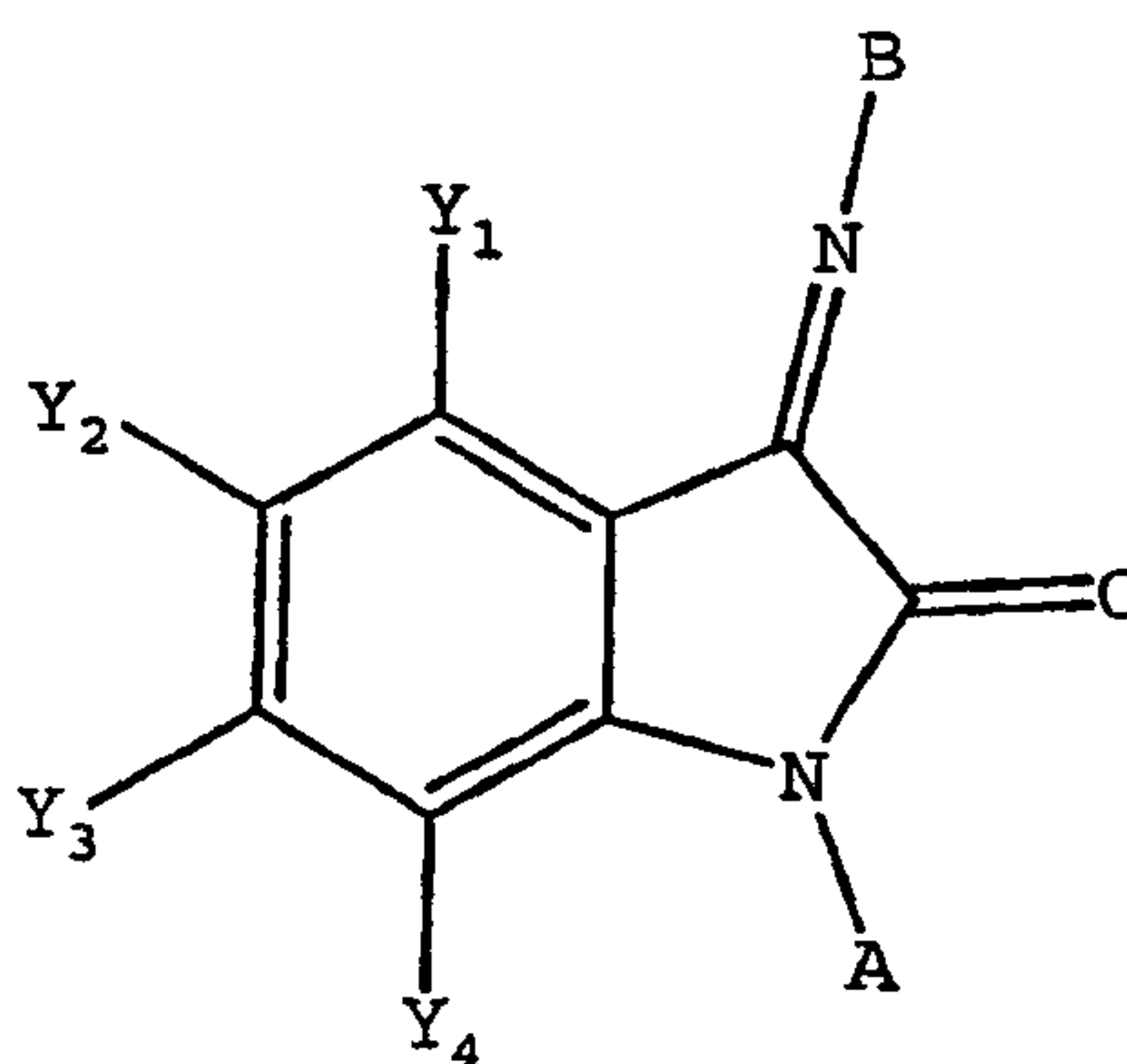
10

wherein each R₂₂ is independently H, F, Cl, or straight chained or branched C₁-C₄ alkyl;

or a pharmaceutically acceptable salt thereof.

15

The invention provides a compound having the structure:



20

wherein each of Y₁, Y₂, Y₃, and Y₄ is independently - H; straight chained or branched C₁-C₇ alkyl,

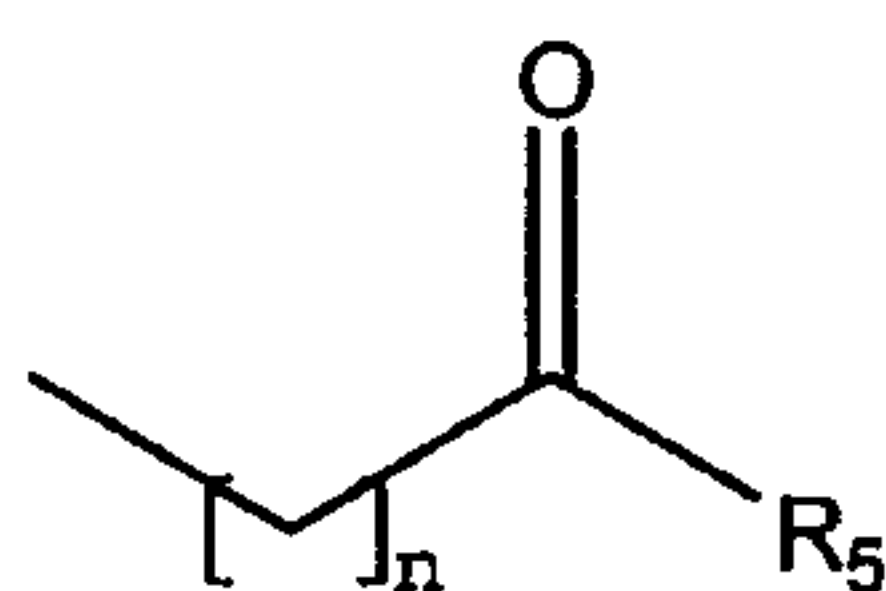
monofluoroalkyl or polyfluoroalkyl; straight chained
or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
cycloalkyl, or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -
I; -NO₂; -N₃; -CN; -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -
5 N(R₄)₂, -CON(R₄)₂, or -COOR₄; aryl or heteroaryl; or
any two of Y₁, Y₂, Y₃ and Y₄ present on adjacent
carbon atoms can constitute a methylenedioxy group;

wherein each R₄ is independently -H; straight chained
10 or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇
cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

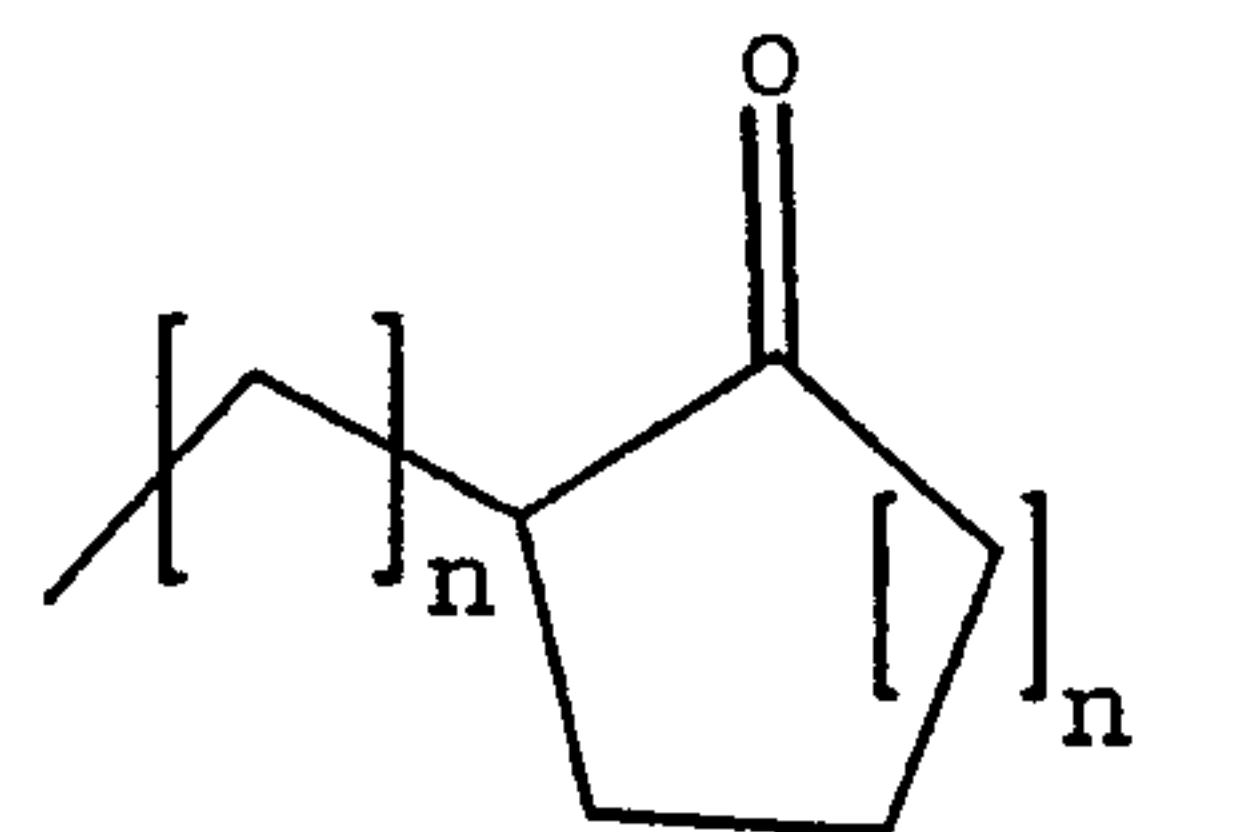
wherein A is A', straight chained or branched C₁-C₇
15 alkyl, aryl, heteroaryl, aryl(C₁-C₆)alkyl or
heteroaryl(C₁-C₆)alkyl;

wherein A' is

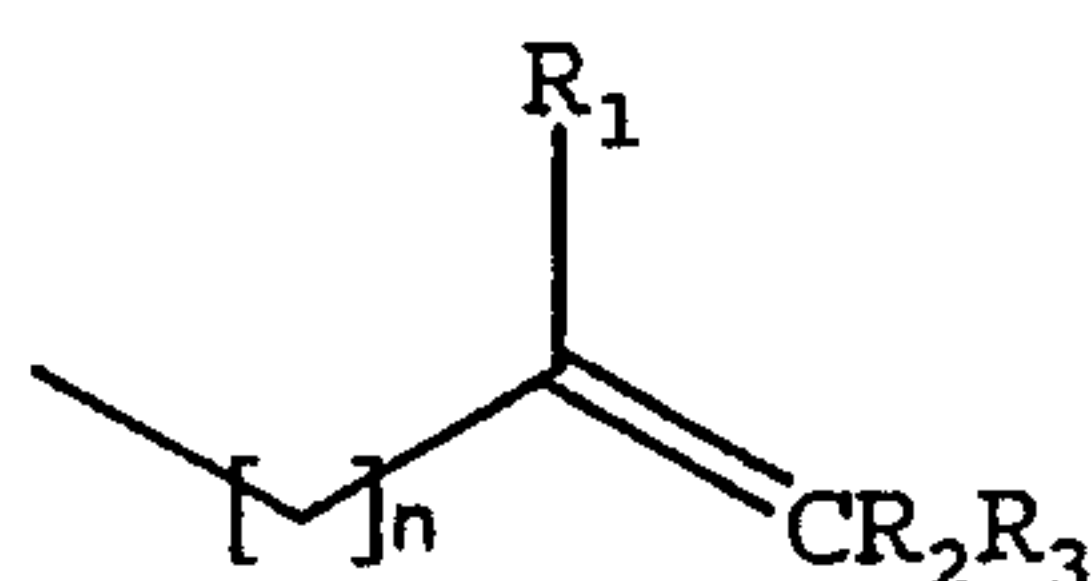
20



;



;



; or



;

25

WO 02/060392

PCT/US02/04608

118

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;

5

wherein R_3 is H, straight chained or branched C_1 - C_7 alkyl, -F, -Cl, -Br, -I, - NO_2 , -CN, -OR₆ aryl or heteroaryl;

10

wherein R_5 is straight chained or branched C_1 - C_7 alkyl, -N(R_4)₂, -OR₆ or aryl;

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

15

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;

20

wherein n is an integer from 1 to 4 inclusive;

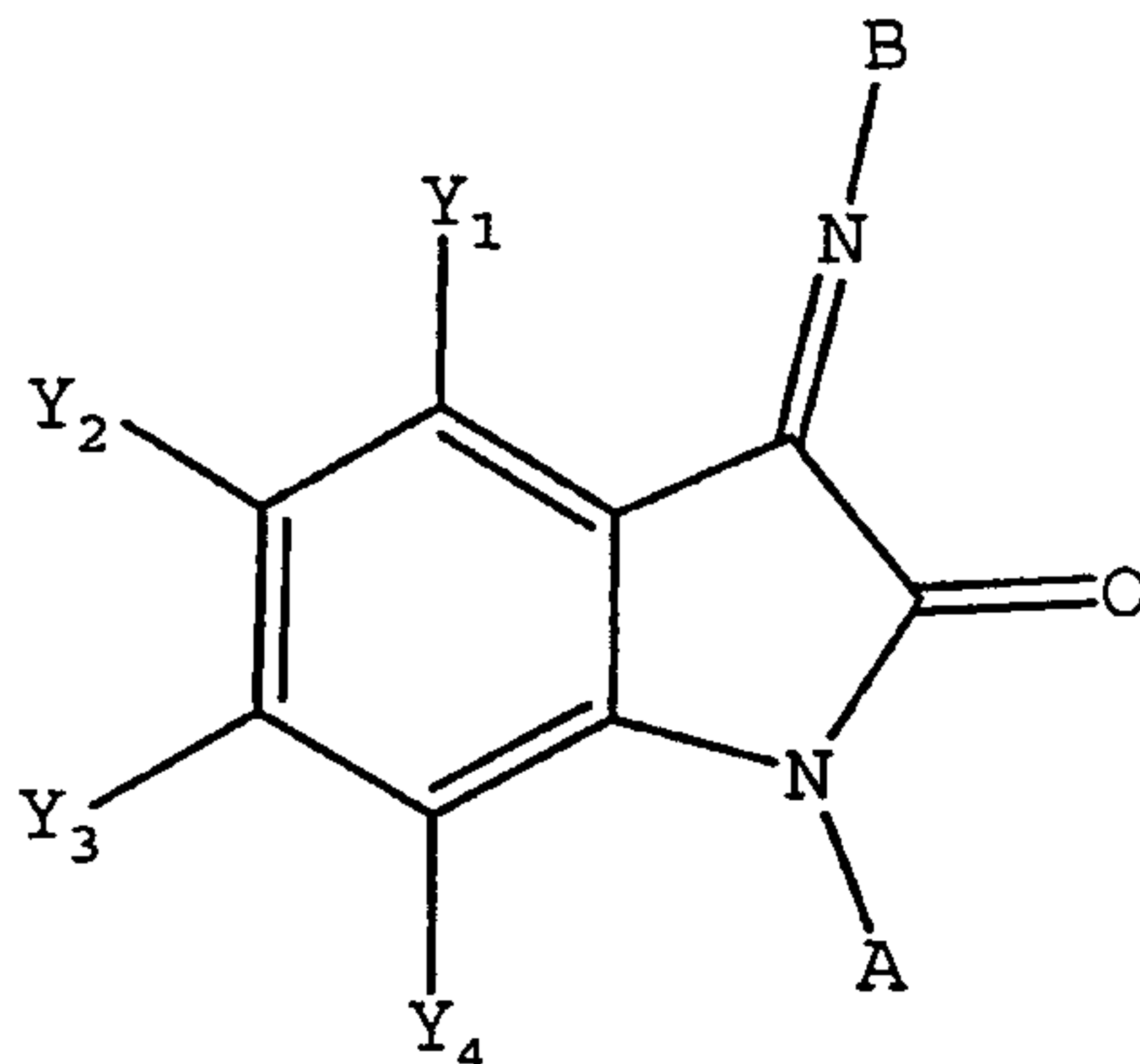
25

or a pharmaceutically acceptable salt thereof.

30

The invention provides a compound having the structure:

119



5 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 , - $NCOR_4$, -
 10 $N(R_4)_2$, - $CON(R_4)_2$, 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;

15 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;

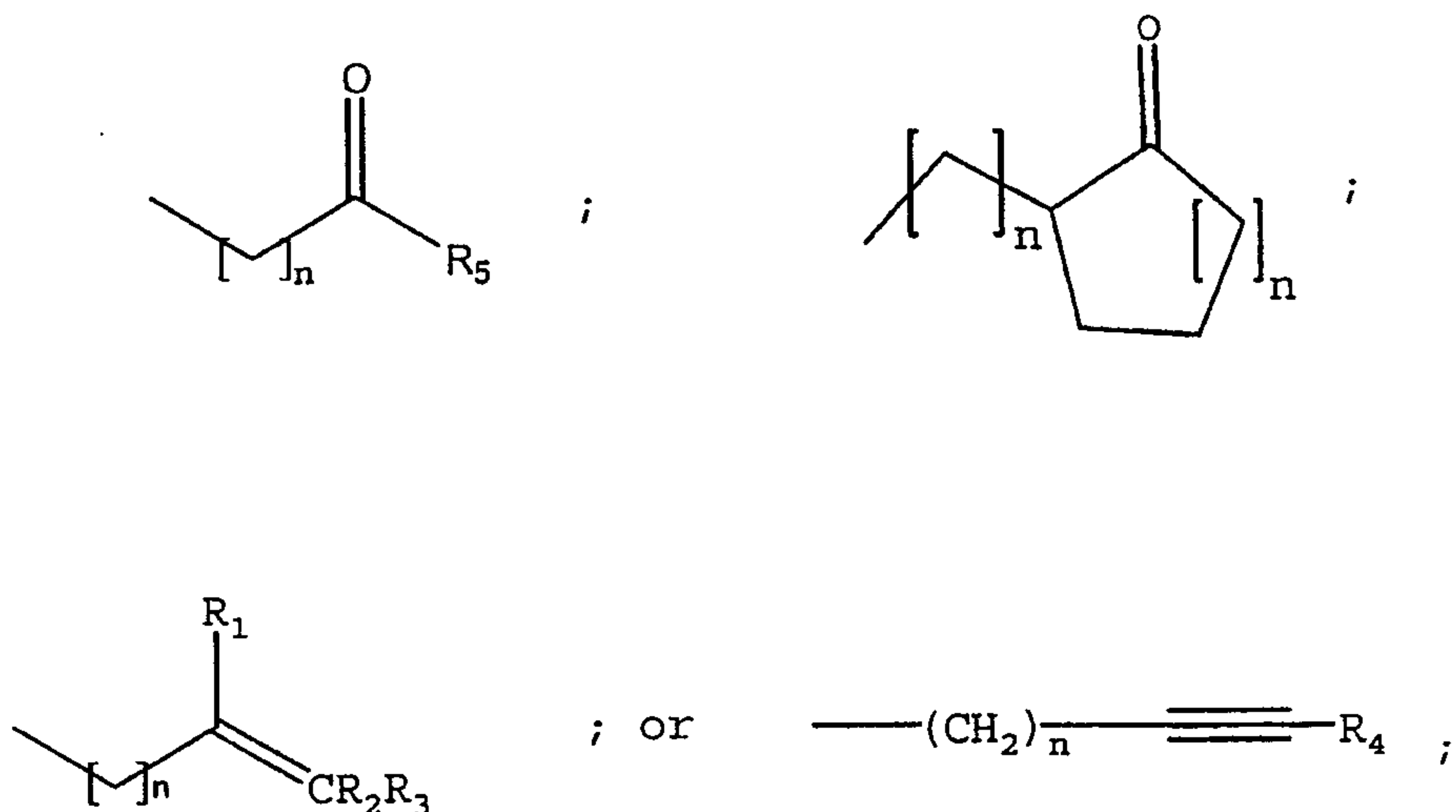
20 wherein A is A', straight chained or branched C_1 - C_7
 alkyl, aryl, heteroaryl, aryl(C_1 - C_6)alkyl or
 heteroaryl(C_1 - C_6)alkyl;

wherein A' is

WO 02/060392

PCT/US02/04608

120



5

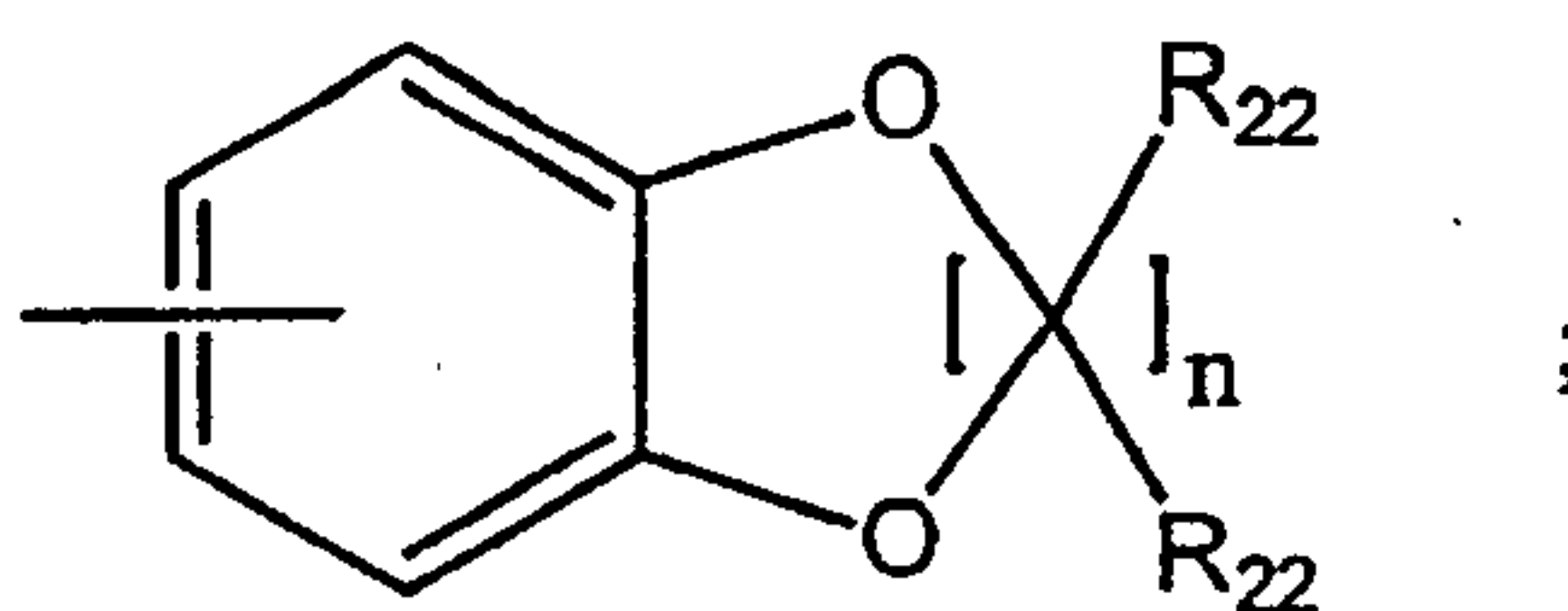
wherein B is aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, tricyclic heteroaryl or Q_6 ;

10

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

15

wherein Q_6 is



20

wherein n is an integer from 1 to 4 inclusive;

WO 02/060392

PCT/US02/04608

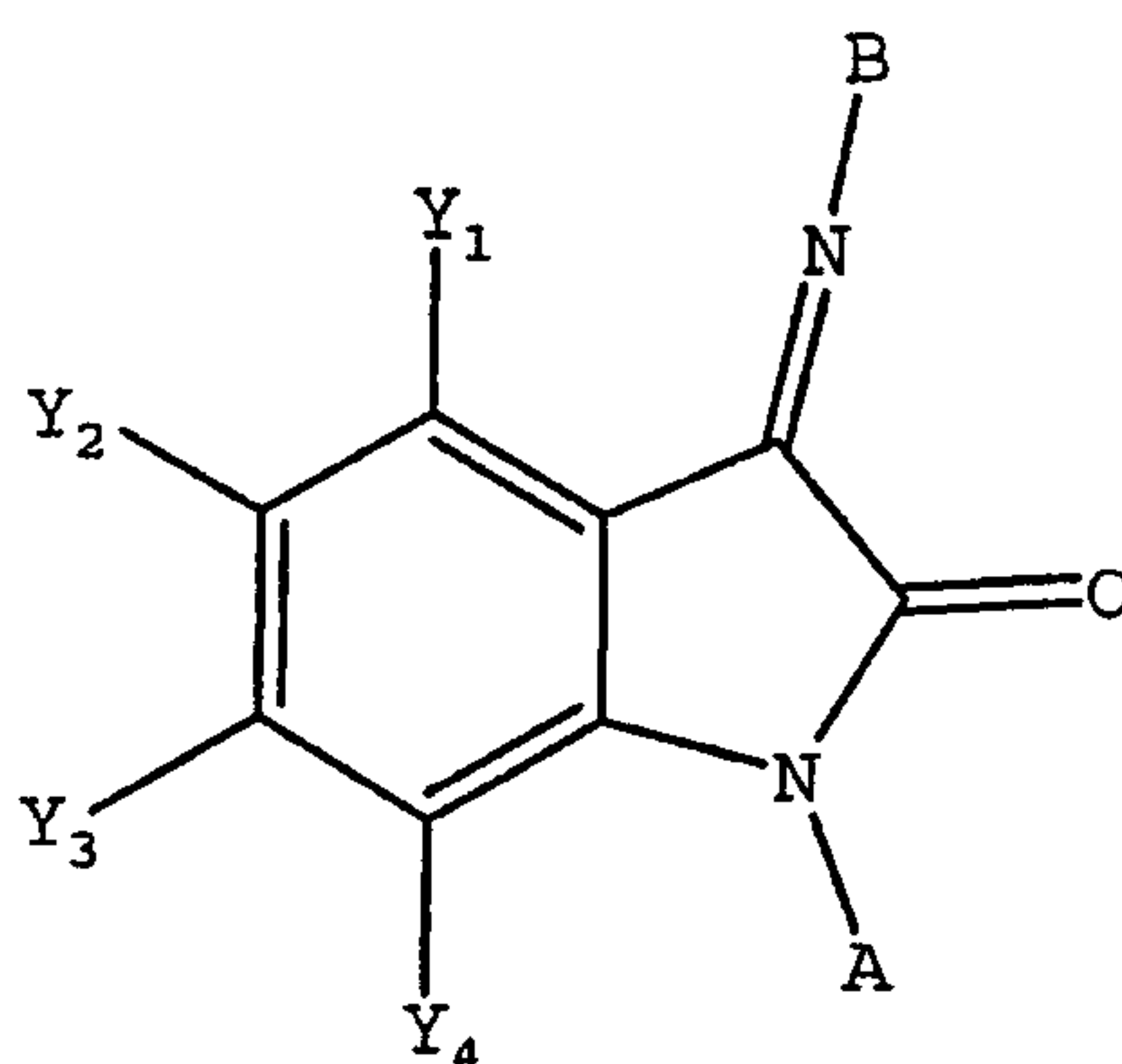
121

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

5

or a pharmaceutically acceptable salt thereof.

10 The invention provides a compound having the structure:



15

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;

20

25

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

WO 02/060392

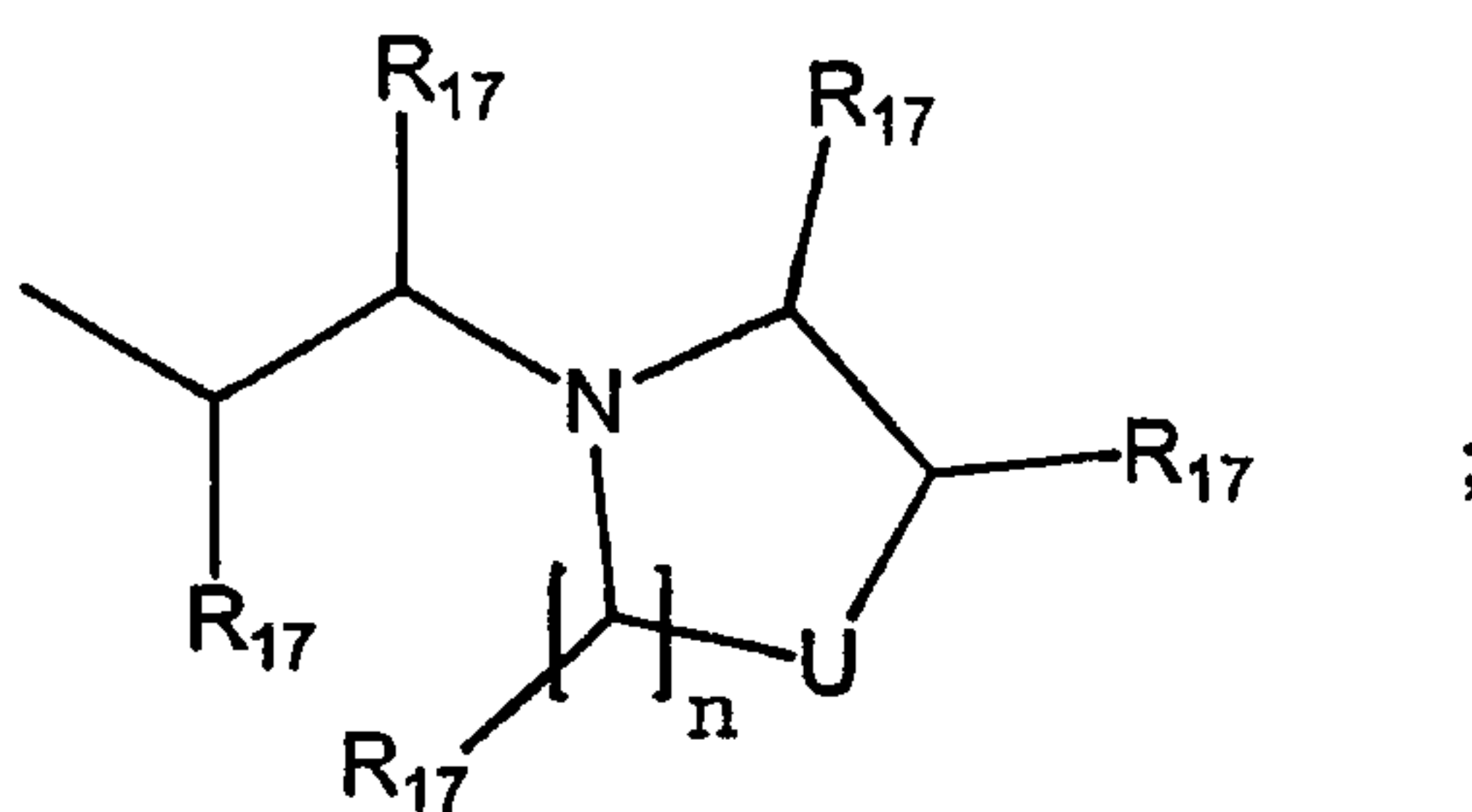
PCT/US02/04608

122

alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

5 wherein A is Q₃, Q₄, Q₅, aryl substituted with an aryl or heteroaryl, heteroaryl substituted with an aryl or heteroaryl, or (CHR₁₇)_n-Z;

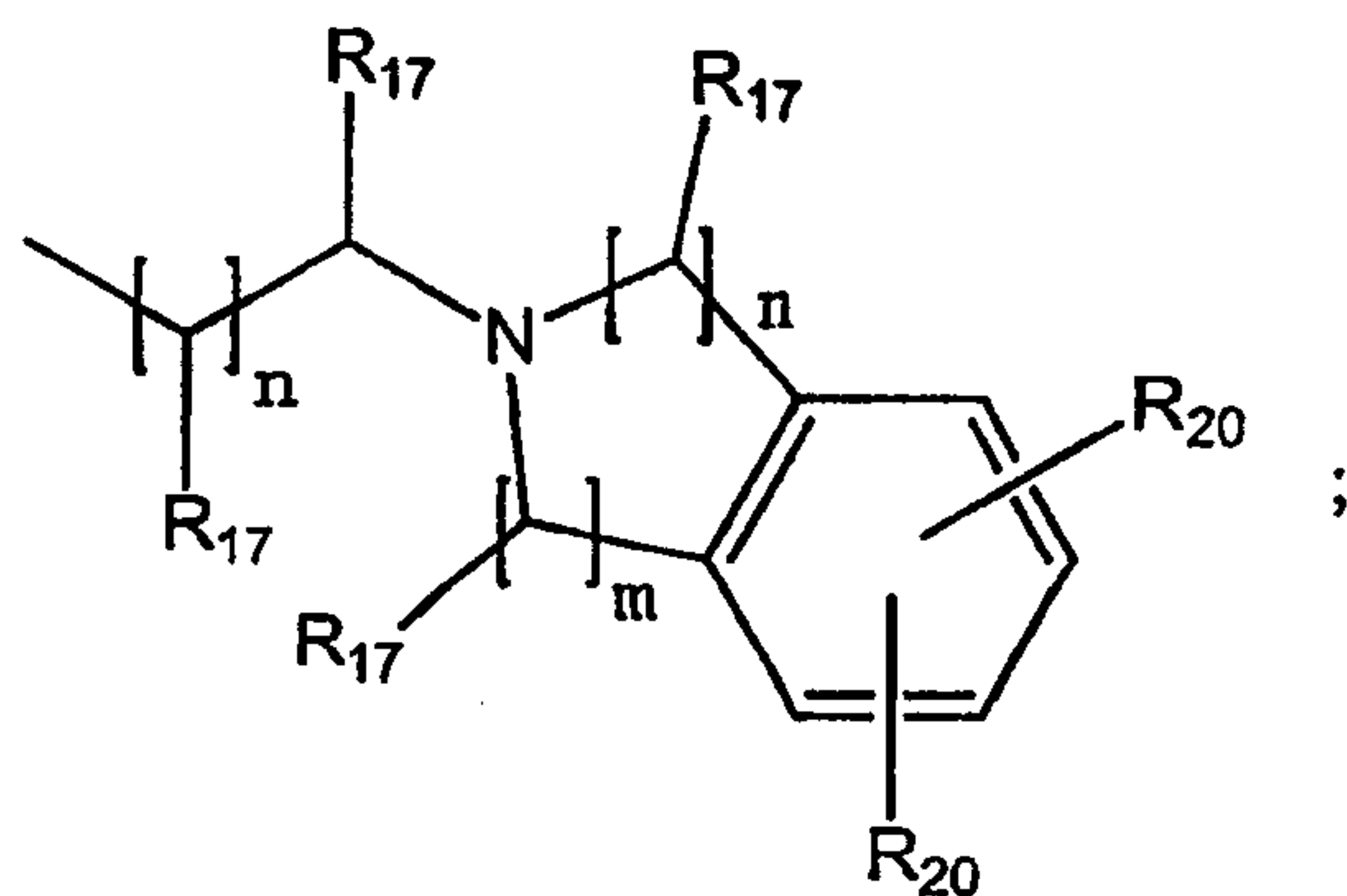
wherein Q₃ is



10

15

wherein Q₄ is

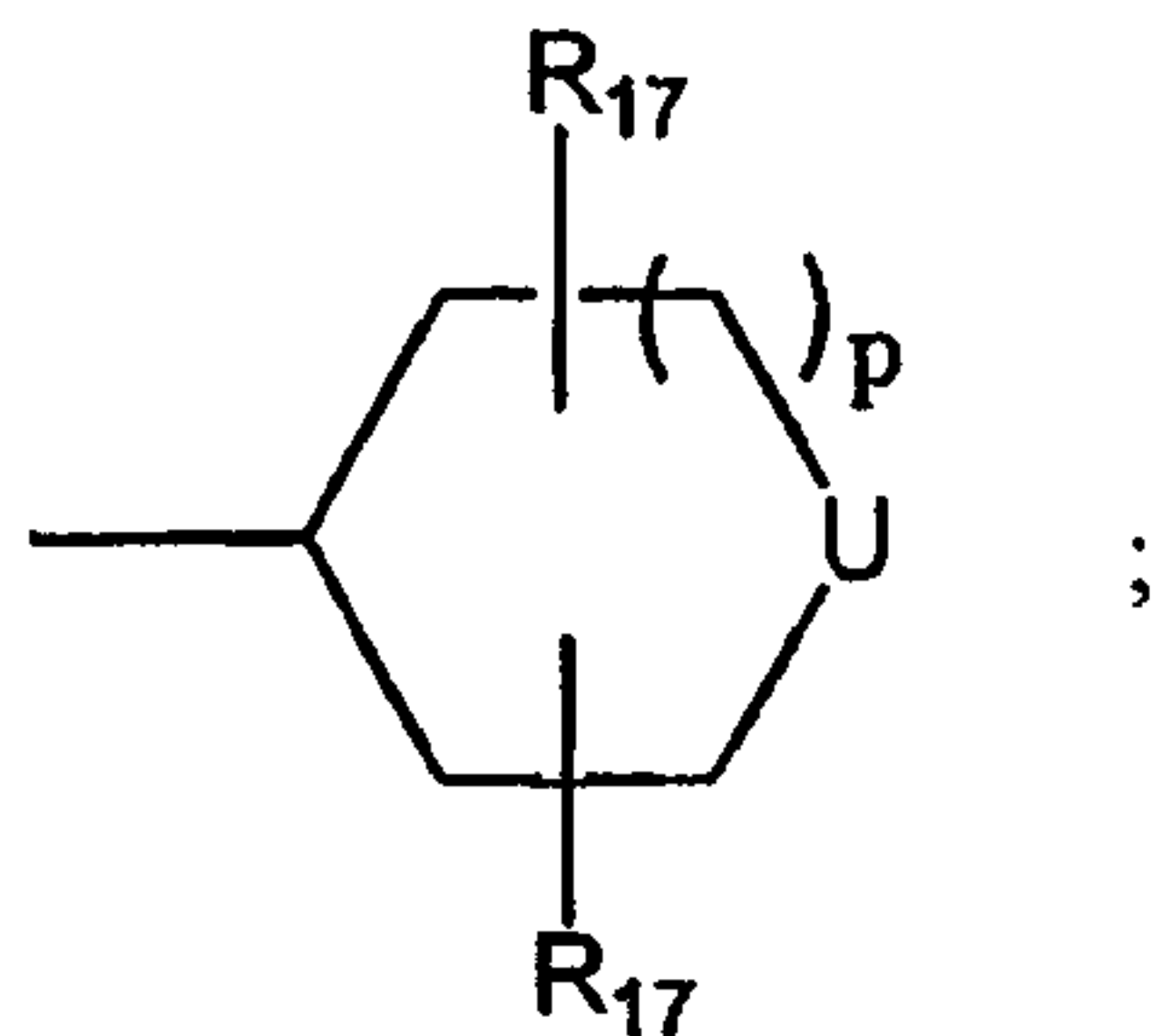


wherein Q₅ is

WO 02/060392

PCT/US02/04608

123



5 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 $(CH_2)_n-O-$
 10 $(CH_2)_m-CH_3$;

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; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R_{20} groups present on adjacent carbon atoms can join together to form a
 15 methylenedioxy group;
 20

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;
 25

WO 02/060392

PCT/US02/04608

124

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;

5

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

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

10

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

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

15

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

20

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

25

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;

30

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 10 μ M; and

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

WO 02/060392

PCT/US02/04608

126

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

- 5 (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 FiguresFigure 1: Rat Forced Swim Test Results (Immobility: Normal Rats)

5 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 intraperitoneal administration (n = 5 for each treatment condition). One hour later, rats were examined in a 5
10 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
15 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)

20 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 intraperitoneal administration (n = 5 for each treatment
25 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
30 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 intraperitoneal 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 intraperitoneal 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

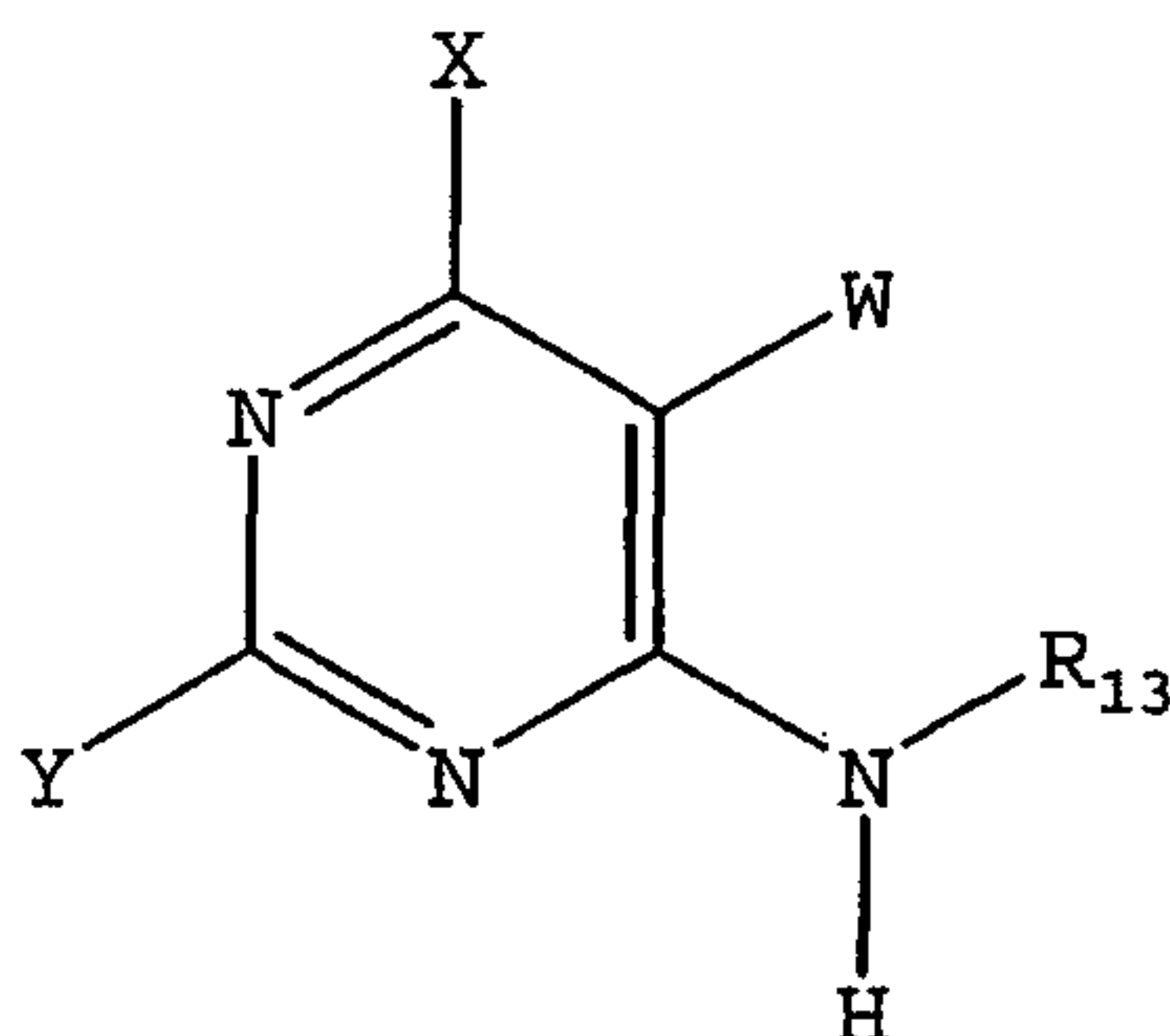
92 was increased to 100 mg/kg, the amount of social interaction time was significantly less than measured after chlordiazepoxide at 5 mg/kg ip or Example 92 at 30 mg/kg ip ($p < 0.01$). Significance in all cases was
5 determined by ANOVA and Student-Nerman-Keuls.

Figure 5: Western Blot Results

In order to establish the specificity of the anti-GAL3 antiserum, membranes prepared from COS-7 cells
10 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-
15 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
20 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
25 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.

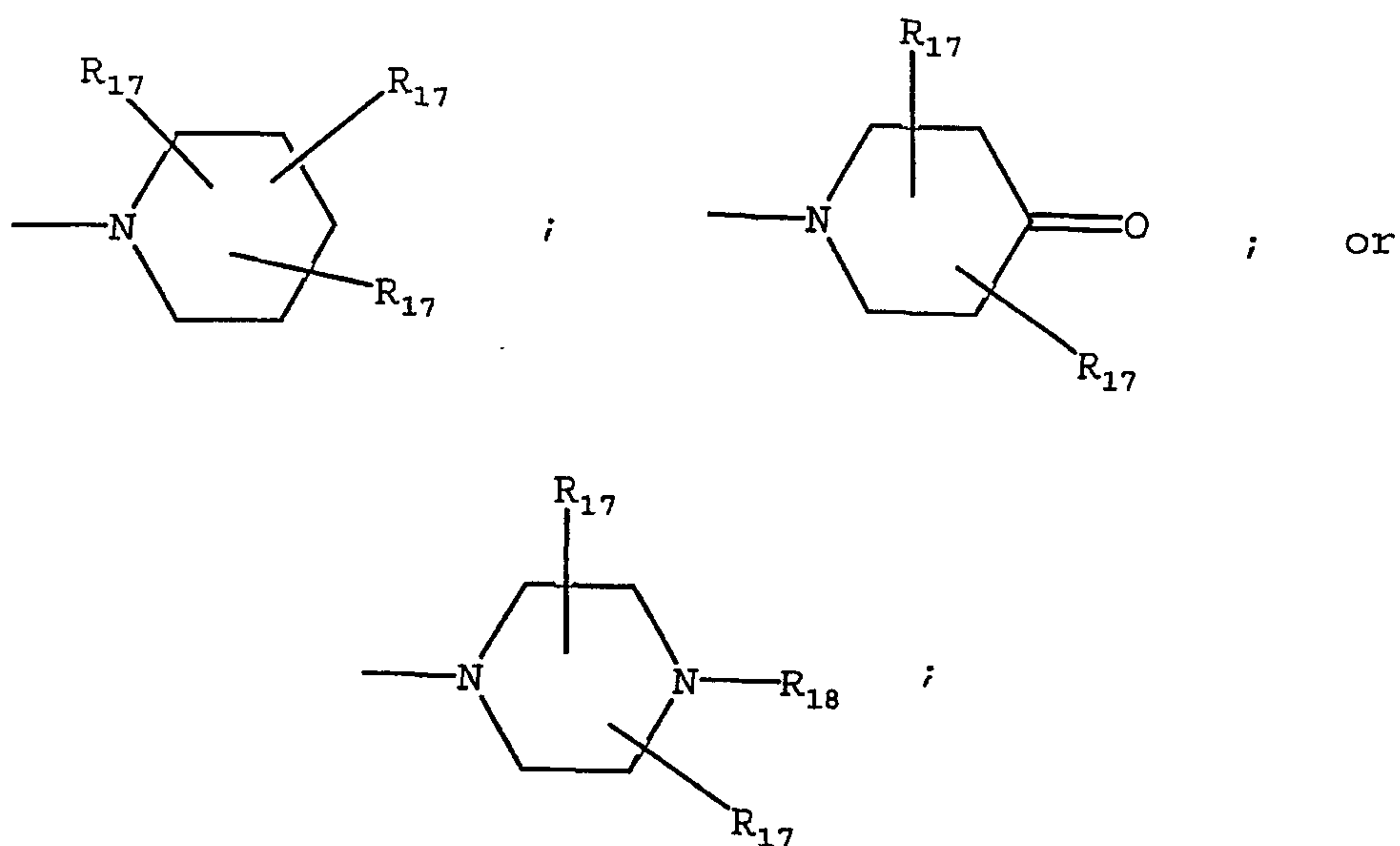
Detailed Description of the Invention

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; NR₁₁R₁₂;



wherein R₁₁ is H, straight chained or branched C₁-C₇ alkyl,

WO 02/060392

PCT/US02/04608

131

$(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$, aryl, or aryl $(\text{C}_1\text{-C}_6)$ alkyl;

wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$, or $\text{-(CH}_2)_m\text{-Z}$;

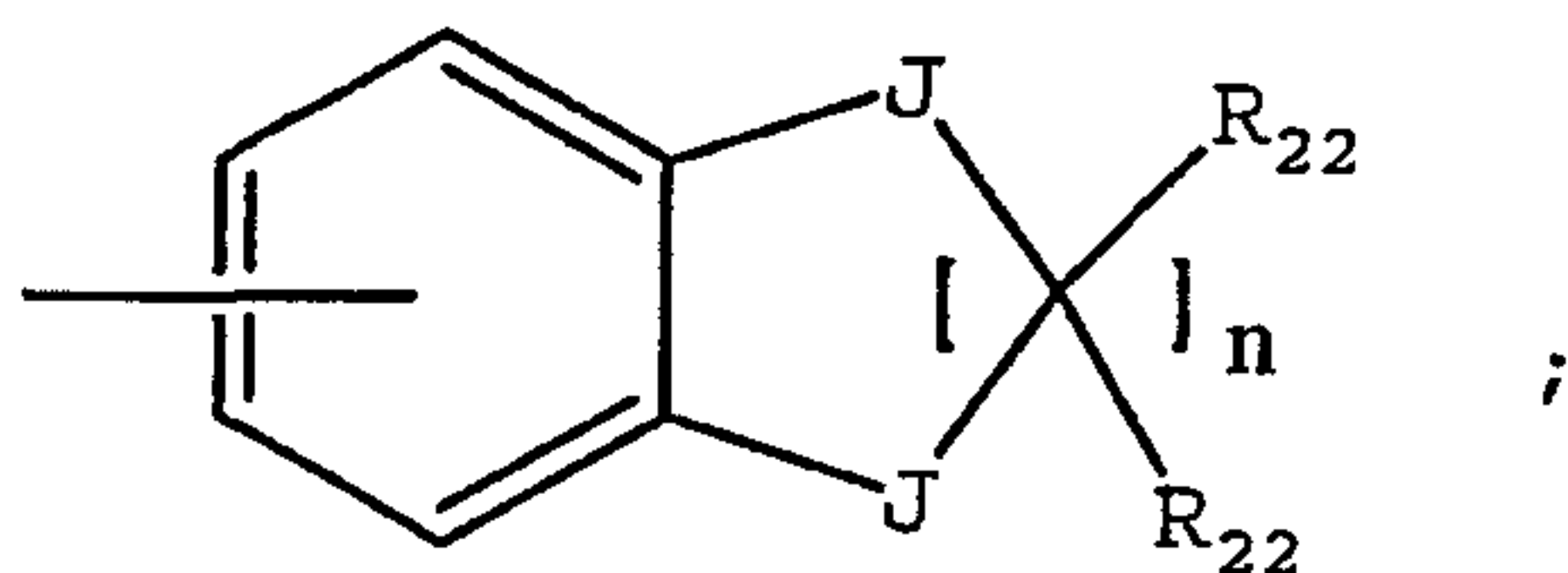
5

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, heteroaryl, aryl, aryl $(\text{C}_1\text{-C}_6)$ alkyl, Q_1 or Q_2 ;

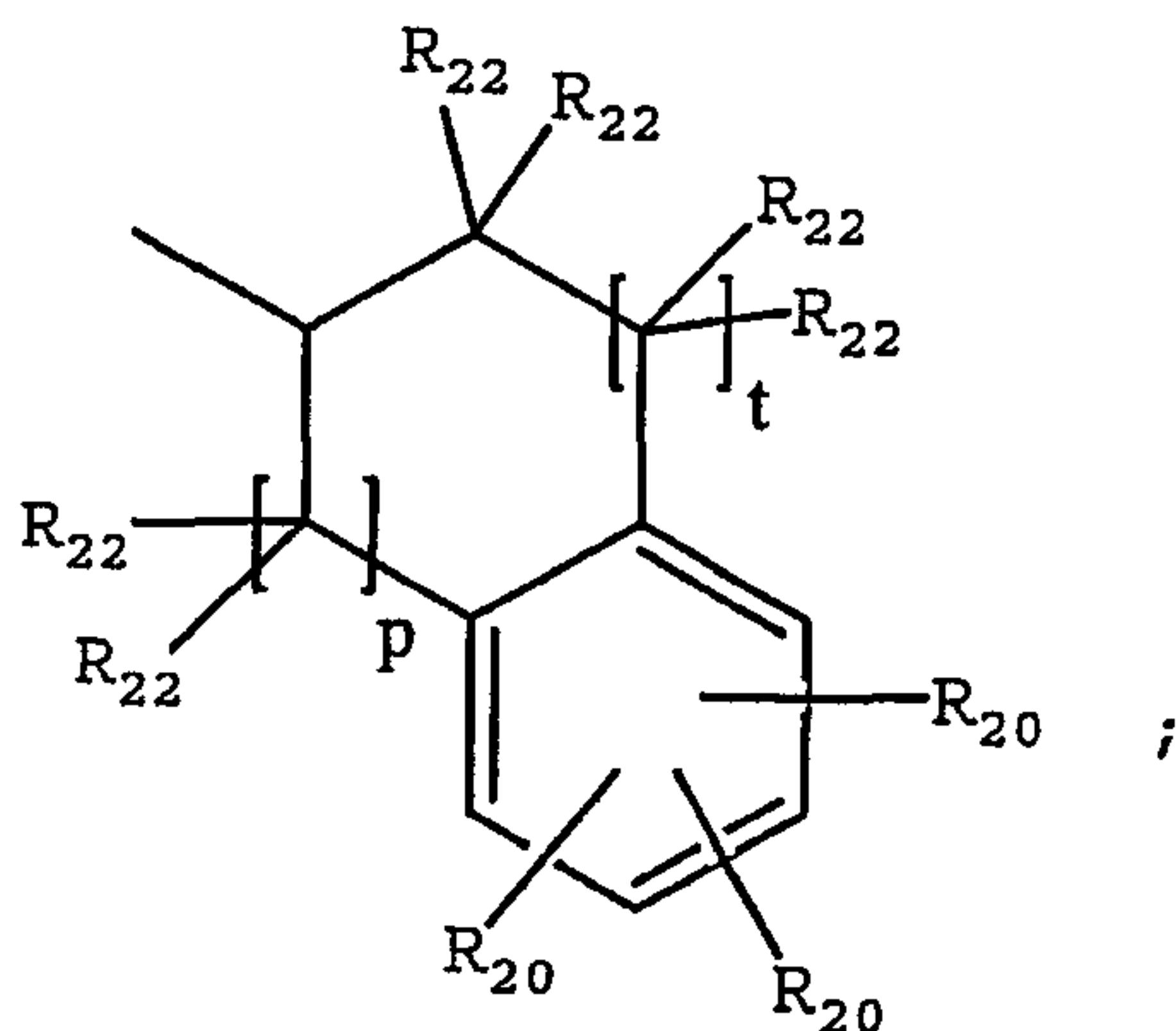
10 wherein aryl may be substituted with one or more $\text{C}_1\text{-C}_{10}$ straight chained or branched alkyl, aryl, heteroaryl, or $\text{N}(\text{R}_{19})\text{-Z}$;

wherein Q_1 is

15



wherein Q_2 is



20

wherein each J is independently O , S , $\text{C}(\text{R}_{22})_2$ or NR_4 ;

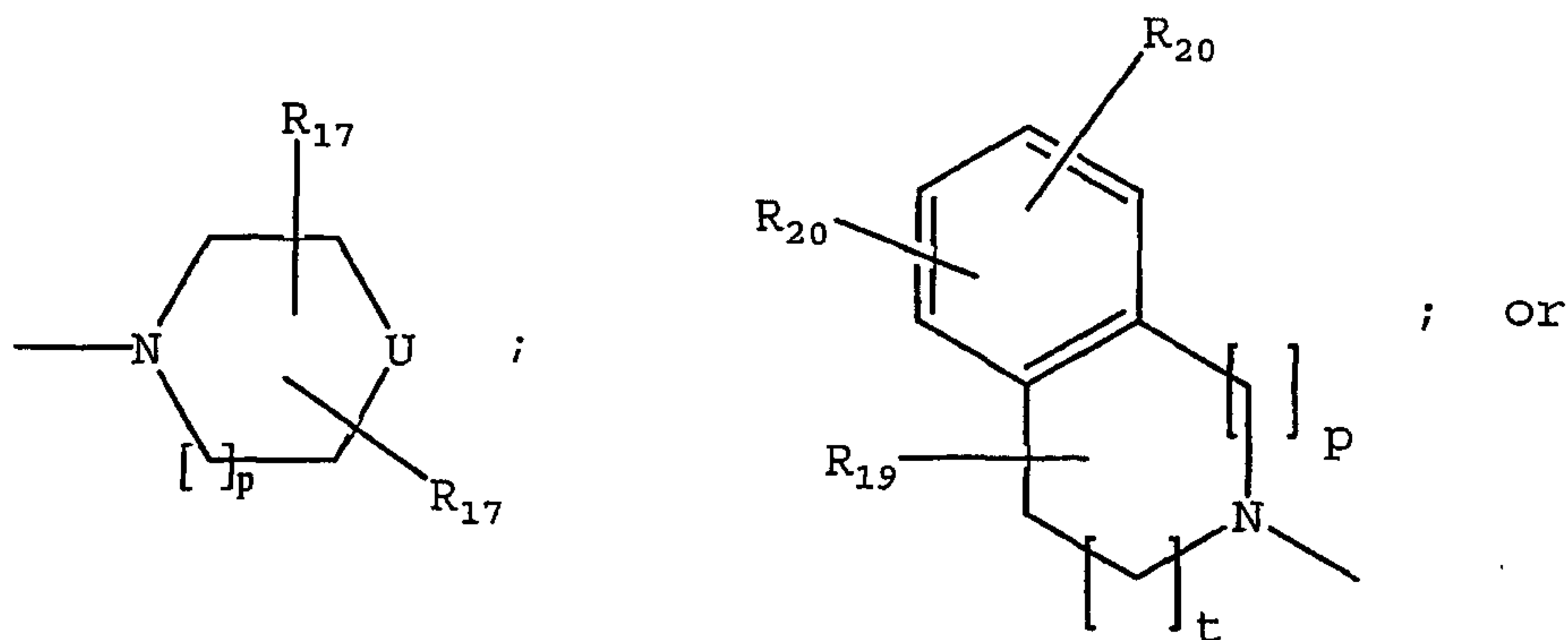
WO 02/060392

PCT/US02/04608

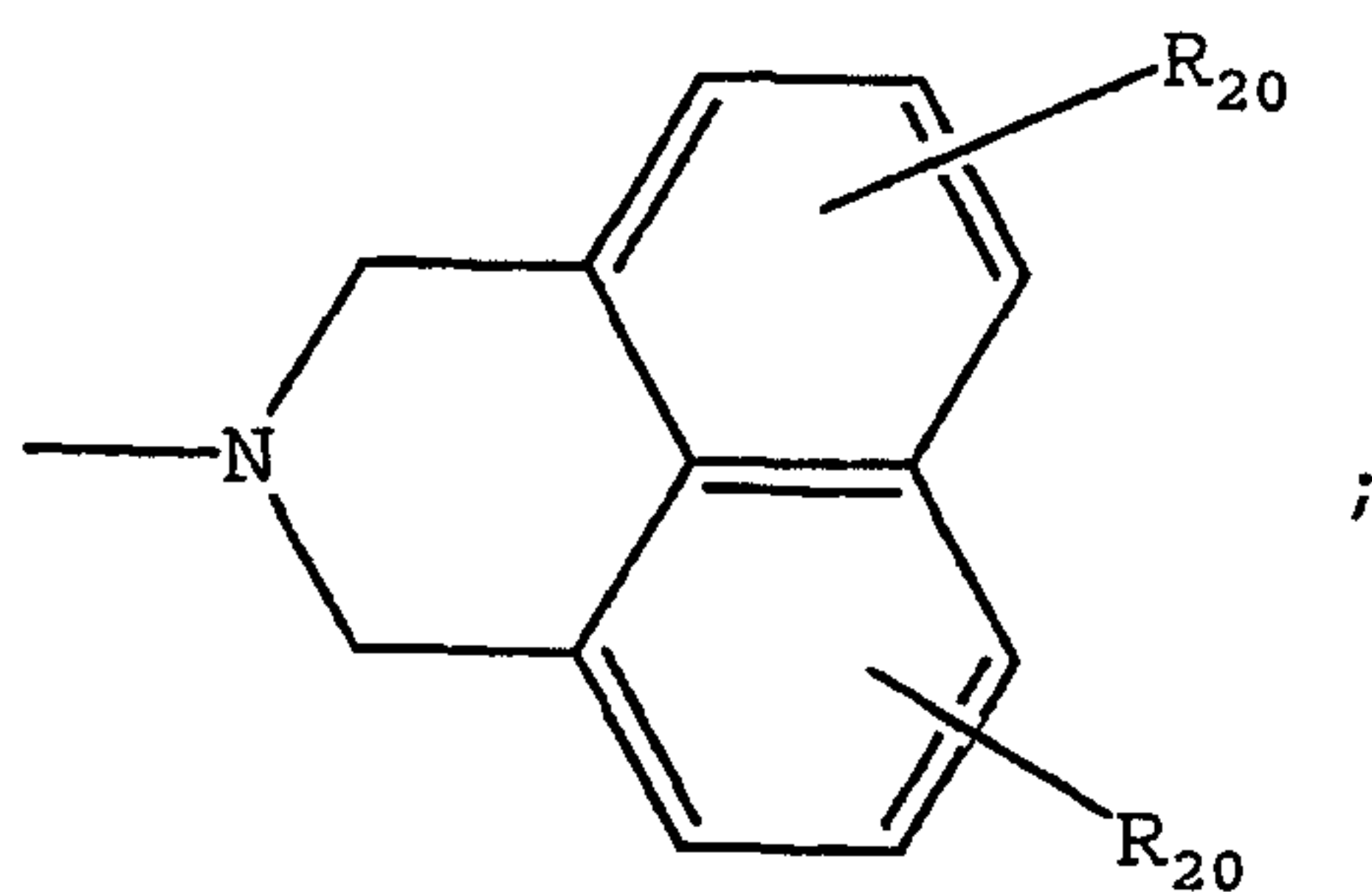
132

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 $NR_{14}R_{15}$;



10



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 $(C(R_{19})_2)_m-Z$;

15

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 $(C(R_{19})_2)_m-Z$;

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

straight chained or branched C₁-C₇ monofluoroalkyl,
 straight chained or branched C₁-C₇ polyfluoroalkyl,
 straight chained or branched C₂-C₇ alkenyl, straight
 chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -
 5 (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

wherein each R₁₇ is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁,
 -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or
 branched C₁-C₇ alkyl, straight chained or branched C₁-C₇
 10 monofluoroalkyl, straight chained or branched C₁-C₇
 polyfluoroalkyl, straight chained or branched C₂-C₇
 alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇
 cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

15 wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, -
 (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

wherein each R₁₉ is independently H, or straight chained
 or branched C₁-C₆ alkyl;

20

wherein each R₂₀ is independently -H; straight chained or
 branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
 C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I;
 25 -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -
 CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups
 present on adjacent carbon atoms can join together to
 form a methylenedioxy group;

30 wherein each R₂₁ is independently -H; straight chained or
 branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-

C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, or aryl(C₁-C₆)alkyl;

wherein each R₂₂ is independently H, F, Cl or C₁-C₄
5 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;
10

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

15 wherein t is 1 or 2;

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

wherein Z is C₃-C₁₀ cycloalkyl, C₄-C₇ cyclic ether, C₄-C₇
20 cyclic thioether, aryl, or heteroaryl; or

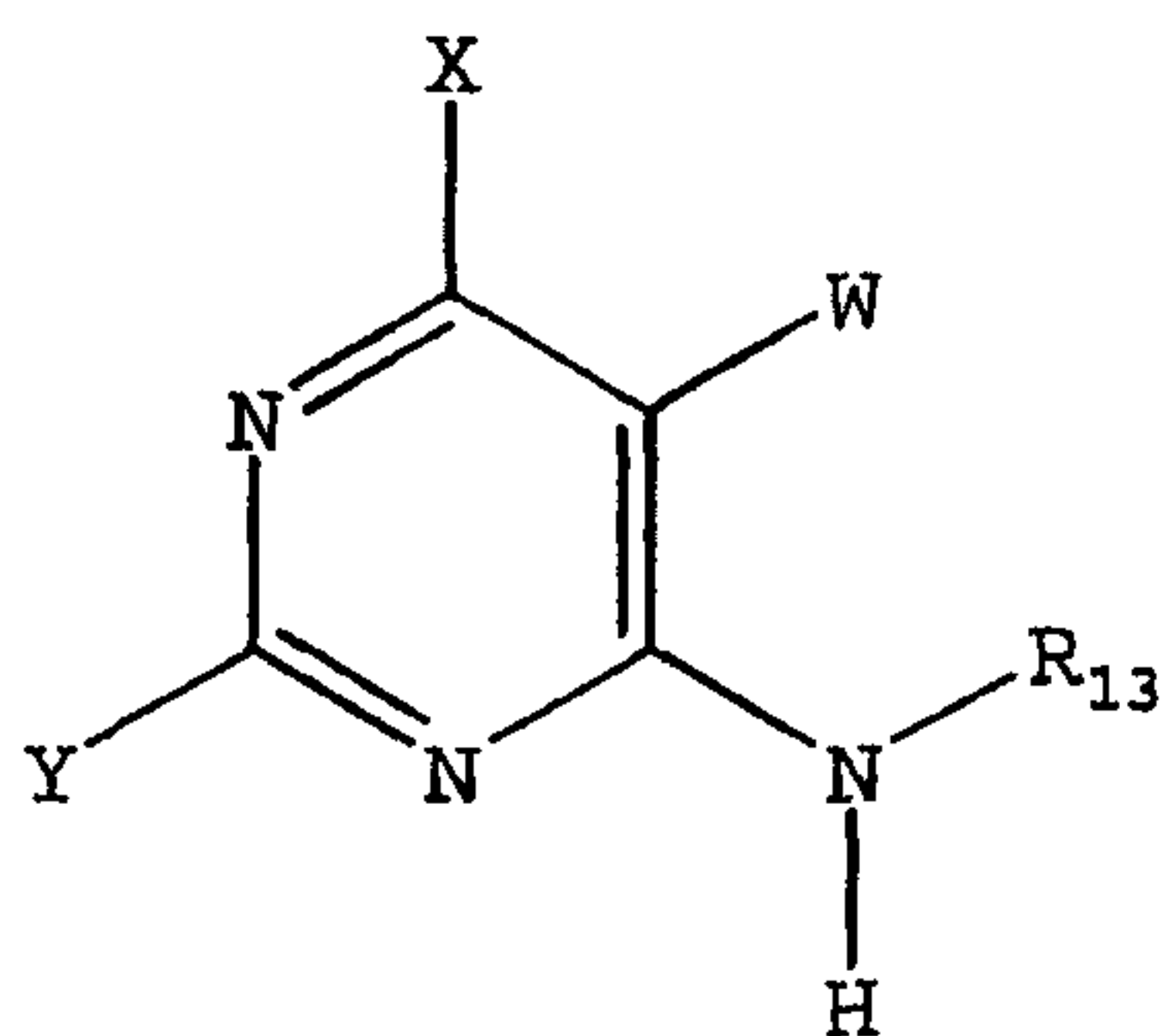
a pharmaceutically acceptable salt thereof.

25 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:

WO 02/060392

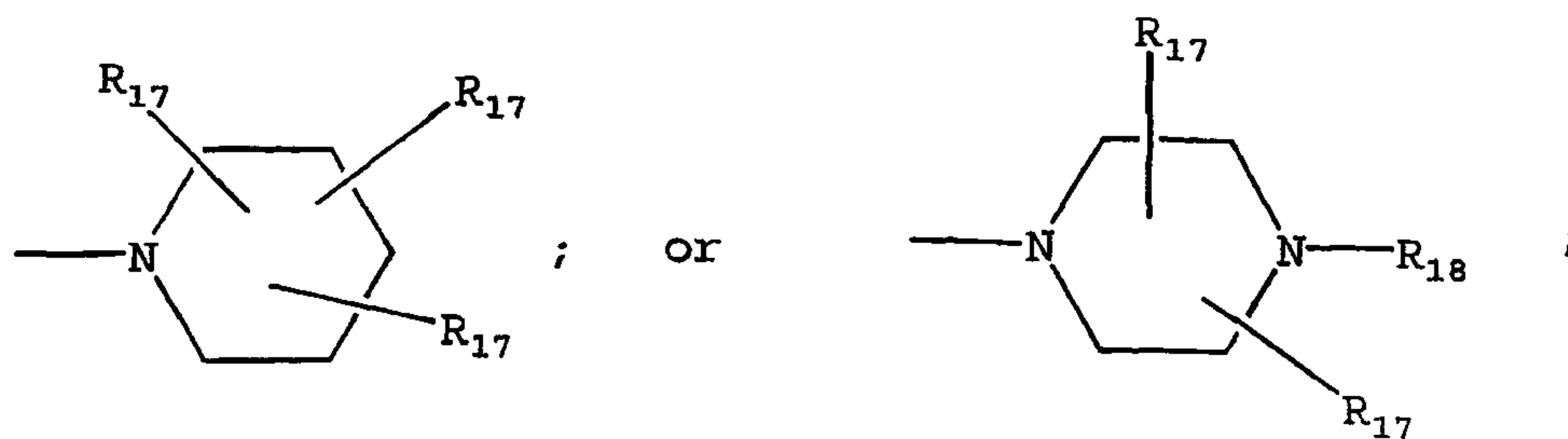
PCT/US02/04608

135



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

5 wherein X is $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

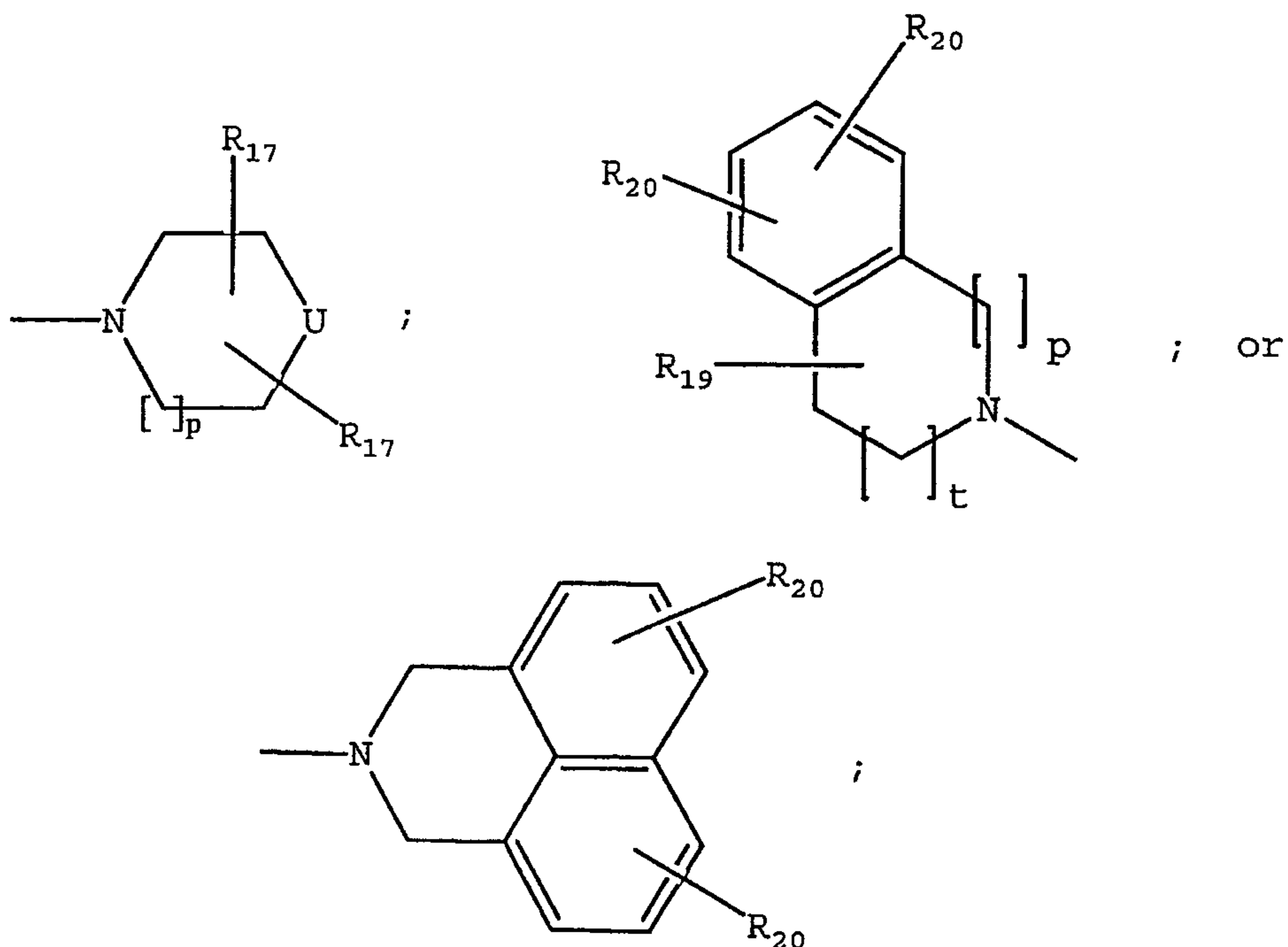
10 wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $-(\text{CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

15

wherein Y is $\text{NR}_{14}\text{R}_{15}$;

136



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 $(C(R_{19})_2)_m-Z$;

5

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 $-NSO_2R_{16}$;

10

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

15

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;

WO 02/060392

PCT/US02/04608

138

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

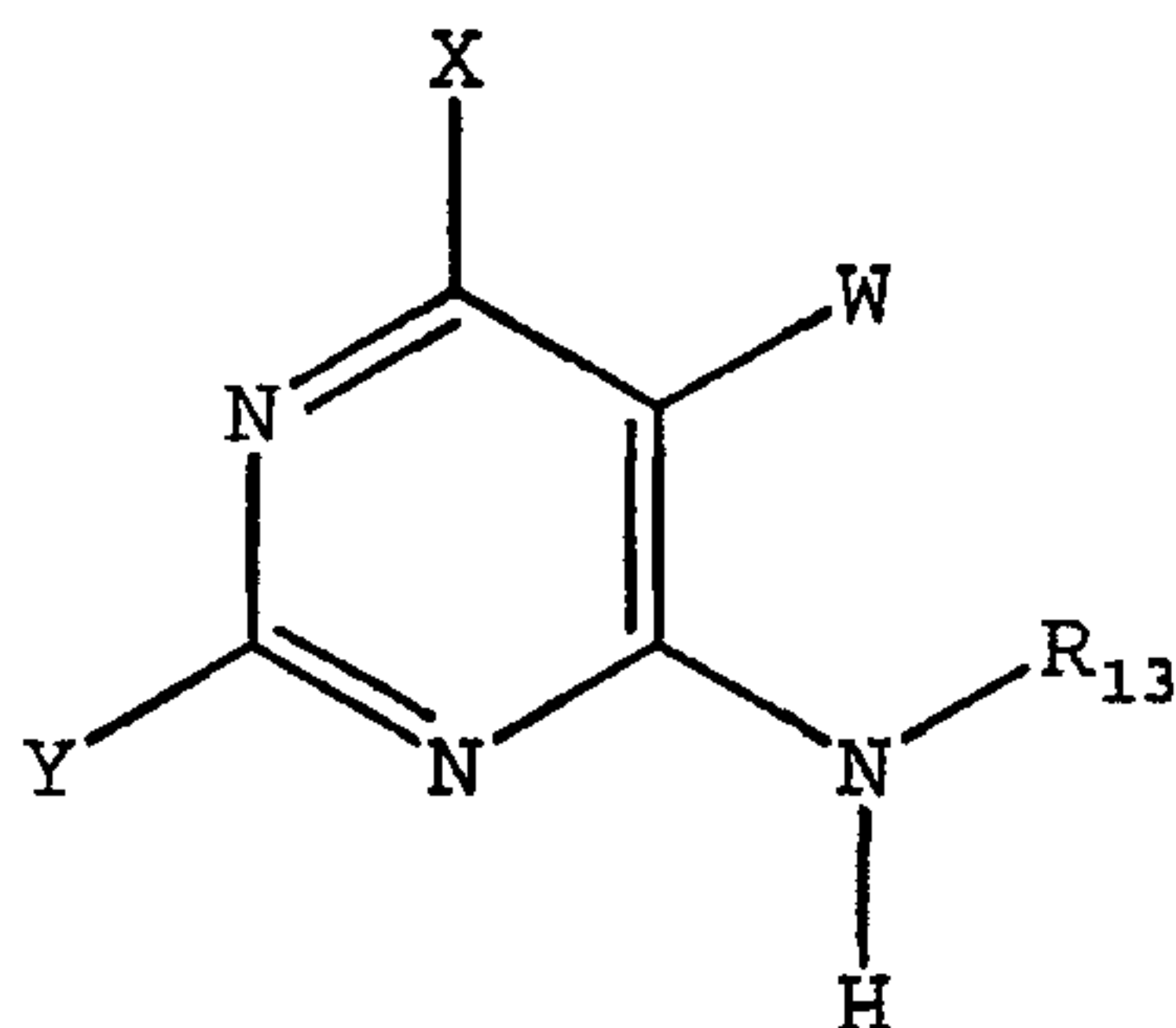
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

10

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

15 structure:



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

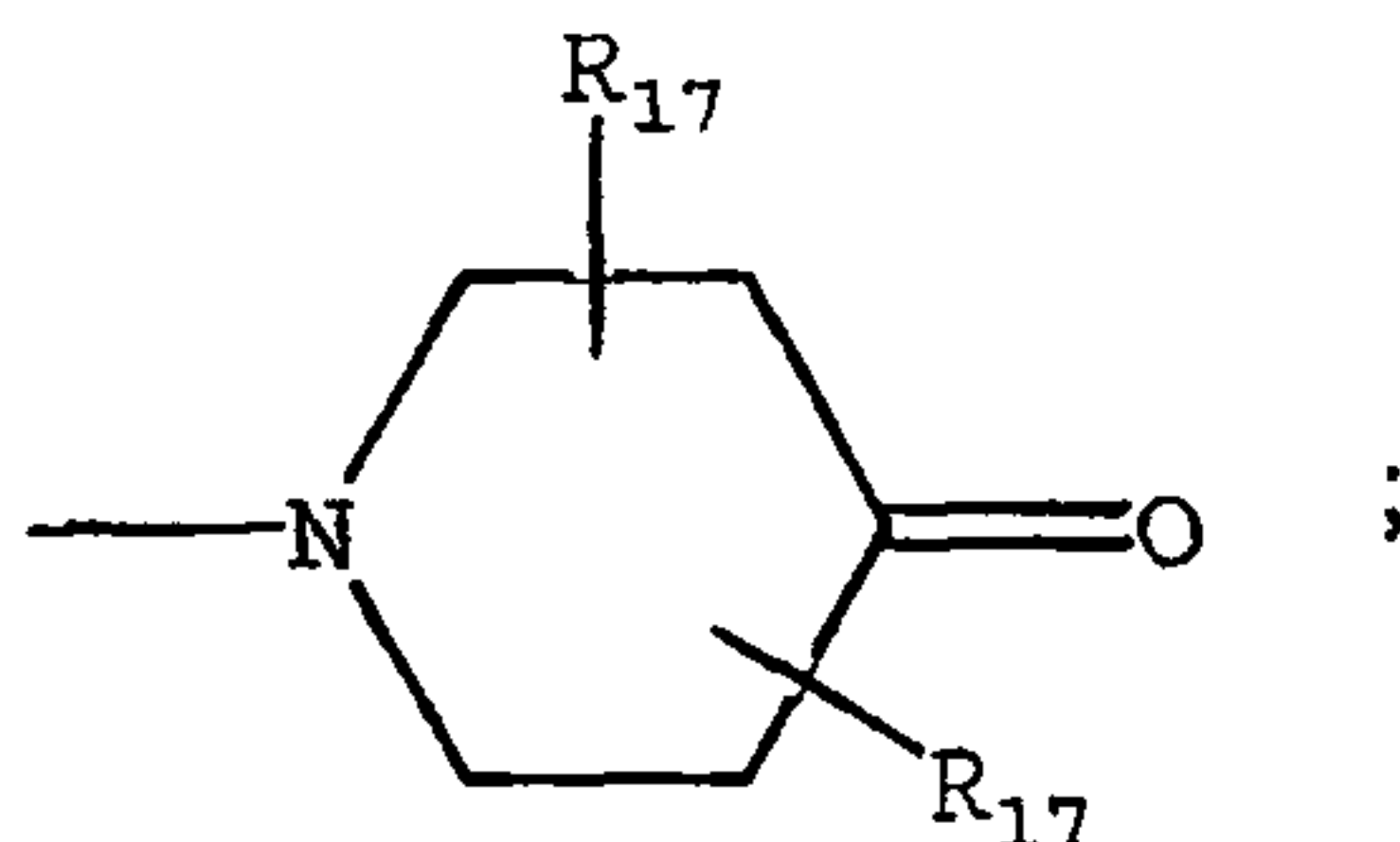
20

wherein X is $N(CH_3)_2$ or

WO 02/060392

PCT/US02/04608

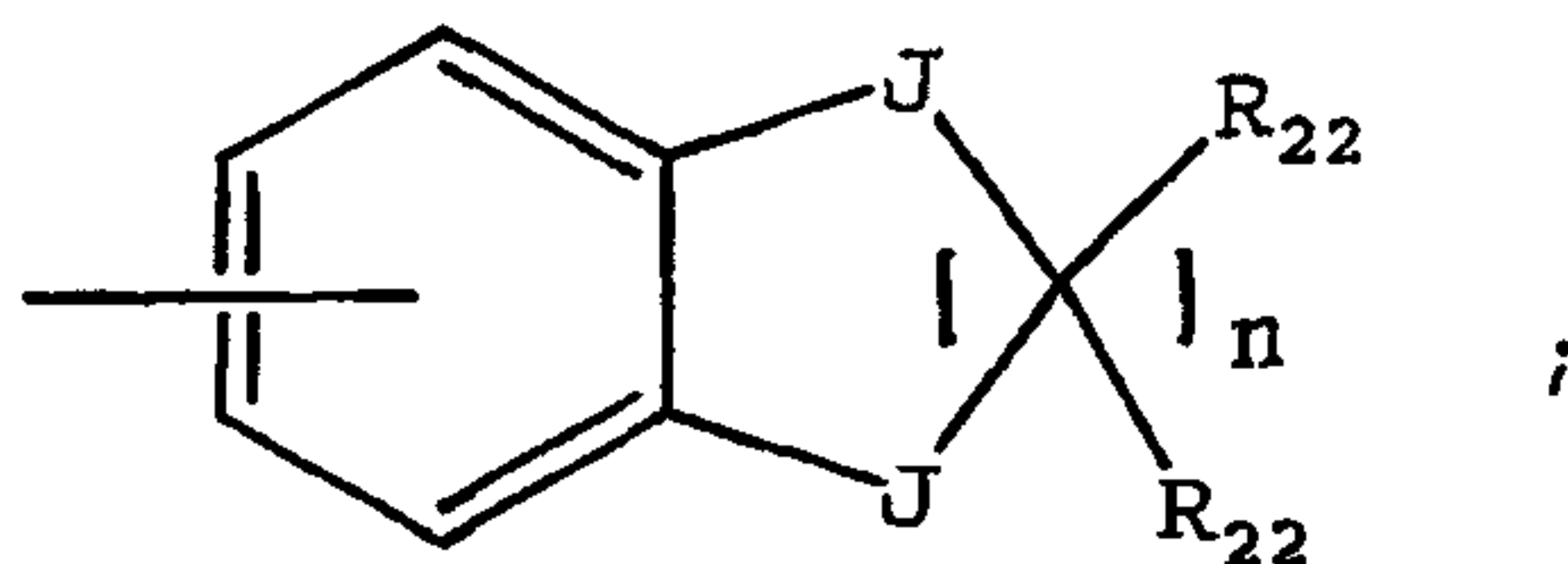
139



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

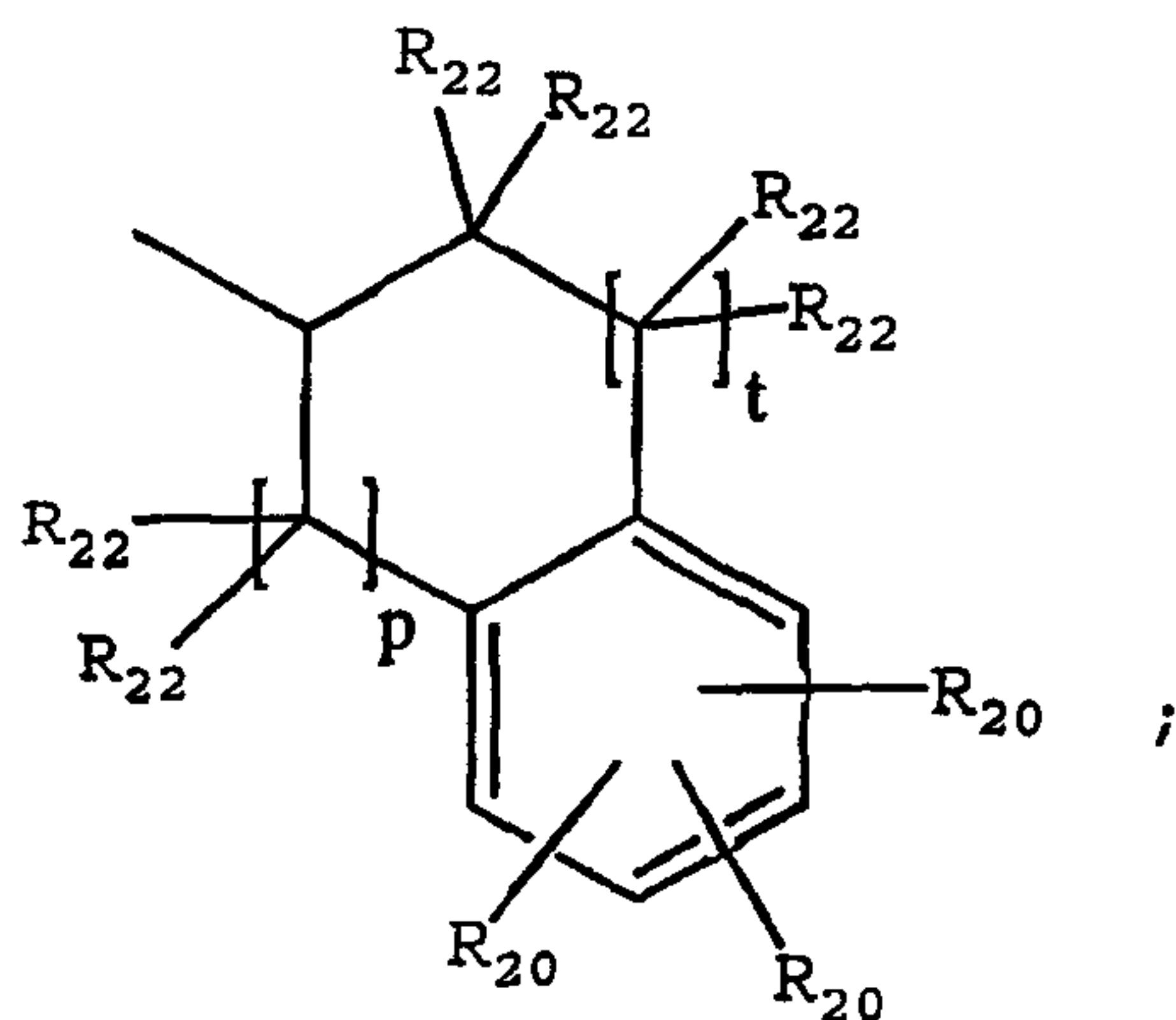
5

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

10 wherein Q_1 is

wherein Q_2 is

15



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

WO 02/060392

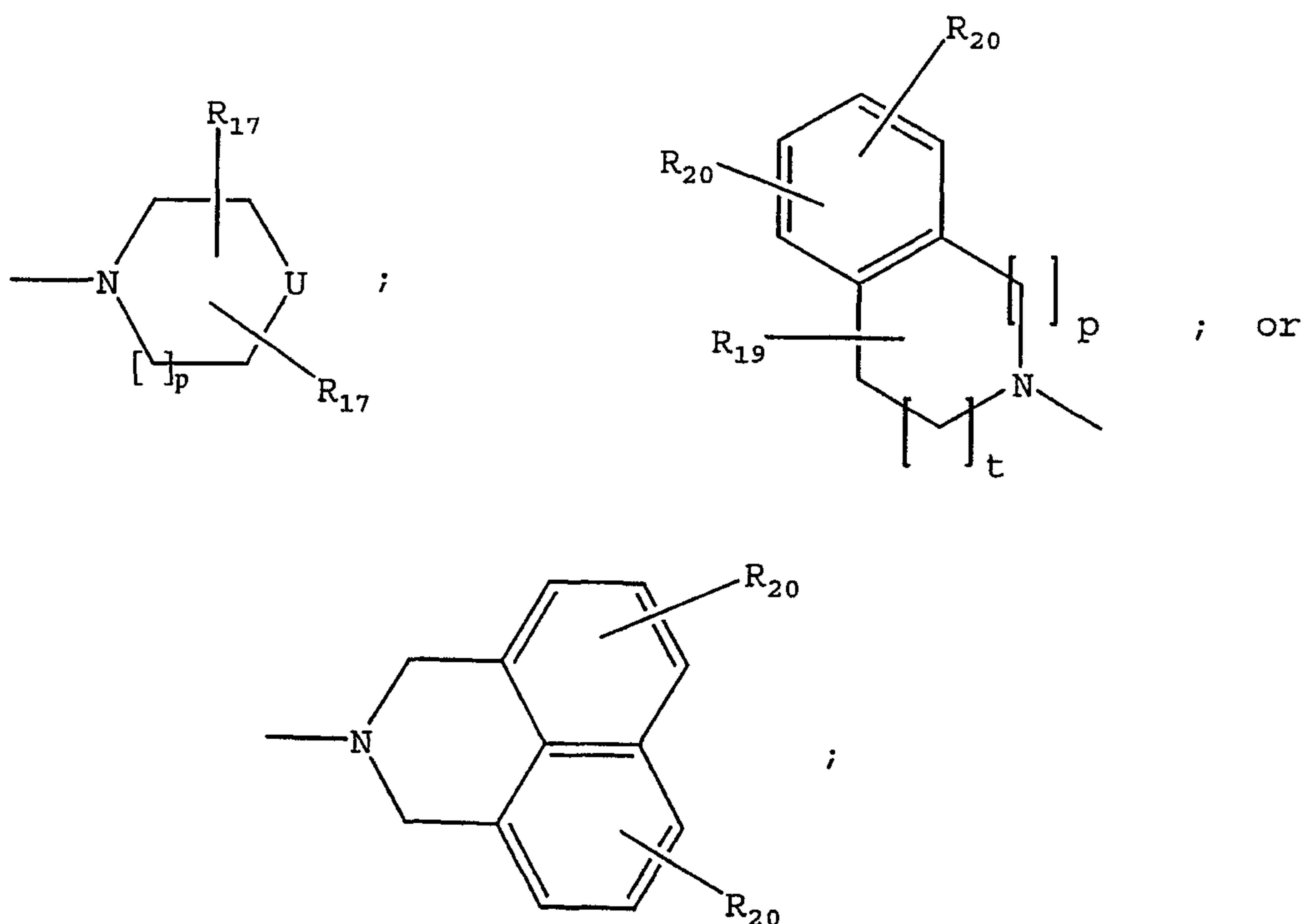
PCT/US02/04608

140

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;

5

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



- 10 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 $(C(R_{19})_2)_m-Z$;

15

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,
 5 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; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$,
 10 $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, 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
 15 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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

20 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;
 25 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
 30 form a methylenedioxy group;

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

WO 02/060392

PCT/US02/04608

142

branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-
C₆)alkyl;

5

wherein each R₂₂ is independently H, F, Cl or C₁-C₄
straight chained or branched alkyl;

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

10

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

wherein p is an integer from 0 to 2 inclusive;

15

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

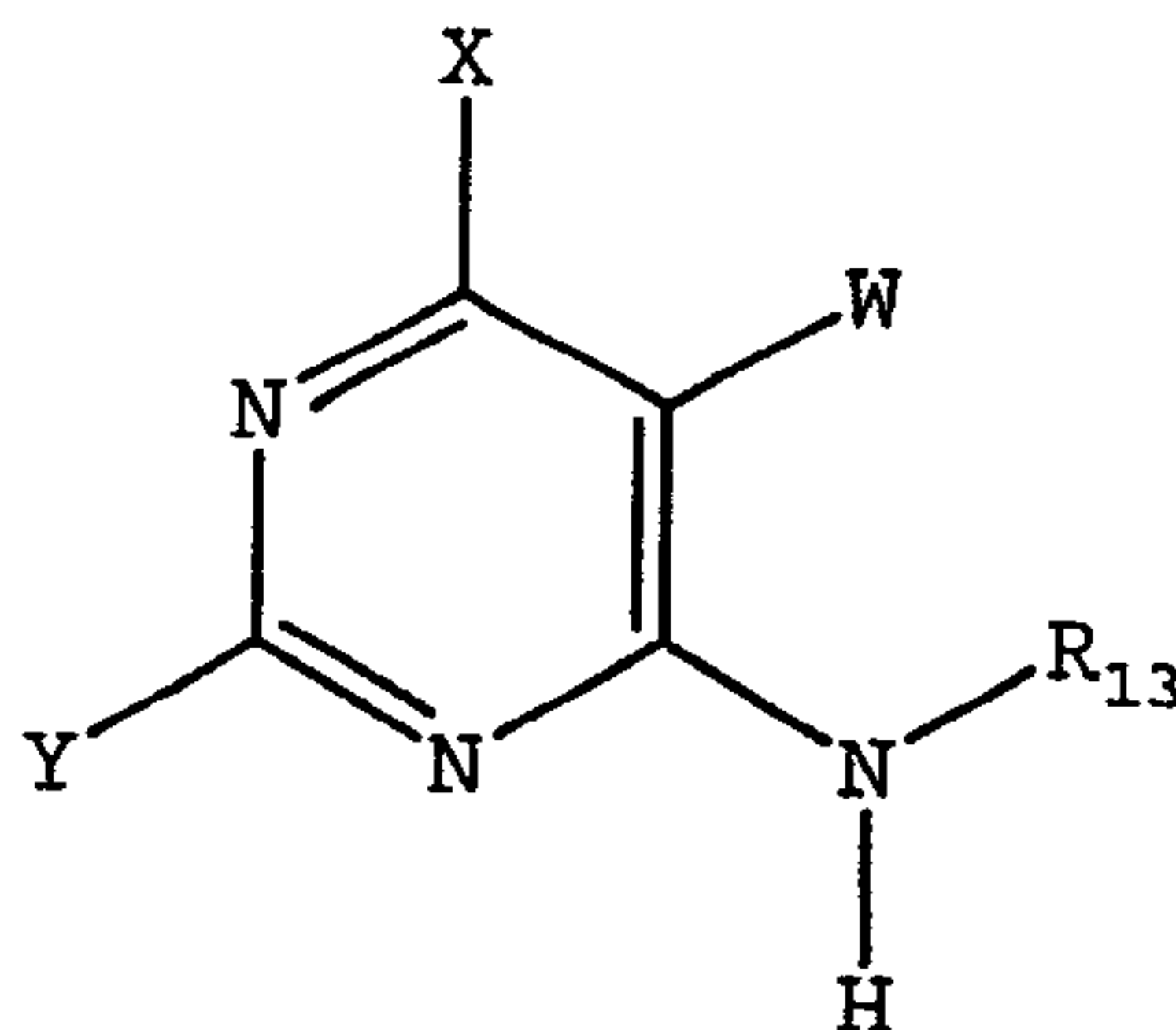
a pharmaceutically acceptable salt thereof.

20

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

25

structure:



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

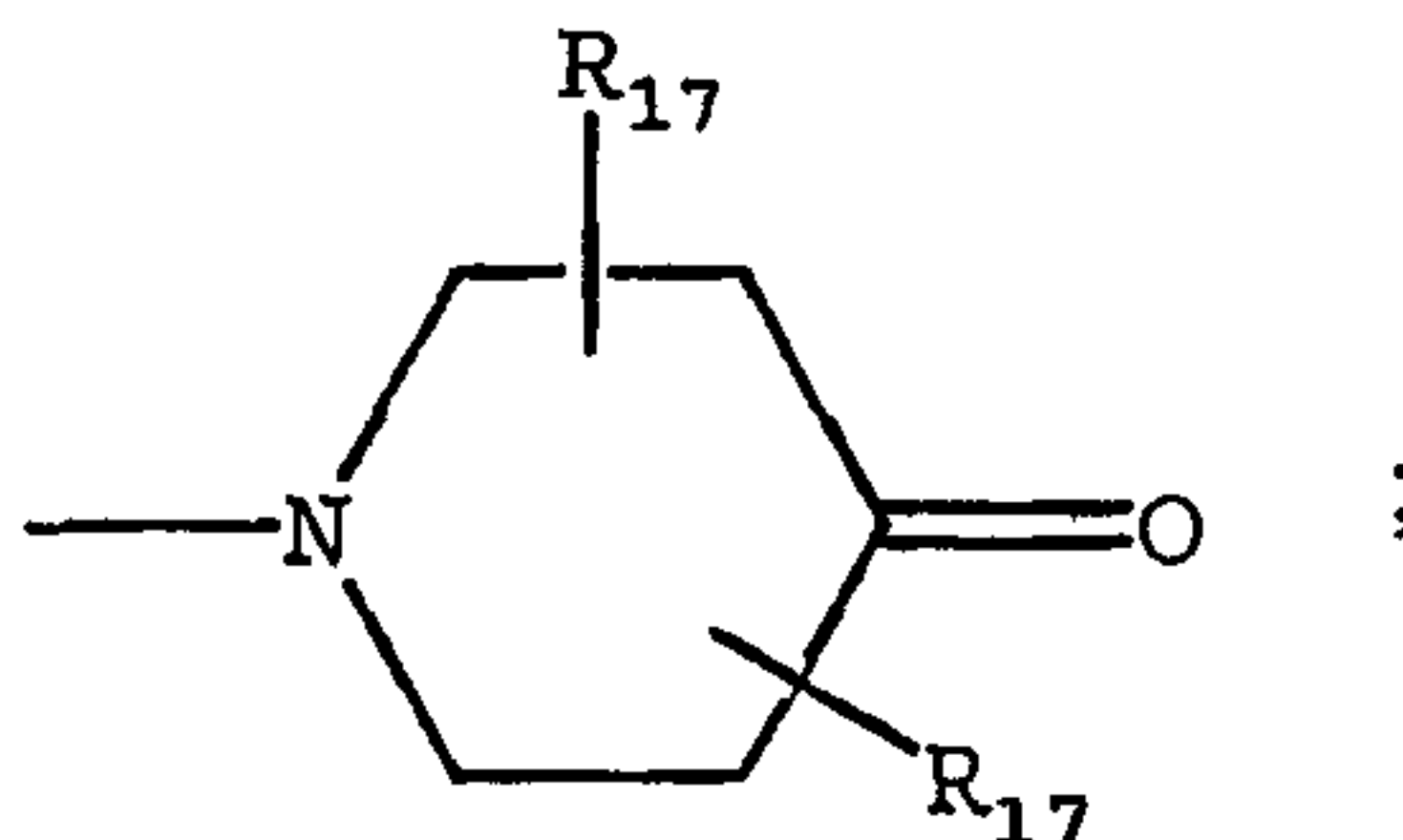
WO 02/060392

PCT/US02/04608

143

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;

10 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 $(C(R_{19})_2)_m-Z$;

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

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

20 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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

25

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 C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

5 wherein each R₁₉ is independently H, or straight chained or branched C₁-C₆ alkyl;

wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
 10 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

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

15

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

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

20 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
 25 bicyclo[2.2.2]octane. In addition, the bicyclic alkyl ring systems may be substituted with one or more of the following: -F, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇
 30 alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, -N(R₂₁)₂, -OR₂₁, -COR₂₁, -

CO_2R_{21} , $-\text{CON}(\text{R}_{21})_2$ or $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$.

As used in the present invention, the term "cycloalkyl" includes, $\text{C}_3\text{-C}_7$ cycloalkyl moieties which may be substituted with one or more of the following: -F, -NO₂, -CN, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{C}_3\text{-C}_7$ monofluorocycloalkyl, $\text{C}_3\text{-C}_7$ polyfluorocycloalkyl, $\text{C}_5\text{-C}_7$ cycloalkenyl, $-\text{N}(\text{R}_4)_2$, $-\text{OR}_4$, $-\text{COR}_4$, $-\text{NCOR}_4$, $-\text{CO}_2\text{R}_4$, $-\text{CON}(\text{R}_4)_2$ or $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$.

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with one or more of the following: -F, -NO₂, -CN, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{C}_3\text{-C}_7$ monofluorocycloalkyl, $\text{C}_3\text{-C}_7$ polyfluorocycloalkyl, $\text{C}_5\text{-C}_7$ cycloalkenyl, $-\text{N}(\text{R}_4)_2$, $-\text{OR}_4$, $-\text{COR}_4$, $-\text{NCOR}_4$, $-\text{CO}_2\text{R}_4$, $-\text{CON}(\text{R}_4)_2$ or $(\text{CH}_2)_n\text{-O-}(\text{CH}_2)_m\text{-CH}_3$.

25

As used in the present invention, the term "cycloalkenyl" includes, $\text{C}_5\text{-C}_7$ cycloalkenyl moieties which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl, straight

30

chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

5

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.

15

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, indolizinyll, 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.

25

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, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or

30

branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

5

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

10 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, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇
15 monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -
20 SR₄, -OCOR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

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

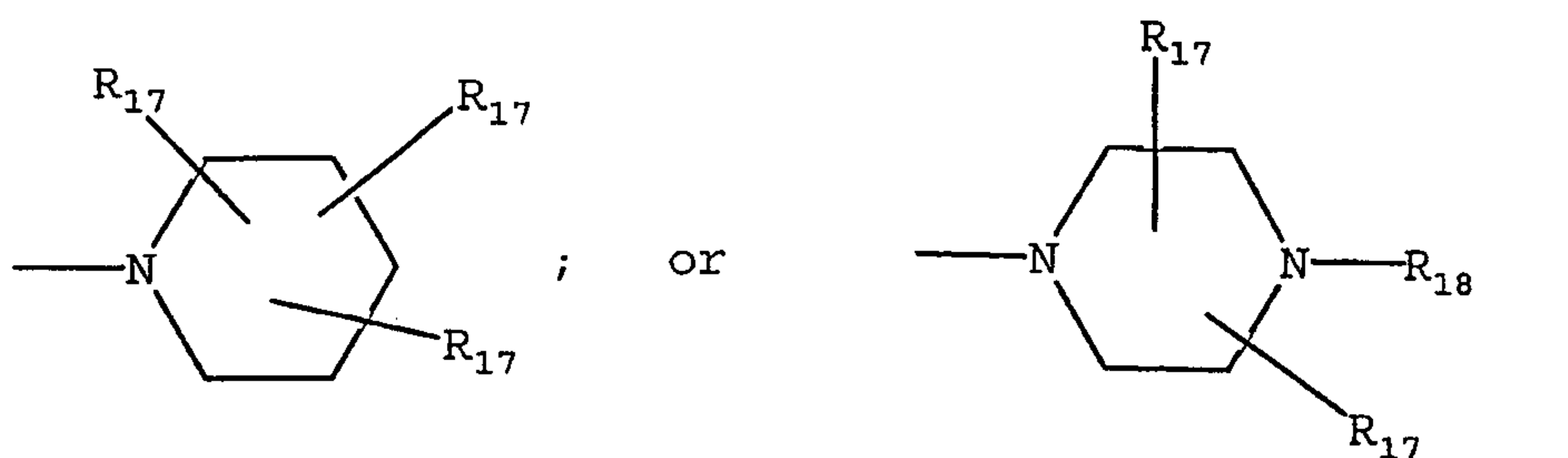
In one embodiment of any of the methods described herein,
30 the compound can be administered orally.

In one embodiment, X is:

WO 02/060392

PCT/US02/04608

148

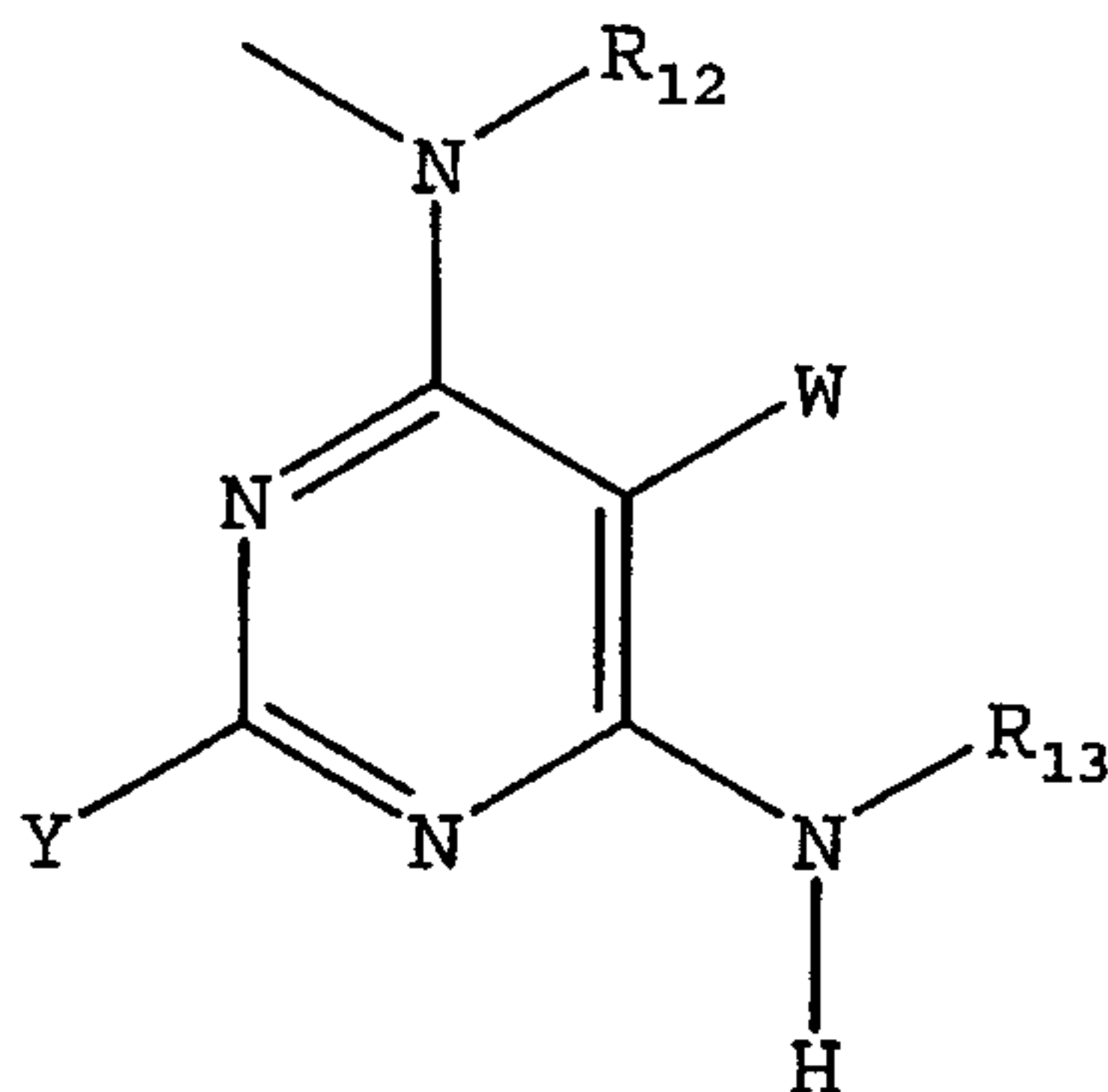


5

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:

10



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

15

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 $(CH_2)_q-O-(CH_2)_m-CH_3$.

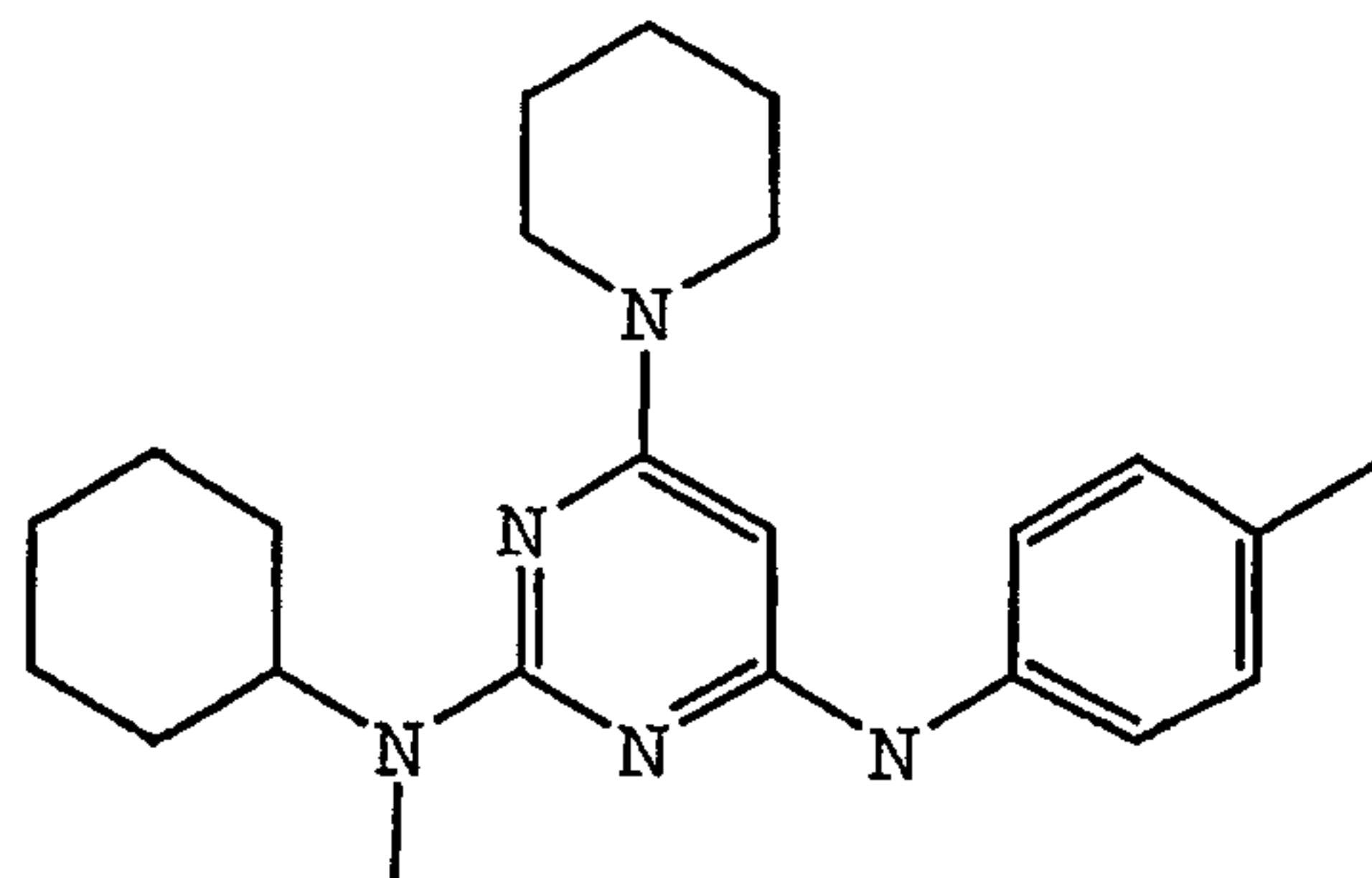
20

WO 02/060392

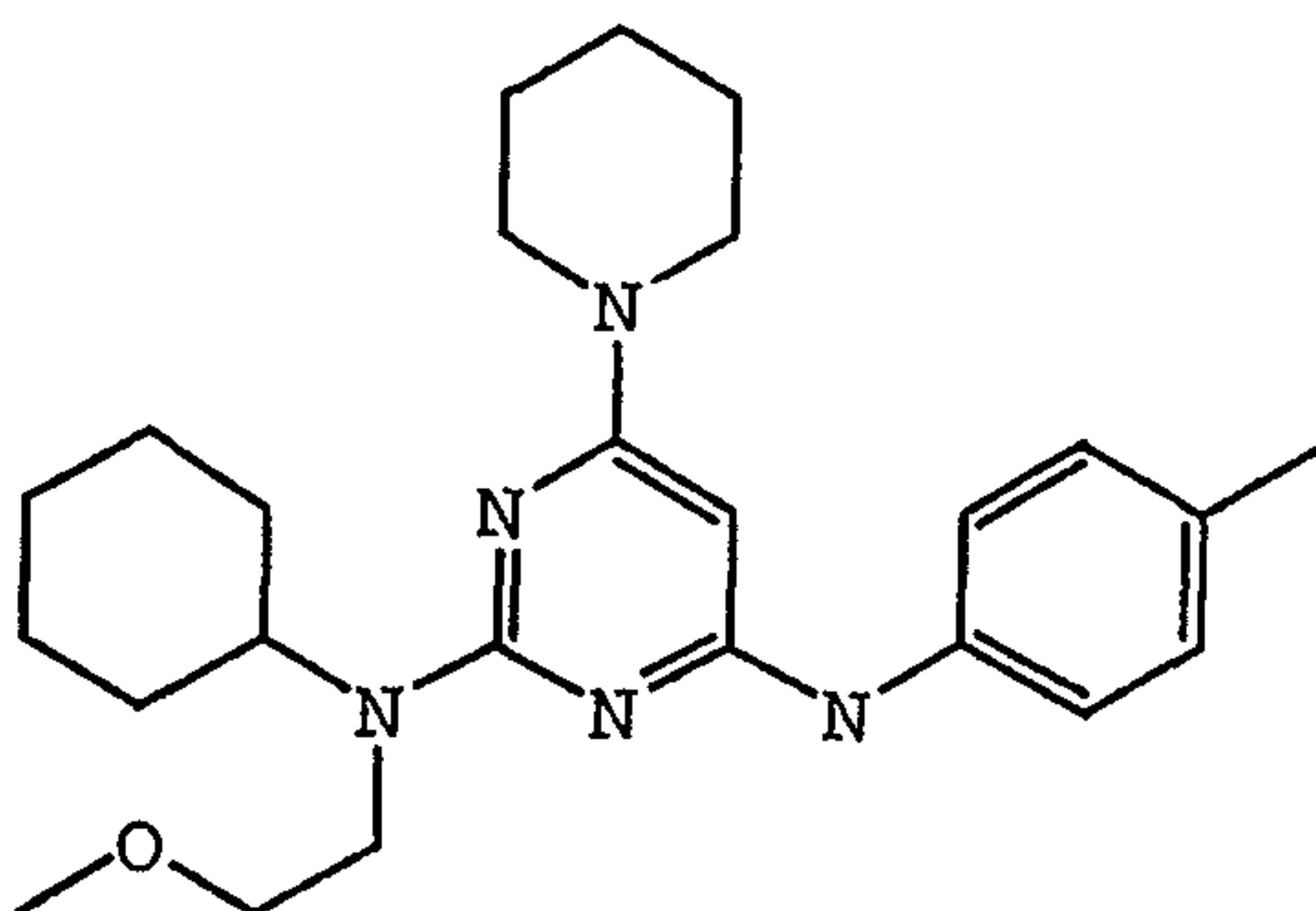
PCT/US02/04608

149

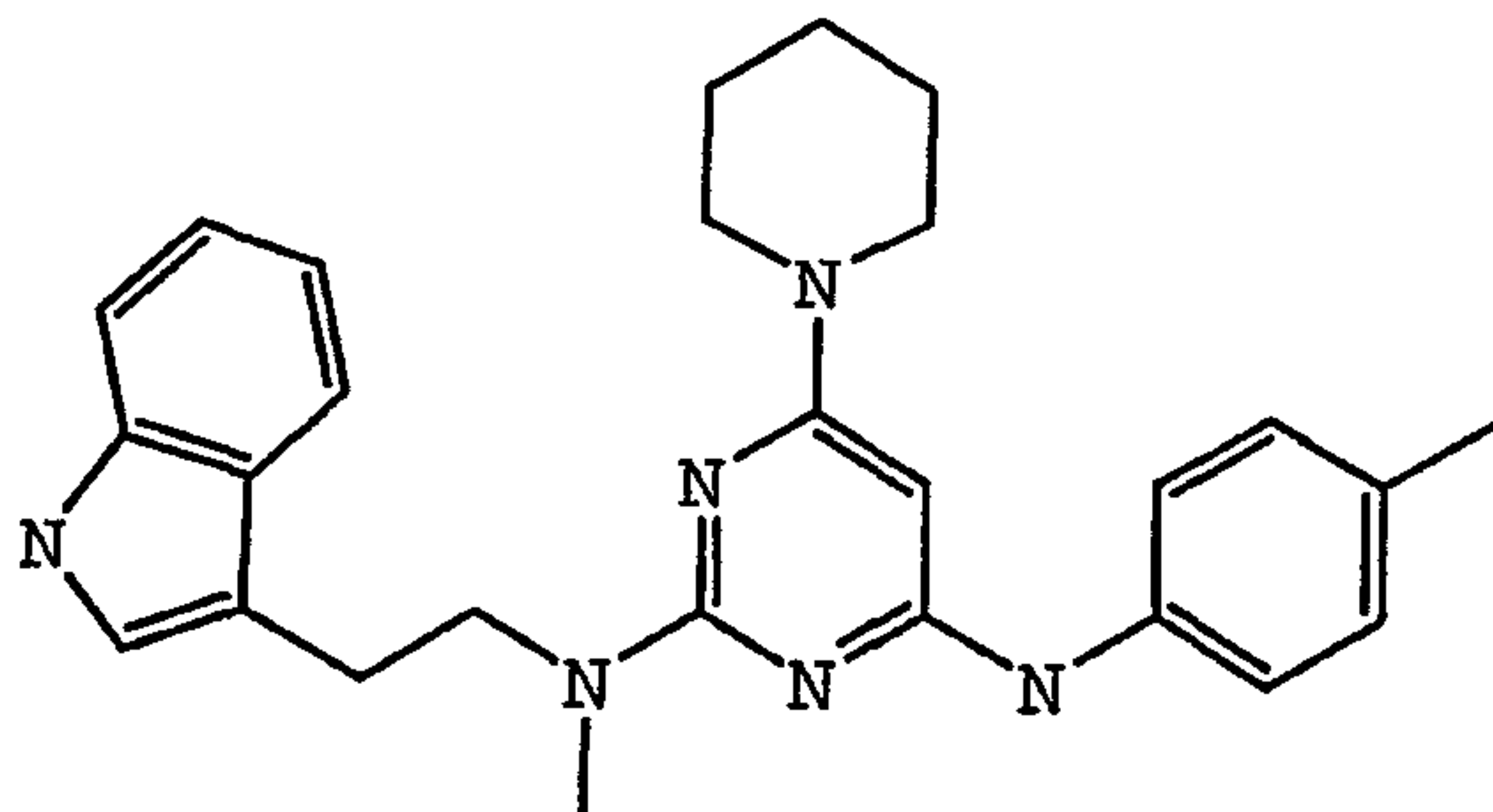
In one embodiment, the compound is selected from the group consisting of:



;



;

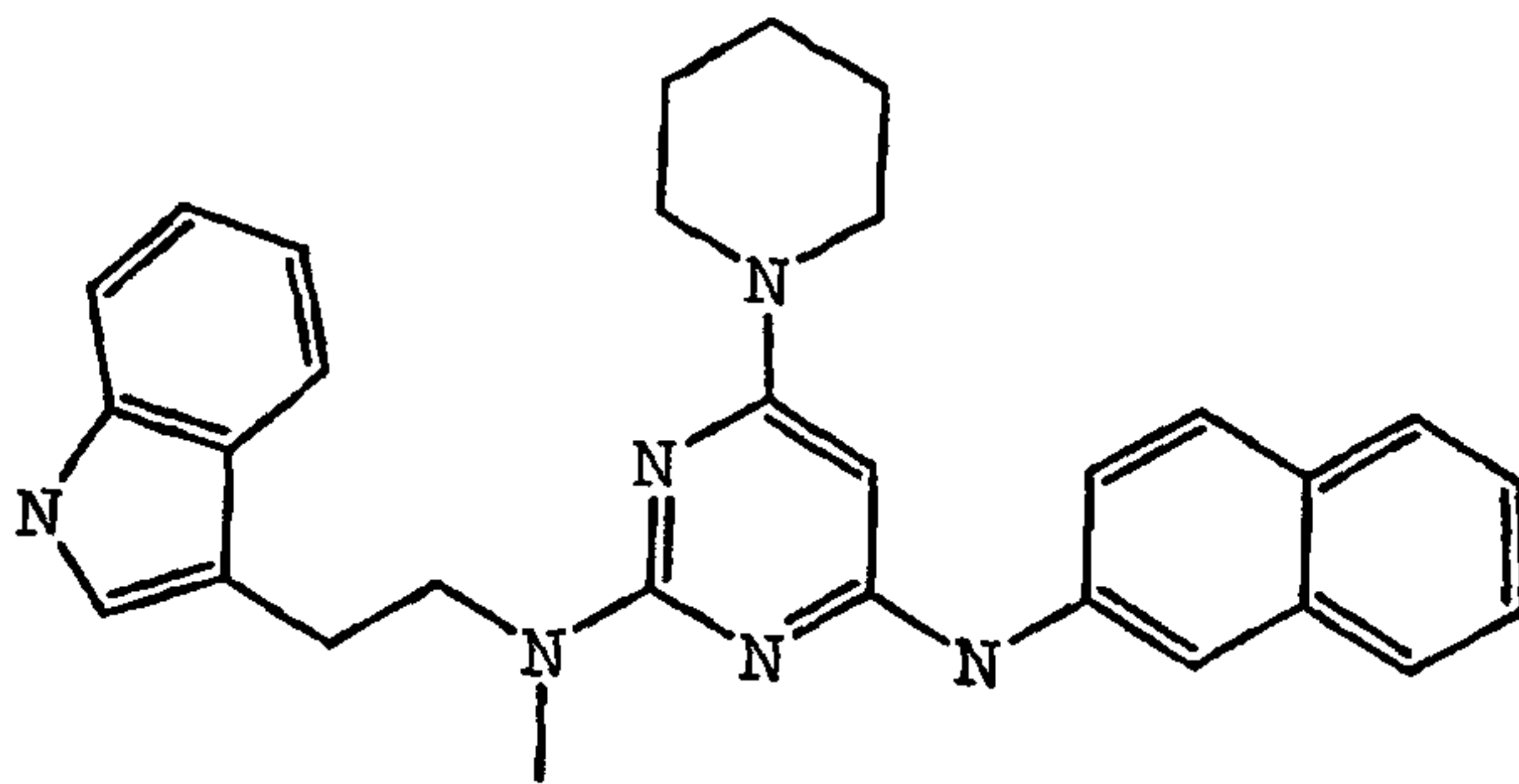


;

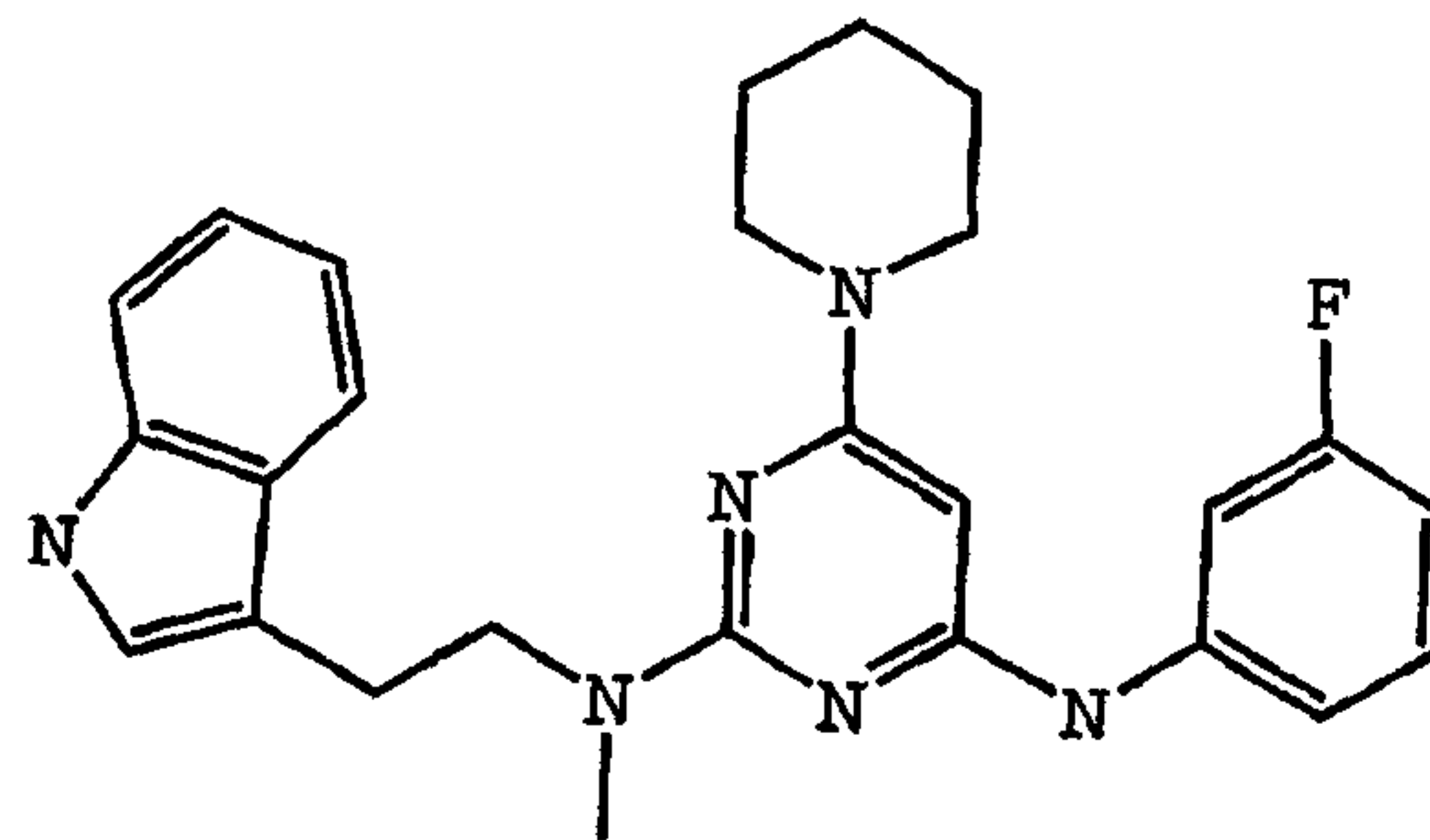
WO 02/060392

PCT/US02/04608

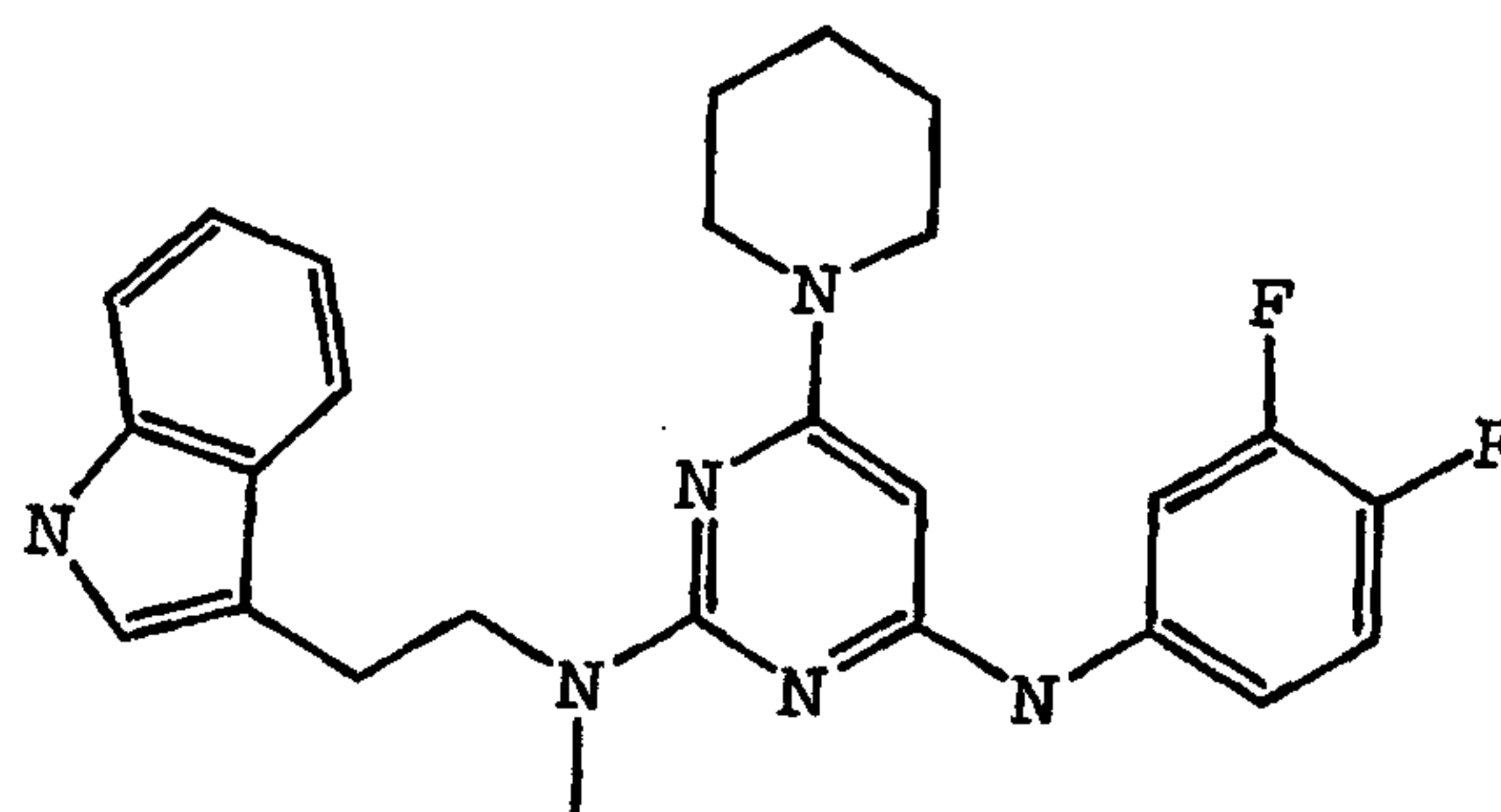
150



i



i

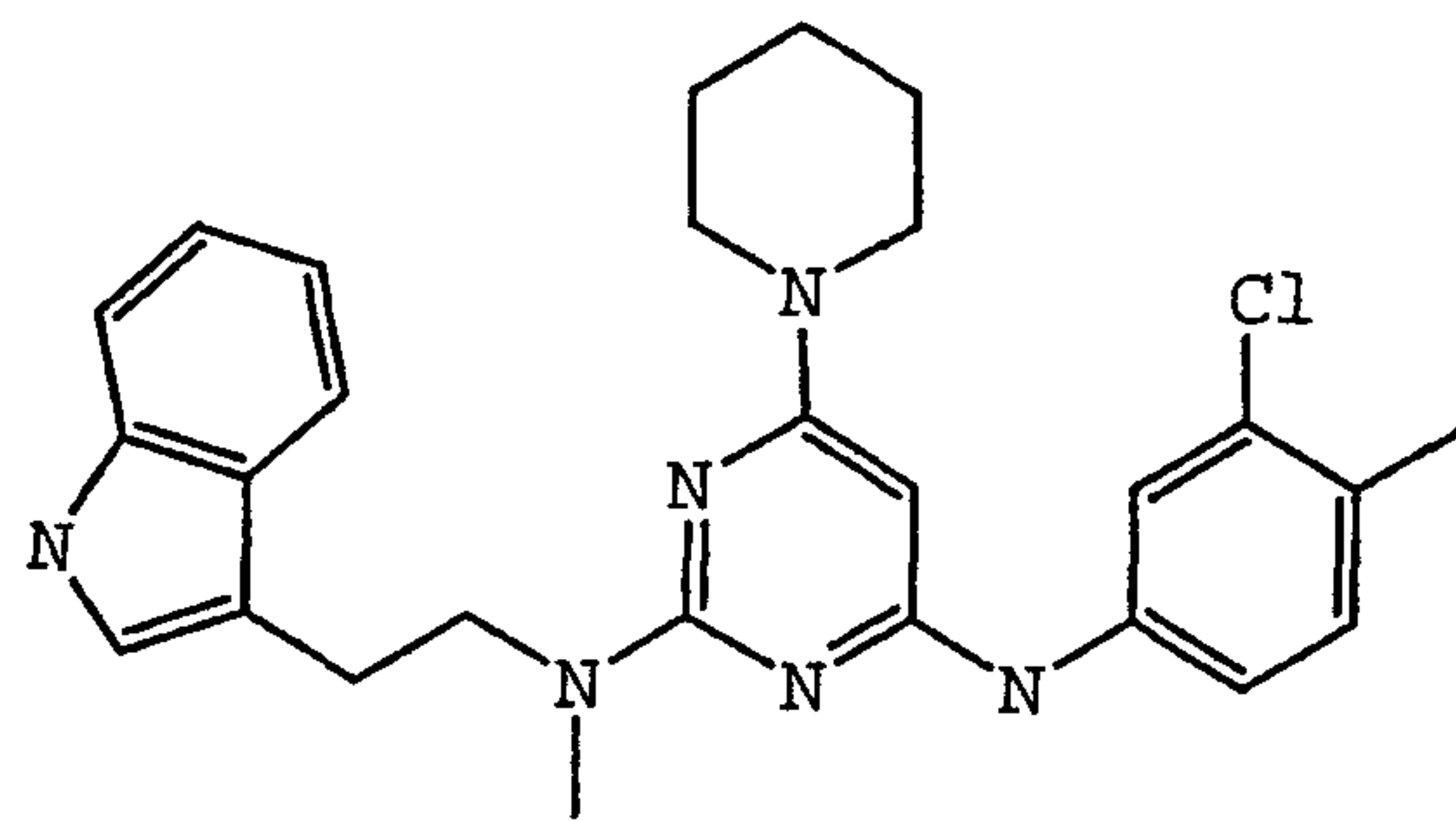


i

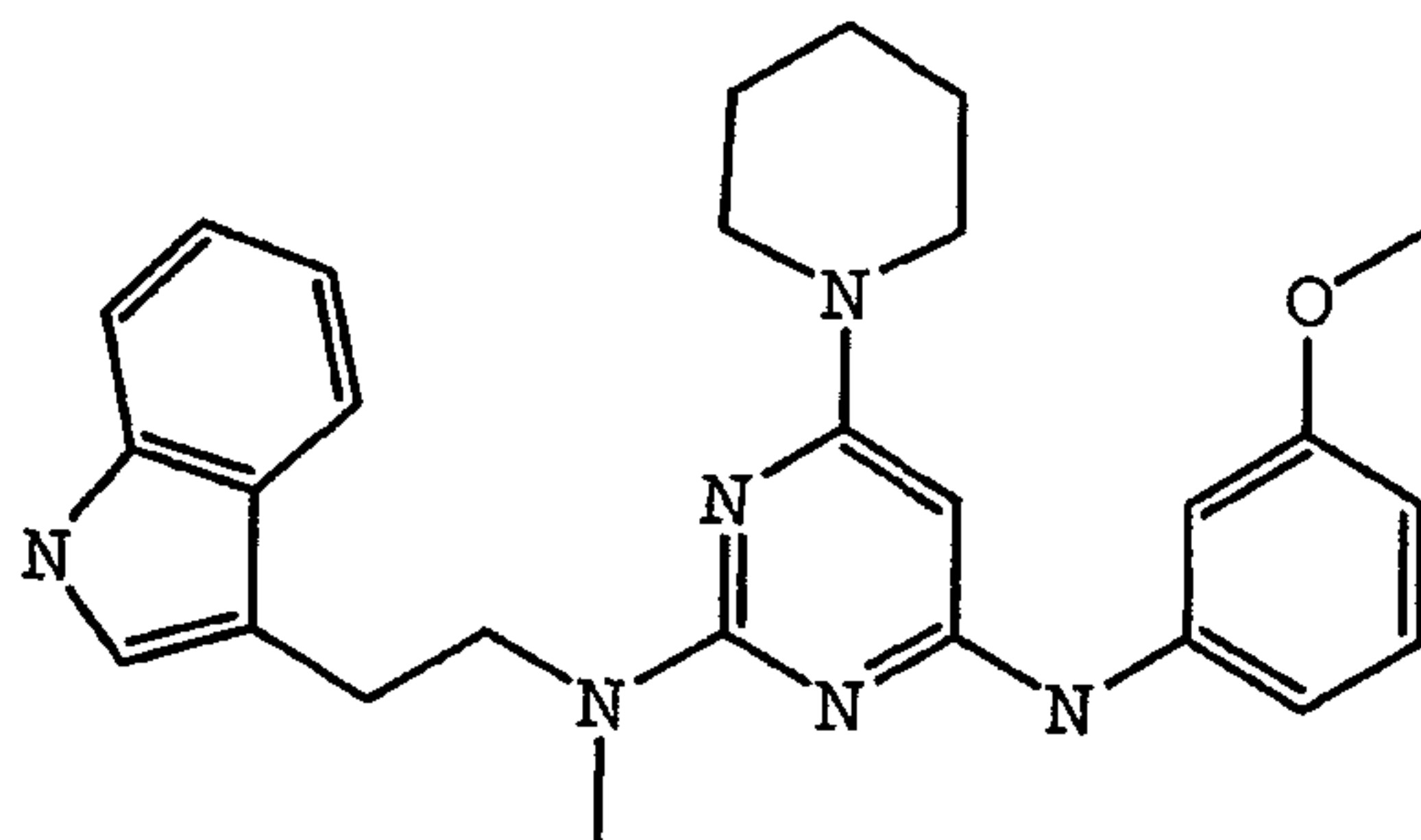
WO 02/060392

PCT/US02/04608

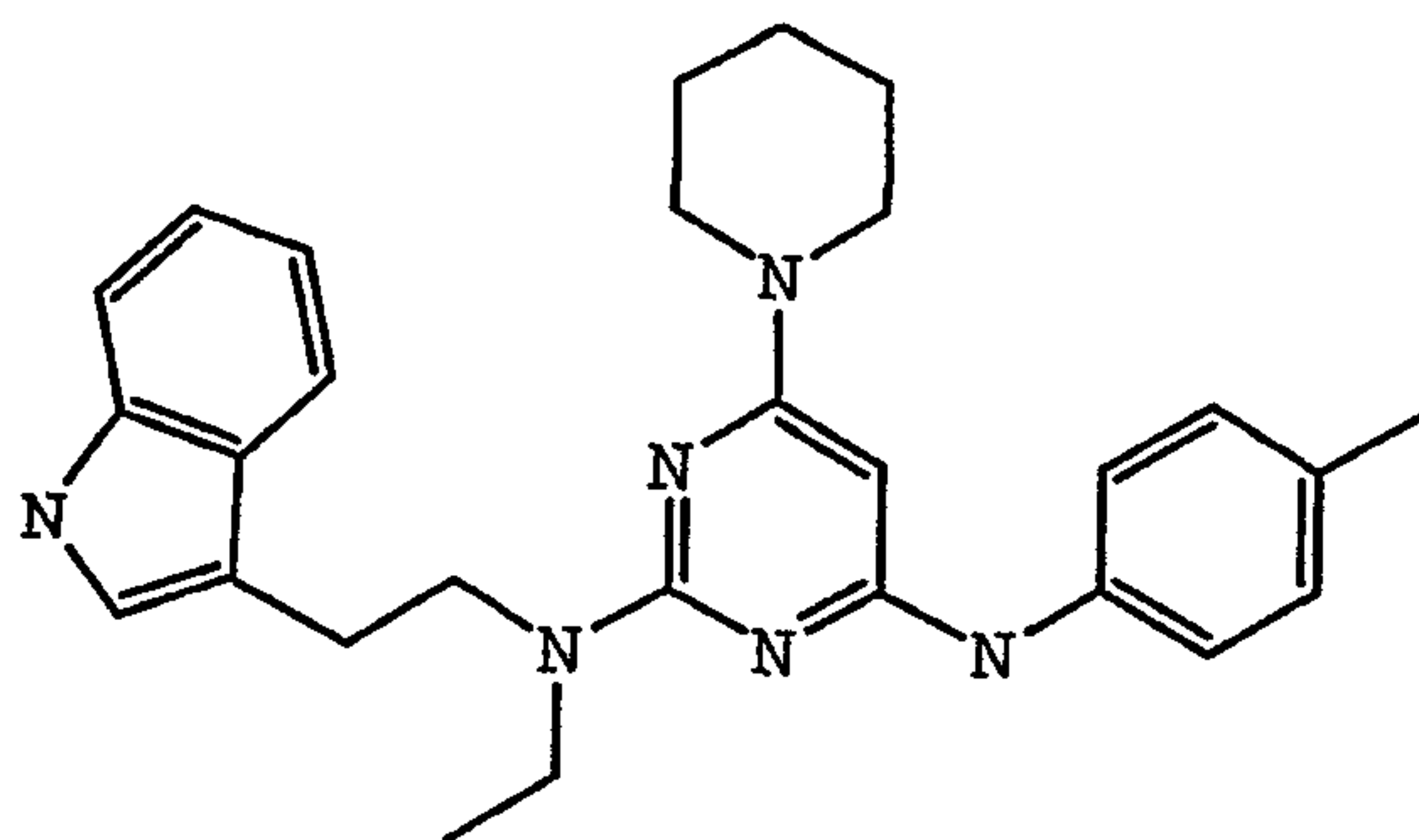
151



;



;

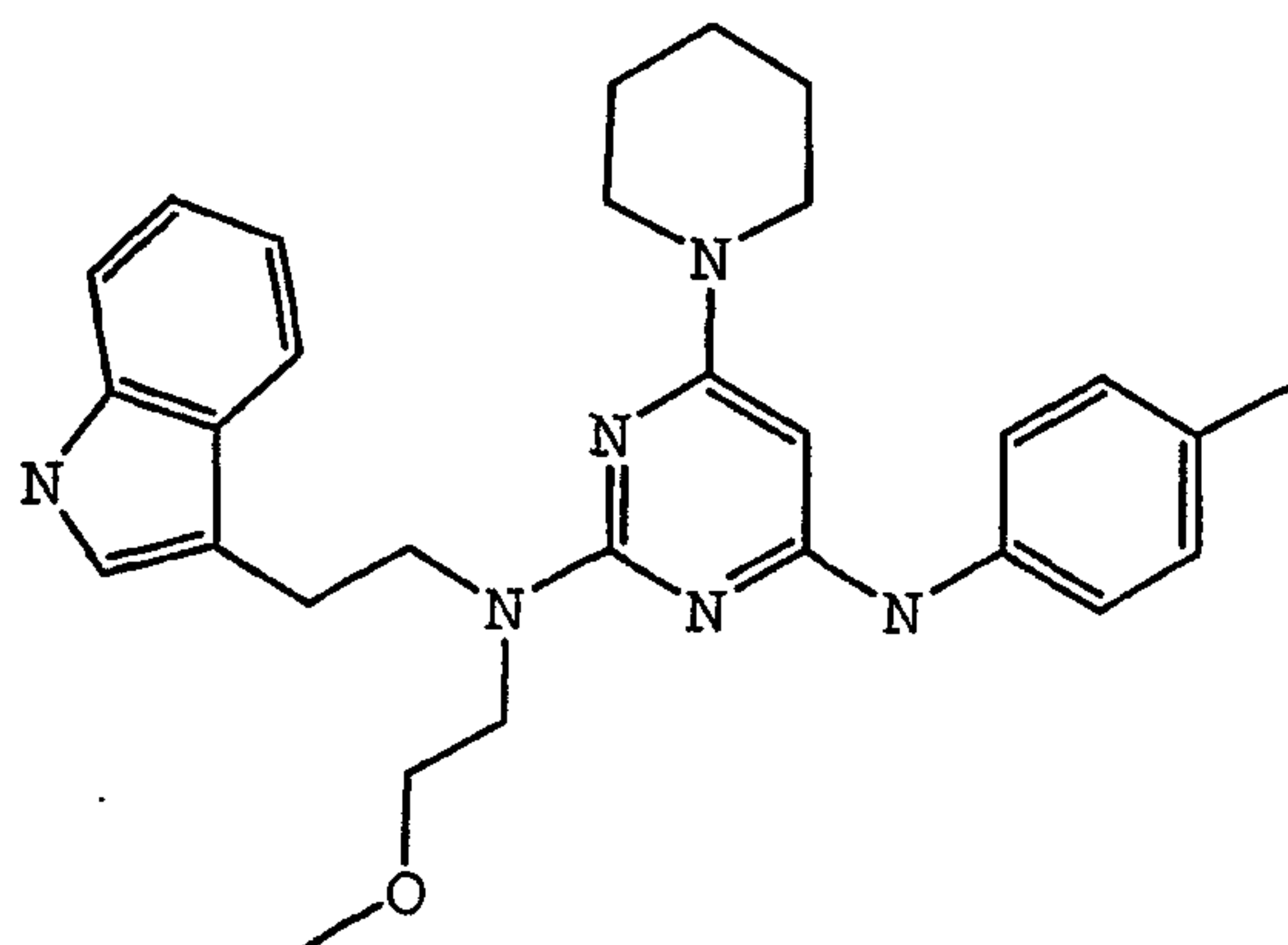


;

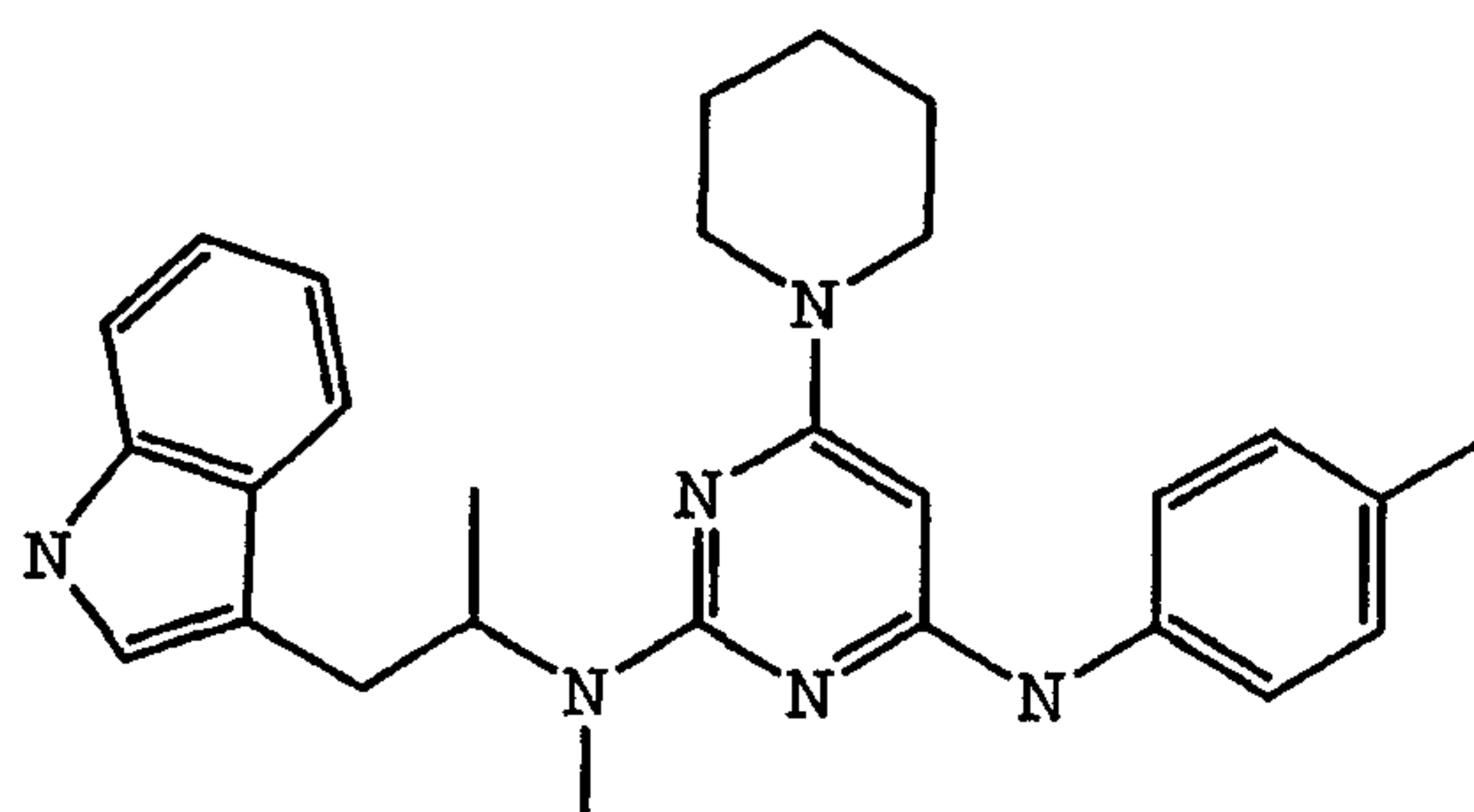
WO 02/060392

PCT/US02/04608

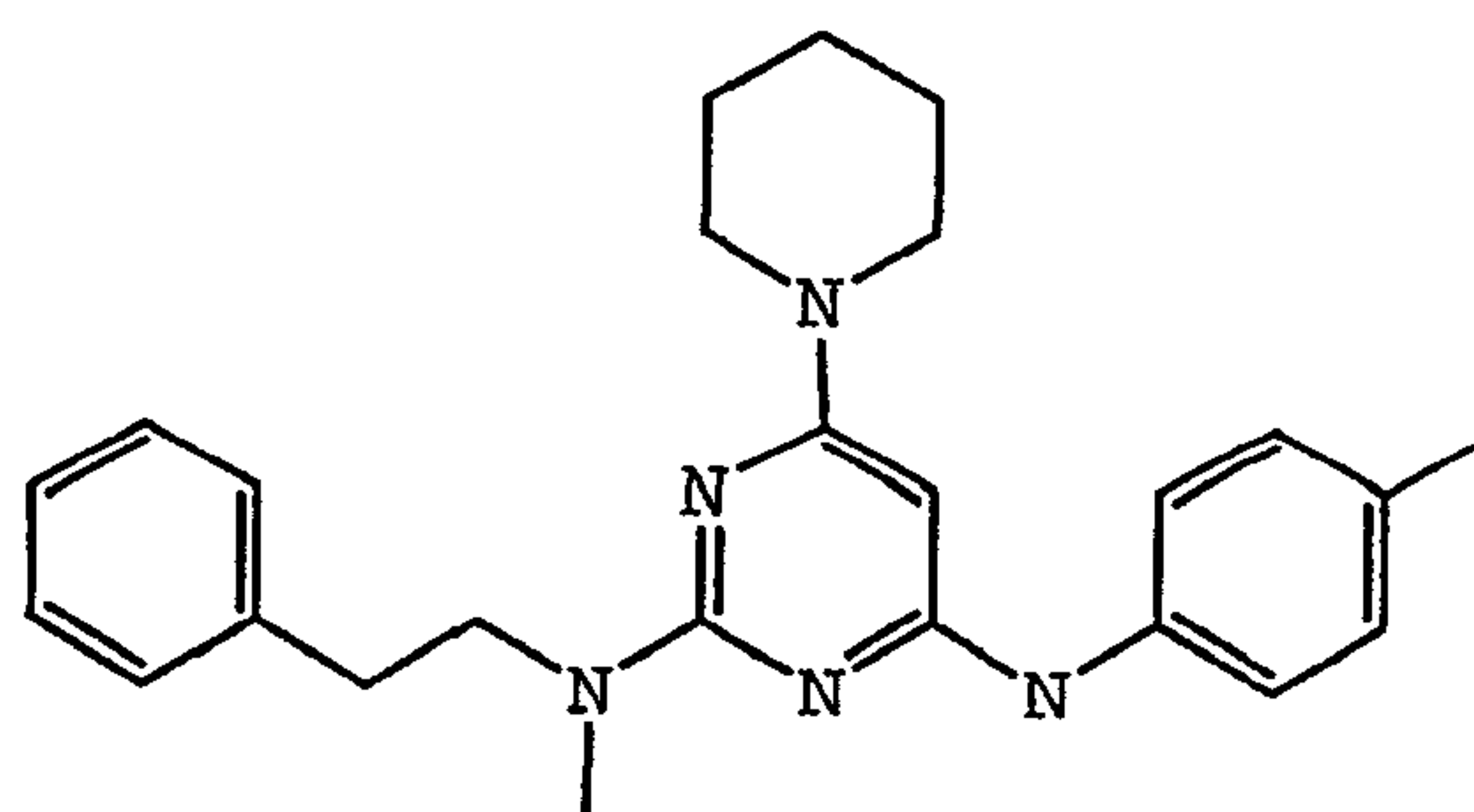
152



;



; and



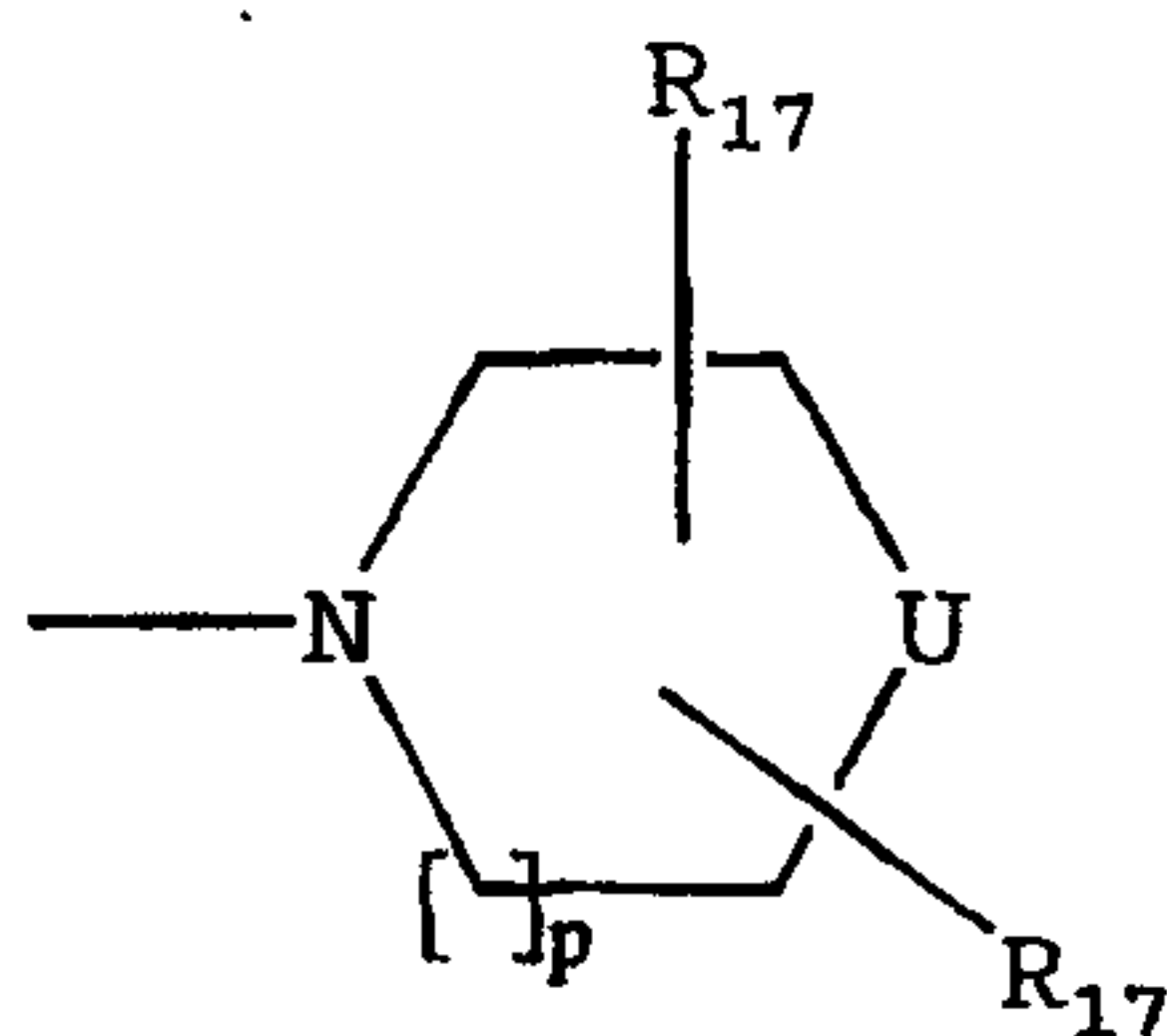
5

In one embodiment, Y is

WO 02/060392

PCT/US02/04608

153

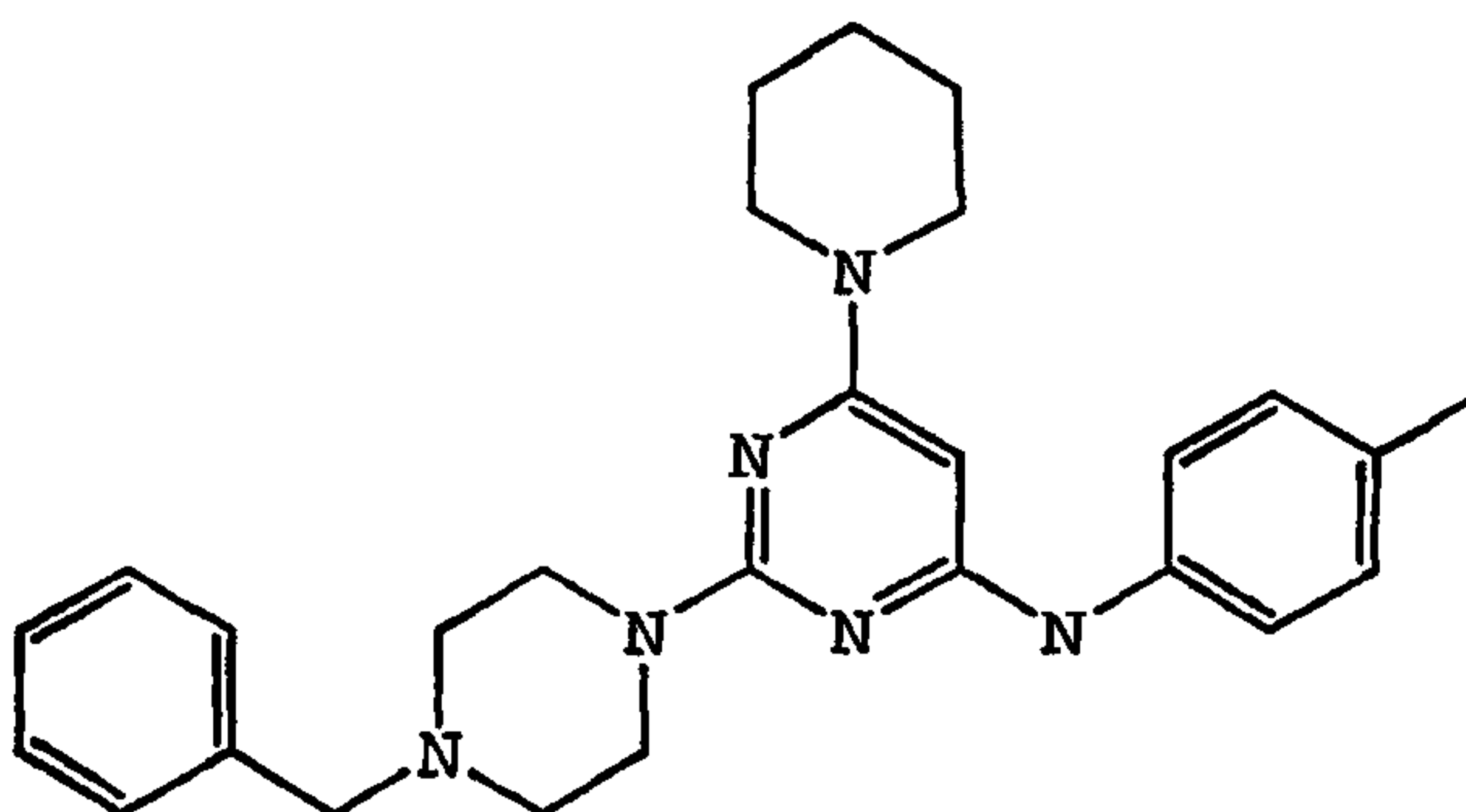


In one embodiment, U is NR_{16} .

5 In one embodiment, R_{16} is $(\text{CH}_2)_m\text{-Z}$.

In one embodiment, Z is aryl or heteroaryl.

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

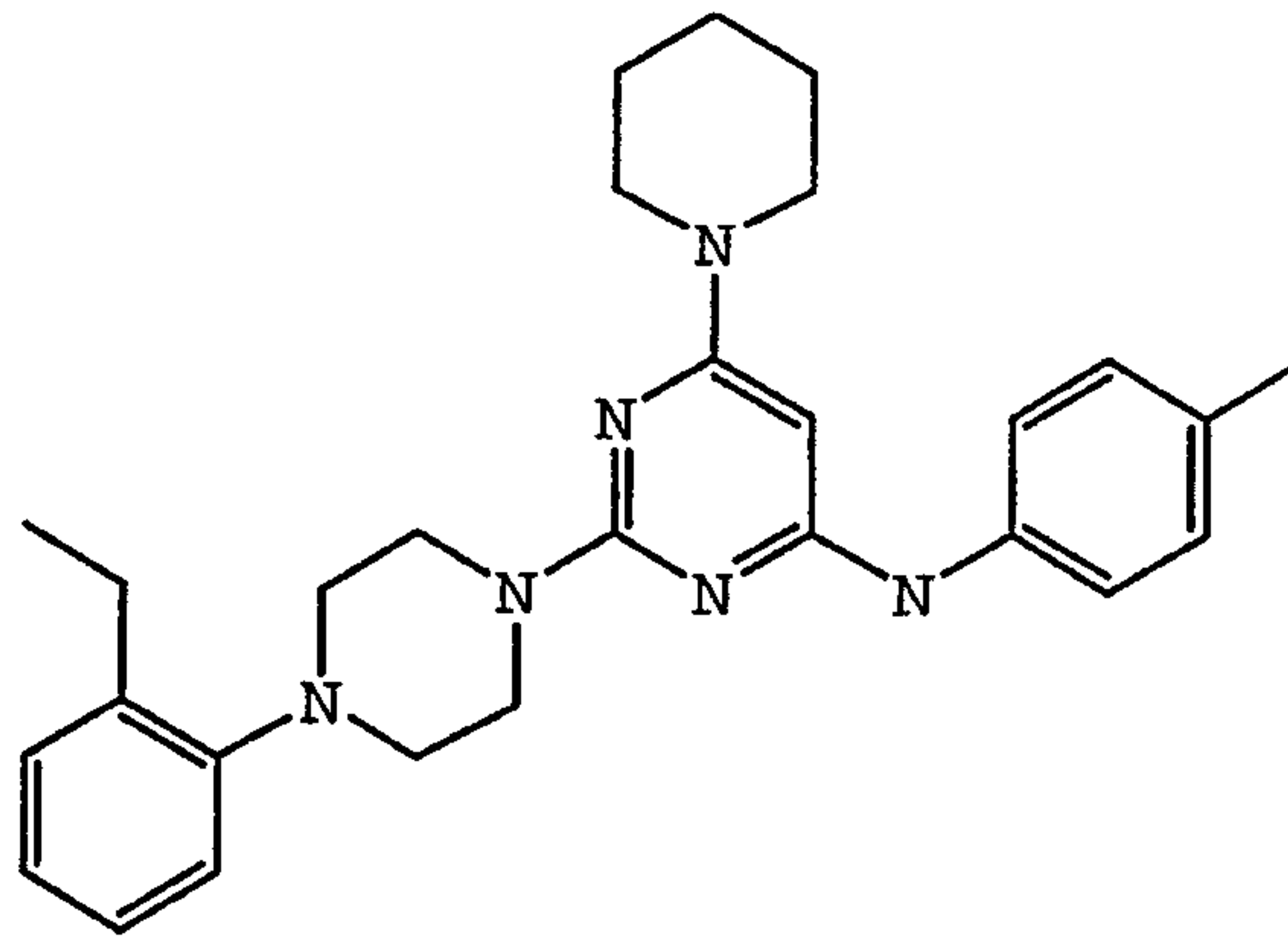
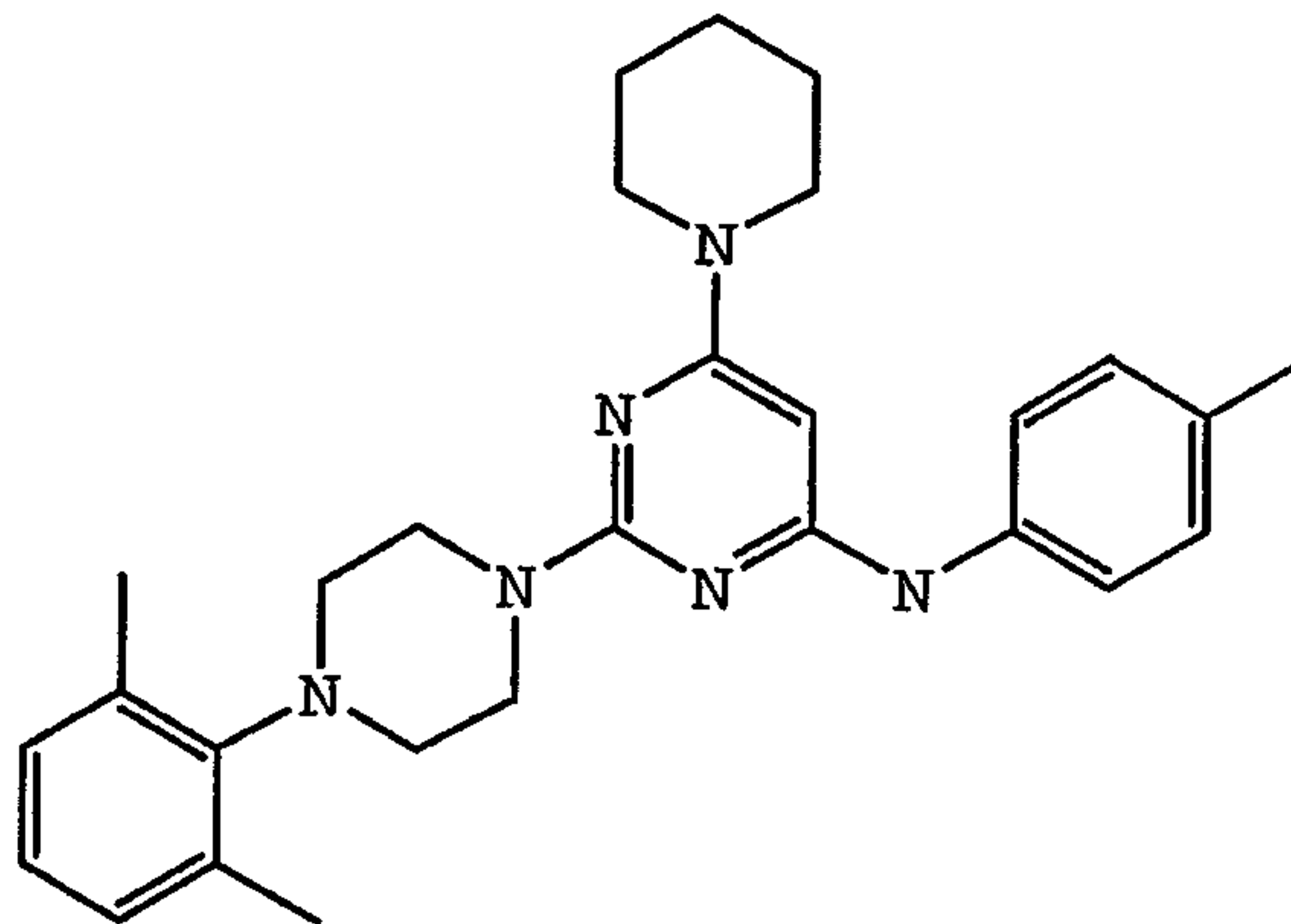


15

WO 02/060392

PCT/US02/04608

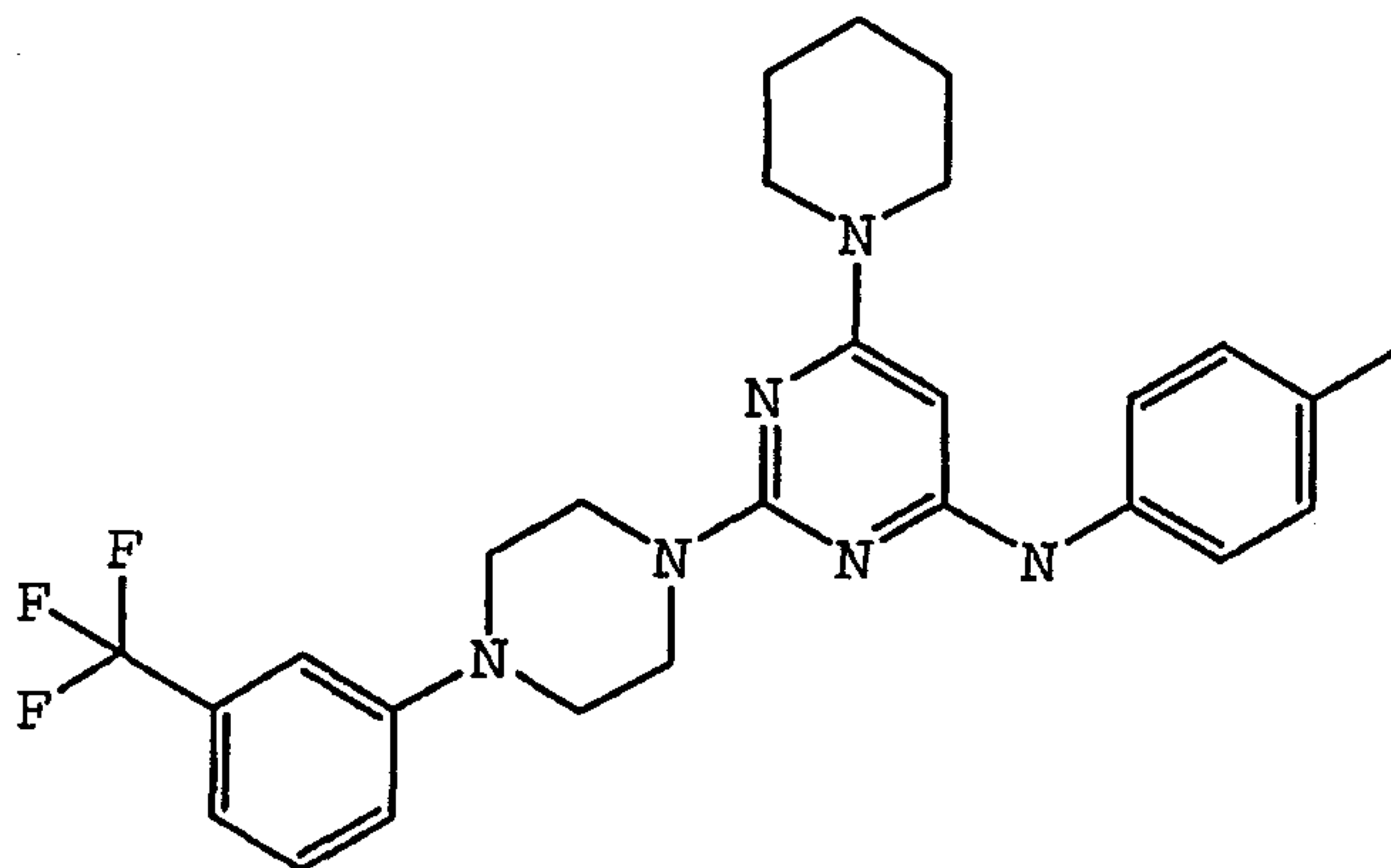
154

*i**i*

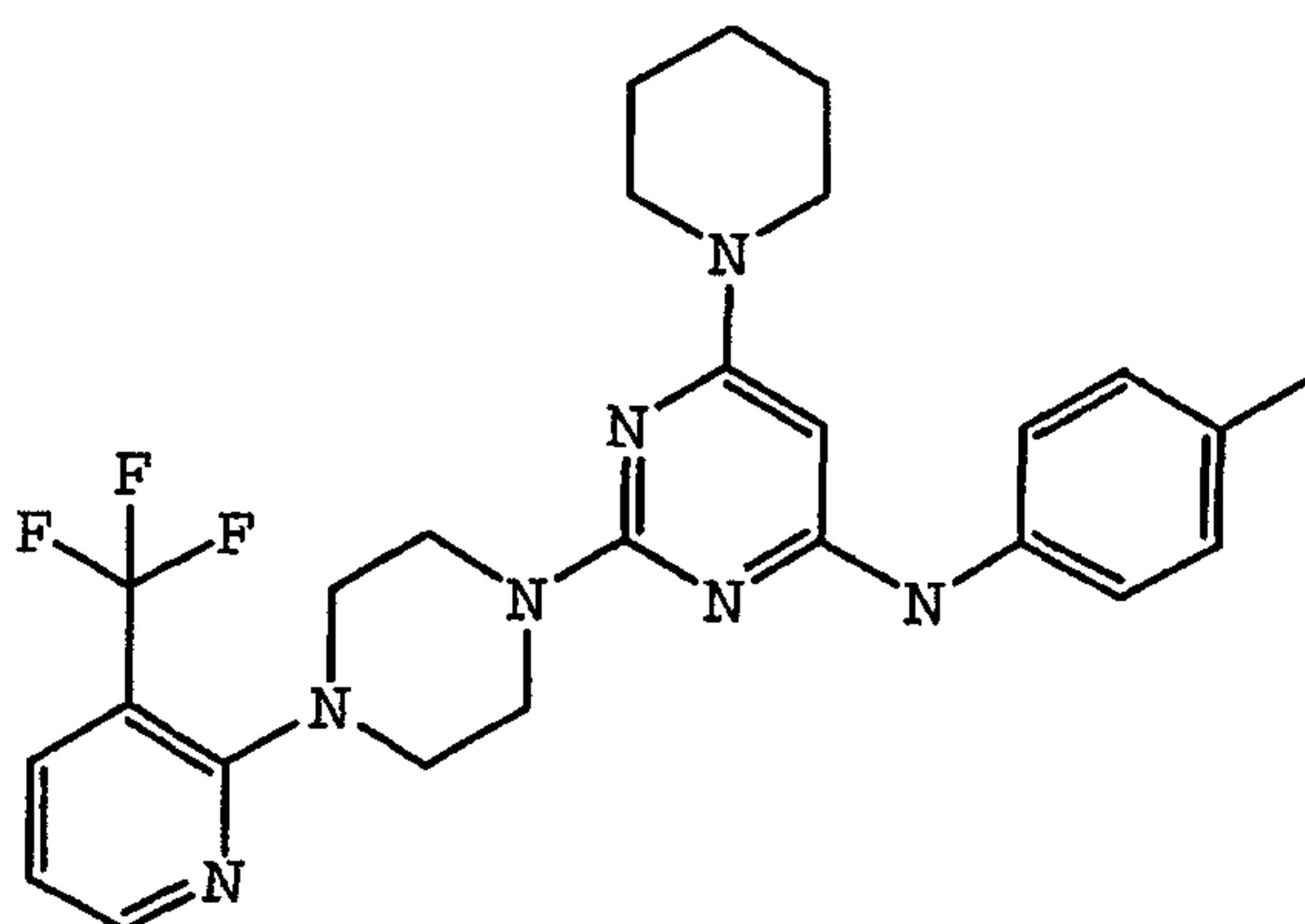
WO 02/060392

PCT/US02/04608

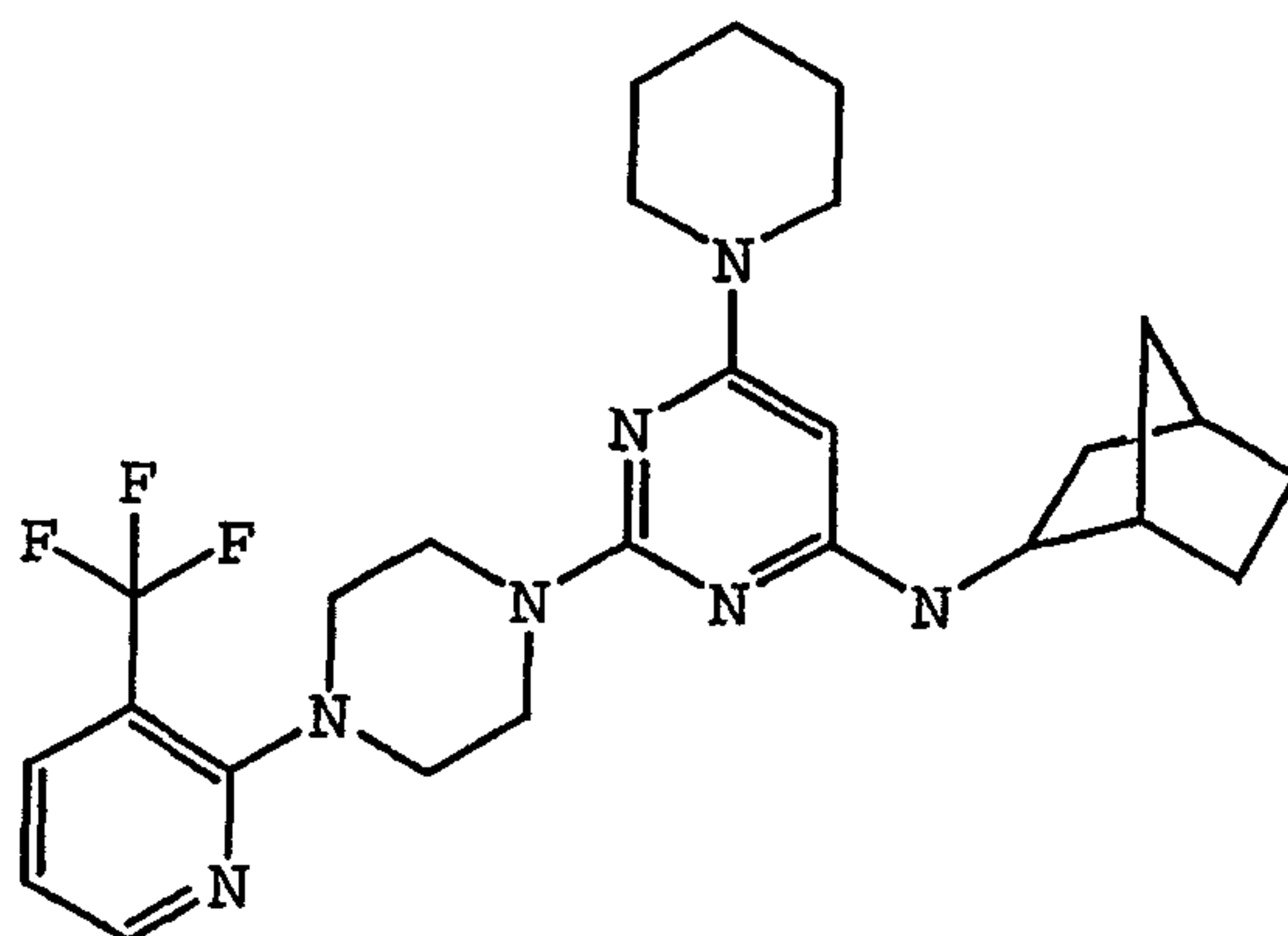
155



;



; and

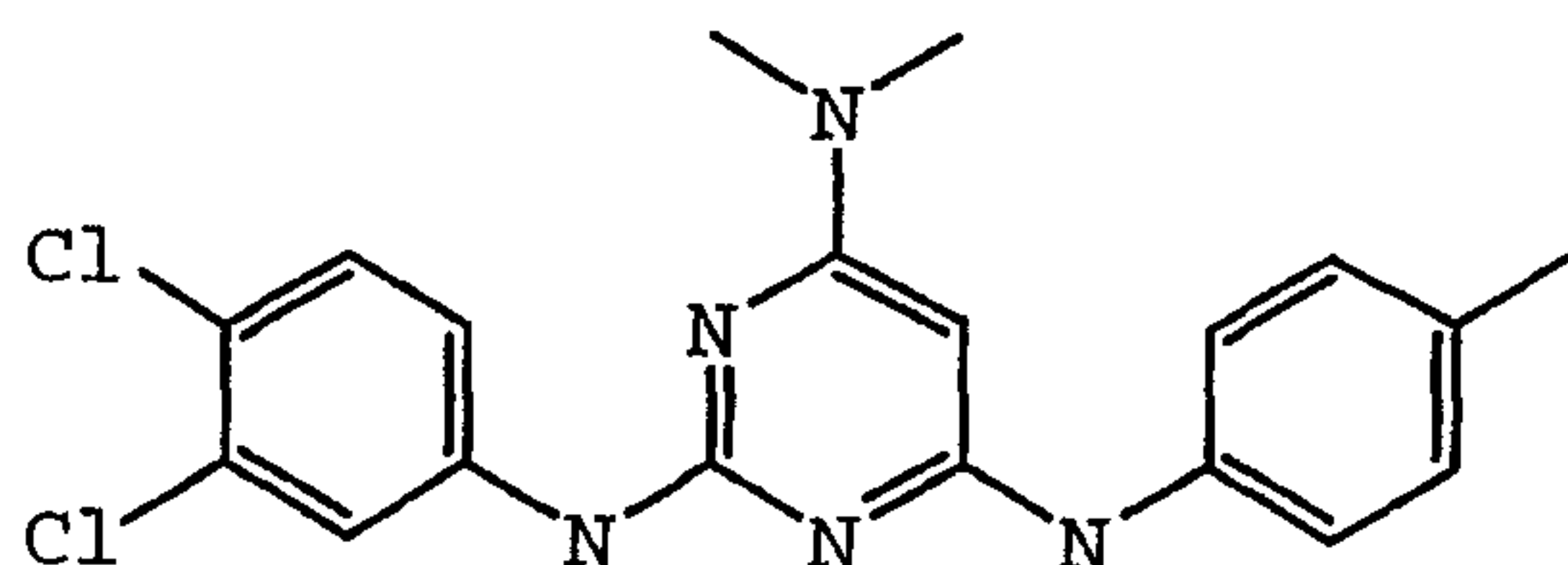


WO 02/060392

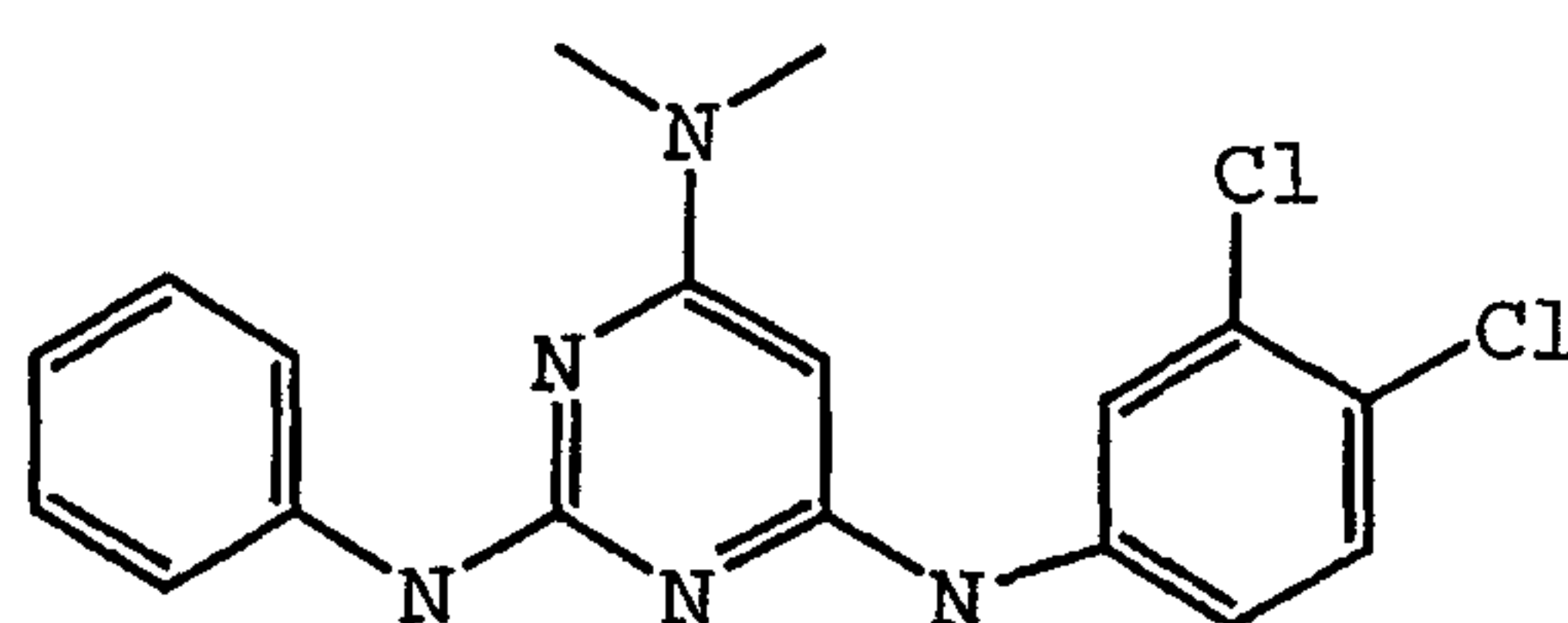
PCT/US02/04608

156

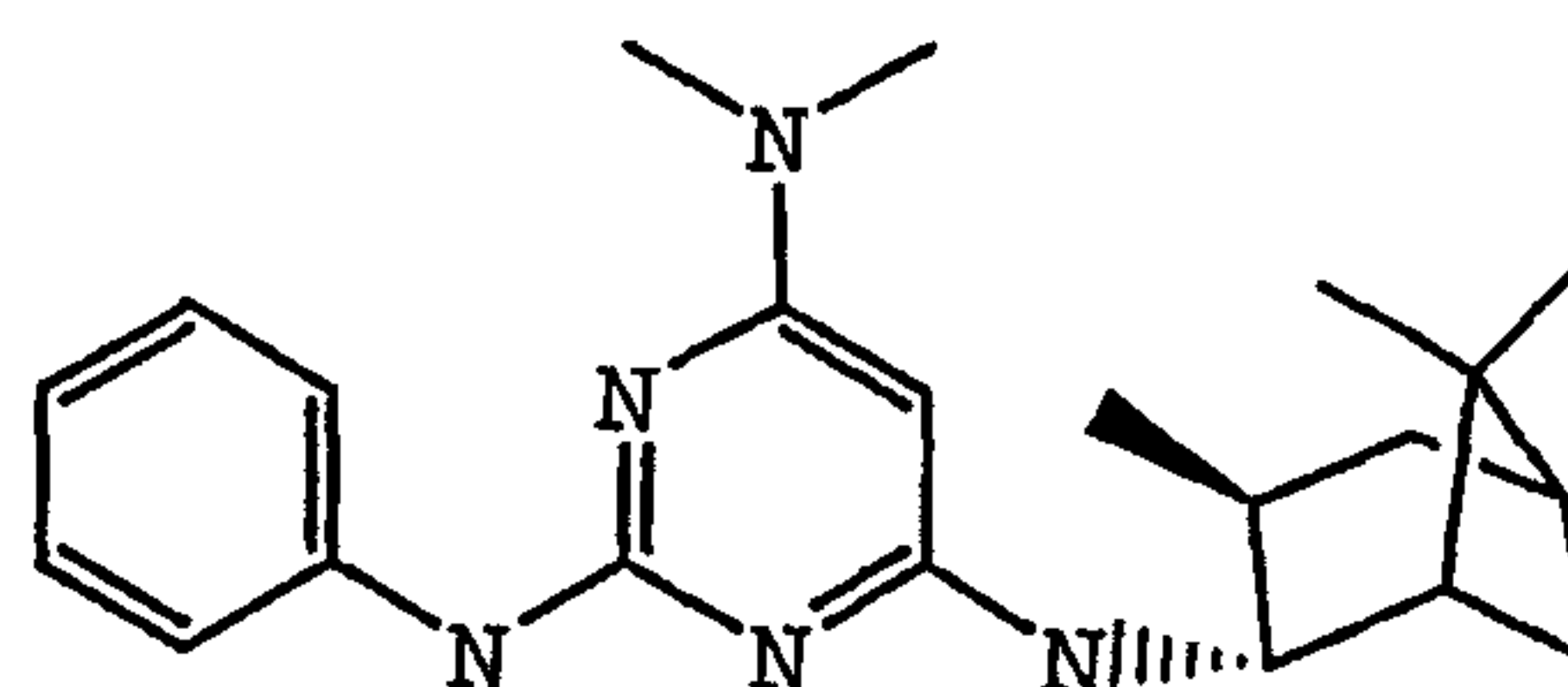
In one embodiment, the compound is selected from the group consisting of:



i



i

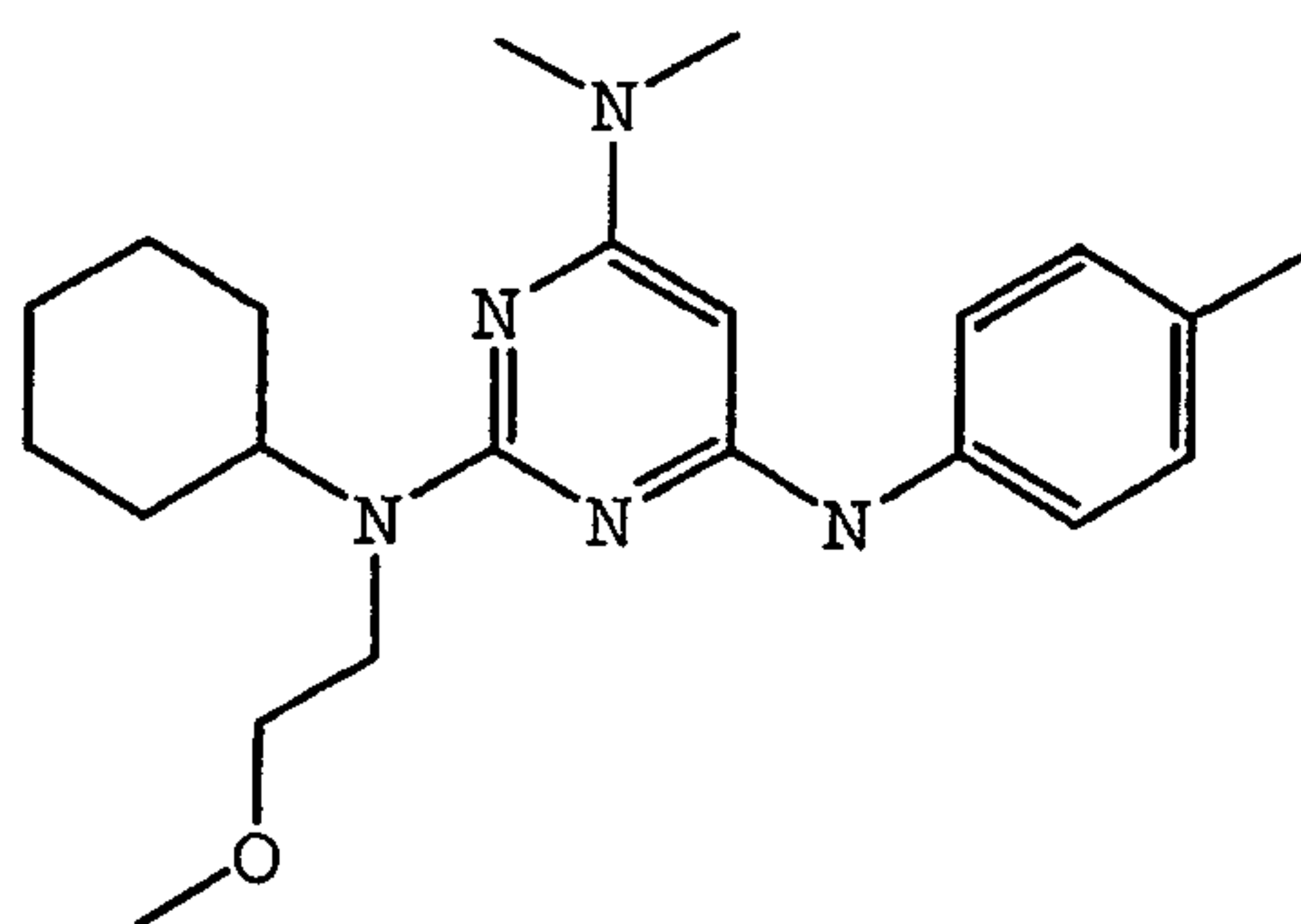


i

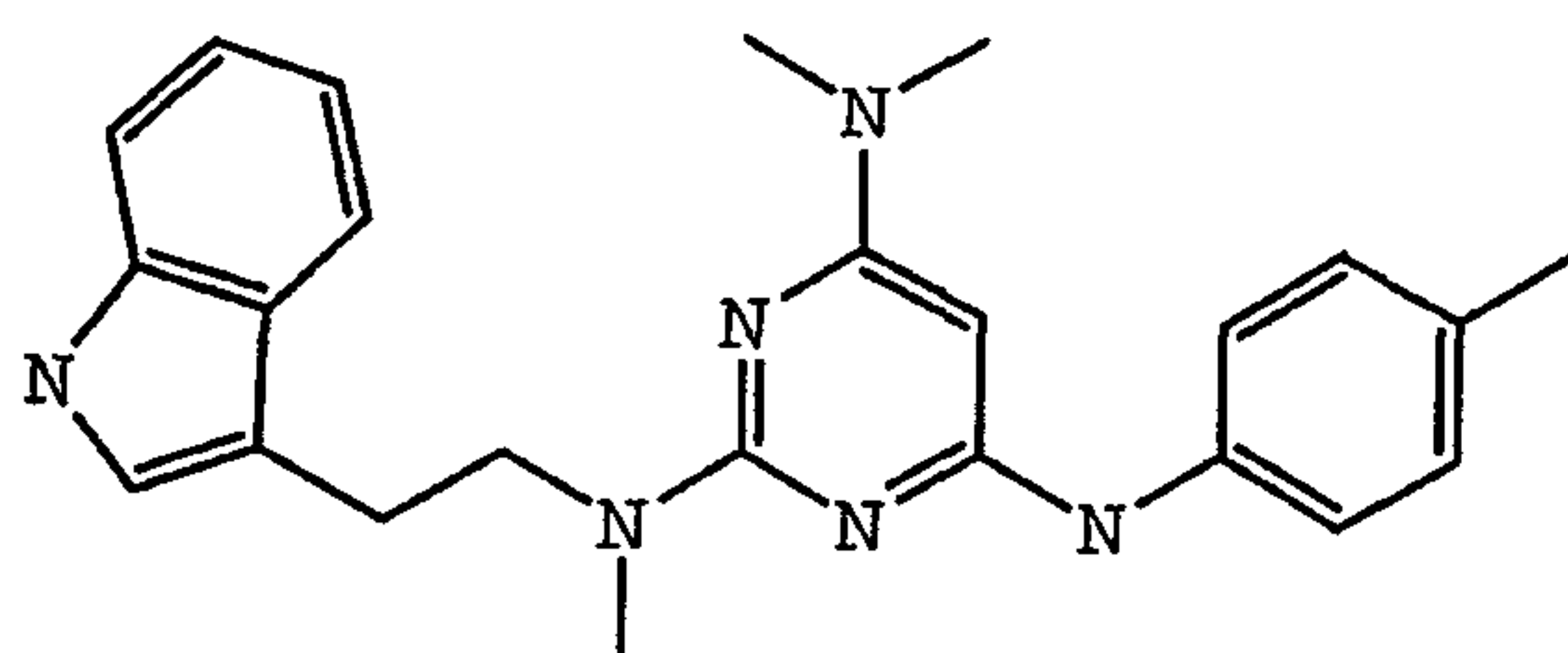
WO 02/060392

PCT/US02/04608

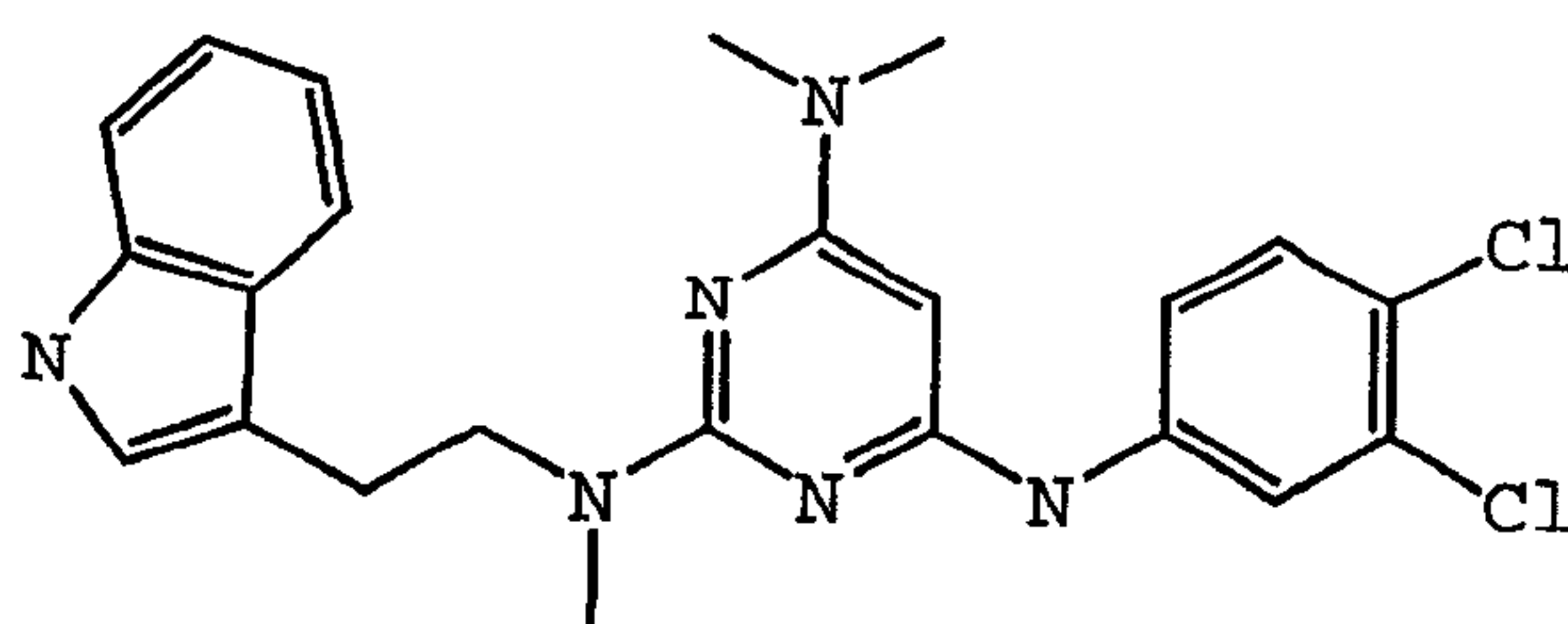
157



;



; and

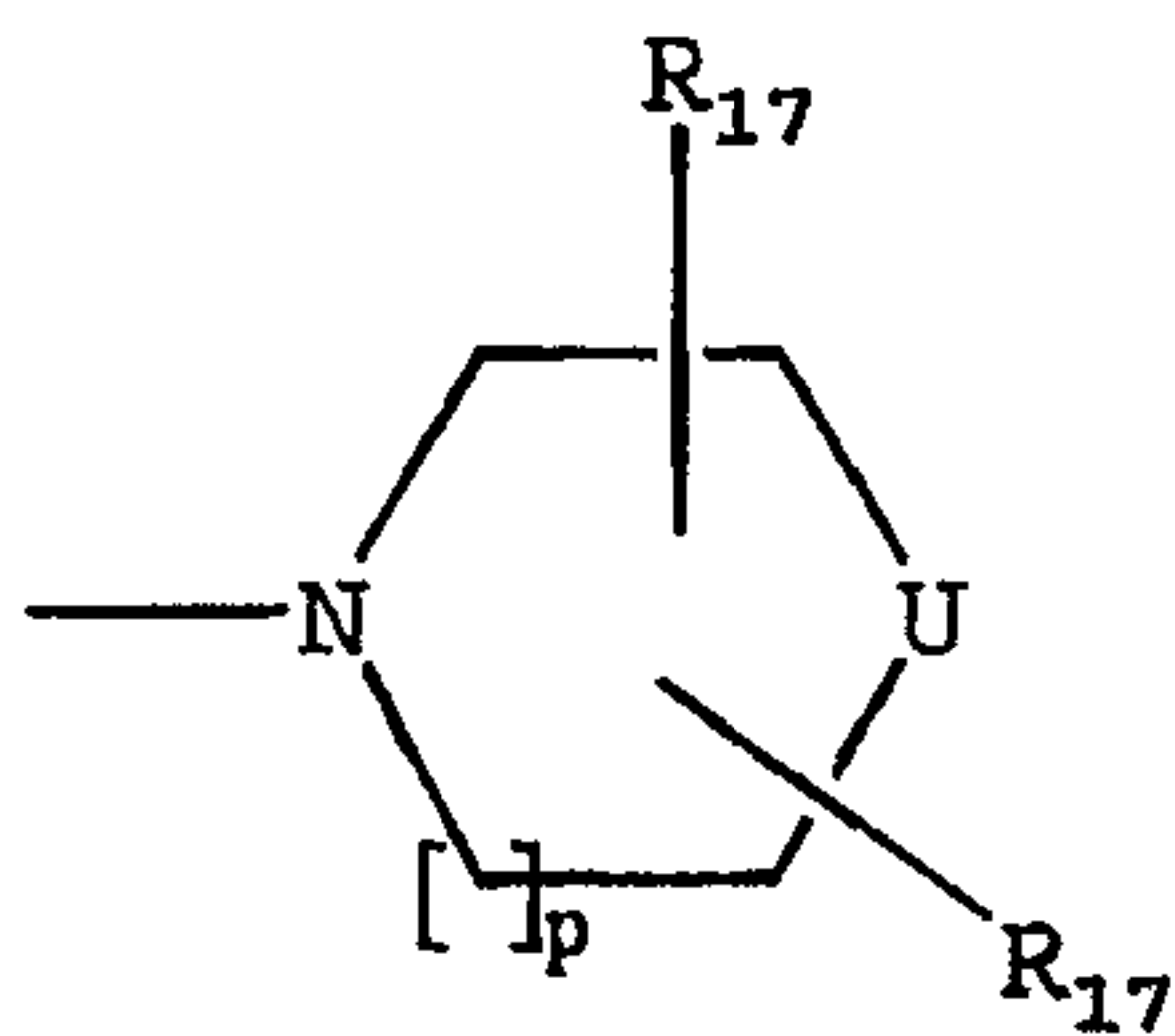


WO 02/060392

PCT/US02/04608

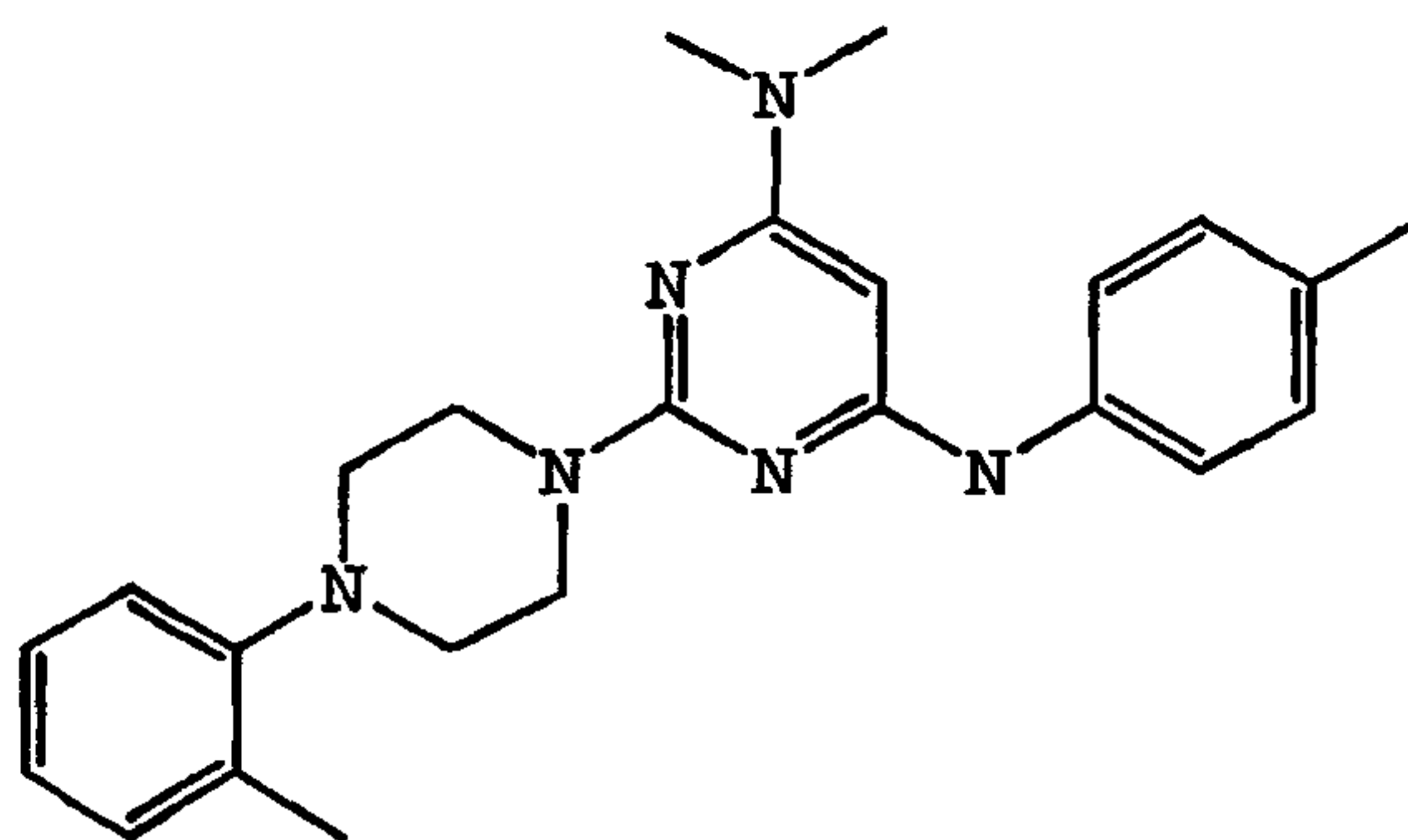
158

In one embodiment, Y is

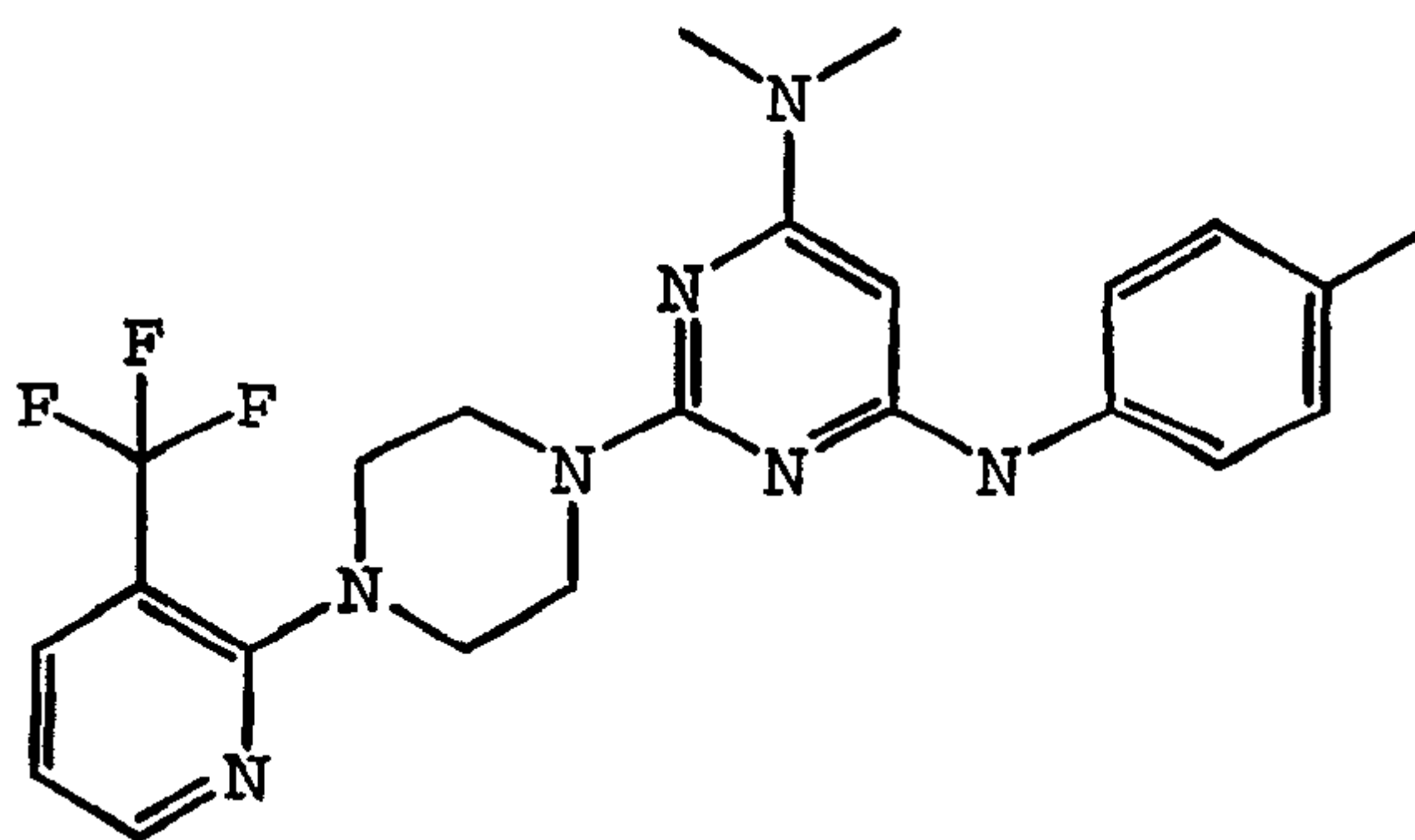


5 In one embodiment, U is NR_{16} .

In one embodiment, the compound is



; OR

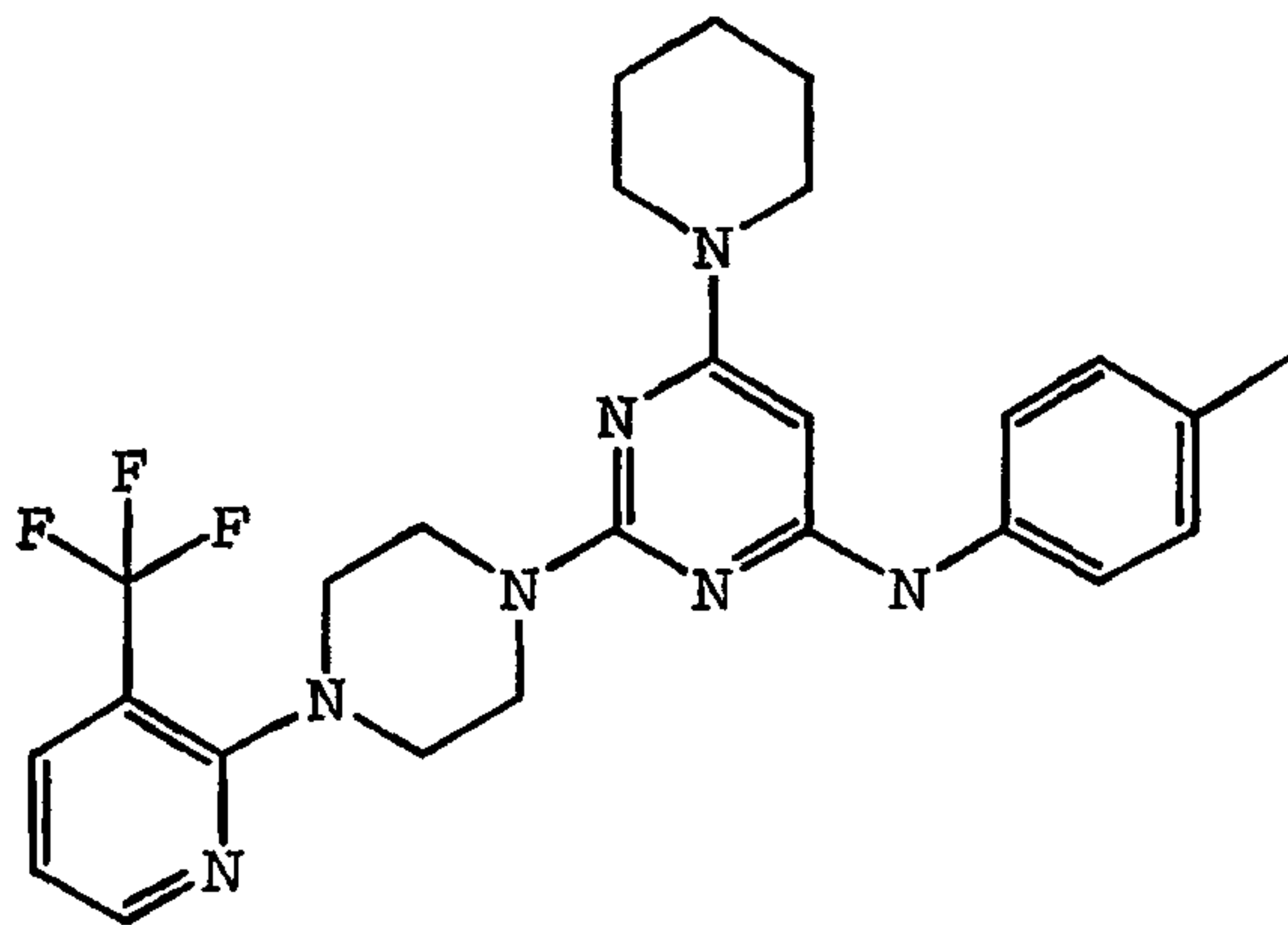


WO 02/060392

PCT/US02/04608

159

In one embodiment, the compound is



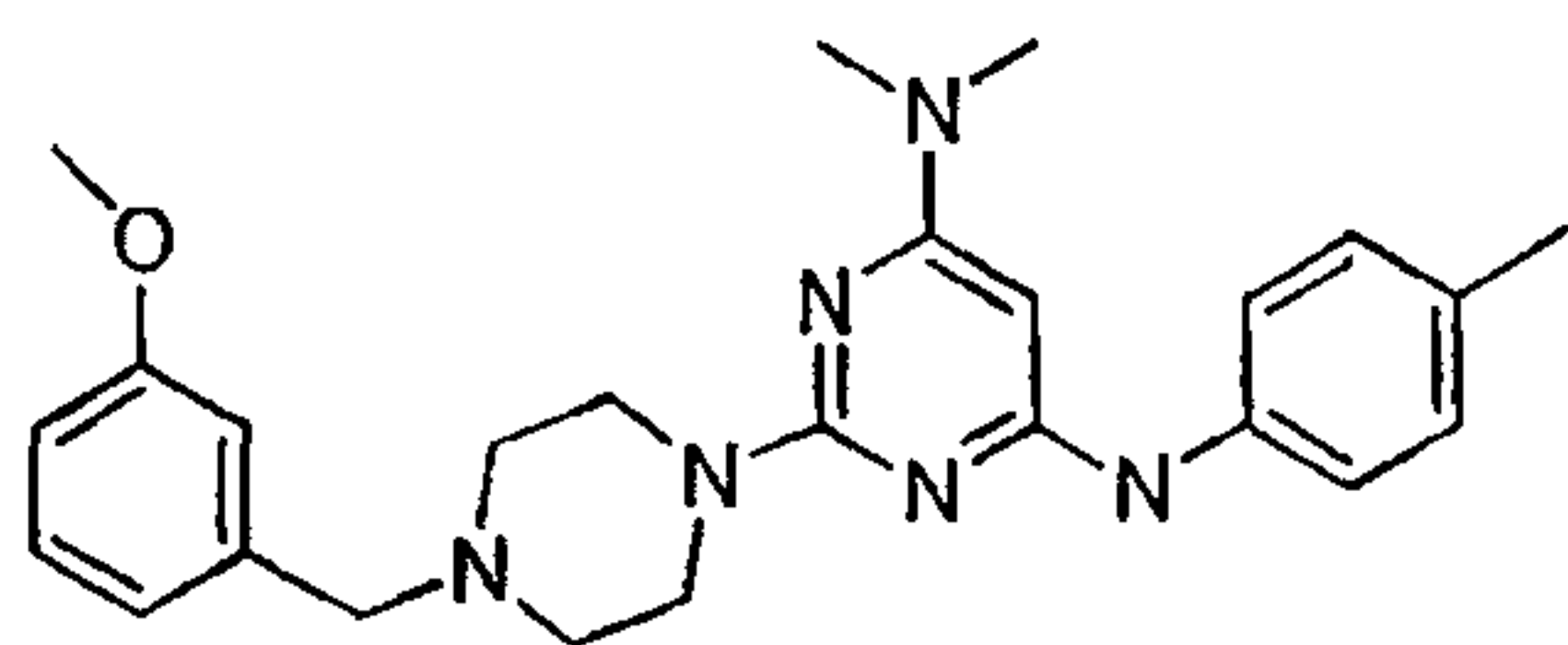
5

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

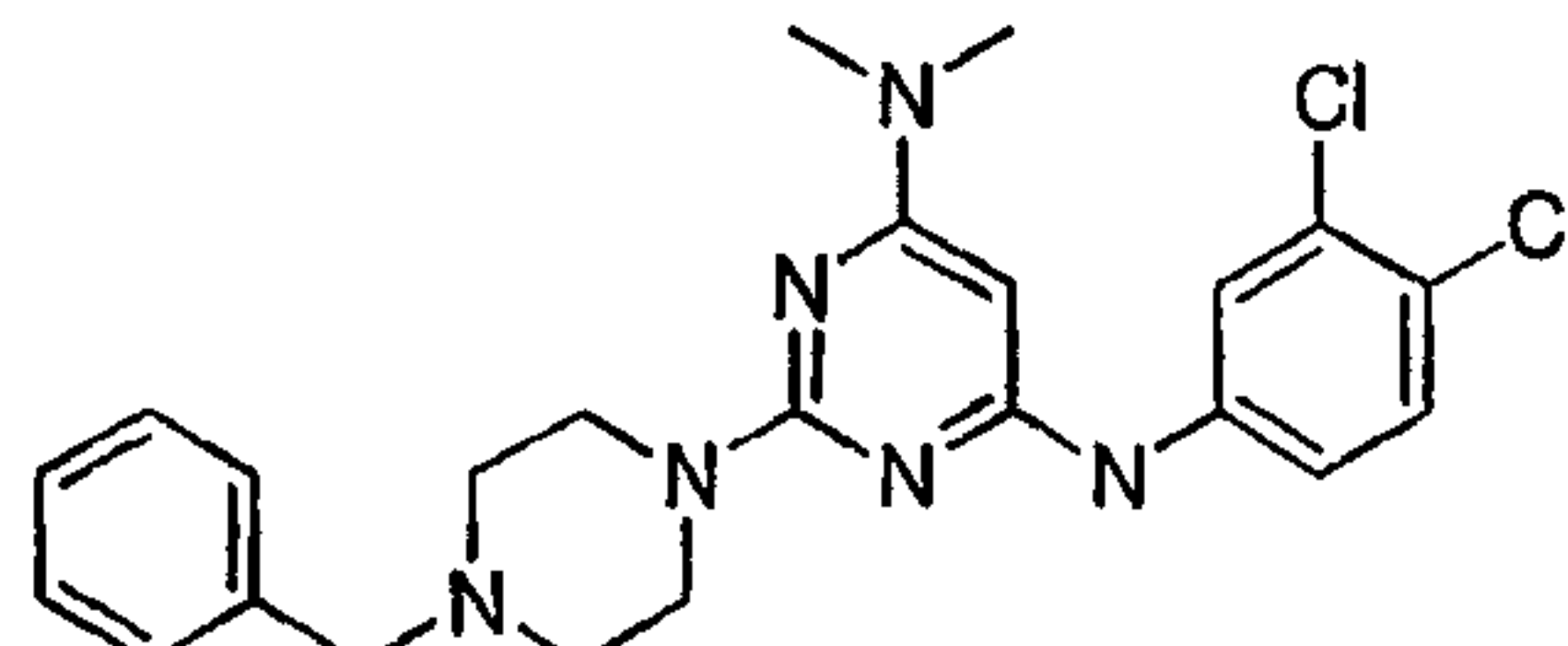
WO 02/060392

PCT/US02/04608

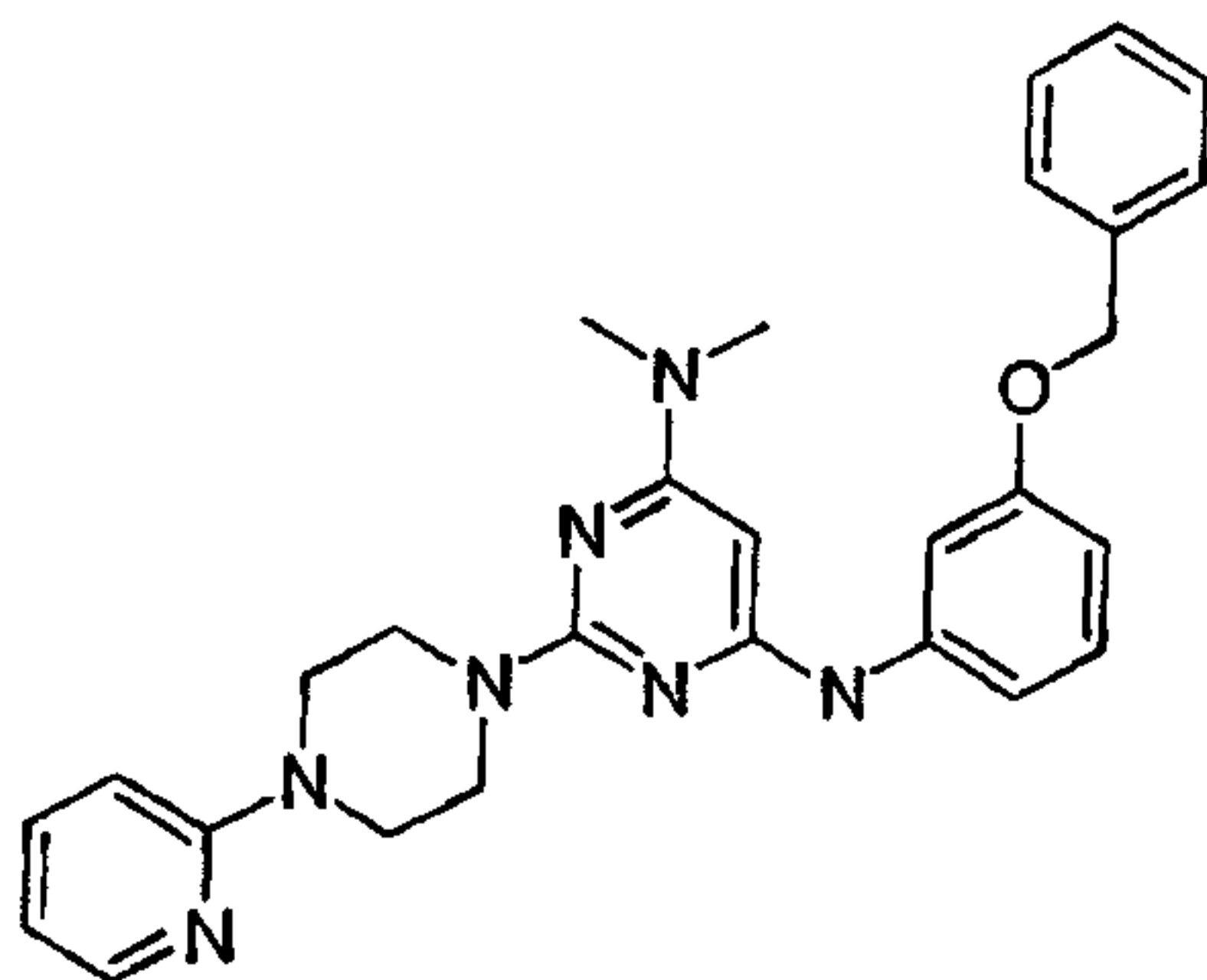
160



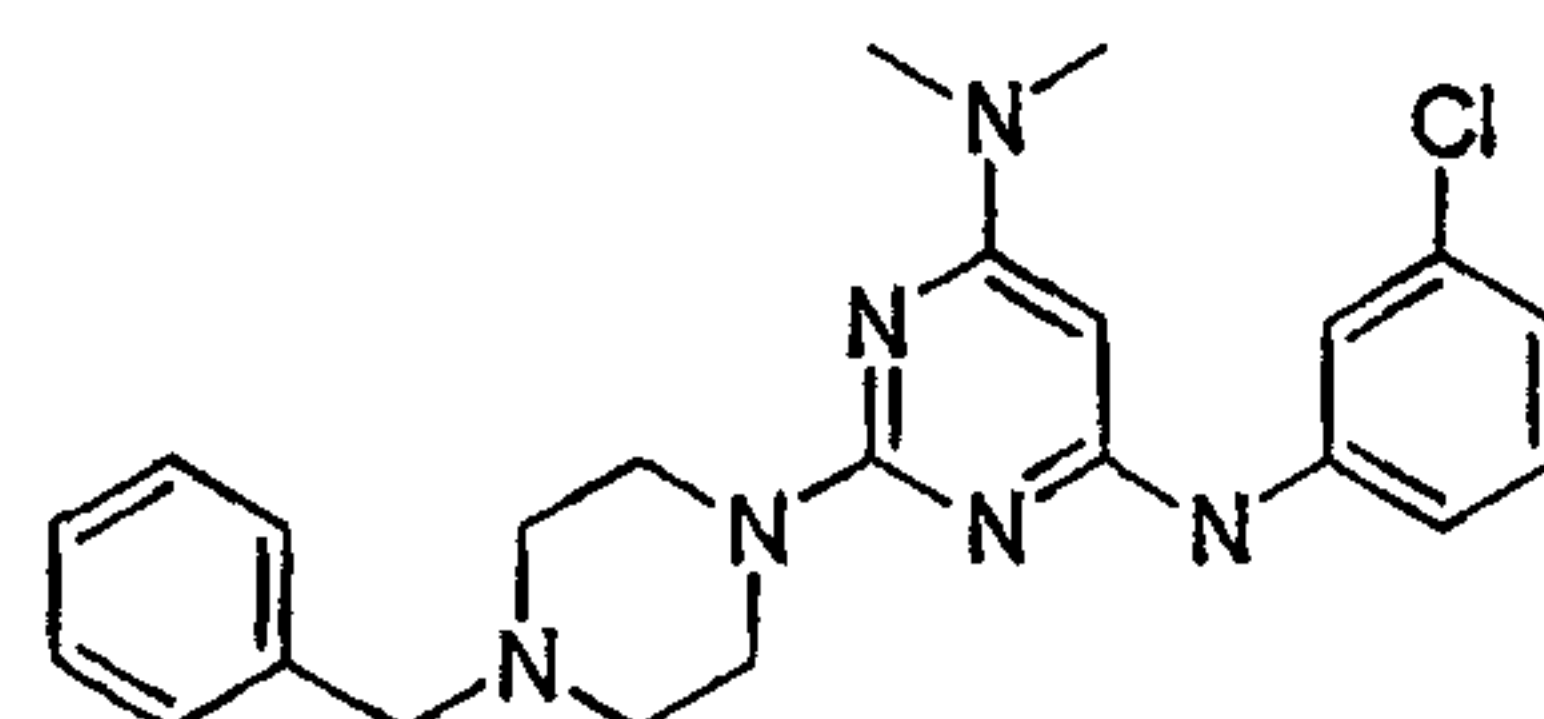
;



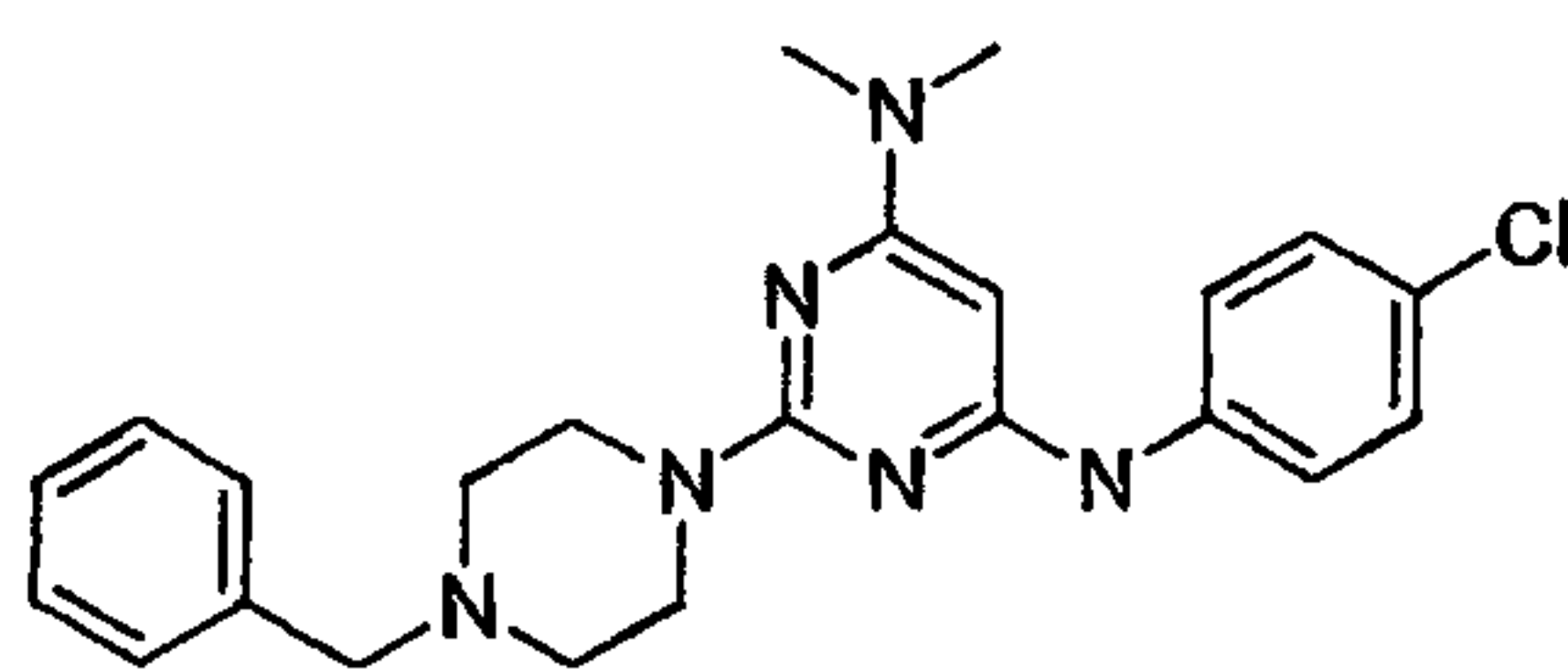
;



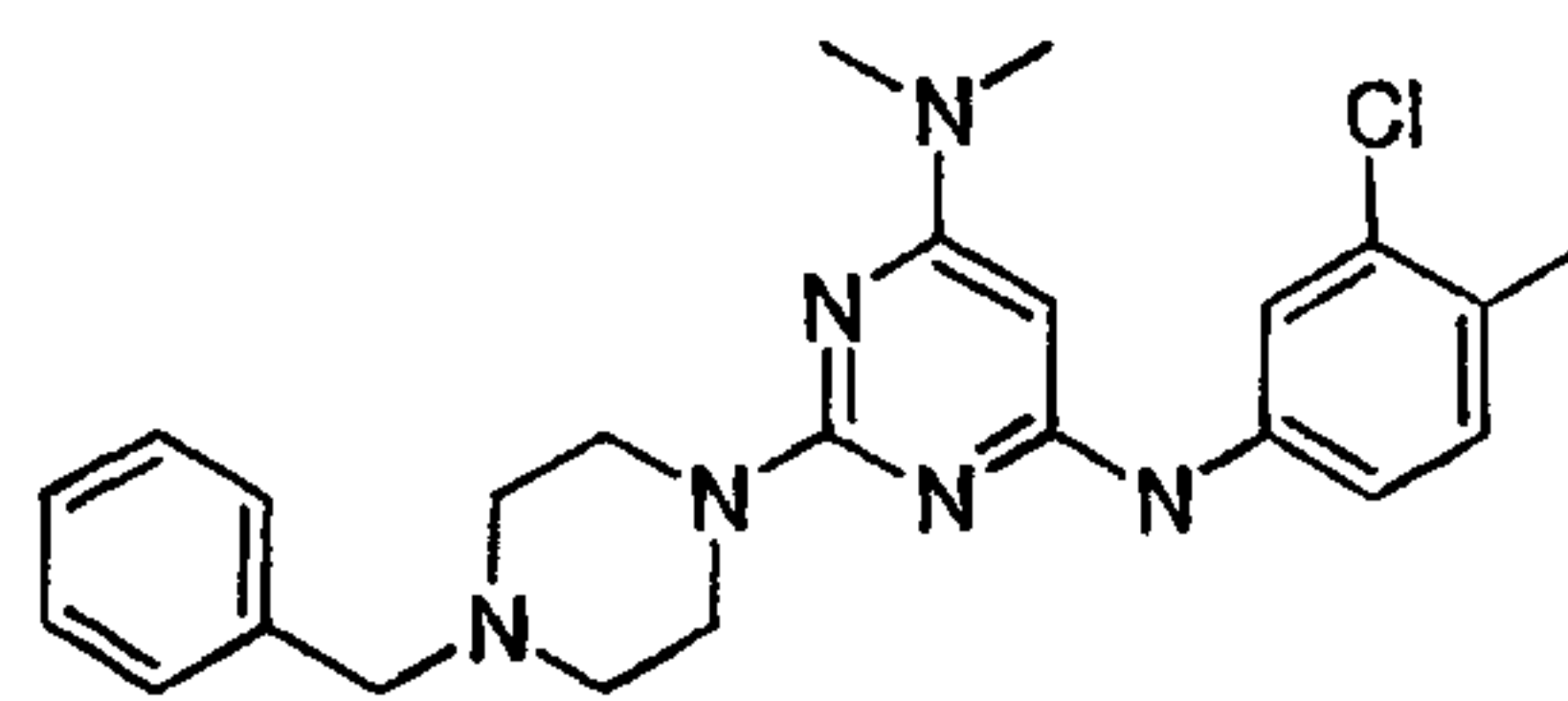
;



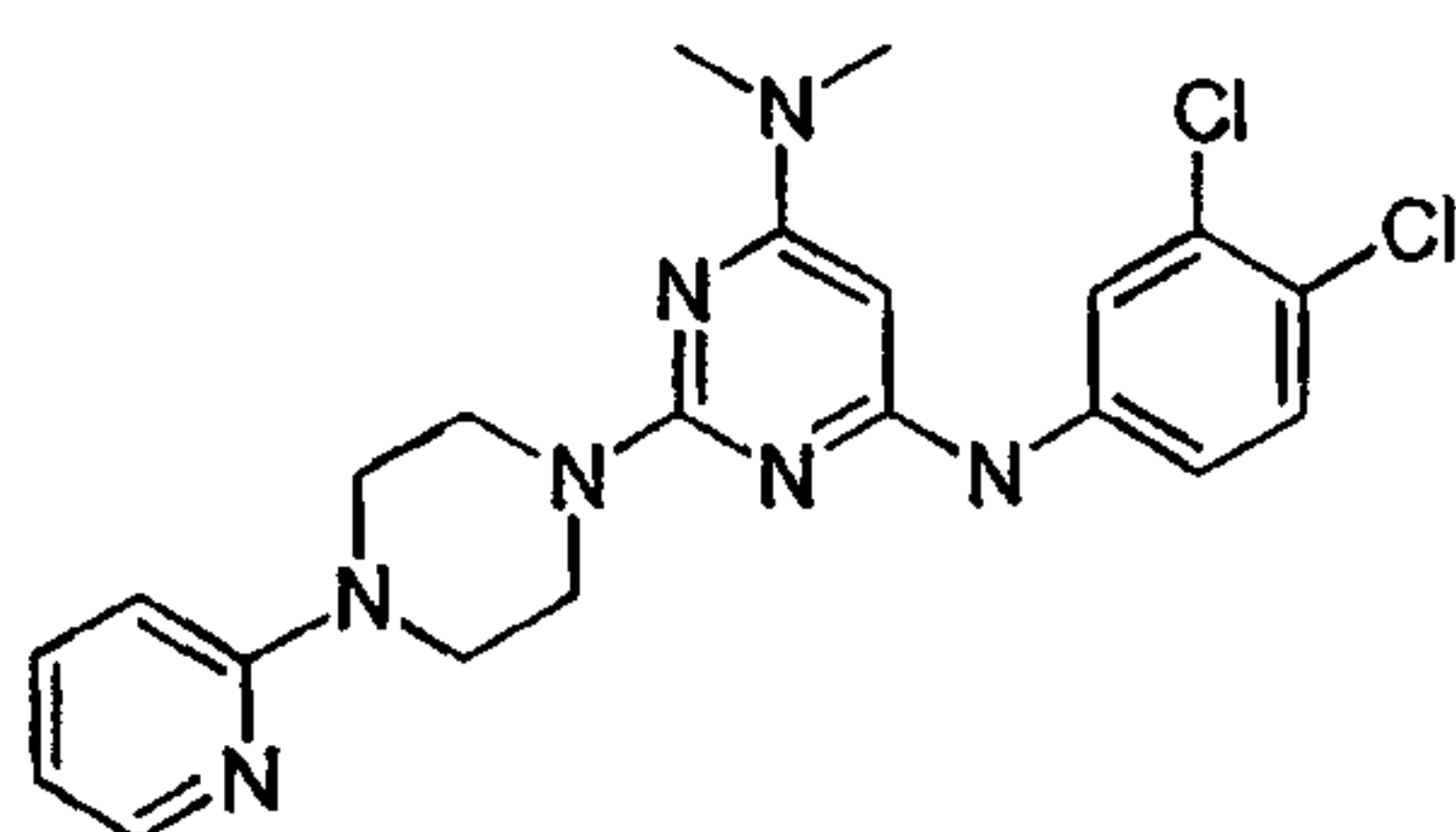
;



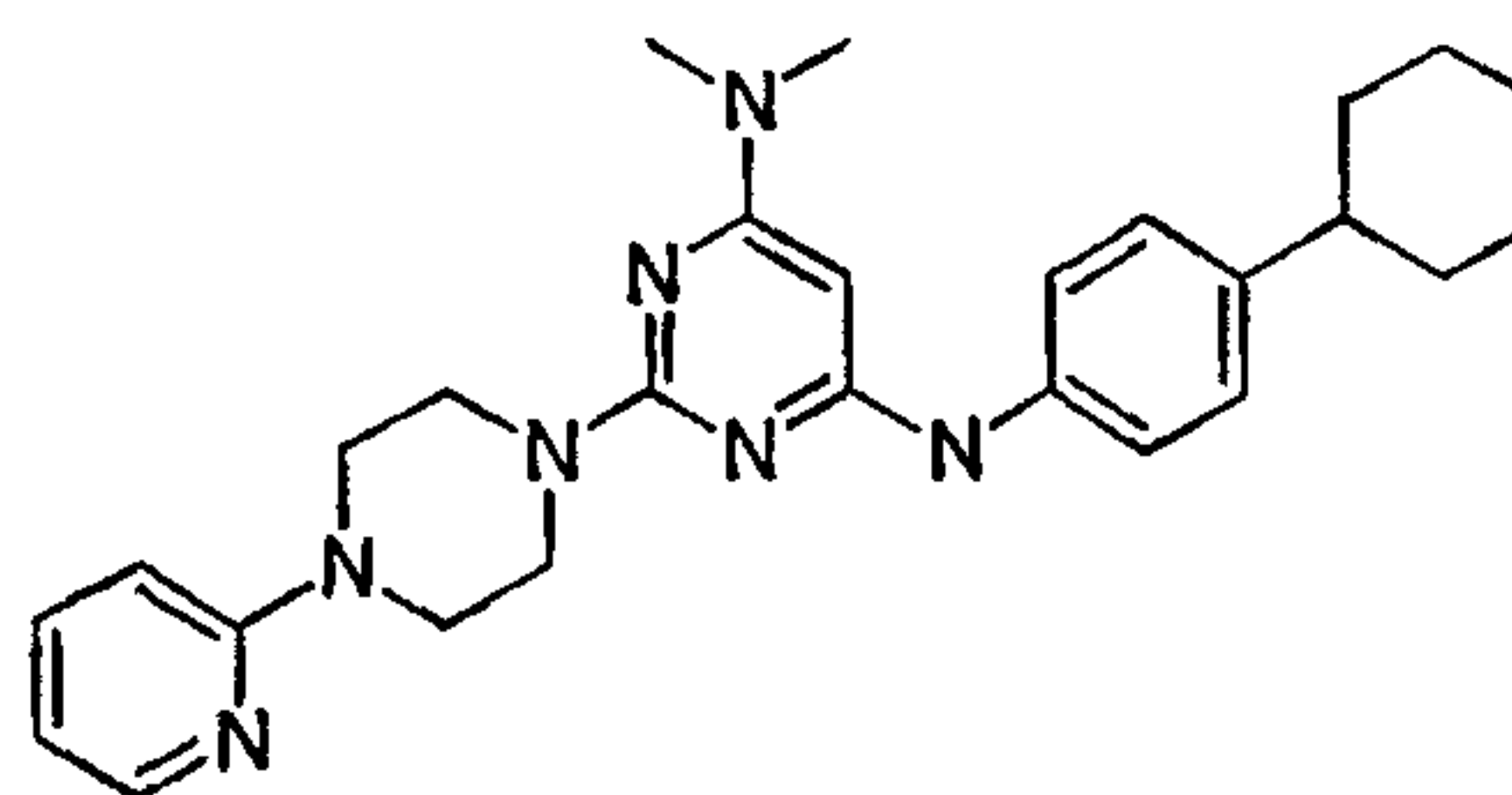
;



;



; and

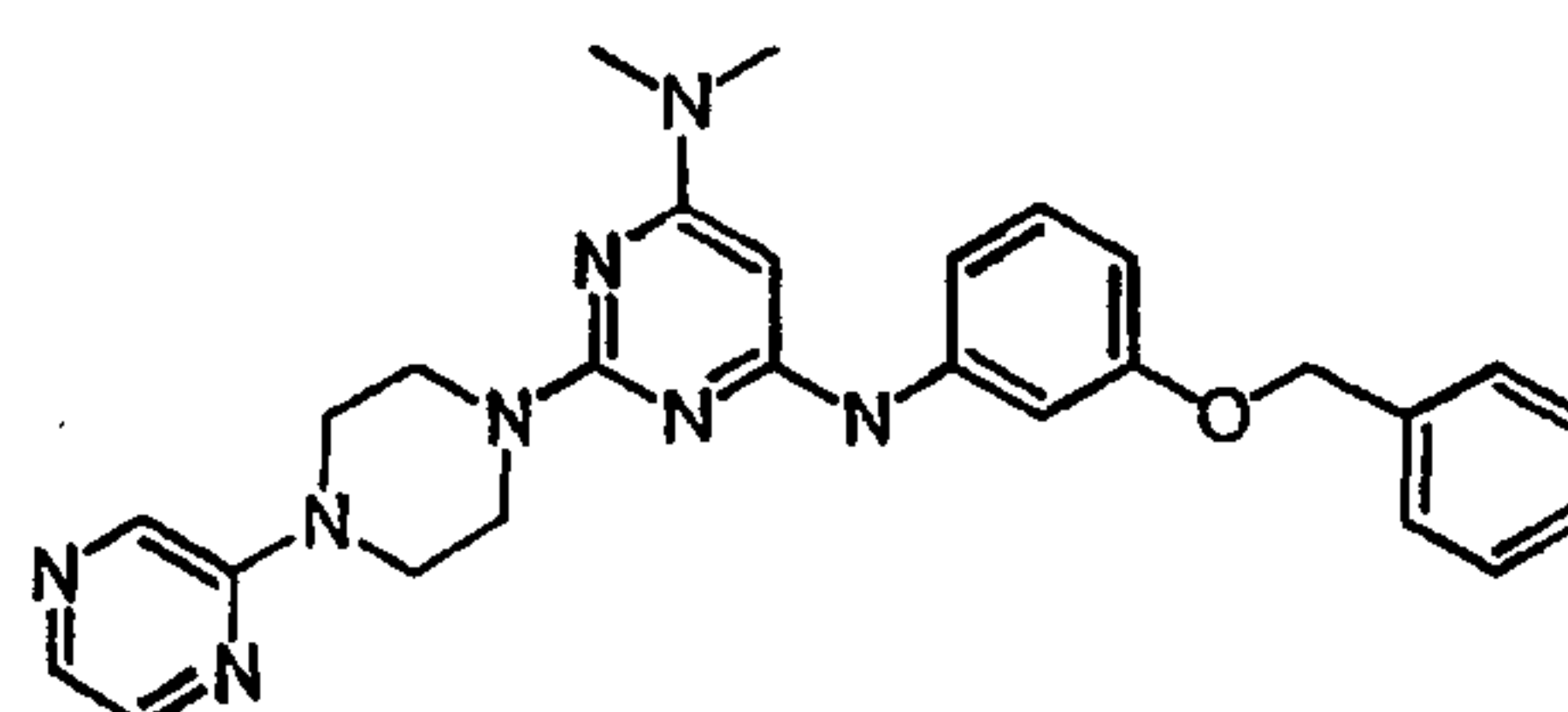
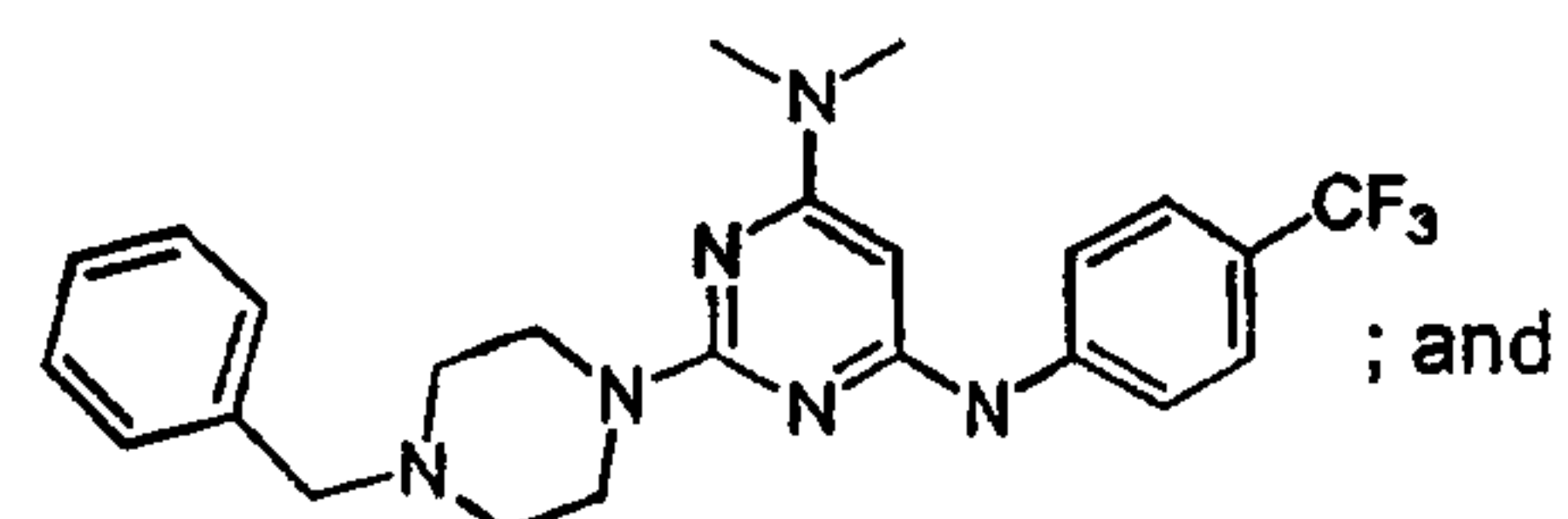
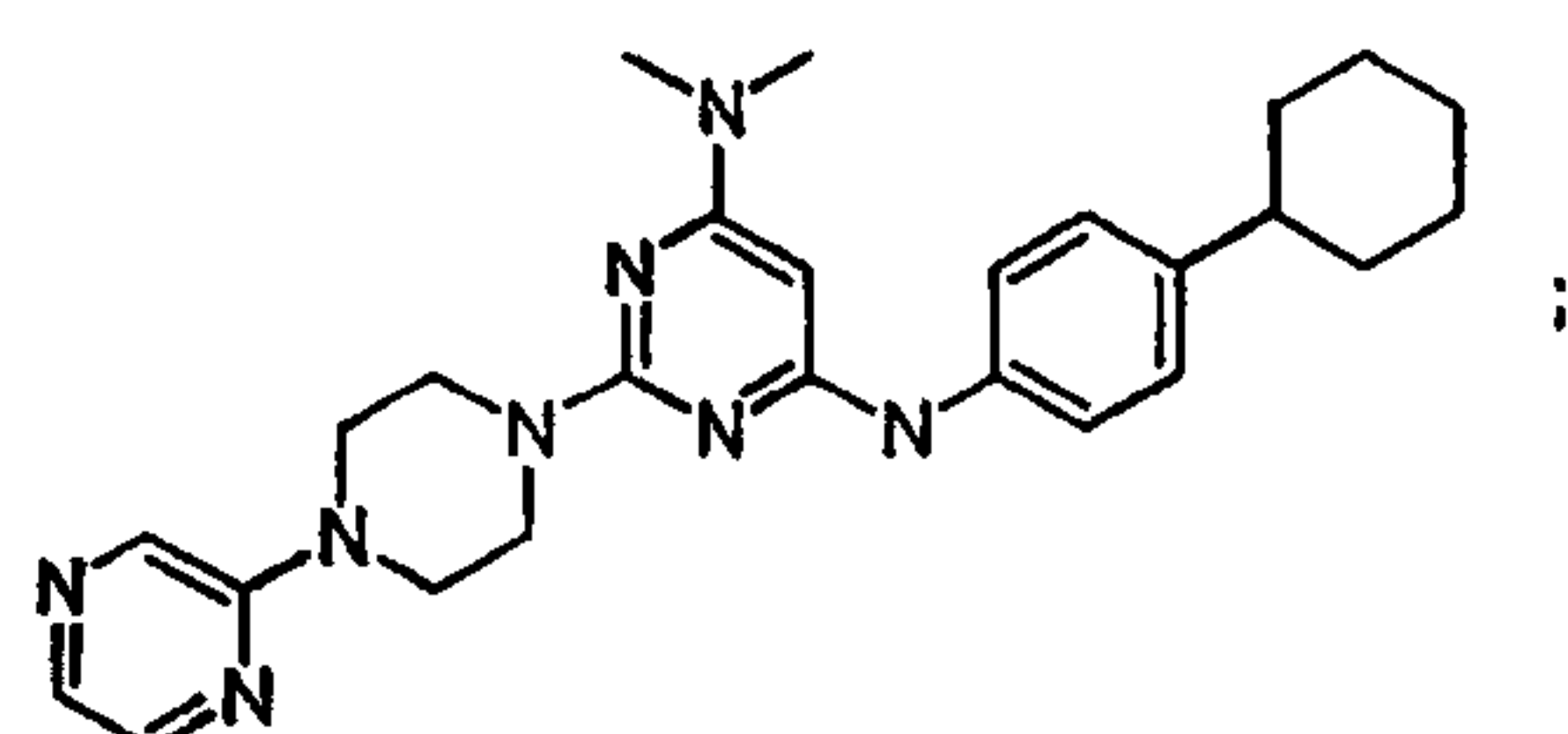
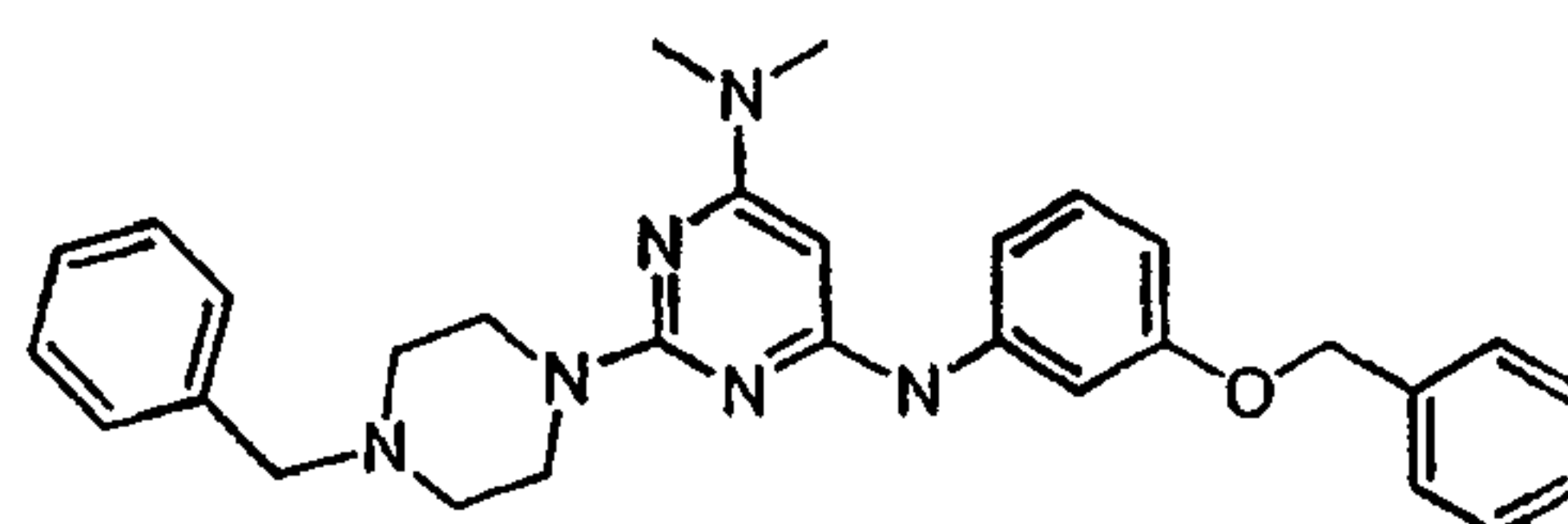
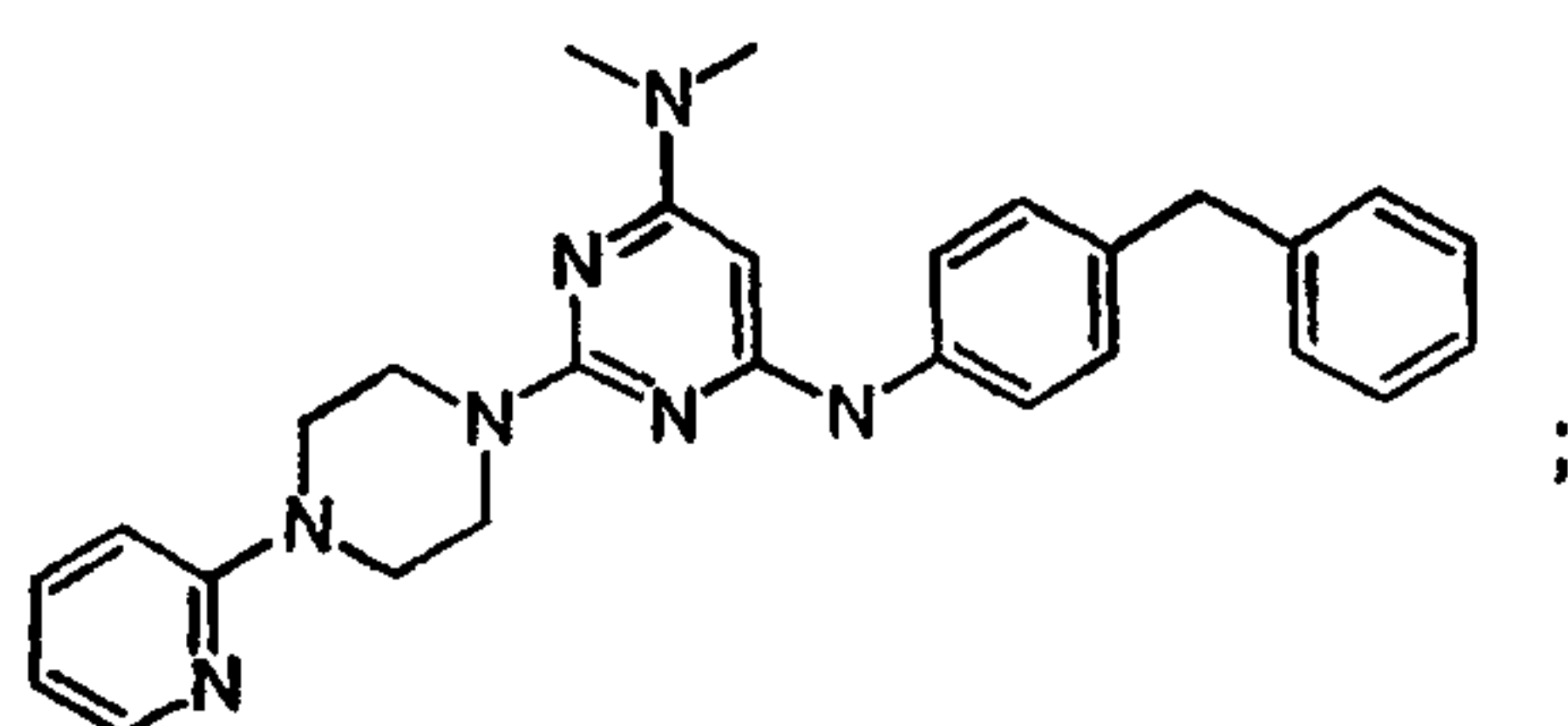
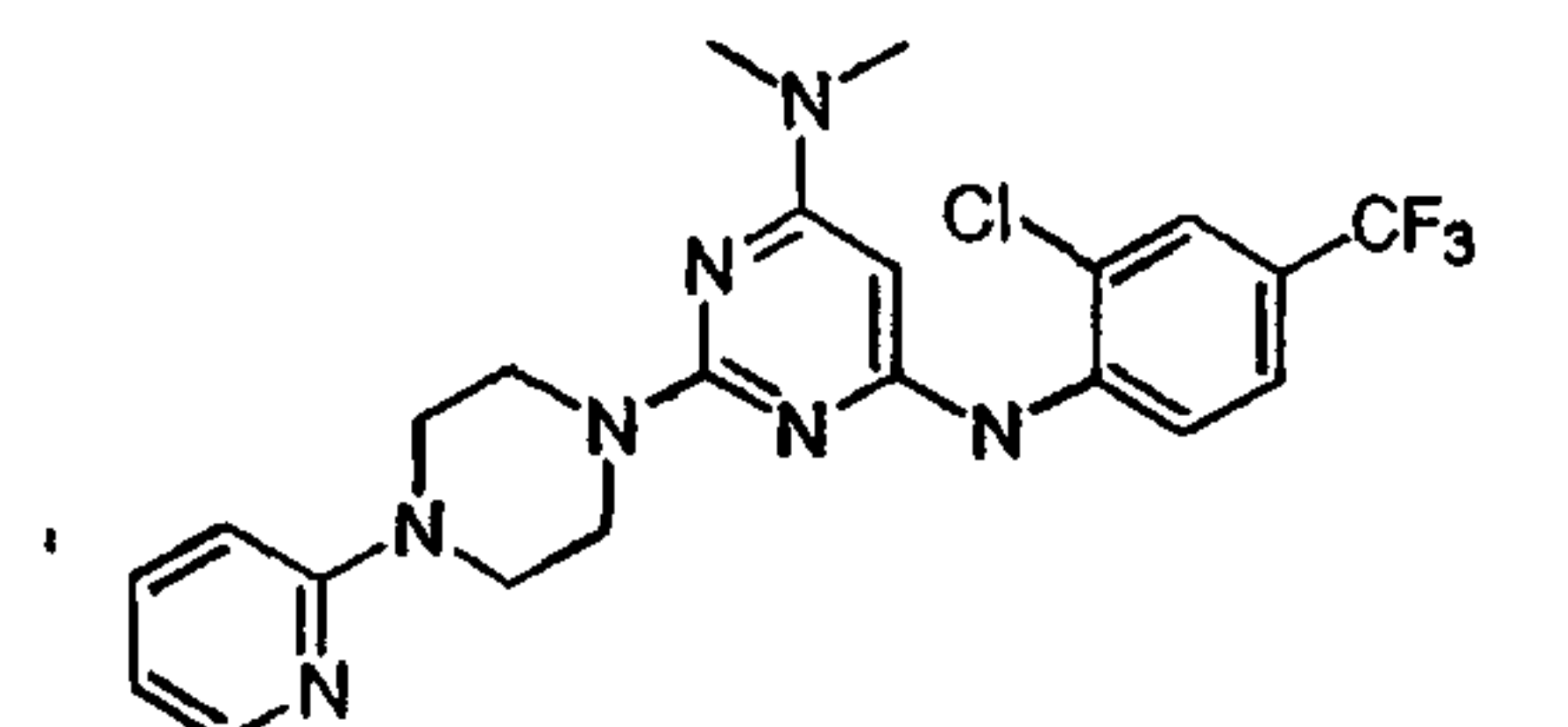
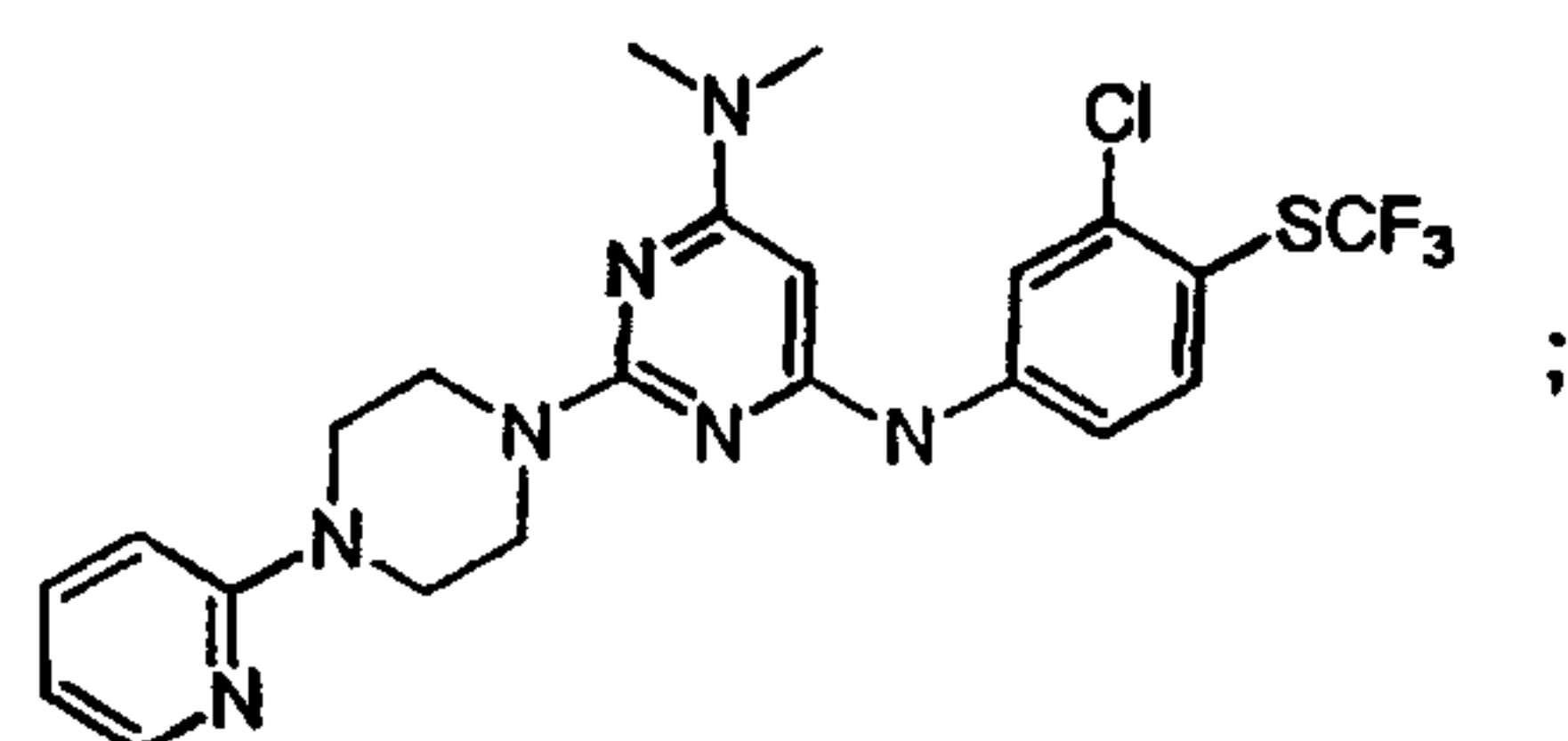
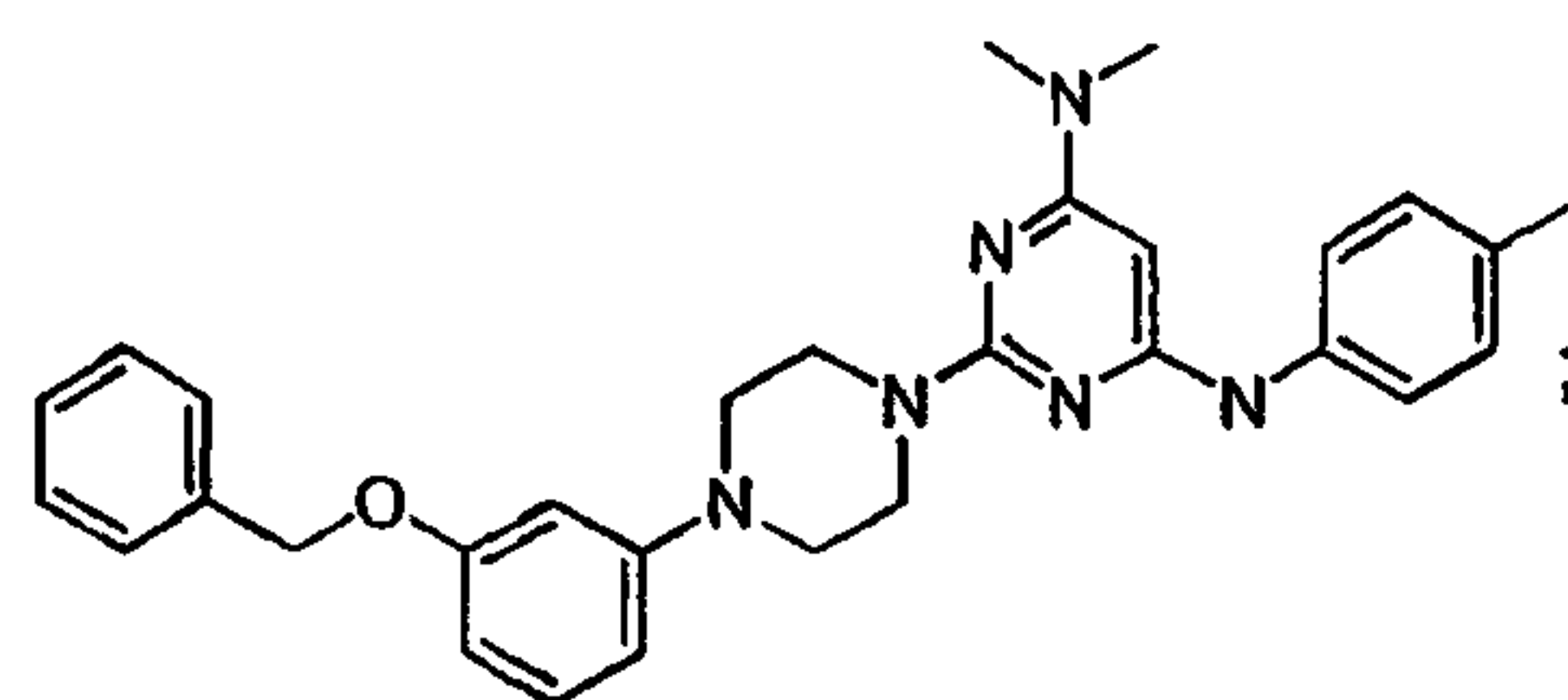
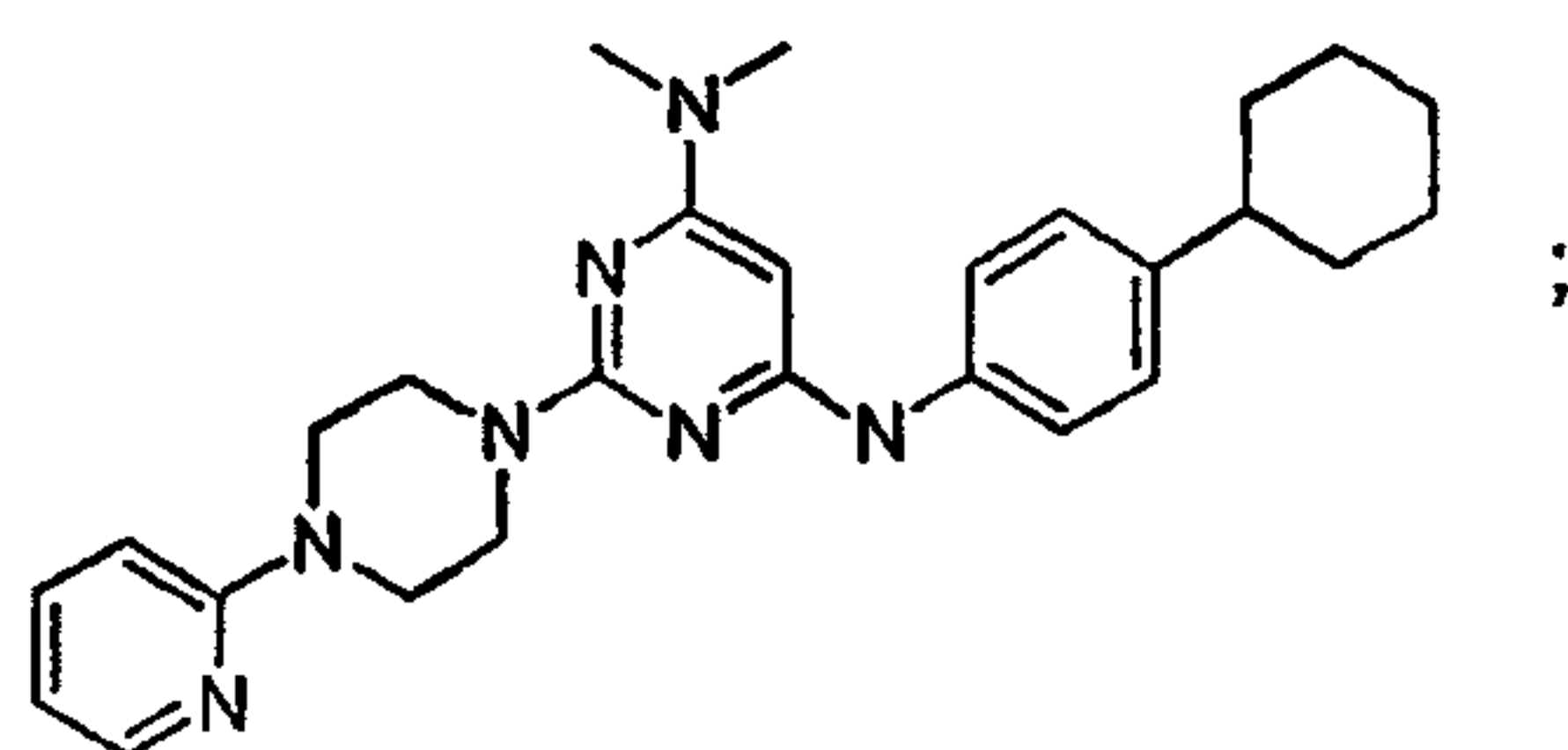


- 5 In one embodiment, the compound is selected from the group consisting of:

WO 02/060392

PCT/US02/04608

161



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

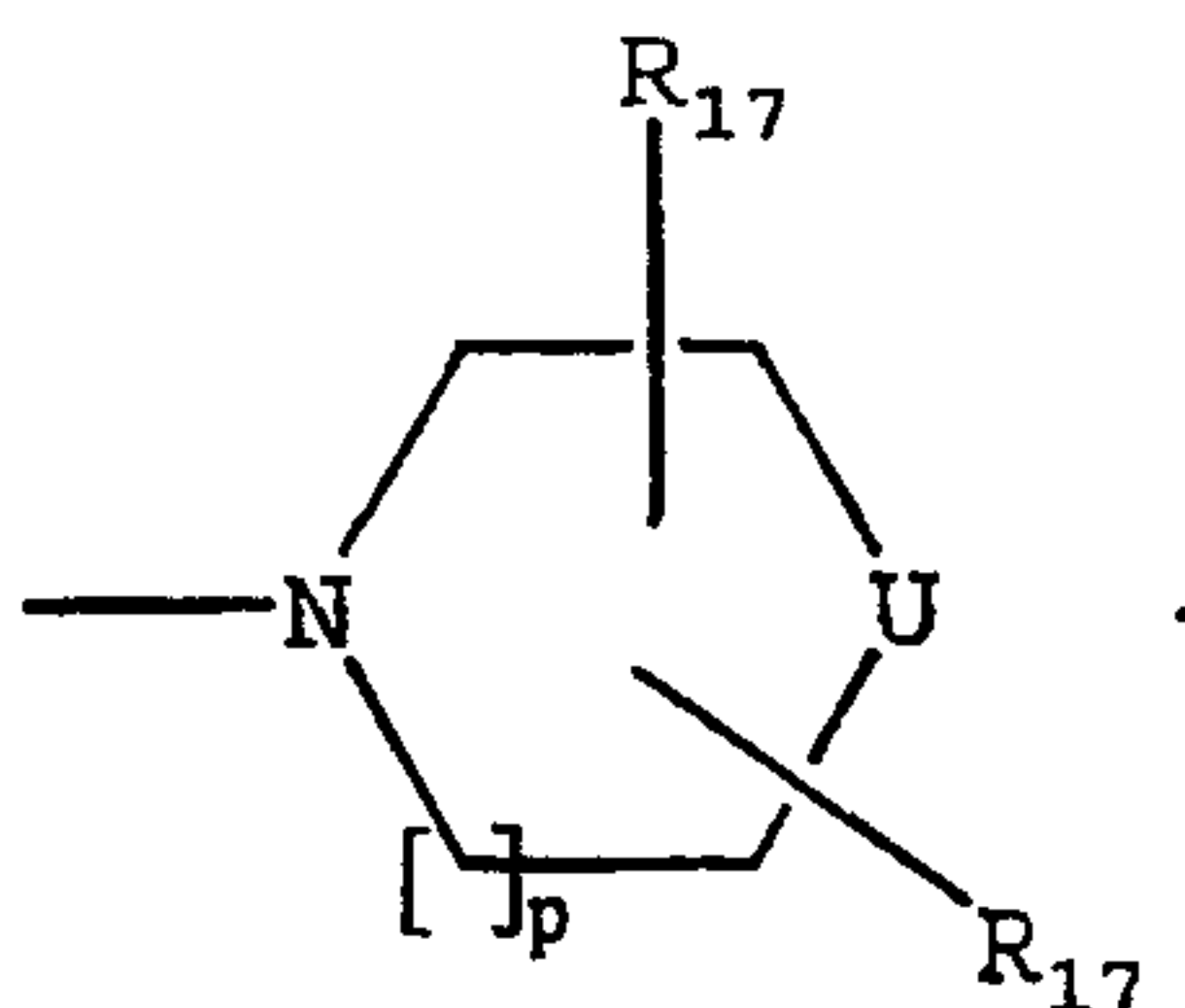
5

In one embodiment, Y is

WO 02/060392

PCT/US02/04608

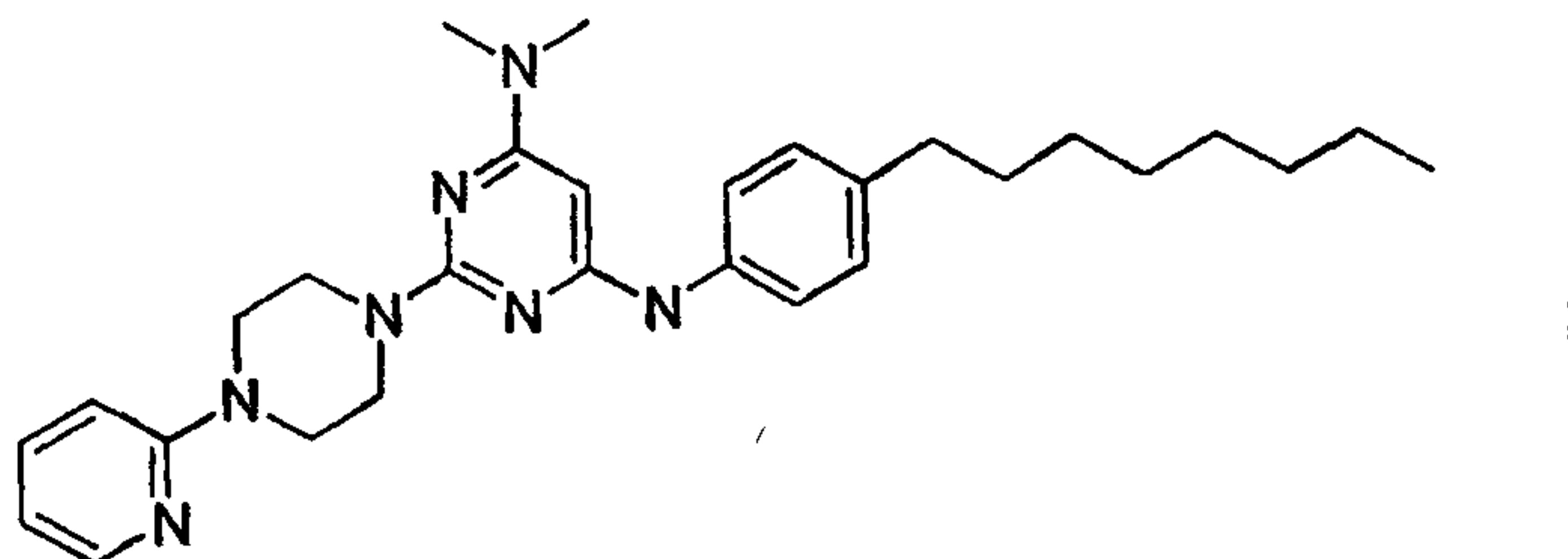
162



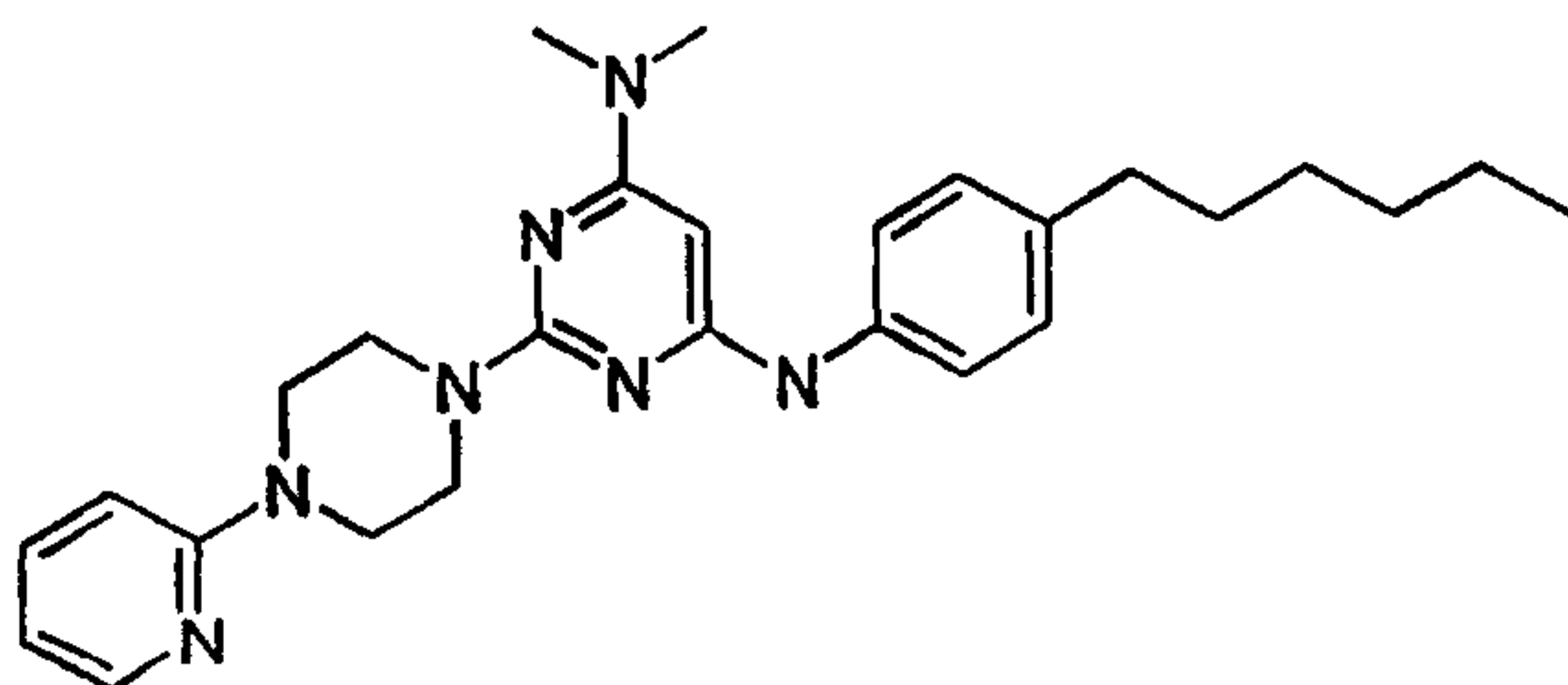
In one embodiment, R_{13} is an aryl substituted with a C_1 - C_{10} straight chained alkyl.

5

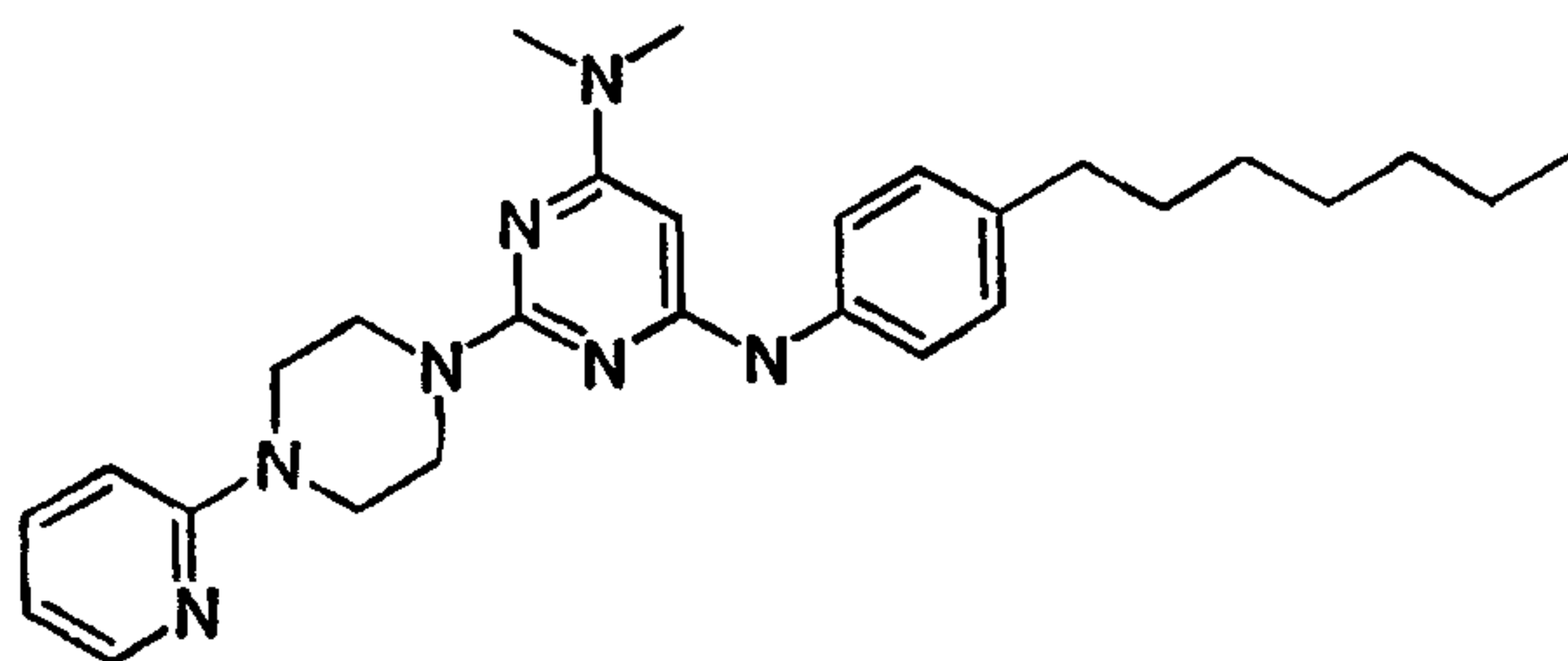
In one embodiment, the compound is selected from a group consisting of:



;

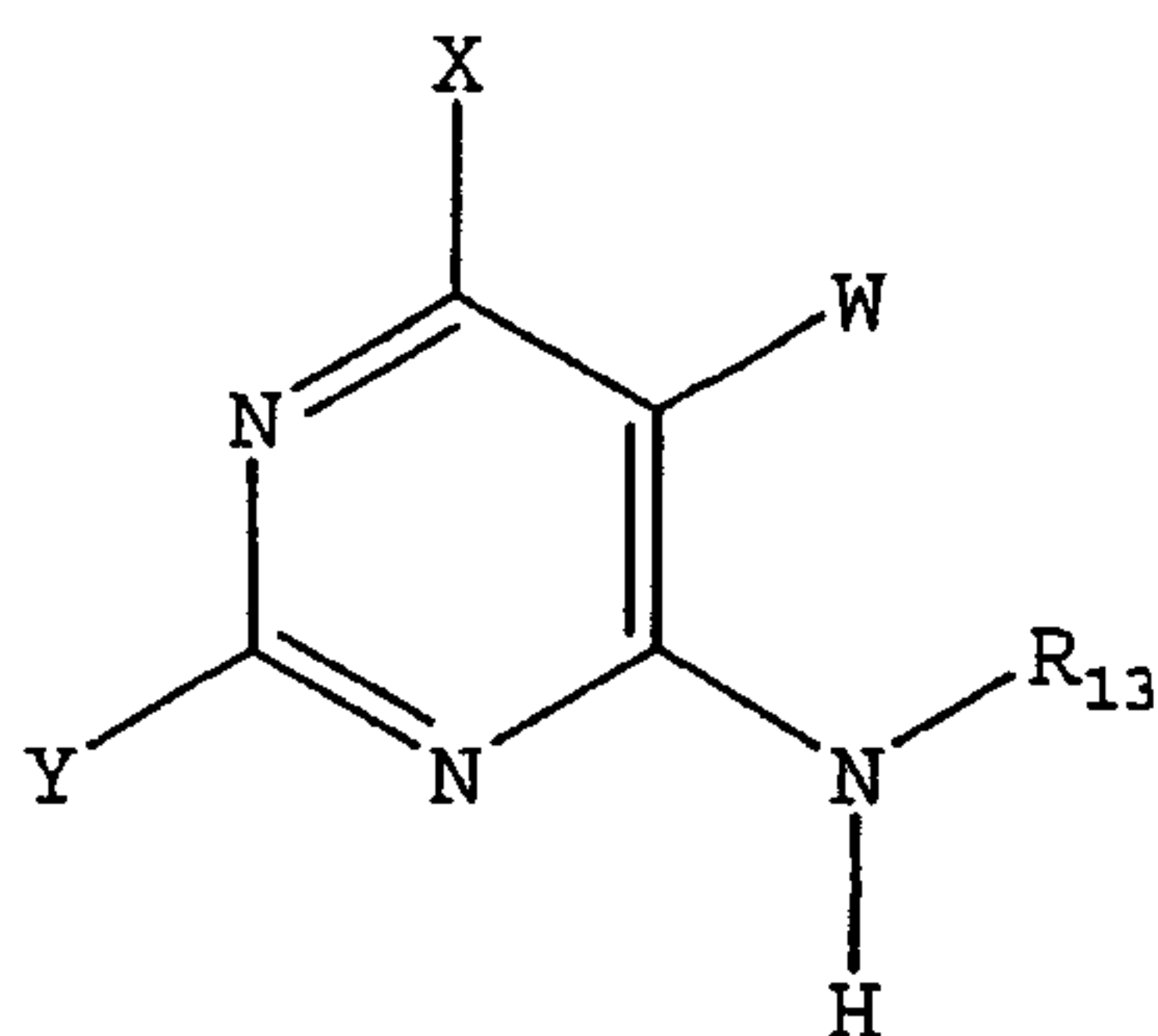


; and



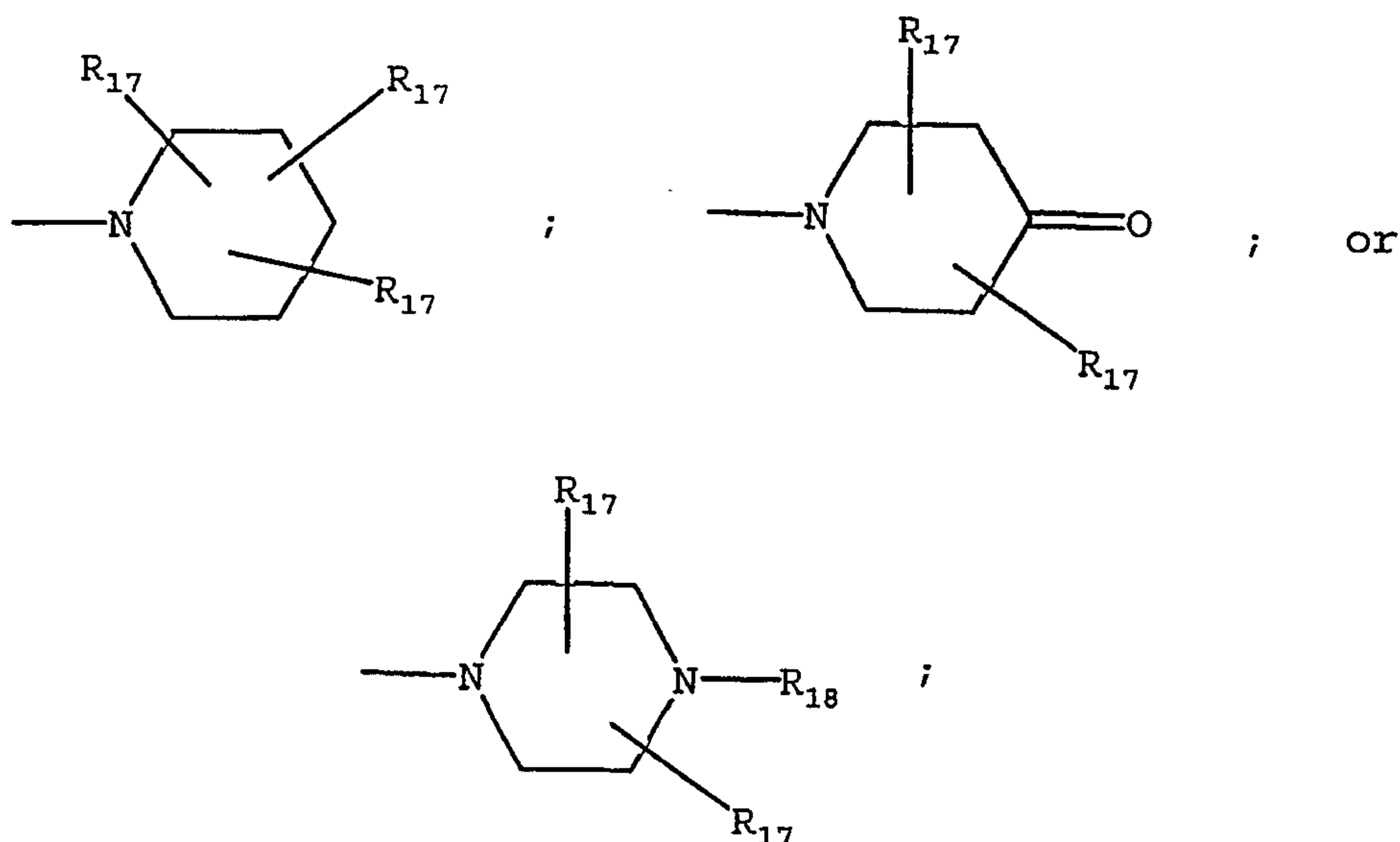
10

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
 5 subject's anxiety wherein the compound has the structure:



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

10 wherein X is; $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl, or aryl $(\text{C}_1\text{-C}_6)$ alkyl;

WO 02/060392

PCT/US02/04608

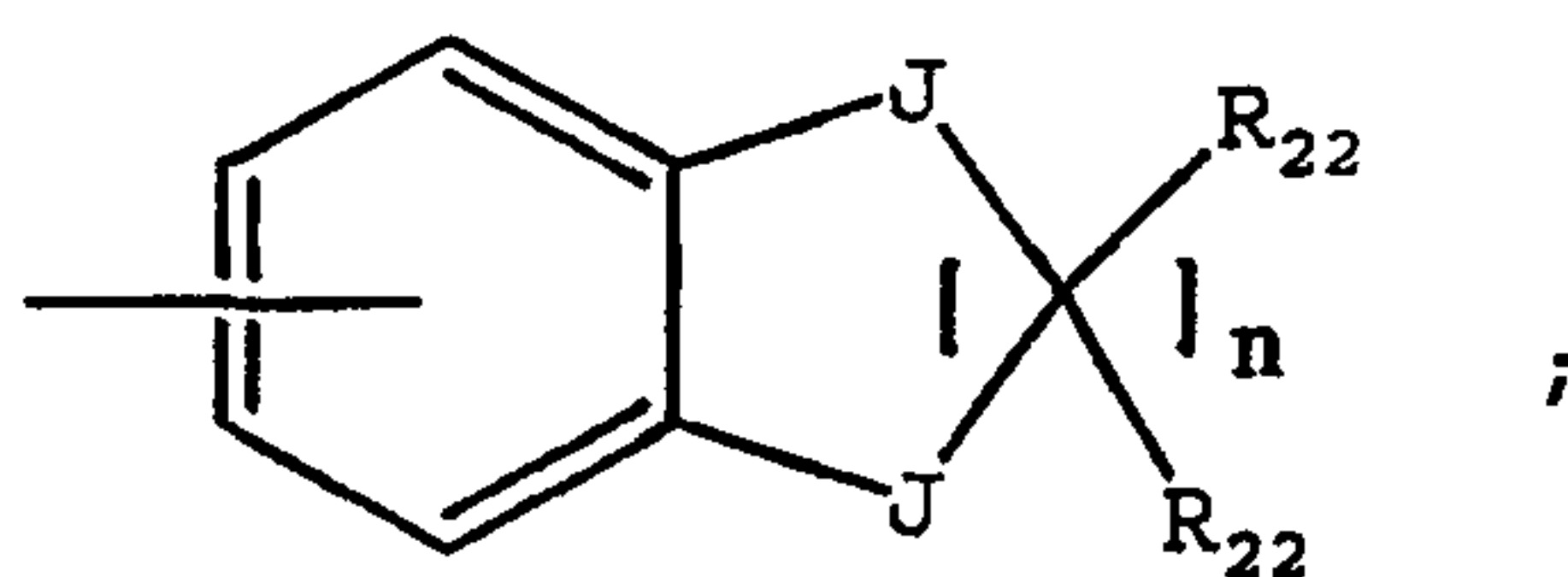
164

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 ;

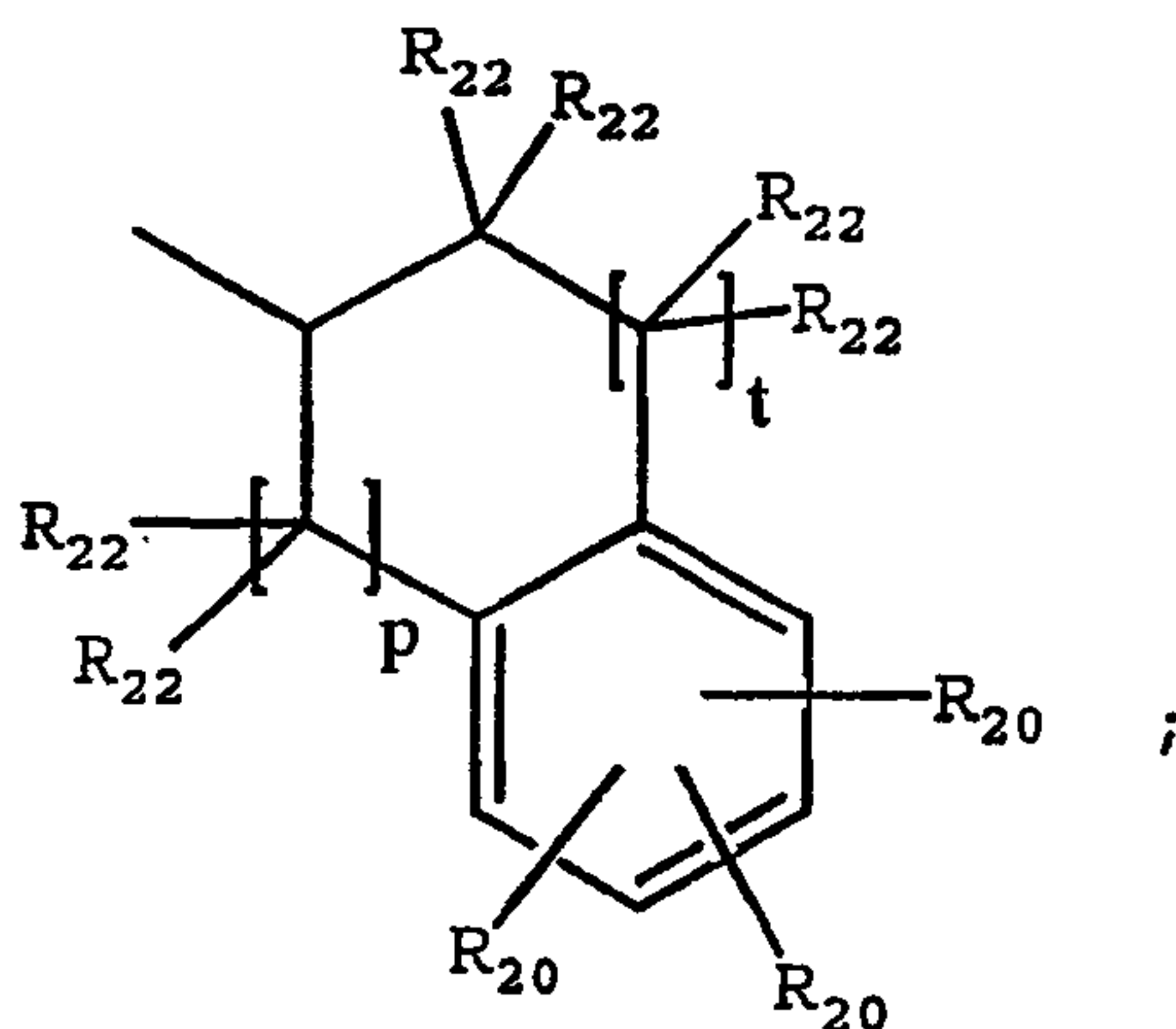
wherein aryl may be substituted with one or more C_1 - C_{10} straight chained or branched alkyl, aryl, heteroaryl, or $N(R_{19})-Z$;

wherein Q_1 is



15

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,

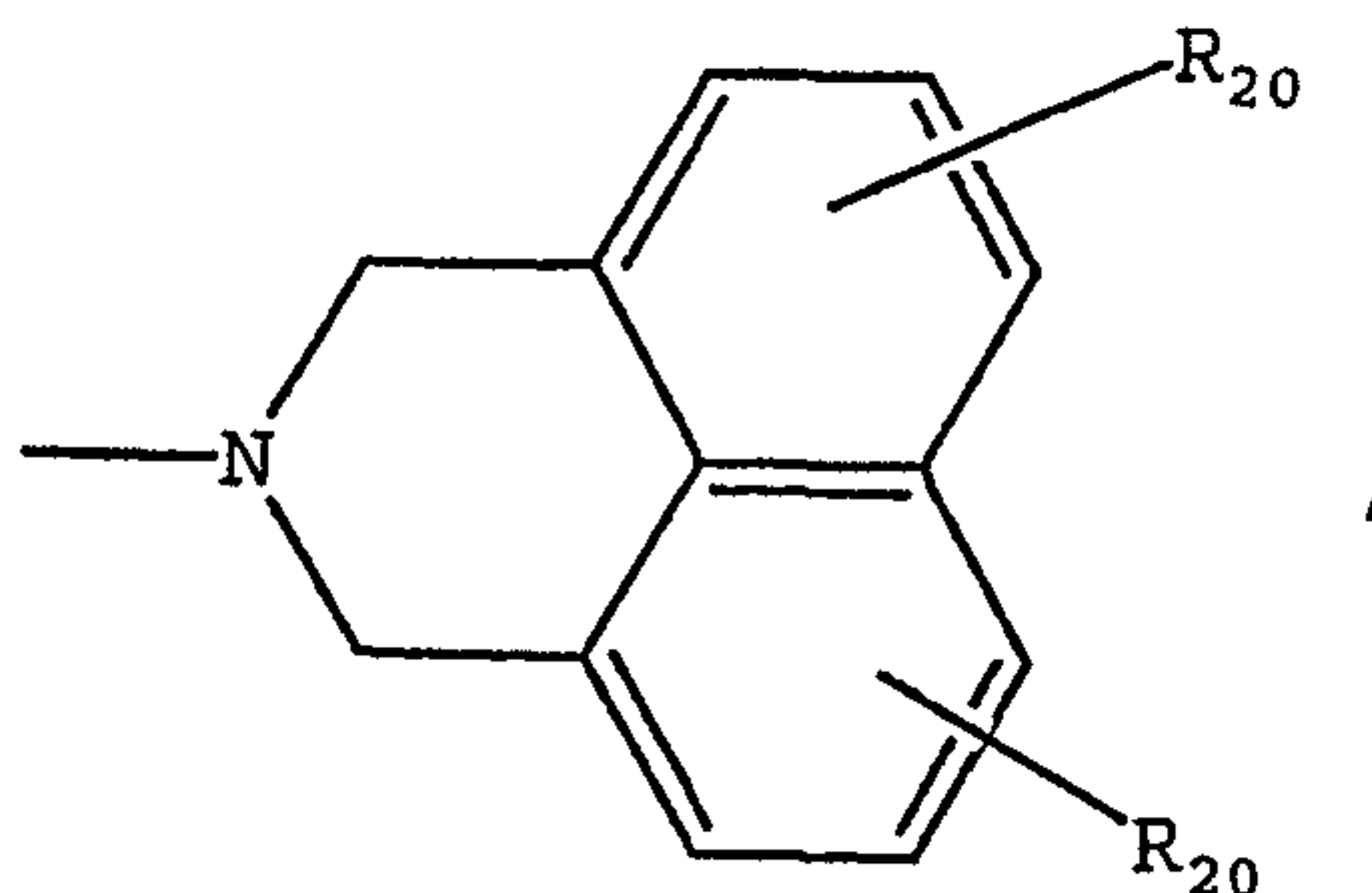
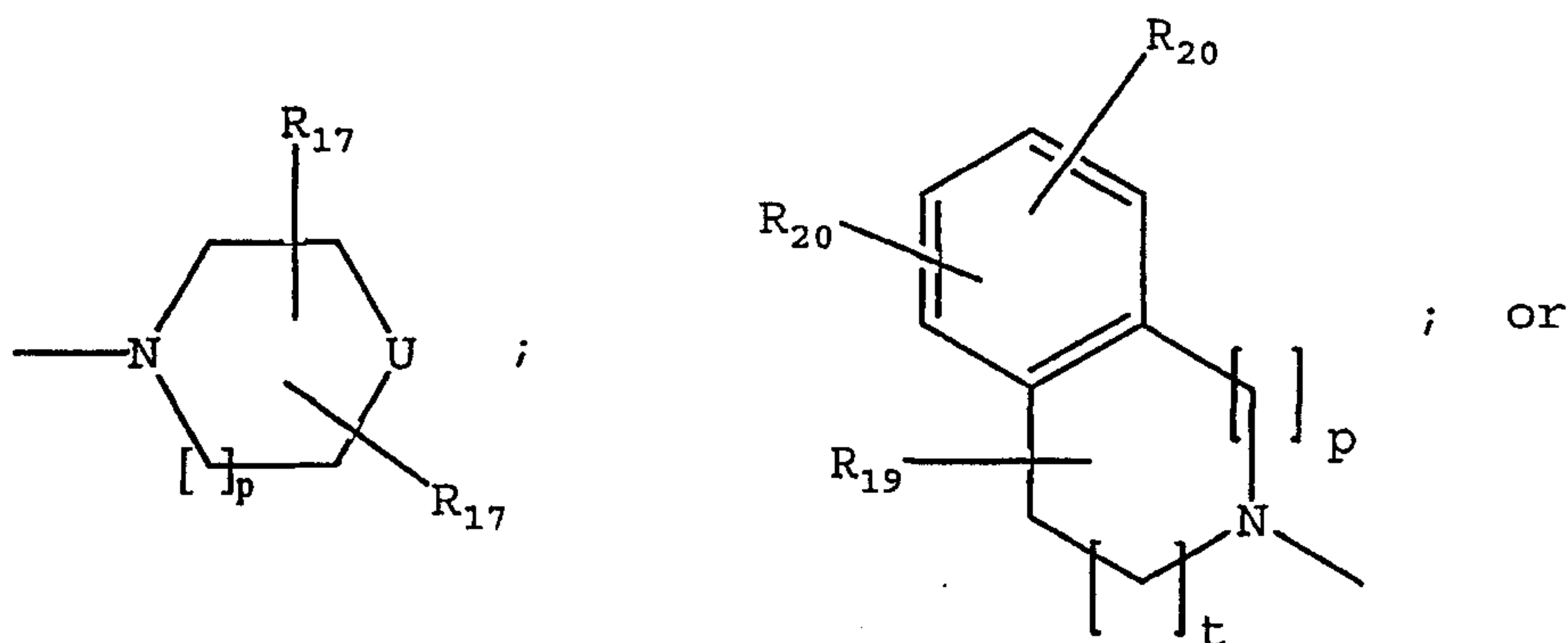
WO 02/060392

PCT/US02/04608

165

monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl or aryl;

5 wherein Y is NR₁₄R₁₅;



10

wherein R₁₄ is H, straight chained or branched C₁-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

15 wherein R₁₅ is straight chained or branched C₃-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, (C(R₁₉)₂)_mN(R₁₆)₂ or (C(R₁₉)₂)_m-Z;

20 wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl,

straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

- 5 wherein each R₁₇ is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15

wherein each R₁₉ is independently H, or straight chained or branched C₁-C₆ alkyl;

- wherein each R₂₀ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

- wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, or aryl(C₁-C₆)alkyl;

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

5 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;

10

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2;

15 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

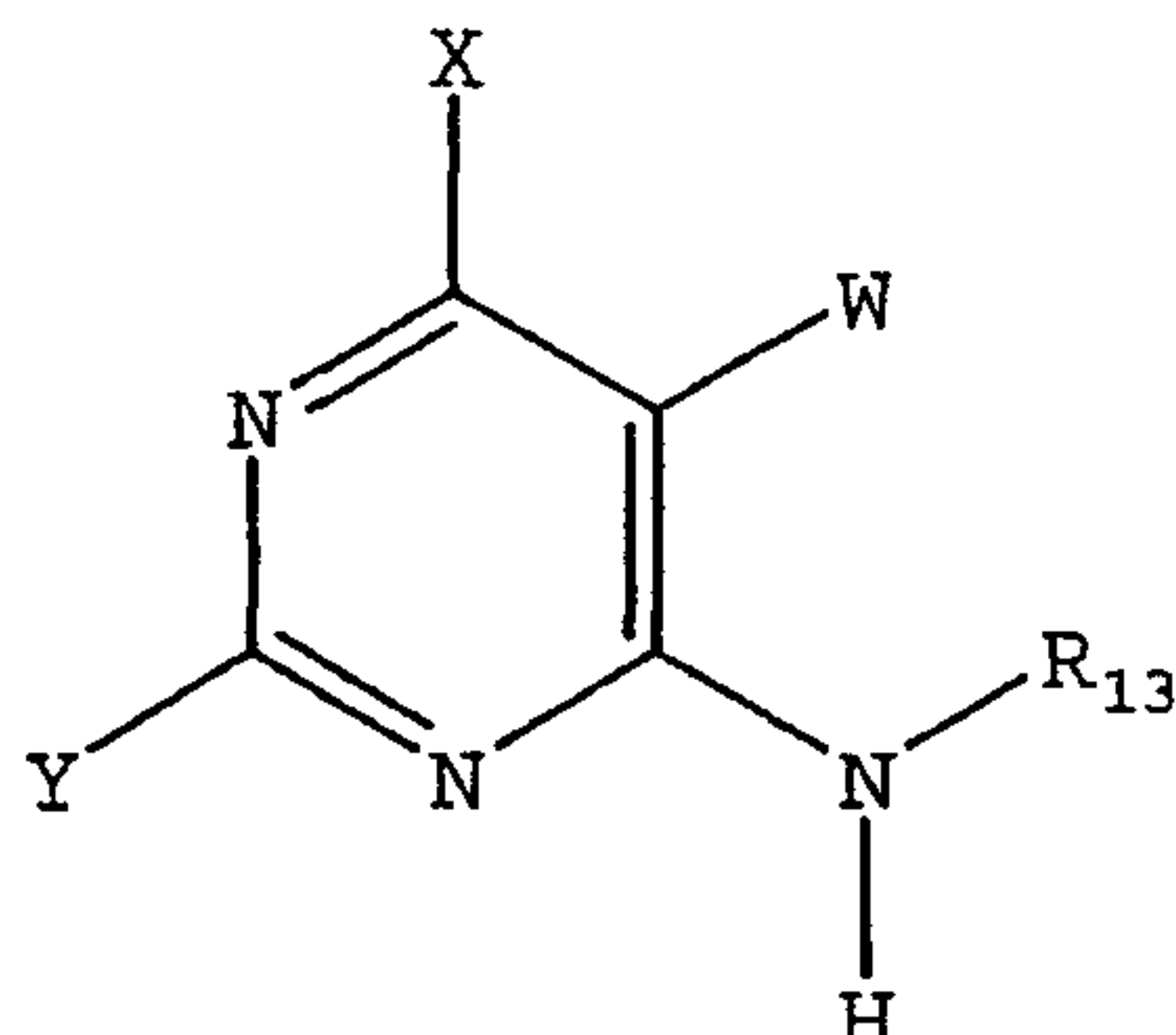
20 a pharmaceutically acceptable salt thereof.

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

WO 02/060392

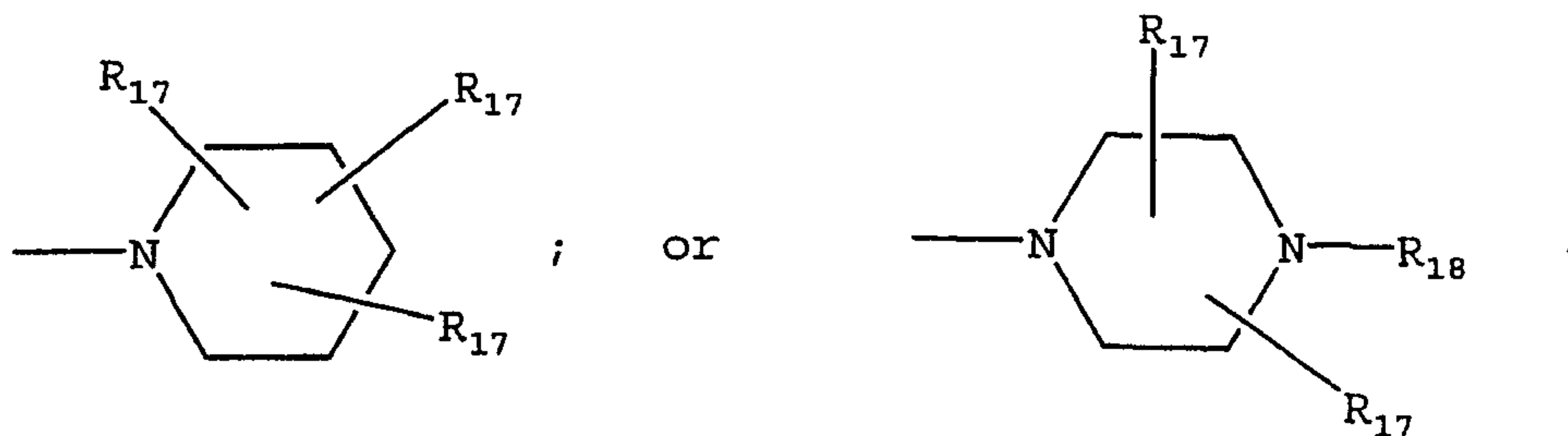
PCT/US02/04608

168



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

5 wherein X is $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

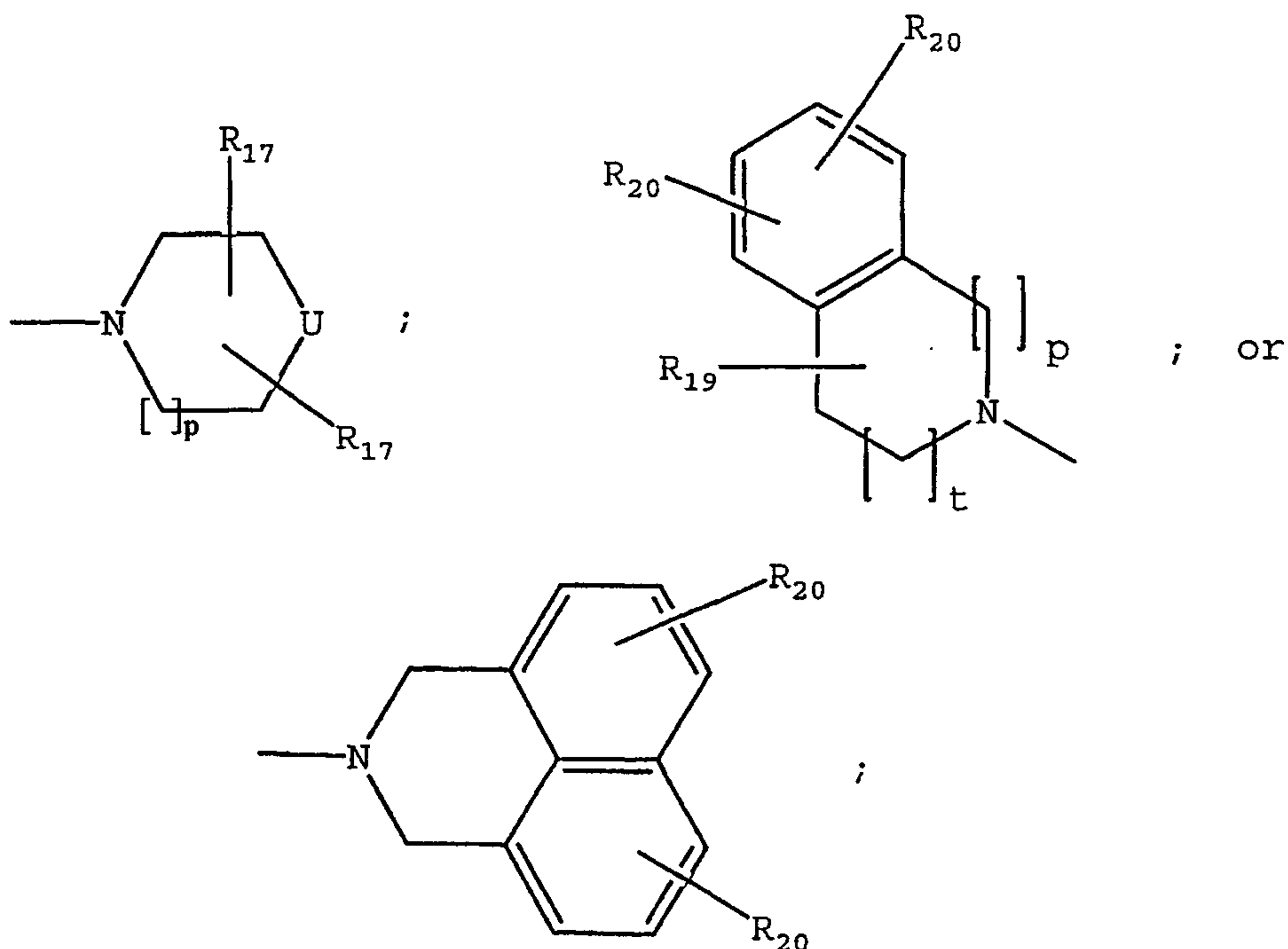
10 wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $-(\text{CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

15

wherein Y is $\text{NR}_{14}\text{R}_{15}$;

169



wherein R₁₄ is H, straight chained or branched C₁-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

5

wherein R₁₅ is straight chained or branched C₃-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

10

wherein Z is C₃-C₁₀ cycloalkyl, aryl, or heteroaryl;

wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15

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;

WO 02/060392

PCT/US02/04608

171

wherein p is an integer from 0 to 2 inclusive;

wherein q is an integer from 2 to 4 inclusive;

5

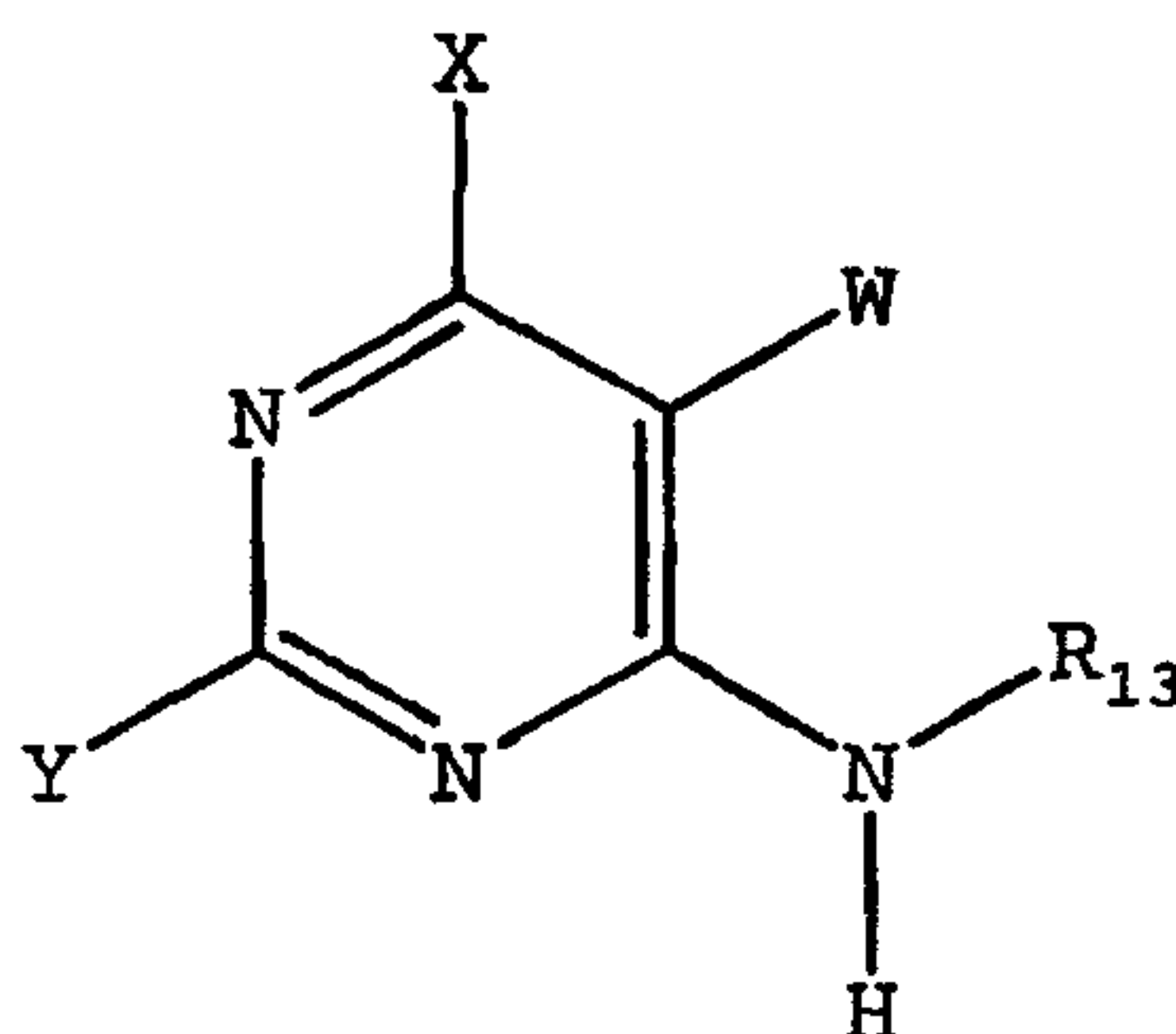
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

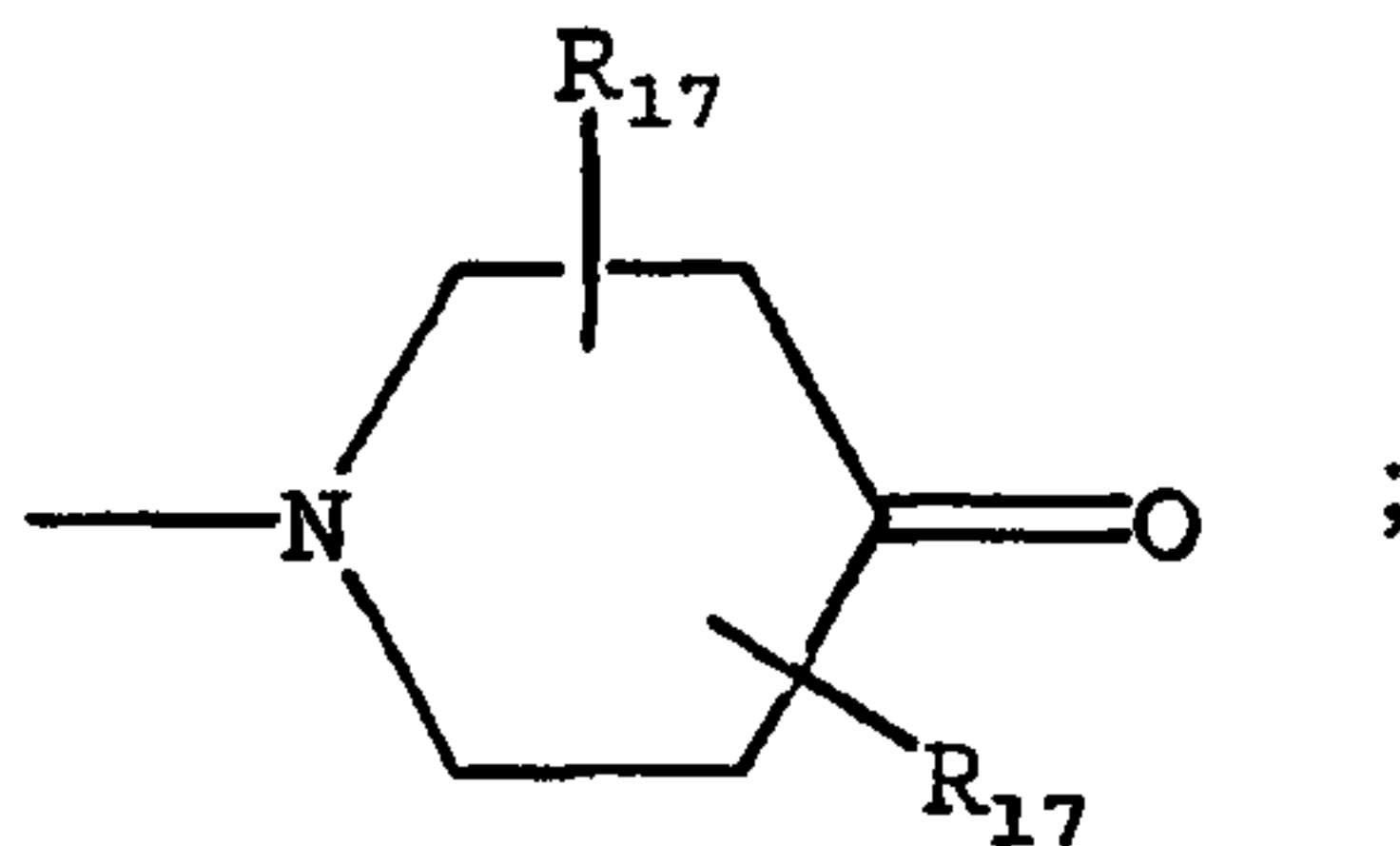
10

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:

15



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

20 wherein X is N(CH₃)₂ or

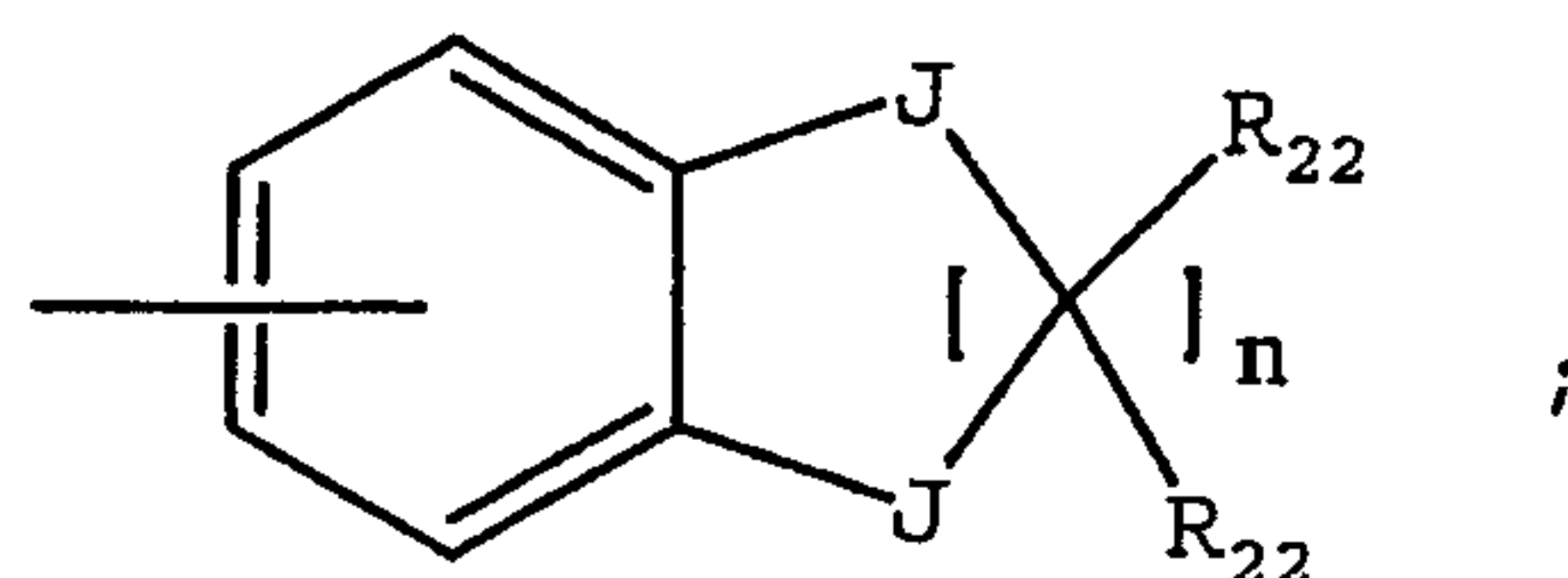
172

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

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

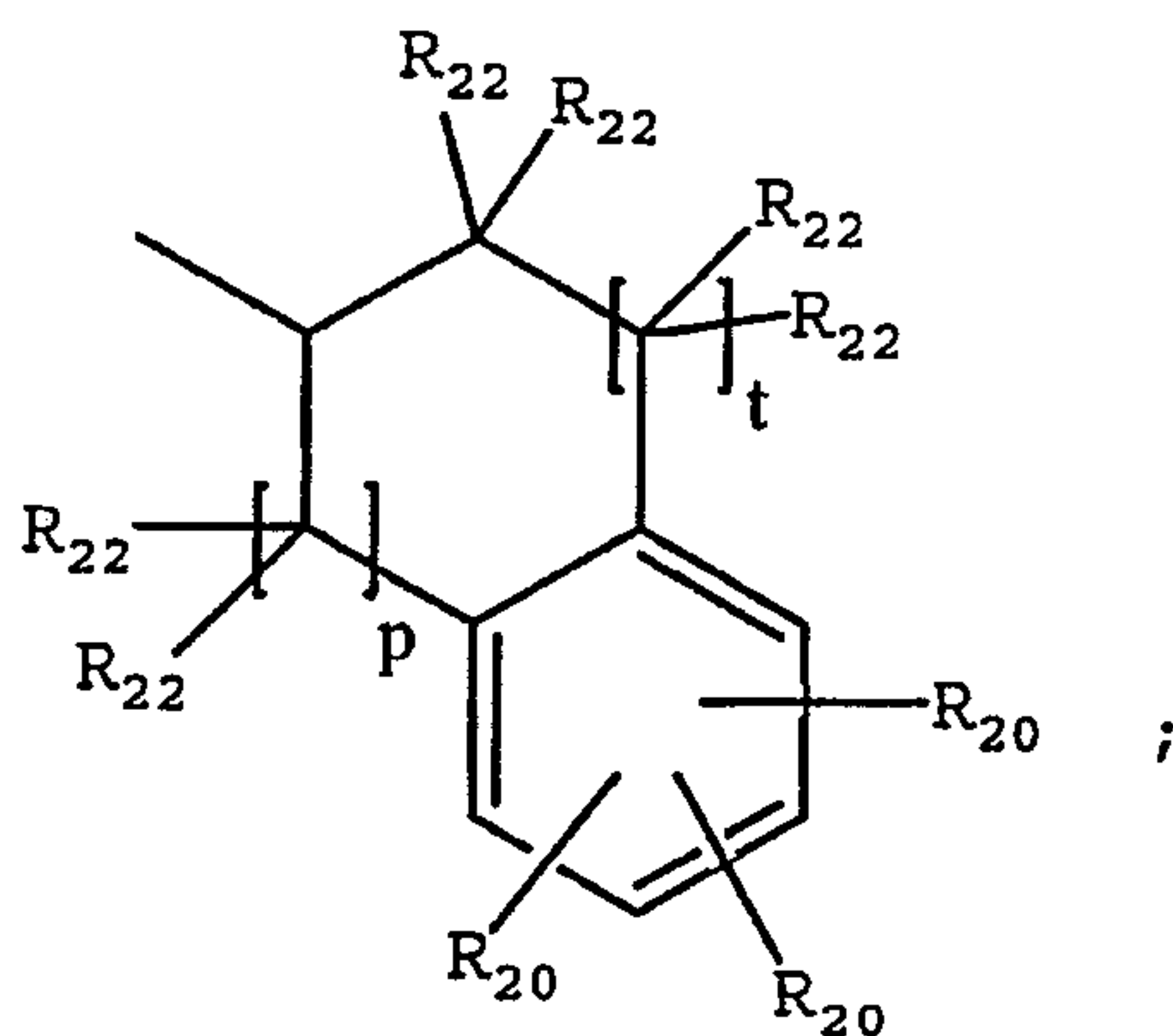
wherein Q_1 is

10



wherein Q_2 is

15



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

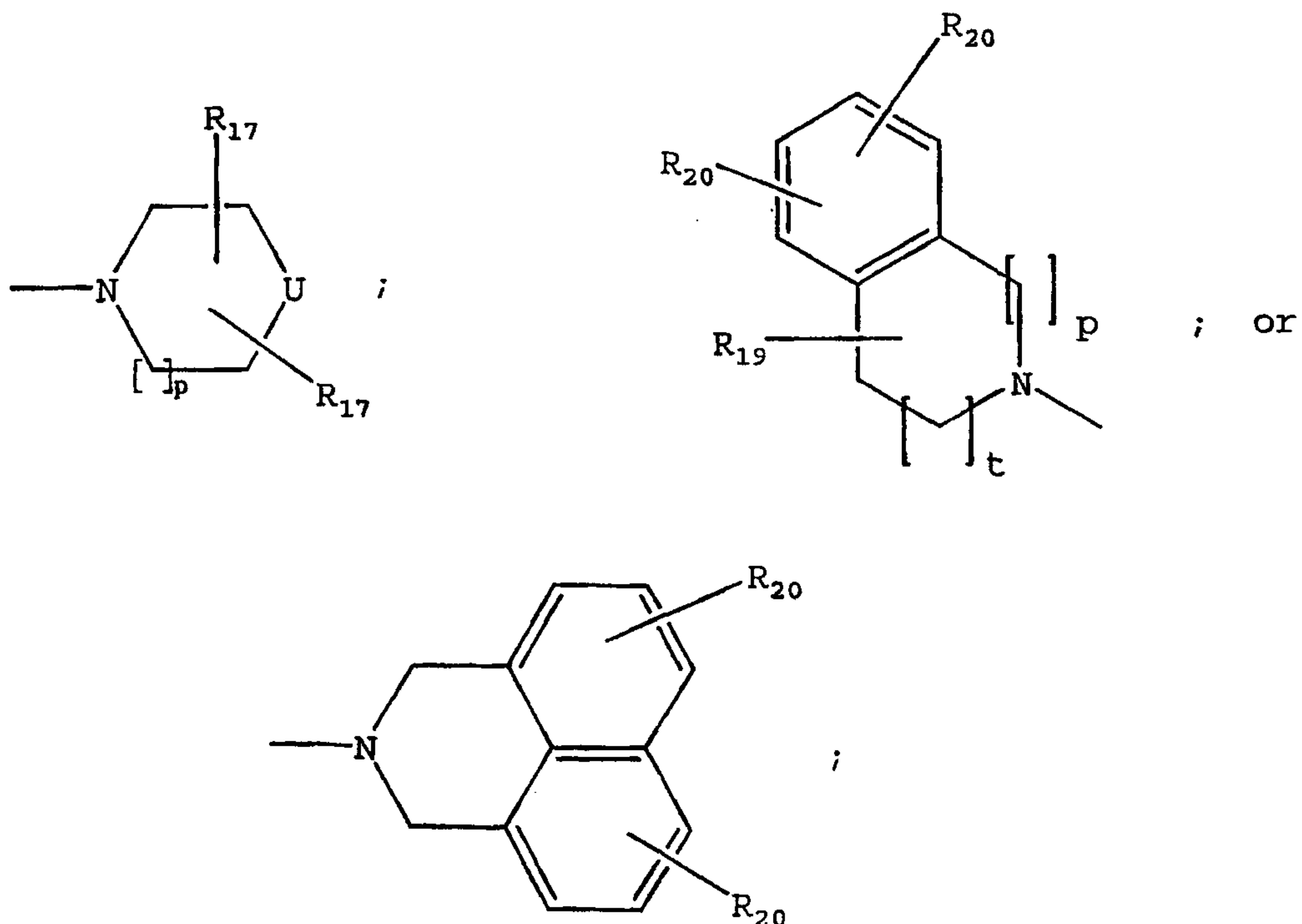
- 20 wherein R_4 is -H; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, C_5 - C_7 cycloalkenyl or aryl;

WO 02/060392

PCT/US02/04608

173

wherein Y is $\text{NR}_{14}\text{R}_{15}$;



5

wherein R_{14} is H, straight chained or branched $\text{C}_1\text{-C}_6$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

wherein R_{15} is straight chained or branched $\text{C}_3\text{-C}_6$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

10

wherein U is O, -NR_{16} , S, $\text{C}(\text{R}_{17})_2$, or $\text{-NSO}_2\text{R}_{16}$;

wherein Z is $\text{C}_3\text{-C}_{10}$ cycloalkyl, aryl, or heteroaryl;

15

wherein R_{16} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl,

straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

- 5 wherein each R₁₇ is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15

wherein each R₁₉ is independently H, or straight chained or branched C₁-C₆ alkyl;

- wherein each R₂₀ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups present on adjacent carbon atoms can join together to form a methylenedioxy group;

- wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

WO 02/060392

PCT/US02/04608

175

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;

5

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

wherein p is an integer from 0 to 2 inclusive;

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

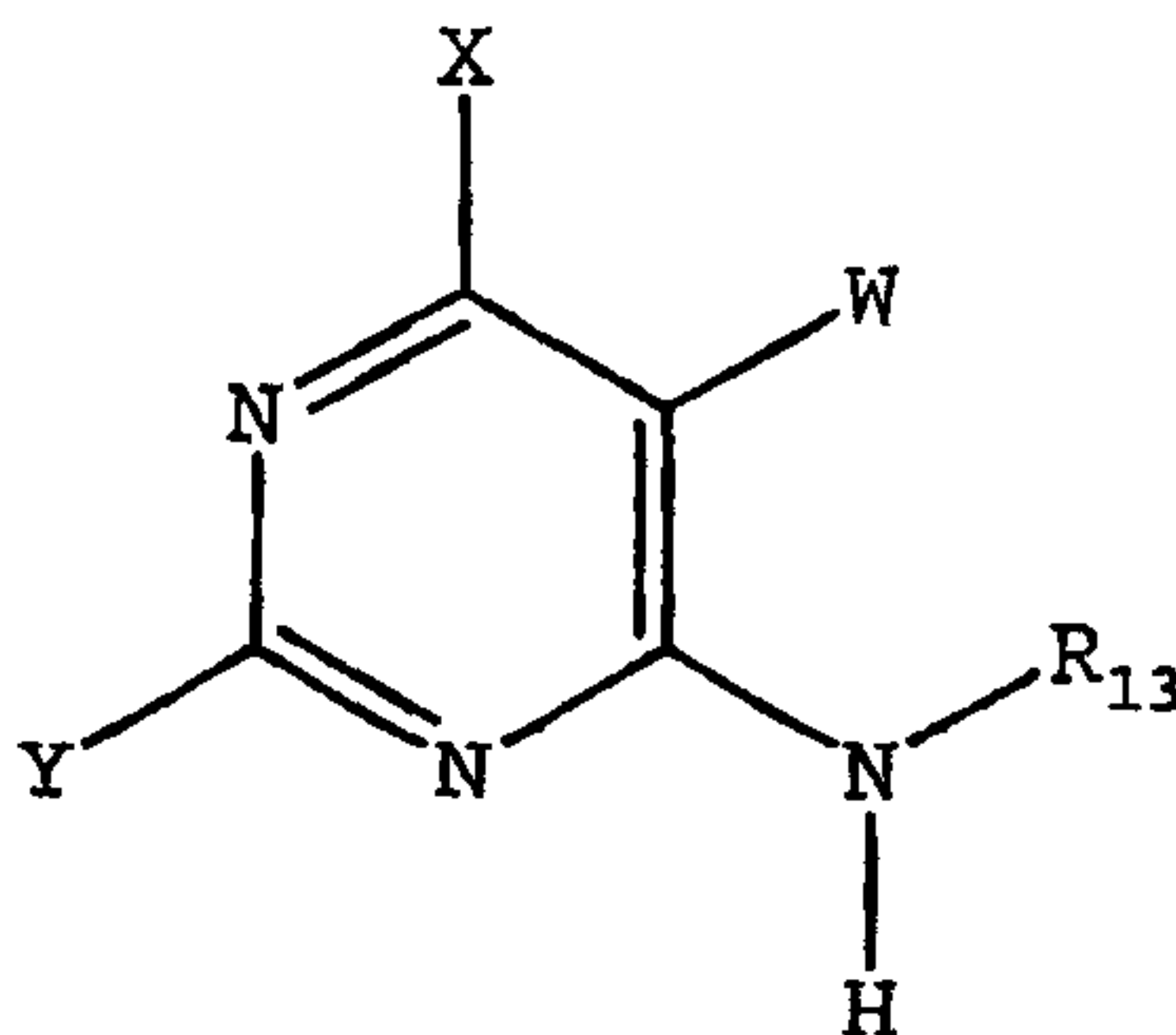
wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

15

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:

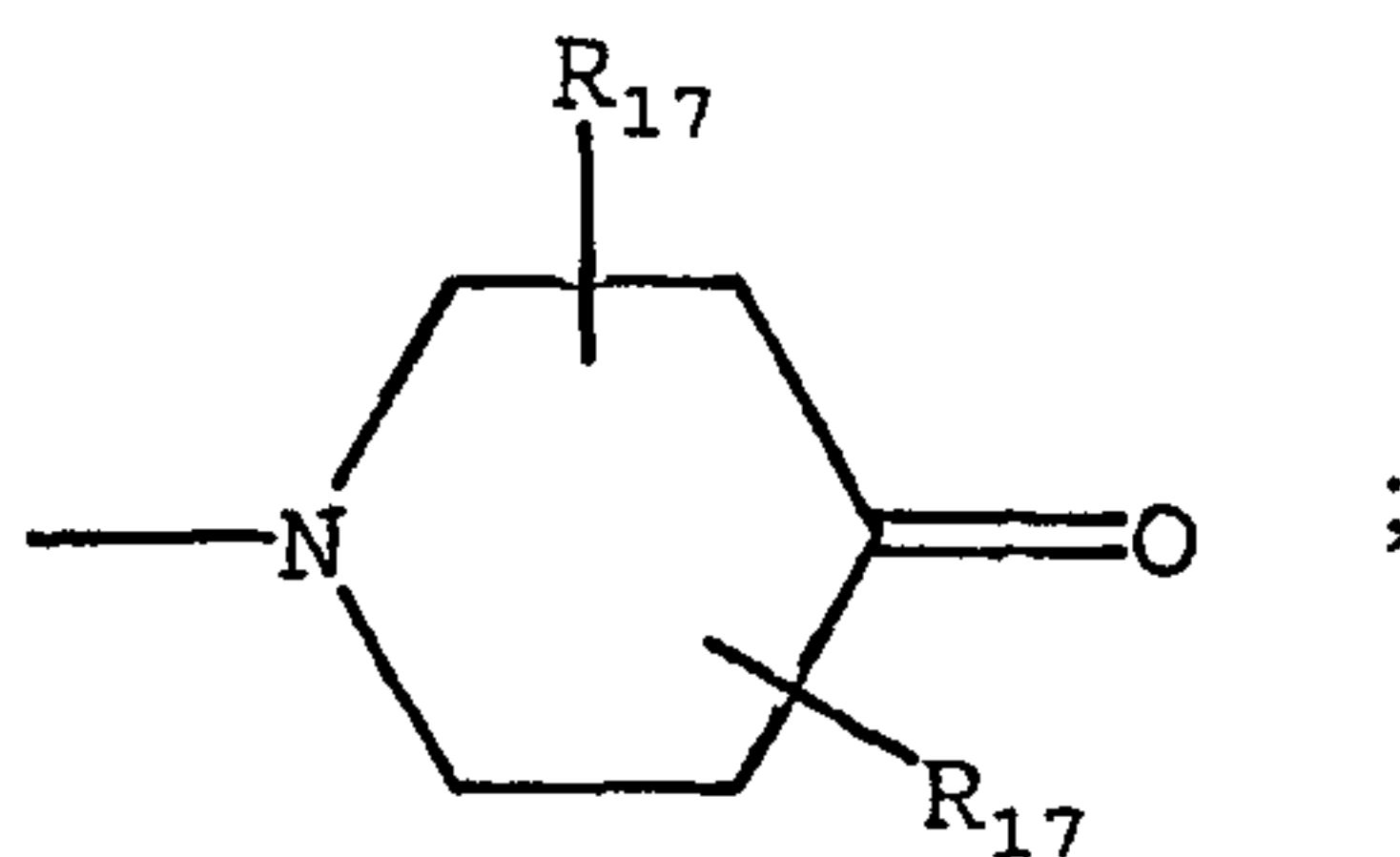
20



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

25 wherein X is $N(CH_3)_2$ or

176



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

5

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 $(C(R_{19})_2)_m-Z$;

10

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

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

15 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, -
20 $(CH_2)_m-Z$, 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 $(CH_2)_n-O-(CH_2)_m-CH_3$;

25

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

5 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;

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

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

15 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, 20 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, -NO₂, -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, -OR₂₁, -COR₂₁, -CO₂R₂₁, -CON(R_{21})₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

30

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, -NO₂,
 -CN, straight chained or branched C₁-C₇ alkyl, straight
 chained or branched C₁-C₇ monofluoroalkyl, straight
 chained or branched C₁-C₇ polyfluoroalkyl, straight
 5 chained or branched C₂-C₇ alkenyl, straight chained or
 branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇
 monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇
 cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -
 CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

10

As used in the present invention, the term "cyclohexyl"
 includes, cyclohexyl groups which may be substituted with
 one or more of the following: -F, -NO₂, -CN, straight
 chained or branched C₁-C₇ alkyl, straight chained or
 15 branched C₁-C₇ monofluoroalkyl, straight chained or
 branched C₁-C₇ polyfluoroalkyl, straight chained or
 branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇
 alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇
 polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -
 20 COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

As used in the present invention, the term "cycloalkenyl"
 includes, C₅-C₇ cycloalkenyl moieties which may be
 substituted with one or more of the following: -F, -Cl,
 25 -Br, -I, -NO₂, -CN, straight chained or branched C₁-C₇
 alkyl, straight chained or branched C₁-C₇ monofluoroalkyl,
 straight chained or branched C₁-C₇ polyfluoroalkyl,
 straight chained or branched C₂-C₇ alkenyl, straight
 chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇
 30 monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇
 cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -
 CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

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, indolizinylyl, 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, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

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

5

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, -NO₂, -CN, straight chained
10 or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇
15 polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

20 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.

25 In one embodiment, the compound can be administered orally.

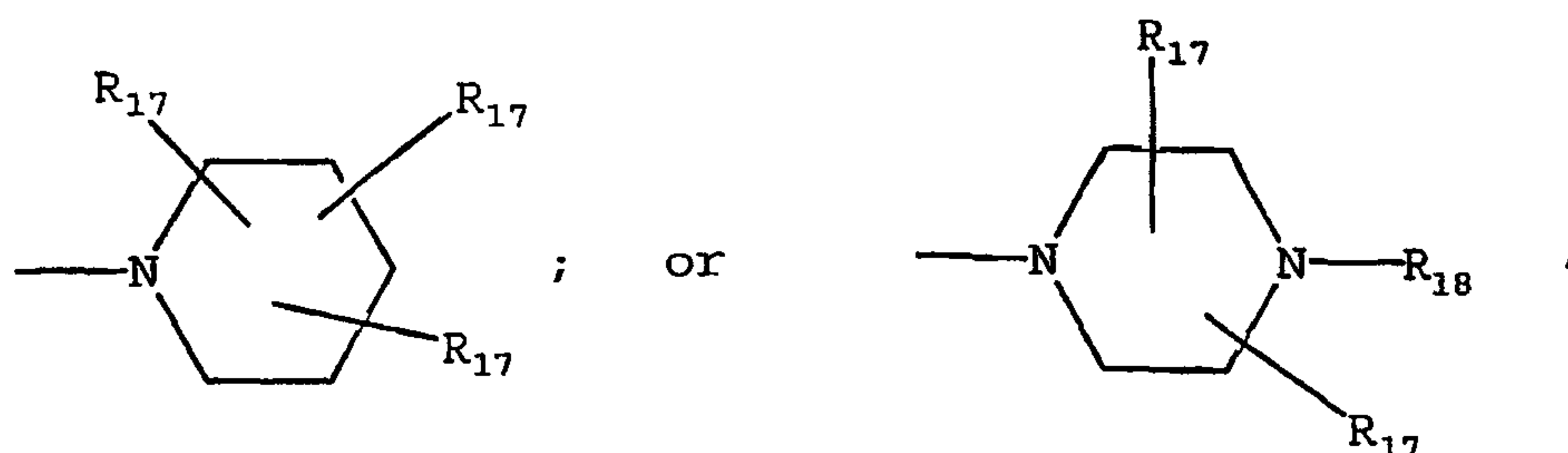
In one embodiment, X is:

30

WO 02/060392

PCT/US02/04608

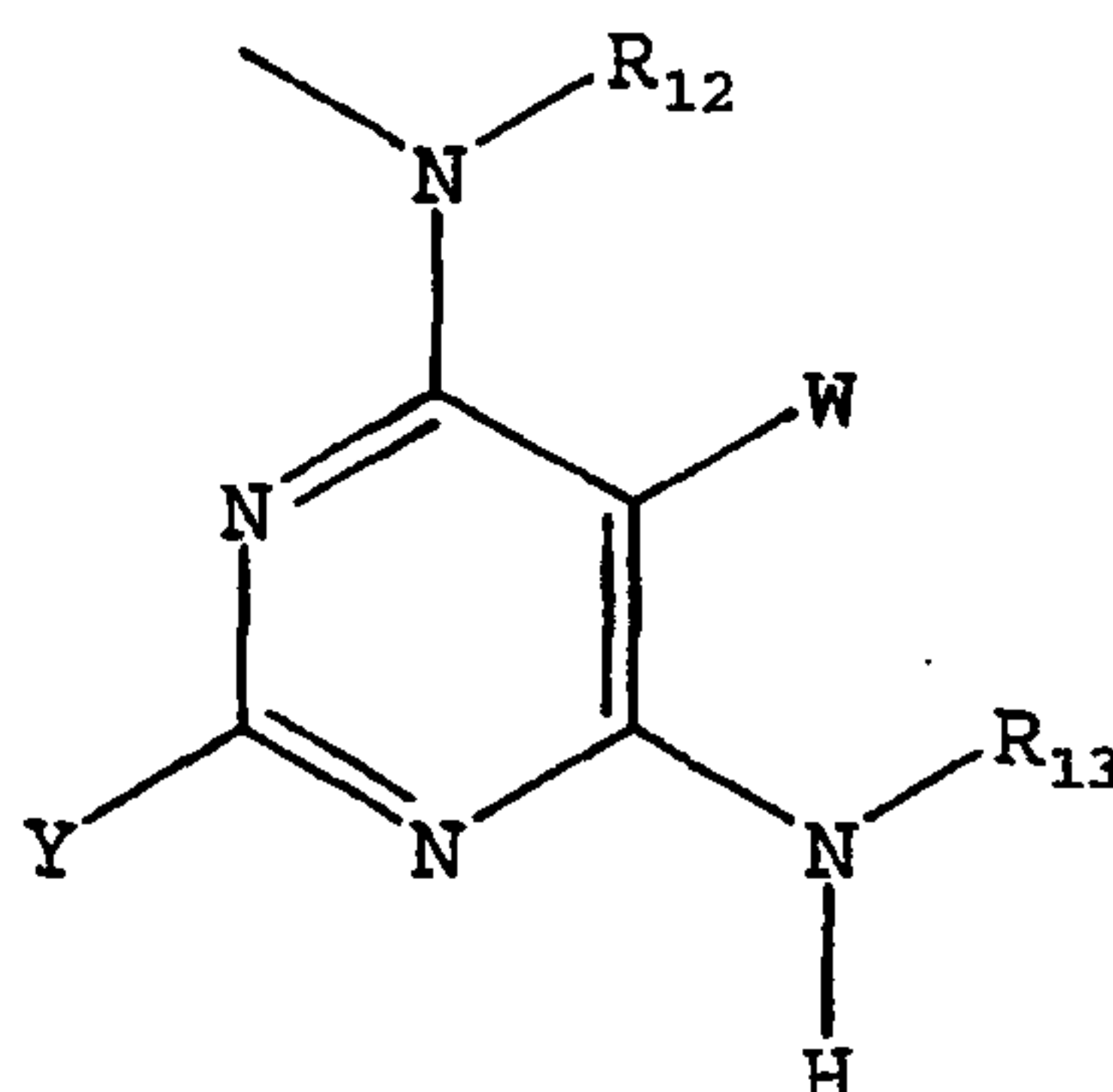
181



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

5

In one embodiment, the compound has the structure:



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

10

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

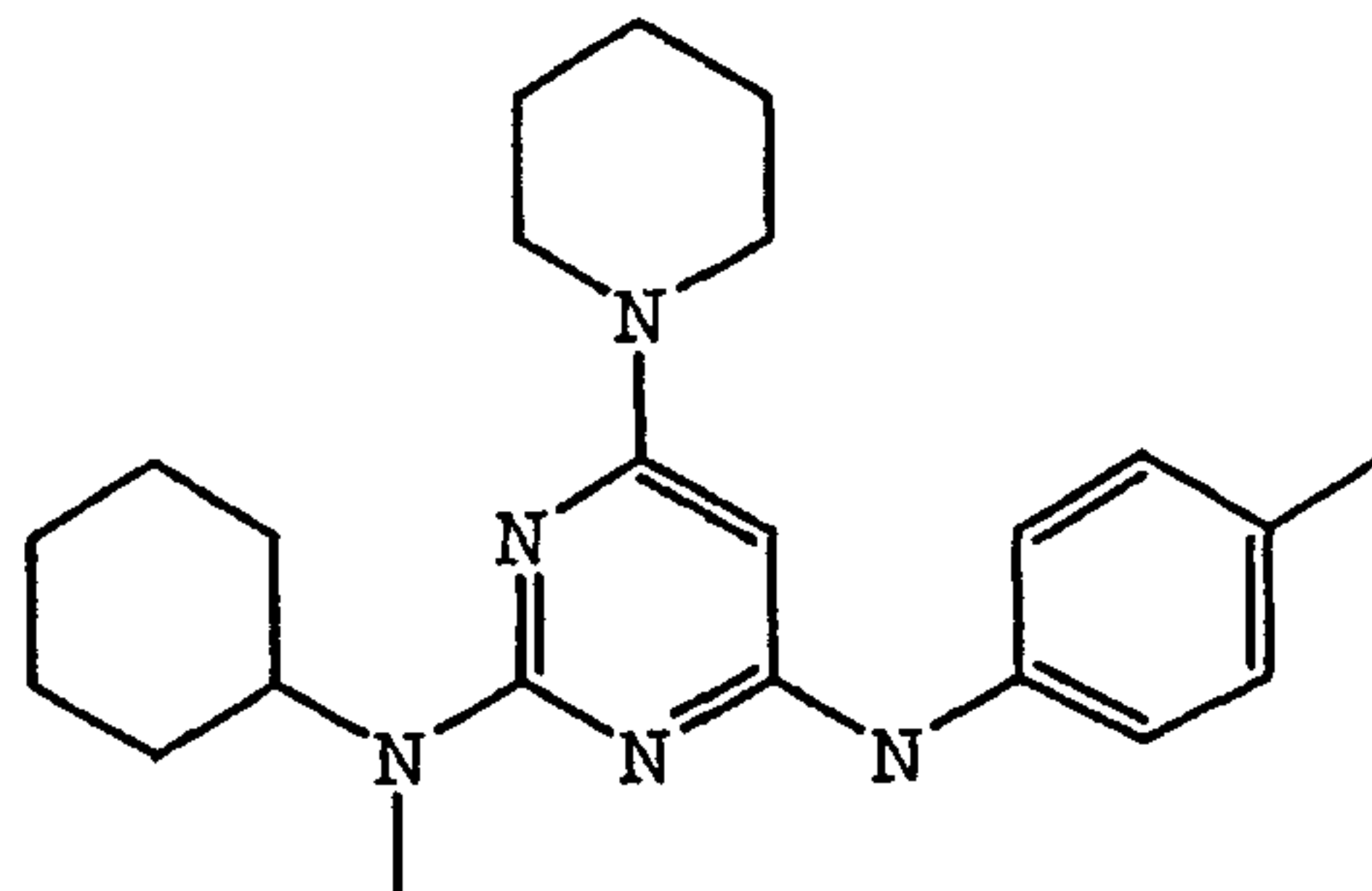
15

WO 02/060392

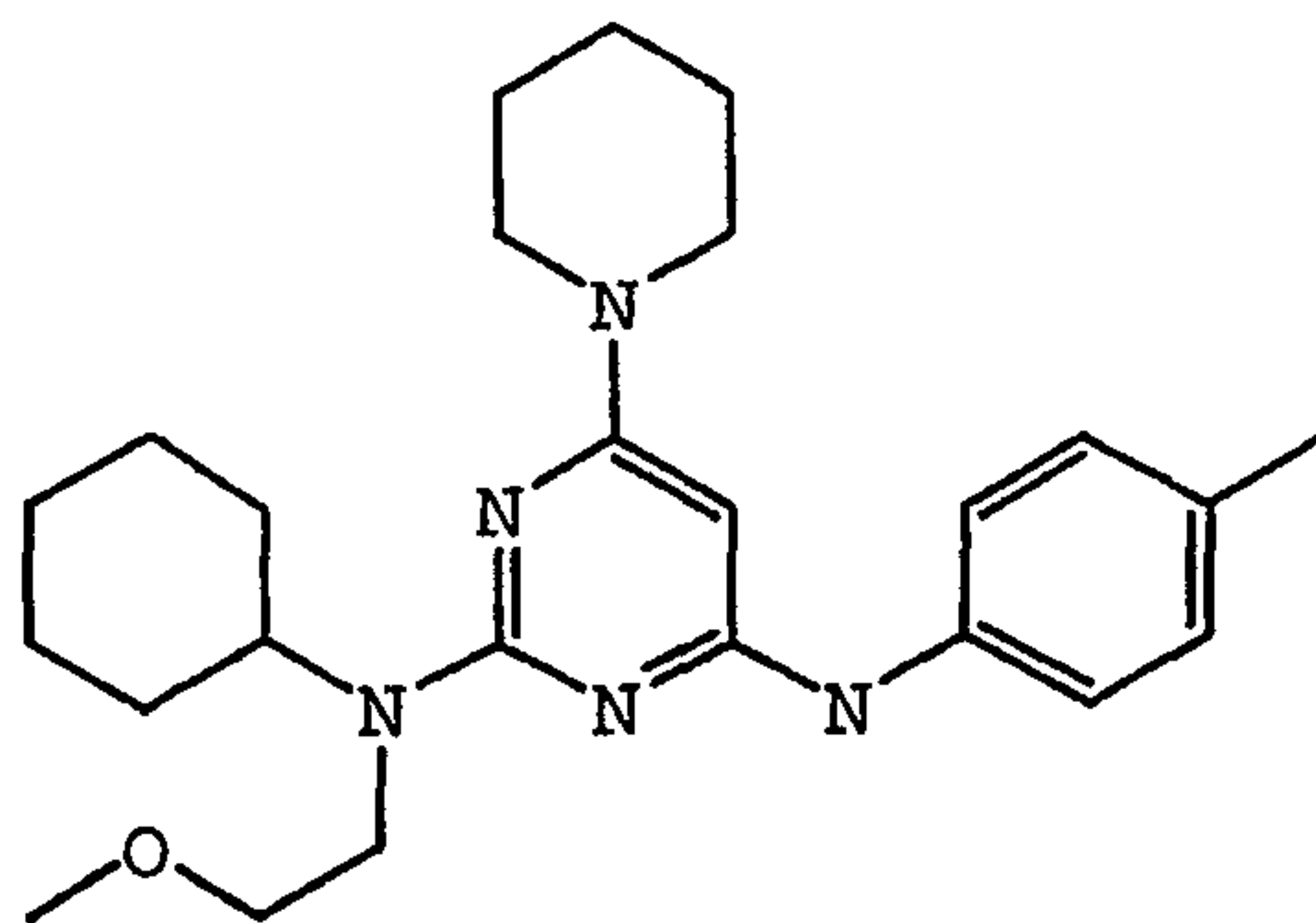
PCT/US02/04608

182

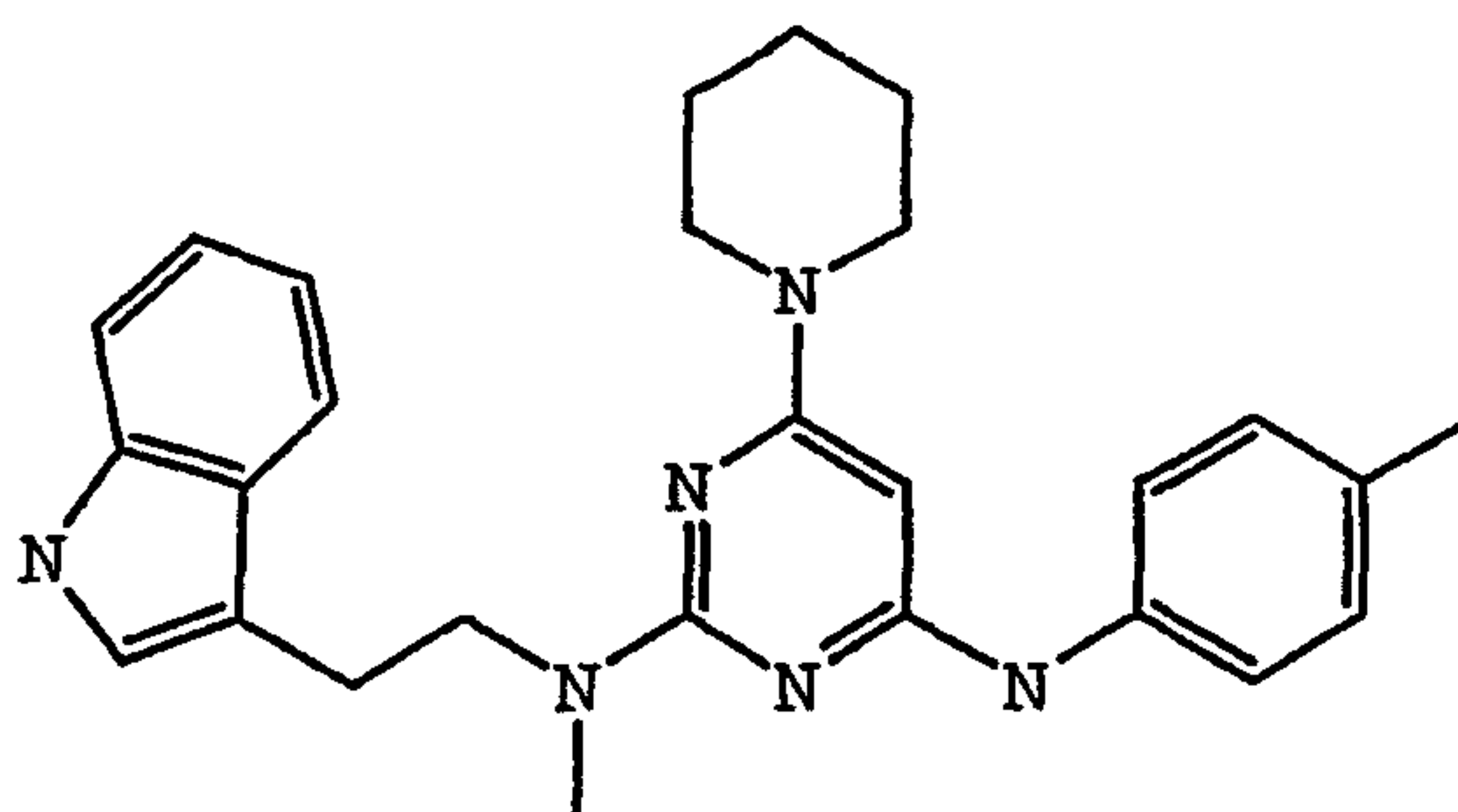
In one embodiment, the compound is selected from the group consisting of:



i



i

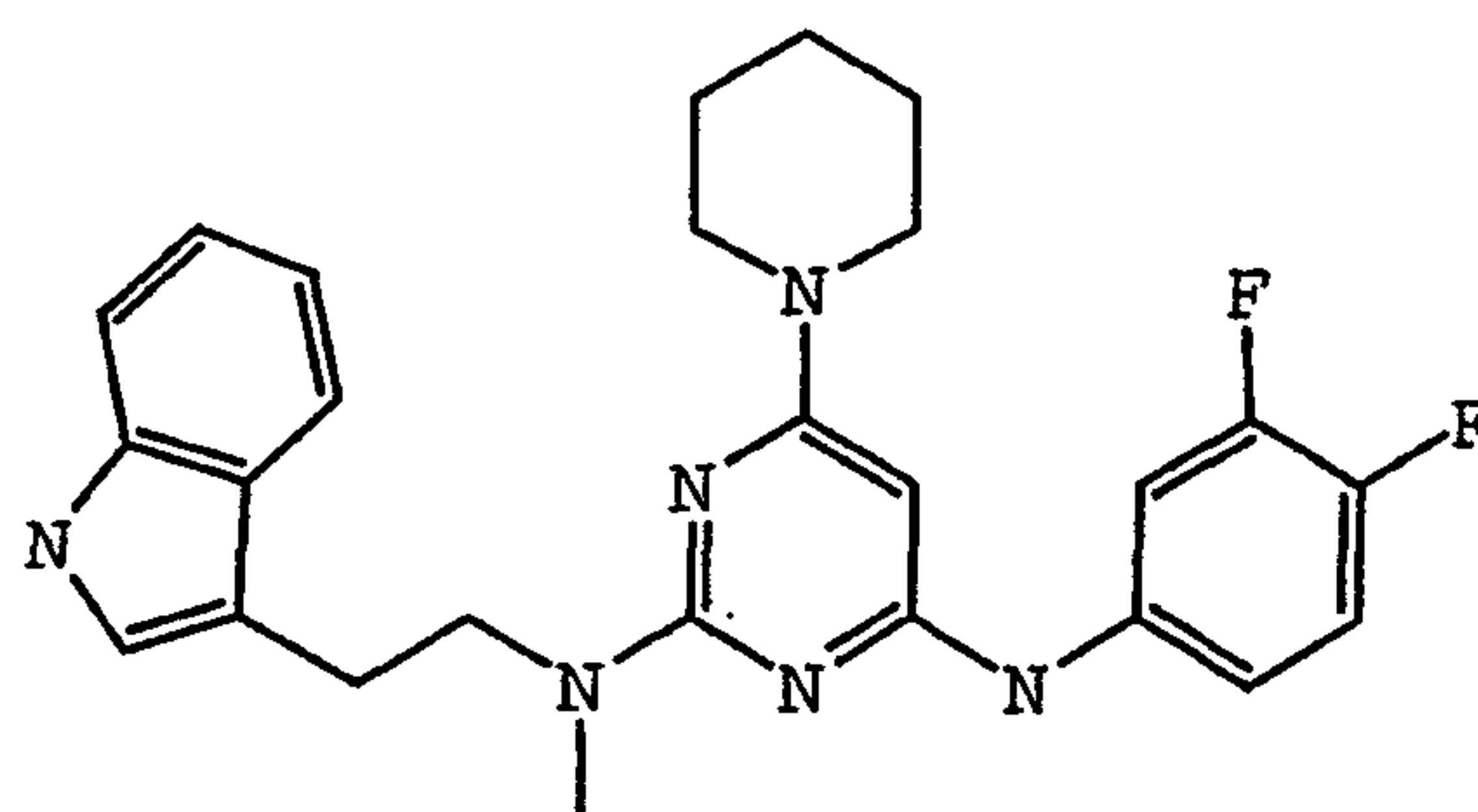
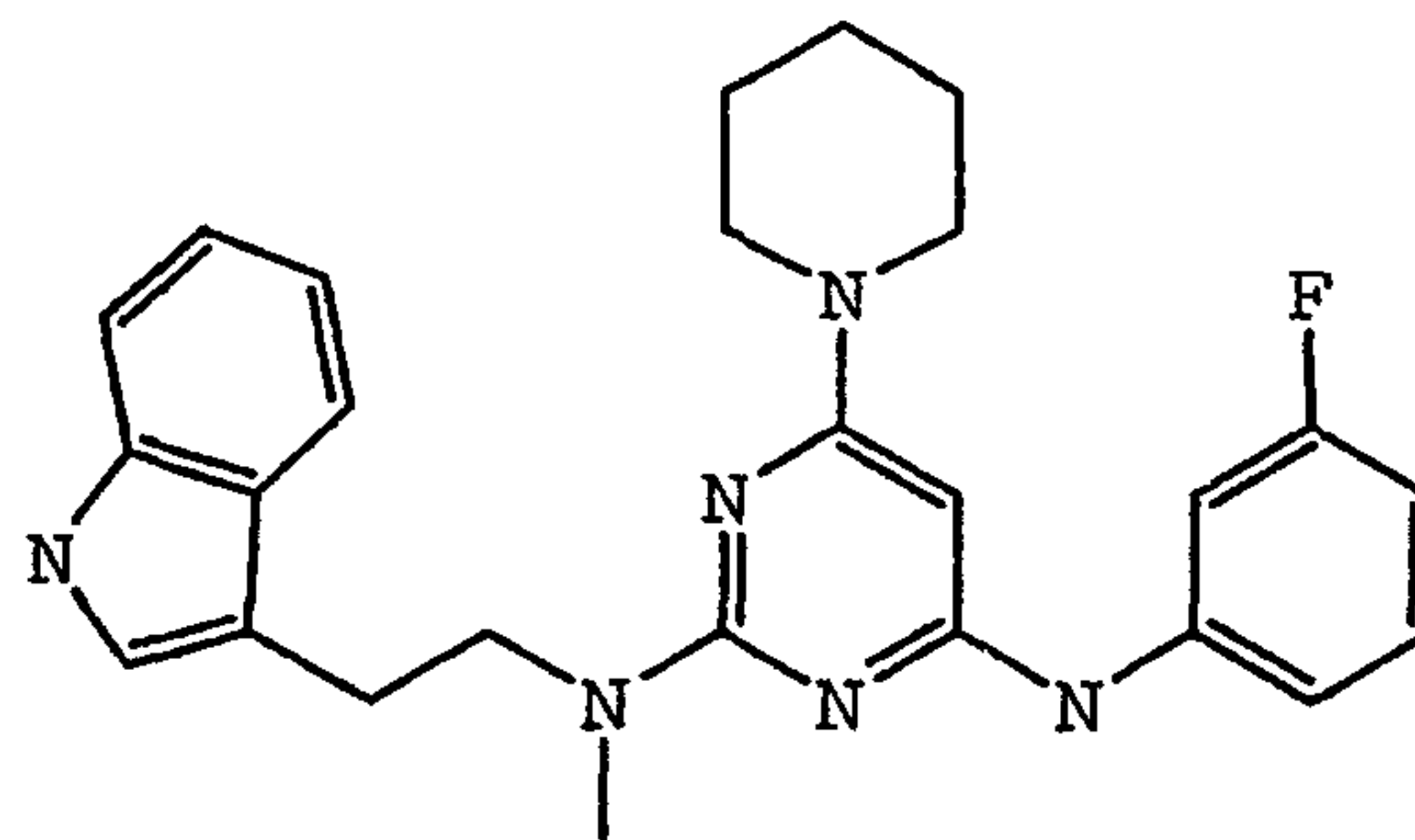
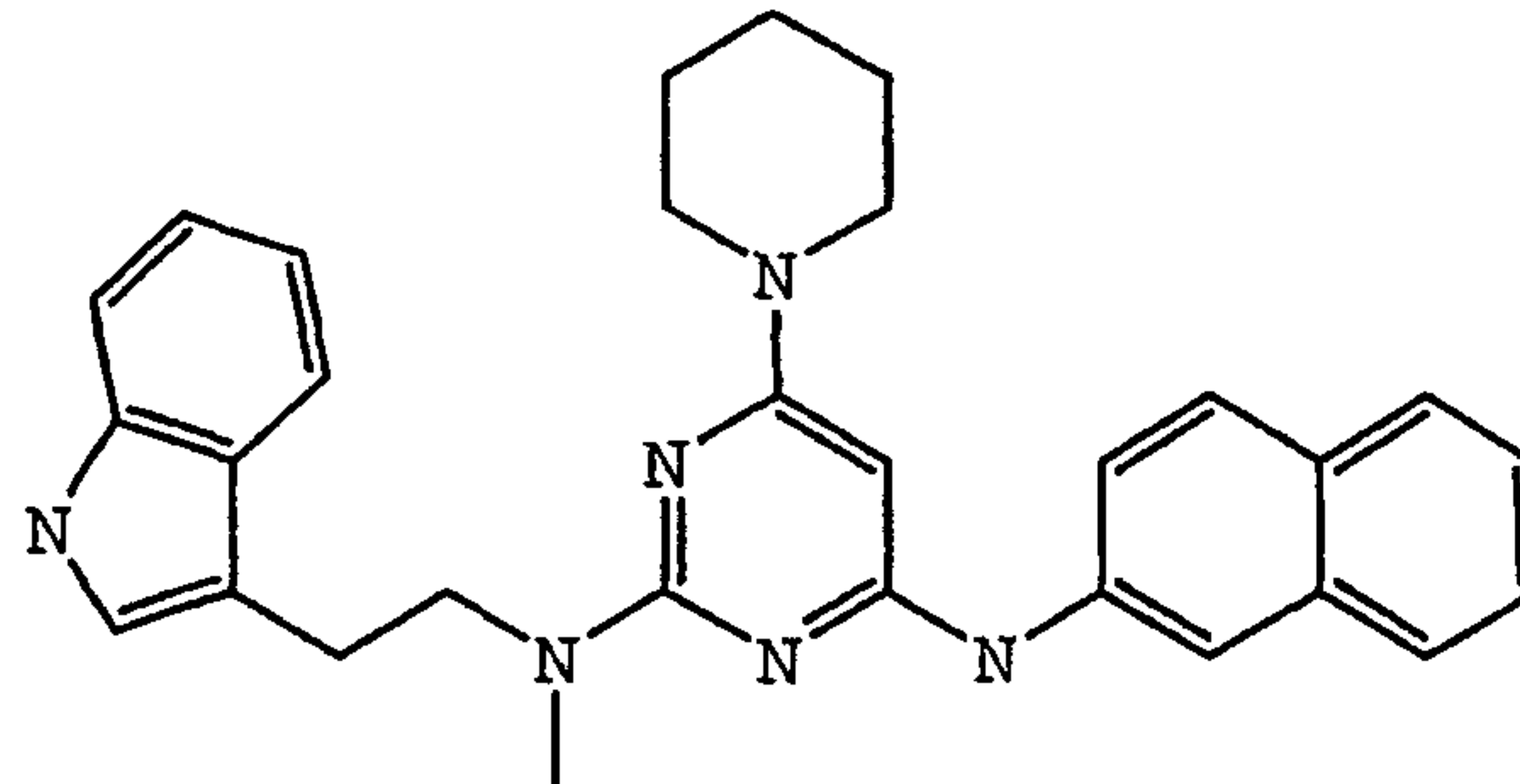


i

WO 02/060392

PCT/US02/04608

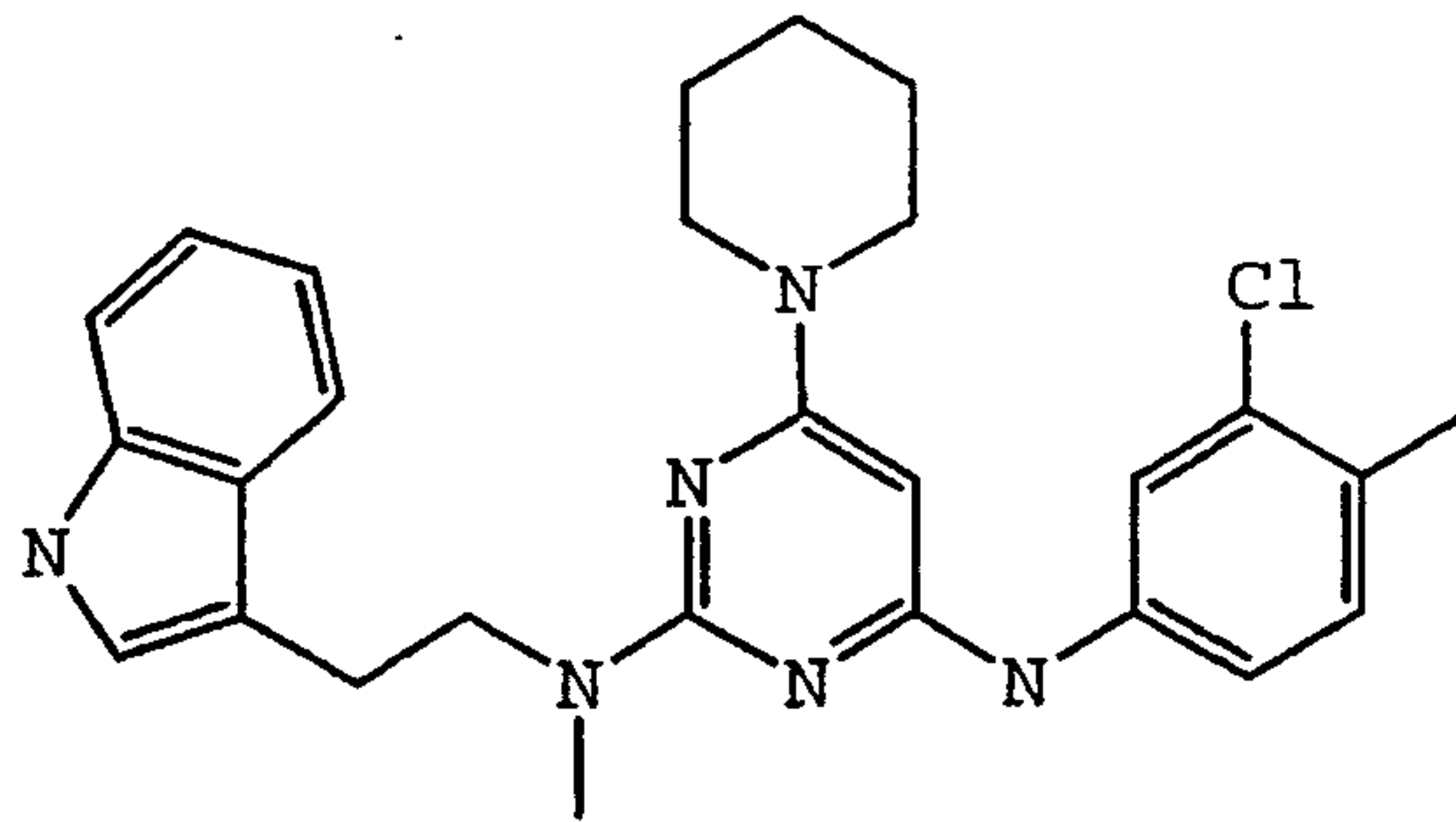
183



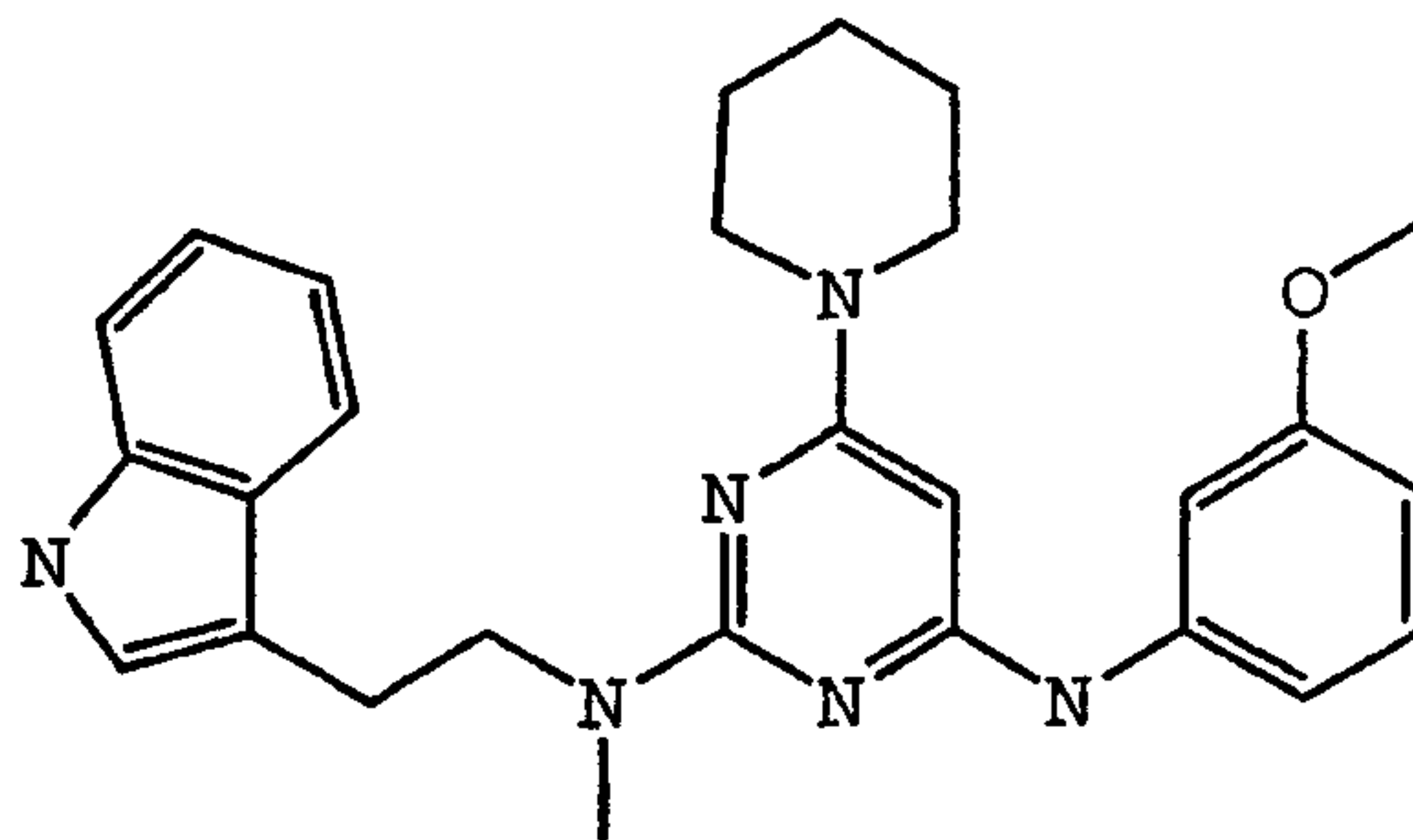
WO 02/060392

PCT/US02/04608

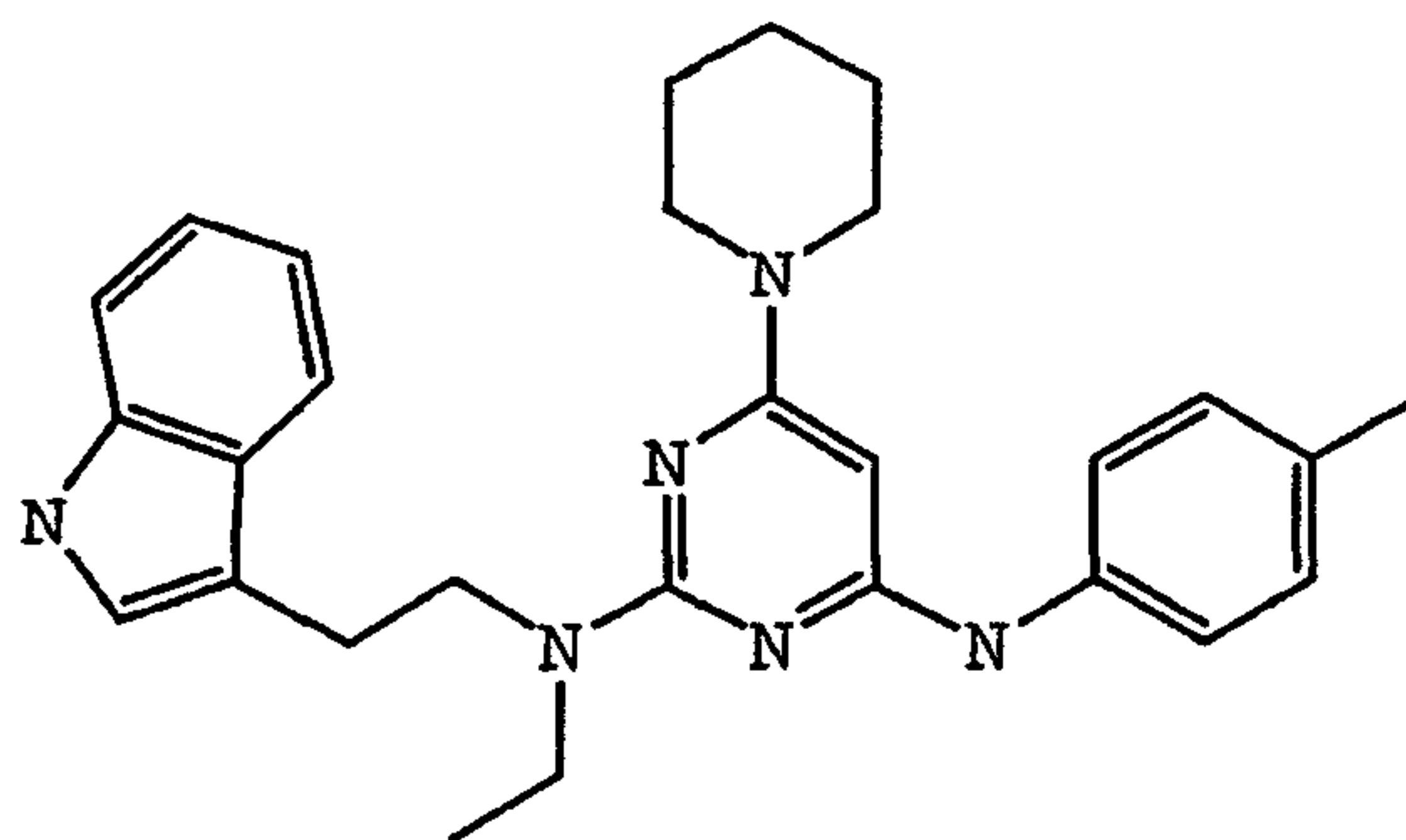
184



i



i

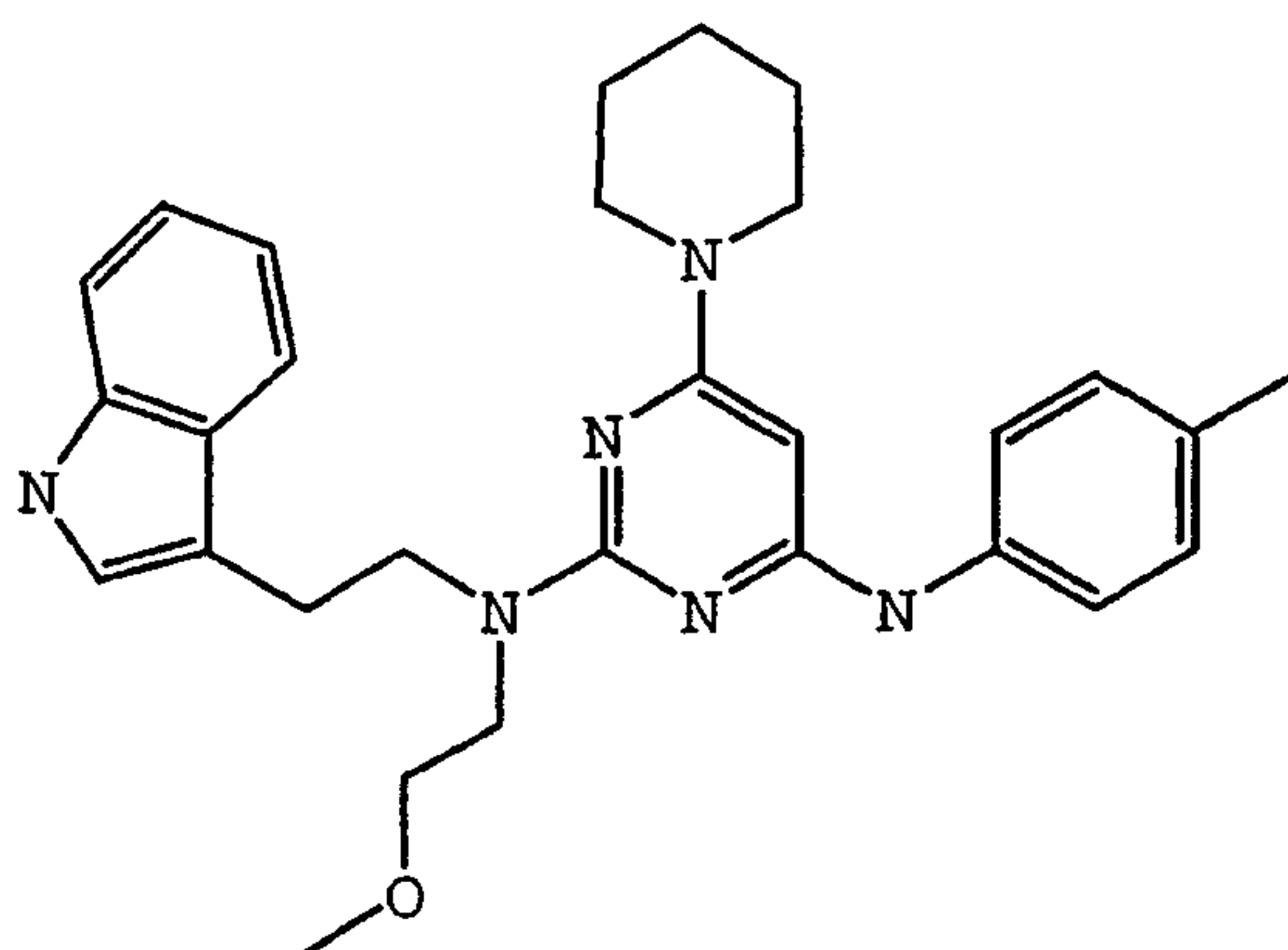


i

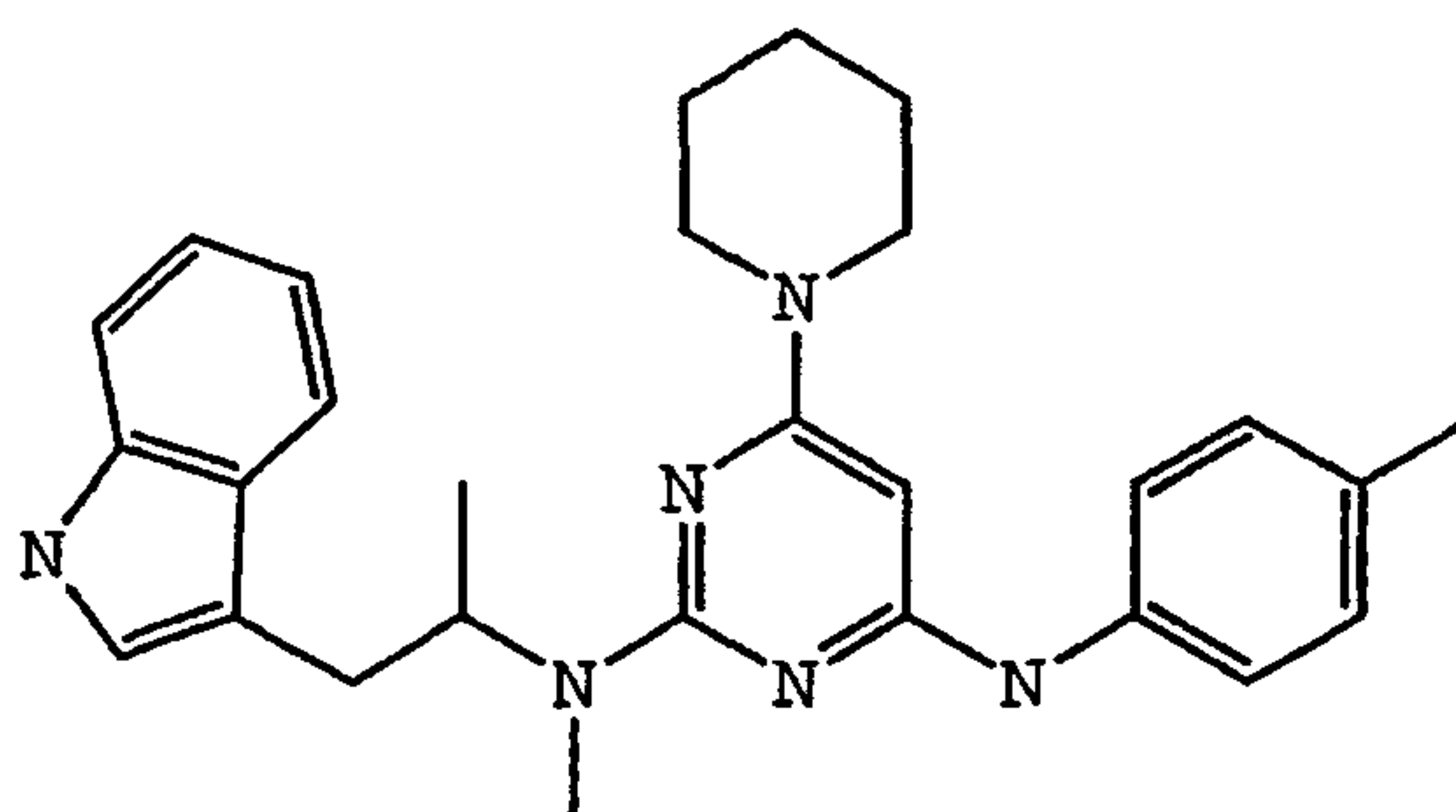
WO 02/060392

PCT/US02/04608

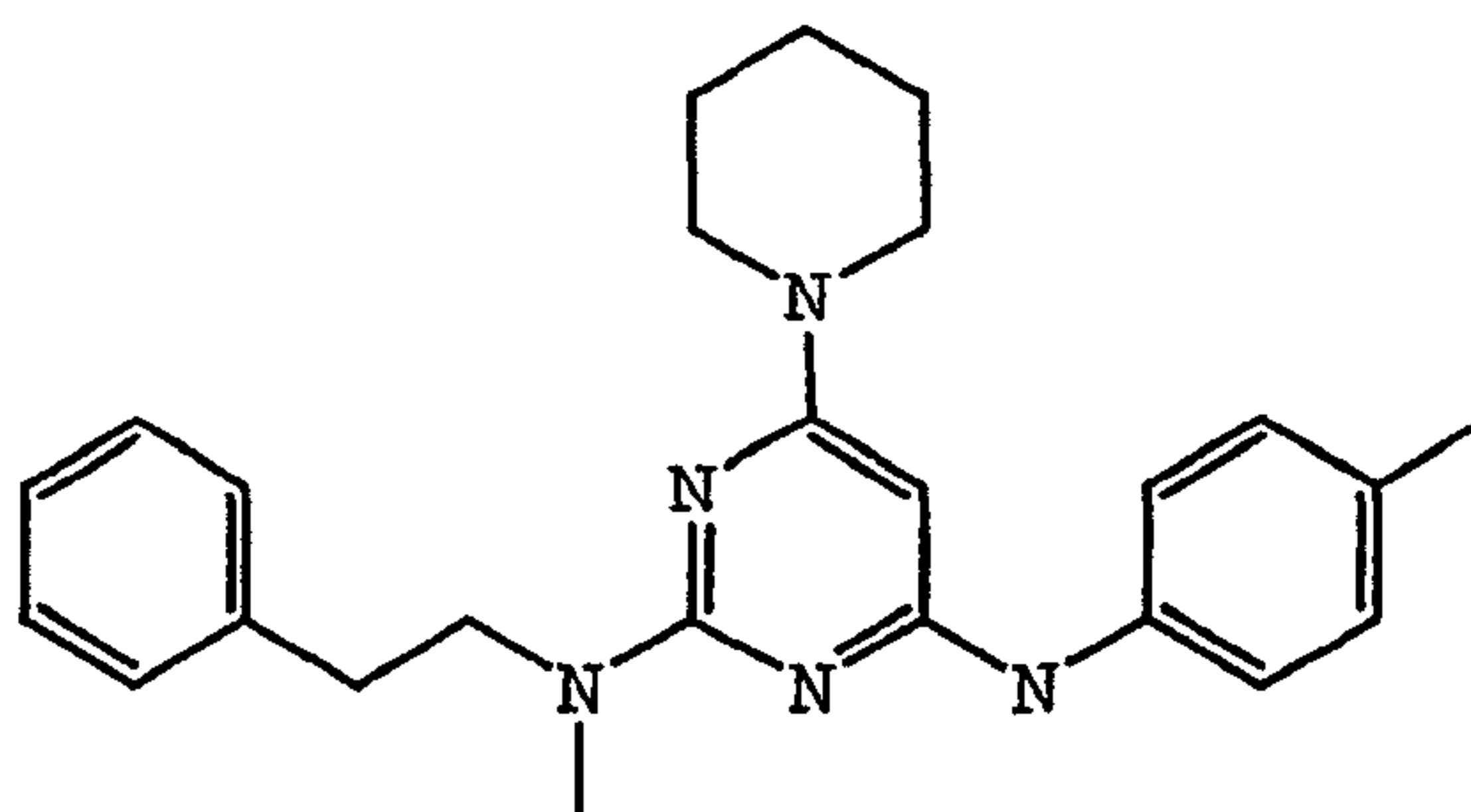
185



;



; and



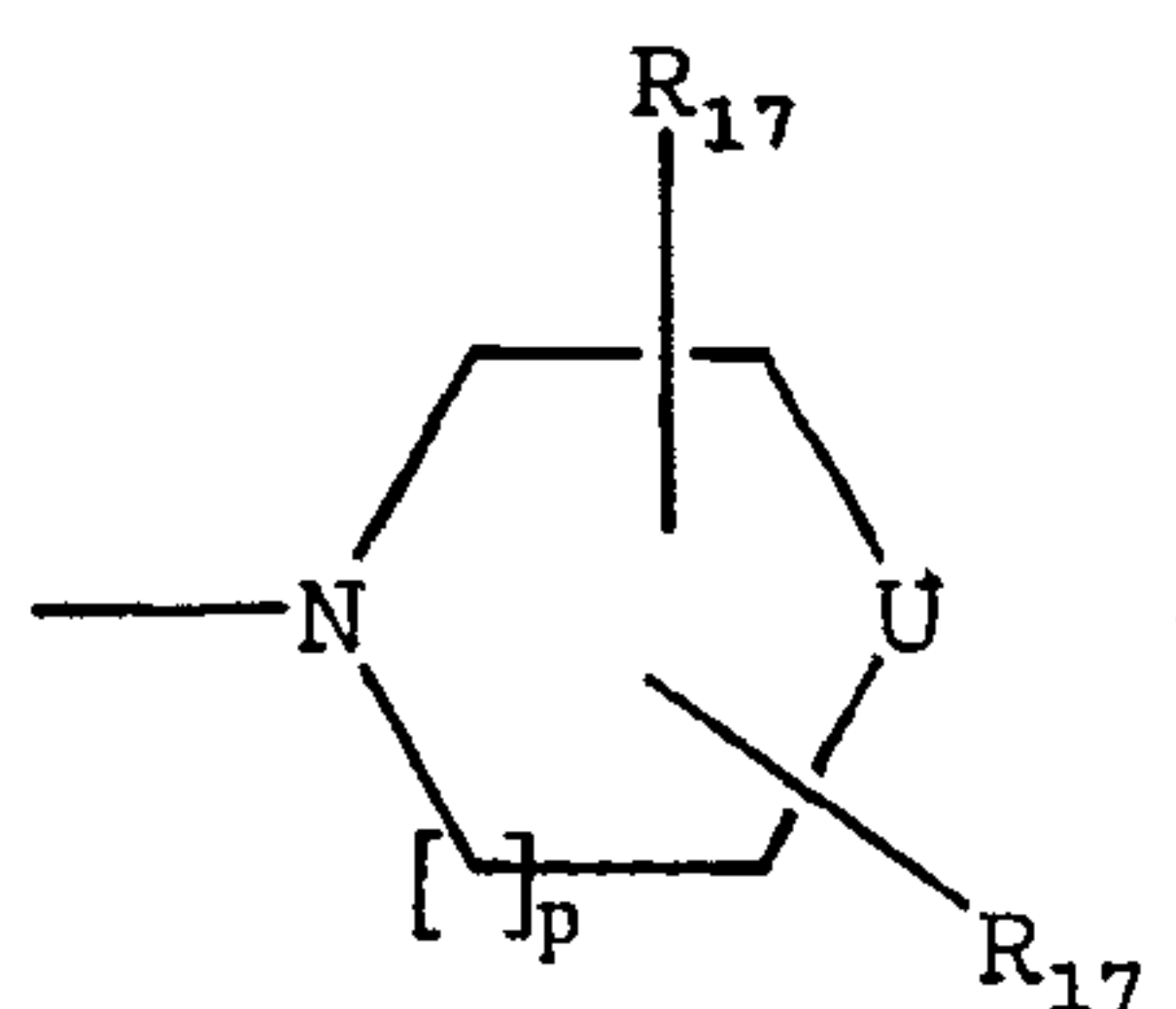
5

In one embodiment, Y is

WO 02/060392

PCT/US02/04608

186

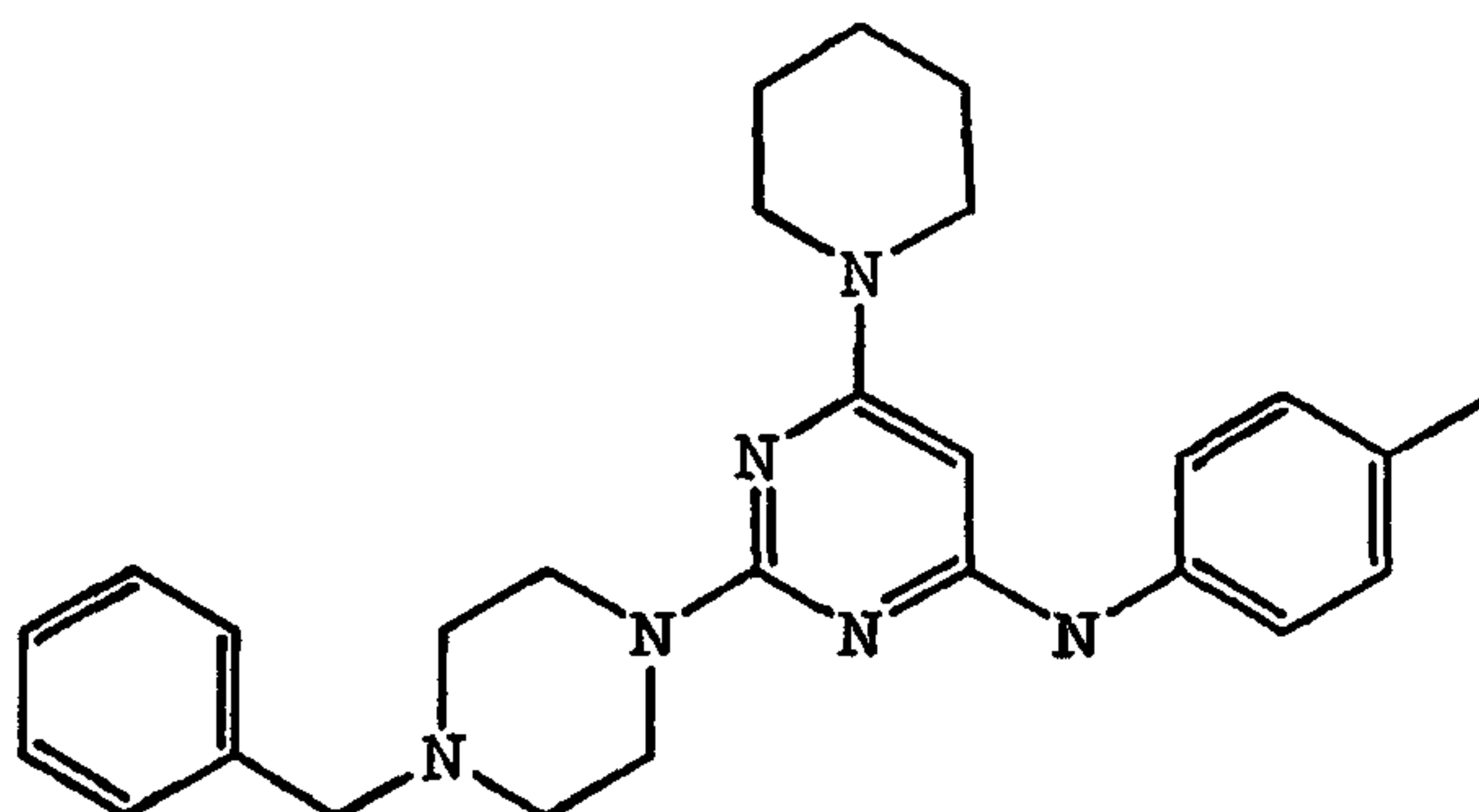


In one embodiment, U is NR_{16} .

5 In one embodiment, R_{16} is $(\text{CH}_2)_m\text{-Z}$.

In one embodiment, Z is aryl or heteroaryl.

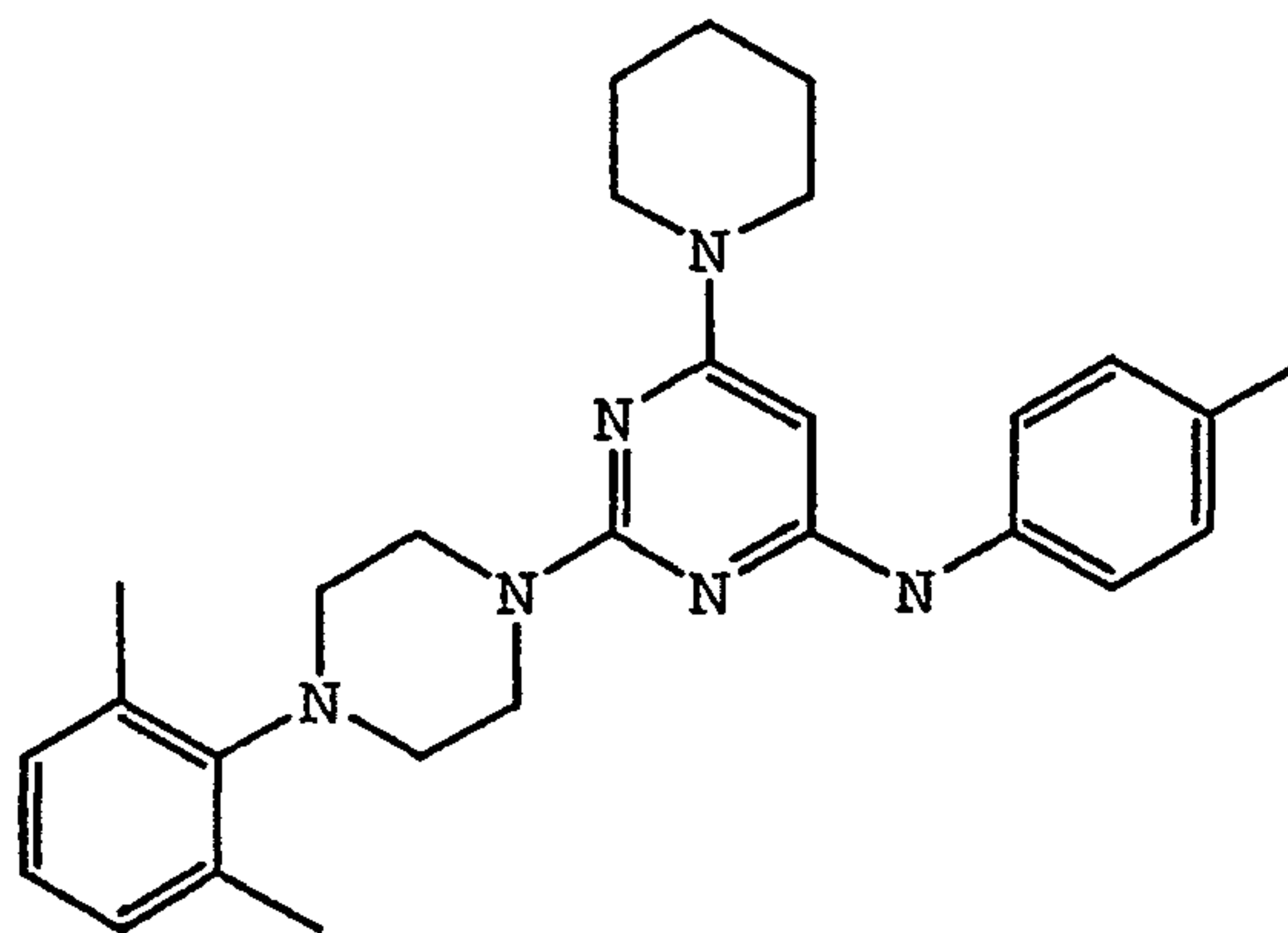
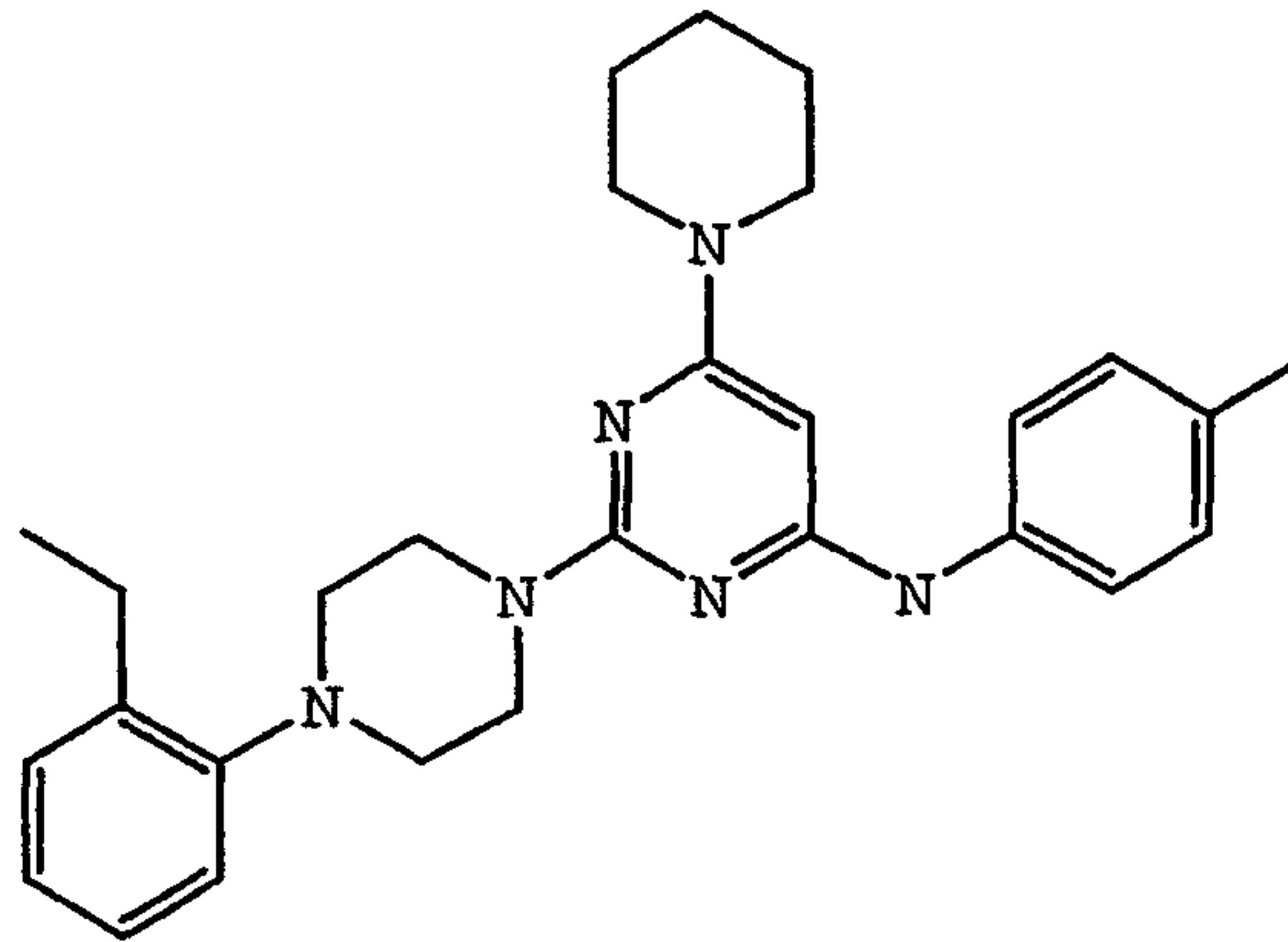
In one embodiment, the compound is selected from the
10 group consisting of:



WO 02/060392

PCT/US02/04608

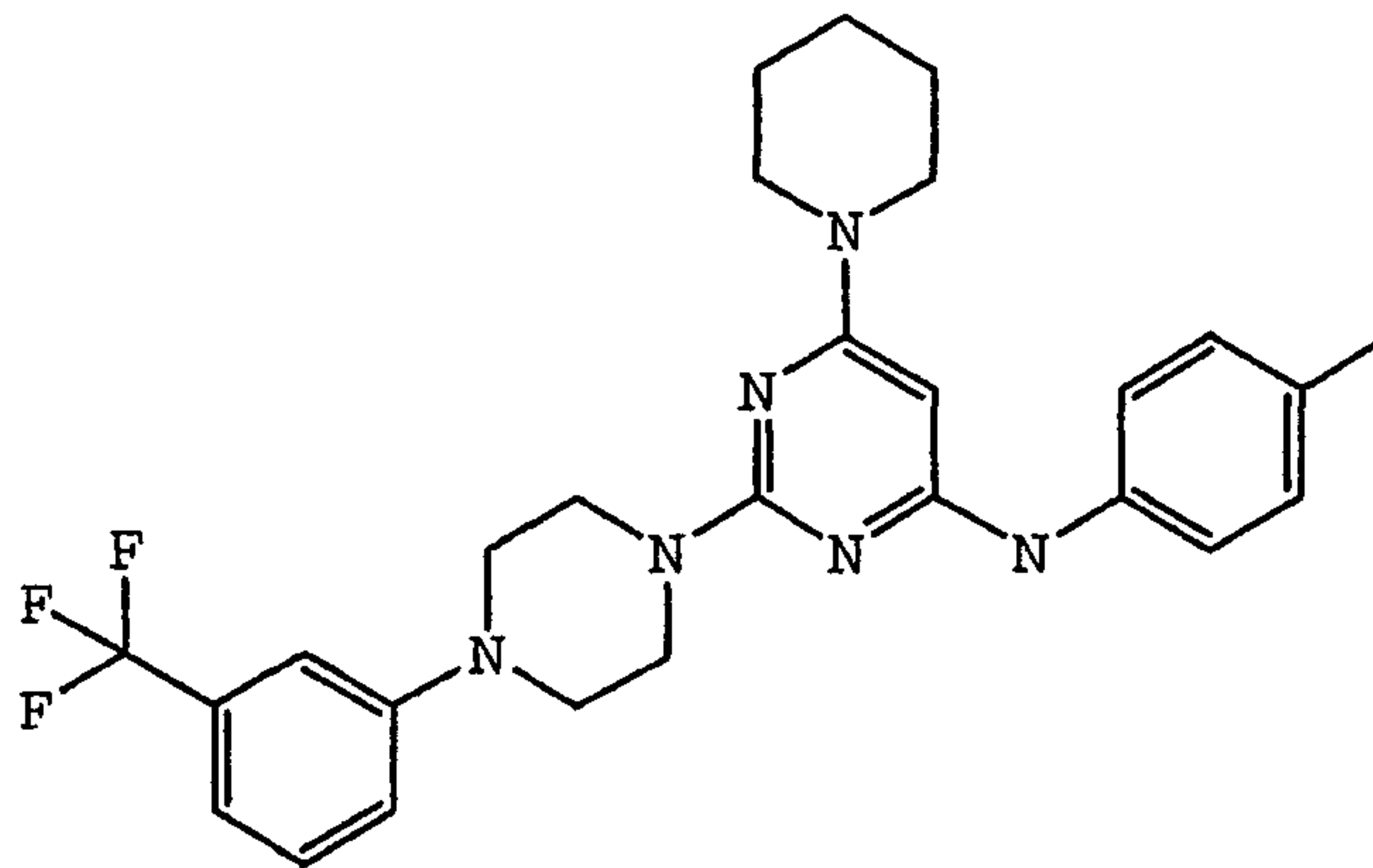
187



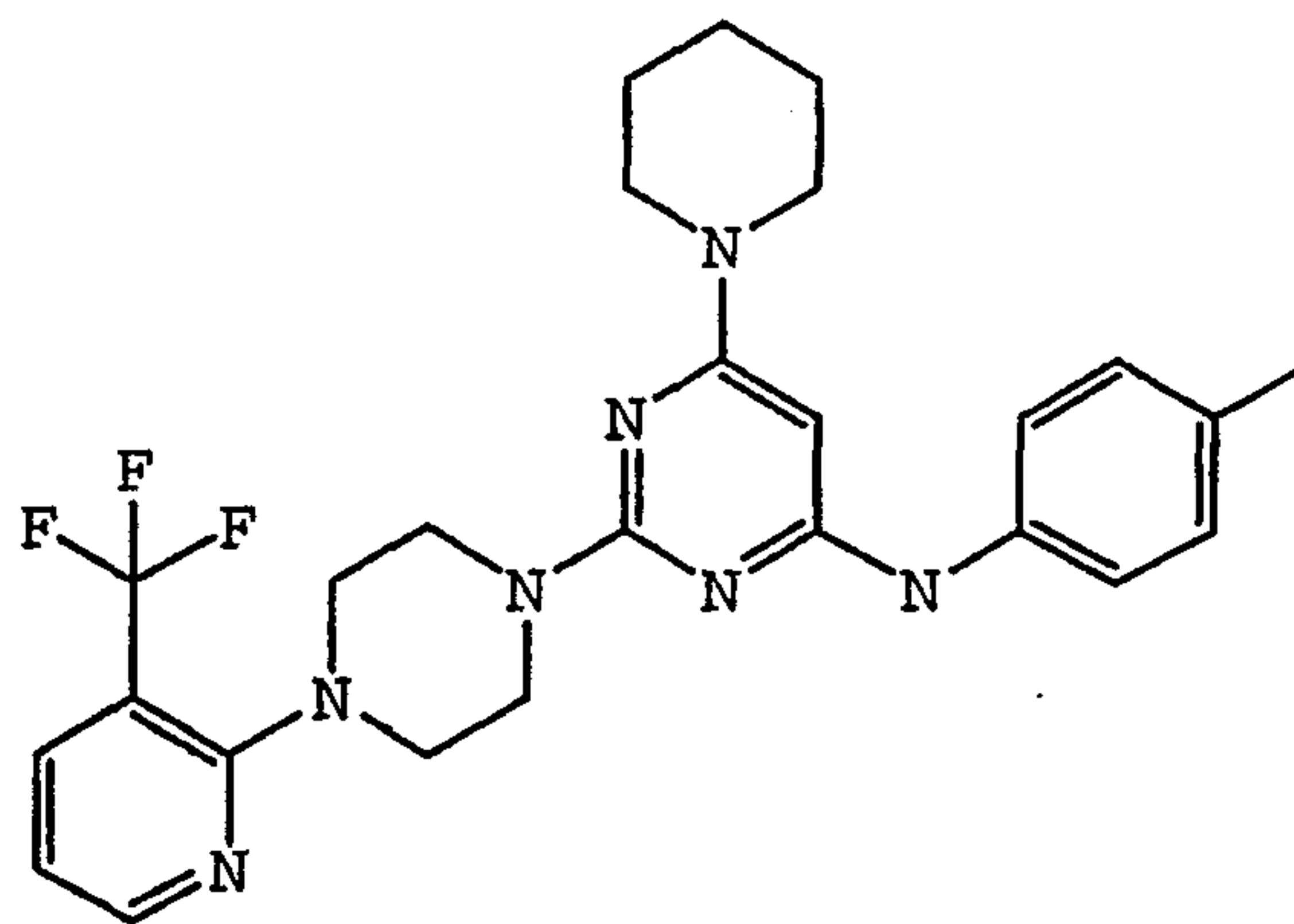
WO 02/060392

PCT/US02/04608

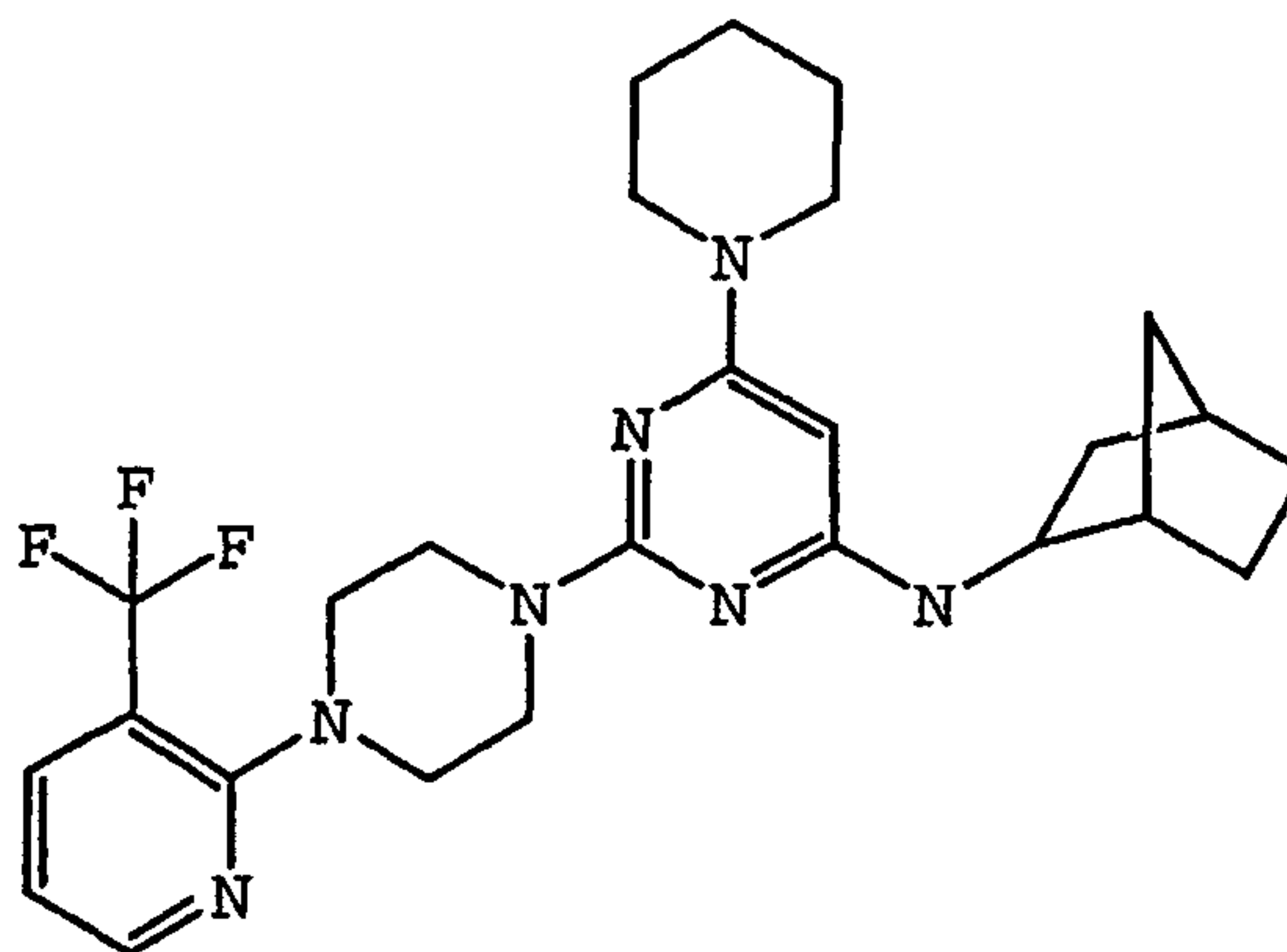
188



;



; and

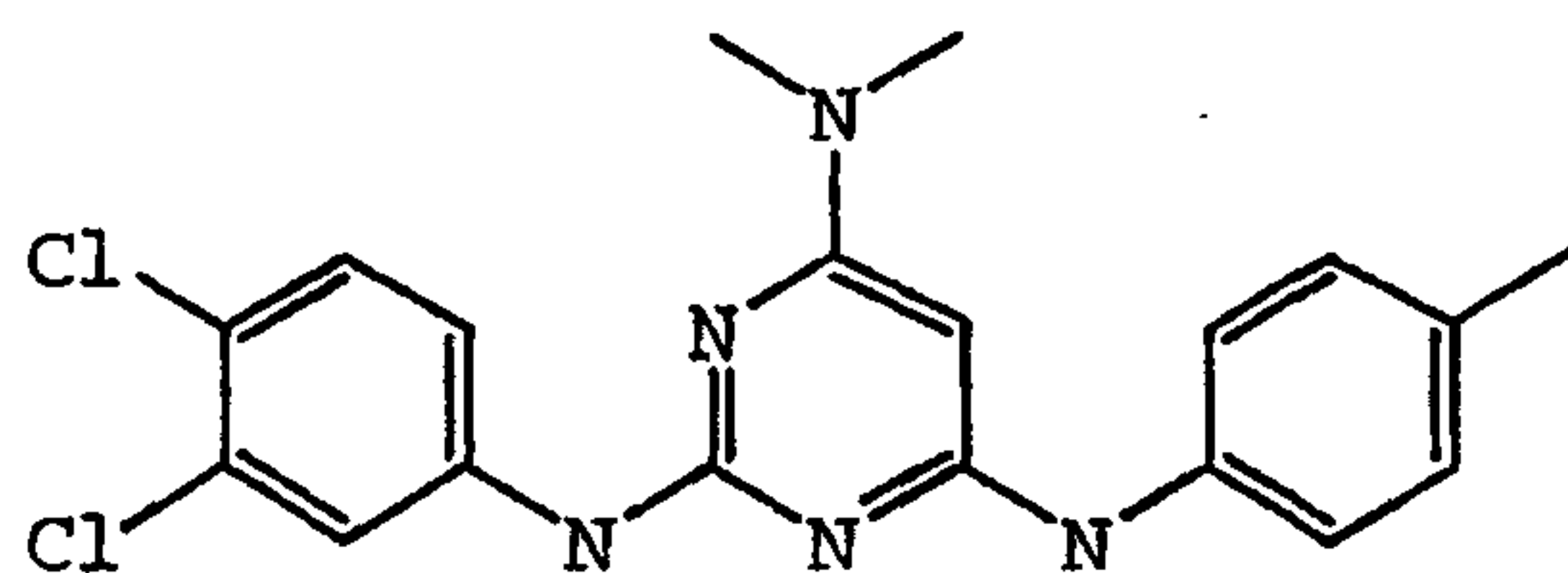


WO 02/060392

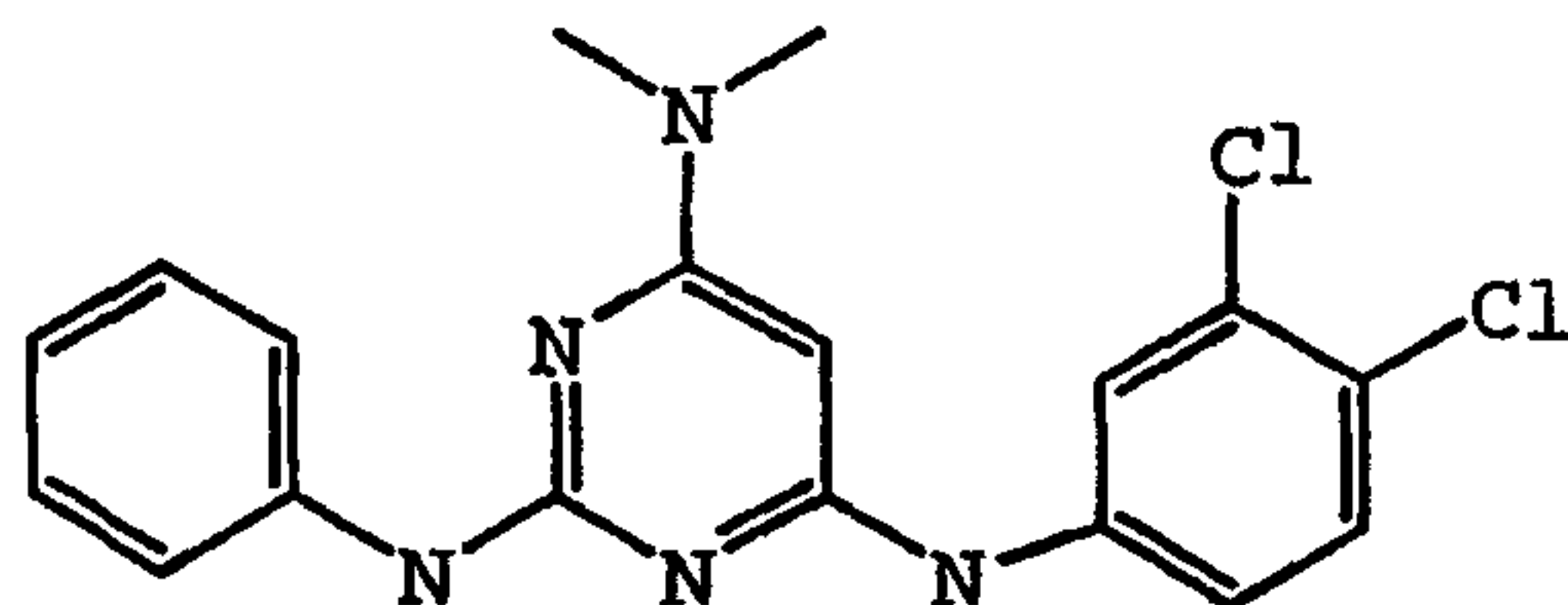
PCT/US02/04608

189

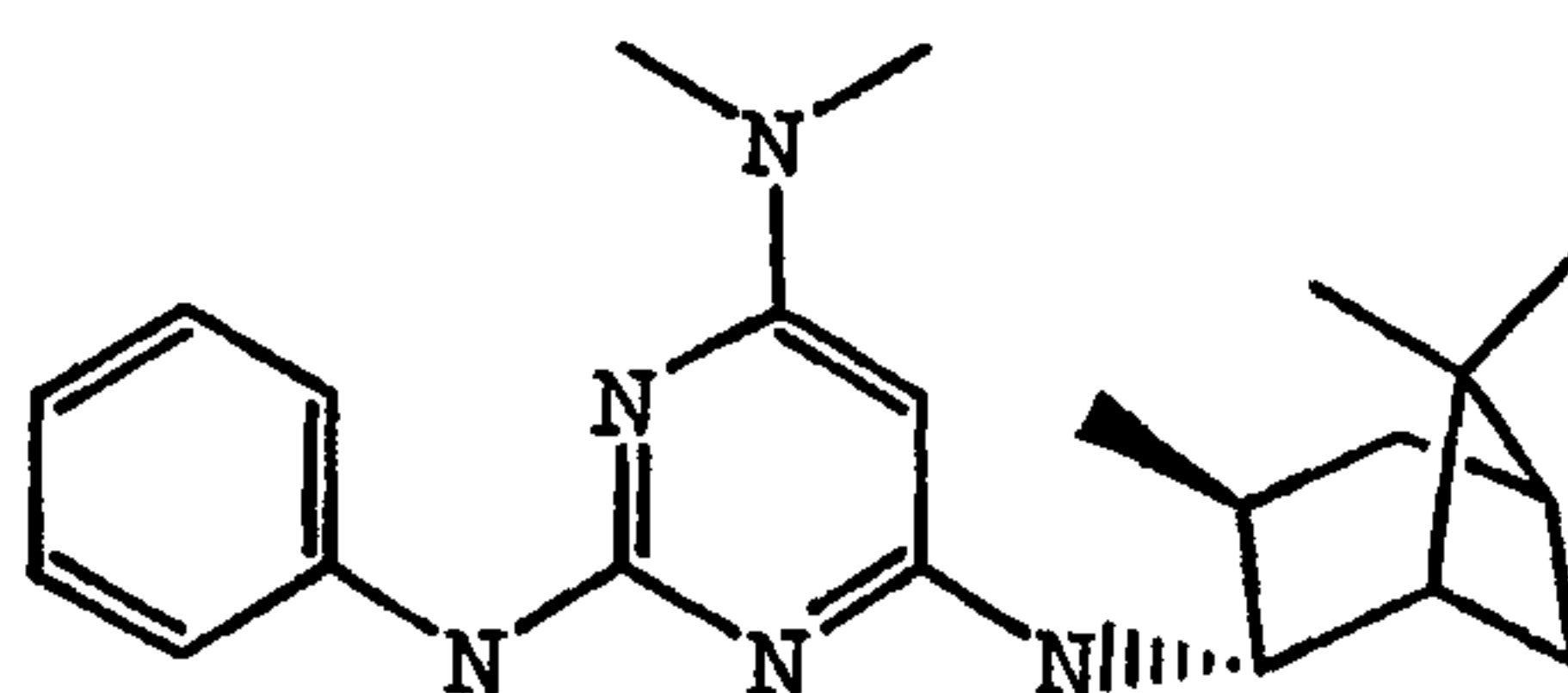
In one embodiment, the compound is selected from the group consisting of:



;



;

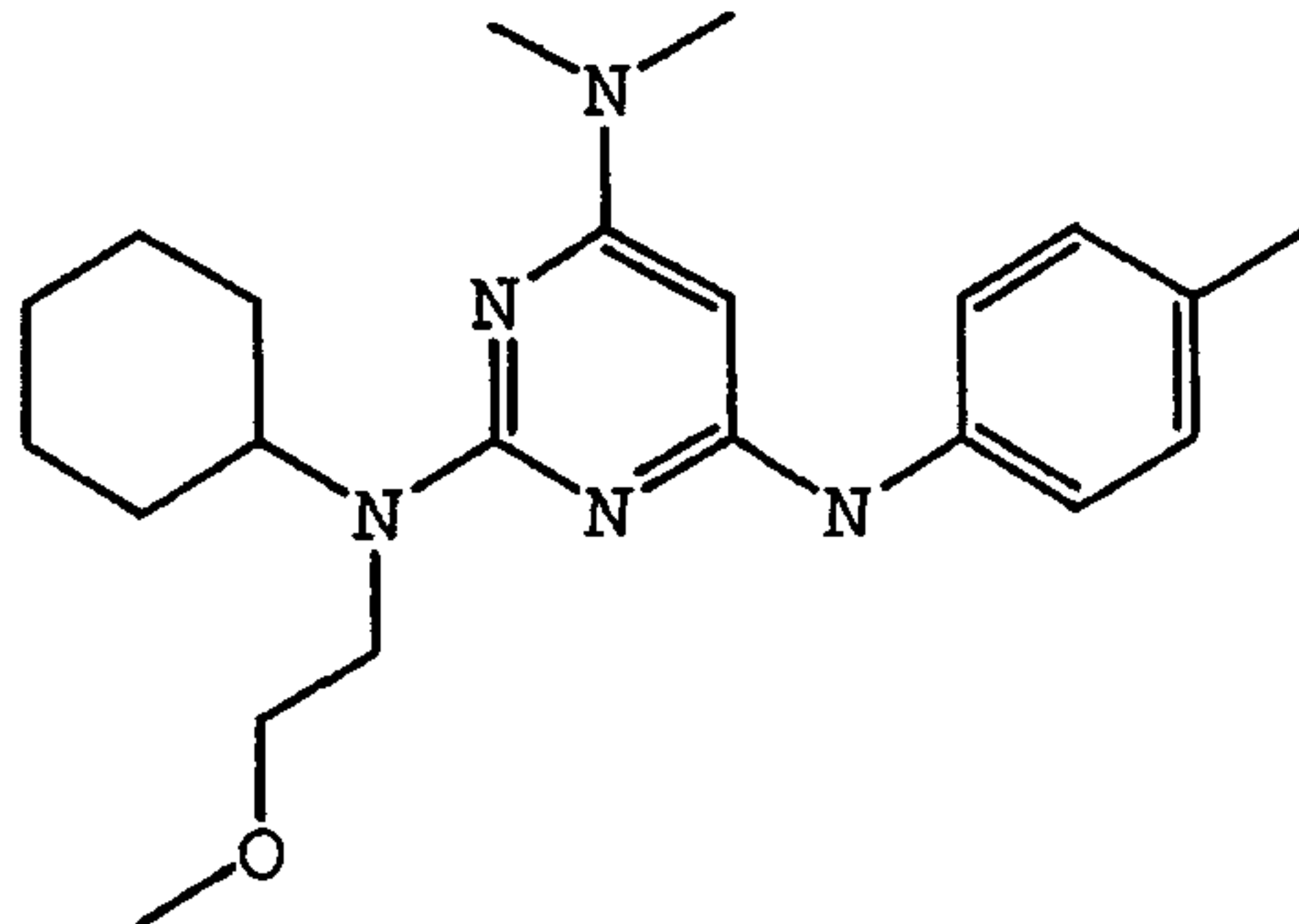


;

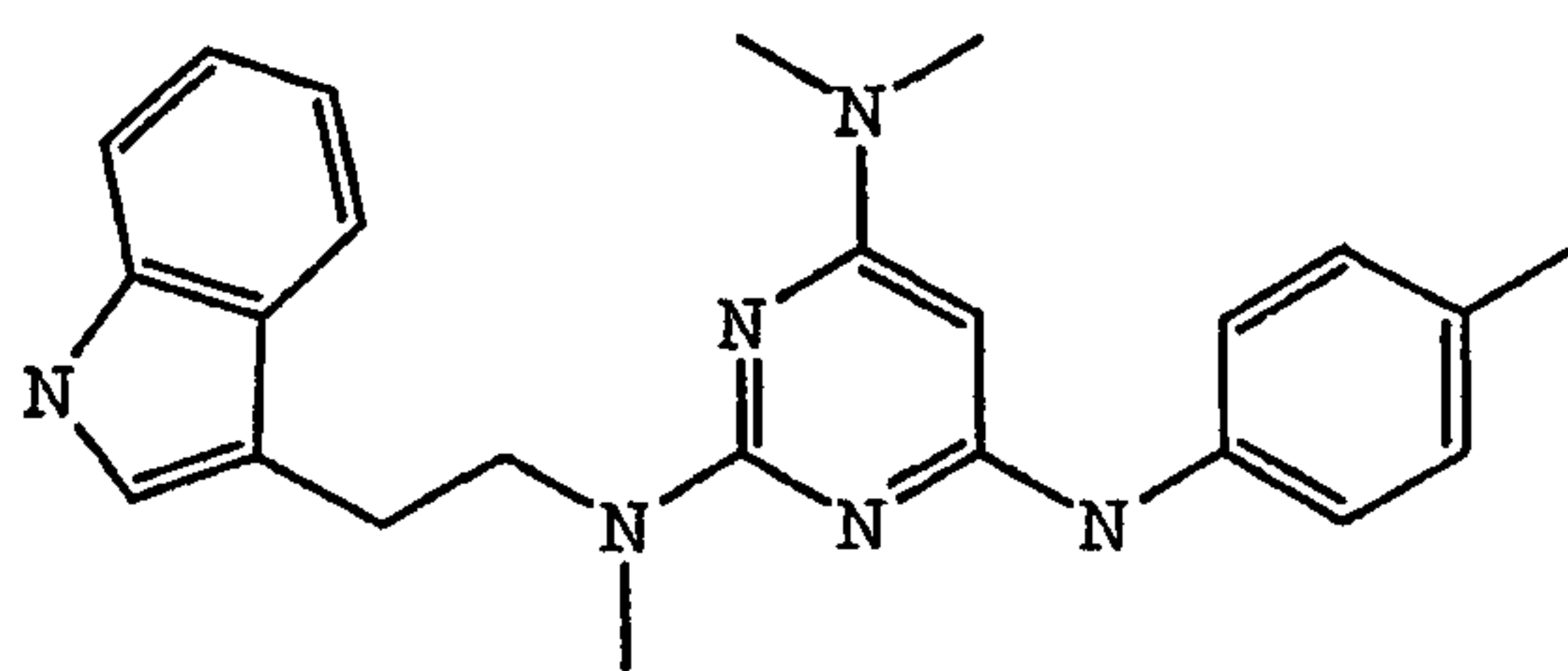
WO 02/060392

PCT/US02/04608

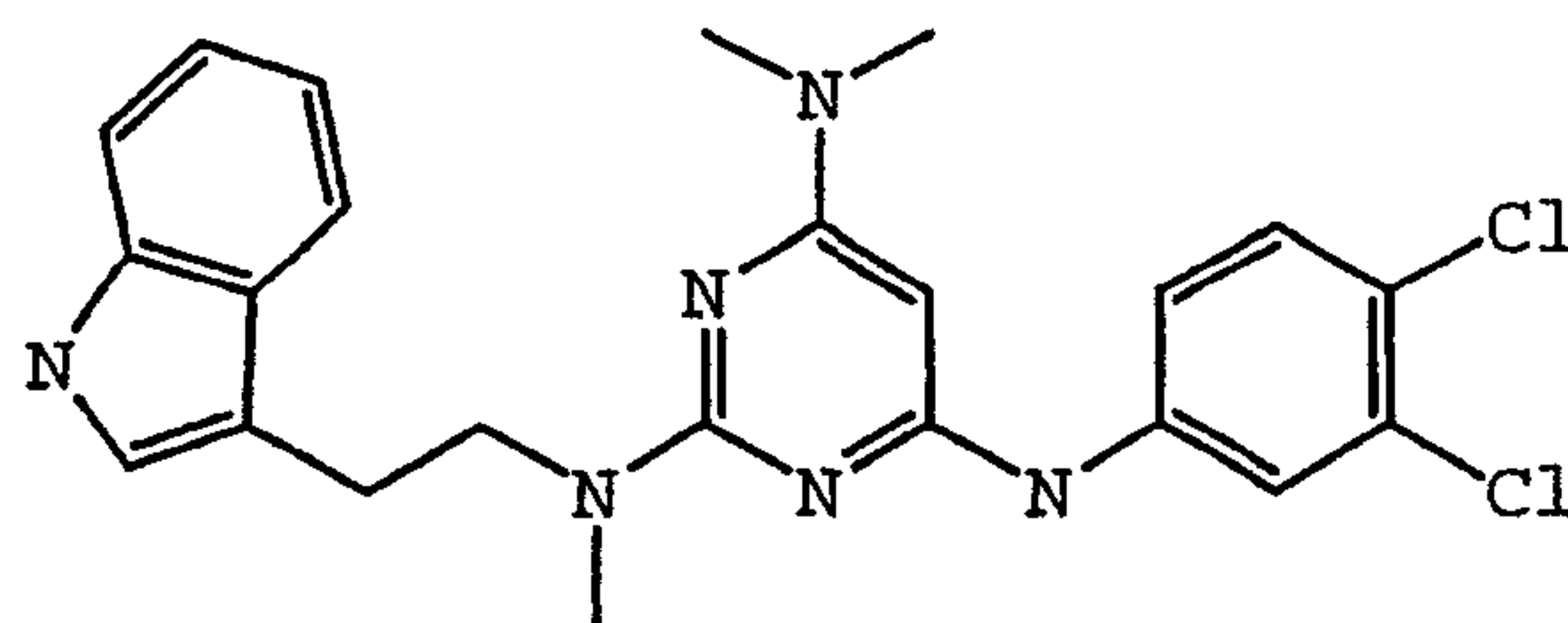
190



;



; and

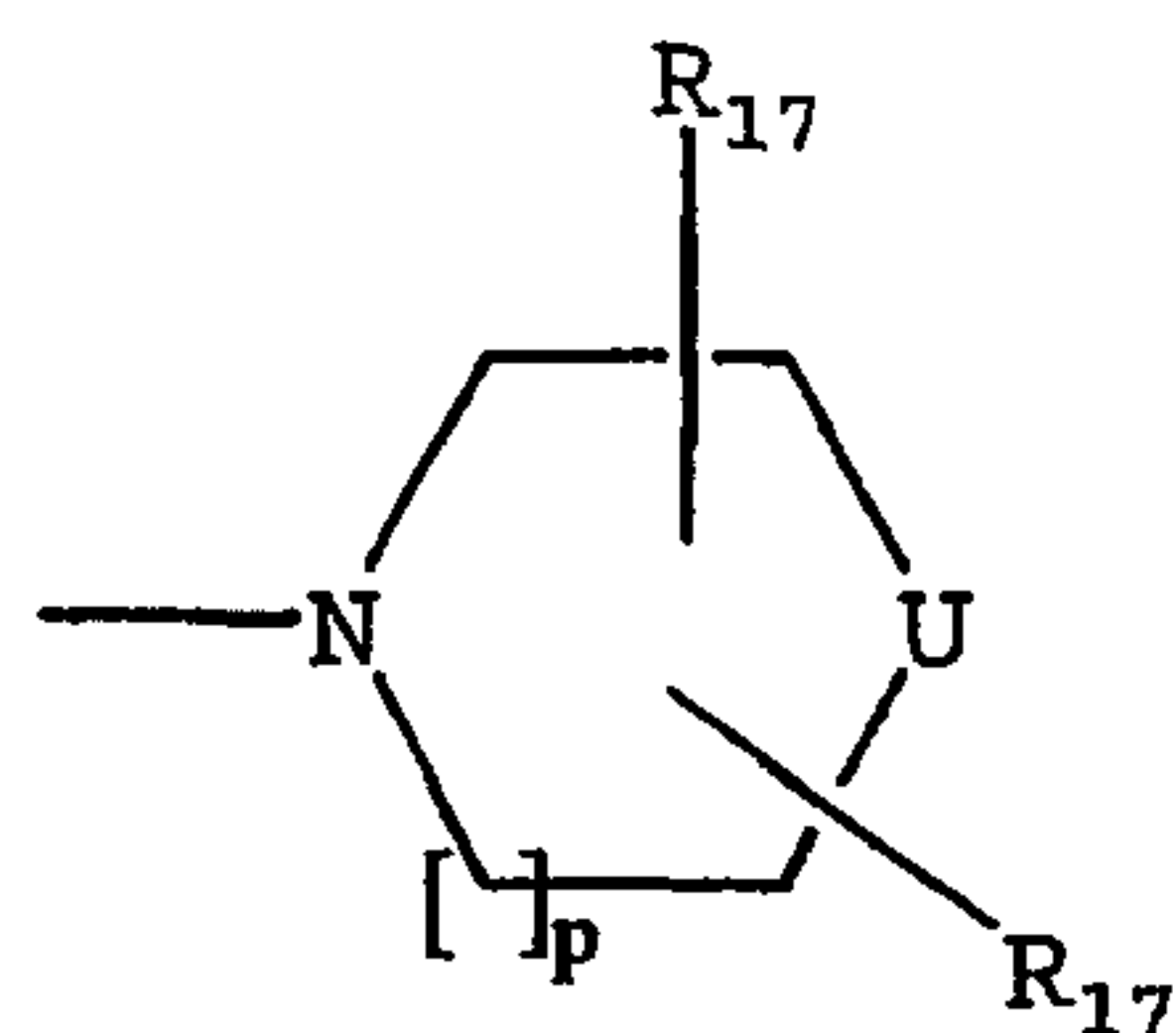


In one embodiment, Y is

WO 02/060392

PCT/US02/04608

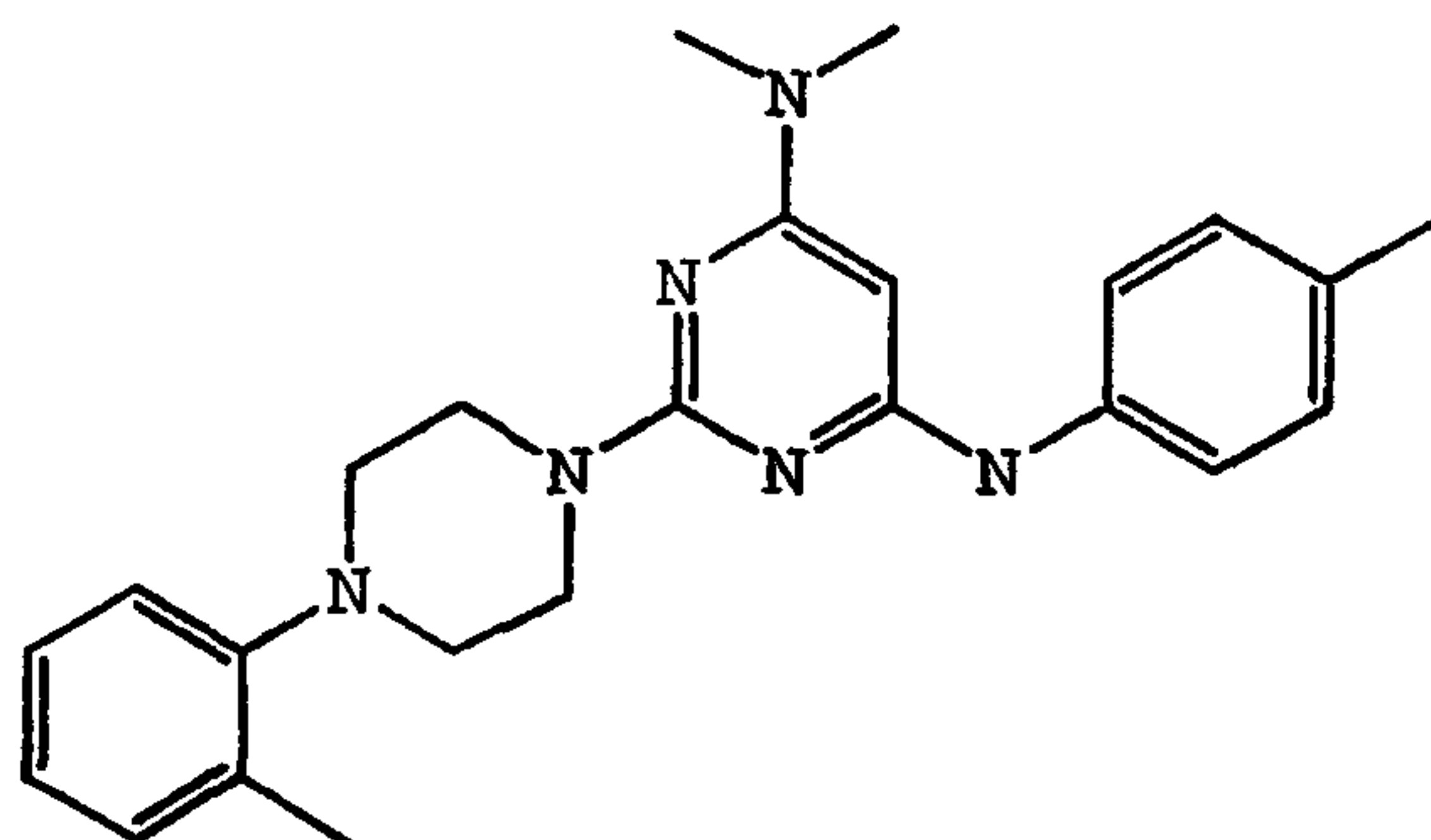
191



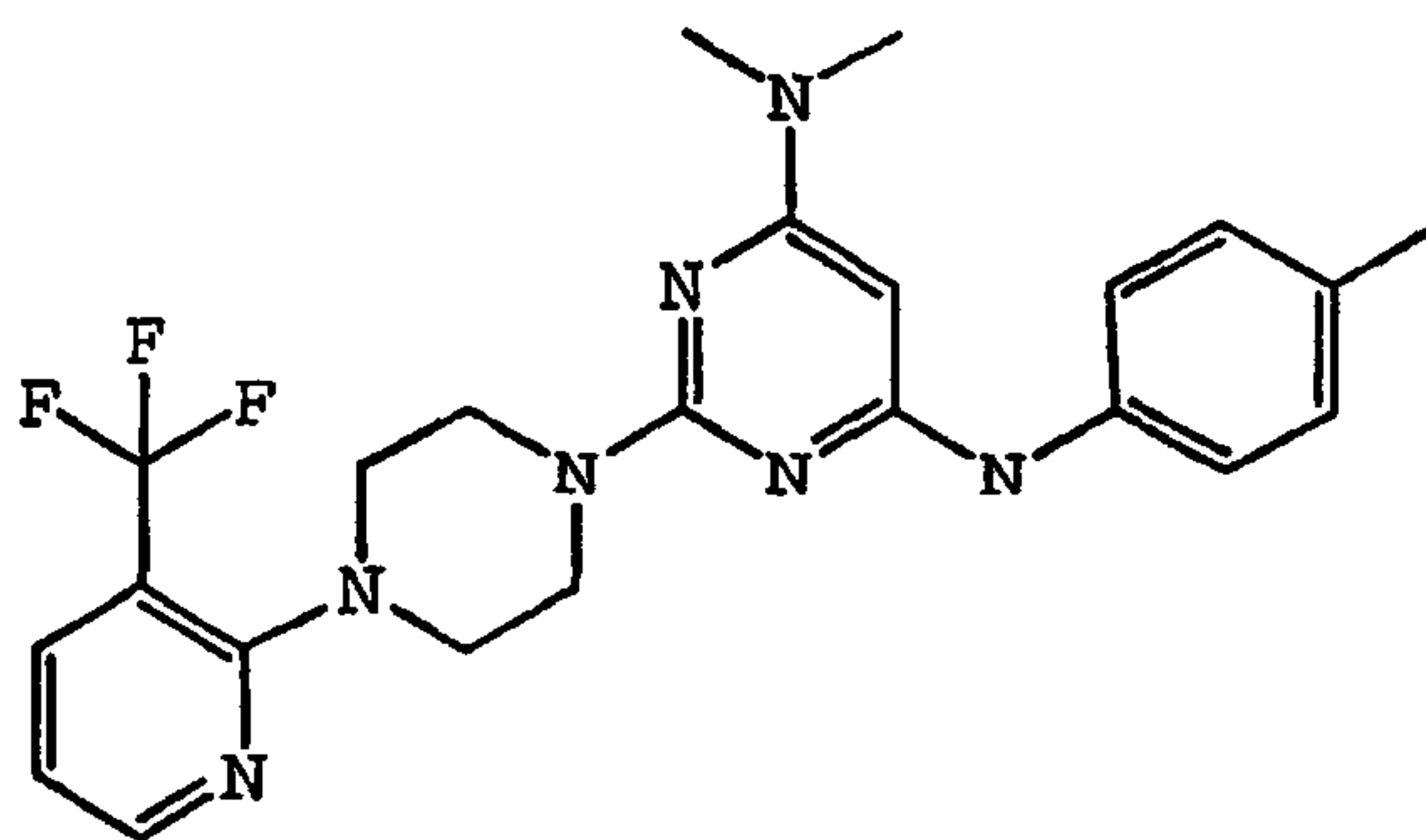
In one embodiment, U is NR_{16} .

5

In one embodiment, the compound is



; or

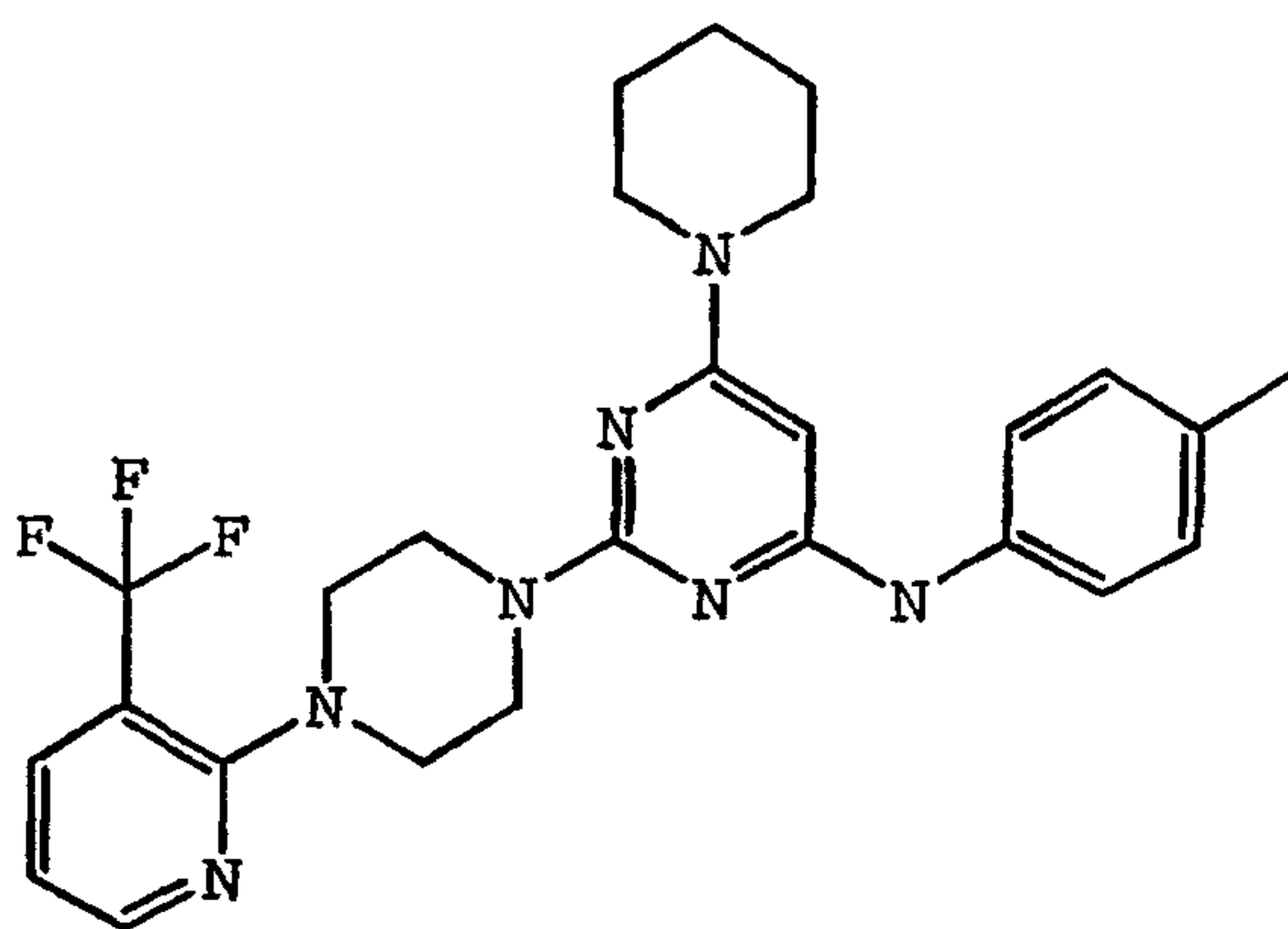


WO 02/060392

PCT/US02/04608

192

In one embodiment, the compound is



5

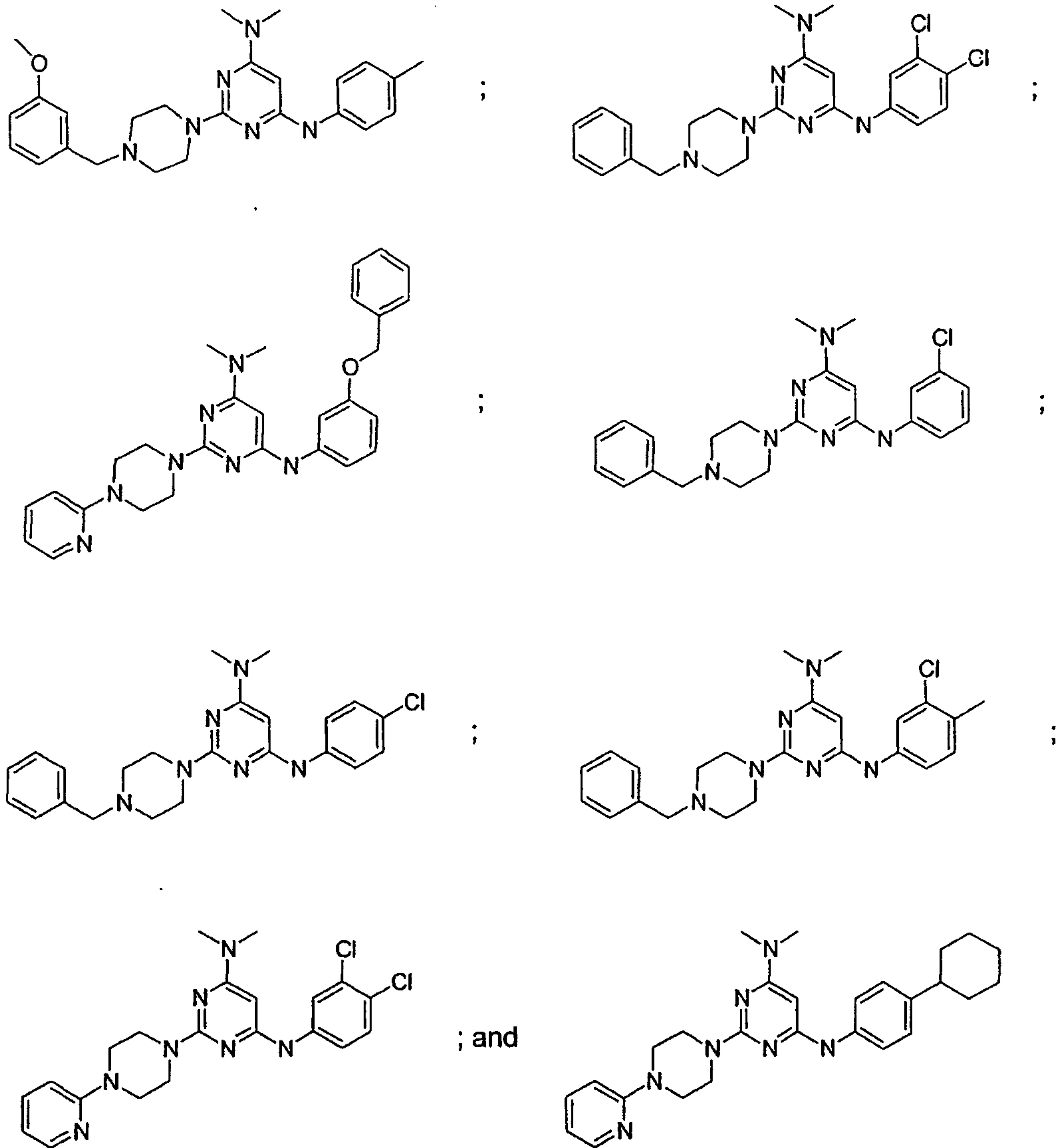
In one embodiment, the compound is selected from the group consisting of:

10

WO 02/060392

PCT/US02/04608

193

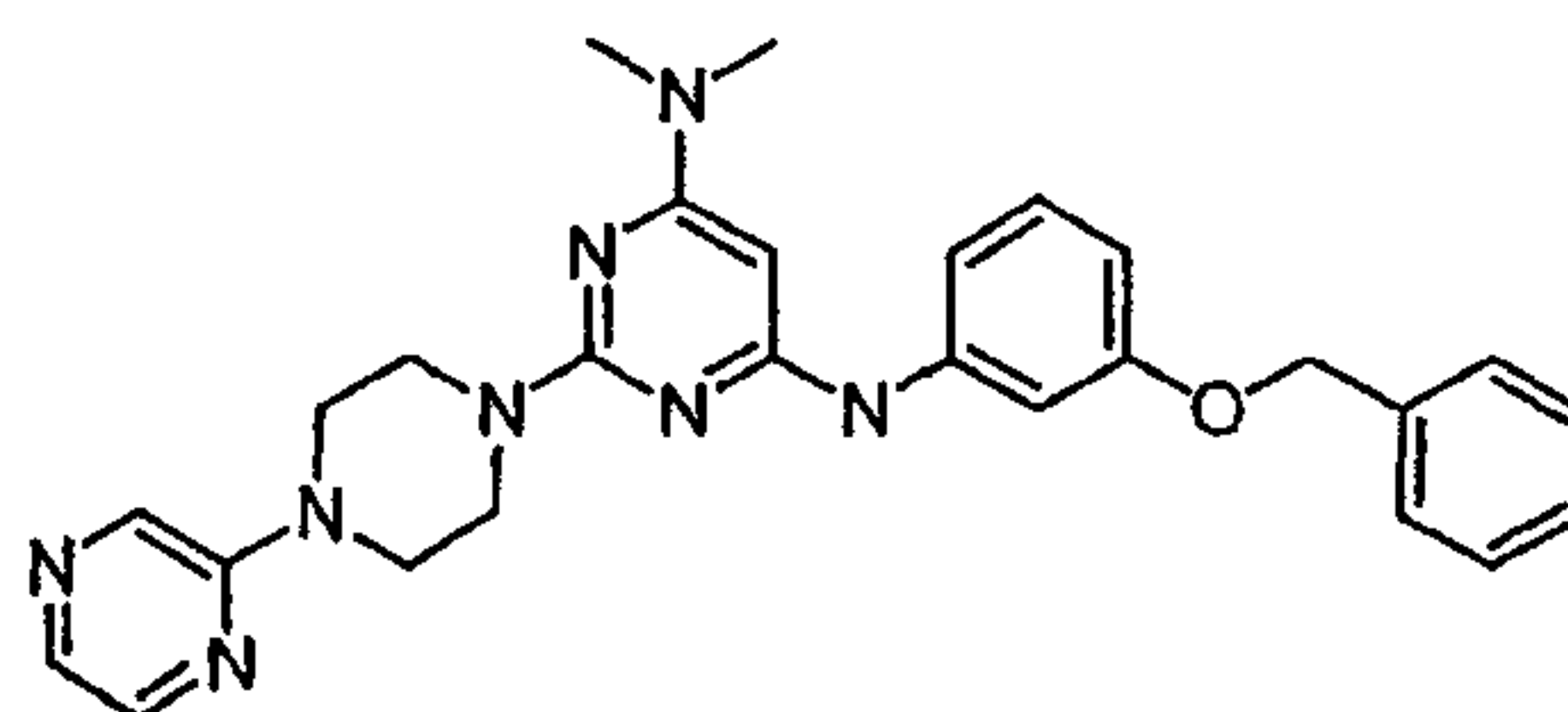
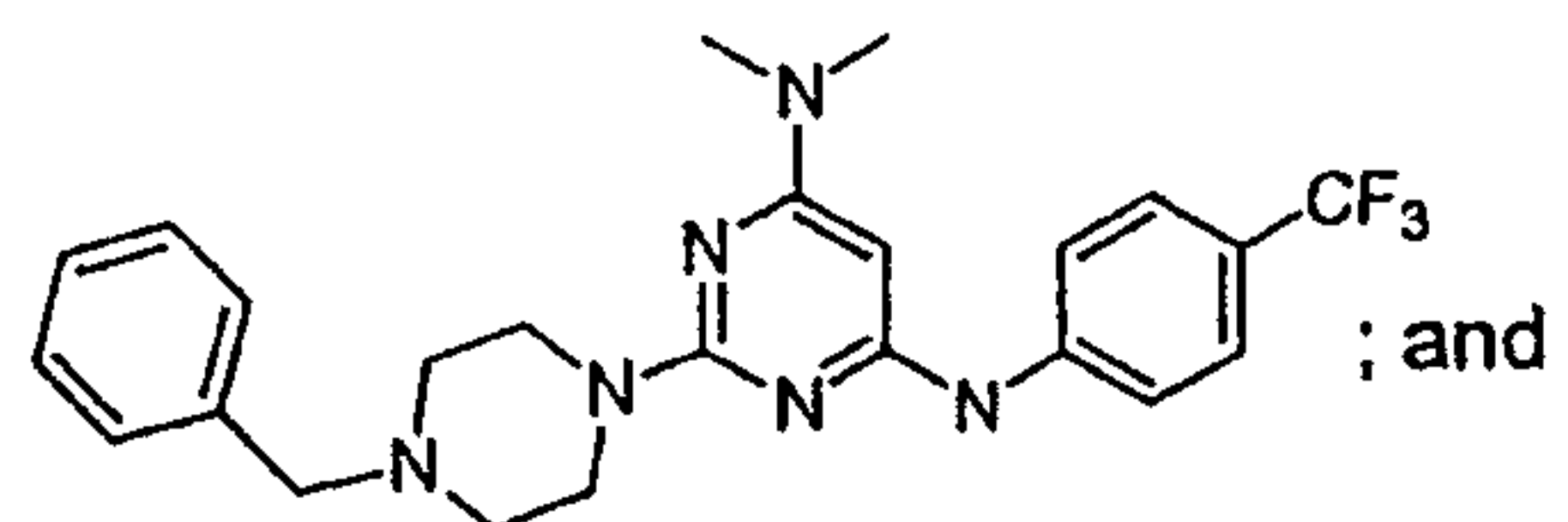
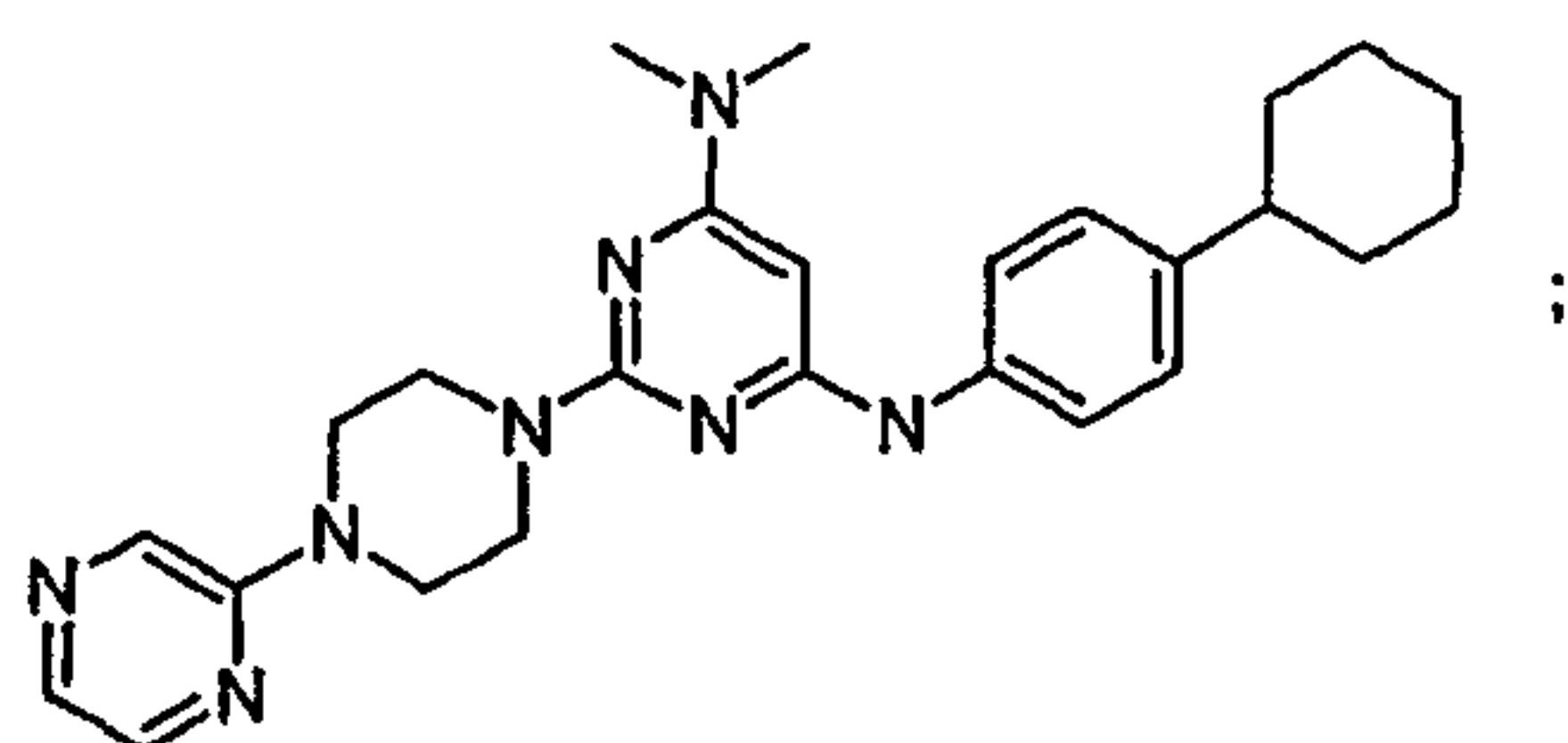
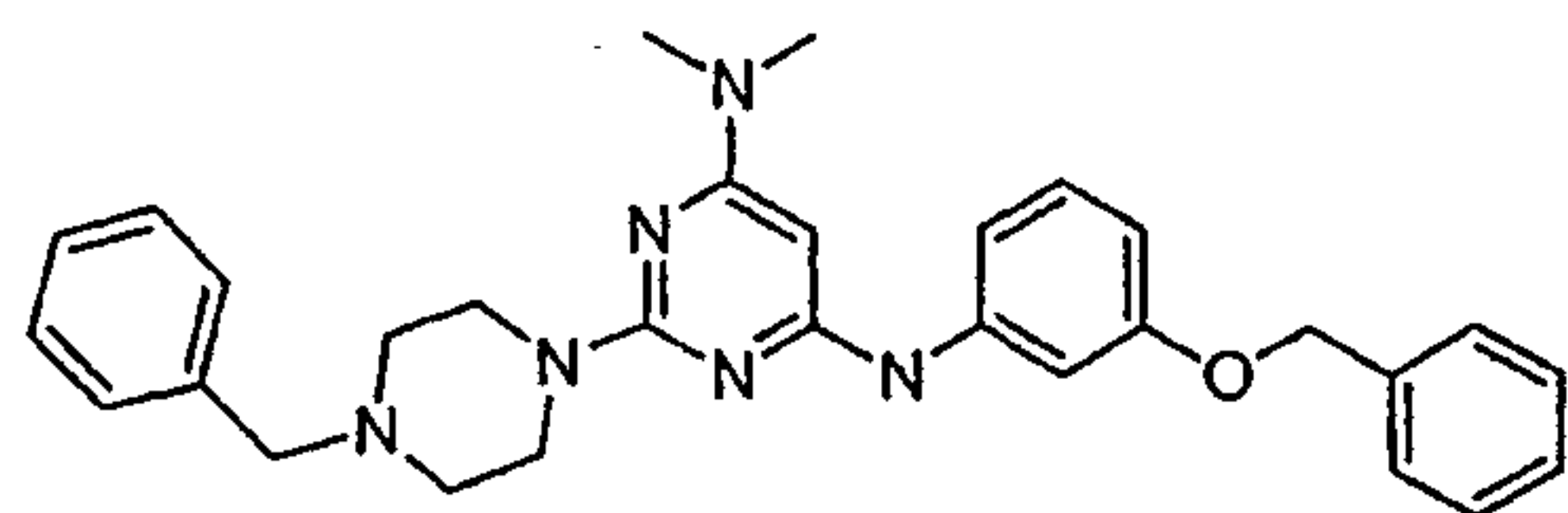
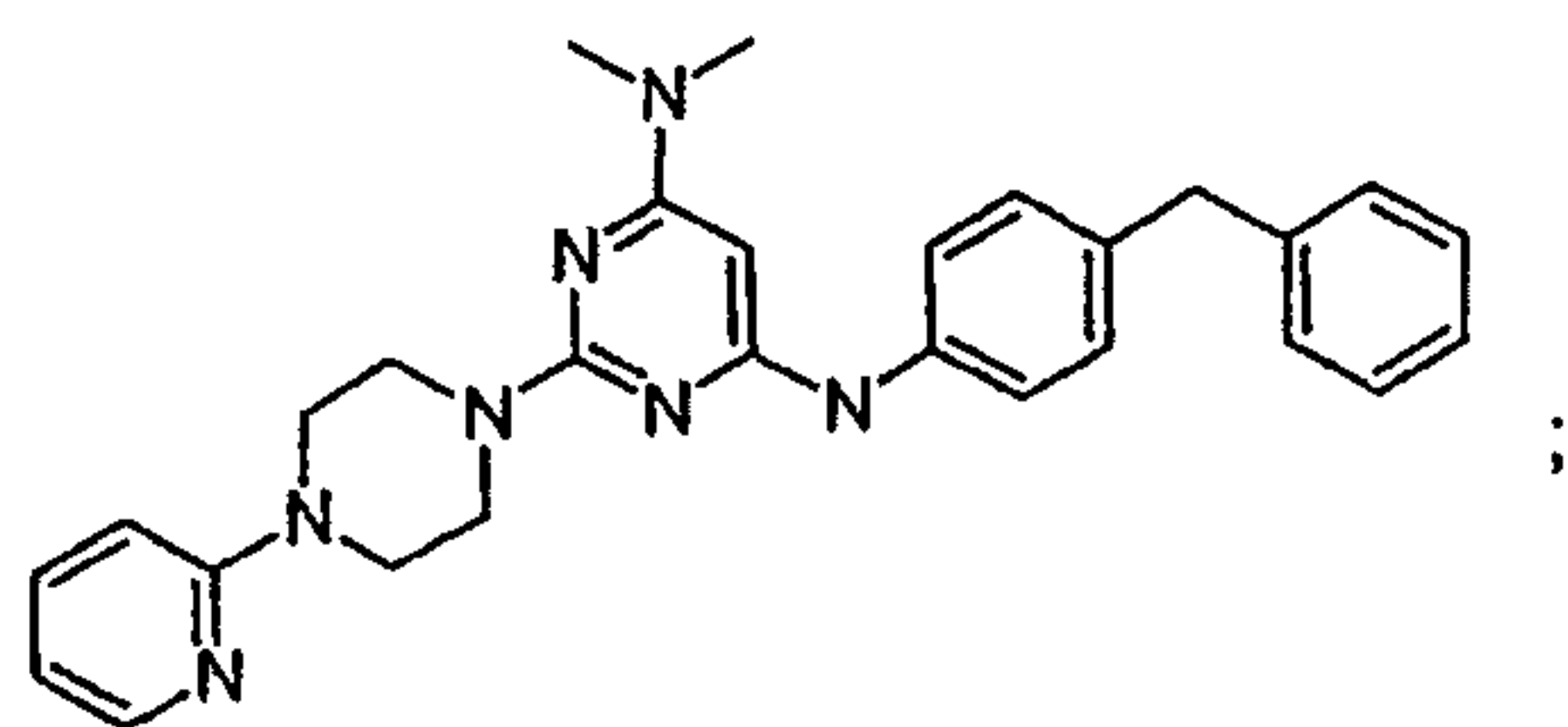
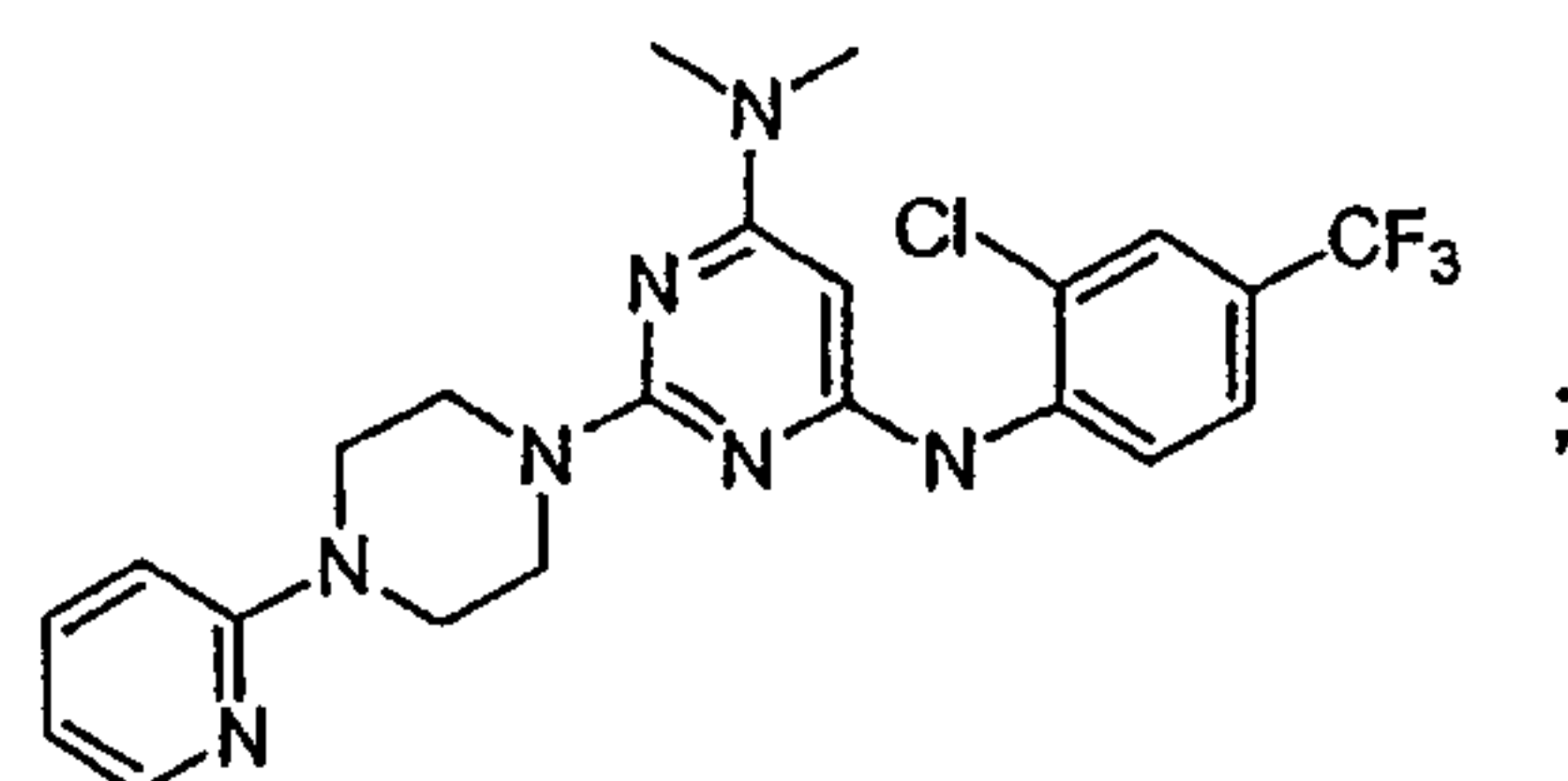
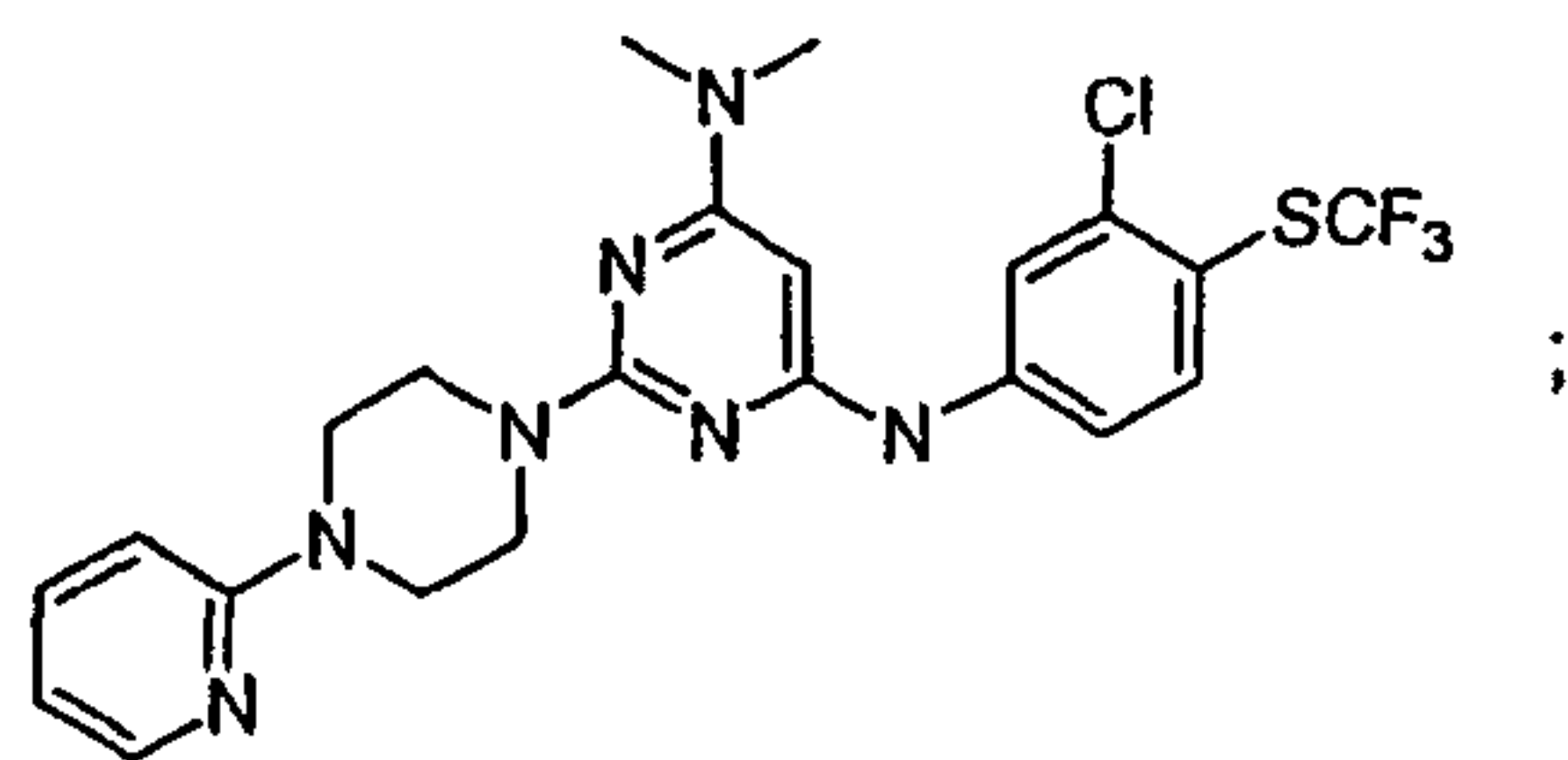
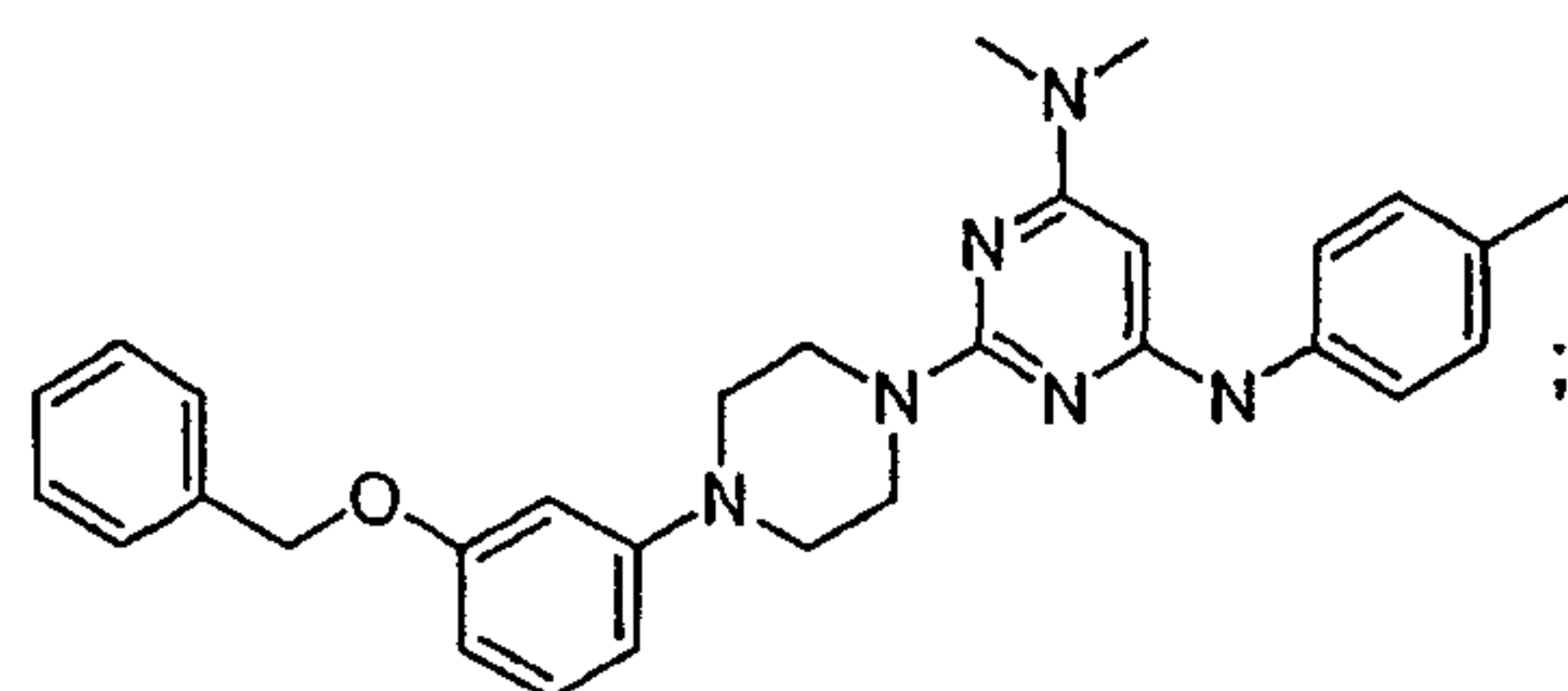
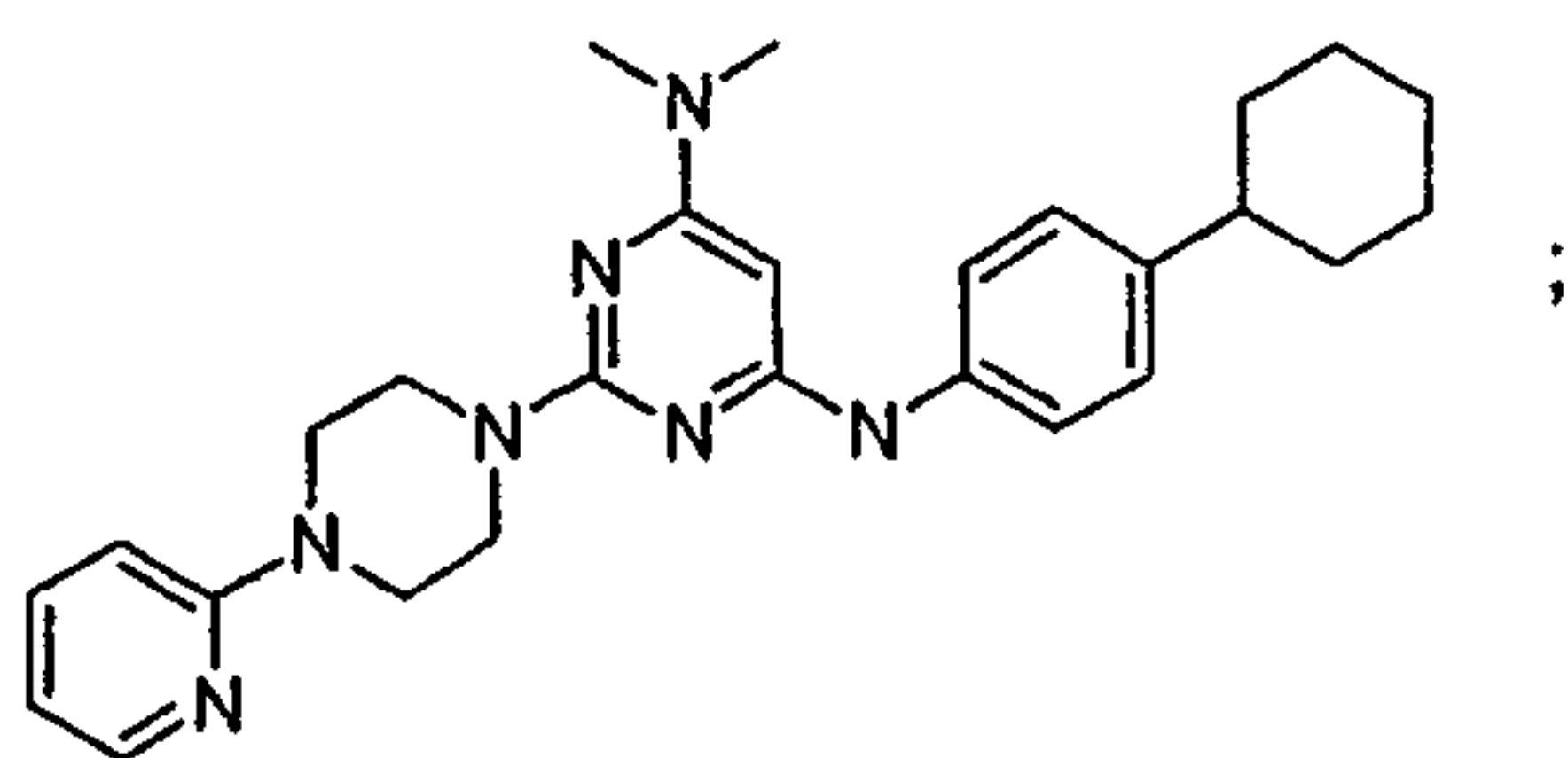


5 In one embodiment, the compound is selected from the group consisting of:

WO 02/060392

PCT/US02/04608

194



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

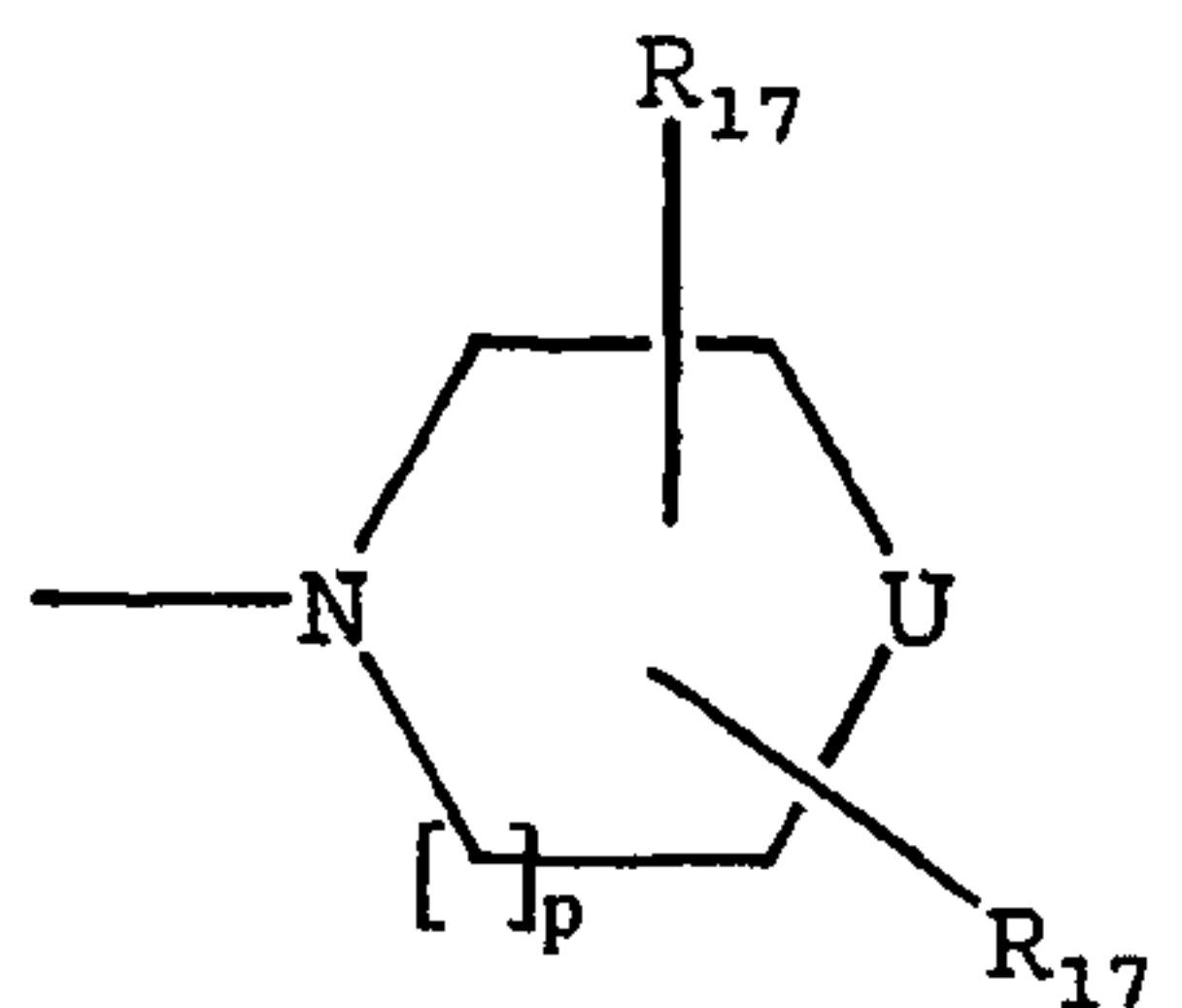
5

In one embodiment, Y is

WO 02/060392

PCT/US02/04608

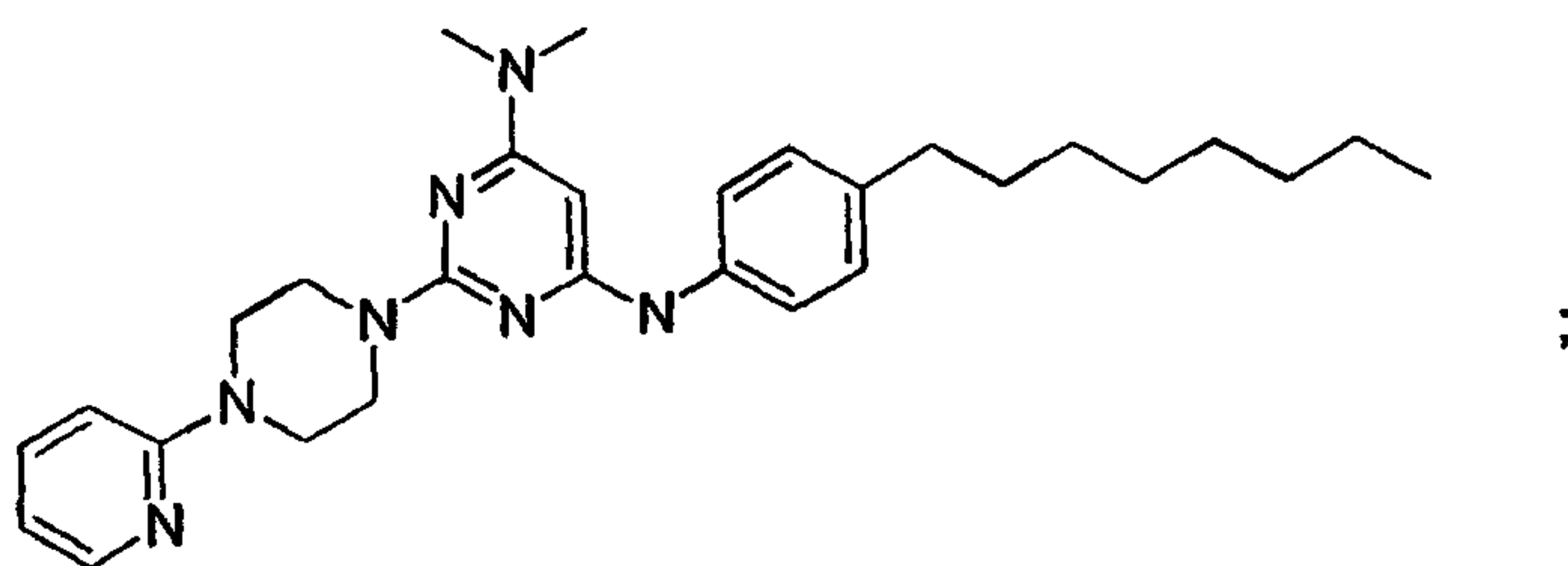
195



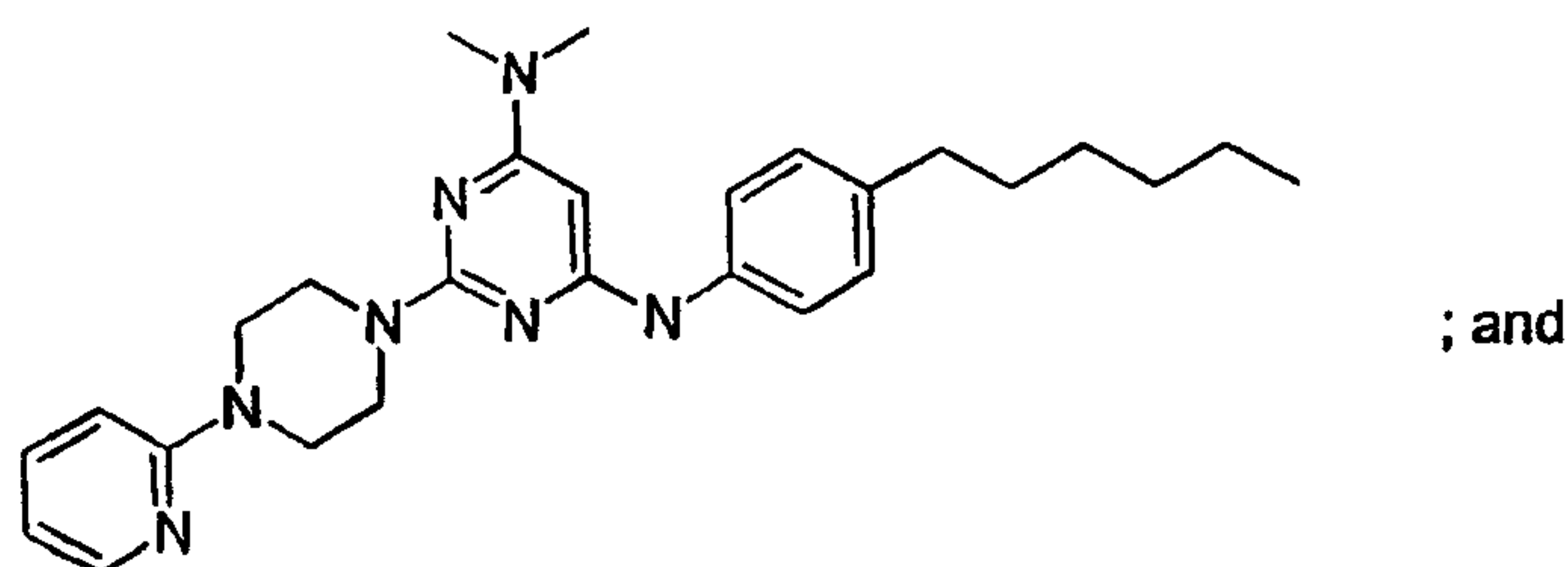
In one embodiment, R_{13} is an aryl substituted with a C_1 - C_{10} straight chained alkyl.

5

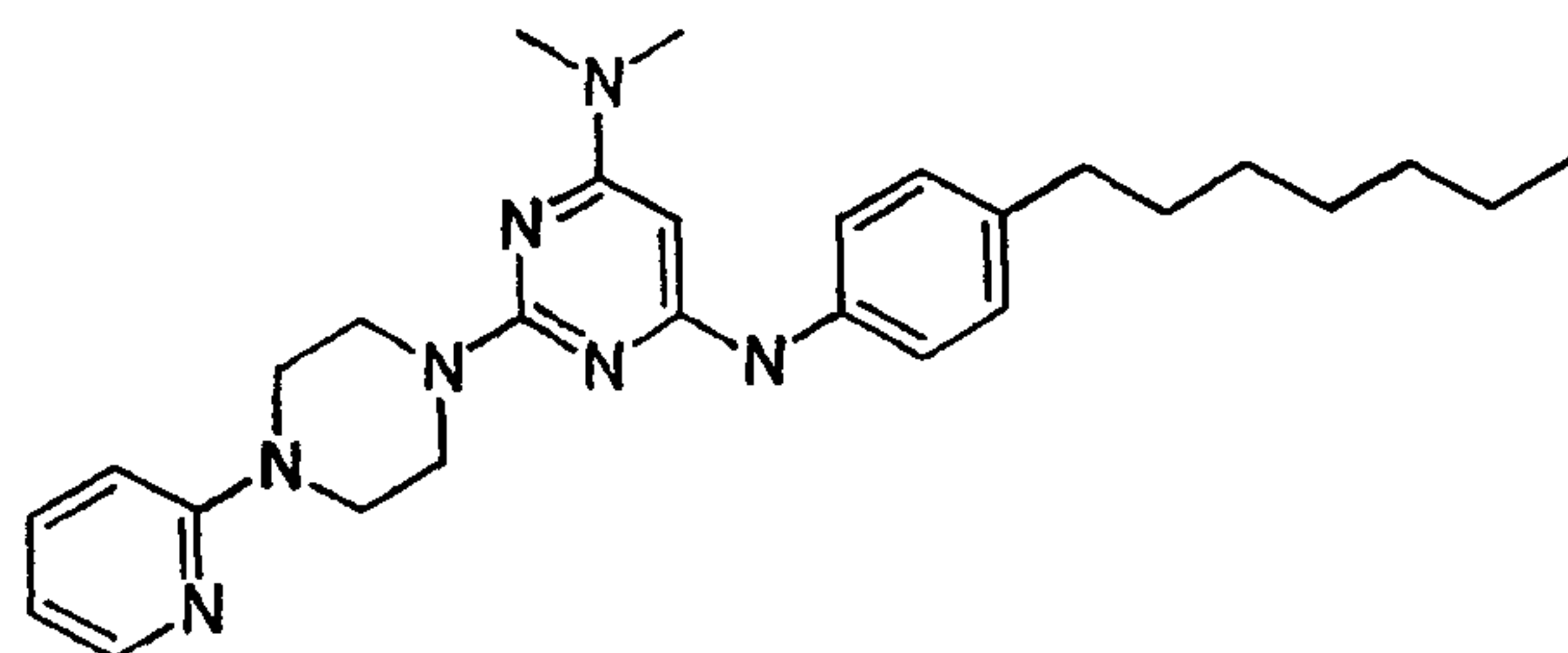
In one embodiment, the compound is selected from a group consisting of:



;

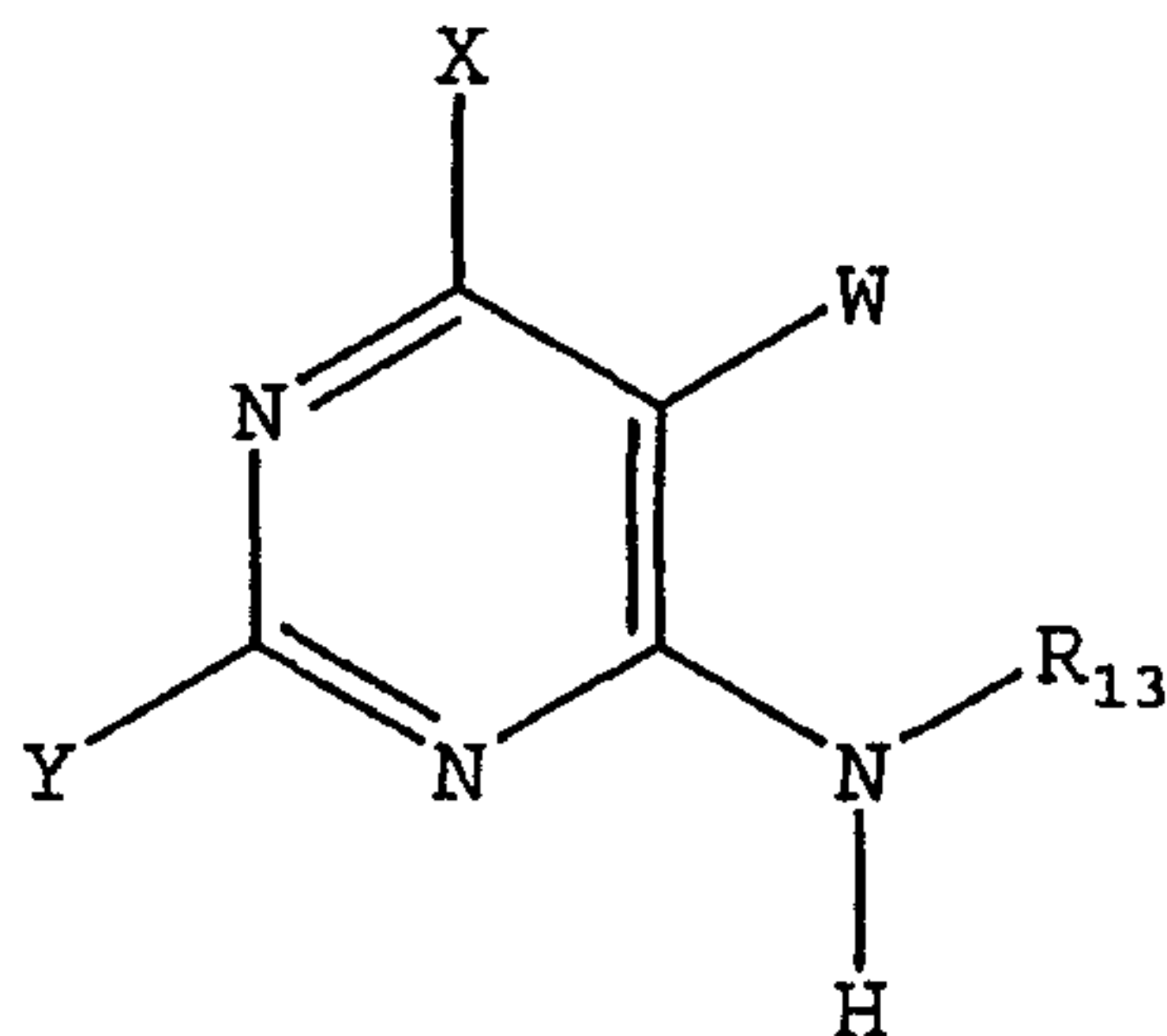


; and



10

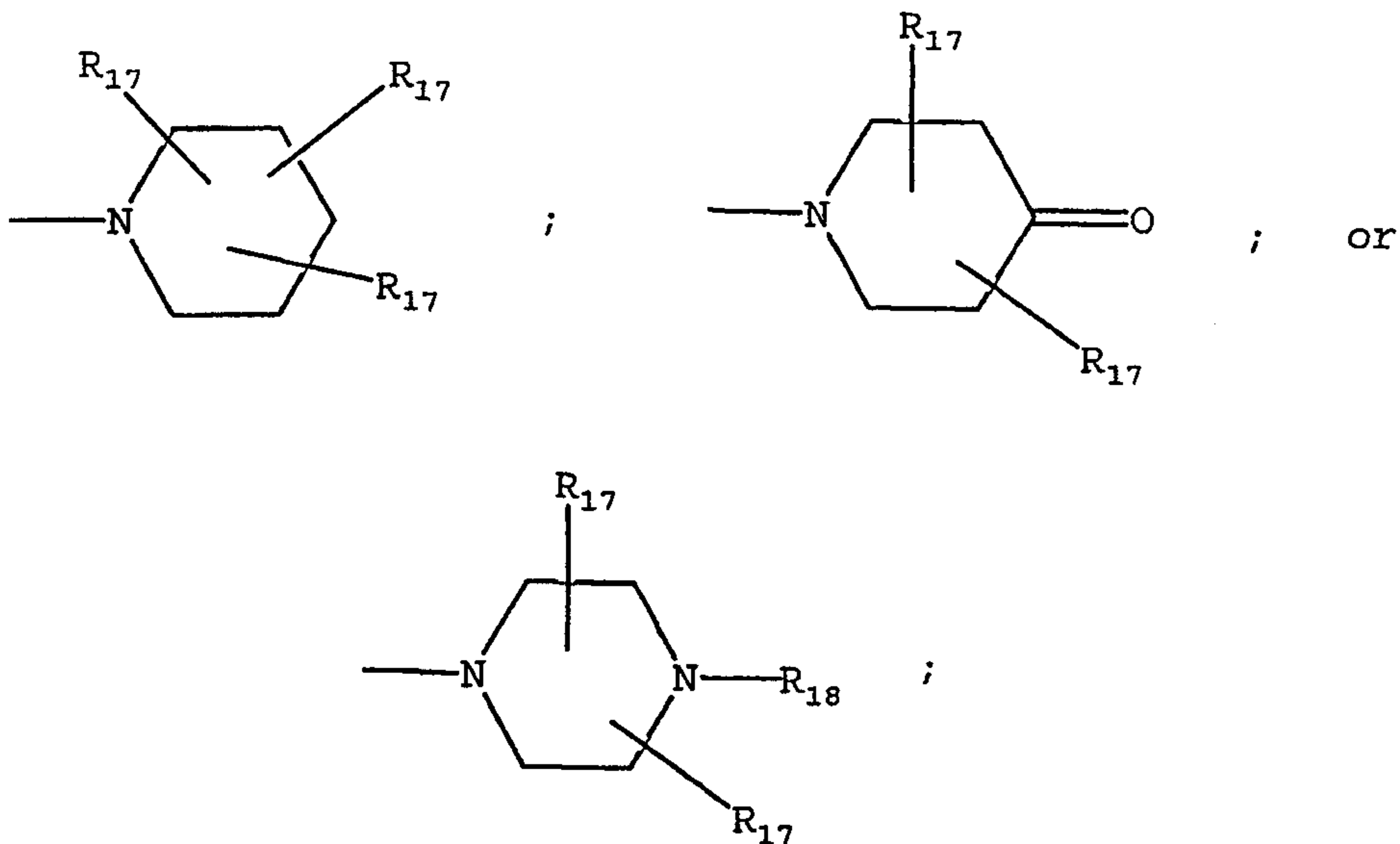
The invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure:



5

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

wherein X is; $\text{NR}_{11}\text{R}_{12}$;



10

wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl, or aryl $(\text{C}_1\text{-C}_6)$ alkyl;

wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl,

WO 02/060392

PCT/US02/04608

197

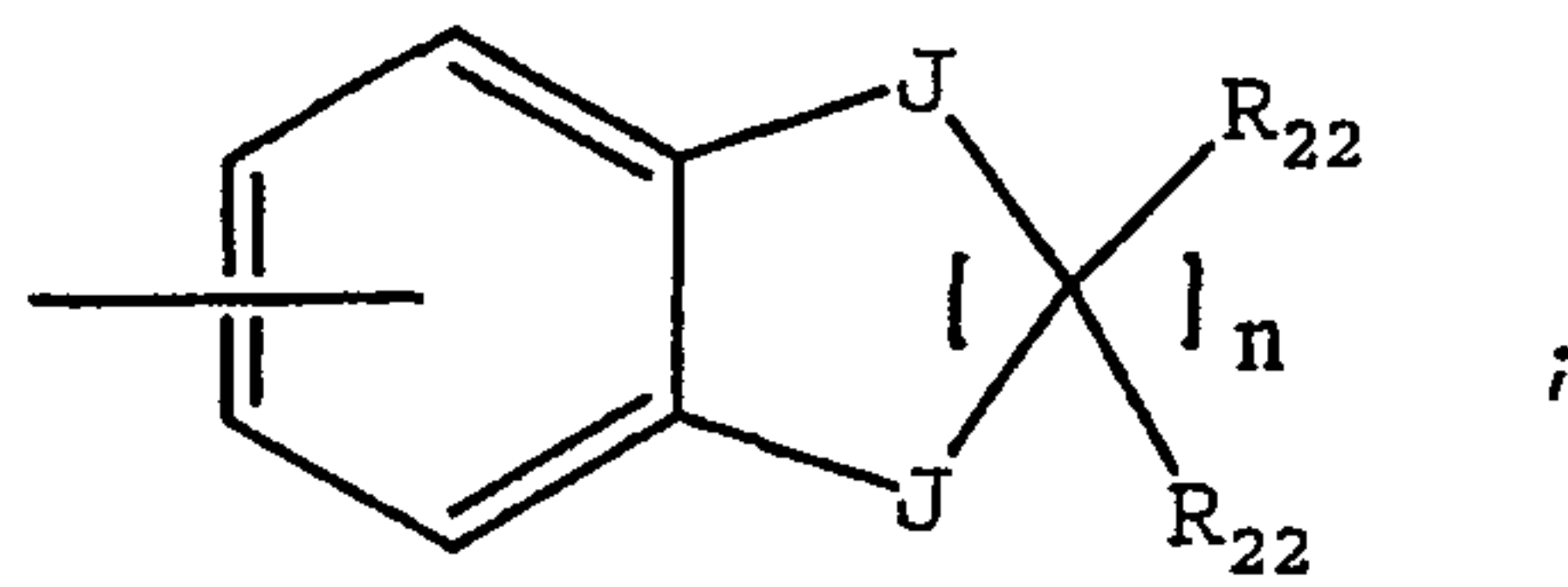
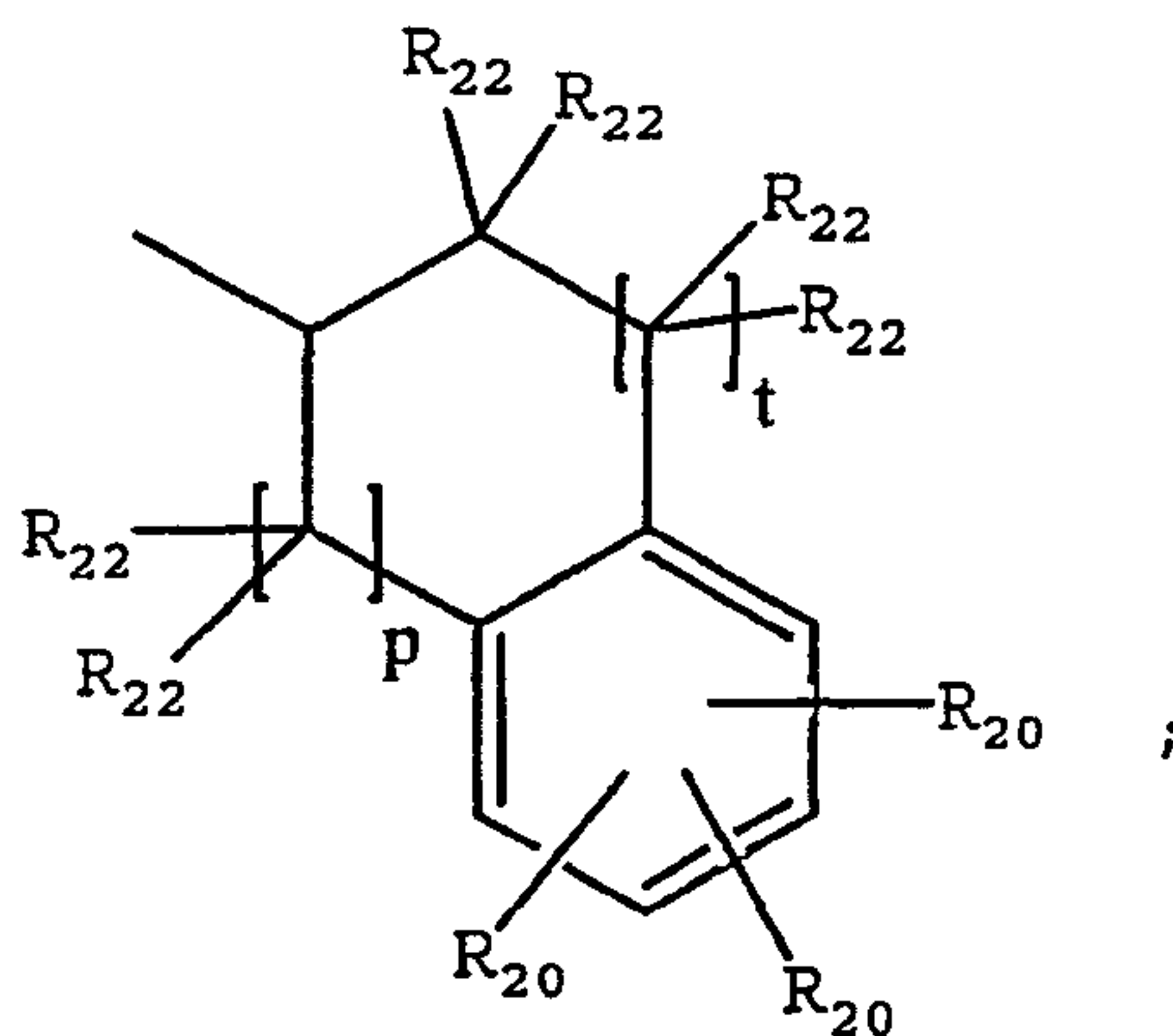
$(\text{CH}_2)_q\text{-O-}(\text{CH}_2)_m\text{-CH}_3$, or $\text{-(CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl, noradamantyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, heteroaryl, aryl, aryl($\text{C}_1\text{-C}_6$)alkyl, Q_1 or Q_2 ;

wherein aryl may be substituted with one or more $\text{C}_1\text{-C}_{10}$ straight chained or branched alkyl, aryl, heteroaryl, or $\text{N(R}_{19})\text{-Z}$;

10

wherein Q_1 is

15 wherein Q_2 is

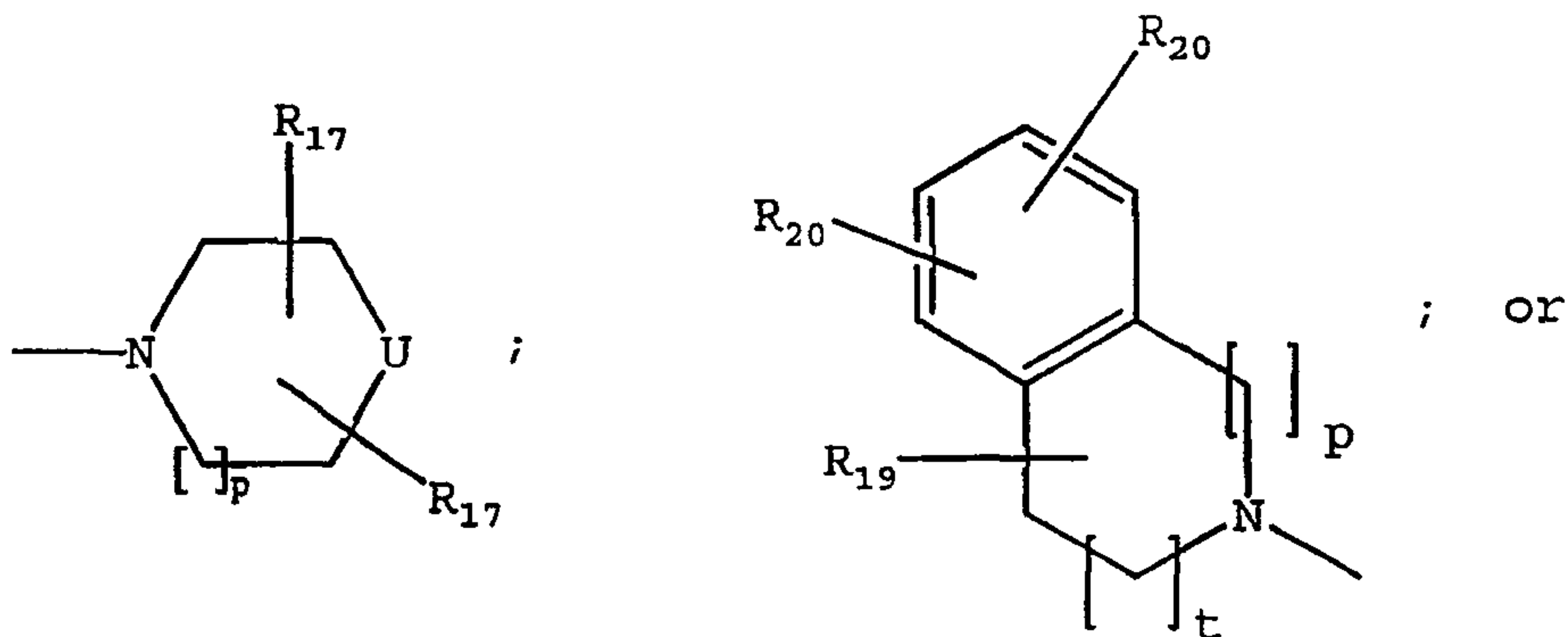
wherein each J is independently O, S, $\text{C(R}_{22})_2$ or NR_4 ;

20

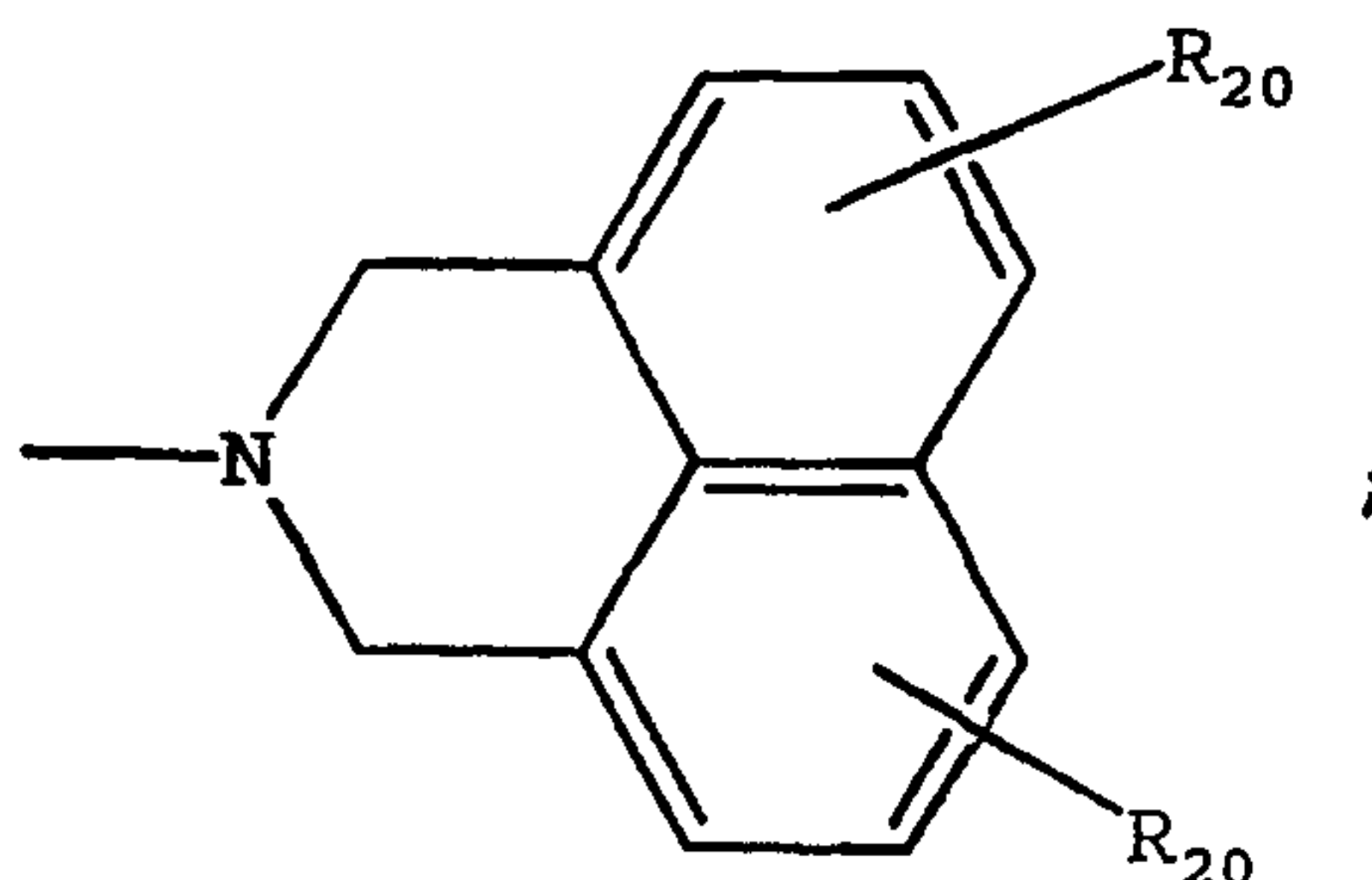
wherein R_4 is H; straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or

branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl or aryl;

wherein Y is NR₁₄R₁₅;



5



10 wherein R₁₄ is H, straight chained or branched C₁-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

wherein R₁₅ is straight chained or branched C₃-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, (C(R₁₉)₂)_mN(R₁₆)₂ or
15 (C(R₁₉)₂)_m-Z;

wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl,
20 straight chained or branched C₂-C₇ alkenyl, straight

chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -
(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

wherein each R₁₇ is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁,
5 -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or
branched C₁-C₇ alkyl, straight chained or branched C₁-C₇
monofluoroalkyl, straight chained or branched C₁-C₇
polyfluoroalkyl, straight chained or branched C₂-C₇
alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇
10 cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, -
(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15 wherein each R₁₉ is independently H, or straight chained
or branched C₁-C₆ alkyl;

wherein each R₂₀ is independently -H; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
20 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I;
-NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -
CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups
present on adjacent carbon atoms can join together to
25 form a methylenedioxy group;

wherein each R₂₁ is independently -H; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
30 C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl, or aryl(C₁-
C₆)alkyl;

WO 02/060392

PCT/US02/04608

200

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;

5

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

wherein p is an integer from 0 to 2 inclusive;

10 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 $-NSO_2R_{16}$;

15

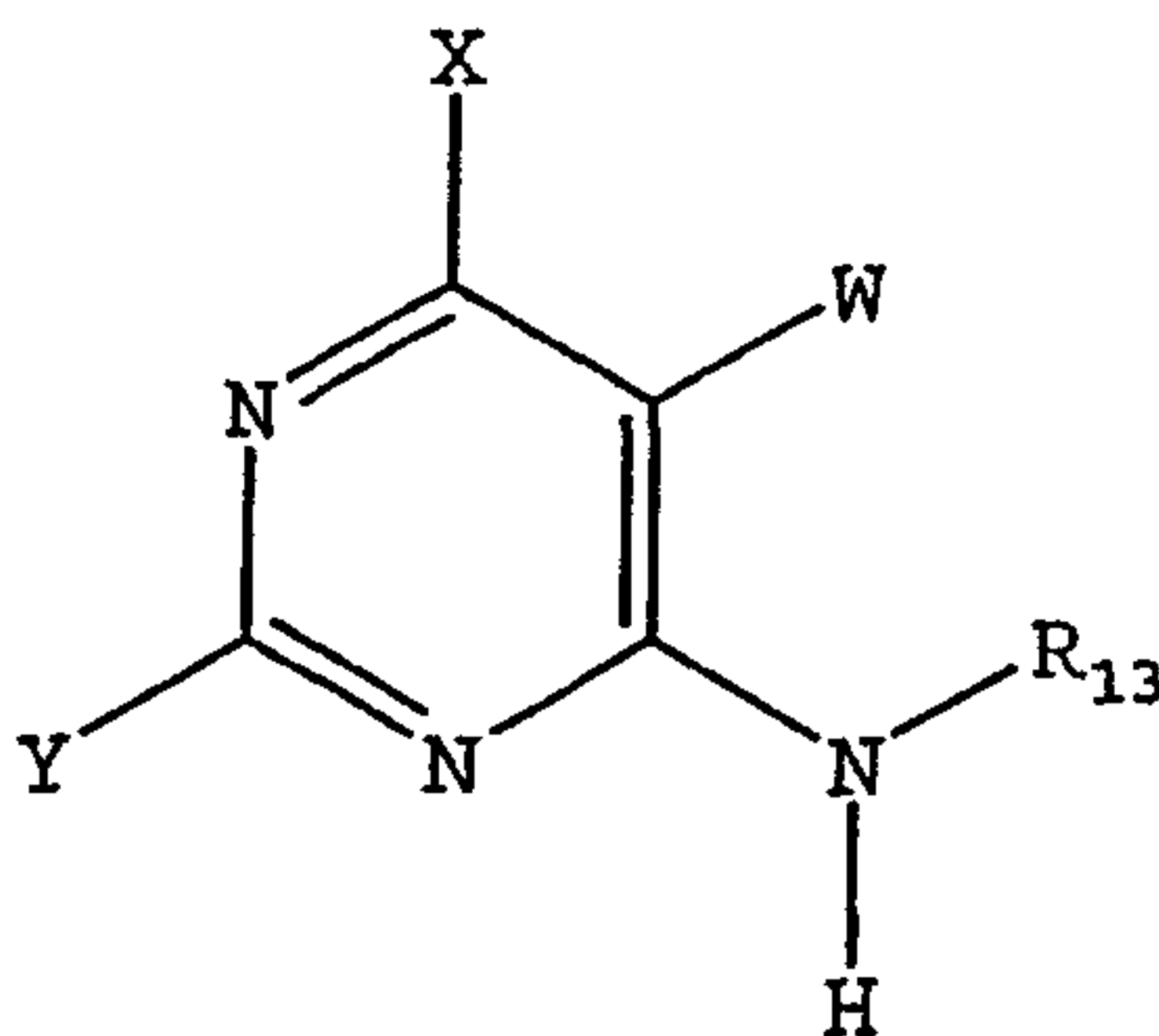
wherein Z is C_3-C_{10} cycloalkyl, C_4-C_7 cyclic ether, C_4-C_7 cyclic thioether, aryl, or heteroaryl; or

a pharmaceutically acceptable salt thereof.

20

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

25



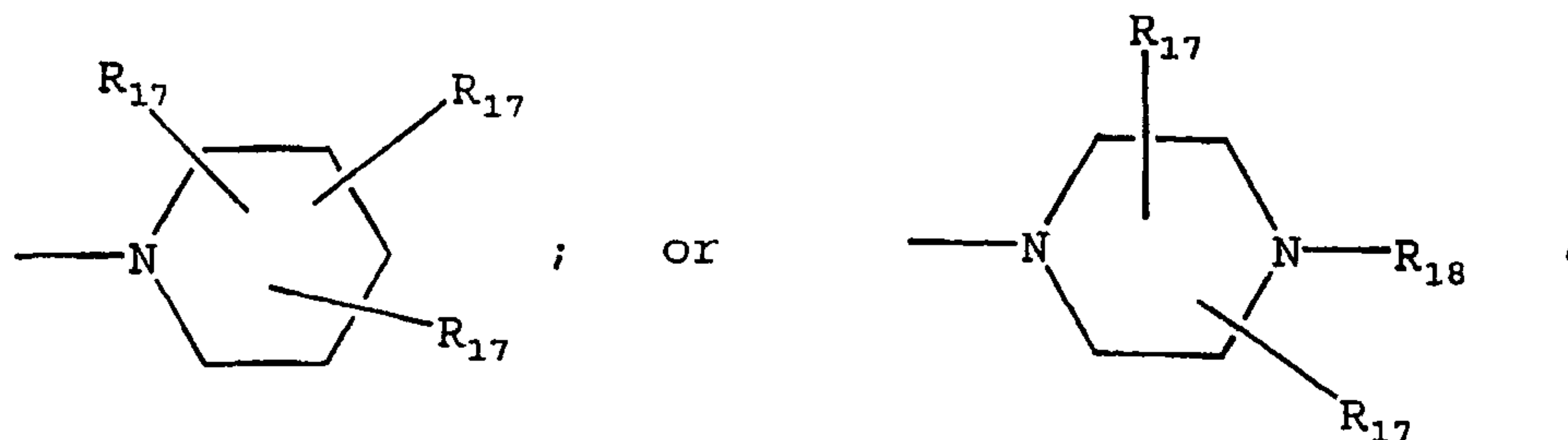
WO 02/060392

PCT/US02/04608

201

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

wherein X is $\text{NR}_{11}\text{R}_{12}$;



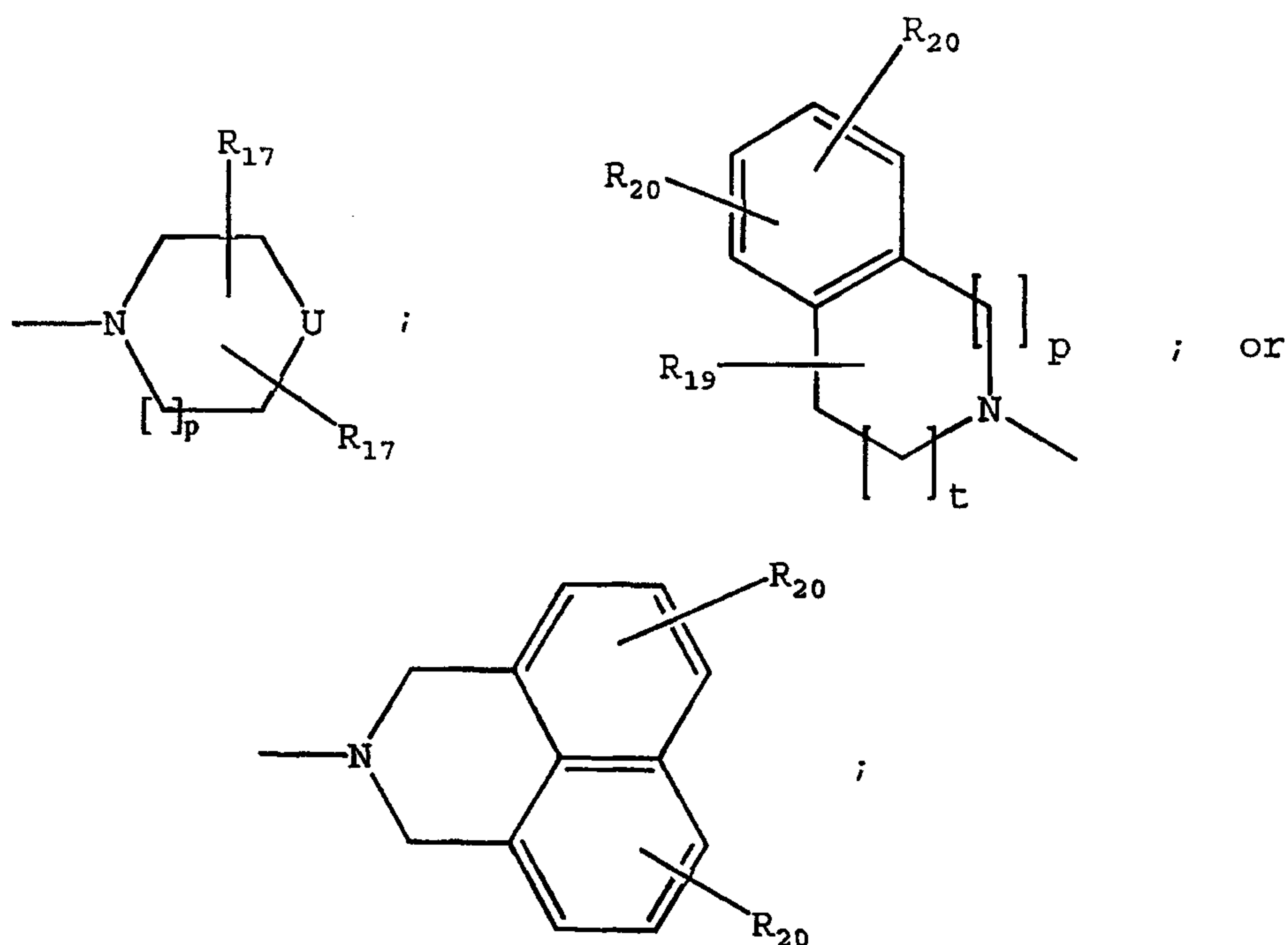
5

wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl,
10 $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $-(\text{CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

15 wherein Y is $\text{NR}_{14}\text{R}_{15}$;



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 $(C(R_{19})_2)_m-Z$;

5

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 $-NSO_2R_{16}$;

10

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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

15

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;

WO 02/060392

PCT/US02/04608

204

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

wherein p is an integer from 0 to 2 inclusive;

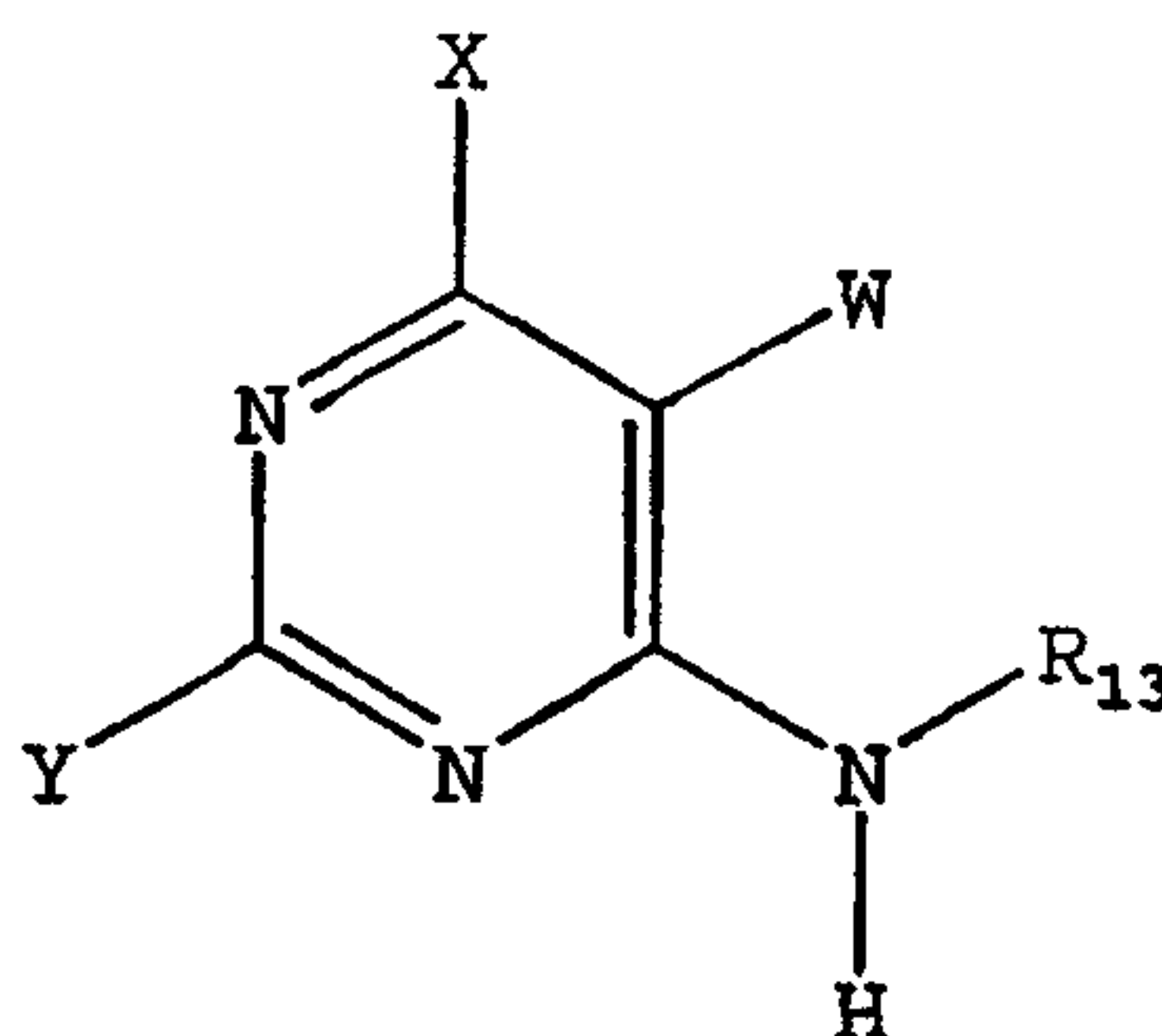
5

wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

10 a pharmaceutically acceptable salt thereof.

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



20

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

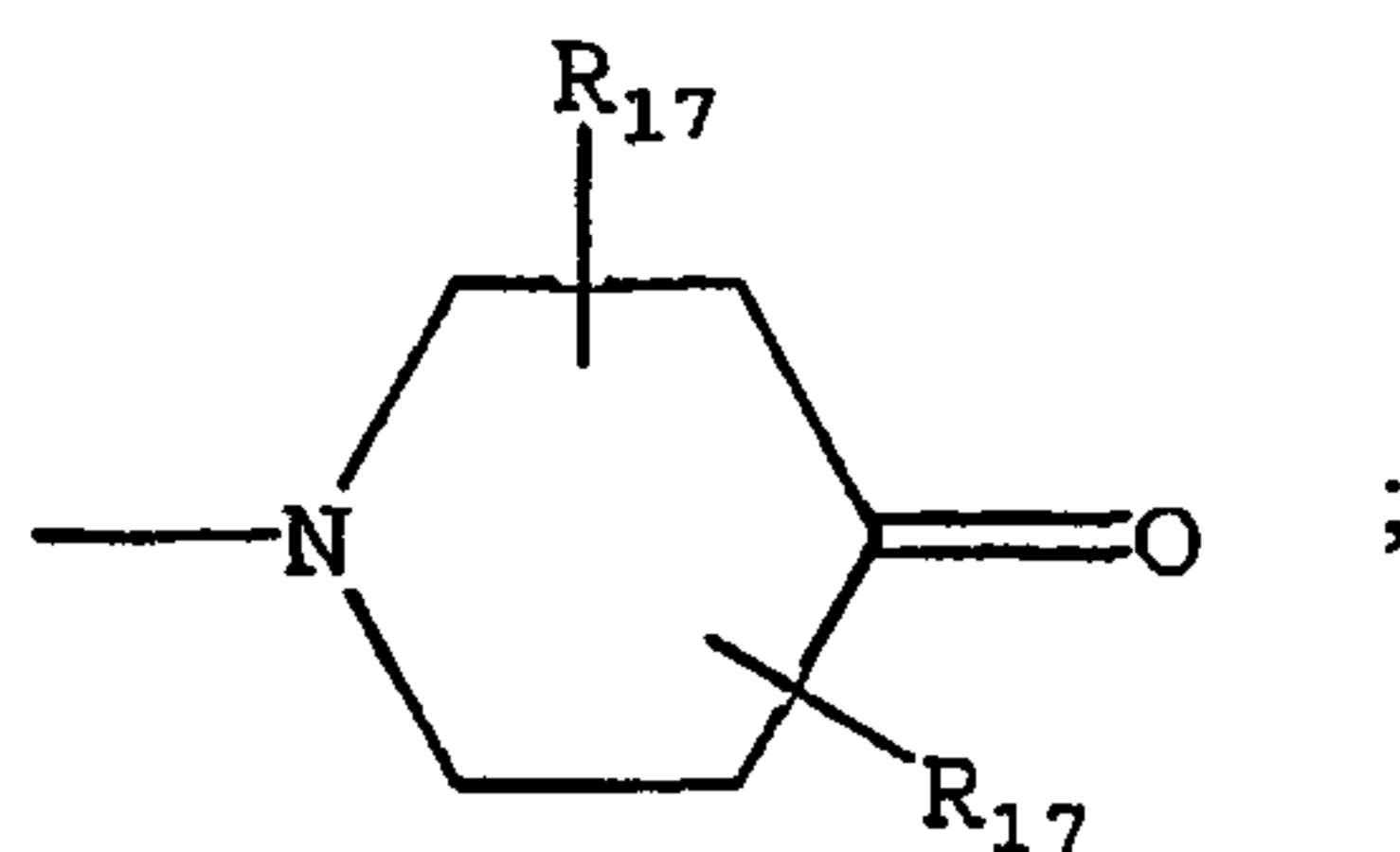
wherein X is N(CH₃)₂ or

25

WO 02/060392

PCT/US02/04608

205

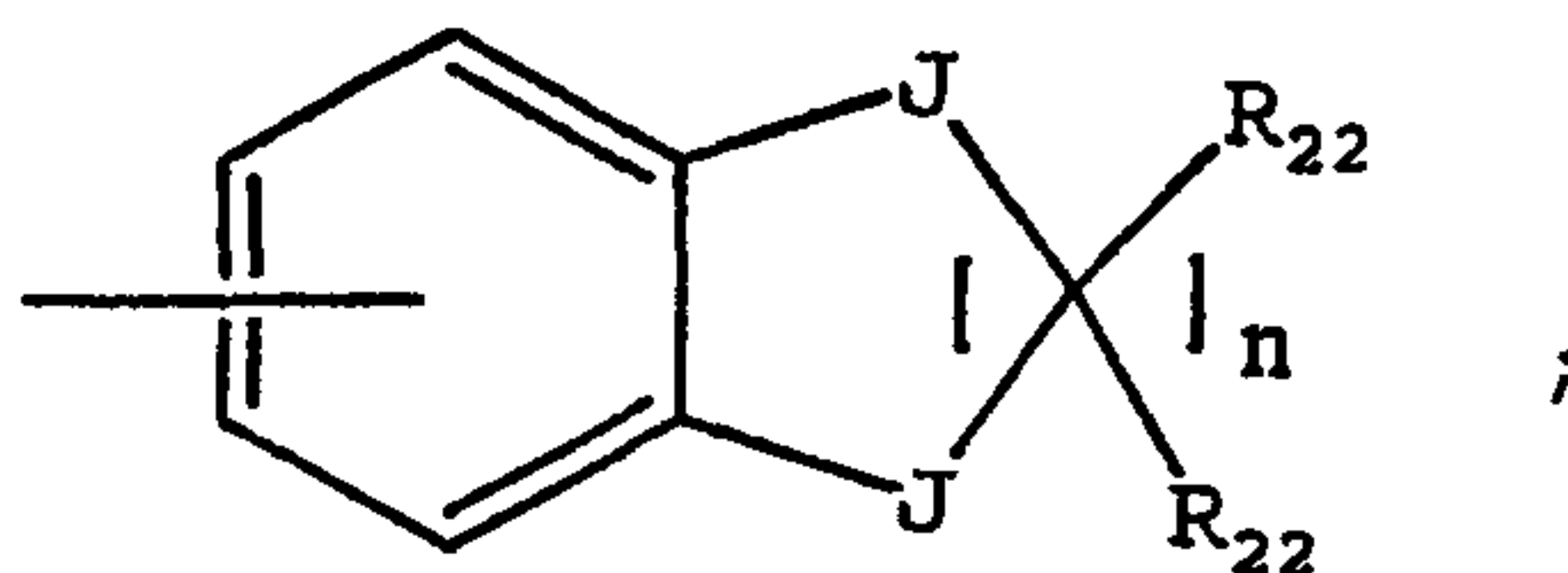


wherein R₁₃ is an aryl, adamantyl, noradamantyl, C₃-C₁₀ cycloalkyl, heteroaryl, Q₁ or Q₂;

5

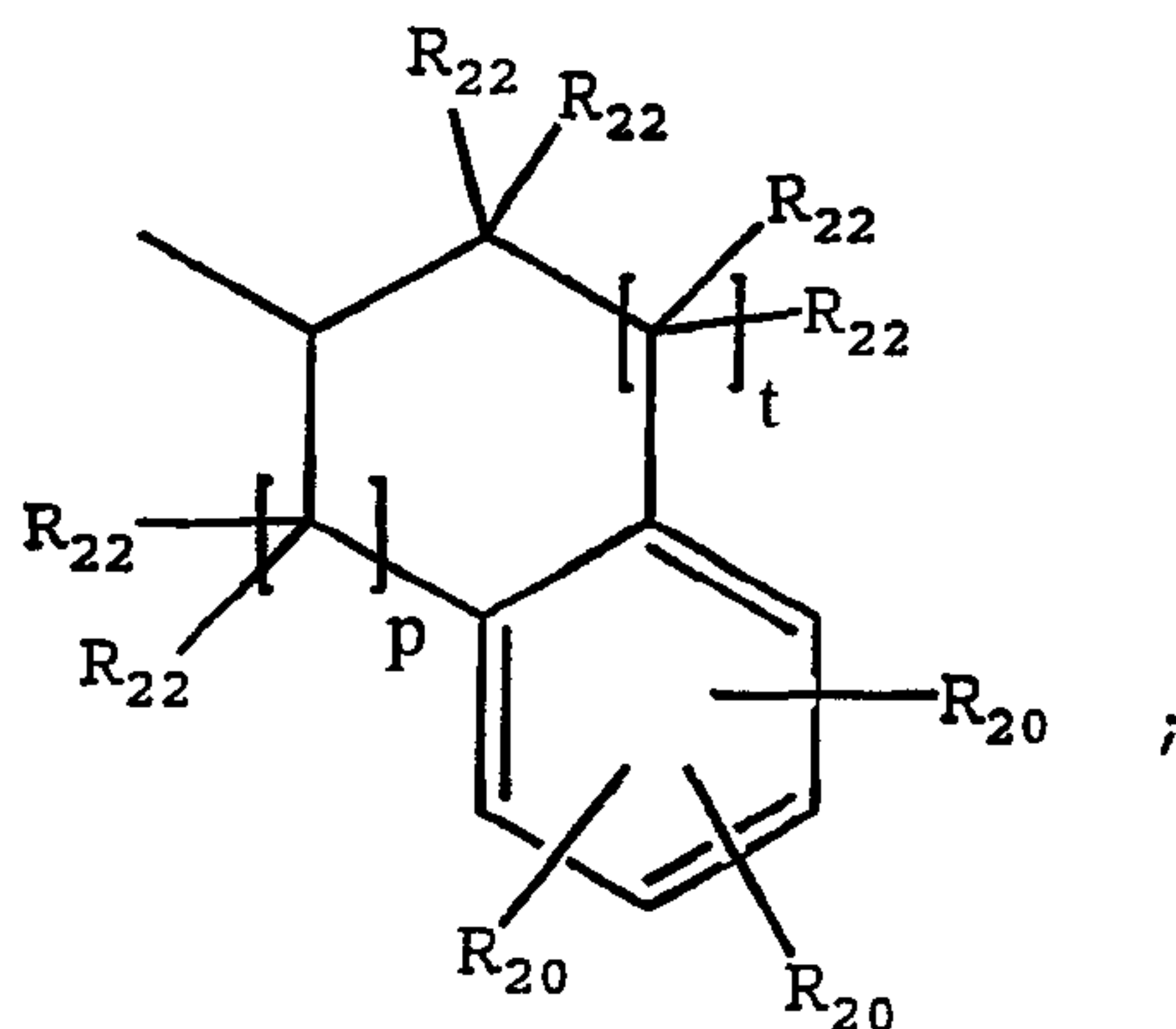
wherein aryl may be substituted with one or more C₁-C₁₀ straight chained or branched alkyl, aryl, heteroaryl, or N(R₁₉)-Z;

10 wherein Q₁ is



wherein Q₂ is

15



wherein each J is independently O, S, C(R₂₂)₂ or NR₄;

WO 02/060392

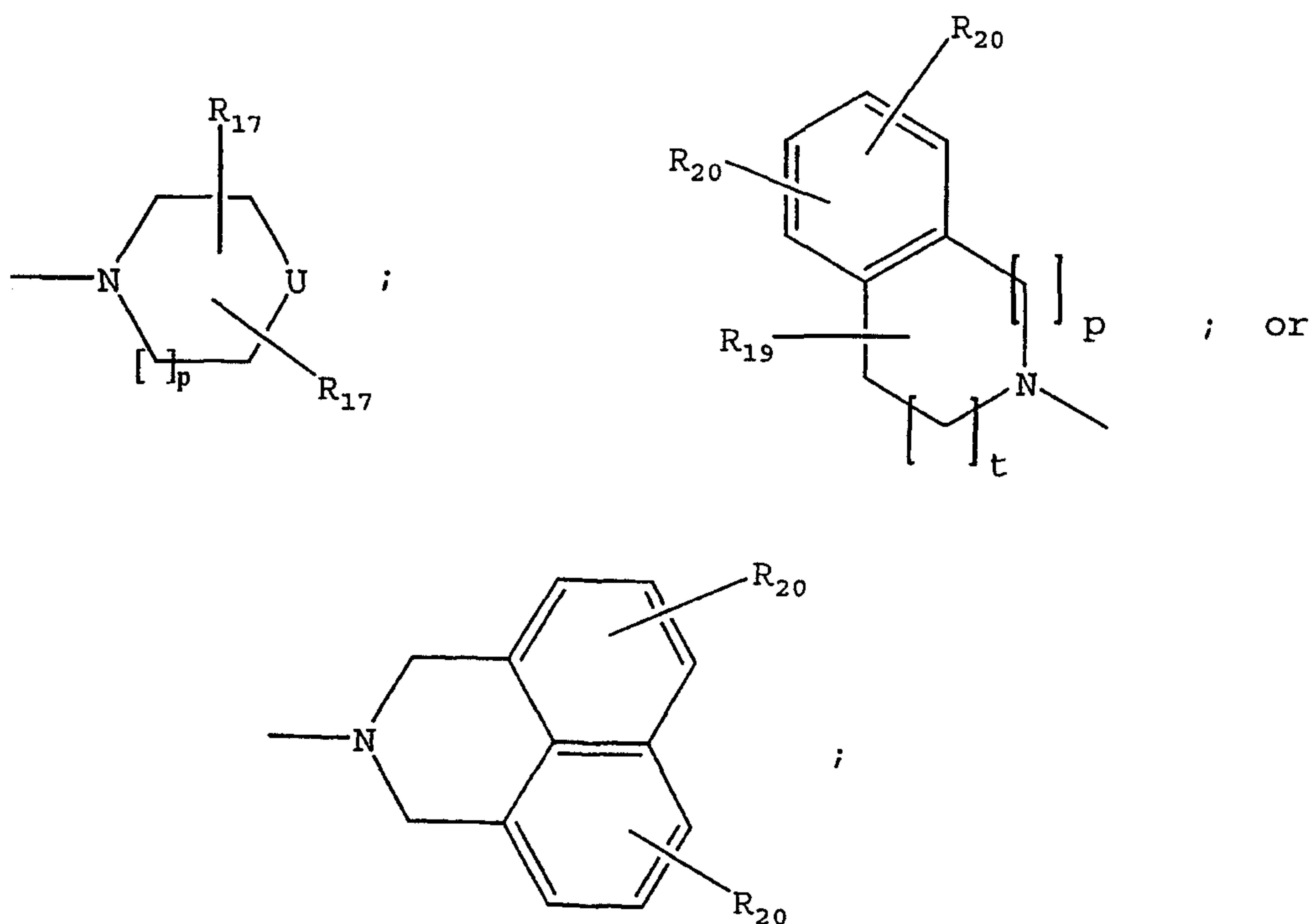
PCT/US02/04608

206

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;

5

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



- 10 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 $(C(R_{19})_2)_m-Z$;

15

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, 5 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; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$, 10 $-NCOR_{21}$, $-N(R_{21})_2$, $-CON(R_{21})_2$, $-COOR_{21}$, 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 15 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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

20 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; 25 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 30 form a methylenedioxy group;

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

branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-
C₆)alkyl;

5

wherein each R₂₂ is independently H, F, Cl or C₁-C₄
straight chained or branched alkyl;

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

10

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

wherein p is an integer from 0 to 2 inclusive;

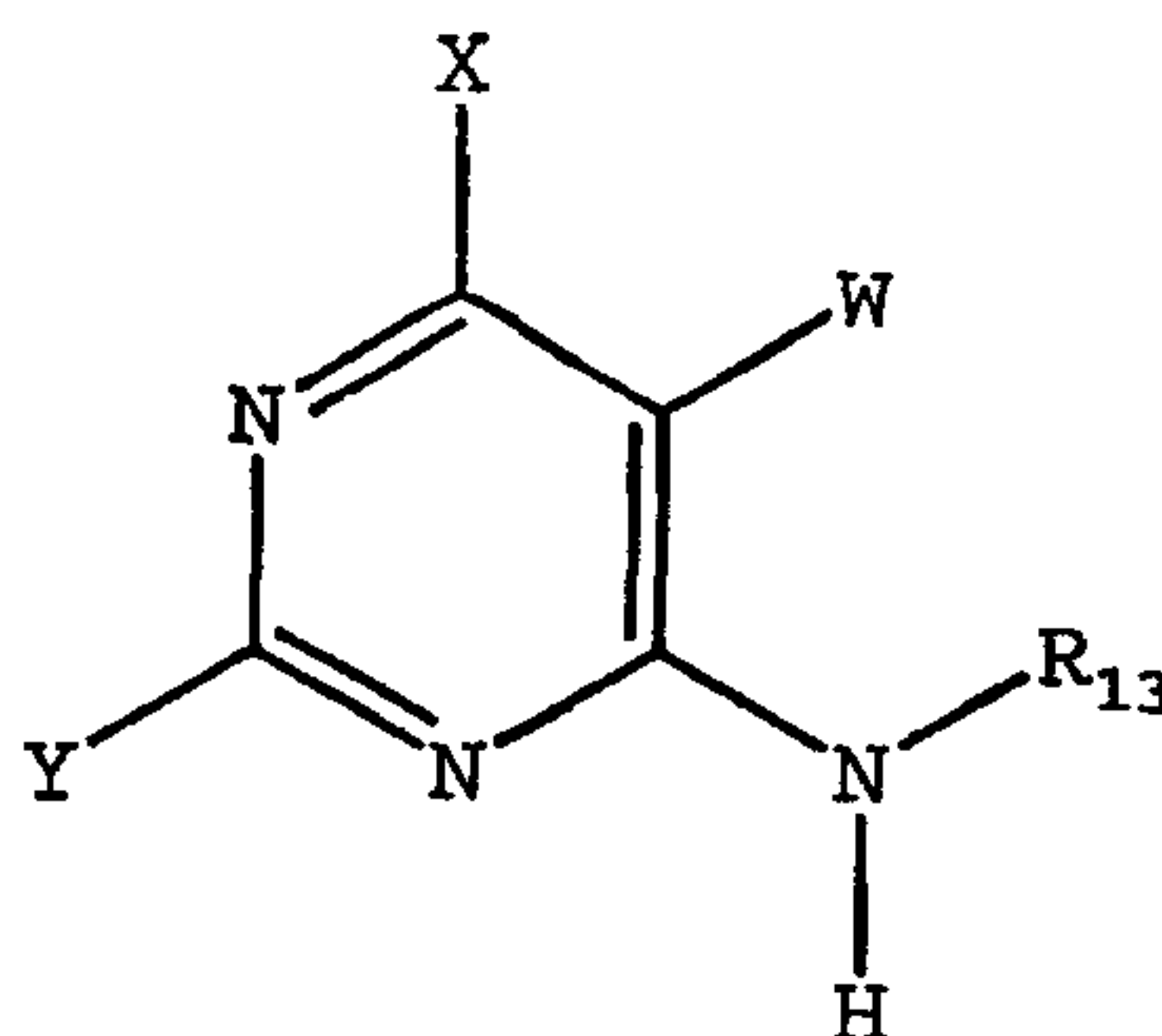
15 wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

20

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



25

WO 02/060392

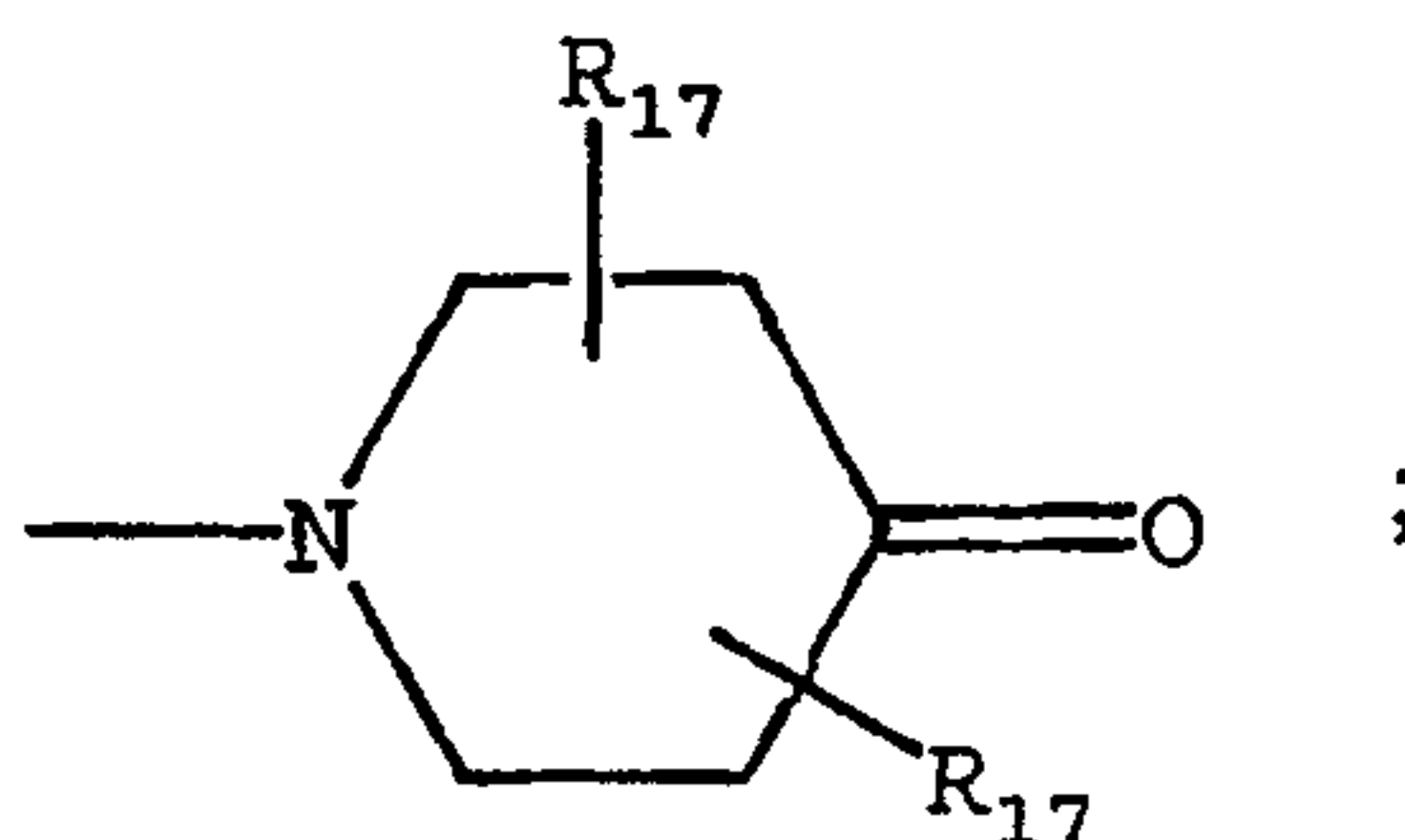
PCT/US02/04608

209

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

5

wherein X is $N(CH_3)_2$ or



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

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

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

20 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, 25 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; $-OR_{21}$, $-OCOR_{21}$, $-COR_{21}$,

-NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

wherein each R₁₉ is independently H, or straight chained or branched C₁-C₆ alkyl;

10

wherein each R₂₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-C₆)alkyl;

15

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

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

20

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

a pharmaceutically acceptable salt thereof.

25 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, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇

30

polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, -N(R₂₁)₂, -OR₂₁, -COR₂₁, -CO₂R₂₁, -CON(R₂₁)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

5

As used in the present invention, the term "cycloalkyl" includes, C₃-C₇ cycloalkyl moieties which may be substituted with one or more of the following: -F, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight
 10 chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇
 15 cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

As used in the present invention, the term "cyclohexyl" includes, cyclohexyl groups which may be substituted with
 20 one or more of the following: -F, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇
 25 alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

As used in the present invention, the term "cycloalkenyl" includes, C₅-C₇ cycloalkenyl moieties which may be
 30 substituted with one or more of the following: -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched C₁-C₇

alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

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, indolizinyll, 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, -NO₂, -CN,

straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

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, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

25

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.

30

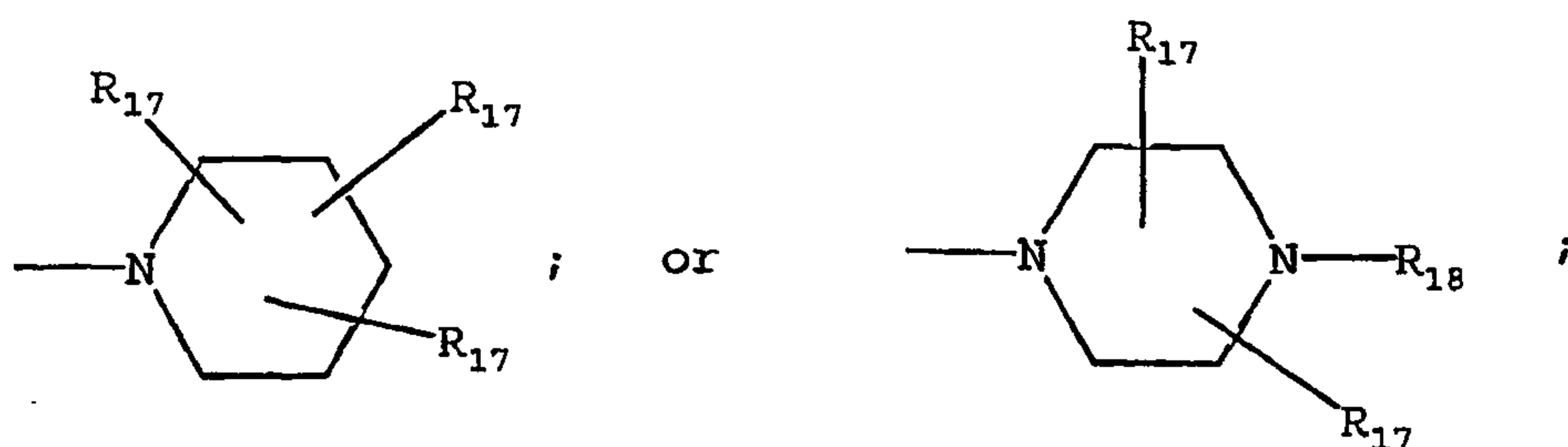
WO 02/060392

PCT/US02/04608

214

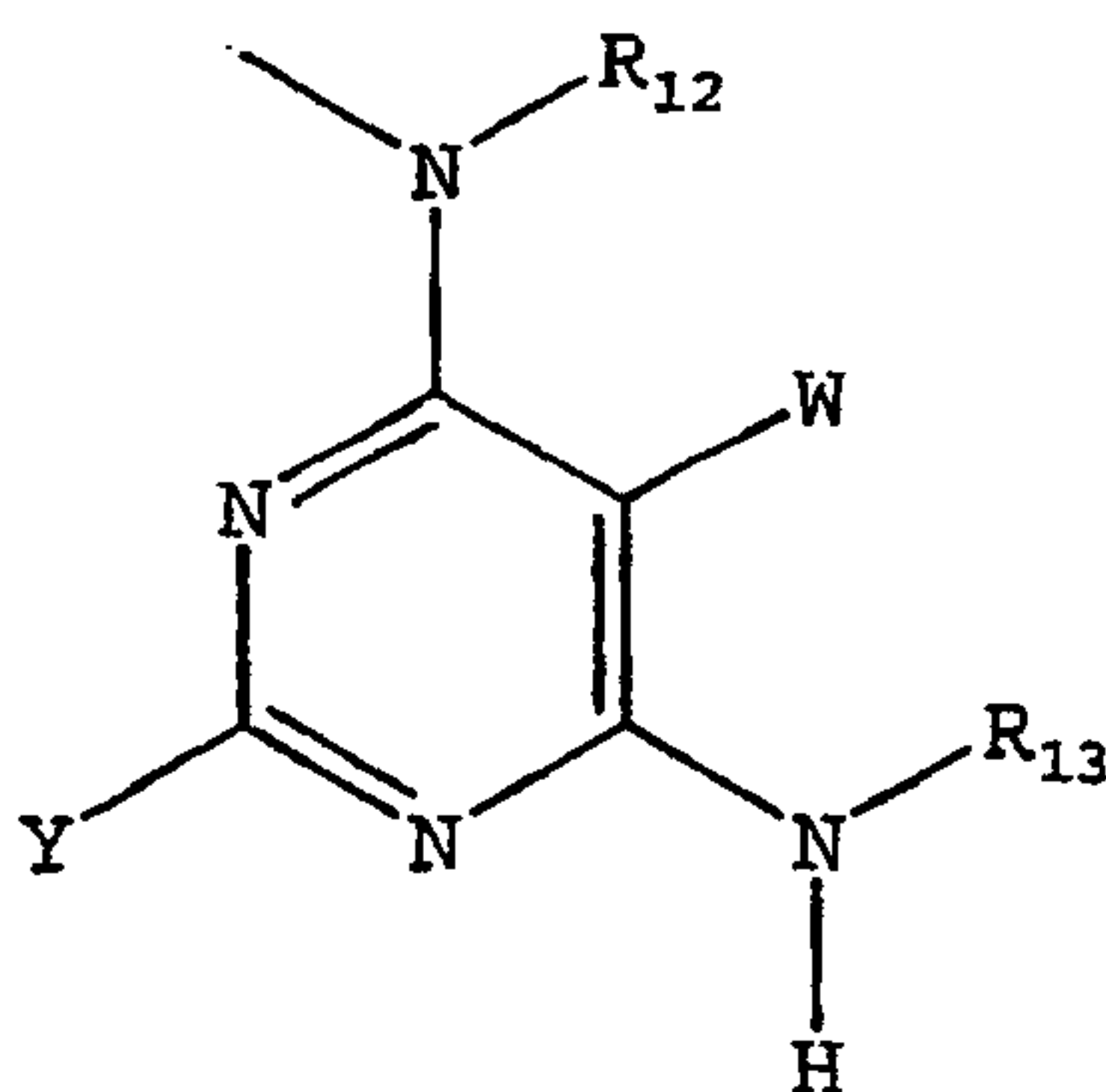
In one embodiment of any of the pharmaceutical compositions described herein, the compound can be administered orally.

5 In one embodiment, X is:



In one embodiment, X is $\text{NR}_{11}\text{R}_{12}$ and R_{11} is H or straight
15 chained or branched $\text{C}_1\text{-C}_7$ alkyl.

In one embodiment, the compound has the structure:



WO 02/060392

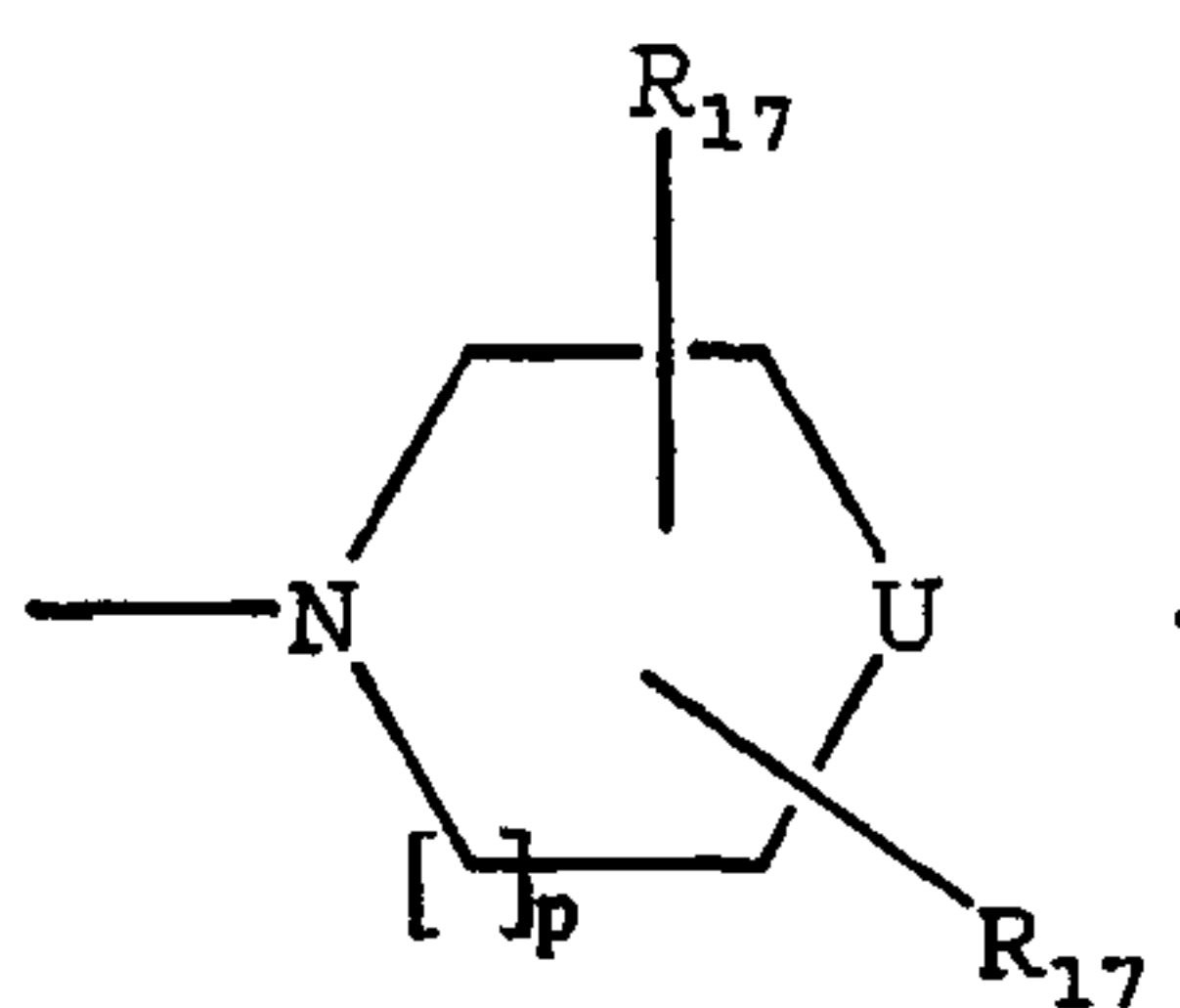
PCT/US02/04608

215

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
5 C_1-C_6 alkyl or $(CH_2)_q-O-(CH_2)_m-CH_3$.

In one embodiment, Y is



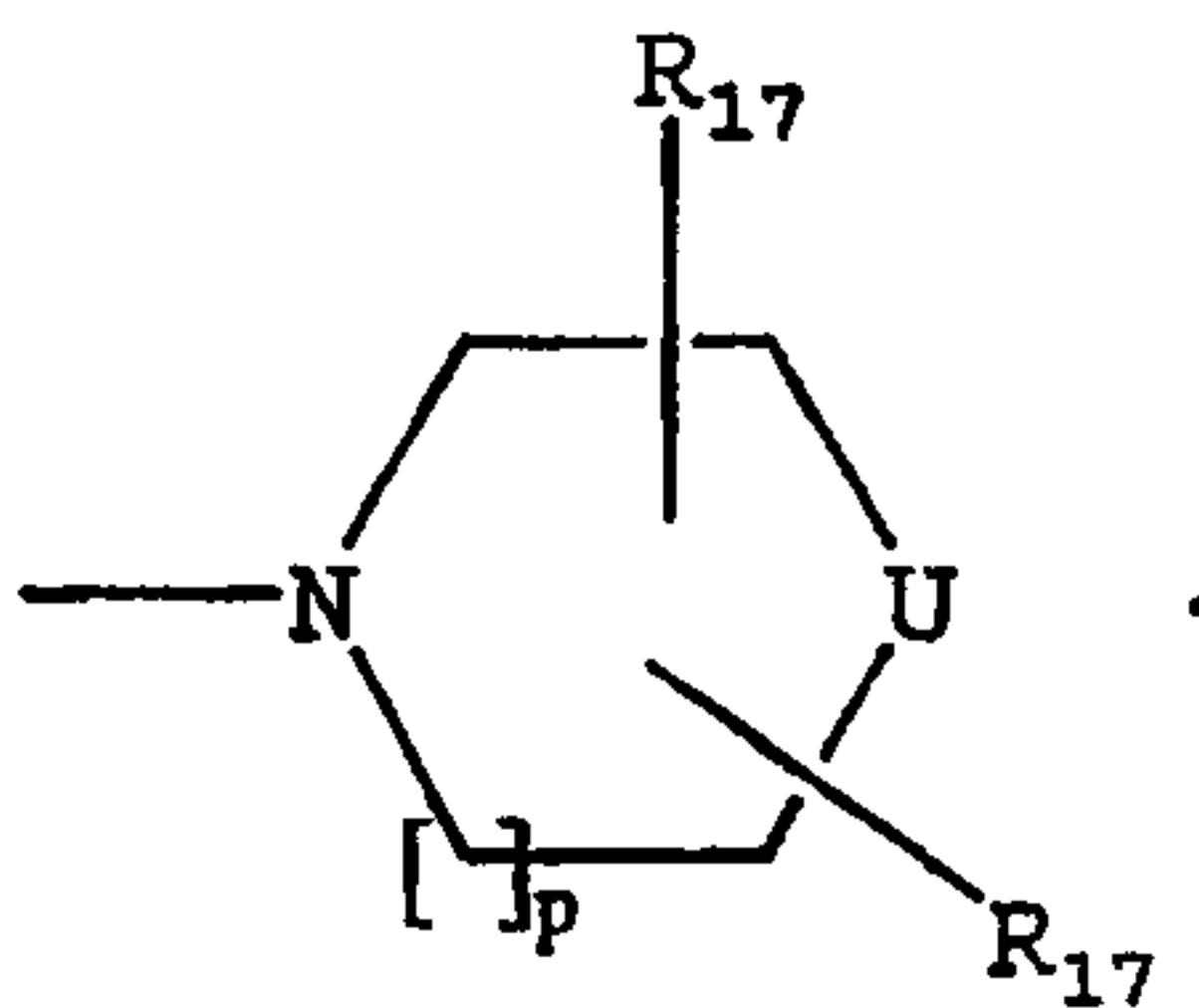
10 In one embodiment, U is NR_{16} .

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

In one embodiment, Z is aryl or heteroaryl.

15

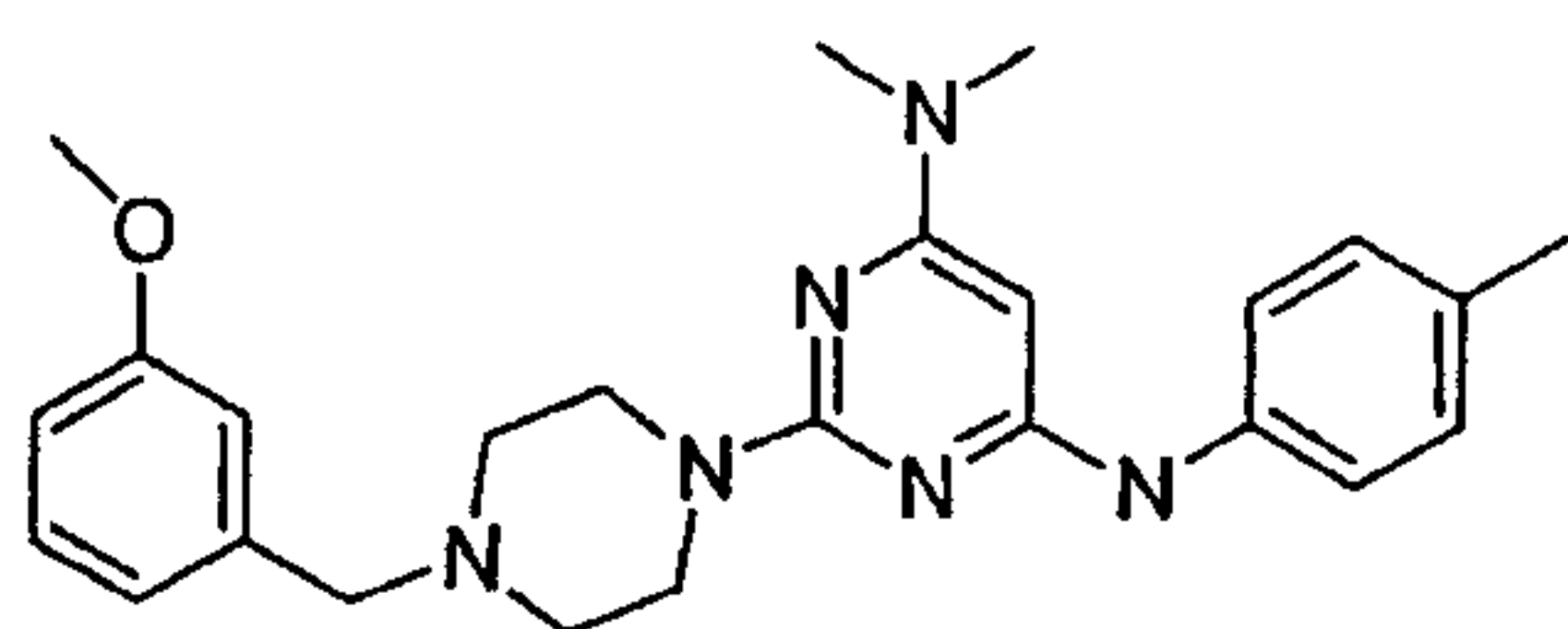
In one embodiment, Y is



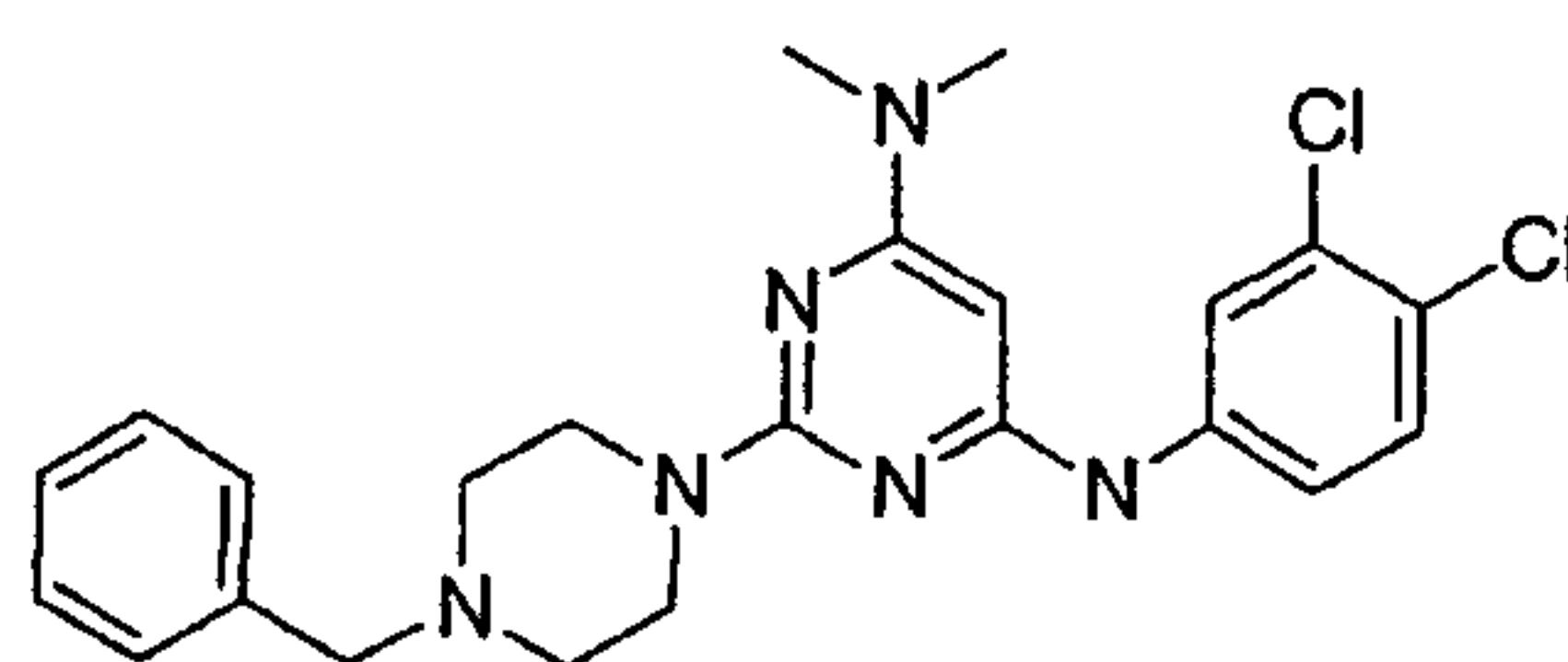
20 In one embodiment, U is NR_{16} .

216

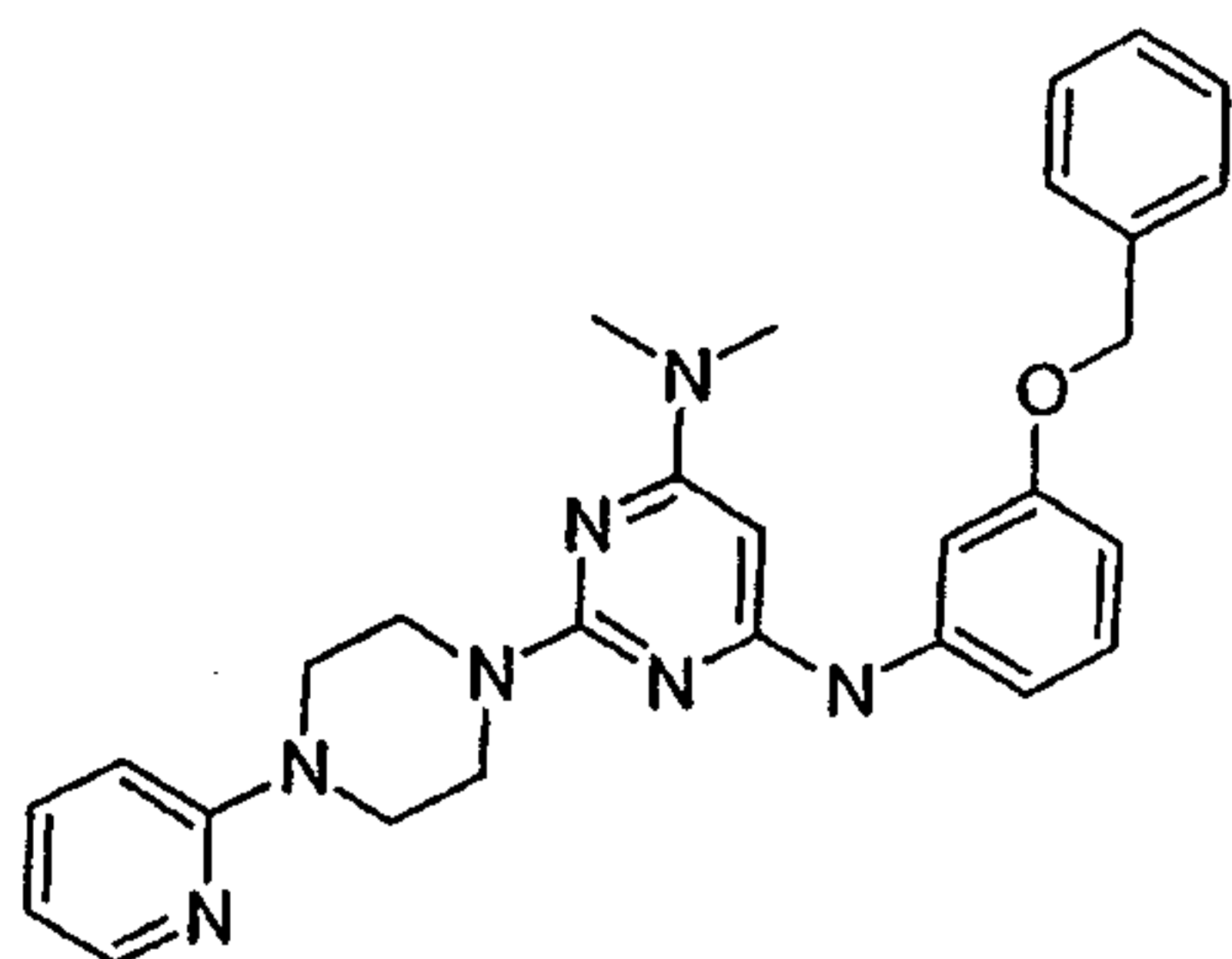
In one embodiment, the compound is selected from the
5 group consisting of:



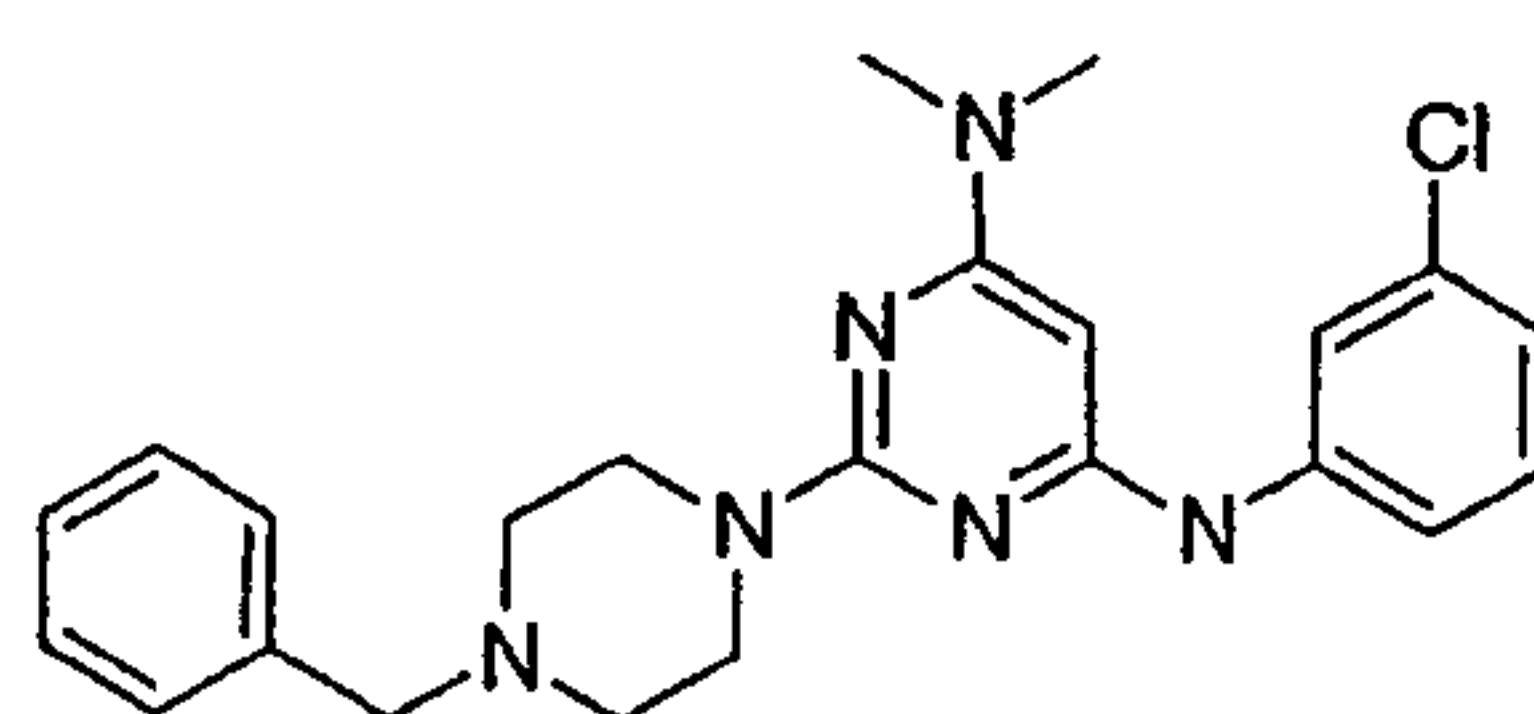
;



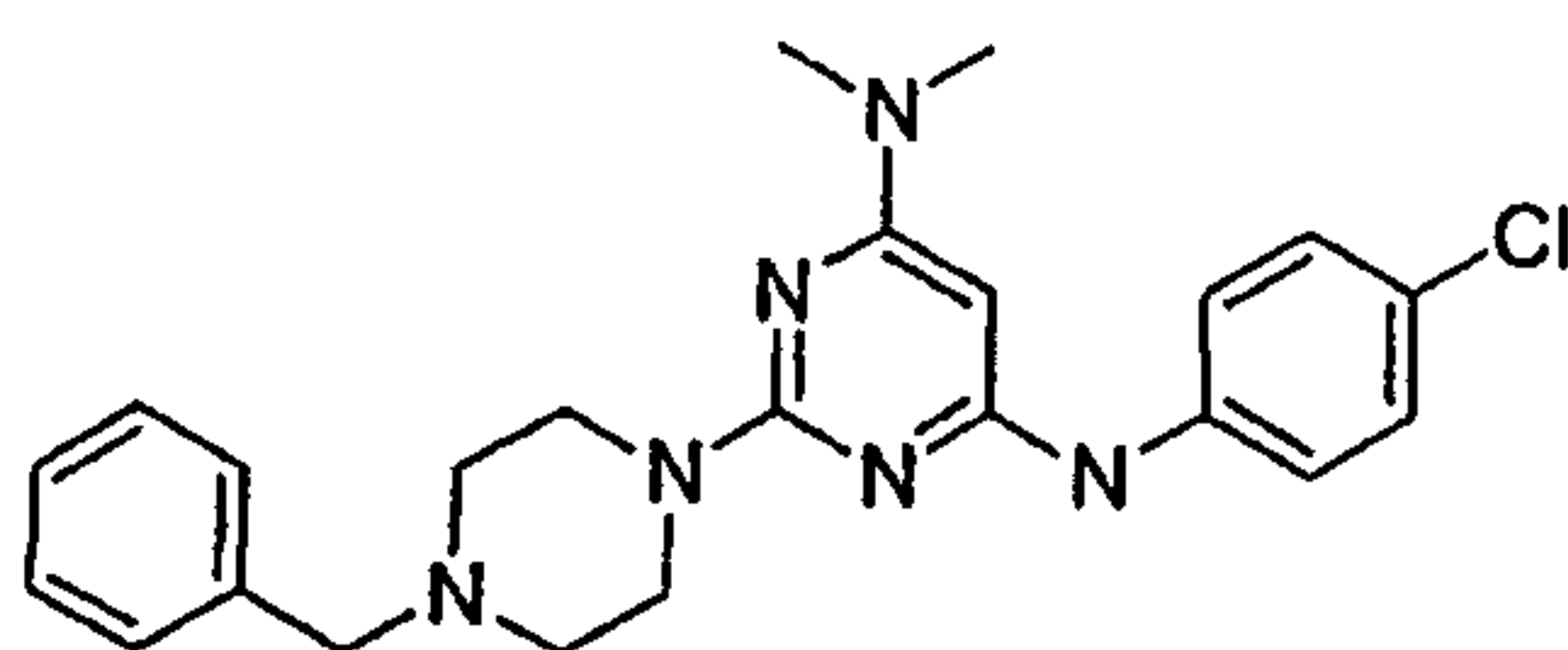
;



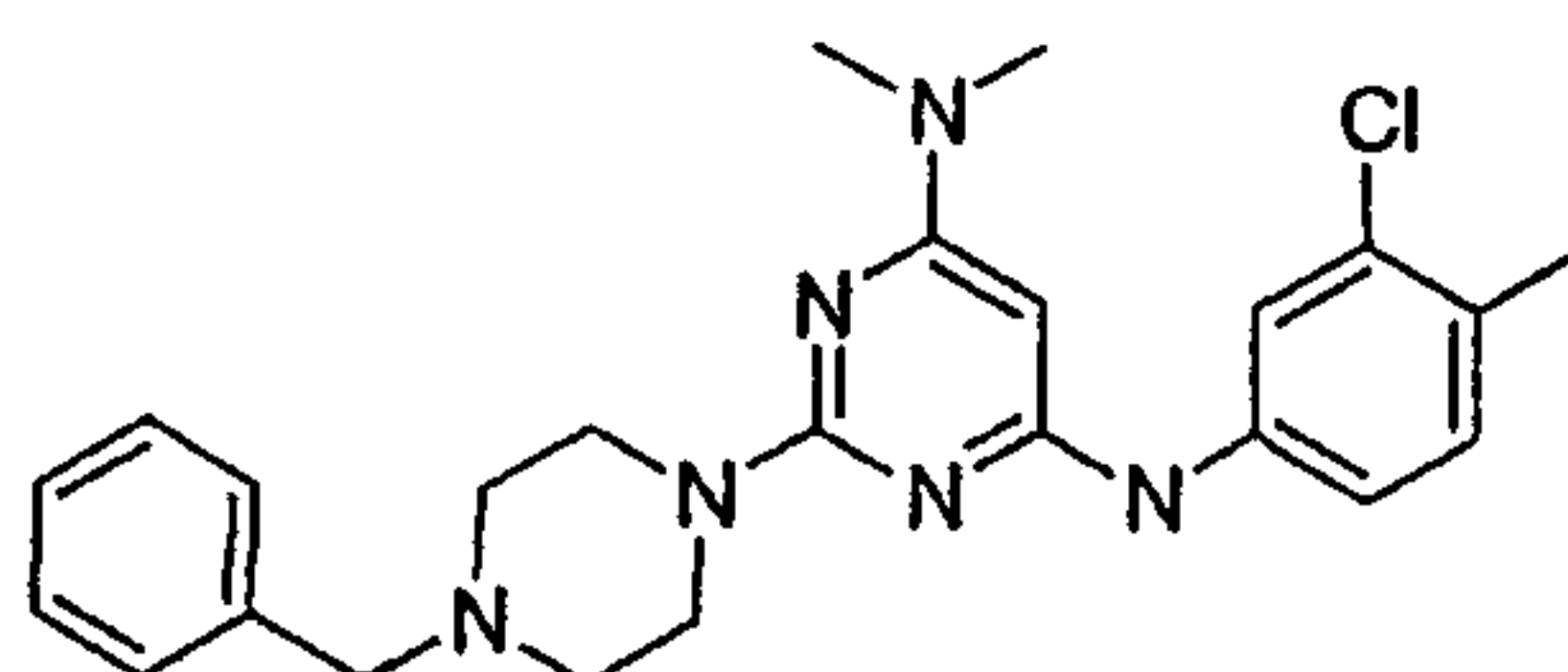
;



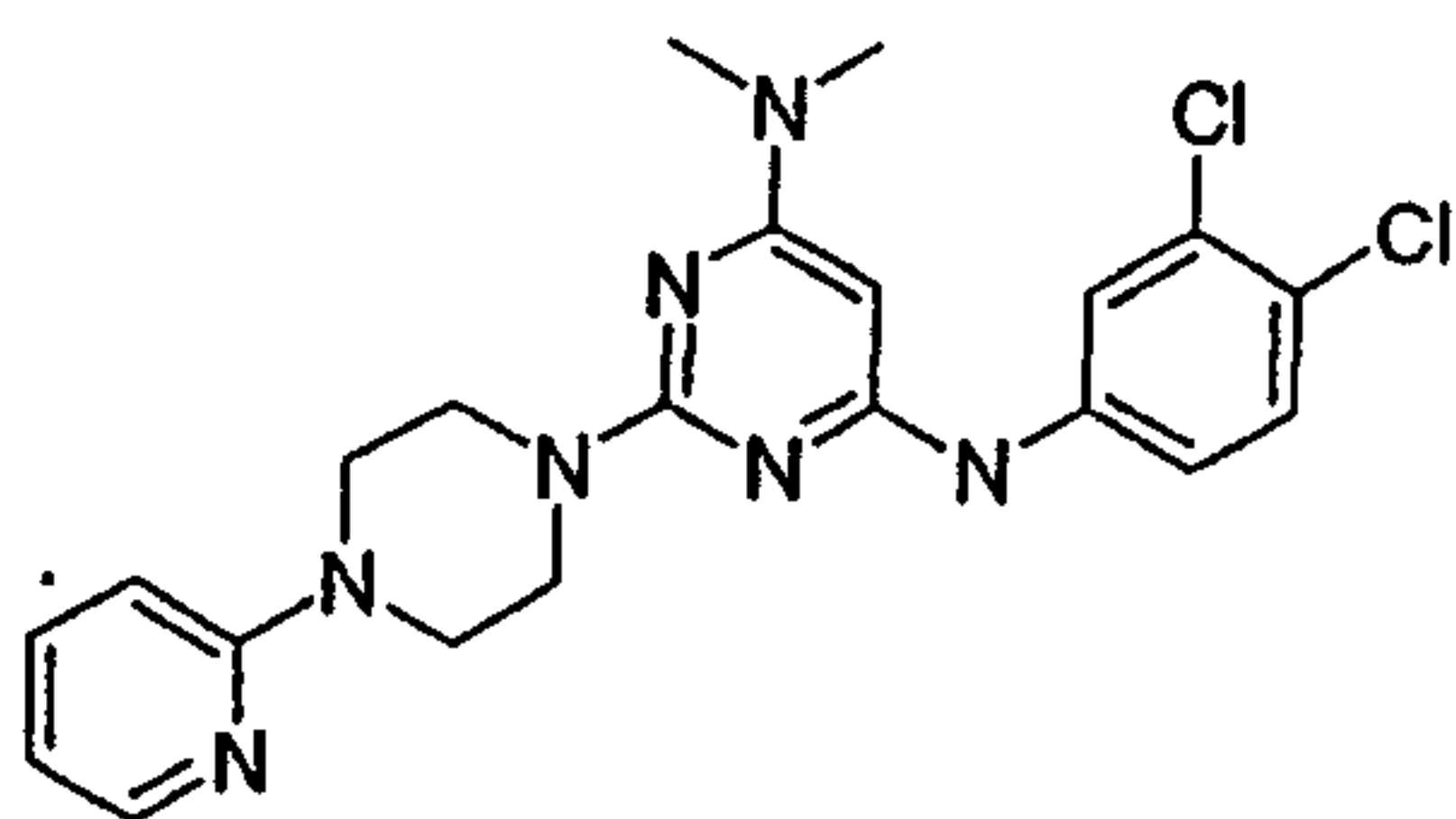
;



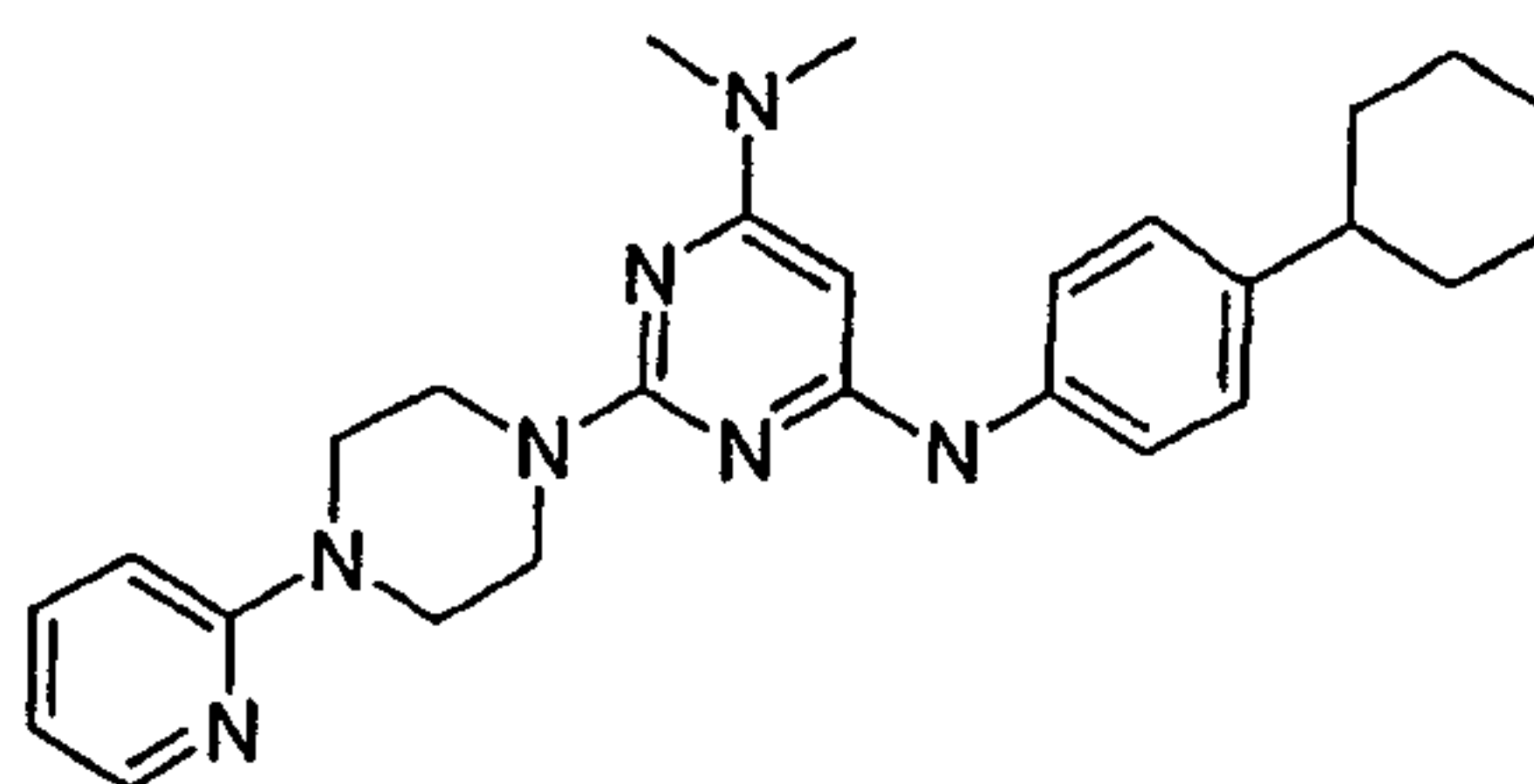
;



;

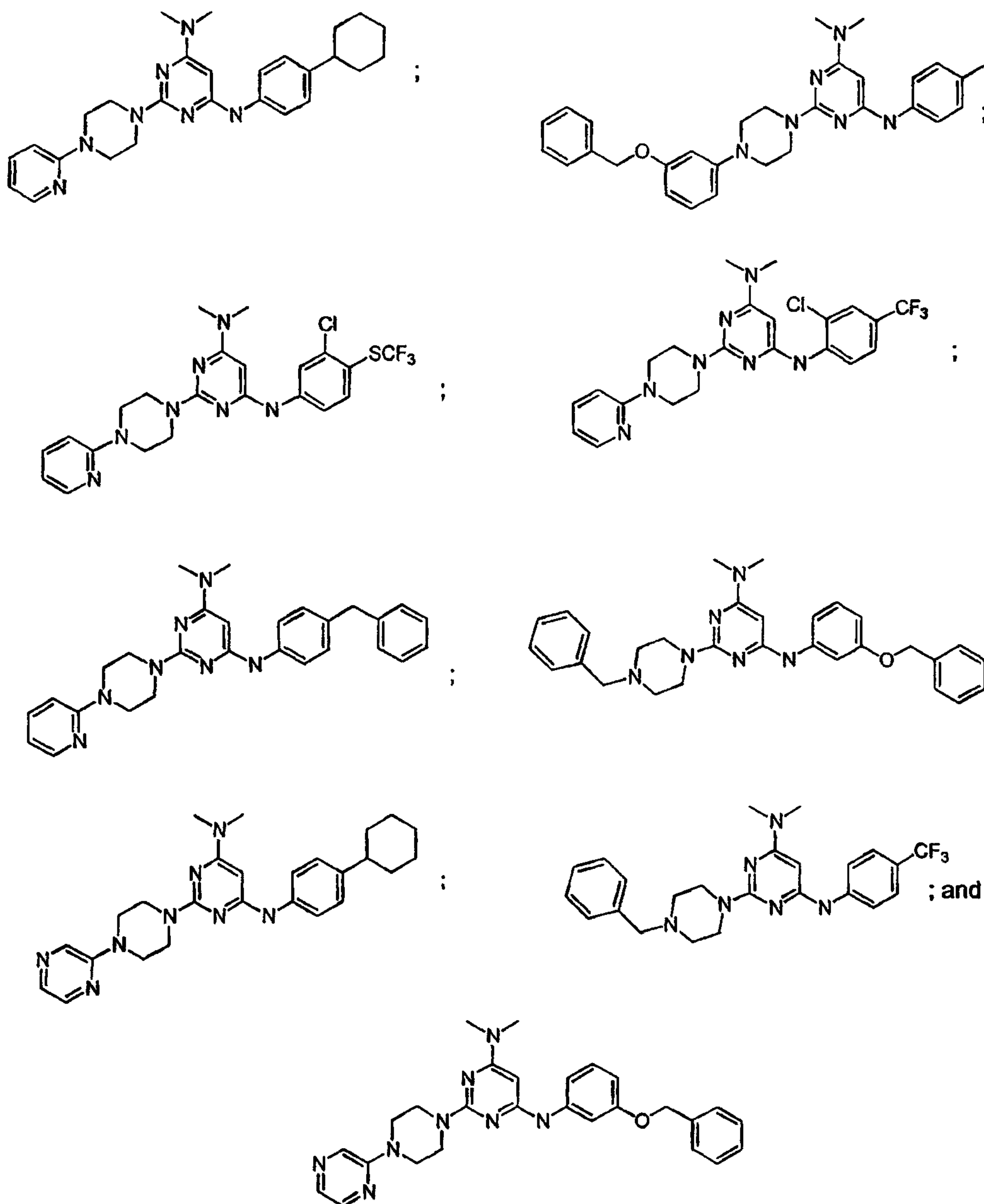


; and



217

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



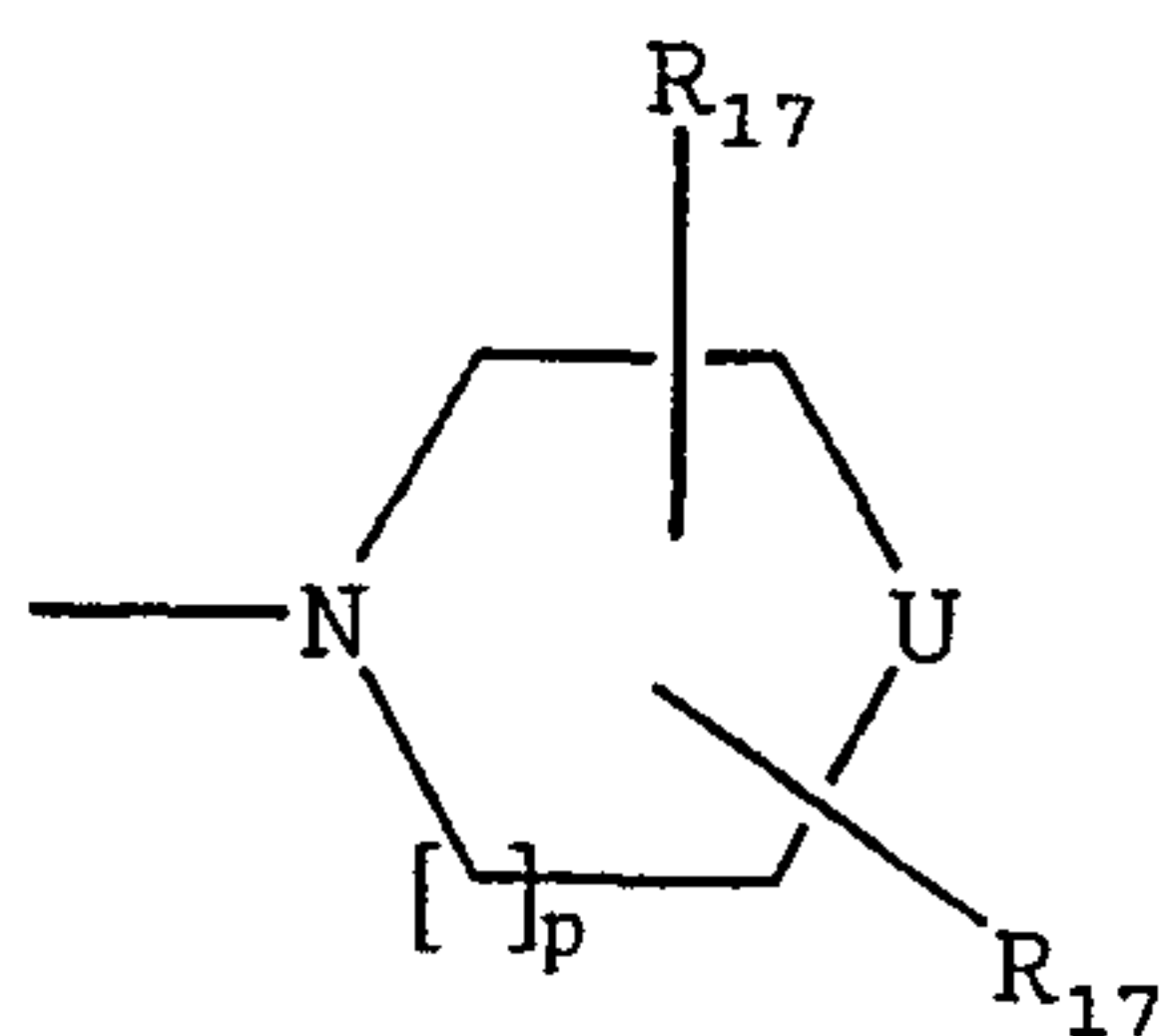
WO 02/060392

PCT/US02/04608

218

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

In one embodiment, Y is



5

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

10

15

20

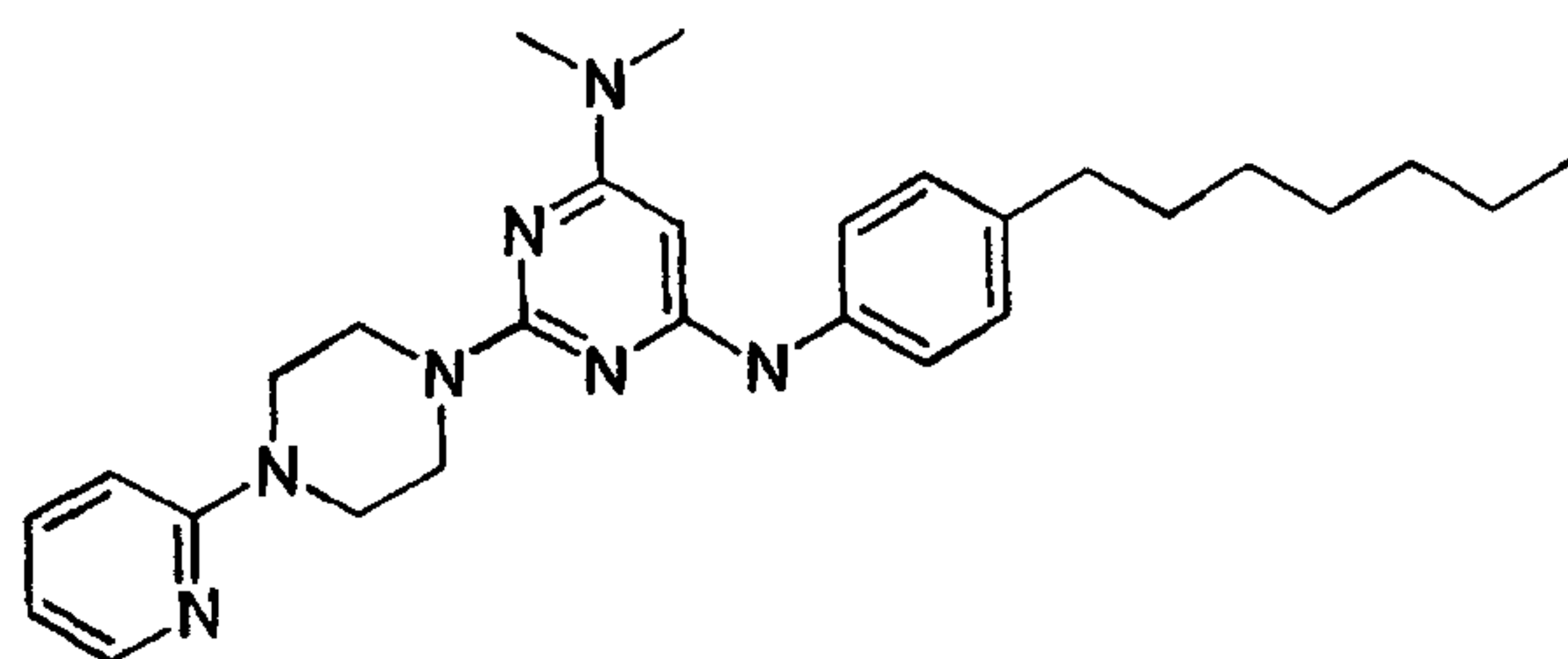
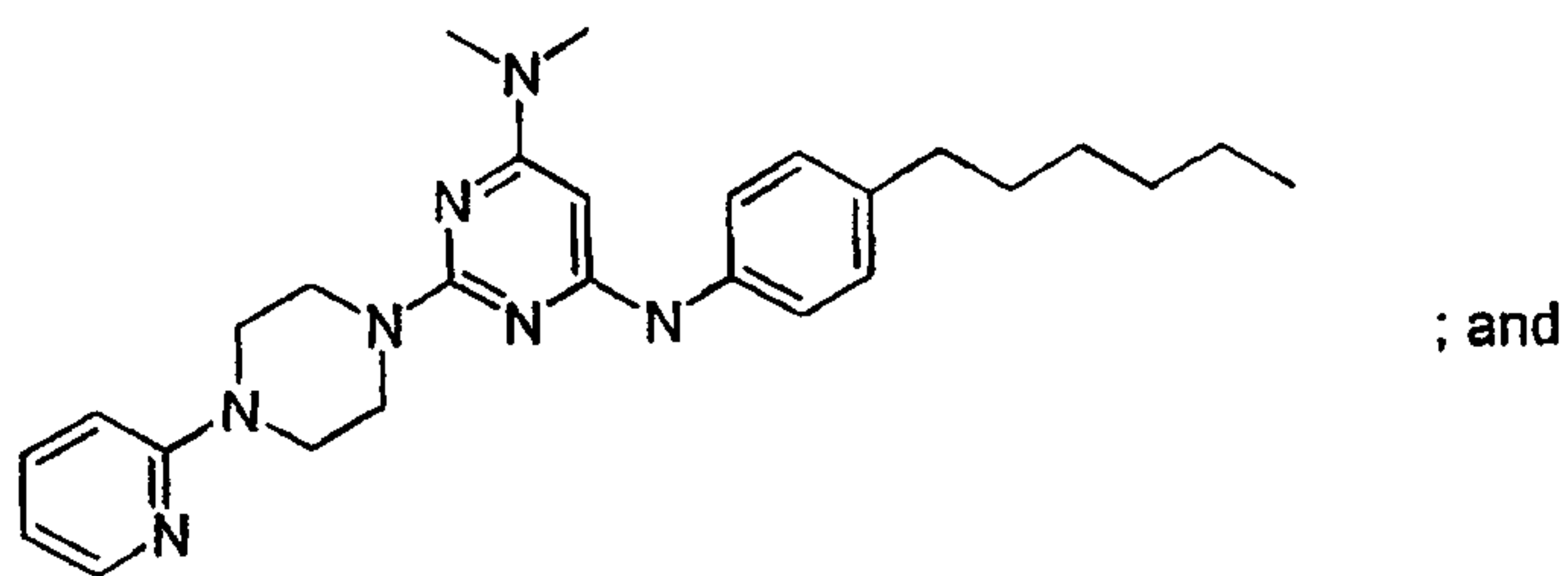
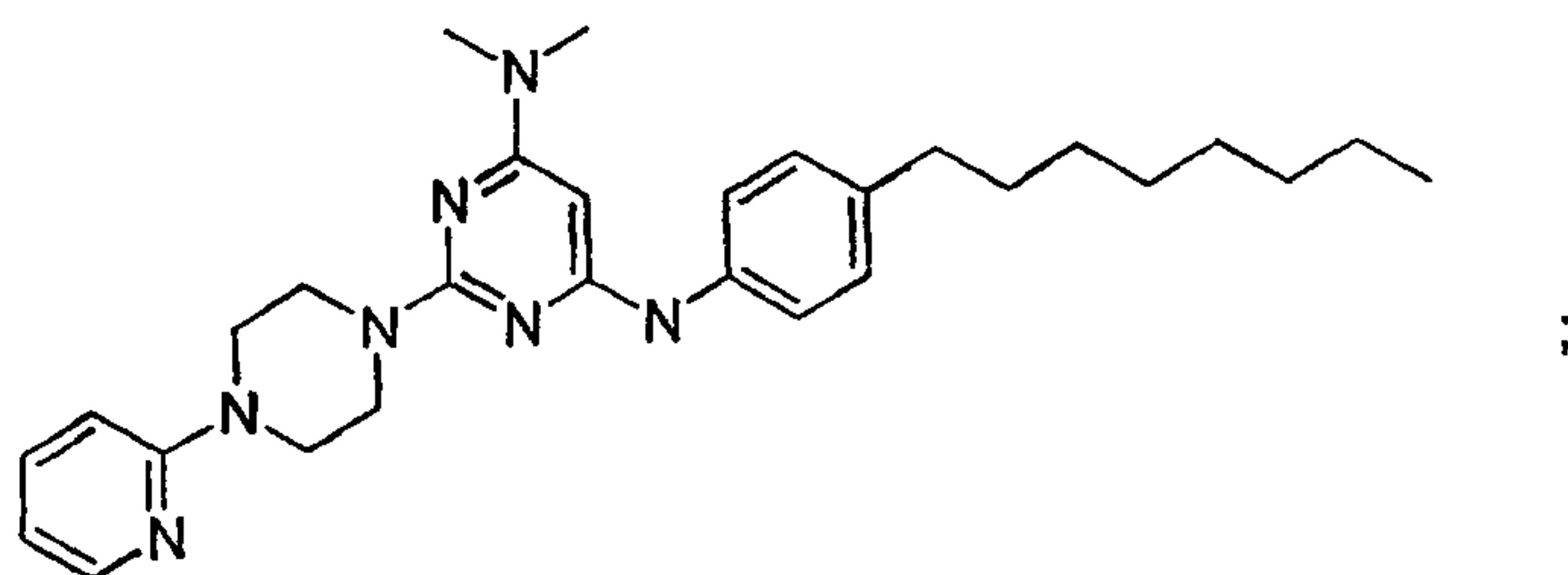
25

WO 02/060392

PCT/US02/04608

219

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



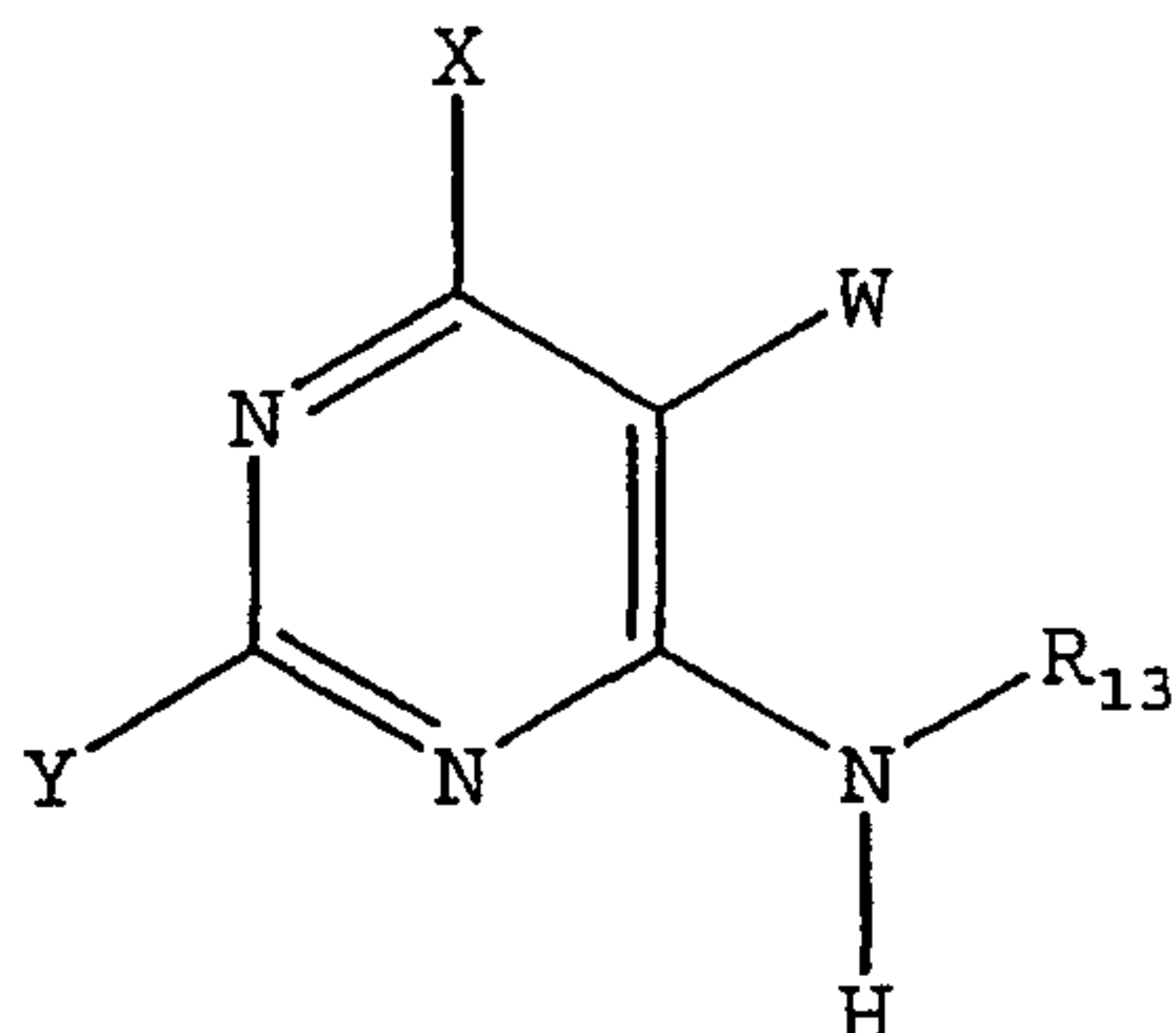
5

10

15

220

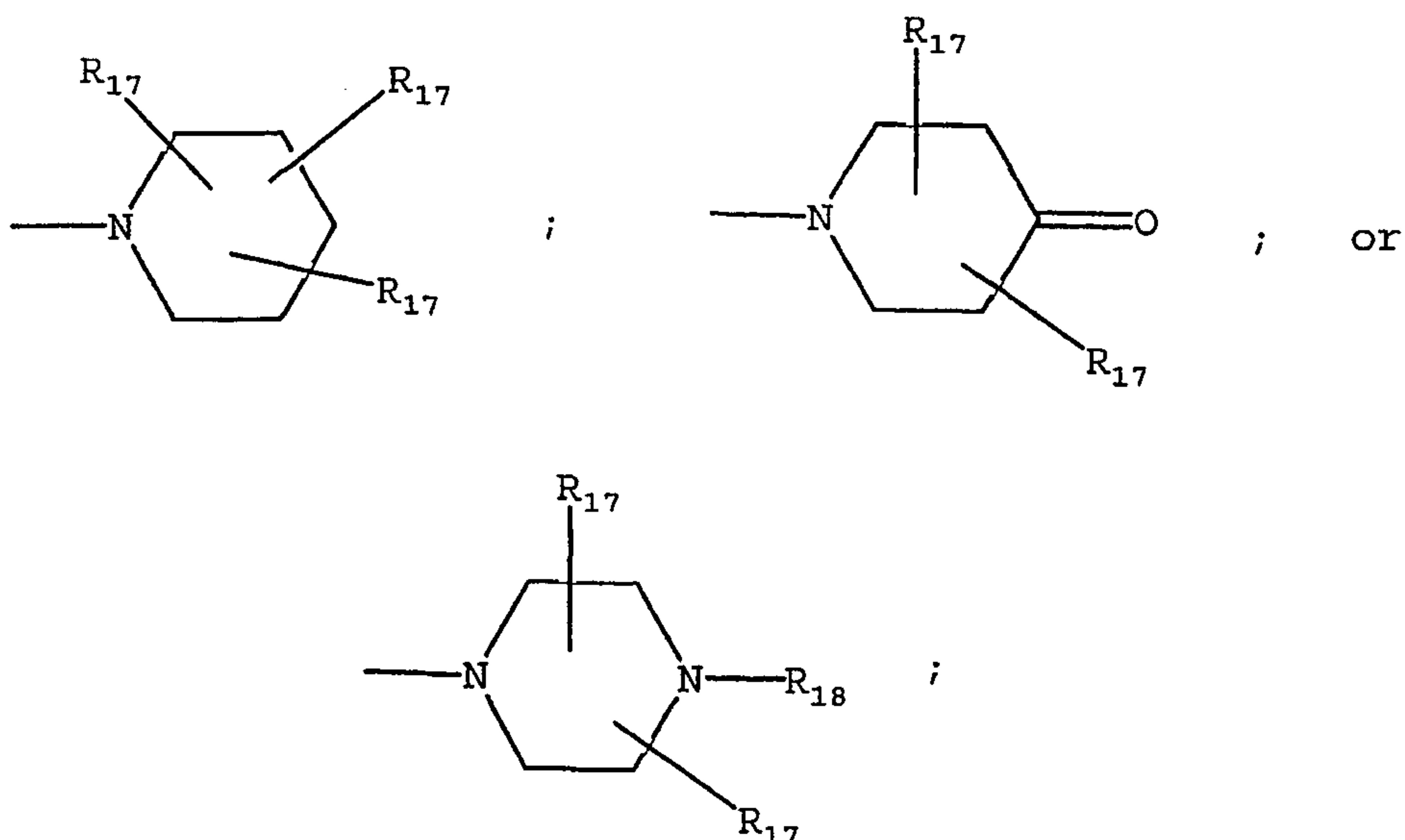
The invention provides a compound having the structure:



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

5

wherein X is; $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl, or aryl $(\text{C}_1\text{-C}_6)$ alkyl;

10

wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $\text{-(CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, adamantyl,

WO 02/060392

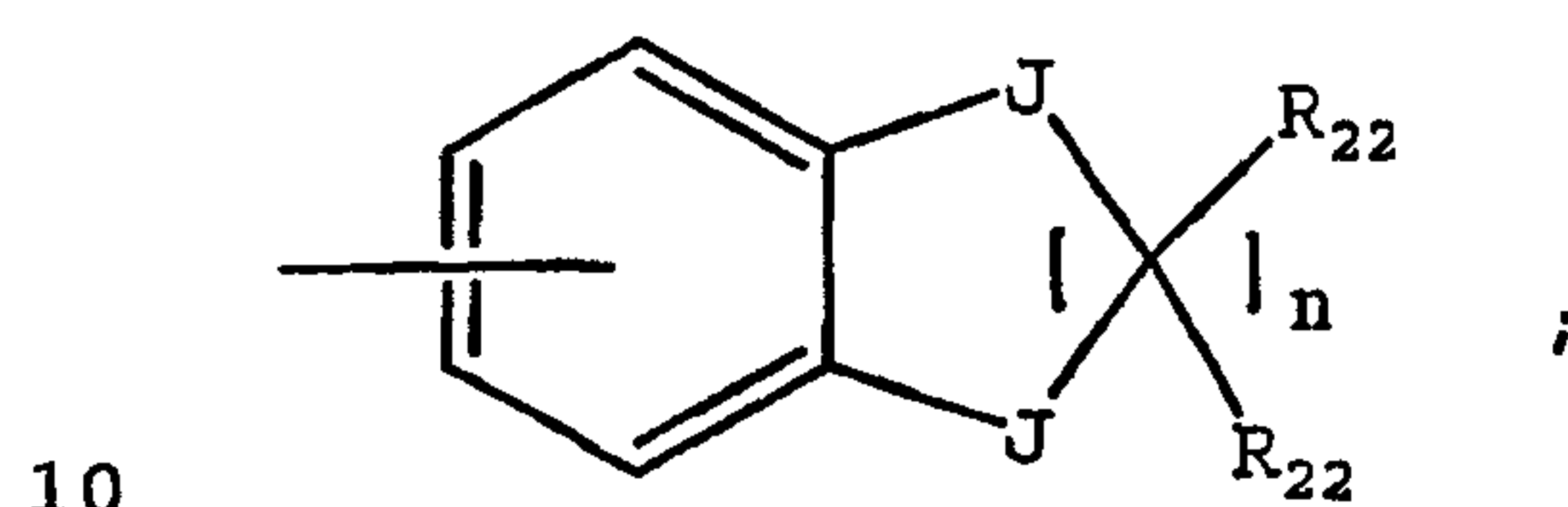
PCT/US02/04608

221

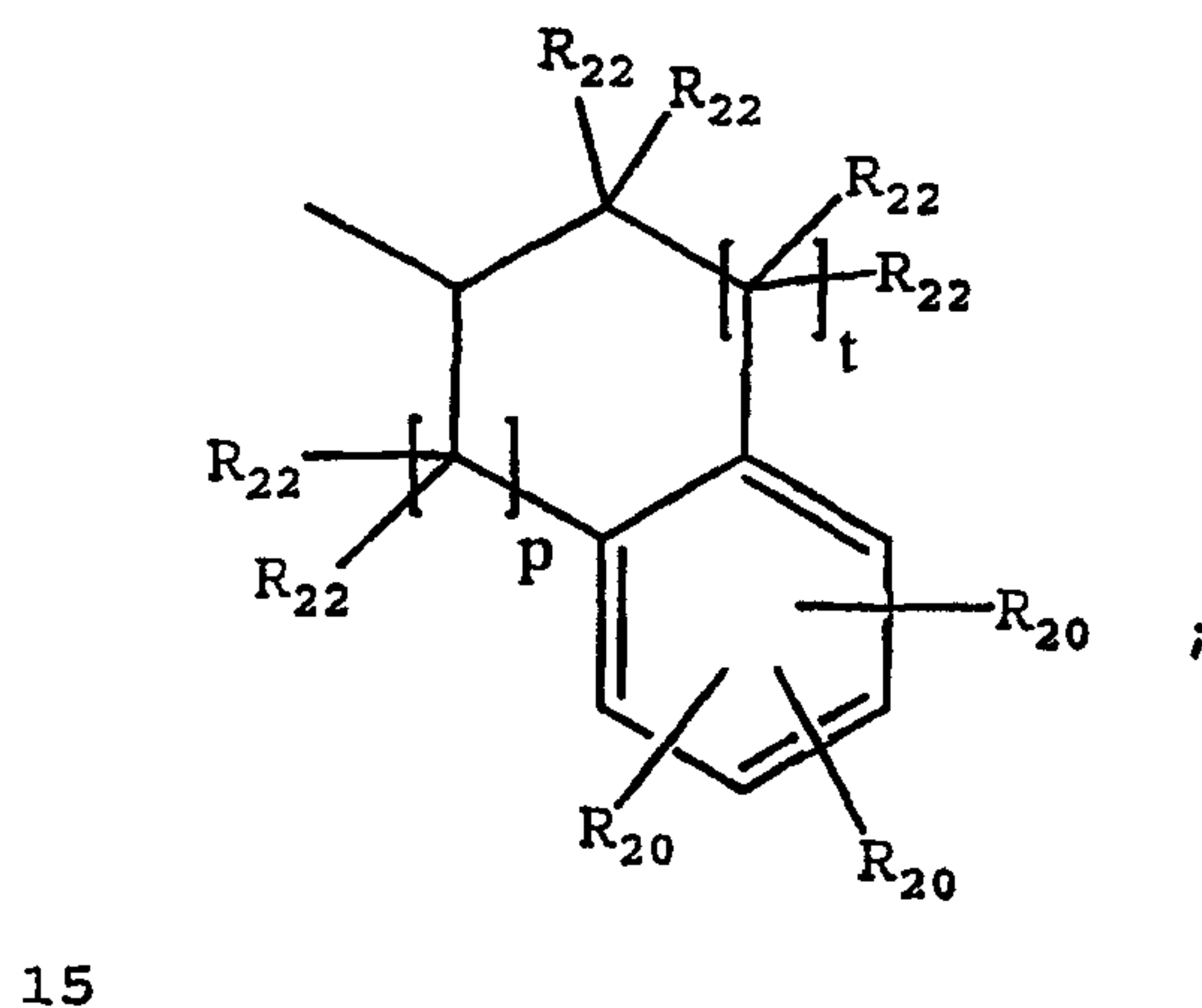
noradamantyl, C₃-C₁₀ cycloalkyl, heteroaryl, aryl, aryl(C₁-C₆)alkyl, Q₁ or Q₂;

wherein aryl may be substituted with one or more C₁-C₁₀
 5 straight chained or branched alkyl, aryl, heteroaryl, or
 N(R₁₉)-Z;

wherein Q₁ is



wherein Q₂ is

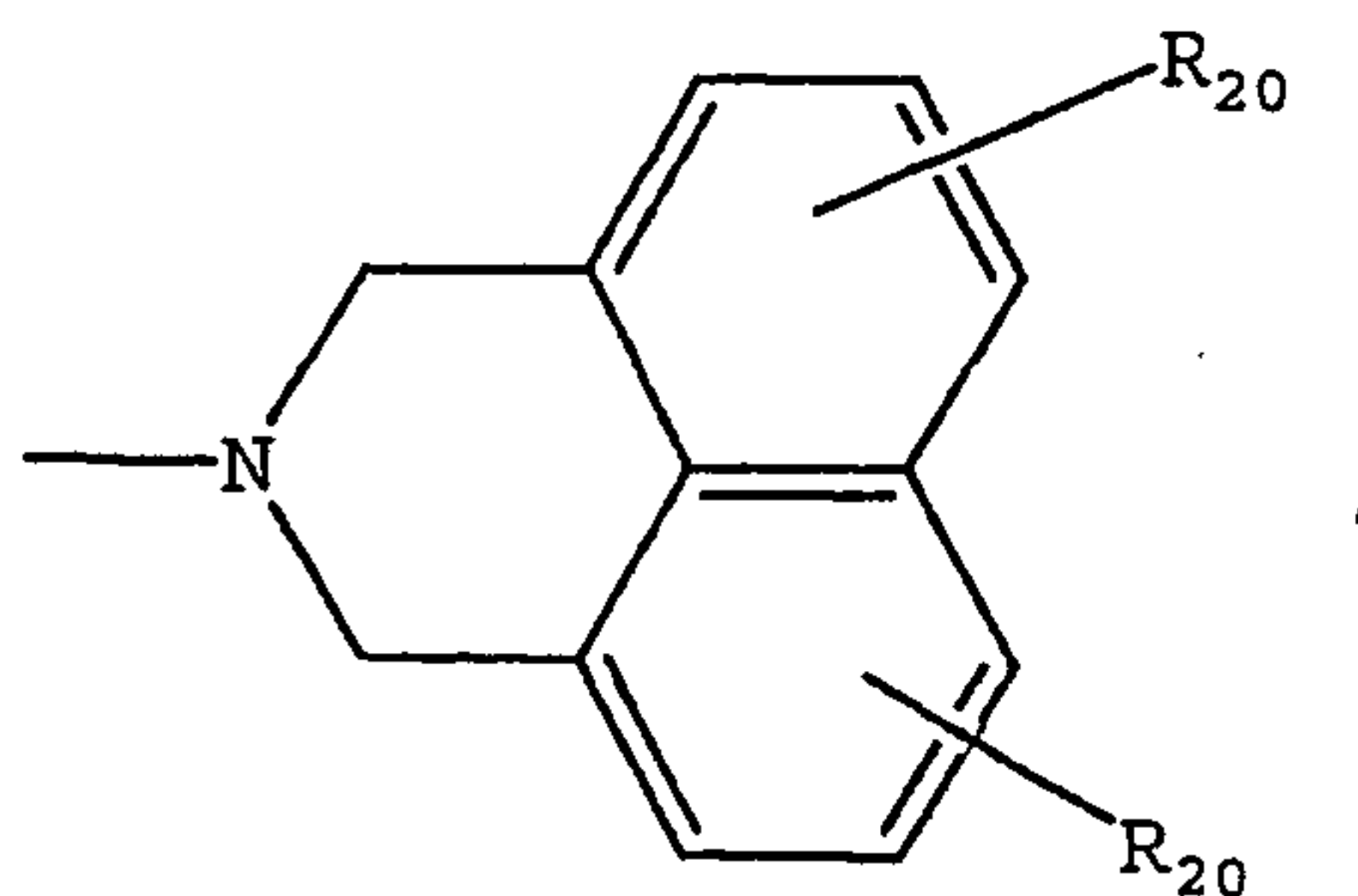
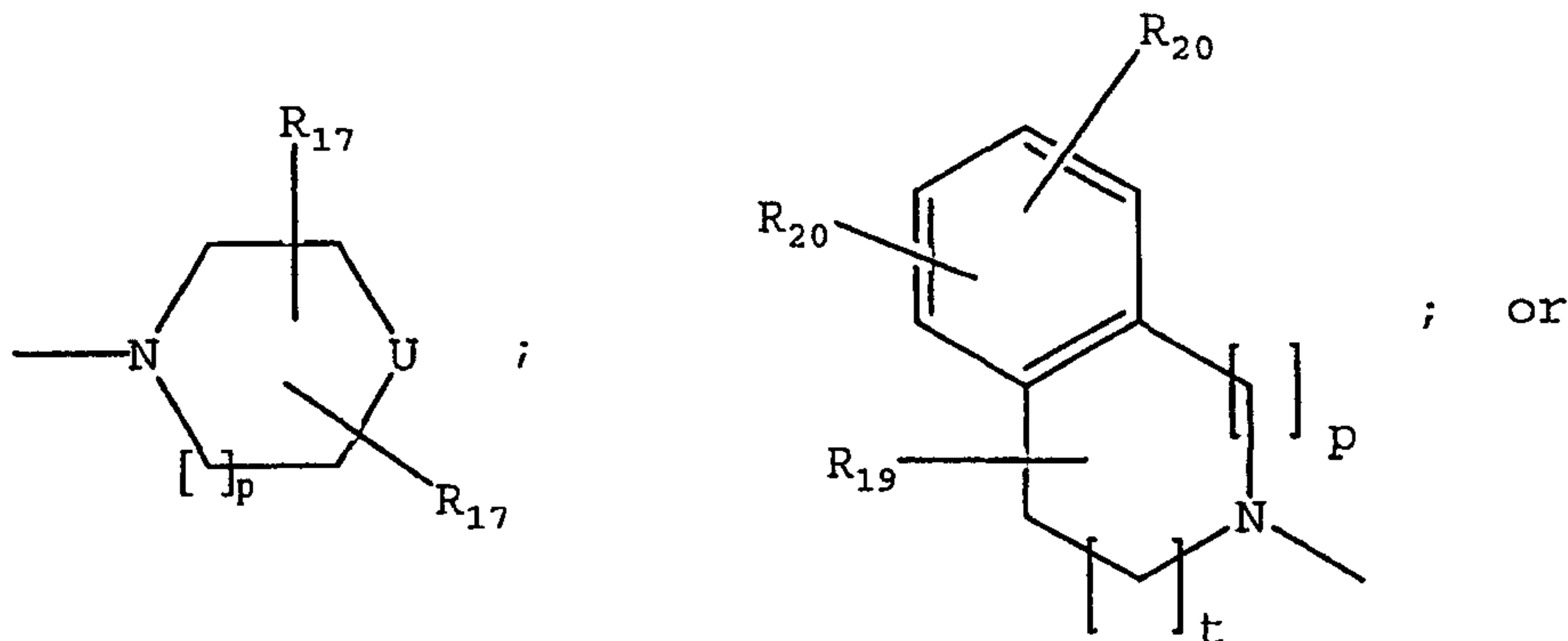


wherein each J is independently O, S, C(R₂₂)₂ or NR₄;

wherein R₄ is H; straight chained or branched C₁-C₇ alkyl,
 monofluoroalkyl or polyfluoroalkyl; straight chained or
 20 branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, C₅-C₇
 cycloalkenyl or aryl;

222

wherein Y is $\text{NR}_{14}\text{R}_{15}$;



5

wherein R_{14} is H, straight chained or branched $\text{C}_1\text{-C}_6$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

- 10 wherein R_{15} is straight chained or branched $\text{C}_3\text{-C}_6$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, $(\text{C}(\text{R}_{19})_2)_m\text{N}(\text{R}_{16})_2$ or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

15 wherein R_{16} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkynyl, $\text{C}_5\text{-C}_7$ cycloalkenyl, $(\text{CH}_2)_m\text{-Z}$, or $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$;

20

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;

WO 02/060392

PCT/US02/04608

224

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

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

5 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;

10

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

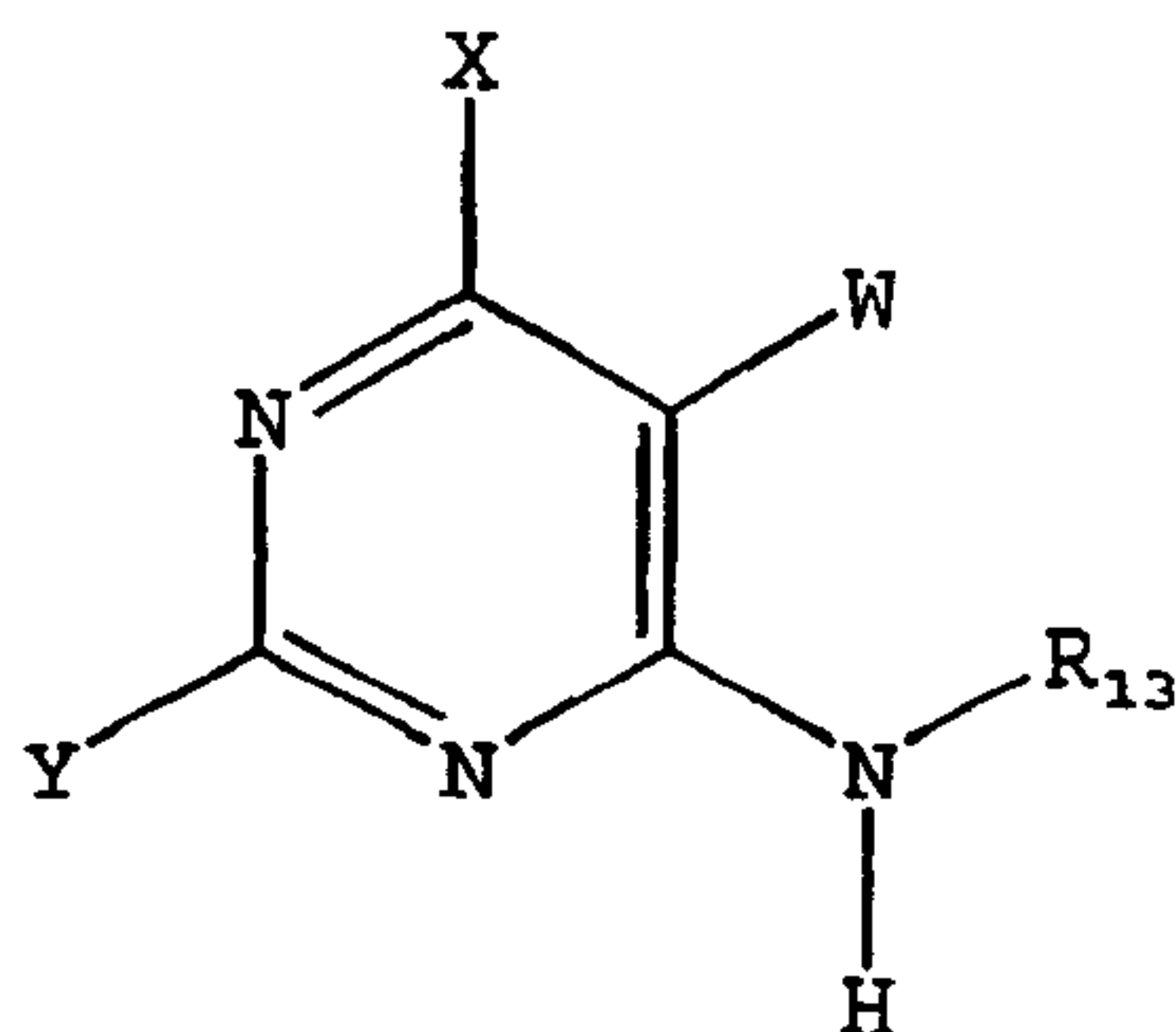
wherein Z is C₃-C₁₀ cycloalkyl, C₄-C₇ cyclic ether, C₄-C₇ cyclic thioether, aryl, or heteroaryl; or

15

a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:

20



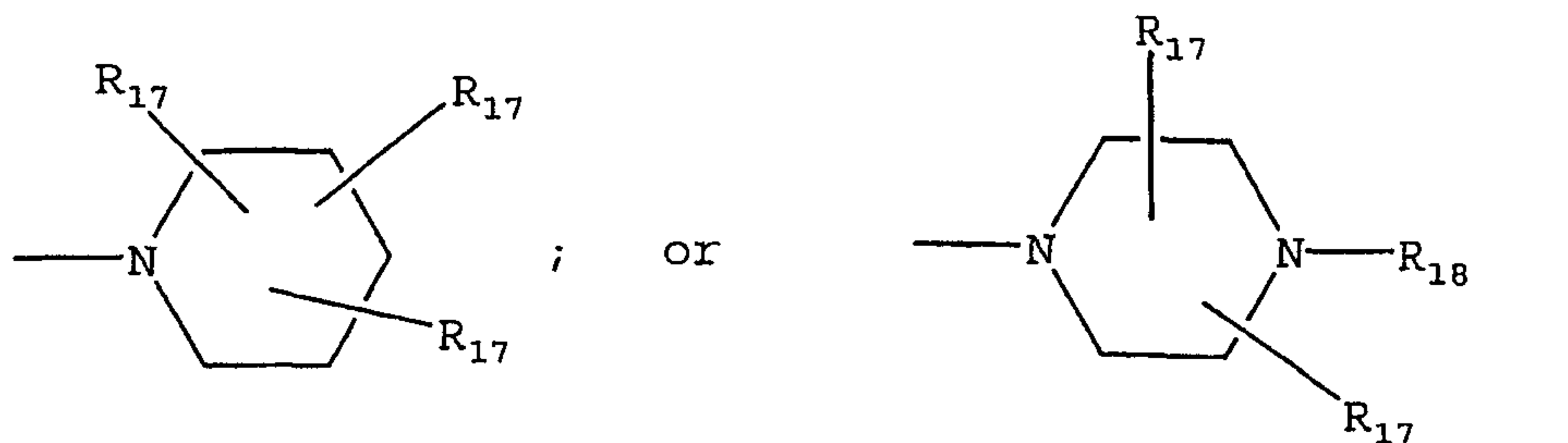
wherein W is H, -F, -Cl, -Br, -I, CN, methyl, ethyl, propyl, methoxy or ethoxy;

WO 02/060392

PCT/US02/04608

225

wherein X is $\text{NR}_{11}\text{R}_{12}$;



wherein R_{11} is H, straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, aryl or aryl($\text{C}_1\text{-C}_6$)alkyl;

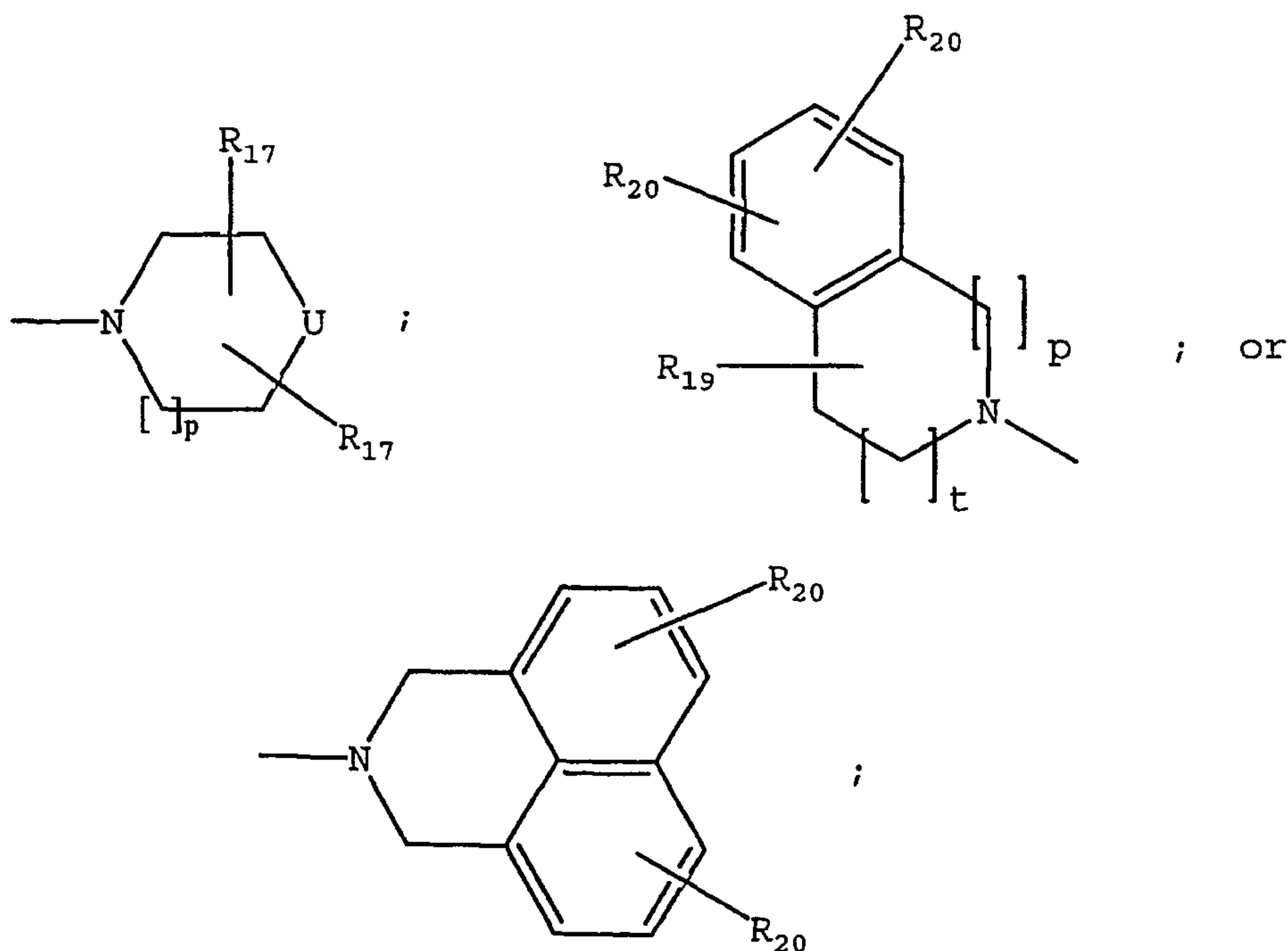
5

wherein R_{12} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, or $\text{-(CH}_2)_m\text{-Z}$;

wherein R_{13} is a bicyclic alkyl ring system, aryl or
 10 aryl($\text{C}_1\text{-C}_6$)alkyl;

wherein Y is $\text{NR}_{14}\text{R}_{15}$;

226



wherein R₁₄ is H, straight chained or branched C₁-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

5

wherein R₁₅ is straight chained or branched C₃-C₆ alkyl, (CH₂)_q-O-(CH₂)_m-CH₃, C₃-C₆ cycloalkyl, or (C(R₁₉)₂)_m-Z;

wherein U is O, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

10

wherein Z is C₃-C₁₀ cycloalkyl, aryl, or heteroaryl;

wherein R₁₆ is straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, - (CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15

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;

WO 02/060392

PCT/US02/04608

228

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

wherein p is an integer from 0 to 2 inclusive;

5

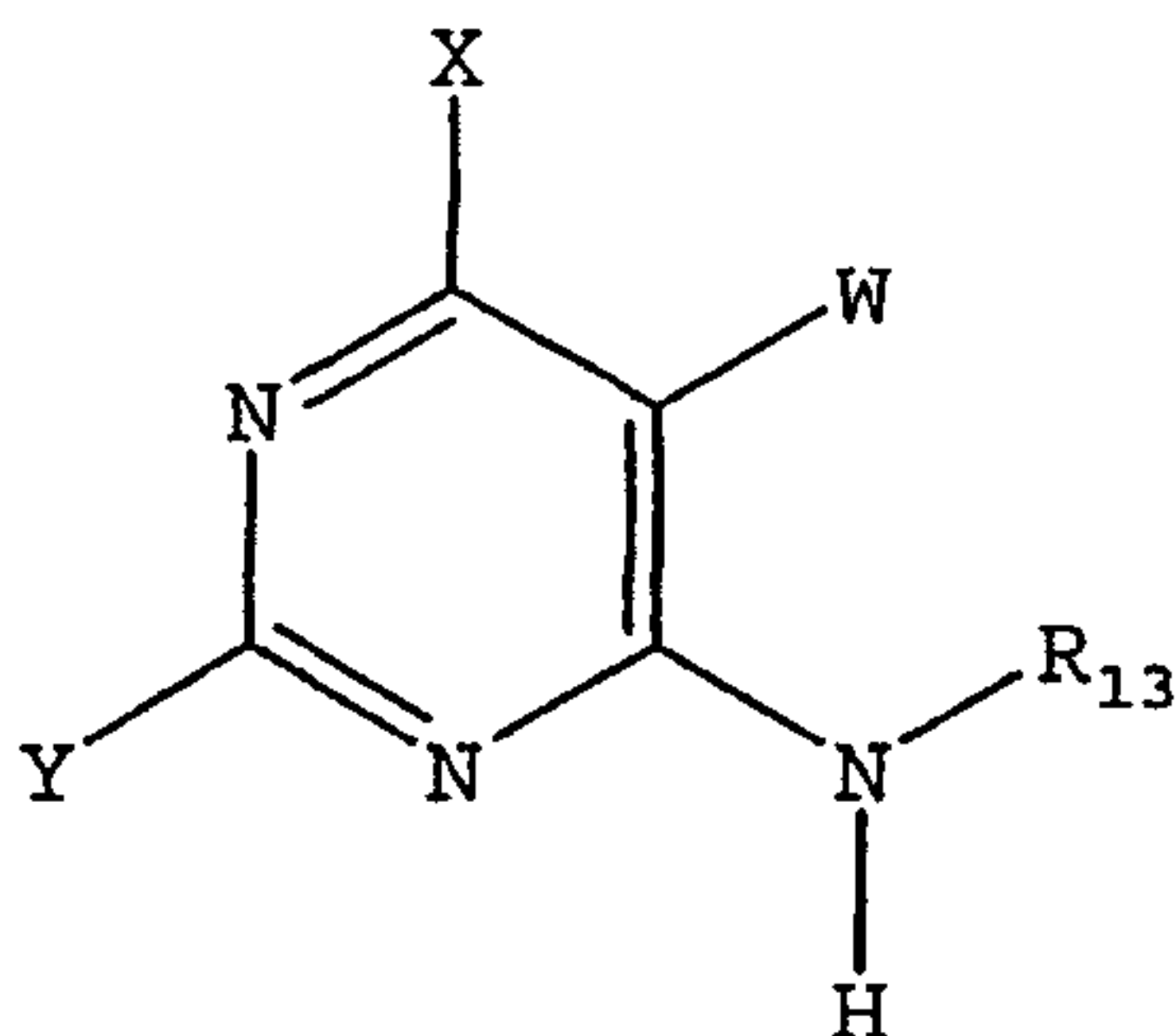
wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

10 a pharmaceutically acceptable salt thereof.

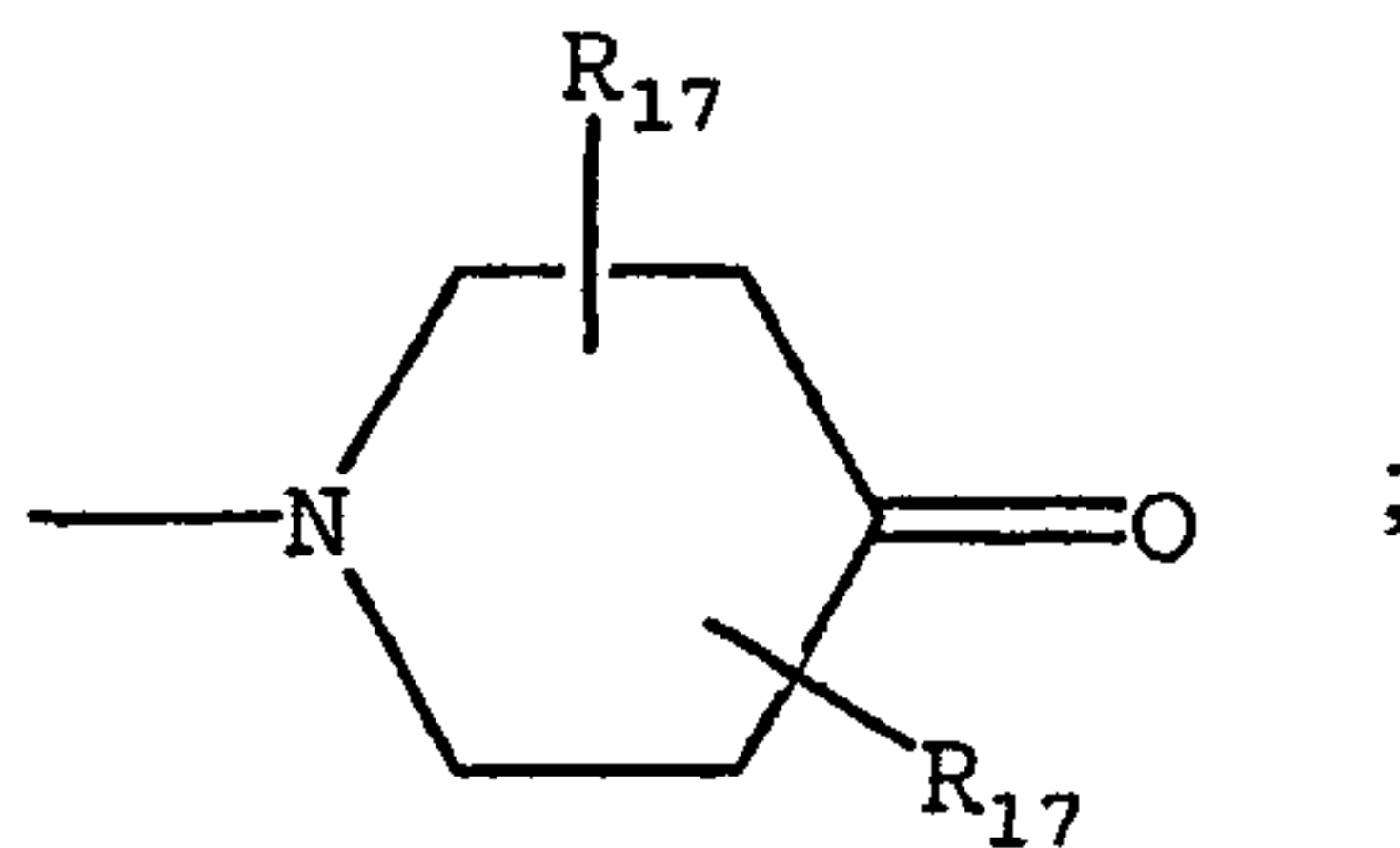
The invention provides a compound having the structure:

15



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

20 wherein X is N(CH₃)₂ or



WO 02/060392

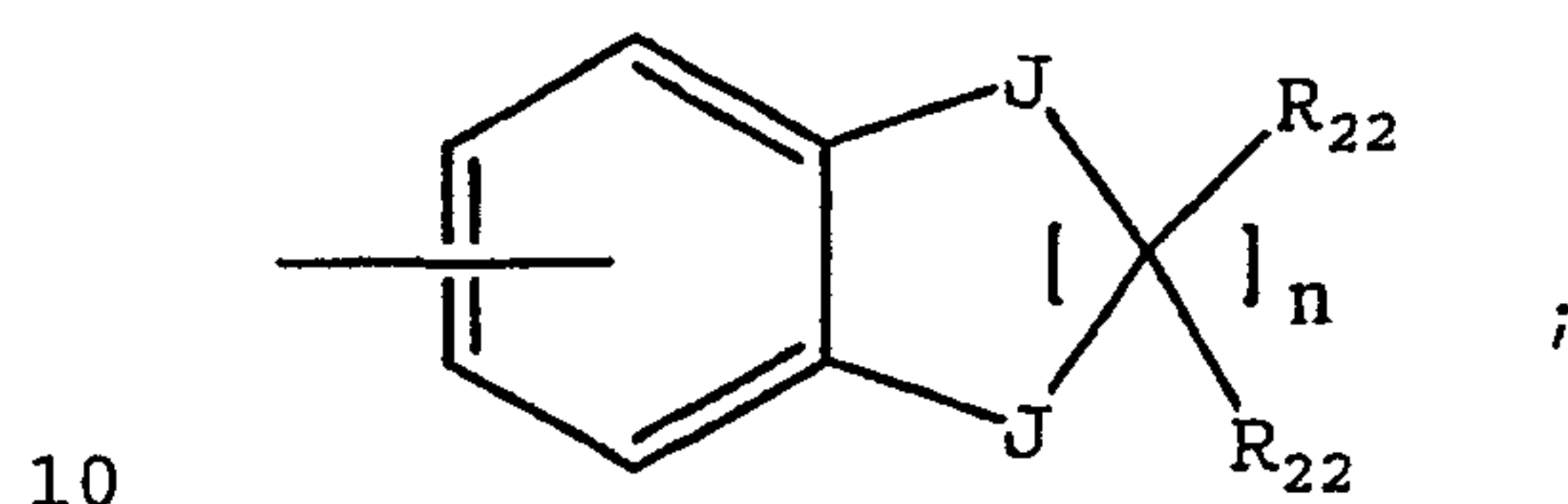
PCT/US02/04608

229

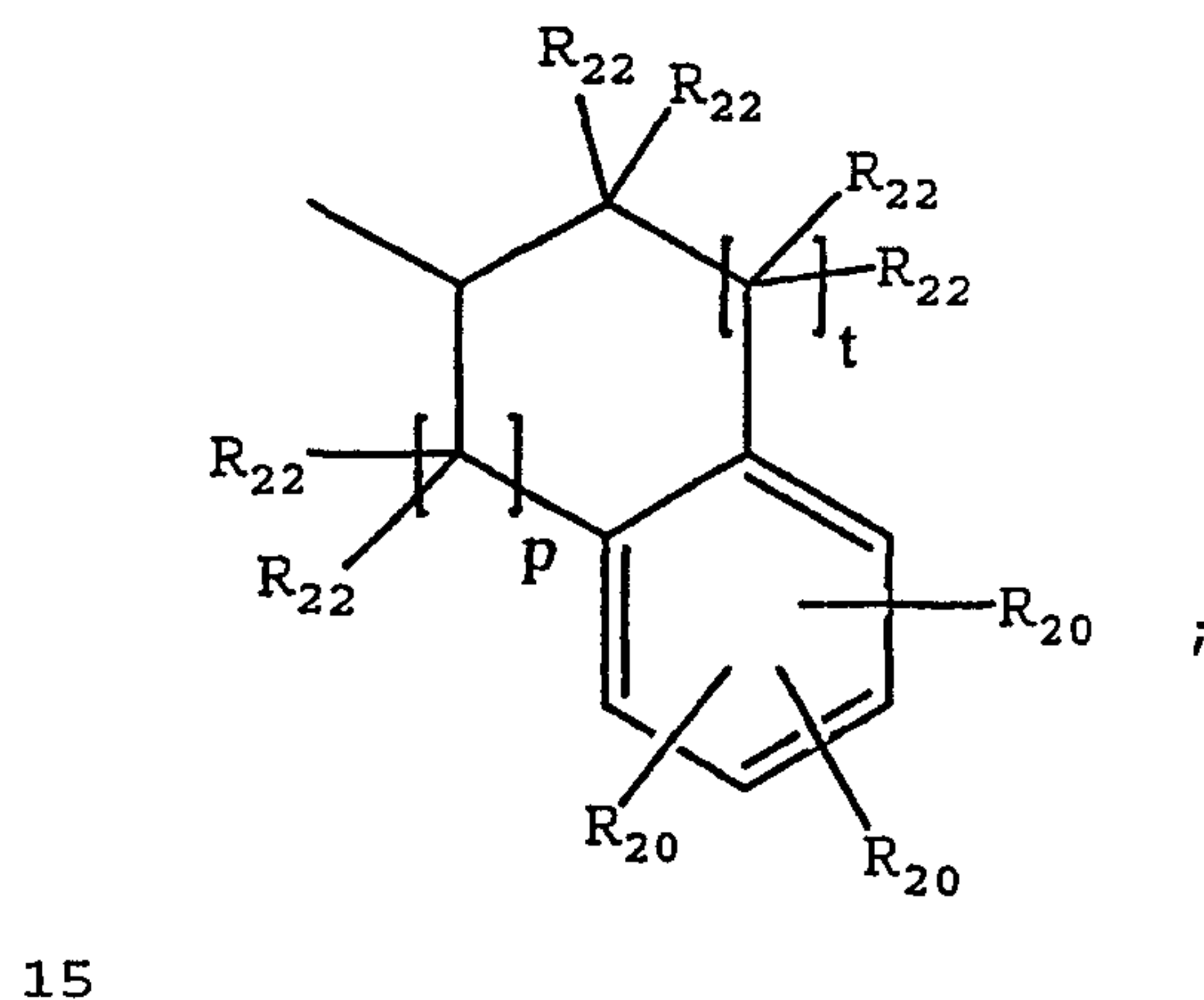
wherein R_{13} is an aryl, adamantyl, noradamantyl, C_3 - C_{10} cycloalkyl, heteroaryl, Q_1 or Q_2 ;

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



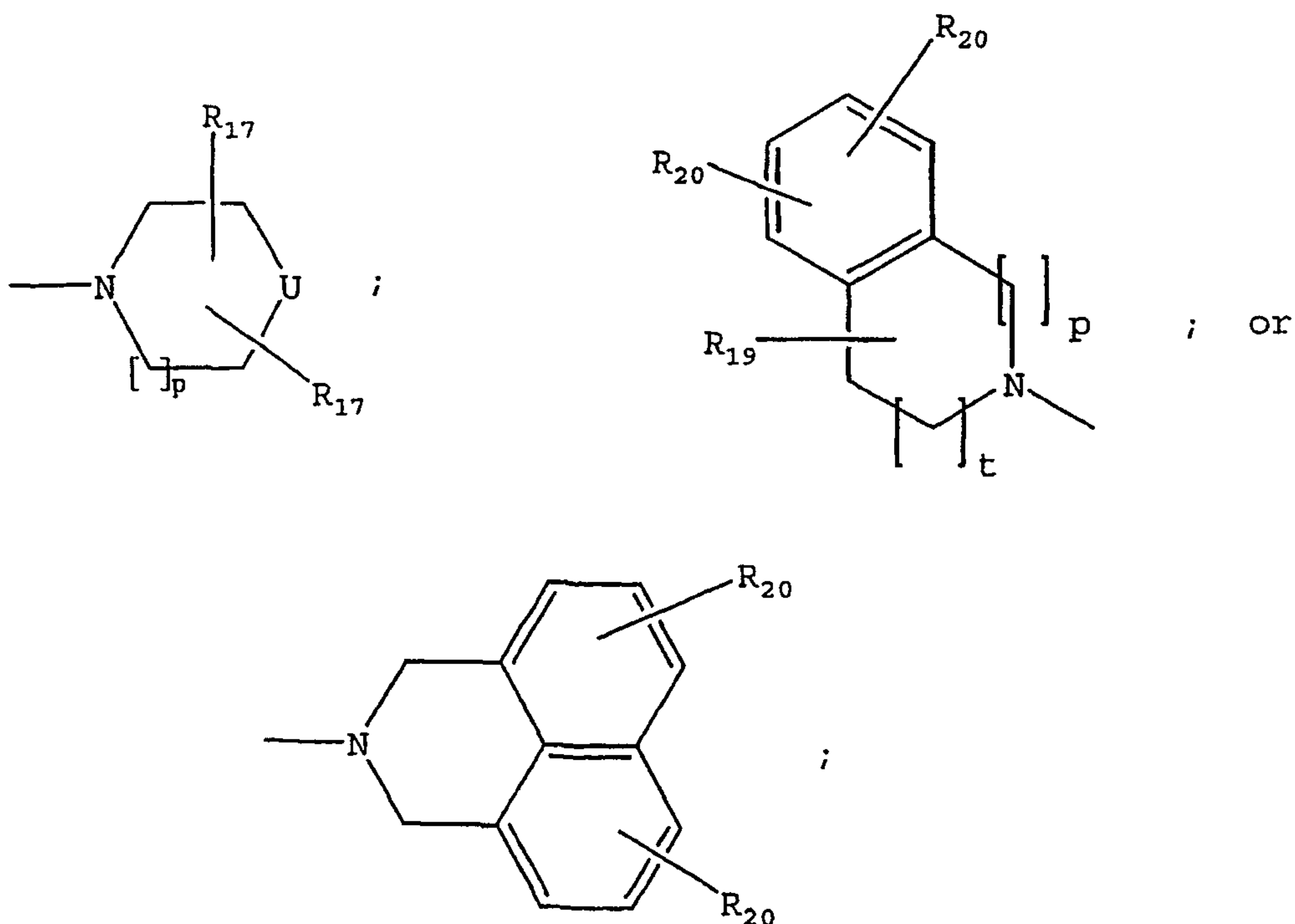
wherein Q_2 is



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
20 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 $\text{NR}_{14}\text{R}_{15}$;



- 5 wherein R_{14} is H, straight chained or branched $\text{C}_1\text{-C}_6$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

wherein R_{15} is straight chained or branched $\text{C}_3\text{-C}_6$ alkyl, $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$, $\text{C}_3\text{-C}_6$ cycloalkyl, or $(\text{C}(\text{R}_{19})_2)_m\text{-Z}$;

10

wherein U is O, -NR_{16} , S, $\text{C}(\text{R}_{17})_2$, or $\text{-NSO}_2\text{R}_{16}$;

wherein Z is $\text{C}_3\text{-C}_{10}$ cycloalkyl, aryl, or heteroaryl;

- 15 wherein R_{16} is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl, straight chained or branched $\text{C}_1\text{-C}_7$ monofluoroalkyl, straight chained or branched $\text{C}_1\text{-C}_7$ polyfluoroalkyl, straight chained or branched $\text{C}_2\text{-C}_7$ alkenyl, straight

chained or branched C₂-C₇ alkynyl, C₅-C₇ cycloalkenyl, -
(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

wherein each R₁₇ is independently H; -OR₂₁, -OCOR₂₁, -COR₂₁,
5 -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, -COOR₂₁, straight chained or
branched C₁-C₇ alkyl, straight chained or branched C₁-C₇
monofluoroalkyl, straight chained or branched C₁-C₇
polyfluoroalkyl, straight chained or branched C₂-C₇
alkenyl, straight chained or branched C₂-C₇ alkynyl, C₅-C₇
10 cycloalkenyl, -(CH₂)_m-Z, or (CH₂)_n-O-(CH₂)_m-CH₃;

wherein R₁₈ is straight chained or branched C₁-C₆ alkyl, -
(CH₂)_m-Z, or (CH₂)_q-O-(CH₂)_m-CH₃;

15 wherein each R₁₉ is independently H, or straight chained
or branched C₁-C₆ alkyl;

wherein each R₂₀ is independently -H; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
20 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl or C₅-C₇ cycloalkenyl; -F, -Cl, -Br, or -I;
-NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -
CON(R₂₁)₂, or -COOR₂₁; aryl or heteroaryl; or two R₂₀ groups
present on adjacent carbon atoms can join together to
25 form a methylenedioxy group;

wherein each R₂₁ is independently -H; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
30 C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-
C₆)alkyl;

WO 02/060392

PCT/US02/04608

232

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;

5

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

wherein p is an integer from 0 to 2 inclusive;

10

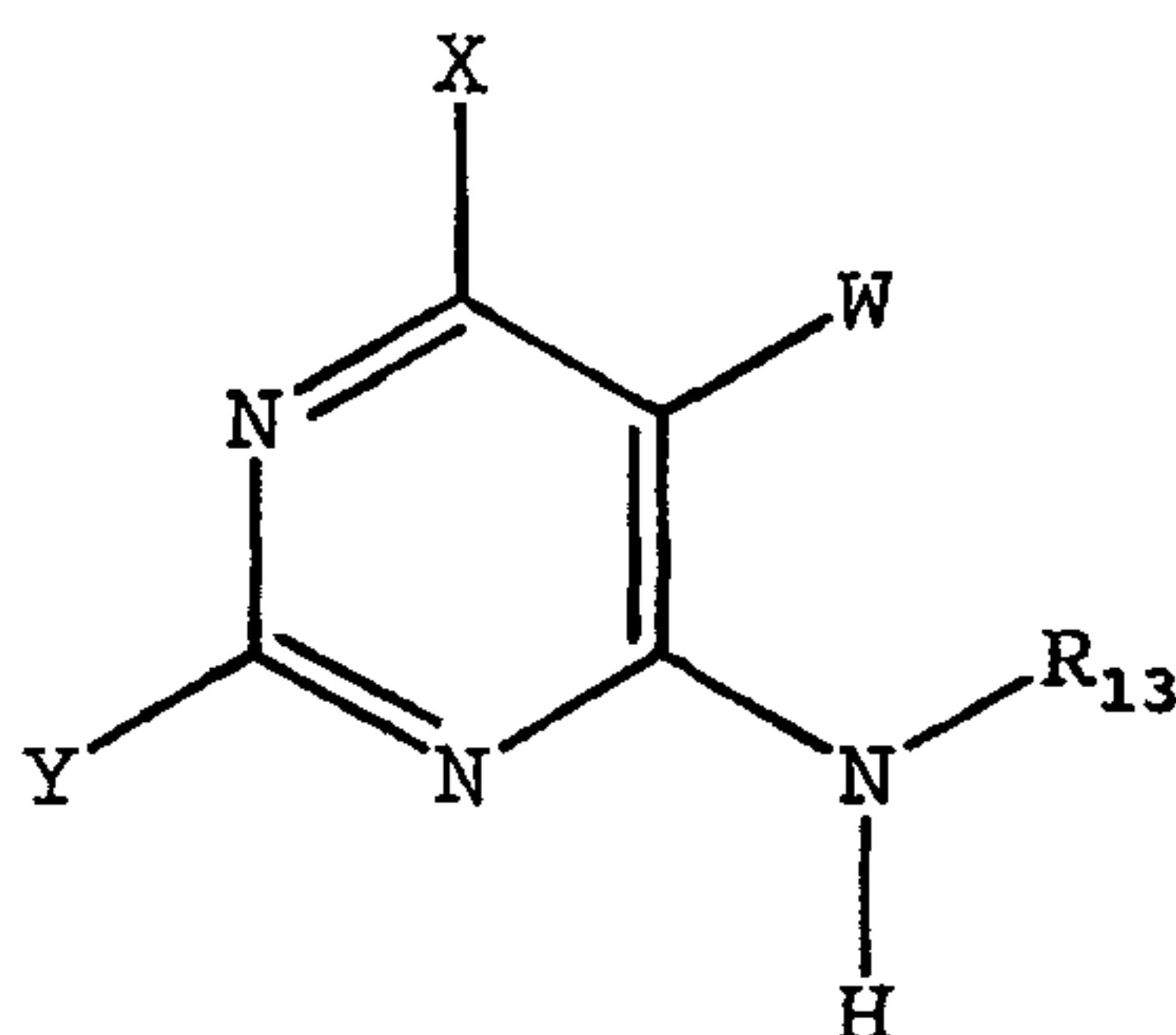
wherein q is an integer from 2 to 4 inclusive;

wherein t is 1 or 2; or

a pharmaceutically acceptable salt thereof.

15

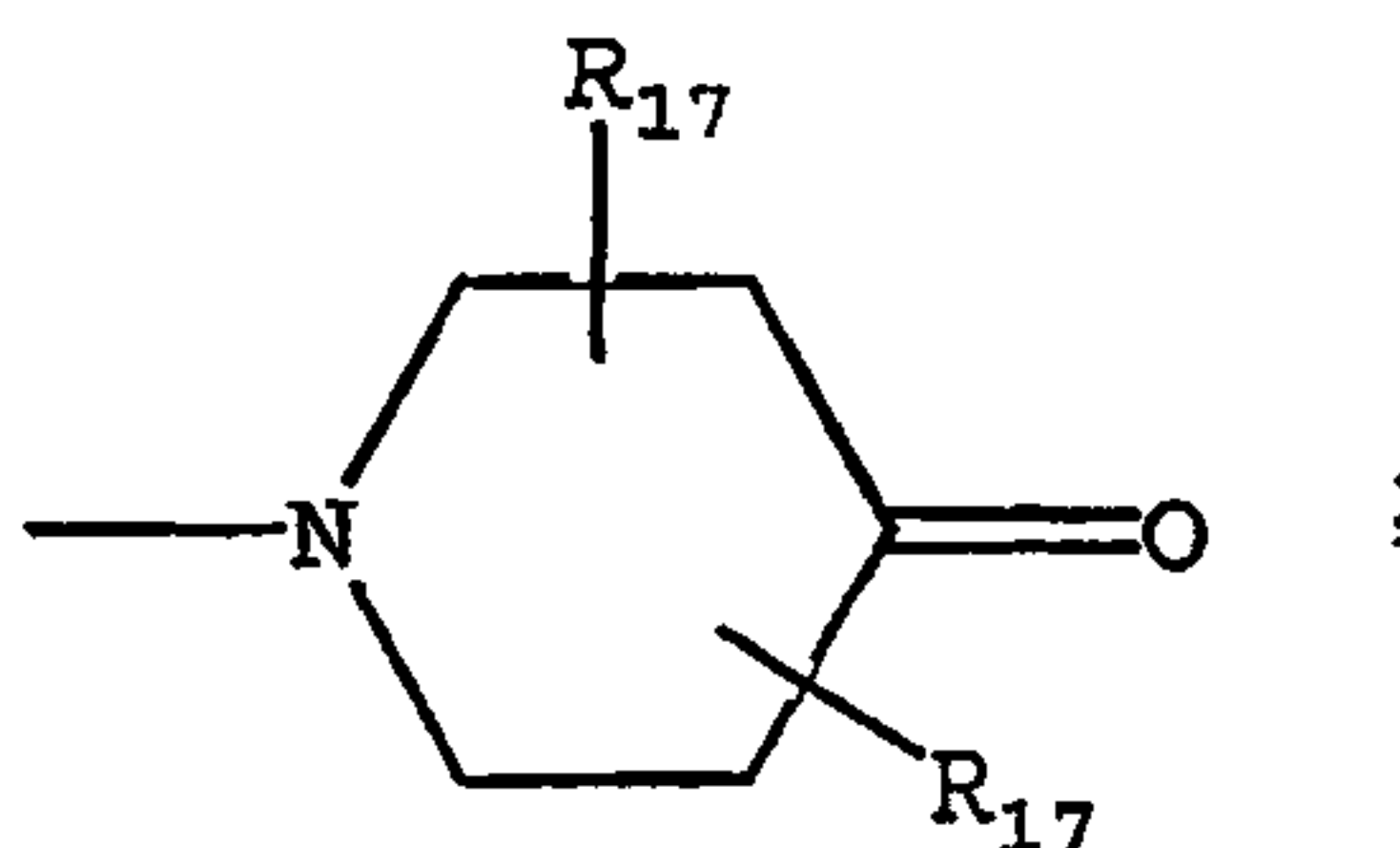
The invention provides a compound having the structure:



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

20

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;

5 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 $(C(R_{19})_2)_m-Z$;

10 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,
 15 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 $(CH_2)_q-O-(CH_2)_m-CH_3$;

20

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
 25 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
 30 or branched C_1 - C_6 alkyl;

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

branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
 C₇ cycloalkyl, C₅-C₇ cycloalkenyl, aryl or aryl(C₁-
 C₆)alkyl;

5

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

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

10

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
 15 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, -NO₂, -CN, straight chained or branched
 20 C₁-C₇ alkyl, straight chained or branched C₁-C₇
 monofluoroalkyl, straight chained or branched C₁-C₇
 polyfluoroalkyl, straight chained or branched C₂-C₇
 alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇
 cycloalkyl, C₅-C₇ cycloalkenyl, -N(R₂₁)₂, -OR₂₁, -COR₂₁, -
 25 CO₂R₂₁, -CON(R₂₁)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

As used in the present invention, the term "cycloalkyl"
 includes, C₃-C₇ cycloalkyl moieties which may be
 substituted with one or more of the following: -F, -NO₂,
 30 -CN, straight chained or branched C₁-C₇ alkyl, straight
 chained or branched C₁-C₇ monofluoroalkyl, straight
 chained or branched C₁-C₇ 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, $-N(R_4)_2$, $-OR_4$, $-COR_4$, $-NCOR_4$, $-CO_2R_4$, -
 5 $CON(R_4)_2$ 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
 10 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
 15 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
 20 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
 25 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 $(CH_2)_n-O-(CH_2)_m-CH_3$.

30 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, 5 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 10 heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyll, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, 15 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 20 moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or 25 branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

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

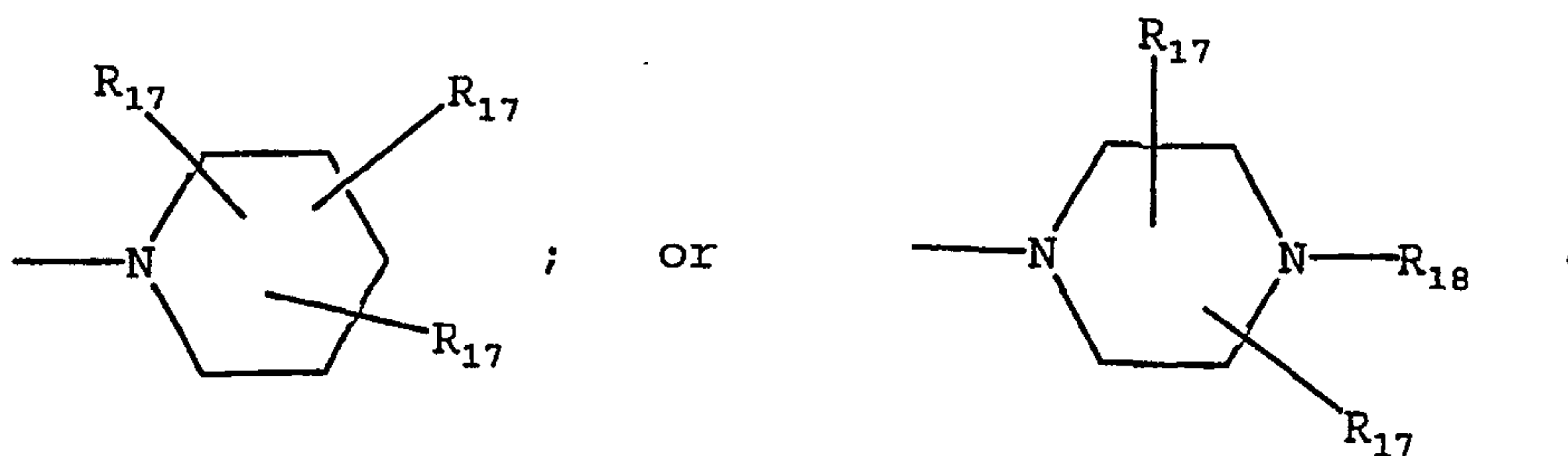
In the present invention the term "aryl" is phenyl or naphthyl. The term "aryl" also includes phenyl and naphthyl which may be substituted with one or more of the following: -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₄)₂, -OR₄, -SR₄, -OCOR₄, -COR₄, -NCOR₄, -CO₂R₄, -CON(R₄)₂ or (CH₂)_n-O-(CH₂)_m-CH₃.

15

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.

25

In one embodiment, X is:



WO 02/060392

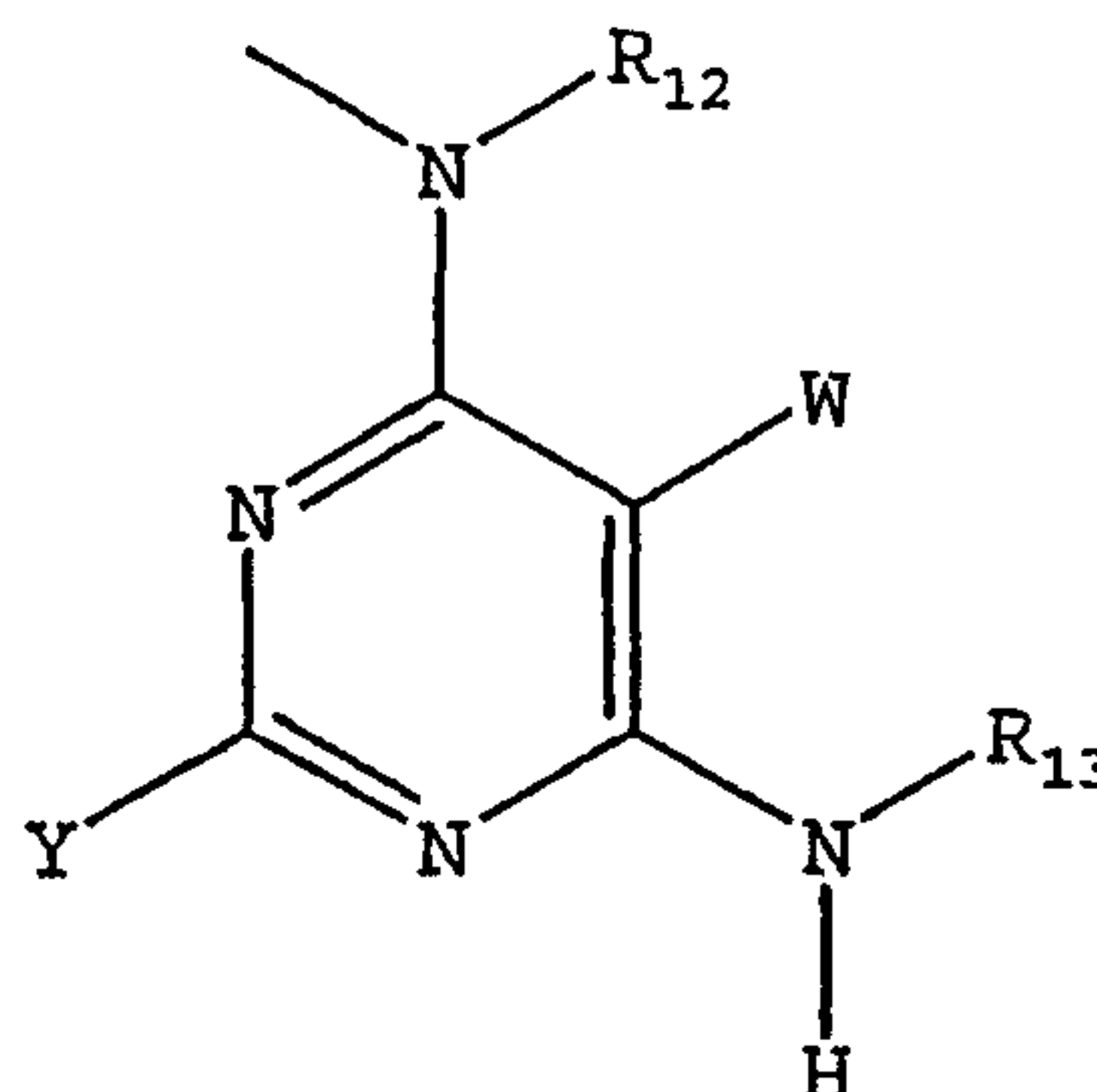
PCT/US02/04608

238

In one embodiment, X is $\text{NR}_{11}\text{R}_{12}$ and R_{11} is H or straight chained or branched $\text{C}_1\text{-C}_7$ alkyl.

5

In one embodiment, the compound has the structure:

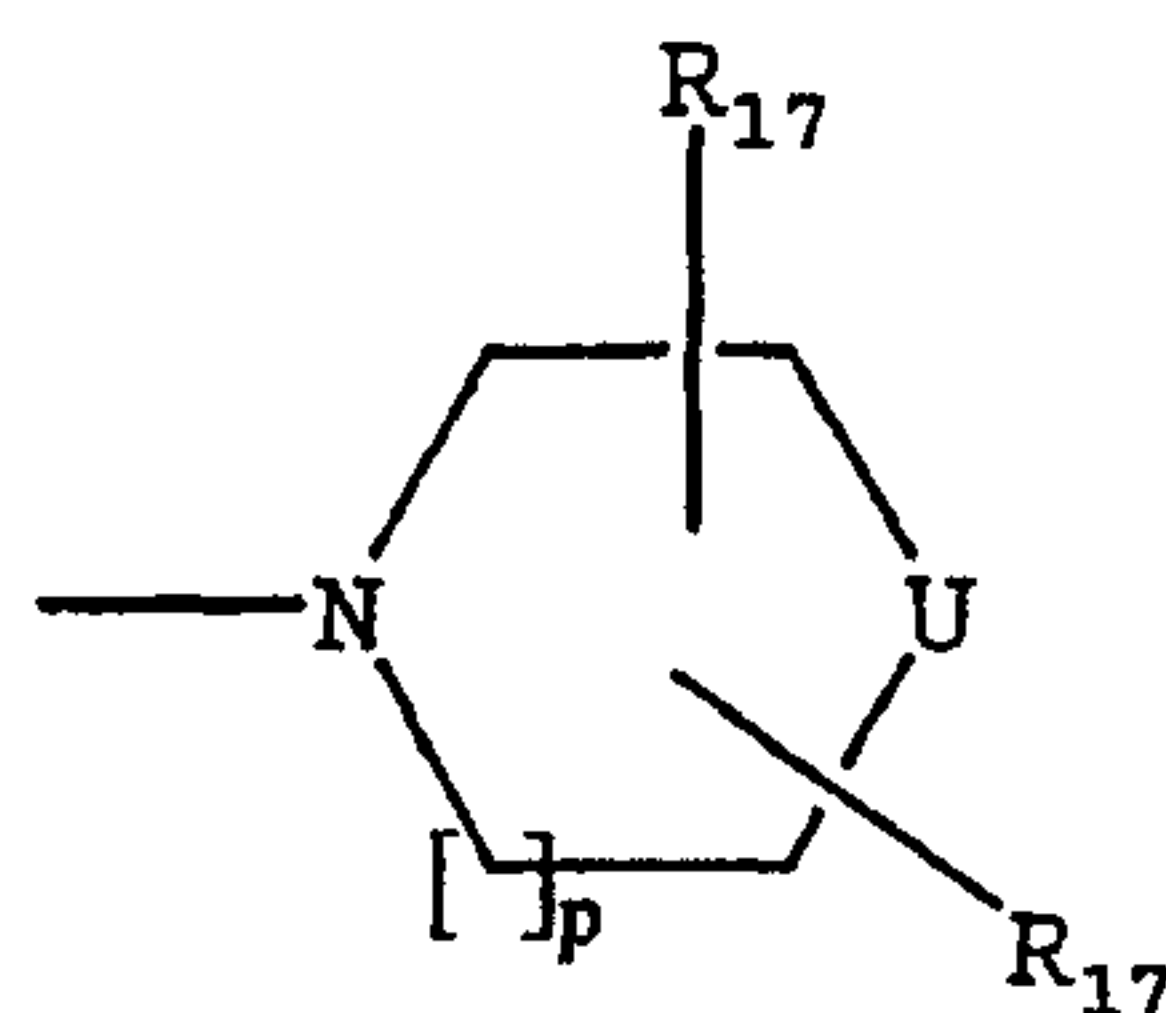


In one embodiment, R_{13} is a bicyclic alkyl ring system, cyclohexyl or aryl.

10

In one embodiment, R_{14} is H, straight chained or branched $\text{C}_1\text{-C}_6$ alkyl or $(\text{CH}_2)_q\text{-O-(CH}_2)_m\text{-CH}_3$.

15 In one embodiment, Y is



In one embodiment, U is NR_{16} .

WO 02/060392

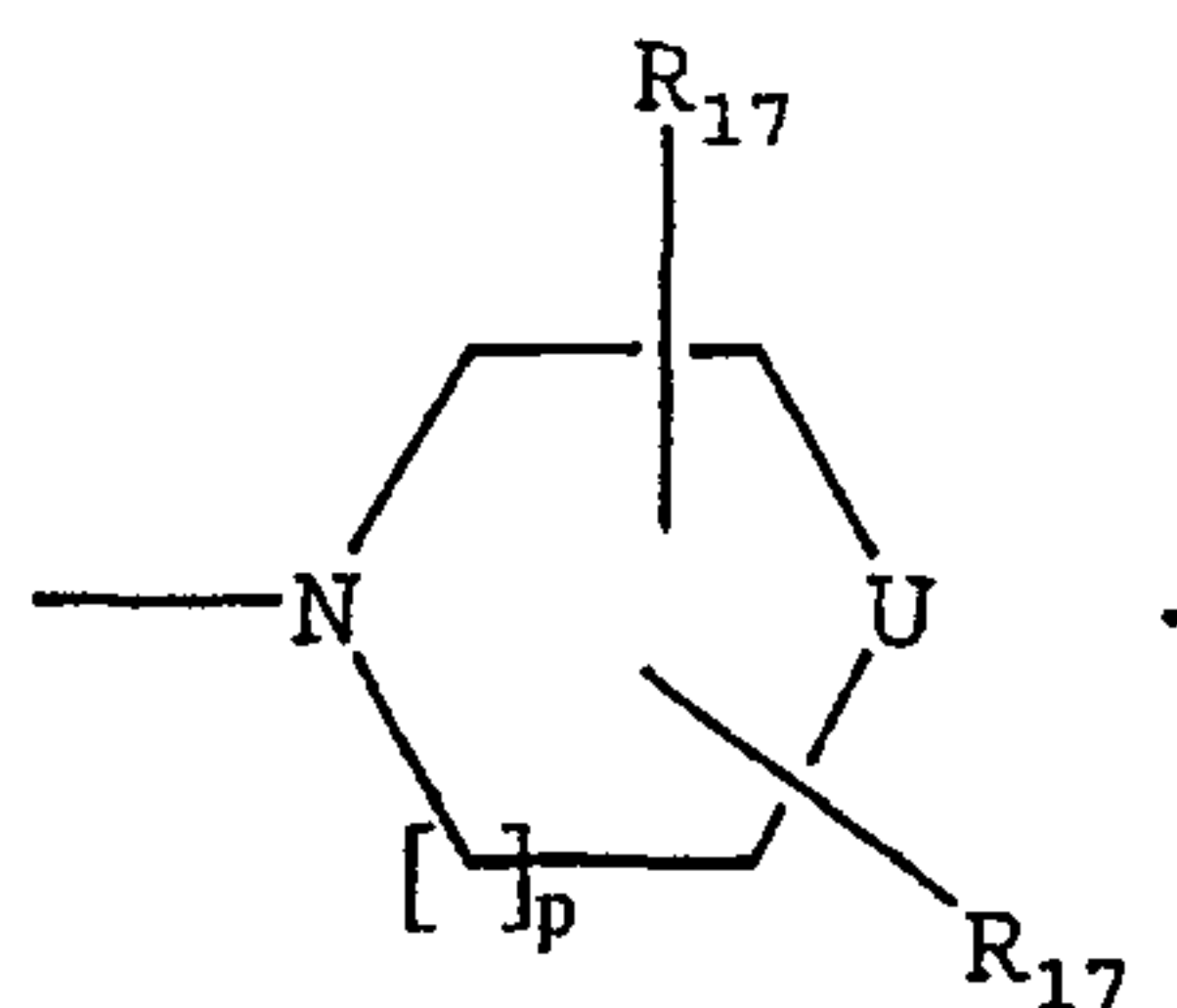
PCT/US02/04608

239

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

In one embodiment Z is aryl or heteroaryl.

5 In one embodiment, Y is



In one embodiment, U is NR_{16} .

10

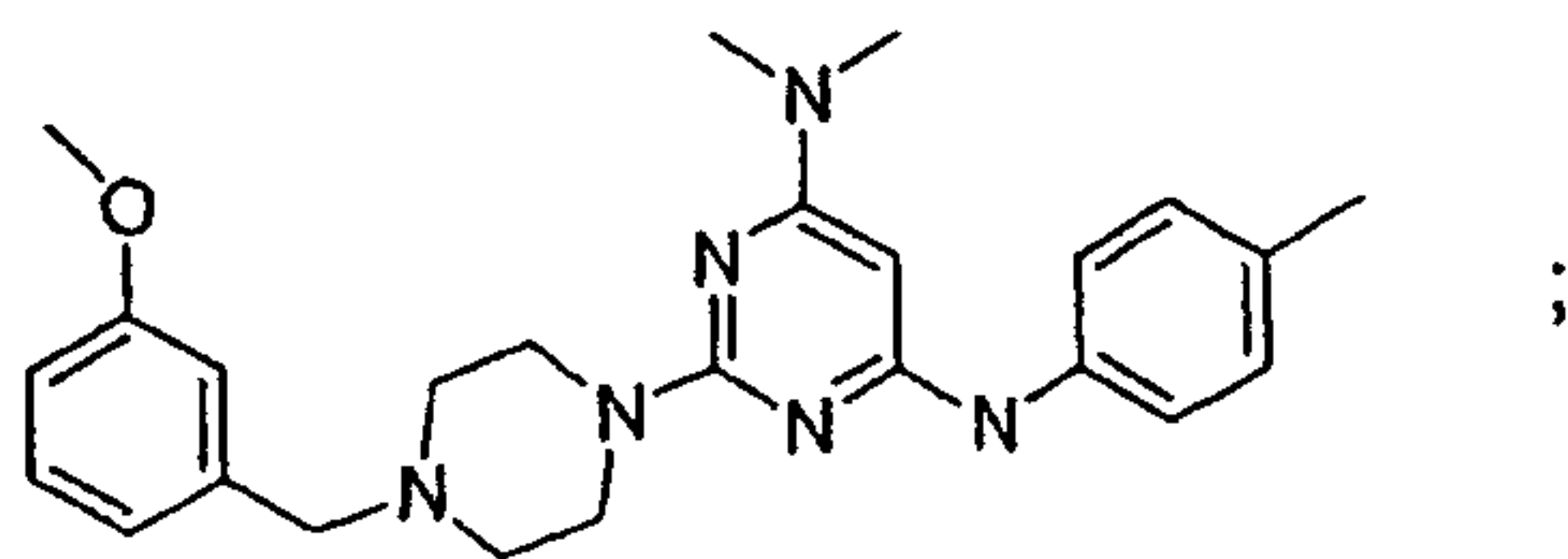
In one embodiment, the compound is selected from the group consisting of:

15

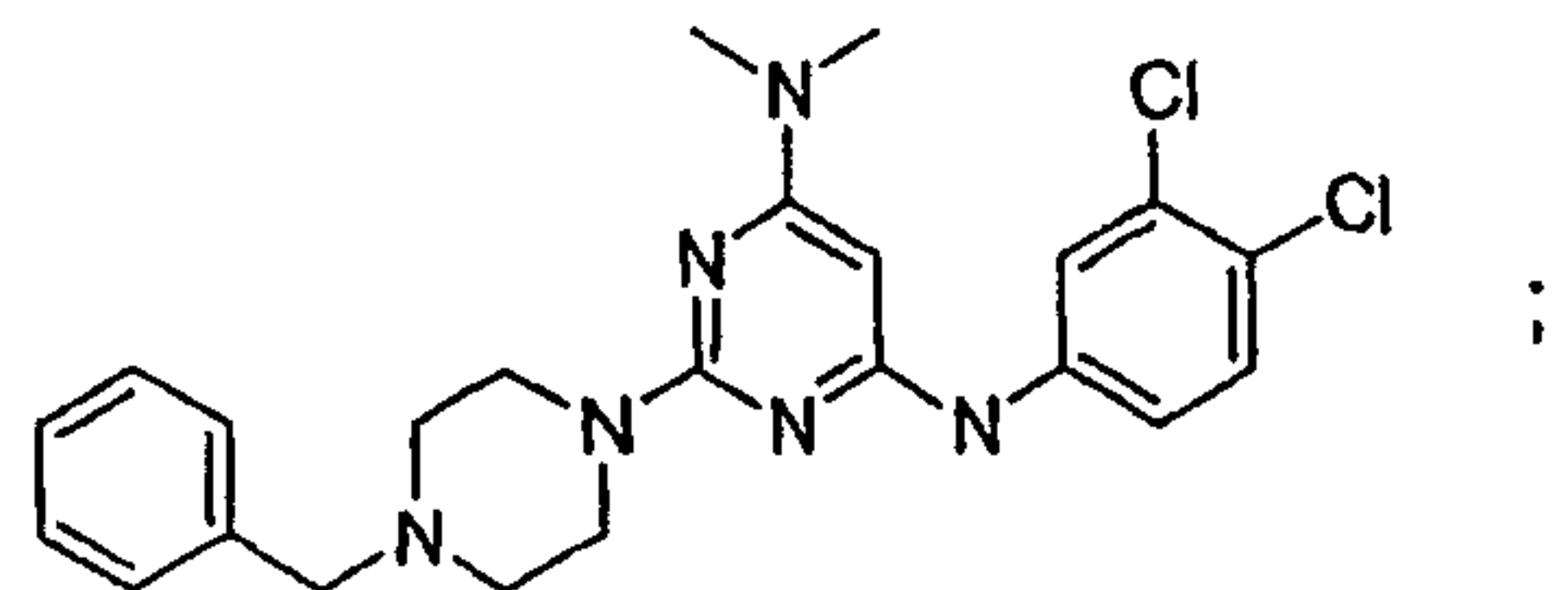
WO 02/060392

PCT/US02/04608

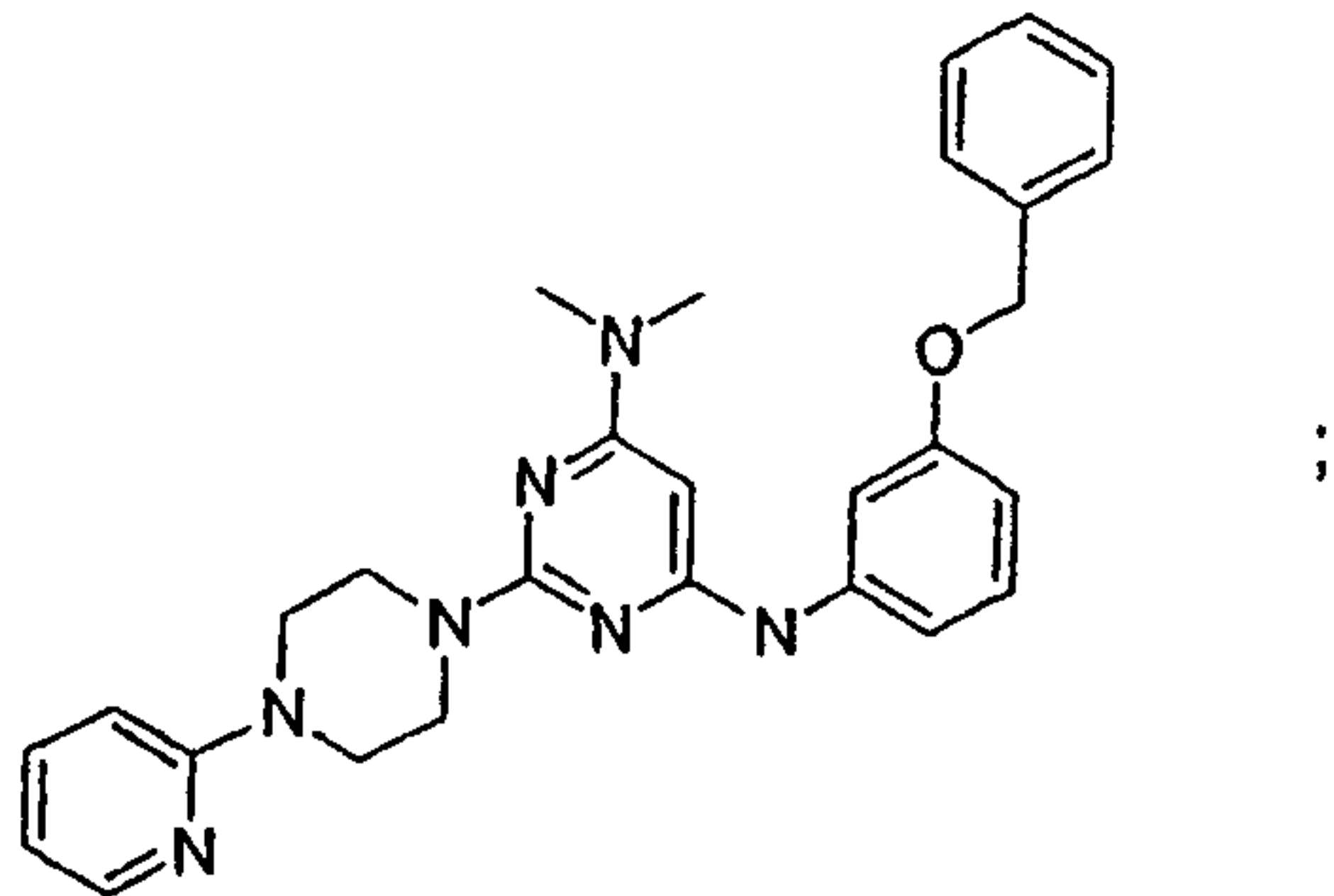
240



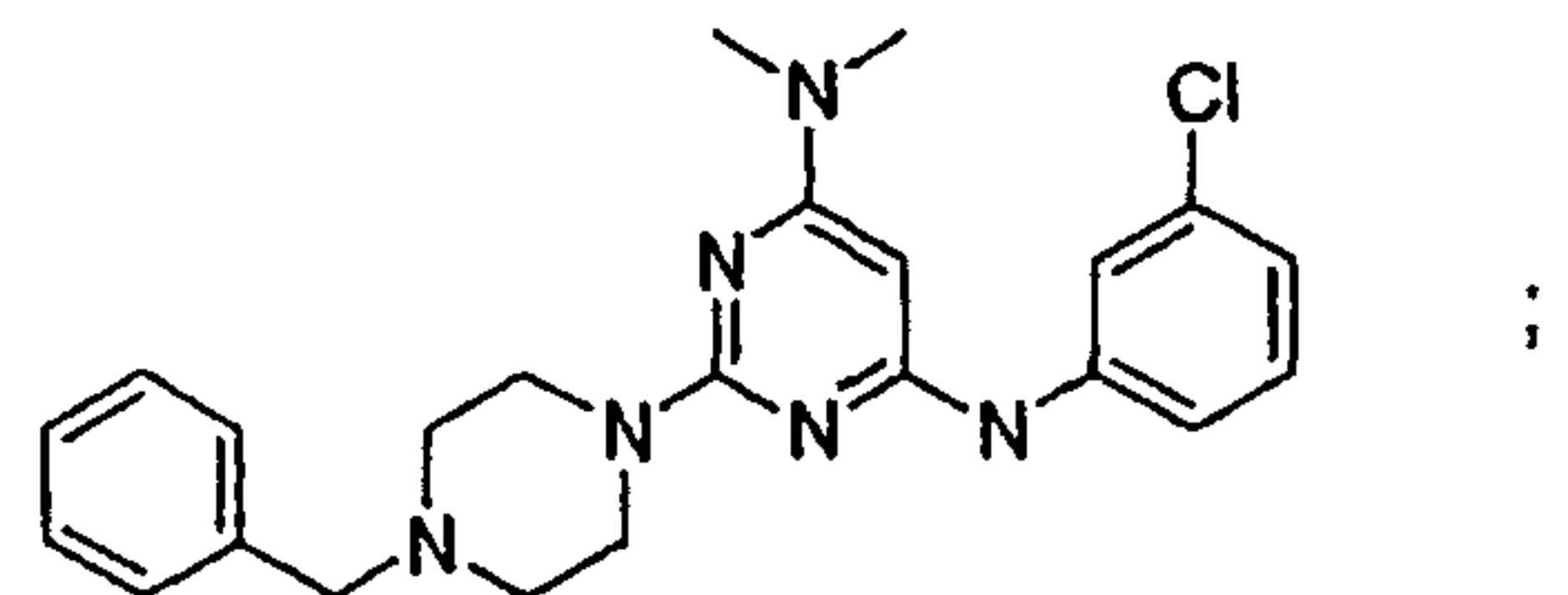
;



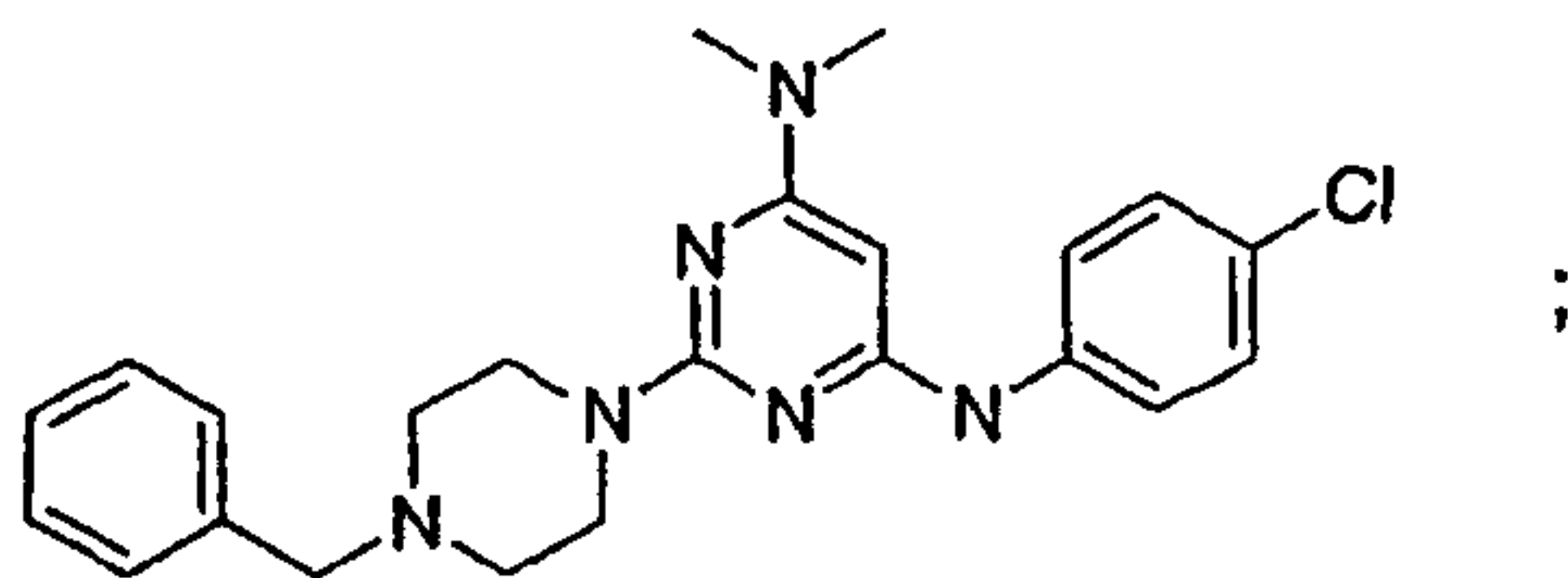
;



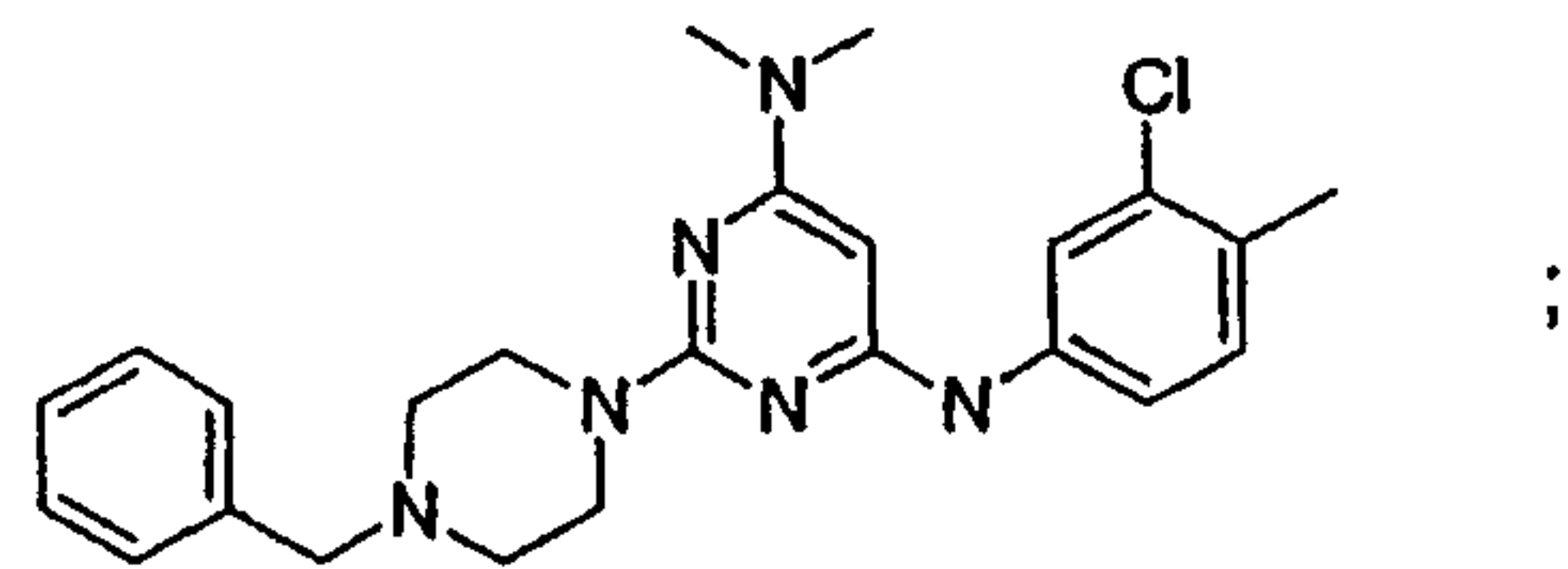
;



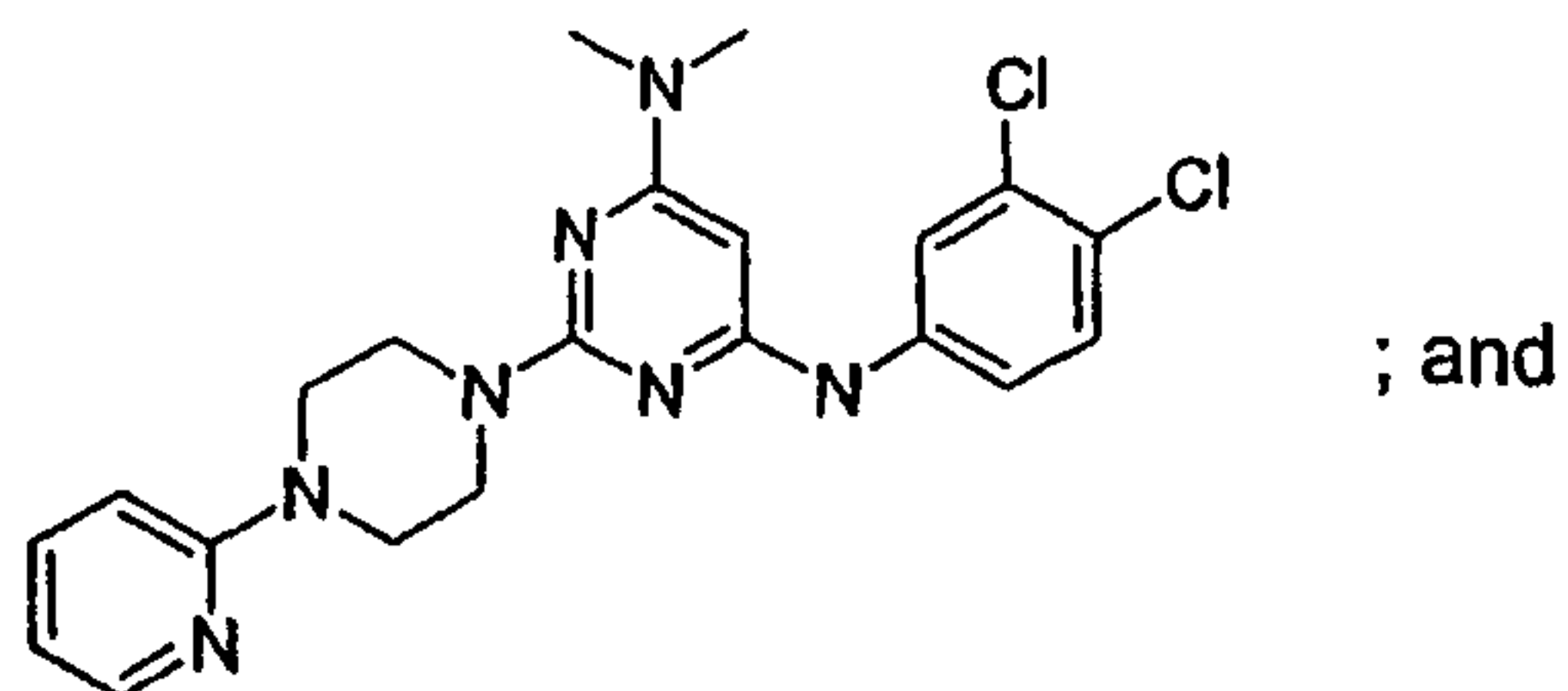
;



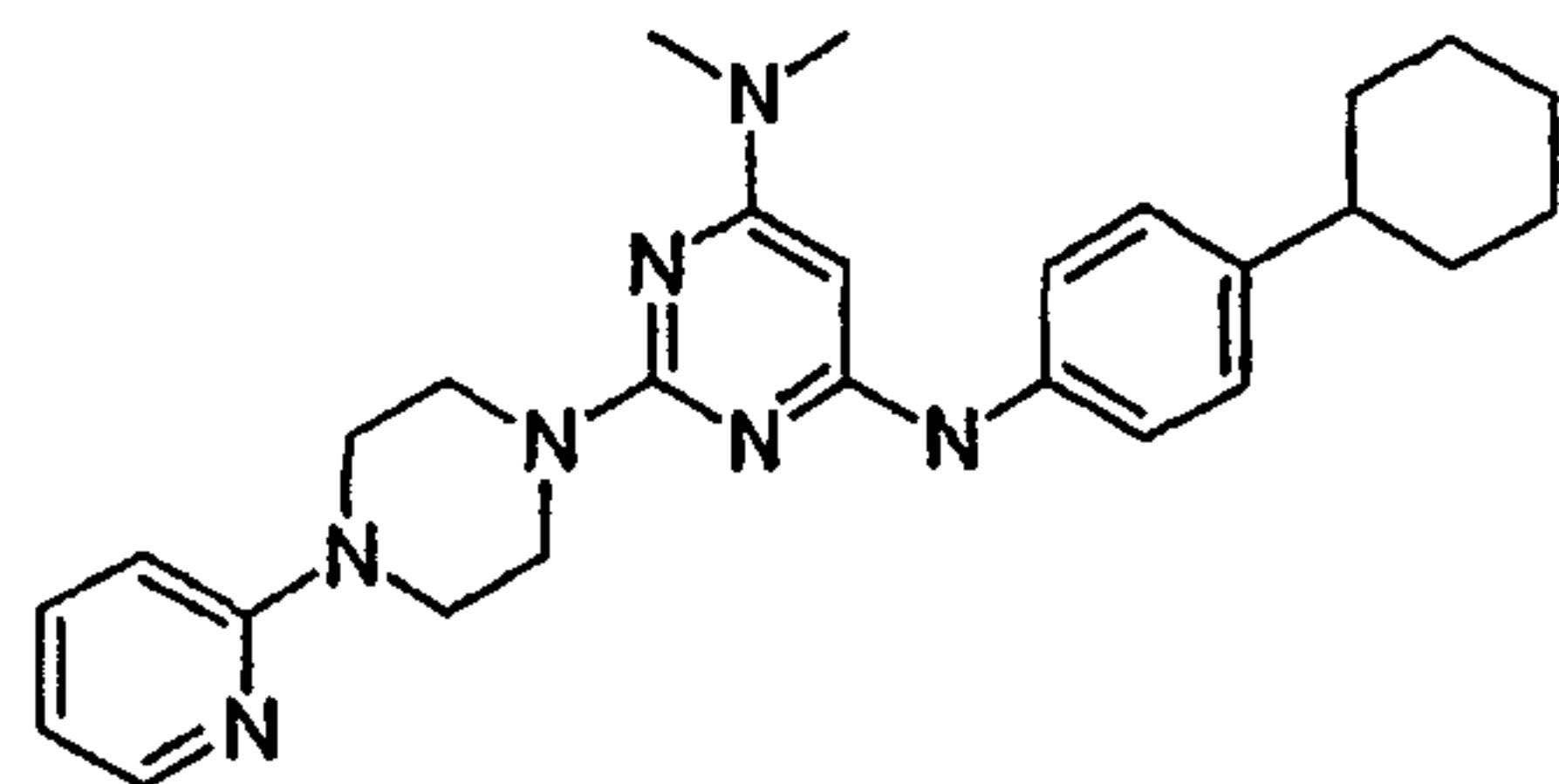
;



;



; and

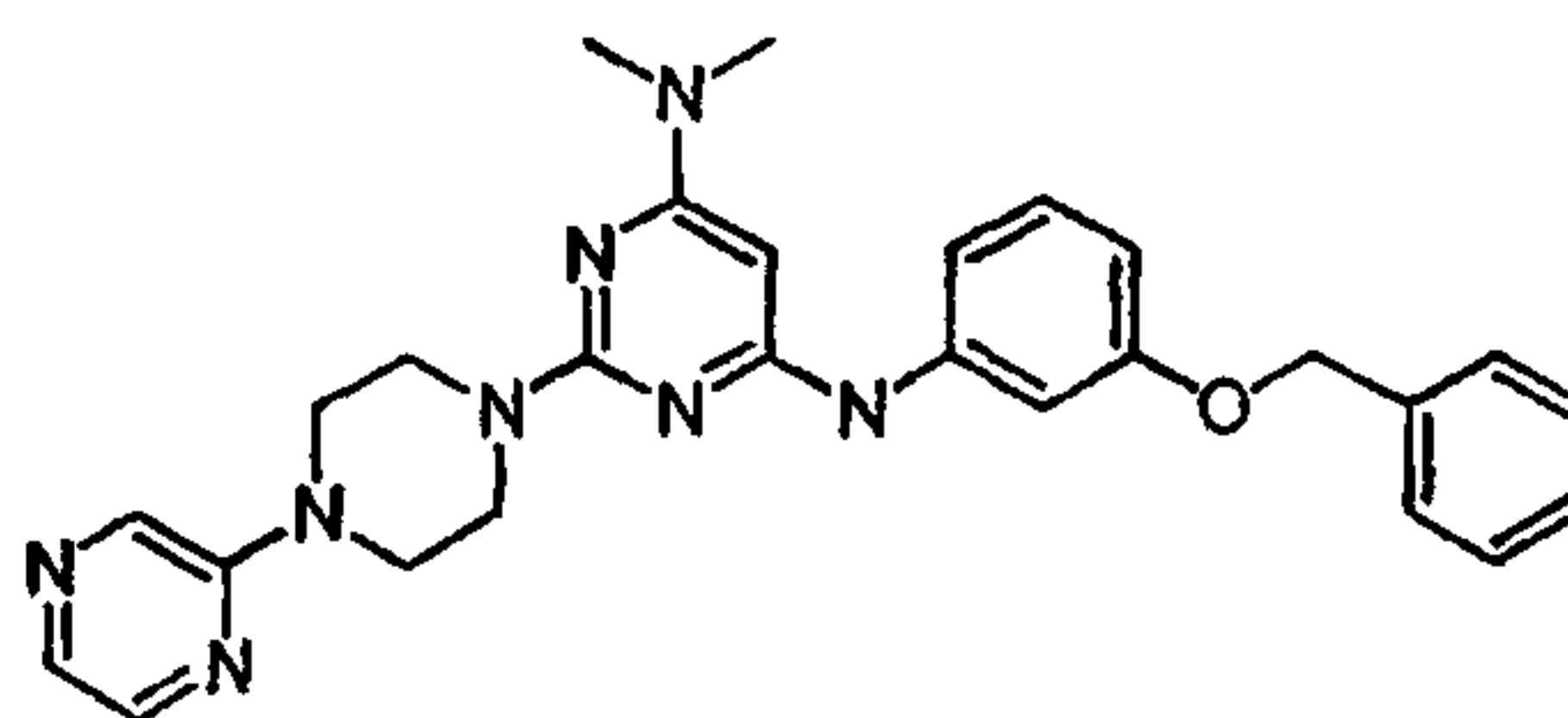
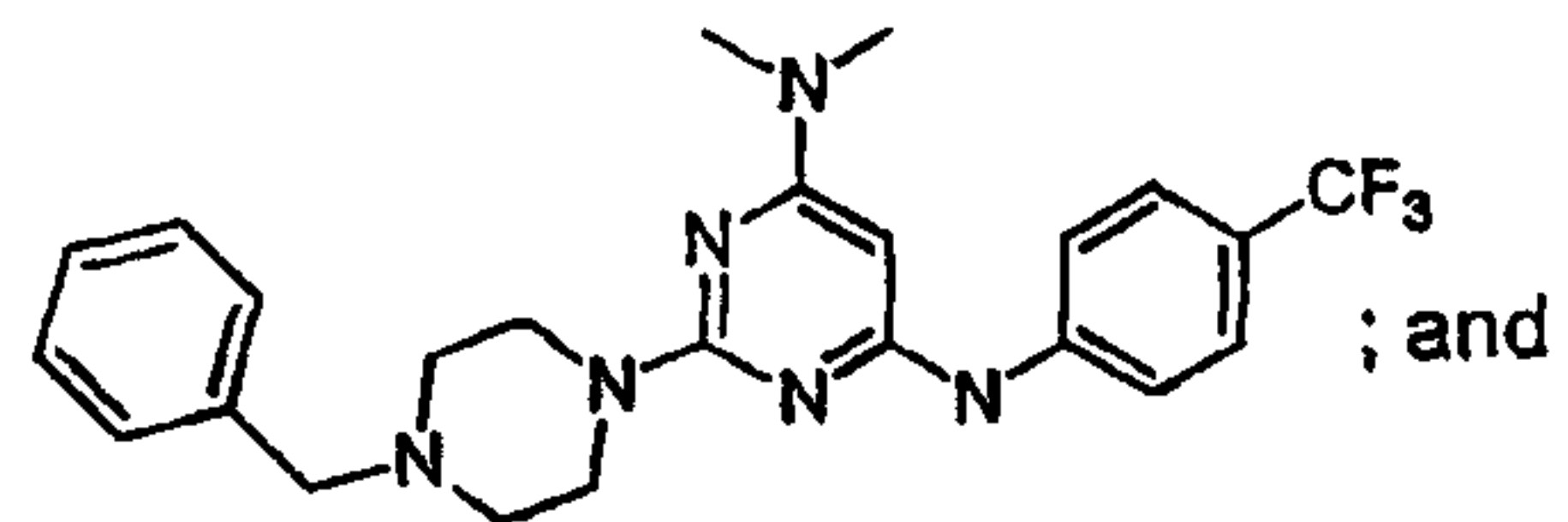
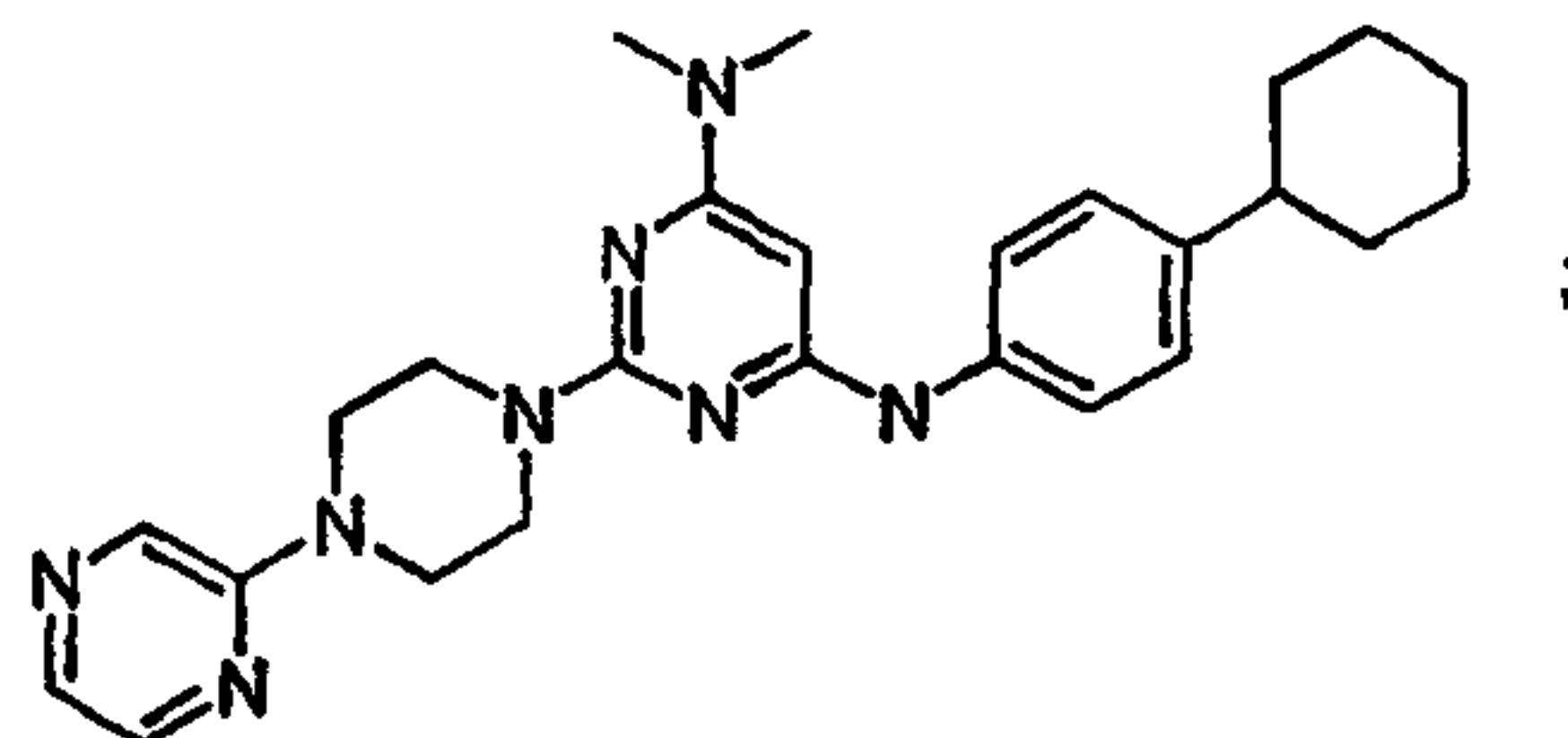
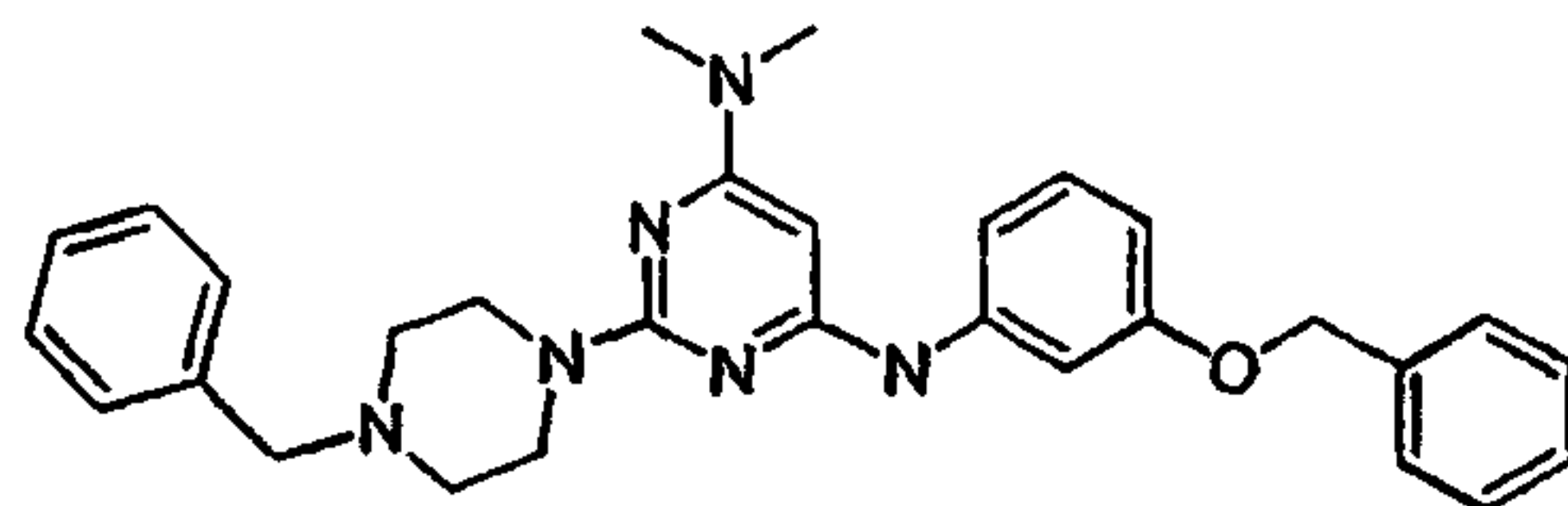
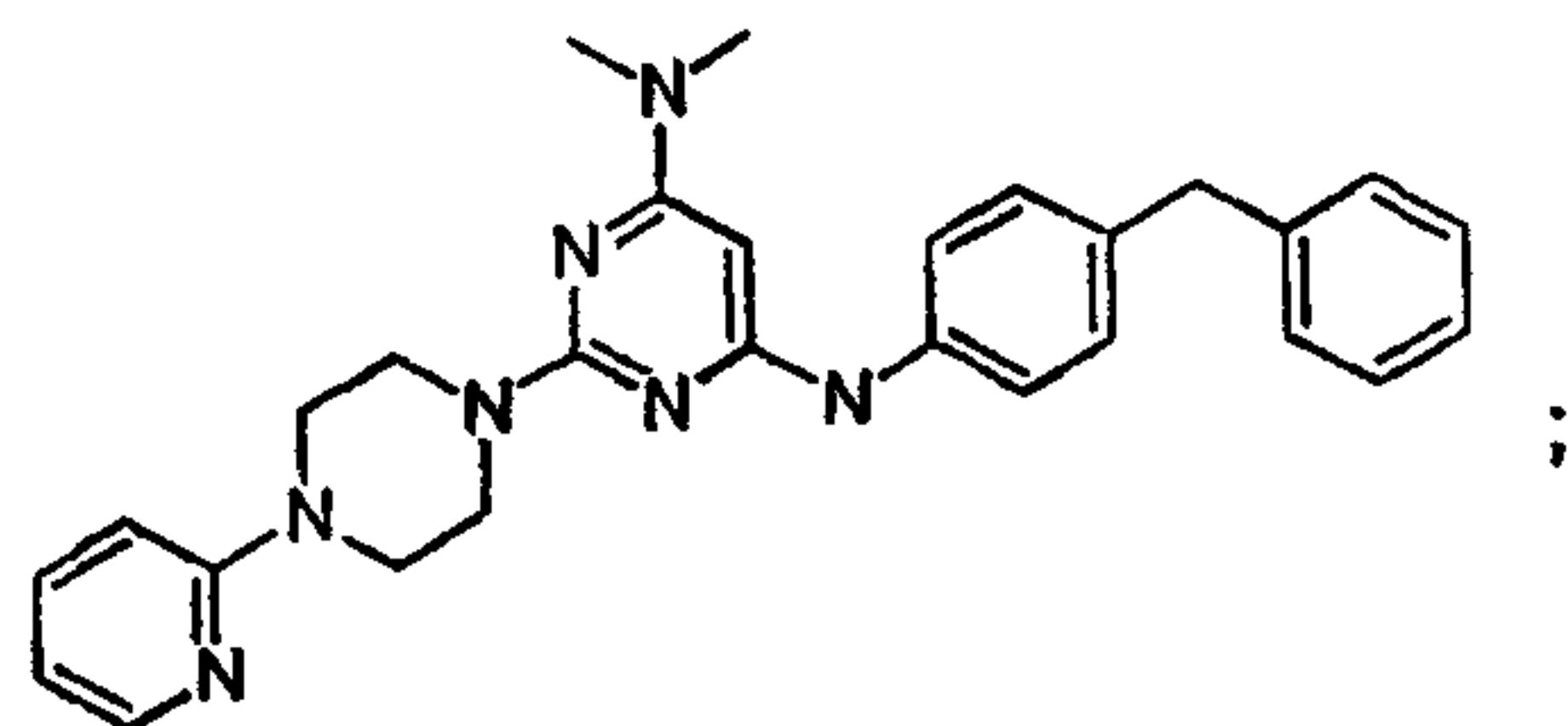
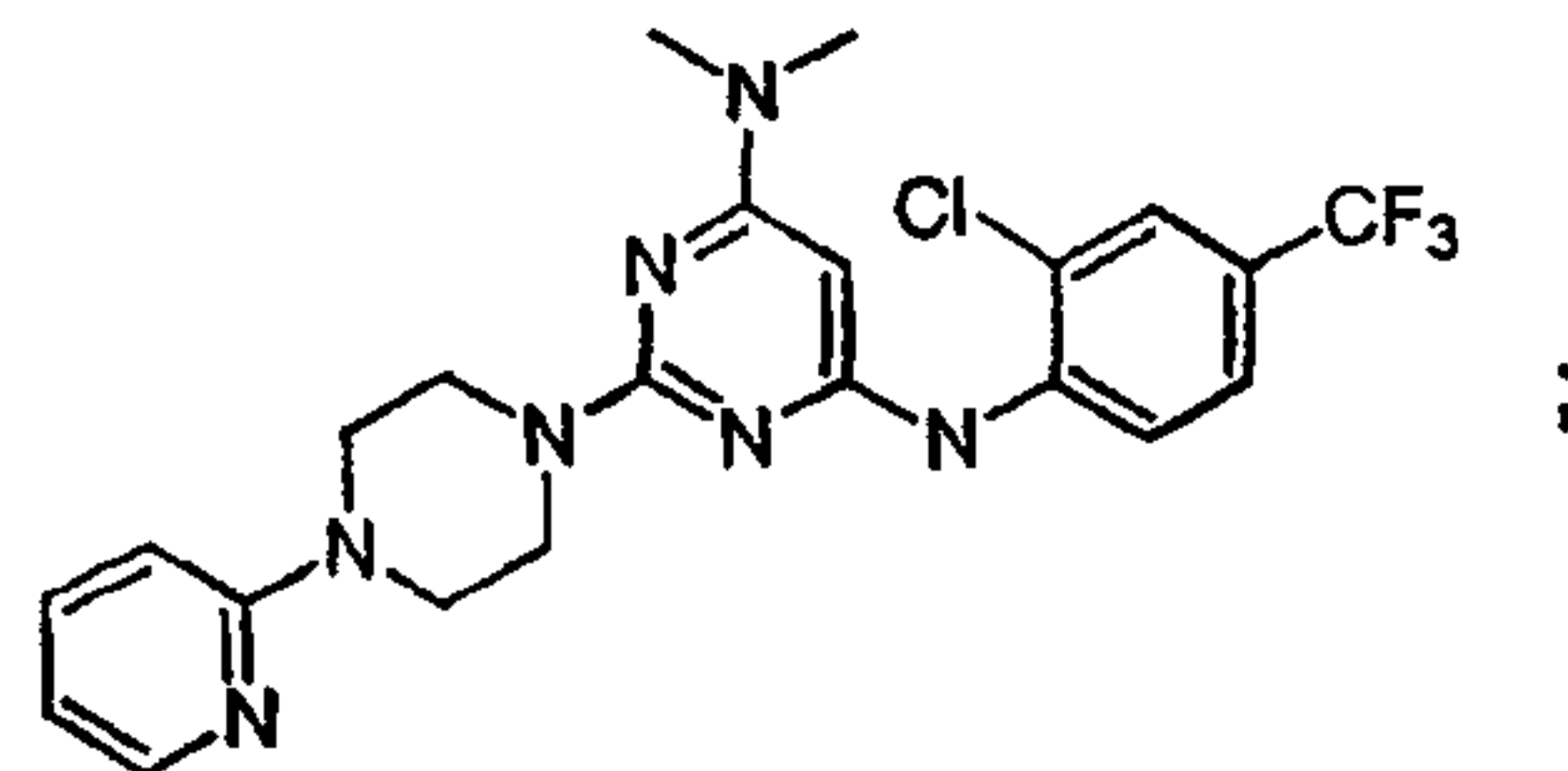
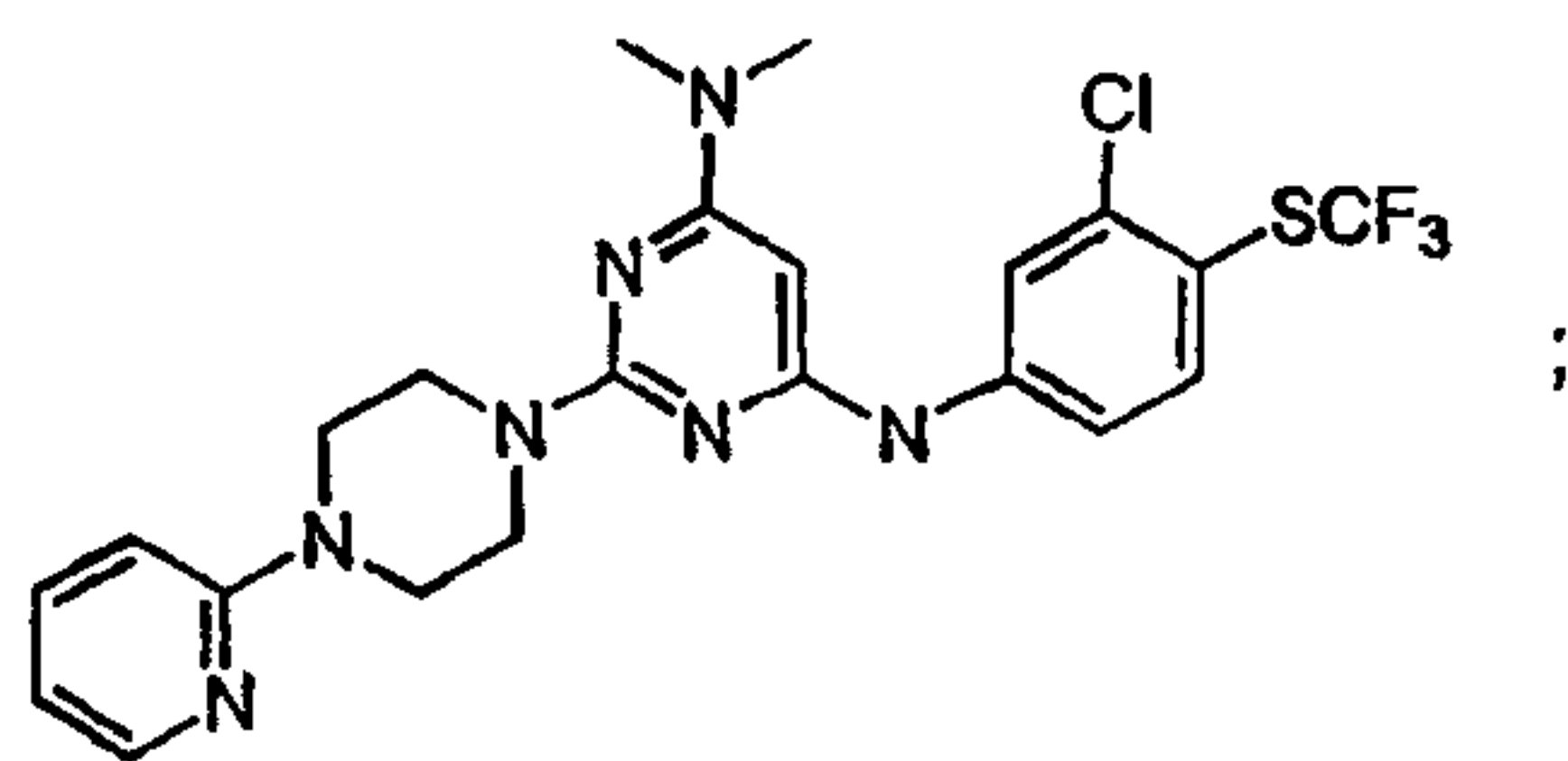
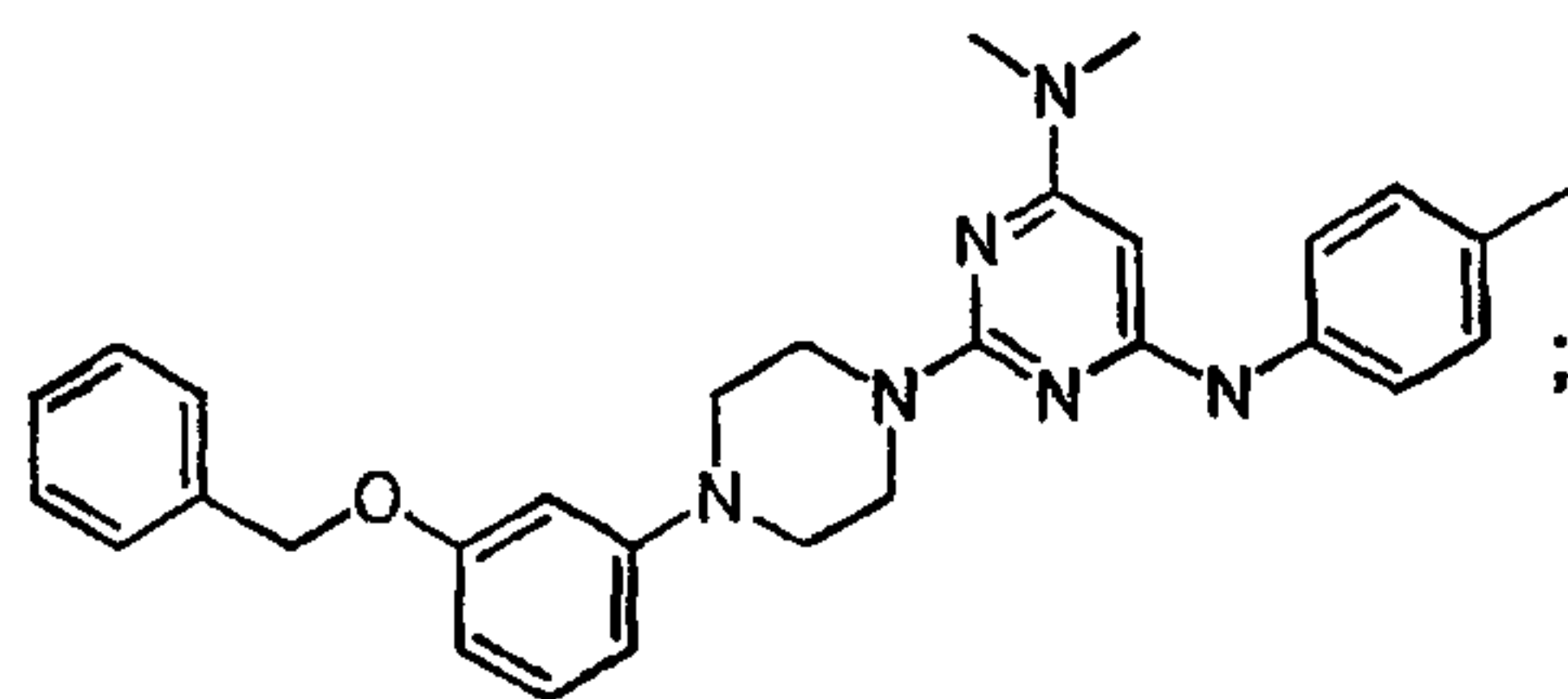
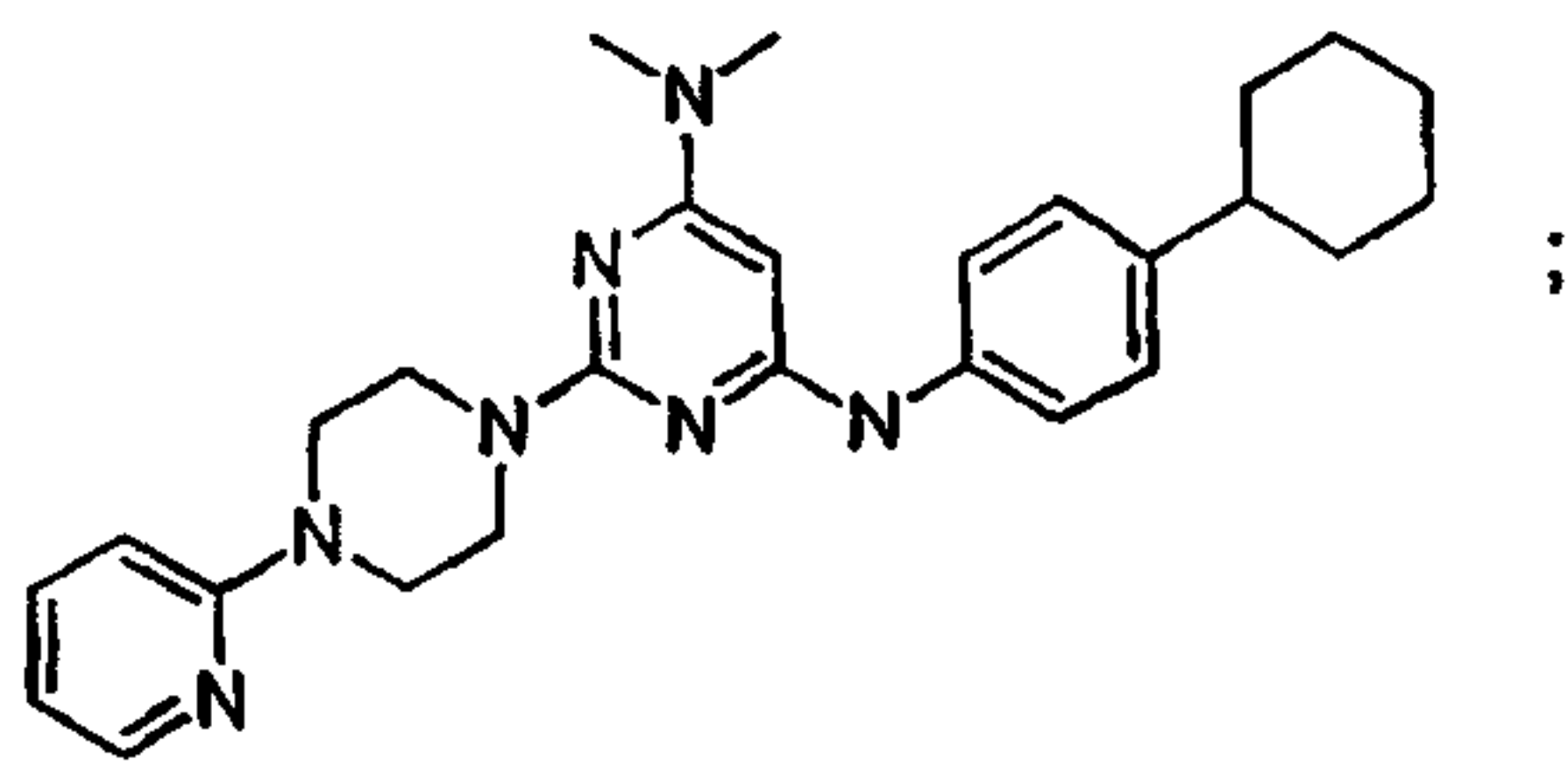


In one embodiment, the compound is selected from the group consisting of:

WO 02/060392

PCT/US02/04608

241



5

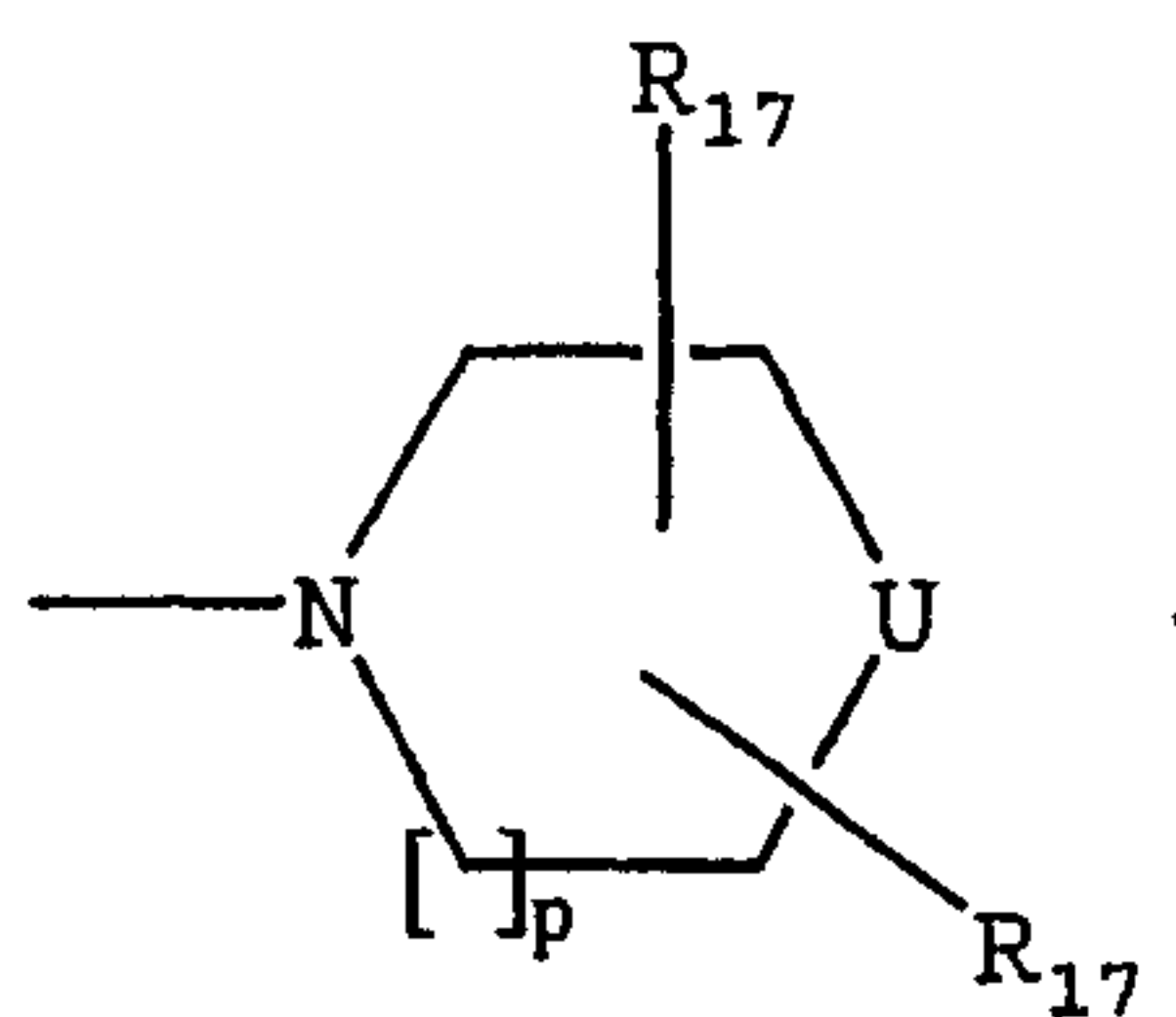
In one embodiment, X is N(CH₃)₂.

WO 02/060392

PCT/US02/04608

242

In one embodiment, Y is



5

In one embodiment, R₁₃ is an aryl substituted with a C₁-C₁₀ straight chained alkyl.

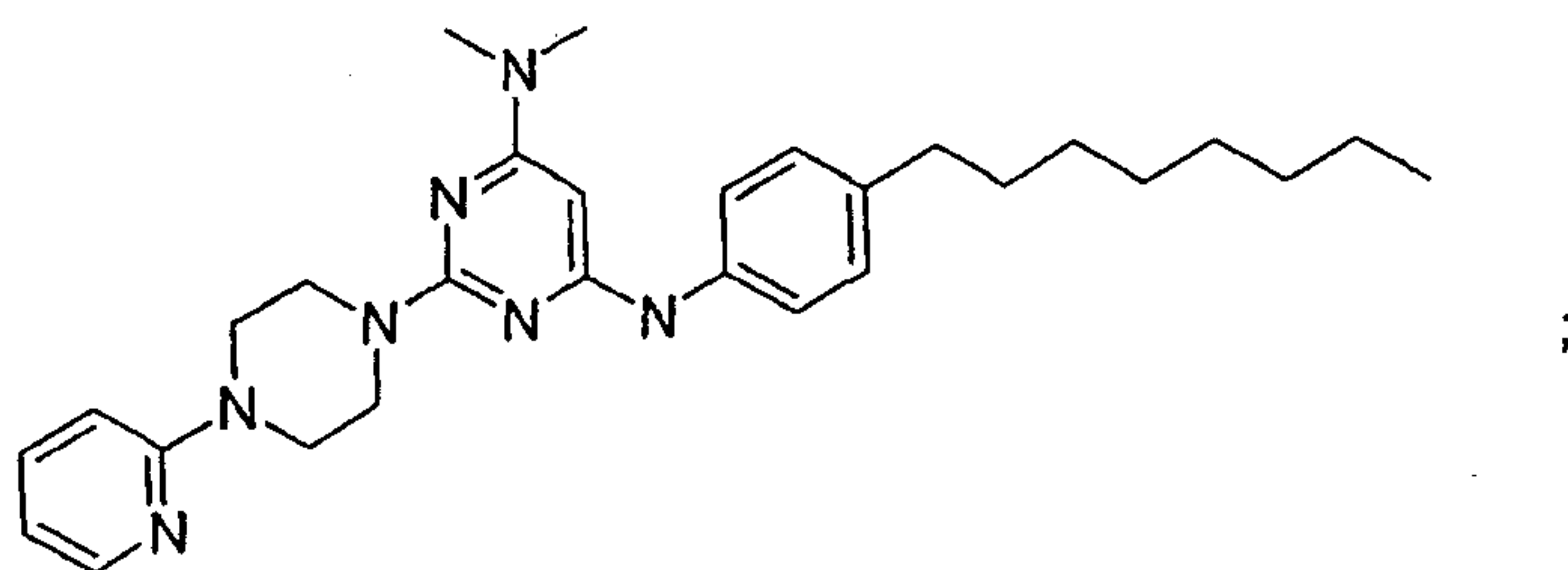
10

15

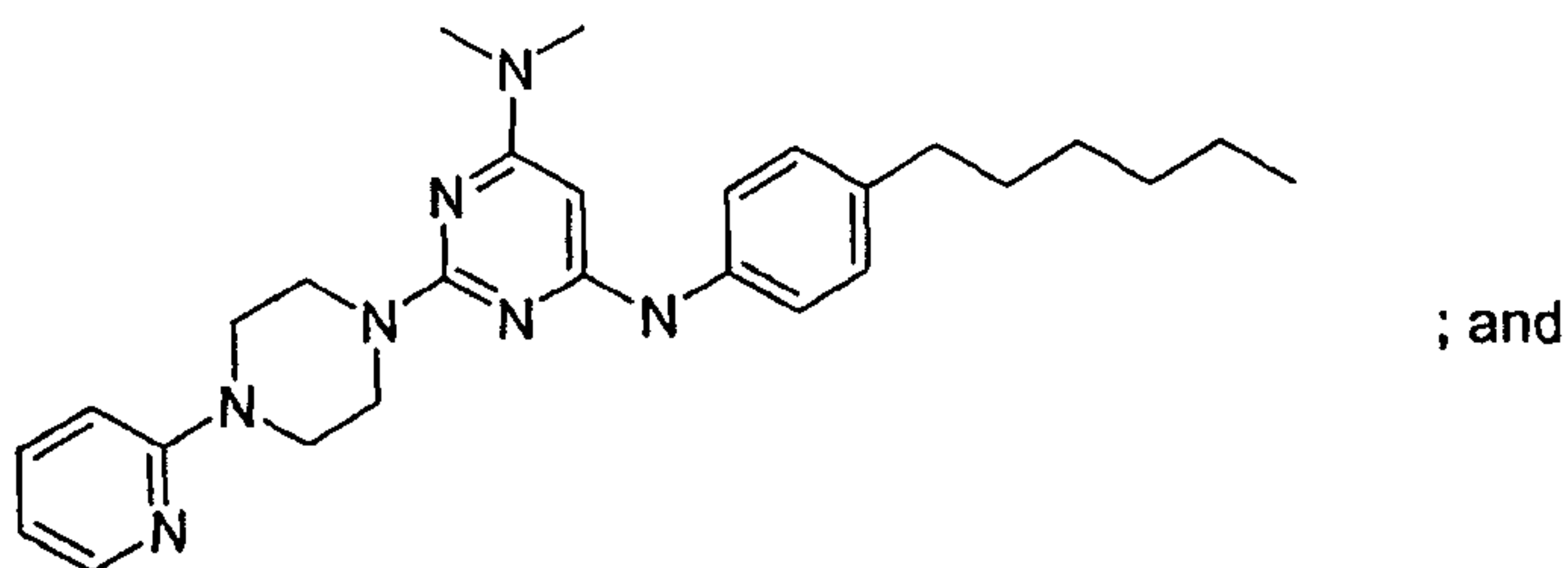
20

25

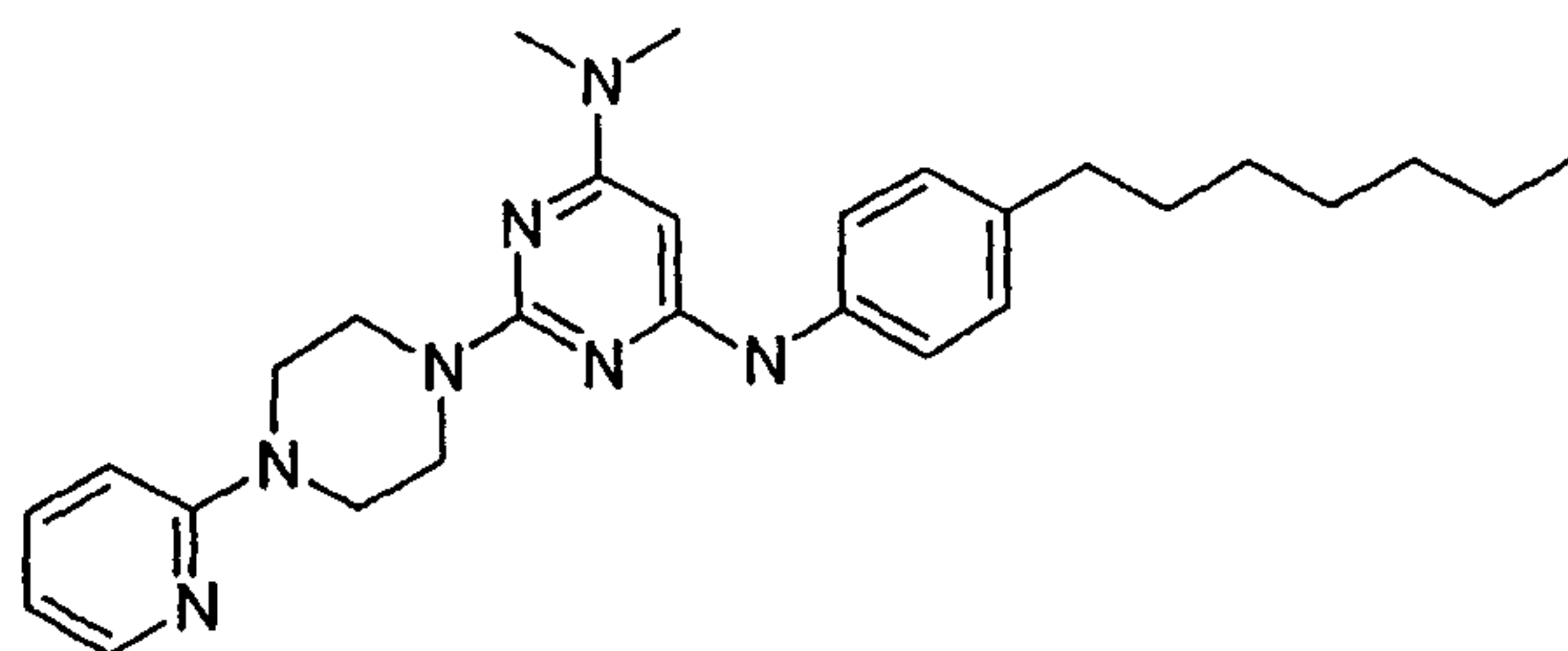
In one embodiment, the compound is selected from a group consisting of:



;



; and



5

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.

WO 02/060392

PCT/US02/04608

244

The invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of any of the compounds
5 described herein and a pharmaceutically acceptable carrier.

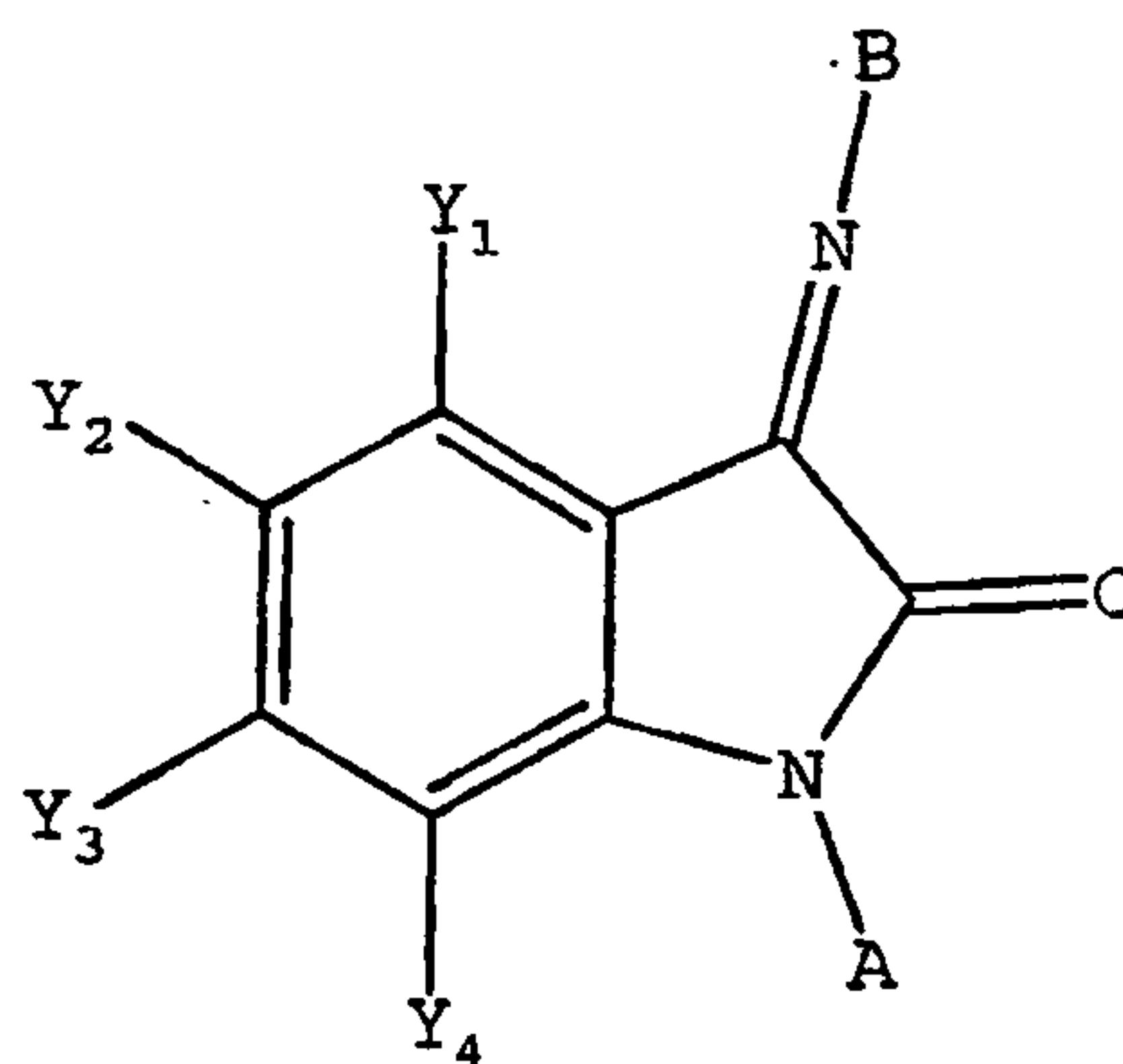
The invention provides a method of treating a subject suffering from depression which comprises administering
10 to the subject an amount of any of the compounds described herein effective to treat the subject's depression.

The invention provides a method of treating a subject
15 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
20 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.

25

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



10 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 -
 15 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;

20 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;

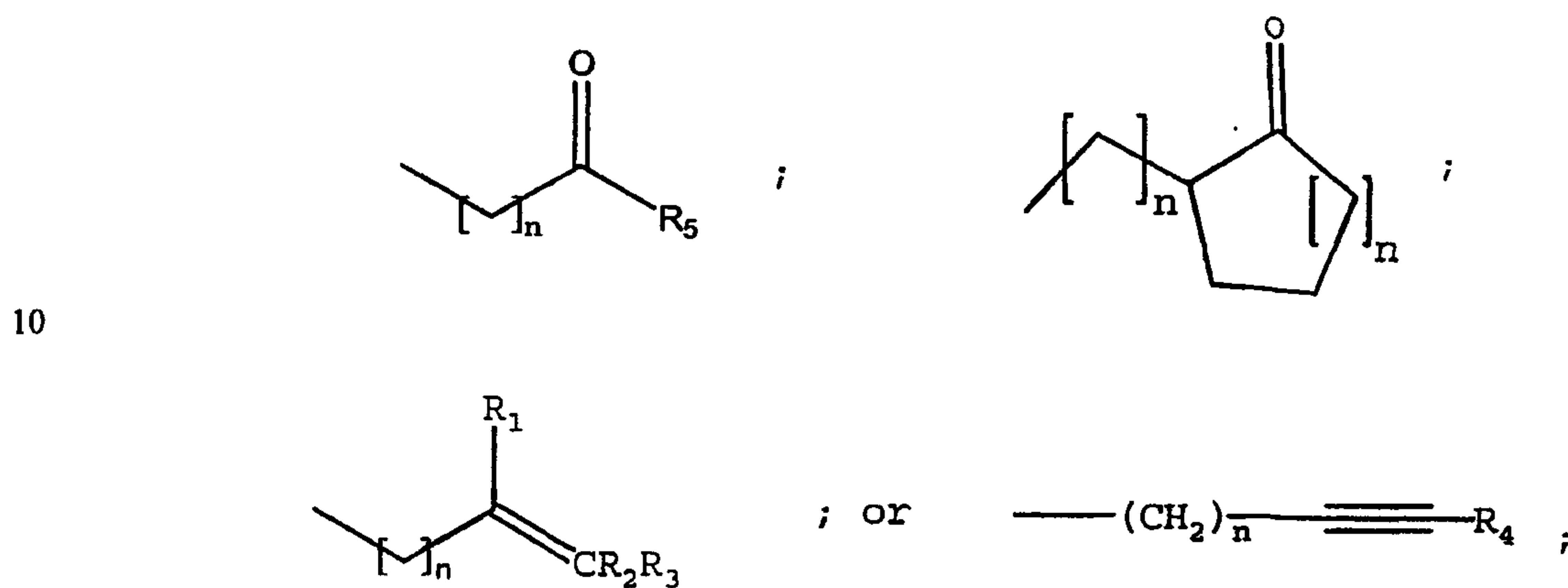
WO 02/060392

PCT/US02/04608

246

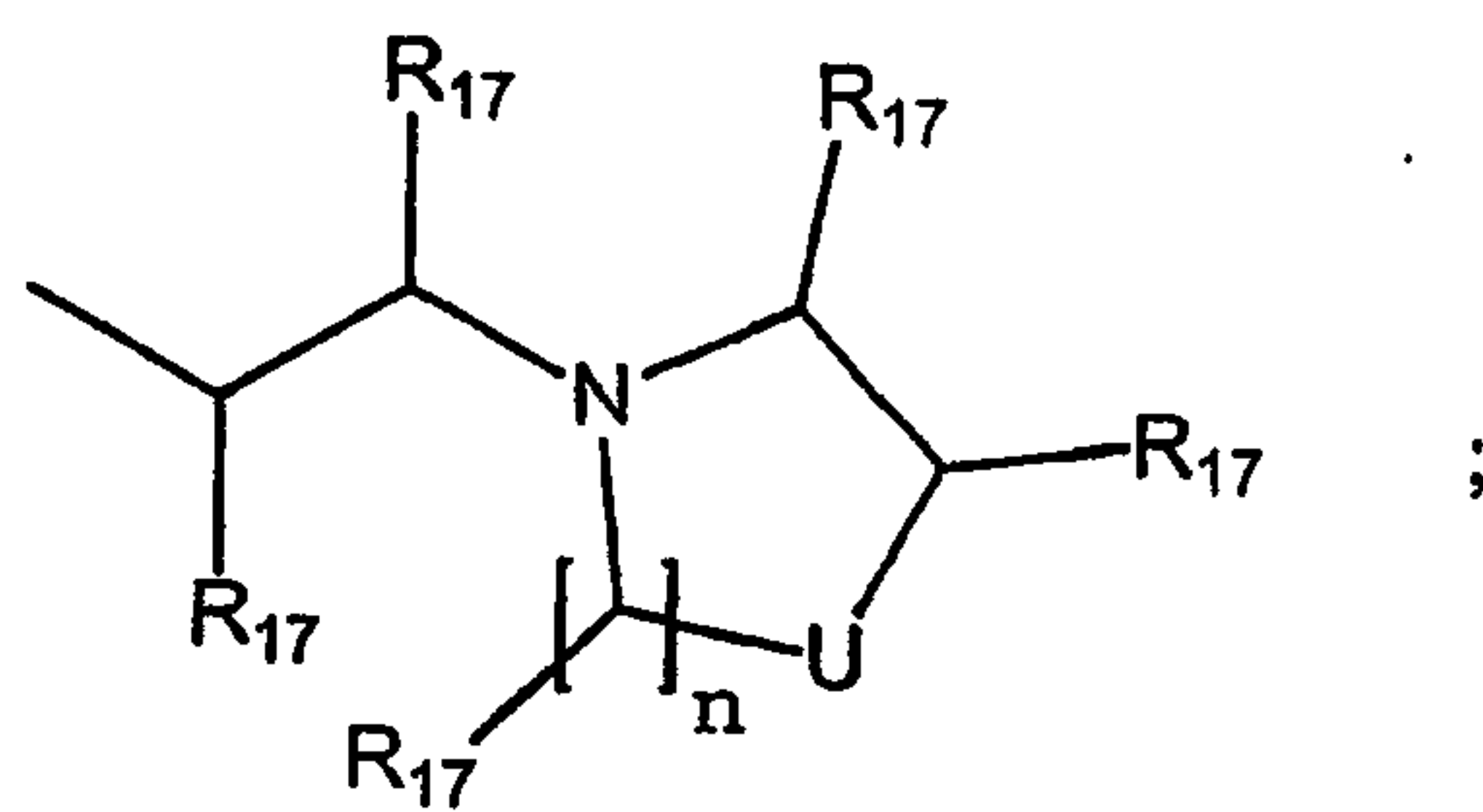
wherein A is A', Q₃, Q₄, Q₅, straight chained or
 branched C₁-C₇ alkyl, aryl, heteroaryl, aryl(C₁-
 C₆)alkyl, heteroaryl(C₁-C₆)alkyl, aryl substituted
 5 with an aryl or heteroaryl, heteroaryl substituted
 with an aryl or heteroaryl; or (CHR₁₇)-(CHR₁₇)_n-Z;

wherein A' is



wherein Q₃ is

15



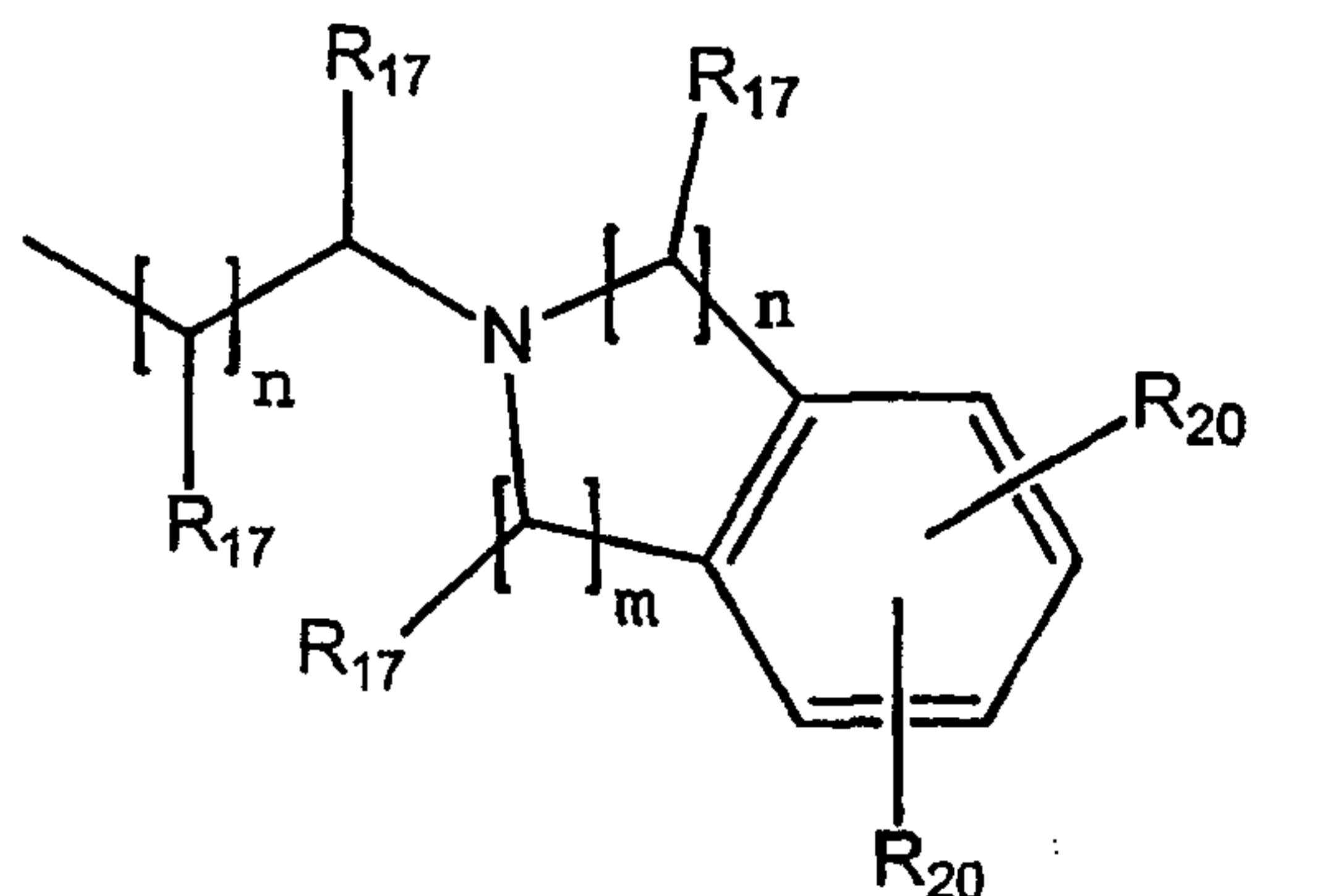
20

WO 02/060392

PCT/US02/04608

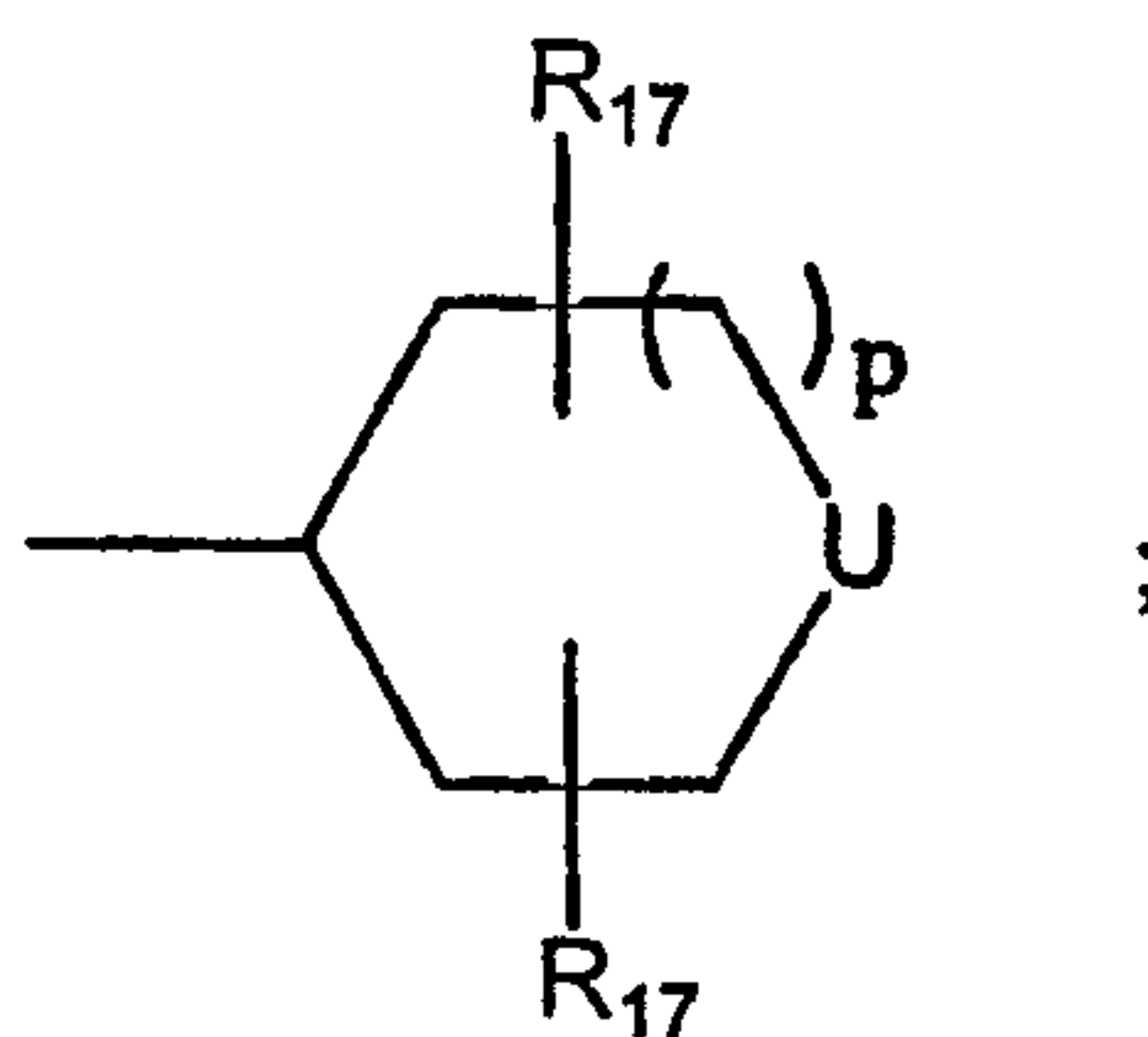
247

wherein Q₄ is



5

wherein Q₅ is



10

wherein R₁ and R₂ are each independently H, straight chained or branched C₁-C₇ alkyl, -F, -Cl, -Br, -I, -NO₂, or -CN;

15

wherein R₃ is H, straight chained or branched C₁-C₇ alkyl, -F, -Cl, -Br, -I, -NO₂, -CN, -OR₆, aryl or heteroaryl;

20

wherein R₅ is straight chained or branched C₁-C₇ alkyl, -N(R₄)₂, -OR₆ or aryl;

wherein R₆ is straight chained or branched C₁-C₇ 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; -NO₂; -N₃; -CN; -OR₂₁, -OCOR₂₁, -COR₂₁, -NCOR₂₁, -N(R₂₁)₂, -CON(R₂₁)₂, or -COOR₂₁; 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, -NR₁₆, S, C(R₁₇)₂, or -NSO₂R₁₆;

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __3__

NOTE: For additional volumes please contact the Canadian Patent Office.

What is claimed is:

1. Use of a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist for treating depression in a subject, 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 10 μ M; and

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

provided that the GAL3 receptor antagonist is not a 1,5-Disubstituted 3-(5-aryl-1,3,4-oxadiazolyl-2-)iminoindolin-2-one compound.

2. The use of claim 1, wherein the 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.

3. The use of claim 2, wherein the 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.

4. The use of claim 3, wherein the 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.

5. The use of claim 4, wherein the 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.
6. The use of any one of claims 1 to 5, wherein the 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.
7. The use of any one of claims 1 to 6, wherein 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 5HT₆ and human 5HT₇ receptors.
8. The use of any one of claims 1 to 7, wherein 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 H₁ receptor.
9. The use of any one of claims 1 to 8, wherein 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 D₁, D₂, D₃, D₄ and D₅ receptors.
10. The use of any one of claims 1 to 9, wherein 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.
11. The use of any one of claims 1 to 10, wherein 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.

12. The use of any one of claims 1 to 11, wherein the 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 5HT₄ receptor.
13. The use of any one of claims 1 to 12, wherein the 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.
14. The use of any one of claims 1 to 13, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 30 percent at a concentration of 10 μ M.
15. The use of any one of claims 1 to 14, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 30 percent at a concentration of 10 μ M.
16. The use of any one of claims 1 to 13 and 15, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase A greater than 15 percent at a concentration of 10 μ M.
17. The use of any one of claims 1 to 14, wherein the receptor antagonist does not inhibit the activity of central monoamine oxidase B greater than 15 percent at a concentration of 10 μ M.
18. Use of a composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a GAL3 receptor antagonist for treating anxiety in a subject, 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;

provided that the GAL3 receptor antagonist is not a 1,5-Disubstituted 3-(5-aryl-1,3,4-oxadiazolyl-2-)iminoindolin-2-one compound.

19. The use of claim 18, wherein the 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.

20. The use of claim 19, wherein the 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.

21. The use of claim 20, wherein the 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.

22. The use of claim 21, wherein the 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.

23. The use of any one of claims 18 to 22, wherein the 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.

24. The use of any one of claims 18 to 23, wherein 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 SHT_{1F}, human 5HT_{2A}, rat 5HT_{2C}, human 5HT₆ and human 5HT₇ receptors.

25. The use of any one of claims 18 to 24, wherein 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 H₁ receptor.

26. The use of any one of claims 18 to 25, wherein 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 D₁, D₂, D₃, D₄ and D₅ receptors.

27. The use of any one of claims 18 to 26, wherein 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.

28. The use of any one of claims 18 to 27, wherein 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.

29. The use of any one of claims 18 to 28, wherein the 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 5HT₄ receptor.

30. The use of any one of claims 18 to 29, wherein the 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.

Application number/numéro de demande: 2671776

Figures: 5

Pages: 5/5

Unscannable Item(s) received with this application.

To inquire if you can order a copy of the unscannable item(s),

Please visit the CIPO Website at [HTTP://CIPO.GC.CA](http://CIPO.GC.CA)

Item(s) ne pouvant être balayés.

Documents reçus avec cette demande ne pouvant être balayés.

Pour vous renseigner si vous pouvez commander

une copie des items ne pouvant être balayés,

veuillez visiter le site web de l'OPIC au [HTTP://CIPO.GC.CA](http://CIPO.GC.CA)

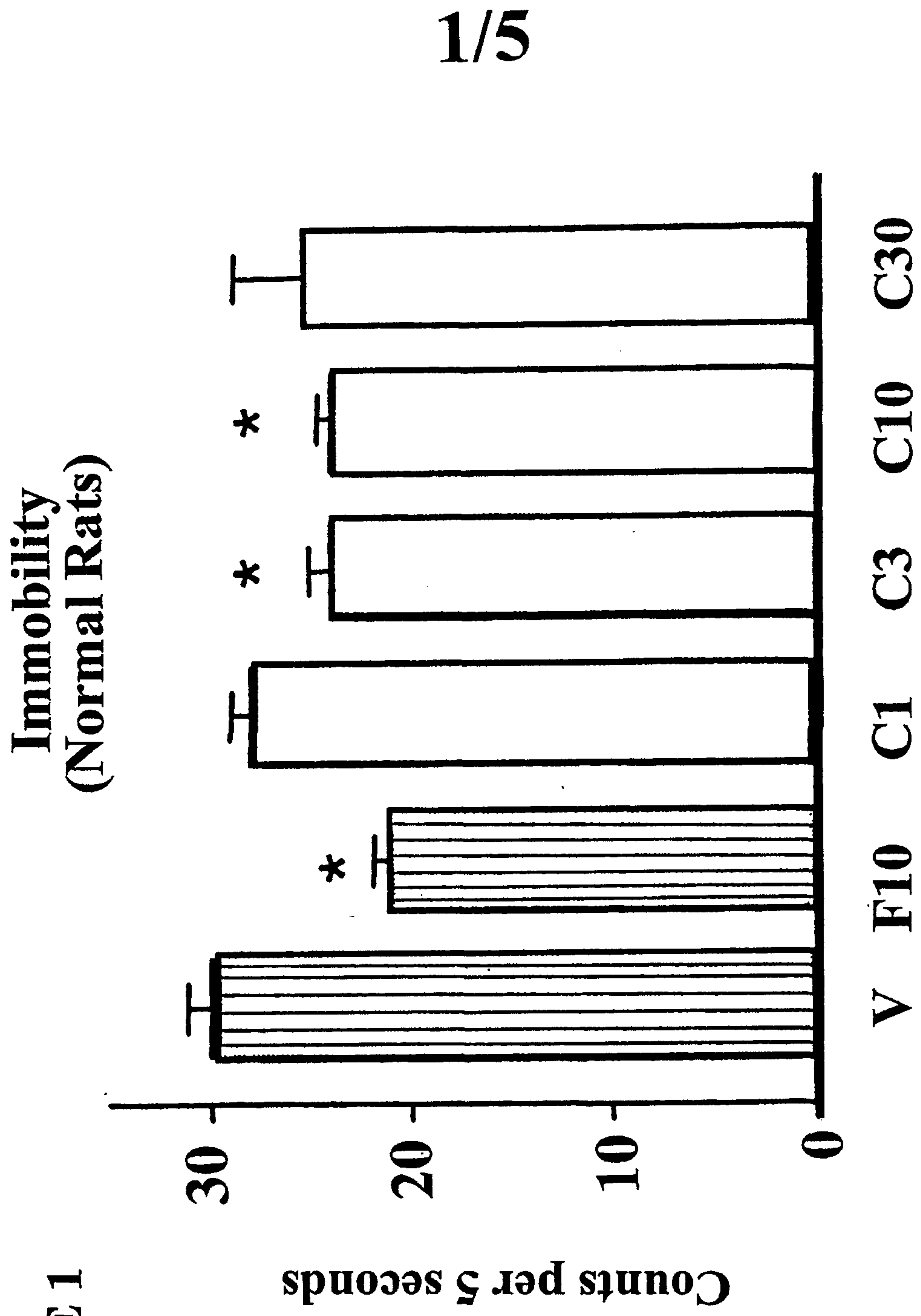


FIGURE 1

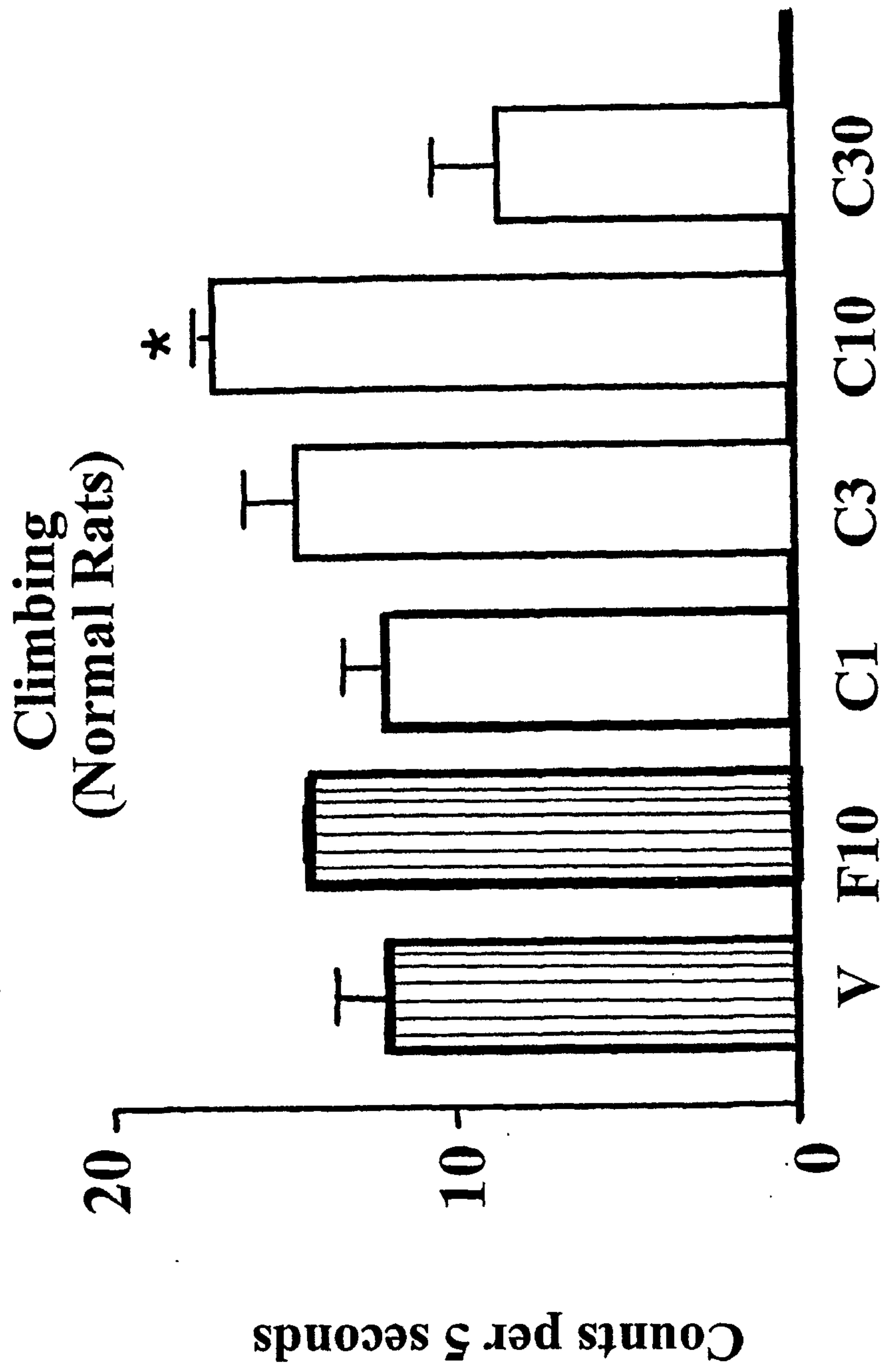
FIGURE 2

FIGURE 3