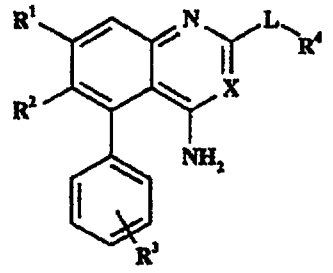
Quinoline and quinazoline compounds useful in therapy

This invention relates to novel compounds useful in therapy, particularly in the treatment of benign prostatic hyperplasia.

International Patent Application WO 89/05297 discloses a number of substituted quinazoline compounds which are indicated as inhibitors of gastric acid secretion.

According to the present invention, there is provided a compound of formula I,



I

wherein

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;

R^2 represents H or C_{1-6} alkoxy optionally substituted by one or more fluorine atoms;

R^3 represents one or more groups independently selected from H, halogen, C_{1-4} alkoxy and CF_3;

in addition, R^2 and one R^3 group may together represent $-OCH_2-$, the methylene group being attached to the ortho-position of the pendant phenyl ring;

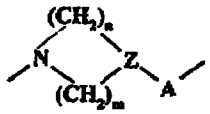
R^4 represents a 4-, 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $SO_2NR^8R^9$ and $NHSO_2(C_{1-4}$ alkyl), and when S is a member of the ring system, it may be substituted by one or two oxygen atoms;

R^8 and R^9 independently represent H or C_{1-4} alkyl;

X represents CH or N; and

L is absent,

or represents a cyclic group of formula Ia,



Ia

in which N is attached to the 2-position of the quinoline or quinazoline ring;

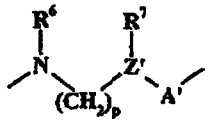
A is absent or represents CO or SO_2;

Z represents CH or N;

m represents 1 or 2, and in addition, when Z represents CH, it may represent 0; and

n represents 1, 2 or 3, provided that the sum of m and n is 2, 3, 4 or 5;

or represents a chain of formula Ib,



Ib

in which N is attached to the 2-position of the quinoline or quinazoline ring;

A' and Z' have the same significance as A and Z above, respectively;

R^6 and R^7 independently represent H or C_{1-4} alkyl; and

p represents 1, 2 or 3, and in addition, when Z' represents CH, it may represent 0;

or a pharmaceutically acceptable salt thereof (referred to together herein as "the compounds of the invention").

Pharmaceutically acceptable salts include acid addition salts, such as hydrochloride and hydrobromide salts, and phosphate salts.

Alkyl and alkoxy groups that R^{1-4} may represent or include can be straight chain, branched chain, cyclic, or a combination thereof.

Heterocyclic groups that R^4 represents may be saturated or unsaturated.

The compounds of the invention may be optically active. In particular, they may exhibit atropisomerism about the bond joining the pendant phenyl ring to the rest of the molecule when an R^3 substituent is in the 2- or 3- position of the phenyl ring. The invention includes all optical isomers of the compounds of formula I, and all diastereoisomers thereof.

Preferred groups of compounds that may be mentioned include those in which:

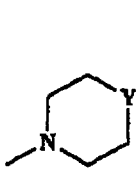
(a) R^1 represents methoxy;

(b) R^2 represents methoxy;

(c) R^2 and an R^3 group together represent $-OCH_2-$;

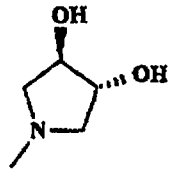
(d) R^3 represents H or 4-fluoro;

(e) R^4 represents a group having the formula II, III, IV, V or VI,



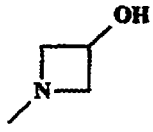
II

,



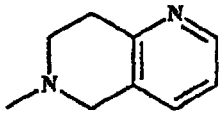
III

,



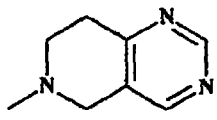
IV

,



V

or



VI

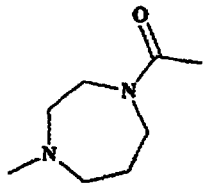
wherein

Y represents O, CH_2, SO_2, NR^5 or CHF; and

R^5 represents H or C_{1-4} alkyl;

the group of formula II being of particular interest, especially when Y represents O; and

(f) L represents a group of formula VII,

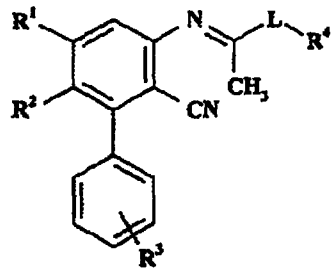


VII

or is absent, this latter preference being of particular interest when R^4 represents a group of formula V or VI.

According to the invention, there is also provided a process for the production of a compound of the invention, which comprises:

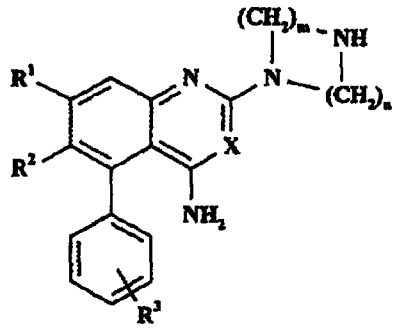
(a) when X represents CH, cyclizing a compound of formula X,



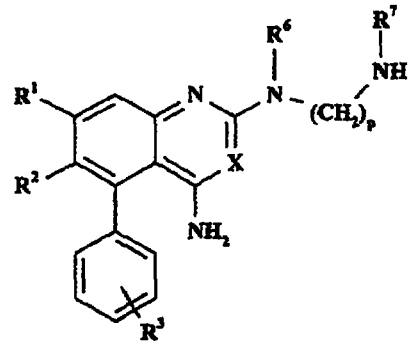
X

in which R^{1-4} and L are as defined above;

(b) when A or A' is present, and Z or Z' represents N, reacting a compound of formula XIIIa or XIIIb, as appropriate,

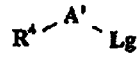


XIIIa



XIIIb

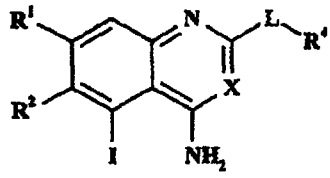
in which R^{1-3}, R^6, R^7, X, m, n and p are as defined above, with a compound of formula XIV,



XIV

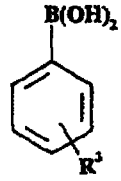
in which R^4 is as defined above, A' represents CO or SO_2 and Lg represents a leaving group;

(c) reacting a compound of formula XVIII,



XVIII

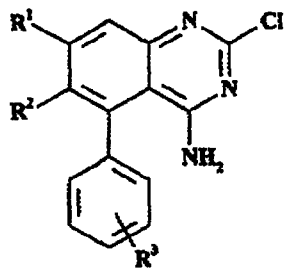
in which R^1, R^2, R^4, X and L are as defined above, with a compound of formula XIX,



XIX

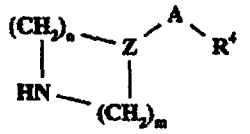
in which R^3 is as defined above; or

(d) when X represents N, reacting a compound of formula XXII,

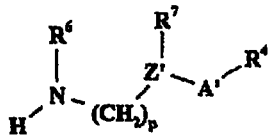


XXII

in which R^{1-3} are as defined above, with a compound of formula XXIIIa or XXIIIb, as appropriate,



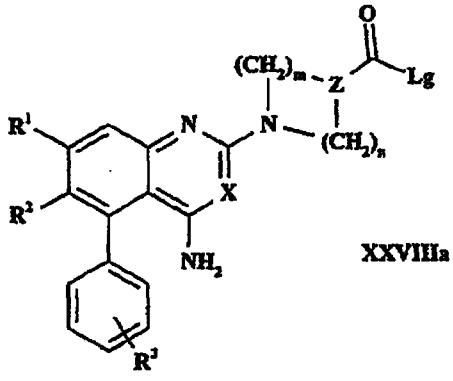
XXIIIa



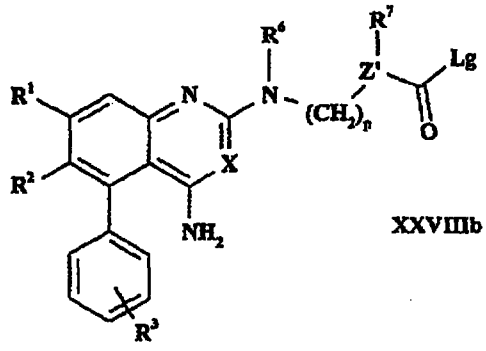
XXIIIb

in which R^4, R^6, R^7, A, A', Z, Z', m, n and p are as defined above;

(e) when A or A' represents CO, reacting a compound of formula XXVIIIa or XXVIIIb, as appropriate,



XXVIIIa



XXVIIIb

in which R^{1-3}, R^6, R^7, X, Z, Z', m, n and p are as defined above, and Lg is a leaving group, with a compound of formula XXIX,

$$HR^{4a} \qquad \text{XXIX}$$

in which R^{4a} represents the groups defined by R^4 above which contain a nucleophilic nitrogen atom in the ring, this nucleophilic nitrogen atom being attached to H;

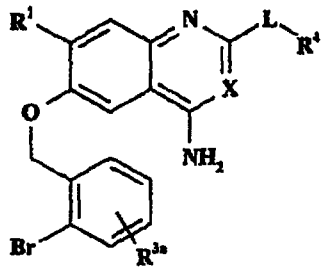
(f) conversion of a compound of formula I in which L represents a cyclic group of formula Ia, to a corresponding compound of formula I in which L represents a chain of formula Ib in which R^6 and R^7 each represent H, by the action of a strong base;

(g) when A or A' is absent and Z or Z' represents N, reacting a compound of formula XIIIa or XIIIb, as defined above, with a compound of formula XXX,

R^4-Hal XXX

in which R^4 is as defined above and Hal represents a halogen atom attached to the ring; or

(h) when R^2 and one R^3 group together represent -OCH_2-, cyclization of a compound of formula XXXI,



XXXI

in which R^1, R^4, X and L are as defined above, and R^{3a} has the same meaning as R^3 above except that R^2 and an R^{3a} group do not together represent -OCH_2-;

and where desired or necessary converting the resulting compound of the invention into a pharmaceutically acceptable salt or vice versa.

In process (a), the cyclization may be carried out in the presence of a strong base (for example lithium diisopropylamide) in a solvent which does not adversely affect the reaction (for example tetrahydrofuran) around room temperature and quenched with water.

In process (b), suitable leaving groups are OH and Cl. When the compound of formula XIV is a carboxylic acid, the reaction may be carried out in the presence of conventional coupling agents [for example 1-hydroxybenzotriazole monohydrate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 4-methylmorpholine] in a solvent which does not adversely affect the reaction (for example CH_2Cl_2) at or around room temperature. When the leaving group is Cl, the reaction may be carried out in a solvent which does not adversely affect the reaction (for example CH_2Cl_2) around 0°C.

In process (c), the reaction may be carried out in the presence of a palladium catalyst [for example tetrakis(triphenylphosphine)palladium] in a solvent which does not adversely

affect the reaction (for example a mixture of toluene, ethanol and 1N aqueous sodium carbonate) at an elevated temperature (for example the reflux temperature of the solvent).

In process (d), the reaction may be carried out in a solvent which does not adversely affect the reaction (for example n-butanol) in the presence of a base (for example triethylamine) at an elevated temperature (for example 100°C).

In process (e), suitable leaving groups include Cl. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example THF) in the presence of a base (for example triethylamine) at room temperature.

The reaction may also be carried out without isolating the compound of formula XXVIIIa or XXVIIIb, by reacting a compound of formula XIIIa or XIIIb with triphosgene and a compound of formula XXIX. In this case the leaving group is -Cl. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example CH_2Cl_2) in the presence of a base (for example triethylamine) at or around room temperature.

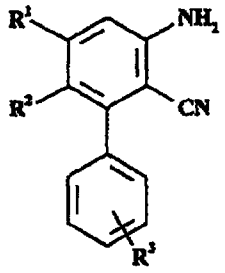
In process (f), suitable strong bases include lithium diisopropylamide. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example THF).

In process (g), the reaction may be carried out in a solvent which does not adversely affect the reaction (for example a mixture or n-BuOH and dimethylacetamide) in the presence of a base (for example triethylamine) at an elevated temperature (for example 80°C).

In process (h), suitable reagents are sodium carbonate with palladium acetate. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example dimethylacetamide) at an elevated temperature (for example 130°C).

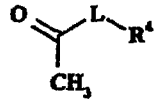
It will be apparent to those skilled in the art that in the processes described above [for example process (c)], and in the methods given below for preparation of the starting materials used in the above processes, when R^2 and R^3 are present in different molecules, they cannot together represent $-OCH_2-$.

Compounds of formula X [see process (a)] may be prepared by reaction of a compound of formula XI,



XI

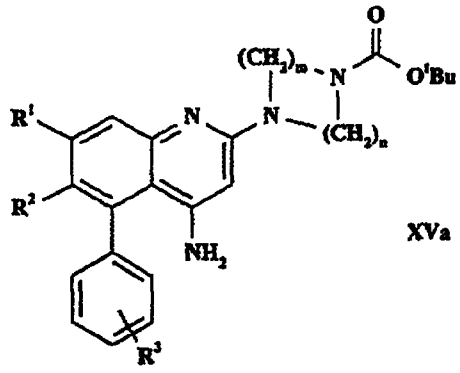
in which R^{1-3} are as defined above, with a combination of a compound of formula XII,



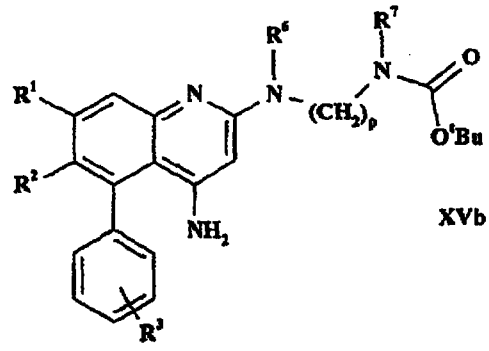
XII

in which R^4 and L are as defined above, and phosphorous oxychloride in dichloromethane at the reflux temperature of the solvent.

Compounds of formula XIIIa or XIIIb [see process (b)] in which X represents CH may be prepared from compounds of formula XVa or XVb, as appropriate,



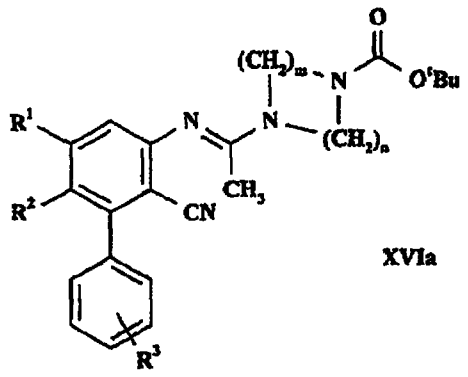
XVa



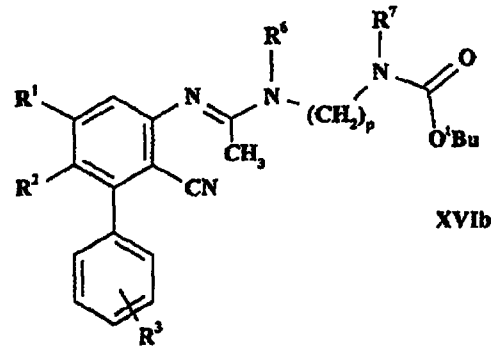
XVb

in which R^{1-3}, R^6, R^7, m, n and p are as defined above, by bubbling HCl gas through a solution of the compound in dichloromethane.

Compounds of formula XVa or XVb may be prepared from compounds of formula XVIa or XVIb, as appropriate,



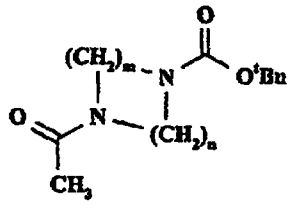
XVIa



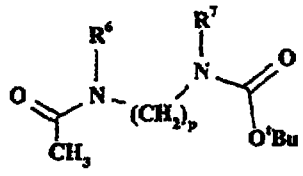
XVIb

in which R^{1-3}, R^6, R^7, m, n and p are as defined above, by cyclization using potassium hydroxide or lithium diisopropylamide at an elevated temperature (such as 90°C) in DMSO, quenching with water.

Compounds of formula XVIa or XVIb may be prepared by reacting a compound of formula XI, as defined above, with a compound of formula XVIIa or XVIIb, as appropriate,



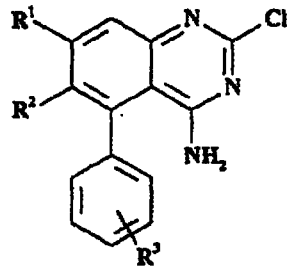
XVIIa



XVIIb

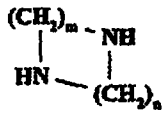
in which R^6, R^7, m, n and p are as defined above, by the method described above for producing compounds of formula X.

Compounds of formula XIIIa or XIIIb in which X represents N may be prepared by reacting a compound of formula XXII,

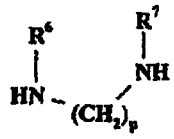


XXII

in which R^{1-3} are as defined above, with a compound of formula XXIIa or XXIIb, as appropriate,



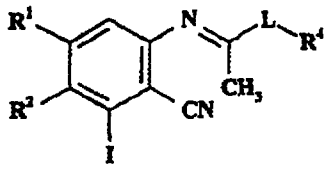
XXIIa



XXIIb

in which R^6, R^7, m, n and p are as defined above, using the conditions mentioned for process (d) above.

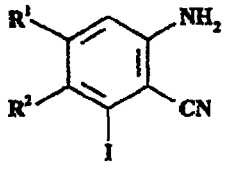
Compounds of formula XVIII [see process (c)] in which X represents CH may be prepared by cyclization of a compound of formula XX,



XX

in which R^1, R^2, R^4 and L are as defined above, using the reaction conditions mentioned in process (a) above.

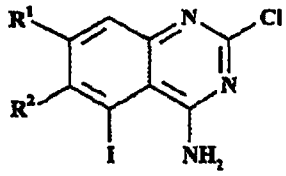
Compounds of formula XX may be prepared by reacting a compound of formula XXI,



XXI

in which R^1 and R^2 are as defined above, with a compound of formula XII as defined above, using the method described above for the preparation of compounds of formula X.

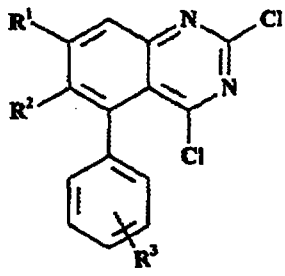
Compounds of formula XVIII in which X represents N may be prepared by reacting a compound of formula XXVII,



XXVII

in which R^1 and R^2 are as defined above, with a compound of formula XXIIIa or XXIIIb, as appropriate, as defined above, using the reaction conditions mentioned above for process (d).

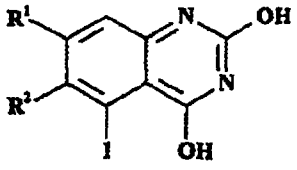
Compounds of formula XXII [see process (d)] may be prepared from a compound of formula XXIV,



XXIV

in which R^{1-3} are as defined above, by reaction with a saturated solution of ammonia in methanol.

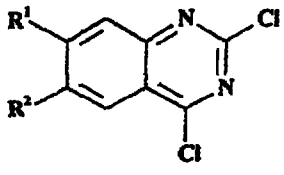
Compounds of formula XXIV may be prepared from a compound of formula XXV,



XXV

in which R^1 and R^2 are as defined above, by reaction with a compound of formula XIX as defined above using the reaction conditions described above for process (c), followed by reaction with $POCl_3$ and N,N-dimethylaniline.

Compounds of formula XXV may be prepared from a compound of formula XXVI,

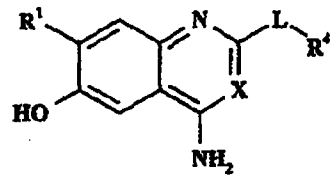


XXVI

in which R^1 and R^2 are as defined above, using conventional techniques.

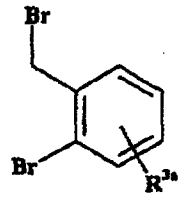
Compounds of formula XXVIIIa and XXVIIIb [see process (e)] in which Lg represents Cl may be prepared from compounds of formula XIIIa or XIIIb, as appropriate, by reaction with triphosgene. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example CH_2Cl_2) in the presence of a base (for example triethylamine) at around -10°C.

Compounds of formula XXXI [see process (h)] may be prepared from compounds of formula XXXII,



XXXII

in which R^1, R^4, L and X are as defined above, by reaction with a compound of formula XXXIII,



XXXIII

wherein R^{3a} is as defined above, in the presence of sodium hydride in DMF at room temperature.

Compounds of formula XXXII are analogous to compounds of formula I, and may be prepared using analogous methods. For example, when X represents CH, the compounds may be prepared by cyclizing a compound analogous to those of formula X using process (a). When X represents N, the compounds may be prepared from a compound analogous to those of formula XXII and a compound of formula XXIIIa or XXIIIb, as appropriate, using process (d).

Compounds of formulae XI, XII, XIV, XVIIa, XVIIb, XIX, XXI, XXIIa, XXIIb, XXIII, XXVI, XXIX, XXX and XXXIII are either known or are available using known techniques.

The intermediate compounds of formulae X, XIIIa, XIIIb, XVIII, XXII, XXVIIIa, XXVIIIb and XXXI form a further aspect of the invention.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be

achieved by conventional techniques, for example as described in 'Protective Groups in Organic Synthesis' by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991.

The compounds of the invention are useful because they possess pharmacological activity in animals. In particular, the compounds are useful in the treatment of a number of conditions including hypertension, myocardial infarction, male erectile dysfunction, hyperlipidaemia, cardiac arrhythmia and benign prostatic hyperplasia. The latter condition is of greatest interest. Thus, according to another aspect of the invention, there is provided a method of treatment of benign prostatic hyperplasia which comprises administering a therapeutically effective amount of a compound of the invention to a patient suffering from such a disorder. The use of the compounds of the invention as pharmaceuticals, and the use of the compounds of the invention in the manufacture of a medicament for the treatment of benign prostatic hyperplasia, are also provided.

The compounds of the invention may be administered by any convenient route, for example orally, parenterally (*e.g.* intravenously, transdermally) or rectally. The daily dose required will of course vary with the particular compound used, the particular condition being treated and with the severity of that condition. However, in general a total daily dose of from about 0.01 to 10mg/kg of body weight, and preferably about 0.05 to 1mg/kg, is suitable, administered from 1 to 4 times a day.

The compounds of the invention will generally be administered in the form of a suitable pharmaceutical formulation. Thus, according to another aspect of the invention, there is provided a pharmaceutical formulation including preferably less than 50% by weight of a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. The pharmaceutical formulation is preferably in unit dose form. Such forms include solid dosage forms, for example tablets, pills, capsules, powders, granules, and suppositories for oral, parenteral or rectal administration; and liquid dosage forms, for example sterile parenteral solutions or suspensions, suitably flavoured syrups, flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil and peanut oil, and elixirs and similar pharmaceutical vehicles.

Solid formulations may be prepared by mixing the active ingredient with pharmaceutical carriers, for example conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums and other diluents, for example water, to form a homogeneous preformulation formulation in which the active ingredient is uniformly dispersed so that it may be readily subdivided into equally effective unit dosage forms containing typically from 0.1 to about 500mg of the active ingredient. The solid dosage forms may be coated or otherwise compounded to prolong the action of the formulation.

The formulations of the invention may also contain a human 5-α reductase inhibitory compound [see International Patent Application WO 95/28397], or a compound of the invention could be presented in a pharmaceutical pack also containing a human 5-α reductase inhibitory compound as a combined preparation for simultaneous, separate or sequential use.

The compounds of the invention may be tested in the screens set out below.

Contractile responses of human prostate

Prostatic tissue was cut into longitudinal strips (approximately 3x2x10 mm) and suspended in organ baths under a resting tension of 1 g in Krebs Ringer bicarbonate of the following composition (mM): NaCl (119), KCl (4.7), $CaCl_2$ (2.5), KH_2PO_4 (1.2), $MgSO_4$ (1.2), $NaHCO_3$ (25), glucose (11), and gassed with 95% O_2/5% CO_2. The solution also contained 10 mM cocaine and 10 mM corticosterone. Tissues were exposed to a sensitising dose of (-)-noradrenaline (100 mM) and washed over a 45 minute period. Isometric contractions were obtained in response to cumulative additions of (-)-noradrenaline to obtain control curves in all tissues. A further curve was then generated in the presence or absence of antagonist (incubated for 2 hours). Antagonist affinity estimates (pA_2) were determined using a single concentration of competing antagonist, pA_2 = -log [A]/(DR-1) where the dose ratio (DR), relative to corresponding controls, was produced by a single concentration of antagonist [A], assuming competitive antagonism and Schild regression close to unity.

Anaesthetised dog model of prostatic pressure and blood pressure

Mature male beagles (12-15 kg body weight) were anaesthetised with sodium pentobarbitone (30-50 mg/kg i.v.) and a tracheal cannula was inserted. Subsequent anaesthesia was maintained using pentobarbitone infusion. The animals were respirated with air using a Bird Mk8 respirator (Bird Corp., Palm Springs, CA, U.S.A.) adjusted to maintain blood gasses in the range pO_2 90-110 mm Hg, pCO_2 35-45 mm Hg, pH 7.35-7.45. Body temperature was maintained at 36-37.5°C using a heated operating table. Catheters were placed into the left femoral artery for recording blood pressure and into the left femoral vein for compound administration. Heart rate was recorded via the lead II E.C.G. A laparotomy was performed to cannulate both ureters to prevent change of fluid volume within the bladder. A 7F cardiac catheter (with a 1.5 ml capacity balloon tip) was inserted into the bladder via the urethra. The balloon was filled with air and the catheter withdrawn until the balloon became lodged in the prostate, which was confirmed by digital pressure. Balloon pressure was recorded via a Druck transducer. Prostatic pressure and haemodynamic parameters were made on a Grass Polygraph (Grass Instruments, Quincy, Mass, U.S.A.) and the data measured on line using a Motorola 68000-based microcomputer system (Motorola Inc., Temple, AZ, U.S.A.). Compounds were made up in PEG 300 and administered i.v. through a catheter in the femoral vein. Responses to phenylephrine (1-16 μg/kg i.v. in saline) were obtained to generate control dose-response curves (two control curves for each experiment). Compounds were administered (in terms of compound base) at 10-300 μg/kg i.v. 5 min before construction of phenylephrine curves (constructed up to a maximum dose of 128 μg/kg in the presence of test compound).

Due to α_1-related dysrhythymic properties of phenylephrine, absolute maximal responses were not obtained but were taken as 10 % greater than the control response obtained with 16 μg/kg phenylephrine. Drug concentrations were calculated on the basis of molar weight of compound/kg body weight thus allowing a "pseudo pA_2"

calculation by Schild analysis using dose ratios derived from shifts in the phenylephrine dose-response curves.

The compounds of the invention may have the advantage that they are more potent, have a longer duration of action, have a broader range of activity, are more stable, have fewer side effects or are more selective (in particular they may have beneficial effects in benign prostatic hyperplasia without causing undesirable cardiovascular effects, for example because they are able to selectively antagonise prostatic subreceptors of the α_1-adrenoceptor), or have other more useful properties than the compounds of the prior art.

The invention is illustrated by the following examples, in which the following abbreviations are used:

DMA = dimethylacetamide

DMF = dimethylformamide

DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone

EtOAc = ethyl acetate

EtOH = ethanol

h = hour

MeOH = methanol

min = minute

n-BuOH = n-butanol

THF = tetrahydrofuran

tlc = thin layer chromatography

Intermediate 1

1-(t-Butyloxycarbonyl)-1,4-diazepane

To a solution of homopiperazine (100g, 1.0 mol) and triethylamine (210ml, 152g, 1.5mol) in CH_2Cl_2 (500ml) at 0°C was added a solution of di-(t-butyl) dicarbonate (195g, 0.89mol) in CH_2Cl_2 (300ml). The mixture was allowed to warm to room temperature and stirred for 18h after which time the CH_2Cl_2 was evaporated under reduced pressure. The resulting residue was partitioned between ether and 2N citric acid and the aqueous layer was extracted with ether (4x200ml). The aqueous layer was basified with 2N aqueous NaOH

and then extracted with CH_2Cl_2 (4x400ml). The combined CH_2Cl_2 extracts were washed with H_2O (2x), saturated brine (1x) and dried over $MgSO_4$. Evaporation under reduced pressure followed by azeotroping with CH_2Cl_2 (4x) gave the title compound as a yellow waxy solid (94.3g, 53%). R_f 0.25 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 201 (MH^+). Found: C,58.86; H,10.03; N,13.58; $C_{10}H_{20}N_2O_2$ 0.05.CH_2Cl_2 requires C, 59.02; H, 9.91; N,13.70%.

Intermediate 2

1-(t-Butyloxycarbonyl)-4-(4-morpholinecarbonyl)-1,4-diazepane

A solution of Intermediate 1 (92.0g, 0.46mol) and triethylamine (96.0ml, 69.7g, 0.69mol) in CH_2Cl_2 (500ml) at 0°C was treated dropwise with a solution of 4-morpholinecarbonyl chloride (64.0ml, 82.0g, 0.55mol) in CH_2Cl_2 (100ml) and the reaction was stirred at room temperature under N_2 for 18h. The reaction mixture was then diluted with CH_2Cl_2 (400ml) and washed with 2N citric acid (3x400ml), saturated brine (1x500ml), dried over $MgSO_4$ and evaporated to give the title compound as an off-white solid (141.7g, 98%). R_f 0.80 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 314 (MH^+). Found: C,57.50; H,8.69; N,13.41; $C_{15}H_{27}N_3O_4$ requires C, 57.50; H, 8.69; N,13.41%.

Intermediate 3

1-(4-Morpholinecarbonyl)-1,4-diazepane hydrochloride

A solution of Intermediate 2 (140.0g, 0.44mol) in CH_2Cl_2/MeOH (1/1, v/v, 600ml) at 0°C was saturated with HCl gas and the reaction mixture was stirred at room temperature under N_2 for 18h after which time the reaction mixture was evaporated under reduced pressure and slurried in EtOAc to give, after filtration, a white hygroscopic solid. This was further purified by slurrying in acetone, filtering, washing with ether and drying in vacuo at 60°C to give the title compound as a colourless solid (99.0g, 90%). R_f 0.41 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 214 (MH^+). Found: C,47.50; H,8.10; N,16.55; $C_{10}H_{19}N_3O_2$ HCl 0.2.H_2O requires C, 47.41; H, 8.12; N,16.59%.

Intermediate 4

1-Acetyl-4-(4-morpholinecarbonyl)-1,4-diazepane

To a solution of Intermediate 3 (50g, 0.2mol) and triethylamine (42ml, 30.5g, 0.3mol) in CH_2Cl_2 (400ml) at 5°C was added acetic anhydride (23ml, 24.9g, 0.24mol) dropwise over 15min and the reaction was then stirred for a further 2h at room temperature under N_2. Dilution with CH_2Cl_2 (600ml) was followed by washing with saturated aqueous sodium bicarbonate (2x200ml) and the combined aqueous layers extracted with CH_2Cl_2 (1x100ml). The CH_2Cl_2 layers were combined and washed with saturated brine, dried over $MgSO_4$ and evaporated to give a light brown oil. This was dissolved in CH_2Cl_2 (300ml) and treated with triethylamine (8ml, 5.8g, 0.06mol) and EtOH (5ml), stirred for 1h at room temperature then washed with saturated sodium bicarbonate and the aqueous layer extracted with CH_2Cl_2 (5x). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and evaporated under reduced pressure to give a yellow oil which was then azeotroped with CH_2Cl_2 (4x) to give the title compound as a yellow oil (47.1g, 92%). R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 256 (MH^+). Found: C,52.62; H,8.18; N,15.02; $C_{12}H_{21}N_3O_3$ 0.3.CH_2Cl_2 requires C, 52.61; H, 7.75; N,14.96%.

Example 1

4-Amino-5-(2-chlorophenyl)-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

(a) 5-(2-Chlorophenyl)-4-cyano-3-nitroanisole

5-Bromo-4-cyano-3-nitroanisole [prepared by the method of Harrison *et al*, J.Chem.Soc.C, 1769 (1966)] (250mg, 0.86mmol) and 2-chlorophenylboronic acid (150mg, 0.96mmol) were dissolved in a mixture of toluene (10ml), EtOH (5.6ml), and 1N aqueous sodium carbonate (1.7ml). The solution was placed under a nitrogen atmosphere and tetrakis(triphenylphosphine)palladium (30mg, 0.03mmol) added. After refluxing for 3h, the solvent was removed from the reaction mixture under reduced pressure. The residue was partitioned between H_2O (50ml) and EtOAc (50ml) and the EtOAc layer washed with H_2O (2x50ml), and dried over $MgSO_4$. Following removal of the solvent, the crude material was purified on silica gel, eluting with hexane/ether (1/1, v/v). This gave the

subtitle compound as a colourless gum (252mg, 100%). R_f 0.38 (hexane/ether 1:1, v/v). MS m/z 306 and 308 (MNH_4^+).

(b) 3-Amino-5-(2-chlorophenyl)-4-cyanoanisole

The product of step (a) (300mg, 1.0mmol) was dissolved in DMF (3ml) and a solution of sodium dithionite hydrate added (500mg, 2.9mmol in 6ml of H_2O). The solution became warm and some solid precipitated out of solution. After stirring for 30 min at room temperature, 15ml of H_2O and 2N HCl were added. This mixture was extracted with EtOAc (2x30ml), neutralised using 2N NaOH and re-extracted with EtOAc (2x30ml). The combined EtOAc extracts were dried over $MgSO_4$ and the solvent removed to give the crude product. This was purified on silica gel, eluting with CH_2Cl_2/MeOH (98/2, v/v) to give the subtitle compound as colourless gum (190mg, 74%). R_f 0.29 (hexane/ether 1/1, v/v). MS m/e 276 and 278 (MNH_4^+).

(c) 6-(2-Chlorophenyl)-4-methoxy-2-{1-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]ethylideneamino}benzonitrile

The product of step (b) (190mg, 0.74mmol) was dissolved in CH_2Cl_2 (5ml) and phosphorous oxychloride (0.082ml, 0.86mmol) added in one portion to the stirred solution, at room temperature. After 20 min, a solution of Intermediate 4 (380mg, 1.5mmol) in CH_2Cl_2 (5ml) was added to the reaction mixture, and the mixture heated to reflux for 14h. After cooling to room temperature, a further 30ml of CH_2Cl_2 was added, and this solution washed with 2N aqueous NaOH (2x20ml), dried over $MgSO_4$, and the solvent removed to give the subtitle compound as a colourless gum (155mg, 43%). R_f 0.26 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 496 (MH^+).

(d) 4-Amino-5-(2-chlorophenyl)-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

The product of step (c) (155mg, 0.31mmol) was dissolved in dry THF (5ml), under a dry nitrogen atmosphere, and the solution cooled to -78°C. A 1.5M solution of lithium diisopropylamide in THF (0.25ml, 0.38mmol) was added to the reaction which was allowed to warm to room temperature. Analysis by tlc indicated that starting material remained, hence the solution was re-cooled to -78°C and a further 0.25ml of the lithium

diisopropylamide solution added. After warming to room temperature, the mixture was again analysed by tlc and then quenched with H_2O (0.5ml). EtOAc was added (30ml) and the solution washed with H_2O (2x20ml), dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (92/7/1, v/v) to give the title compound as a white foam (50mg, 31%). R_f 0.25 (CH_2Cl_2/MeOH 9/1, v/v). MS m/z 496 (M^+). ^1H NMR ($CDCl_3$) δ: 2.05 (2H, m), 3.14 (2H, m), 3.45 (2H, t), 3.60 (6H, m), 3.70 (2H, t), 3.82 (2H bs), 3.86-3.99 (5H, m), 5.75 (1H, s), 6.47 (1H, s), 7.0 (1H, s), 7.28-7.45 (3H, m), 7.45-7.51 (1H, m). Found C, 60.75; H, 6.02; N, 13.13; $C_{26}H_{30}ClN_5O_3.0.25CH_2Cl_2$ requires C,60.96; H, 5.94; N, 13.54%.

Example 2

4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-phenylquinoline

(a) 4-Cyano-3-nitro-5-phenylanisole

The subtitle compound was prepared by the method of Example 1(a), but using phenylboronic acid. The crude material was triturated with 20ml of ether, and recrystallised from EtOAc to give a white crystalline solid (83%). m.p. 175-176°C. R_f 0.44 (hexane/ether 1:1, v/v). MS m/z 169 (no M^+ observed).

(b) 3-Amino-4-cyano-5-phenylanisole

Reduction of the product of step (a) using the procedure of Example 1(b) gave the subtitle compound (41%) yellow gum. R_f 0.30 (hexane/ether 1:1, v/v). MS m/z 242 (no M^+ observed).

(c) 4-Methoxy-2-{1-[4-(morpholine-4-carbonyl)-1,4-diazepan-1-yl]ethylideneamino}-6-phenylbenzonitrile

The subtitle compound was obtained as a white foam from the product of step (b) in 87% yield using the procedure described in Example 1(c). R_f 0.66 (CH_2Cl_2/MeOH 9/1, v/v). MS m/z 462 (MH^+).

(d) 4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-phenylquinoline

The title compound (87%) was obtained as an off-white powder from the product of step (c) using the procedure described in Example 1(d). R_f 0.16 (CH_2Cl_2/MeOH 9/1, v/v). MS m/z 462 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.05 (2H, m), 3.16 (4H, m), 3.48 (2H, t), 3.56-3.68 (6H, m), 3.71 (2H, t), 3.87-3.99 (7H, m), 5.73 (1H, s), 6.54 (1H, s), 7.01 (1H, bs), 7.41 (5H, s). Found C, 66.89; H, 6.78; N, 14.42; $C_{26}H_{31}N_5O_3$ 0.1.CH_2Cl_2 requires C, 66.69; H, 6.69; N, 14.90%

Example 3

4-Amino-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-phenylquinoline

(a) 2-(3,4-Dimethoxyphenyl)-4,4-dimethyl-Δ^2-oxazoline

The subtitle compound was prepared from 3,4-dimethoxybenzoic acid according to the method of Meyers *et al.*, J.Org.Chem., 39, 2787, (1974).

(b) 2-(3,4-Dimethoxy-2-iodophenyl)-4,4-dimethyl-Δ^2-oxazoline

nButyllithium (2.5M in hexane, 8.9ml, 22.3mmol) was added dropwise to a solution of the product of step (a) (4.2g, 17.8mmol) in dry ether (200ml) at 0°C and the reaction was stirred under N_2 for 2h. This was followed by the dropwise addition of iodine (5.46g, 21.5mmol) in ether (100ml) and the reaction was allowed to warm to room temperature over 1h. The reaction mixture was poured onto H_2O, the ether layer was separated, washed with saturated aqueous sodium thiosulphate solution (1x) followed by saturated brine (1x) then dried over $MgSO_4$ and evaporated under reduced pressure to give the subtitle compound as a yellow oil (5.2g, 80%). R_f 0.60 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v); MS m/z 362 (MH^+).

(c) 3,4-Dimethoxy-2-iodobenzonitrile

To a solution of the product of step (b) (5.2g, 14.4mmol) in pyridine (30ml) was added $POCl_3$ (2.7ml, 4.4g, 28.8mmol) and the reaction was heated to 85°C for 18h. The reaction mixture was cooled, partitioned between saturated aqueous sodium carbonate solution

(300ml) and then extracted with ether (2x100ml). The ether layer was washed with 2N HCl (2x75ml) followed by H_2O (1x) and then dried over $MgSO_4$ and evaporated under reduced pressure to afford a yellow oil. This was purified by slurrying with hexane and filtering to give the subtitle compound as an off-white solid (2.82g, 68%). R_f 0.80 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 307 (MH^+). Found: C,38.03; H,2.88; N,4.64; $C_9H_8NO_2I$ 0.05.hexane requires C,38.05; H,2.97; N,4.77%.

(d) 3,4-Dimethoxy-2-iodo-6-nitrobenzonitrile

Nitronium tetrafluoroborate (1.73g, 13.0mmol) was added portionwise to a solution of the product of step (c) (2.67g, 9.2mmol) in acetonitrile (40ml) at 0°C. The reaction was stirred for 0.5h under N_2 and then poured into saturated aqueous sodium bicarbonate solution and extracted with EtOAc (1x). The organic layer was washed with saturated brine (1x), dried over $MgSO_4$ and evaporated under reduced pressure to give a residue which was slurried in hexane and filtered to give the subtitle compound as an off-white solid (2.51g, 82%). R_f 0.46 (EtOAc/hexane 1/1, v/v). MS m/z 352 (MNH_4^+).

(e) 3,4-Dimethoxy-6-nitro-2-phenylbenzonitrile

The subtitle compound was prepared from the product of step (d) by the method of Example 1(a) using phenylboronic acid. The subtitle compound (81%) was obtained as a light yellow solid. R_f 0.46 (EtOAc/hexane 1/1, v/v). MS m/z 302 (MNH_4^+). Found: C,63.23; H,4.23; N,9.86; $C_{15}H_{12}N_2O_4$ requires C,63.38; H,4.23; N,9.86%.

(f) 6-Amino-3,4-dimethoxy-2-phenylbenzonitrile

The subtitle compound was prepared from the product of step (e) by the method of Example 1(b). The crude product was purified on silica gel, eluting with EtOAc/hexane (1/1, v/v) to give the subtitle compound (60%) as a light yellow solid. R_f 0.40 (EtOAc/hexane 1/1, v/v). MS m/z 272 (MNH_4^+). Found: C,70.30; H,5.50; N,10.80; $C_{15}H_{14}N_2O_2$ 0.1.H_2O requires C,70.37; H,5.55; N,10.95%.

(g) 3,4-Dimethoxy-6-{1-[4-(morpholine-4-carbonyl)-1,4-diazepan-1-yl]ethylideneamino}-2-phenylbenzonitrile

The subtitle compound was prepared from the product of step (f) and Intermediate 4 by the method of Example 1(c). The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH (95/5, v/v) to give the subtitle compound (87%) as a colourless foam. MS m/z 492 (MH^+). Found: C,64.75; H,6.74; N,13.67; $C_{27}H_{33}N_5O_4$ 0.15.CH_2Cl_2 requires C,60.64; H,6.61; N,13.89%.

(h) 4-Amino-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-phenylquinoline

The title compound was prepared from the product of step (g) using the method of Example 1(d). The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH3 (90/10/1, v/v) to give the subtitle compound (46%) as a colourless foam. R_f 0.30 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 492 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.05 (2H, m), 3.16 (4H, m), 3.35 (2H, m), 3.48 (3H, s), 3.63 (6H, m), 3.74 (2H, m), 3.87 (2H, bs), 3.97 (2H, m), 4.00 (3H, s), 5.68 (1H, s), 7.13 (1H, bs), 7.39 (2H, m), 7.45 (3H, m). Found: C,63.02; H,6.62; N,13.35; $C_{27}H_{33}N_5O_4$ 0.35.CH_2Cl_2 requires C,63.02; H,6.47; N,13.44%.

Example 4

4-Amino-6,7-dimethoxy-5-(4-fluorophenyl)-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

(a) 3,4-Dimethoxy-2-(4-fluorophenyl)-6-nitrobenzonitrile

The subtitle compound was prepared by the method of Example 1(a) from the compound of Example 3(d) and 4-fluorophenylboronic acid. The subtitle compound (83%) was obtained as a light yellow solid. R_f 0.17 (toluene). MS m/z 303 (MH^+). Found: C,59.19; H,3.63; N,8.84; $C_{15}H_{12}N_2O_4$ 0.15.H_2O requires C,59.04; H,3.71; N,9.18%.

(b) 6-Amino-3,4-dimethoxy-2-(4-fluorophenyl)benzonitrile

The subtitle compound was prepared by the method of Example 1(b) from the product of step (a). The subtitle compound (85%) was obtained as a white solid. R_f 0.73 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 273 (MH^+). Found: C,66.09; H,4.79; N,10.28; $C_{15}H_{13}N_2O_2F$ requires C,66.16; H,4.81; N,10.28%.

(c) 3,4-Dimethoxy-2-(4-fluorophenyl)-6-{1-[4-(morpholine-4-carbonyl)-1,4-diazepan-1-yl]ethylideneamino}benzonitrile

The subtitle compound was prepared by the method of Example 1(c) from the product of step (b) and Intermediate 4. The subtitle compound (83%) was obtained as a colourless solid. mp 174-176°C. R_f 0.12 (EtOAc). MS m/z 510 (MH^+). Found: C,63.61; H,6.35; N,13.68; $C_{27}H_{32}N_5O_4F$ requires C,63.67; H,6.33; N,13.74%.

(d) 4-Amino-6,7-dimethoxy-5-(4-fluorophenyl)-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

The title compound was prepared by the method of Example 1(d) from the product of step (c). The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (95/5/0.5, v/v) and then triturated with EtOAc and filtered to give the subtitle compound (41%) as a colourless solid. mp 189-192°C. R_f 0.15 (CH_2Cl_2/MeOH/0.88NH_3 95/5/0.5, v/v). MS m/z 510 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 2.05 (2H, m), 3.13 (4H, m), 3.32 (2H, m), 3.48 (3H, s), 3.63 (6H, m), 3.74 (2H, m), 3.77-4.23 (4H, bm), 4.00 (3H, s), 5.71 (1H, s), 7.15 (2H, m), 7.23 (1H, bs), 7.32 (2H, m). Found: C,63.07; H,6.41; N,13.17; $C_{27}H_{32}N_5O_4F$ 0.25.H_2O 0.15EtOAc requires C,62.82; H,6.39; N,13.28%.

Example 5

(R/S)-4-Amino-2-[4-(1,4-benzodioxan-2-carbonyl)-1,4-piperazin-1-yl]-6,7-dimethoxy-5-phenylquinoline

(a) 1-Acetyl-4-(t-butyloxycarbonyl)piperazine

The subtitle compound was prepared by the methods of Intermediates 1 and 2 but using piperazine in place of homopiperazine and acetyl chloride in place of 4-morpholinecarbonyl chloride.

(b) 6-{1-[4-(t-Butyloxycarbonyl)-1,4-piperazin-1-yl]ethylideneamino}-3,4-dimethoxy-2-phenylbenzonitrile

The subtitle compound was prepared by the method of Example 1(c) from the compound of Example 3(f) and the product of step (a). The crude product was purified on silica gel,

eluting with CH_2Cl_2/MeOH (97/3, v/v). The subtitle compound (96%) was obtained as a foam. R_f 0.35 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 465 (MH^+).

(c) 4-Amino-2-[4-(t-butyloxycarbonyl)-1,4-piperazin-1-yl]-6,7-dimethoxy-5-phenylquinoline

To a solution of the product of step (b) (270mg, 0.58mmol) in DMSO (3ml) was added KOH flake (33mg,0.58mmol) and the reaction mixture heated to 90°C for 4h after which time the reaction was cooled, poured onto H_2O and extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give the subtitle compound as a foam (65mg, 24%). R_f 0.15 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 465 (MH^+).

(d) 4-Amino-6,7-dimethoxy -5-phenyl-2-(1,4-piperazin-1-yl)quinoline

HCl was bubbled through a solution of the product of step (c) (580mg, 1.25mmol) in CH_2Cl_2 at 0°C. After 15 min the reaction mixture was evaporated under reduced pressure and the residue was purified on silica gel, eluting initially with CH_2Cl_2/MeOH/0.88NH_3 (92/7/1, v/v) followed by CH_2Cl_2/MeOH/0.88NH_3 (90/10/1) to give the subtitle compound as a light brown foam (380mg, 84%). R_f 0.16 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 365 (MH^+).

(e) (R/S)-4-Amino-2-[4-(1,4-benzodioxan-2-carbonyl)-1,4-piperazin-1-yl]-6,7-dimethoxy-5-phenylquinoline

(R/S)-1,4-Benzodioxan-2-carboxylic acid (50mg, 0.28mmol) was added to a solution of 1-hydroxybenzotriazole monohydrate (40mg, 0.30mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (70mg, 0.38mmol) in CH_2Cl_2. This was followed by the sequential addition of 4-methylmorpholine (0.6ml, 0.55mmol) and the product of step (d) (100mg, 0.28mmol) and the reaction mixture was stirred at room temperature under N_2 for 20h after which time it was washed with H_2O, saturated aqueous sodium bicarbonate and then saturated brine. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified on silica gel, eluting initially with EtOAc/hexane (1/1, v/v) followed by EtOAc to give the title compound as a foam (120mg, 79%). R_f 0.30 (EtOAc/hexane 1/1, v/v). MS m/z 527 (MH^+). ^1H NMR ($CDCl_3$) δ: 3.41-

4.05 (2H, b) 3.52 (3H, s), 3.73 (4H, m) 3.90 (4H, m), 4.00 (3H, s), 4.35 (1H, dd), 4.50 (1H, dd), 4.87 (1H, dd), 5.80 (1H, s), 6.89 (4H, m), 7.16 (1H, m), 7.42 (5H, m). Found: C,66.08; H,5.94; N,9.64; $C_{30}H_{30}N_4O_5$ 0.5.EtOAc 0.5.H_2O requires C,66.25; H,6.04; N,9.66%.

Example 6

4-Amino-2-[4-(furan-2-carbonyl)-1,4-piperazin-1-yl]-6,7-dimethoxy-5-phenylquinoline

The title compound was prepared by the method of Example 5(e) from the compound of Example 5(d) and 2-furancarboxylic acid. The title compound (74%) was obtained as a foam. R_f 0.30 (EtOAc/hexane 1/1, v/v). MS m/z 459 (MH^+). ^1H NMR ($CDCl_3$) δ: 3.41-4.05 (2H, b), 3.52 (3H, s), 3.73 (4H, m), 3.90 (4H, m), 4.00 (3H, s), 4.35 (1H, dd), 4.50 (1H, dd), 4.87 (1H, dd), 5.80 (1H, s), 6.89 (4H, m), 7.16 (1H, m), 7.42 (5H, m). Found: C,65.03; H,5.92; N,11.03; $C_{30}H_{30}N_4O_5$ 0.4.EtOAc H_2O requires C,64.73; H,6.10; N,10.94%.

Example 7

(R/S)-4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(tetrahydrofuran-2-carbonyl)-1,4-piperazin-1-yl]quinoline

The title compound was prepared by the method of Example 5(e) from the compound of Example 5(d) and (R/S)-tetrahydrofuran-2-carboxylic acid. The crude product was purified on silica gel eluting with CH_2Cl_2/MeOH/0.88NH_3 (95/4.5/0.5, v/v) to give the title compound (53%) as a white foam. R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 463 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.82-2.05 (3H, m), 2.35 (1H, m), 3.20-4.00 (12H, m), 3.48 (3H, s), 4.00 (3H, s), 4.63 (1H, m), 5.78 (1H, s), 7.10 (1H, s), 7.35-7.48 (5H, m). Found: C,65.57; H,6.51; N,11.60; $C_{26}H_{30}N_4O_4$ 0.2.CH_2Cl_2 requires C,65.62; H,6.39; N,11.68%.

Example 8

4-Amino-6,7-dimethoxy-2-[4-(furan-2-carbonyl)-1,4-diazepan-1-yl]-5-phenylquinoline

(a) 1-Acetyl-4-(t-butyloxycarbonyl)-1,4-diazepane

The subtitle compound was prepared by the methods of Intermediates 1 and 2 but using acetyl chloride in place of 4-morpholinecarbonyl chloride. The subtitle compound (82%) was obtained as a yellow oil. R_f 0.28 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 243 (MH^+).

(b) 6-{1-[4-(t-Butyloxycarbonyl)-1,4-diazepan-1-yl]ethylideneamino}-3,4-dimethoxy-2-phenylbenzonitrile

The subtitle compound was prepared by the method of Example 1(c) from the compound of Example 3(f) and the product of step (a). The subtitle compound (41%) was obtained as a pale yellow foam. R_f 0.21 (CH_2Cl_2/MeOH 97.5/2.5, v/v). MS m/z 479 (MH^+).

(c) 4-Amino-2-[4-(t-butyloxycarbonyl)-1,4-diazepan-1-yl]-6,7-dimethoxy-5-phenylquinoline

The subtitle compound was prepared by the method of Example 1(d) from the product of step (b). The subtitle compound (63%) was obtained as a pale orange foam. R_f 0.51 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 479 (MH^+).

(d) 4-Amino-6,7-dimethoxy-2-(1,4-diazepan-1-yl)-5-phenylquinoline

The subtitle compound was prepared by the method of Example 5(d) from the product of step (c). The subtitle compound was obtained in quantitative yield as a pale orange solid. R_f 0.07 (CH2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 379 (MH^+).

(e) 4-Amino-6,7-dimethoxy-2-[4-(furan-2-carbonyl)-1,4-diazepan-1-yl]-5-phenylquinoline

The title compound was prepared by the method of Example 5(e) from the product of step (d) and 2-furancarboxylic acid. The product was purified by slurrying in EtOAc to give the title compound (72%) as a white solid. R_f 0.58 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 473 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 2.10 (2H, m), 3.50 (3H, s), 3.74 (4H, m), 3.81 (2H, m), 4.00 (8H, m), 5.71 (1H, s), 6.45 (1H, s), 7.01 (1H, bs), 7.65 (1H, bs), 7.44 (5H, m). Found: C,67.57; H,5.90; N,11.63; $C_{27}H_{28}N_4O_4$ 0.5 H_2O requires C,67.34; H,6.07; N,11.63%.

Example 9

4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(tetrahydropyran-4-carbonyl)-1,4-diazepan-1-yl]quinoline

The title compound was prepared by the method of Example 5(e) from the compound of Example 5(d) and tetrahydropyran-4-carboxylic acid. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH (90/10, v/v) to give the title compound (44%) as a white solid. R_f 0.41 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 491 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.74 (1H, m) 1.84-2.15 (3H, m), 2.68 (1H, m), 3.21 (1H, m), 3.50 (8H, m), 3.80 (7H, m), 4.01 (5H, m), 5.68 (1H, s), 7.65 (1H, bs), 7.21-7.55 (6H, m). Found: C,66.97; H,7.09; N,10.77; $C_{28}H_{34}N_4O_4$ 0.75 H_2O requires C,66.71; H,7.10; N,11.11%.

Example 10

4-Amino-5-(4-chlorophenyl)-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

(a) 6-Amino-3,4-dimethoxy-2-iodobenzonitrile

The subtitle compound was prepared by the method of Example 2(b) from the compound of Example 3(d). The subtitle compound (81%) was obtained as a colourless solid. R_f 0.55 (EtOAc/hexane 1/1, v/v). MS m/z 322 (MNH_4^+).

(b) 3,4-Dimethoxy-2-iodo-6-{1-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]ethylideneamino}benzonitrile

The subtitle compound was prepared by the method of Example 1(c) from the product of step (a) and Intermediate 4. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH (97/3, v/v) to give the subtitle compound (87%) as a colourless solid. R_f 0.15 (CH_2Cl_2). MS m/z 542 (MH^+). Found: C,46.00; H,5.17; N,12.44; $C_{21}H_{28}N_5O_4I$ 0.1.CH_2Cl_2 requires C,46.08; H,5.17; N,12.74%.

(c) 4-Amino-6,7-dimethoxy-5-iodo-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

The subtitle compound was prepared by the method of Example 1(d) from the product of step (b) except that the reaction was carried out in THF/DMPU (5/1, v/v). The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH (98/2, v/v). The subtitle compound (65%) was obtained as a light brown solid. R_f 0.50 (CH_2Cl_2/MeOH/0.88NH_3

90/10/1, v/v). MS m/z 542 (MH^+). Found: C,45.71; H,5.26; N,12.44; $C_{21}H_{28}N_5O_4I$ 0.25.CH_2Cl_2 requires C,45.37; H,5.07; N,12.46%.

(d) 4-Amino-5-(4-chlorophenyl)-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

The title compound was prepared by the method of Example 1(a) from the product of step (c)

and 4-chlorophenylboronic acid. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v). The title compound (40%) was obtained as a pale yellow foam. R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 526, 528 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.06 (2H, m), 3.15 (4H, m), 3.35 (2H, m), 3.50 (3H, s), 3.53-3.68 (6H, m), 3.74 (2H, m), 3.97 (5H, m), 4.32 (2H, bs), 5.71 (1H, s), 7.29 (2H, d), 7.45 (2H, d), 7.69 (1H, bs). Found: C,57.34; H,5.71; N,10.97; $C_{27}H_{32}N_5O_4Cl$ 0.67.CH_2Cl_2 requires C,57.02; H,5.76; N,12.02%.

Example 11

4-Amino-5-(3,5-dichlorophenyl)-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

The title compound was prepared by the method of Example 1(a) from the compound of Example 10(c) and 3,5-dichlorophenylboronic acid. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v). The title compound (24%) was obtained as a pale yellow foam. R_f 0.50 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 560, 562, 564 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.06 (2H, m), 3.15 (4H, m), 3.35 (2H, m), 3.55 (3H, s), 3.65 (6H, m), 3.74 (2H, m), 3.99 (7H, m), 5.76 (1H, s), 7.10-7.55 (3H, m), 7.45 (1H, s). Found: C,54.04; H,5.31; N,10.70; $C_{27}H_{32}N_5O_4Cl_2$ 0.6.CH_2Cl_2 0.6.MeOH requires C,53.64; H,5.49; N,11.10%.

Example 12

4-Amino-6,7-dimethoxy-5-(4-methoxyphenyl)-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

The title compound was prepared by the method of Example 1(a) from the compound of Example 10(c) and 4-methoxyphenylboronic acid. The crude product was purified on silica

gel, eluting with CH_2Cl_2/MeOH (95/5, v/v). The title compound (30%) was obtained as a pale yellow foam. R_f 0.20 (CH_2Cl_2/MeOH 9/1, v/v). MS m/z 522 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.06 (2H, m), 3.16 (4H, m), 3.35 (2H, m), 3.50 (3H, s), 3.53-3.80 (8H, m), 3.80-4.13 (4H, m), 3.90 (6H, s), 5.71 (1H, bs), 7.00 (2H, d), 7.06 (1H, bs), 7.31 (2H, d). Found: C,61.75; H,6.63; N,12.34; $C_{28}H_{35}N_5O_5$ 0.2.CH_2Cl_2 0.7.H_2O requires C,61.45; H,6.73; N,12.71%.

Example 13

4-Amino-5-[3,5-bis(trifluoromethyl)phenyl]-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

The title compound was prepared by the method of Example 1(a) from the compound of Example 10(c) and 3,5-bis(trifluoromethyl)phenylboronic acid. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v). The title compound (24%) was obtained as a pale yellow foam. R_f 0.50 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 628 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.06 (2H, m), 3.16 (4H, m), 3.35 (2H, m), 3.48 (3H, s), 3.61 (6H, m), 3.77 (2H, m), 4.00 (7H, m), 5.80 (1H, s), 7.10 (1H, bs), 7.84 (2H, s), 7.95 (1H, s). Found: C,53.51; H,5.06; N,10.03; $C_{29}H_{31}N_5O_4F_6$ 0.4.CH_2Cl_2 0.3.MeOH requires C,53.10; H,4.92; N,10.43%.

Example 14

4-Amino-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-[(4-trifluoromethyl)phenyl]quinoline

The title compound was prepared by the method of Example 1(a) from the compound of Example 10(c) and 4-(trifluoromethyl)phenylboronic acid. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v). The title compound (10%) was obtained as a pale yellow foam. R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 560 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.06 (2H, m), 3.03-4.13 (2H, b), 3.13 (4H, m), 3.34 (2H, m), 3.48 (3H, s), 3.65 (6H, m), 3.76 (2H, m), 4.03 (5H, m), 5.74 (1H, s), 7.16 (1H, bs), 7.50 (2H, d), 7.71 (2H, d). Found: C,56.46; H,5.78; N,11.43; $C_{28}H_{32}N_5O_4F_3$ 0.5.CH_2Cl_2 requires C,56.85; H,5.52; N,11.63%.

Example 15

4-Amino-5-(3-chlorophenyl)-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

The title compound was prepared by the method of Example 1(a) from the compound of Example 10(c) and 3-chlorophenylboronic acid. The crude product was purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88 NH_3 (90/10/1, v/v) followed by trituration with ether. The title compound (43%) was obtained as a colourless foam. R_f 0.34 (CH_2Cl_2/MeOH/0.88 NH_3 90/10/1, v/v); MS m/z 526, 528 (MH^+). ^1H NMR ($CDCl_3$) δ 2.06 (2H, m), 3.15 (4H, m), 3.35 (2H, m), 3.52 (3H, s), 3.40-3.80 (8H, m), 3.99 (7H, m), 5.77 (1H, s), 7.10-7.50 (4H, m), 7.23 (1H, s). Found: C,59.82; H,6.58; N,11.96. $C_{27}H_{32}N_5O_4Cl$ 0.25.CH_2Cl_2 0.5.ether requires C,60.11; H,6.47; N,11.99%.

Example 16

4-Amino-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-phenylquinazoline

(a) 2,4-Dichloro-6,7-dimethoxy-5-nitroquinazoline

To a suspension of 2,4-dichloro-6,7-dimethoxyquinazoline (30.0g, 0.12 mol) in acetonitrile (550ml) at 0°C was added nitronium tetrafluoroborate (25.9g, 0.19mol) portionwise over 15min. The reaction was stirred for 0.75h and then evaporated under reduced pressure. The resulting solid was suspended in a mixture of saturated aqueous sodium bicarbonate and EtOAc and the solid filtered, dissolved in CH_2Cl_2, dried over $MgSO_4$ and evaporated to give the subtitle compound as a pale yellow solid (27g). Further material was obtained by separating the organic layer of the filtrate, washing with H_2O (1x), saturated brine (1x), drying over $MgSO_4$ and filtering through a pad of silica. Subsequent evaporation under reduced pressure, trituration with EtOAc and filtration gave the subtitle compound as a pale yellow solid (3.9g, overall yield 88%). R_f 0.24 (ether/hexane 1/1, v/v).

(b) 2,4-Dihydroxy-6,7-dimethoxy-5-nitroquinazoline

The product of step (a) (27.3g, 90mmol) was suspended in a mixture of glacial acetic acid (150ml) and H_2O (5ml) and the reaction mixture was heated to 150°C for 0.5h after which time a further portion of H_2O (5ml) was added and heating continued. After a total of 1.5h heating, a third portion of H_2O (5ml) was added and heating maintained for a further 0.5h.

The reaction mixture was then cooled and the solid was filtered, washed with ether and dried in vacuo at 80°C to give the subtitle compound as a pale yellow solid (22.2g, 93%). R_f 0.38 (EtOAc/MeOH 95/5, v/v). MS m/z 285 (MNH_4^+).

(c) 5-Amino-2,4-dihydroxy-6,7-dimethoxyquinazoline

A mixture of the product of step (b) (35.0g, 0.13mol) and 10% palladium on carbon (4.0g) was suspended in glacial acetic acid (200ml) and hydrogenated at 50psi (3.4 atm) and 50°C for 2.5 days. The reaction was then cooled, suspended in MeOH/CH_2Cl_2 (1/1,v/v, 1L) and filtered. The residue was transferred to a soxhlet apparatus and continually extracted with MeOH for 3 days. Evaporation afforded a grey solid which was dissolved in 2N NaOH, filtered through a pad of silica, washing with H_2O. The filtrate was then acidified with concentrated HCl. The resulting precipitate was isolated by filtration, washing sequentially with H_2O and acetone, then dried in vacuo at 60°C to give the subtitle compound as a white solid (22.7g, 73%). R_f 0.42 (EtOAc/MeOH 95/5, v/v). MS m/z 238 (MH^+).

(d) 2,4-Dihydroxy-6,7-dimethoxy-5-iodoquinazoline

To a suspension of the product of step (c) (5.5g, 23.2 mmol) in concentrated HCl (10ml) at -10°C was added H_2O (10ml), followed by an aqueous solution of sodium nitrite (2.4g, 34.8mmol in 10ml), the temperature being maintained below 0°C. The resultant yellow diazonium salt was cautiously added to a solution of potassium iodide (40.0g, 0.23mol), copper (I) iodide (4.4g, 23mmol) in H_2O (100ml) heated to 90°C and heating was maintained after the addition was complete until gas evolution ceased. The mixture was then cooled, filtered and the solid residue washed sequentially with H_2O and aqueous sodium thiosulphate. The crude product was purified on silica gel, eluting initially with EtOAc/MeOH (95/5, v/v) followed by EtOAc/MeOH/AcOH (95/5/1, v/v) affording a solid which was suspended in MeOH and filtered to give the subtitle compound as a yellow/orange solid (2.2g, 27%) which was contaminated with the compound of step (b) (0.4g). R_f 0.16 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 366 (MNH_4^+).

(e) 2,4-Dihydroxy-6,7-dimethoxy-5-phenylquinazoline

The subtitle compound was prepared by the method of Example 1(a) from the product of step (d) (5.7/1 mixture of compounds, w/w) and phenylboronic acid. The crude product

was purified on silica gel eluting with CH_2Cl_2/MeOH (95/5, v/v) to give the subtitle compound (95%) as an orange powder which was contaminated (5% w/w) with the compound of step (b). R_f 0.16 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 299 (MH^+).

(f) 2,4-Dichloro-6,7-dimethoxy-5-phenylquinazoline

The mixture produced in step (e) (95/5, w/w, 1.75g, 5.6mmol of the subtitle compound of step (e)) was suspended in $POCl_3$ (10ml, 16.5g, 109mmol) and the mixture treated with N,N-dimethylaniline (1.86ml, 1.79g, 14.7mmol) and heated at reflux for 1.5h. After cooling, excess $POCl_3$ was evaporated under reduced pressure and the residue azeotroped with toluene (2x) then partitioned between EtOAc and H_2O. The organic layer was separated and washed sequentially with H_2O (3x), saturated brine (1x), dried over $MgSO_4$ and filtered through a pad of silica, washing with EtOAc to give, on evaporation, the subtitle compound as a yellow gum. R_f 0.83 (EtOAc).

(g) 4-Amino-2-chloro-6,7-dimethoxy-5-phenylquinazoline

The product of step (f) was suspended in a saturated solution of ammonia in MeOH and the reaction was stirred under N_2 for 3h after which time CH_2Cl_2 was added until all the solid present dissolved. The reaction mixture was then stirred for a further 2.5 days at room temperature, the solvent removed under reduced pressure and the resulting solid suspended in MeOH and isolated by filtration, washing with ether and then drying in vacuo at 60°C. This gave the subtitle compound as a white solid (1.12g, 65% from the product of step (e)). R_f 0.39 (EtOAc). MS m/z 316, 318 (MH^+).

(h) 4-Amino-6,7-dimethoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-phenylquinazoline

To a solution of the product of step (g) (200mg, 0.63mmol) in n-BuOH (10ml) was added Intermediate 3 (250mg, 1.0mmol) and triethylamine (0.22ml, 160mg, 1.58 mmol) and the reaction heated to 100°C under N_2 for 18h. After cooling, the reaction mixture was partitioned between EtOAc and 2N NaOH, the organic layer separated, washed with saturated brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified on silica gel, eluting with EtOAc and the resulting solid was then suspended in a minimal volume of EtOAc, filtered and dried in vacuo at 60°C to give the

title compound as a white solid (180mg, 58%). R_f 0.40 (EtOAc/MeOH 95/5, v/v). MS m/z 493 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.00 (2H, m), 3.16 (4H, m), 3.35 (2H, m), 3.48 (3H, s), 3.52 (2H, m), 3.65 (4H, m), 3.84 (2H, m), 3.94 (2H, m), 3.97 (3H, s), 4.52 (2H, bs), 6.92 (1H, s), 7.35 (2H, m), 7.40-7.52 (3H, m). Found: C,62.82; H,6.52; N,16.70; $C_{26}H_{32}N_6O_4$ 0.25.H_2O requires C,62.85; H,6.59; N,16.91%.

Alternative route to 4-Amino-2-chloro-6,7-dimethoxy-5-phenylquinazoline [the compound of step (g)]

(Aa) 4-Amino-6,7-dimethoxy-2-hydroxy-5-phenylquinazoline

Trifluoroacetic acid (8.1ml, 0.10mol) was added dropwise to a stirred solution of the compound of Example 3(f) (12.9g, 0.051mol) and sodium cyanate (6.6g, 0.10mol) in CH_2Cl_2 (200ml) and the reaction was left to stir at room temperature under N_2 for 18h, after which time an orange precipitate was formed. The solid was isolated by filtration, washing with hexane, dried by suction and then combined with a mixture of 2N aqueous NaOH (250ml) and MeOH (250ml). The mixture was heated on a steam bath until the solid had dissolved and after cooling, the solution was acidified with concentrated HCl and warmed on a steam bath until dissolution was complete. The solution was cooled and neutralised with K_2CO_3 and the precipitated solid was isolated by filtration, washing with H_2O, MeOH, CH_2Cl_2 and finally ether to give the subtitle compound as a colourless solid (12.4g, 82%). MS m/z 298 (MH^+).

(Ab) 4-Amino-2-chloro-6,7-dimethoxy-2-hydroxy-5-phenylquinazoline

DMF (6.4ml, 0.083mol) was added dropwise to $POCl_3$ (19.3ml, 0.21mol). Once the mixture had cooled, the product of step (Aa) (12.34g, 0.042mol) was added and the temperature was maintained at 90°C for 3h and then stirred at room temperature for 18h after which time, the reaction was cautiously quenched with ice. The reaction was then basified with excess 2N NaOH, the temperature was allowed to reach 60°C and this was maintained for 1h. The reaction mixture was then cooled and the precipitate was isolated by filtration and dried in vacuo at 60°C to afford the subtitle compound as an off-white solid (10.2g, 78%).

Example 17

4-Amino-6,7-dimethoxy-2-{4-[1-(3S,4S-dihydroxypyrrolidine)carbonyl]-1,4-diazepan-1-yl}-5-phenylquinazoline hydrochloride

(a) *N*-Benzyl-3S,4S-bis(t-butyldimethylsilyloxy)pyrrolidine

The subtitle compound was prepared by the method of Arakawa *et al* Chem.Pharm.Bull.,39, 2219 (1991).

(b) 1-{1-(3S,4S-Bis(t-butyldimethylsilyloxy)pyrrolidine)carbonyl}-1,4-diazepane

To a stirred solution of the product of step (a) (12.0g, 28mmol) in toluene (150ml) was added a solution of phosgene in toluene (1.93M, 18ml, 34mmol). The resulting suspension was heated at reflux for 6h after which time the solvent was removed under reduced pressure and the residue redissolved in THF (200ml). The solution was cooled to 0°C and then added to a solution of homopiperazine (15.0g, 150mmol) in THF (100ml). The resultant solution was heated to 60°C for 1h and stirred at room temperature for 18h. The solvent was removed under reduced pressure and the residue partitioned between CH_2Cl_2 (200ml) and H_2O (100ml). The organic layer was washed with saturated brine (50ml) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified on silica gel, eluting initially with CH_2Cl_2/MeOH/0.88NH_3 (96/3.5/0.5, v/v) followed by CH_2Cl_2/MeOH/0.88NH_3 (92/7/1, v/v) to give the subtitle compound as an oil which slowly crystallised on standing (7.64g, 60%). R_f 0.2 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 459 (MH^+).

(c) 4-Amino-6,7-dimethoxy-2-{4-[1-(3S,4S-dihydroxypyrrolidine)carbonyl]-1,4-diazepan-1-yl}-5-phenylquinazoline hydrochloride

To a solution of the compound of Example 16(g) (200mg, 0.63mmol) and triethylamine (0.22ml, 1.7mmol) in n-BuOH (10ml) was added the product of step (b) (350mg, 0.76mmol) and the reaction mixture was heated to 100°C under N_2 for 18h. The reaction was then cooled and evaporated under reduced pressure and HCl was bubbled through a solution of the residue in CH_2Cl_2 for 20min. The reaction mixture was then evaporated under reduced pressure, partitioned between EtOAc and H_2O and the aqueous layer extracted repeatedly with EtOAc. The aqueous layer was then basified with 2N NaOH,

extracted with CH_2Cl_2 and the organic layer dried over $MgSO_4$ and evaporated to give a gum which was treated with ethereal HCl. The resulting precipitate was filtered, washing with ether, to give the title compound as a white foam, (210mg, 61%). R_f 0.1 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 509 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.58-2.23 (2H, bm), 3.03-4.35 (2H, bm), 3.23 (4H, m), 3.48 (3H, s), 3.52 (3H, m), 3.71 (4H, m), 4.02 (3H, s), 4.11 (4H, m), 5.16 (1H, bs), 7.32 (2H, m), 7.52 (3H, m), 8.45 (1H, s), 12.59 (1H, bs). Found: C,55.42; H,6.32; N,13.90; $C_{26}H_{32}N_6O_5$ HCl H_2O 0.5EtOAc requires C,55.40; H,6.48; N,13.84%.

Example 18

4-Amino-6,7-dimethoxy-2-[4-(3-hydroxyazetidine-1-carbonyl)-1,4-diazepan-1-yl]-5-phenylquinazoline hydrochloride

A suspension of the compound of Example 16(g) (205 mg, 0.65mmol) in n-BuOH was treated with homopiperazine (1.3g, 13.0mmol) and the reaction heated to reflux under N_2 for 18h. After cooling, the reaction mixture was partitioned between EtOAc and 2N NaOH, the organic layer separated, washed with H_2O (5x) then evaporated under reduced pressure azeotroping with toluene (3x) to give a foam (280mg). This was dissolved in CH_2Cl_2 (50ml), triethylamine (0.11ml, 0.78mmol) was added and the solution stirred with 4Å molecular sieves for 2h before adding dropwise over 1h to a solution of triphosgene (68.0mg, 0.23mmol) in CH_2Cl_2 (10ml) at -5°C. This was then treated with a fine suspension of 2-azetidinol [prepared according to method of Chatterjee *et al*, J.Chem.Soc.Chem.Commun., 93 (1968)] (142mg, 1.3mmol) and triethylamine (0.32ml, 2.3mmol) in THF, pre-stirred with 4Å molecular sieves for 2h. The reaction mixture was subsequently stirred for 3 days at room temperature under N_2 after which time it was partitioned between CH_2Cl_2 and 1N NaOH, the organic layer washed with saturated brine, dried over $MgSO_4$ and evaporated. Purification of the crude product on silica gel, eluting initially with EtOAc/MeOH (95/5, v/v) then CH_2Cl_2/MeOH/0.88NH_3 (90/10/1) followed by treatment with ethereal HCl gave the title compound as a white foam (153mg, 46%). MS m/z 479 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.61, 1.84 (2H, two m), 3.10 (1H, m), 3.18-3.40 (3H, m), 3.40-3.73 (4H, m), 3.55 (3H, s), 3.90 (3H, bm), 4.10 (3H, s), 4.35 (2H, bm), 5.03 (0.5H, bm), 5.21 (1H, bs), 5.26 (0.5H, bm), 5.66 (0.5H, bm), 6.58 (0.5H, bm), 7.40 (2H,

m), 7.55 (3H, m), 8.50 (1H, bs), 12.97 (1H, bs). Found: C,53.94; H,6.40; N,14.06; $C_{25}H_{30}N_6O_4$ HCl 0.4.ether 2.5H_2O requires C,54.14; H,6.78; N,14.25%.

Example 19

4-Amino-2-[4-(1,4-benzodioxan-2-carbonyl)-1,4-piperazin-1-yl]-6,7-dimethoxy-5-phenylquinazoline

(a) 4-Amino-6,7-dimethoxy-5-phenyl-2-(1,4-piperazin-1-yl)quinazoline

To a stirred suspension of the compound of Example 16(g) (420mg, 1.3mmol) in n-BuOH (10ml) was added piperazine (2.29g, 27mmol) and the reaction heated to 80°C for 3h. After cooling, the reaction mixture was partitioned between EtOAc and 2N NaOH, the organic layer was washed sequentially with H_2O (2x) and saturated brine (1x), then dried over $MgSO_4$ and evaporated under reduced pressure. The residue was azeotroped with toluene (1x) then CH_2Cl_2 (2x) to give the subtitle compound as a foam (455mg, 94%). R_f 0.4 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 366 (MH^+).

(b) (R/S)-4-Amino-2-{4-(1,4-benzodioxan-2-carbonyl)-1,4-piperazin-1-yl}-6,7-dimethoxy-5-phenylquinazoline

The title compound was prepared by the method of Example 5(e) from the product of step (a) and (R/S)-1,4-benzodioxan-2-carboxylic acid. The title compound (61%) was obtained as a foam. R_f 0.69 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 528 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 3.42-4.16 (8H, b) 3.48 (3H, s), 4.00 (3H, s), 4.35 (1H, dd), 4.48 (1H, dd), 4.87 (1H, dd), 5.80 (1H, s), 6.89 (4H, m), 6.97 (1H, s), 7.16 (1H, m), 7.39 (2H, m), 7.50 (3H, m). Found: C,64.31; H,5.58; N,12.61; $C_{29}H_{29}N_5O_5$ 0.2.EtOAc 0.5.H_2O requires C,64.54; H,5.70; N,12.63%.

Example 20

4-Amino-6,7-dimethoxy-5-(4-fluorophenyl)-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinazoline

(a) 2,4-Dichloro-6,7-dimethoxy-5-iodoquinazoline

The subtitle compound was prepared by the method of Example 16(f) from the compound of Example 16(d). The subtitle compound was obtained as a solid (contaminated with 2,4,5-trichloroquinazoline). R_f 0.16 (hexane/EtOAc 4/1, v/v).

(b) 4-Amino-2-chloro-6,7-dimethoxy-5-iodoquinazoline

This was prepared by the method of Example 16(g) from the contaminated product of step (a). The subtitle compound (61% from the compound of Example 16(d)) was obtained as a yellow solid (contaminated with the 5-chloro analogue). R_f 0.11 (hexane/EtOAc 4/1, v/v). MS m/z 366 (MH^+).

(c) 4-Amino-6,7-dimethoxy-5-iodo-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinazoline

This was prepared by the method of Example 16(h) from the product of step (b) (3/2 mixture, w/w) and Intermediate 3. The crude product was purified on silica gel, eluting initially with hexane followed by EtOAc/hexane (1/1, v/v). The subtitle compound (28% based on the compound of step (b)) was obtained as an orange foam (contaminated with the 5-chloro analogue). R_f 0.41 (EtOAc). MS m/z 543 (MH^+).

(d) 4-Amino-6,7-dimethoxy-5-(4-fluorophenyl)-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinazoline

This was prepared by the method of Example 1(a) from the product of step (c) (1.2/1 mixture, w/w) and 4-fluorophenylboronic acid. The crude product was purified on silica gel, eluting initially with hexane/EtOAc (4/1, v/v) followed by EtOAc. The title compound (63% based on the compound of step (c)) was obtained as a white foam. R_f 0.18 (EtOAc). MS m/z 511 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.00 (2H, m), 3.14 (4H, m), 3.35 (2H, m), 3.48 (3H, s), 3.55 (2H, m), 3.66 (4H, m), 3.84 (2H, m), 3.94 (2H, m), 3.97 (3H, s), 4.52 (2H, bs), 6.90 (1H, bs), 7.16 (2H, m), 7.32 (2H, m). Found: C,60.91; H,6.32; N,15.73; $C_{26}H_{31}N_6O_4F$ 0.2.EtOAc requires C,60.90; H,6.17; N,15.91%.

Example 21

4-Amino-6,7-dimethoxy-2-{1-[4-(4-morpholinecarbonyl)piperidine]}-5-phenylquinazoline

The title compound was prepared by the method of Example 16(h) from the compound of Example 16(g) and 4-(4-morpholinecarbonyl)piperidine (see US patent 4,022,791). The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2/EtOH/0.88 NH_3 (96/3.5/0.5, v/v). Recrystallisation from EtOAc gave the title compound (25%) as a colourless solid. R_f 0.10 (CH_2Cl_2/MeOH/0.88 NH_3 96/3.5/0.5 v/v). MS m/z 478 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.75-1.95 (4H, m), 2.70 (1H, m), 2.90 (2H, m), 3.50 (3H, s), 3.55-3.75 (8H, m), 4.00 (3H, s), 4.60 (2H, m), 6.95 (1H, bs), 7.40 (2H, m), 7.50 (3H, m). Found: C,65.34; H,6.56; N,14.55. $C_{26}H_{31}N_5O_4$ requires C,65.39; H,6.54; N,14.66%.

Example 22

4-Amino-2-{4-[1-(3S,4S-dihydroxypyrrolidine)carbonyl)]-1,4-diazepan-1-yl}-6,7-dimethoxy-5-phenylquinoline

(a) 6-{1-[(4-Benzyl)-1,4-diazepan-1-yl]ethylideneamino}-3,4-dimethoxy-2-phenylbenzonitrile

The subtitle compound was prepared by the method of Example 1(c) from the compound of Example 3(f) and 1-acetyl-4-benzyl-1,4-diazepane [Sutton, J. Med. Chem., 13, 1026 (1970)] to give the subtitle compound (83%) as an orange glass. R_f 0.36 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 469 (MH^+).

(b) 4-Amino-2-(4-benzyl-1,4-diazepan-1-yl)-6,7-dimethoxy-5-phenylquinoline

A solution of the product of step (a) (440mg, 0.94mmol) in dimethoxyethane (10ml) was treated with potassium t-butoxide (316mg, 2.82mmol) and reaction mixture heated at reflux for 5h. When cool, the mixture was partitioned between EtOAc and H_2O. The organic layer was dried over MgSO4 and evaporated at reduced pressured to an oil. Trituration with MeOH and filtration gave the subtitle compound as a pale pink solid, (300mg, 68%). R_f 0.39 (CH_2Cl_2/MeOH/0.88 NH_3 92/7/1 v/v). ^1H NMR ($CDCl_3$) δ: 1.95(2H, m), 2.65(2H, m), 2.8(2H, m), 3.5(3H, s), 3.65(3H, s), 3.7-3.9(6H, m), 4.00(3H, s), 5.7(1H,s), 7.1(1H, bs), 7.2-7.35(5H, m), 7.4(5H, m).

(c) 4-Amino-2-(1,4-diazepan-1-yl)-6,7-dimethoxy-5-phenylquinoline

A mixture of the product of step (b) (700mg, 1.5mmol), palladium hydroxide (20%w/w, 140mg) and acetic acid (0.17ml, 3.0mmol) in EtOH (30ml) was hydrogenated at 345 kPa (50psi) and room temperature for 18h. The reaction was filtered through Arbocel® and the filtrate evaporated under reduced pressure to yield the subtitle compound as a buff solid (487mg, 86%). R_f 0.10 (CH_2Cl_2/MeOH/0.88 NH_3 90/10/1, v/v). ^1H NMR(CDCl3) δ: 1.95(2H, m), 2.85(2H, m), 3.05(2H, m), 3.50(3H, s), 3.75-3.85(6H, m), 4.0(3H, s), 5.7(1H, s), 7.15(1H, s), 7.45(5H, m).

(d) 4-Amino-2-(4-chlorocarbonyl-1,4-diazepan-1-yl)-6,7-dimethoxy-5-phenylquinoline

To a solution of triphosgene (128mg, 0.43mmol) in CH_2Cl_2 (10ml) at -10°C was added dropwise a solution of the product of step (c) (442mg, 1.17mmol) and triethylamine (0.195ml, 142mg, 1.4mmol) in CH_2Cl_2 (20ml) over 1h. The mixture was stirred at -10°C for a further 1h and then evaporated under reduced pressure to yield the subtitle compound as a brown foam (514mg, 100%) which was used without further treatment.

(e) 4-Amino-2-{4-[1-(3S,4S-dihydroxypyrrolidine)carbonyl]-1,4-diazepan-1-yl}-6,7-dimethoxy-5-phenylquinoline

A mixture of the product of step (d) (257mg,0.58mmol), 3S,4S-bis (t-butyldimethylsilyl-oxy)pyrrolidine [Nagel, Angew. Chem. Int. Ed. Engl., 23, 435 (1984)] (213mg, 0.64mmol) and triethylamine (0.098ml, 71mg, 0.7mmol) in THF (20ml) was refluxed for 18h. When cool, the mixture was partitioned between EtOAc and aqueous saturated sodium hydrogen carbonate solution. The aqueous layer was washed again with EtOAc and finally CH_2Cl_2. The combined organics were dried over $MgSO_4$ and evaporated at reduced pressure. The crude material was purified on silica gel eluting with a gradient eluent of 3-7% MeOH in CH_2Cl_2. The purified material was treated with a methanolic solution of HCl [prepared by adding acetyl chloride (0.07ml) cautiously to MeOH (3ml)] and stirred at room temperature for 2.5h. The mixture was basified with aqueous saturated $NaHCO_3$ and evaporated under reduced pressure. The residue was extracted with CH_2Cl_2, the extract evaporated under reduced pressure and the crude product purified on silica gel eluting with CH_2Cl_2/MeOH/ 0.88 NH_3 (92/7/1, v/v) to yield the title compound (30mg, 10%) as a colourless solid. R_f 0.25 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 508 MH^+. ^1H

NMR(d_6-DMSO) δ: 1.87(2H, m), 3.12(2H, m), 3.34(3H, s), 3.4(2H,m), 3.52(3H,m), 3.68-3.9(8H,m), 4.6(2H,bs), 4.87(2H,m), 5.85(1H,s), 6.93(1H,s), 7.3(2H, m), 7.45(3H,m).

Example 23

4-Amino-6,7-dimethoxy-2-[4-(4-fluoropiperidinecarbonyl)-1,4-diazepan-1-yl]-5-phenylquinoline

A mixture of the compound of Example 22(d) (257mg, 0.58mmol), 4-fluoropiperidine hydrochloride, [J.Org. Chem. 44, 771 (1979)] (90mg, 0.64mmol) and triethylamine (0.18ml, 1.29mmol) in THF (20ml) was heated at reflux for 18h. When cool the reaction was evaporated under reduced pressure and then partitioned between EtOAc and saturated aqueous sodium bicarbonate. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification on silica gel eluting with a gradient eluent of 3-7% MeOH in CH_2Cl_2 afforded the title compound as a foam (102mg, 35%). R_f 0.31 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v). MS m/z 508 (MH^+). NMR ($CDCl_3$) δ: 1.75-1.95(4H, m), 2.05(2H, m), 3.1(2H, m), 3.35(4H, m), 3.45-4.05(12H, m), 4.70 and 4.85(1H, m), 5.70(1H, s), 7.1(1H, bs) 7.45(5H, m). Found: C,64.54; H,6.76; N,12.59. $C_{28}H_{34}N_5O_3F$ 0.5EtOAc 0.5.H_2O requires C,64.27; H,7.01; N,12.49%.

Example 24

4-Amino-6,7-dimethoxy-2-[4-(4-morpholinesulphonyl)-1,4-diazepan-1-yl]-5-phenylquinazoline

(a) 1-(t-Butyloxycarbonyl)-4-{4-morpholinesulphonyl}-1,4-diazepane

The subtitle compound was prepared by the method of Intermediate 2 from Intermediate 1 and 4-morpholinesulphonyl chloride [Repine *et al* J. Med. Chem., 34, 1935 (1991)]. The reaction mixture was partitioned between CH_2Cl_2 and 1N NaOH . The organic phase was washed again with 1N HCl, then H_2O and dried over $MgSO_4$ and evaporated under reduced pressure. Purification on silica gel eluting with CH_2Cl_2/MeOH/0.88 NH_3 (98/1.25/0.25, v/v) initially and then (96/3.5.0.5, v/v) gave the subtitle compound as a gum (53%). R_f 0.44 (CH_2Cl_2/MeOH/0.88 NH_3 96/3.5/0.5, v/v). MS m/z 350 (MH^+). ^{1}H NMR($CDCl_3$) δ: 1.4(9H, s), 1.9(2H, m), 3.17(4H, m), 3.22(2H, m), 3.4(2H, m), 3.5(2H, m), 3.73(6H, m).

(b) 1-(4-Morpholinesulphonyl)-1,4-diazepane hydrochloride

The subtitle compound was prepared by the method of Intermediate 3 from the product of step (a). The subtitle compound (97%) was obtained as a white solid. R_f 0.09 (CH_2Cl_2/MeOH/0.88 NH_3 92/7/1, v/v). MS m/z 250 (MH^+). NMR(d_6-DMSO) δ: 2.1(2H ,m), 3.1(4H, m), 3.4(4H, m), 3.62(8H, m), 9.2(2H, b).

(c) 4-Amino-6,7-dimethoxy-2-[4-(morpholinesulphonyl)-1,4-diazepan-1-yl]}-5-phenylquinazoline

The title compound was prepared by the method of Example 16(h) from the product of step (b) and the compound of Example 16(g). The mixture was purified on silica gel eluting with 3% MeOH in CH_2Cl_2. Evaporation under reduced pressure and recrystallisation from EtOAc/hexane gave the title compound (33%) as a colourless solid. R_f 0.27 (CH_2Cl_2/MeOH 95/5 v/v). MS m/z 529 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.03(2H, m), 3.08(4H, m), 3.37(2H, m), 3.47(3H, s), 3.53(2H, m), 3.63(4H, m), 3.9(2H, m), 3.95(2H, m), 3.98(3H, s), 4.56(2H, s), 6.9(1H, s), 7.37(2H, m), 7.44(3H, m). Found C,56.23; H,6.06; N,15.56. $C_{25}H_{32}N_6O_5S$ 0.5.H_2O requires C,56.42; H,6.14; N,15.79%.

Example 25

4-Amino-2-(7-aminosulfonyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-6,7-dimethoxy-5-phenylquinazoline

To a solution of the compound of Example 16(g) (500mg,1.6mmol) and triethylamine (0.66ml, 4.8mmol) in a mixture of n-BuOH (10ml) and DMA (3ml) was added 1,2,3,4-tetrahydroisoquinoline-7-sulfonamide hydrochloride (R.G. Pendleton *et al*, The Journal of Pharmacology and Experimental Therapeutics, 208, 24, 1979) (597mg, 2.4mmol) and the reaction mixture was heated to 100°C under N_2 for 18h. The reaction was then cooled, partitioned between 2N aqueous NaOH and EtOAc, the organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was triturated with ether/hexane and the resulting solid isolated by filtration to give the title compound as a light yellow solid, (360mg, 46%). R_f 0.62 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 492 (MH^+). ^1H NMR (D_6-DMSO) δ: 2.87 (2H, dd), 3.37 (3H, s), 3.90 (3H, s), 4.00

(2H, dd), 4.94 (2H, s), 6.90 (1H, s), 7.20-7.40 (6H, m), 7.45-7.65 (6H, m). Found: C,60.47; H,5.39, N,13.72; $C_{25}H_{25}N_5O_4S$ 0.3.H_2O requires C,60.42; H,5.19, N,14.09%.

Example 26

4-Amino-6,7-dimethoxy-5-phenyl-2-(3-pyridinemethylamino)quinazoline

To a solution of the compound of Example 16(g) (300mg, 0.95mmol) and triethylamine (0.60ml, 5.7mmol) in a mixture of n-BuOH (10ml) and DMA (2ml) was added 3-(aminomethyl)pyridine and the reaction mixture was heated to 100°C under N_2 for 24h after which time, a further portion of DMA (2ml) was added and heating continued for a subsequent day. The reaction was then cooled, partitioned between H_2O and CH_2Cl_2, the organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v) to give the title compound as a colourless foam, (65mg, 18%). R_f 0.52 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 388 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 3.45 (2H, dd), 3.97 (3H, s), 4.65 (2H, bs), 4.71 (2H, bs), 5.40 (1H, bs), 6.94 (1H, s), 7.15-7.30 (2H, m), 7.39 (2H, m), 7.50 (3H, m), 7.71 (1H, d), 8.50 (1H, d), 8.61 (1H, s). Found: C,65.48; H,5.51, N,16.68; $C_{22}H_{21}N_5O_2$ 0.1.MeOH 0.25.CH_2Cl_2 requires C,65.18; H,5.36, N,17.00%.

Example 27

4-Amino-6,7-dimethoxy-5-(4-fluorophenyl)-2-[4-(morpholinecarbonylamino)-1-propaneamino]quinoline

To a solution of the compound of Example 4 (150mg, 0.29mmol) in THF (5ml) at 0°C under N_2 was added a 1.5M solution of lithium diisopropylamide in cyclohexane (0.2ml, 0.3mmol) and the reaction was allowed to reach room temperature and stirred for 1h. This was followed by the addition of further portions of lithium diisopropylamide (0.4ml, 0.6mmol) and a final portion of lithium diisopropylamide (0.2ml, 0.3mmol) after a further 2h. The reaction was then stirred at room temperature for a further 3h, after which time it was quenched with H_2O, the product extracted into 2N aqueous HCl, the aqueous layer separated, neutralised with sodium bicarbonate, extracted with CH_2Cl_2 (3x) dried over

$MgSO_4$ and evaporated under reduced pressure. The resulting residue was purified by chromatography on silica, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v) to give the title compound as an off-white solid (82mg, 58%). R_f 0.17 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 484 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.95 (2H, m), 3.27 (2H, m), 3.37 (2H, m), 3.48 (3H, s), 3.55 (2H, m), 3.65 (4H, m), 3.90 (5H, bm), 3.99 (3H, s), 5.08 (1H, m), 5.70 (1H, s), 7.03-7.23 (3H, m), 7.31-7.44 (2H, m). Found: C,60.72; H,6.37, N,13.38; $C_{25}H_{30}N_5O_4F$ 0.35.ether 0.7.H_2O requires C,60.73; H,6.74, N,13.41%.

Example 28

4-Amino-6,7-dimethoxy-5-(3-fluorophenyl)-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]quinoline

To a solution of the compound of Example 10(b) (200mg, 0.37mmol) and 3-fluorophenylboronic acid (62mg, 0.44mmol) in a mixture of toluene (9ml), 1M aqueous Na_2CO_3 (1.5ml) and EtOH (5ml) was added tetrakis(triphenylphosphine)palladium (13mg, 0.44mmol) and the reaction was heated to reflux for 1h. The reaction was then cooled, partitioned between EtOAc and H_2O, the organic layer dried over $MgSO_4$ and evaporated to afford a brown residue. This was dissolved in 1,2-dimethoxyethane, the solution purged with N_2 and then potassium t-butoxide (124mg, 1.1mmol) was added and the reaction heated to reflux for 1h. After cooling, the reaction mixture was partitioned between EtOAc and H_2O, the organic layer was dried over $MgSO_4$ and evaporated in vacuo. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH/0.88 NH_3 (96/3.5/0.5, v/v) to afford the title compound as a brown foam (136mg, 72%). R_f 0.39 (CH_2Cl_2/MeOH/0.88 NH_3 92/7/1, v/v). MS m/z 510 (MH^+). ^1HNMR ($CDCl_3$) δ: 2.03 (2H, m), 3.16 (4H, m), 3.34 (2H, m), 3.50 (3H, s), 3.59 (2H, m), 3.65 (4H, m), 3.71 (2H, m), 3.80 (2H, bs), 3.94 (2H, m), 3.99 (3H, s), 5.74 (1H, s), 7.06 (1H, bs), 7.10-7.20 (3H, m), 7.41 (1H, s). Found: C,62.70; H,6.22; N,13.18. $C_{27}H_{32}N_5O_4F$ 0.5.H_2O requires C,62.53; H,6.41; N,13.50%.

Example 29

4-Amino-6,7-dimethoxy-2-(1-methylpiperidin-4-yl)-5-phenylquinoline

The title compound was prepared by the method of Example 5(e) from the compound of Example 8(d) and 1-methylpiperidine-4-carboxylic acid [Rogers *et al* Molecular Pharmacology 36, 333 (1989)]. The product was purified by chromatography on silica gel, eluting with EtOAc/diethylamine (90/10, v/v) to afford the title compound (63%) as an orange solid. R_f 0.15 (CH_2Cl_2/MeOH/0.88 NH_3 92/7/1, v/v). MS m/z 504 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 1.35 (4H, m), 2.06 (2H, m), 2.23 (3H, s), 2.30 (2H, m), 2.42 (1H, m), 2.80-2.95 (2H, m), 3.50 (3H, s), 3.59 (2H, m), 3.78 (6H, m), 3.95-4.13 (2H, bs), 4.00 (3H, s), 5.68 (1H, s), 7.13 (1H, bs), 7.38 (2H, m), 7.45 (3H, m). Found: C,67.03; H,7.37; N,12.87. $C_{29}H_{37}N_5O_3$ 0.5.H_2O 0.5.EtOAc requires C,66.88; H,7.60; N,12.58%.

Example 30

4-Amino-6,7-dimethoxy-2-[3-(morpholinecarbonylamino)ethaneamino]-5-phenylquinazoline

(a) 4-Amino-2-(3-aminoethaneamino)-6,7-dimethoxy-5-phenyl-quinazoline

This was prepared by the method of Example 16(h) from the compound of Example 16(g) and 10 mole equivalents of 1,2-ethanediamine, in the presence of catalytic potassium iodide. The subtitle compound (66%) was obtained as a colourless foam. R_f 0.42 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 340 (MH^+).

(b) 4-Amino-6,7-dimethoxy-2-[3-(morpholinecarbonylamino)ethaneamino]-5-phenylquinazoline

A solution of the product of step (a) (343mg, 1.0mmol) in CH_2Cl_2 (3ml) at 0°C under N_2 was treated with N-methylmorpholine (0.14ml, 1.3mmol) followed by the dropwise addition of a solution of 4-morpholinecarbonyl chloride (0.11ml, 1.1mmol) in CH_2Cl_2 (1ml). The reaction was allowed to reach room temperature and stirred for 18h. The reaction was then quenched with H_2O, extracted with CH_2Cl_2, the organic layer separated, washed with saturated brine, dried over $MgSO_4$ and evaporated. Purification on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether afforded the title compound as a colourless foam (185mg, 34%). R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 453 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 3.32-3.80 (13H, mm), 4.00 (5H, s), 5.34 (3H, b), 5.94 (1H, bs), 7.03 (1H, bs), 7.32 (2H, m), 7.55

(3H, m). Found: C,53.68; H,6.16; N,16.45; $C_{23}H_{28}N_6O_4$ 0.1.ether CH_2Cl_2 requires C,53.77; H,5.73, N,16.43%.

Example 31

4-Amino-6,7-dimethoxy-2-[4-(morpholinecarbonylamino)-1-*N*-methylpropaneamino]-5-phenylquinazoline

(a) 4-Amino-2-(4-amino-1-*N*-methylpropaneamino)-6,7-dimethoxy-5-phenylquinazoline

This was prepared by the method of Example 16(h) from the compound of Example 16(g) and 10 mole equivalents of N-methyl-1,3-propanediamine, in the presence of catalytic potassium iodide. The subtitle compound (17%) was obtained as a colourless foam. R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 368 (MH^+).

(b) 4-Amino-6,7-dimethoxy-2-[4-(morpholinecarbonylamino)-1-*N*-methylpropaneamino]-5-phenylquinazoline

The title compound was prepared by the method of Example 30(b) from the product of step (a) and 4-morpholinecarbonyl chloride. The crude product was purified on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to afford the title compound (49%) as a colourless foam. R_f 0.56 (CH_2Cl_2/MeOH/0.88NH_3, 90/10/1, v/v). MS m/z 481 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.81 (2H, m), 3.13 (3H, s), 3.32 (6H, m), 3.50 (3H, s), 3.65 (4H, m), 3.84 (2H, m), 4.00 (3H, s), 4.71 (2H, bs), 5.65 (1H, bs), 7.00 (1H, bs), 7.35 (2H, m), 7.48 (3H, m). Found: C,58.84; H,6.68; N,15.69; $C_{25}H_{32}N_6O_4$ 0.2.ether 0.5.CH_2Cl_2 requires C,58.72; H,6.56; N,15.63%.

Example 32

(R/S)-4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(tetrahydrofuran-2-carbonylamino)-1-*N*-methylpropaneamino]quinazoline

The title compound was prepared by the method of Example 5(e) from the product of Example 31(a) and (R,S)-tetrahydrofuran-2-carboxylic acid. The crude product was purified on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by

trituration with ether to afford the title compound (57%) as a colourless foam. R_f 0.51 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 466 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.58 (1H, m), 1.71-1.97 (3H, m), 2.23 (2H, m), 2.94 (1H, m), 3.16 (3H, s), 3.39 (1H, m), 3.50 (3H, s), 3.71 (1H, m), 3.84 (1H, m), 3.89-4.05 (2H, m), 4.00 (3H, s), 4.40 (1H, t), 5.15 (2H, b), 7.05 (1H, bs), 7.40 (2H, m), 7.50 (3H, m), 8.39 (1H, bs). Found: C,63.71; H,6.85; N,14.64; $C_{25}H_{31}N_5O_4$ 0.1.CH_2Cl_2 requires C,63.59; H,6.63; N,14.77%.

Example 33

4-Amino-6,7-dimethoxy-2-[4-(morpholinecarbonylamino)-1-propaneamino]-5-phenylquinazoline

(a) 4-Amino-2-(4-amino-1-propaneamino)-6,7-dimethoxy-5-phenylquinazoline

The subtitle compound was prepared by the method of Example 16(h) from the compound of Example 16(g) and 10 mole equivalents of 1,3-propanediamine, in the presence of catalytic potassium iodide. The subtitle compound (72%) was obtained as a colourless foam. R_f 0.11 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 354 (MH^+).

(b) 4-Amino-6,7-dimethoxy-2-[4-(morpholinecarbonylamino)-1-propaneamino]-5-phenylquinazoline

The title compound was prepared by the method of Example 30(b) from the product of step (a) and 4-morpholinecarbonyl chloride. The crude product was purified on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to afford the title compound (71%) as a colourless solid. R_f 0.40 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 467 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.80 (2H, m), 3.39 (6H, m), 3.50 (3H, s), 3.58 (2H, m), 3.68 (4H, m), 4.00 (3H, s), 4.90 (2H, bs), 5.50 (1H, bs), 5.80 (1H, bs), 6.90 (1H, s), 7.37 (2H, m), 7.52 (3H, m). Found: C,58.69; H,6.49; N,16.53; $C_{24}H_{30}N_6O_4$ 0.4.CH_2Cl_2 requires C,58.54; H,6.20; N,16.79%.

Example 34

(R/S)-4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(tetrahydrofuran-2-carbonylamino)-1-propaneamino]quinazoline

The title compound was prepared by the method of Example 5(e) from the product of Example 33(a) and (R/S)-tetrahydrofuran-2-carboxylic acid. The crude product was purified on silica gel, eluting with (CH_2Cl_2/MeOH 90/10, v/v) followed by trituration with toluene to afford the title compound (52%) as a colourless foam. R_f 0.70 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 452 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.67 (2H, m), 1.90 (2H, m), 2.23 (2H, m), 3.06 (1H, m), 3.35 (2H, m), 3.50 (3H, s), 3.61 (2H, m), 3.87 (1H, m), 3.99 (3H, s), 4.01 (1H, bs), 4.40 (1H, t), 5.35 (2H, b), 7.03 (1H, bs), 7.39 (2H, m), 7.52 (3H, m), 8.20 (1H, bs). Found: C,63.18; H,6.50; N,14.66; $C_{24}H_{29}N_5O_4$. 0.1.toluene 0.5.H_2O requires C,63.16; H,6.61; N,14.91%.

Example 35

4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(2-pyrimidineamino)-1-propaneamino]quinazoline

The product of Example 33(a) (230mg, 0.65mmol) was added to a solution of 2-chloropyrimidine (82mg, 0.72mmol) and triethylamine (0.11ml, 0.78mmol) in a mixture of n-BuOH (3ml) and DMA (1ml). The reaction was heated to 80°C under N_2 for 18h, after which the reaction was cooled, washed with H_2O, extracted with CH_2Cl_2, then washed with saturated brine. The organic layer was separated and dried over $MgSO_4$ and the product purified by silica gel chromatography, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether. The title compound was obtained as a colourless foam (110mg, 34%). R_f 0.57 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 432 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.84 (2H, m), 3.41 (2H, m), 3.48 (3H, s), 3.55 (2H, m), 3.99 (3H, s), 6.4-8.4 (2H, b), 6.42 (1H, t), 6.90 (1H, bm), 7.05 (1H, s), 7.35 (2H, m), 7.52 (3H, m), 8.16 (2H, bs). Found: C,57.75; H,5.70; N,20.04; $C_{23}H_{25}N_7O_2$ 0.75.CH_2Cl_2 requires C,57.59; H,5.39; N,19.80%.

Example 36

4-Amino-6,7-dimethoxy-5-phenyl-2-[3-(2-pyridyl)ethaneamino]quinazoline

The title compound was prepared by the method of Example 16(h) from the compound of Example 16(g) and 5 mole equivalents of 2-(2-aminoethyl)pyridine in the presence of catalytic potassium iodide. The product was purified by silica gel chromatography, eluting

with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to afford the title compound (31%) as a colourless foam. R_f 0.27 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 402 (MH^+). ^1H NMR ($CDCl_3$) δ: 3.09 (2H, t), 3.45 (3H, s), 3.84 (2H, q), 4.00 (3H, s), 5.00 (2H, bs), 6.00-6.60 (1H, b), 6.99 (1H, s), 7.05 (1H, dd), 7.40 (1H, d), 7.35 (2H, m), 7.50 (3H, m), 7.59 (1H, t), 8.55 (1H, d). Found: C,63.48; H,5.84; N,15.77; $C_{23}H_{23}N_5O_2$. 0.5.CH_2Cl_2 requires C,63.57; H,5.45; N,15.78%.

Example 37

4-Amino-2-[4-(furan-2-carbonyl)-1,4-piperazin-1-yl]-6,7-dimethoxy-5-phenylquinazoline

The title compound was prepared by the method of Example 5(e) from the compound of Example 19(a) and furan-2-carboxylic acid. The product was purified by chromatography on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to give the title compound (66%) as a foam. R_f 0.67 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 460 (MH^+). ^1H NMR ($CDCl_3$) δ: 3.50 (3H, s), 3.74 (2H, m), 3.80-4.05 (6H, m), 3.97 (3H, s), 4.66 (2H, bs), 6.48 (1H, bs), 7.00 (2H, m), 7.39 (2H, m), 7.50 (4H, m). Found: C,65.71; H,6.42; N,14.80; $C_{25}H_{25}N_5O_4$ 0.5.ether requires C,65.30; H,6.09; N,14.11%.

Example 38

(R/S)-4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(tetrahydrofuran-2-carbonyl)-1,4-piperazin-1-yl]quinazoline

The title compound was prepared by the method of Example 5(e) from the compound of Example 19(a) and (R/S)-tetrahydrofuran-2-carboxylic acid. The product was purified by chromatography on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to give the title compound (52%) as a foam. R_f 0.58 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 464 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.81-2.16 (4H, m), 3.09-4.08 (10H, m), 3.50 (3H, s), 4.00 (3H, s), 4.61 (3H, bm), 6.97 (1H, s), 7.37 (2H, m), 7.50 (3H, m). Found: C,63.14; H,6.52; N,14.00; $C_{25}H_{29}N_5O_4$ 0.2.CH_2Cl_2 0.3.ether requires C,63.07; H,6.53; N,13.88%.

Example 39

(R/S)-4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(tetrahydropyran-2-carbonyl)-1,4-piperazin-1-yl]quinazoline

The title compound was prepared by the method of Example 5(e) from the compound of Example 19(a) and (R/S)-tetrahydropyran-2-carboxylic acid [Nelson *et al* J. Org. Chem. 21, 798 (1956)]. The product was purified by chromatography on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to give the title compound (59%) as a solid. R_f 0.48 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 478 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.44-2.02 (6H, m), 3.40-4.16 (10H, m), 3.50 (3H, s), 3.98 (3H, s), 4.11 (1H, dd), 4.60 (2H, bm), 6.94 (1H, s), 7.38 (2H, m), 7.50 (3H, m). Found: C,64.43; H,6.45; N,13.85; $C_{26}H_{31}N_5O_4$ 0.1.CH_2Cl_2 0.3.ether requires C,64.51; H,6.82; N,13.71%.

Example 40

4-Amino-6,7-dimethoxy-2-[4-(morpholinecarbonyl)-1,4-piperazin-1-yl]-5-phenylquinazoline

Morpholinecarbonyl chloride (0.07ml, 0.66mmol) was added to a stirred solution of the compound of Example 19(a) (220mg, 0.60mmol) and 4-methylmorpholine (0.08ml, 0.72mmol) in CH_2Cl_2 (5ml) at 0°C under N_2. The reaction was stirred for 18h, after which it was washed with H_2O, extracted with CH_2Cl_2, washed with saturated brine and the organic layer dried over $MgSO_4$ and evaporated. The product was purified on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to afford the title compound as a solid (230mg, 70%). R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 479 (MH^+). ^1H NMR ($CDCl_3$) δ: 3.30 (12H, m), 3.50 (3H, s), 3.84 (4H, m), 3.98 (3H, s), 4.60 (2H, bm), 6.97 (1H, s), 7.38 (2H, m), 7.48 (3H, m). Found: C,60.33; H,6.24; N,15.43; $C_{25}H_{30}N_6O_4$ 0.3.CH_2Cl_2 0.5.ether requires C,60.35; H,6.61; N,15.46%.

Example 41

4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(thiomorpholine-1,1-dioxide-4-carbonyl)-1,4-diazepan-1-yl]quinazoline

(a) Thiomorpholine-1,1-dioxide hydrochloride

2-Chloroethyl chloroformate (0.72ml, 6.7mmol) was added dropwise to a solution of 4-methylthiomorpholine-1,1-dioxide (1.0g, 6.7mmol) in toluene (10ml) at 0°C under N_2. After 10min, the reaction was warmed and maintained at reflux for 2h. On cooling, the reaction mixture was evaporated, partitioned between EtOAc and H_2O, the organic layer separated and washed sequentially with dilute HCl and saturated brine, the organic layer dried over Na_2SO_4 and evaporated. The residue was taken up in MeOH (10ml) and heated at reflux for 2h, after which time the reaction mixture was evaporated and triturated with EtOAc to afford the subtitle compound (415mg, 36%) as a solid. R_f 0.34 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 136 (MH^+).

(b) 4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(thiomorpholine-1,1-dioxide-4-carbonyl)-1,4-diazepan-1-yl]quinazoline

The title compound was prepared by the method of Example 18 using the product of step (a) in place of azetidinol. The product was purified by chromatography on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to give the title compound (25%) as a foam. R_f 0.58 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 541 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 1.97 (2H, m), 3.00 (4H, m), 3.40 (2H, m), 3.50 (3H, s), 3.55-3.73 (6H, m), 3.84 (2H, m), 3.90-4.06 (2H, m), 3.98 (3H, s), 4.59 (2H, bm), 6.90 (1H, s), 7.38 (2H, m), 7.50 (3H, m). Found: C,55.90; H;5.82; N,14.35; $C_{26}H_{32}N_6O_5S$ 0.3.CH_2Cl_2 0.2.ether requires C,55.82; H,5.98; N,14.40%.

Example 42

(R/S)-4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(tetrahydropyran-2-carbonyl)-1,4-diazepan-1-yl]quinazoline

(a) (R/S)-1-(t-Butyloxycarbonyl)-4-(tetrahydropyran-2-carbonyl)-1,4-diazepane

The subtitle compound was prepared by the method of Example 5(e) with Intermediate 1 and (R/S)-tetrahydropyran-2-carboxylic acid. The subtitle compound (73%) was obtained as a solid. R_f 0.67 (CH_2Cl_2). MS m/z 312 (MH^+).

(b) (R/S)-1-(Tetrahydropyran-2-carbonyl)-1,4-diazepane hydrochloride

The subtitle compound was prepared by the method of Intermediate 3 from the product of step (a). The subtitle compound was obtained in quantitative yield as a hygroscopic solid. MS m/z 213 (MH^+).

(c) (R/S)-4-Amino-6,7-dimethoxy-5-phenyl-2-[4-(tetrahydropyran-2-carbonyl)-1,4-diazepan-1-yl]quinazoline

The title compound was prepared by the method of 16(h) from the product of step (b) and the compound of Example 16(g). The product was purified by chromatography on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to afford the title compound (43%) as a foam. R_f 0.61 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 492 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.06-2.16 (8H, m), 3.16-4.40 (11H, m), 3.47 (3H, s), 3.98 (3H, s), 4.59 (2H, bm), 6.95 (1H, bs), 7.38 (2H, m), 7.50 (3H, m). Found: C,65.60; H,7.20; N,12.32; $C_{27}H_{33}N_5O_4$ 0.8.ether requires C,65.84; H,7.50; N,12.71%.

Example 43

(S)-4-Amino-6,7-dimethoxy-2-[2-(morpholinecarbonyl)pyrrolidin-1-yl]-5-phenylquinazoline

The title compound was prepared by the method of 16(h) from (S)-proline morpholine amide [prepared according to the method of Asami, Bull. Chem. Soc. Jpn., 63, 721 (1990), replacing Cbz-(S)-proline with tBoc-(S)-proline] and the compound of Example 16(g). The product was purified by chromatography on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v) followed by trituration with ether to afford the title compound (53%) as a foam. R_f 0.39 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 464 (MH^+). ^1H NMR ($CDCl_3$) δ: 1.99 (2H, m), 2.02 (2H, m), 3.48 (3H, s), 3.60 (6H, m), 3.84 (4H, m), 3.97 (3H, s), 4.58 (2H, bm), 5.02 (1H, bs), 6.95 (1H, bs), 7.35 (2H, m), 7.47 (3H,

m). Found: C,63.68; H;6.54; N,13.92; $C_{25}H_{29}N_5O_4$ 0.5.ether 0.1. CH_2Cl_2 requires C,63.72; H,6.75; N,13.70%.

Example 44

4-Amino-6,7-dimethoxy-5-phenyl-2-(5,6,7,8-tetrahydro-1,6-naphthyrid-6-yl)quinazoline

The title compound was prepared by the method of 16(h) from 5,6,7,8-tetrahydro-1,6-naphthyridine [Shiozawa *et al.* Chem. Pharm. Bull., 32, 2522 (1984)] and the compound of Example 16(g). The product was purified by chromatography on silica gel, eluting with (CH_2Cl_2/MeOH/0.88NH_3 93/7/1, v/v) followed by trituration with ether to afford the title compound (33%) as a foam. R_f 0.50 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 492 (MH^+). ^{1}H NMR ($CDCl_3$) δ: 3.10 (2H, t), 3.48 (3H, s), 3.98 (3H, s), 4.18 (2H, t), 4.66 (2H, bs), 5.00 (2H, s), 7.01 (1H, s), 7.13 (1H, dd), 7.39 (2H, m), 7.50 (4H, m), 8.42 (1H, d). Found: C,68.05; H;5.80; N,15.89; $C_{25}H_{23}N_5O_2$ 0.1.CH_2Cl_2 0.4.ether requires C,68.35; H,6.07; N,15.51%.

Example 45

4-Amino-6,7-dimethoxy-5-phenyl-2-(5,6,7,8-tetrahydro-1,3,6-triazanaphth-6-yl)quinazoline

(a) 1-(t-Butyloxycarbonyl)-3-(*N,N*-dimethylmethylidene)-4-piperidone

Dimethylformamide dimethyl acetal (5.82ml, 0.044mol) was added to a stirred solution of 1-Boc-4-piperidone [Ashwood *et al* J. Chem. Soc., Perkin 1, 641 (1995)] (8.73g, 0.044mol) in DMF (80ml) and the reaction mixture was heated to 80°C under N_2 for 18h. After cooling, the DMF was removed under reduced pressure and the residue was partitioned between EtOAc and H_2O, the organic layer washed with H_2O and saturated brine, then dried over $MgSO_4$ and evaporated to afford the subtitle compound as a solid (8.44g, 76%). R_f 0.33 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 255 (MH^+).

(b) 6-(t-Butyloxycarbonyl)-(5,6,7,8-tetrahydro-1,3,6-triazanaphthalene)

Sodium (762mg, 0.033mol) was added to EtOH (150ml) followed by formamidine acetate (3.45g, 0.033mol) and the reaction was stirred at room temperature under N_2 for 30min. A

solution of the product of step (a) (8.43g, 0.033M) in EtOH (50ml) was then added and the reaction heated to reflux for 18h after which time the mixture was cooled and concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O, the organic layer washed with saturated brine and dried over $MgSO_4$. Purification on silica gel, eluting with CH_2Cl_2/MeOH (96/4, v/v) afforded the subtitle compound as an oil (5.09g, 65%). R_f 0.57 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 236 (MH^+).

(c) 5,6,7,8-Tetrahydro-1,3,6-triazanaphthalene

HCl was bubbled through a solution of the product of step (b) (4.80g, 0.020mol) in a mixture of MeOH and ether (50ml, 1/1, v/v) at 0°C until saturated. The mixture was then allowed to reach room temperature over 2h, after which time a precipitate formed. This was isolated by decanting off the supernatant solution, washing with ether (2x) and drying in vacuo to afford the subtitle compound as a colourless solid (2.85g, 81%). R_f 0.13 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 136 (MH^+).

(d) 4-Amino-6,7-dimethoxy-5-phenyl-2-(5,6,7,8-tetrahydro-1,3,6-triazanaphth-6-yl)quinazoline

The title compound was prepared by the method of 16(h) from the product of step (c) and the compound of Example 16(g). The product was purified by chromatography on silica gel, eluting with (EtOAc/hexane 7/1, v/v) followed by trituration with ether to afford the title compound (42%) as a light yellow foam. R_f 0.48 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 415 (MH^+). ^1H NMR ($CDCl_3$) δ: 3.03 (2H, t), 3.50 (3H, s), 4.00 (3H, s), 4.21 (2H, t), 4.68 (2H, bs), 5.00 (2H, s), 7.00 (1H, s), 7.37 (2H, m), 7.50 (3H, m), 8.55 (1H, s), 8.99 (1H, s). Found: C,65.77; H,5.48; N,19.31; $C_{23}H_{22}N_6O_2$ 0.2.ether 0.25.H_2O requires C,65.90; H,5.69; N,19.37%.

Example 46

4-Amino-6,7-dimethoxy-2-[(4-methanesulfonamido)isoindolin-2-yl]-5-phenylquinazoline

(a) 4-Methanesulfonamidophthalimide

Methanesulfonylchloride (2.6ml, 0.034mol) was added dropwise to a stirred suspension of 4-aminophthalimide (5.0g, 0.031mol) in pyridine (50ml). The mixture was stirred for 48h

under N_2 at room temperature, after which time the solid formed was isolated by filtration, washing well with H_2O and CH_2Cl_2 and then dried in vacuo to afford the subtitle compound as a colourless solid (5.67g, 76%). R_f 0.52 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 241 (MH^+).

(b) 4-(Methanesulfonamido)isoindoline hydrochloride

Borane.THF complex (1M solution in THF, 106ml, 0.11mol) was added dropwise to a stirred suspension of the product of step (a) in THF (100ml) and the reaction heated to reflux for 18h. The reaction mixture was then cooled to 0°C and MeOH (50ml) was added cautiously, followed by 6N HCl (70ml). The mixture was then extracted with CH_2Cl_2 (3x) and the aqueous layer evaporated to dryness. The residue was taken up into CH_2Cl_2/MeOH (95/5, v/v) and the inorganic solid filtered off. The filtrate was concentrated to give a solid which was triturated with CH_2Cl_2 and dried in vacuo to afford the subtitle compound as a colourless solid (2.67g, 46%). R_f 0.09 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 213 (MH^+).

(c) 4-Amino-6,7-dimethoxy-2-[(4-methanesulfonamido)isoindolin-2-yl]-5-phenylquinazoline

The title compound was prepared by the method of 16(h) from the product of step (b) and the compound of Example 16(g). The product was purified by chromatography on silica gel, eluting with (EtOAc/hexane 7/1, v/v) followed by trituration with ether to afford the title compound (41%) as a solid. R_f 0.52 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 492 (MH^+). ^1H NMR ($CDCl_3$) δ: 3.03 (3H, s), 3.50 (3H, s), 4.00 (3H, s), 4.71 (2H, bs), 4.90 (4H, bs), 7.03 (1H, s), 7.13 (1H, d), 7.21 (1H, s), 7.30 (1H, d), 7.40 (2H, m), 7.52 (4H, m). Found: C,59.87; H,5.51; N,12.72; $C_{25}H_{25}N_5O_4S$ 0.8.EtOAc requires C,60.26; H,5.63; N,12.46%.

Example 47

(S)-4-Amino-6,7-dimethoxy-2-[3-(morpholinecarbonyl)pyrrolidin-1-yl]-5-phenylquinazoline

(a) (R/S)-1-(t-Butyloxycarbonyl)-3-(morpholinecarbonyl)pyrrolidine

The subtitle compound was prepared by the method of Example 5(e) with (R/S)-1-Boc-pyrrolidine-3-carboxylic acid [MacLeod *et al* J. Med. Chem., 33, 2052 (1990)] and morpholine. The subtitle compound (62%) was obtained as an oil. R_f 0.69 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 285 (MH^+).

(b) (R/S)-3-(Morpholinecarbonyl)pyrrolidine hydrochloride

The subtitle compound was prepared by the method of Example 45(c). The subtitle compound (64%) was obtained as a colourless solid. R_f 0.07 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 185 (MH^+).

(c) (S)-4-Amino-6,7-dimethoxy-2-[3-(morpholinecarbonyl)pyrrolidin-1-yl]-5-phenylquinazoline

The title compound was prepared by the method of 16(h) from the product of step (b) and the compound of Example 16(g). The product was purified by chromatography on silica gel, eluting with (CH_2Cl_2/MeOH/NH_3 90/10/1, v/v) followed by trituration with ether to afford the title compound (41%) as a solid. R_f 0.52 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 464 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.13 (1H, m), 2.35 (1H, m), 3.26(1H, m), 3.47 (3H, s), 3.52-3.76 (10H, m), 3.84 (1H, m), 3.98 (3H, s), 4.00 (1H, m), 4.70 (2H, bs), 7.05 (1H, s), 7.38 (2H, m), 7.45 (3H, m). Found: C,62.55; H,6.28; N,14.27; $C_{25}H_{29}N_5O_4$ 0.25. CH_2Cl_2 requires C,62.55; H,6.13; N,14.45%.

Example 48

4-Amino-6,7-dimethoxy-5-(2-methoxyphenyl)-2-(5,6,7,8-tetrahydro-1,6-naphthyrid-6-yl)quinazoline

(a) 4-Amino-6,7-dimethoxy-5-iodo-2-(5,6,7,8-tetrahydro-1,6-naphthyrid-6-yl)quinazoline

The subtitle compound was prepared by the method of 16(h) from 1,2,3,4-tetrahydro-1,6-naphthyridine and the compound of Example 20(b).The subtitle compound was obtained in quantitative yield as a brown foam. R_f 0.35 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 464 (MH^+).

(b) 4-Amino-6,7-dimethoxy-5-(2-methoxyphenyl)-2-(5,6,7,8-tetrahydro-1,6-naphthyrid-6-yl)quinazoline

The title compound was prepared by the method of Example 1(a) with 2-methoxyphenylboronic acid and the product of step (a). The product was purified by trituration with EtOAc/hexane to afford the title compound (18%) as an off-white solid. R_f 0.33 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 444 (MH^+). ^1H NMR (D_6-DMSO) δ: 3.06 (2H, m), 3.50 (3H, s), 3.74 (3H, s), 4.00 (3H, s), 4.21 (2H, m), 4.74 (2H, s), 4.99 (2H, s), 6.90-7.16 (4H, m), 7.22 (1H, d), 7.39-7.55 (2H, m), 8.40 (1H, d). Found: C,66.52; H,5.84; N,14.83; $C_{25}H_{25}N_5O_3$ 0.5.H_2O 0.1.hexane requires C,66.67; H,5.73; N,15.20%.

Example 49

4-Amino-11-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-9H-[2]benzopyrano-[3,4-c]quinazoline

(a) 3-Benzyloxy-4-methoxybenzonitrile

3-Benzyloxy-4-methoxybenzaldehyde (50g, 0.21mol) was added to a solution of sodium acetate (33.9g, 0.41mol) and hydroxylamine hydrochloride (28.73g, 0.41mol) in acetic acid (200ml) and the resulting suspension was heated to reflux for 18h. After cooling, the reaction mixture was partitioned between CH_2Cl_2 and H_2O and the aqueous phase was further extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the subtitle compound as a buff-coloured solid (43.9g, 89%). R_f 0.70 (toluene/EtOAc 4/1, v/v).

(b) 5-Benzyloxy-4-methoxy-2-nitro-benzonitrile

A solution of the product of step (a) (43.8g, 0.18mol) in glacial acetic acid (87ml) was added dropwise to concentrated nitric acid (70% w/w, 244ml) with periodic cooling to maintain the reaction temperature below 30°C. Once the addition was complete, the reaction was stirred for a further 30min, after which time the mixture was poured into H_2O (1L) and stirred for 30min. The resulting precipitate was isolated by filtration, washing with H_2O followed by drying in vacuo at 50°C to afford the subtitle compound as a white solid (35.1g, 68%). R_f 0.70 (EtOAc/hexane 1/1, v/v).

(c) 2-Amino-5-benzyloxy-4-methoxybenzonitrile

To a solution of the product of step (b) (35.0g, 0.12mol) in CH_2Cl_2 (500ml) was added tetra-n-butylammonium chloride (20.3g, 0.074mol) followed by a solution of sodium dithionite hydrate (118.0g, 0.61mol) in H_2O (400ml) and the mixture was stirred vigorously for 2h at room temperature. A further quantity of sodium dithionite hydrate (47.2g) was then added and stirring continued for 1h. The reaction mixture was then basified with 2N aqueous NaOH and the phases separated. The aqueous layer was extracted twice more with CH_2Cl_2 and the combined organic layers dried over $MgSO_4$ and concentrated in vacuo to a volume of 60ml. Treatment with excess ethereal HCl led to the precipitation of an orange solid which was washed with ether and then dissolved in a mixture of CH_2Cl_2 and 2N aqueous NaOH. The phases were separated and the organic layer concentrated in vacuo and then dissolved in EtOAc and passed through a 5cm plug of silica gel, eluting with EtOAc. On evaporation and drying in vacuo, the subtitle compound was obtained as a yellow solid (26.7g, 85%). R_f 0.76 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 255 (MH^+).

(d) 4-Amino-6-benzyloxy-2-hydroxy-7-methoxyquinazoline

A solution of the product of step (c) (26.7g, 0.10mol) in CH_2Cl_2 was treated with sodium cyanate (17.1g, 0.26mol) and trifluoroacetic acid (20.9ml, 0.26mol) was added dropwise to the resulting mixture at room temperature. After 45min, the mixture was diluted with CH_2Cl_2 (1L) and stirred for a further 18h. The mixture was then concentrated in vacuo and partitioned between MeOH and 2N aqueous NaOH and stirred for 2h. The MeOH was then removed in vacuo and the yellow solid isolated by filtration, washing sequentially with H_2O, acetone and ether to afford the subtitle compound as a yellow solid (18.0g, 54%). A further quantity of product was obtained by concentration of the filtrate, acidification with concentrated HCl (95ml), warming on a steam bath for 5min, cooling and neutralisation with solid potassium carbonate. The solid obtained was isolated by filtration, washing sequentially with H_2O, EtOH and ether to afford the subtitle compound as a yellow solid (12.11g, 93% combined yield). R_f 0.23 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 298 (MH^+).

(e) 4-Amino-6-benzyloxy-2-chloro-7-methoxyquinazoline

DMF (7.9ml, 0.10mol) was added dropwise to $POCl_3$ with stirring. After 10min, the product of step (d) was added portionwise and the resulting mixture heated at 90°C for 1.5h, then cooled and poured into EtOAc (750ml). The mixture was neutralised by the portionwise addition of aqueous sodium carbonate and the phases were separated. The organic layer was evaporated to dryness and the residue combined with the organic phase which was then treated with aqueous NaOH to basify (pH10) and the mixture was heated at 90°C for 2h. After cooling, the mixture was partitioned between CH_2Cl_2 (1L) and H_2O (1L), the organic phase washed with H_2O, dried over $MgSO_4$ and evaporated to give a pale yellow solid. Trituration with isopropanol afforded the subtitle compound as a colourless solid (4.64g, 29%). R_f 0.64 (EtOAc/MeOH 95/5, v/v). MS m/z 316, 318 (MH^+).

(f) 2-Amino-6-benzyloxy-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]

The subtitle compound was prepared by the method of 16(h) from the product of step (e) and the compound of Example 16(g). The product was purified on silica gel eluting with EtOAc/MeOH (9/1, v/v) to afford the subtitle compound (46%) as a foam. R_f 0.67 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 493 (MH^+).

(g) 2-Amino-6-hydroxy-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]

The product of step (f) (360mg, 0.73mmol) was dissolved in EtOH (60ml), 10% palladium on charcoal (100mg, 0.09mmol) was added and the reaction mixture hydrogenated at room temperature at a pressure of 414 kPa (60psi). for 18h. The reaction mixture was filtered and concentrated in vacuo and the residue purified on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (92/7/1, v/v) to afford the subtitle compound as a foam (135mg, 47%). R_f 0.33 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 403 (MH^+).

(h) 2-Amino-6-(o-bromobenzyloxy)-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]

Sodium hydride (60% dispersion in mineral oil, 100mg, 2.5mmol) was added to DMF (20ml) and this was followed by the addition of the product of step (g) (1.0g, 2.5mmol) and the reaction was stirred at room temperature for 20min. o-Bromobenzyl bromide (625mg, 2.5mmol) was then added to the reaction which was left to stir for 1h, after which time it was quenched with H_2O, extracted with EtOAc (2x), the combined organic layers washed

with H_2O, dried over $MgSO_4$ and evaporated to afford the product as a foam (1.2g, 84%). R_f 0.48 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 571, 573 (MH^+).

(i) 4-Amino-11-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-9H-[2]benzopyrano-[3,4-c]quinazoline

To a solution of the product of step (i) (1.2g, 2.0mmol) in DMA (10ml) was added sodium carbonate (254mg, 2.4mmol) and palladium acetate (45mg, 0.2mmol) and the reaction mixture was heated to 130°C for 48h under N_2. The reaction mixture was then cooled partitioned between EtOAc and H_2O and the organic layer dried over $MgSO_4$ and evaporated. The product was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH/0.88NH_3 (95/5/0.5, v/v) followed by trituration with hexane to afford the title compound as a light yellow solid (114mg, 12%). R_f 0.76 (CH_2Cl_2/MeOH/0.88NH_3 84/14/2, v/v). MS m/z 491 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.06 (2H, m), 3.18 (4H, m), 3.42 (2H, m), 3.60 (2H, m), 3.68 (4H, m), 3.94 (2H, m), 4.00 (5H, m), 4.90 (2H, bs), 5.09 (2H, s), 6.87 (1H, s), 7.21-7.52 (4H, m). Found: C,62.18; H,6.34; N,14.66; $C_{26}H_{30}N_6O_4$. 0.6.hexane 0.5. CH_2Cl_2 requires C,61.84; H,6.74; N,14.38%.

Example 50

4-Amino-11-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-9H-[2]benzopyrano-[3,4-c]quinoline

(a) 3-(o-Bromobenzyloxy)-4-methoxybenzonitrile

To a solution of 2-bromobenzyl alcohol (16.50g, 88.2mmol) in DMF (100ml) was added sodium hydride (60% dispersion in mineral oil, 2.94g, 73.5mmol) and this was followed by 3-fluoro-4-methoxybenzonitrile (8.88g, 58.8mmol) and the resulting mixture was heated to 90°C for 2h under N_2. After cooling, the mixture was partitioned between ether and H_2O, the organic layer washed sequentially with 0.5N HCl and saturated brine and then dried over $MgSO_4$. Trituration with ether/pentane (1/3, v/v) afforded the subtitle compound as an off-white solid (13.35g, 71%). R_f 0.27 (hexane/EtOAc 5/1, v/v). MS m/z 318, 320 (MH^+).

(b) 1-Cyano-6H-dibenzo[b,d]pyran

The subtitle compound was prepared by the method of Example 49(i) from the product of step (a). The product was purified by chromatography on silica gel, eluting with hexane/EtOAc (4/1, v/v) followed by trituration with hexane/EtOAc (4/1, v/v) to afford the subtitle compound (41%) as a colourless solid. R_f 0.16 (hexane/EtOAc, 4/1, v/v). MS m/z 238 (MH^+).

(c) 1-Cyano-2-nitro-6H-dibenzo[b,d]pyran

The subtitle compound was prepared by the method of Example 16(a) from the product of step (b). The product was purified by chromatography on silica gel, eluting with CH_2Cl_2 to afford the subtitle compound (42%) as a pale yellow solid. R_f 0.26 (hexane/ CH_2Cl_2 1/2, v/v). MS m/z 283 (MH^+).

(d) 2-Amino-1-cyano-6H-dibenzo[b,d]pyran

The subtitle compound was prepared by the method of Example 49(c) from the product of step (c). The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (98/2, v/v) to afford the subtitle compound (85%) as a yellow solid. R_f 0.81 (CH_2Cl_2/MeOH/0.88NH_3 93/7/1, v/v). MS m/z 253 (MH^+).

(e) 1-Cyano-2-{1-[4-(morpholine-4-carbonyl)-1,4-diazepan-1-yl]ethylideneamino}-6H-dibenzo[b,d]pyran

The subtitle compound was prepared by the method of Example 1(c) from the product of step (d) and Intermediate 4. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (97/3, v/v) to afford the subtitle compound (97%) as a yellow foam. R_f 0.56 (CH_2Cl_2/MeOH/0.88NH_3 93/7/1, v/v). MS m/z 490 (MH^+).

(f) 4-Amino-11-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-9H-[2]benzopyrano-[3,4-c]quinoline

The title compound was prepared by the method of Example 1(d) from the product of step (e). The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (9/1, v/v) followed by dissolution in CH_2Cl_2 and precipitation with toluene to afford the subtitle compound (40%) as a yellow solid. R_f 0.35 (CH_2Cl_2/MeOH/0.88NH_3 93/7/1, v/v). MS m/z 490 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.10 (2H, m), 3.16 (4H, m), 3.40 (2H, m), 3.65

(6H, m), 3.77 (2H, m), 3.98 (2H, m), 4.01 (3H, s), 4.35 (2H, s), 4.90 (1H, d), 5.30 (1H, d), 5.94 (1H, s), 7.05 (1H, s), 7.21-7.52 (4H, m). Found: C,65.86; H,6.33, N,13.30; $C_{27}H_{31}N_5O_4$. 0.2.toluene 0.5.H_2O requires C,65.98; H,6.55, N,13.55%.

Example 51

4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-phenyl-6-(2,2,2-trifluoroethoxy)quinoline

(a) 4-Methoxy-3-(2,2,2-trifluoroethoxy)benzoic acid, methyl ester

To a mixture of isovanillic acid methyl ester (33.0g, 0.18mol) and potassium carbonate (41.4g, 0.30mol) in DMF (100ml) was added a solution of trifluoroethyl triflate [Burdon *et al* Tetrahedron 21, 1 (1965)] (65.0g, 0.28mol) in CH_2Cl_2. The mixture was stirred at room temperature for 18h then evaporated to 50ml, the mixture partitioned between ether and H_2O, the organic layer washed with H_2O and saturated brine, then dried over $MgSO_4$ and evaporated. The resulting solid was triturated with hexane to give the subtitle compound as an off-white solid (42.55g, 90%). R_f 0.47 (CH_2Cl_2). MS m/z 265 (MH^+).

(b) 4-Methoxy-3-(2,2,2-trifluoroethoxy)benzoic acid

The product of step (a) (42.3g, 0.16mol) was dissolved in MeOH (500ml) and 2N aqueous NaOH (160ml, 0.32mol) was added and the mixture stirred at room temperature for 3h and then at 50°C for 1h. After cooling, the solution was concentrated in vacuo, treated with 2N HCl and extracted with EtOAc (3x). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to give the subtitle compound as a colourless solid (40.4g, quantitative). R_f 0.13 (hexane/EtOAc 1/1, v/v). MS m/z 251 (MH^+).

(c) 2-[4'-Methoxy-3'-(2,2,2-trifluoroethoxyphenyl)]-4,4-dimethyl-Δ^2-oxazoline

The subtitle compound was prepared by the method of Example 3(a) from the product of step (b). The product was purified on silica gel, eluting with CH_2Cl_2/MeOH (95/5) to give the subtitle compound (80%) as a colourless solid. R_f 0.54 (EtOAc). MS m/z 304 (MH^+).

(d) 2-[2'-Iodo-4'-methoxy-3'-(2,2,2,-trifluoroethoxyphenyl)]-4,4-dimethyl-Δ^2-oxazoline

The subtitle compound was prepared by the method of Example 3(b) from the product of step (c). The product was purified on silica gel, eluting with EtOAc/hexane (3/2, v/v) followed by trituration with ether/hexane (1/3, v/v) to give the subtitle compound (26%) as a colourless solid. R_f 0.27 (EtOAc/hexane 1/1, v/v). MS m/z 430 (MH^+).

(e) 2-Iodo-4-methoxy-3-(2,2,2-trifluoroethoxy)benzonitrile

The subtitle compound was prepared by the method of Example 3(c) from the product of step (d). The product was triturated with ether/hexane (1/3, v/v) to give the subtitle compound (97%) as a colourless solid. R_f 0.50 (EtOAc/hexane 1/1, v/v). MS m/z 358 (MH^+).

(f) 2-Iodo-4-methoxy-6-nitro-3-(2,2,2-trifluoroethoxy)benzonitrile

The subtitle compound was prepared by the method of Example 3(d) from the product of step (e). The product was triturated with ether to give the subtitle compound (61%) as a colourless solid. R_f 0.25 (EtOAc/hexane 1/2, v/v). MS m/z 403 (MH^+).

(g) 2-Amino-6-iodo-4-methoxy-5-(2,2,2-trifluoroethoxy)benzonitrile

The subtitle compound was prepared by the method of Example 49(c) from the product of step (f). The subtitle compound (70%) was obtained as a colourless solid. R_f 0.74 (CH_2Cl_2/MeOH/0.88NH_3 93/7/1, v/v). MS m/z 373 (MH^+).

(h) 2-Iodo-4-methoxy-6-{1-[4-(morpholine-4-carbonyl)-1,4-diazepan-1-yl]ethylideneamino}-3-(2,2,2-trifluoroethoxy)benzonitrile

The subtitle compound was prepared by the method of Example 1(c) from the product of step (g) and Intermediate 4. The product was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1, v/v) followed by crystallisation from EtOAc to give the subtitle compound (64%) as a colourless solid. R_f 0.12 (EtOAc). MS m/z 610 (MH^+).

(i) 4-Amino-5-iodo-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-6-(2,2,2-trifluoroethoxy)quinoline

The subtitle compound was prepared by the method of Example 1(d) from the product of step (h). The product was purified by chromatography on silica gel eluting with

CH_2Cl_2/MeOH (9/1, v/v) to give the subtitle compound (20%) as a colourless solid. R_f 0.15 (CH_2Cl_2/MeOH 9/1, v/v). ^1H NMR ($CDCl_3$) δ: 2.06 (2H, m), 3.16 (4H, m), 3.32 (2H, m), 3.58 (2H, m), 3.65 (4H, m), 3.70 (2H, m), 3.90 (2H, m), 3.97 (3H, s), 4.37 (2H, t), 5.55 (2H, bs), 5.90 (1H, s), 7.05 (1H, bs).

(j) 4-Amino-7-methoxy-2-[4-(4-morpholinecarbonyl)-1,4-diazepan-1-yl]-5-phenyl-6-(2,2,2-trifluoroethoxy)quinoline

The subtitle compound was prepared by the method of Example 1(a) from the product of step (i) and phenylboronic acid. The product was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (9/1, v/v) to give the subtitle compound (55%) as a foam. R_f 0.12 (CH_2Cl_2/MeOH 9/1, v/v). MS m/z 560 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.06 (2H, m), 3.16 (4H, m), 3.35 (2H, m), 3.55-3.80 (8H, m), 3.82-4.13 (9H, m), 5.70 (1H, s), 7.65 (1H, bs), 7.37 (2H, m), 7.45 (3H, m).

Example 52

2-Amino-6,7-dimethoxy-5-phenyl-2-(5,6,7,8-tetrahydro-1,3,7-triazanaphth-7-yl)quinazoline

(a) 1-Trityl-3-piperidone

Trityl chloride (13.1g, 47.0mmol) was added to a stirred suspension of 3-piperidone hydrochloride (5.79g, 42.7mmol) and triethylamine (14.9ml, 107mmol) in CH_2Cl_2 (100ml) and the reaction was stirred for 16h under N_2 at room temperature. The resulting mixture was filtered and the filtrate washed sequentially with H_2O and 5% aqueous citric acid, dried over $MgSO_4$ and evaporated under reduced pressure. Trituration with pentane afforded the subtitle compound as a colourless solid (4.8g, 33%). R_f 0.23 (CH_2Cl_2/pentane 2/3, v/v). ^1H NMR ($CDCl_3$) δ: 2.05 (2H, m), 2.35 (2H, m), 2.45 (2H, m), 2.85 (2H, s), 7.06-7.55 (15H, m).

(b) 4-(*N,N*-Dimethylmethylidene)-1-trityl-3-piperidone

The subtitle compound was prepared by the method of Example 45(a) from the product of step (a). Crystallisation from ether afforded the subtitle compound (52%) as a colourless

solid. R_f 0.23 (CH_2Cl_2/pentane 2/3, v/v). ^1H NMR ($CDCl_3$) δ: 2.35 (2H, t), 2.87 (2H, t), 2.97 (2H, s), 3.13 (6H, s), 7.13 (3H, m), 7.24 (7H, m), 7.50 (6H, m).

(c) 7-Trityl-(5,6,7,8-tetrahydro-1,3,7-triazanaphthalene)

The subtitle compound was prepared by the method of Example 45(b) from the product of step (b). The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/ether (9/1, v/v) to afford the subtitle compound (51%). R_f 0.33 (CH_2Cl_2/ether 85/15, v/v). ^1H NMR ($CDCl_3$) δ: 2.60 (2H, t), 2.97 (2H, t), 3.58 (2H, s), 7.06-7.37 (8H, m), 7.52 (7H, m), 8.45 (1H, s), 8.90 (1H, s)

(d) 5,6,7,8-Tetrahydro-1,3,7-triazanaphthalene hydrochloride

The subtitle compound was prepared by the method of Example 45(c) from the product of step (c). The product crystallised from MeOH/ether to afford the subtitle compound (65%) as an orange hygroscopic solid. ^1H NMR (d_6-DMSO) δ: 3.06 (2H, m), 3.40 (2H, m), 4.26 (2H, s), 8.68 (1H, s), 9.00 (1H, s), 9.96 (2H, bs).

(e) 2-Amino-6,7-dimethoxy-5-phenyl-2-(5,6,7,8-tetrahydro-1,3,7-triazanaphth-7-yl)quinazoline

The title compound was prepared by the method of 16(h) from the product of step (d) and the compound of Example 16(g). The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH (95/5, v/v) to afford the title compound (36%) as a foam. R_f 0.16 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 415 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.90 (2H, m), 3.50 (3H, s), 4.00 (3H, s), 4.16 (2H, m), 4.65 (2H, bs), 5.05 (2H, s), 7.00 (1H, s), 7.38 (2H, m), 7.50 (3H, m), 8.50 (1H, s), 9.02 (1H, s). Found: C,63.56; H,5.20; N,18.97; $C_{23}H_{22}N_6O_2$ 0.3.CH_2Cl_2 requires C,63.49; H,5.17; N,19.06%.

Example 53

4-Amino-6,7-dimethoxy-2-(4-methoxy-5,6,7,8-tetrahydro-1,3,7-triazanaphth-7-yl)-5-phenylquinazoline

(a) 7-Benzyl-4-chloro-5,6,7,8-tetrahydro-1,3,7-triazanaphthalene

7-Benzyl-4-hydroxy-5,6,7,8-tetrahydro-1,3,7-triazanaphthalene [Ozdowska *et al* Rocz. Chem. Ann. Soc. Chim. Pol. 50,1771 (1976)] 95.0g, 15.9mmol) was added to $POCl_3$ and the mixture heated to 100°C for 1h. The reaction was cooled, concentrated under reduced pressure and the residue quenched with ice. After neutralising with K_2CO_3 the product was extracted with CH_2Cl_2, the organic layer washed with H_2O, dried over $MgSO_4$ and evaporated to give the subtitle compound as a brown oil (3.33g, 81%). R_f 0.45 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v).

(b) 7-Benzyl-4-methoxy-5,6,7,8-tetrahydro-1,3,7-triazanaphthalene

Sodium (380mg, 16.5mmol) was added portionwise to MeOH (7ml) and the solution was added dropwise to a solution of the product of step (a) (3.3g, 12.7mmol) in THF (30ml). After stirring at room temperature for 18h, the reaction mixture was concentrated under reduced pressure, partitioned between H_2O and CH_2Cl_2, the aqueous layer extracted with CH_2Cl_2 and the combined organic layers dried over $MgSO_4$. Evaporation under reduced pressure afforded the subtitle compound as a brown oil (3.1g, 95%). R_f 0.64 (CH_2Cl_2/MeOH/0.88NH_3 92/7/1, v/v).

(c) 4-Methoxy-5,6,7,8-tetrahydro-1,3,7-triazanaphthalene

To a solution of the product of step (b) (3.1g, 12.0mmol) in EtOH (40ml) was added palladium hydroxide (20%, w/w, 614mg) and the mixture was hydrogenated at 345kPa [50psi] pressure for 18h, after which time a further portion of EtOH (40ml) and palladium hydroxide (614mg) was added and the hydrogenation continued for a further 18h. Filtration, evaporation under reduced pressure and chromatography on silica gel, eluting with CH_2Cl_2/MeOH (90/10, v/v) afforded the subtitle compound as a pale orange oil (1.09g, 55%). R_f 0.06 (CH_2Cl_2/MeOH 95/5, v/v). MS m/z 166 (MH^+).

(d) 4-Amino-6,7-dimethoxy-2-(4-methoxy-5,6,7,8-tetrahydro-1,3,7-triazanaphth-7-yl)-5-phenylquinazoline

The title compound was prepared by the method of 16(h) from the product of step (c) and the compound of Example 16(g) in the presence of 1mol equivalent of ammonium chloride. The product was purified by chromatography on silica gel, eluting with EtOAc to afford the title compound (10%) as a foam. R_f 0.42 (EtOAc/MeOH 95/5, v/v). MS m/z 445

(MH^+). ^1H NMR ($CDCl_3$) δ: 2.74 (2H, t), 3.48 (3H, s), 3.98 (3H, s), 4.00 (3H, s), 4.10 (2H, t), 4.61 (2H, bs), 4.95 (2H, s), 6.97 (1H, s), 7.38 (2H, m), 7.50 (3H, m), 8.57 (1H, s). Found: C,63.88; H,5.59; N,17.82; $C_{24}H_{24}N_6O_3$ 0.2.EtOAc 0.3.H_2O requires C,63.71; H,5.65; N,17.98%.

Example 54

4-Amino-6,7-dimethoxy-2-[6-(2-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridyl)]-5-phenylquinazoline

(a) 2-Methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine hydrochloride

A mixture of 3-bromo-4-piperidone hydrobromide [Scarponi *et al* Farmaco, Ed. Sci. 43, 575 (1988)] (2.58g, 0.01mol) and thioacetamide (940mg, 0.013mol) in EtOH (100ml) was heated at reflux for 3h. After cooling, the reaction mixture was cooled and evaporated under reduced pressure and the resulting residue triturated with acetone to afford a solid. This was dissolved in H_2O, washed with EtOAc (3x), the aqueous phase was basified with saturated aqueous Na_2CO_3 and extracted with EtOAc (5x), the combined organic extracts washed with saturated brine and dried over $MgSO_4$. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2/MeOH/0.88NH_3 (90/10/1, v/v) followed by conversion to the hydrochloride salt with ethereal HCl to give, on filtration and drying in vacuo, the subtitle compound as a white solid (380mg, 20%). R_f 0.67 (CH_2Cl_2/MeOH/0.88NH_3 90/10/1, v/v). MS m/z 155 (MH^+)

(b) 4-Amino-6,7-dimethoxy-2-[6-(2-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridyl)]-5-phenylquinazoline

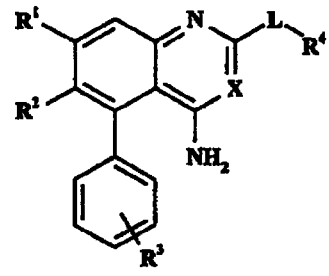
The title compound was prepared by the method of 16(h) from the product of step (a) and the compound of Example 16(g). The product was purified by chromatography on silica gel, eluting with EtOAc, followed by trituration with ether to afford the title compound (11%) as a solid. R_f 0.24 (EtOAc). MS m/z 434 (MH^+). ^1H NMR ($CDCl_3$) δ: 2.66 (3H, s) 2.90 (2H, t), 3.50 (3H, s), 3.97 (3H, s), 4.16 (2H, t), 4.61 (2H, bs), 4.97 (2H, s), 6.95 (1H, s), 7.38 (2H, m), 7.48 (3H, m).

Example 55

The compound of Example 17 was tested in the first screen described above ("*Contractile responses of human prostate*") and found to have a pA_2 value of 8.5.

Claims:

1. A compound of formula I,



I

wherein

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;

R^2 represents H or C_{1-6} alkoxy optionally substituted by one or more fluorine atoms;

R^3 represents one or more groups independently selected from H, halogen, C_{1-4} alkoxy and CF_3;

in addition, R^2 and one R^3 group may together represent $-OCH_2-$, the methylene group being attached to the ortho-position of the pendant phenyl ring;

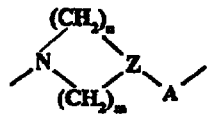
R^4 represents a 4-, 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $SO_2NR^8R^9$ and $NHSO_2(C_{1-4}$ alkyl), and when S is a member of the ring system, it may be substituted by one or two oxygen atoms;

R^8 and R^9 independently represent H or C_{1-4} alkyl;

X represents CH or N; and

L is absent,

or represents a cyclic group of formula Ia,



Ia

in which N is attached to the 2-position of the quinoline or quinazoline ring;

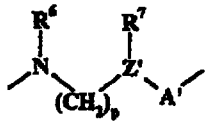
A is absent or represents CO or SO_2;

Z represents CH or N;

m represents 1 or 2, and in addition, when Z represents CH, it may represent 0; and

n represents 1, 2 or 3, provided that the sum of m and n is 2, 3, 4 or 5;

or represents a chain of formula Ib,



Ib

in which N is attached to the 2-position of the quinoline or quinazoline ring;

A' and Z' have the same significance as A and Z above, respectively;

R^6 and R^7 independently represent H or C_{1-4} alkyl; and

p represents 1, 2 or 3, and in addition, when Z' represents CH, it may represent 0;

or a pharmaceutically acceptable salt thereof.

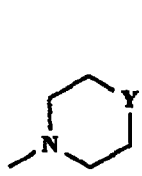
2. A compound as claimed in claim 1, wherein R^1 represents methoxy.

3. A compound as claimed in claim 1 or claim 2, wherein R^2 represents methoxy.

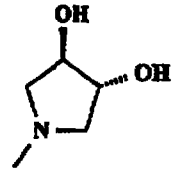
4. A compound as claimed in claim 1 or claim 2, wherein R^2 and an R^3 group together represent $-OCH_2-$.

5. A compound as claimed in any one of the preceding claims, wherein R^3 represents H or 4-fluoro.

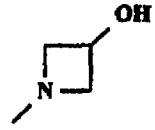
6. A compound as claimed in any one of the preceding claims, wherein R^4 represents a group having the formula II, III, IV, V or VI,



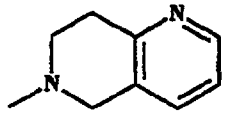
II ,



III ,

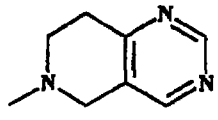


IV ,



V

or



VI

wherein

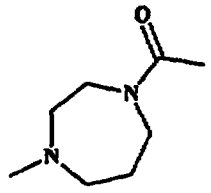
Y represents O, CH_2, SO_2, NR^5 or CHF; and

R^5 represents H or C_{1-4} alkyl.

7. A compound as claimed in claim 6, wherein R^4 represents a group of formula II.

8. A compound as claimed in claim 7, wherein Y represents O.

9. A compound as claimed in any one of the preceding claims, wherein L is absent or represents a group of formula VII,



VII

10. A pharmaceutical formulation including a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

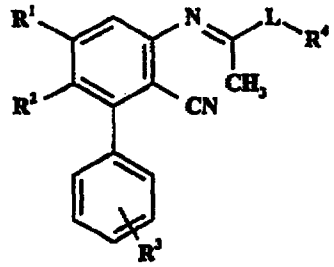
11. A compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

12. The use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of benign prostatic hyperplasia.

13. A method of treatment of benign prostatic hyperplasia, which comprises administration of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment.

14. A process for the production of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, which comprises:

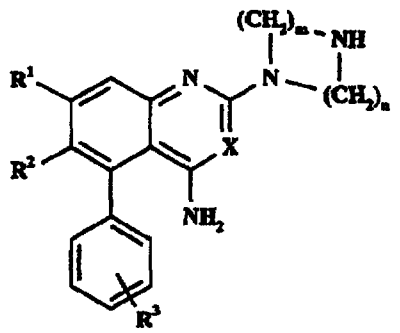
(a) when X represents CH, cyclizing a compound of formula X,



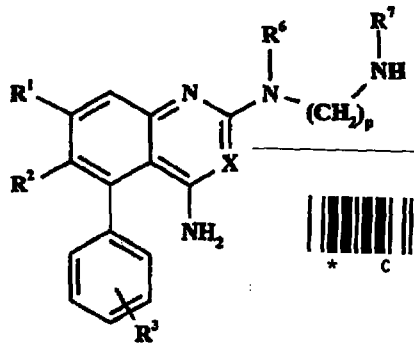
X

in which R^{1-4} and L are as defined in claim 1;

(b) when A or A' is present, and Z or Z' represents N, reacting a compound of formula XIIIa or XIIIb, as appropriate,



XIIIa



XIIIb

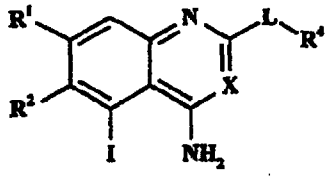
in which R^{1-3}, R^6, R^7, X, m, n and p are as defined in claim 1, with a compound of formula XIV,



XIV

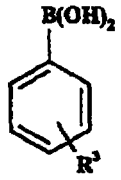
in which R^4 is as defined in claim 1, A' represents CO or SO_2 and Lg represents a leaving group;

(c) reacting a compound of formula XVIII,



XVIII

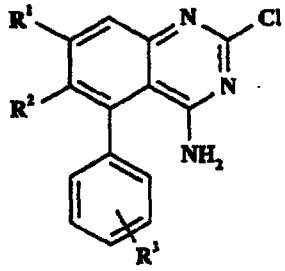
in which R^1, R^2, R^4, X and L are as defined in claim 1, with a compound of formula XIX,



XIX

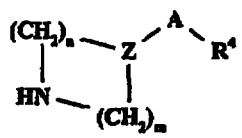
in which R^3 is as defined in claim 1; or

(d) when X represents N, reacting a compound of formula XXII,

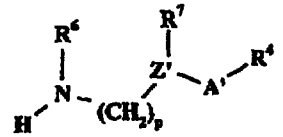


XXII

in which R^{1-3} are as defined in claim 1, with a compound of formula XXIIIa or XXIIIb, as appropriate,



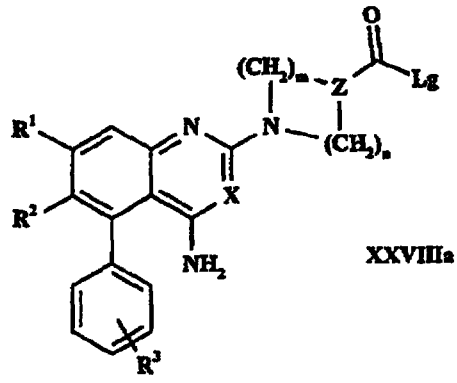
XXIIIa



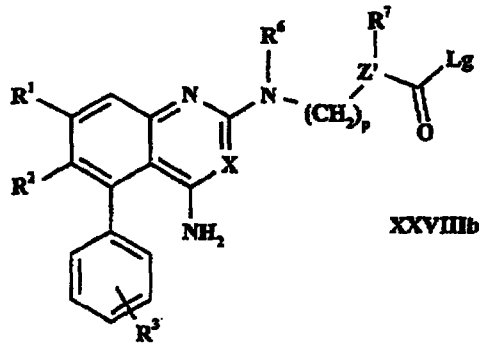
XXIIIb

in which R^4, R^6, R^7, A, A', Z, Z', m, n and p are as defined in claim 1;

(e) when A or A' represents CO, reacting a compound of formula XXVIIIa or XXVIIIb, as appropriate,



XXVIIIa



XXVIIIb

in which R^{1-3}, R^6, R^7, X, Z, Z', m, n and p are as defined in claim 1, and Lg is a leaving group, with a compound of formula XXIX,

$$HR^{4a} \qquad \text{XXIX}$$

in which R^{4a} represents the groups defined by R^4 in claim 1 which contain a nucleophilic nitrogen atom in the ring, this nucleophilic nitrogen atom being attached to H;

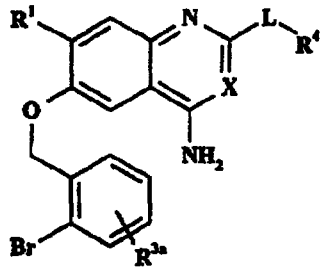
(f) conversion of a compound of formula I in which L represents a cyclic group of formula Ia, to a corresponding compound of formula I in which L represents a chain of formula Ib in which R^6 and R^7 each represent H, by the action of a strong base;

(g) when A or A' is absent and Z or Z' represents N, reacting a compound of formula XIIIa or XIIIb, as defined above, with a compound of formula XXX,

$$R^4\text{-Hal} \qquad \text{XXX}$$

in which R^4 is as defined in claim 1 and Hal represents a halogen atom attached to the ring; or

(h) when R^2 and one R^3 group together represent $-OCH_2-$, cyclization of a compound of formula XXXI,



XXXI

in which R^1, R^4, X and L are as defined in claim 1, and R^{3a} has the same meaning as R^3 in claim 1 except that R^2 and an R^{3a} group do not together represent $-OCH_2-$;

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable salt or vice versa.

15. Compounds of formulae X, XIIIa, XIIIb, XVIII, XXII, XXVIIIa, XXVIIIb and XXXI as defined in claim 12.