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COMMONWEALTH of AUSTRALIA
Patents Act 1952

APPLICATION FOR A STANDARD PATENT

I/We

Glaxo Group Limited

of

Clarges House, 6-12 Clarges Street, London, W1Y 8DH, United Kingdom

hereby apply for the grant of a Standard Patent for an invention entitled:

~~Medicaments~~ The use of lactam derivatives in the treatment of depression

which is described in the accompanying complete specification.

Details of basic application(s):-

Number	Convention Country	Date
88 20653.7	United Kingdom	1 September 1988

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this THIRTY FIRST day of AUGUST 1989

To: THE COMMISSIONER OF PATENTS

Keith Leslie
.....
a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

Davies & Collison, Melbourne

M 012003 310889

AUSTRALIAN PATENT OFFICE

N367

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention

Insert title of invention.

entitled : MEDICAMENTS

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

I ~~We~~ BARRY ANTHONY NEWSAM, a British Subject, of Clarges House, 6/12, Clarges Street, London, W1Y 8DH, ENGLAND.

do solemnly and sincerely declare as follows :-

Cross out whichever of paragraphs 1(a) or 1(b) does not apply

1(a) relates to application made by individual(s)
1(b) relates to application made by company; insert name of applicant company.

1. (a) I am / ~~We are~~ ~~the applicant for the patent~~

or (b) I am authorized by

Glaxo Group Limited

the applicant..... for the patent to make this declaration on its behalf.

Cross out whichever of paragraphs 2(a) or 2(b) does not apply

2(a) relates to application made by inventor(s)
2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventors.

2. (a) I am / ~~We are~~ ~~the actual inventor of the invention~~

or (b)

Ian Harold Coates, 20, Mandeville Road, Hertford, Hertfordshire, England.
Alexander William Oxford, 60, Green Drift, Royston, Hertfordshire, England.
Peter Charles North, 60, Downlands, Royston, Hertfordshire, England.
Michael Brian Tyers, c/o Glaxo Group Research Ltd, Priory Street, Ware, Hertfordshire, England.

~~is~~ are the actual inventor...s..... of the invention and the facts upon which the applicant.....
~~is~~ are entitled to make the application are as follows :-

State manner in which applicant(s) derive title from inventor(s)

The invention was assigned to the applicant by the said inventors by virtue of an assignment.

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ~~was~~ were made

in United Kingdom on the 1st September, 1988

by Glaxo Group Limited

in ..... on the .....

by .....

in ..... on the .....

by .....

4. The basic application..... referred to in paragraph 3 of this Declaration ~~was~~ were the first application..... made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at London, England this 25th day of ~~September~~ 1989

Signature of declarant(s) (no attestation required)

GLAXO GROUP LIMITED
by their Attorney:

.....

.....

Barry Anthony Newsam

Note: Initial all alterations.

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-40968/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 627770

(54) Title
IMIDAZOLE DERIVATIVES FOR USE IN TREATMENT OF DEPRESSION

International Patent Classification(s)
(51)[5] **A61K 031/445** **A61K 031/55**

(21) Application No. : **40968/89** (22) Application Date : **31.08.89**

(30) Priority Data

(31) Number	(32) Date	(33) Country
8820653	**01.09.88**	**GB UNITED KINGDOM**

(43) Publication Date : **08.03.90**

(44) Publication Date of Accepted Application : **03.09.92**

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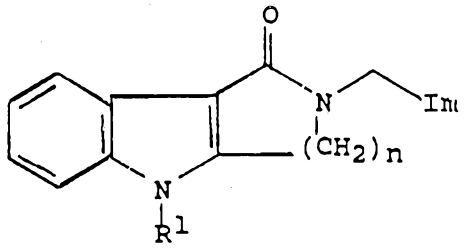
(56) Prior Art Documents
AU 613662 21742/88 A61K

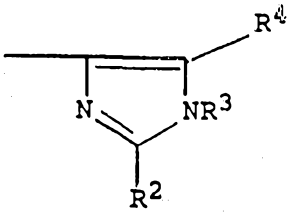
(57) Claim

1. A method for the treatment of depression which comprises administering to a human or animal subject in need thereof an effective amount of a compound of formula (I)

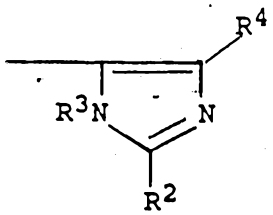


(I)

wherein Im represents an imidazolyl group of the formula:



or



and R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, phenylC_{1-3}alkyl, phenylmethoxymethyl, phenoxyethyl, phenoxymethyl, $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ or $-SO_2R^5$ (wherein R^5 and R^6, which may be the same or different, each

.../2

represents a hydrogen atom, a C_{1-6}alkyl or C_{3-7}cycloalkyl group, or a phenyl or phenylC_{1-4}alkyl group, in which the phenyl group is optionally substituted by one or more C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy groups or halogen atoms, with the proviso that R^5 does not represent a hydrogen atom when R^1 represents a group $-CO_2R^5$ or $-SO_2R^5$);

one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl, phenyl or phenylC_{1-3}alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

and n represents 2 or 3,

or a physiologically acceptable salt or solvate thereof.

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COMPLETE SPECIFICATION

NAME & ADDRESS OF APPLICANT:

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NAME(S) OF INVENTOR(S):

Ian Harold COATES
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Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

~~Medicaments~~ The use of lactam derivatives in the treatment of depression

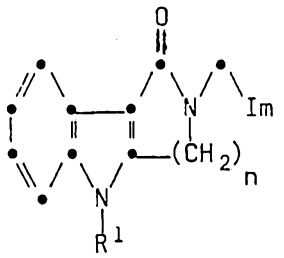
The following statement is a full description of this invention, including the best method of performing it known to me/us:-

AUSTRALIAN PATENT OFFICE

This invention relates to a further medical use for a group of heterocyclic compounds and pharmaceutical compositions containing them. In particular it relates to the use of certain lactam derivatives in the treatment of depression.

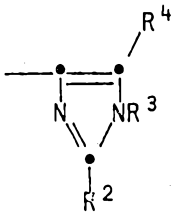
Compounds which are antagonists of 5-HT at 5-HT_3 receptors have been described previously for use in the treatment of depression in, for example, published European Patent Applications Nos. 276559 and 278173, and in German Offenlegungsschrift No. 3740352.

The present invention relates to the use, in this indication, of a particular group of compounds which are antagonists of 5-HT at 5-HT_3 receptors, as defined by the general formula (I).



(I)

In the above formula Im represents an imidazolyl group of formula:



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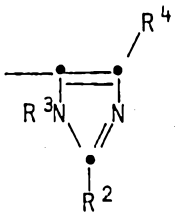

and R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, phenyl, phenylC_{1-3}alkyl, phenylmethoxymethyl, phenoxyethyl, phenoxymethyl, $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ or $-SO_2R^5$ (wherein R^5 and R^6, which may be the same or different, each represents a hydrogen atom, a C_{1-6} alkyl or C_{3-7} cycloalkyl group, or a phenyl or phenylC_{1-4}alkyl group, in which the phenyl group is optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy groups or halogen atoms, with the proviso that R^5

does not represent a hydrogen atom when R^1 represents a group $-CO_2R^5$ or $-SO_2R^5$);

one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl, phenyl or phenylC_{1-3}alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

and n represents 2 or 3.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates. The solvates may, for example, be hydrates.

Compounds defined by the general formula (I) are the subject of published European Patent Application No. 306323, which was unpublished at the priority date of the present application.

The compounds of formula (I) are potent and selective antagonists of 5-hydroxytryptamine (5-HT) at 'neuronal' 5-HT receptors of the type located on terminals of primary afferent nerves. Receptors of this type are now designated as 5-HT_3 receptors and are also present in the central nervous system. 5-HT occurs widely in the neuronal pathways in the central nervous system and disturbance of these 5-HT containing pathways is known to alter behavioural syndromes such as mood, psychomotor activity, appetite and memory.

The potent and selective antagonism of 5-HT at 5-HT_3 receptors by compounds for use according to the invention has been demonstrated by their ability to inhibit 3-(5-methyl-1H-imidazol-4-yl)-1-[1-(methyl-t_3)-1H-indol-3-yl]-1-propanone binding in rat entorhinal cortex homogenates (following the general procedure described by G. Kilpatrick et al. in Nature, 1987, 330, 746), and/or by their ability to inhibit the 5-HT-induced depolarisation of the rat isolated vagus nerve preparation.

Compounds which are antagonists of 5-HT at 5-HT_3 receptors, such as the compounds of formula (I), are of use in the treatment of a human or animal subject suffering from anxiety, a psychotic disorder

such as schizophrenia, or nausea and vomiting. The compounds are also useful in the treatment of gastric stasis; symptoms of gastrointestinal dysfunction such as occur with dyspepsia, peptic ulcer, reflux oesophagitis, flatulence and irritable bowel syndrome; migraine; and pain.

We have now found that the compounds of formula (I) and their physiologically acceptable salts and solvates, may be used in the treatment of depression.

Accordingly the invention provides a method of treatment of ~~a human or animal subject suffering from~~ depression which comprises administering to a human or animal subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof. The treatment of humans is particularly important.

References in this specification to treatment include prophylactic treatment as well as the acute alleviation of symptoms.

The use of all optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof, and all the geometric isomers of compounds of formula (I), is embraced by the invention.

A particular group of compounds of formula (I) for use according to the invention is that wherein R^1 represents a hydrogen atom or a group selected from C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, phenyl or phenylC_{1-3} alkyl (n and Im being as defined in formula (I)).

A preferred group of compounds of formula (I) for use according to the invention is that wherein R^1 represents a hydrogen atom or a C_{1-4} alkyl, C_{3-4}alkenyl, C_{3-4}alkynyl, C_{5-6}cycloalkyl, C_{5-6}cycloalkylmethyl, phenylC_{1-2} alkyl, phenylmethoxymethyl, N,N-diC_{1-3}alkylcarboxamido or C_{1-3}alkylsulphonyl group; R^2 represents a hydrogen atom; and R^3 and R^4 each represent a hydrogen atom or a C_{1-3} alkyl group.

A particularly preferred group of compounds of formula (I) for use according to the invention is that wherein R^1 represents a methyl, n-propyl, prop-2-ynyl, cyclopentyl, cyclopentylmethyl, benzyl or N,N-dimethylcarboxamido group; R^2 and R^3 each represent a hydrogen atom; and R^4 represents a methyl group.

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Within the above preferred and particularly preferred groups of compounds, an especially important group of compounds is that in which n represents 2.

Preferred compounds for use according to the invention are:

2,3,4,5-tetrahydro-5-(phenylmethyl)-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one;

5-cyclopentyl-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one;

2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-propyl-1H-pyrido[4,3-b]indol-1-one;

5-(cyclopentylmethyl)-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one;

3,4,5,6-tetrahydro-6-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-azepino[4,3-b]indol-1(2H)-one;

2,3,4,5-tetrahydro-N,N-dimethyl-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1-oxo-5H-pyrido[4,3-b]indole-5-carboxamide;

2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propynyl)-1H-pyrido[4,3-b]indol-1-one;

and their physiologically acceptable salts and solvates.

A particularly preferred compound for use according to the invention is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one and its physiologically acceptable salts and solvates. Preferred salts of this compound are the hydrochloride and maleate, of which the hydrochloride is particularly preferred.

~~In a further aspect, the invention provides a pharmaceutical~~ composition which comprises an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate (e.g. hydrate) thereof, for use in human or veterinary medicine, paticularly human medicine, for the treatment ~~of~~ depression.

In a yet further aspect, the invention provides for the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment ~~of depression.~~

AUSTRALIAN PATENT OFFICE

Pharmaceutical compositions for use in ~~accordance with~~ the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

Thus the compounds of formula (I) and their physiologically acceptable salts and solvates may be formulated for oral, buccal, parenteral, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose). Oral administration is preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage

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form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of formula (I) may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A proposed dose of a compound of formula (I) for use according to the invention for administration to man (of approximately 70kg body weight) is 0.001 to 100mg, for example 0.01 to 50mg, of the active ingredient per unit dose, expressed as the weight of free base. A preferred dose of active ingredient per unit dose is 0.001 to 10mg. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

Compounds of general formula (I) and physiologically acceptable salts or solvates thereof, may be prepared by the methods described in published European Patent Application No. 306323.

The following examples illustrate the preparation of 2,3,4,5-tetrahydro-3-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one and its hydrochloride salt, covered by

formula (I). Temperatures are in ^{0}C. Thin layer chromatograpy (t.l.c.) was carried out on silica. Organic extracts were dried, where indicated, over magnesium sulphate or sodium sulphate.

Example 1

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A suspension of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (400mg) in dry dimethoxyethane (50mℓ) was treated with sodium hydride (60% dispersion in oil; 100mg), and the mixture was stirred at 60^0 under nitrogen for 6h. 4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (474mg) was added and the reaction mixture was stirred at 60^0 under nitrogen overnight. 2N Hydrochloric acid (10mℓ) and water (10mℓ) were then added, and the mixture was heated at reflux for 6h. After cooling, the mixture was basified with 2N sodium hydroxide and the resulting mixture was extracted with ethyl acetate (2x50mℓ). The combined, dried organic extracts were concentrated onto flash column chromatography (FCC) silica and purified by FCC eluting with dichloromethane:ethanol: 0.88 ammonia (150:8:1) to give the title compound (352mg) as a solid, t.l.c. (dichloromethane:ethanol:0.88 ammonia 100:8:1) Rf 0.28. ^{1}H-N.m.r.(DMSO-d_6): δ 2.2 (3H,s), 3.04 (2H,t), 3.62 (2H,t), 3.72 (3H,s), 4.53 (2H,s), 7.1-7.28 (2H,m), 7.43 (1H,s), 7.47-7.55 (1H,dd), 7.94-8.03 (1H,dd).

Example 2

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (1.00g) was suspended in ethanol (40ml) and concentrated hydrochloric acid (1.00ml) was added. The mixture was warmed to 40^0 and charcoal (0.25g) was added. The resulting suspension was stirred and warmed for 5 min. and then filtered. The filtrate was evaporated in vacuo to ca. 20ml and was allowed to cool to 20^0. Ether (40ml) was added with stirring over 5 min., and the

mixture was stored at 4^0 overnight. The resulting precipitate was filtered off, washed with ether (2x10ml), dried in vacuo at room temperature for 2h and then at 70^0 for 7 h to give the title compound (0.95g), m.p. 288-291^0.

Analysis Found: C,61.4; H,5.8; N,16.7; Cl, 10.7;
$C_{17}H_{18}N_4O.HCl$ requires C,61.7; H,5.8; N,16.9; Cl, 10.7%

The following examples illustrate pharmaceutical formulations for use according to the invention, containing, as the active ingredient, 2,3,4,5-tetrahydro-5- methyl-2-[(5-methyl-1H-imidazol-1-yl)methyl]-1H-pyrido- [4,3-b]indol-1-one (Compound A) in the form of its free base or hydrochloride salt (1.124g of the hydrochloride is equivalent to 1g of the free base). Other physiologically acceptable salts and/or solvates of Compound A, and other compounds of formula (I) and their physiologically acceptable salts and/or solvates may be formulated in a similar manner.

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Direct Compression

(i) Tablet

	mg/tablet
Compound A free base	0.50
Calcium Hydrogen Phosphate BP*	87.25
Croscarmellose Sodium NF	1.80
Magnesium Stearate BP	0.45
Compression weight	90.00

* of a grade suitable for direct compression.

The active ingredient is passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3 tablet machine fitted with 5.5mm, flat bevelled edge punches.

(ii) Tablet	mg/tablet
Compound A hydrochloride	0.562
Microcystalline cellulose NF	31.250
Lactose (anhydrous) NF	111.303
Pregelatinised maize starch BP	6.250
Magnesium Stearate	0.625
Compression weight	150.0

* of a grade suitable for direct compression.

The active ingredient is passed through a 60 mesh sieve, blended with the lactose, microcystalline cellulose, pregelatinised maize starch and magnesium stearate. The resultant mix is compressed into tablets using a suitable tablet machine fitted with 7.0mm, normal concave punches.

Sub-Lingual Tablet	mg/tablet
Compound A hydrochloride	0.562
Compressible Sugar NF	63.938
Magnesium Stearate BP	0.5
Compression Weight	65.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using suitable punches.

Tablets of other strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

Wet Granulation

Conventional Tablet	mg/tablet
Compound A hydrochloride	0.562
Lactose BP	152.938
Starch BP	30.000
Pregelatinised Maize Starch BP	15.000
Magnesium Stearate BP	1.500
Compression Weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 8mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

Sub-Lingual Tablet	mg/tablet
Compound A hydrochloride	0.562
Mannitol BP	58.438
Hydroxypropylmethylcellulose	5.000
Magnesium Stearate BP	1.000
Compression Weight	65.0

The active ingredient is sieved through a suitable sieve and blended with the mannitol and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended into tablets using suitable punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to mannitol or the compression weight and punches to suit.

CAPSULES

	mg/capsule
Compound A hydrochloride	0.562
* Starch 1500	98.438
Magnesium Stearate BP	1.000
Fill Weight	100.0

* a form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitabled machinery. Other doses may be prepared by altering the fill weight an if necessary changing the capsule size to suit.

SYRUP

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup

	mg/5ml dose
Compound A hydrochloride	0.562
Sucrose BP	2750.0
Glycerine BP	500.0
Buffer, Flavour, Colour, Preservative	as required
Purified Water BP to	5.0ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup is clarified by filtration.

B. Sucrose-Free	mg/5ml dose
Compound A hydrochloride	0.562
Hydroxypropylmethylcellulose USP (viscosity type 4000)	22.5
Buffer) Flavour) Colour) Preservative) Sweetener)	as required
Purified Water BP to	5.0ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

INJECTION FOR INTRAVENOUS ADMINISTRATION

(i)

	mg/mℓ	
Compound A free base	0.05	0.5
Sodium Chloride BP	as required	as required
Water for Injection	1.0mℓ	1.0mℓ

(ii)

	mg/mℓ	
Compound A hydrochloride	0.0562	0.562
Sodium Chloride BP	as required	as required
Water for Injection BP to	1.0mℓ	1.0mℓ

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively, suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively, the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

SUPPOSITORY

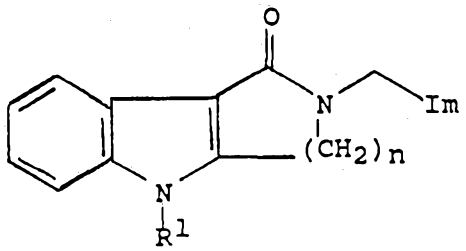
(i)	Compound A free base	0.5mg
	* Witepsol H15 to	1.0g
(ii)	Compound A hydrochloride	0.562mg
	* Witepsol H15 to	1.0g

* Witepsol H15 is a proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient is prepared in the molten Witepsol and filled, using suitable machinery, into 1g size suppository moulds.

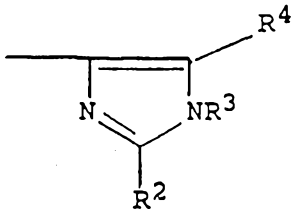
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for the treatment of depression which comprises administering to a human or animal subject in need thereof an effective amount of a compound of formula (I)

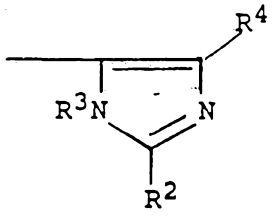


(I)

wherein Im represents an imidazolyl group of the formula:



or



and R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, phenylC_{1-3}alkyl, phenylmethoxymethyl, phenoxyethyl, phenoxymethyl, $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ or $-SO_2R^5$ (wherein R^5 and R^6, which may be the same or different, each represents a hydrogen atom, a C_{1-6}alkyl or C_{3-7}cycloalkyl group, or a phenyl or phenylC_{1-4}alkyl group, in which the phenyl group is optionally substituted by one or more C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy groups or halogen atoms, with the proviso that R^5 does not represent a hydrogen atom when R^1 represents a group $-CO_2R^5$ or $-SO_2R^5$);

one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl, phenyl or phenylC_{1-3}alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

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and n represents 2 or 3,
or a physiologically acceptable salt or solvate thereof.

2. A method according to claim 1 in which in the compound of formula (I) R^1 represents a hydrogen atom or a C_{1-4}alkyl, C_{3-4}alkenyl, C_{3-4}alkynyl, C_{5-6}cycloalkyl, C_{5-6}cycloalkylmethyl, phenylC_{1-2}alkyl, phenylmethoxymethyl, N,N-diC_{1-3}alkylcarboxamido or C_{1-3}alkylsulphonyl group; R^2 represents a hydrogen atom; and R^3 and R^4 each represent a hydrogen atom or a C_{1-3} alkyl group.

3. A method according to claim 1 in which in the compound of formula (I) R^1 represents a methyl n-propyl, prop-2-ynyl, cyclopentyl, cyclopentylmethyl, benzyl or N,N-dimethylcarboxamido group; R^2 and R^3 each represent a hydrogen atom; and R^4 represents a methyl group.

4. A method according to claim 1 in which in the compound of formula (I), n is 2.

5. A method according to claim 1 in which said compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

6. A method according to claim 5 in which said compound is used in the form of its hydrochloride salt.

7. A method according to claim 1 in which said compound of formula (I) is selected from
2,3,4,5-tetrahydro-5-(phenylmethyl)-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one;
5-cyclopentyl-2,3,4,5-tetrahydro-2-[5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one;
2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-propyl-1H-pyrido[4,3-b]indol-1-one;

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5-(cyclopentylmethyl)-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one;
3,4,5,6-tetrahydro-6-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-azepino[4,3-b]inol-1(2H)-one;
2,3,4,5-tetrahydro-N,N-dimethyl-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1-oxo-5H-pyrido[4,3-b]indole-5-carboxamide;
2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propynyl)-1H-pyrido[4,3-b]indol-1-one;
and physiologically acceptable salts and solvates thereof.

8. A method according to any one of claims 1 to 7 in which the compound of formula (I) is administered in a form adapted for oral administration.

9. A method according to any one of claims 1 to 8 in which the compound of formula (I) is administered in a unit dose form containing from 0.001 to 100mg of the said compound per unit dose.

10. A method according to any one of claims 1 to 9 in which the compound of formula (I) is administered in a unit dose form containing from 0.001 to 10mg of the said compound per unit dose.

DATED this 7th day of May, 1992
Glaxo Group Limited
By Its Patent Attorneys
DAVIES COLLISON CAVE

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