Title: THERAPEUTIC USE OF SELECTIVE NORADRENALINE REUPTAKE INHIBITORS

Abstract: Selective noradrenaline reuptake inhibitors are used in the treatment of nausea, emesis and related conditions, e.g. as caused by opiates or by chemotherapy.
THERAPEUTIC USE OF SELECTIVE NORADRENALINE REUPTAKE INHIBITORS

Field of the Invention

This invention relates to a new therapeutic use of selective noradrenaline reuptake inhibitors.

Background of the Invention

Noradrenaline (norepinephrine), serotonin and dopamine are monoamine neurotransmitters. Noradrenaline has been shown to modulate delayed nausea resulting from chemotherapy (see Fredrikson et al., Br. J. Cancer, 1994, 70, 642-645). Selective noradrenaline reuptake inhibitors (NRIs), for example reboxetine, desipramine, maprotiline and lofepramine, are used in the treatment of depression.

WO01/01973 describes the use of selective NRIs for the treatment of central nervous system disorders such as alcohol addiction, nicotine addiction, depression, anxiety, schizophrenia, migraine, narcolepsy, Tourette syndrome and incontinence. The compounds have a pharmacological selectivity of serotonin (Kᵢ) / noradrenaline (K) of at least 5000.

WO02/053140 discloses the combination of a NRI such as reboxetine and a neuroleptic agent such as clozapine, for the treatment of schizophrenia. WO02/076461 discloses the combination of reboxetine and citalopram, for the treatment of treatment-resistant depression.

Reboxetine is a NRI and also an anti-depressant with fewer side-effects than the traditional tricyclic anti-depressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). It is marketed as a racemic mixture of R,R-(-) and S,S-(+) enantiomers.

Reboxetine potently inhibits presynaptic noradrenaline reuptake inhibition (Kᵢ of 8 nM), and exhibits >8 fold selectivity over serotonin or dopamine reuptake inhibition and >100 fold selectivity over alpha-1 adrenergic, H₁-histaminergic or M₁-muscarinic receptor-binding in vitro (see Int. J. Med. Toxicol. 2000; 3(4): 26).

Patients treated with reboxetine have been shown to experience significantly reduced nausea and sexual dysfunction, adverse events that are common among those taking SSRIs or noradrenaline serotonin reuptake inhibitors (SNRIs).

Summary of the Invention

The present invention is based on the discovery that prophylactic or therapeutic administration of a selective noradrenaline reuptake inhibitor can prevent or diminish the nausea and emesis side-effects associated with
administration of emetogens such as opiates or cytotoxic agents.

A first aspect of the invention is the use of a selective NRI for the manufacture of a medicament for the treatment or prevention of nausea or emesis (including anticipatory nausea and vomiting, and morning sickness), vomiting, drowsiness, somnolence, dizziness, motion sickness, respiratory depression, blurred vision, hallucination, dehydration, constipation or euphoria. Such conditions and symptoms may be treated by administration of the active compound alone, i.e. as a monotherapy.

Another aspect of the invention is a pharmaceutical composition comprising a selective NRI, one or more other therapeutic agents, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the invention is a product comprising a selective NRI and one or more other therapeutic agents as a combined preparation for separate, simultaneous or sequential use in therapy associated with the or at least one of the therapeutic agents.

Selective NRIs may be effective in the treatment or prevention of conditions resulting from the administration of emetogenic compounds, for example opiates or cytotoxic agents. Nausea and emesis are examples of such conditions. A composition or product of the invention may comprise, for example, cis-platin (an anti-cancer agent), morphine (a painkiller) and a selective NRIs; both cis-platin and morphine are emetogenic agents.

Description of the Preferred embodiments

The term "selective noradrenaline reuptake inhibitor" (selective NRI) as used herein refers to a compound which is an inhibitor of noradrenaline reuptake and which has a selectivity of serotonin reuptake (IC₅₀) noradrenaline reuptake (IC₅₀) of at least 8.

By way of example, the active selective NRI that is used in the invention is a compound of formula I

![Chemical structure](image)

wherein R¹ and R² are the same or different and are each hydrogen, alkyl, -
alkyl-cycloalkyl, -alkyl-alkenyl, -alkyl-alkynyl, -alkyl-aryl or -alkyl-heteroaryl;

R³ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, CF₃, halogen, cyano, alkoxy, -O-aryl, -O-heteroaryl or hydroxy;

R⁴ is hydrogen, alkyl, alkenyl, alkynyl, halogen, CF₃, cyano, alkoxy or hydroxy; and

n is 1 or 2;

or an active metabolite or pharmaceutically acceptable salt thereof.

With regard to formula (I), R¹ is preferably alkyl, more preferably ethyl. R² is preferably hydrogen, R³ and R⁴ are preferably each hydrogen.

The term "alkyl" as used herein refers to a straight or branched chain alkyl moiety having from one to six carbon atoms, and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl and the like. "C₁₆ alkyl" has the same meaning.

The term "alkenyl" as used herein refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition at least one double bond, of either E or Z stereochemistry where applicable. This term includes for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2- methyl-2-propenyl etc. "C₂-₅ alkenyl" has the same meaning.

The term "alkynyl" as used herein refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition at least one triple bond. "C₂-₅ alkynyl" has the same meaning.

The term "alkoxy" as used herein refers to a straight or branched chain alkoxy group containing one to six carbon atoms, and includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like. "C₁-₆ alkoxy" has the same meaning.

The term "aryl" as used herein refers to optionally substituted aromatic ring systems comprising six to ten ring atoms, and optionally substituted polycyclic ring systems having two or more cyclic rings at least one of which is aromatic. This term includes for example, phenyl and naphthyl.

The term "cycloalkyl" as used herein refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "heteroaryl" as used herein refers to aromatic ring systems of five to ten atoms or which at least one atom is selected from O, N and S and includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.

The term "halogen" as used herein refers to F, Cl, Br or I.

Preferred compounds of formula (I) include:

2R-{[(R)-(2-ethoxyphenoxy)-phenyl][methyl]-morpholine;
2S-[(S)-(2-ethoxyphenoxy)-phenylmethyl]-morpholine; and
(+/-)-2R*-[(R*)-(2-ethoxyphenoxy)-phenylmethyl]-morpholine
("reboxetine");
each of the following general structure

[Chemical structure image]

Other active selective NRI compounds that may be used in the
invention are desipramine, protriptyline, oxaprotiline, norclomipramine,
lofepramine, miansarin, viloxazine, nisoxetine and neprotiline. Many of those
compounds are chiral, and the given names (also reboxetine) are used herein
to describe racemic, non-racemic and any single enantiomeric or
diastereomeric form. Reference to these and any other compounds for use in
the invention includes salts, prodrugs and active metabolites thereof.

More specifically, compounds of interest are:
(+/-)-2R*-[(R*)-(2-ethoxyphenoxy)phenylmethyl]morpholine
("reboxetine");
2(S)-[(S)-(2-ethoxyphenoxy)phenylmethyl]morpholine;
10,11-dihydro-N-methyl-5H-dibenz[b,f]azepine-5-propanamine
("desipramine");
N-methyl-5H-dibeno[a,d]cycloheptene-5-propanamine ("protriptyline");
3-chloro-10,11-dihydro-N-methyl-5H-dibenz[b,f]azepine-5-propanamine
("norclomipramine");
alpha-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol
("oxaprotiline");
R( )-alpha-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-
ethanol;
1-(4-chlorophenyl)-2-[[3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-
yl)propyl]methylamino]ethanone ("lofepramine");
1,2,3,4,10,14b-hexahydro-2-methyl dibenzofuro[1,2-a]azepine
("miansarin");
2-[2-ethoxyphenoxy)-methyl]morpholine ("viloxazine");
(+/-)-gamma-(2-methoxyphenoxy)-N-methyl-benzene propanamine
("nisoxetine"); and

\[ N\text{-methyl-9,10-ethanoanthracene-9(10H)-propanamine ("maprotiline")} \]

A compound for use in the invention may be known, or prepared by a suitable method known to one skilled in the art. The compounds may be prepared in racemic form, or prepared in individual enantiomeric form by specific synthesis or resolution as will be appreciated in the art. The compounds may, for example, be resolved into their enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid followed by fractional crystallisation and regeneration of the free base. Alternatively, the enantiomers of the novel compounds may be separated by HPLC using a chiral column.

A compound of the invention may be in a protected amino or protected form. The term "protected amino" as used herein refers to amino groups which are protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzylxycarbonyl, tert-butoxycarbonyl, acetyl or like group, or in the form of a phthalimido or like group.

Some compounds of formula (I) may exist in the form of solvates, for example hydrates, which also fall within the scope of the present invention.

Compounds of formula (I) may be in the form of pharmaceutically acceptable salts, for example, addition salts of inorganic or organic acids. Such inorganic acid addition salts include, for example, salts of hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid and sulphuric acid. Organic acid addition salts include, for example, salts of acetic acid, benzenesulphonic acid, benzoic acid, camphorsulphonic acid, citric acid, 2-(4-chlorophenoxy)-2-methylpropionic acid, 1,2-ethanedisulphonic acid, ethanesulphonic acid, ethylenediaminetetraacetic acid (EDTA), fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, N-glycolylasparaginic acid, 4-hexylresorcinol, hippuric acid, 2-(4-hydroxybenzoyl)benzoic acid, 1-hydroxy-2-naphthoic acid, 3-hydroxy-2-naphthoic acid, 2-hydroxyethanesulphonic acid, lactobionic acid, n-dodecyl sulphate, maleic acid, malic acid, mandelic acid, methanesulphonic acid, methyl sulphate, mucic acid, 2-naphthalenesulphonic acid, pamoic acid, pantothenic acid, phosphanilic acid ((4-aminophenyl)phosphonic acid), picric acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, terephthalic acid, p-toluenesulphonic acid, 10-undecenoic acid and the like. The compounds are preferably in the form of salts of methanesulphonic acid.

It will be appreciated that such salts, provided that they are pharmaceutically acceptable, may be used in therapy. Such salts may be
prepared by reacting the compound with a suitable acid in a conventional manner.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a salt if appropriate or possible under the circumstances.

The activity and selectivity of the compounds may be determined by any suitable assay known in the art.

The compounds may be used in the treatment or prevention of numerous ailments, conditions and diseases including, but not limited thereto, those described above.

In therapeutic use, the active compound may be administered orally, intravenously, rectally, parenterally, by inhalation (pulmonary delivery), topically, ocularly, nasally, or to the buccal cavity. Oral or intravenous administration is preferred. Thus, the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably, a unit dose comprises the active ingredient in an amount of 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the disease undergoing treatment.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oily suspensions. The pharmaceutical composition containing the active
ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example starch gelatin, acacia, microcrystalline cellulose or polyvinyl pyrrolidone; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long-chain aliphatic alcohols, for example heptadecaethylenoxyacetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or
more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable sweetening, flavouring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland
fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid, find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compositions for topical administration are also suitable for use in the invention. The pharmaceutically active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as light liquid paraffin, dispersed in a aqueous medium using surfactants. An ointment may be prepared by mixing the active compound with a topical vehicle such as a mineral oil or wax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally.
CLAIMS
1. Use of a selective noradrenaline reuptake inhibitor for the manufacture of a medicament for the treatment or prevention of a condition which is nausea or linked to nausea.
2. Use according to claim 1, wherein the inhibitor exhibits a selectivity of serotonin reuptake (IC$_{50}$/noradrenaline reuptake (IC$_{50}$) of at least 8.
3. Use according to claim 1 wherein the inhibitor is selected from desipramine, protriptyline, oxaprotiline, norclomipramine, lofepramine, miansarin, viloxazine, nisoxetine and neprotiline.
4. Use according to claim 1 or claim 2, wherein the inhibitor is a compound of formula (I)

![Chemical Structure](image)

wherein R$^1$ and R$^2$ are the same or different and are each hydrogen, alkyl, -alkyl-cycloalkyl, -alkyl-alkenyl, -alkyl-alkynyl, -alkyl-aryl or -alkyl-heteroaryl; 
R$^3$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, CF$_3$, halogen, cyano, alkoxy, -O-aryl, -O-heteroaryl or hydroxy; 
R$^4$ is hydrogen, alkyl, alkenyl, alkynyl, halogen, CF$_3$, cyano, alkoxy or hydroxy; and 
n is 1 or 2; or a pharmaceutically acceptable salt thereof.
5. Use according to claim 4, wherein R$^1$ is ethyl and/or R$^2$ is hydrogen.
6. Use according to claim 1, wherein the inhibitor is selected from 2R-[(R)-(2-ethoxyphenoxy)phenylmethyl]morpholine; 2S-[(S)-(2-ethoxyphenoxy)phenylmethyl]morpholine; and (+/-)-2R*-(R*)-(2-ethoxyphenoxy)phenylmethyl]morpholine ("reboxetine").
7. Use according to any preceding claim, which is a monotherapy for the said condition.
8. Use according to any preceding claim, wherein the condition is emesis, motion sickness, anticipatory nausea, vomiting or morning sickness.
9. Use according to claim 8, wherein the condition is emesis.
10. Use according to claim 8, wherein the condition is post-operative nausea or vomiting.
11. Use according to any preceding claim, wherein the condition is associated with one or more of drowsiness, somnolence, dizziness, respiratory depression, blurred vision, hallucination, constipation and euphoria.
12. Use according to any preceding claim, wherein the subject is also receiving an emetogenic agent.
13. Use according to claim 12, wherein the emetogenic agent is an opiate or cytotoxic drug.
14. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 5, an emetogenic agent, e.g. as defined in claim 13, and a pharmaceutically acceptable diluent or carrier.
15. A product comprising a compound as defined in any of claims 1 to 5 and an emetogenic agent, e.g. as defined in claim 13, as a combined preparation for separate, simultaneous or sequential use in therapy for which the emetogenic agent is effective.
CONFIRMATION COPY

13th May 2004

Dear Sirs,

Re: International Patent Application No. PCT/GB03/05693
AMEDIS PHARMACEUTICALS LTD.

I refer to you invitation to pay additional search fees dated 19th April 2004 which was sent to Gill Jennings & Every. Please note that I am now the agent for this application as indicated in the notification of the recording of a change from WIPO dated 24th March 2004.

The applicant wishes to pay all eight additional search fees. Please debit the eight additional search fees from deposit account No. 2805.0059 (Carpmaels & Ransford).

In box 3 of the invitation, the International Searching Authority indicated that the compound “neprotiline” referred to claim 3 could not be found in any database. I hereby request correction of the term “neprotiline” found on page 4, line 10 and in claim 3 of the application to “maprotiline” under Rule 91 PCT. Copies of the corrected pages are enclosed.

As recognised by the International Searching Authority, the term “neprotiline” is obviously an error since no selective noradrenaline reuptake inhibitor (NRI) having this name exists. As shown below, it is also obvious from reading the application that nothing could have been intended by “neprotiline” except “maprotiline”.

Page 1 of the application indicates that it relates to a new therapeutic use of NRIs and lines 9-11 of page 1 refer to known NRIs, stating:

Selective noradrenaline reuptake inhibitors (NRIs), for example reboxetine, desipramine, maprotiline and lofepramine, are used in the treatment of depression. (Emphasis added).

FACSIMILE MESSAGE

To: EPO Hague
Fax No.: 00 31 70 340 3016

This fax consists of 4 sheets. If a sheet is missing or has been imperfectly received, please contact us immediately (Tel: 020-7242 8692; Fax: 020-7405 4198). If you are not the addressee, please contact us immediately and then destroy this fax.
Pages 4-5 of the application as filed provide a list of the given names and chemical formulae of preferred NRIs that may be used in the invention, stating:

Other active selective NRI compounds that may be used in the invention are desipramine, protriptyline, oxapriline, nortriamipramine, lofepramine, miansarin, viloxazine, nisoxetine and maprotiline. Many of those compounds are chiral, and the given names (also reboxetine) are used herein to describe racemic, non-racemic and any single enantiomeric or diastereomeric form. Reference to these and any other compounds for use in the invention includes salts, prodrugs and active metabolites thereof.

More specifically, compounds of interest are:
(+/-)-2R*-(R*)-(2-ethoxyphenoxy)phenyl(methyl)morpholine ("reboxetine");
2(S)-[(S)-(2-ethoxyphenoxy)phenyl(methyl)morpholine;
10,11-dihydro-N-methyl-5H-dibenzo[b,f]azepine-5-propanamine
("desipramine");
N-methyl-5H-dibenzo[a,d]cycloheptene-5-propanamine ("protriptyline");
3-chloro-10,11-dihydro-N-methyl-5H-dibenzo[b,f]azepine-5-propanamine
("nortriamipramine");
alpha-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol
("oxapriline");
R(-)-alpha-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol;
1-(4-chlorophenyl)-2-[[3-(10,11-dihydro-5H-dibenzo[b,f]azepine-5-yl)propyl]methylamino]ethanone ("lofepramine");
1,2,3,4,10,14b-hexahydro-2-methylbenzo[c,f]pyrazino[1,2-a]azepine
("miansarin");
2-[(2-ethoxyphenoxy)-methyl]morpholine ("viloxazine");
(+/-)-gamma-(2-methoxyphenoxy)-N-methyl-benzenepranamine
("nisoxetine");
and N-methyl-9,10-ethanoanthracene-9(10H)-propanamine ("maprotiline").

It is clear that the terms "maprotiline" and "neprotiline" are used in this paragraph to refer to one chemical compound. The skilled person reading the application would be aware that "maprotiline" was a NRI that had been used previously for treating depression as indicated on page 1 of the application whereas no NRIs called "neprotiline" existed. It would therefore be obvious to the skilled person that, where the term "neprotiline is used on page 4 and in claim 3 of the application, nothing else could have been intended except "maprotiline." The request for correction thus satisfies the requirements of Rule 91 PCT.

This application is due to publish soon after 24th June 2004. I therefore look forward to receiving confirmation that the request for correction is allowable as soon as possible to enable the corrected pages to be included in the application as published.

Yours truly,

MERCER, CHRISTOPHER PAUL

Enc: copies of amended pages 4 and 10
2S-[(S)-(2-ethoxyphenoxy)-phenylmethyl]-morpholine; and
(+/-)-2R*-[((R*)-(2-ethoxyphenoxy)-phenylmethyl]-morpholine
("reboxetine");

each of the following general structure

![Chemical Structure](Image)

Other active selective NRI compounds that may be used in the
invention are desipramine, protriptyline, oxaprotiline, norclomipramine,
lofepramine, miansarin, viloxazine, nisoxetine and maprotiline. Many of those
compounds are chiral, and the given names (also reboxetine) are used herein
to describe racemic, non-racemic and any single enantiomeric or
diastereomeric form. Reference to these and any other compounds for use in
the invention includes salts, prodrugs and active metabolites thereof.

More specifically, compounds of interest are:

(+/-)-2R*-[((R*)-(2-ethoxyphenoxy)phenylmethyl]morpholine
("reboxetine");

2(S)-[(S)-(2-ethoxyphenoxy)phenylmethyl]morpholine;
10,11-dihydro-N-methyl-5H-dibenz[b,f]azepine-5-propanamine
("desipramine");

N-methyl-5H-dibeno[a,d]cycloheptene-5-propanamine ("protriptyline");
3-chloro-10,11-dihydro-N-methyl-5H-dibenz[b,f]azepine-5-propanamine
("norclomipramine");
alpha-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-ethanol
("oxaprotiline");
R(-)-alpha-[(methylamino)methyl]-9,10-ethanoanthracene-9(10H)-
ethanol;
1-(4-chlorophenyl)-2-[3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-
yl)propyl[methylamino]ethanone ("lofepramine");
1,2,3,4,10,14b-hexahydro-2-methyldibenzo[c,f]pyrazino[1,2-a]azepine
("miansarin");
2-[(2-ethoxyphenoxy)-methyl]morpholine ("viloxazine");
(+/-)-gamma-(2-methoxyphenoxy)-N-methyl-benzenepropanamine
CLAIMS

1. Use of a selective noradrenaline reuptake inhibitor for the manufacture of a medicament for the treatment or prevention of a condition which is nausea or linked to nausea.

2. Use according to claim 1, wherein the inhibitor exhibits a selectivity of serotonin reuptake (IC\textsubscript{50})/noradrenaline reuptake (IC\textsubscript{50}) of at least 8.

3. Use according to claim 1 wherein the inhibitor is selected from desipramine, protriptyline, oxaprotiline, norclomipramine, lofepramine, miansarin, viloxazine, nisoxetine and maprotiline.

4. Use according to claim 1 or claim 2, wherein the inhibitor is a compound of formula (I)

\[
\text{OR}^1
\]

\[
\text{OR}^2
\]

\[
\text{R}^3
\]

\[
\text{R}^4
\]

\[
\text{NR}^2
\]

(\text{I})

wherein \( R^1 \) and \( R^2 \) are the same or different and are each hydrogen, alkyl, -alkyl-cycloalkyl, -alkyl-alkenyl, -alkyl-alkynyl, -alkyl-aryl or -alkyl-heteroaryl;

\( R^3 \) is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, CF\textsubscript{3}, halogen, cyano, alkoxy, -O-aryl, -O-heteroaryl or hydroxy;

\( R^4 \) is hydrogen, alkyl, alkenyl, alkynyl, halogen, CF\textsubscript{3}, cyano, alkoxy or hydroxy; and

\( n \) is 1 or 2;

or a pharmaceutically acceptable salt thereof.

5. Use according to claim 4, wherein \( R^1 \) is ethyl and/or \( R^2 \) is hydrogen.

6. Use according to claim 1, wherein the inhibitor is selected from

\( 2R-[(R)-(2-ethoxyphenoxy)phenylmethyl]morpholine; \)

\( 2S-[(S)-(2-ethoxyphenoxy)phenylmethyl]morpholine; \)

(\text{"reboxetine"}).

7. Use according to any preceding claim, which is a monotherapy for the said condition.

8. Use according to any preceding claim, wherein the condition is emesis, motion sickness, anticipatory nausea, vomiting or morning sickness.