METHOD OF TREATING ANXIETY-RELATED DISORDERS WITH 2-AMINOCYCLOALIPHATIC AMIDE COMPOUNDS

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Field of Search .................. 514/408, 409, 514/411

References Cited
U.S. PATENT DOCUMENTS
4,098,904 7/1978 Szumskovicz ............... 424/324
4,145,435 3/1979 Szumskovicz ............... 424/274

FOREIGN PATENT DOCUMENTS
2225325 5/1990 United Kingdom

OTHER PUBLICATIONS
C.A.: vol. 112 (1); #10001t; Gue et al. (1990).

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ABSTRACT
A method for combatting anxiety in a subject in need of such treatment is provided. The method comprises administering to the subject a 2-aminocycloaliphatic amide kappa opioid agonist in an effective anxiety-combatting amount.

6 Claims, 2 Drawing Sheets
FIG. 1.

FIG. 2.

FIG. 3.
**FIG. 4.**

**FIG. 5.**
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METHOD OF TREATING
ANXIETY-RELATED DISORDERS WITH
2-AMINOCYCLOALIPHATIC AMIDE
COMPOUNDS

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under Grant No. AFOSR-89-0531 awarded by the Air Force
Office of Scientific Research. The Government has certain
rights in this invention.

FIELD OF THE INVENTION

This invention relates generally to methods for treating
anxiety in subjects in need of such treatment, and more
specifically relates to treating anxiety by administering a
kappa opioid receptor agonist to such a subject.

BACKGROUND OF THE INVENTION

Anxiety and anxiety-related disorders are extremely com-
mon. Anxiety-related conditions can be relatively mild or
can be sufficiently severe as to be quite disabling. Also
noteworthy is that anxiety, while infrequently a “disease” in
itself, is an almost inevitable and often exacerbating conse-
quence of many other medical-and surgical conditions.

The most common treatment for anxiety is to administer
one of a class of anxiolytic agents. The most common of
these are benzodiazepines such as diazepam and alprazolam.
Benzodiazepines can act to counteract anxiety by depressing
the electrical afterdischarge in the limbic system, and may
possibly inhibit neurotransmission mediated by gamma-
aminobutyric acid (GABA). Gilman et al., The Pharmaceutical
Basis of Therapeutics 434 (Gilman et al., eds., 7th ed.,
McMillan Publishing Co., New York 1985). These com-
ounds have proven to be effective at reducing anxiety, but
they also have significant depressant effects and act as
skeletal muscle relaxers. These side effects can render these
compounds unsuitable for many patients, particularly those
whose anxiety is coupled to another form of illness.

British Patent No. 2 225 325 to Gozzini et al. discloses an
opioid peptide with high affinity for delta opioid receptors.
Administration of the peptide is said to control pain and the
symptoms of depression and anxiety. No mention is made
therein of reduced sedative effects.

In view of the foregoing, it is an object of the present
invention to provide new treatment methods for combating
the effects of anxiety, along with compositions for carrying
out the same.

SUMMARY OF THE INVENTION

These and other objects are satisfied by the present
invention, which as a first aspect comprises a method of
treating anxiety in a subject in need of such treatment by
administering a kappa opioid receptor agonist (the “active
compound agent”) to such a subject in an amount effective
to combat anxiety. Preferably, the subject is a human subject.
Preferably, the compound is a compound of formula I

\[
\text{wherein:\nR is C1 to C3-alkyl;}
\]

\[
\text{R1 is C1 to C3-alkyl, and R2 is C1 to C6-alkyl,}
\]

\[
\text{—CH2CF3, C3 to C6-(allylic)alkenyl, C2 to C5-hybroxyalkyl, C3 to C6-cycloalkylmethyl, phenyl-C1 to C3-alkyl, or alternatively R1}
\]

\[
\text{and R2 together with the nitrogen atom to which they are}
\]

\[
\text{bonded form a saturated, monocyclic, heterocyclic ring}
\]

\[
\text{containing only carbon and nitrogen ring atoms and}
\]

\[
\text{containing from 3 to 4 carbon atoms, the said saturated}
\]

\[
\text{monocyclic heterocyclic ring being optionally substitu-
}\]

\[
\text{ted in the 3-position of the ring with hydroxy, C1 to C3}
\]

\[
\text{alkyl, C1 to C3-alkoxy, or C1 to C3-alkanoyloxy;}
\]

\[
\text{R3 is hydrogen or methyl;}
\]

\[
\text{R4 is hydrogen or methyl, or R3 and R4 together with the}
\]

\[
\text{carbon atom to which they are bonded form a cyclo-
}\]

\[
\text{propylene ring;}
\]

\[
m is 1 to 4;
\]

\[
n is 2 to 4; and
\]

\[
\text{Q is 1-naphthyl, 2-naphthyl or a moiety of formula II}
\]

\[
\text{wherein each of X, Y and Z is hydrogen, a halogen having}
\]

\[
an atomic number of from 9 to 35, trifluoromethyl, C2 to
\]

\[
C3-alkyl, C1 to C3-alkoxy, azido or phenyl, and at least
\]

\[
one of X, Y and Z is a substituent other than hydrogen,
\]

\[
and when one of X, Y and Z is azido, phenyl, C1 to C3-alkoxy
\]

\[
or trifluoromethyl, the remaining X, Y and Z moieties are
\]

\[
hydrogen; and the pharmaceutically acceptable salts thereof.
\]

\[
It has been discovered that the administration of a kappa
\]

\[
opioid receptor agonist can combat anxiety. Preferably, the
\]

\[
administered compound is a compound of formula I, which
\]

\[
has the particular advantage of having reduced or no seda-
\]

\[
tive effect on the subject.
\]

A second aspect of the present invention is the use of an
active compound as given above for the preparation of a
medicament for the treatment of anxiety, as described
herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a bar graph showing the spontaneous locomotor
activity of rats in the open cell test administered one of three
different dosages of U-50,488H or saline. Note that U-50,
488H is referred to as U-50 in the figure legends.

FIG. 2 is a bar graph showing the number of entries onto
the open arm of a plus-maze of rats administered one of
three different dosages of U-50,488H or saline.

FIG. 3 is a bar graph showing the time spent on the open
arm of a plus-maze by rats administered one of three
different dosages of U-50,488H or saline.

FIG. 4 is a bar graph showing the number of entries onto
the open arm of a plus-maze of rats administered peripheral
saline and intrahippocampal saline, peripheral saline and
intrahippocampal Nor-BNI, peripheral U-50,488H and
intrahippocampal saline, or peripheral U-50,488H and intrahip-

FIG. 5 is a bar graph showing the time spent on the open
arm of a plus-maze by rats administered peripheral saline
and intrahippocampal saline, peripheral saline and intrahip-
pocampal Nor-BNI, peripheral U-50,488H and intrahippocampal saline, or peripheral U-50,488H and intrahippocampal Nor-BNI.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "anxiety" is intended to refer to a condition of apprehension, uncertainty, dread, or fear unattached to a clearly defined stimulus accompanied by numerous physiological and psychological symptoms such as tachycardia, dyspnea, tension, restlessness, inattentiveness, and loss of appetite, skeletal motor function, initiative, cognitive logic, short- and long-term memory, and the like. Practice of the method of the present invention can combat, i.e., reduce or alleviate, some, most, or all of these physiological symptoms.

A suitable subject to be treated by the present method is an animal, such as a human or other mammal (e.g., house pets such as dogs and cats, or other commercially valuable or domestic animals), which experience anxiety-related symptoms due to some external or internal stimulus that are desirably combated. Preferably, the subject is human.

A kappa opioid receptor is but one of at least three recognized types of opioid receptors present in the central nervous system, the others being mu receptors and delta receptors, each of which is so designated for historical reasons. Kappa receptors are generally found in areas of the brain associated with pain perception and regulation of water balance and food intake, and administration of agonists for kappa receptors have shown analgesic effects. Kappa opioid receptors agonists selectively and stereospecifically bind kappa opioid receptor agonists as opposed to agonists of mu and delta receptors, which have essentially no affinity for kappa opioid receptors. Pleurvy, Brit. J. Anaesthesia 66:370-380 (1991). Thus, kappa opioid receptor agonists employed in carrying out the present invention are administered at a dosage effective to evoke an anxiolytic response mediated by the kappa opioid receptor, but essentially ineffective to evoke any anxiolytic response mediated by delta or mu opioid receptor.

As a result of the inventors' research, it has been discovered that the administration of agonists selective for kappa opioid receptors can combat anxiety in subjects in need of such treatment. Exemplary agonists include: the peptide products and active fragments of the prohormone prodynorphin, which include dynorphins such as dynorphin 1-13, dynorphin 1-9, dynorphin 1-17, and dynorphin 1-8, as well as leumorphin and beta-neo-morphin; azocines such as ketocyclazocine, ethylketocyclazocine, brexazocine, and pentazocine; tiifuadom; U-52,066; U-69,503; MR 2034; nalorphine; pentazocine; buprenorphine; BC 3016; compounds of formula I above, wherein R, R1, R2, R3, Q, X, Y, and Z are as defined above, and the pharmaceutically acceptable salts thereof. As used herein to refer to prodynorphin products, "active fragments" are peptides derived from these products which have N-terminal, C-terminal, or both N-terminal and C-terminal residues deleted, but nevertheless retain the biological activity of the products as described herein.

For compounds of formula I, it is preferred that R be methyl. It is also preferred that n be equal to 2, and that m be equal to 1. R3 and R2 are preferably hydrogen.

R1 and R2 preferably together with the nitrogen atom to which they are bonded form a saturated monocyclic heterocyclic ring containing only carbon atoms and nitrogen atoms. The ring can be optionally substituted at the 3-position with hydroxy, C1 to C3-alkyl, C1 to C3-alkoxy-, or C1 to C3-alkanoyloxy, although preferably the ring is unsubstituted. In a particularly preferred embodiment, R1 and R2 form a pyrrolidinyl moiety.

Q is preferably a compound of formula II in which at least one of X, Y, and Z is a halogen having an atomic number of from 9 to 35. More preferably, Q is 3, 4-dichlorophenyl.

The compounds of formula I can be stereoisomeric so that the nitrogen atom bound to R1 and R2 and the amide nitrogen are on the same side of the cycloalkylphatic ring (the cis-configuration) or on opposite sides (the trans-configuration). Preferably, the compounds of formula I are in the trans-configuration.

A particularly preferred compound of Formula I is trans-N-[2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-2-(3,4-dichlorophenyl) acetamide, which is shown in formula III.

![Formula III](image)

Compounds of Formula I and their preparation are known and are set forth in detail in U.S. Pat. No. 4,145,435, issued 20 Mar. 1979 to Szmuszkovicz, the content of which is incorporated herein by reference in its entirety.

The preparation of prodynorphin products and active fragments thereof is known to those skilled in this art. They may be produced by recombinant means in cells which do not typically produce these products, and by culture of cells which ordinarily produce these products, either in the form of the prohormone prodynorphin or the active products thereof.

Techniques for the preparation of the azocines, tifuadom, nalorphine, and buprenorphine are known to those skilled in this art.

The present invention extends to non-physiologically acceptable salts of the selective agonists of kappa opioid receptors which may be used in the preparation of the pharmacologically active compounds of the invention. The physiologically acceptable salts of kappa opioid receptor agonists include salts derived from bases. Base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine, and salts with amino acids such as arginine and lysine.

Quaternary ammonium salts can be formed, for example, by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, with dialkyl sulphates, with long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides, and with aralkyl halides, such as benzyl and phenethyl bromides.

In the manufacture of a medicament according to the invention, hereinafter referred to as a "formulation," the kappa opioid receptor agonists and the physiologically acceptable salts thereof, or the acid derivatives of either thereof (referred to as the "active compound") are typically
admixed with, among other things, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.5% to 95% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixing the components.

The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above).

Suitable solid diluents or carriers for the solid oral pharmaceutical dosage unit forms are selected from the group consisting of lipids, carbohydrates, proteins and mineral solids, for example, starch, sucrose, lactose, kaolin, dicalcium phosphate, gelatin, acacia, corn syrup, corn starch, talc and the like.

Capsules, both hard and soft, are filled with compositions of these amino-amide active ingredients in combination with suitable diluents and excipients, for example, edible oils, talc, calcium carbonate and the like, and also calcium stearate.

In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Liquid preparations for oral administration are prepared in water or aqueous vehicles which advantageously contain suspending agents, for example, methylcellulose, acacia, polyvinylpyrrolidone, polyvinyl alcohol and the like.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. The formulation should be sufficiently fluid that easy syringeability exists. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Such preparations should be stable under the conditions of manufacture and storage, and ordinarily contain in addition to the basic solvent or suspending liquid, preservatives in the nature of bacteriostatic and fungistic agents, for example, parabens, chlorobutanol, benzyl alcohol, phenol, thimerosal, and the like.

In many cases, it is preferable to include osmotically active agents, for example, sugars or sodium chloride in isotonic concentrations. Injectable formulations according to the invention generally contain from 0.1 to 5% w/w of active compound and are administered at a rate of 0.1 ml/min/kg.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w, for example, from 0.5 to 2% w/w.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1 to 0.2M concentration with respect to the said active compound.

Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, Pharmaceutical Research 3 (6), 318, (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis(tris) buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

The kappa opioid receptor agonist is administered in an anxiety-combating amount. The dose can vary depending on the agonist selected for administration, the subject, the route of administration, and other factors. Preferably, the compound is administered in an amount of between about 0.1 mg/kg and 1 g/kg, and more preferably is administered in an amount of between about 0.01 μg/kg and 0.1 g/kg.

The invention is illustrated in greater detail in the following non-limiting examples. In the Examples, "g" means grams, "mg" means milligrams, "kg" means kilograms, "mm" means millimeters, "cm" means centimeters, "μm" means micrometers, "ml" means milliliters, "μl" means microliters, and "°C." means degrees Celsius.

EXAMPLE 1

Maintenance of Test Subjects

Male Sprague-Dawley rats (Harlan, Indianapolis, Ind.) weighing from 224 g to 340 g were housed 3 or 4 to a cage in a room maintained at 22°-23°C. under 12 hours light/12 hours dark conditions (lights on at 6 am). Rat chow and
water were provided ad libitum. One day prior to behavioral testing the test animals were moved to the testing room so that the handling of cages would be minimized on the test day. The testing room was maintained at the identical temperature and light/dark schedule as the colony room. Approximately 2 hours prior to testing the room lights were attenuated to the level maintained through testing.

**EXAMPLE 2**

Introduction of Anxiolytic Agents to Rats

Each animal was anesthetized with 2.0 ml/kg equithesin solution intraperitoneally, with a methoxyflurane overlay applied when supplemental anesthesia was required. Following standard aseptic surgical procedures previously described in Myers et al., Chronic Methods: Intraventricular Infusion, Cerebrospinal Fluid Sampling and Push-Pull Perfusion, in 3 Methods in Psychology 281–315 (Academic Press, New York 1977), bilateral craniotomy holes were drilled over predetermined sites so that a thin-walled 23 gauge stainless steel guide tube could be lowered through the dura. The tubes were positioned just dorsal to the intended hippocampal injection sites using the stereotaxic coordinates AP −3.5, lateral 3.5 and DV −3.5 mm relative to Bregma. See Paxinos et al., The Rat Brain (Academic Press, New York 1982).

After 3–4 anchor screws were placed in the calvarium, cranialplastic cement was packed around the cannulae-pedestal assembly. A 27 gauge stylet of the same length as the guide was inserted in the tube to prevent its occlusion. A protective cap was screwed onto the pedestal. A recovery period of at least seven days elapsed before the beginning of the experiments.

**EXAMPLE 3**

Drugs and Experimental Groups

Subjects were divided into four groups. The first group received either U-50,488H (trans-3,4-dichloro-N-methyl-N-
[2-pyrrolidinyl]cyclohexy]benzene-acetamide methanesulfonate hydrate or saline vehicle intraperitoneally 20 minutes prior to testing. Drugs were delivered in a saline vehicle; dosages are as given in the figures. The second group received Naloxone or saline vehicle i.p. 35 minutes prior to testing and 15 minutes prior to i.p. administration of U-50,488H (the compound of Formula III) or saline vehicle. U-50,488H was purchased as the methanesulfonate from Research Biochemicals, Inc., One Strathmore Road, Natick, Mass., 01760-2418 U.S.A. (Tel. (508) 651-8151). The third group received bilateral intra-hippocampal injections of Nor-Binaltorphine (Nor-BNI) or distilled water vehicle over a 5 minute period between 15 and 20 minutes prior to testing. Injections were carried out as described in Example 4. U-50,488H or saline vehicle was administered i.p. immediately following the first bilateral hippocampal injection and immediately preceding the second. The fourth group received intra-hippocampal and i.p. vehicle only; these injections coincided with appropriate time points as described above for group three. Following the injections each rat was returned to its cage until the time of testing.
compared to the degree of stress or anxiety experienced by
the animal being tested.

EXAMPLE 8

Histological and Statistical Analysis of Specimens
At the conclusion of the experiments, each rat was given
an overdose of sodium pentobarbital and perfused transcor-
inally with normal saline followed by 10% buffered forma-
lin. After the brain was removed, sections were cut in the
coronal plane at 40 μm on a cryotome, mounted and stained
for nissi. Anatomical maps of the sites of microinjection
were then constructed after their identification by light
microscopy.

The results were analyzed statistically by paired students
T-tests on the differences between control and treatment
groups for all measures and doses. Results were considered
to be statistically significant at the level of p<0.05.

EXAMPLE 9

Locomotor Activity of U-50,488H Injected Rats in
Open Field Testing

The open field is a behavioral test widely used to measure
components of exploratory activity such as rearing, hole
poking, and the like, but can also be utilized for the
determination of sedative effects of compounds by measur-
ing spontaneous locomotor activity. FIG. 1 shows the results
of open field testing for rats receiving different 3 doses of
U-50,488H tested compared to the saline control group.

There were no measurable differences in the 5 minute open
field test of locomotor activity for all groups. This finding for
spontaneous locomotor behavior between all groups is con-
sistent with that expected from a compound which demon-
strates no sedative effects.

EXAMPLE 10

Locomotor Activity of Rats Injected with
U-50,488H in Plus-Maze Testing

The number of times a rat will enter an open arm of a
plus-maze compared to the total number of entries in all
arms (expressed as a percentage) is thought to measure the
willingness of an animal to explore an environment that may
be perceived as threatening. This measure can also reflect
sedative effects of the test compound in that drugs known to
cause sedation will lower this percentage. FIG. 2 illustrates
the dose-dependent effects of U-50,488H on the percentage
of open/total arm entries on the elevated plus-maze. Signifi-
cant (95% confidence level) differences were observed in the
percentage of open/total entries for the 0.01 and 0.1 mg/kg
U-50,488H treatment groups. The treatment group receiving
1.0 mg/kg showed no difference compared to the saline
control group. A compound with sedative actions causes a
reduction in the total number of entries by this plus-maze
measure. No U-50,488H-treated experimental groups pro-
duced an open arm/total arm ratio below that of the saline
control. This result provides further evidence that sedative
effects at the doses tested are absent.

EXAMPLE 11

Anxiety Levels of U-50,488H-Injected Rats in
Plus-Maze Testing

In elevated plus-maze testing, the key index for measur-
ing anxiety is the percentage of time spent on the open arm
to the total time on all arms. There is a direct relationship
between the relative amount of time spent on the open arms
and the anxiolytic efficacy of a given compound. FIG. 3
reveals an inverse dose-dependent response in the percent-
ages of open/total time for each dose. This effect was most
significant (99% confidence level) for the 0.01 mg/kg dose.

EXAMPLE 12

Activity of Antagonists Against U-50,488H

Nor-binaltorphine (nor-BNI) is a highly selective antago-
nist of the kappa subtype of opioid receptor. Because it was
hypothesized that peripherally administered U-50,488H was
acting predominantly within the hippocampus to elicit its
anxiolytic effects, it would follow that bilateral injections of
a selective antagonist to U-50,488H (nor-BNI) directly into
the hippocampal formation may ameliorate this effect.

As previously mentioned, the measurement on the plus-
maze most sensitive to the detection of anxiolysis is the ratio
of open/total time spent on the maze, whereas the percentage
of open/total entries is more a reflection of locomotor
activity or willingness to explore novelty. Therefore, the
reversal of U-50,488H-induced anxiolysis would be most
evident in the open/total time measurement.

As can be seen in FIG. 4, nor-BNI injected directly into
the hippocampus with or without peripheral U-50,488H (0.1
mg/kg U-50,488H) had little to no effect on open/total
entries compared with saline control values. Intrahippocam-
pal saline and peripheral U-50,488H, however, demonstrated
a significant increase (95% confidence level) in the open/
total entries. This results confirms the findings of Example
11 that indicate that U-50,488H by itself has potent anxi-
olytic properties, even following intrahippocampal injec-
tions of vehicle.

FIG. 5 presents data for the open/total time percentage for
rats (a) injected intrahippocampally with Nor-BNI and i.p.
with U-50,488H, (b) injected intrahippocampally with Nor-
BNI and i.p. with vehicle, (c) injected intrahippocampally
with vehicle and i.p. with U-50,488H, and (d) injected
intrahippocampally with vehicle and i.p. with vehicle. The
data reveals a significant difference (90% confidence level)
in anxiolytic effect from saline control for the peripheral
U-50,488H/central saline treatment group. Of greatest inter-
est is the complete reversal of the U-50,488H effect by the
bilateral intrahippocampal injection of the antagonist Nor-
BNI. Also note that Nor-BNI by itself had no effect on
behavior.

These results provide compelling evidence that U-50,
488H is endowed with potent anxiolytic properties. The data
suggest that the anxiolytic effects of U-50,488H are medi-
ated by a mechanism involving the kappa subtype of opioid
receptor. Further, the site of action for this effect can, in large
part, be localized to the hippocampal formation. These
conclusions are supported by the demonstration that the
anxiolysis induced by U-50,488H can be completely
reversed following bilateral injections, directly into the
hippocampal formation, of the selective kappa opioid
antagonist nor-BNI, and that nor-BNI by itself has no
measurable effects.
The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

That which is claimed is:

1. A method of treating anxiety in subjects in need of such treatment comprising administering to said subject a kappa opioid receptor agonist in an effective anxiety-combating amount, wherein said kappa opioid receptor agonist is a compound of the formula:

   \[
   \begin{align*}
   \text{R} & \quad \text{is C1 to C3 alkyl;} \\
   \text{R}_1 & \quad \text{is C1 to C3 alkyl, and R}_2 \text{ is C1 to C6 alkyl, --CH}_2\text{CF}_3, \\
   \text{C3 to C6(allylic)alkenyl, C2 to C5 hyroxylalkyl, C3 to} \\
   \text{C6 cycloalkyl, C3 to C4 cycloalkylmethyl, phenyl C1} \\
   \text{to C3 alkyl, or alternatively R}_1 \text{ and R}_2 \text{ together with the} \\
   \text{nitrogen atom to which they are bonded form a saturated, monocyclic, heterocyclic ring containing only} \\
   \text{carbon and nitrogen ring atoms and containing from 3} \\
   \text{to 4 carbon atoms; said saturated monocyclic heterocyclic} \\
   \text{ring being optionally substituted in the 3 position of the ring with hydroxy, C1 to C3 alkyl, C1 to C3} \\
   \text{alkoxy, or C1 to C3 alkanoyloxy;}} \\
   \text{R}_3 & \quad \text{is hydrogen or methyl;} \\
   \text{R}_4 & \quad \text{is hydrogen or methyl, or R}_3 \text{ and R}_4 \text{ together with the} \\
   \text{carbon atom to which they are bonded form a cyclo} \\
   \text{propylene ring;}} \\
   \text{m} & \quad \text{is 1 to 4;} \\
   \text{n} & \quad \text{is 2 to 4;} \\
   \text{Q} & \quad \text{is 1-naphthyl, 2-naphthyl or a moiety of formula II} \\
   \end{align*}
   \]

wherein each of X, Y and Z is hydrogen, a halogen having an atomic number of from 9 to 35, trifluoromethyl, C2 to C3 alkyl, C1 to C3 alkyloxy, azido or phenyl, and at least one of X, Y and Z is a substituent other than hydrogen, and when one of X, Y and Z is azido, phenyl, C1 to C3 alkyloxy or trifluoromethyl, the remaining X, Y and Z moieties are hydrogen, and the pharmaceutically acceptable salts thereof.

2. A method of treating anxiety according to claim 1 wherein:

   R is C1 to C3-alkyl;

   R1 is C1 to C3-alkyl, and R2 is C1 to C6-alkyl, --CH2CF3, C3 to C6(allylic)alkenyl, C2 to C5 hydroxalkyl, C3 to C6-cycloalkyl, C3 to C4-cycloalkylmethyl, phenyl-C1 to C3-alkyl, or alternatively R1 and R2 together with the nitrogen atom to which they are bonded form a saturated, monocyclic, heterocyclic ring containing only carbon and nitrogen ring atoms and containing from 3 to 4 carbon atoms; said saturated monocyclic heterocyclic ring being optionally substituted in the 3 position of the ring with hydroxy, C1 to C3 alkyl, C1 to C3-alkoxy, or C1 to C3 alkanoyloxy; R3 and R4 are each hydrogen;

   n is 2;

   m is 1; and

   Q is 3,4 dichlorophenyl; and the pharmaceutically acceptable salts thereof.

3. A method of treating anxiety according to claim 1 wherein:

   R is methyl;

   R1 is C1 to C3-alkyl, and R2 is C1 to C6-alkyl, --CH2CF3, C3 to C6(allylic)alkenyl, C2 to C5-hydroxalkyl, C3 to C6-cycloalkyl, C3 to C4-cycloalkylmethyl, phenyl-C1 to C3-alkyl, or alternatively R1 and R2 together with the nitrogen atom to which they are bonded form a saturated, monocyclic, heterocyclic ring containing only carbon and nitrogen ring atoms and containing from 3 to 4 carbon atoms; said saturated monocyclic heterocyclic ring being optionally substituted in the 3 position of the ring with hydroxy, C1 to C3 alkyl, C1 to C3-alkoxy, or C1 to C3 alkanoyloxy; R3 and R4 are each hydrogen;

   n is 2;

   m is 1; and

   Q is 3,4 dichlorophenyl; and the pharmaceutically acceptable salts thereof.

4. A method of treating anxiety according to claim 1 wherein:

   R is C1 to C3-alkyl;

   R1 and R2 together with the nitrogen atom to which they are bonded form a saturated monocyclic heterocyclic ring containing from 3 to 4 ring carbon atoms;

   R3 and R4 are each hydrogen;

   n is 2;

   m is 1; and

   Q is a moiety of formula II.

5. A method of treating anxiety according to claim 1 wherein said compound is trans-N-[2-(1-pyridinyl)cyclohexyl]-N-methyl-2-(3,4-dichlorophenyl)acetamide or a pharmaceutically acceptable salt thereof.

6. A method of treating anxiety according to claim 1 wherein:

   X is hydrogen or methyl, or X and Z together with the carbon atom to which they are bonded form a cyclopropyl ring;

   Y is hydrogen or methyl; and

   Q is 1-naphthyl, 2-naphthyl or a moiety of formula II.

wherein each of X, Y and Z is hydrogen, a halogen having an atomic number of from 9 to 35, or azido; and pharmaceutically acceptable salts thereof.
R is C1 to C3-alkyl;
R1 is C1 to C3-alkyl, and R2 is C1 to C6-alkyl,
—CH2CF3, C3 to C6-(allylic)alkenyl, C2 to C5-hydroxyalkyl, C3 to C6-cycloalkyl, C3 to C4-cycloalkyl-
-lmethyl, phenyl-C1 to C3-alkyl, or alternatively R1 and
R2 together with the nitrogen atom to which they are
bonded form a saturated, monocyclic, heterocyclic ring
containing only carbon and nitrogen ring atoms and
containing from 3 to 4 carbon atoms; said saturated
monocyclic heterocyclic ring being optionally substi-
tuted in the 3-position of the ring with hydroxyl, C1 to
C3 alkyl, C1 to C3-alkyloxyl, or C1 to C3-alkanoyloxyl;
R3 and R4 are each hydrogen;
n is 2 to 4;
m is 1; and
Q is a moiety of formula II

wherein at least one of X, Y and Z is a halogen having
an atomic number of from 9 to 35; and pharmaceuti-
cally acceptable salts thereof.

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