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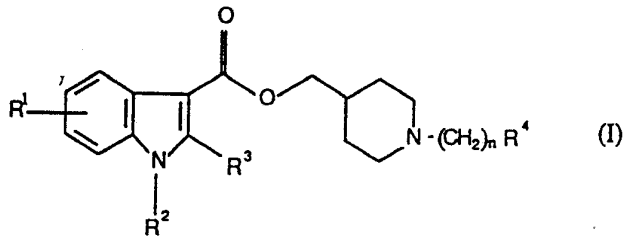
(54) Title: 3-PIPERIDINYLMETHYLCARBOXYLATE SUBSTITUTED INDOLES



(I)

(57) Abstract

Indole derivatives of formula (I) wherein R^1 represents a hydrogen or a halogen atom, or a C_{1-6}alkyl, C_{1-6}alkoxy or hydroxy group; R^2 represents a hydrogen atom or a C_{1-6}alkyl, $-CH_2C_{2-5}$alkenyl or $-CH_2C_{2-5}$alkynyl group; R^3 represents a hydrogen atom or a C_{1-6}alkyl or C_{1-6}alkoxy group; n represents 2 or 3; R^4 represents a group selected from cyano, hydroxyl, C_{1-6}alkoxy, phenoxy, $C(O)C_{1-6}$alkyl, $C(O)C_6H_5$, $-CONR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$ or $-NR^5SO_2R^6$ (wherein each of R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl or phenyl group); and quaternary ammonium derivatives, piperidine N-oxides and pharmaceutically acceptable salts and solvates thereof; which compounds are potent and specific antagonists of 5-hydroxytryptamine (5-HT; seretonin).

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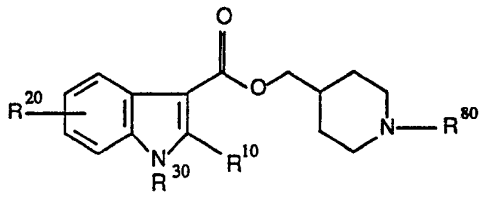
3-Piperidinylmethylcarboxylate substituted indoles

This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

British Patent Specification No. 2152049 describes inter alia compounds of formula

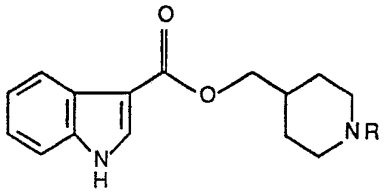


wherein

R^{10} and R^{20} independently represent hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxy, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, mercapto or C_{1-4}alkylthio; R^{30} represents hydrogen, C_{1-4}alkyl, C_{3-5}alkenyl, aryl or aralkyl; and R^{80} represents hydrogen, C_{1-7}alkyl, C_{3-5}alkenyl or benzyl.

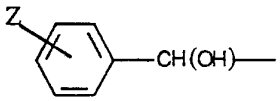
These compounds are stated to exhibit serotonin M receptor antagonist activity.

European Patent Specification No. 229391 describes inter alia compounds of formula



wherein

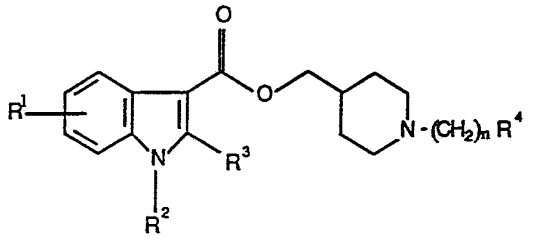
R represents hydrogen, lower alkyl, optionally substituted benzyl, optionally substituted benzoyl, pyridyl, 2-hydroxyethyl, pyridylmethyl or



where Z represents halogen, which compounds are claimed to be of use in preventing dementias and sequelae of cerebrovascular diseases.

The present invention relates to novel compounds which are potent and specific antagonists of 5-hydroxytryptamine (5-HT;serotonin).

Thus, the present invention provides an indole derivative of formula (I):



(I)

wherein R^1 represents a hydrogen or a halogen atom, or a C_{1-6}alkyl, C_{1-6}alkoxy or hydroxy group;

R^2 represents a hydrogen atom or a C_{1-6}alkyl, $-CH_2C_{2-5}$alkenyl or $-CH_2C_{2-5}$alkynyl group;

R^3 represents a hydrogen atom or a C_{1-6}alkyl or C_{1-6}alkoxy group;

n represents 2 or 3;

R^4 represents a group selected from cyano, hydroxyl, C_{1-6}alkoxy, phenoxy, $C(0)C_{1-6}$alkyl, $C(0)C_6H_5$, $-CONR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$ or $-NR^5SO_2R^6$ (wherein each of R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl or phenyl group);

and quaternary ammonium derivatives, piperidine N-oxides and pharmaceutically acceptable salts and solvates thereof.

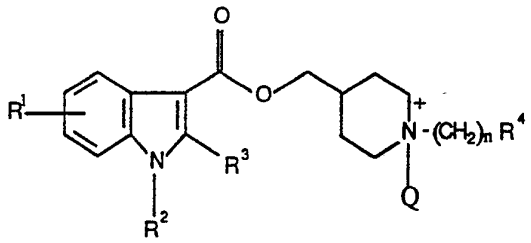
Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates),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

Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in

obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. The solvates may, for example, be hydrates.

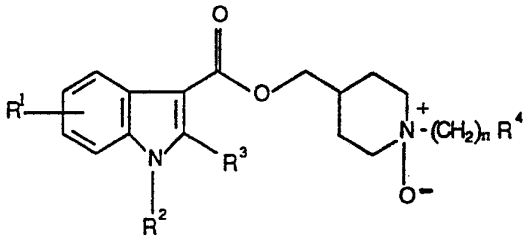
References hereafter to a compound according to the invention includes both compounds of formula (I) and their quaternary ammonium derivatives, piperidine N-oxides and pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

Quaternary ammonium derivatives of compounds of formula (I) are compounds of formula



where Q represents C_{1-6}alkyl (e.g. methyl).

Piperidine N-oxides of compounds of formula (I) are compounds of formula



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), are embraced by the invention.

Referring to the general formula (I), a C_{1-6}alkyl group may be a straight chain or branched chain alkyl group, for example, methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl, 2-methylprop-2-yl, pentyl, pent-3-yl or hexyl. A $-CH_2C_{2-5}$alkenyl group may be, for example, a propenyl or butenyl group. A $-CH_2C_{2-5}$alkynyl group may be, for example, a prop-2-ynyl group. When R^1 represents a halogen atom this may be, for example, a fluorine, chlorine, bromine or iodine atom. R^1 may be attached at

either the 4-, 5-, 6- or 7- (e.g. the 4-, 5-,or 7- more preferably the 5- or 7-, most preferably the 5-) position of the indole ring.

A preferred class of compounds of formula (I) is that in which R^4 is a group selected from cyano, C_{1-6}alkoxy, phenoxy, $C(0)C_{1-6}$alkyl, $C(0)C_6H_5$, $-CONR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$ or $-NR^5SO_2R^6$ (wherein each of R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl or phenyl group);

Another preferred class of compounds formula (I) is that in which R^4 represents a group -CN, hydroxy, $-C_{1-6}$alkoxy (e.g. methoxy), $-CONR^5R^6$ (e.g. $CONH_2$), $-NR^5COR^6$ (e.g. NHCOMe), $-SO_2NR^5R^6$ (e.g. SO_2NHMe) or $-NR^5SO_2R^6$ (e.g. $NHSO_2Me$ or $NHSO_2Ph$).

Another preferred class of compounds of formula (I) is that in which R^4 represents a group -CN, $-C_{1-6}$alkoxy (e.g. methoxy), $-CONR^5R^6$ (e.g. $CONH_2$), $-NR^5COR^6$ (e.g. NHCOMe), $-SO_2NR^5R^6$ (e.g. SO_2NHMe) or $-NR^5SO_2R^6$ (e.g.$NHSO_2Me$ or $NHSO_2Ph$).

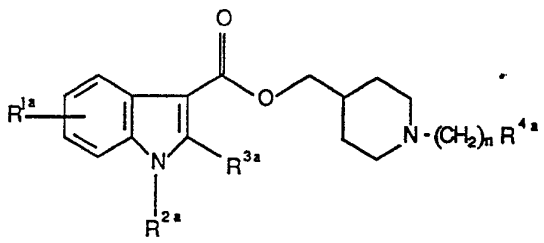
A further preferred class of compounds of formula (I) is that in which R^1 represents a hydrogen atom, a halogen (e.g. fluorine) atom or a C_{1-6}alkyl (e.g. methyl) group. Furthermore, when R^1 represents a halogen (e.g. fluorine) atom or a C_{1-6}alkyl (e.g. methyl) group this is preferably attached at the 5-, or 7- position (e.g. the 5-position) of the indole ring.

Another preferred class of compounds of formula (I) is that in which R^2 represents a hydrogen atom or a C_{1-6}alkyl (e.g. methyl) group.

Yet another preferred class of compounds of formula (I) is that in which R^3 represents a hydrogen atom or a C_{1-6}alkoxy (e.g. methoxy) group.

Another preferred class of compounds of formula (I) is that in which n represents 2.

In a preferred aspect, the present invention provides compounds of formula (Ia)



(Ia)

wherein

R^{1a} represents a hydrogen or a halogen atom, or a C_{1-6}alkyl, or C_{1-6}alkoxy group;

R^{2a} represents a hydrogen atom or a C_{1-6}alkyl group;

R^{3a} represents a hydrogen atom or a C_{1-6}alkyl or C_{1-6}alkoxy group;

n represents 2 or 3;

R^{4a} represents a group selected from CN, -C_{1-6}alkoxy, -$C(O)C_{1-6}$alkyl, -$CONR^{5a}R^{6a}$, -$NR^{5a}COR^{6a}$, -$SO_2NR^{5a}R^{6a}$ or -$NR^{5a}SO_2R^{6a}$ (wherein each of R^{5a} and R^{6a} independently represent a hydrogen atom or a C_{1-6}alkyl group); and quaternary ammonium derivatives, piperidine N-oxides and pharmaceutically acceptable salts and solvates thereof.

A preferred class of compound of formula (Ia) is that in which R^{1a} is attached at the 4-, 5- or 7- (e.g. the 5- or 7-, most preferably the 5-) position of the indole ring.

A further preferred class of compounds of formula (Ia) is that in which R^{1a} represents a hydrogen or a halogen (e.g. fluorine) atom or a C_{1-6}alkyl (e.g. methyl) group. Furthermore, when R^{1a} represents a halogen (e.g. fluorine) atom or a C_{1-6}alkyl (e.g. methyl) group this is preferably attached at the 5-, or 7- position (e.g. the 5-position) of the indole ring.

Another preferred class of compounds of formula (Ia) is that in which R^{2a} represents a hydrogen atom or a methyl group.

Yet another preferred class of compounds of formula (Ia) is that in which R^{3a} represents a hydrogen atom or a C_{1-6}alkoxy (e.g. methoxy) group.

Another preferred class of compounds of formula (Ia) is that in which n represents 2.

Another preferred class of compounds of formula (Ia) is that in which R^{4a} represents a group -CN, -C_{1-6}alkoxy (e.g. methoxy), -$CONR^{5a}R^{6a}$ (e.g. $CONH_2$), -$NR^{5a}COR^{6a}$ (e.g.NHCOMe), -$SO_2NR^{5a}R^{6a}$ (e.g.SO_2NHMe) or -$NR^{5a}SO_2R^{6a}$ (e.g.$NHSO_2$Me or $NHSO_2$Ph).

A preferred group of compounds of formula (Ia) is that in which R^{1a} represents a hydrogen or halogen (e.g. fluorine) atom or a C_{1-6}alkyl (e.g. methyl) group (e.g. a fluorine atom or a methyl group in the 5-position of the indole ring), R^{2a} represents a hydrogen atom or a C_{1-6}alkyl (e.g. methyl) group, R^{3a} represents a hydrogen atom or a C_{1-6}alkoxy (e.g. methoxy) group, n represents 2, and R^{4a} represents a group -$S0_2NR^{5a}R^{6a}$(e.g.SO_2NHMe) or $NR^{5a}SO_2R^{6a}$ (e.g.$NHSO_2$Me or $NHSO_2$Ph).

Specific compounds according to the invention are:-

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H- indole-3-carboxylate;

[1-(2-Hydroxyethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3- carboxylate;

[1-[2-(Methylamino)sulphonyl]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-(2-Methoxyethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-(3-Amino-3-oxopropyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-(2-Cyanoethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[2-(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1H-indole-3-carboxylate;

[1-[2-(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1H-indole-3-carboxylate;

[1-[2-(Acetylamino)ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[3-[(Methylsulphonyl)amino]propyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Phenylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-5-methyl-1H-indole-3-carboxylate;

[1-[2-[Methyl(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate N-oxide;

1-Methyl-4-[[[(1-methyl-1H-indol-3-yl)carbonyl]oxy]methyl]-1-[2-[(methylsulphonyl)amino]ethyl]piperidinium iodide;

4-[[[(2-Methoxy-1H-indol-3-yl)carbonyl]oxy]methyl]-1-methyl-1-2-[2-[(methylsulphonyl)amino]ethyl]piperidinium iodide; and pharmaceutically acceptable salts, more particularly the hydrochloride, methanesulphonate and maleate salts, and solvates thereof.

The compounds of the invention are antagonists of 5-HT both in vitro and in vivo and are thus of use in the treatment of conditions mediated by 5-HT.

In particular the compounds of the invention inhibit the 5-HT induced contraction of guinea-pig colon (essentially following the general procedure described by C.J. Elswood et.al in Br. J. Pharmac., 1990, 100, (Proc.Suppl.) 485P and Eur. J. Pharmac., 1991, 196, 149-155 in the presence of ondansetron and methysergide) and the 5-HT-induced secretion in rat colon (as described by K T Bunce et.al in Br.J. Pharmac., 1991, 102, 811-816), and are thus useful in the treatment of 5-HT mediated disorders in which there is a disturbance of gastrointestinal function. Conditions involving disturbance of intestinal function include for example irritable bowel syndrome and its associated pain, excessive

gastrointestinal secretion, and/or diarrhoea for example diarrhoea associated with excessive gastrointestinal secretion, cholera infection and carcinoid syndrome. The compounds of the invention may also be useful in the treatment of emesis.

The compounds of the invention have been shown to be 5-HT_4 antagonists in vitro as demonstrated by their ability to inhibit the 5-HT-induced relaxation of the rat oesophagus preparation (essentially following the general procedure described by J J Reeves et al in Br. J Pharmac., 1989, 98, (Proc.Suppl.), 800P and 1991, 103, 1067-1072) and are thus of use in the treatment of conditions capable of amelioration by antagonism of such receptors. 5-HT_4 receptors have been found in for example the digestive and urinary tracts, brain and cardiovascular system of mammals including man and are thus believed to be associated with conditions involving the digestive and urinary tracts (e.g. urinary incontinence), cardiovascular system and CNS disorders.

Thus the compounds of the invention may also be useful in the treatment of movement disorders (e.g. Parkinsonism), psychoses such as schizophrenia, mania, dementia or other cognitive disorders e.g. Alzheimer's disease; depression; and dependency on drugs or substances of abuse.

The compounds of the invention have been shown to be active in the rat social interaction test as described by B J Jones et al in Br J Pharmac., 1988, 93, 985-93 and are thus of use in the treatment of anxiety.

In a further aspect the invention therefore provides a compound of formula (I) or a quaternary ammonium derivative, piperidine N-oxide or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine. It will be appreciated that use in therapy embraces but is not necessarily limited to use of a compound of the invention as an active therapeutic substance.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a quaternary ammonium derivative, piperidine N-oxide or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by 5-hydroxytryptamine, in particular conditions capable of amelioration by antagonism of 5-HT_4 receptors.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, comprising administration of an effective amount of a compound of formula (I) or a quaternary ammonium derivative, piperidine N-oxide or a pharmaceutically acceptable salt or solvate thereof in particular in the treatment of conditions mediated by 5-hydroxytryptamine, in particular conditions capable of amelioration by antagonism of 5-HT_4 receptors.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds according to the invention may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition comprising a compound of formula (I) or a quaternary ammonium derivative, piperidine N-oxide or a pharmaceutically acceptable salt or solvate thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in conventional manner using pharmaceutically acceptable carriers.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral, topical, implant or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

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 the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage 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 the invention 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.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention 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.

For intranasal and pulmonary administration, the compounds according to the invention may be formulated as solutions or suspensions for administration via a

suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

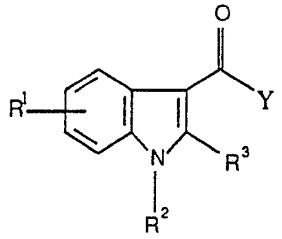
For topical and percutaneous administration, the compounds according to the invention may be formulated as solutions, suspensions, creams or ointments and be included in systems that provide controlled release.

A proposed dose of the compounds of the invention for administration to man (of approximately 70kg body weight) is 1mg to 100mg, of the active ingredient per unit dose expressed as the weight of free base, which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art.

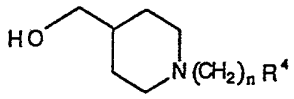
Compounds of formula (I), and quaternary ammonium derivatives, piperidine N-oxides and pharmaceutically acceptable salts or solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R^1 to R^4 and n are as previously defined for compounds of formula (I) unless otherwise stated.

According to a first general process (A), a compound of formula (I) may be prepared by reacting a compound of formula (II):



(II)

or a protected derivative thereof, wherein Y represents a leaving atom or group such as a halogen (e.g. chlorine) atom or an imidazolide group, or a group R^7CO_2- (wherein R^7 represents an alkyl or fluoroalkyl group such as trifluoromethyl or t-butyl), with a compound of formula (III) :

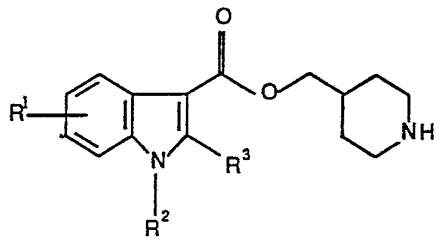


(III)

or an alkali metal (e.g. lithium) alkoxide thereof, optionally in the presence of a strong acid such as methanesulphonic acid.

The reaction is conveniently effected in an inert organic solvent such as an ether (e.g. tetrahydrofuran) or a halogenated hydrocarbon (e.g. dichloromethane) at a temperature between -80^{0}C and the reflux temperature of the solvent.

According to another general process (B), a compound of formula (I) may be prepared by alkylating a compound of formula (IV) :



(IV)

or a protected derivative thereof, with a compound of formula (V) :

$$L(CH_2)_nR^4 \qquad (V)$$

wherein L represents a leaving atom or group such as a halogen (e.g. bromine or iodine) atom, or an acyloxy (e.g. trifluoroacetyloxy) or a sulphonyloxy (e.g. p-toluenesulphonyloxy) group; or a protected derivative thereof, in the presence of a base such as a tertiary amine (e.g. diisopropylethylamine or triethylamine).

The reaction is conveniently effected in an inert organic solvent such as acetonitrile, a substituted amide (e.g. dimethylformamide) or an aromatic

hydrocarbon (e.g. toluene), at an elevated temperature, for example at the reflux temperature of the solvent.

According to another general process (C), a compound of formula (I) may be converted into another compound of formula (I) using conventional techniques.

Thus, for example, a compound of formula (I) where R^3 represents a C_{1-6}alkoxy (e.g. methoxy) group may be prepared by reacting a compound of formula (I) wherein R^3 represents a hydrogen atom with N-chlorosuccinimide followed by an appropriate alcohol (e.g. methanol). The reaction conveniently takes place in a suitable solvent such as chlorinated hydrocarbon (e.g. chloroform) at ambient temperature.

In addition, compounds of formula (I) where R^2 is a hydrogen atom may be converted into another compound of formula (I) wherein R^2 represents a C_{1-6}alkyl (e.g. methyl) group with a suitable alkylating agent such as an alkyliodide (e.g. methyliodide).

Similarly, compounds of formula (I) where R^4 represents a group containing an -NH- moiety may be converted into another compound of formula (I) wherein R^4 contains a -N(C_{1-6}alkyl)- moiety (e.g. -N(CH_3)-) using a suitable alkylating agent as described above. The reaction conveniently takes place in a suitable solvent such as an ether (e.g. tetrahydrofuran) at ambient temperature and in the presence of a strong base such as sodium hydride.

Also, quaternary ammonium salts of compounds of formula (I) may be prepared by reacting non-quaternary compounds of formula (I) with a suitable quaternising agent such as Q-L (where L is a leaving group as defined above e.g. a halogen (e.g. iodine) atom and Q is as defined above). The reaction conveniently takes place in a suitable solvent such as a chlorinated hydrocarbon (e.g. chloroform) at ambient temperature.

Piperidine N-oxides of compounds of formula (I) may be prepared by reacting an appropriate piperidine compound of formula (I) with a suitable oxidising agent such as 3-chloro peroxybenzic acid. Oxidation conveniently takes place in a suitable solvent such as a halogenated hydrocarbon (e.g. chloroform) at ambient temperature.

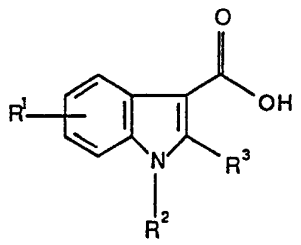
It should be appreciated that in the above transformations it may be necessary or desirable to protect any sensitive groups in the molecule of the compound in question to avoid undesirable side reactions. For example, it may be necessary to protect the indole nitrogen atom, for example with an arylmethyl (e.g. trityl), alkyl (e.g. t-butyl), alkoxymethyl (e.g. methoxymethyl), acyl (e.g. benzyloxycarbonyl) or a sulphonyl (e.g. N,N-dimethylaminosulphonyl or p-toluenesulphonyl) group. When R^4 represents a hydroxyl group it may be necessary to protect the hydroxyl group, for example with an arylmethyl (e.g. benzyl or trityl) group.

It may be necessary to protect compounds where R^4 contains a sensitive group such as an amine group. Such groups may be protected for example using an acyl group (e.g. benzyloxycarbonyl) or a silyl group (e.g. trimethylsilyl).

Thus according to another general process (D), a compound of general formula (I) may be prepared by the removal of any protecting groups from a protected form of a compound of formula (I). Deprotection may be effected using conventional techniques such as those described in 'Protective Groups in Organic Synthesis' by T. W. Greene (John Wiley and Sons, 1981).

For example, considering the N-protecting groups first, a trityl group may be cleaved by acid hydrolysis (e.g. using dilute hydrochloric or acetic acid). An alkoxyalkyl group may be removed using a mineral acid (e.g. dilute hydrochloric acid). An acyl (e.g. benzyloxycarbonyl) group may be removed by hydrolysis under acidic or basic conditions (e.g. using hydrogen bromide or sodium hydroxide or, where milder conditions are required, sodium carbonate or cesium carbonate). A sulphonyl group may be removed by alkaline hydrolysis. An arylmethyl OH-protecting group may be cleaved under acidic or basic conditions (e.g. with dilute acetic acid, hydrobromic acid or boron tribromide) or by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal).

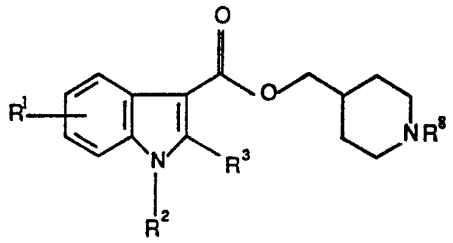
Compounds of formula (II) may be prepared, for example, by reacting a compound of formula (VI) :



(VI)

with a suitable halogenating reagent (e.g. oxalyl chloride or thionyl chloride), an imidazole derivative (e.g. N,N-carbonyldiimidazole), or an anhydride (e.g. trifluoroacetic or t-butyl anhydride).

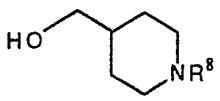
Compounds of formula (IV) may be prepared, for example, by reacting a compound of formula (VII)



(VII)

wherein R^8 is a C_{1-6}alkyl (e.g. methyl) group with a chloroformate (e.g. a-chloroethylchloroformate, vinylchloroformate or ethylchloroformate) at an elevated temperature, with subsequent heating of the reaction mixture at reflux temperature with an alcohol (e.g. methanol).

Compounds of formula (VII) may be prepared according to the method of general process (A), by reacting a compound of formula (II) with a compound of formula (VIII)

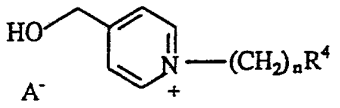


(VIII)

in which R^8 is a C_{1-6}alkyl (e.g. methyl) group.

Compounds of formulae (III), (V), (VI) and (VIII) are either known, or may be prepared from known compounds by conventional procedures.

In addition, compounds of formula (III) may be prepared by reduction of the corresponding compounds of formula (IX)



(IX)

wherein A^- represents an associated anion such as a halide (e.g. bromide) anion. Reduction may be conveniently effected by hydrogenation in the presence of a suitable catalyst, such as rhodium on alumina, in the presence of a suitable solvent, for example under aqueous conditions.

Compounds of formula (IX) may be prepared by alkylation of 4-pyridine methanol using a suitable alkylating agent of formula (V) as defined hereinbefore. The reaction conveniently takes place in the presence of sodium iodide in a suitable solvent such as an alcohol (e.g. isopropanol) at the reflux temperature of the solvent.

Where it is desired to isolate a compound of the invention as a salt, for example a physiologically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate acid, preferably with an equivalent amount, in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. tetrahydrofuran).

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compound of formula (I) using conventional methods.

The compounds of the invention may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent to give the corresponding solvates.

Individual enantiomers of the compounds of the invention may be obtained by resolution of a mixture of enantiomers (e.g a racemic mixture) using conventional means, such as an optically active resolving acid; see for example 'Stereochemistry of Carbon Compounds' by E.L.Eliel (McGraw Hill, 1962) and 'Tables of Resolving Agents' by S. H. Wilen.

The various general methods described above may be used for the introduction of the desired groups at any stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the

reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

The invention is further illustrated by the following Intermediates and Examples. All temperatures are in ^{0}C. Thin layer chromatography (t.l.c.) was carried out on silica, and flash column chromatography (FCC) on silica (Merck 9385). Solvent System A as used for chromatography denotes dichloromethane:ethanol:0.88 ammonia solution. Organic extracts were dried, where indicated, over magnesium sulphate.

Intermediate 1

(1-Methyl-4-piperidinyl)methyl 1-methyl-1H-indole-3-carboxylate

1-Methylindole-3-carboxylic acid (1.74g) was suspended in dry dichloromethane (50ml). Oxalyl chloride (0.9ml) was added and the mixture was stirred for 1h. The solvent was removed in vacuo to leave the acid chloride as a solid. 4-Hydroxymethyl-1-methylpiperidine (1.40g) in dry THF (20ml) was cooled to -78^0 under nitrogen. n-Butyllithium (1.64M; 6.0ml) was added, and the solution was stirred for 1h. The acid chloride in dry THF (20ml) was added, and the mixture was allowed to warm to room temperature over 2h. The mixture was then diluted with ether (200ml), washed with 8% aqueous sodium bicarbonate solution (200ml), dried, and the solvent was removed in vacuo to leave a solid which was triturated with ether to give the title compound (1.25g), m.p. 102-104^0.

Intermediate 2

4-Piperidinylmethyl 1-methyl-1H-indole-3-carboxylate

(1-Methyl-4-piperidinyl)methyl 1-methyl-1H-indole-3-carboxylate (2.40g) and a-chloroethylchloroformate (15ml) were heated together at 50^0 for 2h. Methanol (20ml) was then added, and the mixture was heated at reflux for 0.5h. The solvent was removed in vacuo to leave a solid which was purified by FCC eluting with System A (100:8:1) to give the title compound (1.43g), m.p. 126-130^0.

Intermediate 3

N-[2-[4-(Hydroxymethyl)-1-piperidinyl]ethyl]methanesulphonamide

4-Piperidine methanol (1.60g) was dissolved in dry acetonitrile (40ml), N,N-diisopropylethylamine (5ml) was added, followed by N-(2-bromoethyl)methanesulphonamide (2.95g) in acetonitrile (10ml), and the resulting mixture heated at reflux for 2h. The solvent was removed in vacuo to leave a gum. This was purified by FCC eluting with System A (75:8:1) to give the title compound (1.80g) as a solid, m.p. 81-82^0.

Intermediate 4

[1-[2-[(Methylsulphonyl)[(phenylmethoxy)carbonyl]amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1H-indole-3-carboxylate

[1-[2-[(Methylsulphonyl)amino]ethyl]-4- piperidinyl]methyl 2-methoxy-1H-indole-3-carboxylate (440mg) was dissolved in acetonitrile (10ml) and 4-N,N-dimethylaminopyridine (654mg) was added, followed by benzylchloroformate (0.61ml) and the mixture stirred at room temperature for 18h. 6.5% Methanolic ammonia (10ml) was added, and the mixture stirred for 1h. The mixture was poured into 2M sodium carbonate solution (100ml), extracted with ethyl acetate (2x100ml), dried and the solvent evaporated in vacuo to leave a pale yellow gum. FCC eluting with System A (300:10:1) gave the title compound (359mg) a white foam.

T.l.c. (System A, 300:10:1) Rf 0.32

Intermediate 5

[1-[2-[(Methylsulphonyl)[(phenylmethoxy)carbonyl]amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1-methyl-1H-indole-3-carboxylate

[1-[2-[(Methylsulphonyl)[(phenylmethoxy)carbonyl]amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1H-indole-3-carboxylate (327mg) was dissolved in dry THF (6ml). Tetra n-butylammonium fluoride 1M solution in THF (2.4ml) was added, followed by methyliodide (0.15ml) and the resulting solution stirred for 30min. The mixture was poured into 2M sodium carbonate solution (100ml), extracted with ethyl acetate (2x100ml), dried and the solvent removed in vacuo to

leave a brown foam. FCC eluting with ether:cyclohexane:triethylamine (30:10:4) gave the title compound (130mg) as a white foam.

T.l.c. (ether:cyclohexane:triethylamine, 30:10:4) Rf 0.19

Intermediate 6

[1-(Phenylmethyl)-4-piperidinyl]methyl 1H-indole-3-carboxylate

1H-Indole-3-carboxylic acid (3.0g) was suspended in dry dichloromethane (60ml) under nitrogen. Oxalyl chloride (2ml) was added, and the mixture stirred for 2h. The solvent was removed in vacuo to leave the acid chloride as an orange solid. 1-Benzyl-4-hydroxymethylpiperidine (4.11g) in dry tetrahydrofuran (60ml) was cooled to -78° under nitrogen, n-butyl lithium 1.64M (11.3ml) was added, and the mixture stirred for 30min. The acid chloride in dry tetrahydrofuran (60ml) was added dropwise, and the resulting solution stirred for 1h at -78° then allowed to warm to room temperature over 2h. The mixture was diluted with dichloromethane (250ml), washed with 2M potassium carbonate solution (2x250ml), dried, and the solvent removed in vacuo to leave a brown gum. FCC using System A (300:8:1) as eluant gave a pale yellow solid which was triturated with cyclohexane:ether (2:1) to give the title compound (4.5g) as a white solid, m.p. 106°-107.5°.

Intermediate 7

(4-Piperidinyl)methyl 1H-indole-3-carboxylate

[1-(Phenylmethyl)-4-piperidinyl]methyl 1H-indole-3-carboxylate (2.0g) in ethanol (60ml) was added to a pre-hydrogenated suspension of palladium on charcoal 10% (100mg) in ethanol (50ml) and the mixture stirred under an atmosphere of hydrogen for 24h. The mixture was filtered, and the filtrate evaporated in vacuo to leave the title compound as a white solid, (1.45g) m.p. 185°-187°.

Intermediate 8

4-(Hydroxymethyl) - 1 - [2-[(methylsulphonyl)amino]ethyl]pyridinium bromide

A stirred solution of 4-pyridine-methanol (90g) and N-2-bromethylmethane sulphonamide (207g) with sodium iodide (12.6g) in isopropanol (2000ml) was

heated under reflux, under nitrogen for 5 days. The mixture was cooled to room temperature. The solid material was then collected, washed with isopropanol (2 x 100 ml) and dried in vacuo at 50-55° for 10h. The title compound (231.2g) was obtained as a white crystalline solid. The material was then recrystallised from methanol (1200ml) to give the title compound (219g) m.p. 176-17°.

Intermediate 9

N-[2-[4-(Hydroxymethyl)-1-piperidinyl]ethyl]methanesulphonamide

A solution of 4-(Hydroxymethyl) - 1 - [2-[(methylsulphonyl) amino]ethyl]pyridinium bromide (120g) in water (1700ml) was hydrogenated in the presence of 5% rhodium on alumina (12g) for (5x8h). The catalyst was filtered off and washed with water (ca. 200ml). The solvent was then removed in vacuo. The residual oil (140g) was then purified by FCC using System A (50:8:1) as the eluent. After a small amount of the fast running material was collected the solvent ratio was increased to a 25:8:1 mixture. The title compound (62g) was isolated as a near colourless oil which crystallised under vacuo to give a colourless crystalline solid, m.p. 86-88°.

Example 1

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H- indole-3-carboxylate

To a solution of 4-piperidinylmethyl 1-methyl-1H-indole-3- carboxylate (200mg) in dry acetonitrile (6ml) was added diisopropylethylamine (0.26ml) followed by N-(2-bromoethyl)-methanesulphonamide (178mg), and the mixture was heated at reflux for 2h. The cooled mixture was poured into 2M sodium hydroxide solution (150ml), extracted with ether (2x150ml), dried, and the solvent was removed in vacuo to leave a gum which was purified by FCC eluting with System A (200:8:1) to give the title compound (86mg), m.p. 95-97°.

Analysis Found: C,57.8; H,7.0; N,10.4;

$C_{19}H_{27}N_3O_4S$ requires C,58.0; H,6.9; N,10.7%.

Example 2

[1-(2-Hydroxyethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3- carboxylate

To a solution of 4-piperidinylmethyl 1-methyl-1H-indole-3- carboxylate (200mg) in acetonitrile (6ml) was added diisopropylethylamine (0.19ml), followed by 2-iodoethanol (0.07ml), and the mixture was heated at reflux overnight. The solvent was then removed in vacuo, and the residue was partitioned between ether (80ml) and 2M sodium hydroxide (50ml). The organic phase was dried and the solvent was removed in vacuo to leave a solid which was crystallised from ether to give the title compound (51mg), m.p. 127-128^0, t.l.c. (System A, 200:8:1) Rf 0.10.

Example 3

[1-[2-(Methylamino)sulphonyl]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate maleate

A mixture of 4-piperidinylmethyl 1-methyl-1H-indole-3-carboxylate (200mg), diisopropylethylamine (0.25ml), and N-methylethene sulphonamide (107mg), in dry acetonitrile (6ml) was heated at reflux under nitrogen for 2h. The solvent was then removed in vacuo to give a solid (310mg) which was purified by FCC eluting with System A (400:10:1) to give the free base of the title compound (250mg) as a solid, m.p. 128-129^0, t.l.c. (System A, 400:10:1) Rf 0.33.

A sample of the free base (220mg) was dissolved in dichloromethane (2ml) and treated with a solution of maleic acid (68mg) in absolute ethanol (1ml). The resultant solid was filtered off and washed with dry ether (3x20ml) to give the title compound (280mg), m.p. 170-171^0.

Analysis	Found: C,54.3; H,6.2; N,8.2;
$C_{19}H_{27}N_3O_4S.C_4H_4O_4$	requires C,54.2; H,6.1; N,8.3%

Example 4

[1-(2-Methoxyethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate

A mixture of 4-piperidinylmethyl 1-methyl-1H-indole-3-carboxylate (200mg), diisopropylethylamine (0.25ml), and bromoethyl methylether (0.08m) in dry acetonitrile (6ml) was heated at reflux under nitrogen for 2h. The solvent was then

removed in vacuo to give an oil (340mg), which was purified by FCC eluting with System A (400:10:1) to give the title compound (210mg) as a solid, m.p. 151-153^0, t.l.c. (System A, 400:10:1) Rf 0.35.

Example 5

[1-(3-Amino-3-oxopropyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate

A mixture of 4-piperidinylmethyl 1-methyl-1H-indole-3-carboxylate (250mg), diisopropylethylamine (0.32ml), and acrylamide (78mg), in dry acetonitrile (7.5ml) was heated at reflux under nitrogen for 24h. The solvent was then removed in vacuo to give an oil (355mg) which was purified by FCC eluting with System A (200:10:1) to give the title compound (295mg) as a solid, m.p. 126-127^0.

Analysis	Found C,66.1; H,7.6; N,11.8;
$C_{19}H_{25}N_3O_3$	requires C,66.5; H,7.3; N,12.2%.

Example 6

[1-(2-Cyanoethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate maleate

A mixture of 4-piperidinylmethyl 1-methyl-1H-indole-3-carboxylate (750mg), diisopropylethylamine (0.96ml) and acrylonitrile (0.22ml) in dry acetonitrile (20ml) was heated at reflux under nitrogen for 24h. The solvent was then removed in vacuo to give an oil (880mg) which was purified by FCC eluting with System A (500:10:1) to give the free base of the title compound (825mg) as a solid, m.p. 94-95^0.

A sample of the free base (175mg) was dissolved in dichloromethane (2ml) and treated with a solution of maleic acid (68mg), in absolute ethanol (1ml). The solvent was removed in vacuo and the residue was triturated with dry ether (3x5ml) to give the title compound (235mg) as a solid, m.p. 174-175^0.

Analysis	Found: C,62.7; H,6.2; N,9.4;
$C_{19}H_{23}N_3O_2.C_4H_4O_4$	requires C,62.6; H,6.2; N,9.5%.

Example 7

[1-[2-(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1H-indole-3-carboxylate

4-Piperidinylmethyl 1H-indole-3-carboxylate (1.31g) was dissolved in hot acetonitrile (50ml). Diisopropylethylamine (1.76ml) was added followed by N-(2-bromoethylmethanesulphonamide) (1.0g) and the resulting mixture was stirred at room temperature for ca. 72h. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (250ml). The solution was then washed with 2M potassium carbonate solution (2x250ml), dried, and solvent was removed in vacuo to leave a gum, which was purified by FCC eluting with System A (150:8:1) to give the title compound as a solid, m.p. 114-116^0.

Assayfound: C,57.2; N,6.7; N,10.9;

$C_{18}H_{25}N_3O_4S$ requires C,57.0; H,6.6; N,11.1%.

Example 8

[1-[2-(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1H-indole-3-carboxylate

To a solution of [1-[2-(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1H-indole-3-carboxylate (1.0g) in chloroform (30ml) was added N chlorosuccinimide (525mg), and the resulting solution was stirred for 3h. Methanol (5ml) was added and the solution was stirred overnight. The mixture was then diluted with dichloromethane (200ml), washed with 2M sodium carbonate solution (200ml), dried and the solvent was removed in vacuo to leave a gum which was purified by FCC (200:8:1) to give a solid (410mg). Crystallisation of this solid twice from methanol:ether (1:10) gave the title compound (230mg), m.p. 131.5-134^0, t.l.c. (System A, 200:8:1) Rf O.38.

Example 9

[1-[2-(Acetylamino)ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate maleate

A mixture of 4-piperidinylmethyl 1-methyl-1H-indole-3-carboxylate (250mg), diisopropylethylamine (0.32ml), and N-(2-chloroethyl) acetamide (0.11ml) in dry acetonitrile (7.5ml) was heated at reflux under nitrogen for 48h. The solvent was then removed in vacuo to give an oil (ca. 550mg) which was purified by FCC

eluting with System A (200:10:1) to give an oil (127mg). This material was dissolved in dichloromethane (2ml) and treated with a solution of maleic acid (43mg), in absolute ethanol (1ml). The solvent was removed in vacuo and the residue was triturated with dry ether (5x5ml) to give the title compound (150mg) as a solid, m.p. 151-152^0.

Analysis	Found: C,60.8; N,6.6; N,8.6;
$C_{20}H_{27}N_3O_3.C_4H_4O_4$	requires C,60.9; H,6.6; N,8.9%.

Example 10

[1-[3-[(Methylsulphonyl)amino]propyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate maleate

A mixture of 4-piperidinylmethyl 1-methyl-1H-indole-3-carboxylate (250mg), diisopropylethylamine (0.32ml) and N-(3-bromopropyl)methanesulphonamide (238mg) in dry acetronitrile (7.5ml) was heated at reflux under nitrogen for 2.5h. The solvent was removed in vacuo to give an oil (ca.625mg), which was purified by FCC eluting with System A (200:10:1) to give an oil (200mg). This material was dissolved in dichloromethane (3ml) and treated with a solution of maleic acid (60mg) in absolute ethanol (1ml). The solvent was removed in vacuo and the residue was triturated with dry ether (3 x 10ml) to give the title compound (250mg) as a solid, m.p. 159-160^0.

Analysis	Found: C,55.1; H,6.4; N,7.9%
$C_{20}H_{29}N_3O_4S.C_4H_4O_4$	requires C,55.1; H,6.4; N,8.0%

Example 11

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-1H-indole-3-carboxylate

Trifluoroacetic anhydride (0.47ml) was added dropwise to a stirred suspension of 5-fluoroindole-3-carboxylic acid (500mg) in dry dichloromethane (25ml) under nitrogen. After 1h the suspension was treated with methane sulphonic acid (0.22ml) followed immediately with a suspension of N-[2-[4-(hydroxymethyl)-1-piperidinyl]ethyl]methanesulphonamide (792mg) in dry dichloromethane (20ml).

The solution was stirred for 2.5h then poured into 8% sodium bicarbonate solution (100ml). The organic layer was separated and the aqueous phase extracted with dichloromethane (2 x 50ml). The combined organic extracts were dried, filtered and evaporated to give an oil (21.1g). This was purified by FCC eluting with System A (250:10:1) to give the title compound (635mg) as a foam, t.l.c. (System A, 250:10:1) Rf 0.17.

Analysis	Found: C,53.9; H,6.2; N,10.1%
$C_{18}H_{24}FN_3O_4S$	requires C,54.4; H,6.1; N,10.6%.

Example 12

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate hydrochloride

N-chlorosuccinimide (302mg) was added to a stirred solution of [1-[2-[(methylsulphonyl)amino]ethyl]-4-piperidinyl methyl 5-fluoro-1H-indole-3-carboxylate (600mg) in chloroform (20ml) under nitrogen. After 3h the solvent was removed in vacuo and the residue treated with methanol (10ml). The solution was stirred under nitrogen for 1h and the solvent removed in vacuo to give an oil (950mg). This was purified by FCC eluting with System A (200:10:1) to give a foam (395mg). This material was dissolved in dichloromethane/ethanol (5ml) and treated with an excess of ethereal hydrogen chloride solution. The solvent was removed in vacuo and the residue triturated with dry ether (5 x 10ml) to give the title compound (400mg) as a solid, m.p. 207-209^0.

Analysis	Found: C,49.1; H,6.0; N,8.8%
$C_{19}H_{26}FN_3O_5S.HCl$	requires C,49.2; H,5.9; N,9.1%.

Example 13

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1-methyl-1H-indole-3-carboxylate

[1-[2-[(Methylsulphonyl)[(phenylmethoxy)carbonyl]amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1-methyl-1H-indole-3-carboxylate (130mg) was dissolved in dry THF (1ml) and methanol (2ml). Cesium carbonate (75mg) was

added and the mixture stirred for 1h. The mixture was poured into 2M sodium carbonate solution (100ml), extracted with ethyl acetate (2x100ml), dried and the solvent removed in vacuo to leave a yellow gum. FCC eluting with System A (300:8:1) gave the title compound (65mg) as a white crystalline solid, m.p.103-104°.

T.l.c. (System A, 300:8:1) Rf 0.26.

Example 14

[1-[2-[(Phenylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate

To 4-piperidinylmethyl 1-methyl-1H-indole-3-carboxylate (0.5g) in acetonitrile (30ml) was added diisopropylethylamine (0.48ml) followed by N-(2-bromoethyl)benzenesulphonamide (0.48g) and the reaction mixture heated at reflux for 3h. The cooled reaction mixture was diluted with dichloromethane (200ml) and washed with 2M sodium carbonate (200ml), dried and the solvent removed in vacuo to give a yellow oil. This was purified by FCC eluting with System A (200:8:1). The solvent was removed in vacuo to give the free base as an amorphous white foam (0.64g). Ethyl acetate (20ml) was added whereupon crystallisation occurred, the mixture was diluted with ether, filtered and dried in vacuo to give the title compound (0.508g) as an off-white crystalline solid m.p. >240°.

γmax (Nujol) 3125, 1691, 1536, 953, 745, 694 cm^{-1}

Assay Found:	C,63.6; H,6.4; N,9.2;
$C_{24}H_{29}N_3O_4S$ requires:	C,63.3; H,6.4; N,9.2%

Example 15

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-1-methyl-1H-indole-3-carboxylate hydrochloride

Trifluoroacetic anhydride (0.32ml) was added dropwise to a stirred suspension of 5-fluoro-1-methylindole-3-carboxylic acid (220mg) in dry dichloromethane (10ml) under nitrogen. After 10min the brown solution was treated with methane sulphonic

acid (0.15ml) followed immediately with a suspension of N-[2-[-4-(hydroxymethyl)-1-piperidinyl]ethyl]methanesulphonamide (539mg) in dry dichloromethane (15ml). The solution was stirred for 1h, poured into 8% sodium bicarbonate solution (50ml) and extracted with dichloromethane (3x25ml). The combined extracts were dried, filtered and evaporated to give a brown oil (550mg). FCC with System A (250:10:1) as the eluent gave a pink foam (300mg). This material was dissolved in dichloromethane (5ml) and treated with an excess of ethereal hydrogen chloride solution. The solvent was removed in vacuo and the residue triturated with dry ether (5x10ml) to give the title compound as a pink solid (320mg) m.p. 223-4°

T.l.c. (System A 250:10:1), Rf 0.22

Water assay Found 0.44%w/w = 0.11mol.H_2O

Similarly prepared:-

Example 16

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-methyl-1H-indole-3-carboxylate (1.28g), T.l.c. System A (75:8:1), Rf 0.53

Assay Found: C,57.0; H,7.2; N,10.3;

$C_{19}H_{27}N_3O_4S.0.4H_2O$ requires: C,57.0; H,7.0; N,10.5%

Water assay indicates presence of 0.8mol equiv. of water.

From 5-methyl-1H-indole-3-carboxylic acid (1.00g).

Example 17

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-5-methyl-1H-indole-3-carboxylate

N-Chlorosuccinimide (0.18g) was added to a stirred solution of [1-[2-[(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-methyl-1H-indole-3-carboxylate (0.35g) in chloroform (10ml) under nitrogen. After stirring at room temperature for 4.75h, the solvent was removed in vacuo and the residue was treated with methanol (5ml). The solution was stirred under nitrogen at room temperature for 1.5h, and the solvent was then removed in vacuo to give a yellow residue. After

storing overnight in the refrigerator, the residue was purified by FCC eluting with System A (100:8:1). The appropriate fractions were combined and concentrated in vacuo to give the title compound (0.16g) as an off-white crystalline solid (0.16g) m.p.167-169°.

T.l.c. (System A 100:8:1), Rf 0.20

Assay Found: C,56.5; H,7.1; N,9.6;

$C_{20}H_{29}N_3O_4S$ requires: C,56.7; H,6.9; N,9.9%

Example 18

1-Methyl-4-[[[(1-methyl-1H-indol-3-yl)carbonyl]oxy]methyl]-1-[2-[(methylsulphonyl)amino]ethyl]piperidinium iodide

A sample of [1-[2-[(methylsulphonyl)amino]ethyl]-4-piperidinyl] methyl 1-methyl-1H-indole-3-carboxylate maleate (0.5g) was partitioned between 2N sodium hydroxide (30ml) and chloroform (15ml). The organic layer was separated, the aqueous extracted twice with chloroform and the combined organic solution dried. After filtration the chloroform solution was treated with methyl iodide (1ml) and stirred at room temperature for 2 days. By t.l.c. (System A 75:8:1) there was still starting material present. The heterogeneous mixture was stirred under gentle reflux for 5h. The reaction mixture was filtered whilst still warm, the solid was washed with chloroform and dried in vacuo to give the title compound as a white solid (0.31g) with m.p. 186-189°.

Analysis Found: C,44.8; H,5.65; N,7.7;

$C_{20}H_{30}IN_3O_4S$ requires C,44.8; H,5.65; N,7.85%

Example 19

4-[[[(2-Methoxy-1H-indol-3-yl)carbonyl]oxy]methyl]-1-methyl-1-2-[2-[(methylsulphonyl)amino]ethyl]piperidinium iodide

[1-[2-(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1H-indole-3-carboxylate hydrochloride (250mg) was treated with 8% sodium bicarbonate (10ml) and the aqueous extracted with chloroform (3x10ml). The combined organic

extracts were dried and filtered. The solution was treated with methyl iodide (1ml) and stirred under nitrogen at 50° to 55° for 18h. Additional methyl iodide (1ml) was added and the solution stirred at reflux for 8h. The mixture was left to stand for 16h then concentrated in vacuo. The resultant cream foam was dissolved in hot isopropanol (ca. 60ml) and left to stand overnight. The solution was concentrated in vacuo (to ca. 10ml) and the residue collected by filtration. After drying in vacuo the title compound was obtained a cream foam (0.232g).γ max (Nujol) 3415, 3154, 1675, 1557 cm^{-1}

Assay Found: C,42.9; H,5.7; N,7.0;

$C_{20}H_{13}IN_3O_5S.0.35C_3H_8O.0.7H_2O$ requires C,43.2; H,5.9; N,7.2%

Water assay Found 2.24%w/w water (0.7mol equiv.)

Example 20

[1-[2-[Methyl(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate

[1-[2-(Methylsulphonyl)amino]ethyl-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate (700mg) was dissolved in dry tetrahydrofuran (50ml). Sodium hydride 70% dispersion in mineral oil (73mg) was added and the mixture stirred for 1h. Methyl iodide (0.11ml) was added and the resulting mixture stirred under nitrogen for 5h. The mixture was poured into 2M sodium carbonate solution (200ml), extracted with ether (2x200ml), dried, and the solvent removed in vacuo to leave the title compound (420mg) as a white solid, m.p.=144°-145.5°.

T.l.c. System A (200:8:1), Rf 0.30

Example 21

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate methanesulphonate

A solution of [1-[2-[(methylsulphonyl)amino]ethyl]-4-piperidinyl] methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate (500mg) in absolute ethanol (15ml) was treated with a solution of methanesulphonic acid (113mg) in absolute ethanol (2ml). The

solvent was removed in vacuo and the oily residue triturated with dry ether (3x50ml) to give the title compound as a white solid (610mg) m.p. 184-185°.

T.l.c. System A (150:10:1), Rf 0.24

Example 22

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate maleate

A solution of [1-[2-[(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate (500mg) in absolute ethanol (15ml) was treated with a solution of maleic acid (137mg) in absolute ethanol (2ml). The solvent was removed in vacuo and the oily residue triturated with dry ether (3x50ml) to give the title compound as a white solid (635mg), m.p. 96-7°.

T.l.c. System A (150:10:1), Rf 0.24.

Example 23

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate N-oxide

3-Chloroperoxybenzoic acid (505mg) was added to a stirred solution of 1-[(2-sulphonamidomethyl)ethyl]-4-piperidinylmethyl 5-fluoro-1H-indole-3-carboxylate (500mg) in dry chloroform (25ml) under nitrogen. After 16h 0.1N hydrochloric acid (25ml) was added and the organic layer separated. The aqueous was washed with chloroform (25ml) then evaporated in vacuo to give a yellow oil (~600mg). FCC with System A (25:10:1) as the eluent gave a yellow oil which was triturated with dry ether (3x25ml) to give impure title compound (150mg) as a pale yellow solid, m.p. 113-6° (foamed).

The above material was crystallised from isopropanol to give the title compound as a pale brown solid (48mg).

Analysis found:	C,52.3; H,6.8; N,8.3;
$C_{19}H_{26}FN_3O_6S.0.75^{i}PrOH$ requires:	C,52.2; H,6.6; N,8.6%

Pharmacy Examples

Example 1 - Tablets

a) Compound of the invention	5.0mg
Lactose	95.0mg
Microcrystlline Cellulose	90.0mg
Cross-linked polyvinylpyrrolidone	8.0mg
Magnesium Stearate	2.0mg
Compression weight	200.0mg

The compound of the invention. microcrystalline cellulose, lactose and cross linked polyvinylpyrrolidone are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

b) Compound of the invention	5.0mg
Lactose	165.0mg
Pregelatinised Starch	20.0mg
Cross-linked polyvinylpyrrolidone	8.0mg
Magnesium Stearate	2.0mg
Compression weight	200.0mg

The compound of the invention, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Example 2 - Capsules

a) Compound of the invention	5.0mg
Pregelatinised Starch	193.0mg
Magnesium Stearate	2.0mg
Fill weight	200.0mg

The compound of the invention and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate, (meshed through a 250 micron sieve). The blend is filled into hard gelatine capsules of a suitable size.

b) Compound of the invention	5.0mg
Lactose	177.0mg
Polyvinylpyrrolidone	8.0mg
Cross-linked polyvinylpyrrolidone	8.0mg
Magnesium Stearate	2.0mg
Fill weight	200.0mg

The compound of the invention and lactose are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granules. The resultant blend is filled into hard gelatine capsules of a suitable size.

Example 3 - Syrup

a) Compound of the invention	5.0mg
Hydroxypropyl Methylcellulose	45.0mg
Propyl Hydroxybenzoate	1.5mg
Butyl Hydroxybenzoate	0.75mg
Saccharin Sodium	5.0mg
Sorbitol Solution	1.0ml

Suitable Buffers	qs
Suitable flavours	qs
Purified Water to	10.ml

The hydroxypropyl methylcellulose is dispersed in a portion of hot purified water together with the hydroxybenzoates and the solution is allowed to cool to room temperature. The saccharin sodium flavours and sorbitol solution are added to the bulk solution. The compound of the invention is dissolved in a portion of the remaining water and added to the bulk solution. Suitable buffers may be added to control the pH in the region of maximum stability. The solution is made up to volume, filtered and filled into suitable containers.

Example 4 - Injection Formulation

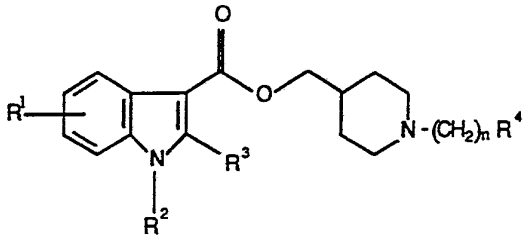
	% w/v
Compound of the invention	1.00
Water for injections B.P. to	100.00

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included.

The solution is prepared, clarified and filled into appropriate sized 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.

Claims

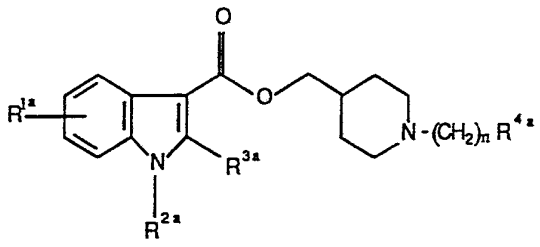
1. Compounds of formula (I)



(I)

wherein R^1 represents a hydrogen or a halogen atom, or a C_{1-6}alkyl, C_{1-6}alkoxy or hydroxy group;
R^2 represents a hydrogen atom or a C_{1-6}alkyl, $-CH_2C_{2-5}$alkenyl or $-CH_2C_{2-5}$alkynyl group;
R^3 represents a hydrogen atom or a C_{1-6}alkyl or C_{1-6}alkoxy group;
n represents 2 or 3;
R^4 represents a group selected from cyano, hydroxyl, C_{1-6}alkoxy, phenoxy, $C(0)C_{1-6}$alkyl, $C(0)C_6H_5$, $-CONR^5R^6$, $-NR^5COR^6$, $-SO_2NR^5R^6$ or $-NR^5SO_2R^6$ (wherein each of R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl or phenyl group);
and quaternary ammonium derivatives, piperidine N-oxides and pharmaceutically acceptable salts and solvates thereof.

2. A compound as claimed in claim 1 wherein the compound of formula (I) is a compound of formula (Ia)



(Ia)

wherein
R^{1a} represents a hydrogen or a halogen atom, or a C_{1-6}alkyl, or C_{1-6}alkoxy group;

R^{2a} represents a hydrogen atom or a C_{1-6}alkyl group;
R^{3a} represents a hydrogen atom or a C_{1-6}alkyl or C_{1-6}alkoxy group;
n represents 2 or 3;
R^{4a} represents a group selected from CN, $-C_{1-6}$alkoxy, $-C(O)C_{1-6}$alkyl, $-CONR^{5a}R^{6a}$, $-NR^{5a}COR^{6a}$, $-SO_2NR^{5a}R^{6a}$ or $-NR^{5a}SO_2R^{6a}$ (wherein each of R^{5a} and R^{6a} independently represent a hydrogen atom or a C_{1-6}alkyl group); and quaternary ammonium derivatives, piperidine N-oxides and pharmaceutically acceptable salts and solvates thereof.

3. A compound as claimed in claim 1 or claim 2 in which R^1 or R^{1a} is in the 5-position of the indole ring.

4. A compound as claimed in any of claims 1 to 3 in which R^1 or R^{1a} is a hydrogen or fluorine atom or a methyl group.

5. A compound as claimed in any of claims 1 to 4 in which R^2 or R^{2a} is a hydrogen atom or a methyl group.

6. A compound as claimed in any of claims 1 to 5 in which R^3 or R^{3a} is a hydrogen atom or a methoxy group.

7. A compound as claimed in any of claims 1 to 6 in which n is 2.

8. A compound as claimed in any of claims 1 to 7 in which R^4 or R^{4a} is a group $NR^5SO_2R^6$ or $NR^{5a}SO_2R^{6a}$.

9. [1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H- indole-3-carboxylate;
[1-(2-Hydroxyethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;
[1-[2-(Methylamino)sulphonyl]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;
[1-(2-Methoxyethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;
[1-(3-Amino-3-oxopropyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-(2-Cyanoethyl)-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[2-(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1H-indole-3-carboxylate;

[1-[2-(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1H-indole-3-carboxylate;

[1-[2-(Acetylamino)ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[3-[(Methylsulphonyl)amino]propyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Phenylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 2-methoxy-5-methyl-1H-indole-3-carboxylate;

[1-[2-[Methyl(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate;

[1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate N-oxide;

1-Methyl-4-[[[(1-methyl-1H-indol-3-yl)carbonyl]oxy]methyl]-1-[2-[(methylsulphonyl)amino]ethyl]piperidinium iodide;

4-[[[(2-Methoxy-1H-indol-3-yl)carbonyl]oxy]methyl]-1-methyl-1-2-[2-[(methylsulphonyl)amino]ethyl]piperidinium iodide; and pharmaceutically acceptable salts and solvates thereof.

10. [1-[2-[(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 5-fluoro-2-methoxy-1H-indole-3-carboxylate and pharmaceutically acceptable salts and solvates thereof.

11. The compound of claim 10 in the form of its hydrochloride salt.

12. The compound of claim 10 in the form of its methanesulphonate salt.

13. The compound of claim 10 in the form of its maleate salt.

14. A compound as claimed in any of claims 1 to 13 for use in therapy.

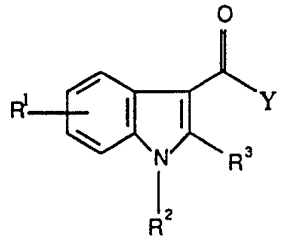
15. A method for treatment of conditions mediated by -5-hydroxytryptamine, in particular conditions capable of amelioration by antagonism of 5-HT_4 receptors, comprising administration of an effective amount of a compound of formula (I) as claimed in any one of claims 1 to 13.

16. The use of a compound as claimed in any of claims 1 to 13 in the preparation of a medicament for use in the treatment of conditions mediated by 5-hydroxytryptamine, in particular conditions capable of amelioration by antagonism of 5-HT_4 receptors.

17. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 13 together with a pharmaceutically acceptable carrier.

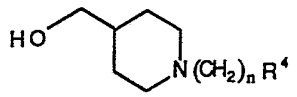
18. A process for the preparation of a compound of formula (I) as claimed in claim 1, which process comprises :-

(A) reacting a compound of formula (II):



(II)

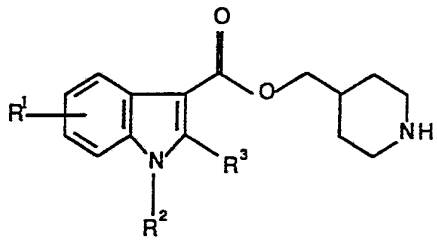
or a protected derivative thereof, wherein Y represents a leaving atom or group, with a compound of formula (III) :



(III)

or an alkali metal alkoxide thereof, wherein R^1, R^2, R^3, R^4 and n are as defined in claim 1;

(B) alkylating a compound of formula (IV) :



(IV)

or a protected derivative thereof, with a compound of formula (V)

$$L(CH_2)_nR^4 \quad (V)$$

wherein L represents a leaving atom or group and R^1, R^2, R^3, R^4 and n are as defined in claim 1, or a protected derivative thereof, in the presence of a base;

(C) converting a compound of formula (I) into another compound of formula (I);

(D) removing any protecting groups from a protected form of a compound of formula (I).

INTERNATIONAL SEARCH REPORT

International Applica. . No PCT/EP 92/00371

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 401/12 A 61 K 31/40

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 401/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	GB,A,2152049 (SANDOZ LTD) 31 July 1985, see the claims; page 1, lines 14-17 (cited in the application)	1,17
A	EP,A,0229391 (EISAI CO., LTD) 22 July 1987, see the claims (cited in the application)	1,17
A	EP,A,0144986 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD) 19 June 1985, see page 12, lines 4-11; claims	1,17
A	EP,A,0230718 (BEECHAM GROUP PLC) 5 August 1987, see page 19, lines 1-16; page 28	1,17

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
31-03-1992	28.04.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Els Vonk

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] **OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND ~~UNSEARCHABLE~~ [1] INCOMPLETELY**

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

1. [X] Claim numbers 15 partially because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] **OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING** [2]

This International Searching Authority found multiple Inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200371

SA 56434

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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