Description

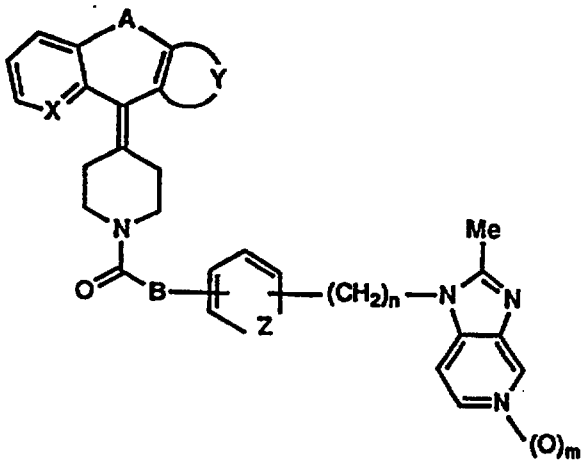
This invention relates to imidazopyridines, specifically to certain 4-substituted-1-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzene and -alkylbenzene derivatives. The compounds possess both and -alkylbenzene derivatives. The compounds possess both histamine (H_1) and platelet activating factor (PAF) antagonist activities and have clinical utility in the treatment of allergic inflammatory conditions of both the respiratory tract, such as allergic rhinitis, sinusitis and asthma, and skin, such as atopic dermatitis and urticaria.

The acute symptoms of allergic rhinitis, e.g. sneezing, nasal and ocular secretion and itching, are generally well controlled by H_1-antagonists. However, these agents elicit little or no relief of the congestion caused both by vasodilation and the oedema due to increased vascular permeability. Furthermore, H_1-antagonists do not affect the accumulation of inflammatory cells which contribute to both the delayed response and the hyperresponsiveness to allergen in chronic disease. The potent oedemogenic activity of PAF together with its known release from and activation of many types of inflammatory cells indicates that a PAF antagonist would be effective against the histamine-independent congestion and inflammatory features of allergic rhinitis. The compounds of the invention are both PAF and H_1-antagonists and thus have the potential to ameliorate all the major symptoms of chronic allergic rhinitis.

In addition, while histamine contributes to the acute bronchoconstriction to allergen in asthma, it has little effect on either the delayed bronchoconstrictor responses or the non-specific bronchial hyperresponsiveness associated with the accumulation of inflammatory cells in the lower airways. The involvement of PAF in this inflammatory response, together with its bronchoconstrictor activity, supports the potential role for a dual PAF/H_1 antagonist in the treatment of asthma. Similarly, a dual PAF/H_1 antagonist would be expected to be superior to antihistamines alone for the treatment of allergic cutaneous diseases, such as atopic dermatitis and urticaria, since, while antihistamines reduce itching and reddening, they are less effective against the wheal response associated with the influx of inflammatory cells. The compounds of the invention would also be expected to be of value in the treatment of other conditions in which pathophysiological changes are mediated both by histamine as well as histamine-independent inflammatory events.

In our European patent application no 0310386 we disclose a series of dihydrppyridine PAF antagonists wherein the 2-position substituent includes in particular a (2-methylimidazo[4,5-c]pyrid-1-yl)phenyl group. United States patent no 3326924 discloses certain aza-dibenzocycloheptenes as antihistamines including 3-aza-5-(4-piperidylidene)-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene and its 4-aza analogue (5,6-dihydro-11-(4-piperidyl-idene)-11H-benzo[5,6]cyclohepta[1,2-b]pyridine) as well as 7 and 8-chloro and 7,8 and 9-methyl derivatives thereof.

According to the present invention there are provided compounds having the general formula:



(I)

and pharmaceutically acceptable salts thereof wherein:

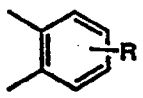
X is CH or N;

Z is CH=CH or S;

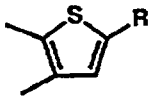
A is CH_2CH_2, CH=CH, $CH(OH)CH_2$, or $COCH_2$;

B is a direct link or $-CH_2-$, $-CH(CH_3)-$ or $-C(CH_3)_2-$, or when Z is CH=CH, B may form a cyclopentane ring fused

to the attached benzene ring;
Y completes a fused ring which is



or

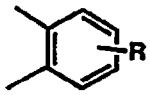


wherein R is H, halo or C_1-C_4 alkyl;
n is 0, 1 or 2;
and m is 0 or 1.

In the above definition, the term halo means fluoro, chloro, bromo or iodo; alkyl and alkoxy groups of 3 or more carbon atoms may be straight or branched-chain, and the linking group A may be attached in either sense when it is asymmetric. When the compounds contain asymmetric centres the compounds can exist as enantiomers and diastereoisomers. Such isomers may be separable by physical methods, e.g. by fractional crystallisation or chromotograhy of the parent compounds or of a suitable salt or derivatives thereof. The invention includes all the enantiomers whether separated or not.

The pharmaceutically acceptable acid addition salts of the compounds of the formula (I) which form such salts are those formed from acids which form non-toxic acid addition salts, for example the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate and tartrate salts.

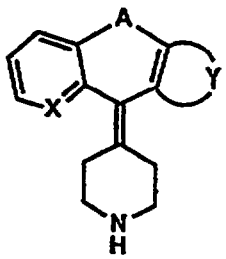
In preferred embodiments of the invention, X is N, Z is CH=CH and Y completes a benzo-fused ring of formula:



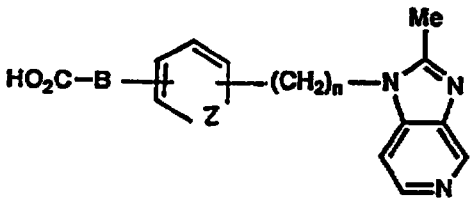
particularly when R is H or Cl. B is preferably a direct link or CH_2 and n is 0 and m is 0. Particularly preferred are compounds wherein R is Cl, B is a direct link, A is CH_2CH_2, n is 0 and m is O.

The compounds 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]-pyrid-11-ylidene)-1-[4-(2-methylimidazo-[4,5-c]pyrid-1-yl)-benzoyl]piperidine is especially preferred.

The compounds of the invention wherein m is 0 may be prepared by the following route which involves reaction of a piperidine derivative of formula (II) with an acid (or activated derivative thereof) of formula (III).



+



(II) (III)

The reaction of the compounds of formula (II) and (III) is achieved using conventional amide coupling techniques. Thus in one process the reaction is achieved with the reactants dissolved in an organic solvent, e.g. dichloromethane, using a diimide condensing agent, for example 3-(dimethylaminopropyl)-1-ethylcarbodiimide, or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of 1-hydroxybenzotriazole and an organic base such as N-methylmorpholine. The reaction is generally complete after a period of from 2 to 24 hours at room temperature and the product is then isolated by conventional procedures, i.e. by washing with water, or filtration, to remove the urea byproduct and evaporation of the solvent. The product may be further purified by crystallisation or chromatography if necessary.

A number of subsequent transformation reactions are possible. Thus reduction of the product wherein A

is $COCH_2$, for example with sodium borohydride, yields the corresponding compound wherein A is $CH(OH)CH_2$. N-oxides (wherein m is 1) are prepared by oxidation of the corresponding imidazopyridine (m = O) using, for example, 3-chloroperbenzoic acid.

The starting materials of formula (II) are prepared by literature methods following the procedures described by Engelhardt et al in J. Med. Chem., 1965, 8, 829; by Waldvogel et al in Helvetica Chimica Acta, 1976, 59, 866 and in U.S. patent no 3326924. The starting materials of formula (III) are prepared following the procedures as described in European patent 0310386 and as described in the preparations given hereinafter.

The activity of the compounds of the invention as H_1 antagonists is shown by their ability to inhibit histamine-induced contraction of guinea pig trachea in vitro. Testing is performed as follows:-

Spirally-cut guinea pig trachea strips are suspended under tension (2 g) in tissue baths containing 15 ml of continuously gassed (95% O_2, 5% CO_2) Krebs buffer (118 mM NaCl, 4.62 mM KCl, 1.16 mM $MgSO_4$, 1.18 mM KH_2PO_4, 25mM $NaHCO_3$, 11 mM glucose, 2.5 mM $CaCl_2$) containing indomethacin (2 μM)). Following an equilibration period of 45 minutes, histamine dihydrochloride is added to the tissue bath, to a final concentration of 10^{-5} M, and the resulting contraction recorded isometrically. Following contraction for 30 minutes, the tissue is washed with buffer until fully relaxed to baseline. This is followed by a further histamine contraction (30 minutes) and wash. Tissues are contracted with histamine for a third time but not washed. Following 30 minutes sustained contraction the first dose of test compound is added to the tissue bath and effects recorded for 20 minutes. Increasing cumulative doses of compound are added every 20 minutes and the effects quantified. An IC_{50} value is calculated as the concentration of the compound required to relax the third sustained histamine contraction by 50 percent.

The activity of the compounds of the invention as PAF antagonists is shown by their ability to inhibit the platelet aggregating activity of PAF in vitro. Testing is performed as follows:

Blood samples are taken from a rabbit into 0.1 vol (77 mM) disodium ethylenediamine tetraacetic acid and the samples centrifuged at 150 x g for 15 minutes to obtain platelet rich plasma. The plasma is further centrifuged at 2000 x g for 10 minutes to give a platelet pellet which is washed with a buffer solution (4 mM KH_2PO_4, 6mM Na_2HPO_4, 100 mM NaCl, 55mM glucose and 0.1% bovine serum albumin, pH 7.25) and finally resuspended in buffer solution to a concentration of 2 x 10^8 platelets/ml. The washed platelets are pre-incubated with stirring for 2 minutes at 37°C in an aggregometer in the presence of an ADP scavenging system (1 mM creatinine phosphate, 27 U/ml creatinine phosphokinase and 10 mM $MgCl_2$), 1 mM $CaCl_2$ and either vehicle alone (dimethylsulphoxide) or vehicle containing the particular compound under test. C_{18}-PAF is added at a sufficient concentration to give a maximum aggregating response in the absence of test compound (10^{-8} to 10^{-9} M), and the platelet aggregation is measured by following the increase in light transmission of the solution. The experiment is repeated in the presence of a range of concentrations of the test compound and the concentration of compound required to reduce the response to 50% of its maximum value is recorded as the IC_{50} value.

The activity of the compounds of formula (I) as dual PAF and H_1 antagonists is demonstrated in vivo by their ability to inhibit increases in cutaneous vascular permeability induced by intradermal injections of PAF or histamine in mice. Animals are dosed orally or intravenously with test compound. Forty five minutes (for oral) or 10 minutes (for i.v.) after dosing, each animal is given a single intradermal injection of either histamine (13.5 nmoles) or PAF (30 pmoles) on its dorsal side, directly behind the head. Immediately following the injection, Evans Blue dye (250 μl, 6.25 mg/ml) is injected intravenously. After thirty minutes the animals are killed with a lethal injection of pentobarbitone, the dorsal skin removed, and areas of intradermal blueing punched out. The extent of blueing is measured by extracting the dye from the skin punches with formamide for 24 hours at 70°C and recording absorption at 620 nm in a spectrophotometer. The ID_{50} is calculated as the dose of compound which reduces absorbance (blueing) by 50% compared to untreated controls.

For therapeutic use the compounds of the formula (I) will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For administration to man in the curative or prophylactic treatment of allergic and inflammatory conditions, oral dosages of the compounds will generally be in the range of from 2-1000 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules will contain from 1 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration would typically be within the range 1 to 10 mg per single dose as required. For the treatment of

allergic asthma and rhinitis, intranasal administration or inhalation via a nebuliser or aerosol may be the preferred route of drug administration. Dose levels by this route would be within the range 0.1 to 50 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Thus in a further aspect, the invention provides a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable diluent or carrier.

The invention also includes a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use in medicine, in particular in the treatment of allergic and inflammatory conditions in a human being.

The preparation of the compounds of formula (I) will now be more particularly illustrated by reference to the following experimental Examples. The purity of compounds was routinely monitored by thin layer chromatography using Merck Kieselgel 60 F_{254} plates. ^{1}H-Nuclear magnetic reasonance spectra were recorded using either a Nicolet QE-300 or a Bruker AC-300 spectrometer and were in all cases consistent with the proposed structures.

Chemical shifts are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: s, singlet; d, doublet; t, triplet; m, multiplet and br, broad.

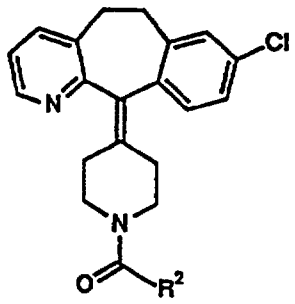
EXAMPLE 1

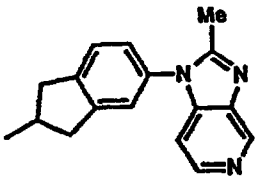
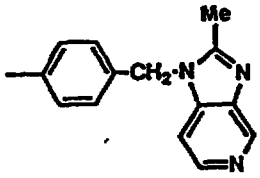
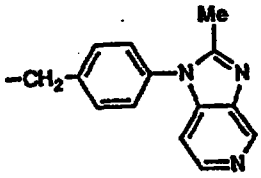
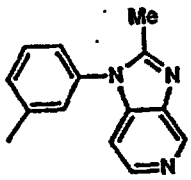
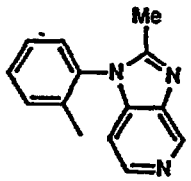
4-(8-Chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]-pyrid-11-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl]piperidine hemihydrate

A solution of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyrid-11-ylidene)piperidine (224 mg, 0.75 mmol) and 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoic acid (190 mg, 0.75 mmol) in dichloromethane (12 ml) was treated sequentially with 1-hydroxybenzotriazole hydrate (102 mg, 0.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (290 mg, 1.5 mmol) and 4-methylmorpholine (165 µl; 1.5 mmol). The mixture was stirred at room temperature for 16 hours, washed with water, dried over magnesium sulphate and evaporated. The residue was purified by chromatography on silica using dichloromethane plus 3-4% methanol as eluant. Appropriate fractions were combined and evaporated to give the title compound (113 mg, 27%) as a colourless foam which was characterised as a hemihydrate. Found: C,71.1; H,5.2; N,12.3. $C_{33}H_{28}ClN_5O$. 0.5 H_20 requires C,71.4; H,5.3; N,12.6%.

EXAMPLES 2-6

The following Examples were prepared by reacting 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-piperidine with the appropriate acid using the method described in Example 1 and were characterised in the form indicated.



Example No	R^2	Form characterised	Analysis (%) (Theoretical in brackets) C	H	N
2		foam, hemi-hydrate	72.8 (72.6	5.7 5.6	11.7 11.8)
3		foam, hemi-hydrate	71.9 (71.7	5.4 5.5	12.0 12.3)
4		foam, hemi-hydrate	71.9 (71.7	5.6 5.5	12.3 12.3)
5		foam, 0.25 EtOAc	72.0 (71.9	5.3 5.1	12.3 12.6)
6		foam, 0.25 EtOAc	71.5 (71.9	5.5 5.1	12.4 12.6)

EXAMPLE 7

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]piperidine hemihydrate

This was prepared as described in Example 1 using 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine hydrochloride (see J. Med. Chem., 1965, 8, 829) instead of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine.The title compound was obtained as a colourless foam and was characterised as a hemihydrate. Found: C,78.9; H,5.6; N,11.0. $C_{34}H_{28}N_4O$. 0.5 H_2O requires C,78.9; H,5.8; N,10.8%.

EXAMPLE 8

1-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzoyl]-4-(10-oxo-9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-piperidine

This was prepared as described in Example 1 using 4-(10-oxo-9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-piperidine (see Helv. Chim. Acta, 1976, 59, 866) instead of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)piperidine. The title compound was obtained as a colourless foam which was characterised as a monohydrate. Found: C,70.1; H,5.1; N,10.1. $C_{32}H_{28}N_4O_2S$. H_2O requires C,70.0; H,5.1; N,10.2%.

EXAMPLE 9

4-(8-Chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]-pyrid-11-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl-5-oxide)benzoyl]piperidine

A solution of 3-chloroperbenzoic acid (50%; 126 mg, 0.37 mmol) in dichloromethane (3 ml) was added dropwise over 10 minutes to a stirred, ice-cooled solution of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-1-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)benzoyl]piperidine hemihydrate (200 mg, 0.37 mmol) (Example 1). The mixture was stirred at 0°C for 19 hours, treated with a further portion of 3-chloroperbenzoic acid (25 mg), stirred with ice-cooling for a further 25 hours, washed with saturated aqueous sodium hydrogen carbonate solution and water, dried over magnesium sulphate and evaporated. The residue was purified by chromatography on silica using dichloromethane plus 5% methanol plus 0.1 - 0.5% saturated aqueous ammonia solution as eluant. Appropriate fractions were combined and evaporated to give the title compound (44 mg, 21%) as a colourless glass, m.p. 176-180°C, which was characterised by its ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ = 9.03(1H,s), 8.39(1H,d,J=8Hz), 8.04(1H,s), 7.64(2H,d,J=8Hz), 7.37(2H,d,J=8Hz), 6.95-7.25(6H,m), 3.25-4.15(4H,m), 1.7-3.0(8H,m).

EXAMPLE 10

4-(10-Hydroxy-9,10-dihydro-4-benzo[4,5]cyclohepta[1,2-b]-thiophen-4-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl]piperidine

A solution of 1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl]-4-(10-oxo-9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]-thiophen-4-ylidene)piperidine (200 mg, 0.38 mmol) (Example 8) and sodium borohydride (200 mg) in methanol (20 ml) was stirred at room temperature for 4 hours and evaporated. The residue was partitioned between dichloramethane and water and the organic layer was washed with water, dried over magnesium sulphate and evaporated. The residue was triturated with hexane to give the title compound (70 mg, 35%) as a colourless foam which was characterised as a dihydrate. Found: C,67.9; H,5.4; N,9.6. $C_{32}H_{28}N_4O_2S$. 2 H_2O requires C,67.5; H,5.6; N,9.9%.

EXAMPLE 11

4-(8-Chloro-5,6-dihydro-6-oxo-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl]piperidine

This was prepared as described in Example 1 using 4-(8-chloro-5,6-dihydro-6-oxo-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)piperidine (see J. Org. Chem., 1990, 55, 3341) instead of 4-(8-chloro-5,6-dihydro-

11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)piperidine. The title compound was obtained as a colourless gum which was characterised containing 1.5 equivalents of water. Found: C,67.2; H,5.2; N,11.4. $C_{33}H_{28}ClN_5O_2$. 1.5 H_2O requires C,67.0; H,4.9; N,11.9%.

EXAMPLE 12

4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]piperidine

This was prepared as described in Example 1 using 4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine (see EP-A-0347123, 1989) instead of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine. The title compound was obtained as a colourless foam (248 mg, 48%) which was characterised as a hemihydrate. Found: C,78.4; H,5.9; N,10.7. $C_{34}H_{30}N_4O$. 0.5 H_2O requires C,78.5; H,6.0; N,10.8%.

EXAMPLE 13

4-(8-Chloro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-1-[4-(2-nethylimidazo[4,5-c]pyrid-1-yl)benzoyl]-piperidine

This was prepared as described in Example 1 using 4-(8-chloro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-piperidine (see WO 88/03138, 1988) instead of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-piperidine. The title compound was obtained as a colourless gum, Rf 0.25 (silica, solvent system: CH_2Cl_2,CH_3OH,NH_4OH; 98:7:1), which was characterised by its mass spectrum. M/e, M+ = 543 ($C_{33}H_{26}ClN_5O$).

EXAMPLE 14

4-(5,6-Dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]-piperidine

This was prepared as described in Example 1 using 4-(5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-piperidine (see J. Med. Chem, 1972, 15, 750) instead of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11--ylidene)piperidine. The title conp:ind was obtained as a beige solid, m.p. 243-245°C, which was characterised containing 0.67 equivalents of water. Found: C,75.7; H,5.9; N,13.4. $C_{33}H_{29}N_5O$. 0.67 H_2O requires C,75.7; H,5.8; N,13.4%.

EXAMPLE 15

4-(8-Chloro-5,6-dihydro-6-hydroxy-11H-benzo[5,6]cyclohepta-[1,2-b]-pyrid-11-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]piperidine

This was prepared as described in Example 10 by sodium borohydride reduction of 4-(8-chloro-5,6-dihydro-6-oxo-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-1-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)benzoyl]-piperidine (see Example 11). The title compound was obtained as a colourless gum, Rf 0.30 (silica, solvent system: CH_2Cl_2, CH_3OH, NH_4OH; 93:7:1), which was characterised by its mass spectrum. M/e, M+ = 561 ($C_{33}H_{28}ClN_5O_2$).

EXAMPLE 16

4-(8-Chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]-pyrid-11-ylidene)-1-[5-(2-methylimidazo[4,5-c]pyrid-1-yl)-thien-2-oyl] piperidine

This was prepared as described in Example 1 using 5-(2-methylimidazo-[4,5-c]pyrid-1-yl)thiophene-2-carboxylic acid (see Preparation 8; 185 mg) instead of 4-(2-methylimidazo[4,5-c]-pyrid-1-yl)benzoic acid. The title compound was obtained as a tan coloured foam (121 mg, 38.5%) which was characterised as a sesquihydrate. Found: C,64.3; H,4.8; N,12.0. $C_{31}H_{26}ClN_5OS$. 1.5 H_2O requires C,64.3; H,5.0; N,12.1%.

EXAMPLE 17

4-(8-Methyl-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]-pyrid-11-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl]piperidine

This was prepared as in Example 1 using 4-(8-methyl-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)- piperidine (see J. Med. Chem, 1991, 34, 457-461; 300 mg) instead of 4-(8-chlro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)piperidine. The title compound was obtained as a glass (270 mg, 49.6%) which was characterised containing 0.25 moles of dichloromethane. Found: C,74.8; H,6.0; N,12.7. $C_{34}H_{31}N_5O$. 0.25 CH_2Cl_2 requires C,75.2; H,5.8; N,12.8%.

EXAMPLE 18

4-(8-Chloro-5,6-dihydro-5-oxo-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl]piperidine

This was prepared as described in Example 1 using 4-(8-chloro-5,6-dihydro-5-oxo-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)piperidine (see J. Org. Chem, 1990, 55, 3341; 80 mg) instead of 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)piperidine. The title compound was obtained as a tan coloured foam (60 mg, 43.5%). Rf 0.08 (silica; solvent system: $CH_3CO_2C_2H_5$, CH_3OH, NH_4OH; 80:20:1). m/e, M+= 559 ($C_{33}H_{28}ClN_5O_2$).

EXAMPLE 19

4-(8-Chloro-5,6-dihydro-5-hydroxy-11H-benzo[5,6]cyclohepta-[1,2-b]pyrid-11-ylidene)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl]piperidine

This was prepared as described in Example 10 by sodium borohydride reduction of 4-(8-chloro-5,6-dihydro-5-oxo-11H-benzo-[5,6]cyclohepta[1,2-b]pyrid-11-ylidene)-1-[4-(2-methyimidazo[4,5-c]pyrid-1-yl)benzoyl]piperidine (from Example 18; 40 mg). The title compound was obtained as a yellow foam (35 mg, 87%) which was characterised as a hydrate containing 0.33 equivalents of ethyl acetate. Found: C,67.7; H,5.2; N,11.4. $C_{33}H_{28}ClN_5O_2$. H_2O. 0.33 $C_4H_8O_2$ requires C,67.7; H,5.1; N,11.5%.

PREPARATION 1

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzoic acid

A mixture of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzonitrile (see EP-0310386) (12.0 g, 51.3 mmol) and sodium hydroxide (22.0 g, 0.55 mmol) in a mixture of ethanol (55 ml) and water (55 ml) was heated under nitrogen at reflux for 1.5 hours, cooled and concentrated under reduced pressure. The brown residue was dissolved in ice-water and glacial acetic acid (33 ml) was added. The resulting precipitate was collected, washed with water and dried under vacuum at 70°C to give the title compound (9.1 g, 70%) as a buff coloured solid which was characterised by its ^{1}H-NMR spectrum. ^{1}H NMR (DMSO-d_6), 2.50(3H,s), 7.25(1H,d,J=5Hz), 7.72(2H,d,J=8Hz), 8.16(2H,d,J=8Hz), 8.30(1H,d,J=5Hz), 8.92(1H,s).

PREPARATION 2

Ethyl 4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl acetate

a) Ethyl 4-aminophenylacetate (17.7 g, 0.1 mole) and sodium hydrogen carbonate (8.4 g, 0.1 mole) were stirred in ethanol (200 ml). 4-Chloro-3-nitropyridine (15.9 g, 0.1 mole) was added as a solution in ethanol (50 ml) and the mixture stirred at room temperature for 3 hours. The mixture was then evaporated to low volume and poured into ethyl acetate (500 ml) and the solution washed with water (200 ml). The organic phase was then extracted with 0.5M hydrochloric acid and the combined aqueous extracts basified with 2M sodium hydroxide and extracted with dichloromethane. The combined organic extracts were dried over sodium sulphate, filtered and evaporated to dryness. The residue was recrystallised from aqueous ethanol to give ethyl 4-(3-nitropyrid-4-ylamino)phenyl acetate (7.32 g), m.p. 124-126°C. A further 8.56 g was recovered from the mother liquors.

b) The above product (15.7 g) was hydrogenated at 60 p.s.i. (4.1 bar) over 5% palladium on charcoal for 3 hours at room temperature. Filtration and evaporation of the solvent gave ethyl 4-(3-aminopyrid-4-ylamino)phenyl acetate (14.1 g).

c) Ethyl 4-(3-aminopyrid-4-ylamino)phenyl acetate (14.1 g, 52 mmol), acetic acid (100 ml) and acetic anhydride (100 ml) were mixed and heated at reflux under nitrogen for 1.5 hours. The cooled solution was evaporated to dryness and basified with 10% aqueous sodium carbonate solution then extracted with dichloromethane. The combined organic extracts were evaporated to dryness and purified by chromatography on silica eluting with dichloromethane/ethanol to give ethyl 4-(2-methylimidazo[4,5-c]-pyrid-1-yl)phenyl acetate (13.6 g).

PREPARATION 3

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenylacetic acid

A solution of ethyl 4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenylacetate (750 mg, 2.54 mmol) and sodium hydroxide (160 mg, 4.0 mmol) in a mixture of ethanol (5 ml) and water (5 ml) was stirred at room temperature for 16 hours and evaporated. The residue was taken up in water, acidified with 2M hydrochloric acid to pH 4-5 and extracted into 1-buanol. The combined 1-butanol extracts were evaporated and the residue triturated with diethyl ether. The resulting solid was collected, washed with hexane and dried to give the title compound (267 mg, 39%) as a buff solid, m.p. 226-230°C, which was characterised by its ^{1}H-NMR spectrum. ^{1}H-NMR (d_6-DMSO) δ = 8.86(1H,s), 8.23(1H,d,J=8Hz), 7.48(4H,s), 7.15(1H,d,J=8Hz), 3.70(2H,s), 2.42(3H,s).

PREPARATION 4

4-[(2-Methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoic acid

Ethyl 4-[(2methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoate (EP-A-0330327) was hydrolysed following the procedure described in Preparation 3 above to give the title compound as a colourless solid which was used directly in Example 3.

PREPARATION 5

5-(2-Methylimidazo[4,5-c]pyrid-1-yl)indane-2-carboxylic acid

(a) Fuming nitric acid (40 ml, 1.5 g/ml) was added dropwise with stirring to acetic anhydride (80 ml) keeping the temperature of the mixture at 0°C. After the addition was complete 2-cyanoindane (11.33 g, 79.5 mmol), (J. Chem. Soc. (B), (1969), 1197) was added dropwise with stirring over 30 minutes maintaining the reaction temperature between -5° and 0°C. The mixture was stirred for a further 15 minutes then poured onto ice. The mixture was extracted with dichloromethane (4 x 150 ml) and the extracts were washed with saturated aqueous sodium bicarbonate (3 x 150 ml), dried over magnesium sulphate and the solvent evaporated under reduced pressure. The residue was recrystallised from ethanol to give 2-cyano-5-nitroindane (12.09 g, 81%) as a yellow solid, m.p. 80-82°C.

(b) A solution of 2-cyano-5-nitroindane (11.90 g, 63.3 mmol) in methanol/dichloromethane = 1:1 (200 ml) was hydrogenated over 10% palladium on charcoal (1.2 g) at 30 p.s.i. and 20°C for 5 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 5-amino-2-cyanoindane (10.4 g) which was used directly for the next reaction. A portion, recrystallised from ethanol, formed pinkish needles, m.p. 73-76°C.

(c) 4-Chloro-3-nitropyridine (11.46 g, 72.3 mmol) was added to a suspension of 5-amino-2-cyanoindane (10.4 g, 65.7 mmol) in ethanol (150 ml) at room temperature. The mixture was stirred overnight at room temperature and then poured into excess ice-cold aqueous ammonia. The yellow solid was filtered off, partially digested in hot ethanol (150 ml), cooled, and re-filtered to give 2-cyano-5-(3-nitropyrid-4-ylamino)indane (13.61 g, 74%).

(d) 2-Cyano-5-(3-nitropyrid-4-ylamino)indane (12.46 gm, 44.5 mmol) was suspended in methanol/ dichloromethane = 1:1 (750 ml) and hydrogenated at 20°C and 30 p.s.i. over 10% palladium on charcoal (1.25 g) for 2 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 5-(3-aminopyrid-4-ylamino)-2-cyanoindane (12.28 g, ca quantitative) as a yellow solid, m.p. 98-100°C.

(e) A mixture of 5-(3-aminopyrid-4-ylamino)-2-cyanoindane (12.28 g, ca 44.5 mmol from step (d) above),

acetic acid (70 ml) and acetic anhydride (70 ml) was heated at reflux under nitrogen for 1.75 hours, cooled, and concentrated under reduced pressure. The residual brown gum was dissolved in 2M hydrochloric acid (40 ml) and washed with ethyl acetate (50 ml). The aqueous layer was rendered basic by the addition of 2M aqueous sodium hydroxide, and the product was extracted into dichloromethane. The combined extracts were washed with water (50 ml), dried over magnesium sulphate and the solvent evaporated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/ methanol (7:1), to give a brown gum, which was recrystallised from ethyl acetate/methanol, to give the 2-cyano-5-(2-methylimidazo[4,5-c]pyrid-1-yl)indane as an off-white powder (9.67 g, 79%), m.p. 174-176°C. Found: C,74.4; H,5.2; N,20.7. $C_{17}H_{14}N_4$ requires C,74.4; H,5.1; N,20.4%.

(f) A mixture of 2-cyano-5-(2-methylimidazo[4,5-c]pyrid-1-yl)-indane (739 mg, 2.70 mmol), 50% aqueous sodium hydroxide (1 ml) and methanol (6 ml) was heated at reflux under nitrogen for 9 hours, cooled, poured onto ice, and the pH of the solution was adjusted to pH5 by the addition of 2M hydrochloric acid. The resulting precipitate was collected by filtration and dried under vacuum to give the title compound, (426 mg, 54%) as a colourless solid, m.p. 264-267°C. Found: C,68.9; H,5.1; N,14.1; $C_{17}H_{15}N_3O_2$. 0.2 H_20 requires C,68.8; H,5.2; N,14.1%.

PREPARATION 6

3-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzoic acid

a) A solution of ethyl 3-aminobenzoate (3.3 g, 20 mmol) and 4-chloro-3-nitropyridine (3.17 g, 20 mmol) in ethanol (150 ml) was stirred at room temperature for 16 hours and then cooled in an ice-bath. The resulting precipitate was collected, washed with ice-cold ethanol and dried to give ethyl 3-(3-nitro-4-pyridylamino)benzoate hydrochloride (4.17 g) as a yellow crystalline solid, m.p. 201-204°C. Found: C,5.2; H,4.4; N,12.9. $C_{14}H_{13}N_3O_4$. HCl requires C,51.9; H,4.3; N,13.0%. The mother liquors were evaporated and the residue recrystallised from ethanol to give a further 1.2 g of product.

b) The above product (5.2 g) was partitioned between ethyl acetate and 10% aqueous sodium carbonate solution and the organic layer was washed with water, dried over magnesium sulphate and evaporated. The residue was dissolved in ethanol (300 ml) and the solution was stirred under an atmosphere of hydrogen (40 p.s.i., 2.76 bar) at room temperature in the presence of 5% palladium on charcoal for 16 hours. The mixture was filtered and the filtrate was evaporated to give ethyl 3-(3-amino-4-pyridylamino)benzoate (4.8 g) as a colaurless solid; m.p. 89-91°C.

c) A solution of the above product (4.8 g) in acetic acid (25 ml) and acetic anhydride (25 ml) was heated under reflux for two hours and evaporated. The residual oil was poured into water, basified with solid sodium carbonate and extracted into ethyl acetate. The combined organic extracts were washed with saturated sodium chloride solution, dried over magnesium sulphate and evaporated. The residue was recrystallised from ethyl acetate to give ethyl 3-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoate (2.9 g) as a colourless solid, m.p. 120-121°C. Found: C,69.1; H,5.4; N,14.8. $C_{16}H_{15}N_3O_2$ requires C,68.3; H,5.3; N,14.9%.

d) A mixture of the above product (1.0 g) and 2M aqueous sodium hydroxide solution (2.2 ml) in ethanol (10 ml) was stirred at room temperature for 18 hours. The ethanol was removed under vacuum and the remaining aqueous solution was neutralised to pH6 with 2M hydrochloric acid. The resulting precipitate was collected, washed with ice-cold water and diethyl ether and dried to give 3-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoic acid (830 mg) as a colourless powder, m.p. 205-206°C, which was characterised containing 0.75 equivalents of water. Found: C,62.8; H,4.5; N,15.5. $C_{13}H_{11}N_3O_2$. 0.75 H_20 requires C,63.0; H,4.7; N,15.7%.

PREPARATION 7

2-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzoic acid

a) A solution of ethyl 2-aminobenzoate (3.17 g, 20 mmol) and 4-chloro-3-nitropyridine (2.8 ml) in ethanol (150 ml) was stirred at room temperature for 60 hours. The resulting precipitate was collected, washed with ethanol and dried to give ethyl 2-(3-nitro-4-pyridylamino)benzoate hydrochloride (3.9 g) as a yellow crystalline solid, m.p. 192-205°C.

The mother liquors were evaporated and the residue was recrystallised from ethanol to give a further 1.5 g of product.

b) The above product (5.3 g) was partitioned between ethyl acetate and 10% aqueous sodium carbonate solution and the organic layer was washed with water, dried over magnesium sulphate and evaporated.

The residue was dissolved in ethanol (800 ml) and the solution was stirred under an atmosphere of hydrogen (40 p.s.i., 2.76 bar) at room temperature in the presence of 5% palladium on charcoal for 16 hours. The mixture was filtered and the filtrate evaporated to give ethyl 2-(3-amino-4-pyridylamino)benzoate (5.1 g) as a colourless oil.

c) A solution of the above product (5.0 g) in acetic acid (25 ml) and acetic anhydride (25 ml) was heated under reflux for 4 hours and evaporated. The residual oil was poured into water, basified with solid sodium carbonate and extracted into ethyl acetate. The combined organic extracts were washed with saturated sodium chloride solution, dried over magnesium sulphate and evaporated. The residue was recrystallised from ethyl acetate to give ethyl 2-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoate (3.20 g) as colourless crystals, m.p. 125-127°C.

d) A mixture of the above product (1.0 g) and 2M aqueous sodium hydroxide solution (2.2 ml) in ethanol (10 ml) was stirred at room temperature for 18 hours. The ethanol was removed under vacuum and the remaining aqueous solution neutralised to pH6 with 2M hydrochloric acid. The resulting precipitate was collected, washed with ice-cold water and diethyl ether and dried to give 2-(2-methylimidazo[4,5-c3]pyrid-1-yl)benzoic acid (760 mg) as a colourless powder, m.p. 181-183°C, which was characterised containing 0.75 equivalents of water. Found: C,63.4; H,4.8; N,15.8. $C_{13}H_{11}N_3O_2$. 0.75 H_20 requires C,63.0; H,4.7; N,15.7%.

PREPARATION 8

5-(2-Methylimidazo[4,5-c]pyrid-1-yl)thiophene-2-carboxylic acid

a) A solution of 2-cyano-5-nitrothiophene (Berichte, 1943, 76B 419; 7.3 g, 47 mmol) in ethanol (150 ml) was hydrogenated at 20 p.s.i. (1.4 bar) over 30% palladium on charcoal for 4.5 hours at roon temperature. Filtration gave a solution of 2-amino-5-cyanothiopene in ethanol which was used immediately.

b) A solution of the above product (5.8 g, 47 mmol) in ethanol was stirred with 4-chloro-3-nitropyridine (8.89 g, 56 mmol) under nitrogen in the dark for 18 hours. Dichloromethane (100 ml) and triethylamine (13 ml, 94 mmol) were added, followed by silica (50 g) and the solvent removed under vacuum. The residue was added to a chromatography column, eluting initially with dichloromethane and then with dichloromethane plus 10% ethyl acetate. The product containing fractions were evaporated and the dark red solid was suspended in ethanol (100 ml) and the mixture heated to reflux for 30 minutes. After cooling, the solid was filtered off and dried under vacuum to yield 4-(5-cyanothien-2-yl)amino-3-nitropyridine (6.1 g, 52%). Found: C,48.77; H,2.42; N,23.37. $C_{10}H_6N_4O_2S$ requires C,48.77; H,2.46; N,22.75%.

c) The above product was hydrogenated at 20 p.s.i. (1.4 bar) over 30% palladium on charcoal for 4 hours at room temperature. Filtration and evaporation of the solvent gave 3-amino-4-(5-cyanothien-2-yl)aminopyridine (5.35 g, 100%) which was used immediately in the cyclisation step, following the procedure described in Preparation 2c, to give 2-cyano-5-(2-methylimidazo-[4,5-c]pyrid-1-yl)thiophene (2.25 g, 46%). ^{1}H NMR ($CDCl_3$), δ = 9.10(1H,s), 8.53(1H,d,J=6Hz), 7.75(1H,d,J=4Hz), 7.26(1H,d,J=6Hz), 7.20(1H,d,J=4Hz), 2.62(3H,s).

d) A solution of 2-cyano-5-(2-methylimidazo[4,5-c]pyrid-1-yl)-thiophene (2.7 g, 11 mmol) and sodium hydroxide (1.76 g, 44 mmol) in a mixture of ethanol (23 ml) and water (5 ml) was heated under reflux for 2 hours. The pH was adjusted to 6 with 2N hydrochloric acid and the reaction diluted to 500 ml with water. The solution was divided into two equal portions and each portion was passed through a column of XAD-2 ion-exchange resin (350 g) eluting with water initially, followed by methanol and water (1:1). The product containing fractions were combined and the solvent evaporated under vacuum. The residue was taken up in boiling isopropyl alcohol, filtered and the solvent evaporated under vacuum; azeotroping with toluene yielded the title compound (1.8 g, 63%). ^{1}H NMR ($DMSOd_6$), δ = 8.91(1H,s), 8.36(1H,d,J=5.5Hz), 7.79(^{1}H,d,J=4.0Hz), 7.47(1H,d,J=6Hz), 7.40(1H,d,J=6Hz), 2.55(3H,s).

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound having the formula:-

The residue was dissolved in ethanol (800 ml) and the solution was stirred under an atmosphere of hydrogen (40 p.s.i., 2.76 bar) at room temperature in the presence of 5% palladium on charcoal for 16 hours. The mixture was filtered and the filtrate evaporated to give ethyl 2-(3-amino-4-pyridylamino)benzoate (5.1 g) as a colourless oil.

c) A solution of the above product (5.0 g) in acetic acid (25 ml) and acetic anhydride (25 ml) was heated under reflux for 4 hours and evaporated. The residual oil was poured into water, basified with solid sodium carbonate and extracted into ethyl acetate. The combined organic extracts were washed with saturated sodium chloride solution, dried over magnesium sulphate and evaporated. The residue was recrystallised from ethyl acetate to give ethyl 2-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoate (3.20 g) as colourless crystals, m.p. 125-127°C.

d) A mixture of the above product (1.0 g) and 2M aqueous sodium hydroxide solution (2.2 ml) in ethanol (10 ml) was stirred at room temperature for 18 hours. The ethanol was removed under vacuum and the remaining aqueous solution neutralised to pH6 with 2M hydrochloric acid. The resulting precipitate was collected, washed with ice-cold water and diethyl ether and dried to give 2-(2-methylimidazo[4,5-c3]pyrid-1-yl)benzoic acid (760 mg) as a colourless powder, m.p. 181-183°C, which was characterised containing 0.75 equivalents of water. Found: C,63.4; H,4.8; N,15.8. $C_{13}H_{11}N_3O_2$. 0.75 H_2O requires C,63.0; H,4.7; N,15.7%.

PREPARATION 8

5-(2-Methylimidazo[4,5-c]pyrid-1-yl)thiophene-2-carboxylic acid

a) A solution of 2-cyano-5-nitrothiophene (Berichte, 1943, 76B 419; 7.3 g, 47 mmol) in ethanol (150 ml) was hydrogenated at 20 p.s.i. (1.4 bar) over 30% palladium on charcoal for 4.5 hours at roon temperature. Filtration gave a solution of 2-amino-5-cyanothiopene in ethanol which was used immediately.

b) A solution of the above product (5.8 g, 47 mmol) in ethanol was stirred with 4-chloro-3-nitropyridine (8.89 g, 56 mmol) under nitrogen in the dark for 18 hours. Dichloromethane (100 ml) and triethylamine (13 ml, 94 mmol) were added, followed by silica (50 g) and the solvent removed under vacuum. The residue was added to a chromatography column, eluting initially with dichloromethane and then with dichloromethane plus 10% ethyl acetate. The product containing fractions were evaporated and the dark red solid was suspended in ethanol (100 ml) and the mixture heated to reflux for 30 minutes. After cooling, the solid was filtered off and dried under vacuum to yield 4-(5-cyanothien-2-yl)amino-3-nitropyridine (6.1 g, 52%). Found: C,48.77; H,2.42; N,23.37. $C_{10}H_6N_4O_2S$ requires C,48.77; H,2.46; N,22.75%.

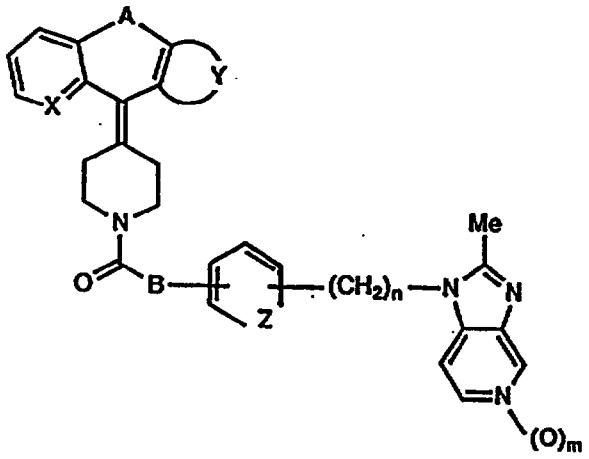
c) The above product was hydrogenated at 20 p.s.i. (1.4 bar) over 30% palladium on charcoal for 4 hours at room temperature. Filtration and evaporation of the solvent gave 3-amino-4-(5-cyanothien-2-yl)amino-pyridine (5.35 g, 100%) which was used immediately in the cyclisation step, following the procedure described in Preparation 2c, to give 2-cyano-5-(2-methylimidazo-[4,5-c]pyrid-1-yl)thiophene (2.25 g, 46%). ^{1}H NMR ($CDCl_3$), δ = 9.10(1H,s), 8.53(1H,d,J=6Hz), 7.75(1H,d,J=4Hz), 7.26(1H,d,J=6Hz), 7.20(1H,d,J=4Hz), 2.62(3H,s).

d) A solution of 2-cyano-5-(2-methylimidazo[4,5-c]pyrid-1-yl)-thiophene (2.7 g, 11 mmol) and sodium hydroxide (1.76 g, 44 mmol) in a mixture of ethanol (23 ml) and water (5 ml) was heated under reflux for 2 hours. The pH was adjusted to 6 with 2N hydrochloric acid and the reaction diluted to 500 ml with water. The solution was divided into two equal portions and each portion was passed through a column of XAD-2 ion-exchange resin (350 g) eluting with water initially, followed by methanol and water (1:1). The product containing fractions were combined and the solvent evaporated under vacuum. The residue was taken up in boiling isopropyl alcohol, filtered and the solvent evaporated under vacuum; azeotroping with toluene yielded the title compound (1.8 g, 63%). ^{1}H NMR ($DMSOd_6$), δ = 8.91(1H,s), 8.36(1H,d,J=5.5Hz), 7.79(^{1}H,d,J=4.0Hz), 7.47(1H,d,J=6Hz), 7.40(1H,d,J=6Hz), 2.55(3H,s).

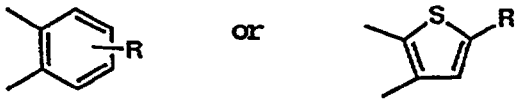
Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound having the formula:-

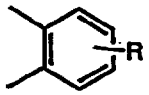


or a pharmaceutically acceptable salt thereof wherein:
X is CH or N;
Z is CH=CH or S;
A is CH_2CH_2, CH=CH, $CH(OH)CH_2$, or $COCH_2$;
B is a direct link or $-CH_2-$, $-CH(CH_3)-$ or $C(CH_3)_2$-, or when
Z is CH=CH, B may form a cyclopentane ring fused to the attached benzene ring;
Y completes a fused ring which is



wherein R is H, halo or C_1-C_4 alkyl;
n is 0, 1 or 2;
and m is 0 or 1.

2. A compound as claimed in claim 1 wherein X is N, Z is CH=CH and Y completes a fused benzene ring of formula:



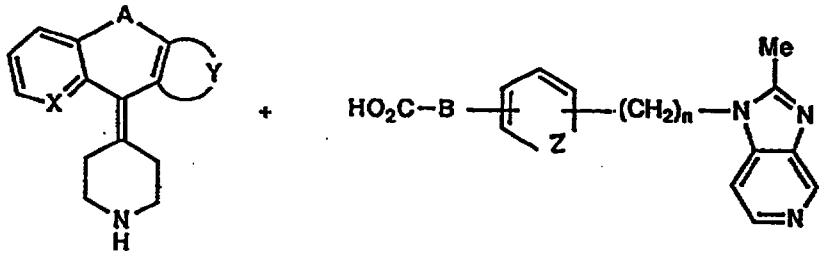
3. A compound as claimed in claim 2 wherein B is a direct link or CH_2.

4. A compound as claimed in claim 3 wherein n is 0 and m is 0.

5. A compound as claimed in claim 4 wherein R is Cl, B is a direct link, and A is CH_2CH_2.

6. The compound 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyrid-11-ylidene)-1-[4-(2-methylimidazo-[4,5-c]pyrid-1-yl)benzoyl]piperidine.

7. A process for preparing a compound of the formula (I) as claimed in claim 1 which comprises reacting a piperidine derivative of formula (II) with an acid of formula (III), or an activated derivative thereof:



(II) (III)

wherein X, Y, Z, A, B and n are as previously defined in claim 1, and optionally oxidising to yield compounds wherein m is 1.

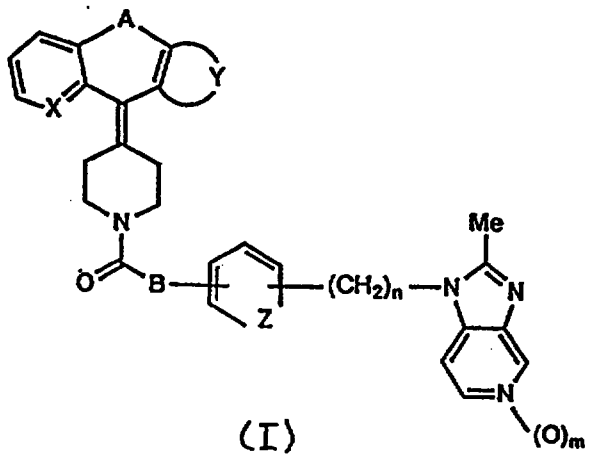
8. A pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6, together with a pharmaceutically acceptable diluent or carrier.

9. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6 for use in medicine, in particular for use in the treatment of allergic inflammatory conditions in humans including allergic rhinitis, sinusitis, asthma, atopic dermatitis and urticaria.

10. The use of a compound of the formula (I) as claimed in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating allergic inflammatory conditions in humans.

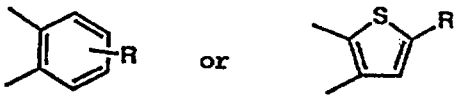
Claims for the following Contracting States : ES, GR

1. A process for preparing a compound having the formula-:

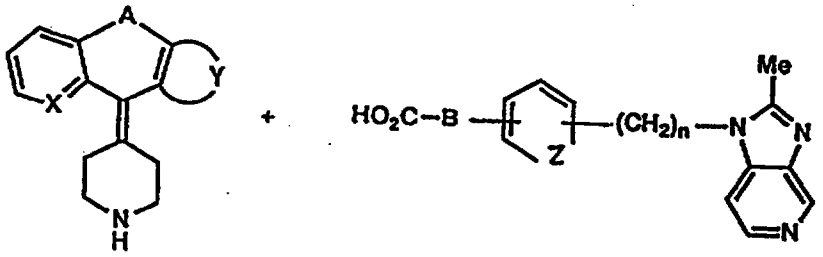


(I)

or a pharmaceutically acceptable salt thereof wherein:
X is CH or N;
Z is CH=CH or S;
A is CH_2CH_2, CH=CH, $CH(OH)CH_2$, or $COCH_2$;
B is a direct link or $-CH_2-$, $-CH(CH_3)-$ or $-C(CH_3)_2-$, or when
Z is CH=CH, B may form a cyclopentane ring fused to the attached benzene ring;
Y completes a fused ring which is



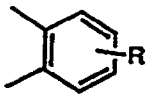
wherein R is H, halo or C_1-C_4 alkyl;
n is 0, 1 or 2;
and m is 0 or 1,
which comprises reacting a piperidine derivative of formula (II) with an acid of formula (III) or an activated derivative thereof:



(II) (III)

wherein X, Y, Z, A, B, and n are as previously defined in claim 1, and if desired oxidising to yield compounds wherein m is 1, and optionally forming a pharmaceutically acceptable salt thereof.

2. A process as claimed in claim 1 wherein X is N, Z is CH=CH and Y completes a fused benzene ring of formula:



3. A process as claimed in claim 2 wherein B is a direct link or CH_2.

4. A process as claimed in claim 3 wherein n is 0 and m is 0.

5. A process as claimed in claim 4 wherein R is Cl, B is a direct link, and A is CH_2CH_2.

6. A process as claimed in claim 1 wherein the compound of formula (I) is 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-ylidene)-1-[4-(2-methylimidazo-[4,5-c]pyrid-1-yl)benzoyl]piperidine.

7. A process as claimed in claim 1 wherein the reaction is performed in an organic solvent at room temperature in the presence of a diimide coupling reagent.

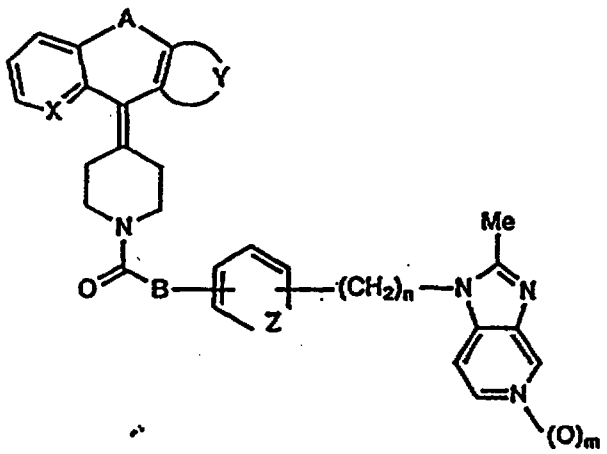
8. A process as claimed in claim 2 wherein the coupling reagent is 3-(dimethylaminopropyl)-1-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide.

* C L M S *

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung mit der Formel

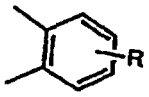


oder ein pharmazeutisch akzeptables Salz davon, worin:
X für CH oder N steht;
Z für CH=CH oder S steht;
A für CH_2CH_2, CH=CH, $CH(OH)CH_2$ oder $COCH_2$ steht;
B eine direkte Bindung oder $-CH_2-$, $-CH(CH_3)-$ oder $-C(CH_3)_2-$bedeutet, oder, wenn Z für CH=CH steht, B einen Cyclopentanring bilden kann, der mit dem daran befindlichen Benzolring verschmolzen ist;
Y einen verschmolzenen Ring vervollständigt, der



ist, worin R für H, Halogen oder C_1-C_4-Alkyl steht;
n 0, 1 oder 2 ist;
und m 0 oder 1 ist.

2. Verbindung nach Anspruch 1, worin X für N steht, Z für CH=CH steht und Y einen verschmolzenen Benzolring der Formel



vervollständigt.

3. Verbindung nach Anspruch 2, worin B eine direkte Bindung oder CH_2 bedeutet.

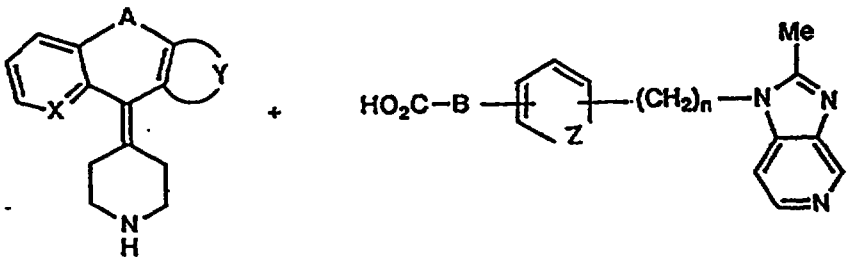
4. Verbindung nach Anspruch 3, worin n 0 ist und m 0 ist.

5. Verbindung nach Anspruch 4, worin R für Cl steht, B eine direkte Bindung bedeutet und A für CH_2CH_2 steht.

6. Die Verbindung 4-(8-Chlor-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyrid-11-yliden)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl]-piperidin.

7. Verfahren zur Herstellung einer Verbindung der Formel (I) nach Anspruch 1, welches die Umsetzung ei-

nes Piperidinderivats der Formel (II) mit einer Säure der Formel (III) oder einem aktivierten Derivats davon:



(II) (III)

worin X, Y, Z, A, B und n der zuvor in Anspruch 1 angegebenen Definition entsprechen, und gegebenenfalls eine Oxidierung zum Erhalt von Verbindungen, worin m 1 bedeutet, umfaßt.

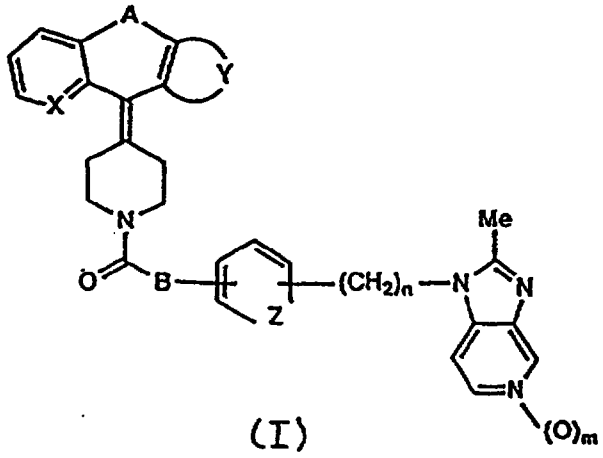
8. Pharmazeutische Zusammensetzung umfassend eine Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz davon nach einem der Ansprüche 1 bis 6, zusammen mit einem pharmazeutisch akzeptablen Verdünnungs- oder Trägermittel.

9. Verbindung der Formel (I) oder ein pharmazeutisch akzeptables Salz davon nach einem der Ansprüche 1 bis 6 zur Verwendung in der Medizin, insbesondere zur Verwendung bei der Behandlung allergischer entzündlicher Erkrankungen des Menschen, einschließlich allergischer Rhinitis, Sinusitis, Asthma, atopischer Dermatitis und Urticaria.

10. Verwendung einer Verbindung der Formel (I) nach einem der Ansprüche 1 bis 6 oder eines pharmazeutisch akzeptablen Salzes davon zur Herstellung eines Medikaments zur Behandlung allergischer entzündlicher Erkrankungen des Menschen.

Patentansprüche für folgende Vertragsstaaten : ES, GR

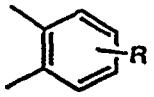
1. Verfahren zur Herstellung einer Verbindung mit der Formel:



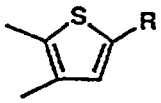
(I)

oder eines pharmazeutisch akzeptablen Salzes davon, worin:
X für CH oder N steht;
Z für CH=CH oder S steht;

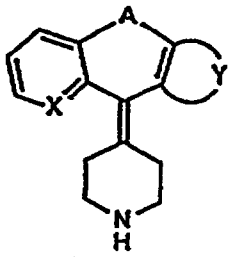
A für CH_2CH_2, CH=CH, $CH(OH)CH_2$ oder $COCH_2$ steht;
B eine direkte Bindung oder $-CH_2-$, $-CH(CH_3)-$ oder $-C(CH_3)_2-$ bedeutet, oder, wenn Z für CH=CH steht, B einen Cyclopentanring bilden kann, der mit dem daran befindlichen Benzolring verschmolzen ist;
Y einen verschmolzenen Ring vervollständigt, der



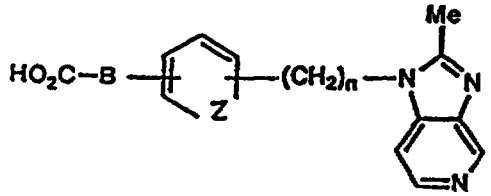
oder



ist, worin R für H, Halogen oder C_1-C_4-Alkyl steht;
n 0, 1 oder 2 ist;
und m 0 oder 1 ist, welches die Umsetzung eines Piperidinderivats der Formel (II) mit einer Säure der Formel (III) oder einem aktivierten Derivat davon



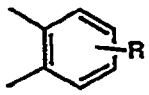
+



(II) (III)

worin X, Y, Z, A, B und n der zuvor in Anspruch 1 angegebenen Definition entsprechen, und gewünschtenfalls eine Oxidierung zum Erhalt von Verbindungen, worin m 1 bedeutet, und gegebenenfalls die Bildung eines pharmazeutisch akzeptablen Salzes davon umfaßt.

2. Verfahren nach Anspruch 1, worin X für N steht, Z für CH=CH steht und Y einen verschmolzenen Benzolring der Formel



vervollständigt.

3. Verfahren nach Anspruch 2, worin B eine direkte Bindung oder CH_2 bedeutet.

4. Verfahren nach Anspruch 3, worin n 0 ist und m 0 ist.

5. Verfahren nach Anspruch 4, worin R für Cl steht, B eine direkte Bindung bedeutet und A für CH_2CH_2 steht.

6. Verfahren nach Anspruch 1, worin die Verbindung der Formel (I) 4-(8-Chlor-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyrid-11-yliden)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl]-piperidin ist.

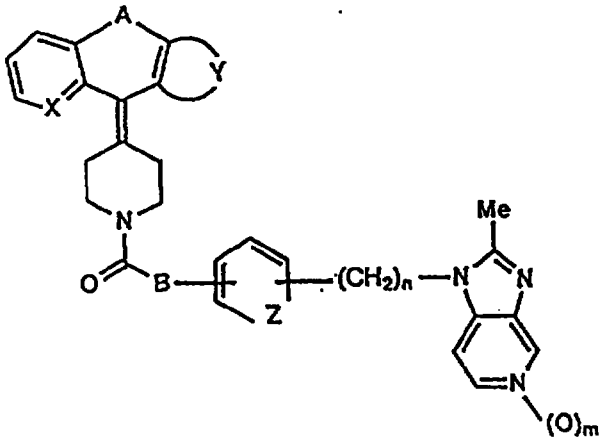
7. Verfahren nach Anspurch 1, worin die Umsetzung in einem organischen Lösungsmittel bei Raumtemperatur in Gegenwart eines Diimidkupplungsreagens durchgeführt wird.

8. Verfahren nach Anspruch 2, worin das Kupplungsreagens 3-(Dimethylaminopropyl)-1-ethylcarbodiimid oder N,N'-dicylcohexylcarbodiimid ist.

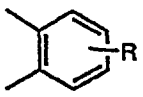
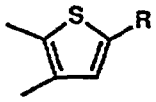
Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule :

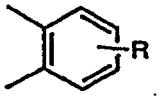


ou sel pharmaceutiquement acceptable d'un tel composé, dans laquelle :
X représente CH ou N ;
Z représente CH=CH ou S ;
A représente CH_2CH_2, CH=CH, $CH(OH)CH_2$, ou $COCH_2$;
B est une liaison directe ou un groupe $-CH_2-$, $-CH(CH_3)-$ ou $-C(CH_3)_2-$, ou lorsque Z représente CH=CH, B peut former un noyau cyclopentane fusionné avec le noyau benzénique attaché ;
Y complète un noyau fusionné qui est

 ou 

où R représente H, halogéno ou alkyle en C_1-C_4 ;
n représente 0, 1 ou 2 ; et
m représente 0 ou 1.

2. Composé selon la revendication 1, dans lequel X représente N, Z représente CH=CH et Y complète un noyau benzénique fusionné de formule :



3. Composé selon la revendication 2, dans lequel B est une liaison directe ou CH_2.

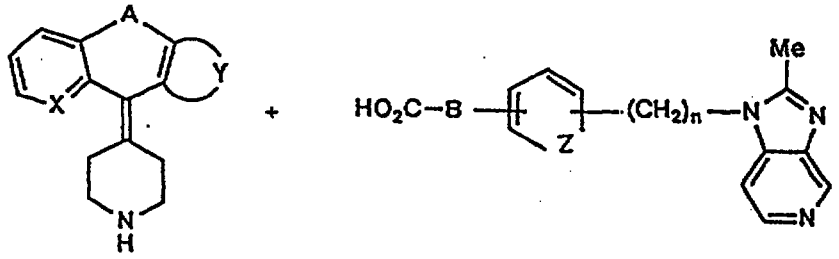
4. Composé selon la revendication 3, dans lequel n représente 0 et m représente 0.

5. Composé selon la revendication 4, dans lequel R représente Cl, B est une liaison directe, et A représente CH_2CH_2.

* C L M S *

6. 4-(8-chloro-5,6-dihydro-11H-benzo(5,6)-cyclohepta-(1,2-b)pyrid-11-ylidène)-1-(4-(2-méthylimidazo(4,5-c)pyrid-1-yl)benzoyl)pipéridine.

7. Procédé de préparation d'un composé de formule (I) selon la revendication 1, qui consiste à faire réagir un dérivé pipéridine de formule (II) avec un acide de formule (III), ou avec un dérivé activé d'un tel acide :



(II) (III)

où X, Y, Z, A, B et n sont tels que précédemment définis dans la revendication 1, et éventuellement à procéder à une oxydation pour obtenir les composés dans lesquels m représente 1.

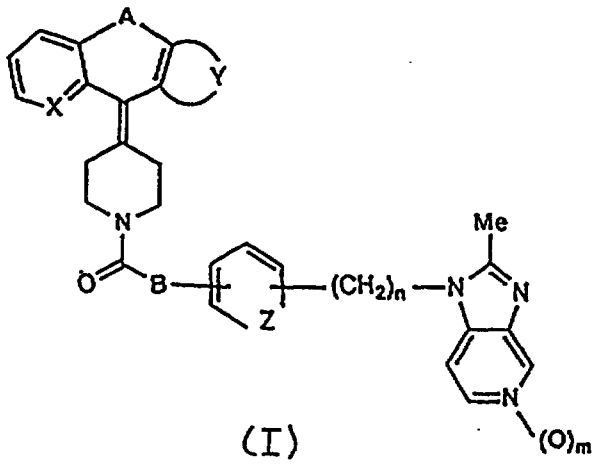
8. Composition pharmaceutique comprenant un composé de formule (I), ou un sel pharmaceutiquement acceptable d'un tel composé, selon l'une quelconque des revendications 1 à 6, avec un diluant ou un véhicule pharmaceutiquement acceptable.

9. Composé de formule (I), ou sel pharmaceutiquement acceptable d'un tel composé, selon l'une quelconque des revendications 1 à 6, pour une utilisation en médecine, en particulier pour une utilisation dans le traitement d'états inflammatoires allergiques chez l'homme y compris les rhinites allergiques, la sinusite, l'asthme, les dermatites atopiques et l'urticaire.

10. Utilisation d'un composé de formule (I) selon l'une quelconque des revendications 1 à 6, ou d'un sel pharmaceutiquement acceptable d'un tel composé, pour la fabrication d'un médicament pour le traitement des états inflammatoires allergiques chez l'homme.

Revendications pour les Etats contractants suivants : ES, GR

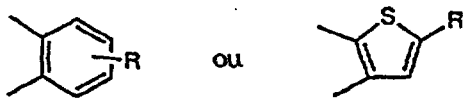
1. Procédé de préparation d'un composé de formule :



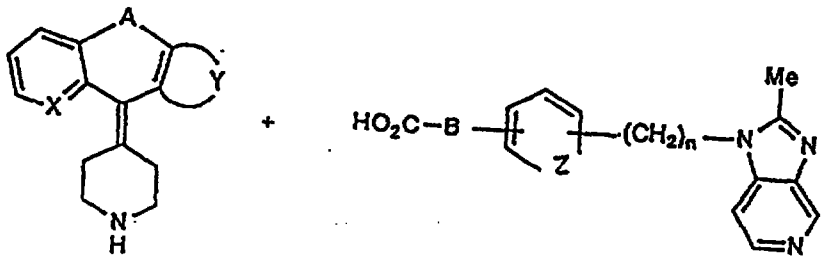
(I)

ou d'un sel pharmaceutiquement acceptable d'un tel composé, dans laquelle :
X représente CH ou N ;

Z représente CH=CH ou S ;
A représente CH_2CH_2, CH=CH, $CH(OH)CH_2$, ou $COCH_2$;
B est une liaison directe ou un groupe $-CH_2-$, $-CH(CH_3)-$ ou $-C(CH_3)_2-$, ou lorsque Z représente CH=CH, B peut former un noyau cyclopentane fusionné avec le noyau benzénique attaché ;
Y complète un noyau fusionné qui est



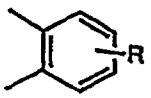
où R représente H, halogéno ou alkyle en C_1-C_4 ;
n représente 0, 1 ou 2 ; et
m représente 0 ou 1,
qui consiste à faire réagir un dérivé pipéridine de formule (II) avec un acide de formule (III), ou avec un dérivé activé d'un tel acide :



(II) (III)

où X, Y, Z, A, B et n sont tels que précédemment définis dans la revendication 1, et éventuellement à procéder à une oxydation pour obtenir les composés dans lesquels m représente 1 et, le cas échéant, à former un sel pharmaceutiquement acceptable de tels composés.

2. Procédé selon la revendication 1, dans lequel X représente N, Z représente CH=CH et Y complète un noyau benzénique fusionné de formule :



3. Procédé selon la revendication 2, dans lequel B est une liaison directe ou CH_2.

4. Procédé selon la revendication 3, dans lequel n représente 0 et m représente 0.

5. Procédé selon la revendication 4, dans lequel R représente Cl, B est une liaison directe, et A représente CH_2CH_2.

6. Procédé selon la revendication 1, dans lequel le composé de formule (I) est la 4-(8-chloro-5,6-dihydro-11H-benzo(5,6)cyclohepta(1,2-b)pyrid-11-ylidène)-1-'4-(2-méthyl-imidazo(4,5-c)pyrid-1-yl)benzoyl)pipéridine.

7. Procédé selon la revendication 1, dans lequel la réaction est mise en oeuvre dans un solvant organique à la température ambiante en présence d'un réactif de couplage diimide.

8. Procédé selon la revendication 7, dans lequel le réactif de couplage est le 3-(diméthylaminopropyl)-1-éthylcarbodiimide ou le N,N'-dicyclohexylcarbodiimide.