(54) Title: NEUROPEPTIDE Y5 RECEPTOR ANTAGONISTS FOR TREATING DEPRESSION, ANXIETY AND DEMENTIA

(57) Abstract: This invention relates to the treatment and/or prevention of depression and/or anxiety disorders and/or dementia by the administration of a Neuropeptide Y Y5 antagonist. The present invention further provides for the use of a medicament for carrying out these methods.
BACKGROUND OF THE INVENTION

This invention relates to the treatment and/or prevention of depression and/or anxiety disorders and/or dementia by the administration of a Neuropeptide Y Y5 antagonist.

A major depressive episode has been defined as being a period of at least two weeks during which, for most of the day and nearly every day, there is either depressed mood or the loss of interest or pleasure in all, or nearly all activities. The individual may also experience changes in appetite or weight, sleep and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating or making decisions; and recurrent thoughts of death or suicidal ideation, plans or attempts. One or more major depressive episodes may give rise to a diagnosis of major depressive disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, American Psychiatric Association, 1994).

Treatment regimens commonly include the use of tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), some psychotrophic drugs, lithium carbonate, and electroconvulsive therapy (ECT) (see R. J. Baldessarini in Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 19, McGraw-Hill, 1996 for a review). More recently, new classes of antidepressant drugs are being developed including selective serotonin reuptake inhibitors (SSRIs), specific monoamine reuptake inhibitors and 5-HT1A receptor agonists and antagonists.

The most established drug treatment for the management of depressive illness are the tricyclic antidepressants. For instance, depressed patients with prominent sleep disturbance and anxiety may be treated with a sedating tricyclic antidepressant such as amitriptyline; for other patients, less sedating compounds such as imipramine or desipramine can be used. As well as inhibiting the uptake of noradrenaline and 5-hydroxytryptamine, tricyclic antidepressants also possess antagonist properties at a variety of neurotransmitter receptors, including muscarinic cholinergic receptors, α1-adrenoceptors and H1-histamine receptors. These receptor antagonist effects account for much of the side-effect profile of the tricyclic antidepressants, and in particular, their anticholinergic side-effects which are particularly troublesome in patients with prostatic enlargement or glaucoma. Other
side-effects include dry mouth, tachycardia, difficulty in visual accommodation, constipation, urinary retention, sexual dysfunction, cognitive impairment, postural hypotension, and weight gain.

Monoamine oxidase inhibitors are generally prescribed for patients who have failed to respond to tricyclic antidepressants or electroconvulsive therapy. As with tricyclic antidepressants, there are a number of side-effects associated with the use of MAOIs including dizziness, muscular twitching, insomnia, confusion, mania, tachycardia, postural hypotension, hypertension, dry mouth, blurred vision, impotence, peripheral edema, hepatocellular damage and leucopenia.

Of the new classes of antidepressant, selective serotonin reuptake inhibitors are increasingly prescribed, particularly in patients where the use of tricyclic antidepressants is contraindicated because of their anticholinergic and cardiotoxic effects. SSRIs such as fluoxetine, fluvoxamine, sertraline and paroxetine are generally non-sedating. Furthermore, SSRIs do not stimulate appetite and may therefore be appropriate in patients in whom weight gain would be undesirable. However, SSRIs are not without their own side-effects, including nausea, diarrhea, dry mouth, reduced appetite, dyspepsia, vomiting, headache, nervousness, insomnia, anxiety, tremor, dizziness, fatigue, decreased libido, pharyngitis, dyspnea, skin rash and sexual dysfunction.

Whatever drug is used, there is a delay of usually two, three or even four weeks before a therapeutic effect is observed. This period of delay may be particularly difficult for a patient suffering from a major depressive illness.

Anxiety is an emotional condition characterized by feelings such as apprehension and fear accompanied by physical symptoms such as tachycardia, increased respiration, sweating and tremor. It is a normal emotion but when it is severe and disabling it becomes pathological.

Anxiety disorders are generally treated using benzodiazepine sedative-antianxiety agents. Potent benzodiazepines are effective in panic disorder as well as in generalized anxiety disorder, however, the risks associated with the drug dependency may limit their long-term use, 5-HT₁A receptor partial agonists also have useful anxiolytic and other psychotropic activity, and less likelihood of sedation and dependence (See, e.g., R.J. Balderssarini in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 18, McGraw-Hill, 1996, for a review).
Dementia is a syndrome due to disease of the brain, usually a chronic or progressive nature, in which there is a disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Consciousness is not clouded.

Impairments of cognitive functioning are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior or motivation. This syndrome occurs in Alzheimer’s disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain.

In view of the short-comings of existing antidepressant therapy, there is a need for new, safe and effective treatment for depression and anxiety.

Neuropeptide Y (NPY) is a 36 amino acid peptide that is a member of the pancreatic polypeptide family, which also includes pancreatic polypeptide (PP) and peptide YY (PYY). NPY is located throughout the central and peripheral nervous systems and affects a diverse range of biological functions, including central endocrine secretion, vascular and smooth muscle activity, appetite, memory, anxiety, blood pressure regulation and reproduction. See, e.g., Karla, et al., Phys. & Behavior 50, 5 (1991).

fashion is an agonist whereas one that competitively reverses the NPY inhibition of forskolin-stimulated cAMP production is an antagonist.

Neuropeptide Y itself is the archetypal substrate for the NPY receptors and its binding can elicit a variety of pharmacological and biological effects \textit{in vitro} and \textit{in vivo}. When administered to the brain of live animals (intracerebroventriculally (icv) or into the amygdala), NPY produces anxiolytic effects in established animal models of anxiety such as the elevated plus-maze, Vogel punished drinking and Geller-Seifert’s bar-pressing conflict paradigms (Heilig, M. et al. \textit{Psychopharmacology} 1989, 98, 524; Heilig, M. et. al. \textit{Reg. Peptides} 1992, 41, 61; Heilig M. et. al. \textit{Neuropsychopharmacology} 1993, 8, 357). Thus compounds that mimic NPY are postulated to be useful for the treatment of anxiolytic disorders.

The immunoreactivity of neuropeptide Y is notably decreased in the cerebrospinal fluid of patients with major depression and those of suicide victims (Widdowson, P.S. et. al. \textit{Journal of Neurochemistry} 1992, 59, 73), and rats treated with tricyclic antidepressants display significant increases of NPY relative to a control group (Heilig, M. et. al. \textit{European Journal of Pharmacology} 1988, 147, 465). These findings suggest that an inadequate NPY response may play a role in some depressive illnesses, and that compounds that regulate the NPY-ergic system may be useful for the treatment of depression.

Neuropeptide Y improves memory and performance scores in animal models of learning (Flood, J. F. et. al. \textit{Brain Research} 1987, 421, 280) and therefore may serve as a cognition enhancer for the treatment of neurodegenerative diseases such as Alzheimer’s Disease (AD) as well as AIDS-related and senile dementia.

Elevated plasma levels of NPY are present in animals and humans experiencing episodes of high sympathetic nerve activity such as surgery, newborn delivery and hemorrhage (Morris, M. J. et. al. \textit{Journal of Autonomic Nervous System} 1986, 17, 143). Thus chemical substances that alter the NPY-ergic system may be useful for alleviating migraine, pain and the condition of stress.

\textbf{SUMMARY OF THE INVENTION}

The present invention relates to the use of a NPY Y5 antagonist for treating depression in a mammal. Accordingly, the present invention provides a method for treating depression in a mammal comprising the administration of NPY Y5 antagonist. The present invention further provides a pharmaceutical composition
for treating depression. The present invention further provides a method of manufacture of a medicament useful in the treatment or prevention of depression.

The present invention is further directed to the use of a NPY Y5 antagonist for treating anxiety in a mammal. Accordingly, the present invention provides a method for treating anxiety in a mammal comprising the administration of NPY Y5 antagonist. The present invention further provides a pharmaceutical composition for treating anxiety. The present invention further provides a method of manufacture of a medicament useful in the treatment or prevention of anxiety.

The present invention is further directed to the use of a NPY Y5 antagonist for treating dementia in a mammal. Accordingly, the present invention provides a method for treating dementia in a mammal comprising the administration of NPY Y5 antagonist. The present invention further provides a pharmaceutical composition for treating dementia. The present invention further provides a method of manufacture of a medicament useful in the treatment or prevention of dementia.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the use of a NPY Y5 antagonist for treating depression in a mammal. The present invention also relates to the use of a NPY Y5 antagonist for treating anxiety in a mammal. The present invention also relates to the use of a NPY Y5 antagonist for treating dementia in a mammal.

Illustrating the invention is the use of a CNS penetrant NPY Y5 antagonist for the treatment of depression, anxiety and/or dementia.

Further illustrating the invention is the use of an orally active NPY Y5 antagonist for the treatment of depression, anxiety and/or dementia.

Further illustrating the invention is the use of a non-peptidyl NPY Y5 antagonist for the treatment of depression, anxiety and/or dementia.

Also illustrating the invention is the use of a NPY Y5 antagonist for the treatment of major depressive disorder.

Exemplifying the invention is the use of a NPY Y5 antagonist for the treatment of depression including depressive disorders, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, anxiety and phobias; seasonal affective disorder; or bipolar
disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder.

Further exemplifying the invention is the use of a NPY Y5 antagonist for the treatment of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalized anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer’s disease, senile dementia, dementia of the Alzheimer’s type, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson’s disease, Huntington’s disease, Pick’s disease, Creutzfeldt-Jakob disease, or due to multiple etiologies; Parkinson’s disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglyclidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delirium, withdrawal delirium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down’s syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid hemorrhage or cerebral edema.
The present invention is also concerned with treatment and prevention of these conditions, and with the use of a NPY Y5 antagonist, combinations, and compositions thereof, for the manufacture of a medicament useful for treating or preventing these conditions.

The NPY Y5 antagonists of use in the present invention may be any NPY Y5 antagonist known from the art.

The NPY Y5 antagonist may be peptidal or non-peptidal in nature, however, the use of a non-peptidal NPY Y5 antagonist is preferred. In addition, for convenience the use of an orally active NPY Y5 antagonist is preferred.

In the present invention, it is preferred that the NPY Y5 antagonist active upon the central nervous system (CNS), such as the brain, following systemic administration, i.e. that it readily penetrates the CNS. Accordingly, a preferred NPY Y5 antagonist for use in the present invention is a CNS-penetrating NPY Y5 antagonist.

Non-limiting examples of NPY Y5 receptor antagonists include compounds of the formula:

![Chemical Structure](image)

wherein A is selected from the group consisting of aryl or heteroaryl, wherein said aryl and heteroaryl groups may be optionally substituted on either the carbon or hetero atom, the substituent being selected from the group consisting of halogen, nitro, lower alkyl, halo(lower)alkyl, hydroxy(lower)alkyl, cyclo(lower)alkyl, lower alkenyl, lower alkoxy, halo(lower)alkoxy, lower alkylthio, carboxyl, lower alkanoyl, lower alkoxy carbonyl, lower alkylene optionally substituted with oxo, and a group represented by formula of -Q-D;

D is selected from the group consisting of aryl or heteroaryl, wherein said aryl and heteroaryl groups may be optionally substituted, the substituent being selected from the group consisting of halogen, cyano, lower alkyl, halo(lower)alkyl,
hydroxy(lower)alkyl, hydroxy, lower alkoxy, halo(lower)alkoxy, lower alkylamino, di-lower alkylamino, lower alkanoyl and aryl;  
n is an integer from 0 to 1;  
Q is selected from the group consisting of a single bond or carbonyl;  
T, U, V and W are each independently selected from the group consisting of nitrogen or a methylene group, said nitrogen or methylene group may be optionally substituted with a substituent selected from the group consisting of: halogen, lower alkyl, hydroxy, and lower alkoxy;  
X is selected from the group consisting of methylene or nitrogen;  
Y is selected from the group consisting of nitrogen and oxygen, wherein said nitrogen may be optionally substituted with lower alkyl or oxygen; and the pharmaceutically acceptable salts and esters thereof. These compounds are further described and methods of preparing them can be found in International Publication Number WO 01/14376, and in US Patent Nos. 6,326,375, and 6,335,345, which are hereby incorporated by reference in their entirety.  

Non-limiting examples of NPY Y5 receptor antagonists include compounds of the formula:

\[ \text{or a pharmaceutically acceptable salt thereof, wherein;} \]

V, W, X and Z are independently selected from CH and N;  
R\(^1\) is H, C\(_{1-3}\) alkyl, C\(_{1-3}\) alkoxy, F, or Cl;  
R\(^2\) is S(O)\(^n\) R\(^6\), COR\(^6\) or CHO, wherein  
n is 0, 1 or 2; and  
R\(^6\) is N(R\(^3\))\(_2\) or C\(_{1-3}\) alkyl;  
R\(^3\) is independently H or C\(_{1-3}\) alkyl;
Ar is aryl or heteroaryl;
R⁴ and R⁵ are independently selected from:
(1) hydrogen,
(2) aryl, either unsubstituted or substituted with
   (a) halo
   (b) C₁-₃ alkoxy,
   (c) N(C₁-₃ alkyl)₂,
   (d) C₂-₄ alkanoyl, or
   (e) aryl;
(3) nitro,
(4) C₁-₅ alkyl,
(5) C₁-₅ alkoxy,
(6) hydroxy-C₁-₃ alkyl,
(7) carboxy,
(8) halo,
(9) C₁-₅ alkylthio,
(10) C₁-₅ ethoxycarbonyl,
(11) pyridylcarbonyl,
(12) benzoyl,
(13) phenyl-C₁-₃ alkoxy,
(14) pyridyl, either unsubstituted or substituted with C₁-₃ alkyl or C₁-₃ alkoxy,
(15) C₃-₆ cycloalkyl,
(16) oxazolyl,
(17) thiazolyl,
(18) triazolyl,
(19) phenoxy, and
(20) C₂-₆ alkanoyl.

These compounds are further described and methods of preparing them can be found in International Publication Number WO 00/27845, and U.S. Patent Nos. 6,191,160, and 6,313,298, which is hereby incorporated by reference in their entirety.
Non-limiting examples of NPY Y5 receptor antagonists include compound L-152,804 of the formula:


The above compounds are only illustrative of the NPY Y5 antagonists which are currently under investigation. As this listing of groups of compounds is not meant to be comprehensive, the methods of the present invention may employ any NPY Y5 antagonist and is not limited to any particular structural class of compound.

A suitable selection cascade for NPY Y5 antagonists of use according to the present invention is as follows:

(i) Determine affinity for human Y5 receptor in radioligand binding studies (Assay 1); select compounds with IC\(_{50} \leq 10\)nM, preferably IC\(_{50} \leq 2\)nM, especially IC\(_{50} \leq 1\)nM.

(ii) Determine ability of compounds to penetrate CNS by their ability to inhibit bovine pancreatic polypeptide (bPP)-induced food intake in Sprague-Dawley rats. Select compounds that inhibit (bPP)-induced food intake ID\(_{50} \leq 30\)mg/kg p.o., and preferably ID\(_{50} \leq 10\) mg/kg p.o. when administered 1 hour prior to central bPP agonist challenge.

Yet further preferred compounds of use in the present invention may be selected from those compounds which satisfy the NPY Y5 receptor binding criteria of step (i) which, in addition, have \(\leq 5\)-fold shift in affinity when incubated in the presence of human serum albumin (HSA) to show non-specific protein binding.

Examples of NPY Y5 receptor antagonists of use in the present invention are the compounds described in US 6,191,160, US 6,313,298 and
Suitable pharmaceutically acceptable salts of the NPY Y5 antagonists of use in the present invention include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group. Where the compound carries an acidic group, for example a carboxylic acid group, the present invention also contemplates salts thereof, preferably non-toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium and calcium salts thereof.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other. Similarly, the use of a particular variable within a noted structural formula is intended to be independent of the use of such variable within a different structural formula.

Full descriptions of the preparation of the NPY Y5 antagonists which are employed in the present invention may be found in the references cited herein.

The identification of a compound as a NPY Y5 antagonist, in particular a CNS penetrant NPY Y5 antagonist, and thus able to have utility in the present invention may be readily determined without undue experimentation by methodology well known in the art, such as the assays described herein.

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a NPY Y5 antagonist and one or more other pharmacologically active agents suitable for the treatment of the specific condition. The NPY Y5 antagonist and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination. For example, the present compound may employed directly in combination with the other active agent(s), or it may be administered prior, concurrent or subsequent to the administration of the other active agent(s). In general,
the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

It will be appreciated that for the treatment of depression or anxiety, the NPY Y5 antagonist may be used in conjunction with other anti-depressant or anti-anxiety agents.

Suitable classes of anti-depressant agent include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical anti-depressants.

Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Another norepinephrine reuptake inhibitor of use in the present invention is reboxetine.

Suitable selective serotonin reuptake inhibitors include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof. Suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof.


Suitable atypical anti-depressants include: buproprion, lithium, nefazodone, trazodone and vloxazine, and pharmaceutically acceptable salts thereof. Another suitable atypical antidepressant is sibutramine.

Other antidepressants of use in the present invention include adinazolam, alaproclate, amineptine, amitriptyline/chlordiazepoxide combination,
atipamezole, azamianserin, bazinaprine, befuraline, bifemelane, binodaline, bipenamol, brofaromine bupropion, caroxazone, ceniclamine, cianopramine, cimoxatone, citalopram, clemeprrol, clovoxamine, dazepinil, deanol, demexiptiline, dibenzepin, dothiepin, droxidopa, enexefine, estazolam, etoperidone, femoxetine, fengabine, fezolamine, fluotracen, idazoxan, indalpine, indeloxazine, iprindole, levoprotidine, litoxetine, lofepramine, medifoxamine, metapramine, metralindole, mianserin, milnacipran, minaprine, mirtazapine, montirelin, nebracetam, nefopam, nialamide, nomifensine, norfluoxetine, orotirelin, oxaflozane, pinazepam, pirlindone, pizotyline, ritanserin, rolipram, sercloremine, setiptiline, sibutramine, sulbutiamine, sulpiride, teniloxazine, thozalinone, thymoliberin, tianeptine, tiflucarbine, tofenacin, tofisopam, tolaxatone, tomooxetine, veralipride, viquamine, zimelidine and zometapine, and pharmaceutically acceptable salts thereof, and St. John’s wort herb, or Hypericum perforatum, or extracts thereof.

Suitable classes of anti-anxiety agent include benzodiazepines and 5-HT1A agonists or antagonists, especially 5-HT1A partial agonists, and corticotropin releasing factor (CRF) antagonists. In addition to benzodiazepines, other suitable classes of anti-anxiety agent are nonbenzodiazepine sedative-hypnotic drugs such as zolpidem; mood-stabilizing drugs such as clobazam, gabapentin, lamotrigine, loreclezole, oxcarbamazepine, stiripentol and vigabatrin; and barbiturates.

Suitable benzodiazepines include: alprazolam, chlor Diazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam, and pharmaceutically acceptable salts thereof.

Suitable 5-HT1A receptor agonists or antagonists include, in particular, the 5-HT1A receptor partial agonists bupriprine, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an anti-depressant or anti-anxiety agent, together with at least one pharmaceutically acceptable carrier or excipient.

The present invention further includes the use of a NPY Y5 antagonist in the manufacture of a medicament useful in the treatment or prevention of depression, anxiety, or dementia.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an anti-
depressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of depression and/or anxiety.

For the treatment of the clinical conditions and diseases noted above, the compounds of this invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Preferably the compositions containing an the NPY Y5 antagonists of use according to the present invention are in unit dosage forms such as tablets, pills, capsules, wafers and the like. Additionally, the NPY Y5 antagonists of use according to the present invention may be presented as granules or powders for extemporaneous formulation as volume defined solutions or suspensions. Alternatively, the NPY Y5 antagonists of use according to the present invention may be presented in ready-prepared volume defined solutions or suspensions. Preferred forms are tablets and capsules.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such
materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil or soybean oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions of the present invention may also be administered via the buccal cavity using conventional technology, for example, absorption wafers.

Compositions in the form of tablets, pills, capsules or wafers for oral administration are particularly preferred.

In the treatment of a condition in accordance with the present invention, an appropriate dosage level will generally be about 0.01 μg to 50 mg per kg patient body weight per day which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 μg to about 25 mg/kg per day; more preferably about 0.5 μg to about 10 mg/kg per day. For example, for achieving a circadian rhythm phase-shifting effect, resetting the internal circadian clock, shortening the time of reentrainment of circadian rhythms, alleviating a circadian rhythm disorder or enhancing the quality of sleep, a suitable dosage level is about 0.1 μg to 25 mg/kg per day, preferably about 0.5 μg to 10 mg/kg per day, and especially about 1 μg to 5 mg/kg per day. In larger mammals, for example humans, a typical indicated dose is about 300 μg to 400 mg orally. A compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day. When using an injectable formulation, a suitable dosage level is about 0.1 μg to 10 mg/kg per day, preferably about 0.5 μg to 5 mg/kg per day, and especially about 1 μg to 1 mg/kg per day. In larger mammals, for example humans, a typical indicated dose is about 100 μg to 100 mg i.v. A compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day.

Pharmaceutical compositions of the present invention may be provided in a solid dosage formulation preferably comprising about 100 μg to 500 mg active ingredient, more preferably comprising about 100 μg to 250 mg active ingredient.
The pharmaceutical composition is preferably provided in a solid dosage formulation comprising about 100 μg, 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg or 250 mg active ingredient.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

It will be appreciated that the amount of the NPY Y5 antagonist required for use in the treatment or prevention of major depressive disorders will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the patient’s physician or pharmacist.

As used herein, the term “depression” includes major depressive episodes, major depressive disorder and seasonal affective disorder.

As used herein, the term “major depressive disorder” includes single or recurrent major depressive episodes, with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset and, in the case of recurrent episodes, with or without interepisode recovery and with or without seasonal pattern.

Other mood disorders encompassed within the term “major depressive disorder” include dysthymic disorder with early or late onset and with or without atypical features; dementia of the Alzheimer’s type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood.

Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

A “major depressive episode” is defined as at least two weeks of depressed mood or loss of interest, which may be accompanied by other symptoms of depression. The symptoms must persist for most of the day (i.e. for at least two thirds of the patients’ waking hours), nearly every day (i.e. for at least ten out of fourteen days) for at least two consecutive weeks. A “depressed mood” is often described by the patient as feeling sad, hopeless, helpless or worthless. The patient may also appear sad to an observer, for example, through facial expression, posture, voice and
tearfulness. In children and adolescents, the mood may be irritable. A “loss of interest” is often described by the patient as feeling less interested in hobbies or not feeling any enjoyment in activities that were previously considered to be pleasurable.

A major depressive episode may be accompanied by other symptoms of depression including significant weight loss when not dieting or weight gain (e.g. a change of more than 5% body weight in one month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate; or indecisiveness; and recurrent thoughts of death, recurrent suicidal ideation with or without a specific plan, or a suicide attempt.

As used herein, the term “seasonal affective disorder” refers to a type of depressive disorder which is a cyclic, seasonal condition in which the signs and symptoms of the disorder usually appear during the winter. Signs and symptoms of the disorder include depression, loss of energy, anxiety, irritability, headaches, increased sleep, loss of interest in sex, overeating (especially foods high in carbohydrates), weight gain, and difficulty concentrating and processing information. The patient is usually free of the symptoms during spring and summer, but some patients do have exacerbated symptoms of depression in the spring. Others may experience periods of mania or hypomania, a less intense form of mania, during the summer. Characteristics of mania may include persistent elevated mood, hyperactivity, and inflated self-esteem.

As used herein, the term “treatment” refers both to the treatment and to the prevention or prophylactic therapy of the aforementioned conditions.

As used herein, the term “CNS-penetrating” refers to a compound that is active upon the central nervous system (CNS), such as the brain, following systemic administration.

As used herein, the term “orally active” refers to a compound which when given by mouth results in at least 5% of the dose being absorbed into the systemic circulation.
EXAMPLE 1

Y5 receptor antagonist assay:

To identify a potent Y5 antagonist for treatment of depression and/or anxiety in humans, the cloned human Y5 receptor is used in the primary assay. Vectors expressing either the 455 amino acid form (See, e.g., US 5,602,024) or a 10 amino acid, N-terminally shorter form (See, e.g., US 5,919,901) can be introduced into cell lines to obtain cells which express the human Y5 receptor. Binding of [125]PYY (NEN) to membrane preparations from cells expressing the cloned human Y5 receptor are performed in 0.2 ml of 25 mM Tris buffer (pH 7.4) containing 10 mM MgCl₂, 1 mM PMSF, 0.1% bacitracin and 0.5% bovine serum albumin. Membranes (10 - 300 µg/ml) prepared from LMtk-, COS-7, HEK or CHO cells expressing Y5 receptors, are incubated at 25°C for 120 min with [125]PYY (25 pM) in the presence of several concentrations of compounds to be evaluated. Bound and free peptides are separated by filtration using a GF/C glass filter presoaked with 0.3% polyethylenimine. The remaining radioactivity on the filter is quantitated using a TopCount™ (Packard Instruments Co. Inc.). Specific binding of [125]PYY is defined as the difference between total binding and nonspecific binding in the presence of 1 µM PYY. The binding IC₅₀ is calculated using GraphPad Prism (Ver. 3.0).

The functional potency of Y5 antagonists can be determined using various assays which measure inhibition of second messenger pathways. NPY increases intracellular Ca²⁺ concentration via activation of Y5 receptors through coupling to Goαq5. The potency of a Y5 antagonist in blocking NPY mediated Ca²⁺ increase can be used as a measure of its functional antagonist activity. For example, CHO cells expressing both NPY Y5 receptors and Goαq5 are seeded (40,000 cells per well) into 96-well plate 24 hr before assay. Cells are loaded for 1 hr with a Ca²⁺-sensitive fluorescent dye, Fluo-4-AM in assay buffer (Hank’s Balanced Salts Solution (HBSS) containing 20 mM HEPES, 0.5% BSA and 2.5 mM probenecid, pH 7.4), washed 3 times with the assay buffer, then returned to the incubator for 1 hr before assay on a fluorometric imaging plate reader, FLIPRTM (Molecular Device, California). The NPY-induced maximum change in fluorescence over baseline is determined and the dose which induces a 50% increase in fluorescence is defined as the EC₅₀ dose for NPY. To evaluate Y5 antagonists, the assay is repeated with the EC₅₀ dose of NPY in the presence of various concentrations of a Y5 antagonist to
generate a functional IC50. The concentration-response curves are fitted using GraphPad Prism (Ver. 3.0). Using these assays, potent Y5 antagonists with a binding IC50 and/or functional IC50 of less than 1 μM can be identified. Useful antagonists would also have to possess other characteristics such as selectivity over the other NPY receptors, good systemic exposure, sufficient half-life and brain penetration.

EXAMPLE 2
Effect of a Y5 antagonist on bovine pancreatic polypeptide (bPP)-induced food intake in Sprague-Dawley rats.

To affect depression or anxiety a Y5 antagonist must penetrate into the CNS and functionally block the NPY Y5 receptors. This assay measures the ability of NPY Y5 antagonists to block the action of an ICV dose of bPP, a NPY Y5 agonist.

Materials and Methods:

Male Sprague-Dawley rats aged 7 weeks (Charles River, Japan) were maintained under the controlled temperature (23 ± 3 °C), humidity (55 ± 15%) and light-dark cycle (7:00-19:00 light on). Rats were housed individually with ad libitum access food (CE-2, Clea Japan) and tap water.

Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p., Dainabot, Japan). A permanent stainless steel guide cannula for intracerebroventricular (ICV) injection (21 gauge, 10 mm long) was stereotaxically implanted into the right lateral ventricle. The stereotaxic coordinates used were as follows: 0.9 mm posterior and 1.2 mm lateral to the bregma and 1.5 mm ventral to the brain surface.

Animals were allowed at least 6-day recovery postoperatively before the start of feeding experiment. The day before the experiment, they were handled and underwent mock injection, and nocturnal food intake was measured. Rats which ate more than 15 g during the night before the experiment were used for the following experiment.

Test compounds were suspended in 0.5 % methylcellulose and orally administered by gavage. Administration of test compounds usually began at 10:00. Dosing volume was 5 ml/kg. One hour after the drug administration, bovine pancreatic polypeptide (PP, 5 μg/10 μl/1 min) was ICV injected through a stainless steel injector (26 gauge) attached to a 50 μl Hamilton microsyringe by polyethylene
tubing. The injector extended 2 mm beyond the end of the guide cannula. Bovine PP was dissolved in 10 mM PBS containing 0.05% BSA. Two hour post-injection food intake was measured for each rat.

Results:

A Y5 antagonist was orally administered 1 hour prior to the ICV-injection of bPP in satiated male Sprague-Dawley rats. Effective compounds suppressed bPP-induced food intake in a dose-dependent manner, with a minimum effective dose between 3 and 50 mg/kg.

EXAMPLE 3

Separation-Induced Vocalization a rodent model of depression and anxiety

Male and female guinea-pigs pups are housed in family groups with their mothers and littermates throughout the study. Experiments are commenced after weaning when the pups are 2 weeks old. Before entering an experiment, the pups are screened to ensure that a vigorous vocalization response is reproducibly elicited following maternal separation. The pups are placed individually in an observation cage (55cm x 39cm x 19cm) in a room physically isolated from the home cage for 15 minutes and the duration of vocalization during this baseline period is recorded. Only animals which vocalize for longer than 5 minutes are employed for drug challenge studies (approximately 50% of available pups may fail to reach this criterion). On test days each pup receives an oral dose or an s.c. or i.p. injection of test compound or vehicle and is then immediately returned to the home cage with its mother and siblings for 30 to 60 minutes (or for up to 4 hours following an oral dose, dependent upon the oral pharmacokinetics of the test compound) before social isolation for 15 minutes as described above. The duration of vocalization on drug treatment days is expressed as a percentage of the pre-treatment baseline value for each animal. The same subjects are retested once weekly for up to 6 weeks. Between 6 and 8 animals receive each test compound at each dose tested.

CNS-penetrant NPY Y5 receptor antagonists of use in the present invention are also effective in the attenuation of separation-induced vocalizations by guinea-pig pups as hereinafter defined. Essentially, a vocalization response in guinea-pig pups is induced by isolation from their mothers and littermates, which response is attenuated when a
CNS-penetrant NPY Y5 receptor antagonist is administered subcutaneously 30 minutes prior to isolation, wherein vocalizations during the first 15 minutes of isolation are attenuated with an ID$_{50} \leq 20$mg/kg, preferably with an ID$_{50} \leq 10$mg/kg, and especially with an ID$_{50} \leq 5$mg/kg.

In an alternative method, the NPY Y5 receptor antagonist is administered orally, 2 hours prior to isolation, wherein vocalizations during the first 15 minutes of isolation are attenuated with an ID$_{50} \leq 20$mg/kg, preferably with an ID$_{50} \leq 10$mg/kg, and especially with an ID$_{50} \leq 5$mg/kg.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.
WHAT IS CLAIMED IS:

1. A method for treating depression in a mammal which comprises administering to the mammal an effective amount of a NPY Y5 antagonist.

2. A method for treating anxiety in a mammal which comprises administering to the mammal an appropriate amount of a NPY Y5 antagonist.

3. A method for treating dementia in a mammal which comprises administering to the mammal an appropriate amount of a NPY Y5 antagonist.

4. The method of Claim 1 wherein the mammal is a human.

5. The method of Claim 1 wherein the NPY Y5 antagonist is an orally active NPY Y5 antagonist.

6. The method of Claim 1 wherein the NPY Y5 antagonist is a non-peptidal NPY Y5 antagonist.

7. The method of Claim 1 wherein the NPY Y5 antagonist is a CNS-penetrating NPY Y5 antagonist.

8. The method of Claim 2 wherein the mammal is a human.

9. The method of Claim 8 wherein the neuropeptide Y Y5 antagonist is a CNS-penetrating NPY Y5 antagonist.

10. The method of Claim 3 wherein the mammal is a human.

11. The method of Claim 10 wherein the neuropeptide Y Y5 antagonist is a CNS-penetrating NPY Y5 antagonist.

12. A method for preventing depression in a mammal comprising administration to said mammal an effective amount of a NPY Y5 antagonist, or a pharmaceutically acceptable salt or ester thereof.
13. A method for preventing dementia in a mammal comprising administration to said mammal an effective amount of a NPY Y5 antagonist, or a pharmaceutically acceptable salt or ester thereof.

14. A method for preventing anxiety in a mammal comprising administration to said mammal an effective amount of a NPY Y5 antagonist, or a pharmaceutically acceptable salt or ester thereof.

15. The use of an effective amount of a NPY Y5 antagonist, or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament useful for the treatment of depression in a mammal.

16. The use of an effective amount of a NPY Y5 antagonist, or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament useful for the treatment of dementia in a mammal.

17. The use of an effective amount of a NPY Y5 antagonist, or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament useful for the treatment of anxiety in a mammal.
### A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC.

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

| EPO-Internal, PAJ, WPI Data, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data |

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 00 27845 A (BANYU PHARMA CO LTD ;FUKURODA TAKAHIRO (JP); KANATANI AKIO (JP); F) 18 May 2000 (2000-05-18) cited in the application page 34, line 1 - line 9; claim 1; examples 19,20</td>
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</tr>
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**Further documents are listed in the continuation of box C.**

**Patent family members are listed in annex.**

* Special categories of cited documents:
  
  **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
  
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  **P** document published prior to the international filing date but later than the priority date claimed
  
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  **X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  
  **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
  
  **A** document member of the same patent family

Date of the actual completion of the international search: 5 March 2003

Date of mailing of the international search report: 13/03/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer: Vandenbogaerde, A
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### 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. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
   Although claims 1-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. X 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:  
   see FURTHER INFORMATION sheet PCT/ISA/210

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).

### 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.
Continuation of Box I.2

The subject-matter of present claims 1-17 is defined by means of the functional feature, namely NPY Y5 antagonist.

Because of the character of the functional feature, it cannot be guaranteed that the performed search is complete.

It cannot be excluded that compounds fulfilling the requirements of the functional feature have not been identified as doing so in the prior art. If such compounds have not been identified in the application either, they have not been covered by the search.

The search has been carried out, based on the functional feature per se as well as the examples given in the application, namely 3 classes of compounds described on page 7-11 of the present application.

It is further pointed out that the substantive examination can only be carried out to the same extent as the search.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
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