



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/445, 45/06	A1	(11) International Publication Number: WO 92/18127 (43) International Publication Date: 29 October 1992 (29.10.92)
(21) International Application Number: PCT/US92/02811 (22) International Filing Date: 14 April 1992 (14.04.92) (30) Priority data: 685,749 15 April 1991 (15.04.91) US (71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US). (72) Inventor: COOK, Leonard ; 6 Radburn Lane, Newark, DE 19711 (US). (74) Agents: FERGUSON, Blair, Q. et al.; The du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), PL, SE (European patent). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE OF SIGMA RECEPTOR ANTAGONISTS TO ENHANCE THE EFFECTS OF ANTIPSYCHOTIC DRUGS (57) Abstract The invention relates to a method of treating psychosis in a mammal which comprises administering to the mammal an effective amount of a dopamine receptor antagonist antipsychotic and a sigma receptor antagonist having greater affinity for sigma receptors than for dopamine receptors, in an amount effective to selectively enhance the antipsychotic effects of the dopamine receptor antagonist relative to the adverse side effects of the dopamine receptor antagonist.		

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TITLE

5 Use of Sigma Receptor Antagonists to Enhance the
 Effects of Antipsychotic Drugs

BACKGROUND OF THE INVENTION

10 Schizophrenia is a psychosis marked by withdrawn,
 bizarre, and sometime delusional behavior. About 1% of
 the United States population, 2,400,000 people, suffer
 from the disease. About 25% of all the beds used for
 any medical treatment in the United States are used by
 schizophrenia patients. The estimated medical costs in
15 the United States for treatment of schizophrenia run as
 high as \$40 billion a year.

 Several classes of drugs are currently marketed for
 use in the symptomatic treatment of psychoses. Certain
 antipsychotics, referred to as neuroleptics, are known
20 to produce unwanted extrapyramidal side effects,
 including acute dystonia, akathisia, parkinsonian
 syndrome, anticholinergic effects, hypotension,
 increased prolactin levels, malignant syndrome, perioral
 tremor, and tardive dyskinesia. The parkinsonian
25 syndrome and tardive dyskinesia side effects are thought
 to be mediated by the antagonist effect of the drug on
 dopamine receptors (Goodman and Gilman's The
 Pharmacological Basis of Therapeutics, 8th Edition,
 Pergamon Press, 1990). Tardive dyskinesia, an often
30 irreversible syndrome consisting of involuntary movement
 or rigidity of the muscles, is caused by standard
 neuroleptics at an estimated rate of 4 cases per 100
 patient years of treatment.

 Because of the limitations of currently available
35 antipsychotic drugs, the search continues for compounds

with fewer deleterious side effects and better efficacy (Abou-Gharbia and Moyer, "Novel Antipsychotic Agents", in Annual Reports in Medicinal Chemistry, Volume 25, pp 1-10, Academic Press, 1990).

- 5 Effective neuroleptics include the phenothiazine derivatives chlorpromazine hydrochloride (Thorazine), triflupromazine hydrochloride (Vesprin), mesoridazine besylate (Serentil), thioridazine hydrochloride (Mellaril, Millazine), acetophenazine maleate (Tindal),
- 10 fluphenazine (Permitil, Prolixin), perphenazine (Trilafon), trifluoperazine hydrochloride (Stelazine, Suprazine), chlorprothixene (Taractan), and thiothixene hydrochloride (Navane). Other antipsychotics include haloperidol and haloperidol decanoate (Haldol,
- 15 Halperon), loxapine succinate (Loxitane), molindone hydrochloride (Moban), and pimozone (Orap). The pharmacology of these drugs is reviewed in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th Edition, Pergamon Press, 1990 and in Physicians' Desk
- 20 Reference, 45th Edition, Medical Economics, 1991.

Antipsychotics also include "atypical" antipsychotics, such as the dibenzodiazepine clozapine (Clozaril), which have little extrapyramidal side effects.

- 25 Neuroleptic drugs, which are the primary antipsychotic drugs used in the treatment of schizophrenia, are thought to exert their therapeutic effects by binding to and blocking dopamine receptors, primarily D₂ receptors (Snyder and Largent (1989) J.
- 30 Neuropsychiatry 1:7-15). Most marketed antipsychotics are neuroleptics and are referred to as dopamine receptor antagonist antipsychotics. Some neuroleptics, such as cinuperone, tiospirone, and haloperidol, are known to nonselectively antagonize both sigma and

dopamine D₂ receptors (Snyder and Largent (1989) J. Neuropsychiatry 1:7-15).

SUMMARY OF THE INVENTION

- 5 In the present invention, sigma receptor antagonists having greater affinity for sigma receptors than for dopamine receptors were discovered to enhance the antipsychotic effects of dopamine receptor antagonist antipsychotics relative to the adverse side
- 10 effects of the dopamine receptor antagonist antipsychotic. It has been discovered that sigma receptor antagonists with greater affinity for sigma receptors than dopamine receptors will selectively potentiate the measures of psychotherapeutic properties
- 15 of dopamine receptor antagonist antipsychotics and will not potentiate the measures reflecting unwanted short and long-term neurological side effects produced by these dopamine receptor antagonist antipsychotics, such as extrapyramidal symptoms or tardive dyskinesia.
- 20 The present invention, therefore, provides a means of maintaining or enhancing the psychotherapeutic properties of a dopamine receptor antagonist antipsychotic drug without enhancing their usual neurological side effects. This can be accomplished by
- 25 employing lower doses of the dopamine receptor antagonist antipsychotic when administered in combination or concurrently with a sigma receptor antagonist having greater affinity for sigma receptors than for dopamine receptors.
- 30 The method of the present invention improves the therapeutic ratio of classical dopamine receptor antagonist antipsychotics and also offers the potential of a broader therapeutic profile by the combination of the therapeutic properties of a sigma receptor
- 35 antagonist with the therapeutic properties of a dopamine

receptor antagonist antipsychotic, when administered in combination or concurrently with a sigma receptor antagonist having greater affinity for sigma receptors than for dopamine receptors.

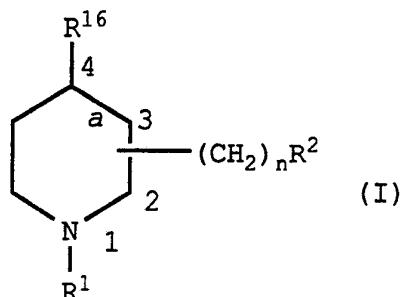
- 5 Effective dopamine receptor antagonist antipsychotics useful in the method of the invention include the phenothiazine derivatives chlorpromazine hydrochloride (Thorazine), triflupromazine hydrochloride (Vesprin), mesoridazine besylate (Serentil),
- 10 thioridazine hydrochloride (Mellaril, Millazine), acetophenazine maleate (Tindal), fluphenazine (Permitil, Prolixin), perphenazine (Trilafon), trifluoperazine hydrochloride (Stelazine, Suprazine), chlorprothixene (Taractan), thiothixene hydrochloride (Navane). Other
- 15 antipsychotics include haloperidol and haloperidol decanoate (Haldol, Halperon), loxapine succinate (Loxitane), molindone hydrochloride (Moban) and pimozide (Orap). The pharmacology, including dosage and
- 20 formulation, of these drugs is reviewed in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th Edition, Pergamon Press, 1990 and in Physicians' Desk Reference, 45th Edition, Medical Economics, 1991.

- Sigma receptor antagonists having greater affinity for sigma receptors than for dopamine receptors include
- 25 compounds having an inhibition constant, K_i , of 500 nM or less for sigma receptors and having at least a 5-fold greater affinity for sigma receptors relative to dopamine receptors. The sigma receptor antagonists useful in the present invention preferably have a K_i for
- 30 sigma receptors of less than 100 nM and at least a 50 to 100-fold greater affinity for sigma receptors than for dopamine receptors.

- Unlike neuroleptics, the sigma receptor antagonists useful in the method of the present invention lack or
- 35 have relatively weak dopamine receptor-blocking activity

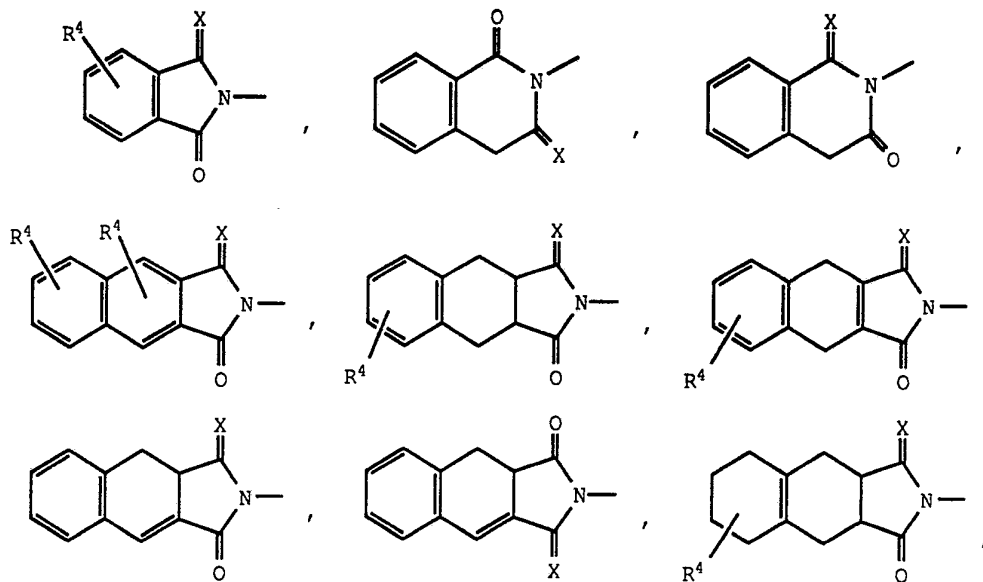
and, unlike neuroleptics, elicit their effects primarily without directly antagonizing the dopamine receptor system.

The sigma receptor antagonist compounds useful in this invention include (N-phthalimidoalkyl) piperidines of the formula:

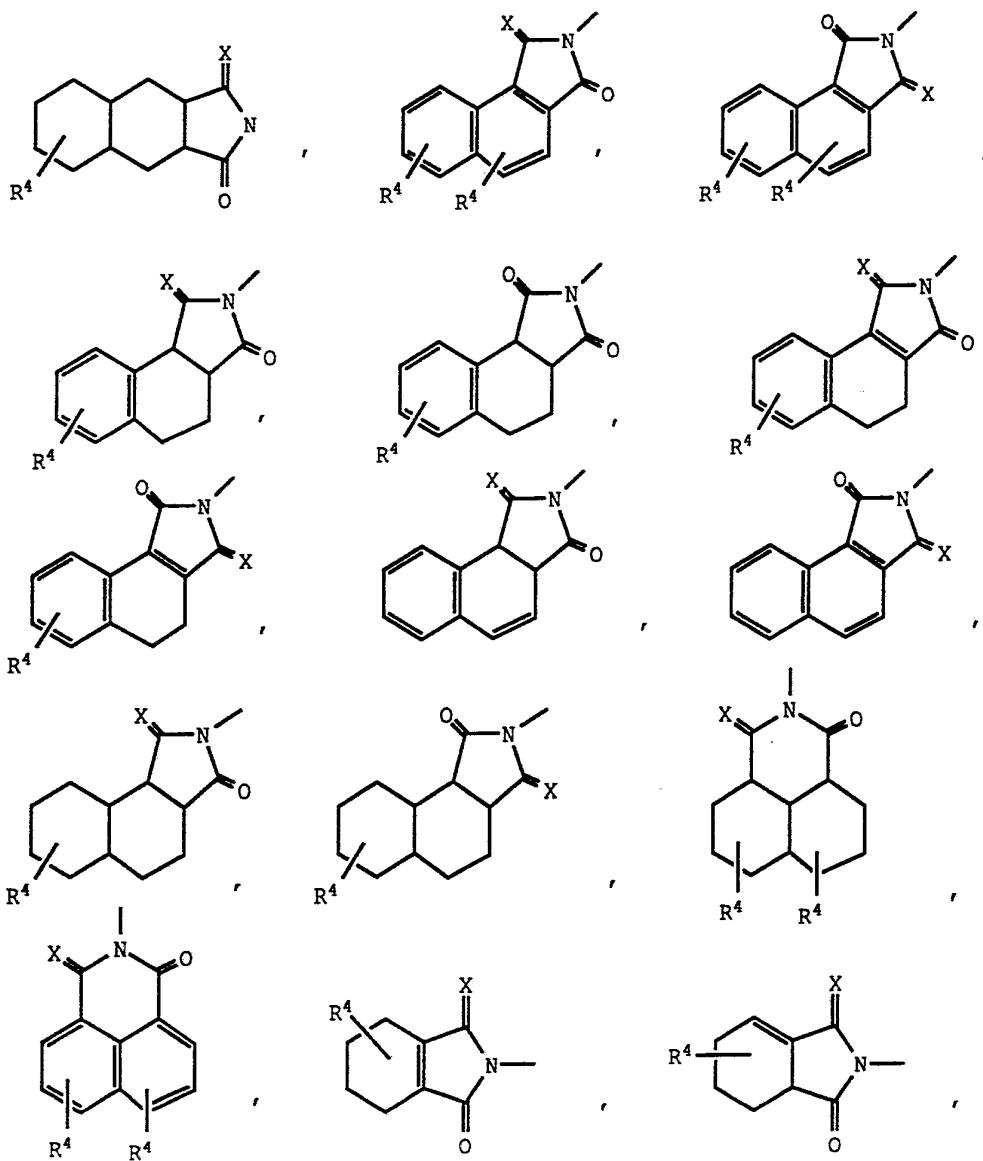


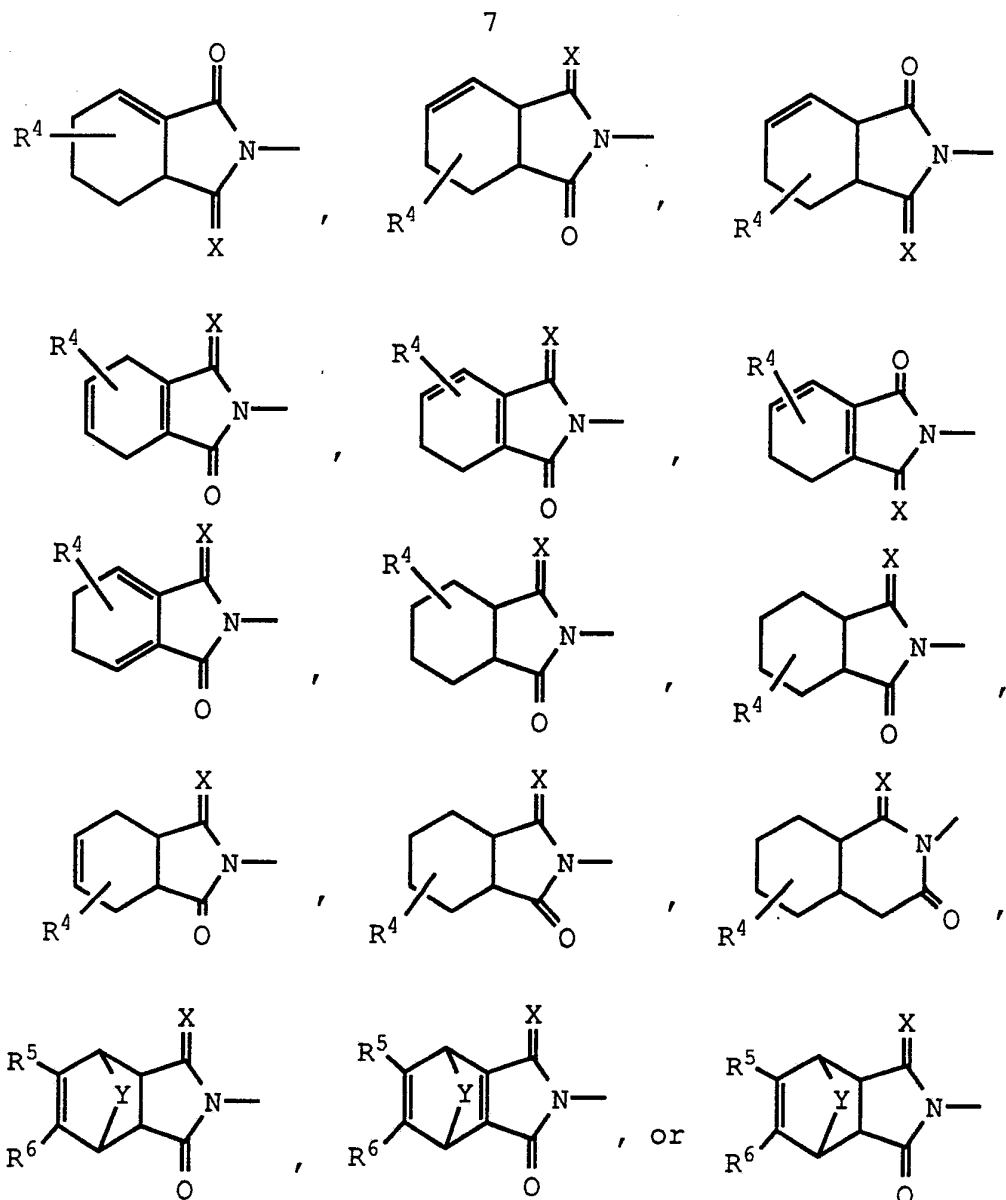
or a pharmaceutically acceptable salt or an N-oxide thereof wherein:

- 10 a is a single or double bond, provided that when a is a double bond then $R^2(CH_2)_n$ is attached at C-4;
 n is 0-4, provided that when $(CH_2)_nR^2$ is attached to the 2-position of the piperidine ring then n is 2-4;
 R^1 is $(CH_2)_mR^3$ or $(CH_2)_pAr$, where m is 1-4 and p is 1-4;
 15 R^2 is



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R^3 is cycloalkyl of 3 to 8 carbon atoms;

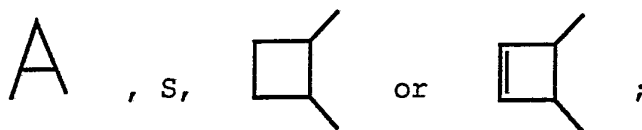
- 5 R^4 is 1-4 substituents independently selected from the group consisting of H, halogen, NO_2 , NH_2 , haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, $\text{C}_1\text{-C}_3$ alkyl, NHCOR^7 , NHCO-phenyl , OH, OR^8 and Ar' ;

- R^5 and R^6 independently are H, alkyl of 1 to 3 carbon atoms, Ar'' or taken together are $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$;
- 10 R^7 and R^8 independently are H or alkyl of 1 to 3 carbon atoms;

X is O; H_2 ; H, OH; R^9 , OH; Ar''' , OH; H, R^9 ; or H, OR^9 ;

8

Y is CH_2 , CHR^{10} , $\text{C}(\text{R}^{10})_2$, O, CH_2CH_2 , $(\text{CH}_2)_3$,

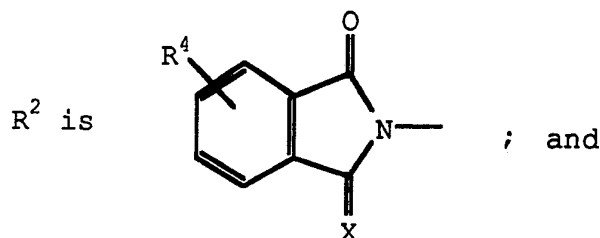


- 5 Ar, Ar', Ar'' and Ar''' independently are phenyl optionally substituted with 1-5 substituents independently selected from the group consisting of:
- 10 H, halogen, OH, alkoxy of 1 to 3 carbon atoms, $\text{NR}^{11}\text{R}^{12}$, SH, $\text{S}(\text{O})_t\text{R}^{13}$, where t is 0-2, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkyl of 1 to 3 carbon atoms, CO_2H , carboalkoxy of 2 to 6 carbon atoms, CN, NO_2 , SO_2NH_2 , SO_3H , $\text{CO}_2\text{NR}^{14}\text{R}^{15}$, naphthyl, pyridyl, pyrimidyl,
- 15 quinolyl or isoquinolyl;
- R^9 and R^{10} independently are alkyl of 1 to 3 carbon atoms;
- $\text{R}^{11}\text{-R}^{15}$ independently are H or alkyl of 1 to 3 carbon atoms;
- 20 R^{16} is H; OH; O-alkyl of 1-6 carbons; O-acyl of 1-8 carbons; alkyl of 1-12 carbons; phenyl substituted with one or two substituents independently selected from F, Cl, Br, I, alkyl, perfluoroalkyl, alkoxy, aryloxy, alkylthio, arylthio, perfluoroalkoxy,
- 25 perfluoroalkylthio, and dialkylamino (alkyl and alkoxy 1-12 carbons; aryl 6-12 carbons); 1- and 2-naphthyl substituted with one or two substituents independently selected from F, Cl, Br, I, alkyl, perfluoroalkyl, alkoxy, aryloxy, alkylthio,
- 30 arylthio, perfluoroalkoxy, perfluoroalkylthio, and dialkylamino (alkyl and alkoxy 1-12 carbons; aryl 6-12 carbons); 2- and 3- pyrrolyl; 2- and 3- furyl; 2- and 3- thienyl; 2,3, and 4-pyridyl; 2- and 3-

benzofuryl; 2- and 3- indolyl; 2- and 3-
benzothienyl; 2, 3, and 4- quinolyl; and 1, 3, and
4-isoquinolyl;

with the following provisos:

- 5 (1) when R^1 is $(CH_2)_pAr$ (where p is 1);



$(CH_2)_nR^2$, ($n=0$), is attached at the C-4
position on the piperidine ring;
then X cannot be H_2 or O.

- (2) R^{16} is H, OH, alkyl or aryl when $(CH_2)_n R^2$ is
attached to the 4-position of the
piperidine ring.

15 Some compounds useful in the present invention can
exist as optical isomers and both the racemic mixtures
of these isomers as well as the individual optical
isomers which confer activity are within the scope of
compounds useful in the present invention.

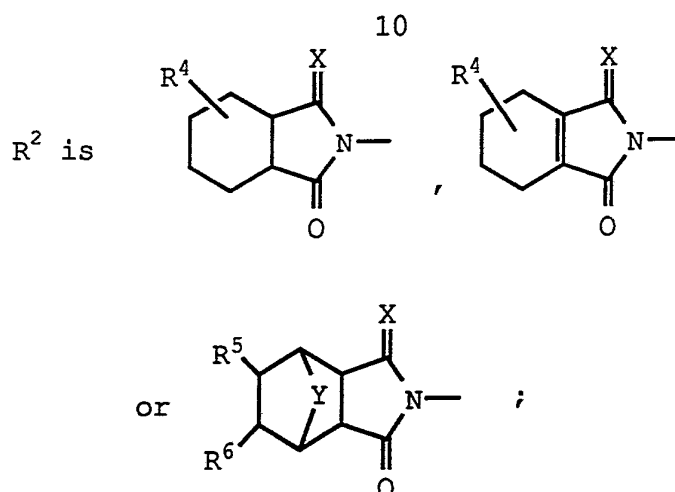
20 In addition some compounds useful in the present
invention can exist as cis or trans isomers and although
these are not all specifically set forth, the cis and
trans fused compounds as known to those skilled in the
art, are within the scope of this invention.

25 Preferred compounds useful in the method of the
present invention are compounds of Formula (I) for which
one or more of the following occur:

n is 1-4;

R^1 is $(CH_2)_pAr$;

30 p is 1-2;



(CH₂)_n² is attached at the C-4 position of the piperidine ring;

5

X is 0 or H_2 ;

R^4, R^5 and R^6 are all H;

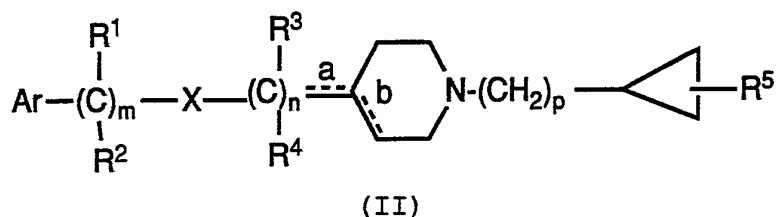
Ar is phenyl; or

Y is $(\text{CH}_2)_3$ or O.

More preferred compounds useful in the present
10 invention are the compounds of formula (I) wherein n is
1.

The selective sigma receptor antagonist compounds useful in the present invention also include cycloalkylpiperidines of the formula:

15



or a pharmaceutically acceptable salt thereof, wherein:

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m is 0 to 3;
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20

n is 0 to 3;

provided that m and n are not both 0;

p is 0 to 3;

25

X is O, S, SO, SO₂, NR⁶, CR⁷R⁸, C, or CHO;

- 5 R^1 , R^3 and R^7 independently are H, alkyl of 1 to 5 carbon atoms, halogen, $NR^{10}R^{11}$, OH, CO_2H , carboalkoxy of 2 to 6 carbon atoms, CN, Ar^1 , alkoxy of 1 to 5 carbon atoms or alkylthio of 1 to 5 carbon atoms;
- R^2 , R^4 and R^8 independently are H, alkyl of 1 to 5 carbon atoms, carboalkoxy of 2 to 6 carbon atoms, CN, alkoxy of 1 to 5 carbon atoms or Ar^1 ;
- 10 provided that R^1 , R^2 , R^3 and R^4 are not alkoxy of 1 to 5 carbon atoms, alkylthio of 1 to 5 carbon atoms, $NR^{10}R^{11}$ or OH when X is O, S, SO, SO_2 or NR^6 ;
- R^5 is H, alkyl, halogen, OH or alkenyl;
- 15 R^6 is H, alkyl of 1 to 5 carbon atoms or Ar^1 ;
- Ar and Ar^1 independently are naphthyl, pyridyl, pyrimidyl, indolyl, quinolinyl, isoquinolinyl, or phenyl optionally substituted with alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, SH, $S(O)_t$ alkyl of 1 to 3 carbon atoms, where t is 1, 2 or 3, dialkylamino of 2 to 6 carbon atoms, halogen, OH, alkylamino of 1 to 3 carbon atoms, NH_2 ,
- 20 CN, NO_2 , SO_3H , tetrazole, CO_2H , carboalkoxy of 2 to 6 carbon atoms, $CONH_2$, SO_2NH_2 , COR^9 , $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, Ar^2 , OAr^2 or SAr^2 ;
- 25 Ar^2 is naphthyl or phenyl optionally substituted with alkyl of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkoxy of 1 to 3 carbon atoms, halogen or alkylthio of 1 to 3 carbon atoms;
- 30 R^9 , R^{10} , R^{11} , R^{12} and R^{13} independently are H, alkyl of 1 to 5 carbon atoms or phenyl or R^{10} and R^{11} taken together are an alkylene chain
- 35

12

of 3 to 6 carbon atoms or R¹² and R¹³ taken together are an alkylene chain of 3 to 6 carbon atoms; and

5 a or b is a double bond or a single bond, provided that both are not double bonds.

Preferred compounds useful in the present invention include those compounds of Formula (II) wherein:

X is C(O), CHOH or O;

m is 0;

10 n and p are 1;

R³-R⁵ are H; and/or

Ar is phenyl optionally substituted with halogen, OCH₃, NH₂, NO₂ or another phenyl group.

15 Pharmaceutical compositions comprising an effective amount of a compound of Formula I or II and a pharmaceutically acceptable carrier are useful in the method of the present invention.

Other sigma receptor antagonists lacking or having relatively weak dopamine receptor-blocking activity are
20 expected to be useful in the method of the invention. Examples of other sigma receptor antagonists lacking or having weak dopamine receptor-blocking activity and expected to be useful in this invention are rimcazole (also known as BW234U) (Ferris et al. (1982) J. Pharm.
25 Pharmacol. 34: 388-390; Ferris et al. (1986) Life Sciences 38: 2329-2337; U.S. patent 4,400,383; U.S. patent 4,588,728), remoxipride (Ogren et al. (1984) European Journal of Pharmacology 102: 439-474; U.S. patent 4,232,037; Snyder and Largent (1989) J.
30 Neuropsychiatry 1: 7-15), and BMY14802 (Taylor and Dekleva (1987) Drug Development Research 11: 65-70; U.S. patent 4,605,655). The above identified patents are hereby incorporated by reference.

35 Other sigma receptor antagonists lacking or having relatively weak dopamine receptor-blocking activity and

expected to be useful in the method of the invention include the compounds claimed in copending, commonly assigned U.S. patent applications USSN 07/506961, filed 3/28/90 and USSN 07/500573, filed 3/28/90, the
5 disclosures of which are hereby incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effect of haloperidol (Haldol) alone and haloperidol (Haldol) + Ex. No. 504 on
10 avoidance behavior and escape behavior in pole climb avoidance in rats.

DETAILED DESCRIPTION OF THE INVENTION

15 We have discovered that sigma receptor antagonists having greater affinity for sigma receptors than for dopamine receptors are useful to enhance the antipsychotic effects of dopamine receptor antagonist antipsychotics relative to the adverse side effects of
20 the dopamine receptor antagonist antipsychotic. It has been discovered that sigma receptor antagonists with greater affinity for sigma receptors than dopamine receptors will selectively potentiate the measures of psychotherapeutic properties of dopamine receptor
25 antagonist antipsychotics and will not potentiate the measures reflecting unwanted short and long-term neurological side effects produced by these dopamine receptor antagonist antipsychotics, such as extrapyramidal symptoms or tardive dyskinesia.

30 The present invention, therefore, provides a means of maintaining or enhancing the psychotherapeutic properties of a dopamine receptor antagonist antipsychotic drug without enhancing their usual neurological side effects. This can be accomplished by
35 employing lower doses of the dopamine receptor

antagonist antipsychotic, when administered in combination or concurrently with a sigma receptor antagonist having greater affinity for sigma receptors than for dopamine receptors.

- 5 The method of the present invention improves the therapeutic ratio of dopamine receptor antagonist antipsychotics and also offers the potential of a broader therapeutic profile by the combination of the therapeutic properties of a sigma receptor antagonist
10 with the therapeutic properties of a dopamine receptor antagonist antipsychotic.

Effective neuroleptics useful in the method of the invention include the phenothiazine derivatives chlorpromazine hydrochloride (Thorazine),
15 triflupromazine hydrochloride (Vesprin), mesoridazine besylate (Serentil), thioridazine hydrochloride (Mellaril, Millazine), acetophenazine maleate (Tindal), fluphenazine (Permitil, Prolixin), perphenazine (Trilafon), trifluoperazine hydrochloride (Stelazine,
20 Suprazine), chlorprothixene (Taractan), thiothixene hydrochloride (Navane). Other antipsychotics include haloperidol and haloperidol decanoate (Haldol, Halperon), loxapine succinate (Loxitane), molindone hydrochloride (Moban) and pimozide (Orap). The
25 pharmacology, including dosage and formulation, of these drugs is reviewed in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th Edition, Pergamon Press, 1990 and in Physicians' Desk Reference, 45th Edition, Medical Economics, 1991.

- 30 Sigma receptor antagonists having greater affinity for sigma receptors than for dopamine receptors useful in the present invention include compounds having an inhibition constant, K_i , of 500 nM or less for sigma receptors and having at least a 5-fold greater affinity
35 for sigma receptors relative to dopamine receptors. The

sigma receptor antagonists useful in the present invention preferably have a K_i for sigma receptors of less than 100 nM and at least a 50 to 100-fold greater affinity for sigma receptors than for dopamine
5 receptors.

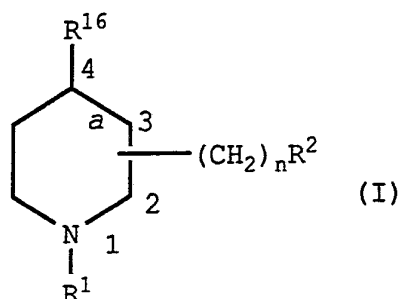
Unlike neuroleptics, the sigma receptor antagonists useful in the method of the present invention lack or have relatively weak dopamine receptor-blocking activity.

10 Typical dopamine receptor antagonist antipsychotic agents, such as haloperidol and chlorpromazine, produce effects in many behavioral paradigms. Some of these behaviors can be said to be reflective of the therapeutic effects of the drugs based upon correlations
15 with clinical potency and the spectrum of clinically useful agents that demonstrate activity. Other behaviors can be said to be reflective of unwanted side-effect liability based upon similar correlations. The conditioned avoidance response, in many forms, has been
20 used to predict antipsychotic efficacy. Inhibition of conditioned avoidance is associated with the therapeutic properties of antipsychotics. In contrast, inhibition of conditioned escape behavior has been associated with non-specific sedative effects. The induction of
25 catalepsy by typical antipsychotics is associated with the production of sedative and extrapyramidal side-effects in man.

Our results indicate that sigma receptor antagonists having greater affinity for sigma receptors
30 than for dopamine receptors will potentiate the therapeutic properties while not effecting the unwanted side-effect properties of dopamine antagonist antipsychotics. These results have profound significance for the treatment of psychosis since it is
35 the severe side-effects that are the major limitation to

the use of typical dopamine receptor antagonist antipsychotics. The addition of a sigma receptor antagonist to treatment with the typical dopamine receptor antagonist antipsychotic is expected to enhance the therapeutic efficacy and therefore produce a greater therapeutic index than the dopamine receptor antagonist antipsychotic alone.

The sigma receptor antagonist compounds useful in this invention include (N-phthalimidoalkyl) piperidines of the formula:



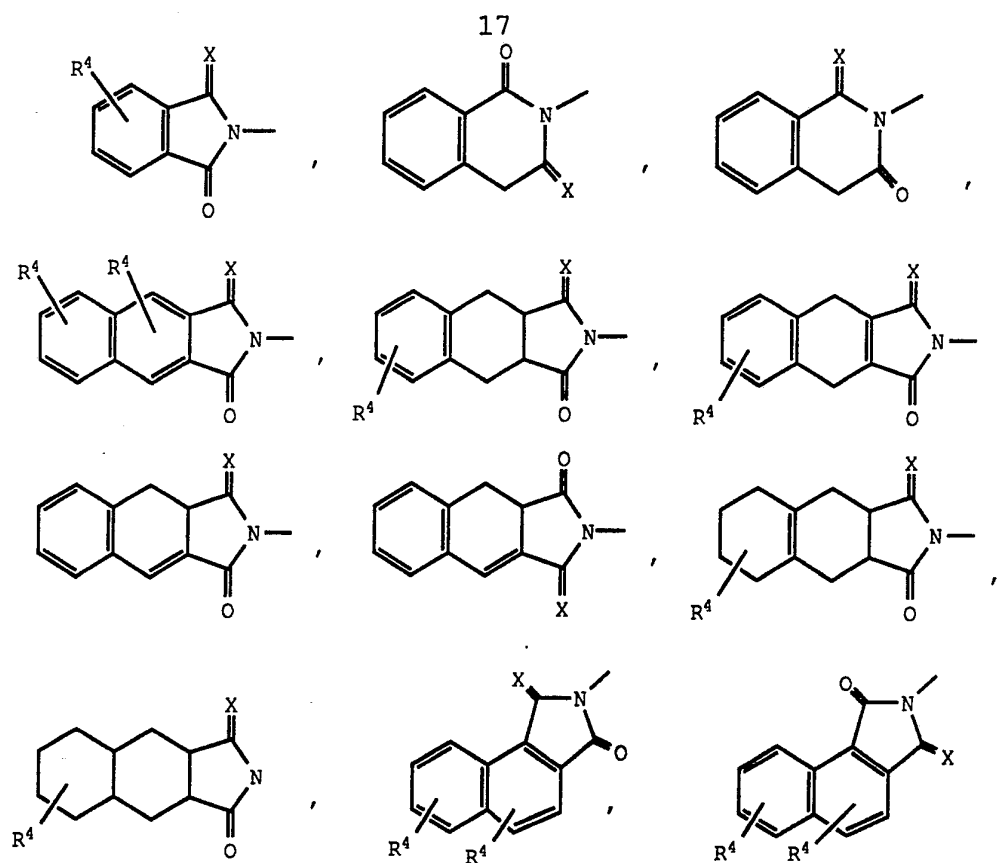
or a pharmaceutically acceptable salt or an N-oxide thereof wherein:

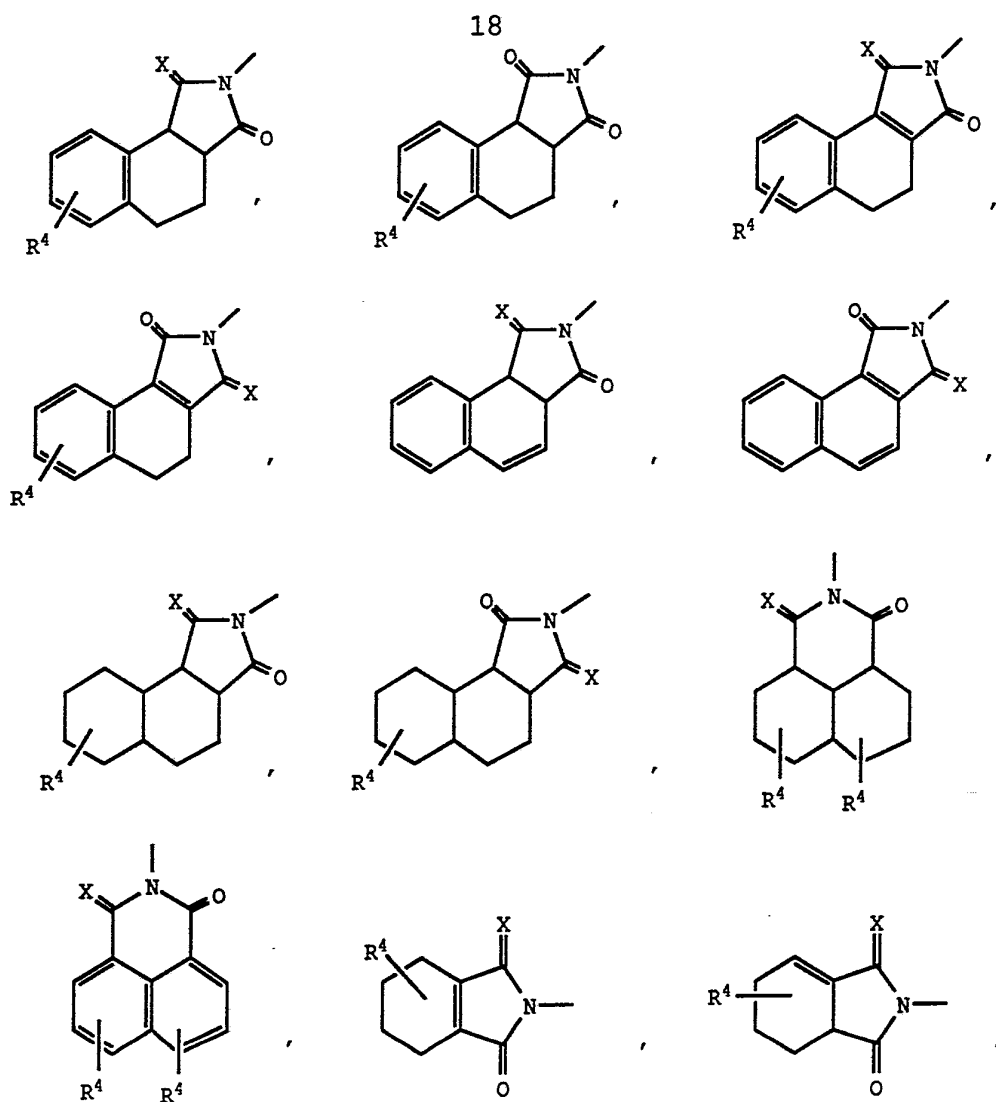
a is a single or double bond, provided that when a is a double bond then $R^2(CH_2)_n$ is attached at C-4;

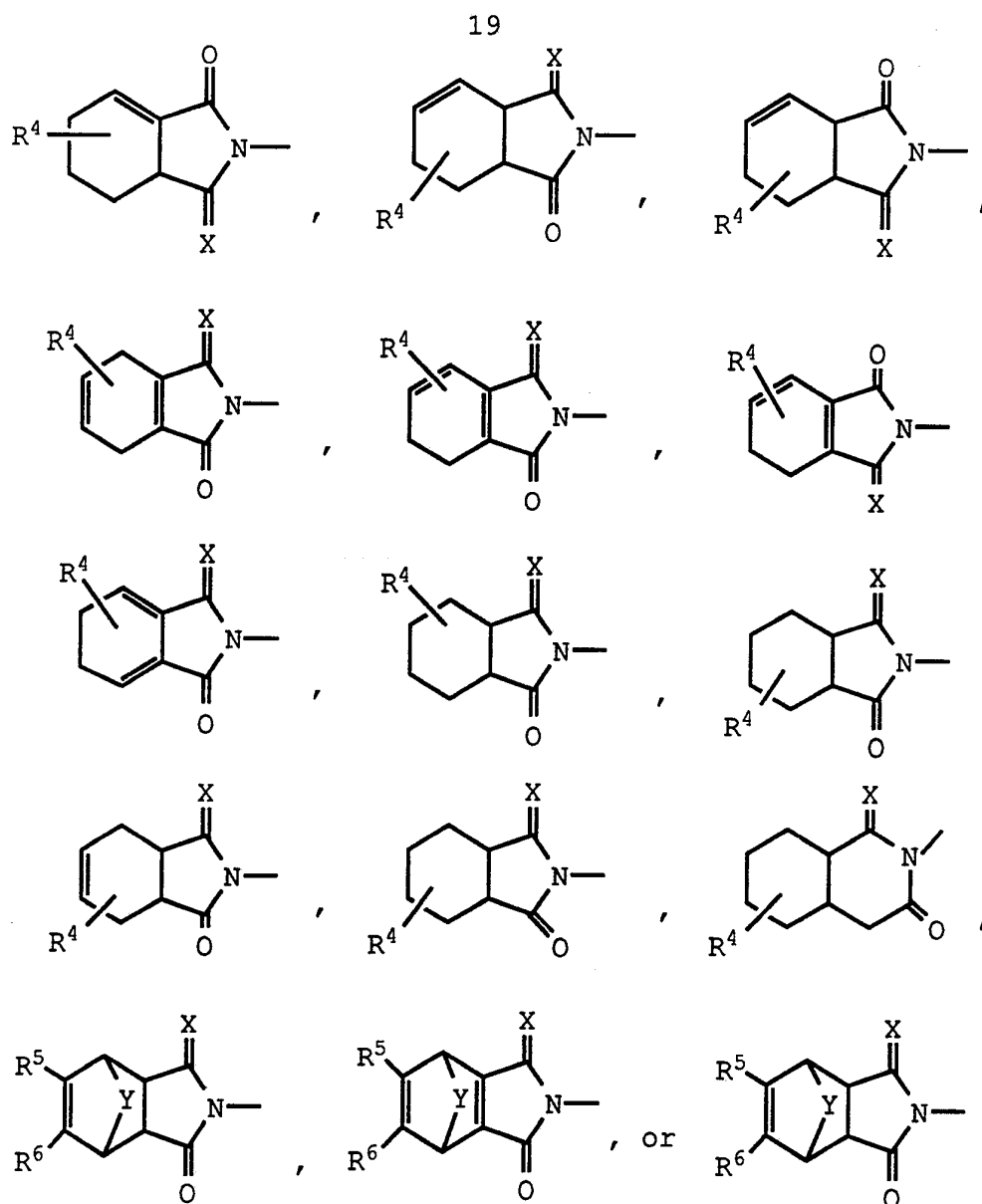
n is 0-4, provided that when $(CH_2)_nR^2$ is attached to the 2-position of the piperidine ring then n is 2-4;

R^1 is $(CH_2)_mR^3$ or $(CH_2)_pAr$, where m is 1-4 and p is 1-4;

R^2 is







R^3 is cycloalkyl of 3 to 8 carbon atoms;

R^4 is 1-4 substituents independently selected from the group consisting of H, halogen, NO_2 , NH_2 , haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, $\text{C}_1\text{-C}_3$ alkyl, NHCOR^7 , NHCO-phenyl , OH, OR^8 and Ar' ;

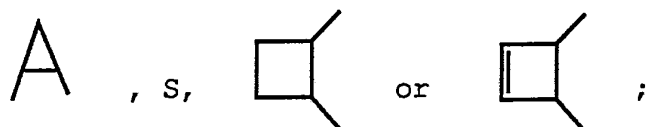
R^5 and R^6 independently are H, alkyl of 1 to 3 carbon atoms, Ar'' or taken together are $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$;

R^7 and R^8 independently are H or alkyl of 1 to 3 carbon atoms;

X is O; H_2 ; H, OH; R^9 , OH; Ar''' , OH; H, R^9 ; or H, OR^9 ;

20

Y is CH_2 , CHR^{10} , $\text{C}(\text{R}^{10})_2$, O, CH_2CH_2 , $(\text{CH}_2)_3$,



- 5 Ar, Ar', Ar'' and Ar''' independently are phenyl optionally substituted with 1-5 substituents independently selected from the group consisting of:
- 10 H, halogen, OH, alkoxy of 1 to 3 carbon atoms, $\text{NR}^{11}\text{R}^{12}$, SH, $\text{S}(\text{O})_t\text{R}^{13}$, where t is 0-2, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkyl of 1 to 3 carbon atoms, CO_2H , carboalkoxy of 2 to 6 carbon atoms, CN, NO_2 , SO_2NH_2 , SO_3H , $\text{CO}_2\text{NR}^{14}\text{R}^{15}$, naphthyl, pyridyl, pyrimidyl,
- 15 quinolyl or isoquinolyl;
- R^9 and R^{10} independently are alkyl of 1 to 3 carbon atoms;
- $\text{R}^{11}\text{-R}^{15}$ independently are H or alkyl of 1 to 3 carbon atoms;
- 20 R^{16} is H; OH; O-alkyl of 1-6 carbons; O-acyl of 1-8 carbons; alkyl of 1-12 carbons; phenyl substituted with one or two substituents independently selected from F, Cl, Br, I, alkyl, perfluoroalkyl, alkoxy, aryloxy, alkylthio, arylthio, perfluoroalkoxy,
- 25 perfluoroalkylthio, and dialkylamino (alkyl and alkoxy 1-12 carbons; aryl 6-12 carbons); 1- and 2-naphthyl substituted with one or two substituents independently selected from F, Cl, Br, I, alkyl, perfluoroalkyl, alkoxy, aryloxy, alkylthio,
- 30 arylthio, perfluoroalkoxy, perfluoroalkylthio, and dialkylamino (alkyl and alkoxy 1-12 carbons; aryl 6-12 carbons); 2- and 3-pyrrolyl; 2- and 3-furyl; 2- and 3-thienyl; 2,3, and 4-pyridyl; 2- and 3-

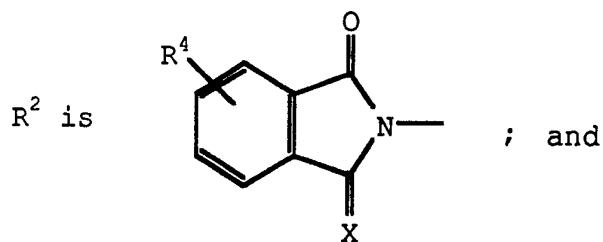
21

benzolfuryl; 2- and 3- indolyl; 2- and 3-
benzothienyl; 2, 3, and 4- quinolyl; and 1, 3, and
4-isoquinolyl;

with the following provisos:

5

(1) when R^1 is $(CH_2)_pAr$ (where p is 1);



10

$(CH_2)_nR^2$, ($n=0$), is attached at the C-4
position on the piperidine ring;
then X cannot be H_2 or O .

15

(2) R^{16} is H , OH , alkyl or aryl when $(CH_2)_n R^2$ is
attached to the 4-position of the
piperidine ring.

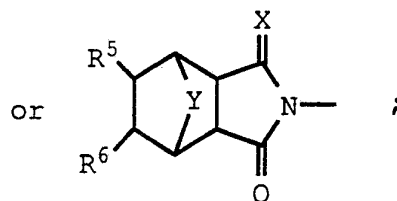
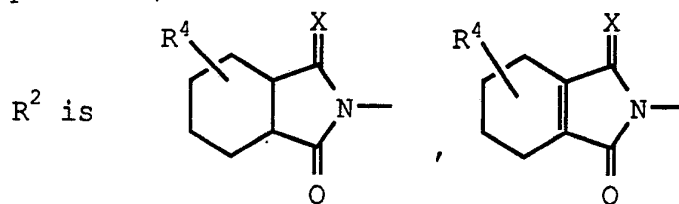
Preferred compounds useful in the method of the
present invention are compounds of Formula (I) for which
one or more of the following occur:

20

n is 1-4;

R^1 is $(CH_2)_pAr$;

p is 1-2;



$(CH_2)_nR^2$ is attached at the C-4 position of the
piperidine ring;

X is O or H₂;

5 R^4 , R^5 and R^6 are all H;

Ar is phenyl; or

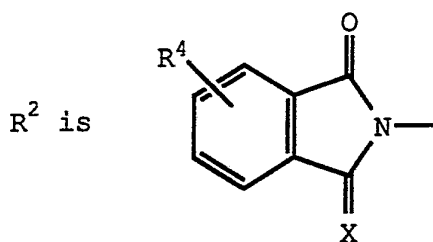
Y is $(CH_2)_3$ or O.

More preferred compounds useful in the present
invention are the compounds of formula (I) wherein n is
10 1.

Specifically preferred compounds useful in the
present invention are compounds of formula (I) wherein:

(1) $(CH_2)_nR^2$ is attached at the C-4 position of
the piperidine ring;

15 n is 1;



X is O;

20 R^4 is H;

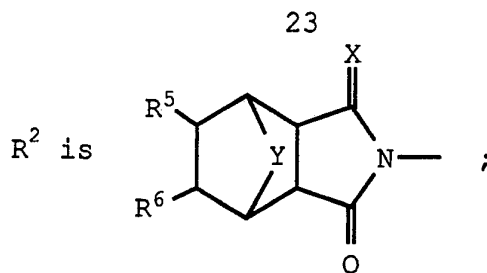
R^1 is $(CH_2)_pAr$;

p is 2; and

Ar is phenyl.

25 (2) $(CH_2)_nR^2$ is attached at the C-4 position of
the piperidine ring;

n is 1;



X is O;

Y is $(CH_2)_3$ and R^5 and R^6 are H;

R^1 is $(CH_2)_pAr$;

p is 2; and

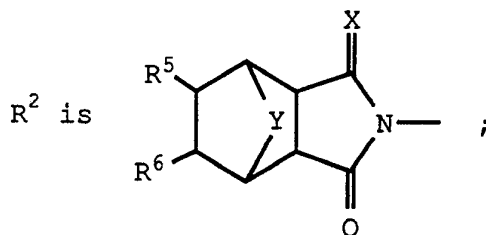
Ar is phenyl.

5

(3) $(CH_2)_nR^2$ is attached at the C-4 position of
the piperidine ring;

n is 1;

10



15

X is O;

Y is O;

R^5 and R^6 are H;

R^1 is $(CH_2)_pAr$;

p is 2; and

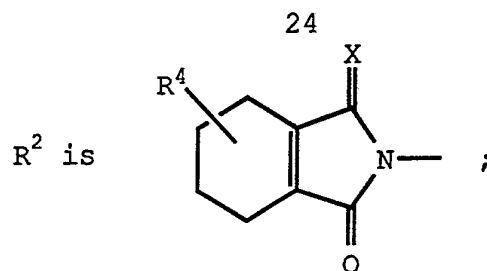
Ar is phenyl.

20

(4) $(CH_2)_nR^2$ is attached at the C-4 position of
the piperidine ring;

n is 1;

25



X is H₂;

R⁴ is H;

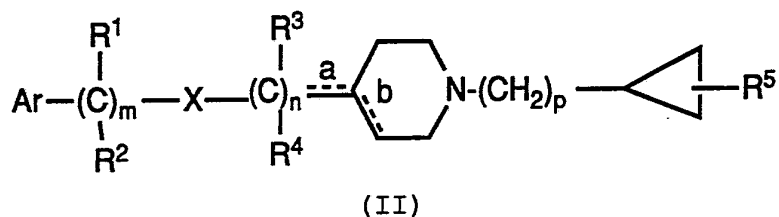
5

R¹ is (CH₂)_pAr;

p is 2; and

Ar is phenyl.

The selective sigma receptor antagonist compounds
 10 useful in the present invention also include
 cycloalkylpiperidines of the formula:



15 or a pharmaceutically acceptable salt thereof, wherein:

m is 0 to 3;

n is 0 to 3;

provided that m and n are not both 0;

p is 0 to 3;

20

X is O, S, SO, SO₂, NR⁶, CR⁷R⁸, C, or CHO⁹H;

R¹, R³ and R⁷ independently are H, alkyl of 1 to 5
 carbon atoms, halogen, NR¹⁰R¹¹, OH, CO₂H,

25

carboalkoxy of 2 to 6 carbon atoms, CN, Ar¹,
 alkoxy of 1 to 5 carbon atoms or alkylthio of
 1 to 5 carbon atoms;

R², R⁴ and R⁸ independently are H, alkyl of 1 to 5
 carbon atoms, carboalkoxy of 2 to 6 carbon

30

atoms, CN, alkoxy of 1 to 5 carbon atoms or

Ar¹;

provided that R¹, R², R³ and R⁴ are not alkoxy of 1 to 5 carbon atoms, alkylthio of 1 to 5 carbon atoms, NR¹⁰R¹¹ or OH when X is O, S, SO, SO₂ or NR⁶;

R⁵ is H, alkyl, halogen, OH or alkenyl;

R⁶ is H, alkyl of 1 to 5 carbon atoms or Ar¹;

Ar and Ar¹ independently are naphthyl, pyridyl, pyrimidyl, indolyl, quinolinyl, isoquinolinyl, or phenyl optionally substituted with

alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, SH, S(O)_t alkyl of 1 to 3 carbon atoms, where t is 1, 2 or 3,

dialkylamino of 2 to 6 carbon atoms, halogen, OH, alkylamino of 1 to 3 carbon atoms, NH₂, CN, NO₂, SO₃H, tetrazole, CO₂H, carboalkoxy of 2 to 6 carbon atoms, CONH₂, SO₂NH₂, COR⁹, CONR¹²R¹³, SO₂NR¹²R¹³, Ar², OAr² or SAR²;

Ar² is naphthyl or phenyl optionally substituted with alkyl of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkoxy of 1 to 3 carbon atoms, halogen or alkylthio of 1 to 3 carbon atoms;

R⁹, R¹⁰, R¹¹, R¹² and R¹³ independently are H, alkyl of 1 to 5 carbon atoms or phenyl or R¹⁰ and R¹¹ taken together are an alkylene chain of 3 to 6 carbon atoms or R¹² and R¹³ taken together are an alkylene chain of 3 to 6 carbon atoms; and

a or b is a double bond or a single bond, provided that both are not double bonds.

Preferred compounds useful in the present invention include those compounds of Formula (II) wherein:

X is C(O), CHOH or O;

m is 0;

n and p are 1;

R³-R⁵ are H; and/or

5 Ar is phenyl optionally substituted with halogen,
OCH₃, NH₂, NO₂ or another phenyl group.

Specifically preferred compounds useful in the
present invention are:

- (a) 1-(cyclopropylmethyl)-4-(2'-(4"-fluorophenyl)-2'-
oxoethyl) piperidine
- 10 (b) 1-(cyclopropylmethyl)-4-(2'-(4"-fluorophenyl)-2'-
oxoethyl) piperidine, hydrobromide salt
- (c) 1-(cyclopropylmethyl)-4-(2'-(4"-chlorophenyl)-2'-
oxoethyl) piperidine
- (d) 1-(cyclopropylmethyl)-4-(2'-(4"-chlorophenyl)-2'-
15 oxoethyl) piperidine, hydrobromide salt
- (e) 1-(cyclopropylmethyl)-4-(4'-
fluorophenoxymethyl)piperidine
- (f) 1-(cyclopropylmethyl)-4-(4'-
fluorophenoxymethyl)piperidine,
20 hydrochloride salt
- (g) 1-(cyclopropylmethyl)-4-(4'-chlorophenoxy-
methyl)piperidine
- (h) 1-(cyclopropylmethyl)-4-(4'-chlorophenoxy-
methyl)piperidine, hydrochloride salt
- 25 (i) 1-(cyclopropylmethyl)-4-(4'-
nitrophenoxymethyl)piperidine
- (j) 1-(cyclopropylmethyl)-4-(2'-(4'''-biphenyl)-2'-
oxoethyl)piperidine
- (k) 1-(cyclopropylmethyl)-4-(2'-(4'''-biphenyl)-2'-
30 oxoethyl)piperidine, hydrobromide salt.

Pharmaceutical compositions comprising an effective
amount of a compound of Formula I or II and a
pharmaceutically acceptable carrier are useful in the
method of the present invention.

The preparation of the (N-phthalimidoalkyl) piperidine compounds of Formula I is described in copending, commonly assigned U.S. patent application USSN 07/570199, filed 8/20/90, the disclosure of which
5 is hereby incorporated by reference. The compound referred to herein as Ex. No. 504 is designated as the compound of Example No. 504 in USSN 07/570199.

The preparation of the 1-cycloalkyl piperidine compounds of Formula II is described in copending,
10 commonly assigned U.S. patent application USSN 07/602024, filed 10/23/90, the disclosure of which is hereby incorporated by reference. The compound referred to herein as Ex. No. 3 is referred to as Example No. 3 in USSN 07/428097.

15 Other sigma receptor antagonists lacking or having relatively weak dopamine receptor blocking activity are expected to be useful in the method of the present invention. Examples of other sigma receptor antagonists having greater affinity for sigma receptors than for
20 dopamine receptors which are expected to be useful in the present invention are rimcazole (also known as BW234U) (Ferris et al. (1982) J. Pharm. Pharmacol. 34: 388-390; Ferris et al. (1986) Life Sciences 38: 2329-2337; U.S. patent 4,400,383; U.S. patent 4,588,728),
25 remoxipride (Ogren et al. (1984) European Journal of Pharmacology 102: 439-474; U.S. patent 4,232,037; Snyder and Largent (1989) J. Neuropsychiatry 1: 7-15), and BMY14802 (Taylor and Dekleva (1987) Drug Development Research 11: 65-70; U.S. patent 4,605,655). The above
30 identified patents are hereby incorporated by reference.

Other sigma receptor antagonists lacking or having relatively weak dopamine receptor blocking activity and expected to be useful in the method of the invention include the compounds of copending, commonly assigned
35 U.S. patent applications USSN 07/506961, filed 3/28/90

and USSN 07/500573, filed 3/28/90, the disclosures of which are hereby incorporated by reference.

Example 1

5 The typical dopamine antagonist antipsychotic haloperidol is very active in mouse and rat tests predictive of therapeutic antipsychotic activity and in tests predictive of side-effect liability. We tested the combination of the representative sigma receptor
10 antagonist Ex. No. 3 and haloperidol in a test predictive of antipsychotic therapeutic effects (inhibition of conditioned avoidance) and a test predictive of antipsychotic side-effect liability (induction of catalepsy). In this set of experiments
15 haloperidol alone at 0.4 mg/kg p.o. inhibited conditioned avoidance behavior by 45%. However, in combination with Ex. No. 3 (3.8 mg/kg p.o.) haloperidol inhibited conditioned avoidance behavior by 85% ($p < .01$). Ex. No. 3 at this dose alone does not inhibit
20 conditioned avoidance behavior.

 Haloperidol produces a dose related (0.3 to 3.0 mg/kg p.o.) induction of catalepsy ($ED_{50} = 1.13$ mg/kg p.o.). The addition of Ex. No. 3 (3.8 mg/kg p.o.) did not significantly change the cataleptogenic response to
25 haloperidol at any dose.

 These results indicate that Ex. No. 3 enhances the therapeutic efficacy of dopamine antagonist antipsychotic agents, such as haloperidol, without altering the side-effect liability, thus enhancing the
30 therapeutic index of haloperidol and lending greater safety to its clinical use. This is very significant for the treatment of psychosis, as it is the side-effects associated with the typical antipsychotic agents that are the major limitation to their use.

Materials and Methods

Conditioned Avoidance and Escape Response: A modification of the method of Cook and Weidley (1957) was used. The apparatus is a Coulbourn Instrument large modular test cage measuring 10" x 11" x 12" with a pole suspended from the top center and a grid floor connected to a Coulbourn Instrument programmable shocker delivering a 0.75 mA pulsed current. The animals, male CDF rats (Charles River) weighing 250-350 g, are trained to a high degree of avoidance in a paradigm where they are required to climb the pole to avoid a footshock. Each animal is run 3 trials a day, 1 trial 30 min after drug administration, 1 trial 60 min after drug administration and 1 trial 90 min after drug administration. A trial consists of the animal being placed in the cage, after 10 sec the footshock comes on for 15 seconds. The animal is then removed from the cage. The animal is considered to have avoided the footshock when it climbs the pole within the first 10 sec of being placed in the cage (before the shock comes on). The animal is considered to have escaped when it climbs the pole during shock delivery. The animal is considered to have omitted when it fails to climb the pole during the trial.

Induction of Catalepsy: A modification of the method of Costall and Naylor (1975) was used. Rats, male CD rats (Charles River) weighing 250-300 g, are treated with test drugs and standards and tested for the presence of catalepsy 30 min, 60 min, and 90 min after treatment. To test for catalepsy each rat is placed with its front paws over a 10 cm high horizontal bar. The intensity of catalepsy is measured by the length of time it takes the animal to move both forelegs to the table. A time of 20 sec is considered maximal catalepsy.

Ex. No. 3 fumarate is suspended in 0.25% methycellulose. Haloperidol is dissolved in glacial acetic acid. Both compounds are injected p.o. at a rate of 0.1 ml/100 gm body weight. The data reported is for 60 min pretreatment. All doses and ED₅₀'s are expressed as the free base equivalent.

Catalepsy data was analyzed using Kruskal-Wallis and Mann-Whitney U Tests. ED₅₀'s were calculated using Litchfield-Wilcoxon. Conditioned avoidance behavior was analyzed by the Fisher Exact Test.

As shown in Table 1, Ex. No. 3 at 3.8 mg/kg p.o. significantly ($p < .01$) potentiated the effect of haloperidol (0.4 mg/kg p.o.) on inhibition of conditioned avoidance responding in the rat. Therefore, Ex. No. 3 potentiated a measure of the therapeutic efficacy of the typical antipsychotic haloperidol.

TABLE 1

The effect of Ex. No. 3 + haloperidol on conditioned avoidance responding in the rat. Ex. No. 3 and haloperidol are given p.o. 60 min. before testing. Animals are trained to avoid a footshock in a pole climb apparatus.

		% Antagonism of Avoidance
25	<u>Treatment</u>	<u>N</u>
	haloperidol, 0.4 mg/kg	
	+ Vehicle	20
		45
	haloperidol, 0.4 mg/kg	
30	<u>+ Ex. No. 3, 3.8 mg/kg</u>	<u>20</u>
		85*

* $p = .008$: Fisher Exact Test

Example 2

We tested the combination of the sigma receptor antagonist Ex. No. 504 and the typical antipsychotic

haloperidol in a test predictive of antipsychotic therapeutic effects (inhibition of conditioned avoidance) and a test predictive of antipsychotic side-effects liability (induction of catalepsy).

- 5 In this set of experiments haloperidol at 0.4 mg/kg p.o. did not inhibit conditioned avoidance behavior. However, in combination with Ex. No. 504, 3.9 mg/kg p.o., haloperidol inhibited conditioned avoidance behavior by 60% ($p < .01$). Ex. No. 504 at this dose alone
10 does not inhibit conditioned avoidance behavior.

- Haloperidol produced a dose related (0.3 to 3.0 mg/kg p.o.) induction of catalepsy ($ED_{50} = 0.88$ mg/kg p.o.). The addition of Ex. No. 504, 3.9 mg/kg p.o., antagonized or did not significantly change the
15 cataleptogenic response to haloperidol at any dose.

- These results suggest that Ex. No. 504 enhances the therapeutic efficacy of typical dopamine antagonist antipsychotic agents like haloperidol without altering the side-effect liability, thus enhancing the
20 therapeutic index of haloperidol and lending greater safety to its clinical use.

Materials and Methods

- The same materials and methods were used to
25 evaluate Ex. No. 504 in conditioned avoidance response and the induction of catalepsy as described in Example 1.

- Ex. No. 504 HBr is suspended in 0.25% methycellulose. Haloperidol is dissolved in glacial
30 acetic acid. Both compounds are injected p.o. at a rate of 0.1 ml/100 gm body weight. The data reported is for 60 min pretreatment. All doses and ED_{50} 's are expressed as the free base equivalent.

- As shown in Table 2, Ex. No. 504 at 3.9 mg/kg p.o.
35 significantly ($p < .01$) potentiated the effect of

haloperidol (0.4 mg/kg p.o.) on the inhibition of conditioned avoidance response in the rat.

TABLE 2

5 The effect of Ex. No. 504 + haloperidol on conditioned avoidance responding in the rat. Ex. No. 504 and haloperidol are given p.o. 60 min. before testing. Animals are trained to avoid a footshock in a pole climb apparatus.

10

Treatment	N	% Antagonism of Avoidance
haloperidol, 0.4 mg/kg + vehicle	10	0
haloperidol, 0.4 mg/kg + Ex. No. 504, 3.9 mg/kg	10	60*

15

20 * p = .005: Fisher Exact Test

Example 3

The effect of the sigma receptor antagonist Ex. No. 504 in affecting the dose response curve of haloperidol in the conditioned avoidance response (pole climb) was tested. Ex. No. 504 (3.9 mg/kg p.o.) produced a statistically significant 3-fold lowering in the ED₅₀ (more potent) of haloperidol for inhibition of avoidance behavior, with no significant change in the ED₅₀ of haloperidol for inhibition of conditioned escape behavior (Figure 1). The ED₅₀ of haloperidol alone for inhibition of conditioned avoidance behavior was 0.94 mg/kg p.o. In combination with Ex. No. 504 (3.9 mg/kg p.o.) the ED₅₀ of haloperidol was 0.32 mg/kg p.o.

25

30

The ED₅₀ of haloperidol alone for inhibition of escape behavior was 11.5 mg/kg p.o. and the addition of Ex. No. 504 (3.9 mg/kg p.o.) did not produce a significant change in the effect of haloperidol on
5 conditioned escape behavior.

Inhibition of conditioned avoidance behavior is considered reflective of psychotherapeutic properties and inhibition of conditioned escape behavior is considered reflective of the unwanted sedative and motor
10 incapacitation side effects produced by typical antipsychotic drugs like haloperidol. Ex. No. 504 does not inhibit conditioned avoidance or escape behavior by itself.

These results suggest that sigma receptor
15 antagonists, such as Ex. No. 504, selectively enhance the therapeutic efficacy of typical dopamine antagonist antipsychotic agents like haloperidol without effecting certain side-effects, thus enhancing the therapeutic index of the antipsychotic agent. The addition of a
20 sigma receptor antagonist, such as Ex. No. 504, to treatment with the typical dopamine receptor antagonist antipsychotics, such as haloperidol, is expected to selectively enhance the therapeutic efficacy and therefore produce a greater therapeutic index than the
25 dopamine receptor antagonist antipsychotic alone.

Dosage Forms

Daily dosage ranges from 1 mg to 2000 mg. Dosage forms (compositions) suitable for administration
30 ordinarily will contain 0.5-95% by weight of the active ingredient based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs,

syrups, and suspensions; it can also be administered parenterally in sterile liquid dosage forms.

5 Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric-coated for selective disintegration in the gastrointestinal tract.

10 Liquids dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

15 In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

20 Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., a standard reference text in this field.

CLAIMS

What is claimed is:

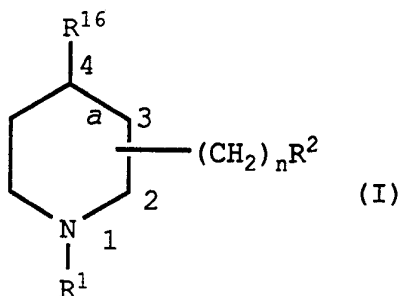
1. A method of treating psychosis in a mammal comprising administering to the mammal: (a) an effective
5 amount of a dopamine receptor antagonist antipsychotic, and (b) a sigma receptor antagonist having greater affinity for sigma receptors than for dopamine receptors, in an amount effective to enhance the antipsychotic effects of the dopamine receptor
10 antagonist relative to the adverse side effects of the dopamine receptor antagonist.
2. A method of Claim 1 wherein the dopamine receptor antagonist antipsychotic is selected from the group
15 consisting of chlorpromazine hydrochloride, triflupromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine, perphenazine, trifluoperazine hydrochloride, chlorprothixene, thiothixene
20 hydrochloride, haloperidol, haloperidol decanoate, loxapine succinate, molindone hydrochloride, and pimozide.
3. A method of Claim 1 wherein the sigma receptor
25 antagonist has an inhibition constant K_i for sigma receptors of at least 500 nM and has at least a 5-fold greater affinity for sigma receptors relative to dopamine receptors.
- 30 4. A method of Claim 1 wherein the sigma receptor antagonist has an inhibition constant K_i for sigma receptors of at least 500 nM and has at least a 10-fold greater affinity for sigma receptors relative to dopamine receptors.

5. A method of Claim 1 wherein the sigma receptor antagonist has an inhibition constant K_i for sigma receptors of at least 500 nM and has at least a 50-fold greater affinity for sigma receptors relative to dopamine receptors.
6. A method of Claim 1 wherein the sigma receptor antagonist has an inhibition constant K_i for sigma receptors of at least 500 nM and has at least a 100-fold greater affinity for sigma receptors relative to dopamine receptors.
7. A method of Claim 1 wherein the sigma receptor antagonist has an inhibition constant K_i for sigma receptors of at least 100 nM and has at least a 5-fold greater affinity for sigma receptors relative to dopamine receptors.
8. A method of Claim 1 wherein the sigma receptor antagonist has an inhibition constant K_i for sigma receptors of at least 100 nM and has at least a 10-fold greater affinity for sigma receptors relative to dopamine receptors.
9. A method of Claim 1 wherein the sigma receptor antagonist has an inhibition constant K_i for sigma receptors of at least 100 nM and has at least a 50-fold greater affinity for sigma receptors relative to dopamine receptors.
10. A method of Claim 1 wherein the sigma receptor antagonist has an inhibition constant K_i for sigma receptors of at least 100 nM and has at least a 100-fold greater affinity for sigma receptors relative to dopamine receptors.

11. A method according to Claim 1 wherein the sigma receptor antagonist is selected from the group consisting of BMY14802, rimcazole, and remoxipride.

5

12. A method of Claim 1, wherein the sigma receptor antagonist is a compound having the formula:



10

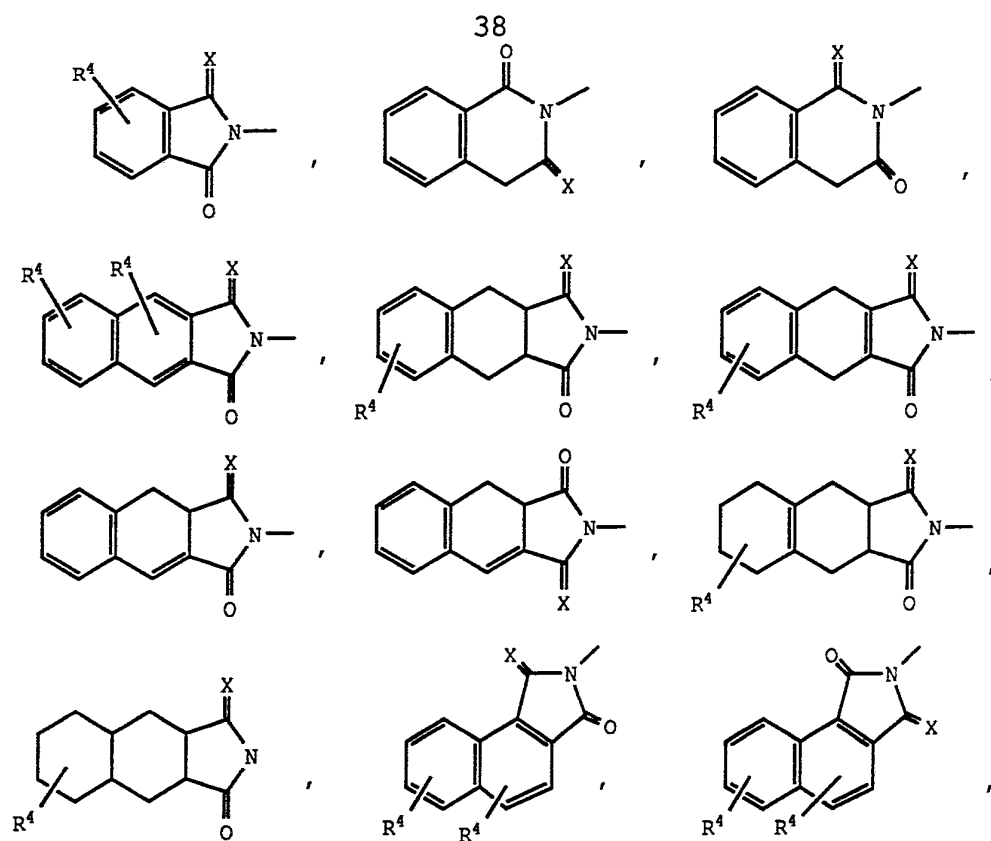
or a pharmaceutically acceptable salt or an N-oxide thereof wherein:

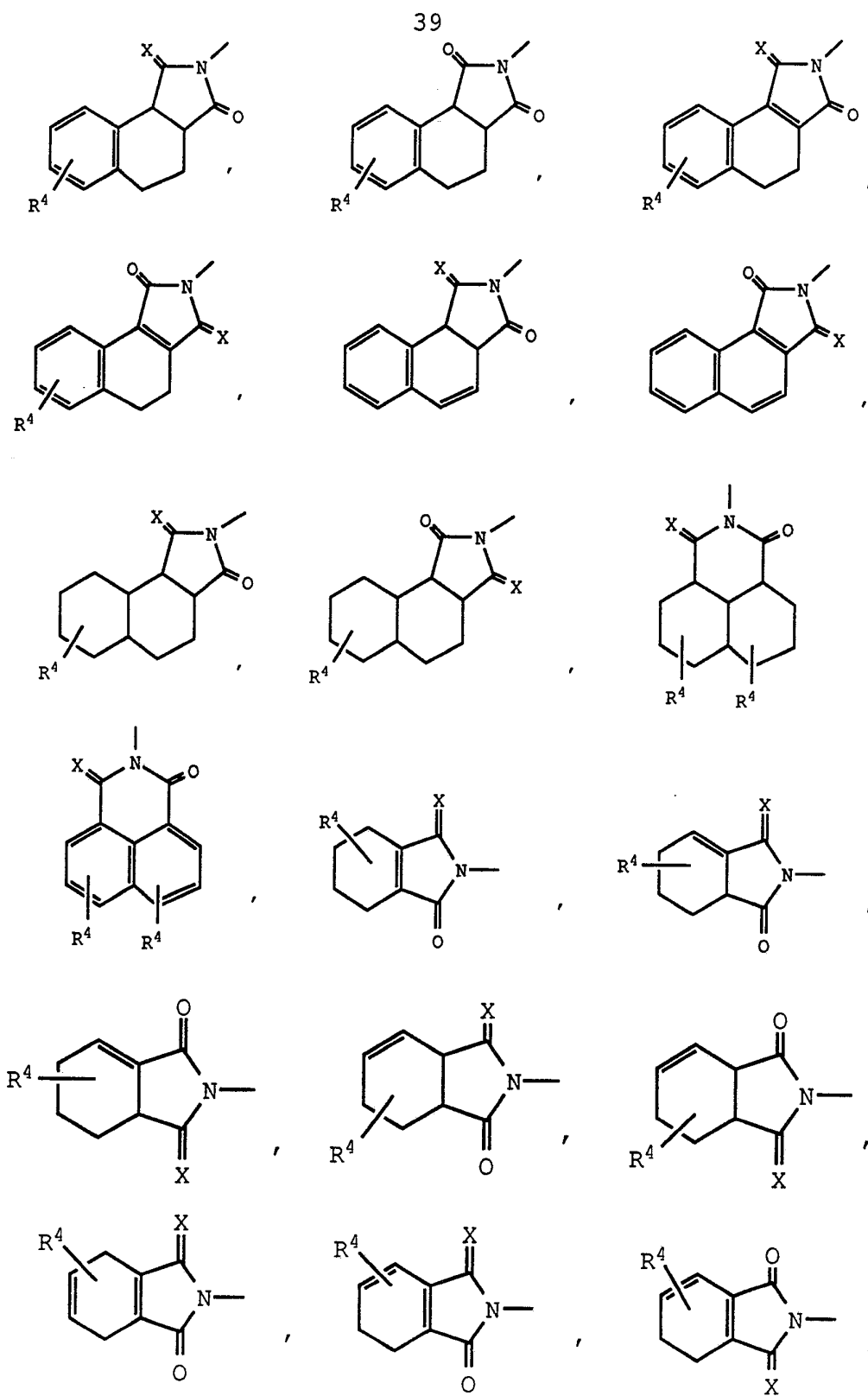
a is a single or double bond, provided that when a is a double bond then R²(CH₂)ₙ is attached at C-4;

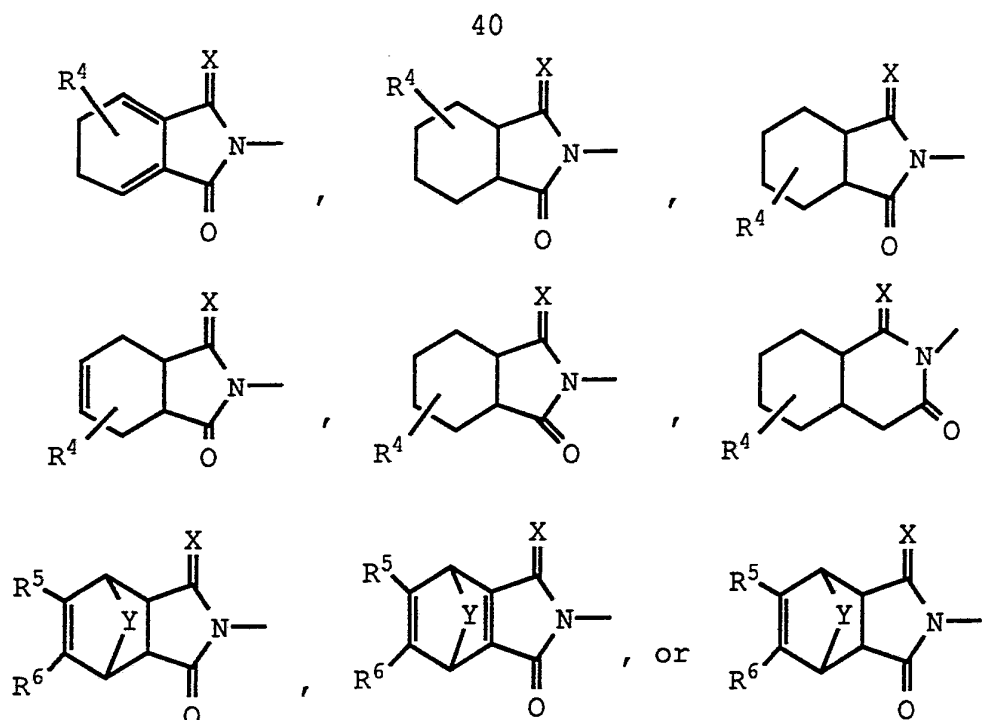
15 n is 0-4, provided that when (CH₂)ₙR² is attached to the 2-position of the piperidine ring then n is 2-4;

R¹ is (CH₂)ₘR³ or (CH₂)ₚAr, where m is 1-4 and p is 1-4;

R² is







R^3 is cycloalkyl of 3 to 8 carbon atoms;

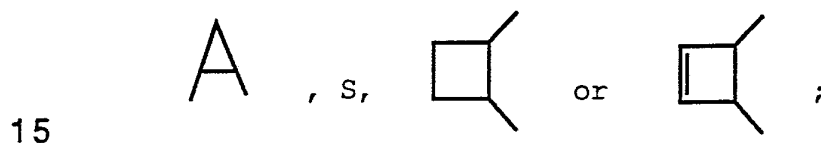
5 R^4 is 1-4 substituents independently selected from the group consisting of H, halogen, NO_2 , NH_2 , haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, C_1 - C_3 alkyl, $NHCOR^7$, $NHCO$ -phenyl, OH, OR^8 and Ar' ;

R^5 and R^6 independently are H, alkyl of 1 to 3 carbon atoms, Ar'' or taken together are $-CH=CH-CH=CH-$;

10 R^7 and R^8 independently are H or alkyl of 1 to 3 carbon atoms;

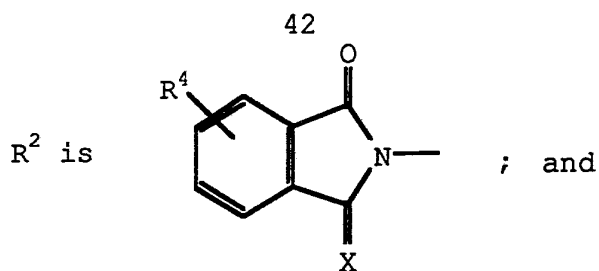
X is O; H_2 ; H, OH; R^9 , OH; Ar''' , OH; H, R^9 ; or H, OR^9 ;

Y is CH_2 , CHR^{10} , $C(R^{10})_2$, O, CH_2CH_2 , $(CH_2)_3$,



20 Ar , Ar' , Ar'' and Ar''' independently are phenyl optionally substituted with 1-5 substituents independently selected from the group consisting of:

- H, halogen, OH, alkoxy of 1 to 3 carbon atoms, $\text{NR}^{11}\text{R}^{12}$, SH, $\text{S(O)}_t\text{R}^{13}$, where t is 0-2, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkyl of 1 to 3 carbon atoms, CO_2H , carboalkoxy of 2 to 6 carbon atoms, CN, NO_2 , SO_2NH_2 , SO_3H , $\text{CO}_2\text{NR}^{14}\text{R}^{15}$, naphthyl, pyridyl, pyrimidyl, quinolyl or isoquinolyl;
- 5 R^9 and R^{10} independently are alkyl of 1 to 3 carbon atoms;
- 10 $\text{R}^{11}\text{-R}^{15}$ independently are H or alkyl of 1 to 3 carbon atoms;
- R^{16} is H; OH; O-alkyl of 1-6 carbons; O-acyl of 1-8 carbons; alkyl of 1-12 carbons; phenyl substituted with one or two substituents independently selected from F, Cl, Br, I, alkyl, perfluoroalkyl, alkoxy, aryl, arylthio, perfluoroalkoxy, perfluoroalkylthio, and dialkylamino (alkyl and alkoxy 1-12 carbons; aryl 6-12 carbons); 1- and 2-naphthyl substituted with one or two substituents independently selected from F, Cl, Br, I, alkyl, perfluoroalkyl, alkoxy, aryl, arylthio, perfluoroalkoxy, perfluoroalkylthio, and dialkylamino (alkyl and alkoxy 1-12 carbons; aryl 6-12 carbons); 2- and 3- pyrrolyl; 2- and 3- furyl; 2- and 3- thienyl; 2,3, and 4-pyridyl; 2- and 3-benzofuryl; 2- and 3- indolyl; 2- and 3-benzothienyl; 2, 3, and 4- quinolyl; and 1, 3, and 4-isoquinolyl;
- 20 provided however that:
- 25
- 30 (1) when R^1 is $(\text{CH}_2)_p\text{Ar}$ (where p is 1);



$(CH_2)_n R^2$, ($n=0$), is attached at the C-4 position on the piperidine ring; then X cannot be H_2 or O.

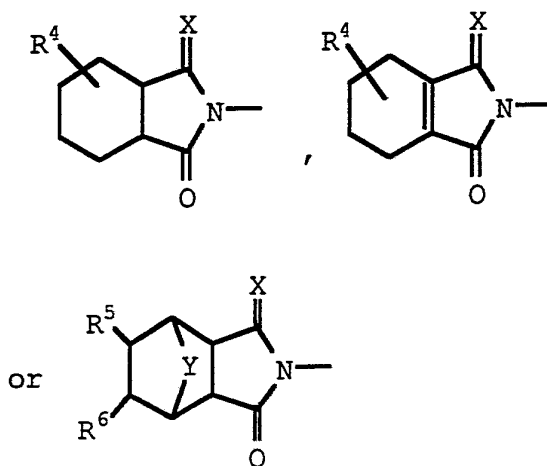
(2) R^{16} is H, OH, alkyl or aryl when $(CH_2)_n R^2$ is attached to the 4-position of the piperidine ring.

10

13. A method of Claim 12 wherein n is 1-4.

14. A method of Claim 12 wherein R^1 is $(CH_2)_p Ar$.

15. A method of Claim 12 wherein R^2 is selected from the group consisting of



where X, Y, R^4 , R^5 and R^6 are as defined in Claim 12.

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16. A method of Claim 12 wherein $(CH_2)_nR^2$ is attached at the C-4 position of the piperidine ring.

17. A method of Claim 12 wherein X is O or H₂.

5

18. A method of Claim 12 wherein R⁴, R⁵ and R⁶ are all H.

19. A method of Claim 12 wherein p is 1 or 2.

10

20. A method of Claim 12 wherein Ar is phenyl.

21. A method of Claim 12 wherein Y is $(CH_2)_3$ or O.

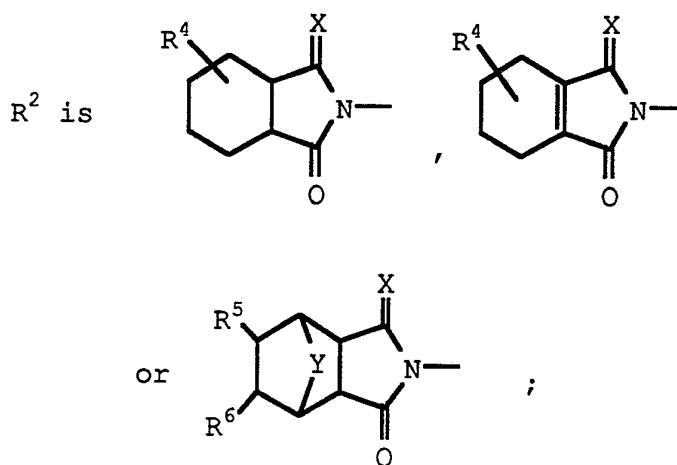
15 22. A method of Claim 12 wherein:

n is 1-4;

R¹ is $(CH_2)_pAr$;

p is 1-2;

20



$(CH_2)_nR^2$ is attached at the C-4 position of the piperidine ring; and/or

25

X is O or H₂;

R⁴, R⁵ and R⁶ are all H;

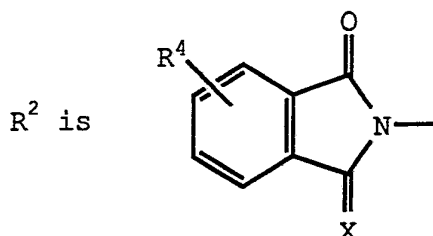
Ar is phenyl;

44

Y is $(\text{CH}_2)_3$ or O.

23. A method of Claim 22 wherein:
n is 1;

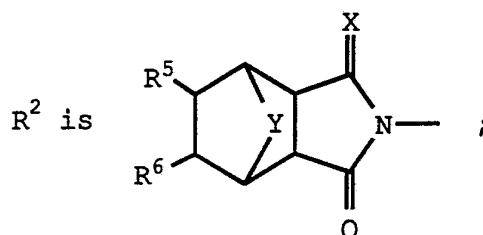
5



X is O; and
p is 2.

10

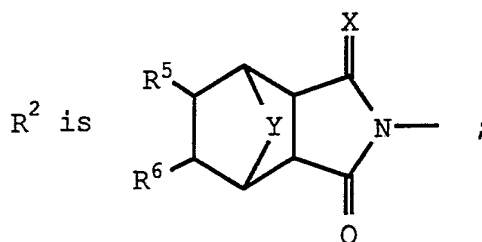
24. A method of Claim 22 wherein:
n is 1;



15

X is O;
Y is $(\text{CH}_2)_3$; and
p is 2.

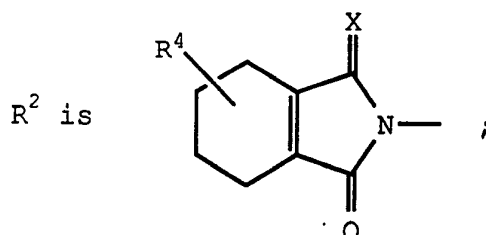
- 20 25. A method of Claim 22 wherein:
n is 1;



X is O;
Y is O; and
p is 2.

5

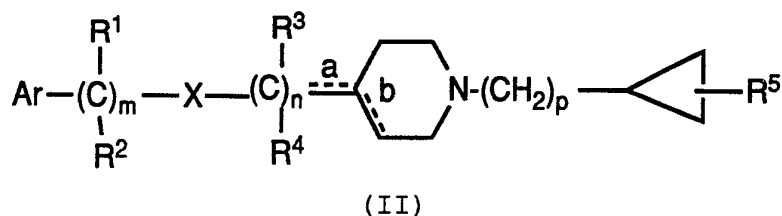
26. A method of Claim 22 wherein:
n is 1;



10

X is H₂; and
p is 2.

27. A method of Claim 1 wherein the sigma receptor
15 antagonist is a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein:

20

m is 0 to 3;
n is 0 to 3;
provided that m and n are not both 0;
p is 0 to 3;

25

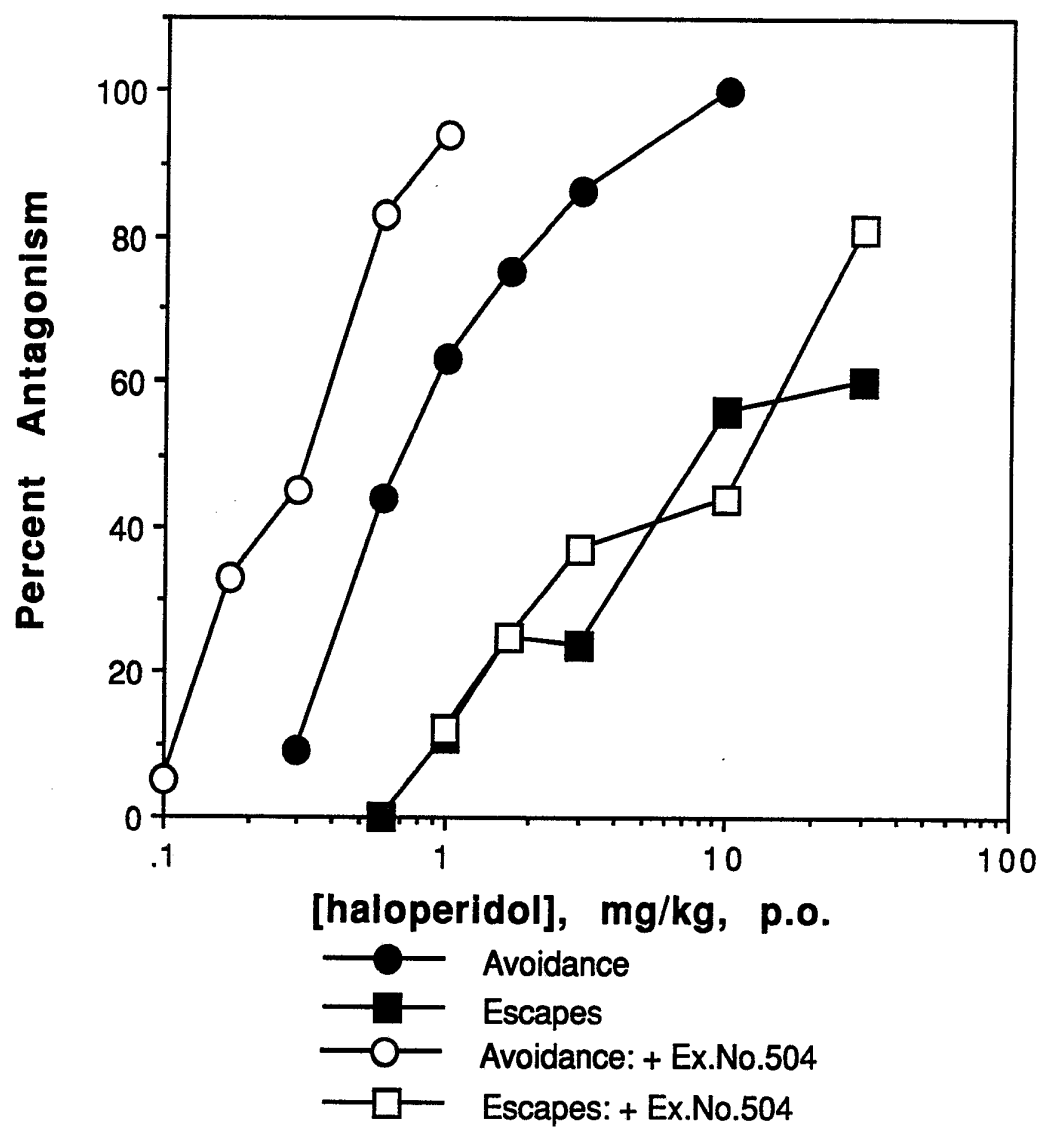
X is O, S, SO, SO₂, NR⁶, CR⁷R⁸, C, or CHOH;
R¹, R³ and R⁷ independently are H, alkyl of 1 to 5
carbon atoms, halogen, NR¹⁰R¹¹, OH, CO₂H,
carboalkoxy of 2 to 6 carbon atoms, CN, Ar¹,
30 alkoxy of 1 to 5 carbon atoms or alkylthio of

- 1 to 5 carbon atoms;
R², R⁴ and R⁸ independently are H, alkyl of 1 to 5 carbon atoms, carboalkoxy of 2 to 6 carbon atoms, CN, alkoxy of 1 to 5 carbon atoms or Ar¹;
5 provided that R¹, R², R³ and R⁴ are not alkoxy of 1 to 5 carbon atoms, alkylthio of 1 to 5 carbon atoms, NR¹⁰R¹¹ or OH when X is O, S, SO, SO₂ or NR⁶;
10 R⁵ is H, alkyl, halogen, OH or alkenyl;
R⁶ is H, alkyl of 1 to 5 carbon atoms or Ar¹;
Ar and Ar¹ independently are naphthyl, pyridyl, pyrimidyl, indolyl, quinolinyl, isoquinolinyl, or phenyl optionally substituted with
15 alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, SH, S(O)_t alkyl of 1 to 3 carbon atoms, where t is 1, 2 or 3, dialkylamino of 2 to 6 carbon atoms, halogen,
20 OH, alkylamino of 1 to 3 carbon atoms, NH₂, CN, NO₂, SO₃H, tetrazole, CO₂H, carboalkoxy of 2 to 6 carbon atoms, CONH₂, SO₂NH₂, COR⁹, CONR¹²R¹³, SO₂NR¹²R¹³, Ar², OAr² or SAr²;
Ar² is naphthyl or phenyl optionally substituted
25 with alkyl of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkoxy of 1 to 3 carbon atoms, halogen or alkylthio of 1 to 3 carbon atoms;
R⁹, R¹⁰, R¹¹, R¹² and R¹³ independently are H,
30 alkyl of 1 to 5 carbon atoms or phenyl or R¹⁰ and R¹¹ taken together are an alkylene chain of 3 to 6 carbon atoms or R¹² and R¹³ taken together are an alkylene chain of 3 to 6 carbon atoms; and
35 a or b is a double bond or a single bond, provided

that both are not double bonds.

28. A method of Claim 27 wherein:
- 5 X is CO, CHOH or O;
m is 0;
n and p are 1;
R³-R⁵ are H; and/or
Ar is phenyl optionally substituted with halogen,
10 OCH₃, NH₂, NO₂ or another phenyl group.
29. A method according to Claim 27 wherein the compound
is 1-(cyclopropylmethyl)-4-(2'-(4"-fluorophenyl)-2'-
oxoethyl) piperidine.
- 15 30. A method according to Claim 27 wherein the compound
is 1-(cyclopropylmethyl)-4-(2'-(4"-chlorophenyl)-2'-
oxoethyl) piperidine.
- 20 31. A method according to Claim 27 wherein the compound
is 1-(cyclopropylmethyl)-4-(4'-fluorophenoxymethyl)
piperidine.
32. A method according to Claim 27 wherein the compound
25 is 1-(cyclopropylmethyl)-4-(4'-chlorophenoxy-
methyl)piperidine.
33. A method according to Claim 27 wherein the compound
is 1-(cyclopropylmethyl)-4-(4'-nitrophenoxy-
30 methyl)piperidine.
34. A method according to Claim 27 wherein the compound
is 1-(cyclopropylmethyl)-4-(2'-(4' '-biphenyl)-2'-
oxoethyl)piperidine.

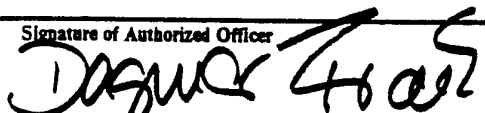
Figure 1



INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 92/02811

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 A 61 K 31/445 A 61 K 45/06		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0011606 (CIBA-GEIGY AG) 28 May 1980, see claim 10 ----	1-34
A	WO,A,8303541 (UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC.) 27 October 1983, see claims 1,2 ----	1-34
A	FR,A,2358881 (SYNTHELABO.) 17 February 1978, see claim 1 ----	1-34
A	EP,A,0337136 (MERRELL DOW PHARMACEUTICALS INC.) 18 October 1989, see page 2, lines 1-21 -----	1-34
¹⁰ Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
11-08-1992	04. 09. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/02811

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Remark: Although claims 1-34
are directed to a method of treatment of (diagnostic
method practised on) the human/animal body the search has
been carried out and based on the alleged effects of the
compound/composition.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

see annex

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX

PCT/US 92/02811

In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description, with the exception of the compound referred to as "example no. 3" which is not sufficiently described. (PCT art. 6, Guidelines; Part B, chapt. II.7, last sentence and chapt. III.3.7)

Claims searched incompletely: 1-34.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9202811

SA 60268

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 21/08/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0011606	28-05-80	JP-A- 55073679	03-06-80
		US-A- 4284638	18-08-81
WO-A- 8303541	27-10-83	US-A- 4508715	02-04-85
		EP-A- 0105361	18-04-84
		JP-T- 59500563	05-04-84
FR-A- 2358881	17-02-78	AU-B- 508753	03-04-80
		AU-A- 2715177	25-01-79
		BE-A- 856937	19-01-78
		CA-A- 1077846	20-05-80
		DE-A- 2732614	26-01-78
		GB-A- 1556567	28-11-79
		JP-A- 53026327	11-03-78
		LU-A- 77796	25-10-77
		NL-A- 7708055	24-01-78
		SE-A- 7708349	21-01-78
EP-A- 0337136	18-10-89	AU-A- 3133889	21-09-89
		JP-A- 1275530	06-11-89