(12) UK Patent Application (19) GB (11) 2 276 165 (13) A

(43) Date of A Publication 21.09.1994

(21) Application No 9305523.4

(22) Date of Filing 17.03.1993

(71) Applicant(s)
Glaxo Group Limited

(Incorporated in the United Kingdom)

Glaxo House, Berkeley Avenue, GREENFORD, Middlesex, UB6 0NN, United Kingdom

(72) Inventor(s)
William Leonard Mitchell
John Bradshaw
Alexander William Oxford
John Watson Clitherow

(74) Agent and/or Address for Service
C L Brewer
Glaxo Holdings plc, Glaxo House, Berkeley Avenue, GREENFORD, Middlesex, UB6 0NN, United Kingdom

(51) INT CL[5]
C07C 237/40 , A61K 31/135 31/165 31/395 , C07C 215/50 215/74 233/80 323/36 , C07D 207/04 211/06 295/00

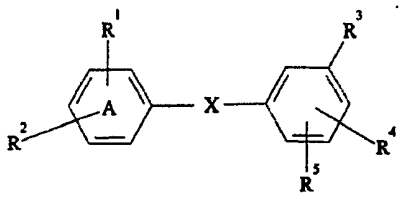
(52) UK CL (Edition M)
C2C CAA CKH CKN CKP CKR CKZ CLG CRC C1341 C1532 C1562 C1626 C202 C215 C22Y C220 C221 C225 C226 C227 C246 C25Y C250 C251 C252 C255 C270 C271 C280 C281 C282 C29X C29Y C30Y C304 C305 C31Y C313 C314 C315 C32Y C322 C323 C338 C34Y C342 C351 C353 C355 C36Y C360 C361 C362 C364 C365 C366 C367 C368 C37Y C373 C45Y C455 C52X C57Y C593 C594 C603 C610 C613 C62X C620 C623 C624 C628 C63X C630 C634 C65X C650 C652 C658 C660 C662 C668 C669 C678 C680 C682 C699 C80Y C800 C802
U1S S1318 S2413 S2414 S2415 S2417 S2418

(56) Documents Cited
EP 0533266 A **EP 0142283 A2**

(58) Field of Search
UK CL (Edition M) **C2C CKH CKJ**
INT CL[5] **C07C , C07D**
ONLINE DATABASE: CAS ONLINE

(54) **Aniline and benzanilide compounds.**

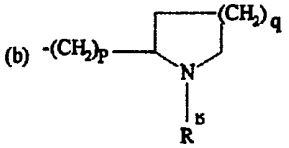
(57) Compounds of the general formula (I):-

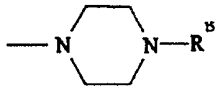


(I)

or a physiologically acceptable salt or solvate thereof, in which
R^1 represents a hydrogen atom or a halogen atom or a C_{1-6}alkyl or C_{1-6}alkoxy group;
R^2 represents a hydrogen atom or a halogen atom, or C_{1-6}alkyl, hydroxy C_{1-6}alkyl, hydroxyC_{3-6}alkenyl, hydroxy C_{3-6}alkynyl, C_{1-6}alkylthio, hydroxy, $-(CH_2)_kOR^6$, $-(CH_2)_kCOR^7$, $-(CH_2)_kCR^7{=}NOR^9$, $-CO_2R^7$, $-O(CH_2)_mR^8$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-SO_2NR^{11}R^{12}$ or C_{5-7}cycloalkyl (optionally substituted by a hydroxy or an oxo group);
R^3 represents a group selected from

(a) 

(b)  or

(c)  ;

(57) continued overleaf

The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1990.

GB 2 276 165 A

(57) cont

R^4 and R^5, which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy, C_{1-6}alkoxy or C_{1-6}alkyl group;

R^6 represents a C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-4}alkanoyl group;

R^7 represents a hydrogen atom or a C_{1-6}alkyl group;

R^8 represents a C_{1-6}alkoxy, $-CO_2R^7$ or $-CONR^9R^{10}$ group;

R^9 and R^{10}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-6}alkyl group, or $-NR^9R^{10}$ forms a saturated heterocyclic ring which has 5 or 6 ring members, may optionally be substituted by an oxo group and, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom or a group -NH- or $-NR^{16}$-;

R^{11}, R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-6}alkyl group;

R^{16} represents a C_{1-6}alkyl, $-COR^7$ or $-CO_2R^7$ group;

X represents -CONH-, -NHCO-, $-CH_2NH-$ or $-NHCH_2-$;

k represents zero or an integer from 1 to 6;

m represents an integer from 1 to 6;

n represents an integer from 2 to 4;

p represents an integer from 1 to 3; and

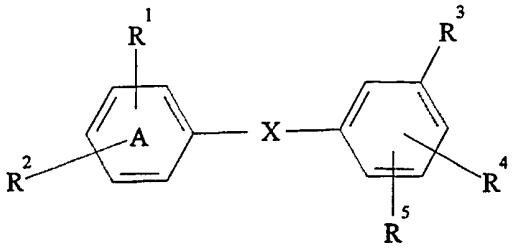
q represents an integer from 1 to 3;

are $5\text{-}HT_{1D}$ antagonists useful in the treatment of CNS disorders, endocrine disorders and sexual dysfunction.

CHEMICAL COMPOUNDS

This invention relates to novel aniline and benzanilide derivatives, to processes for their preparation, and to pharmaceutical compositions containing them.

According to the present invention there is provided compounds of the general formula (I) :-



(I)

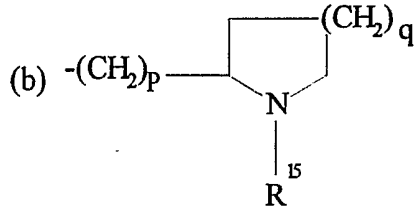
or a physiologically acceptable salt or solvate thereof, in which

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

R^2 represents a hydrogen atom or a halogen atom, or C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyC_{3-6}alkenyl, hydroxyC_{3-6}alkynyl, C_{1-6}alkylthio, hydroxy, $-(CH_2)_kOR^6$, $-(CH_2)_kCOR^7$, $-(CH_2)_kCR^7{=}NOR^9$, $-CO_2R^7$, $-O(CH_2)_mR^8$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-SO_2NR^{11}R^{12}$ or C_{5-7}cycloalkyl (optionally substituted by a hydroxy or an oxo group);

R^3 represents a group selected from

(a) $-(CH_2)_n NR^{13} R^{14}$,

(b)  or

(c)  ;

R^4 and R^5, which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy, C_{1-6}alkoxy or C_{1-6}alkyl group;

R^6 represents a C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-4}alkanoyl group;

R^7 represents a hydrogen atom or a C_{1-6}alkyl group;

R^8 represents a C_{1-6}alkoxy, $-CO_2R^7$ or $-CONR^9R^{10}$ group;

R^9 and R^{10}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-6}alkyl group, or $-NR^9R^{10}$ forms a saturated heterocyclic ring which has 5 or 6 ring members, may optionally be substituted by an oxo group and, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom or a group -NH- or $-NR^{16}$-;

R^{11}, R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-6}alkyl group;

R^{16} represents a C_{1-6}alkyl, $-COR^7$ or $-CO_2R^7$ group;

X represents -CONH-, -NHCO-, $-CH_2NH-$ or $-NHCH_2-$;

k represents zero or an integer from 1 to 6;

m represents an integer from 1 to 6;

n represents an integer from 2 to 4;

p represents an integer from 1 to 3; and

q represents an integer from 1 to 3.

It is to be understood that the present invention encompasses all geometric and optical isomers of the compounds of general formula (I) and their mixtures including the racemic mixtures thereof.

Physiologically acceptable salts of the compounds of formula (I) include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, citrates, oxalates, maleates, salicylates, fumarates, succinates, lactates, glutarates, glutaconates, acetates or tricarballylates) and, where appropriate, inorganic base salts such as alkali metal salts (for example sodium salts).

In the compounds of formula (I), the term "C_{1-6}alkyl" or "C_{1-6}alkoxy" as a group or part of a group means that the group is straight or branched and consists of 1 to 6 carbon atoms. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy. The term "halogen" means fluorine, chlorine, bromine or iodine.

Within the above definition, when or $-NR^9R^{10}$ represents a saturated heterocyclic ring, this contains 5 or 6 ring members, one of which (when there are 6 ring members) may be an oxygen or a sulphur atom or a group -NH- or $-NR^{16}$-. Suitable heterocyclic groups are a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group.

Where a saturated heterocyclic ring is formed by the group $-NR^9R^{10}$ and said ring is substituted by an oxo group, suitable heterocyclic groups include a 2-oxo-1-pyrrolidinyl, 4-oxo-3-thiazolidinyl or 2-oxo-tetrahydro-1,3-thiazinyl group.

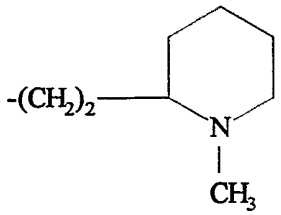
The group R^2 may preferably be attached in the meta or more particularly the para position of the phenyl ring A relative to the group X.

Another preferred group of compounds of general formula (I) is that wherein R^2 represents a hydrogen atom; a halogen atom; or a C_{1-6}alkyl, especially methyl, ethyl or propyl, group; a hydroxyC_{1-6}alkyl, especially 3-hydroxypropyl, 4-hydroxybutyl or 4-hydroxypentyl, group; a hydroxyC_{3-6}alkynyl, especially 4-hydroxybut-1-ynyl or 4-hydroxypent-1-ynyl, group; a C_{1-6}alkylthio, especially methylthio, group; hydroxy; $-(CH_2)_kOR^6$, where R^6 is a C_{1-6}alkyl, especially methyl, ethyl, propyl or butyl, group, or a hydroxyC_{1-6}alkyl, especially 3-hydroxypropyl, group and k is zero; $-(CH_2)_kCOR^7$ where R^7 is a C_{1-6}alkyl, especially methyl, group and k is zero, 1, 2 or 3; $-CO_2R^7$ where R^7 is a hydrogen atom or a C_{1-6}alkyl, especially ethyl, group; $-O(CH_2)_mR^8$ where R^8 is $-CO_2R^7$ (where R^7 is a hydrogen atom or a C_{1-6}alkyl, especially ethyl, group) or $-CONH_2$ and m is 4; $-NR^9R^{10}$ where $-NR^9R^{10}$ forms a pyrrolidinyl, morpholinyl, piperazinyl or piperazinecarboxylate group; $-CONH_2$; or a C_{5-7}cycloalkyl, especially cyclohexyl, group, optionally substituted by a hydroxy or an oxo group.

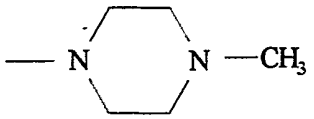
Also preferred is the group of compounds of general formula (I) wherein R^1 is a hydrogen atom or a C_{1-6}alkyl, especially methyl, group.

Another preferred group of compounds of general formula (I) is that wherein R^1 is attached at a position ortho to the group R^2 in general formula (I).

A further preferred group of compounds of general formula (I) is that wherein R^3 represents $-(CH_2)_3N(CH_3)_2$, $-(CH_2)_3NHCH_3$,



or



Another preferred group of compounds of general formula (I) is that wherein R^4 is attached in the para-position relative to the group X.

A further preferred group of compounds of general formula (I) is that wherein R^4 is a halogen atom, especially a fluorine or chlorine atom, or a hydroxy or C_{1-6}alkoxy, especially methoxy, group.

Also preferred is the group of compounds of general formula (I) wherein R^5 is a hydrogen atom or a fluorine atom.

A yet further preferred group of compounds of general formula (I) is that wherein R^{13}, R^{14} and R^{15} each represent a C_{1-6}alkyl, especially methyl, group.

Also preferred is the group of compounds of general formula (I) wherein X is -NHCO- or -CONH-.

Another preferred group of compounds of general formula (I) is that wherein n is 3.

A further preferred group of compounds of general formula (I) is that wherein p is 2.

Preferred compounds of general formula (I) include:

N-[4-[(5-amino-5-oxopentyl)oxy]phenyl]-3-[(dimethylamino)propyl]-4-methoxy benzamide;

3-[3-(dimethylamino)propyl]-4-methoxy-N-[4-(4-oxopentyl)phenyl]benzamide;

methyl 4-[4-[[[3-[3-(dimethylamino)propyl]-4-methoxyphenyl]carbonyl]amino]phenyl]-4-piperazinecarboxylate;

N-(4-ethoxyphenyl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide;

and their physiologically acceptable salts and solvates

Particularly preferred compounds of general formula (I) include:

3-[3-(dimethylamino)propyl]-N-[4-(4-hydroxy-1-butynyl)phenyl]-4-methoxybenzamide;

3-[3-(dimethylamino)propyl]-N-[4-(4-hydroxybutyl)phenyl]-4-methoxybenzamide;

3-[3-(dimethylamino)propyl]-N-(4-hydroxyphenyl)-4-methoxybenzamide;

3-[3-(dimethylamino)propyl]-N-[4-(4-hydroxy-1-pentynyl)phenyl]-4-methoxybenzamide;

cis-3-[3-(dimethylamino)propyl]-N-[4-(4-hydroxycyclohexyl)phenyl]-4-methoxybenzamide;

3-[3-(dimethylamino)propyl]-4-methoxy-N-[4-(4-oxocyclohexyl)phenyl]benzamide;

N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-4-(4-oxocyclohexyl)benzamide;

and their physiologically acceptable salts and solvates.

5-Hydroxytryptamine (serotonin) is a neurotransmitter which is widely distributed within the central nervous system (CNS), platelets and the gastrointestinal tract. Changes in transmission in serotonergic pathways in the CNS are known to modify, for example, mood, psychomotor activity, appetite, memory and blood pressure. Release of 5-hydroxytryptamine from platelets can mediate vasospasm while changes in free 5-hydroxytryptamine levels in the gastrointestinal tract can modify secretion and motility.

Abundant pharmacological studies have led to the discovery of multiple types of receptors for 5-hydroxytryptamine, thus providing a molecular basis to the diversity of its actions. These receptors are classed as 5-HT_1, 5-HT_2 and 5-HT_3, with 5-HT_1 receptors being sub-classified as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D} and 5-HT_{1D}(like) receptors. The identification of these classes and sub-classes of receptor is based mainly on radioligand binding studies.

Compounds having a selective antagonist action at 5-HT_{1D} receptors such as those described herein may exhibit a beneficial effect on subjects suffering from CNS disorders.

In the present specification, a 5-HT_{1D} antagonist is a non-naturally occurring (synthetic) compound that specifically and selectively antagonises 5-HT_{1D} receptors, i.e. blocks the specific actions of 5-hydroxytryptamine mediated by 5-HT_{1D} receptors. Such compounds may be identified by a high level of affinity (pKi $\geq$ 8) in the <u>in vitro</u> human cortex and guinea-pig striatum radioligand binding assays described by Hoyer *et al*, Neuroscience Letters, 1988, <u>85</u>, p357-362. Activity at 5-HT_{1D} receptors may be

confirmed *in vivo* using the guinea pig rotation model described by G A Higgins *et al*, Br. J. Pharmacol., 1991, 102, p305-310.

The affinity of a compound for 5-HT_{1A}, 5-HT_{1C} and/or 5-HT_2 receptors is measured using the *in vitro* tests described in the following publications:

5-HT_{1A}	Gozlan *et al*, Nature, 1983, 305, p140-142
5-HT_{1C}	Pazos *et al*, Eur. J.Pharmacol., 1984, 106, p531-538
5-HT_2	Humphrey *et al*, Br. J. Pharmacol, 1988, 94, p1123-1132 (rabbit aorta model).

Thus, for example, compounds of the present invention have been shown to inhibit 5-hydroxytryptamine induced contraction of the dog isolated saphenous vein and to antagonise the 5-hydroxytryptamine induced inhibition of neurotransmission in central and peripheral neurones.

5-HT_{1D} antagonists, and in particular the compounds of the present invention, may therefore be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal affective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviour, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

5-HT_{1D} antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, according to a second aspect of the invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

According to a further aspect of the present invention, we therefore provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

According to another aspect of the invention, we provide the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a therapeutic agent for the treatment of the aforementioned disorders.

According to a further aspect of the invention, we provide, a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof.

In particular, according to another aspect of the present invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as tricyclic antidepressants (e.g. amitriptyline, dothiepin, doxepin, trimipramine, butriptyline, clomipramine, desipramine, imipramine, iprindole, lofepramine, nortriptyline or protriptyline), monoamine oxidase inhibitors (e.g. isocarboxazid, phenelzine or tranylcyclopramine) or 5-HT reuptake inhibitors (e.g. fluvoxamine, sertraline, fluoxetine or paroxetine), and/or antiparkinsonian agents such as dopaminergic antiparkinsonian agents (e.g. levodopa, preferably in combination with a peripheral decarboxylase inhibitor e.g. benserazide or carbidopa), or a dopamine agonist (e.g. bromocriptine, lysuride or pergolide). It is to be understood that the present invention covers the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof in combination with one or more other therapeutic agents.

Thus there is provided in a further or alternative aspect of the present invention a compound of general formula (I) or a physiologically acceptable salt or solvate thereof and an antidepressant agent in the presence of each other in the human or non-human animal body for use in the treatment of the aforementioned disorders.

While it is possible that a compound of general formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The compounds of general formula (I) and their physiologically acceptable salts and solvates may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof. Such compositions may be presented for use in a conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Thus, the compositions according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methylcellulose, glucose/sugar syrup, gelatin, hydroxypropyl methylcellulose,

carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

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

The composition according to the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dose form 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.

For administration by inhalation either orally or nasally the compositions according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The pharmaceutical formulations according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compositions according to the invention may be prepared by mixing the various ingredients using conventional means.

It will be appreciated that the amount of a compound of general formula (I) required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or veterinarian. In general, however, a proposed dose of the compounds of the invention for administration in man is 0.5 to 1000mg, preferably 1 to 200mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

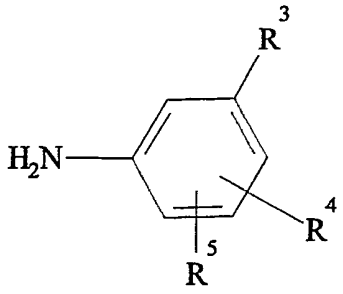
The compounds of the invention may be prepared by a number of processes as described in the following. In describing the processes which may be used for preparing the compounds of general formula (I) or intermediates useful in the preparation thereof, any of R^1-R^{16}, k, m, n, p and q in the various formulae are as defined in general formula (I) unless otherwise stated.

It will be appreciated that in the following methods for the preparation of compounds of general formula (I), for certain reaction steps it may be necessary to protect various reactive substituents in the starting materials for a particular reaction and subsequently to remove the protecting group. Such protection and subsequent deprotection may be particularly pertinent where R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and/or R^{15} in intermediates used to prepare compounds of general formula (I) are hydrogen atoms. Standard protection and deprotection procedures can be employed, for example formation of a phthalimide (in the case of a primary amine), benzyl, trityl, benzyloxycarbonyl or trichloroethoxycarbonyl derivatives. Subsequent removal of the protecting group is achieved by conventional procedures. Thus a phthalimide group may be removed by treatment with hydrazine or a primary amine, for example methylamine. Benzyl or benzyloxycarbonyl groups may be removed by hydrogenolysis in the presence of a catalyst e.g. palladium, and trichloroethoxycarbonyl derivatives may be removed by treatment with zinc dust. Trityl groups may be removed under acidic conditions using standard procedures.

It may also be necessary in some cases to protect carboxylic acid groups (e.g. as esters) or aldehyde or ketone groups (e.g. as acyclic or cyclic acetals or ketals or as thioacetals or thioketals). Subsequent removal of these protecting groups is achieved by conventional procedures. Thus for example alkyl esters may be removed under conditions of acidic or basic hydrolysis, benzyl esters may be removed by hydrogenolysis in the presence of a catalyst e.g. palladium. Acyclic or cyclic acetals or ketals may be removed under conditions of acidic hydrolysis and thioacetals and thioketals may be removed using a mercuric salt.

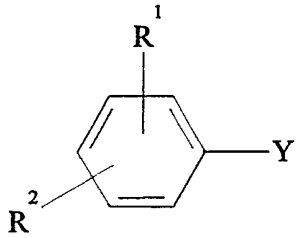
Hydroxyl groups may also need protection and these may be adequately protected under amenable conditions as their esters or trialkylsilyl, tetrahydropyran and benzyl ethers. Such derivatives may be deprotected by standard procedures.

According to one general process (1A), the compounds of general formula (I) in which X represents the group -CONH-, may be prepared by a carbonylation reaction involving an aniline (II)



(II)

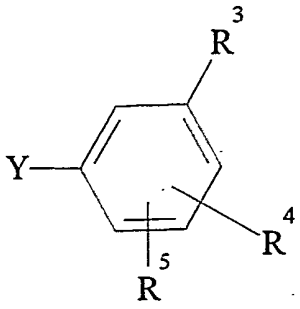
(where R^3, R^4 and R^5, are as defined in general formula (I)) and a halophenyl compound (III)



(III)

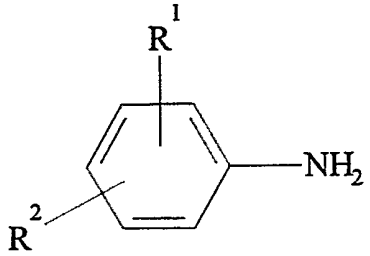
(where R^1 and R^2 are as defined in general formula (I) and Y is a bromine or iodine atom or the group $-OSO_2CF_3$) .

Alternatively, according to the general process (1B), the compounds of general formula (I), in which X represents the group -NHCO-, may be prepared by a carbonylation reaction involving a halophenyl compound (IV)



(IV)

(where R^3, R^4, and R^5 are as defined in general formula (I) and Y represents a bromine or iodine atom or the group $-OSO_2CF_3$) and an aniline of formula (V)



(V)

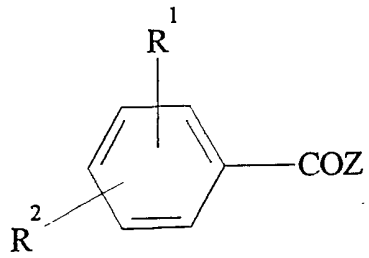
(where R^1 and R^2 are as defined in general formula (I)).

Both reactions take place, for example, in the presence of carbon monoxide using a palladium salt as a catalyst. The reaction is effected in the presence of a suitable base e.g. a trialkylamine such as triethylamine or tri-n-butylamine and may be conducted in a suitable solvent such as an amide e.g. dimethylformamide or a nitrile e.g. acetonitrile at a temperature within the range of -10^0C to $+150^0$C.

Suitable palladium salts for the reaction include triarylphosphine palladium (II) salts such as bis(triphenylphosphine)palladium (II) chloride.

According to another general process (2A), the compounds of general formula (I), in which X represents the group -CONH-, may be prepared by reacting an aniline of formula

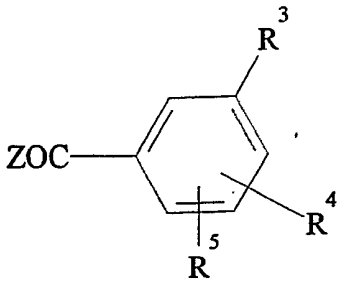
(II) with an activated carboxylic acid derivative of formula (VI)



(VI)

(where Z is a leaving group).

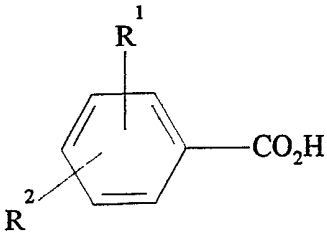
Alternatively, according to the general process (2B), the compounds of general formula (I), in which X represents the group -NHCO-, may be prepared by reacting an aniline of formula (V) with an activated carboxylic acid derivative of formula (VII)



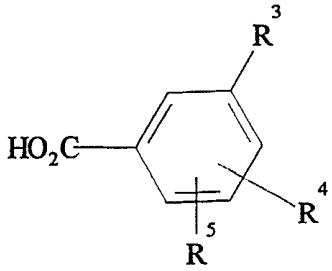
(VII)

(where Z is a leaving group).

Suitable activated carboxylic acid derivatives represented in formulae (VI) and (VII) include acyl halides (e.g. acid chlorides) and acid anhydrides including mixed anhydrides. These activated derivatives may be formed from the corresponding acids of formulae (VIII) or (IX)



(VIII)



(IX)

respectively, by well known procedures. For example, acid chlorides may be prepared by reaction with phosphorus pentachloride, thionyl chloride or oxalyl chloride and acid anhydrides may be prepared by reaction with an appropriate acid anhydride (e.g.

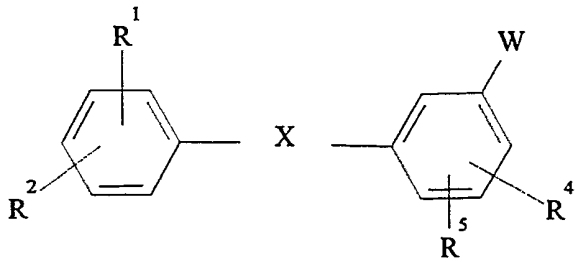
trifluoroacetic anhydride), an acid chloride (e.g. acetyl chloride), an alkyl or aralkyl haloformate (e.g. ethyl or benzyl chloroformate) or methanesulphonyl chloride.

Activated carboxylic acid derivatives of formulae (VI) and (VII) may also be prepared *in situ* by the reaction of the corresponding acids of formulae (VIII) and (IX), respectively, with a coupling reagent such as 1,1'-carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazide.

The conditions under which the activated carboxylic acid derivatives of formulae (VI) and (VII) are formed and subsequently reacted with the anilines of formulae (II) and (V), respectively, will depend upon the nature of the activated derivative. However, in general the reaction between the compounds (II) and (VI), or (V) and (VII), may be carried out in a non-aqueous medium such as, for example, dimethylformamide, tetrahydrofuran, acetonitrile or a halohydrocarbon such as dichloromethane at a temperature within the range -25°C to +120°C. The reaction may optionally be carried out in the presence of a base such as triethylamine or pyridine and the base may also be used as the solvent for reaction.

Where acid chlorides are used, the reaction may be carried out using the Schotten-Baumann technique in the presence of a suitable base, for example, aqueous sodium hydroxide, conveniently at a temperature between 0°C and 100°C, for example, room temperature.

According to another general process (3), the compounds of general formula (I) in which R^3 represents the group (a), may be prepared by reducing a compound of formula (X)



(X)

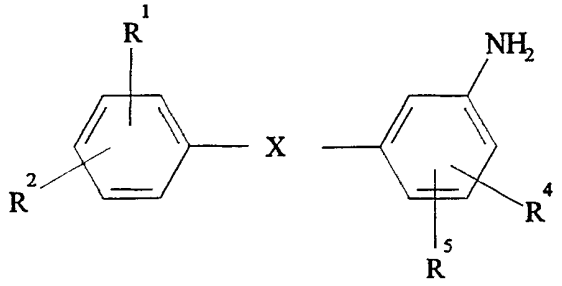
(where W represents a group convertible to the group $-(CH_2)_nNR^{13}R^{14}$ under reducing conditions).

Examples of the type of group W which may be converted into the group $-(CH_2)_nNR^{13}R^{14}$ are: $-(CH_2)_{n-1}CN$, $-(CH_2)_{n-1}CHO$, and when n is 3, $-C\equiv CCN$, $-CH=CHCN$, $-CH=CHCHO$, $-CH=CHCH_2NR^{13}R^{14}$ or $-C\equiv CCH_2NR^{13}R^{14}$. When W contains an aldehyde as defined above, the conversion is carried out in the presence of an appropriate amine of formula $NHR^{13}R^{14}$. When W contains a nitrile as defined above, the conversion may be carried out in the presence of an amine of formula $NHR^{13}R^{14}$, with the proviso that R^{13} and R^{14} do not both represent a hydrogen atom, in order to obtain a secondary or tertiary amine of general formula (I).

The reaction may be effected using an alkali or alkaline earth metal borohydride, e.g. sodium borohydride, or hydrogen and a metal catalyst such as palladium or platinum or oxides thereof. The reaction may be carried out at a temperature between 0°C and 100°C, conveniently at room temperature, and preferably in a solvent.

Suitable solvents for chemical reduction include ethers e.g. tetrahydrofuran, or alcohols e.g. ethanol. Suitable solvents for catalytic reduction include alcohols e.g. ethanol, ethers e.g. dioxan, amides e.g. dimethylformamide or a mixture of solvents e.g. ethanol/dimethylformamide.

According to another general process (4), the compounds of general formula (I) in which R^3 represents the group (c), may be prepared by treating a compound of formula (XI)



(XI)

with an amine dihalide of formula (XII)

$$R^{15}N(CH_2CH_2Hal)_2 \qquad (XII)$$

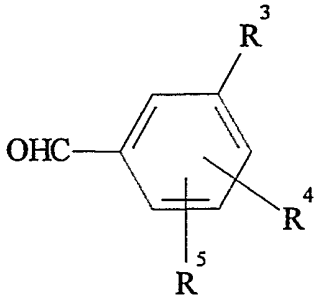
(where Hal is a chlorine, bromine or iodine atom).

The reaction may conveniently take place in the presence of a polar solvent such as an alcohol (e.g. n-butanol) or a nitrile (e.g. acetonitrile), optionally in the presence of a base, for example, an alkali metal carbonate such as sodium carbonate or potassium carbonate, or alternatively in a non-polar solvent (e.g. chlorobenzene) in the absence of a base. The reactions may conveniently be carried out at an elevated temperature, for example, reflux.

According to another general process (5), the compounds of general formula (I) in which X represents either of the groups $-NHCH_2-$ or $-CH_2NH-$ may be prepared by reduction of the corresponding compounds of general formula (I) in which X represents the groups -NHCO- or -CONH-, respectively, except that the reaction cannot be used to prepare compounds in which R^2 represents another group reducible under the reaction conditions, for example, $CONR^9R^{10}$, $SO_2NR^{11}R^{12}$, CO_2H, or $(CH_2)_kCOR^7$.

The reduction may be effected using a suitable metal hydride such as lithium aluminium hydride in a solvent e.g. an ether (such as tetrahydrofuran) at a temperature in the range of -10°C to +100°C.

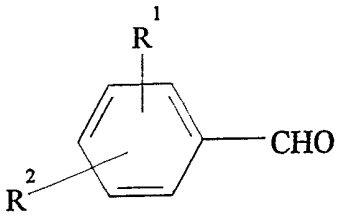
According to another general process (6A), the compounds of general formula (I) in which X represents the group $-NHCH_2-$ may be prepared by reacting an aniline of formula (V) with an aldehyde of formula (XIII)



(XIII)

under reducing conditions.

Alternatively, according to general process (6B), the compounds of general formula (I) in which X represents the group $-CH_2NH-$ may be prepared by reacting an aniline of formula (II) with an aldehyde of formula (XIV)



(XIV)

under reducing conditions.

Both reactions may conveniently take place in the presence of a solvent such as an alcohol e.g. methanol or ethanol using for example a hydride reducing agent such as an alkali or alkaline earth metal borohydride (e.g. sodium borohydride or sodium cyanoborohydride). The reactions may be carried out at a temperature in the range from 0° to 60°C, conveniently at room temperature.

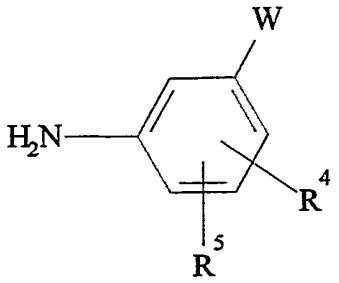
Compounds of general formula (I) in which R^2, R^4 and R^5 have a particular meaning may be converted into another compound of the invention by standard methods of interconversion.

For instance, when R^2 represents a hydroxy or alkoxy group and/or when R^4 and/or R^5 represents hydroxy or alkoxy these groups may be interchanged by standard methods of O-alkylation or O-dealkylation. Thus, for example, a compound in which R^4 represents hydroxy may be prepared by treating a corresponding compound in which R^4 represents methoxy with a reagent system capable of removing the methyl group e.g. a mercaptide such as sodium ethylmercaptide in a solvent such as dimethylformamide, lithium iodide in collidine, boron tribromide in a halohydrocarbon solvent e.g. methylene chloride or molten pyridine hydrochloride.

When R^2 represents a hydroxymethyl group this may be converted by oxidation into a corresponding compound of general formula (I) in which R^2 represents a group $-(CH_2)_kCHO$ or CO_2H. Thus, for example, oxidation may be effected using a suitable oxidising agent such as a manganese oxidising agent (e.g. manganese dioxide) in a solvent such as an ether (e.g. 1,4-dioxan) at a suitable temperature up to reflux, a chromium oxidising agent (e.g. Jones reagent) or pyridinium dichromate in a suitable solvent such as a halohydrocarbon (e.g. methylene chloride).

When R^2 represents an aldehyde group this may be converted by oxidation into a corresponding compound of general formula (I) in which R^2 represents a group CO_2H. Thus, for example, oxidation may be effected using a suitable oxidising agent such as a source of silver (I) (e.g. silver nitrate) in aqueous alkali optionally in the presence of a cosolvent such as an alcohol (e.g. methanol).

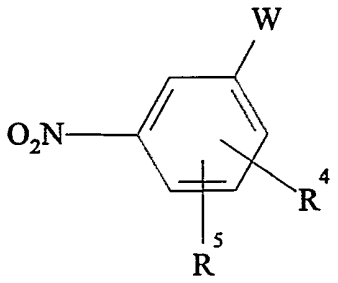
Intermediates of formula (II), in which R^3 represents the group $-(CH_2)_nNR^{13}R^{14}$, may be prepared by reduction of a compound of formula (XV)



(XV)

(where W is as defined in formula (X)) under the reducing conditions described for process (3).

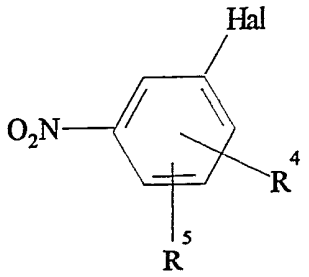
Compounds of formula (XV) may be prepared by reduction of the corresponding nitro compounds of formula (XVI)



(XVI)

Suitable reducing conditions include, for example, catalytic hydrogenation using a metal catalyst such as palladium oxide on a support such as charcoal, optionally in a solvent such as an alcohol (e.g. ethanol) or an ether (e.g. tetrahydrofuran). Under such conditions, the group W may also be reduced and hence the intermediates of formula (II) may be prepared directly from the compounds of formula (XVI) without prior isolation of the compounds of formula (XV).

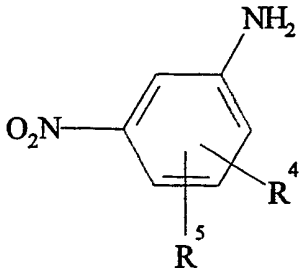
The nitro compounds of formula (XVI) may be prepared from the corresponding halo compounds of formula (XVII)



(XVII)

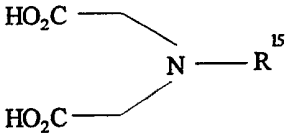
(where Hal is bromine or iodine) using standard methodology.

Intermediates of formula (II) in which R^3 represents the group (c) may be prepared from the corresponding compound of formula (XVIII)



(XVIII)

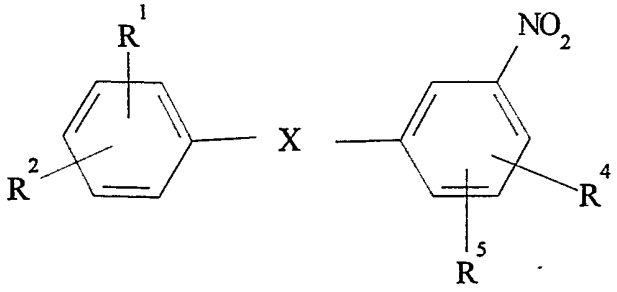
by reaction with a compound of formula (XIX)



(XIX)

in the presence of acetic anhydride, followed by reduction of the diketopiperazine intermediate thus formed using, for example, borane. The reaction may be carried out at a temperature between 50°C and reflux, and optionally in a solvent such as an ether, e.g. tetrahydrofuran. The nitro group may be subsequently converted into an amine using standard methodology.

Intermediates of formula (XI) may be prepared by reduction of the corresponding nitro compound of general formula (XXI)

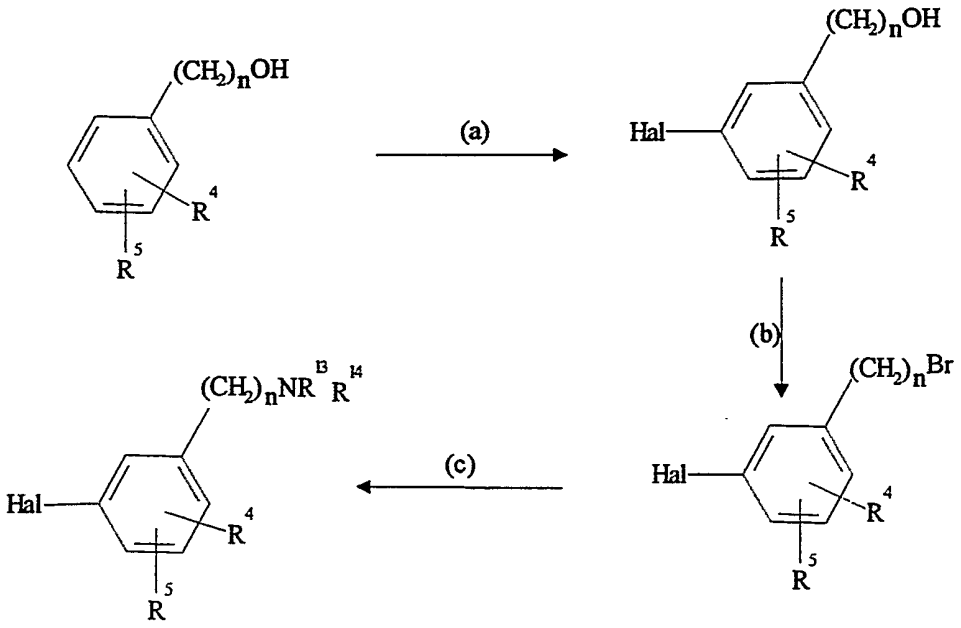


(XXI)

The reduction may be effected by catalytic hydrogenation using a metal catalyst such as palladium or platinum or oxides thereof, preferably, in a solvent such as an alcohol e.g. ethanol, or alternatively by using Raney nickel and hydrazine in a solvent such as an alcohol e.g. ethanol.

Intermediates of of formula (XXI) in which X is, for example, -CONH-, may be prepared by condensing a compound of formula (VI) or (VII) (in which R^3 represents a nitro group) with a compound of formula (XVIII) or (V), respectively, under the conditions of general process (2A).

Intermediates of formula (IV) in which R^3 is the group (a), may be prepared by the following reaction sequence:



Step (a) is carried out using suitable halogenating conditions, for example, when Hal represents iodine the iodine atom may be introduced using iodine monochloride in a solvent such as methylene chloride;

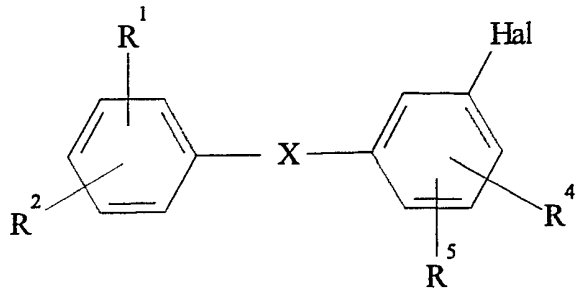
step (b) is carried out under standard brominating conditions such as using phosphorous tribromide in a halohydrocarbon solvent or using carbon tetrabromide in the presence of triphenylphosphine; and

step (c) is carried out using an amine $R^{13}R^{14}NH$ in a suitable solvent such as ethanol, preferably in the presence of a base;

with the proviso that either R^4 or R^5 is a directing group (i.e. fluorine, chlorine, hydroxy, C_{1-6}alkoxy or C_{1-6}alkyl) in a position either ortho or para to the group $-(CH_2)_nOH$.

Intermediates of formula (X), in which X is -CONH-, may be prepared by reaction of a compound of formula (XV) with a compound of either formula (III) or (VI) according to the method of general process (1) or (2), respectively.

Alternatively, intermediates of formula (X), in which W is -CH=CHCHO, -CH=CHCN, $-CH=CHCH_2NR^{13}R^{14}$ or $-C\equiv CCH_2NR^{13}R^{14}$, may be prepared from a compound of formula (XXII)



(XXII)

(wherein Hal is the only bromine or iodine atom in the molecule) by reaction with an alkene: $H_2C=CHCHO$, $H_2C=CHCH_2NR^{13}R^{14}$ or $H_2C=CHCN$; or an alkyne: $HC\equiv CCH_2NR^{13}R^{14}$.

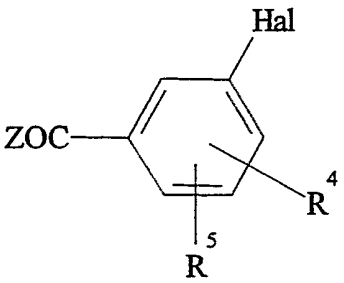
The reaction may be effected in the presence of a palladium reagent and preferably in the presence of a base. The palladium reagent may be, for example, a palladium salt derived from an organic acid (e.g. an acetate) or derived from an inorganic acid (e.g. a chloride or bromide), a palladium complex such as a triarylphosphine palladium complex (e.g. triphenylphosphine or tri(2-methylphenyl)phosphine palladium complex), or a finely

divided palladium metal such as palladium on charcoal. The triarylphosphine palladium complex may be generated *in situ* by reacting a palladium salt (e.g. palladium acetate) with the appropriate triarylphosphine.

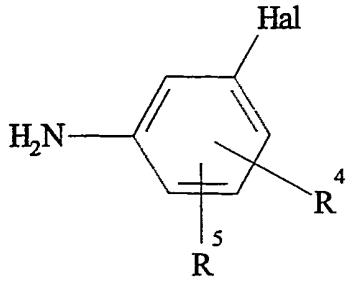
Suitable bases include tertiary amines (e.g. triethylamine or tri-n-butylamine) or alkali metal (e.g. sodium or potassium) carbonates, bicarbonates and acetates.

The reaction may be effected in the presence or absence of a solvent. Suitable solvents include nitriles (e.g. acetonitrile), amides (e.g. dimethylformamide, N-methylpyrrolidinone) and water. The reaction may conveniently be carried out at a temperature between room temperature and 200°C, preferably between 50°C and 160°C.

Compounds of formula (XXII) may be prepared by the reaction of a compound of formula (V) or (VI) with a compound of formula (XXIII) or (XXIV), respectively,



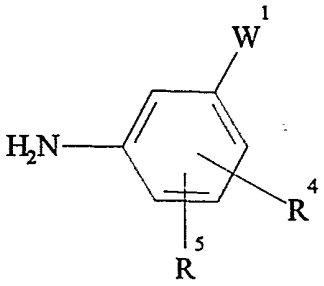
(XXIII)



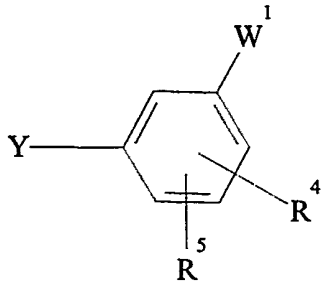
(XXIV)

according to the method of general process (2).

Alternatively, intermediates of formula (X) in which W is $-(CH_2)_{n-1}CN$ or $-(CH_2)_{n-1}CHO$ may be prepared by the reaction of a compound of formula (III) or (V) with a compound of formula (XXV) or (XXVI), respectively,



(XXV)

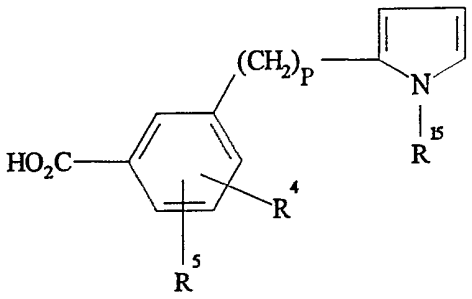


(XXVI)

(wherein W^1 represents $-(CH_2)_{n-1}CN$ or $-(CH_2)_{n-1}CHO$), according to the method of general process (1).

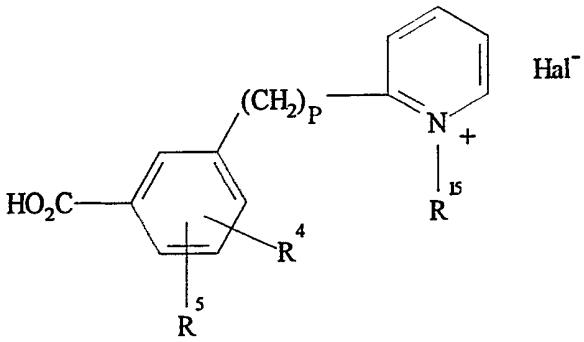
Intermediates of formulae (XXV) and (XXVI) in which W^1 contains a nitrile group may be prepared from the corresponding halo (e.g. bromo) compound using standard methodology.

Intermediates of formula (IX) wherein R^3 represents the group (b) and in which q is 1 may be prepared by reducing a compound of formula (XXVII)



(XXVII)

Similarly, intermediates of formula (IX) wherein R^3 represents the group (b) and in which q is 2, may be prepared by reducing a salt of formula (XXVIII)

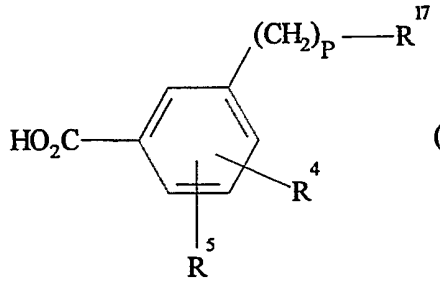


(XXVIII)

(wherein Hal^- is a halide ion e.g. an iodide ion).

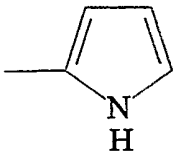
These reductions may be effected under standard conditions of hydrogenation e.g. using hydrogen in the presence of a catalyst such as palladium or platinum or oxides thereof. The reaction may be carried out at any suitable temperature, for example, from 0^0 to 100^0C, conveniently at room temperature, and preferably in a solvent. Suitable solvents include alcohols (e.g. ethanol), ethers (e.g. dioxan or dimethoxyethane), amides (e.g. dimethylformamide) or esters (e.g ethyl acetate) or a mixture of solvents (e.g. ethanol/dimethylformamide).

The compounds of formulae (XXVII) and (XXVIII) may be prepared from compounds of formula (XXIX)

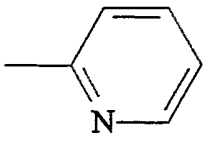


(XXIX)

(where R^{17} represents

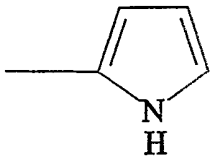


and



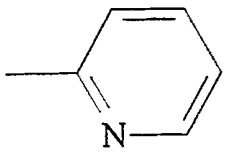
, respectively .

Thus, compounds of formula (XXVII) may be prepared from compounds of formula (XXIX) where R^{17} represents



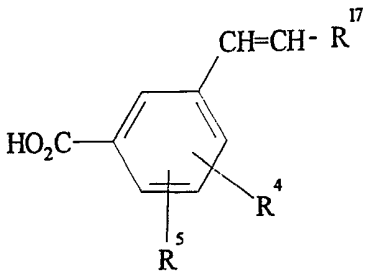
by treating the compound of formula (XXIX) with, for example, an alkali metal amide such as potassium amide or sodium amide in liquid ammonia, an alkali metal hydride such as sodium hydride or potassium hydride in a suitable solvent such as an ether (e.g. tetrahydrofuran) or an amide (e.g. dimethylformamide) or with n-butyllithium in hexane, followed by an alkylation step using a halide R^{15} Hal (where Hal is a halogen atom e.g. chlorine, bromine or iodine) in a suitable solvent such as an ether (e.g. dimethoxyethane) or an amide (e.g. dimethylformamide).

Compounds of formula (XXVIII) may be prepared from compounds of formula (XXIX) where R^{17} is



by reaction with a halide R^{15} Hal (where Hal is chlorine, bromine or iodine), in a suitable solvent such as a ketone (e.g. acetone), a nitrile (e.g. acetonitrile) or an alcohol (e.g. ethanol).

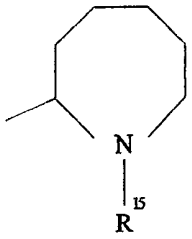
Intermediates of formula (XXIX) in which p is 2 may be prepared by reducing a compound of formula (XXX)



(XXX)

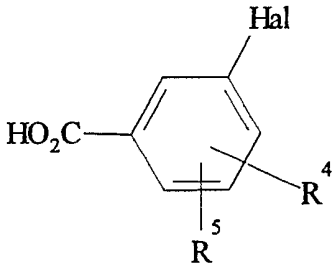
(where R^{17} is as defined in formula (XXIX) above).

Additionally, intermediates of formula (IX) wherein R^3 represents the group (b) and where p is 2 and q is 3 may be prepared by reducing a compound of formula (XXX) where R^{17} represents



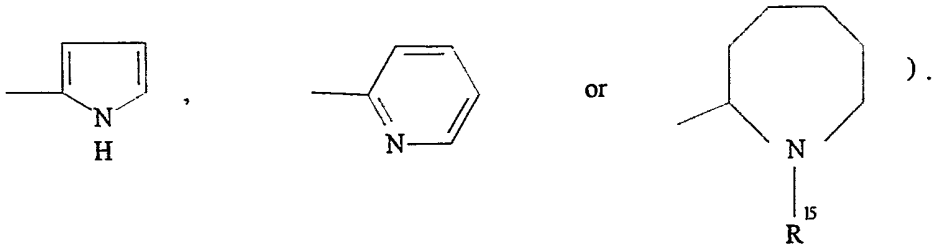
The reduction of compounds of formula (XXX) may be effected using hydrogen and a metal catalyst such as palladium or platinum or oxides thereof in a suitable solvent.

Compounds of formula (XXX) may be prepared from a compound of formula (XXXI)



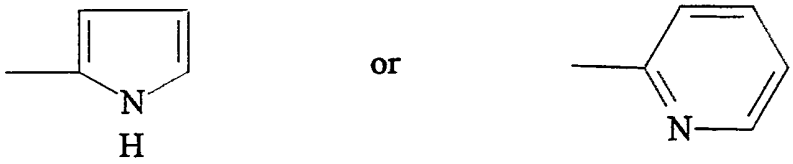
(XXXI)

(where Hal is bromine or iodine) by reaction with an appropriate alkene of formula CH_2=CH-R^{17} (where R^{17} represents

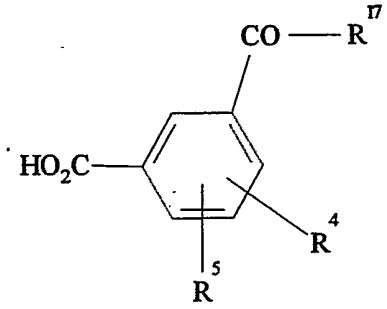


The reaction may be effected in the presence of a palladium reagent such as palladium acetate and preferably in the presence of a base such as a tertiary amine e.g. triethylamine. The reaction may be effected in the presence or absence of a solvent. Suitable solvents include nitriles (e.g. acetonitrile), amides (e.g. dimethylformamide) and water.

Intermediates of formula (XXIX) in which R^{17} represents



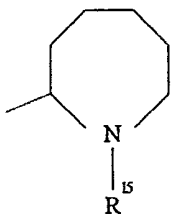
and p is 1 may be prepared by reducing a compound of formula (XXXII)



(XXXII)

(where R^{17} is as defined in formula (XXIX) above).

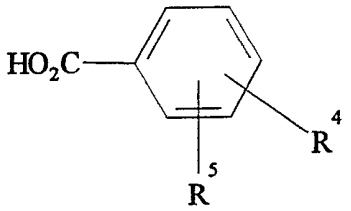
Intermediates of formula (IX) wherein R^3 represents the group (b) and where p is 1 and q is 3 may be prepared by reducing a compound of formula (XXXII) where R^{17} is



The reduction of compounds of formula (XXXII) may be effected using hydrogen and a metal catalyst such as palladium or platinum or oxides thereof or using hydrazine

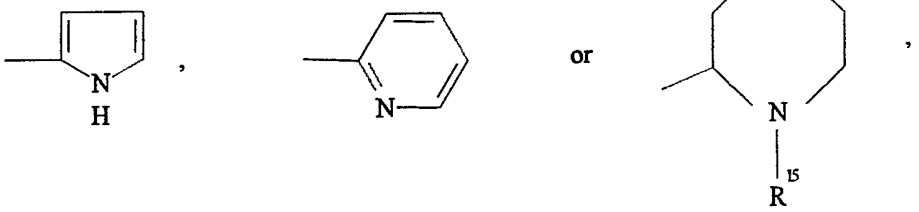
hydrate and a base (e.g. an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide).

Compounds of formula (XXXII) may be prepared from a compound of formula (XXXIII)



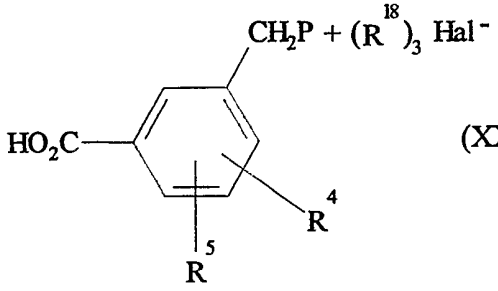
(XXXIII)

by a Friedel Craft reaction involving an acyl halide of the formula Hal-CO-R^{17} (where R^{17} represents



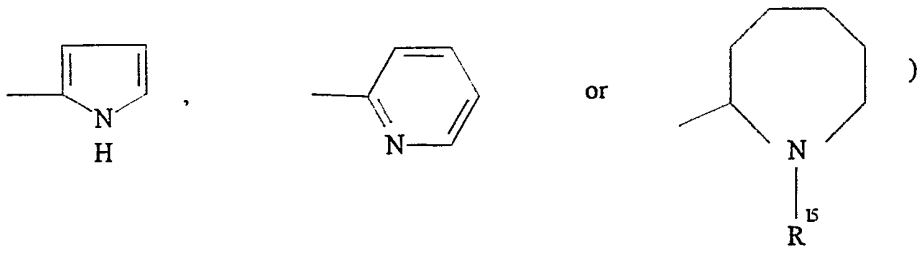
and Hal represents chlorine or bromine) with the proviso that at least one of the positions on the phenyl ring meta in relation to the carboxyl group is unoccupied.

Alternatively, intermediates of formula (XXX) may be prepared by the reaction of a phosphonium salt of a halide of formula (XXXIV)



(XXXIV)

(where Hal^- represents a halide (e.g. chloride) ion and R^{18} represents, for example, an aryl or alkoxy group) with an aldehyde of the formula $R^{17}CHO$ (where R^{17} represents



in the presence of a suitable strong base such as an alkoxide (e.g. potassium t-butoxide) and in the presence of a suitable solvent such as an ether (e.g. tetrahydrofuran) at ambient temperature.

Suitable phosphonium salts include aryl phosphonium salts such as triphenylphosphonium salts (where R^{18} represents an aryl group) which may be prepared according to established procedures.

It will be appreciated that, where necessary, a halogen substituent may be converted into a carboxyl group using standard methodology thus, for example, compounds of formula (VIII) or (IX) may be prepared from an intermediate of formula (III) or (IV), respectively, by lithiation using, for example, n-butyl lithium followed by quenching with carbon dioxide.

The aldehydes of formula (XIII) or (XIV) may be prepared from an intermediate of formula (IV) or (III), respectively, by lithiation using, for example, n-butyl lithium followed by formylation using, for example, dimethylformamide.

Intermediates of formulae (III), (XII), (XVII) (XVIII), (XIX), (XXIII), (XXIV), (XXXI) and (XXXIII) are either known compounds or may be prepared by standard methodology or methods analogous to those described herein.

Physiologically acceptable acid addition salts of the compounds of general formula (I) may be prepared by treating the corresponding free base with a suitable acid using conventional methods. Thus, for example, a generally convenient method of forming the acid addition salts is to mix appropriate quantities of the free base and the acid in an appropriate solvent e.g. an alcohol such as ethanol or an ester such as ethyl acetate.

Inorganic basic salts of compounds of general formula (I) may be prepared by treating the corresponding acid of general formula (I) (i.e. a compound of general formula

(I) in which R^2 represents the group CO_2H) with a suitable base using conventional methods.

Salts of compounds of general formula (I) may also be converted into different physiologically acceptable salts of compounds of general formula (I) using conventional methods.

The invention is illustrated but not limited by the following examples in which temperatures are in °C. Thin layer chromatography (T.l.c.) was carried out on silica plates.

The following abbreviations are used :

DMF-dimethylformamide; TEA-triethylamine; HMPA-hexamethylphosphoramide; THF-tetrahydrofuran; MSC-methanesulphonyl chloride; BTPC- bis(triphenylphosphine) palladium (II) chloride; PdOC - pre-reduced palladium oxide on carbon; PtOC-pre-reduced platinum oxide on carbon; LAH-lithium aluminium hydride; DMSO-dimethylsulphoxide; SPC-Short path chromatography carried out on silica (Merck 7747) unless otherwise stated. FCC-Flash column chromatography carried out on silica (Merck 9385). 'Dried' refers to drying using sodium sulphate or magnesium sulphate unless otherwise stated.

The following solvent systems were used:

System A-dichloromethane:ethanol:0.88 ammonia; System B-dichloromethane:ethanol; System C-hexane:diethyl ether; System D-dichloromethane:hexane; System E- ethyl acetate:ethanol:triethylamine; System F-dichloromethane:methanol:0.88 ammonia; System G -ethyl acetate:methanol:triethylamine.

Intermediate 1

5-Bromo-2-methoxybenzenepropanenitrile

A vigorously stirred mixture of 4-bromo-2-(2-bromoethyl)-1-methoxybenzene (29.89g) and sodium cyanide (5.48g) in DMF (80ml) was heated at 105 to 115° under nitrogen for 21h. Sodium cyanide (3.00g) was added and heating continued for 8h. The cooled mixture was poured into water (500ml), extracted with ether (3x200ml), and the

combined, dried extracts were evaporated onto silica gel (Merck 7734). This was purified by FCC eluting with System C (19:1 to 7:3) to give firstly 4-bromo-2-ethenyl-1-methoxybenzene as an oil, and secondly the title compound (11.2g) as white crystals, m.p. 62 - 64°.

Intermediate 2

(E)-3-(2-Cyanoethenyl)-4-methoxybenzoic acid, mixture with (Z) isomer (2:1).

A stirred mixture of 3-iodo-4-methoxybenzoic acid (18.06g), acrylonitrile (5.4ml), TEA (22.5ml), palladium (II) acetate (300mg), and acetonitrile (30ml) was heated at 100° in an autoclave. After 36h, the reaction was incomplete. Half of the reaction mixture was removed, treated with palladium (II) acetate (300mg) and this mixture heated at 100° for 18h in an autoclave. The cooled reaction mixture was filtered, evaporated, and the residue treated with water (l00ml), aqueous saturated sodium bicarbonate (150ml), and 2M-sodium hydroxide (50ml). The mixture was extracted with ethyl acetate (l00ml) and the organic extract discarded. The aqueous extract was acidified to pH 1 by the addition of 2M-hydrochloric acid, extracted with ethyl acetate and the combined, dried extracts were evaporated. The residue was crystallised from ether to give the title compound (3.37g) as cream microcrystals.

Analysis Found: C,64.75; H,4.65; N,6.8

$C_{11}H_9NO_3$ requires: C,65.0; N,4.45; N,6.9%

Intermediate 3

(E)-3-(2-Cyanoethenyl)-4-methoxy-N-(4-propylphenyl)benzamide

A stirred suspension of Intermediate 2 (4.00g) in dry THF (35ml) was treated with TEA (5.5ml) at room temperature under nitrogen, and after l0min, MSC (1.52ml) was added dropwise at -5° to 0° over l0min. After 1.5h, 4-propylbenzeneamine (2.66g) in THF (15ml) was added over l0min, and after 1.5h at -5°, the mixture was stirred at room temperature for 16h. The reaction mixture was evaporated, treated with ethyl acetate (350ml), and washed with a mixture of 2M hydrochloric acid (l00ml) and brine (50ml), followed by 2M hydrochloric acid (50ml), then aqueous saturated sodium bicarbonate

(2x80ml). The dried organic layer was evaporated and the residue crystallised from ethyl acetate to give the title compound (2.47g) as cream needles.

Analysis Found: C,75.25; H,6.25; N,8.7

$C_{20}H_{20}N_2O_2$ requires: C,75.0; H,6.3; N,8.75%

Intermediate 4

(E)-3-(2-Cyanoethenyl)-4-methoxy-N-(4-propoxyphenyl)benzamide

A stirred suspension of Intermediate 2 (4.00g) in dry THF (35ml) was treated with TEA (5.5ml) at room temperature under nitrogen and after 10min MSC (1.52ml) was added dropwise at -5 to 0° over 10min. After 1.5h, 4-(propoxy)benzeneamine (2.97g) in dry THF (15ml) was added over 10min, and after 1.5h at -5°, the mixture was stirred at room temperature for 22h. The reaction mixture was evaporated and treated with a mixture of 2M hydrochloric acid (100ml), brine (100ml), and ethyl acetate (1 litre). The precipitate was filtered off, washed with aqueous saturated sodium bicarbonate (40ml), followed by water (50ml), and air dried for 30min. The organic layer of the above filtrate was washed with aqueous saturated sodium bicarbonate (2x100ml), dried, added to the above precipitate, and evaporated. A portion of the residue was crystallised twice from acetonitrile to give the title compound (290mg) as white needles, m.p. 204.5 - 207.5°.

Intermediate 5

(E) Ethyl 4-[[[3-(2-cyanoethenyl)-4-methoxyphenyl]carbonyl]amino]benzoate

A suspension of Intermediate 2 (11.0g) in dry THF (100ml) was treated with TEA (15.1ml) at room temperature under nitrogen with stirring and, after 20 min, MSC (4.2ml) was added dropwise at -5° to 0° over 20 min. After 1.5h, ethyl 4-aminobenzoate (8.94g) in dry THF (30ml) was added over 20 min, and after 1.5h at -5°, the mixture was stirred at room temperature for 3 days. The mixture was evaporated, treated with aqueous saturated sodium bicarbonate (250ml), and the precipitate collected. The precipitate was washed with 2M-hydrochloric acid (250ml), followed by water (50ml), air-dried for 1h, and dried in vacuo over phosphorus pentoxide at 50° for 16h. The solid was crystallised from acetonitrile to give the title compound (4.71g) as cream needles m.p. 234-237.5°.

Intermediate 6

3-(2-Cyanoethyl)-N-(4-ethoxyphenyl)-4-methoxybenzamide

A vigorously stirred mixture of Intermediate 1 (5.00g), 4-ethoxybenzeneamine (5.71g), tri-n-butylamine (20ml), and BTPC (0.80g) was heated at 100° under carbon monoxide for 16h. The cooled mixture was treated with 2M hydrochloric acid (200ml) and the mixture extracted with ethyl acetate (4x200ml). The combined organic extracts were washed with 2M hydrochloric acid (200ml), dried and evaporated. The residue was purified by FCC, eluting with dichloromethane:methanol (100:1 to 50:1) to give a white solid. The solid was adsorbed from methanol onto silica gel (Merck 7734, 80g) and purified by SPC (Merck 7729) eluting with dichloromethane:methanol (200:1 to 100:1) to give a white solid which crystallised from ethanol to give pure title compound (0.50g) as fine white needles, m.p. 165.5 - 166.5°

Intermediate 7

3-(2-Cyanoethyl)-4-methoxy-N-phenylbenzamide

A vigorously stirred mixture of Intermediate 1 (5.00g), benzeneamine (3.87g), tri-n-butylamine (20ml), and BTPC (0.80g) was heated at 90° under carbon monoxide for 16h. The cooled mixture was treated with 2M hydrochloric acid (200ml) and the mixture extracted with ethyl acetate (4 x 200ml). The combined, dried organic extracts were evaporated onto silica gel (Merck 7734) and then purified by SPC eluting with ethyl acetate:hexane (1:4 to 1:0) to give a cream crystalline solid which was treated with refluxing ethyl acetate (500ml) and clarified by filtration. The solution was evaporated and the residue crystallised from ethyl acetate to give the title compound (3.60g) as fine white needles m.p. 157-158°.

Intermediate 8

3-[3-(Dimethylamino)propyl]4-methoxybenzoic acid

A solution of Intermediate 2 (2.00g) in a mixture of 33% ethanolic dimethylamine (60ml) and DMF (l0ml) was hydrogenated at room temperature and pressure over 10% PdOC

(2.00g) in ethanol (l0ml) for 2.25h. The catalyst was filtered off, replaced with fresh catalyst (2.0g) and hydrogenation continued for a further 19.25h. The catalyst was filtered off, the filtrate concentrated in vacuo, and the residual white oil was triturated with hexane (3x200ml). The resultant white solid was filtered off and dried. A portion of this material (1.20g) was crystallised from acetonitrile (65ml) to give the title compound (0.84g) as white crystals m.p. 140-141.5°.

Intermediate 9

3-(Cyanomethyl)-N-(4-ethoxyphenyl)-4-methoxybenzamide

A mixture of 5-bromo-2-methoxybenzeneacetonitrile (580mg), 4-ethoxyaniline (705mg) and BTPC (l00mg) in tri-n-butylamine (6ml) was stirred at 90° under an atmosphere of carbon monoxide for 24h and left to stand for 3 days. The suspension was partitioned between 2N hydrochloric acid (60ml) and ethyl acetate (3x25ml). The combined organic extracts were washed with 2N hydrochloric acid (25ml), water (25ml) and brine (25ml), dried and concentrated in vacuo. FCC of the residual brown solid eluting with chloroform:methanol (100:1) afforded a white solid (0.55g). Crystallisation of this solid from isopropyl acetate (5ml) gave the title compound (0.23g) as fine white needles, m.p. 147-148°.

Intermediate 10

5-Iodo-2-methoxybenzenepropanol

A solution of iodine monochloride (17.0g) in dichloromethane (55ml) was added dropwise, under nitrogen, over a period of 0.5h to a stirred, ice-cooled solution of 2-methoxybenzenepropanol (l0.0g) in dichloromethane (50ml). The dark solution was stirred, with ice-cooling for 1.25h and then washed with 20% sodium thiosulphate solution. The pale yellow organic solution was then dried and concentrated in vacuo to give the title compound (16.38g) as a pale pink solid m.p. 68-70°.

Intermediate 11

2-(3-Bromopropyl)-4-iodo-l-methoxybenzene

A solution of triphenylphosphine (18.5g) in dichloromethane (120ml) was added dropwise under nitrogen to a stirred, cooled solution of Intermediate 10 (13.3g) and carbon tetrabromide (19.2g) in dichloromethane (200ml). The orange solution was stirred, with external cooling, for 2h and then concentrated in vacuo. FCC of the residual orange solid (Merck 7734) eluting with hexane afforded the title compound (15.35g) as a colourless oil. T.l.c. (hexane) Rf 0.39.

Intermediate 12

5-Iodo-2-methoxy-N,N-dimethylbenzenepropanamine hydrochloride

A solution of Intermediate 11 (500mg) in a mixture of 33% ethanolic dimethylamine (10ml) and ethanol (2ml) was stirred at reflux under nitrogen for 2h, allowed to cool, and then concentrated in vacuo. FCC of the residual white solid eluting with System A (200:10:1) afforded a colourless oil which contained the free base of the title compound (272mg) as a white solid. This material was dissolved in refluxing ethanol (1ml) and ethereal hydrogen chloride (0.5ml) was added. The stirred solution was diluted with dry ether (10ml) and the resultant solid filtered off, washed with dry ether and dried in vacuo at 60° for 20h to give the title compound (195mg) as a white solid m.p. 143-144°.

Intermediate 13

Ethyl 5-(4-nitrophenoxy)pentanoate

To a stirred solution of 4-nitrophenol (5.56g) in dry DMF (30ml) kept at 10-15° was added portionwise sodium hydride 80% in oil (1.26g). Ethyl 5-bromopentanoate (8.36g) was added and the mixture stirred at 80° for 2h. The solution was evaporated to dryness in vacuo and the oily residue mixed with water (120ml) and sodium carbonate (2g). The mixture was extracted with ethyl acetate (2x70ml) and the extracts washed with brine (40ml) and then dried. After 1h, the mixture was filtered and the filtrate evaporated in vacuo to give the title compound (9.905g) as a dark oil.

T.l.c. System C (6:4) Rf 0.4

Intermediate 14

Ethyl 5-(4-aminophenoxy)pentanoate

To a solution of Intermediate 13 (2.67g) in ethanol (30ml) was added Raney Nickel (lg). Hydrazine hydrate (2ml) was added slowly in portions to the stirred suspension at room temperature. The mixture was heated on a steam bath for 15 minutes then cooled. The suspension was filtered under nitrogen and the filtrate evaporated to dryness in vacuo to give a slowly darkening oil consisting of the title compound (2.414g).

T.l.c. System A (150:8:1) Rf 0.66

Intermediate 15

5-(4-Aminophenoxy)pentanamide

A mixture of Intermediate 14 (1.172g) in methanolic ammonia (saturated; 8ml) was kept at room temperature for 7 days. The solution was evaporated to dryness and the residue suspended in ether. The suspension was filtered and the solid residue washed with ether and dried to give the title compound (0.412g) m.p. 134-136°.

Intermediate 16

4-(3-Hydroxypropoxy)benzeneamine

3-(4-Nitrophenoxy)propanol (4.1g) was dissolved in ethanol (80ml). This solution was added to PdOC (10%, 2.05g) in ethanol (50ml) and the mixture stirred under 1 atmosphere of hydrogen for 4h. The reaction mixture was then filtered through celite, washing the celite pad thoroughly with ethanol, and the filtrate evaporated in vacuo to give a light brown solid. This was crystallised from toluene (25ml) to give the title compound as a beige coloured solid (1.4g) m.p. 87°C.

Intermediate 17

4-[4-[Bis(phenylmethyl)amino]phenyl]4-hydroxycyclohexanone

Butyllithium (98.0 ml of a 1.59M solution in hexane) was added dropwise at -60 to -65° under nitrogen to a stirred solution of N-(4-bromophenyl) -N-(phenylmethyl)benzenemethanamine (50.00g) in dry THF (500 ml) over 30 min. After 2h at -60 to -65° the solution was added via a cannula to a stirred solution of

1,4-cyclohexanedione (15.9g) in dry THF (200 ml) at -50 to -65° over 15 min and stirring continued for 1.5h. The solution was allowed to reach 23° over 20 min and then poured into aqueous saturated ammonium chloride (500 ml). The mixture was evaporated, treated with water (1.3 litres), and extracted with ethyl acetate (5x600 ml). The combined, dried organic extracts were evaporated and the residue adsorbed from ethanol (600ml) onto silica gel (Merck 7734, 250g). Purification by SPC eluting with a gradient of hexane:ethyl acetate (4:1 to 55:45) afforded a yellow solid. This was adsorbed from dichloromethane (150ml) onto silica gel (Merck 7734, 60g) and further purified by SPC eluting with a gradient of dichloromethane:ethanol (100:0 to 97:3) which afforded firstly impurities and secondly a cream-coloured solid (11.14g). A portion of the solid (1.00g) was crystallised from ethanol (5ml) to give the title compound as a white crystalline solid (492mg), m.p. 115.5-117.5°.

Intermediate 18

1-[4-[Bis(phenylmethyl)amino]phenyl]-1,4-cyclohexanediol Isomer II

Sodium borohydride (1.40g) was added to a stirred solution of Intermediate 17 (11.44g) in dry THF (160 ml) and ethanol (160 ml) under nitrogen at 0° over 5 min. After 45 min at 0°, the reaction mixture was stirred at 23° for 2.5h, and then treated with 2N hydrochloric acid (100 ml). Aqueous saturated sodium bicarbonate (300 ml) was added, the mixture evaporated, and the residue treated with water (300 ml). The mixture was extracted with ethyl acetate (2x400 ml), and the combined, dried organic extracts were evaporated onto silica gel (Merck 7734, 80 ml). Purification by SPC eluting with a gradient of ethyl acetate:hexane (3:7 to 1:0) afforded firstly impurities, then 1-[4-[bis(phenylmethyl)amino]phenyl]-1,4-cyclohexanediol isomer I (1.13g). Further elution afforded the title compound (3.08g) as fine cream crystals.

Analysis Found C,80.6; H, 7.5; N,3.3

$C_{26}H_{29}NO_2.0.12C_{26}H_{27}NO.0.1H_2O$ requires : C,80.7; H,7.5; N,4.6%

Water Assay Found: 0.4% w/w H_2O = 0.1 mol H_2O

Intermediate 19

Cis-4-(4-aminophenyl)cyclohexanol

A solution of Intermediate 18 (2.96g) in ethanol (260ml) was added to a stirred suspension of dry 10% palladium on carbon (2.0g) in ethanol (40ml) and hydrogenated at room temperature and pressure until uptake ceased. The catalyst was filtered off and the filtrate concentrated to 100ml. The concentrate was added to a stirred suspension of dry 10% palladium on carbon (2.0g) in ethanol (40ml) and further hydrogenated at room temperature and pressure for 18h. The catalyst was filtered off and the filtrate adsorbed onto silica gel (Merck 7734, 30ml). Purification by SPC (Merck 7729) eluting with a gradient of ethyl acetate:exane (25:75 to 40:60) afforded firstly impurities followed by the title compound (391mg). This was crystallised from ethyl acetate (5ml) to give the title compound as cream crystals (96mg).

T.l.c. ethyl acetate:hexane (1:1), Rf 0.14.

Intermediate 20

1-(4-Nitrophenyl)-4-(phenylmethyl)piperazine, maleate

A stirred mixture of 1-(4-nitrophenyl)piperazine (15.0g), benzyl bromide (12.96g), anhydrous sodium carbonate (11.45g) and 1-butanol (150ml) under nitrogen was heated at reflux overnight. The reaction mixture was cooled, evaporated and the mixture diluted with 2N sodium carbonate (200ml). The mixture was extracted with ethyl acetate (5x300ml), dried and evaporated to dryness to yield a yellow, feathery solid (18.57g). The solid was then absorbed from ethanol (200ml) onto silica gel (Merck 7734, 160g). Purification by FCC eluting with triethylamine:ethyl acetate:hexane (1:30:69) afforded the free base of the title compound (12.72g) as a yellow solid. A portion of the free base (400mg) was treated with maleic acid (230mg) in ethanol (20ml) and heated to reflux at effect solution. On cooling the precipitate was collected to give the title compound as fine yellow crystals (530mg) m.p. 127-129°.

Intermediate 21

4-[4-(Phenylmethyl)-1-piperazinyl]benzenamine

A solution of Intermediate 20 (7.91g) in DMF (150ml) was added to PtOC (5%, 1.98g) and hydrogenated at room temperature and pressure until uptake ceased. The catalyst was filtered off and the filtrate evaporated to yield a brown solid (5.77g). FCC eluting with System A (3:30:967) gave the title compound (4.87g) as a pale brown foam, m.p.133-135°.

Intermediate 22

3-[3-(Dimethylamino)propyl]-4-methoxy-N-[4-(4-phenylmethyl-1-piperazinyl)phenyl] benzamide

The hydrochloride salt of Intermediate 8(4.29g) was treated with thionyl chloride (25ml), heated to reflux for 5min and then evaporated. The residue was coevaporated with toluene (2x25ml), treated with Intermediate 21 (4.2g) followed by pyridine (25ml) and the stirred mixture heated at 100°C under nitrogen for 5h. When cool aqueous saturated sodium bicarbonate (25ml) was added and the mixture evaporated. After addition of ethanol (20ml) and evaporation onto silica (80g, Merck 7734) the product was purified by FCC eluting with System A (923:70:7 to 912:80:82) which afforded the title compound (1.32g) as pale brown, feathery crystals. A mixed fraction of product and acid (4.38g) was also isolated for further purification.

The mixed fraction was adsorbed from ethanol (40ml) onto silica gel (Merck 7734, 20g) and purified by SPC eluting with System A (923:70:7 to 912:80:8) which afforded the title compound (4.03g) as pale brown, feathery crystals, m.p. 167-169°.

Intermediate 23

N-(4-Ethoxyphenyl)-3-nitro-4-methoxybenzamide

TEA (2.8ml) was added to a solution of 4-methoxy-3-nitrobenzoic acid (3.94g) in dry THF (100ml) chilled in an ice bath and treated with MSC (1.55ml). The suspension was stirred for 2.5h then a further quantity of TEA (2.8ml) was added followed by p-phenetidine (3.02g), and the mixture stirred and allowed to warm to room temperature over 5.25h. The solvent was removed and the residue partitioned between ethyl acetate (150ml) and water (50ml). The organic layer was separated and washed successively with

2N hydrochloric acid, 2N sodium carbonate and water and dried. Removal of the solvent afforded a solid which was triturated with cyclohexane and dried in vacuo to give the title compound (4.12g) m.p. 159-161°.

Intermediate 24

3-Amino-N-(4-ethoxyphenyl)-4-methoxybenzamide

A solution of Intermediate 23 (3.16g) in ethanol (270ml) was added to PdOC (50% aqueous paste, 0.4g) in ethanol (30ml) and hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen ceased. The catalyst was removed by filtration and the filter bed extracted with hot ethanol (l00ml). The filtrate was concentrated to a low volume whereupon the product crystallised. This was collected and washed with ether to give the title compound (2.14g) m.p. 170-172°.

Intermediate 25

Methyl 4-methoxy-3-(4methyl-1-piperazinyl)benzoate hydrochloride

A suspension of 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (1.92g) and methyl 3-amino-4-methoxybenzoate (1.81g) in n-butanol was refluxed with stirring for l9h. Anhydrous sodium carbonate (0.54g) was added and refluxing continued for 8.5h. The solvent was then removed to give an oil which was taken up in water (50ml) and 2N hydrochloric acid (50ml) and extracted with ethyl acetate (2x50ml). The acid solution was then basified with sodium bicarbonate and reextracted with ethyl acetate (3x50ml). The extracts were dried and concentrated to a semi-solid (2.47g) which was absorbed from System A (200:8:1) (5ml) onto Kieselgel G (l00g). Elution with the same solvent gave starting material and minor basic impurities. Further elution with System A (100:8:1) (450ml) gave first minor impurities and later fractions afforded the free base of the desired product as a gum (0.48g). This was taken up in methanol (5ml), filtered and treated with ethereal hydrogen chloride and diluted to 25ml with ethyl acetate. A cream coloured solid separated and was collected giving the title compound (0.56g), m.p. 190-194°.

Intermediate 26

4-Methoxy-3-(4-methyl-1-piperazinyl)benzoic acid hydrazide

The free base of Intermediate 25 (2g) in methanol (20ml) was treated with hydrazine hydrate (4ml) and refluxed under nitrogen for 16h. The solution was evaporated and then adsorbed from ethanol onto silica gel [Merck Art. 7734, 5g]. Purification by SPC eluting with System A (91:9:0.9) gave the title compound as an off-white solid (0.764g).

T.l.c. System A (90:10:0.1), Rf 0.2.

Intermediate 27

4-Methoxy-3-(4-methyl-1-piperazinyl)benzenamine

A solution of Intermediate 26 (0.73g) in water (30ml) was mixed with concentrated hydrochloric acid (0.6ml), the solution cooled to 0 to 5°C and a solution of sodium nitrite (0.219g) in water (10ml) added during 5min. The solution was stirred at 0 to 5°C for 20min, then 1h at 23°C, and treated with concentrated hydrochloric acid (40ml) and acetic acid (40ml). The mixture was heated at reflux for 2h, cooled and poured into aqueous sodium hydroxide (5N; 260ml). The mixture was extracted with ethyl acetate (3x500ml), and the combined, dried organic extracts were evaporated to give the title compound as a gum (0.190g).

T.l.c. System A (95:5:0.5), Rf 0.2.

Intermediate 27 was also made by the alternative two-step reaction as follows:

(a) 1-Methyl-4-(2-methoxy-5-nitrophenyl)piperazine

1-(2-Methoxyphenyl)-4-methylpiperazine (5.36g) was acidified with 5N sulphuric acid and the excess water evaporated in vacuo. Concentrated sulphuric acid (95-98%, 22ml) was added and the mixture stirred at room temperature until homogeneous. To the stirred, dark solution was added portionwise at room temperature potassium nitrate (3.07g) in ten portions at intervals of approximately 5min. The mixture was stirred at room temperature for 4h then poured onto ice (500ml) and the mixture made slightly alkaline with anhydrous sodium carbonate. The basic mixture was extracted with ethyl

acetate (4xl50ml) and the combined extracts dried. After lh the mixture was filtered and the filtrate evaporated to dryness in vacuo. The dark red residue was diluted with ether (200ml) and the solid which separated (0.51g) was filtered off and discarded. The filtrate was evaporated to dryness and the oily residue mixed with ether (300ml) and the suspension filtered. The filtrate was evaporated to dryness to give a red gum which very slowly solidified to give the title compound (5.45g)

T.1.c System A (150:8:1), Rf 0.45

(b) 4-Methoxy-3-(4-methyl-1-piperazinyl)benzeneamine

To a solution of the product of step (a) (5.07g) in ethanol (70ml) was added a paste of Raney Nickel in water (2g). To the warmed suspension was added, with constant agitation, hydrazine hydrate (5ml) dropwise during 20min with occasional warming. After the main effervescence had ceased, the suspension was heated for 15min and then filtered with the aid of ethanol under nitrogen. The residues were kept moist and washed with ethanol and the combined filtrate and washings were evaporated to dryness with the aid of ethanol. The dark residue was reevaporated with ethanol (20ml), resuspended in ether (40ml) and the mixture filtered. The residue was washed with ether and dried to give a solid consisting of the title compound (2.365g)

T.l.c. System A (70:8:1), Rf 0.25.

Intermediate 28

(E)-4-Methoxy-3-[2-(2-pyridinyl)ethenyl]benzoic acid

A mixture of 3-iodo-4-methoxybenzoic acid (2.0g), 2-vinylpyridine (l.0ml), TEA (2.5ml), acetonitrile (3.3ml) and palladium acetate (0.15g) were heated at 115 - 120° for 48h. The reaction mixture was filtered through celite, and the pad was washed with ethyl acetate (50ml). The filtrate was extracted with saturated aqueous sodium bicarbonate solution (50ml), and the aqueous layer was washed with ethyl acetate (2x50ml). The aqueous extract was neutralised using 2N hydrochloric acid resulting in the formation of a cream-coloured precipitate. The precipitate was removed and dried in vacuo.

Recrystallisation from ethanol gave the title compound (0.68g) as a white microcrystalline solid, m.p. 187-191°.

Intermediate 29

4-Methoxy-3-[2-(2-pyridinyl)ethyl]benzoic acid

Intermediate 28 (98mg) was dissolved in glacial acetic acid (5ml). This solution was added to PdOC (50% aqueous paste, 40mg) in glacial acetic acid (4ml) and the mixture was stirred under 1 atmosphere of hydrogen for 90 min. The catalyst was removed by filtration through celite, and the filtrate was evaporated in vacuo to give an off-white solid. The solid was crystallised from ethanol to give the title compound (80mg) as a white microcrystalline powder, m.p. 193-196°.

Intermediate 30

4-Methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzoic acid

Intermediate 29 (200mg) was dissolved in DMF (l0ml) and methyl iodide (0.2ml) was added. The mixture was kept at room temperature for 70h. Further methyl iodide (0.lml) was added, and the mixture kept at room temperature for 22h. A further portion of methyl iodide (0.lml) was added and the mixture was kept at room temperature for 20h. The solution was evaporated in vacuo to remove the excess methyl iodide, and Adams catalyst (25mg) was added. The mixture was hydrogenated at 50 psi for 6h. The catalyst was removed by filtration and the solvent was evaporated in vacuo. Re-evaporation with ethyl acetate, followed by trituration with ethyl acetate gave the hydroiodide of the title compound as a white powder (282mg). Purification of a sample of the hydroiodide by FCC eluting with isopropanol:ether:water:aqueous ammonia (20:20:8:1) gave the title compound as a white solid, m.p. 162-165°.

Intermediate 31

(E)-3-(2-Methoxy-5-nitrophenyl)2propenenitrile mixture with (Z) (1:1)

A solution of 2-iodo-1-methoxy-4-nitrobenzene (500g), acrylonitrile (0.14ml), TEA (0.62ml) and acetonitrile (1.2ml), was treated with palladium acetate (28mg) and heated

at 110° for 16h. When cool the mixture was poured into aqueous saturated sodium bicarbonate (30ml), extracted into ethyl acetate (3x30ml), and the combined, dried organic extracts were evaporated and purified by SPC eluting with System C (4:1 to 7:3) to give the title compound (128mg) as white crystals.

T.l.c. System C (2:1) Rf 0.11

Intermediate 32

5-Amino-2-methoxy-N,N-dimethylbenzenepropanamine

A solution of Intermediate 31 (4.33g) in dry THF (80ml) and ethanolic dimethylamine (33% w/v, 80ml) was added to a suspension of 10% PdOC (2.00g) in ethanol (30ml) and the stirred mixture hyrogenated at room temperature and pressure for 5h. The catalyst was filtered off and the filtrate evaporated. A solution of the filtrate in ethanolic dimethylamine (100ml) was added to a suspension of 10% PdOC (2.00g) in ethanol (30ml) and the stirred mixture hydrogenated at room temperature and pressure for 16h. The catalyst was once again replenished as above and hydrogenation continued for 70h. The catalyst was filtered off and the filtrate was purified by SPC with gradient elution using System A (945:50:5 to 912:80:8) to afford the title compound (3.20g) as a light brown oil.

T.l.c. System A(89:10:1) Rf 0.12.

Intermediate 33

3,4-Dimethoxy-5-nitrobenzoic acid

To a solution of potassium permanganate (3.05g) in water (100ml) was added to a solution of 3,4-dimethoxy-5-nitrobenzaldehyde (2.7g) in acetone (80ml). The mixture was then stirred at 20° for 18h whereupon the acetone was evaporated and the residue acidified (2N HCl) and was then decolourised by the addition of sodium metabisulphite The mixture was then extracted with ethyl acetate (3x200ml) and the dried extracts evaporated to give the title compound as a colourless solid (2.08g) m.p. 197-198°.

Intermediate 34

Methyl 3,4-dimethoxy-5-nitrobenzoate

Intermediate 33 (lg) was dissolved in methanol:conc. sulphuric acid (9:1; 20ml) and was stirred at 20 for 2h, and was then heated to reflux for 2h. The cooled mixture was added to 8% $NaHCO_3$ solution (50ml). The methanol was then evaporated and the residue extracted with ethyl acetate (2x75ml). The dried extracts were evaporated to give the title compound as a cream solid (lg), m.p. 75-76.

Intermediate 35

Methyl 3-amino-4,5-dimethoxybenzoate

A solution of Intermediate 34 (990mg) in ethanol (15ml) was hydrogenated over 10% PdC for about 5h. The mixture was filtered and was evaporated to give a pale pink oil which crystallised to give the title compound (883mg).

T.l.c. ethyl acetate:hexane (1:2) Rf 0.15.

Intermediate 36

Butyl 3,4-dimethoxy-5-(4-methyl-1-piperazinyl)benzoate

A mixture of Intermediate 35 (868mg), sodium carbonate (1.74g) and 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (791mg) in n-butanol (35ml) was heated to reflux for 48h. The mixture was allowed to cool and the solvent evaporated. Water (40ml) was added and the mixture extracted with ethyl acetate (2x50ml). The dried extracts were evaporated to give a red oil (1.55g) which was chromatographed on silica gel eluting with System A (200:8:1) to give the title compound as red oil (276mg)

T.l.c. System A (200:8:1) Rf 0.24

Intermediate 37

Methyl 3,4-dimethoxy-5-(4-methyl-1-piperazinyl)benzoate

A mixture of Intermediate 36 (1.9g), 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (1.73g) and sodium carbonate (3.81g) in 3-methyl-3-pentanol (70ml) was heated to reflux for 42h. The solvent was evaporated and the residue partitioned between

water (100ml) and ethyl acetate (2xl00ml). The dried extracts were evaporated to give a pale yellow oil (2.2g). This material was chromatographed eluting with System A (200:8:1) to give the title compound as a pale yellow oil which crystallised on standing (369mg).

T.l.c. System A (200:8:1) Rf 0.3

Intermediate 38

3,4-Dimethoxy-5-(4-methyl-1-piperazinyl)benzoic acid hydrazide

Intermediate 37 (651mg) was dissolved in methanol (15ml) containing hydrazine hydrate (2ml) and was heated to reflux for 18h. The cooled mixture was evaporated and the residue partitioned between water (30ml) and dichloromethane (2x30ml). The dried extracts were evaporated to give the title compound as a colourless solid (520mg).

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

Intermediate 39

3,4-Dimethoxy-5-(4-methyl-1-piperazinyl)benzenamine

Intermediate 38 (510mg) in water (5ml) was treated with conc. HCl (5ml), cooled (0°), and a solution of sodium nitrite (144mg) in water (2ml) added over 5min. Stirring was continued at 0° for 20min, then at 20° for lh. Conc. HCl (5ml) and glacial acetic acid (5ml) were then added, and the mixture heated to reflux for 2h. The cooled mixture was poured into 2N NaOH (l00ml) and was then extracted with ethyl acetate (2xl00ml). The dried extracts were evaporated to give a brown oil. This was chromatographed eluting with System A (100:8:1) to give the title compound as a red-brown oil which crystallised (139mg).

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

Example 1

(a) 3-[3-(Dimethylamino)propyl]-4-methoxy-N-(4-propylphenyl)benzamide hydrochloride

A solution of Intermediate 3 (2.90g) in dimethylamine (33% w/v in ethanol 160ml) and DMF (70ml) was added to a stirred suspension of 10% PdOC (2.5g) in ethanol (30ml) and the mixture hydrogenated at room temperature and pressure for 3 days. The mixture was filtered, the filtrate added to a stirred suspension of 10% PdOC (2g) in ethanol (30ml) and the mixture hydrogenated at room temperature and pressure for 2 days. The mixture was filtered and the filtrate evaporated. The residue was purified by SPC (Merck 7729) eluting with System E (89:10:1) to give the free base of the title compound (1.85g). A solution of the free base (578mg) in hot ethyl acetate (l0ml) was acidified with ethereal hydrogen chloride, diluted with ether (l0ml), and stirred at room temperature for 2h to give the title compound (527mg) as white crystals m.p. 175-178°.

Analysis Found: C,67.4; H,8.3; N,7.0; Cl,9.1.

$C_{22}H_{30}N_2O_2$.HCl requires C,67.6; H,8.0; N,7.2; Cl,9.1%.

Similarly were prepared:

(b) 3-[3-(Dimethylamino)propyl]-4-methoxy-N-(4-propoxyphenyl)benzamide hydrochloride (121mg) m.p. 189-192°.

Analysis Found : C,64.7; H, 7.8;N,6.8;Cl,8.9.

$C_{22}H_{30}N_2O_3$ .HCl requires C,64.9;H, 7.7;N,6.9;Cl,8.7%.

From the corresponding free base (452mg) with purification by crystallisation from ethanol. The free base (1.47g) was obtained as above in Example l(a) from Intermediate 4 (3.04g) and ethanolic dimethylamine (190ml).

(c) Ethyl 4-[[[3-[3-(dimethylamino)propyl]-4-methoxyphenyl]carbonyl]amino]benzoate hydrochloride (350mg)

T.l.c. (free base) System E (89:10:1) Rf 0.25;

Analysis Found: C,62.5;H,7.3;N,6.5.

$C_{22}H_{28}N_2O_4$.HCl requires C,62.8;H,6.9;N,6.7%

From the corresponding free base (420mg). The free base (2.45g) was obtained as above in Example l(a) from Intermediate 5 (4.66g) and ethanolic dimethylamine (300ml) except that the residue was purified by SPC eluting with System E (94:5:1).

Example 2

(a) 3-[3-(Dimethylamino)propyl]-N-(4-ethoxyphenyl)-4-methoxybenzamide hydrochloride

A suspension of Intermediate 6 (2.35g) in ethanolic dimethylamine (25% w/v, 800ml) was added to 5% PtOC (2.0g) in ethanol (20ml) and the rapidly stirred mixture hydrogenated at room temperature and pressure. The catalyst was filtered off and the filtrate evaporated. The resultant white solid was purified by FCC eluting with System G (88:10:2) to give the free base of the title compound (1.60g). T.l.c. System G (88:10:2) Rf 0.15.

The free base of the title compound (760mg) was dissolved in ethanolic hydrogen chloride (15ml), ether (75ml) was added, and the precipitate filtered off to give the title compound (460mg)as fine white crystals, m.p. 184-188°.

Analysis Found: C,61.25;H,7.15;N,6.6;Cl,12.65.

$C_{21}H_{28}N_2O_3.1.5HCl$ requires C,61.35;H,7.25;N,6.8;Cl,12.95%.

Similarly were prepared :

(b) 3-[3 (Dimethylamino)propyl]-4-methoxy-N-phenylbenzamide hydrochloride (492mg) m.p. 159-161.5°.

T.l.c. System G (93:5:2) Rf 0.18.

From the corresponding free base (517mg) except that the acidified solution was evaporated and the residue triturated with ethyl acetate instead of adding ether. The free base (m.p. 117.5-119.5°) was obtained (3.28g) as above in Example 3(a) from Intermediate 8 (3.78g) and ethanolic dimethylamine (200ml) except that purification was carried out using FCC eluting with System G (93:5:2).

(c) 3-[2-(Dimethylamino)ethyl]-N-(4-ethoxyphenyl)-4-methoxybenzamide hydrochloride (0.84g) m.p. 212-213°.

T.l.c. System A (150:10:1) Rf 0.30.

From the corresponding free base (0.80g). The free base was obtained (2.21g) as above in Example 3(a) from Intermediate 9 (2.5g) and ethanolic dimethylamine (50ml) except that purification was carried out using FCC eluting with System A (150:10:1).

Example 3

2-Methoxy-N,N-dimethyl-5-[[(4-propoxyphenyl)amino]methyl]benzenepropanamine maleate

A solution of Example 1(b) (992mg) in dry THF (25ml) was added under nitrogen to a stirred suspension of LAH (254mg) in dry THF (10ml) and the mixture heated under reflux for 2h. The cooled mixture was cautiously treated with a solution of water (3ml) in THF (12ml), evaporated, and the residue treated with brine (60ml) and ethyl acetate (60ml). The precipitate was filtered off and washed with ethyl acetate (420ml). The washings were used (in seven portions) to extract the aqueous layer of the filtrate and the combined, dried organic layers were evaporated. The residual oil was purified by SPC (Merck 7729) eluting with System A (945:50:5) to give firstly an oil and secondly the pure free base of the title compound (616mg) as an oil. T.l.c. System A (89:10:1) Rf 0.36.

A stirred mixture of the free base of the title compound (582mg) and maleic acid (158mg) in ethanol (8ml) was heated to reflux, filtered and the filtrate on cooling gave the title compound (361mg) as white needles, m.p. 102-104°.

Analysis Found: C,66.4;H,7.8;N,5.7.

$C_{22}H_{32}N_2.O_2C_4H_4O_4$ requires C,66.1;H,7.7;N,5.9%.

Example 4

5-[[(4-Ethoxyphenyl)amino]methyl]-2-methoxy-N,N-dimethylbenzenepropanamine maleate

A slurry of Example 3(a) (1.018g) in THF (20ml) was added dropwise under nitrogen with stirring and ice-cooling to a slurry of LAH (0.14g) in THF (5ml). The mixture was heated under reflux for 3h, cooled to 5°, and further LAH (0.14g) was added. The mixture was heated under reflux for a further 16h, and then at 0°, water (5ml) in THF (20ml) was added dropwise. The mixture was diluted with water (70ml), acidified to pHl by the addition of aqueous 2M hydrochloric acid, and then basified to pH9 by the addition of aqueous saturated sodium bicarbonate. The mixture was extracted with ethyl acetate (3x90ml), and the combined, dried extracts were evaporated. The residual oil was purified by FCC eluting with System G (93:5:2 to 90:8:2) to give the free base of the title compound (712mg) as a pale yellow oil. T.l.c. System G (88:10:2) Rf 0.2.

The free base of the title compound (582mg) was treated with a solution of maleic acid (197mg) in ethanol (15ml) and the solution evaporated. The resultant solid was stirred in ether (40ml) and filtered off to give the title compound (710mg) as buff crystals, m.p. 105-110°.

Analysis Found: C,65.2;H,7.6;N,6.0.

$C_{21}H_{30}N_2O_2.C_4H_4O_4$ requires C,65.5;H,7.45;N,6.1%.

Example 5

5-[[(4-Ethoxyphenyl)amino]methyl]-2-methoxy-N,N-dimethylbenzeneethanamine maleate

A solution of Example 3(c) (800mg) in dry THF (10ml) was added dropwise under nitrogen to a stirred suspension of LAH (270mg) in dry THF (5ml). The mixture was heated to reflux, stirred for 3.5h, and then cooled in ice. The suspension was carefully diluted sequentially with aqueous THF (15%H_2O; 5ml), water (7ml) and ethyl acetate (7ml), saturated with solid sodium chloride and filtered. The two phases in the filtrate were separated, and the organic layer washed with brine (10ml), dried and concentrated in vacuo. FCC of the residual colourless oil eluting with System A (150:10:1) afforded a colourless oil (670mg). A portion of this oil (570mg) was dissolved in refluxing absolute ethyl acetate (2ml) and a solution of maleic acid (210mg) in refluxing absolute ethanol (1ml) was added. The stirred solution was diluted with dry ether (25ml), and the resultant

solid was filtered off, washed with dry ether (2xl0ml) and dried in vacuo at 60° to give the title compound (560mg) as a fawn solid. T.l.c. System A (150:10:1) Rf 0.29.

Analysis Found: C,64.1;H,7.8;N,6.1.

$C_{20}H_{28}N_2O_2.C_4H_4O_4$ $0.25H_2O$ requires C,64.2;H,7.3;N,6.2%.

Example 6

2-Methoxy-N,N-dimethyl-5-[(phenylamino)methyl]benzenepropanamine 4-methylbenzenesulphonate

A solution of the free base of Example 3(b) (1.0g) in THF (20ml) was added over 2 min to a stirred slurry of LAH (0.30g) in THF (l0ml) under nitrogen, and the mixture heated under reflux for 2h. When cool, water (5ml) in THF (20ml) was added dropwise over 5min, with ice-cooling, and the resultant mixture filtered, washing the precipitate with THF (50ml). The filtrate was evaporated, treated with water (20ml), and extracted with ethyl acetate (3x40ml). The combined, dried organic extracts were evaporated and purified by FCC eluting with System G (95:3:2) to afford the free base of the title compound as a colourless oil (857mg). A hot solution of the free base of the title compound (691mg) in ethanol (l0ml) was added to a hot solution of 4-methylbenzenesulphonic acid monohydrate (441mg) in ethanol (l0ml) and the solution filtered whilst hot. On cooling the title compound (845mg) crystallised as fine white needles, m.p. 148.5-150.5°.

Analysis Found: C,66.3;H,7.25;N,5.9;S,6.85.

$C_{19}H_{26}N_2O.C_7H_8O_3S$ requires C,66.35;H,7.3;N,5.95;S,6.8%.

Example 7

N-(4-Butoxyphenyl)-3-[3-(dimethylamino)propyl]-4-methoxybenzamide hydrochloride

MSC (0.4ml) was added under nitrogen to a stirred, ice-cooled suspension of Intermediate 8 (1.0g) and TEA (1.5ml) in dry THF (25ml) and dry DMF (l0ml). The mixture was stirred at 0° for 0.25h, a solution of 4-butoxybenzeneamine (0.85g) in dry DMF (10ml) was added, and stirring continued for 25h at room temperature. The resultant mixture was partitioned between 2N sodium carbonate (l00ml) and ethyl acetate

(3x50ml). The combined organic layers were washed with 2N sodium carbonate (70ml), water (70ml) and brine (70ml), dried and concentrated in vacuo. The residual brown solid (1.54g) was purified by SPC (Merck 7729) eluting with System A (150:10:1), to give a yellow solid (173mg). This material was dissolved in refluxing ethyl acetate (2ml), allowed to cool, and stirred while ethereal hydrogen chloride (lml) was added, followed by dry ether (2ml). The resultant solid was washed with dry ether (3x5ml), filtered off, and dried in vacuo at 60° for 24h to give the title compound (0.12g) as a white solid m.p. 190-192°.

Analysis Found : C,65.6;H,8.0;N,6.6.

$C_{23}H_{32}N_2O_3.HCl$ requires C,65.6;H,7.9;N,6.65%.

Example 8

3-[3-(Dimethylamino)propyl]-4-methoxy-N-[4-(1-pyrrolidinyl)phenyl]benzamide dihydrochloride

MSC (0.75ml) was added under nitrogen to a stirred, ice-cooled suspension of Intermediate 8 (1.5g) and TEA (5.00ml) in a mixture of dry THF (25ml) and dry DMF (l0ml). The mixture was stirred at 0° for lh, and then 4-(1-pyrrolidinyl)benzeneamine dihydrochloride (2.75g) was added. The mixture was stirred at 0° for lh, at room temperature for 26h, and then left to stand for 72h. The dark mixture was partitioned between 2N sodium carbonate (150ml) and ethyl acetate (3x75ml) and the combined organic layers were washed with 2N sodium carbonate (l00ml) and water (l00ml). The organic solution was dried and concentrated in vacuo. The residual black oil (3.07g) was purified by SPC (Merck 7729) eluting with System A (150:10:1) to give a black solid. Crystallisation from ethyl acetate (2.5ml) gave a grey solid (135mg).

This material was dissolved in refluxing ethyl acetate (2ml), allowed to cool, and stirred while ethereal hydrogen chloride (lml) and dry ether (l0ml) were added. The precipitated gum was triturated with dry ether (4x5ml), and the resultant solid was filtered off, washed with dry ether (2x5ml) and dried in vacuo at 60° for 18h to give the title compound (138mg) as a grey solid.

T.l.c. System A(150:10:1) Rf 0.32.

Analysis found: C,59.35;H,7.6;N,8.4.

$C_{23}H_{31}N_3O_2.2HCl.0.75H_2O.\ 0.2C_4H_8O_2\ 0.1C_4H_{10}O$ C,59.0;H;7.6;N,8.5%

Example 9

2-Methoxy-N,N-dimethyl-5-[[(4-methylphenyl)amino]methyl]benzenepropanamine 4-methylbenzenesulphonate

A solution of the free base of Example l(c) (l.l0g) in dry THF (20ml) was added to a stirred suspension of LAH (0.54g) in dry THF (20ml) under nitrogen and the mixture stirred at reflux for 5h. When cool, a solution of water (5ml) in THF (15ml) was added cautiously. The mixture was then evaporated, and the residue treated with brine (l00ml). The mixture was shaken with ethyl acetate (l00ml), filtered, and the filtrate separated. The residue was washed with ethyl acetate (500ml) and the washings used to extract the aqueous layer of the filtrate (in five portions). The residue was boiled with ethyl acetate (200ml) for 10 min, filtered and the filtrate combined with the above organic extracts. The dried organic phase was evaporated and purified by FCC eluting with System E (94:5:1) to afford the free base of the title compound as a light yellow oil (210mg) T.l.c. System E, (89:10:1) Rf 0.19.

A hot solution of 4-methylbenzenesulphonic acid monohydrate (85mg) in ethanol (5ml) was added to the free base of the title compound (147mg) and on cooling, the title compound (108mg) separated as fine cream needles m.p. 142-144°

Analysis found: C,66.9;H,7.5;N,5.7;S,6.4.

$C_{20}H_{28}N_2O.C_7H_8O_3S$ requires C,66.9;H,7.5;N,5.8;S,6 6%

Example 10

3-[3-(Dimethylamino)propyl]-4-methoxy-N-[4-(methylthio)phenyl]benzamide maleate

A mixture of the free base of Intermediate 12 (2.0g), 4-methylthioaniline (1.36g), tri-n-butylamine (4.8ml) and BTPC (0.40g) was heated at 120°, with stirring under carbon monoxide for 18h. The reaction mixture was poured into 8% aqueous sodium bicarbonate (80ml) and extracted with ethyl acetate (5x70ml). The combined, dried organic extracts were evaporated to yield a yellow/brown oil. This was purified by SPC eluting with

System A (945:50:5) to yield a white solid (0.64g). The solid was recrystallised from acetonitrile (10ml) to give the free base of the title compound (0.34g) as a white solid. A portion of this material (250mg) was dissolved in hot ethanol (l0ml) and maleic acid (9Omg) in ethanol (2ml) was added. The resultant yellow solution was evaporated and the solid residue recrystallised from ethanol (2ml) to give the title compound (225mg) as white crystals, m.p. 147-149°.

Analysis Found: C,60.8; H,6.4; N,5.8.

$C_{24}H_{30}N_2O_6S$ requires C,60.7; H,6.4; N,5.9%.

Similarly prepared:

Example 11

N-(4-Chlorophenyl)-3-[3-(dimethylamino)propyl]-4-methoxybenzamide, maleate (0.23g), m.p. 137-138°.

Analysis Found: C,59.7; H,5.9; N,5.9.

$C_{23}H_{27}ClN_2O_6$ requires C,59.7; H,5.9; N,6.1%.

From the free base of Intermediate 12 (2.0g) and 4-chlorobenzeneamine (1.25g) with additional solvent DMF (2ml). A portion (0.30g) of the free base of the title compound (0.495g) was used to prepare the title compound.

Example 12

N-(4-Bromophenyl)-3-[3-(dimethylamino)propyl]-4-methoxybenzamide maleate (131mg), T.l.c System A (97:3:0.3) Rf 0.25,

Analysis Found: C,54.5; H,5.4; N,5.4.

$C_{19}H_{23}BrN_2O.C_4H_4O_4$ requires C,54.45; H,5.4; N,5.5%.

From 4-bromobenzeneamine (1.88g) and the free base of Intermediate 12 (3.50g) with additional solvent DMF (12ml), with purification by SPC (Merck 7729) using gradient elution with System A (945:50:5 to 923:70:7). A portion (l00mg) of the free base of the title compound (674mg) was used to prepare the title compound.

Example 13

N-[4-(Aminocarbonyl)phenyl]-3-[3-(dimethylamino)propyl-4-methoxybenzamide maleate

A solution of Intermediate 8 (1.0g) in a mixture of dry THF (32ml) and DMF (22ml) was stirred under nitrogen at room temperature, and TEA (1.18ml) was added. The colourless solution was cooled to -10° and MSC (0.32ml) was added. After 1.5h at -10°, 4-aminobenzamide (0.573g) in DMF (8ml) was added and stirring continued for 1h at -10°, 18h at room temperature and 2.5h at reflux. The cooled mixture was evaporated, treated with aqueous saturated sodium bicarbonate (50ml), and extracted with ethyl acetate (5x75ml), and the combined, dried extracts were evaporated to yield a pale brown solid (0.80g). This was dissolved in refluxing methanol (100ml), adsorbed onto silica gel (Merck 7734, 6g) and the resultant silica gel was applied as a plug to FCC eluting with chloroform:ethanol:0.88 ammonia (89:10:1) to afford the free base of the title compound (0.305g) as a white solid. A portion of this solid (0.10g) was dissolved in hot ethanol (10ml) and maleic acid (41mg) in warm ethanol (2ml) was added. The solution was evaporated, and the residual cream solid recrystallised from ethanol (8ml) to give the title compound (0.105g) as white crystals , m.p. 177-179°.

Analysis Found: C,61.4; H,6.1; N,8.8.

$C_{24}H_{27}N_3O_7$ requires C,61.4; H,5.8; N,9.0%.

Example 14

3-[3-(Dimethylamino)propyl]-N-[4-iodophenyl]-4-methoxybenzamide

Intermediate 8 (5.00g) was treated with thionyl chloride (20ml) and stirred at reflux for 7 min. When cool, the solution was evaporated and the residue coevaporated with toluene (2x20ml). 4-Iodoaniline (4.62g) and pyridine were added and the stirred mixture heated under nitrogen at reflux for 1.75h. When cool, aqueous saturated sodium bicarbonate (30ml) was added and the mixture evaporated. The residue was purified by FCC eluting with System A (945:50:5 to 912:80:8) to give the title compound (3.45g). Further elution afforded impure title compound which was recrystallised from ethanol, twice, to give the title compound (1.28g) as buff crystals, m.p. 161.5 - 162.5°

T.l.c. System A (89:10:1) Rf 0.27.

Example 15

3-[3-(Dimethylaminopropyl)]-N-[4-(4-hydroxy-1-butynyl)phenyl]-4-methoxybenzamide

A solution of Example 14 (1.41g), 3-butyn-1-ol (0.68ml), and TEA (3ml) in DMF (3ml) was treated with copper (I) iodide (52mg) and BTPC (95mg) at 23° under nitrogen with stirring. After 30 min aqueous saturated sodium bicarbonate (l0ml) was added. The solution was evaporated and the residue purified by FCC. Elution with System A (912:80:8) afforded an oil which was dissolved in hot ethanol (50ml) and filtered. The filtrate was evaporated and the residue crystallised from ethyl acetate to give the title compound (552mg) as fine white crystals, m.p. 125-126°.

T.l.c. System A (89:10:1) Rf 0.15.

Example 16

3-[3-(Dimethylamino)propyl]-N-[4-(4-hydroxybutyl)phenyl]-4-methoxybenzamide

A solution of Example 15 (580mg) in ethanol (20ml) was added to a suspension of dry 5% palladium oxide on activated carbon (320mg) in ethanol (l0ml) and the stirred mixture hydrogenated at room temperature and pressure until uptake ceased. The catalyst was filtered off and the filtrate evaporated. The residue was crystallised from ethyl acetate (2.5ml) to give the title compound (274mg) as fine white crystals, m.p. 109 -111°

T.l.c. System A (835:150:15) Rf 0.23.

Example 17

3-[3-(Dimethylamino)propyl]-N-[4-(3-hydroxypropyl)phenyl]-4-methoxybenzamide oxalate

A solution of Example 14 (2.00g), 2-propyn-1-ol (0.75ml), and TEA (4ml) in DMF (4ml) was treated with copper (I) iodide (74mg) followed by BTPC (135mg) and stirred under nitrogen. After 30 min, aqueous saturated sodium bicarbonate (20ml) was added, and the mixture evaporated. The residue was purified by FCC eluting with System A (912:80:8 to 890:100:10) to give a yellow oil (1.30g). The oil was further purified by SPC eluting with System A (912:80:8 to 890:100:10) to give 3-[3-(dimethylamino)propyl]-N-[4

(3-hydroxy-1-propynyl)phenyl]-4-methoxybenzamide (1.13g). This was dissolved in ethanol (20ml), added to a suspension of dry 5% PdOC (0.6g) in ethanol (10ml) and hydrogenated at room temperature and pressure until uptake ceased. The catalyst was filtered off and the filtrate evaporated. The residual oil (1.06g) was treated with oxalic acid dihydrate (500mg), followed by ethanol (50ml) and heated to reflux. The solution was filtered, concentrated to 8ml, and heated to reflux. On cooling the title compound (647mg) crystallised as buff crystals.

T.l.c. System A (89:10:1) Rf 0.10.

Analysis Found: C,61.9; H,6.9; N,6.0;

$C_{22}H_{30}N_2O_3.C_2H_2O_4$ .0.27 H_2O requires C,61.9; H,7.05; N,6.0%

Water assay Found: 1.06% w/w H_2O = 27mol.

Example 18

Ethyl 5-[4-[[[3-[3-(dimethylamino)propyl]-4-methoxyphenyl]carbonyl]amino]phenoxy] pentanoate hydrochloride

Thionyl chloride (4ml) was added to the hydrochloride salt of Intermediate 8 (0.82g). The mixture was heated on a steam bath for 5min and the solution evaporated to dryness in vacuo with the aid of toluene (2x5ml) to give 3-[(3-dimethylamino)propyl]-4-methoxybenzoyl chloride hydrochloride. To this was added pyridine (10ml) and Intermediate 14 (0.71g). The mixture was heated on a steam bath for 20min and the pyridine evaporated in vacuo. The residue was mixed with water (20ml), sodium carbonate (3g) was added and the mixture was evaporated to dryness and the residue mixed with water (60ml). The suspension was extracted with ethyl acetate (2x60ml) and the extracts washed with water (20ml). The combined extracts were dried and evaporated in vacuo to give a solid which was suspended in ether (10ml) and filtered. The residue was washed with ether and dried to give a solid consisting of the free base of the title compound. To a solution of the free base (0.4g) in ethyl acetate (3ml) was added excess ethereal hydrogen chloride (4ml). The mixture was evaporated in vacuo to give a solid which was suspended in ether and filtered. The residue was washed with ether and dried to give the title compound (0.415g) m.p. 160-162°.

Analysis Found: C,63.1; H,7.6; N,5.5; Cl,7.2.

$C_{26}H_{36}N_2O_5.HCl$ requires C,63.3; H,7.6; N,5.7; Cl,7.2%.

Similarly prepared:

Example 19

3-[3-(Dimethylamino)propyl]-N-(4-hydroxyphenyl)-4-methoxybenzamide hydrochloride (0.569g) m.p. 215-217°,

Analysis Found: C,61.75; H,7.0; N,7.3; Cl,9.2.

$C_{19}H_{24}N_2O_3.HCl.0.145\ H_2O$ requires C,62.1; H,6.9; N,7.6; Cl,9.65%.

Water Analysis Found 0.71% w/w H_2O equivalent to 0.145mol H_2O

From Intermediate 8 and 4-hydroxybenzenamine (0.33g), except that the free base obtained on evaporation of the ethyl acetate extracts was redisolved in ethyl acetate and treated with an excess of ethereal hydrogen chloride. The suspension waq evaporated to dryness in vacuo and the residue re-evaporated with acetone until the residue became a solid. This was dissolved in boiling ethanol, the solution evaporated to low bulk and the solid which separated on cooling, filtered, washed with ethanol then acetone and dried to give the title compound.

Example 20

3-[3-(Dimethylamino)propyl]-4-methoxy-N-[4-(4-morpholinyl)phenyl]benzamide hydrochloride (0.57g) m.p. 244-246°.

T.l.c. System A (70:8:1) 0.48

From the hydrochloride salt of Intermediate 8 (0.78g) and 4-(4-morpholinyl) benzeneamine (0.53g). Except that the reaction mixture was heated on a steam bath for 15min then poured into water (20ml) and anhydrous sodium carbonate (3g) added. The mixture was evaporated to dryness and the residue re-evaporated with water (20ml). The solid was mixed with water (40ml) and the mixture filtered and the residue washed with water and dried. The solid was crystallised from ethanol:ether to give the free base of the title compound (0.781g) m.p. 173-174°.

To a solution of the base (0.5g) in ethanol (10ml) was added excess of ethereal hydrogen chloride. The solution was evaporated to low bulk (4ml) and then diluted with acetone (25ml). The solid was filtered and the residue washed well with acetone, then ether and dried to give the title compound.

Example 21

5-[4-[[[3-[3-(Dimethylamino)propyl]-4-methoxyphenyl]carbonyl]amino]phenoxy] pentanoic acid hydrochloride (0.412g)

T.l.c. System A (30:19:1) Rf 0.33

Analysis Found: C,61.6; H,7.2; N,6.3.

$C_{24}H_{32}N_2O_5HCl$ requires C,62.0; H,7.15; N,6.0%.

From the hydrochloride salt of Intermediate 8 (0.86g) and 5-(4-aminophenoxy)pentanoic acid (0.63g). The reaction mixture was evaporated in vacuo and the residue re-evaporated with water (20ml) then ethanol (20ml) to give an oily residue. 0.88 Ammonia solution (4ml) was added and the mixture re-evaporated to dryness. The residue was purified by FCC eluting with System F (30:19:1) to give a gummy residue. This was suspended in hot acetone and the powder which formed was filtered, washed with acetone and dried to give the title compound.

Example 22

N-[4-[(5-Amino-5-oxopentyl)oxy]phenyl]-3-[(dimethylamino)propyl]-4-methoxybenzamide maleate (1:1) (0.317g), m.p. 148-149°.

Analysis Found: C,61.4; H,6.6; N,7.3.

$C_{28}H_{37}N_3O_8.0.14\ H_2O$ requires C,61.6; H,6.9; N,7.7%.

Water assay: (0.14mol H_2O)

From Intermediate 8 (0.53g) and Intermediate 15 (0.38g). Charcoal was added to the combined, dried ethyl acetate extracts. The mixture was heated to boiling and filtered and the combined filtrates and washings evaporated in vacuo to give a buff powder (0.362g) which was crystallised from ethyl acetate to give the free base of the title compound (0.307g) m.p. 167-169°.

To a saturated solution of the free base (0.237g) in acetone was added a solution of maleic acid (0.08g) in acetone (8ml). The solid which separated was filtered, washed with acetone and dried to give the title compound.

Example 23

3-[3-(Dimethylamino)propyl]-N-[4-(4-hydroxy-1-pentynyl)phenyl]-4-methoxybenzamide DL-tartrate

A solution of the free base of Example 12 (5.0g), (±)-4-pentyn-2-ol (2.4ml) and TEA (12ml) in DMF (15ml) was treated with copper (I) iodide (0.207g) and BTPC (0.377g) and the reaction stirred under nitrogen at room temperature for 4h. The mixture was stirred at 70-80°C for 3h, then at 110°C for 2.5h. Further (±)-4-pentyn-2-ol (2.4ml), copper (I) iodide (0.103g) and BTPC (0.11g) were added and the mixture stirred at 110°C for 2h. When cool, aqueous sodium bicarbonate (8% w/w, 40ml) was added and the mixture evaporated. The residue was refluxed in ethanol (200ml), adsorbed onto silica gel (Merck 7734, 80ml) and purified by FCC. Gradient elution with System A (467:30:3 to 923:70:7) yielded the free base of the title compound as an orange/brown oil (3.91g). A portion of this (3.88g) was treated with DL-tartaric acid (2.22g) and the title compound crystallized from refluxing ethanol (15ml) (4.59g).

T.l.c. System A (114:10:1) Rf 0.21

Analysis Found: C,59.6; H,6.3 N,4.7.

$C_{24}H_{30}N_2O_3 1.1C_4H_6O_6\ 0.71H_2O$ requires C,59.6; H,6.7; N,4,9%

Water assay Found 2.29% H_2O w/w $\equiv$ 0.71mol H_2O

Example 24

3-[3-(Dimethylamino)propyl]-N-[4-(4-hydroxypentyl)phenyl]-4-methoxybenzamide citrate

A solution of the free base of Example 23 (3.32g) in ethanol (70ml) was added to a prehydrogenated mixture of 10% palladium on carbon (2.01g) in ethanol (20ml) and the stirred mixture hydrogenated at room temperature for 1.25h. The mixture was filtered washing the filter-pad with ethanol (2 litres) and the combined filtrates evaporated. The

residue was adsorbed onto silica gel (Merck 7734, 30ml) from ethanol and purified by FCC. Elution with System A (467:30:3) yielded the free base of the title compound as a hydroscopic brown/orange gum (1.6g) A portion of the free base (0.340g) was treated with citric acid hydrate (0.246g) and the title compound crystallized from ethanol (3ml) as a light brown solid (0.357g)

T.l.c. System A (114:10:1) Rf 0.18.

Analysis Found: C,58.4; H,7.3; N,4.0.

$C_{24}H_{34}N_2O_3 1.3C_6H_8O_7$ $0.31H_2O$ requires C,58.4; H,6.9; N,4.3%.

Water assay found 0.94% H_2O w/w = 0.31mol H_2O.

Example 25

3-[-3-(Dimethylamino)propyl]-4-methoxy-N-[4-(4-oxopentyl)phenyl]benzamide

A solution of sieve-dried DMSO (0.68ml) in sieve-dried dichloromethane (6.2ml) was added dropwise to a stirred solution of oxalyl chloride (0.37ml) in sieve-dried dichloromethane (6.2ml) at -60 to -70°C under nitrogen over 10min. After 10min at -70°C, a solution of the free base of Example 24 (1.178g) in sieve-dried dichloromethane (25ml) was added dropwise at -60 to -70°C over 20min and the solution stirred at -70°C for 20min. TEA (3.0ml) was added at -60 to -70°C over 3min, the cooling bath removed, and the solution stirred for 2h. The solution was poured into aqueous sodium bicarbonate (85ml, 8% w/w) and the organic layer separated. The aqueous phase was extracted with ethyl acetate (3x85ml) and the combined, dried organic extracts evaporated, then adsorbed onto silica gel (Merck 7734, 15ml) from ethanol (100ml). Purification by FCC eluting with a gradient of System A (967:30:3 to 239:10:1) yielded the slightly impure title compound as a yellow brown oil (0.752g). This oil was dissolved in dichloromethane (20ml) and purified by SPC (Merck 7729) eluting with System A (967:30:3) to give the pure title compound as a yellow gum (395g).

T.l.c. System A (114:10:1) Rf 0.43.

Analysis Found: C,71.9; H,8.4; N,6.9.

$C_{24}H_{32}N_2O_3.0.40H_2O$ requires C,71.4; H,8.2; N,6.9%.

Water assay Found 1.80% H_2O w/w = 0.40mol H_2O

Example 26

3-[3-(Dimethylamino)propyl]-N-[4-3-hydroxypropoxy)phenyl]-4-methoxybenzamide

The hydrochloride salt of Intermediate 8 (1.5g) was treated with thionyl chloride (9ml) and stirred at reflux for 20min. When cool, the solution was evaporated and then coevaporated with toluene (2x20ml). The residue was treated with Intermediate 16 (0.9g) followed by pyridine (8ml) and then stirred at 110° under nitrogen for 18h. When cool, aqueous saturated sodium bicarbonate (50ml; 8%) was added and the mixture evaporated. The residue was partially purified by SPC eluting with System A (98:2:0.2). H.p.l.c. purified the mixture and gave the title compound as a brown solid (l.lg) of which a portion (300mg) was recrystallised from ethyl acetate m.p. 118-120°C

Analysis Found: C,67.9; H,7.9; N,7.1.

$C_{22}H_{30}N_2O_4$ 0.05 H_2O 0.1 $CH_3COOC_2H_5$ requires C,67.9; H,7.9; N,7.1%.

Water assay Found 0.24% w/w H_2O = 0.05mol H_2O

Example 27

4-(4-Acetylphenyl)-3-[3-(dimethylamino)propyl]-4-methoxybenzamide hydrochloride

A mixture of Intermediate 8 (0.52g) and thionyl chloride (3ml) was heated for 5 min on a steam bath, then evaporated and then coevaporated in vacuo with toluene (l0ml) and the solid residue was dried under vacuum. The residue was suspended in pyridine (4ml), 4-acetylbenzeneamine (0.27g) added and the mixture heated on a steam bath for 20min. The pyridine was evaporated in vacuo and water (15ml) added. The mixture was re-evaporated to dryness and water (20ml) added. The solid residue was filtered, the residue washed well with water and dried. The solid was disssolved in boiling isopropyl acetate (30ml) and the hot solution filtered. The crystals which separated on cooling were filtered, washed with isopropyl acetate and dried to give the free base of the title compound (0.377g) m.p. 145-146°. To the isopropyl acetate filtrate was added an excess of a solution of hydrogen chloride in ether. The suspension was evaporated to dryness to give a dark solid which was repeatedly extracted with boiling acetone. The extract was filtered whilst boiling and the filtrate evaporated to dryness in vacuo. The residue was

suspended in cold acetone and filtered and the residue was washed with acetone and dried to give the title compound (0.190g) m.p. 225-227°.

Analysis Found: C,63.2; H, 7.1; N,6.8; Cl,8.7

$C_{21}H_{26}N_2O_3.HCl.0.38\ H_2O$ requires C,63.4;H,7.0; N,7.0; Cl,8.9%.

Water Analysis indicates 1.73% w/w H_2O = 0.38mol H_2O.

Example 28

N-(4-Bromophenyl)-3-[3-(dimethylamino)propyl]-4-hydroxybenzamide

To a solution of boron tribromide in dichloromethane (lM; 112.8ml) was added a portion of the free base of Example 12 (1.32g) under nitrogen and the mixture stirred for 5h. Methanol (20ml) was added to the mixture, under nitrogen, to give an orange solution. The solvent was evaporated in vacuo. The residue was adsorbed onto silica gel (Merck 9385, 8g) and applied as a plug to a column of silica gel (Merck 9385). Elution with System A (189:10:1) gave the title compound as a white powder (700mg), m.p. 184-187°

Analysis Found C,57.2; H.5.7; N,7.2.

$C_{18}H_{21}BrN_2O_2$ requires C,57.3; H,5.6; N,7.4%

Example 29

N-(2-Bromophenyl)-3-[3-(dimethylamino)propyl]-4-methoxybenzamide

The hydrochloride salt of Intermediate 8 (lg) was treated with thionyl chloride (7ml) and stirred at reflux for 20 min. When cool, the solution was evaporated and then coevaporated with toluene (2x25ml). The residue was treated with o-bromobenzenamine (660mg), followed by pyridine (8ml) and then stirred at 110° under nitrogen for 5h. When cool, aqueous saturated sodium bicarbonate (70ml) was added and the mixture evaporated. The residue was purified by SPC eluting with System A (98:2:0:2) to give the title compound as a cream coloured solid (1.12g).m.p. 88-90°C.

Analysis Found C,58.3; H,6.2; N,7.1; Br,20.6.

$C_{19}H_{23}BrN_2O_2\ 0.045\ H_2O$ requires C,58.2; H,6.3; N,7.; Br, 20.4%

Water assay Found: 0.2% w/w H_2O = 0.045mol H_2O

Example 30

N-(4-Bromo-3-methylphenyl)-3-[3-(dimethylamino)propyl]-4-methoxybenzamide

A mixture of the hydrochloride salt of Intermediate 8 (2.00g) and thionyl chloride (20ml) was heated at reflux for lh. The excess thionyl chloride was evaporated under reduced pressure. A mixture of the resulting solid and 4-bromo-3-methylbenzenamine (1.50g) in dry pyridine (20ml) was heated at reflux for 30min. The solvent was evaporated and the residue adsorbed onto silica gel. The silica gel residue was purified by FCC eluting with System A (150:8:1) to give the title compound as a brown gum. (2.82g)

T.l.c. System A (100:8:1) Rf 0.30.

Analysis Found: C,59.5; H,6.1; N,6.7.

$C_{20}H_{25}BrN_2O_2$ requires C,59.3; H,6.2; N,6.9%.

Example 31

Cis-3-[3-(Dimethylamino)propyl]-N-4-(4-hydroxycyclohexyl)phenyl]-4-methoxybenzamide citrate

3-[3-(Dimethylamino)propyl]-4-methoxybenzoyl chloride hydrochloride (805 mg) (prepared from the hydrochloride salt of Intermediate 8 and thionyl chloride)was added in portions over 30 min to a stirred solution of Intermediate 19 (511 mg) in pyridine (10 ml) at 0° under nitrogen. After 30 min at 0°, the solution was stirred at 23° for 45 min, then at 80° for 30 min. When cool, aqueous saturated sodium bicarbonate (20 ml) was added and the mixture evaporated. The residue was stirred in hot ethanol (50 ml) and the mixture adsorbed onto silica gel (Merck 7734, 15 ml). Purification by FCC eluting with a gradient of System A (945:50:5 to 912:80:8) afforded the free base of the title compound as a cream foam (1.095g). A portion of the free base (200 mg) and citric acid monohydrate (140mg) were heated in ethanol (9 ml) to reflux, and on cooling the title compound crystallised as a fine white solid (156 mg)

T.l.c. System A (89:10:1) Rf. 0.14.

Analysis Found : C, 60.2; H, 7.1; N, 4.4.

$C_{25}H_{34}N_{34}N_2O_3$. $C_6H_8O_7$.0.86 H_2O requires C, 60.2; H, 7.1; N, 4.5%

Water assay Found : H_2O, 2.52% w/w $\equiv$ 0.86 mol.

Example 32

3-[3-(Dimethylamino)propyl]-4-methoxy-N-[4-(4-oxocyclohexyl)phenyl]benzamide

A solution of sieve-dried DMSO (0.22ml) in dry dichloromethane (2ml) was added dropwise under nitrogen to a stirred solution of oxalyl chloride (0.12ml) in dichloromethane (2ml) at -72° over 5min. After l0min at -72°, a solution of the free base of Example 31 (385mg) in dry dichloromethane (8ml) was added dropwise over 5min and then stirred at -72° for 15min. TEA (0.89ml) was added over 5min and the cooling bath was then removed. After stirring for 1.5h at 23° the solution was poured into aqueous saturated sodium bicarbonate (20ml) and the organic layer was separated. The aqueous phase was extracted with dichloromethane (4x25ml) and the combined, dried organic extracts were evaporated. The residue was adsorbed from ethanol (20ml) onto silica gel (Merck 7734, 15ml) and purified by SPC (Merck 7729) . Gradient elution with System A (945:50:5 to 934:60:6) afforded the crude title compound as a cream foam (219mg). A portion of this (169mg) was crystallised from ethyl acetate (lml) to give the title compound as fine white crystals (50mg), m.p. 131-132.5°.

Analysis Found: C,73.3; H,7.9; N,6.7.

$C_{25}H_{32}N_2O_3$ requires C,73.5; H,7.9; N, 6.9% .

Example 33

3-[3-(Dimethylamino)propyl]-4-methoxy-N-[4-(1-piperazinyl)phenyl]benzamide

A solution of Intermediate 22 (3.67g) in ethanol (200ml) and hydrochloric acid (2N, llml) was added to a pre-reduced suspension of palladium on carbon (5% 4.0g) and hydrogenated at room temperature and pressure overnight. The catalyst was filtered off and sodium bicarbonate added . The mixture was extracted with ethyl acetate (10 x 200 ml), dried and evaporated to yield a creamy white solid. FCC eluting with System A (835:150:15) gave the a pale brown foam which was dried in vacuo. Further purification by SPC eluting with the same eluant as above afforded the title compound (0.418g) as a pale brown foam, m.p. 153-155°.

Analysis Found: C,68.3; H,8.05; N,13.5

$C_{23}H_{32}N_4O_2.0.187\ H_2O.0.16\ C_2H_5OH$ requires; C,6.8; H,8.25; N.13.8

Assay Found 0.83% H_2O (0.187 mol H_2O)

Example 34

Methyl 4-[4-[[[3-[3-(dimethylamino)propyl]-4-methoxyphenyl]carbonyl]amino] phenyl]-1-piperazinecarboxylate, maleate (1:1)

Methyl chloroformate (0.538 ml, 0.066g) in THF (10 ml) was added in portions (1 ml) to a stirred mixture of the product of Example 33 (0.25g) in pyridine (1.0 ml) at 0°C over 48h. After evaporation the residue was adsorbed from ethanol onto silica gel (4g, Merck 7734) and purified by FCC eluting with a gradient of System A (967:30:3 to 835:150:15) to give the free base of the title compound (0.14g). A portion of the free base (0.12g) was treated with maleic acid (0.07g); the minimum of hot ethanol was added to effect solution. On cooling, the precipitate was filtered off to yield the title compound (0.12g) as a pink solid, m.p. 174-177°.

Analysis Found : C, 58.5; H, 6.6; N, 9.2.

$C_{25}H_{34}N_4O_4.C_4H_4O_4.0.78\ H_2O$ requires C, 59.6; H, 6.8; N, 9.6%.

Assay Found 2.39% H_2O = 0.78 mol H_2O.

Example 35

N-(4-Bromophenyl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide

A solution of Intermediate 23 (lg) and sodium hydroxide (0.4g) in aqueous methanol (1:1, 60ml) was boiled under reflux for 3.5h. The clear colourless solution was concentrated, acidified with 2N hydrochloric acid and concentrated to dryness. The residual white solid was then suspended in dry pyridine (l5ml) and the mixture chilled in an ice-salt bath and treated with thionyl chloride (242µl) with stirring. An orange precipitate separated from orange/yellow solution. The mixture was stirred in the ice-salt for lh, then p-bromobenzenamine (573mg) was added and the mixture allowed to reach room temperature. Most of the solid dissolved, then after 30 min, a pale yellow solid separated. Stirring was continued for 18h, then the solution was diluted with water (75ml), followed

by sodium carbonate (2N; 75ml). The aqueous solution was extracted with ethyl acetate (3 x 150ml). The combined organic extracts were washed with brine (150ml) and water (150ml), dried, filtered and evaporated in vacuo to give an oily residue. SPC eluting with System A (98:2:0.2) gave the title compound as a cream-coloured foam (455mg), m.p. 72-73°C.

Analysis Found: C,55.9; H,5.7; N,10.2; Br,18.55.

$C_{19}H_{22}BrN_3O_2$. 0.45 C_2H_6O requires C,56.2; H,5.9; N,9.9; Br, 18. 8%

Example 36

N-(4-Ethoxyphenyl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide dihydrochloride

A suspension of Intermediate 24 (1.43g) and 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (0.96g) in 1-butanol (20ml) was heated to reflux with stirring. Refluxing was continued for 22h., then anhydrous sodium carbonate (0.27g) was added and refluxing continued for 8.5h. A further quantity (0.27g) of sodium carbonate was added and refluxing continued for 6h. The mixture was concentrated to a brown oil which was taken up in water (l00ml) and 2N hydrochloric acid (20ml) and extracted with ethyl acetate (2x50ml). The aqueous solution was then basified with sodium carbonate and re-extracted with ethyl acetate (3x50ml). The extract was dried and removal of the solvent afforded an oil (1.86g). The oil was absorbed from System A (200:8:1, l0ml) onto Kieselgel G (l00g) and eluted with the same solvent (550ml) to return starting material. Later fractions eluted in System A (200:8:1, 200ml; 100:8:1, 200ml and 50:8:1, l00ml) were discarded. Further elution (50:8:1, 350ml) afforded the free base of the title compound as an oil (0.43g). The oil was taken up in ethanol (l0ml) and treated with ethereal hydrogen chloride. The mixture was diluted with ethyl acetate and the resulting solid collected, and washed with ethyl acetate to give the title compound (0.462g). Recrystallisation from methanol:ethyl acetate afforded a sample for analysis (0.390g) T.l.c. System A (50:8:1), Rf 0.37.

Analysis Found: C,57.0;H,6.7;N,9.6.

$C_{21}H_{27}N_3O_3.2HCl$ requires C,57.0;H,6.6;N,9.5%

Example 37

4-Bromo-N-[[4-methoxy-3-(4-methyl-1-piperazinyl)]phenyl]benzamide

A solution of Intermediate 27 (0.168g) in pyridine (3ml) was treated with p-bromobenzoyl chloride (0.25g) and stirred at 110°, under nitrogen, for 5h. Sodium bicarbonate (20ml; 8%) was added and the mixture was evaporated. The residue was pre-adsorbed onto silica gel [Merck Art. 7734 5g] and purified by SPC eluting with System A (97:3:0.3) to give the title compound as a beige solid (0.237g),

m.p. 158.5-159.5°C.

Analysis Found: C,56.4; H,5.7; N,9.9; Br, 19.2.

$C_{19}H_{22}BrN_3O_2$ 0.1 $CH_3CO_2C_2H_5$ requires

C,56.4; H,5.6; N,10.2; Br, 19.3%

Example 38

N-(4-Bromophenyl)-4-methoxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide

Intermediate 30 (1.6g) was treated with thionyl chloride (5ml) and stirred at reflux for 20min. When cool, the solution was evaporated and then coevaporated with toluene (2xl0ml). The residue was treated with p-bromobenzenamine (967mg), followed by pyridine (5ml) and then stirred at 110° under nitrogen for 3h. When cool, aqueous saturated sodium bicarbonate (30ml) was added and the mixture evaporated. The residue was purified by SPC using System A (97:3:0.5) to give the title compound as a cream-coloured solid which was recrystallised from ethanol (1.7g) m.p. 152-154°C.

Analysis Found: C,61.5; H,6.4; N,6.3; Br,18.3

$C_{22}H_{27}BrN_2O_20.0$ $1H_2O$ requires C,61.3; H,6.3; N,6.5; Br;18.5%

Example 39

N-(4-Bromophenyl)-4-hydroxy-3-[2-(1-methyl-2-piperidinyl)ethyl]benzamide

A solution of sodium ethanethiolate was prepared by adding ethanethiol (lml) slowly dropwise to a stirred suspension of sodium hydride (544mg of a 60% w/w dispersion) in dry DMF (8ml). After stirring for lh the solution was treated with a solution of the product of Example 38 (730mg) in warm dry DMF (8ml). The resulting solution was

heated in an oil bath (150°, 6h), cooled and evaporated to dryness. The residue was partially purified by SPC using System A (189:10:1) and then further purified by HPLC to give the title compound (520mg) as a cream coloured foam.

Analysis Found: C,60.4; H,5.9; N,6.4; Br, 19.2.

$C_{21}H_{25}N_2BrO_2$ requires C,60.4; H,6.0; N,6.7; Br, 19.15%

Example 40

4-Iodo-2-methoxy-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]benzamide

A mixture of 4-iodo-2-methoxybenzoic acid (750mg) and thionyl chloride (7ml) was stirred at reflux for 15 min and then evaporated to give 4-iodo-2-methoxybenzoyl chloride. A solution of Intermediate 27 (629mg) in THF (30ml) was treated with a solution of sodium hydroxide (227mg) in water (10ml), followed by the 4-iodo-2-methoxybenzoyl chloride, and the mixture stirred at 23° under nitrogen for 24h. 5M Hydrochloric acid (1.5ml) was added, followed by aqueous saturated sodium bicarbonate (10ml), and the mixture evaporated. The residue was treated with water (50ml), extracted with ethyl acetate (10x100ml), and the combined dried organic extracts were evaporated. The residue was absorbed from hot ethanol (40ml) onto silica gel (Merck 7734,10ml) and purified by FCC eluting with System A (945:50:5) to give a solid (780mg) which crystallised from ethanol (10ml) to give the impure title compound (602mg). A portion of the solid (102mg) was recrystallised from ethanol to give the title compound as fine white crystals (37mg), m.p. 168-170°.

Analysis Found C,49.7; H,5.0; N,8.5; I,26.2.

$C_{20}H_{24}IN_3O_3$ requires C,49.9; H,5.0; N,8.7; I,26.4%

Example 41

4-Bromo-N-[4-hydroxy-3-(4-methyl-1-piperazinyl)phenyl]benzamide

A mixture of the product of Example 37 (0.5g) and pyridine hydrochloride (173mg) was heated at 180-200° for 2h. A further quantity of pyridine hydrochloride (600mg) was added and the mixture was heated at 180-200° for 16h. The resulting residue was partitioned between aqueous sodium carbonate (2N;20ml) and dichloromethane (3x20ml).

The dried extract was evaporated and the residue was purified on a column of silica eluting with System F (240:10:1) to give the title compound as a white foam (150mg)

T.l.c System F (240:10:1), Rf 0.3

Analysis Found: C,53.7; H,5.1; N,10.2;

$C_{18}H_{20}BrN_3O_2 0.6H_2O$ requires: C,53.9; H,5.4; N,10.5%

Example 42

4-Bromo-N-[[4-methoxy-3-(4-methyl-l-piperazinyl)phenyl]-3-methyl]benzamide

4-Bromo-3-methylbenzoic acid (4.86g) in an excess of thionyl chloride (25ml) was heated to reflux for lh. The excess thionyl chloride was then removed by distillation and evaporation. The acid chloride was then added to a mixture of a solution of Intermediate 27 (5.0g) in THF (25ml) and sodium hydroxide (1.8g) in water (30ml). The resulting solution was then stirred at room temperature, under nitrogen, overnight. The solvent was removed by evaporation, water (40ml) added and extracted with dichloromethane (5x50ml), dried and evaporated to give a brown/orange sticky foam. This was purified by FCC eluting with System F (970:20:10) to give the title compound (5.73g).

T.l.c. System F (970:20:10) Rf = 0.11

Analysis Found: C,56.8; H,5.75; N,9.9%

$C_{20}H_{24}N_3BrO_2$ requires C,57.4; H,5.7; N,10.0%

Example 43

4-Bromo-N-[3-[3-(dimethylamino)propyl]-4-methoxyphenyl]benzamide

Sodium hydroxide (ll0mg) in water (5ml), was added to a solution of Intermediate 32 (250mg) and 4-bromobenzoyl chloride (263mg) in THF (5ml) at room temperature, under nitrogen. The solution was stirred at room temperature for 3h. The mixture was evaporated to dryness and water (l0ml) added. This was extracted with ethyl acetate (4x20ml) dried and evaporated to yield a brown/white solid (335mg). This was purified by FCC eluting with ethyl acetate:methanol:ammonia (940:50:10) to give the title compound (218mg) as an off-white solid.

T.l.c. ethyl acetate:methanol:ammonia (940:50:10) Rf 0.10

Analysis found C,57.6; H,6.0; N,6.7

$C_{19}H_{33}BrN_2O_2$ requires C,57.85; H,6.0;N,7.0%

Example 44

4-Bromo-N-[3,4-dimethoxy-5-(4-methyl-1-piperazinyl)phenyl]benzamide

A mixture of Intermediate 39 (134mg) and 4-bromobenzoyl chloride (117mg) in THF (8ml) and water (4ml) was stirred at 20° for 3h in the presence of sodium hydroxide (42mg). The THF was evaporated and the residue was partitioned between water (25ml) and dichloromethane (2x50ml). The dried extracts were evaporated to give an off-white foam (240mg) which was chromatographed eluting with System A (200:8:1) to give the title compound as an off-white foam (210mg).

T.l.c System A (100:8:1) Rf 0.43.

n.m.r. (CDCl) δ 2.36 (3H,s), 2.58 (4H, br.s), 3.17 (4H,br.s),3.82-3.88 (2x3H, 2xs), 6.63 (1H,d), 8.18 (1H,d), 7.63 (2H, 1/2 AA' BB'), 7.68 (1H, br.s), 7.75 (2H, 1/2 AA'BB')

Example 45

4-Butoxy-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]benzamide

A solution of 4-butoxybenzoic acid (291mg) in thionyl chloride (0.5ml) was refluxed under nitrogen for 30 min and evaporated. The residue in THF (5ml) was added in one portion to a solution of Intermediate 27 (300mg) and sodium hydroxide (120mg), THF (10ml) and water (5ml). The solution was stirred for 2h at room temperature, treated with water (50ml), and extracted with dichloromethane (3x50ml). The dried extract was evaporated and the residue was purified on a column of silica eluting with System F (97:3:0.3) to give the title compound as a white foam (426mg)

T.l.c. System F (90:10:1), Rf 0.6.

Analysis Found C,69.4; H,7.8; N,10.4

$C_{23}H_{31}N_3O_3$ requires C,69.5; H, 7.9; N,10.6%

Example 46 (step a)

8-(4-Iodophenyl)-1,4-dioxaspiro[4.5]decan-8-ol

n-Butyllithium (1.64M in hexane, 105ml, 172mmol) was added during 30min to a stirred suspension of 1,4-diiodobenzene (56.7g, 172mmol) in dry THF (500ml) at -63 to -66° under nitrogen. Stirring was continued at -65° for 10min.

A solution of 1,4-cyclohexanedione monoethyleneketal (26.82g, 172mmol) in dry THF (135ml) was added dropwise over 30min at -62 to -66° and stirring continued for 1.25h. Aqueous saturated ammonium chloride (190ml) was added at -66° to -30° and the mixture allowed to warm to +23° over 15h. The mixture was evaporated, treated with water (500ml), and extracted with ethyl acetate (500ml, then 2x250ml). The combined, dried (Na_2SO_4) organic extracts were evaporated and the residue crystallised from ethyl acetate (ca. 100ml) to give the title compound (31.73g) as a colourless oil.

Example 46 (step b)

8-(4-Iodophenyl)-1,4-dioxaspiro[4.5]dec-7-ene

4-Methylbenzenesulphonic acid monohydrate (15.31g, 79.5mmol) was added to a stirred solution of 8-(4-iodophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (29.09g, 80.8mmol) in toluene (500ml) under nitrogen at 75-80°. After 5min, the mixture was rapidly cooled to 23° (solid carbon dioxide/acetone bath) and then treated with aqueous saturated sodium bicarbonate (250ml). The aqueous phase was separated and extracted with ethyl acetate (2x500ml). The combined, dried (Na_2SO_4) organic phases were evaporated onto silica gel (Merck 7734, 200ml), and this applied to a flash column of silica gel (Merck 9385, 15cm wide column). Gradient elution with ether-hexane (5:95→12:88) afforded a solid.

A portion of this (500mg) was stirred in refluxing hexane (25ml) for 5min, filtered, and on cooling the title compound crystallised as fine pale cream crystals (232mg), m.p. 99-105°.

Example 46 (step c)

4-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)benzoic acid

n-Butyllithium (17.4ml of a 1.63M solution in hexane, 28.4mmol) was added over 15min at -73° to -70° to a stirred solution of 8-(4-iodophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (9.71g, 28.4mmol) in dry THF (120ml) under nitrogen. After 15min, carbon dioxide was passed over the solution at -70° to -60° for 20min and the mixture allowed to warm to 23° over 40min. Water (2.5ml) was added, followed by silica gel (Merck 7734, 100ml), and the mixture evaporated. The resultant silica was applied as a plug to a flash column of silica (Merck 9385, 7cm wide) and this eluted with dichloromethane-ethanol-0.88 ammonia (78:20:2→50:45:5) to give impure acid (1.05g),

followed by 4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)benzoic acid (3.20g).

T.l.c. SiO_2 (CH_2Cl_2-EtOH-0.88NH_3, 50:45:5), Rf 0.28,

Example 46 (step d)

Tricyclo[3.3.1.1]decan-1-amine 4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)benzoate

A solution of 4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)benzoic acid 163mg, 0.63mgmmol) in hot ethanol (7ml) was filtered (hyflo) to give solution A. Tricyclo[3.3.1.1]decan-1-amine (150mg, 0.99mmol) was stirred in refluxing ethanol (2ml) and filtered (hyflo) to give solution B. Solution B was added to solution A and on cooling, the precipitate was filtered off to give the title compound as fine cream crystals (90mg) m.p. 230-235° (with darkening).

Example 46 (step e)

4-(1,4-Dioxaspiro[4.5]decan-8-yl)benzoic acid

A solution of 4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)benzoic acid (2.91g, 11.2mmol) in dry THF was added to a mixture of pre-reduced 10% palladium on carbon (3.0g) in dry THF (50ml) and the stirred mixture hydrogenated at room temperature and pressure until uptake ceased (theoretical uptake 269ml, actual uptake 260ml). The catalyst was filtered off (hyflo) and the filtrate evaporated. The residue was stirred in refluxing ethanol (ca 50ml), filtered, and on cooling the filtrate crystallised to give the title compound as fine white crystals (1.56g).

nmr (δ, D_6-DMSO) 1.55-1.85 (8H,m), 2.65 (1H,m), 3.91 (4H,AA'BB'), 7.26 (2H,½AA'BB'), 7.86 (2H,½AA'BB').

Example 46 (step f)

4-(1,4-Dioxaspiro[4.5]decan-8-yl)-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]benzamide

Thionyl chloride (0.20ml, 2.74mmol) was added dropwise under nitrogen at 0° to +3° to a stirred solution of 4-(1,4-dioxaspiro[4.5]decan-8-yl)benzoic acid (800mg, 3.05mmol) in pyridine (12ml) and stirring continued for 1h at 0°, followed by 1h at +23°. The solution was cooled to 0°, treated with 4-methoxy-3-(4-methyl-1-piperazinyl)benzenamine (676mg, 3.05mmol) and allowed to stir at +23° for 19h. Aqueous saturated sodium bicarbonate (20ml) was added and the mixture evaporated. Water (30ml) and ethyl acetate (30ml) were added and after shaking for 5min the mixture was filtered to give solid I. The aqueous layer was separated and further extracted with ethyl acetate (3x50ml). The combined, dried (Na_2SO_4) organic extracts were evaporated and combined with solid I. The mixture was dissolved in hot ethanol (30ml), treated with silica gel (Merck 7734, 20ml), and evaporated. The resultant silica was applied as a plug to a flash column of silica gel (Merck 9385, 6cm wide column) and gradient elution with dichloromethane-ethanol-0.88 ammonia (967:30:3→945:50:5) afforded the crude title compound (387mg, 27%). This crystallised from hot ethyl acetate to give the title compound as fine white crystals (28mg), m.p. 141-143.5°.

Example 46 (step g) [Final Compound]

N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-4-(4-oxocyclohexyl)benzamide

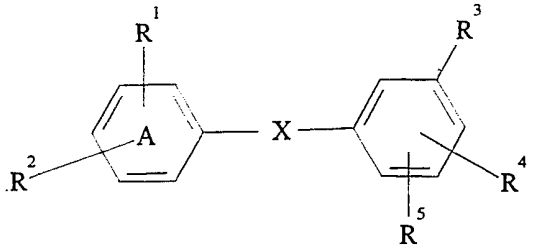
A solution of 4-(1,4-dioxaspiro[4.5]decan-8-yl)-N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]benzamide (288mg, 0.62mmol) in 2M-hydrochloric acid (20ml) was kept at 23° for 1.5h and then basified by pouring it into aqueous 1M-sodium carbonate (30ml). The mixture was extracted with ethyl acetate (3x50ml) and the combined, dried (Na_2SO_4) organic extracts were evaporated. The residue crystallised from ethyl acetate (ca. 4ml) to give the title compound as fine white crystals (120mg), m.p. 176-177.5°.

Analysis Found: C,70.3; H,7.4; N,9.4;

$C_{25}H_{31}N_3O_3$ requires: C,70.3; H,7.2; N,9.0%

Claims

Compounds of the general formula (I) :-



(I)

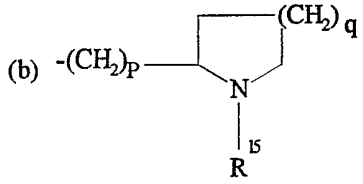
or a physiologically acceptable salt or solvate thereof, in which

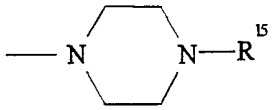
R^1 represents a hydrogen atom or a halogen atom or a C_{1-6}alkyl or C_{1-6}alkoxy group;

R^2 represents a hydrogen atom or a halogen atom, or C_{1-6}alkyl, hydroxy C_{1-6}alkyl, hydroxyC_{3-6}alkenyl, hydroxyC_{3-6}alkynyl, C_{1-6}alkylthio, hydroxy, $-(CH_2)_kOR^6$, $-(CH_2)_kCOR^7$, $-(CH_2)_kCR^7{=}NOR^9$, $-CO_2R^7$, $-O(CH_2)_mR^8$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-SO_2NR^{11}R^{12}$ or C_{5-7}cycloalkyl (optionally substituted by a hydroxy or an oxo group);

R^3 represents a group selected from

(a) $-(CH_2)_n NR^{13} R^{14}$,

(b)  or

(c)  ;

R^4 and R^5, which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy, C_{1-6}alkoxy or C_{1-6}alkyl group;

R^6 represents a C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-4}alkanoyl group;

R^7 represents a hydrogen atom or a C_{1-6}alkyl group;
R^8 represents a C_{1-6}alkoxy, $-CO_2R^7$ or $-CONR^9R^{10}$ group;
R^9 and R^{10}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-6}alkyl group, or $-NR^9R^{10}$ forms a saturated heterocyclic ring which has 5 or 6 ring members, may optionally be substituted by an oxo group and, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom or a group -NH- or $-NR^{16}-$;
R^{11}, R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-6}alkyl group;
R^{16} represents a C_{1-6}alkyl, $-COR^7$ or $-CO_2R^7$ group;
X represents -CONH-, -NHCO-, $-CH_2NH-$ or $-NHCH_2-$;
k represents zero or an integer from 1 to 6;
m represents an integer from 1 to 6;
n represents an integer from 2 to 4;
p represents an integer from 1 to 3; and
q represents an integer from 1 to 3.

2. Compounds as claimed in Claim 1 for use in therapy.

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

Application number
GB 9305523.4

Relevant Technical Fields

(i) UK Cl (Ed.M) C2C CKH CKJ

(ii) Int Cl (Ed.5) C07C C07D

Search Examiner
D S LUCAS

Date of completion of Search
19 MAY 1994

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE DATABASE: CAS ONLINE

Documents considered relevant following a search in respect of Claims :-
1 AND 2

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
A	EP 0533266 A	(GLAXO) see Claim 1	1 and 2
X	EP 0142283 A2	(FISONS) see Example 28	1

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).