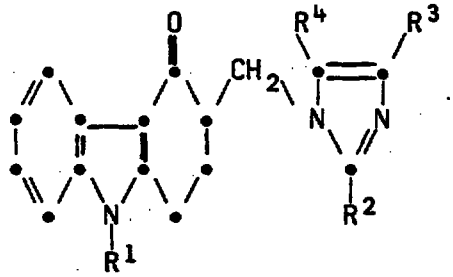
TRICYCLIC KETONES

2202530

This invention relates to tricyclic ketones, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use. In particular the invention relates to compounds which act upon 5-hydroxytryptamine (5-HT) receptors of the type located on terminals of primary afferent nerves.

Compounds having antagonist activity at 'neuronal' 5-HT receptors of the type located on primary afferent nerves have been described previously.

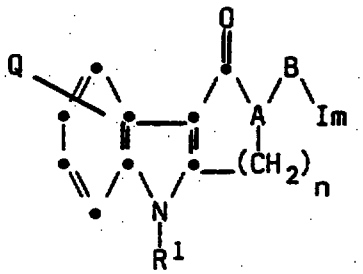
Thus for example published UK Patent Specification No. 2153821A and published European Patent Specification No. 191562 disclose tetrahydrocarbazolones of the general formula



wherein R^1 represents a hydrogen atom or a C_{1-10}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{3-6} alkenyl, C_{3-10}alkynyl, phenyl or phenylC_{1-3}alkyl group, and 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_{2-6}alkenyl 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.

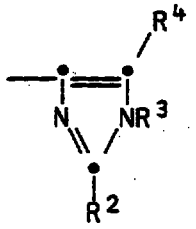
We have now found a novel group of compounds which differ in structure from those described previously, and which are potent antagonists of the effect of 5-HT at 5-HT 'neuronal' receptors.

Thus, in one aspect the present invention provides a tricyclic ketone of the general formula (I):

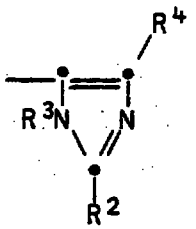


(I)

wherein Im represents an imidazolyl group of the formula:



or



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, $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ 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;
Q represents a hydrogen or a halogen atom, or a hydroxy, C_{1-4} alkoxy, phenylC_{1-3}alkoxy or C_{1-6} alkyl group or a group $-NR^7R^8$ or $-CONR^7R^8$ wherein R^7 and R^8, which may be the same or different, each represents a hydrogen atom or a C_{1-4} alkyl or C_{3-4} alkenyl group, or together with the nitrogen atom to which they are attached form a saturated 5 to 7 membered ring);
n represents 1, 2 or 3;
and A-B represents the group $CH-CH_2$ or $C=CH$; and physiologically acceptable salts and solvates thereof.

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.

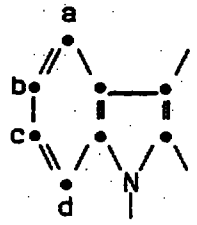
It will be appreciated that when A-B represents $CH-CH_2$ the carbon atom A is asymmetric and may exist in the R- or S- configuration. Furthermore, depending on the nature of the substituents A-B, R^1, R^2, R^3, R^4 and Q, centres of optical and geometric isomerism may occur elsewhere in the molecule. 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), the alkyl groups represented by R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Q may be straight chain or branched chain alkyl groups, for example, methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl or 2-methylprop-2-yl, and, in the case of R^1-R^6 and Q, pentyl, pent-3-yl or hexyl. An alkenyl group may be, for example, a propenyl or butenyl group. An alkynyl group may be, for example, a prop-2-ynyl or oct-2-ynyl group.

It is understood that when R^1 or R^3 represents a C_{3-6}alkenyl group or R^1 represents a C_{3-10} alkynyl group, or R^7 or R^8 represents a C_{3-4} alkenyl group, the double or triple bond may not be adjacent to the nitrogen atom.

A phenylC_{1-3} alkyl group (as such or as part of a phenylC_{1-3}alkoxy group) may be, for example, a benzyl, phenethyl or 3-phenylpropyl group. A cycloalkyl group (as such or as part of a cycloalkylalkyl group) may be, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group. When R^1 represents a C_{3-7} cycloalkyl C_{1-4} alkyl group, the alkyl moiety may be, for example, a methyl, ethyl, propyl, prop-2-yl or butyl group. When Q represents a C_{1-4} alkoxy group it may be, for example, a methoxy group. When Q represents a halogen atom it may be, for example, a

fluorine, chlorine or bromine atom. The substituent Q may be at the a, b, c or d position of the indole moiety :



A preferred class of compounds of formula (I) is that wherein R^1 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl), C_{3-4} alkenyl (e.g. prop-2-enyl), C_{3-4} alkynyl (e.g. prop-2-ynyl), C_{5-6}cycloalkyl (e.g. cyclopentyl), C_{5-6}cycloalkylmethyl (e.g. cyclopentylmethyl), phenylC_{1-2} alkyl (e.g. benzyl), C_{1-3} alkoxycarbonyl (e.g. methoxycarbonyl), N,N-diC_{1-3}alkylcarboxamido (e.g. N,N-dimethylcarboxamido) or phenylsulphonyl group. More preferably R^1 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl), C_{3-4} alkenyl (e.g. prop-2-enyl), C_{3-4} alkynyl (e.g. prop-2-ynyl), C_{5-6}cycloalkylmethyl (e.g. cyclopentylmethyl), phenyl C_{1-2} alkyl (e.g. benzyl), C_{1-3} alkoxycarbonyl (e.g. methoxycarbonyl), or N,N-diC_{1-3}alkylcarboxamido (e.g. N,N-dimethylcarboxamido) group. Most preferably R^1 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl), C_{3-4} alkenyl (e.g. prop-2-enyl), C_{3-4}alkynyl (e.g. prop-2-ynyl), C_{5-6} cycloalkylmethyl (e.g. cyclopentylmethyl), phenylC_{1-2} alkyl (e.g. benzyl) or N,N-diC_{1-3}alkylcarboxamido (e.g. N,N-dimethylcarboxamido) group.

Another preferred class of compounds of formula (I) is that wherein R^2 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl) group, more preferably a hydrogen atom.

Another preferred class of compounds of formula (I) is that wherein R^3 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl) group, more preferably a hydrogen atom.

A further preferred class of compounds of formula (I) is that wherein R^4 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl) group. Most preferably R^4 represents a methyl group.

Another preferred class of compounds of formula (I) is that wherein Q represents a hydrogen atom, a halogen (e.g. fluorine) atom

or a hydroxy, a C_{1-3} alkoxy (e.g. methoxy) or a C_{1-3} alkyl (e.g. methyl) group. More preferably Q represents a hydrogen atom, a halogen (e.g. fluorine) atom or a hydroxy group. Most preferably Q represents a hydrogen or a fluorine atom.

When Q represents a substituent other than a hydrogen atom, Q is preferably at the b- or c- position of the indole moiety.

Another preferred class of compounds of formula (I) is that wherein A-B represent $CH-CH_2$.

A further preferred class of compounds of formula (I) is that wherein n represents 2 or 3, more particularly 2.

A preferred group of compounds of formula (I) is that wherein R^1 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-4}alkenyl, C_{3-4}alkynyl, C_{5-6}cycloalkylmethyl, phenyl C_{1-2} alkyl, C_{1-3}alkoxycarbonyl or N,N-diC_{1-3}alkylcarboxamido group; R^2 and R^3 each represent a hydrogen atom; R^4 represents a hydrogen atom or a C_{1-3} alkyl group; Q represents a hydrogen or a halogen atom or a hydroxy group; A-B represents $CH-CH_2$ or C=CH; and n represents 2 or 3.

A particularly preferred group of compounds of formula (I) is that wherein R^1 represents a hydrogen atom or a methyl, prop-2-enyl, prop-2-ynyl, cyclopentylmethyl, benzyl or N,N-dimethylcarboxamido group; R^2 and R^3 each represent a hydrogen atom; R^4 represents a methyl group; Q represents a hydrogen or a fluorine atom; A-B represents $CH-CH_2$; and n represents 2 or 3.

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 according to the invention are:

6-fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)-methyl]-4H-carbazol-4-one;

1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one;

9-(cyclopentylmethyl)-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one;

1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-(2-propynyl)-4H-carbazol-4-one;
a further preferred compound according to the invention is 6, 7, 8, 9-tetrahydro-5-methyl-9-[(5-methyl-1H-imidazol-4-yl)methyl]-cyclohept[b]indol-10(5H)-one;
and their physiologically acceptable salts and solvates.

A particularly preferred compound according to the invention is 1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one and its physiologically acceptable salts and solvates (e.g. hydrates).

Preferred forms of this compound are the hydrochloride and the maleate. A particularly preferred form is the hydrochloride monohydrate.

It will be appreciated that the invention extends to other physiologically acceptable equivalents of the compounds according to the invention, i.e. physiologically acceptable compounds which are converted in vivo into the parent compound of formula (I).

Compounds of the invention are potent and selective antagonists of 5-HT-induced responses of the rat isolated vagus nerve preparation and thus act as potent and selective antagonists of the 'neuronal' 5-HT receptor type located on primary afferent nerves. Receptors of this type are now designated as 5-HT_3 receptors. Such receptors 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.

Compounds of formula (I), which antagonise the effect of 5-HT at 5-HT_3 receptors, are useful in the treatment of conditions such as psychotic disorders (e.g. schizophrenia and mania); anxiety; and nausea and vomiting, particularly that associated with cancer chemotherapy and radiotherapy. Compounds of formula (I) 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. Compounds of formula (I) may also be used in the treatment of dependency on drugs and substances of abuse, depression and dementia and other cognitive disorders.

Unlike existing drug treatments for certain of the above conditions, the compounds of the invention, because of their high selectivity for 5-HT_3 receptors, would not be expected to produce undesirable side effects. Thus, for example, neuroleptic drugs may exhibit extrapyramidal effects, such as tardive dyskinesia, and benzodiazepines may cause dependence.

According to another aspect, the invention provides a method of treatment of a human or animal subject suffering from a psychotic disorder such as schizophrenia or mania; or from anxiety; nausea or vomiting, particularly that associated with cancer chemotherapy and radiotherapy; gastric stasis; symptoms of gastrointestinal dysfunction such as dyspepsia, reflux oesophagitis, peptic ulcer, flatulence and irritable bowel syndrome; migraine; or pain, which comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound selected from tricyclic ketones derivatives of the general formula (I), their physiologically acceptable salts and solvates (e.g. hydrates), for use in human or veterinary medicine, and formulated for administration by any convenient route.

Such compositions may be formulated in conventional manner using one or more physiologically acceptable carriers and/or excipients.

Thus the compounds according to the invention 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).

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 injection e.g. 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.

In addition to the formulations described previously, the compounds of the invention 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 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 administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

For intranasal administration, the compounds according to the invention may be formulated as solutions 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.

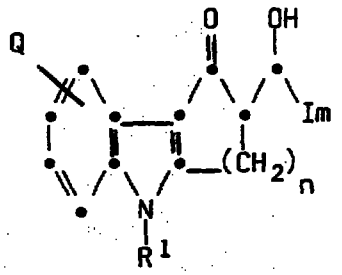
The compounds of formula (I) may also be administered in combination with other therapeutic agents. Thus, for example, in the treatment of gastric stasis, symptoms of gastrointestinal dysfunction, and nausea and vomiting, the compounds of formula (I) may be administered in combination with antisecretory agents such as histamine H_2-receptor antagonists (e.g. ranitidine, sufotidine or loxtidine) or H^+K^+ATPase inhibitors (e.g. omeprazole).

A proposed dose of the compounds of the invention for administration to man (of approximately 70kg body weight) is 0.001 to 100mg, for example 0.01 to 50mg, more preferably 0.1 to 20mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration and the condition being treated. 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.

According to another aspect of the invention, compounds of general formula (I), and physiologically acceptable salts or solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R^1, R^2, R^3, R^4, A, B, Q, n

and Im are as defined for compounds of general formula (I) unless otherwise stated.

According to a first general process (A), a compound of general formula (I) wherein A-B represents the group C=CH, may be prepared by dehydrating a compound of formula (II):

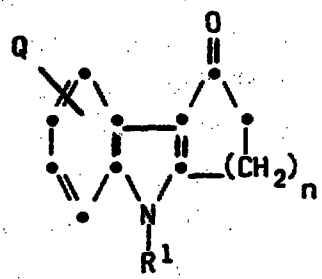


(II)

or a protected derivative thereof, followed where necessary by removal of any protecting groups.

The dehydration process may be effected using conventional methods, for example by using an organic or mineral acid (e.g. p-toluenesulphonic, methanesulphonic, trifluoroacetic or hydrochloric acid) in a suitable solvent such as an ether (e.g. tetrahydrofuran), an alcohol (e.g. methanol), or glacial acetic acid, at a temperature in the range 0 to 100°C.

According to a particular embodiment of this process, a compound of general formula (I), wherein A-B represents the group C=CH, may be prepared directly by the reaction of a compound of formula (III):



(III)

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

OHC - Im (IV)

or a protected derivative thereof, in the presence of a base such as an alkali metal amide (e.g. lithium diisopropylamide) in an inert solvent such as an ether (e.g. tetrahydrofuran). The dehydration is then performed in situ using the appropriate conditions described

above, followed where necessary by deprotection. Compounds of formula (II) may be isolated as intermediates in this particular embodiment of process (A).

According to a further embodiment of this process, a compound of general formula (I), wherein A-B represents the group C=CH, may be prepared by converting the hydroxy group of a compound of formula (II), into a leaving group such as a hydrocarbylsulphonate (e.g. a mesylate or a trifluoromethanesulphonate) using conventional methods, in the presence of a base (e.g. triethylamine or aqueous sodium hydroxide) in a solvent such as an ether (e.g. tetrahydrofuran) or an alcohol (e.g. methanol).

According to another general process (B), a compound of general formula (I) may be converted into another compound of formula (I) using conventional techniques. Such conventional techniques include hydrogenation, alkylation, acylation and acid-catalysed cleavage using protection and deprotection where necessary.

Thus, according to one embodiment of the interconversion process (B), compounds of formula (I) in which A-B represents the group $CH-CH_2$ and R^1 is other than a C_{3-6} alkenyl or a C_{3-10} alkynyl group, and/or Q is other than a benzyloxy group may be prepared by hydrogenating the corresponding compounds in which A-B represents the group C=CH. Hydrogenation may also be used to convert an alkenyl or an alkynyl substituent into an alkyl substituent or an alkynyl into an alkenyl substituent, or a benzyloxy substituent into a hydroxyl group.

Hydrogenation according to general process (B) may be effected using conventional procedures, for example using hydrogen in the presence of a noble metal catalyst (e.g. palladium, Raney nickel, platinum or rhodium). The catalyst may be supported on, for example, charcoal, alumina or alternatively a homogeneous catalyst such as tris(triphenylphosphine)rhodium chloride may be used. The hydrogenation will generally be effected in a solvent such as an alcohol (e.g. methanol or ethanol), an ether (e.g. dioxan), a halogenated hydrocarbon (e.g. dichloromethane) or an ester (e.g. ethyl acetate) or mixtures thereof, and at a temperature in the range -20 to +100^{0}C, preferably 0 to 50^{0}C.

According to another embodiment of the interconversion process (B), a compound of formula (I) in which R^1 represents a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, C_{3-7} cycloalkylC_{1-4}-alkyl or phenyl C_{1-3} alkyl group, or a compound in which at least one of R^2 and R^3 represents a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl or phenyl C_{1-3} alkyl group or a compound in which Q represents a C_{1-4} alkoxy or a phenyl C_{1-3} alkoxy group or a compound in which R^7 and/or R^8 represents a C_{1-4} alkyl or C_{3-4} alkenyl group may be prepared by alkylating a compound of formula (I) where one or more of R^1, R^2, R^3, R^7 and R^8 represent a hydrogen atom, or Q represents a hydroxyl group.

The term 'alkylation' according to general process (B) thus also includes the introduction of other groups such as cycloalkyl, alkenyl or phenalkyl groups.

The above alkylation reactions may be effected using the appropriate alkylating agent selected from compounds of formula R^9Z where R^9 represents a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, C_{3-7} cycloalkylC_{1-4} alkyl, or phenylC_{1-3}alkyl group, and Z represents a leaving atom or group such as a halogen atom (e.g. chlorine, bromine or iodine), an acyloxy group (e.g. trifluoroacetyloxy or acetoxy), or a sulphonyloxy group (e.g. trifluoromethanesulphonyloxy, p-toluenesulphonyloxy or methanesulphonyloxy); or a sulphate of formula $(R^9)_2SO_4$.

The alkylation reaction is conveniently carried out in an inert organic solvent such as a substituted amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene), preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides (e.g. sodium hydride), alkali metal amides (e.g. sodium amide or lithium diisopropylamide), alkali metal carbonates (e.g. sodium carbonate) or an alkali metal alkoxide (e.g. sodium or potassium methoxide, ethoxide or t-butoxide). The reaction may conveniently be effected at a temperature in the range -80 to +100^{0}C, preferably -80 to +50^{0}C.

According to another embodiment of general process (B), a compound of formula (I) wherein R^1 represents $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ or $-SO_2R^5$ may be prepared by acylating a compound of formula (I)

wherein R^1 represents a hydrogen atom. The acylation reactions may be effected using an appropriate acylating agent according to conventional procedures.

Suitable acylating agents include acyl halides (e.g. an acyl, alkylsulphonyl, or arylsulphonyl chloride, bromide or iodide), mixed and symmetrical anhydrides (e.g. a symmetrical anhydride of formula $(R^5CO)_2O$), lower alkyl haloformates (e.g. lower alkyl chloroformates), sulphonates (e.g. hydrocarbylsulphonates such as p-toluenesulphonate), carbamoyl halides (e.g. carbamoyl chlorides of formula R^5R^6NCOCl), carbonates and isocyanates (e.g. isocyanates of formula R^5NCO).

The reaction may conveniently be effected in the presence of a base such as an alkali metal hydride (eg. sodium or potassium hydride), an alkali metal carbonate (e.g. sodium or potassium carbonate), an alkali metal alkoxide (e.g. potassium t-butoxide), butyllithium, lithium diisopropylamide or an organic tertiary amine (e.g. triethylamine or pyridine).

Suitable solvents which may be employed in the acylation of general process (B) include amides (e.g. dimethylformamide or dimethylacetamide), ethers (e.g. tetrahydrofuran or dioxan), halogenated hydrocarbons (e.g. methylene chloride), nitriles (e.g. acetonitrile) and esters (e.g. ethyl acetate). The reaction may conveniently be effected at a temperature of from -10 to +150 °C.

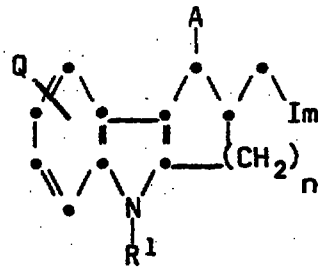
According to a yet further embodiment of general process (B), a compound of formula (I) in which Q represents a hydroxyl group may be prepared from the corresponding compound in which Q represents an alkoxy or benzyloxy group by acid-catalysed cleavage. The reaction may be effected using a Lewis acid such as boron tribromide or aluminium trichloride, in a solvent such as a halogenated hydrocarbon (e.g. dichloromethane). The reaction temperature may conveniently be in the range -80 to +100 °C.

According to another general process (C), a compound of general formula (I), wherein A-B represents the group $CH-CH_2$, may be prepared by reacting a compound of formula (III) or a protected derivative thereof, with a compound of formula (V):

$LCH_2 - Im$ (V)

wherein L represents a leaving atom or group, such as a halogen atom or an acyloxy or sulphonyloxy group as previously defined for Z, or a protected derivative thereof, in the presence of a base, followed where necessary by removal of any protecting groups. Suitable bases include alkali metal hydrides (e.g. sodium or potassium hydride), alkali metal alkoxides (e.g. potassium-t-butoxide) or alkali metal amides (e.g. lithium diisopropylamide). The reaction may conveniently be carried out in an inert solvent such as an ether (e.g. tetrahydrofuran), a substituted amide (e.g. dimethylformamide), or an aromatic hydrocarbon (e.g. toluene) and at a temperature in the range -80 to +50°C.

According to another general process (D), a compound of general formula (I), wherein A-B represents the group $CH-CH_2$, may be prepared by oxidising a compound of formula (VI):



(VI)

wherein A represents a hydrogen atom or a hydroxyl group, or a salt or protected derivative thereof, followed where necessary by removal of any protecting groups.

The oxidation process may be effected using conventional methods and the reagents and reaction conditions should be chosen such that they do not cause oxidation of the indole moiety or other functional groups. Thus, the oxidation process is preferably effected using a mild oxidising agent.

When oxidising a compound of formula (VI) in which A represents a hydrogen atom, suitable oxidising agents include quinones in the presence of water (e.g. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or 2,3,5,6-tetrachloro-1,4-benzoquinone), selenium dioxide, cerium (IV) oxidising reagents (e.g. ceric ammonium nitrate) and chromium (VI)

oxidising agents (e.g. a solution of chromic acid in acetone, for example Jones' reagent, or chromium trioxide in pyridine).

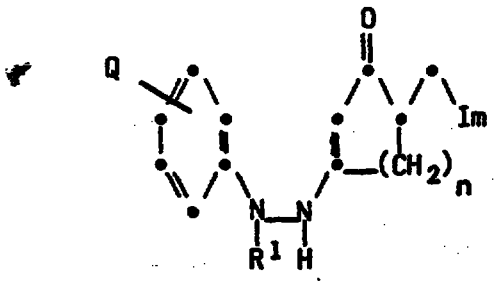
When oxidising a compound of formula (VI) in which A represents a hydroxyl group, suitable oxidising agents include quinones in the presence of water (e.g. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or 2,3,5,6-tetrachloro-1,4-benzoquinone), ketones (e.g. acetone, methylethylketone or cyclohexanone) in the presence of a base (e.g. aluminium t-butoxide), chromium (VI) oxidising agents (e.g. a solution of chromic acid in acetone, for example Jones reagent, or chromium trioxide in pyridine), N-halosuccinimides (e.g. N-chlorosuccinimide or N-bromosuccinimide), dialkylsulphoxides (e.g. dimethylsulphoxide) in the presence of an activating agent such as N,N'-dicyclohexylcarbodiimide or an acyl halide (e.g. oxalyl chloride or tosyl chloride), pyridine-sulphur trioxide complex, and dehydrogenation catalysts (e.g. copper chromite, zinc oxide, copper or silver).

Suitable solvents may be selected from ketones (e.g. acetone or butanone), ethers (e.g. tetrahydrofuran or dioxan), amides (e.g. dimethylformamide), alcohols (e.g. methanol), hydrocarbons (e.g. benzene or toluene), halogenated hydrocarbons (e.g. dichloromethane) and water or mixtures thereof.

The process is conveniently effected at a temperature of -70 to +50°C. It will be understood that the choice of oxidising agent will affect the preferred reaction temperature.

Compounds of formulae (II) and (VI) are novel compounds and constitute a further aspect of the invention.

According to another general process (E), a compound of general formula (I), wherein A-B represents the group $CH-CH_2$, may be prepared by cyclising a compound of formula (VII):



(VII)

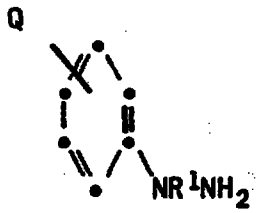
or a salt or protected derivative thereof, followed where necessary by removal of any protecting groups.

It will be appreciated that the compounds of formula (VII) may exist in the corresponding enol hydrazone tautomeric form.

The cyclisation may be carried out in aqueous or non-aqueous media, in the presence of an acid catalyst. When an aqueous medium is employed this may be water or an aqueous organic solvent such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) as well as mixtures of such solvents and the acid catalyst may be, for example, an inorganic acid such as concentrated hydrochloric or sulphuric acid. (In some cases the acid catalyst may also act as the reaction solvent). In an anhydrous reaction medium, which may comprise one or more alcohols or ethers (e.g. as described above), carboxylic acids (e.g. acetic acid) or esters (e.g. ethyl acetate), the acid catalyst will generally be a Lewis acid such as boron trifluoride, zinc chloride or magnesium chloride. The cyclisation reaction may conveniently be carried out at temperatures of from 20 to 200 ^{0}C preferably 50 to 125 ^{0}C.

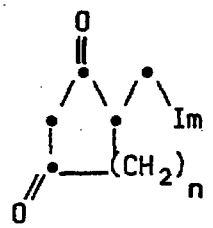
Alternatively the process may be carried out in the presence of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethylether and chloroform according to the method described in 'Reagents for Organic Synthesis', (Fieser and Fieser, John Wiley and Sons 1967).

According to a particular embodiment of process (E), a compound of general formula (I) may be prepared directly by the reaction of a compound of formula (VIII):



(VIII)

or a salt thereof, with a compound of formula (IX):



(IX)

or a protected derivative thereof, using the appropriate conditions as described above, followed where necessary by removal of any protecting groups. Compounds of formula (VII) may be isolated as intermediates in this particular embodiment.

A protected derivative of formula (IX) may for example have one or both of the carbonyl groups protected (e.g. as an enol ether). It will be appreciated that when a compound of formula (IX) is used in which the carbonyl group at the 3-position is protected, it may be necessary to remove the protecting group in order for reaction to occur with the compound of formula (VIII). Deprotection may be carried out by conventional methods, as described hereinafter. If desired, deprotection may be effected in situ.

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 keto group, for example, as a ketal or a thioketal or as an enol ether. It may also be necessary to protect the carbazolone and/or imidazole nitrogen atoms, for example with an arylmethyl (e.g. benzyl or 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 Q represents a hydroxyl group it may be necessary to protect the hydroxyl group, for example with an arylmethyl (e.g. benzyl or trityl) group.

Thus according to another general process (F), 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 Theodora W. Greene (John Wiley and Sons, 1981).

For example a ketal such as an alkyleneketal group may be removed by treatment with a mineral acid such as hydrochloric acid. A thioketal group may be cleaved by treatment with a mercuric salt, (e.g. mercuric chloride), in a suitable solvent, such as ethanol. An enol ether may be hydrolysed in the presence of an aqueous acid (e.g. dilute sulphuric or hydrochloric acid). An arylmethyl N-protecting group may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal) and a trityl group may also be cleaved by acid hydrolysis (e.g. using dilute hydrochloric or acetic acid). An alkoxyalkyl group may be removed using a Lewis acid such as boron tribromide. An acyl group may be removed by hydrolysis under acidic or basic conditions (e.g. using hydrogen bromide or sodium hydroxide). A sulphonyl group may be removed by alkaline hydrolysis. An arylmethyl OH-protecting group may be cleaved under acidic 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 by condensing a compound of formula (III), or a protected derivative thereof, with a compound of formula (IV), or a protected derivative therof, in the presence of a base such as an alkali metal amide (e.g. lithium diisopropylamide) in an inert solvent such as an ether (e.g. tetrahydrofuran).

Compounds of formula (III) may be prepared, for example, by the method or methods analogous to that described by Oikawa and Yonemitsu in J. Org. Chem., 1977, 42, 1213.

Compounds of formula (IV) may be prepared, for example, by oxidation of the corresponding hydroxymethylimidazole of formula (XI):

$$HOCH_2\text{-Im} \qquad (XI)$$

or a protected derivative thereof, with an oxidising agent such as manganese dioxide.

Compounds of formula (V) in which L represents a halogen atom may be obtained by reacting a compound of formula (XI), or a protected

derivative thereof, with a halogenating agent such as thionyl chloride or a phosphorus trihalide (e.g. phosphorus trichloride). Compounds of formula (V) in which L represents an acyloxy group or a sulphonyloxy group may be prepared by reacting a compound of formula (XI) with an appropriate acylating or sulphonylating agent such as an anhydride or a sulphonyl halide (e.g. methanesulphonyl chloride), optionally in the presence of a base (e.g. triethylamine or pyridine).

Compounds of formula (VI) may be prepared, for example, by reacting a compound of formula (I) with an appropriate reducing agent. Thus a compound of formula (VI) wherein A represents a hydrogen atom may be prepared by reacting a compound of formula (I) with a hydride reducing agent such as diisobutylaluminium hydride, or sodium borohydride. When diisobutylaluminium hydride is used, it may be necessary to follow the reaction with an additional hydrogenation step.

Hydrogenation may be effected using conventional procedures, for example, as described in process (B). A compound of formula (VI) wherein A represents a hydroxyl group may be prepared, for example, by reacting a compound of formula (I) with an alkali metal hydride (e.g. lithium hydride).

Compounds of formula (VII) may be prepared, for example, by the reaction of a compound of formula (VIII) or a salt thereof, with a compound of formula (IX), or a protected derivative thereof, in a suitable solvent such as an alcohol, and at a temperature of, for example, from 20 to 100 ^{0}C.

Compounds of formula (IX) may be prepared by reacting a compound of formula (V), or a protected derivative thereof, with the appropriate 1,3-diketone, or a protected derivative thereof, under the conditions referred to in process (C) above.

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

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 aqueous alcohol (e.g. aqueous ethanol), 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.

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.

Examples of optically active resolving acids that may be used to form salts with the racemic compounds include the (R) and (S) forms of organic carboxylic and sulphonic acids such as tartaric acid, di-p-toluoyltartartic acid, camphorsulphonic acid and lactic acid. The resulting mixture of isomeric salts may be separated, for example, by fractional crystallisation into the diastereoisomers and if desired, the required optically active isomer may be converted into the free base.

The methods indicated above for preparing the compounds of the invention can be used as the last main step in the preparative sequence. The same general methods can be used for the introduction of the desired groups at an intermediate 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 Examples. All temperatures are in ^{0}C. Thin layer chromatography (t.l.c.) was carried out on silica, and flash column chromatography (FCC) and

short-path column chromatography (SPCC) on silica (Merck 9385 and Merck 7747 respectively). Solvent System A as used for chromatography denotes dichloromethane:ethanol:0.88 ammonia solution. ^{1}H-N.m.r. spectra were obtained at 250 MHz (integration, multiplicity); multiplicity legend : s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Organic extracts were dried over magnesium sulphate or sodium sulphate. The following abbreviations are used: THF - tetrahydrofuran; DMF - dimethylformamide; IMS - industrial methylated spirits.

MERCK is a Registered Trade Mark.

Intermediate 1

5-Methyl-1-(triphenylmethyl)-1H-imidazole-4-methanol

A solution of triphenylchloromethane (13.1g) in dry DMF (80ml) was added dropwise over 30 min. to a stirred solution of 4-methyl-5-imidazolemethanol hydrochloride (7.0g) and triethylamine (9.52g) in dry DMF (75ml) at room temperature under nitrogen, and stirring was continued for 2.5h. The suspension was poured onto ice (600ml), stirred for 30 min. and filtered. The resulting solid (12.0g) was triturated twice with acetone (2 x 250ml) to give the title compound (8.4g), t.l.c. (System A 94.5:5:0.5) Rf 0.19.

Intermediate 2

5-Methyl-1-(triphenylmethyl)-1H-imidazole-4-carboxaldehyde

A mixture of 5-methyl-1-(triphenylmethyl)-1H-imidazole-4-methanol (4.0g), manganese dioxide (activated) (40g) and dioxan (225ml) was stirred at room temperature overnight. The suspension was filtered and the solid was washed with hot chloroform (1ℓ). The combined filtrates were evaporated in vacuo to leave a solid (4.0g) which was purified by FCC eluting with chloroform to give a solid which was triturated with hexane (ca. 50ml) to give the title compound (2.99g), m.p. 184-188° (decomp.).

Intermediate 3

1,2,3,9-Tetrahydro-3-[hydroxy[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-9-methyl-4H-carbazol-4-one

n-Butyllithium (1.57M; 1.08mℓ) was added at -78° under nitrogen with stirring to a solution of diisopropylamine (0.24mℓ) in dry THF (7mℓ) and stirred at 0° for 30 min. The solution was cooled to -78° and added via a cannula to 1,2,3,9-tetrahydro-9- methyl-4H-carbazol-4-one (282mg) at -78° under nitrogen with stirring. After 1h at -78°, followed by 1h at 0°, the mixture was cooled to -78° and treated with Intermediate 2 (500mg) in THF (6mℓ). After 4h at -78°, the mixture was allowed to warm to 23° and stirred for 14h. The resultant solid (the reaction mixture had evaporated) was cooled to -78° treated with THF (10mℓ), followed by acetic acid (1mℓ), warmed to 0°, and poured into aqueous saturated sodium bicarbonate (50mℓ). The mixture was extracted with dichloromethane (2x60mℓ) and the combined, dried organic extracts were evaporated. The residue was purified by SPCC eluting with System A (967:30:3) to give the title compound (280mg), m.p. 141-147°.

Intermediate 4

3-(3-Fluorophenylhydrazono)-1-cyclohexan-1-ol

3-Fluorophenylhydrazine hydrochloride (9.35g) in water (100mℓ) was treated with 2N aqueous sodium hydroxide (29mℓ) and the resultant solution was added over 2h to a stirred solution of cyclohexan-1,3-dione (6.65g) in water (100mℓ) under nitrogen. This mixture was stirred for 18h and the resultant precipitate was filtered off and then stirred with water (150mℓ). The solid was again filtered off, washed with water (50mℓ) and dried to give a powder (9.90g). This was washed with hexane (2 x 200mℓ) and the solid was collected to give the title compound (5.3g), m.p. 142-144°.

Intermediate 5

7-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

A mixture of glacial acetic acid (25mℓ), 3-(3-fluorophenylhydrazono)-1-cyclohexen-1-ol (1.1g) and fused zinc chloride (1.0g) was heated at 100° for 20h. The cooled reaction mixture was poured into water (35mℓ) and extracted with dichloromethane (2 x 30mℓ). The combined, dried organic extracts were evaporated to give an oil which was purified by SPCC eluting with ethyl

acetate:hexane (3:2) to give the title compound (0.15g) as a powder, m.p. 231-233°.

Intermediate 6

7-Fluoro-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one

A solution of 7-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (1.0g) in dry DMF (8mℓ) was added dropwise to a stirred, ice-cooled suspension of pre-washed (hexane: 2 x 10mℓ) sodium hydride (78% dispersion in oil; 175mg) in dry DMF (5mℓ) under nitrogen and stirring was continued at room temperature for 1.5h. The solution was cooled to 0°, iodomethane (0.35mℓ) was added dropwise and stirring was continued at 0° for 2h. The suspension was poured into 8% aqueous sodium bicarbonate (30mℓ) extracted with dichloromethane (2 x 30mℓ) and the combined, dried organic extracts were evaporated and dried in vacuo at 100° for 18h to give the title compound (1.03g) as a solid, m.p. 174-175°.

Intermediate 7

1,2,3,9-Tetrahydro-3-[(5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl) methyl]-4H-carbazol-4-one

A solution of triphenylchloromethane (4.2g) in dry DMF (40mℓ) was added dropwise to a solution of 1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one (3.5g) and triethylamine (1.75mℓ) in dry DMF (35mℓ) under nitrogen. After stirring for 4h the mixture was poured into water (300mℓ) and extracted with dichloromethane (3x100mℓ). The combined extracts were washed with water (200mℓ), dried and evaporated to give an oil (ca. 9g) which was purified by FCC eluting with System A (200:10:1) to give the title compound (4.57g) as a foam, t.l.c. (System A 200:10:1) Rf 0.32.

Intermediate 8

4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole

A solution of thionyl chloride (1.3mℓ) in dry dichloromethane (10mℓ) was added over 5 min. to a stirred suspension of 5-methyl-1-(triphenylmethyl)-1H-imidazole-4-methanol (5.0g) in a mixture of dichloromethane (100mℓ) and dry DMF (2mℓ) at 0°. The mixture was stirred at 0° for 30 min. and washed consecutively with 8% sodium

bicarbonate (2 x 50mℓ), water (50mℓ), dried and evaporated in vacuo below 40° to give an oil (5g). This was dissolved in ether (100mℓ) and the resulting solution was filtered through a pad of silica which was further eluted with ether (2 x 100mℓ). The combined filtrates were evaporated below 40° to give a foam which was triturated with cold hexane and filtered to give the title compound (4.2g) as a solid, m.p. 133-135°.

Intermediate 9

3-Methoxy-6-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-2-cyclohexen-1-one

n-Butyllithium (1.58M in hexane; 21mℓ) was added at -78° under nitrogen to a stirred solution of diisopropylamine (4.6mℓ) in dry THF (75mℓ) and the solution was stirred at 0° for 30 min. The solution was cooled to -78° and added to a solution of 3-methoxy-2-cyclohexen-1-one (3.4g) in dry THF (25mℓ) at -78° under nitrogen with stirring. After stirring for 1h at -78° and for 30 min. at 0° the solution was cooled to -78° and a solution of 4-(chloromethyl) -5-methyl-1-(triphenylmethyl)-1H-imidazole (10g) in dry THF (100mℓ) was added dropwise with stirring under nitrogen. The solution was stirred at -78° for 3h and at 0° for 30 min., treated with 8% aqueous sodium bicarbonate (400mℓ) and extracted with ethyl acetate (2x300mℓ). The combined, dried organic extracts were evaporated to give an oil (ca. 13g) which was purified by SPCC eluting with System A (967:30:3) to give the title compound (3.28g), m.p. 145-148°.

Intermediate 10

1,2,3,9-Tetrahydro-3-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-9-(phenylmethyl)-4H-carbazol-4-one

A solution of 1,2,3,9-tetrahydro-3-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-4H-carbazol-4-one (500mg) in dry DMF (3mℓ) was added dropwise to a stirred suspension of sodium hydride (73% dispersion in oil; 38mg) in dry DMF (1mℓ) under nitrogen. After 20 min. benzyl bromide (0.14mℓ) was added and the mixture was stirred for 3h. Water (50mℓ) was added and the suspension was extracted with dichloromethane (3 x 25mℓ). The combined, dried organic extracts were evaporated to give an oil (ca. 850mg) which was

purified by FCC (column made up in ethyl acetate:hexane:triethylamine 79:20:1) eluting with ethyl acetate: hexane (4:1) to give the title compound (265mg) as a solid, m.p. 78-80°.

Intermediate 11

9-(Cyclopentylmethyl)-1,2,3,9-tetrahydro-3-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-4H-carbazol-4-one

Using the procedures described above for Intermediate 10, 1,2,3,9-tetrahydro-3-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-4H-carbazol-4-one (500mg) was treated with sodium hydride (73% dispersion in oil; 38mg) and was then stirred with cyclopentanemethanol (p-toluenesulphonate) (292mg) for 24h. Work up and FCC as described above gave the title compound (283mg), m.p. 177-179°.

Intermediate 12

1,2,3,9-Tetrahydro-3-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-9-(2-propynyl)-4H-carbazol-4-one

Propargyl bromide (0.086mℓ) was added to a suspension of 1,2,3,9-tetrahydro-3-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]-methyl]-4H-carbazol-4-one (500mg) and potassium carbonate (265mg) in acetone (10mℓ) and the mixture was stirred under nitrogen for 60h. More propargyl bromide (0.086mℓ) was added and the mixture was stirred at room temperature for 24h and then at reflux for 6h. Water (50mℓ) was added and the suspension was extracted with dichloromethane (3 x 25mℓ). The combined, dried organic extracts were evaporated to give a gum (650mg) which was purified by FCC (column made up in ethyl acetate:hexane:triethylamine 80:19:1) eluting with ethyl acetate: hexane (4:1) to give the title compound (95mg) as a foam, t.l.c. on Et_3N impregnated SiO_2 (ethyl acetate:hexane 4:1) Rf 0.30.

Intermediate 13

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl] 4H-carbazole maleate

A suspension of 1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl) methyl]-9-methyl-4H-carbazol-4-one (0.5g) in dry dichloromethane (150mℓ) at -57° under nitrogen was treated with a solution of diisobutylaluminium hydride (1.0M in cyclohexane; 6mℓ) and the mixture

was stirred for 4h while warming to 5°. Methanol (5mℓ) was added and the mixture was stirred for a further 1h and was then filtered. The gelatinous precipitate was further washed with dichloromethane (50mℓ) and the combined filtrates were evaporated in vacuo. The residual oil (ca. 0.55g) was purified by FCC eluting with System A (95:5:0.5) to give a solid (198mg). A mixture of this solid (175mg) in ethanol (15mℓ) was hydrogenated at room temperature and atmospheric pressure over a stirred suspension of pre-reduced 10% palladium on carbon (50% aqueous paste; 20mg) in ethanol (10mℓ) for 4h. The mixture was filtered, evaporated in vacuo, and the residual gum was partitioned between 0.2N hydrochloric acid (20mℓ) and dichloromethane (20mℓ; discarded). The acidic layer was basified (2N sodium hydroxide) and extracted with chloroform (3x20mℓ). These latter chloroform layers were dried and evaporated in vacuo to leave a gum (155mg) which was dissolved in dichloromethane:methanol (1:1) (15mℓ) and treated with a solution of maleic acid (65mg) in methanol (0.3mℓ). Concentration in vacuo to ca. 2mℓ and dilution with dry ether afforded the title compound (176mg) as a solid, m.p. 175-179° (decomp.).

Intermediate 14

1,2,3,9-Tetrahydro-9-methyl-3-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-4H-carbazol-4-one

A solution of triphenylchloromethane (286mg) in dry DMF (10mℓ) was added dropwise to a stirred solution of 1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one (292mg) and triethylamine (101mg) in dry DMF (20mℓ) and the resulting solution was stirred at room temperature under nitrogen for 3.5h. The reaction mixture was then poured into water (100mℓ) and the resultant suspension was extracted with dichloromethane (3x50mℓ). The combined, dried organic extracts were adsorbed onto FCC silica which was then applied to a column and FCC eluting with System A (150:8:1) gave a solid which was further purified by crystallisation from dichloromethane:hexane (2:1) to give the title compound (304mg), m.p. 193-195°.

Intermediate 15

N,N,5-Trimethyl-4-[(2,3,4,9-tetrahydro-9-methyl-4-oxo-1H-carbazol-3-yl)methyl]-1H-imidazole-1-sulphonamide

A solution of dimethylsulphamoyl chloride (0.16mℓ) in dry dichloromethane was added to a stirred solution of 1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one (438mg) and triethylamine (0.25mℓ) in dry dichloromethane (30mℓ) and the mixture was heated at reflux for 18h. After cooling the reaction mixture was adsorbed onto FCC silica which was then applied to a column and FCC eluting with System A (150:8:1) gave an oil, which solidified to a powder on trituration with dry hexane (30mℓ). This powder was then further purified by dissolution in dry dichloromethane (30mℓ) and crystallisation by addition of dry hexane (10mℓ) to give the title compound (518mg), m.p. 122-124°.

Intermediate 16

1,2,3,9-Tetrahydro-3-[[1-(methoxymethyl)-5-methyl-1H-imidazol-4-yl]-methyl]-9-methyl-4H-carbazol-4-one and 1,2,3,9-tetrahydro-3-[[1-(methoxymethyl)-4-methyl-1H-imidazol-5-yl]methyl]-9-methyl-4H-carbazol-4-one (4:1)

A solution of chloromethyl methyl ether (0.22mℓ) in chloroform (10mℓ) was added to a stirred solution of 1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-methyl-4H-carbazol-4-one (0.44g) and triethylamine (0.5mℓ) in chloroform (30mℓ) under nitrogen. The resulting solution was stirred at 20° for 2h and partitioned between chloroform (25mℓ) and 2N sodium bicarbonate solution (2x30mℓ). The dried organic extract was evaporated and the residue (0.45g) was purified by FCC eluting with System A (200:8:1) to give the title compounds (0.25g) as a gum, t.l.c. (System A 75:8:1) Rf 0.5. N.m.r. ($CDCl_3$) showed the title compounds to be in the ratio of 4:1.

Intermediate 17

Phenylmethyl 5-methyl-4-[(2,3,4,9-tetrahydro-9-methyl-4-oxo-1H-carbazol-3-yl)methyl]-1H-imidazole-1-carboxylate and phenylmethyl

4-methyl-5-[(2,3,4,9-tetrahydro-9-methyl-4-oxo-1H-carbazol-3-yl) methyl]-1H-imidazole-1-carboxylate (97:3)

A solution of carbobenzoxy chloride (0.26mℓ) in chloroform (10mℓ) was added to a stirred solution of 1,2,3,9-tetrahydro -3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-methyl-4H-carbazol-4-one (0.44g) and triethylamine (0.25mℓ) in chloroform (30mℓ) under nitrogen. The resulting solution was stirred at 20° for 2h and partitioned between chloroform (25mℓ) and 2N sodium bicarbonate solution (2x30mℓ). The organic extract was dried and evaporated to leave a gum (0.8g) which was purified by FCC eluting with System A (200:8:1) to give a solid (0.64g) which was crystallised from ethanol (3mℓ) to give the title compounds (0.62g), t.l.c. (System A 200:8:1) Rf 0.47. N.m.r. ($CDCl_3$) showed the title compounds to be in the ratio of 97:3.

Example 1

(E)-1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl) methylene]-4H-carbazol-4-one maleate

A solution of 1,2,3,9-tetrahydro-3-[hydroxy[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-9-methyl-4H-carbazol-4-one (2.70g) in glacial acetic acid (100mℓ) was treated with p-toluenesulphonic acid monohydrate (10.80g) and the stirred solution heated at reflux for 4h. The cool, dark liquid was evaporated, treated with aqueous saturated sodium bicarbonate (250mℓ) and extracted into ethyl acetate (4x250mℓ). The combined, dried organic extracts were evaporated, and purified by SPCC. Elution with System A (978:20:2 → 945:50:5) afforded the free base of the title compound as a light yellow-brown solid (488mg). A hot solution of the free base (87mg) in ethanol (ca. 16mℓ) was treated with a hot solution of maleic acid (38mg) in ethanol (1mℓ), and on cooling the precipitate was collected to give the title compound (81mg), m.p. 205-209°.

Analysis Found: C,65.1; H,5.2; N,10.2;

$C_{18}H_{17}N_3O.C_4H_4O_4$ requires C,64.9; H,5.2; N,10.3%.

Example 2

(E)-1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-carbazol-4-one

Lithium diisopropylamide mono(tetrahydrofuran) (1.5M in cyclohexane; 45mℓ) was added dropwise to a cold (-70°) solution of 1,2,3,9-tetrahydro-4H-carbazol-4-one (5.0g) in dry THF (500mℓ) under nitrogen. The solution was stirred at -70° for 1h whereupon Intermediate 2 (10g) was added and the mixture was allowed to reach room temperature over 3h. It was then cooled to -70° and acetic acid (80mℓ) followed by p-toluenesulphonic acid (51.4g) were added. The resulting solution was heated at reflux for 20h and the solvent was removed in vacuo. The residue was treated with 8% sodium bicarbonate solution (2ℓ) and extracted with dichloromethane (3x1ℓ). The combined, dried organic extracts were evaporated to give a gum (ca. 20.8g) which was purified by FCC eluting with System A (100:10:1) to give the title compound (5.2g), t.l.c. (System A 100:10:1) Rf 0.35.

^{1}H-N.M.r. (d_4-methanol) δ 2.39(3H,s), 3.09(2H,t), 3.50(2H,brt), 7.15-7.25 (2H,m), 7.33-7.43(1H,m), 7.53(1H,brs), 7.69(1H,s), 8.10-8.18(1H,m).

Example 3

(E)-7-Fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-carbazol-4-one

Lithium diisopropylamide mono(tetrahydrofuran) (1.5M in cyclohexane; 3.3mℓ) was added dropwise over 10 min. at -70° under nitrogen to a stirred suspension of 7-fluoro-1,2,3,9-tetrahydro-9-methyl-4H- carbazol-4-one (975mg) in dry THF (30mℓ). After 1.5h a suspension of Intermediate 2 (1.74g) in dry THF (10mℓ) was added and the suspension was stirred at -10° for 2h. The resultant solution was cooled to -70° and acetic acid (12mℓ) was added. The solution was then allowed to warm to -10° and p-toluenesulphonic acid monohydrate (5.8g) was added and the solution was stirred at reflux for 20h. It was then cooled and evaporated and the residue was partitioned between 8% aqueous sodium bicarbonate (100mℓ) and dichloromethane (70mℓ). The suspension was filtered and the resultant solid (1.02g) was crystallised from methanol (100mℓ) to give the title compound (366mg), m.p. 290-295°.

Analysis	Found:	C,69.9; H,5.2; N, 13.2;
$C_{18}H_{16}FN_3O$	requires	C,69.9; H,5.2; N,13.6%.

Example 4

(E)-1,2,3,9-Tetrahydro-6-methoxy-9-methyl-3-[(5-methyl-1H-imidazol-4-yl methylene]-4H-carbazol-4-one

n-Butyllithium (1.39M in hexane; 5.0mℓ) was added dropwise to a cold (-70°) stirred solution of diisopropylamine (0.98mℓ) in dry THF (10mℓ) under nitrogen. The solution was stirred at 0° for 30 min, cooled to -70° and added dropwise to a cold (-70°) stirred solution of 1,2,3,9-tetrahydro-6- methoxy-9-methyl-4H-carbazol-4-one (640mg) in dry THF (20mℓ) under nitrogen and the resultant solution was allowed to reach 0° over 1h. It was then cooled to -70° and a suspension of Intermediate 2 (985mg) in dry THF (10mℓ) was added dropwise and the stirred mixture was allowed to reach room temperature over 3h. It was then cooled to -70° and was treated with acetic acid (8mℓ) followed by p-toluenesulphonic acid (5.3g) and heated at reflux for 16h. The solvent was removed in vacuo and the residue treated with 8% sodium bicarbonate solution (150mℓ) and extracted with dichloromethane (4x50mℓ). The combined, dried organic extracts were evaporated to give a gum (ca. 2g) which was purified by FCC eluting with System A (200:10:1) to give the title compound (220mg) as a solid, m.p. 133-135°, t.l.c. (System A 200:10:1) Rf 0.24.

Example 5

(Z)-6,7,8,9-Tetrahydro-5-methyl-9-[(5-methyl-1H-imidazol-4-yl) methylene]cyclohept[b]indol-10(5H)-one maleate

A solution of lithium diisopropylamide (1.5M in cyclohexane; 3.2mℓ) was added to a cold (-70°) stirred suspension of 5-methyl-6,7,8,9-tetrahydrocyclohept[b]indol-10(5H)-one (0.96g) in dry THF (30mℓ) under nitrogen. The resulting solution was stirred at -70° for 15 min. and then at 20° for 30 min., cooled to -70° and treated with a solution of Intermediate 2 (1.6g) in THF (30mℓ). The reaction mixture was then stirred at -70° for 30 min., at 20° for 1h, cooled to -70° and treated with acetic acid (25mℓ). The resulting solution was heated on a steam bath for 1h and concentrated in vacuo to

ca. 10mℓ and partitioned between saturated potassium carbonate solution (90mℓ) and ethyl acetate (3x90mℓ). The combined, dried organic extracts were evaporated to leave a gum (ca. 2g) which was dissolved in THF (100mℓ) and treated with p-toluenesulphonic acid monohydrate (8.5g) at 100° for 3h. The resultant solution was concentrated *in vacuo* to ca. 5mℓ and partitioned between ethyl acetate (3x90mℓ) and saturated potassium carbonate (90mℓ). The combined, dried organic extracts were evaporated to leave a gum (ca. 2g) which was purified by FCC eluting with System A (200:8:1) to give a gum (ca. 0.75g) which was partitioned between 2N hydrochloric acid (30mℓ) and ethyl acetate (30mℓ). The resultant precipitate, from which the liquid was carefully decanted, was partitioned between saturated potassium carbonate (30mℓ) and ethyl acetate (3x30mℓ). The combined organic extracts were evaporated to give a solid (ca. 260mg) which was crystallised from absolute ethanol (15mℓ) to give the free base of the title compound (0.15g). This solid was dissolved in hot ethanol (30mℓ) and treated with a solution of maleic acid (57mg) in ethanol (2mℓ) to precipitate on cooling the title compound (90mg), m.p. 175-176°.

Analysis Found: C,65.2; H,5.4; N,9.8;
$C_{19}H_{19}N_3O.C_4H_4O_4$ requires C,65.5; H,5.5; N,10.0%.

Example 6

(E)-6,7,8,9-Tetrahydro-5-methyl-9-[(5-methyl-1H-imidazol-4-yl) methylene]cyclohept[b]indol-10(5H)-one

Elution of the FCC column of Example 5 also gave a semi-solid (ca. 0.45g) which was crystallised from absolute ethanol (25mℓ) to give the title compound (0.3g), m.p. 230-232°.

Analysis Found: C,74.3; H,6.3; N,13.6;
$C_{19}H_{19}N_3O$ requires C,74.7; H,6.3; N,13.8%.

Example 7

1,2,3,9-Tetrahydro-9-methyl-3-[(1H-imidazol-4-yl)methylene]-4H-carbazol-4-one

A solution of diisopropylamine (1.54mℓ) in dry THF (20mℓ) at -78° was treated dropwise with n-butyllithium (1.32M in hexane; 8.3mℓ). The mixture was allowed to warm to 0° and was recooled to -78°. It was

then added over 3 min, to a stirred suspension of 1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one (2.0g) in dry THF (80mℓ) at -78°. The resultant suspension was then stirred at -78° for 2h and was then treated with 1-(triphenylmethyl)-1H-imidazole-4-carboxaldehyde (3.72g). The mixture was stirred for a further 2h, whilst it was slowly allowed to warm to room temperature and was then cooled to -78° and quenched with acetic acid (2mℓ). The resultant solution was allowed to warm to room temperature and was poured into 8% aqueous sodium bicarbonate (600mℓ).

The mixture was extracted with dichloromethane (3x150mℓ) and the combined, dried organic extracts were evaporated to give a foam. A solution of this foam and p-toluenesulphonic acid monohydrate (18g) in a mixture of acetic acid (25mℓ) and dry THF (150mℓ) was heated at reflux for 5h. The cooled mixture was added cautiously to 8% aqueous sodium bicarbonate (650mℓ) and was extracted with dichloromethane (3x150mℓ). The combined, dried organic extracts were evaporated to to give a solid which was purified by FCC eluting with System A (100:10:1) to give the title compound (1.42g), m.p. 225-232°.

Analysis Found: C,73.3; H,5.6; N,14.7;

$C_{17}H_{15}N_3O$ requires C,73.6; H,5.5; N,15.1%.

Example 8

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

A solution of 1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-carbazol-4-one (3.50g) in DMF (85mℓ) and ethanol (50mℓ) was added to a pre-reduced suspension of 10% palladium oxide on carbon (3.4g) in ethanol (50mℓ) and hydrogenated at room temperature and atmospheric pressure until uptake ceased (270mℓ). The catalyst was filtered off and the filtrate evaporated. The residue was adsorbed from methanol (170mℓ) onto SPCC silica and applied to an FCC column. Gradient elution with System A (967:30:3→912:80:8) afforded the free base of the title compound as a solid (2.32g). A portion of this solid (500mg) in hot ethanol (15mℓ) was treated with a hot solution of maleic acid (224mg) in ethanol (2mℓ) and on cooling, the

precipitate was collected to give the title compound (415mg), m.p. 130.5-137°, t.l.c. (System A 200:10:1) 0.30.

Analysis Found : C,63.2; H,5.5; N,9.7;

$C_{13}H_{13}N_3O.C_4H_4O_4$ $0.33H_2O$ requires C,63.6; H,5.7; N,10.1%.

Water assay Found : 1.55% w/w $H_2O \equiv 0.33$ mol.

^{1}H-N.m.r. (d_6-DMSO) δ 1.8-1.98(1H,m), 2.1-2.25(1H,m), 2.25(3H,s), 2.68-2.84(2H,m), 2.85-3.3(3H,m), 3.75(3H,s), 6.0(2H,s-maleate), 7.18-7.32(2H,m), 7.57(1H,brd), 8.03(1H,brd), 8.88(1H,s).

Example 9

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

A solution of 1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)-methylene]-4H-carbazol-4-one (5.2g) in ethanol (100mℓ) was hydrogenated at room temperature and atmospheric pressure over a stirred suspension of pre-reduced 10% palladium oxide on carbon catalyst (50% aqueous paste; 1.0g) in ethanol (30mℓ) for 4.5h. The mixture was then filtered and evaporated to give an oil (ca. 5g) which was purified by FCC eluting with System A (100:10:1) to give the free base of the title compound (3.96g) as an oil. A sample (400mg) was dissolved in ethanol (4mℓ) and treated with a solution of maleic acid (170mg) in ethanol (1.25mℓ). The solvent was removed in vacuo and the residue was triturated with dry ether (5 x 25mℓ) to give a solid (555mg). This solid (ca. 500mg) was dissolved in hot methanol (5mℓ) and ethyl acetate (15mℓ) was added. The solution was concentrated to a volume of 10mℓ and allowed to cool. After 1h the precipitated solid was collected to give the title compound (314mg), m.p. 160-162°.

Water Analysis Found : 0.36% w/w $\equiv 0.06$mol H_2O.

Analysis found: C,63.3; H,5.3; N,10.2;

$C_{17}H_{17}N_3O.C_4H_4O_4.0.06H_2O$ requires C,63.6; H,5.4; N,10.6%.

Example 10

7-Fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)-methyl]-4H-carbazol-4-one maleate

A solution of 7-fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-carbazol-4-one (315mg) in ethanol (25mℓ) was hydrogenated at room temperature and atmospheric pressure over pre-reduced 10% palladium oxide on carbon (50% aqueous paste; 300mg) for 2h. The mixture was filtered and evaporated to give a foam which was purified by FCC eluting with System A (912:80:8) to give the free base of the title compound (230mg) as a solid. This was dissolved in hot ethanol (30mℓ) and treated with a solution of maleic acid (85mg) in warm ethanol (3mℓ). The resultant solution was evaporated and the residual oil was triturated with ether (40mℓ) to give a powder (210mg). This was combined with the mother liquors, evaporated, treated with 8% aqueous sodium bicarbonate (25mℓ) and extracted with ethyl acetate (3x20mℓ). The combined, dried organic extracts were evaporated to give a solid which was dissolved in hot ethanol (20mℓ) and diluted with a solution of maleic acid (86mg) in ethanol (3mℓ). The solution was evaporated and the residual solid crystallised from ethanol (5mℓ) to give the title compound (202mg), m.p. 153-156°.

Analysis Found: C,61.6; H,5.2; N,9.6;
$C_{13}H_{18}FN_3O.C_4H_4O_4$ requires C,61.8; H,5.2; N,9.8%.

Example 11

1,2,3,9-Tetrahydro-6-methoxy-9-methyl-3-[(5-methyl-1H-imidazol-4-yl) methyl]-4H-carbazol-4-one

A solution of (E)-1,2,3,9-tetrahydro-6-methoxy-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methylene-4H-carbazol-4-one (200mg) in absolute ethanol (15mℓ) was hydrogenated at room temperature and atmospheric pressure over a stirred suspension of 10% palladium oxide on carbon catalyst (50% aqueous paste; 100mg) in absolute ethanol (5mℓ). The mixture was filtered and evaporated to give a foam (ca. 200mg) which was purified by FCC eluting with System A (200:10:1) to give the title compound (154mg) as a solid, m.p. 227-229°, t.l.c. (System A 200:10:1) Rf 0.26.

Example 12

6,7,8,9-Tetrahydro-5-methyl-9-[(5-methyl-1H-imidazol-4-yl)methyl]-cyclohept[b]indol-10(5H)-one maleate

A solution of (E)- and (Z)- 6,7,8,9-tetrahydro-5-methyl-9-[(5-methyl-1H-imidazol-4-yl)methylene]cyclohept[b]-indol-10(5H)-one (0.4g) in ethanol (250ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium oxide on carbon (100mg) for ca. 5h. The catalyst was filtered off and washed with a further quantity of ethanol (100ml). The filtrates were combined and evaporated to leave a gum (0.4g) which was purified by FCC eluting with System A (200:8:1) to give an oil (0.32g). This was dissolved in absolute ethanol (15ml) and treated with a solution of maleic acid (120mg) in ethanol (5ml). The resulting solution was concentrated to ca. 5ml and diluted with dry ether (5ml) to precipitate the title compound (0.41g), m.p. 160-162°.

Analysis Found: C,64.9; H,6.0; N,9.8;
$C_{19}H_{21}N_3O.C_4H_4O_4$ requires C,65.2; H,6.0; N,9.9%.

Example 13

1,2,3,9-Tetrahydro-9-methyl-3-[(1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

A solution of 1,2,3,9-tetrahydro-9-methyl-3-[(1H-imidazol-4-yl)methylene]-4H-carbazol-4-one (1.37g) in ethanol (100ml) was hydrogenated at atmospheric pressure and room temperature over a 10% palladium on charcoal catalyst (50% aqueous paste; 130mg). After ca. 30 min. a precipitate formed and THF (ca. 30ml) was added to redissolve the precipitate. The mixture was stirred for a further 4h and was then filtered. The filtrate was treated with maleic acid (569mg) and the resultant solution was evaporated to give a solid which was recrystallised from a mixture of methanol and ethyl acetate to give the title compound (1.35g), m.p. 175-177°.

Analysis Found: C,64.2; H,5.5; N,10.6;
$C_{17}H_{17}N_3O.C_4H_4O_4$ requires C,63.8; H,5.4; N,10.6%.

Example 14

1,2,3,4-Tetrahydro-N,N-dimethyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4-oxo-9H-carbazole-9-carboxamide maleate

A solution of Intermediate 7 (500mg) in dry DMF (3mℓ) was added dropwise to a stirred suspension of sodium hydride (52% discersion in oil; 53mg) in dry DMF (1mℓ) under nitrogen. After 20 min. dimethylcarbamyl chloride (0.11mℓ) was added and the mixture was stirred for 2h. Water (50mℓ) was added and the suspension was extracted with dichloromethane (3x25mℓ). The combined, dried organic extracts were evaporated to give an oil (ca. 800mg) which was dissolved in a mixture of THF (10mℓ), acetic acid (10mℓ) and water (10mℓ) and heated at reflux for 1.5h. The mixture was poured into saturated potassium carbonate solution (60mℓ) and extracted with dichloromethane (3x30mℓ). The combined, dried organic extracts were evaporated to give an oil (ca. 800mg) which was purified by FCC eluting with System A (200:10:1) to give a foam (188mg). This was dissolved in ethanol (3mℓ) and treated with a solution of maleic acid (64mg) in ethanol (0.5mℓ). The solvent was removed in vacuo and the residue was triturated with dry ether (5x5mℓ) to give the title compound (195mg), m.p. 157-158°.

Analysis Found: C,61.4; H,5.7; N,11.8;

$C_{20}H_{22}N_4O_2.C_4H_4O_4$ requires C,61.8; H,5.6; N,12.0%.

Examples 15 and 16 were prepared in a similar manner to Example 14.

Example 15

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-(phenylsulphonyl)-4H-carbazol-4-one maleate

Intermediate 7 (500mg) was reacted with benzene sulphonyl chloride (0.15mℓ) to give the title compound (215mg), m.p. 154-156°.

Analysis Found: C,60.3; H,4.7; N,7.5;

$C_{23}H_{21}N_3O_3S.C_4H_4O_4$ requires C,60.6; H,4.7; N,7.9%.

Example 16

Methyl 1,2,3,4-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4-oxo-9H-carbazole-9-acetate maleate

Intermediate 7 (500mg) was reacted with methyl chloroformate (0.09mℓ) to give the title compound (155mg), m.p. 167-168°.

Analysis Found: C,60.8; H,5.0; N,9.1;
$C_{19}H_{19}N_3O_3.C_4H_4O_4$ requires C,60.9; H,5.1; N,9.3%.

Example 17

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-(2-propenyl)-4H-carbazol-4-one maleate

A solution of Intermediate 7 (500mg) in dry DMF (10mℓ) was added dropwise to a stirred suspension of sodium hydride (73% oil dispersion; 36mg) in dry DMF under nitrogen and the resulting suspension was stirred at room temperature for 30 min, then a solution of allyl bromide (121mg) in dry DMF (1mℓ) was added and the resulting solution was stirred at room temperature for 1h. The reaction mixture was then poured into water (500mℓ) and extracted with dichloromethane (4x100mℓ). The combined organic extracts were washed with water (3x250mℓ), dried and concentrated to give an oil which was dissolved in a mixture of THF (5mℓ), water (5mℓ) and acetic acid (5mℓ) and heated at reflux for 1.5h. After cooling, the solution was basified with 2N sodium carbonate solution and then extracted with dichloromethane (2x50mℓ). The combined, dried organic extracts were concentrated to give an oil which was purified by FCC eluting with System A (150:8:1) to give the free base of the title compound (151mg) as a solid. This was dissolved in dry methanol (20mℓ), maleic acid (55mg) was added and the resulting solution was heated on a steam bath for 10 min. The solution was then cooled, and ether (10mℓ) was added to precipitate the title compound (174mg), m.p. 194-196°.

Analysis Found: C,65.7; H,6.0; N,9.3;
$C_{20}H_{21}N_3O.C_4H_4O_4$ requires C,66.1; H,5.8; N,9.65%.

Example 18

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-(cyclopentyl)-4H-carbazol-4-one maleate

A solution of Intermediate 7 (750mg) in dry DMF (30mℓ) was added to a stirred suspension of sodium hydride (73% oil dispersion; 50mg) in dry DMF (5mℓ) under nitrogen and the resulting mixture was stirred

at room temperature for 30 min. A solution of bromocyclopentane (223g) in dry DMF (5mℓ) was added and the resulting solution was stirred at room temperature under nitrogen for 8h and then at 100-110° for a further 18h. After cooling the reaction mixture was poured into water (500mℓ) and the resulting suspension was extracted with dichloromethane (3x100mℓ). The combined organic extracts were washed with water (2x500mℓ), dried and concentrated to give an oil which was adsorbed onto FCC silica. FCC eluting with System A (100:8:1) gave the free base of the title compound as an oil (77mg). This was dissolved in dry methanol (10mℓ), maleic acid (26mg) was added and the resulting solution was heated on a steam bath for 10 min. The solution was cooled and ether (10mℓ) was added to precipitate the title compound (82mg), m.p. 194-196°, t.l.c. (System A 100:8:1) Rf 0.35.

Example 19

1,2,3,9-Tetrahydro-9-methyl-3-[(1-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

1,2,3,9-Tetrahydro-9-methyl-3-[(1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate (600mg) was treated with 8% aqueous sodium bicarbonate (70mℓ) and extracted with dichloromethane (3x25mℓ). The combined, dried organic extracts were evaporated to give a foam (483mg) which was dissolved in dry DMF (25mℓ) at 5° and treated with sodium hydride (73% dispersion in oil; 59mg). The mixture was stirred at 5° for 20 min. and was treated with methyl iodide (0.95mℓ). The solution was stirred for a further 1h and was treated with 8% aqueous sodium bicarbonate (10mℓ). The suspension was diluted with water (120mℓ) and extracted with dichloromethane (3x40mℓ). The combined, dried organic extracts were evaporated to give a solid (641mg) which was purified by FCC. Gradient elution with System A (100:3:0.3 → 100:10:1) gave a wax (432mg) which was purified by high performance liquid chromatography (h.p.l.c.) (Spherisorb 5 sw column 25cm x 20mm) eluting with chloroform:hexane:methanol:water 200:80:15:1 at 20mℓ min^{-1} giving, as the first eluted u.v. active component, an oil (110mg). A solution of this oil and maleic acid (44mg) in ethanol (15mℓ) was evaporated to dryness to give the title compound (154mg) as a solid, m.p. 138-141°, t.l.c. (System A 100:10:1) Rf 0.4.

Example 20

1,2,3,9-Tetrahydro-9-methyl-3-[(3-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

Further elution of the h.p.l.c. column of Example 19 gave a solid (50mg). A solution of this solid and maleic acid (20mg) in ethanol (10mℓ) was evaporated to dryness to give the title compound (70mg), m.p. 122-125°, t.l.c. (System A 100:10:1) Rf 0.4.

Example 21

1,2,3,9-Tetrahydro-6-hydroxy-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

Boron tribromide (1M in dichloromethane; 1.4mℓ) was added dropwise to a cold (0°) stirred solution of 1,2,3,9-tetrahydro-6-methoxy-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl-]-4H-carbazol-4-one (150mg) in dry dichloromethane (15mℓ) under nitrogen. After 1h methanol (10mℓ) was added and the solution was evaporated. The residue was purified by FCC eluting with System A (100:10:1) to give a solid (83mg) which was dissolved in ethanol (ca. 20mℓ) and treated with a solution of maleic acid (32mg) in ethanol (ca. 2mℓ). The solvent was removed in vacuo and the residue was triturated with dry ether (3x25mℓ) to give the title compound (90mg), m.p. 197-199°, t.l.c. (System A 100:10:1) Rf 0.33.

Example 22

3,4-Dihydro-4-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]cyclopent[b]indol-1(2H)-one maleate and hemimaleate

A solution of lithium diisopropylamide (1.5M in cyclohexane; 6mℓ) was added dropwise to a cold (-70°) stirred suspension of 3,4-dihydro-4-methylcyclopent[b]indol-1(2H)-one (1.5g) in dry THF (90mℓ) under nitrogen. The resulting solution was stirred at -70° for 15 min. and at 20° for 30 min. The solution was then recooled to -70° and treated with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (3.0g). The mixture was stirred at -70° for 2h and then at 20° for 2h and quenched with acetic acid (30mℓ) and water (30mℓ). The resulting mixture was left overnight and then heated on a steam bath for 1h, cooled and partitioned between ethyl acetate (200mℓ; discarded) and 2N hydrochloric acid (2x100mℓ). The acidic aqueous layer was basified (to

pH 9) with potassium carbonate and extracted with a mixture of ethyl acetate:ethanol (20:1; 3x150mℓ). The combined, dried organic extracts were evaporated to leave a foam (ca. 2g) which was purified by FCC eluting with System A (150:8:1) to give a solid (0.72g) which was triturated with absolute ethanol (5mℓ). This solid (0.45g) was dissolved in hot absolute ethanol (20mℓ) and treated with a solution of maleic acid (187mg) in ethanol (5mℓ). The resulting solution was concentrated to ca. 5mℓ and diluted with dry ether (10mℓ) to precipitate a solid (0.6g) which was recrystallised from a mixture of ethyl acetate:methanol (15:1; ca. 15mℓ) to give the title compound hemimaleate; 0.2g), m.p. 207-208°.

Water Analysis Found 0.211 % w/w ≡ 0.04 mol H_2O.

Analysis Found: C,67.1;H,5.7;N,12.2;

$C_{17}H_{17}N_3O.0.5C_4H_4O_4.0.04H_2O$ requires C,67.5;H,5.7;N,12.4%.

A second crop of the title compound (full maleate salt; 0.3g) was also obtained, m.p. 143-145°, t.l.c. (System A 75:8:1) Rf 0.26.

Example 23

6-Fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl) methyl]-4H-carbazol-4-one maleate

A solution of 3-methoxy-6-[(5-methyl-1-(triphenylmethyl)-1H-imidazol -4-yl)methyl]-2-cyclohexen-1-one (1.2g) in a mixture of water (15mℓ) and 2N hydrochloric acid (2.7mℓ) was stirred under nitrogen for 18h. 1-Methyl-1-(4-fluorophenyl)hydrazine (378mg) was added and the suspension was stirred at reflux under nitrogen for 2h. The cooled mixture was poured into 8% aqueous sodium bicarbonate (60mℓ) and extracted with ethyl acetate (2x50mℓ). The combined, dried organic extracts were evaporated to give an oil (ca. 1.2g) which was purified by SPCC eluting with System A (923:70:7) to give the free base of the title compound (240mg) as a powder. This was dissolved in hot ethanol (15mℓ), a solution of maleic acid (99mg) in warm ethanol (2mℓ) was added and the resultant solution was evaporated. The solid residue was crystallised from ethanol (6mℓ) to give the title compound (175mg), m.p. 148-150°.

Water Analysis Found 2.17% w/w ≡ 0.53 mol H_2O.
Analysis Found: C,60.5; H,5.2; N,9.4;
$C_{18}H_{18}FN_3O.C_4H_4O_4.0.53H_2O$ requires C,60.5; H,5.3; N,9.6%.

Example 24

1,2,3,9-Tetrahydro-6,9-dimethyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

In a similar manner to that described in Example 23, 3-methoxy-6-[(5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl)methyl]-2-cyclohexen-1-one (1.14g) was reacted with 1-methyl-1-(4-methylphenyl)hydrazine (350mg). Purification by SPCC eluting with System A (934:60:6) gave the free base of the title compound (350mg) as a solid. Maleate formation gave the title compound (205mg), m.p. 150-152°.
Analysis Found: C,64.8; H,5.8; N,9.7;
$C_{19}H_{21}N_2O.C_4H_4O_4$ requires C,65.2; H,6.0; N,9.9%

Example 25

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-(phenylmethyl)-4H-carbazol-4-one maleate

A solution of 1,2,3,9-tetrahydro-3-[[5-methyl-1-(triphenylmethyl)-1H- imidazol-4-yl]methyl]-9-(phenylmethyl)-4H-carbazol-4-one (240mg) in a mixture of acetic acid (7mℓ), water (7mℓ) and THF (7mℓ) was heated at reflux for 2h. The mixture was poured into saturated potassium carbonate solution (40mℓ) and extracted with dichloromethane (3x20mℓ). The combined, dried organic extracts were evaporated to give a solid (256mg) which was purified by SPCC eluting with System A (200:10:1) to give a solid (99mg). This was dissolved in ethanol (3mℓ) and treated with a solution of maleic acid (33mg) in ethanol (1mℓ). The solvent was removed in vacuo and the residue was triturated with dry ether to give the title compound (128mg), m.p. 142-144°.
Water Analysis Found 0.27% w/w ≡ 0.07mol H_2O.
Analysis Found: C,68.7; H,5.6; N,8.5;
$C_{24}H_{23}N_3O.C_4H_4O_4.0.07H_2O$ requires C,69.1; H,5.6; N,8.6%.

Examples 26 and 27 were prepared in a similar manner to Example 25 from the appropriate protected intermediate.

Example 26

9-(Cyclopentylmethyl)-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one maleate

The deprotection of 1,2,3,9-tetrahydro-9-(cyclopentylmethyl)-3-[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl-4H-carbazol-4-one (255mg) gave the free base of the title compound (127mg). Maleate formation gave the title compound (144mg), m.p. 178-180°.

Water Analysis Found: 0.37 % w/w≡0.1mol H_2O

Analysis Found: C,67.3; H,6.2; N,8.9;

$C_{23}H_{27}N_3O.C_4H_4O_4.0.1H_2O$ requires C,67.7; H,6.6; N,8.8%.

Example 27

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-(2-propynyl)-4H-carbazol-4-one maleate

The deprotection of 1,2,3,9-tetrahydro-3-[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl)methyl]-9-(2-propynyl)-4H-carbazol-4-one (90mg) and purification by FCC gave the free base of the title compound (30mg). Maleate formation gave the title compound (40mg), m.p. 189-191°.

Water Analysis Found 1.4% w/w ≡ 0.34mol H_2O.

Analysis Found: C,65.0; H,5.4; N,9.1.

$C_{20}H_{19}N_3O.C_4H_4O_4.0.34H_2O.0.125C_2H_5OH$ requires C,65.4; H,5.5; N,9.4%.

Example 28

(E)-1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl) methylene]-4H-carbazol-4-one methanesulphonate

Lithium diisopropylamide (from n-butyllithium, 1.55M in hexane; (57.3mℓ) and diisopropylamine (11.64mℓ) in THF (45mℓ)) was added dropwise over 15 min. at -5° under nitrogen to a stirred suspension of 1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one (15g) in THF (510mℓ). After 45 min., Intermediate 2 (26.5g) was added in one portion and the resultant solution was stirred at -5 to +5° for 1.75h. The solution was treated with acetic acid at below 20° and stirred for 1h. Methanesulphonic acid (34mℓ) was added and the mixture was stirred and heated under reflux for 16h. The resultant suspension was cooled to

5°, stirred at below 5° for 1h and the solid was filtered off. The product was washed with THF (2x50mℓ) and dried in vacuo at 50° to give a solid (28.5g) which was recrystallised from methanol to give the title compound (17g), m.p. 264.5-267°.

Analysis Found : C,54.5; H,5.3; N,9.75;

$C_{18}H_{17}N_3O.1.4CH_4O_3S$ requires C,54.7; H,5.35; N,9.9%.

Example 29

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

A solution of (E)-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methylene] methanesulphonate (10g) in methanol (150mℓ) and triethylamine (3.6mℓ) was hydrogenated at room temperature and atmospheric pressure over a suspension of pre-reduced 10% palladium oxide on carbon catalyst (aqueous paste; 1g) in methanol (10mℓ). The mixture was then filtered, concentrated to ca. 100mℓ and heated to reflux. Water (50mℓ) was added and the solution was cooled to 0°. The resultant solid was filtered off, washed with water (ca. 50mℓ) and dried in vacuo at 50° to give the title compound (3.80g). The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained for the product of Example 8.

Example 30

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-methyl-4H-carbazol-4-one hydrochloride monohydrate

A suspension of 1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-methyl-4H-carbazol-4-one (20g) in IMS (200mℓ) was heated to boiling and 2N hydrochloric acid (50mℓ) was added. The resulting solution was allowed to cool to 20°, the resultant suspension was stirred for 1h and then cooled at 4° for 2h. The product was filtered off and dried in vacuo at 55° to yield the title compound (20.8g), m.p. ~290° (decomp.).

Analysis Found: C,62.1; H,6.25; N,12.05; Cℓ,9.85;

$C_{18}H_{19}N_3O.HCℓ.H_2O$ requires C,62.5; H,6.4; N,12.15; Cℓ,10.25%.

Example 31

(+)-1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

A solution of (±)-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one (500mg) in warm methanol (30mℓ) was treated with a solution of (+)-2,3-bis-[[(4-methylphenyl) carbonyl]oxy] butanedioic acid (690mg) in methanol (10mℓ) and the solution was allowed to stand at 0^0 for 3 days. It was then filtered to leave a solid which was recrystallised from methanol to give the desired salt (195mg), m.p. 146-148^0. A portion of this salt (186mg) was suspended in water (10mℓ) and potassium carbonate solution (1g in 15mℓ water) was added and the mixture was extracted with dichloromethane (2x40mℓ). The combined, dried organic extracts were evaporated in vacuo to leave the title compound (79.2mg) as a solid, m.p. 230-232^0, $[\alpha]_D^{20}$ = +49.7^0 (c.= 0.41%, $CHCl_3$).

Example 32

(-)-1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

A solution of (±)-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol -4-yl)methyl]-4H-carbazol-4-one (500mg) in warm methanol (30mℓ) was treated with a solution of (-)-2,3-bis-[[(4-methylphenyl) carbonyl]oxy] butanedioic acid (690mg) in methanol (10mℓ) and the solution was allowed to stand at 0^0 for 3 days. It was then filtered to leave a solid which was recrystallised from methanol to give the desired salt (162mg), m.p. 147-149^0. This was suspended in water (15mℓ) and potassium carbonate solution (1g in 10mℓ water) was added, and the mixture was extracted with dichloromethane (2x30mℓ). The combined, dried organic extracts were evaporated in vacuo to leave the title compound (72.5mg) as a solid, m.p. 230-232^0, $[\alpha]_D^{20}$ -48.4^0 (c.= 0.44%, $CHCl_3$).

Example 33

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

A solution of Intermediate 7 (190mg) in dry DMF (1mℓ) was added dropwise to a stirred suspension of sodium hydride (52% dispersion in oil; 20mg) in dry DMF (0.4mℓ) under nitrogen. After 15 min. iodomethane (0.027mℓ) was added and the mixture was stirred for 1.5h. Water (20mℓ) was added and the suspension was extracted with dichloromethane (3x10mℓ). The combined, dried organic extracts were evaporated to give an oil (ca. 300mg) which was dissolved in a mixture of THF (4mℓ), acetic acid (4mℓ) and water (4mℓ) and heated at reflux for 1.5h. The mixture was poured into saturated potassium carbonate solution (20mℓ) and extracted with dichloromethane (3x10mℓ). The combined, dried organic extracts were evaporated to give a semi-solid (ca. 255mg) which was purified by SPCC eluting with System A (200:10:1) to give the title compound (7mg). The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained for the product of Example 8.

Example 34

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

n-Butyllithium (1.45M in hexane; 2.07mℓ) was added dropwise to a cold (-70^0) stirred solution of diisopropylamine (0.42mℓ) in dry THF (20mℓ) under nitrogen. The solution was allowed to reach 0^0 over 30 min, cooled to -70^0 and added to a cold (-70^0) stirred solution of 1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one (500mg) in dry THF (10mℓ under nitrogen. Hexamethylphosphoramide (0.44mℓ) was added and the mixture was allowed to reach 0^0 over 1h. The solution was cooled to -70^0 and a suspension of 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (936mg) in dry THF (15mℓ) was added and the mixture was allowed to reach ca. 20^0 over 2.5h. It was stirred for a further 18h, poured into 8% sodium bicarbonate solution (100mℓ) and extracted with dichloromethane (3x50mℓ). The combined, dried organic extracts were evaporated to give a semi-solid which was treated with a mixture of acetic acid (10mℓ), water (10mℓ) and THF (10mℓ) and heated at reflux for 1.5h. The solution was poured into saturated potassium carbonate solution (100mmℓ) and extracted with dichloromethane (3x50mℓ). The combined, dried organic extracts were evaporated to give a solid (ca. 1.8g) which was purified by SPCC eluting with System A (200:10:1)

to give the title compound (17mg). The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained from the product of Example 8.

Example 35

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl] 4H-carbazole maleate (37mg) was partitioned between 2N bicarbonate (10mℓ) and chloroform (3x15mℓ). The combined, dried organic layers were evaporated to give the free base (26mg) which was dissolved in 10% aqueous THF (4mℓ) at -10° under nitrogen. To this stirred solution, a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (49mg) in dry THF (1.6mℓ) was added dropwise and the reaction mixture was allowed to warm to 0° over 3h. The solution was evaporated in vacuo and purified by FCC eluting with System A (94.5:5:0.5) to give the title compound (10mg) as a solid. The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained for the product of Example 8.

Example 36

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-methyl-4H-carbazol-4-one

3-Methoxy-6-[(5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl) methyl]-2-cyclohexen-1-one (203mg) was treated with a mixture of water (5mℓ) and 2N hydrochloric acid (0.45mℓ) and the resultant solution was stirred at room temperature under nitrogen for 18h. 1-Methyl -1-phenylhydrazine (0.05mℓ) was added dropwise and stirring was continued for 7h. Further 1-methyl-1-phenylhydrazine (0.05mℓ) was added and stirring was continued at room temperature for 5 days. The suspension was poured into 8% aqueous sodium bicarbonate (10mℓ) and extracted with ethyl acetate (3x15mℓ). The combined, dried organic extracts were evaporated to give an oil (ca. 240mg) which was purified by FCC eluting with System A (189:10:1) to give a solid (55mg). A portion of this solid (40mg) was heated at 85° with fused zinc chloride (450mg) in glacial acetic acid (3mℓ) for 5h. The mixture was cooled, poured into 2N aqueous sodium hydroxide (20mℓ) and extracted with ethyl acetate

(3x15mℓ). The combined, dried organic extracts were evaporated to give an oil (ca. 20mg) which was purified by FCC eluting with System A (89:10:1) to give the title compound (5mg). The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained for the product of Example 8.

Example 37

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

A solution of 1,2,3,9-tetrahydro-9-methyl-3-[[5-methyl-(triphenylmethyl)-1H-imidazol-4-yl]methyl]carbazol-4-one (268mg) in a mixture of glacial acetic acid (5mℓ), THF (5mℓ) and water (5mℓ) was heated at 100-110^0 for 8h. After cooling, 2N sodium hydroxide solution (50mℓ) was added and the resulting suspension was extracted with dichloromethane (2x50mℓ). The combined, dried organic extracts were concentrated to give a foam which was purified by FCC eluting with System A (100:8:1) to give the title compound (114mg) as a solid. The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained for the product of Example 8.

Example 38

1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one

A solution of N,N,5-trimethyl-4-[(2,3,4,9-tetrahydro-9-methyl-4-oxo-1H-carbazol-3-yl)methyl]-1H-imidazole-1-sulphonamide (400mg) in 2N hydrochloric acid (30mℓ) and absolute ethanol (5mℓ) was heated at 100-110^0 for 8h. Work up and FCC as described in Example 32 gave the title compound (261mg) as a solid. The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained for the product of Example 8.

Example 39

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-methyl-4H-carbazol-4-one

A solution of the products from Intermediate 16 (0.2g) in 49% hydrobromic acid (3mℓ) was stirred at 20^0 for 30 min. The mixture was

then heated on a steam bath for 30 min. and refluxed gently (at ca. 150°) for 1.5h. The mixture was diluted with water (20mℓ) and washed with ethyl acetate (2x20mℓ; discarded). The acidic aqueous phase was basified (to pH9) with potassium carbonate and extracted with ethyl acetate:ethanol (20:1; 2x30mℓ). The combined, dried organic extracts were evaporated to leave a solid which was triturated with dry ether (5mℓ) to give the title compound (0.09g) as a solid. The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained for the product of Example 8.

Example 40

1,2,3,9-Tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-methyl-4H-carbazol-4-one

A solution of the products from Intermediate 17 (0.5g) in a mixture of absolute ethanol (20mℓ) and 2M hydrochloric acid (10mℓ) was heated on a steam bath for 1h. The resulting solution was concentrated in vacuo to ca. 20mℓ, diluted with water (40mℓ) and washed with ethyl acetate (2x40mℓ; discarded). The acidic aqueous layer was basified (to pH 9) with potassium carbonate and extracted with ethyl acetate:ethanol (20:1; 2x50mℓ). The combined, dried organic extracts were evaporated to give the title compound (0.34g) as a solid. The ^{1}H-n.m.r. and t.l.c. of this material were consistent with those obtained for the product of Example 8.

The following examples illustrate pharmaceutical formulations according to the invention, containing 1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one as the active ingredient. Physiologically acceptable salts and/or solvates of this compound, 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

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

Sub-Lingual Tablet	mg/tablet
Active Ingredient	0.5
Compressible Sugar NF	64.5
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
Active Ingredient	0.5
Lactose BP	153.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
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 7mm 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
Active Ingredient	0.5
Mannitol BP	58.5
Hydroxypropylmethylcellulose	5.0
Magnesium Stearate BP	1.0
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/tablet
Active Ingredient	0.5
* Starch 1500	98.5
Magnesium Stearate BP	1.0
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 suitable machinery. Other doses may be prepared by altering the fill weight and 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
Active Ingredient		0.5
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
Active Ingredient	0.5
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

	mg/mℓ	
Active ingredient	0.05	0.5
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.

METERED DOSE PRESSURISED AEROSOL

Suspension Aerosol	mg/metered dose	Per can
Active Ingredient micronised	0.050	12.0mg
Oleic Acid BP	0.020	4.80mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is mixed with the Trichlorofluoromethane at a temperature of 10-15^{0}C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85mg of suspension are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

Solution Aerosol

	mg/metered dose	Per can
Active Ingredient	0.05	12.0mg
Ethanol BP	7.500	1.80g
Trichlorofluoromethane BP	18.875	4.53g
Dichlorodifluoromethane BP	48.525	11.65g

Oleic Acid BP, on a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included).

The active ingredient is dissolved in the ethanol together with the Oleic Acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoro-methane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

SPAN is a Registered Trade Mark.

Inhalation Cartridges

	mg/cartridge
Active Ingredient (micronised)	0.05
Lactose BP to	25.00

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler.

SUPPOSITORY

Active Ingredient	0.5mg
* Witepsol H15 to	1.0g

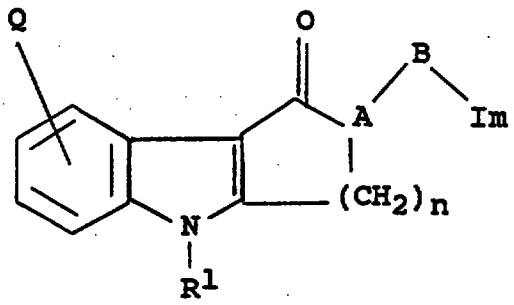
* Witepsol H15 is a proprietary grade of Adeps Solidus Ph. Eur.

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

WITEPSOL is a Registered Trade Mark.

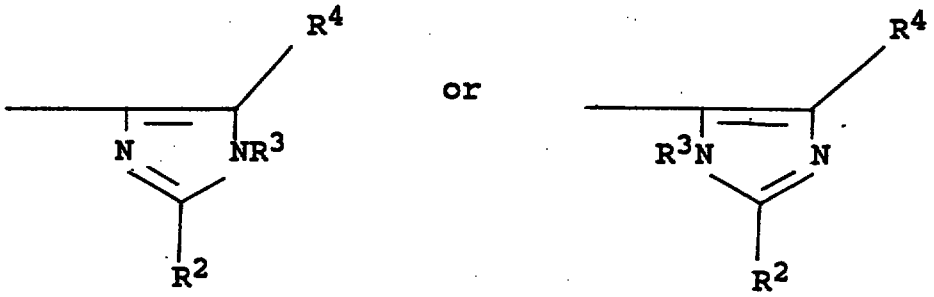
CLAIMS:

1. Compounds of the general formula (I):



(I)

wherein Im represents an imidazolyl group of the formula:



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, $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ or $-SO_2R^5$;

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,

* C L M S *

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;

Q represents a hydrogen or a halogen atom, or a hydroxy, C_{1-4}alkoxy, phenylC_{1-3}alkoxy or C_{1-6}alkyl group or a group $-NR^7R^8$ or $-CONR^7R^8$;

R^7 and R^8, which may be the same or different, each represents a hydrogen atom or a C_{1-4}alkyl or C_{3-4}alkenyl group, or together with the nitrogen atom to which they are attached form a saturated 5 to 7 membered ring;

n represents 1, 2 or 3; and

A-B represents the group $CH-CH_2$ or C=CH;

and physiologically acceptable salts and solvates thereof.

2. Compounds as claimed in claim 1 in which R^1 represents a hydrogen atom or a C_{1-3}alkyl, C_{3-4}alkenyl, C_{3-4}alkynyl, C_{5-6}cycloalkyl, C_{5-6}cycloalkylmethyl, phenyl-C_{1-2}alkyl, C_{1-3}alkoxycarbonyl, N,N-diC_{1-3}alkylcarboxamido or phenylsulphonyl group.

3. Compounds as claimed in claim 1 or 2 in which R^2 represents a hydrogen atom or a C_{1-3}alkyl group.

4. Compounds as claimed in any of claims 1 to 3 in which R^3 represents a hydrogen atom or a C_{1-3}alkyl group.

5. Compounds as claimed in any of claims 1 to 4 in which R^4 represents a hydrogen atom or a C_{1-3}alkyl group.

6. Compounds as claimed in claim 1 or 2 in which R^2 and R^3 each represent a hydrogen atom and R^4 represents a methyl group.

7. Compounds as claimed in any of claims 1 to 6 in which

* C L M S *

Q represents a hydrogen atom, a halogen atom or a hydroxy, C_{1-3}alkoxy or C_{1-3}alkyl group.

8. Compounds as claimed in any of claims 1 to 7 in which A-B represent $CH-CH_2$.

9. Compounds as claimed in any of claims 1 to 8 in which n represents 2 or 3.

10. Compounds as claimed in claim 1 in which R^1 represents a hydrogen atom or a C_{1-3}alkyl, C_{3-4}alkenyl, C_{3-4}-alkynyl, C_{5-6}cycloalkylmethyl, phenylC_{1-2}alkyl, C_{1-3}-alkoxycarbonyl or N,N-diC_{1-3}alkylcarboxamido group; R^2 and R^3 each represent a hydrogen atom; R^4 represents a C_{1-3}alkyl group; Q represents a hydrogen or a halogen atom or a hydroxyl group; A-B represents $CH-CH_2$ or C=CH; and n represents 2 or 3.

11. Compounds as claimed in claim 1 in which R^1 represents a hydrogen atom or a methyl, prop-2-enyl, prop-2-ynyl, cyclopentylmethyl, benzyl or N,N-dimethylcarboxamido group; R^2 and R^3 each represent a hydrogen atom; R^4 represents a methyl group; Q represents a hydrogen or a fluorine atom; A-B represents $CH-CH_2$; and n represents 2 or 3.

12. Compounds as claimed in claim 10 or 11 in which n represents 2.

13. 1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one and physiologically acceptable salts and solvates thereof.

14. The compound of claim 13 in the form of a hydrochloride salt.

* C L M S *

15. 1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one hydrochloride monohydrate.

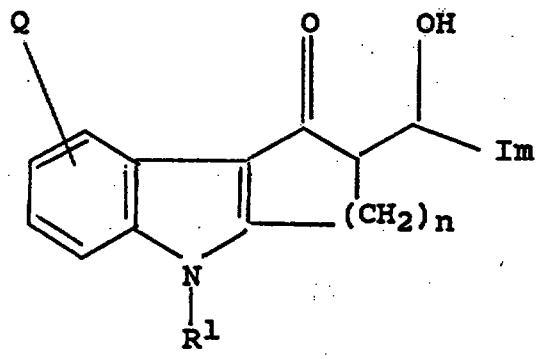
16. (+)-1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one;
(-)-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one;
and physiologically acceptable salts and solvates thereof.

17. 6-Fluoro-1,2,3,9-tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)-methyl]-4H-carbazol-4-one;
1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one;
9-(cyclopentylmethyl)-1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one;
1,2,3,9-tetrahydro-3-[(5-methyl-1H-imidazol-4-yl)methyl]-9-(2-propynyl)-4H-carbazol-4-one;
6,7,8,9-tetrahydro-5-methyl-9-[(5-methyl-1H-imidazol-4-yl)methyl]-cyclohept[b]indol-10(5H)-one;
and physiologically acceptable salts and solvates thereof.

18. A process for the production of a compound of general formula (I) as defined in any of claims 1 to 17 or a physiologically acceptable salt or solvate thereof, which comprises:

(A) for the preparation of a compound of formula (I) in which A-B represents the group C=CH, dehydrating a compound of formula (II)

* C L M S *



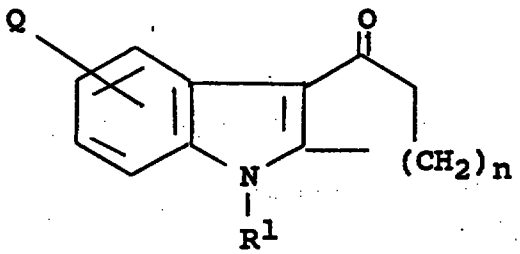
(II)

or a protected derivative thereof, followed if necessary by removal of any protecting groups present; or

* C L M S *

(B) converting a compound of formula (I) into another compound of formula (I) using conventional techniques; or

(C) for the preparation of a compound of formula (I) in which A-B represents the group $CH-CH_2$, reacting a compound of formula (III)



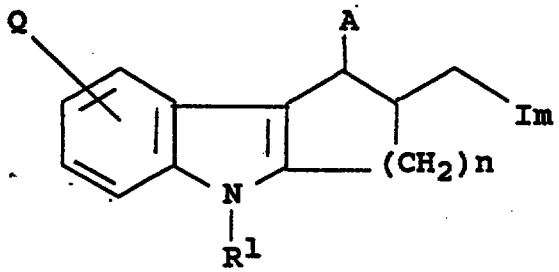
(III)

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

$$LCH_2\text{-}Im \qquad (V)$$

wherein L represents a leaving atom or group, or a protected derivative thereof, in the presence of a base, followed if necessary by removal of any protecting groups present; or

(D) for the preparation of a compound of formula (I) in which A-B represents the group $CH-CH_2$, oxidising a compound of formula (VI)



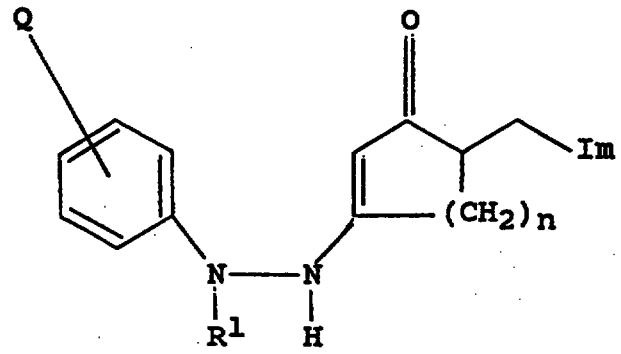
(VI)

wherein A represents a hydrogen atom or a hydroxyl group, or a salt or protected derivative thereof followed if necessary by removal of any protecting groups present; or

(E) for the preparation of a compound of formula

* C L M S *

(I) in which A-B represents the group $CH-CH_2$, cyclising a compound of formula (VII)



(VII)

or a salt or protected derivative thereof, followed if necessary by removal of any protecting groups present; or

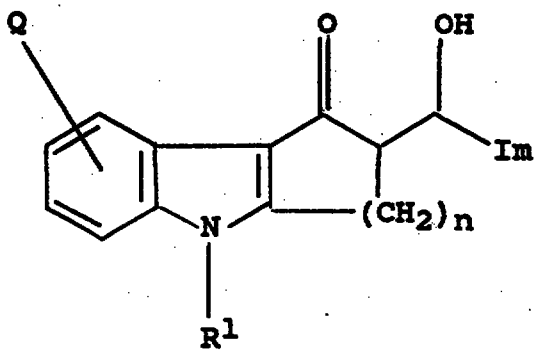
(F) removing protecting group(s) from a protected form of a compound of formula (I);

and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer;

and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

19. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof together with at least one physiologically acceptable carrier or excipient.

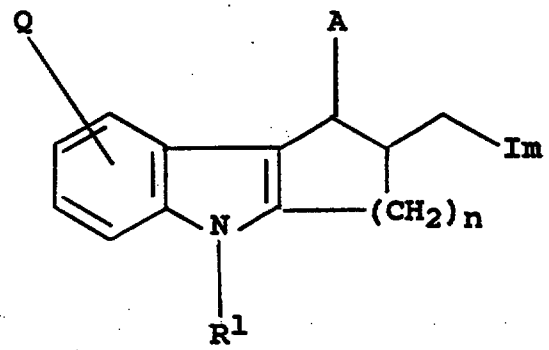
20. Compounds of the general formula (II)



(II)

in which Im, R^1, Q and n are as defined in any of claims 1 to 11.

21. Compounds of the general formula (VI)



(VI)

in which A represents a hydrogen atom or a hydroxyl group and Im, R^1, Q and n are as defined in any of claims 1 to 11.

22. Compounds of the general formula (I) as defined in any of claims 1 to 17 and physiologically acceptable salts and solvates thereof for use in the treatment of a condition caused by disturbance of "neuronal" 5HT function.

23. Compounds of the general formula (I) as defined in any of claims 1 to 17 and physiologically acceptable salts and solvates thereof for use in the treatment of anxiety.

24. Compounds of the general formula (I) as defined in any of claims 1 to 17 and physiologically acceptable salts and solvates thereof for use in the treatment of a psychotic disorder.

25. A pharmaceutical composition for the treatment of a condition caused by disturbance of "neuronal" 5HT function which comprises as active ingredient at least one compound of the general formula (I) as defined in any of claims 1 to 17 or a physiologically acceptable salt or solvate thereof.

26. A pharmaceutical composition for the treatment of

* C L M S *

anxiety which comprises as active ingredient at least one compound of the general formula (I) as defined in any of claims 1 to 17 or a physiologically acceptable salt or solvate thereof.

27. A pharmaceutical composition for the treatment of a psychotic disorder which comprises as active ingredient at least one compound of the general formula (I) as defined in any of claims 1 to 17 or a physiologically acceptable salt or solvate thereof.

28. A therapeutic agent for the treatment of a condition caused by disturbance of "neuronal" 5HT function which comprises as active ingredient at least one compound of the general formula (I) as defined in any of claims 1 to 17 or a physiologically acceptable salt or solvate thereof.

29. A therapeutic agent for the treatment of anxiety which comprises as active ingredient at least one compound of the general formula (I) as defined in any of claims 1 to 17 or a physiologically acceptable salt or solvate thereof.

30. A therapeutic agent for the treatment of a psychotic disorder which comprises as active ingredient at least one compound of the general formula (I) as defined in any of claims 1 to 17 or a physiologically acceptable salt or solvate thereof.

* C L M S *