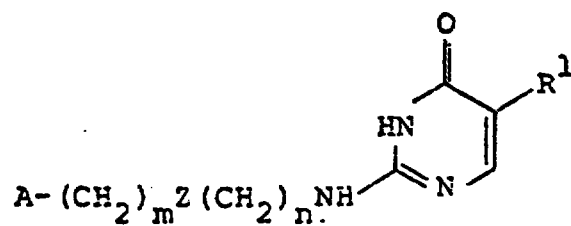


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PYRIMIDONE DERIVATIVES

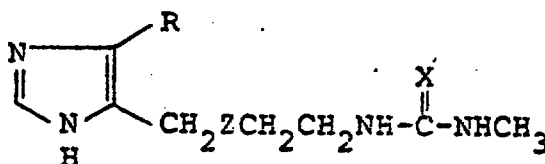
Certain 2,5-disubstituted-4(3H)-pyrimidones
having the formula:



I

wherein A, m, L, n and R¹ are as defined below, and their nontoxic pharmaceutically acceptable salts, are potent histamine H₂-receptor antagonists which inhibit gastric acid secretion and are useful in the treatment of peptic ulcers and other pathological hypersecretory conditions.

Burimamide (IIa) was the first clinically effective histamine H₂-receptor antagonist. It inhibits gastric secretion in animals, including man, but oral absorption is poor.

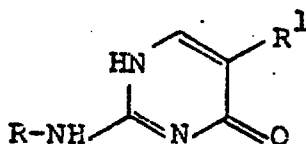


- IIa; R=H, Z=CH₂, X=S Burimamide
 b; R=CH₃, Z=S, X=S Metiamide
 c; R=CH₃, Z=S, X=NCN Cimetidine

Metiamide (IIb), a subsequently evaluated histamine H₂-antagonist, is more potent than burimamide and is orally active in man. Clinical utility was limited, however, owing to toxicity (agranulocytosis). Cimetidine (IIc) is as effective an histamine H₂-antagonist as metiamide, without producing agranulocytosis, and has recently been marketed as an anti-ulcer drug.

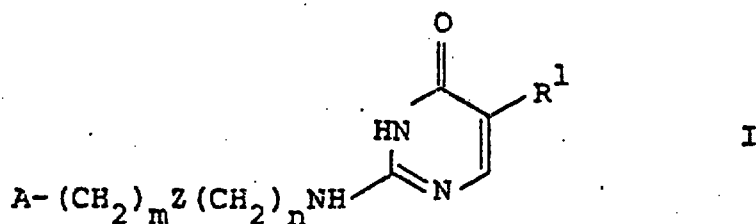
Reviews on the development of histamine H₂-antagonists, including those discussed in the preceding paragraph, may be found in C.R. Ganellin, et al, Federation Proceedings, 35, 1924 (1976), in Drugs of the Future, 1, 13 (1976) and in references cited therein.

A large number of 2,5-disubstituted pyrimidone histamine H₂-receptor antagonists having the general formula:



are known in the art. Thus, European Patent Application No. 4,793, published October 17, 1979,; European Patent Application No. 3,677, published August 22, 1979; European Patent Application No. 15,138, published September 3, 1980; European Patent Application No. 24,873, published March 11, 1981; European Patent Application No. 49,173, published April 7, 1982; and World Patent Application No. 8,000,966, published May 15, 1980 disclose such compounds wherein R can be a group similar to the group substituted on the 2-amino group of the compounds disclosed and claimed herein and R¹ can be hydrogen, alkyl or substituted alkyl. However, none of these applications disclose such compounds substituted at the 5-position with a nitro group or an amino group as is the case with the compounds disclosed and claimed herein.

This application relates to histamine H₂-antagonists which are effective inhibitors of gastric acid secretion in animals, including man, which are useful in the treatment of peptic ulcers and other conditions caused or exacerbated by gastric acidity, and which have the formula:



wherein m is an integer of from zero to 2, inclusive;

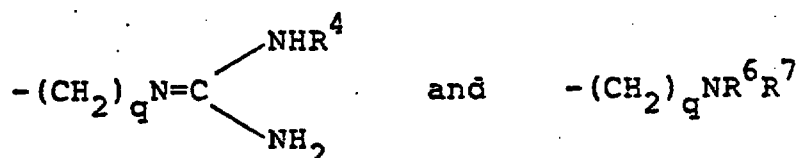
n is an integer of from 2 to 5 inclusive;

Z is sulfur, oxygen or methylene;

R^1 is NO_2 or NR^2R^3 ;

R^2 and R^3 each are independently hydrogen or (lower)alkyl, or, when R^2 is hydrogen, R^3 also may be formyl, carboalkoxy, alkanoyl or benzoyl;

A is phenyl, furyl, thienyl, pyridyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, pyrimidinyl, pyrazolyl, pyridazinyl or pyrazinyl; provided that A contains one or two substituents, the first substituent being selected from



and the second substituent being selected from (lower)-alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive;

R^4 is a hydrogen atom, a (lower)alkyl group optionally substituted by one or more halogen atoms, provided that there is no halogen atom on the carbon atom attached to the nitrogen atom, or a cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, (lower)alkanoyl or benzoyl group;

R^6 and R^7 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, phenyl-(lower)alkyl or (lower)alkoxy(lower)alkyl in which the (lower)alkoxy moiety is at least two carbon atoms removed from the nitrogen atom, or R^6 and R^7 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]non-3-yl;

or 1, 2, 3, 6-tetrahydro-1-pyridyl;

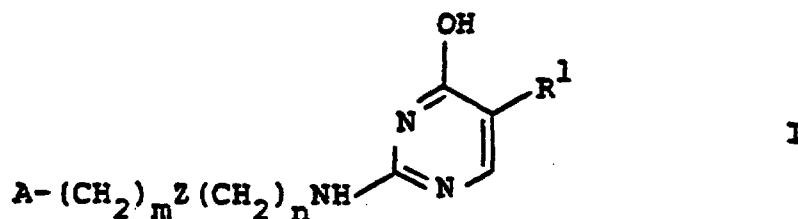
provided that, if R^1 is NO_2 or NH_2 , then $\text{A}-(\text{CH}_2)_m\text{Z}(\text{CH}_2)_n\text{NH}$ is not 3-(3-piperidinomethylphenoxy)propylamino.

The invention also includes nontoxic pharmaceutically acceptable acid addition salts of the formula I compounds just specified.

The invention further includes the monohydrochloride and trihydrochloride salts of 5-amino-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone.

This invention also relates to processes for the preparation of the compounds of Formula I and to intermediates useful in the preparation of the compounds of Formula I.

The present invention includes within its scope all possible tautomeric forms, geometric isomers, optical isomers and zwitterionic forms of the compounds of Formula I, as well as mixtures thereof. Although the compounds of Formula I are shown as 4-pyrimidones, those skilled in the art will appreciate that they, as well as the intermediates for preparing them, may also exist as the tautomeric 4-hydroxypyrimidines, e.g.,



As used herein and in the claims, the term "lower" when used in conjunction with the terms "(lower)-alkyl", "(lower)alkoxy", "(lower)alkanoyl", "(lower)-alkenyl", "(lower)alkynyl", "phenyl(lower)alkyl" and "(lower)alkoxy(lower)alkyl" means straight or branched

chain groups containing from 1 to 6 carbon atoms. Preferably these groups contain from 1 to 4 carbon atoms and, most preferably, they contain 1 to 2 carbon atoms. The term "nontoxic pharmaceutically acceptable salts" is intended to include salts of the compounds of Formula I with any nontoxic pharmaceutically acceptable acid. Such acids are well-known and include hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, maleic, fumaric, succinic, oxalic, benzoic, methanesulfonic, tartaric, citric, camphorsulfonic, levulinic and the like. The salts are made by methods known in the art.

In the compounds of Formula I, R^1 is preferably NO_2 , NH_2 , $NHCO_2C_2H_5$, or $NHCHO$. Substituent A preferably is piperidinomethylphenyl, dimethylaminomethylthienyl, piperidinomethylthienyl, or dimethylaminomethylfuryl. Substituent R^4 preferably is hydrogen, (lower)alkyl or 2,2,-trifluoroethyl. Substituent Z preferably is sulfur or oxygen. It is preferred that m is zero or 1 and n is 2 or 3.

As presently envisaged, the most preferred compounds of Formula 1 are:

- 1) 5-carbethoxyamino-2-[3-(3-piperidino-methylphenoxy)propylamino]-4(3H)-pyrimidone;
- 2) 5-amino-2-[3-(3-piperidinomethylphenoxy)-propylamino]-4(3H)-pyrimidone monohydrochloride;
- 3) 5-amino-2-[3-(3-piperidinomethylphenoxy)-propylamino]-4(3H)-pyrimidone trihydrochloride;
- 4) 5-nitro-2-{2-[(5-dimethylaminomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone;
- 5) 5-nitro-2-{2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone;
- 6) 2-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-5-nitro-4(3H)-pyrimidone;
- 7) 5-amino-2-{2-[(5-dimethylaminomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone;

8) 5-amino-2-{2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone;

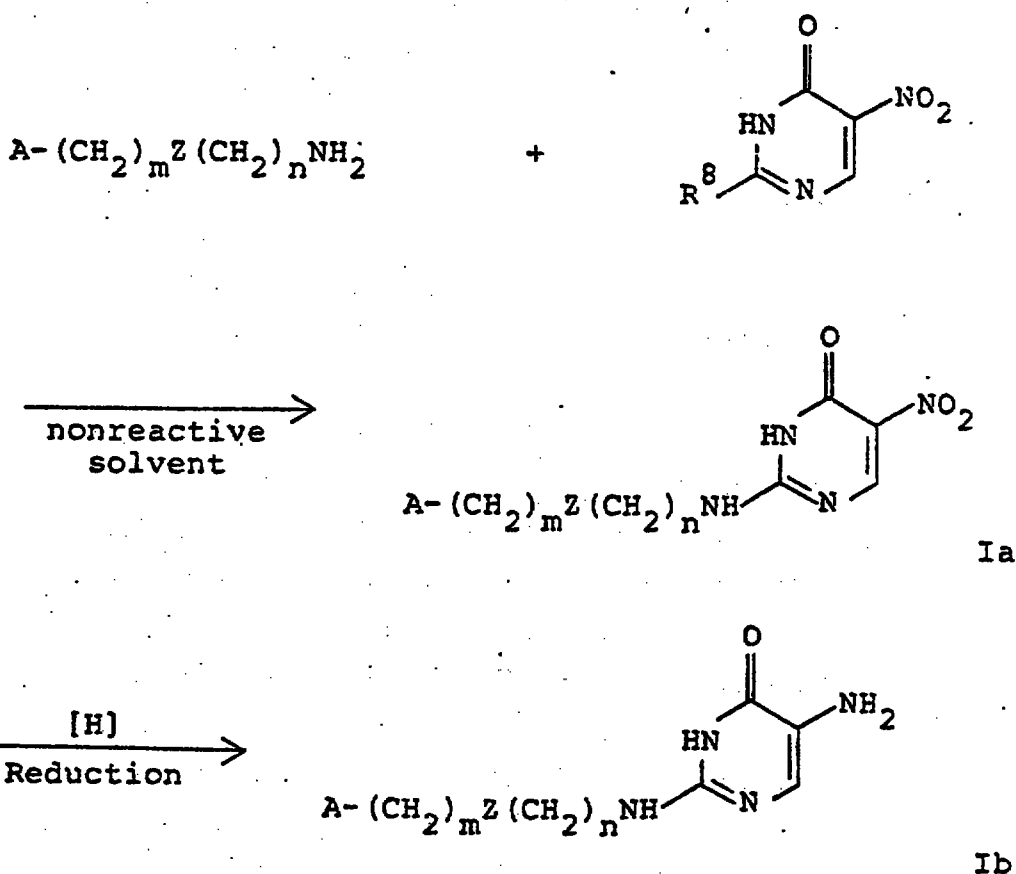
9) 5-amino-2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4(3H)-pyrimidone; and

10) 5-formamido-2-[3-(3-piperidinomethyl-phenoxy)propylamino]-4(3H)-pyrimidone;

and their nontoxic, pharmaceutically acceptable acid addition salts.

The compounds of Formula I may be prepared by various reaction schemes.

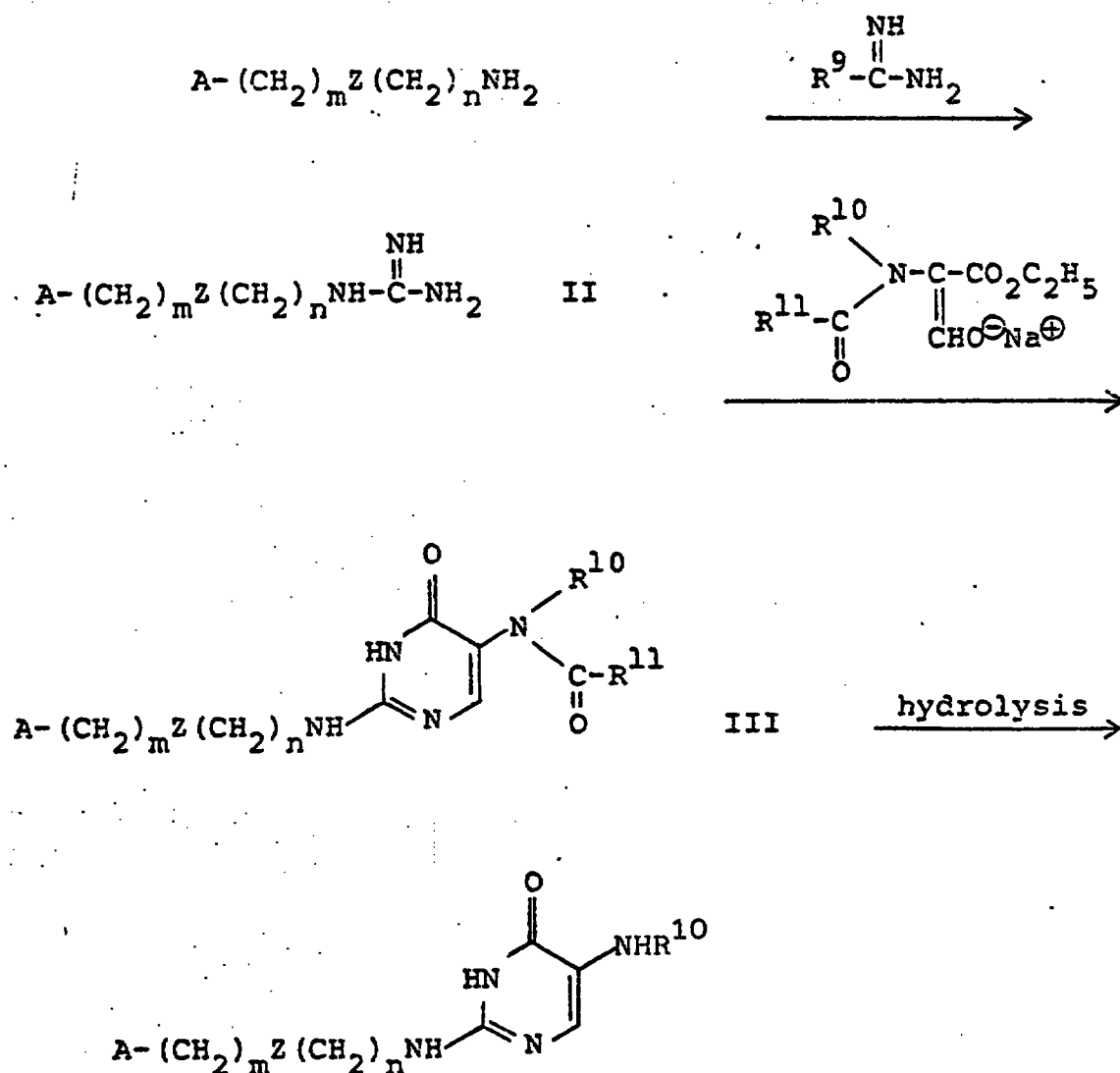
Reaction Scheme 1



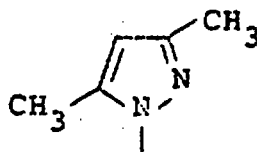
in which R^8 is a good leaving group such as fluoro, chloro, bromo, iodo, alkylthio, nitroamino, phenoxy, substituted phenoxy, alkoxy or the like. Suitable

leaving groups are well known in the art. The reactions are conducted in an inert solvent such as methanol or ethanol. It is preferred to conduct the initial reaction by heating the reactants at reflux. Reduction may be carried out with hydrogen gas in the presence of a suitable catalyst such as Raney nickel or a reducing catalyst such as sodium dithionite.

Reaction Scheme 2

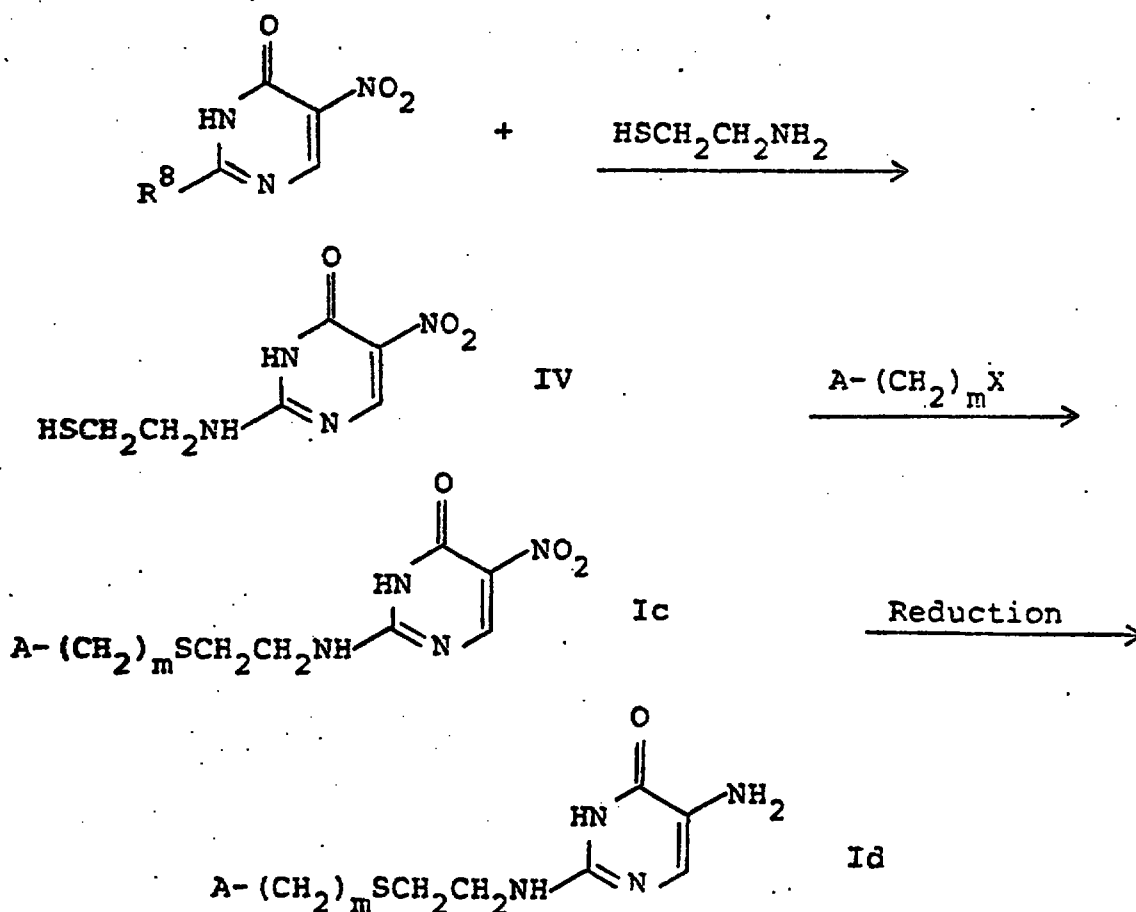


wherein R^9 is thioalkoxy or



R^{10} is H or lower alkyl, and R^{11} is lower alkyl, aryl, alkoxy or aryloxy. The reactions are conducted in an inert solvent such as methanol or ethanol. It is preferred to conduct the initial reaction to obtain a compound of Formula II by heating the reactants at reflux; and to conduct the second reaction to obtain a compound of Formula III at from room temperature up to the reflux temperature of the solvent.

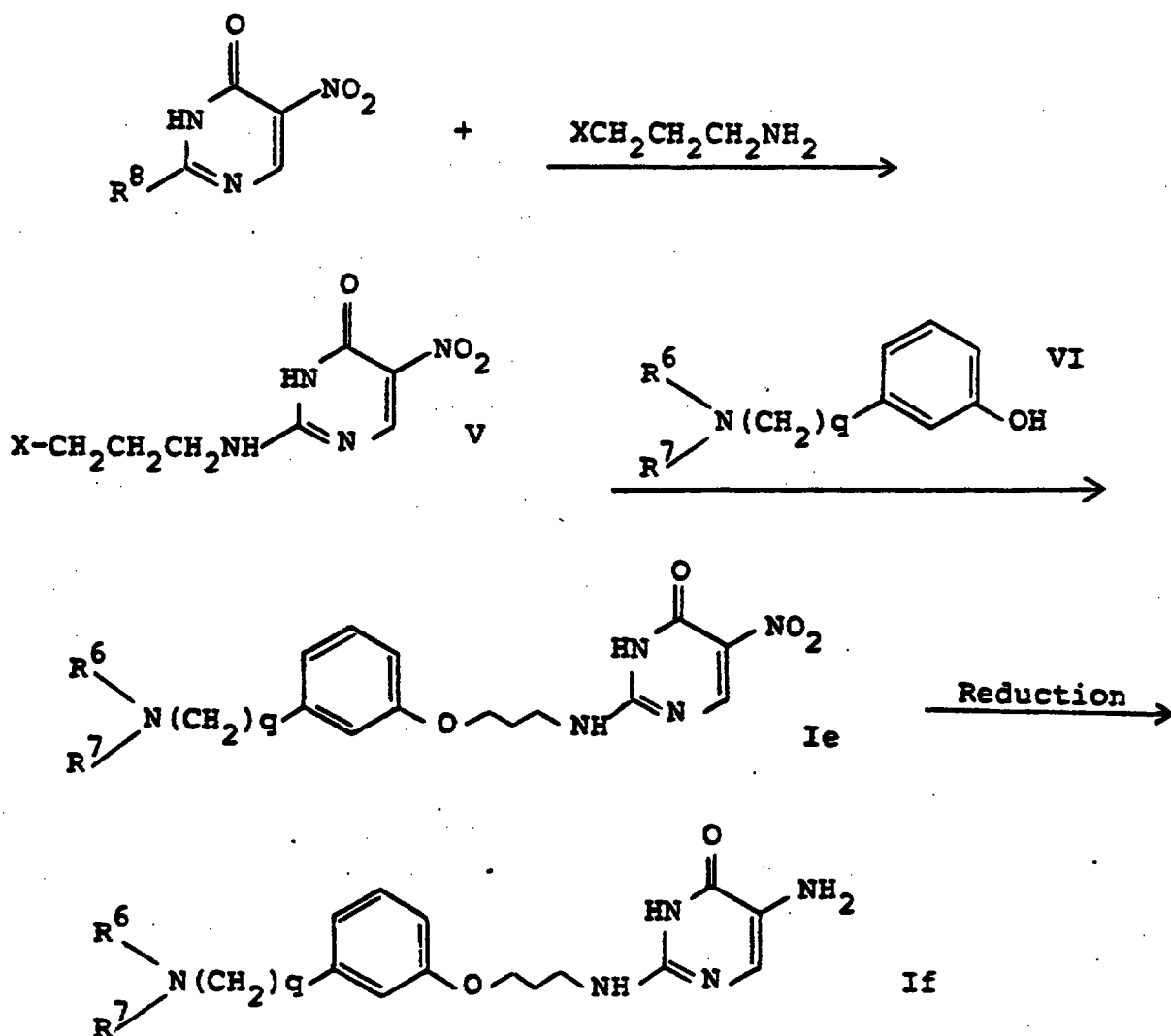
Reaction Scheme 3



wherein R^8 is the same as previously defined and X is a conventional leaving group or hydroxy. Suitable leaving

groups "X" for use in this reaction are well-known to those skilled in the art. They include, for example, fluoro, chloro, bromo, iodo, $-O_3SR^{12}$ wherein R^{12} is (lower)alkyl [e.g., methanesulfonate], $-O_3SR^{13}$ wherein R^{13} is aryl or substituted aryl [e.g., benzenesulfonate, p-bromobenzenesulfonate or p-toluenesulfonate], $-O_3SF$, acetoxy and 2,4-dinitrophenoxy. The first reaction to obtain a compound of Formula IV is preferably conducted in an inert solvent at a temperature ranging between room temperature and the reflux temperature of the solvent; and the second reaction to obtain a compound of Formula Ic is conducted preferably in an inert solvent containing about one equivalent base. When X is hydroxy and m is equal to 1, the reaction is conducted in an acidic medium.

Reaction Scheme 4



wherein q , R^6 , R^7 and R^8 are as previously defined and X is a conventional leaving group as described previously, or hydroxy. When X is hydroxy in compound V, it is converted to a conventional leaving group by reaction with an activating agent such as thionyl chloride, toluene sulfonic acid or the like. The reaction to give V is preferably conducted in an inert solvent at from room temperature to the reflux temperature of the solvent.

Compound V is reacted with compound VI preferably in an inert solvent, preferably in the presence of about one equivalent of base, more preferably in the presence of a phase transfer catalyst such as tetrabutylammonium hydroxide.

For therapeutic use, the pharmacologically active compounds of Formula I will normally be administered as a pharmaceutical composition comprising as the (or an) essential active ingredient at least one such compound in its basic form or in the form of a nontoxic pharmaceutically acceptable acid addition salt, in association with a pharmaceutically acceptable carrier.

The pharmaceutical compositions may be administered orally, parenterally or by rectal suppository. A wide variety of pharmaceutical forms may be employed. Thus, if a solid carrier is used, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. If a liquid carrier is employed, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule, sterile solution for injection, or an aqueous or non-aqueous liquid suspension. The pharmaceutical compositions are prepared by conventional techniques appropriate to the desired preparation.

The dosage of the compounds of this invention will depend not only on such factors as the weight of the patient, but also on the degree of gastric acid inhibition desired and the potency of the particular compound being utilized. The decision as to the particular dosage

to be employed (and the number of times to be administered per day) is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of the specific patient. With the preferred compounds of this invention, each oral dosage unit will contain the active ingredient in an amount of from about 2 mg to about 300 mg, and most preferably from about 4 mg to about 100 mg. The active ingredient will preferably be administered in equal doses from one to four times a day.

Histamine H₂-receptor antagonists have been shown to be effective inhibitors of gastric secretion in animals and man, Brimblecombe et al, J. Int. Med. Res., 3, 86 (1975). Clinical evaluation of the histamine H₂-receptor antagonist cimetidine has shown it to be an effective therapeutic agent in the treatment of peptic ulcer disease, Gray et al, Lancet, 1, 8001 (1977). One of the preferred compounds of this invention has been compared with cimetidine in various tests and has been found to be more potent than cimetidine as a histamine H₂-receptor antagonist as shown in Tables 1 and 2.

Determination of Gastric Antisecretory Activity in the Gastric Fistula Rat

Male Long Evans rats weighing about 240-260 grams at the time of cannula implantation are used. The design and implantation of the stainless steel cannula into the anterior wall of the fore-stomach are carried out essentially as described by Pare et al, Laboratory Animal Science, 27, 244 (1977). The fistula components are designed and the operative procedure is carried out exactly as described in the above reference. Post operatively the animals are individually housed in solid bottom cages with sawdust and are allowed food and water ad libitum throughout the entire recovery period. Animals are not used for test purposes for at least 15 days after the operative procedure.

The animals are fasted but allowed water ad libitum for 20 hours before the testing procedure is to begin. Immediately prior to collection, the cannula is opened and the stomach washed gently with 30-40 ml of warm saline or distilled water to remove any residual contents. The catheter is then screwed into the cannula in place of the plugging screw and the rat is placed in a clear plastic rectangular cage measuring 40 cm long, 15 cm wide and 13 cm high. The bottom of the cage has a slit, approximately 1.5 cm wide and 25 cm long, running down the center, to accommodate the catheter which hangs through it. In this way, the rat is not restricted and can move freely about the cage during collection periods. The remainder of the assay is carried out as described by Ridley et al, Research Comm. Chem. Path. Pharm., 17, 365 (1977).

Gastric secretions collected during the first hour after washing the stomach are discarded as they may be contaminated. For oral evaluation, the catheter is then removed from the cannula and replaced with the plugging screw. Water (2 ml/kg) is administered orally via gastric intubation and the animal is returned to the cage for 45 minutes. After this time the plugging screw is removed and replaced with a catheter to which a small plastic vial has been attached to collect the gastric secretions. A two-hour sample is collected (this represents the control secretion), the catheter is removed and replaced with the plugging screw. The test drug is now administered orally in a volume of 2 ml/kg via gastric intubation. Forty-five minutes later the plugging screw is again removed, replaced with the catheter attached to a small plastic vial and another 2-hour sample is collected. The secretions in the second sample are compared to those of the control sample in order to determine the effects of the test drug.

When test compounds are to be evaluated parenterally, the animal is injected ip or sc with the test

compound vehicle in a volume of 2 ml/kg immediately after discarding the initial 60-minute collection. A two-hour sample is collected (control secretion) and the animals are injected either ip or sc with the test compound in a volume of 2 ml/kg. An additional two-hour sample is collected and its secretions are compared to those of the control period to determine drug effects.

The samples are centrifuged and placed in a graduated centrifuge tube for volume determination. Titratable acidity is measured by titrating a one-ml sample to pH 7.0 with 0.02N NaOH, using an Autoburet and an electrometric pH meter (Radiometer). Titratable acid output is calculated in microequivalents by multiplying the volume in milliliters by the acid concentration in milliequivalents per liter.

Results are expressed as percent inhibition relative to control readings. Dose response curves are constructed and ED₅₀ values are calculated by regression analyses. At least three rats are used at each dosage level and a minimum of three dosage levels are utilized for determination of a dose response curve.

Table 1

Gastric Antisecretory Activity
In The Gastric Fistula Rat

<u>Compound</u>	ED ₅₀ sc <u>μmoles/kg</u>	Potency Ratio <u>(cimetidine = 1.0)</u>
cimetidine	3.48 (2.3-5.5)*	1.0
Example 2	0.15 (0.08-0.2)*	26 (13-50)*

*95% confidence limits.

Determination of Gastric Antisecretory
Activity In The Heidenhain Pouch Dog

Prior to surgery, hematology and blood chemistry profiles are obtained and an assessment made as to the general health of selected female dogs. Dogs are vaccinated with Tissue Vax 5 (DHLP - Pitman-Moore) and housed in general animal quarters for four weeks' observation so incipient diseases may become apparent. Dogs are fasted with water ad libitum 24 hours prior to surgery.

Anesthesia is induced with Sodium Pentothal (Abbott) 25-30 mg/kg iv. Subsequent anesthesia is maintained with methoxyflurane (Pitman-Moore). A mid-line linea alba incision from xiphoid to umbilicus provides good exposure and ease of closure. The stomach is pulled up into the operative field, the greater curvature stretched out at multiple points and clamps placed along the selected line of incision. The pouch is made from the corpus of the stomach so that true parietal cell juice is obtained. About 30% of the corpus volume is resected. The cannula is made of light-weight, biologically-inert material such as nylon or Delrin* with dimensions and attachments after DeVito and Harkins (J. Appl. Physiol., 14, 138 (1959)). Post operatively, dogs are medicated with antibiotics and an analgesic. They are allowed 2-3 months for recovery. Experiments are carried out in the following way: Dogs are fasted overnight (~18 hours) with water ad libitum prior to each experiment. The dogs are placed in a sling and a saphenous vein cannulated for drug administration. Histamine as the base (100 µg/kg/hr) and chlorpheniramine maleate (0.25 mg/kg/hr) are infused continuously (in a volume of 6 ml/hr) with a Harvard infusion pump.

Ninety minutes' infusion are allowed for the dogs to reach a steady state of acid output. At this time the drug or normal saline (control) is administered concomitantly with the secretagogue in a volume of 0.5

* Registered Trade Mark

ml/kg over a 30 second period. When oral studies are to be carried out, the drug is administered via gastric gavage in a volume of 5 ml/kg. Infusion of the secretagogue is continued and 15 minute samples of the gastric juice are taken for 4.5 hours. Each sample is measured to the nearest 0.5 ml and titratable acidity is determined by titrating a 1 ml sample to pH 7.0 with 0.2N NaOH, using an Autoburet and an electrometric pH meter (Radiometer). Titratable acid output is calculated in microequivalents by multiplying the volume in milliliters by the acid concentration in milliequivalents per liter.

Results are expressed as percent inhibition relative to control readings and the response is the average for five dogs at that dose level.

Table 2

Gastric Antisecretory Activity
In The Heidenhain Pouch Dog

<u>Compound</u>	<u>Dose*</u> <u>[μmoles/kg]</u>	<u>% Maximum</u> <u>Inhibition</u>	<u>Potency Ratio</u> <u>[cimetidine = 1.0]</u>
(Intravenous)			
Cimetidine	6.0	94	1.0
Compound of Example 2	0.094	90	50
(Oral)			
Cimetidine	12.0	95	1.0
Compound of Example 2	0.5	86	20

*single dose was used in 5 dogs for compound of Example 2

In addition to the results shown in Table 2, the antisecretory activity of the compound of Example 2 in both the intravenous and oral dog models shows a prolonged duration of action relative to cimetidine.

Example 1

5-Carbethoxyamino-2-[3-(3-piperidinomethylphenoxy)-propylamino]-4(3H)-pyrimidone

A. N-[3-(3-Piperidinomethylphenoxy)propyl]-guanidine nitrate

A solution of 3-(3-piperidinomethylphenoxy)propylamine obtained from the dihydrochloride (7.45 g; 30.0 mmoles) and 3,5-dimethylpyrazole-1-carboxamidinium nitrate (6.04 g; 30.0 mmoles) in 100 ml of absolute ethanol was heated at reflux temperature for 1 hour, then kept at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was triturated with ether, filtered and dried to give 9.82 g of the title compound, mp 74-76°C.

B. 5-Carbethoxyamino-2-[3-(3-piperidinomethylphenoxy)-propylamino]-4(3H)-pyrimidone

A mixture of 3-(3-piperidinomethylphenoxy)propylguanidine nitrate (10.5 g; 29.71 mmoles) [prepared in Step A], and the sodium salt of ethyl carbethoxyaminoformylacetate (6.69 g; 29.8 mmoles) in 57 ml of methanol was treated with 57% sodium hydride dispersion (1.25 g; 29.8 mmoles). The resulting mixture was heated at an oil bath temperature of 60°C for 16 hours. The reaction mixture was evaporated under reduced pressure and the residue taken up with acetonitrile. The turbid solution was filtered, washed with n-pentane and evaporated to

give crude product. The semi-solid product was placed on 250 g of silica gel (230-400 mesh) and chromatographed by flash chromatography using gradient elution of methanol-methylene chloride containing 1% NH_4OH . The appropriate fractions were combined, evaporated and the solid residue recrystallized from acetonitrile to give the title compound, mp 171-173°C.

Anal. Calc'd for $\text{C}_{22}\text{H}_{31}\text{N}_5\text{O}_4$: C, 61.52; H, 7.28; N, 16.31
Found: C, 61.13; H, 7.27; N, 16.24

Example 2

5-Amino-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone

A suspension of 5-carbethoxyamino-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone (1.70 g; 3.96 mmoles) in 11.3 ml (28.3 meq.) of 10% aqueous NaOH was heated at an oil bath temperature of 120°C for 20 minutes. The reaction mixture was neutralized with acetic acid and evaporated under reduced pressure. The residue was placed on 250 g of silica gel (230-400 mesh) and chromatographed by flash chromatography using $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ (80:20:1) as the eluent. The appropriate fractions containing product were combined, evaporated and treated with ethanolic hydrochloric acid, and then diluted with ether to give 0.28 g of the title compound as its hydrochloride salt. The NMR spectrum (100 MHz) in d_6 dimethyl sulfoxide gave the following resonances δ : 7.14 (m, 4H); 6.94 (s, 1H); 4.0 (m, 4H); 3.32 (t, 2H); 2.84 (m, 4H); 1.94 (m, 2H); 1.66 (m, 6H).

Anal. Calc'd for $C_{19}H_{27}N_5O_2 \cdot HCl$: C, 57.93; H, 7.16;
N, 17.78; Cl, 9.00
Found (corr. for 2.37% H_2O): C, 56.67; H, 7.27;
N, 15.60; Cl, 8.87

Example 3

5-Nitro-2-[3-(3-piperidinomethylphenoxy)propylamino]-
4(3H)-pyrimidone

A solution of 3-(3-piperidinomethylphenoxy)propylamine (8.20 g; 33.0 mmoles) and 2-methylthio-5-nitro-4-hydroxypyrimidine (6.20 g; 32.5 mmoles) [prepared according to the procedure described in U.S. Patent 4,241,056] in 35 ml of ethanol was stirred at reflux temperature for 18 hours. The reaction mixture was evaporated under reduced pressure, and the residue was placed on 250 g of silica gel (230-400 mesh) and chromatographed by flash chromatography using a gradient elution of methanol-methylene chloride. The appropriate fractions were combined and evaporated, and the product was recrystallized from tetrahydrofuran to give the title compound, mp 161-164°C.

The NMR spectrum (90 MHz) in d_6 dimethyl sulfoxide shows the presence of approximately 0.25 moles of tetrahydrofuran.

Anal. Calc'd for $C_{19}H_{28}N_5O_4 \cdot 0.25C_4H_8O$:
C, 59.19; H, 6.71; N, 17.27
Found (corr. for 0.19% H_2O):
C, 59.22; H, 6.70; N, 17.54

Example 4

5-Amino-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone

A suspension of 5-nitro-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone (0.50 g; 1.29 mmoles) and a catalytic amount of Raney nickel (approximately 0.7 cm³) in 50 ml of methanol was hydrogenated in a Parr apparatus at 50 psi for 2.75 hours. The reaction mixture was filtered and evaporated, and the residue was placed on 90 g of silica gel (230-400 mesh) and chromatographed by flash chromatography using a gradient elution of methanol-methylene chloride containing 1% NH₄OH. The appropriate fractions were combined and evaporated, and the semi-solid product was acidified with methanolic hydrochloric acid and precipitated with ether to give the title compound as a dihydrochloride salt, mp 182-184°C.

Anal. Calc'd for C₁₉H₂₇N₅O₂·2HCl: C, 50.87; H, 6.63;
N, 15.61; Cl, 19.76
Found (corr. for 1.3% H₂O): C, 49.89; H, 6.56;
N, 15.48; Cl, 19.52

In a separate experiment, the product obtained after flash chromatography was treated with 20 ml of 3.1N methanolic HCl, then evaporated under reduced pressure and dried to give 5.8 g of the title compound as a trihydrochloride salt.

Anal. Calc'd for C₁₉H₂₇N₅O₂·3HCl·0.3CH₄O:
C, 48.65; H, 6.60; N, 14.70; Cl, 22.33
Found (corr. for 1.22% H₂O):
C, 47.54; H, 6.50; N, 14.54; Cl, 21.93

Example 5

5-Nitro-2-[2-[(5-dimethylaminomethyl-3-thienyl)-methylthio]ethylamino]-4(3H)-pyrimidone

A mixture containing 2-[(5-dimethylaminomethyl-3-thienyl)methylthio]ethylamine (2.88 g; 12.5 mmoles) and 2-methylthio-5-nitro-4-hydroxypyrimidine (2.33 g; 12.44 mmoles) in 10 ml of ethanol was heated at reflux temperature for 13 hours. The reaction mixture was evaporated under reduced pressure, and the residue was placed on 150 g of silica gel and chromatographed by flash chromatography using a gradient elution of methanol-methylene chloride. The appropriate fractions gave 2.92 g of product which was recrystallized from tetrahydrofuran to give the title compound, mp 150-153°C.

Anal. Calc'd for $C_{14}H_{19}N_5O_3S_2$: C, 45.51; H, 5.18;
N, 18.96; S, 17.36
Found: C, 45.87; H, 5.20;
N, 19.13; S, 17.45

Example 6

5-Nitro-2-[2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino]-4(3H)-pyrimidone

A mixture containing 2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamine (4.85 g; 17.93 mmoles) and 2-methylthio-5-nitro-4-hydroxypyrimidine (3.30 g; 17.62 mmoles) in 15 ml of ethanol was heated at reflux temperature for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue chromatographed on 190 g of silica gel by flash chromatography

using a gradient elution of methanol-methylene chloride. The appropriate fractions gave 5.86 g of product which was recrystallized from tetrahydrofuran to give the title compound, mp 144-145°C with resolidification and remelting at 193-194°C.

The NMR spectrum (100 MHz) in d_6 dimethyl sulfoxide shows the presence of approximately 0.25 moles of tetrahydrofuran.

Anal. Calc'd for $C_{17}H_{25}N_5O_3S_2 \cdot 0.25C_4H_8O$:

C, 50.56; H, 5.89; N, 16.38; S, 15.00

Found:

C, 50.80; H, 6.07; N, 15.91; S, 14.68

Example 7

2-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]-ethylamino}-5-nitro-4(3H)-pyrimidone

A mixture containing 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine (4.72 g; 22.0 mmoles) and 2-methylthio-5-nitro-4-hydroxypyrimidine (4.0 g; 21.37 mmoles) in 20 ml of ethanol was heated at reflux temperature for 18 hours. The reaction mixture was evaporated under reduced pressure, and the residue was recrystallized from 2-methoxyethanol to give 5.96 g of the title compound, mp 201-204°C.

Anal. Calc'd for $C_{14}H_{19}N_5O_4S$: C, 47.58; H, 5.42;

N, 19.82; S, 9.07

Found: C, 47.22; H, 5.36;

N, 19.76; S, 9.06

Example 8

5-Amino-2-{2-[(5-dimethylaminomethyl-3-thienyl)-methylthio]ethylamino}-4(3H)-pyrimidone

A mixture of 5-nitro-2-{2-[(5-dimethylamino-methyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone (1.3 g; 3.51 mmoles) and a catalytic amount of Raney nickel No. 28 (approximately 1.4 cm³) in 108 ml of methanol was hydrogenated in a Parr apparatus at 50 psi for 2.5 hours. The reaction mixture was filtered, treated with 1.55N methanolic hydrochloric acid (7.0 ml, 10.9 meq.) and then evaporated under reduced pressure. The residue was placed on 85 g of silica gel and chromatographed by flash chromatography using a gradient elution of methanol:CH₂Cl₂:H₂O from 20:80:1 to 30:70:1. The appropriate fractions were combined and treated with 7.0 ml of 1.55N methanolic HCl, and then evaporated under reduced pressure and dried under high vacuum at 56°C for 6 hours to give 0.41 g of the title compound as a trihydrochloride salt which had an indeterminate melting point. The NMR spectrum (100 MHz) in d₆ dimethyl sulfoxide gave the following resonances δ : 8.88 (m, 6H); 8.18 (m, 1H); 7.82 (s, 1H); 7.56 (s, 1H); 7.40 (s, 1H); 4.50 (s, 2H); 3.82 (s, 2H); 3.50 (m, 2H); 2.73 (m, 8H).

Anal. Calc'd for C₁₄H₂₁N₅OS₂·3.5 HCl:

C, 36.00; H, 5.29; N, 14.99; S, 13.73; Cl, 26.57

Found:

C, 36.12; H, 4.77; N, 14.57; S, 13.90; Cl, 25.16

Example 9

5-Amino-2-{2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone

A mixture of 5-nitro-2-{2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone (5.32 g; 12.96 mmoles) and a catalytic amount of Raney nickel No. 28 (approximately 3.5 cm³) in 300 ml of methanol was hydrogenated in a Parr apparatus at 50 psi for 3.0 hours. The reaction mixture was filtered, treated with 1.55N methanolic HCl (24.0 ml; 37.2 meq.) and evaporated under reduced pressure. The residue was placed on 180 g of silica gel and chromatographed by flash chromatography using a gradient elution of methanol-methylene chloride. The appropriate fractions were combined, evaporated and then rechromatographed using a gradient elution of CH₃CN:CH₃OH:CH₂Cl₂ from 7:14:86 to 8:18:80. The appropriate fractions were combined and treated with 20 ml of 1.55N methanolic HCl, and then evaporated under reduced pressure and dried under high vacuum at 56°C to give 2.35 g of the title compound as a trihydrochloride, mp 150-155°C.

Anal. Calc'd for C₁₇H₂₅N₅OS₂·3.25HCl·0.1CH₄O:

C, 40.97; H, 5.76; N, 13.97; S, 12.79; Cl, 22.98

Found (corr. for 1.94% H₂O):

C, 40.77; H, 5.92; N, 14.29; S, 12.52; Cl, 22.80

Example 10

5-Amino-2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4(3H)-pyrimidone

To a solution of 2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-5-nitro-4(3H)-pyrimidone (4.26 g; 12.05 mmoles) in 50 ml of 2-methoxyethanol containing 1.55N methanolic HCl (7.75 ml; 12.01 meq.) was added a catalytic amount of Raney nickel No. 28 (approximately 2.8 cm³), and the mixture was hydrogenated in a Parr apparatus at 50 psi for 1.25 hours. The reaction mixture was filtered, treated with 20 ml of 1.55N methanolic HCl and evaporated under reduced pressure. The residue was placed on 190 g of silica gel and chromatographed by flash chromatography using CH₃OH:CH₃CN:NH₄OH (20:80:1) as eluent. The appropriate fractions were combined and evaporated to dryness. The residue was dissolved in 25 ml (38.8 meq.) of 1.55N methanolic HCl, evaporated under reduced pressure and dried under high vacuum at 56°C to give 3.53 g of the title compound as a trihydrochloride, mp 127-132°C.

Anal. Calc'd for C₁₄H₂₁N₅O₂S·3HCl:

C, 38.85; H, 5.59; N, 16.18; S, 7.41; Cl, 24.58

Found:

C, 38.97; H, 5.59; N, 16.14; S, 7.72; Cl, 23.70

Example 11

5-Formamido-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone

To a suspension of 5-amino-2-[3-(3-piperidino-methylphenoxy)propylamino]-4(3H)-pyrimidone trihydrochloride (1.51 g; 3.23 mmoles) [prepared in Example 4] in 10 ml of acetonitrile and 2 ml of methanol was added 6 ml (43.0 mmoles) of triethylamine. The resulting solution was stirred at ambient temperature for 15 minutes and then evaporated under reduced pressure. The residue was dissolved in 10 ml of acetonitrile and treated with phenylformate (2.17 g; 16.0 mmoles). The reaction mixture was evaporated under reduced pressure and the residue was placed on 120 g of silica gel (230-400 mesh) and chromatographed by flash chromatography using a gradient elution of $\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2:\text{NH}_4\text{OH}$ from 5:95:0.4 to 10:90:0.7. The appropriate fractions were combined and evaporated to give 1.04 g of product. Recrystallization from absolute ethanol yielded the title compound, mp 173-174°C.

Anal. Calc'd for $\text{C}_{20}\text{H}_{27}\text{N}_5\text{O}_3$: C, 62.32; H, 7.06; N, 18.17
Found (corr. for 3.0% H_2O): C, 62.19; H, 6.93; N, 18.56

4 Example 12

The general procedure of Example 3 is repeated and the product thereof is treated by the general procedure of Example 4 except that the 3-(3-piperidino-methylphenoxy)propylamine utilized therein is replaced by an equimolar amount of:

- (a) 3-(3-dimethylaminomethylphenoxy)propylamine,
- (b) 3-(3-diethylaminomethylphenoxy)propylamine,
- (c) 3-(3-pyrrolidinomethylphenoxy)propylamine,
- (d) 3-[3-(2-methylpyrrolidino)methylphenoxy]propylamine,
- (e) 3-[3-(3-methylpyrrolidino)methylphenoxy]propylamine,
- (f) 3-[3-(4-methylpiperidino)methylphenoxy]propylamine,
- (g) 3-(3-morpholinomethylphenoxy)propylamine,
- (h) 3-[3-(N-methylpiperazino)methylphenoxy]propylamine,
- (i) 3-[3-(1,2,3,6-tetrahydro-1-pyridyl)methylphenoxy]-propylamine,
- (j) 3-(3-hexamethyleneiminomethylphenoxy)propylamine,
- (k) 3-(3-heptamethyleneiminomethylphenoxy)propylamine,
- (l) 3-[3-(3-azabicyclo[3.2.2]non-3-yl)methylphenoxy]-propylamine,
- (m) 2-[(5-piperidinomethyl-2-furyl)methylthio]ethylamine,
- (n) 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine,
- (o) 2-[(2-dimethylaminomethylthiazol-4-yl)methylthio]-ethylamine,
- (p) 2-[(5-dimethylaminomethyl-2-thienyl)methylthio]-ethylamine,
- (q) 2-[(5-pyrrolidinomethyl-3-thienyl)methylthio]-ethylamine,
- (r) 3-(5-dimethylaminomethyl-3-thienyloxy)propylamine,
- (s) 3-(5-piperidinomethyl-3-thienyloxy)propylamine,
- (t) 2-[(5-dimethylaminomethyl-4-methyl-2-thienyl)-methylthio]ethylamine,
- (u) 2-[(5-piperidinomethyl-4-methyl-2-thienyl)-methylthio]ethylamine,
- (v) 3-(3-piperidinomethylthiophenoxy)propylamine,
- (w) 2-[(6-dimethylaminomethyl-2-pyridyl)methylthio]-ethylamine,
- (x) 3-(6-piperidinomethyl-2-pyridyloxy)propylamine,
- (y) 3-(6-dimethylaminomethyl-2-pyridyloxy)propylamine,
- (z) 2-[(4-dimethylaminomethyl-2-pyridyl)methylthio]-ethylamine,

- (aa) 2-[(4-piperidinomethyl-2-pyridyl)methylthio]-ethylamine,
- (bb) 3-(4-dimethylaminomethyl-2-pyridyloxy)propylamine, and
- (cc) 3-(4-piperidinomethyl-2-pyridyloxy)propylamine,

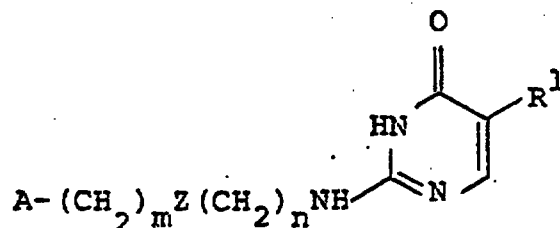
and there is thereby produced:

- (a) 5-amino-2-[3-(3-dimethylaminomethylphenoxy)-propylamino]-4(3H)-pyrimidone,
- (b) 5-amino-2-[3-(3-diethylaminomethylphenoxy)-propylamino]-4(3H)-pyrimidone,
- (c) 5-amino-2-[3-(3-pyrrolidinomethylphenoxy)-propylamino]-4(3H)-pyrimidone,
- (d) 5-amino-2-[3-[3-(2-methylpyrrolidino)methylphenoxy]-propylamino]-4(3H)-pyrimidone
- (e) 5-amino-2-[3-[3-(3-methylpyrrolidino)methylphenoxy]-propylamino]-4(3H)-pyrimidone,
- (f) 5-amino-2-[3-[3-(4-methylpiperidino)methylphenoxy]-propylamino]-4(3H)-pyrimidone,
- (g) 5-amino-2-[3-(3-morpholinomethylphenoxy)-propylamino]-4(3H)-pyrimidone,
- (h) 5-amino-2-[3-[3-(N-methylpiperazino)methylphenoxy]-propylamino]-4(3H)-pyrimidone,
- (i) 5-amino-2-[3-[3-(1,2,3,6-tetrahydro-1-pyridyl)-methylphenoxy]propylamino]-4(3H)-pyrimidone,
- (j) 5-amino-2-[3-(3-hexamethyleneiminomethylphenoxy)-propylamino]-4(3H)-pyrimidone,
- (k) 5-amino-2-[3-(3-heptamethyleneiminomethylphenoxy)-propylamino]-4(3H)-pyrimidone,
- (l) 5-amino-2-[3-[3-(3-azabicyclo[3.2.2]non-3-yl)-methylphenoxy]propylamino]-4(3H)-pyrimidone,
- (m) 5-amino-2-[2-[(5-piperidinomethyl-2-furyl)-methylthio]ethylamino]-4(3H)-pyrimidone,
- (n) 5-amino-2-[2-[(2-guanidinothiazol-4-yl)methylthio]-ethylamino]-4(3H)-pyrimidone,

- (o) 5-amino-2-{2-[(2-dimethylaminomethylthiazol-4-yl)-methylthio]ethylamino}-4(3H)-pyrimidone,
- (p) 5-amino-2-{2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamino}-4(3H)-pyrimidone,
- (q) 5-amino-2-{2-[(5-pyrrolidinomethyl-3-thienyl)-methylthio]ethylamino}-4(3H)-pyrimidone,
- (r) 5-amino-2-[3-(5-dimethylaminomethyl-3-thienyloxy)-propylamino]-4(3H)-pyrimidone,
- (s) 5-amino-2-[3-(5-piperidinomethyl-3-thienyloxy)-propylamino]-4(3H)-pyrimidone,
- (t) 5-amino-2-{2-[(5-dimethylaminomethyl-4-methyl-2-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone,
- (u) 5-amino-2-{2-[(5-piperidinomethyl-4-methyl-2-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone,
- (v) 5-amino-2-[3-(3-piperidinomethylthiophenoxy)-propylamino]-4(3H)-pyrimidone,
- (w) 5-amino-2-{2-[(6-dimethylaminomethyl-2-pyridyl)-methylthio]ethylamino}-4(3H)-pyrimidone,
- (x) 5-amino-2-[3-(6-piperidinomethyl-2-pyridyloxy)-propylamino]-4(3H)-pyrimidone,
- (y) 5-amino-2-[3-(6-dimethylaminomethyl-2-pyridyloxy)-propylamino]-4(3H)-pyrimidone,
- (z) 5-amino-2-{2-[(4-dimethylaminomethyl-2-pyridyl)-methylthio]ethylamino}-4(3H)-pyrimidone,
- (aa) 5-amino-2-{2-[(4-piperidinomethyl-2-pyridyl)-methylthio]ethylamino}-4(3H)-pyrimidone,
- (bb) 5-amino-2-[3-(4-dimethylaminomethyl-2-pyridyloxy)-propylamino]-4(3H)-pyrimidone,
and
- (cc) 5-amino-2-[3-(4-piperidinomethyl-2-pyridyloxy)-propylamino]-4(3H)-pyrimidone.

Claims

1. A compound of the formula:



wherein m is an integer of from zero to 2, inclusive;

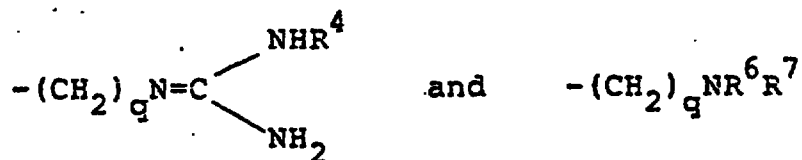
n is an integer of from 2 to 5 inclusive;

Z is sulfur, oxygen or methylene;

$$R^1 \text{ is } NO_2 \text{ or } NR^2R^3;$$

R² and R³ each are independently hydrogen or (lower)alkyl, or, when R² is hydrogen, R³ also may be formyl, carboalkoxy, alkanoyl or benzoyl;

A is phenyl, furyl, thienyl, pyridyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, pyrimidinyl, pyrazolyl, prridaziny1 or pyraziny1; provided that A contains one or two substituents, the first substituent being selected from



and the second substituent being selected from (lower)-alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive;



R^4 is a hydrogen atom, a (lower)alkyl group optionally substituted by one or more halogen atoms, provided that there is no halogen atom on the carbon atom attached to the nitrogen atom, or a cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, (lower)alkanoyl or benzoyl group;

R^6 and R^7 each are independently hydrogen, (lower)-alkyl, (lower)alkenyl, (lower)alkynyl, phenyl(lower)alkyl or (lower)alkoxy(lower)alkyl in which the (lower)alkoxy moiety is at least two carbon atoms removed from the nitrogen atom, or R^6 and R^7 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, homopiperidino, heptamethyleneimino, octamethyleneimino, 3-azabicyclo[3.2.2]non-3-yl or 1,2,3,6-tetrahydro-1-pyridyl;



provided that, if R^1 is NO_2 or NH_2 , then
 $\text{A}-(\text{CH}_2)_m\text{Z}(\text{CH}_2)_n\text{NH}$ is not 3-(3-piperidinomethylphenoxy)
propylamino; or a nontoxic pharmaceutically
acceptable acid addition salt thereof.



* C L M S *

2. A compound of Claim 1 wherein R^1 is NO_2 , NH_2 , $NHCO_2C_2H_5$, or $NHCHO$; substituent A is piperidinomethylphenyl, dimethylaminomethylthienyl, piperidinomethylthienyl, or dimethylaminomethylfuryl; substituent R^4 is hydrogen, (lower)alkyl or 2,2,2-trifluoroethyl substituent Z is sulfur or oxygen; m is zero or 1; and n is 2 or 3.

3. 5-carbethoxy-amino-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone and nontoxic pharmaceutically acceptable acid addition salts thereof.





4. 5-amino-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone monohydrochloride.

5. 5-amino-2-[3-(3-piperidinomethylphenoxy)propylamino]-4(3H)-pyrimidone trihydrochloride.

6. 5-nitro-2-{2-[(5-dimethylaminomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone and nontoxic pharmaceutically acceptable acid addition salts thereof.

7. 5-nitro-2-{2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone and nontoxic pharmaceutically acceptable acid addition salts thereof.

8. 2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-5-nitro-4(3H)-pyrimidone and nontoxic pharmaceutically acceptable acid addition salts thereof.

9. 5-amino-2-{2-[(5-dimethylaminomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone and nontoxic pharmaceutically acceptable acid addition salts thereof.

10. 5-amino-2-{2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino}-4(3H)-pyrimidone and nontoxic pharmaceutically acceptable acid addition salts thereof.

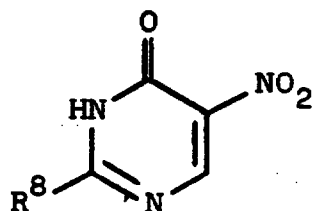
11. 5-amino-2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4(3H)-pyrimidone and nontoxic pharmaceutically acceptable acid addition salts thereof.

12.

5-

formamido-2-[3-(3-piperidinomethylphenoxy)propyl-
amino]-4(3H)-pyrimidone and nontoxic pharmaceutically
acceptable acid addition salts thereof.

- 5 13. A process for the preparation of compounds
of the Formula I, or nontoxic pharmaceutically
acceptable acid addition salts thereof, comprising
reacting, preferably at reflux temperature, a
compound of the formula $A-(CH_2)_mZ(CH_2)_nNH_2$, where
10 A, m, Z and n are as defined in claim 1, with a
compound of the formula



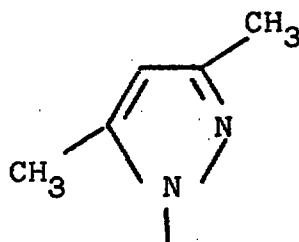
- wherein R^8 is a leaving group, preferably fluoro,
chloro, bromo, iodo, alkylthio, nitroamino, phenoxy,
15 substituted phenoxy or alkoxy, in the presence of
a reaction-inert solvent, preferably methanol or
ethanol, to produce said compound of the Formula I
wherein R^1 is nitro, and, when a compound of the
Formula I wherein R^1 is NR^2R^3 in which R^2 and R^3 are
20 hydrogen is desired, subjecting said compound of
Formula I wherein R^1 is nitro to reduction,
preferably with hydrogen gas and in the presence
of Raney nickel; and, when a compound of said
Formula I wherein R^1 is NR^2R^3 in which R^2 is
25 hydrogen and R^3 is formyl is desired, reacting said
compound of Formula I wherein R^1 is NR^2R^3 in which
 R^2 and R^3 are hydrogen with phenyl formate; and,
if said acid addition salt is desired, preparing
same by methods known per se.



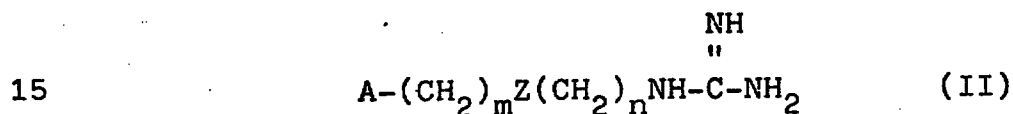
14. A process for producing compounds of the Formula I, as claimed in claim 1, or nontoxic pharmaceutically acceptable acid addition salts thereof, comprising reacting, in a reaction-inert solvent, preferably methanol or ethanol, and preferably at reflux temperature, a compound of the formula $A-(CH_2)_mZ(CH_2)_nNH_2$, wherein A, m, Z and n are as defined in claim 1, with a compound of the formula



wherein R^9 is thioalkoxy or a radical of the formula

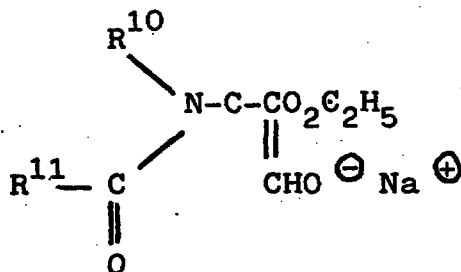


to produce a compound of the Formula II

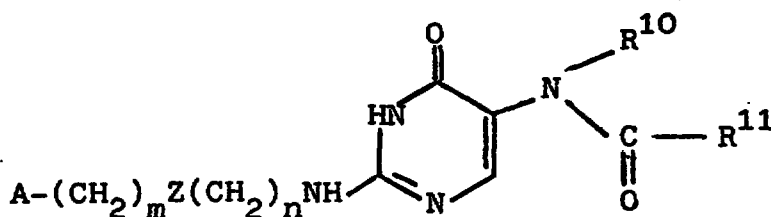


- wherein A, m, Z and n are as previously defined, reacting the compound of Formula II in a reaction-inert solvent, preferably at a temperature of from room temperature to reflux temperature of the solvent, with a compound of the formula
- 20





5 wherein R^{10} is hydrogen or lower alkyl and R^{11} is lower alkyl, aryl, alkoxy or aryloxy, preferably R^{10} being hydrogen and R^{11} being ethoxy, to produce a compound of the Formula III

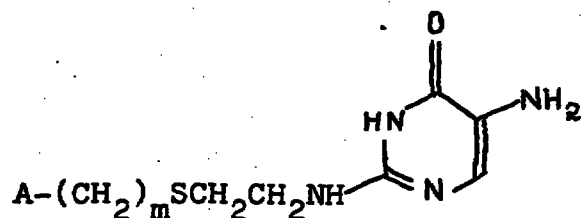


10 wherein A, m, Z, n, R^{10} and R^{11} are as previously defined; and optionally hydrolyzing said compound of Formula III to produce said compound of Formula I wherein R^1 is NR^2R^3 in which R^2 is hydrogen and R^3 is equivalent to R^{10} ; and, if said acid addition salt is desired, preparing same by methods known per se.

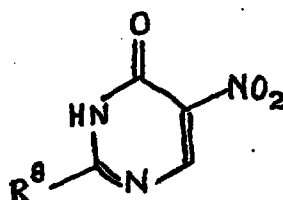


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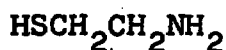
15. A process for producing a compound of the formula Id:-



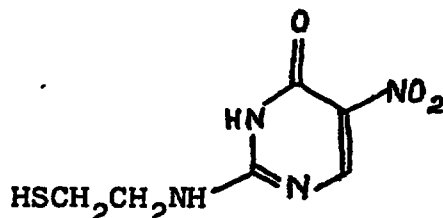
5 wherein A and m are as defined in claim 1, comprising reacting, preferably in an inert solvent and at room temperature to the reflux temperature of the solvent, a compound of the formula:-



10 wherein R⁸ is a leaving group, preferably fluoro, chloro, bromo, iodo, alkylthio, nitroamino, phenoxy, substituted phenoxy or alkoxy, with



15 to produce a compound of the formula IV :-



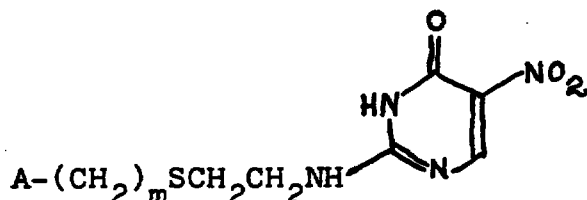
reacting the compound of the formula IV with a compound of the formula





- wherein X is hydroxy or a leaving group, the leaving group preferably being selected from the group consisting of fluoro, chloro, bromo, iodo, $-O_3SR^{12}$ wherein R^{12} is (lower)alkyl (e.g. methylsulfonate), $-O_3SR^{13}$ wherein R^{13} is aryl or substituted aryl (e.g. benzenesulfonate, p-bromobenzenesulfonate or p-toluenesulfonate), $-O_3SF$, acetoxy and 2,4-dinitrophenoxy, to produce a compound of the formula Ic :-

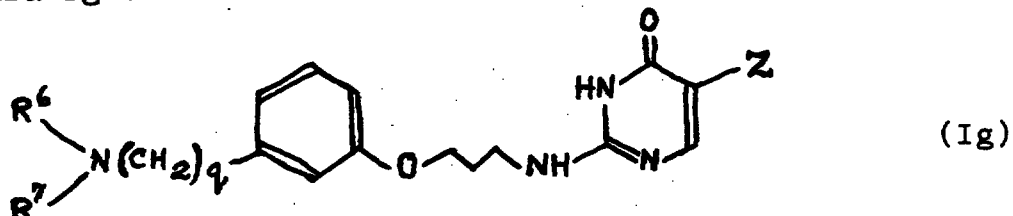
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wherein A and m are as previously defined, and reducing the compound of formula Ic;

- 15 with the proviso that, when X is hydroxy and m is 1, the reaction with $A-(CH_2)_mX$ is carried out in an acidic medium; whereby a compound of the formula Id wherein A and m are as previously defined is produced.

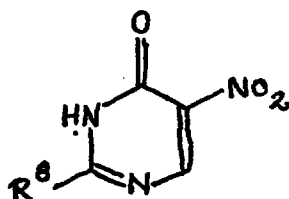
- 20 16. A process for producing a compound of the formula Ig :-



- wherein R^6 , R^7 and q are as defined in claim 1 and Z is NO_2 or NH_2 , comprising reacting, preferably in an inert solvent and at room temperature to the reflux temperature of the

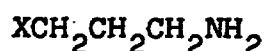


solvent, a compound of the formula



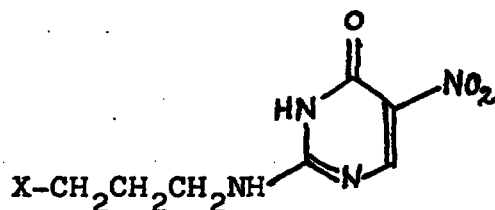
wherein R^8 is a leaving group, with a compound of the formula

5



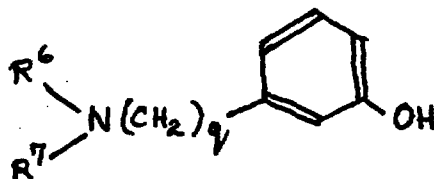
wherein X is hydroxy or a leaving group, the leaving group preferably being selected from the group consisting of fluoro, chloro, bromo, iodo, $-O_3SR^{12}$ wherein R^{12} is (lower)alkyl (e.g. methylsulfonate), $-O_3SR^{13}$ wherein R^{13} is aryl or substituted aryl (e.g. benzenesulfonate, p-bromobenzenesulfonate or p-toluenesulfonate), $-O_3SF$, acetoxy and 2,4-dinitrophenoxy, to produce a compound of the formula V

15



wherein X is as previously defined;
and, when X is other than hydroxy, reacting, preferably in an inert solvent at from room temperature to the reflux temperature of the solvent and in the presence of about one equivalent of base, more preferably in the presence of a phase transfer catalyst, the compound of the formula V with a compound of the formula VI :-





- wherein R^6 , R^7 and q are as defined in claim 1, to produce a compound of the formula Ig wherein Z is NO_2 ; and, when the compound of the formula Ig wherein Z is NH_2 is desired, subjecting the compound of the formula Ig wherein Z is NO_2 to reduction; with the proviso that, when, in compound V, X is hydroxy, the compound of formula V is reacted, prior to reaction with the compound of formula VI, with an activating agent, preferably thionyl chloride or toluene sulfonic acid, to convert such hydroxy group to a leaving group.
17. A process for preparing a compound according to any of claims 1 to 12, substantially as described in any of the foregoing Examples affording a compound as claimed in any of claims 1 to 12.
18. A compound according to any of claims 1 to 12 prepared by a process as claimed in claim 13, 14, 15, 16 or 17.
19. A pharmaceutical composition comprising a compound (or pharmaceutically acceptable salt) according to any of claims 1 to 12, or claim 18, and a pharmaceutically acceptable carrier.

