

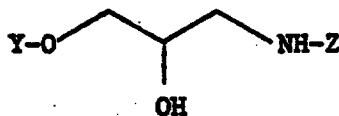
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1-PYRIMIDINYLOXY-3-HETARYLALKYLAMINO-2-PROPANOLS,
PREPARATION, AND USES

The present invention is concerned with heterocyclic carbon compounds of the pyrimidine series and with drug
5 bio-affecting and body-treating processes employing these compounds.

A considerable body of prior art exists encompassing compounds of 3-(aryloxy)-2-hydroxypropylamine series which possess beta-adrenergic receptor blocking activity and/or vasodilating properties and are useful in treatment of cardiovascular diseases. Such compounds
10 can be structurally typified by propranolol, chemically, 1-isopropyl-amino-3-(1-naphthoxy)-2-propanol. Propranolol and some related naphthoxypropanolamines are the subject of U.S. Patent No. 3,337,628 issued August 22, 1967. Numerous subsequent patents have been granted covering carbocyclic ethers in which other aromatic rings or hetero-
15 cyclic systems replace the naphthoxy group of propranolol. Numerous variations have also been disclosed for the amino substituent of the

propanolamine moiety. Reference patents, which are mentioned herein-
below, generally disclose cardiovascular agents possessing the
following generic structure (1):



(1)

wherein Y is aryl or hetaryl, unsubstituted or substituted; and Z is
5 alkyl, alkylphenyl, or alkylhetaryl.

Matier, et al., in U.S. Patent No. 4,321,398 issued March 23,
1982, discloses compounds wherein Y is substituted phenyl and Z is an
alkylthienyl or alkylbenzothienyl moiety.

Attention is also called to the application Serial No.
10 414,748 of Kreighbaum, filed September 3, 1982, which discloses
compounds wherein Y is a substituted pyridine system and Z is an
alkylindolyl moiety.

Frei, et al., South African Patent Application No. 741070,
convention filing date of February 20, 1973, discloses compounds
15 wherein Y is a pyrimidine ring system, either unsubstituted or
substituted with a group selected from a long list of possible
substituents. Z for this series of compounds can be alkyl or alkyl-
phenyl. No hydrazine or hydrazone substituents on the pyrimidine
ring are disclosed in this case.

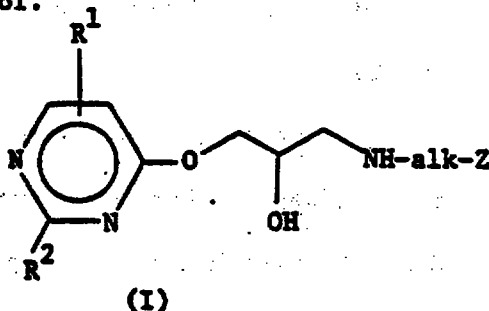
20 Jaeggi, et al., U.S. Patent No. 4,139,623 issued February 13,
1979, also discloses compounds wherein Y is a substituted pyrimidine
ring but Z is alkoxyphenyl or alkoxypyrimidine.

Wasson, et al., disclosed subject matter in divisional patents, U.S. 5,042,586 issued August 16, 1977, and U.S. 4,193,995 issued March 18, 1980, relating to compounds in which Z was alkyl, alkylphenyl, or alkylindolyl but Y was a pyrazine ring system.

5 Similarly, Dorigotti, et al., U.S. Patent No. 4,324,788 issued April 13, 1982, disclosed compounds wherein Z is alkyl, cyclo-alkyl, or alkylphenyl but Y is a hydrazone-substituted pyridazine ring system.

These reference patents can be distinguished from the
10 instant invention in view of one or more of the following distinguishing characteristics. Compounds of the instant invention (1) are comprised of a propoxy-pyrimidine ring structural component, (2) the pyrimidine ring is substituted in the 2- position with a hydrazino or hydrazone moiety, and (3) Z can be alkylthienyl, alkyl-
15 benzothienyl, alkylbenzofuranyl, or alkylbenzimidazolyl in addition to alkylindolyl, alkylphenyl, and alkyl.

This invention concerns a series of cardiovascular agents having vasodilating and beta-adrenergic blocking activities which make them useful as antihypertensive agents. The invention comprises
20 compounds of general formula I and the pharmaceutically acceptable acid addition salts thereof.



In the foregoing structural formula, R^1 can be C_{1-6} alkyl, amino, acylamino, cyano, halogen, or hydrogen; R^2 can be

hydrazino or hydrazono;

alk is C_{1-6} alkylene,

either straight chain or branched; and Z is selected from the group

5 consisting of hydrogen, phenyl, indolyl, thienyl, benzothienyl, benzo-furanyl, and benzimidazolyl.

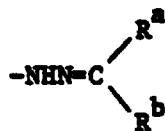
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The invention includes compounds having the foregoing structural Formula I and the acid addition salts thereof. In Formula I, R^1 can be alkyl containing from 1 to 6 carbon atoms, either straight chain or branched, amino, C_{1-4} acylamino, cyano, halogen or hydrogen.

15 In preferred compounds, R^1 is hydrogen, C_{1-4} alkyl, and halogen, especially bromo. R^2 can be

hydrazino or hydrazono.

Hydrazono substituents have the general structure



with R^a and R^b being either the same or different and representing

20 C_{1-3} alkyl or phenyl moieties. In Formula I, alk is an alkylene group containing 1-6 carbon atoms, either straight chain or branched, and is preferably t-butylene. Z is selected from the group consisting of

hydrogen, phenyl, indole, thienyl, benzothienyl, benzofuranyl, and benzimidazolyl. For preferred compounds, Z is phenyl, indolyl, thienyl, or benzothienyl.

5

For medicinal use, the pharmaceutically acceptable acid addition salts (i.e., those salts in which the anion does not contribute significantly to toxicity or pharmacological activity of the organic cation) are preferred. The acid addition salts are obtained either by reaction of an organic base of structure I with an organic or inorganic acid, preferably by contact in solution, or by any of the standard methods detailed in the literature and available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acid, pantoic acid, cyclamic acid, pivalic acid, and the like; useful inorganic acids are hydrohalide acids such as HCl, HBr, HI; sulfuric acid; phosphoric acid; and the like.

It is also to be understood that all the compounds of the present invention embrace all the optical isomer forms, that is, mixtures of enantiomers, e.g., racemic modifications as well as the individual enantiomers and diastereomers. The individual optical isomers of the propanolamine class of compounds of which the instant compounds are members, have most generally been obtained by one of

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four basic methods. These are: 1) the fractional recrystallization of chiral acid salt derivatives; 2) derivatization with a chiral organic reagent, resolution and regeneration of the original compound in optically active form; 3) synthesis of the single optical isomer
5 using chiral intermediates; and 4) column chromatography utilizing chiral stationary phases. The application of these various methods are well known to practitioners in the art.

Biological testing of the subject compounds of Formula I in animals demonstrates that they possess potent vasodilating properties
10 along with varying degrees of adrenergic beta-receptor blocking properties and intrinsic sympathomimetic activity. Preferred members have a particularly desirable combination in the foregoing actions, and ancillary pharmacological effects, or lack thereof, which particularly suits them for specific cardiovascular indications, e.g. use
15 as antihypertensives. The utility of the compounds of Formula I can be demonstrated in various animal models including antagonism of isoproterenol in the anesthetized dog treated intravenously (adrenergic beta-receptor action), the spontaneous hypertensive and DOCA salt hypertensive rat (antihypertensive action), angiotensin-maintained
20 ganglion-blocked rat model (vasodilator action) and in various other animal and laboratory models (cf: Deitchman, et al., Journal Pharmacological Methods, 3, 311-321 (1980)).

For use as antihypertensives, vasodilators, and/or beta-adrenergic blocking agents, therapeutic processes of this invention
25 comprise systemic administration, by both oral and parenteral routes, of an effective, non-toxic amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof. An effective

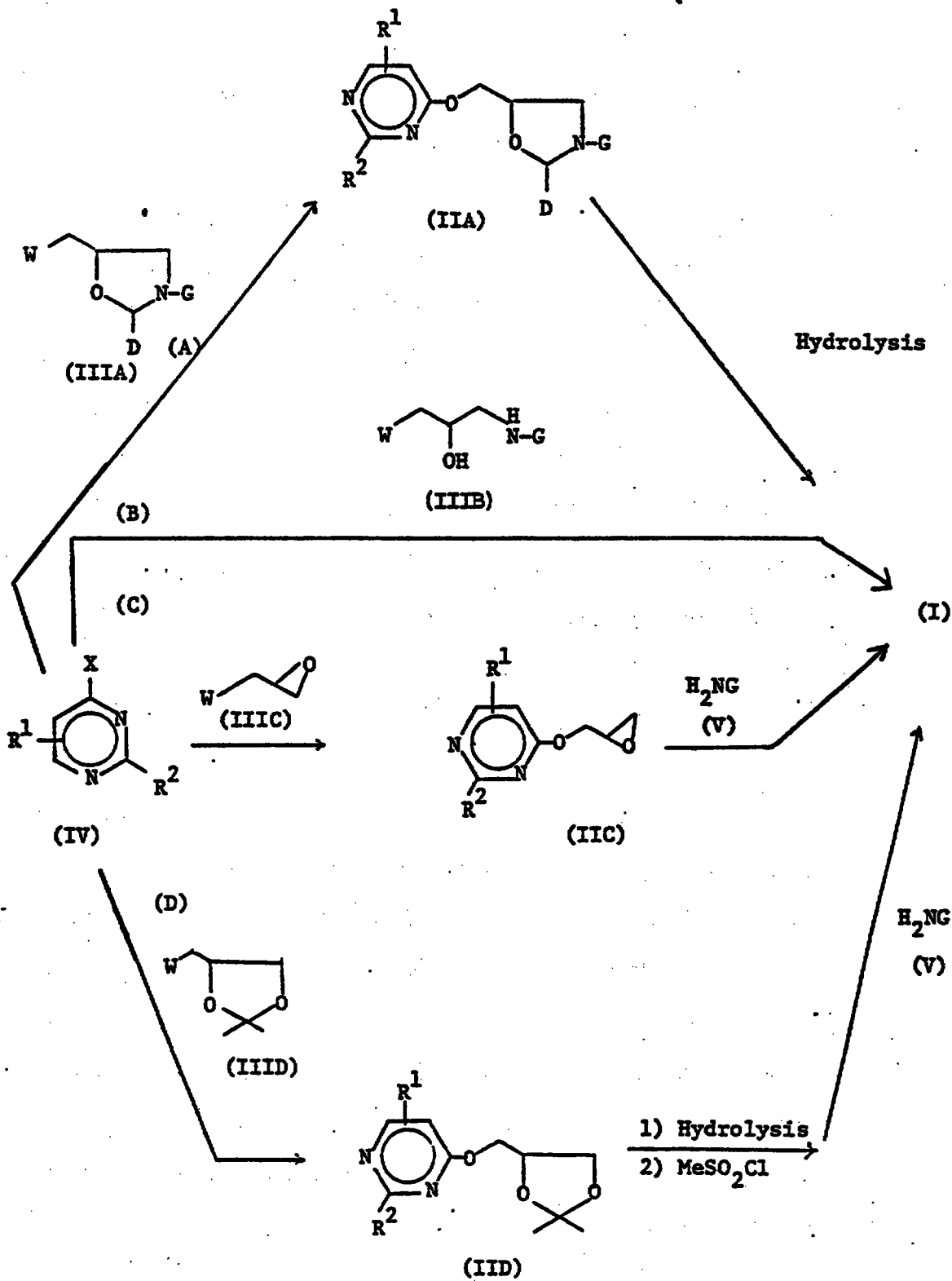
amount is construed to mean a dose which exerts the desired pharmacological activity, such as those stated hereinabove, without undue toxic side effects when administered to a mammal in need of such treatment. Dosage will vary, according to the subject and route of administration selected, with an expected range of about 0.1 mcg to 100 mg/kg body weight for a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof generally providing the desired therapeutic effect.

The basic structure (I) for compounds of the present invention can be assembled by a convenient general process. This process involves the coupling of a X-substituted pyrimidine (IV) with a suitable W-substituted propanol or incipient propanol intermediate (III) followed by hydrolysis and/or aminolysis, if required, with the substituted amino component of the Formula I compound.

Throughout this application, Me stands for a methyl group.

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General Process





In this general process, as illustrated above, D is H or preferably phenyl; G is the radical $[-alk-Z]$; X is hydroxyl or halogen, preferably chloride; W is halogen, preferably chloride, when X is hydroxyl and is hydroxyl when X is halogen. Generally, the hydroxyl-bearing reactant is initially converted to the oxide anion with a strong base prior to reaction with the halogen-bearing intermediate.

This process employs methods known in the prior art for the preparation of 1-(substituted amino)-3-hetaryloxy)-2-propanols as disclosed in the patents and publications cited in "Background of the Invention" section of this disclosure. Basically, the process involves reaction of the appropriately substituted pyrimidine with either: (A) a 3-(G-substituted oxazolidin-5-yl)methanol (or methyl halide) to give IIA, followed by hydrolysis; or (B) a G-substituted aminopropanediol (or halopropanol) of Formula IIIB; or (C) glycidol to give IIC, followed by amination with H_2NG ; or (D) the cyclic ketal to give IID, followed by hydrolysis, activation of the terminal hydroxy, and aminolysis of H_2NG . Method B is preferred in the above process. The hydrolysis steps in the above general process are usually accomplished with dilute mineral acid of from 0.1N to 1N concentration at temperatures of from about 20-100°C. The amination reactions of the general process can be carried out simply by heating an amine of the Formula H_2NG with an epoxy ether (IIC) or a propanediol (from IID) either neat or in the presence of a reaction inert organic solvent. No catalyst or condensation agent is required. Suitable reaction temperatures are from about 60-200°C.

The route "(A)" in the foregoing "General Process" scheme may be performed by reacting the chloropyrimidine (IV) with the potassium salt of 3-(1,1-dimethylethyl)-2-phenyl-5-oxazolidinemethanol (IIIA) followed by acidic hydrolysis of IIA to provide the corresponding structure I product.



To perform route "(B)", chloropropanediol may be treated with an appropriate amine (V) in ethanol, and the anion of the resulting aminopropanediol (IIIB), prepared using a strong base such as sodium hydride or potassium t-butoxide, may be allowed to react with an appropriate chloro pyrimidine to afford a product of structure I.



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In the case of route "(C)", a substituted 4-hydroxy-pyrimidine may be alkylated with epichlorohydrin (IIIC) and the resulting epoxy intermediate(IIC) aminated with the appropriate amine (V) to provide the product of structural Formula I.

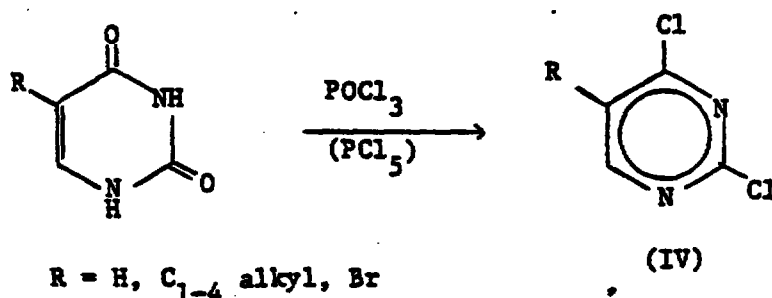


In route "(D)", the anion of the cyclic ketal (IIID) undergoes coupling with a chloropyrimidine (IV). Acid hydrolysis of the pyrimidinyloxy ketal (IID) provides the corresponding pyrimidinyloxypropanediol. Following activation of the terminal hydroxy group, amination with V gives the structure I product.

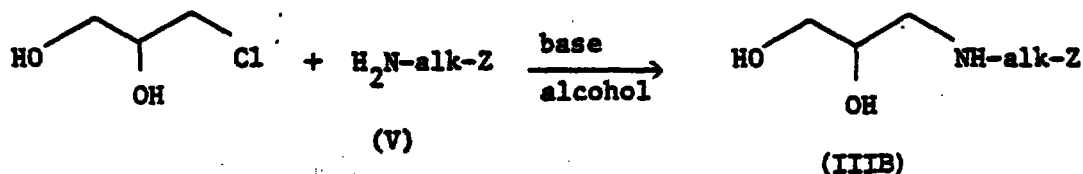


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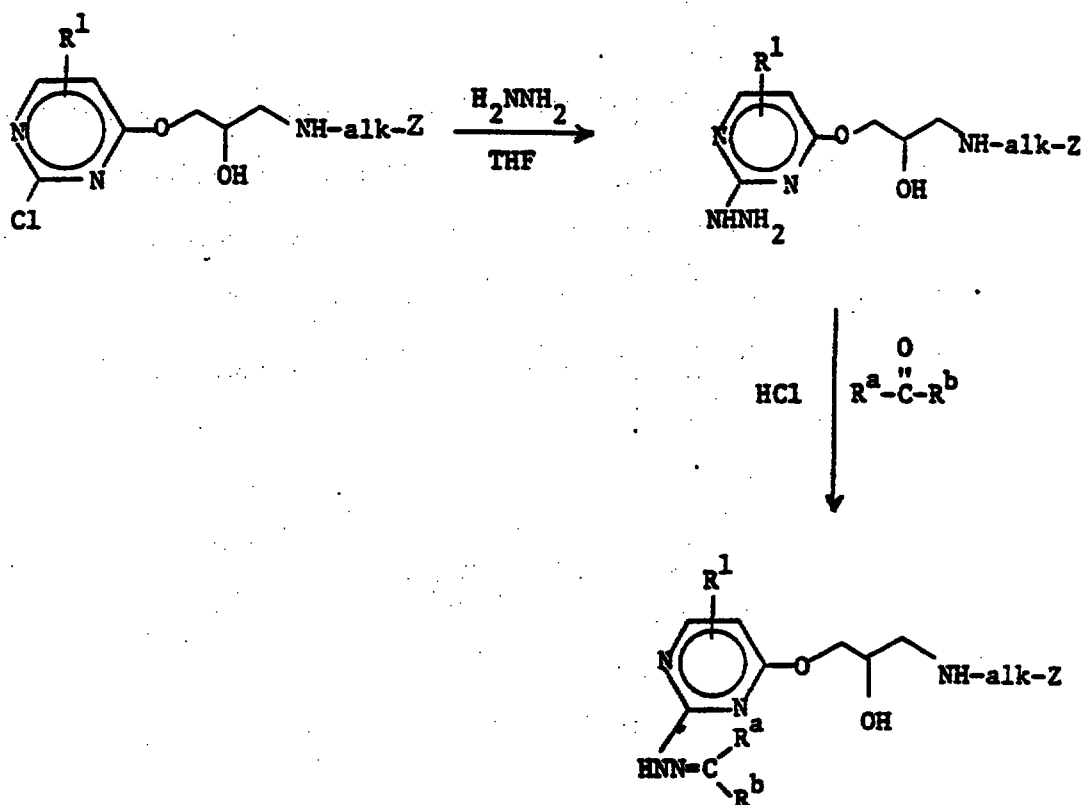
The chemical intermediates utilized in the above syntheses are available commercially or may be prepared using standard methods for their preparation as reported in the literature. For example, uracils can be chlorinated conveniently (cf: Mulvey, et al., J. Heterocycl. Chem., 10, 79 (1973); Koppel, et al., J. Org. Chem., 27, 181 (1962) as shown.



The intermediate heterocyclic alkylaminopropanols (IIIB) which are utilized in the preferred synthetic pathway B are conveniently prepared by reacting an appropriately substituted heterocyclic alkylamine with 3-chloro-1,2-propanediol in refluxing alcohol containing sodium carbonate. This process is illustrated by the reaction shown below which is essentially the first step of pathway B. In this reaction scheme, alk and Z are as defined in Formula I.

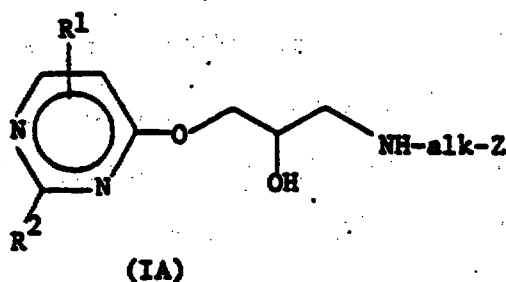


The hydrazino and hydrazone containing compounds of the invention are obtainable from analogous compounds containing a chloro substituent on the pyrimidine ring moiety. These conversions are illustrated in the following scheme.



The present invention includes the preparation of compounds
 5 of Formula IA (specified below)
 by the following processes. Steps a - d in the following discussion cor-
 respond to the pathways A - D discussed hereinbefore.

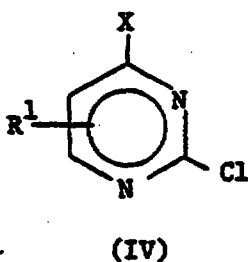
For preparation of a compound of Formula IA



(83)

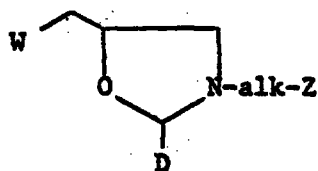
wherein R^1 is hydrogen, C_{1-6} alkyl, amino, C_{1-4} acylamino, cyano or halogen; R^2 is $-NHNH_2$ or $-NHN=C \begin{smallmatrix} R^a \\ R^b \end{smallmatrix}$ with R^a and R^b being the same or different and representing C_{1-3} alkyl or phenyl; alk is C_{1-6} alkylene, either straight chain or branched; and Z is selected from the group consisting of hydrogen, phenyl, indole, thiophene, benzo-
 5 thiophene, benzofuran, and benzimidazole; the process comprises initial use of one of the following variations (1a-d) beginning with a chloropyrimidine compound of structure IV, $R^2=Cl$ and ending with an intermediate of structure I except that R^2 is Cl. The four
 10 method variations shown as a-d below represent optional synthetic pathways which may be selected for the initial step of the process. The process is completed either by introduction of the hydrazine group in Step 2, if the hydrazine product is desired, or with hydrazone formation (Step 3), if a hydrazone product is desired. The total
 15 process comprises (with steps a-d corresponding to A-D described above):

1. Reacting a 2-chloropyrimidine compound of structure IV,



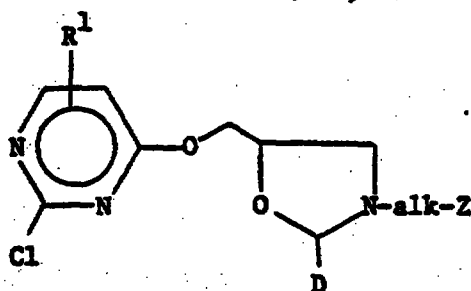
wherein R^1 is hydrogen, C_{1-6} alkyl, amino, C_{1-4} acylamino, cyano, or halogen; and X is hydroxyl or halogen;

a) with an oxazolidine of structure IIIA,



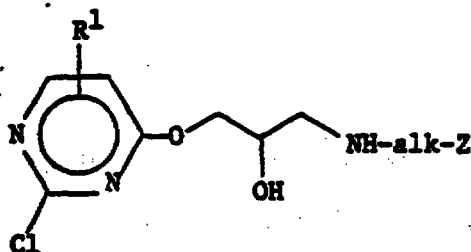
(IIIA)

wherein D is hydrogen or preferably phenyl; -alk and Z are the same as defined hereinabove; and W is halogen, preferably chloride, when X is hydroxyl and W is hydroxyl when X is halogen; to give the intermediate compound of structure IIA,



(IIA)

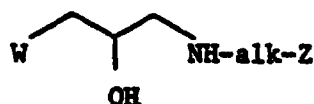
with R^1 , D, alk, and Z corresponding to IIIA as defined above. Hydrolysis of IIA gives the intermediate



which is an analog of a compound I but has $R^2 = Cl$, this being an intermediate

to be used in Step 2.

- b) with an aminopropanediol (or halopropanol) of structure IIIB,



(IIIB)

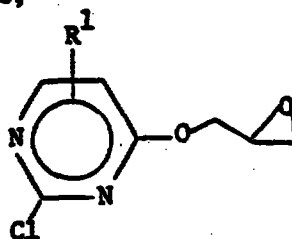
wherein W, alk, and Z are as defined above, (this pathway yielding the "R² = Cl" intermediate directly); or

- c) with glycidol (IIIC),



(IIIC)

with W as defined above to give the intermediate compound IIC,



(IIC)

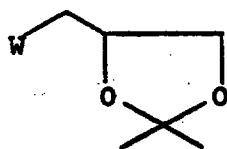
with R¹ as defined above, (amination of IIC with V,



(V)

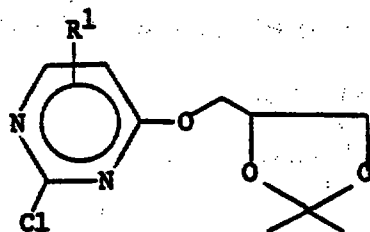
wherein alk and Z are as defined above, yielding the "R² = Cl" intermediate; or

d) with solketal (IIID) .



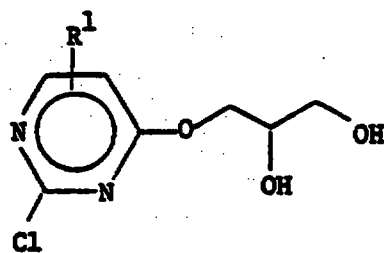
(IIID)

wherein W is as defined above, to give IID,



(IID)

wherein R¹ is as defined above, followed by hydrolysis to give the pyrimidinylxypropanediol compound VI,

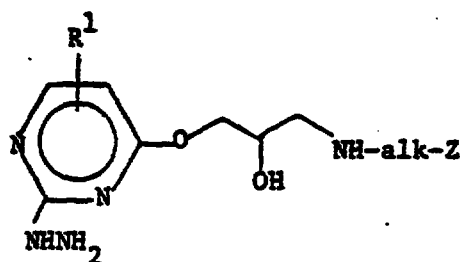


(VI)

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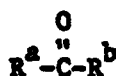
with R¹ as defined above. Treatment of VI with methanesulfonyl chloride to activate the terminal hydroxy group allows ready amination with V to give the "R² = Cl" intermediate.

2. The intermediate compound prepared in Step 1 is treated with hydrazine to give the 2-hydrazino analog of structure I



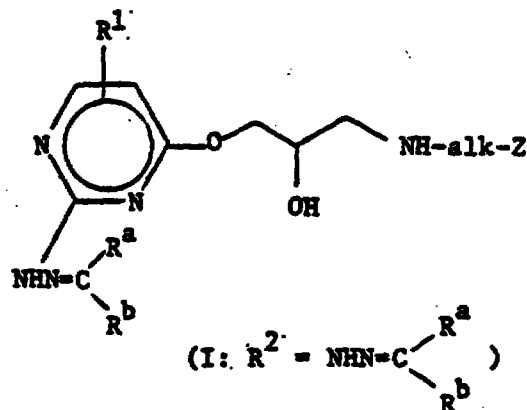
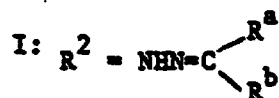
(I: $R^2 = \text{NHNH}_2$)

3. If the desired end product is a hydrazone derivative, then the hydrazine derivative obtained in Step 2 is treated with an appropriate carbonyl compound VII



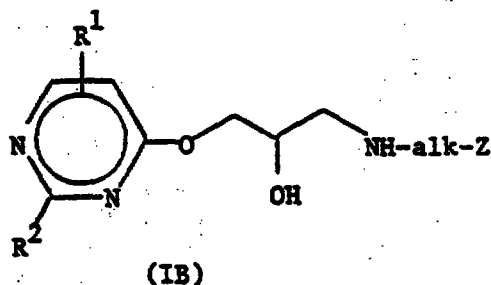
(VII)

with R^a and R^b the same as defined hereinabove, under acidic conditions to obtain the product of structure



(I: $R^2 = \text{NHN}=\text{C} \begin{matrix} \nearrow R^a \\ \searrow R^b \end{matrix}$)

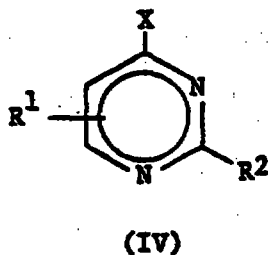
More generally, for the preparation of intermediates which are analogs of the compounds of Formula I but have values of R^2 other than hydrazino and hydrazono, these analogs being compounds of Formula IB



wherein R^1 is hydrogen, C_{1-6} alkyl, amino, C_{1-4} acylamino, cyano, or halogen; R^2 is hydrogen, amino, C_{1-4} acylamino, cyano, halogen, or phenyl;
 5 alk is C_{1-6} alkylene, either straight chain or branched; and Z is selected from the group consisting of indole, thiophene, benzothiophene, benzofuran, and benzimidazole; a procedure may be selected comprising one of the following variations (a-d) (corresponding to A-D above).

The IB synthetic process comprises:

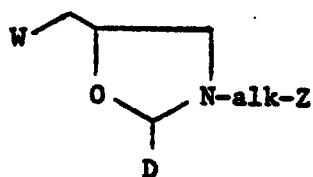
10 Reacting a pyrimidine starting material of structure IV,



wherein R^1 and R^2 are the same as defined above for IB; and X is hydroxyl or halogen;

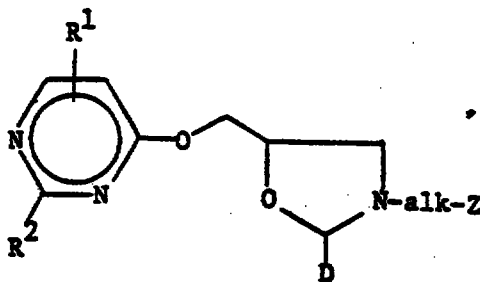
a) with an oxazolidine of structure IIIA,

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(IIIA)

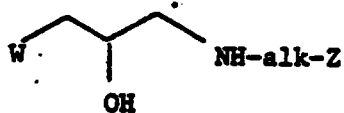
wherein D is hydrogen or preferably phenyl; alk and Z are the same as defined above for IB; and W is halogen, preferably chloride, when X is hydroxyl and W is hydroxyl when X is halogen; to give the intermediate compound of structure IIA,



(IIA)

with R¹, R², D, alk, and Z the same as defined hereinabove, (hydrolysis of IIA giving the analog IB); or

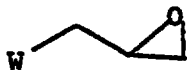
b) with an aminopropanediol (or halopropanolamine) of Formula IIIB,



(IIIB)

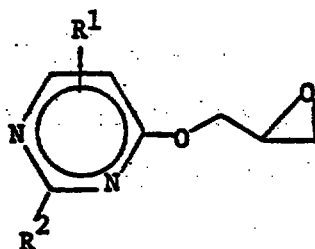
wherein W, alk, and Z are as defined hereinabove, to give the desired IB analog; or

c) with glycidol (IIIC),



(IIIC)

wherein W is as defined above, to give IIC,



(IIC)

wherein R¹ and R² are as defined above, (amination of IIC with V,

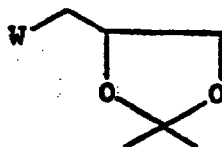


(V)

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wherein alk and Z are as defined above giving IB); or

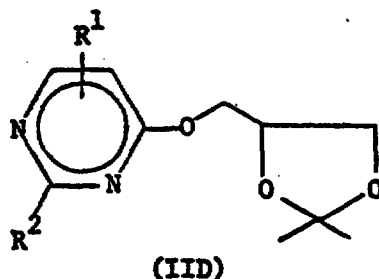
d) with solketal (IIID),



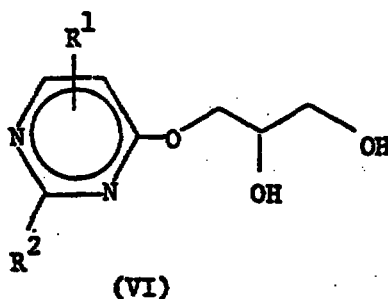
(IIID)

wherein W is as defined above, to give IID,

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wherein R^1 and R^2 are as defined above, (followed by hydrolysis giving VI,



wherein R^1 and R^2 are as defined above). Treatment of VI with methanesulfonyl chloride activates the terminal hydroxy group allowing facile aminolysis by V to give IB.

The compounds of the present invention can be formulated according to conventional pharmaceutical practice to provide pharmaceutical compositions of unit dosage form comprising, for example, tablets, capsules, powders, granules, emulsions, suspensions, and the like. The solid preparations contain the active ingredient in admixture with non-toxic pharmaceutical excipients such as inert diluents, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize, starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for

example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques so as to defy disintegration at absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Liquid .

- 5 preparations suitable for parenteral administration include solutions, suspension, or emulsions of the compounds of Formula I. The aqueous suspensions of the pharmaceutical dosage forms of the compounds of Formula I contain the active ingredient in admixture with one or more non-toxic pharmaceutical excipients known to be suitable in manufacture
- 10 of aqueous suspensions. Suitable excipients are, for example, suspending agents such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia. Suitable dispersing or wetting agents are naturally occurring phosphatides, for example,
- 15 lecithin, polyoxyethylene stearate.

Non-aqueous suspensions may be formulated by suspending the active ingredient in vegetable oil, for example, olive oil, sesame oil, or coconut oil, or in a mineral oil, for example, liquid paraffin. The suspensions may contain a thickening agent such as beeswax, hard

20 paraffin, or cetyl alcohol. Sweetening and flavoring agents generally used in pharmaceutical compositions may also be included such as saccharin, sodium cyclamate, sugar and caramel to provide a palatable oral preparation. The compositions may also contain other absorbing agents, stabilizing agents, wetting agents, and buffers.

Description of Specific Embodiments

The compounds which constitute this invention, their methods of preparation and their biologic actions will appear more fully from a consideration of the following examples and appended

5 claims which are given for the purpose of illustration only and are not to be construed as limiting the invention in sphere or scope. In the following examples, used to illustrate the foregoing synthetic processes, temperatures are expressed in degrees celsius and melting points are uncorrected. The nuclear magnetic resonance (NMR) spectral

10 characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the H NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to

15 multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), or doublet (d). Abbreviations employed are DMSO- d_6 (deuterio-dimethylsulfoxide), $CDCl_3$ (deuteriochloroform), and are otherwise conventional. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification

20 value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight.

Synthesis of Intermediates

A. Intermediates of Formula H₂N-Alk-Z

EXAMPLE 1

α,α -Dimethyl- β -(thienyl)ethaneamine

A mixture of 57% oil emulsion of sodium hydride (3.1 g, 0.07 mole), tetrahydrofuran (68 mL) and diisopropylamine (6.87 g, 0.07 mole) was stirred under nitrogen atmosphere as isobutyric acid (5.98 g, 0.07 mole) was added dropwise. The mixture was heated at reflux for 15 min to complete formation of the salt. After cooling to 0°, a solution of n-butyllithium in hexane (42 mL of 1.6 molar solution, 0.07 mole) was added in small portions while holding the temperature below 10°. The resulting turbid solution was kept at 0° for 15 min and then warmed to 30-35° for 30 min. After again cooling to 0°, 2-chloromethylthiophene (9 g, 0.07 mole) was added dropwise over 15-20 min while holding the temperature between 0 and 5°. The mixture was kept at 0° for 30 min, in the range of 30-35° for 1 hr and was then cooled to 15°. Water (90 mL) was added dropwise and the aqueous layer was separated. The organic phase was washed with a mixture of water (50 mL) and ether (75 mL). The aqueous extracts were combined, washed with ether and then acidified with conc HCl. The oily product was extracted with ether and the combined ether extracts dried (MgSO₄). Removal of the ether in vacuo gave 11.4 g (91%) of 2,2-dimethyl-3-(2-thienyl)propanoic acid of sufficient purity for use.

A solution of 2,2-dimethyl-3-(2-thienyl)propanoic acid (11.2 g, 0.06 mole), diphenylphosphorylazide (16.7 g, 0.06 mole) (Aldrich Chemical Company), and triethylamine (6.14 g, 0.06 mole) in

t-butanol (100 mL) was heated at reflux for 5 hr. The solution was poured into water (300 mL) and the crude material extracted with ether. The combined extracts were washed with brine, dried (MgSO₄) and evaporated to 11.9 g of an oil. This oil was added to a mixture of ethylene glycol (50 mL), H₂O (20 drops) and KOH (10 g). The mixture was heated at reflux for 5 hr, cooled to 25°, diluted with H₂O (300 mL) and acidified to pH 1 with conc HCl. Acid insoluble material was removed by washing with ether. The aqueous solution was then made basic with 50% NaOH solution and the product was extracted with ether. The ether extracts were combined, washed with brine, dried (MgSO₄) and concentrated in vacuo to 6.9 g (74%) of product. The NMR spectrum is consistent with the structure of this intermediate compound.

EXAMPLE 2

15 α,α -Dimethyl- β -(3-benzo{b}thienyl)ethaneamine

2,2-Dimethyl-3-(3-benzo{b}thienyl)propanoic acid was obtained in 82% crude yield from 3-(chloromethyl)benzo{b}thiophene using the procedure for preparation of the corresponding thienyl intermediate as outlined in the first paragraph of Example 1. The yellow viscous oil so obtained exhibited an NMR spectrum consistent with the assigned structure and was sufficiently pure for continued use. Thin layer chromatography on silica plates gave $R_f = 0.7$ (ethyl acetate).

Employing this benzothienyl propanoic acid intermediate in a synthetic procedure analogous to that of the second paragraph in Example 1 resulted in a 71% yield of the crude ethaneamine product with an NMR spectrum consistent with the assigned structure and sufficiently pure for use. Thin layer chromatography on silica plates gave $R_f = 0.6$ (CHCl₃, NH₃).

EXAMPLE 3

1,1-Dimethyl-2-(1H-benzimidazol-2-yl)ethylamine

A solution of o-phenylenediamine (5.4 g, 0.05 mole) and 2,2-dimethylsuccinic acid (7.5 g, 0.05 mole) in 50 mL of 4.8 N HCl was refluxed without condenser until the total volume was reduced to about 20 mL. Evaporation at 100° and 40 torr afforded a green paste which was taken up in 100 mL H₂O and made alkaline (pH 9) with 20% NaOH. The mixture was filtered removing tarry matter and the clear yellow filtrate was concentrated, cooled and the pH adjusted to about 6 by addition of acetic acid. A light yellow solid precipitated and was isolated by filtration and dried in air to give 9 g of α,α -dimethyl-1H-2-benzimidazolepropanoic acid, m.p. 223-226° (dec). Recrystallization from acetonitrile-methyl ethyl ketone-methanol (30-30-40) afforded 6.7 g (61%) of colorless needles, m.p. 266-267° (dec).

A solution containing 11.2 g of this benzimidazolepropanoic acid (0.05 mole), diphenylphosphorylazide (14.0 g, 0.05 mole) and triethylamine (5.0 g, 0.0 mole) in 100 mL of t-butanol was heated at reflux for 10 hr. The volatile material was evaporated at 100° and 30 torr and the residue was diluted with ethanol-methylene chloride. Filtration of the chilled mixture provided a total of 6.5 g of 3,4-dihydro-3,3-dimethylpyrimido[1,6-a]benzimidazol-1(2H)-one as a white solid, m.p. 205-210°. This material can be purified by reprecipitation from acid solution using 20% NaOH to afford white flakes, m.p. 211-215°.

A solution of 0.5 g of this cyclic urea (0.0023 mole) and 1.0 g of 35% KOH (0.22 mole) in 95% ethanol (20 mL) was heated at reflux for 8 hr, after which the mixture was boiled to near dryness

by removing the condenser. Five mL of isopropyl alcohol and 20 mL of water were added and the mixture was boiled to near dryness again.

The crystalline mass obtained by cooling the residue was separated on a Buchner funnel to give 0.4 g of crude product, m.p. 209-214°.

5 Recrystallization from isopropyl alcohol afforded 250 mg, m.p. 209-211°.

EXAMPLE 4

2-(2-Amino-2-methylpropyl)indole

A solution of indol-2-carboxylic acid (10.0 g, 0.06 mole) and thionyl chloride (20.0 g, 0.17 mole) in 130 mL of dry ether was
10 stirred for 12-18 hrs at room temperature under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated to an oily residue which was taken up in 150 mL of dry ether. This ether solution was treated with 80 mL of dimethylamine in 90 mL of ether. The ether was removed by concentration in vacuo and the
15 residue crystallized in isopropyl alcohol. The solid was isolated by filtration to give 4.0 g (34%) of the 2-indolyl amide product, m.p. 181-183°.

This indolyl amide was dissolved in 100 mL tetrahydrofuran and the resulting solution added dropwise to a stirred suspension
20 comprised of 3 g lithium aluminum hydride in 50 mL of tetrahydrofuran under a nitrogen atmosphere. After being refluxed for 2 hr, the reaction mixture was cooled and decomposed with a small amount of water and dilute sodium hydroxide solution. The resulting mixture was filtered and the filtrate concentrated to a residual oil which
25 was taken up in ethanol and treated with a slight excess of dimethyl sulfate. The resulting alcoholic solution was stirred at room temperature for 4 hr and then concentrated in vacuo to dryness giving as residue the trimethylamine quaternary salt.

5 The crude quaternary salt product (3.0 g, 0.01 mole) was combined with NaOH (2.0 g pellets, 0.05 mole) and 2-nitropropane (15 mL) and the mixture was heated at reflux under a nitrogen atmosphere for 1 hr. The resultant dark thick mixture was cooled, diluted with water, acidified with acetic acid to a pH of approximately 6 and then extracted with ether. The ether extracts were combined, washed with water, dried (MgSO_4) and concentrated to a dark residue which was chromatographed on a silica column and diluted with methylene chloride. Removal of the methylene chloride and recrystallization of the crude material from isopropyl alcohol-water gave 0.4 g of 2-(2-methyl-2-nitropropyl)indole as a cream color solid, m.p. 102-103°.

Reduction of this nitro product with Raney Nickel and hydrazine in ethanol yields the desired indole alkylamine as a white solid, m.p. 130-133°.

15 Additional intermediates of this class can either be obtained commercially, prepared by known procedures in the literature (e.g. 2-(3-indolyl)-1,1-dimethylethylamine is prepared by the method of Snyder, et al., J. Am. Chem. Soc., 69, 3140 (1947) from 3-indolyl-methyldimethylamine (gramine) and 2-nitropropane followed by reduction of resulting 2-(3-indolyl)-1,1-dimethylnitroethane); or by modification of the foregoing synthetic examples. By appropriate utilization of these procedures, intermediates wherein Z is benzofuran or positional isomers of thiophene and benzothiophene can be prepared.

99

B. Intermediates of Formula II

The class of intermediates designated as II can be prepared according to methods reported in the literature or by following the procedures outlined in the following examples. Structural variation
5 of these intermediates can be obtained by making appropriate modifications which would be evident to those skilled in the art.

EXAMPLE 5

(IIA) 5-[(2,4-Diamino-6-pyrimidinyl)oxymethyl]-3-
(1,1-dimethylethyl)-2-phenyloxazolidine

10 3-(1,1-Dimethylethyl)-2-phenyl-5-oxazolidinemethanol (8.2 g, 0.035 mole, prepared according to the method disclosed in U.S. Patent 3,998,835 issued December 21, 1976 and assigned to Sandoz, Ltd.) was dissolved in tetrahydrofuran (60 mL) and treated dropwise, under nitrogen, with 24% potassium hydride in mineral oil (5.4 g, 0.032
15 mole). After stirring at 25° for 10 min, the mixture was heated at 45° for 1 hr. 2,4-Diamino-6-chloropyrimidine (4.3 g, 0.03 mole) was added and the mixture heated in a 100 mL stainless steel Parr bomb at 100-105° for 18 hrs. After cooling, a yellow insoluble gum was collected. The filtrate was concentrated to an oil, from which three
20 crops of solid (m.p. 92-105°) were isolated by trituration with CCl₄ and ether.

EXAMPLE 6

(IIIB) 3-[-2-(3-Indolyl)-1,1-dimethyl
ethyl]amino]-1,2-propanediol Hydrate

25 A mixture of α,α -dimethyl- β -(3-indolyl)ethaneamine (10.0 g, 0.053 mole), Na₂CO₃ (11.3 g, 0.106 mole), 3-chloro-1,2-propanediol (7.0 g, 0.064 mole) and ethanol (250 mL) was stirred overnight at reflux. After cooling, the mixture was filtered and concentrated in

vacuo. The residue was dissolved in ethyl acetate, decolorized (Darco G-60), and evaporated to a volume of 100 mL. The solution deposited a white solid which was recrystallized from ethyl acetate to give 7.7 g (55%), m.p. 112-114°.

5

EXAMPLE 7

(IIC) 5-Bromo-2-chloro-4-(oxiranylmethoxy)pyrimidine

A solution of glycidol (13.0 g, 0.175 mole) and 5-bromo-2,4-dichloropyrimidine (40.0 g, 0.175 mole) in dimethylformamide (350 mL) was added dropwise to a stirring nitrogen-flushed, chilled suspension of sodium hydride (from 10.1 g, 0.21 mole, of NaH washed free of mineral oil) in dimethylformamide (350 mL). Following the addition, the reaction mixture was poured into 1:1 brine-water (4.5 l) and extracted with ethyl acetate (5 x 750 mL). Combined extracts were washed with water and brine, dried (MgSO₄) and concentrated in vacuo to give 44.7 g of an oil which solidified. Trituration of the crude product in isopropyl alcohol-isopropyl ether gave 21.9 g (47%) of product, m.p. 69-73°.

20

EXAMPLE 8

(IID) 2-Amino-6-chloro-4-{4-(2,2-dimethyl-1,3-dioxalanyl)methoxy}-pyrimidine

Solketal (20.2 g, 0.152 mole) was added dropwise to a suspension of 24.3% potassium hydride in oil (27.6 g, 0.167 mole) in 500 mL of dry tetrahydrofuran. After hydrogen evolution was complete, a solution of 2-amino-4,6-dichloropyrimidine (25 g, 0.152 mole) in 500 mL tetrahydrofuran was added. The mixture was refluxed for 18 hrs and then the tetrahydrofuran was removed in vacuo and the residue extracted with 600 mL of chloroform. The extract was decolorized

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(Darco G-60), and then filtered. Chilling the filtrate gave 24.3 g (61.4%) of 2-amino-6-chloro-4-{4-(2,2-dimethyl-1,3-dioxalanyl)methoxy}-pyrimidine, m.p. 149-151°.

Synthesis of analogs of the compounds of Formula I, having values of R² other than hydrazino and hydrazono

5 Method A

EXAMPLE 9

1-[(2,4-Diamino-6-pyrimidinyl)oxy]-3-[(1,1-dimethylethyl)amino]-2-propanol Dihydrochloride Hydrate

The oxazolidine intermediate (IIA, prepared in Example 5)
10 was hydrolyzed by stirring with 40 ml. of 1N HCl at 45-50° for 1 hr. After cooling, the solution was washed with ether, made basic with 15% NaOH, and extracted with ethyl acetate. The extracts were dried (K₂CO₃), concentrated in vacuo and the residue dissolved in acetone. The acetone solution was acidified with ethanolic HCl, concentrated,
15 and the residue recrystallized from methanol-isopropyl ether to give 1.4 g (32%), m.p. 221-223° (dec).

Anal. Calcd. for C₁₁H₂₁N₅O₂·2HCl·H₂O: C, 38.16; H, 7.28; N, 20.23. Found: C, 38.32; H, 6.92; N, 20.27.

NMR (DMSO-d₆): 1.34 (9,s); 3.00 (2,m); 4.28 (3,m); 5.48
20 (1,s); 8.05 (4,bs); 8.78 (1,bs); 9.34 (1,bs).

IR (KBr): 785, 1130, 1235, 1380. 1440, 1465, 1550, 1650, 2800, and 2970 cm⁻¹.

Method B

EXAMPLE 10

1-[(2-Amino-6-chloro-4-pyrimidinyl)oxy]-3-[(3-indolyl)-1,1-(dimethylethyl)amino]-2-propanol Hydrochloride

5 3-[2-(3-Indolyl)-1,1-(dimethylethyl)amino]-1,2-propanediol
hydrate (IIB, 11.0 g, 0.042 mole) was added to a solution of potassium
t-butoxide (4.7 g, 0.042 mole) in dry tetrahydrofuran (275 mL).
After the mixture was stirred at reflux for 1.5 hr, a solution of
2-amino-4,6-dichloropyrimidine (6.8 g, 0.042 mole) in tetrahydrofuran
10 (220 mL) was added dropwise in 1 hr. The reaction mixture was stirred
at 25° for 6 hr, allowed to stand overnight, and evaporated to dryness.
The residue was slurried in ethyl acetate and water, the organic
layers dried (MgSO₄) and concentrated to a gummy residue. The gum
was triturated in warm dilute hydrochloric acid, filtered, made basic
15 with dilute sodium hydroxide solution and extracted with ethyl
acetate. After drying (MgSO₄), the ethyl acetate extract was concen-
trated in vacuo, the residue dissolved in isopropyl alcohol and
acidified with ethanolic HCl. The precipitated hydrochloride (7.0 g)
was recrystallized twice from methanol-ethyl acetate to afford 4.9 g
20 (27%) product, m.p. 192-195° (dec).

Anal. Calcd. for C₁₉H₂₄ClN₅O₂·HCl: C, 53.53; H, 5.91;
N, 16.43. Found: C, 53.81; H, 5.92; N, 16.15.

NMR (DMSO-d₆): 1.30 (6,s); 3.05 (4,m); 4.40 (3,m); 6.11
(1,bs); 6.31 (1,s); 7.35 (7,m); 9.00 (1,bs); 9.51 (1,bs); 11.50
25 (1,bs).

IR (KBr): 750, 1145, 1250, 1330, 1430, 1560, 1580, 1625,
2800, 2980, 3330, and 3400 cm⁻¹.

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Method C

EXAMPLE 11

5 1-[(5-Bromo-2-chloro-4-pyrimidinyl)oxy]-3-
 {[1,1-dimethyl-2-(3-benzothienyl)ethyl]
 amino]-2-propanol Hydrochloride

A solution of 1,1-dimethyl-2-(3-benzothienyl)ethaneamine (8.2 g, 0.04 mole) in absolute ethanol (50 mL) was added dropwise to a stirring suspension of 5-bromo-2-chloro-4-(oxiranylmethoxy)pyrimidine (10.6 g, 0.04 mole) in absolute ethanol (100 mL). The mixture was
10 stirred at reflux for 3 hr and the resulting solution acidified with ethanolic HCl. Recrystallization of the crude product from methanol-isopropyl ether gave 6.9 g (34%) product, m.p. 212-213° (dec).

Anal. Calcd. for $C_{19}H_{21}BrClN_3O_2S \cdot HCl$: C, 44.95; H, 4.37; N, 8.28. Found: C, 44.73; H, 4.33; N, 8.15.

15 NMR (DMSO- d_6): 1.31 (6,s); 3.42 (4,m); 4.54 (3,m); 6.05 (1,bs); 7.38 (2,m); 7.61 (1,s); 8.02 (2,m); 8.72 (1,s); 9.05 (1,bs); 9.65 (1,bs).

IR (KBr): 730, 765, 1188, 1220, 1335, 1360, 1435, 1557, 2800, and 2980 cm^{-1} .

20

EXAMPLE 12

4-[3-(1,1-Dimethylethyl)amino-2-hydroxypropoxy]-2-phenyl-5-pyrimidinecarbonitrile Hydrochloride

A mixture of 4-hydroxy-2-phenyl-5-pyrimidinecarbonitrile (Nishigaki, et al, Chem. Pharm. Bull., 18/5, 1003 (1970); 4.0 g, 0.02
25 mole) and epichlorohydrin (40.0 g, 0.44 mole) was stirred at 130-140° for 4 hr. The reaction mixture was concentrated to an oil and the toluene soluble portion taken to dryness. Absolute ethanol (40 mL) and t-butylamine (40 mL) were added to the residue and the solution stirred at reflux for 6 hr. Unreaction epichlorohydrin and ethanol

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were removed by concentration in vacuo. Toluene was added twice to the residue and removed in vacuo. Water (100 mL) was added and insoluble material separated by filtration. The filtrate was made basic with 1N NaOH and the precipitate dissolved in ether. This ether solution was dried (MgSO₄) and acidified with ethanolic HCl to afford the product hydrochloride salt. Two recrystallizations from methanol-acetone gave 0.6 g (12%) of product, m.p. 191-193° (dec).

Method D

EXAMPLE 13

10 1-(2-Amino-4-chloropyrimidin-6-yl)-
 oxy-3-[(1-methylethyl)amino]-2-propanol

To a solution of 2-amino-6-chloro-4-[4-(2,2-dimethyl-1,3-dioxalanyl)methoxy]pyrimidine (IID, Example 8, 22 g) in 95% ethanol (600 mL) was added conc HCl to bring the solution to pH 1 (moistened Hydrion B paper). The solution was heated at 60° in a water bath for 1.5 hr. After cooling to 25°, 20% NaOH solution was added to neutralize the HCl and the ethanol was removed in vacuo. The residue was slurried in H₂O (100 mL), the solid filtered and recrystallized from ethanol to give 11.8 g (62.5%) of 2-amino-6-chloro-4-(2,3-dihydroxypropoxy)-pyrimidine, m.p. 175-177°.

A 10.7 g portion (0.049 mole) of 2-amino-6-chloro-4-(2,3-dihydroxypropoxy)pyrimidine was dissolved in 50 mL pyridine with heating. The pyridine solution was chilled in an ice bath and methanesulfonylchloride (5.5 g, 0.049 mole) was added dropwise while keeping the temperature below 10°. The solution was kept below 10° for 15 min, then a solution of isopropylamine (100 mL) and absolute ethanol (100 mL) were added. After 18 hrs at reflux, the solvent and excess amine were removed in vacuo. Water (approximately 100 mL) was added

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to the residue, followed by 50% NaOH solution making the pH 11. This basic mixture was extracted with ether; the ether extracts combined and dried (MgSO_4) and then concentrated in vacuo to a partially crystallized yellow oil. Recrystallization of this material first
5 from ethyl acetate and then from acetonitrile-isopropyl alcohol gave 2.15 g (17%) of product, m.p. 166-168°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{17}\text{ClN}_4\text{O}_2$: C, 46.07; H, 6.57; N, 21.49.
Found: C, 46.32; H, 6.52; N, 21.18.

NMR ($\text{DMSO}-d_6$): 1.00 (6,d, 6.0 Hz); 2.66 (3,m); 3.88 (2,m);
10 4.29 (2,d, 5.9 Hz); 4.72 (1,bs); 6.25 (1,s); 7.21 (2,bs).

IR (KBr): 795, 1010, 1140, 1250, 1305, 1340, 1445, 1570, 1600, 1650, 2980, 3200, and 3360 cm^{-1} .

Hydrazine/Hydrazone Products

EXAMPLE 14

15 1-[(5-Bromo-2-hydrazino-4-pyrimidinyl)oxy]-3-[(1,1-dimethyl-2-(3-benzothienyl)ethyl)amino]-2-propanol

Hydrazine (2.3 g, 0.071 mole) was added dropwise to a stirred suspension of the substituted chloropyrimidine product prepared in Example 11 (6.0 g, 0.12 mole) in tetrahydrofuran (60 mL).
20 The mixture was vigorously stirred under nitrogen for 16 hr. Excess hydrazine in the form of a bottom layer was removed by pipette and the tetrahydrofuran solution constituting the upper layer was decolorized (Darco) and concentrated in vacuo. The residual oil was dissolved in isopropyl alcohol and crystallization induced by scratching. Filtration
25 provided 4.8 g (80%) of product, m.p. 141-143.5° (dec).

Anal. Calcd. for $\text{C}_{19}\text{H}_{24}\text{BrN}_5\text{O}_2\text{S}$: C, 48.93; H, 5.19; N, 15.02. Found: C, 48.75; H, 5.21; N, 14.82.

NMR (DMSO- d_6): 1.02 (6,s); 2.75 (2,m); 2.90 (2,s); 4.00 (4,m); 4.36 (2,d, 5.8 Hz); 4.92 (1,bs); 7.31 (2,m); 7.42 (1,s); 7.89 (2,m); 8.15 (1,s); 8.26 (1,bs).

IR (KBr): 730, 765, 1235, 1285, 1425, 1580, and 2960 cm^{-1} .

5

EXAMPLE 15

1-{{5-Bromo-2-{2-(1-methylethylidenene)hydrazino}
4-pyrimidinyl}oxy}-3-{{1,1-dimethyl-2-(3-
benzothienyl)ethyl}amino}-2-propanol Dihydrochloride

The hydrazino pyrimidine compound prepared in Example 14
10 (1.6 g, 3.4 mmole) was suspended in isopropyl alcohol (15 mL),
acidified with ethanolic HCl, and warmed while adding acetone (3 mL).
Crystalline dihydrochloride separated from the hot solution. The
mixture was filtered to provide 1.9 g (94%) of analytically pure
product, m.p. 197-199° (dec).

15

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{BrN}_5\text{O}_2\text{S} \cdot 2\text{HCl}$: C, 45.60; H, 5.22;
N, 12.09. Found: C, 45.27; H, 5.27, N, 11.95.

NMR (DMSO- d_6): 1.31 (6,s); 2.10 (6,s); 3.28 (2,m);
3.45 (2,m); 4.60 (3,m); 7.37 (2,m); 7.60 (1,s); 8.02 (2,m); 8.44
(1,s); 9.30 (1,bs); 9.95 (1,bs).

20

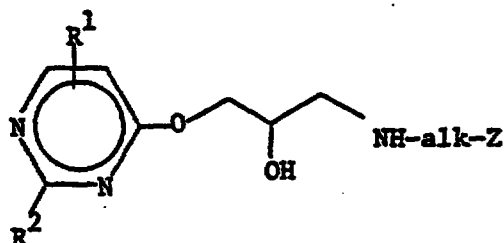
IR (KBr): 760, 1110, 1160, 1425, 1478, 1610, 1640, 2800,
and 2980 cm^{-1} .

Additional product I compounds can be prepared using
methods contained in the foregoing examples. A tabulation of some
selected additional compounds of Formula I, together with some
selected additional analogs of compounds of Formula I having values
of R^2 other than hydrazino and hydrazone, appears in Table 1.

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Table 1

Pyrimidinyloxypropanolamines



	Example No.	R ¹	R ²	alk	Z	m.p. °C
5	16	6-Cl	NH ₂	C(CH ₃) ₂ CH ₂	H	171-172
	17	6-Me	NH ₂	C(CH ₃) ₂ CH ₂	H	202.5-204.5
	18	H	Cl	C(CH ₃) ₂ CH ₂	H	128-143
	19	6-Br	CH ₃ C(=O)NH	CHCH ₃ CH ₂	2-benzofuranyl	-
	20	5-Me	NHN=C(CH ₃)CH ₂ CH ₃	CH ₂ CH ₂	3-benzofuranyl	-
10	21	H	NHNH ₂	C(CH ₃) ₂ CH ₂	H	207-208 (dec)
	22	H	Cl	C(CH ₃) ₂ CH ₂	3-indolyl	213-215
	23	H	NHNH ₂	C(CH ₃) ₂ CH ₂	3-indolyl	141-146 (dec)
	24	6-Me	NHNH ₂	CHCH ₃ CH ₂	2-indolyl	-
	25	6-Br	NHN=C(CH ₃)Ph	CHCH ₃ CH ₂	2-benzimidazolyl	-
15	26	H	Cl	C(CH ₃) ₂ CH ₂	2-thienyl	156.5-158.5
	27	H	Cl	C(CH ₃) ₂ CH ₂	phenyl	165-170
	28	H	NHNH ₂	C(CH ₃) ₂ CH ₂	phenyl	117-120
	29	H	NHNH ₂	C(CH ₃) ₂ CH ₂	2-thienyl	86-110
	30	H	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	2-thienyl	203-205 (dec)
20	31	H	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	phenyl	206-208 (dec)
	32	H	NHNH ₂	C(CH ₃) ₂ CH ₂	3-benzothienyl	125-130
	33	6-Et	CH ₃ C(=O)NH	CHCH ₃ CH ₂	2-benzothienyl	-
	34	H	Cl	C(CH ₃) ₂ CH ₂	3-benzothienyl	208-209 (dec)

Table 1 Continued

Example No.	R ¹	R ²	alk	Z	m.p. °C
35	5-Br	Cl	C(CH ₃) ₂ CH ₂	H	172-174
5 36	5-Br	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	H	200-202 (dec)
37	5-Br	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	2-thienyl	202-203.5 (dec)
38	H	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	3-thienyl	188-190
39	5-Br	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	3-thienyl	201.5-202.5 (dec)
40	5-CH ₃	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	2-thienyl	208-209 (dec)
10 41	5-CH ₃	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	H	217-219
42	5-CH ₃	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	phenyl	202-203
43	5-CH ₃	NHN=C(CH ₃) ₂	C(CH ₃) ₂ CH ₂	3-thienyl	199-201
44	6-CH ₃ O CNH	NHN=CCH ₃ Ph	CHCH ₃ CH ₂	2-indolyl	...

Biological Evaluation

15 These biological tests were used to gauge the antihypertensive profile of a number of the compounds of Formula I as vasodilators with a range of beta-adrenergic blocking activity.

EXAMPLE 45

20 The efficacy of antihypertensive agents other than adrenergic beta-receptor blocking agents is commonly estimated in the spontaneous hypertensive rat. Blood pressure values are determined for test animals prior to and 22 hours after oral doses of 30-100 mg/kg of test compounds. The animals are then dosed again and pressure determinations made 2 and 4 hours later. Heart rate is determined with
25 each pressure measurement as well. A fall in blood pressure at 2 or 4 hours after the second dose in the range of 19-24 mmHg is considered

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"questionable". "Active" and "inactive" designations are decreases greater and less than the range.

EXAMPLE 46

The angiotensin-maintained ganglion-blocked rat model is
5 utilized as a screening test for estimation of the vasodilator
component of activity. Percentage changes in blood pressure in
anesthetized rats 30 minutes after intravenous dosing are determined.
The intravenous dosing is done with test compounds at 3 mg/kg.
Borderline activity is defined as approximately a 10% decrease in
10 blood pressure measured 30 minutes after dosing. "Active" and "inactive"
designations are increases greater and less than that.

EXAMPLE 47

Diastolic blood pressure and heart rate responses to a
fixed challenge dose of isoproterenol are obtained before and 15
15 minutes after graded doses of test compound administered intravenously
over a 3 minute interval to anesthetized dogs. A branch of a femoral
artery and vein are cannulated to record blood pressure and to
administer the drugs which are dissolved in saline. The vagi were
sectioned bilaterally in the mid-cervical region of the neck and the
20 dogs are ventilated mechanically (Harvard respiratory) with room air
at a rate of 20/minute and a stroke volume of 20 mL/kg. Heart rate
is monitored with a cardiometer triggered by the pressure pulse.
All measurements are recorded on a Beckman^{*}R-612 recorder. The drug
effect is expressed in terms of a cumulative dose (microgram/kg)
25 causing 50% inhibition of isoproterenol response.

* Registered Trade Mark

EXAMPLE 48

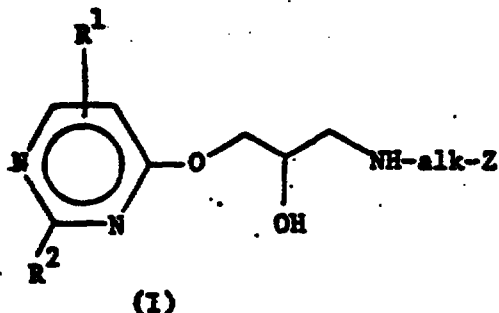
Rats (male Wistar) are anesthetized with a combination of urethane and chloralase intraperitoneally. Following induction of anesthesia, chlorisondamine is injected into the peritoneal cavity to produce ganglion blockage. A femoral artery was cannulated to monitor blood pressure and heart rate and two femoral veins were cannulated to administer compounds. The trachea was intubated and rats were allowed to breath spontaneously. Animals were challenged before and 15 minutes after intravenous administration of test compound with graded doses of isoproterenol and the changes in heart rate recorded. Data were plotted to obtain dose-response curves and the dose of isoproterenol required to elicit a 50 beat per minute (ED_{50}) increase in heart rate was interpolated from the curves. Dose shifts are calculated by dividing the ED_{50} after drug by the ED_{50} before drug.

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CLAIMS

1. A compound of Formula I or an acid addition salt thereof



wherein

R^1 is C_{1-6} alkyl, amino, acylamino, cyano, halogen, or hydrogen;

5 R^2 is hydrazino or hydrazono;

alk is C_{1-6} alkylene, either straight chain or branched; and

10 Z is selected from the group consisting of hydrogen, phenyl, indolyl, thienyl, benzothenyl, benzofuranyl, and benzimidazolyl.

2. A pyrimidine compound according to claim 1 of Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen, C_{1-6} alkyl, amino, C_{1-4} acylamino, cyano, or halogen;

5 R^2 is $-NHNH_2$ or $-NHN=C \begin{matrix} \nearrow R^a \\ \searrow R^b \end{matrix}$, with R^a and R^b being the same or different and representing C_{1-3} alkyl or phenyl;

alk is C_{1-6} alkylene, either straight chain or branched; and

Z is selected from the group hydrogen, phenyl, indolyl, thienyl, benzothenyl, benzofuranyl, and benzimidazolyl.



3. The pyrimidine compound of claim 2 wherein R^1 is selected from the group of hydrogen, C_{1-4} alkyl, and halogen; R^a and R^b are methyl; alk is t-butylene; and Z is selected from the group of phenyl, indolyl, thienyl, and benzothienyl.

4. The pyrimidine compound of claim 3 wherein R^1 is 5-bromo or 5-methyl.

5. The compound of claim 2 which is 1-[(1,1-dimethylethyl)amino]-3-[(2-hydrazino-4-pyrimidinyl)oxy]-2-propanol.

6. The compound of claim 2 which is 1-[(2-hydrazino-4-pyrimidinyl)oxy]-3-[[2-(1H-indol-3-yl)-1,1-dimethylethyl]amino]-2-propanol.

7. The compound of claim 2 which is 1-[(1,1-dimethyl-2-phenylethyl)amino]-3-[(2-hydrazino-4-pyrimidinyl)oxy]-2-propanol.

8. The compound of claim 2 which is 1-[[1,1-dimethyl-2-(2-thienyl)ethyl]amino]-3-[(2-hydrazino-4-pyrimidinyl)oxy]-2-propanol.

9. The compound of claim 2 which is 1-[[1,1-dimethyl-2-(2-thienyl)ethyl]amino]-3-[[2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-2-propanol.



10. The compound of claim 2 which is 1-[(1,1-dimethyl-2-phenylethyl)-amino]-3-[[2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-2-propanol.

11. The compound of claim 2, which is 1-[[1,1-dimethyl-2-(3-benzothienyl)ethyl]amino]-3-[(2-hydrazino-4-pyrimidinyl)oxy]-2-propanol.

12. The compound of claim 2 which is 1-[(5-bromo-2-hydrazino-4-pyrimidinyl)oxy]-3-[[1,1-dimethyl-2-(3-benzothienyl)ethyl]amino]-2-propanol.

13. The compound of claim 2 which is 1-[[5-bromo-2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-3-[[1,1-dimethyl-2-(3-benzothienyl)ethyl]amino]-2-propanol.

14. The compound of claim 2 which is 1-[[5-bromo-2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-3-[(1,1-dimethylethyl)amino]-2-propanol.

15. The compound of claim 2 which is 1-[[5-bromo-2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-3-[[1,1-dimethyl-2-(2-thienyl)ethyl]amino]-2-propanol.

16. The compound of claim 2 which is 1-[[1,1-dimethyl-2-(3-thienyl)-ethyl]amino]-3-[[2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]-oxy]-2-propanol.



17. The compound of claim 2 which is 1-[[5-bromo-2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-3-[[1,1-dimethyl-2-(3-thienyl)ethyl]amino]-2-propanol.

18. The compound of claim 2 which is 1-[[1,1-dimethyl-2-(2-thienyl)ethyl]amino]-3-[[5-methyl-2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-2-propanol.

19. The compound of claim 2 which is 1-[(1,1-dimethylethyl)amino]-3-[[5-methyl-2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-2-propanol.

20. The compound of claim 2 which is 1-[(1,1-dimethyl-2-phenylethyl)amino]-3-[[5-methyl-2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-2-propanol.

21. The compound of claim 2 which is 1-[[1,1-dimethyl-2-(3-thienyl)ethyl]amino]-3-[[5-methyl-2-[2-(1-methylethylidene)hydrazino]pyrimidin-4-yl]oxy]-2-propanol.



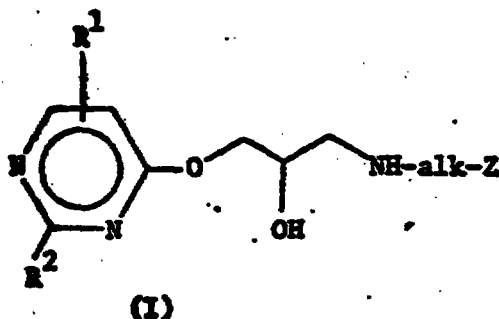
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22. Medication comprising a non-toxic antihypertensive effective dose of a compound claimed in claim 1 or claim 4, for use in a method of countering hypertension in a mammalian host.



23. A pharmaceutical composition in dosage unit form suitable for systemic administration to a mammalian host comprising a pharmaceutical carrier and an amount of a Formula I compound of any of claims 1-21 sufficient to provide an effective but non-toxic antihypertensive dose of from 0.1 mcg to 100 mg of said Formula I compound per kg body weight of said host.

24. A process for preparing a compound of Formula I



or a pharmaceutically acceptable acid addition salt thereof, wherein

R^1 is C_{1-6} alkyl, amino, acylamino, cyano, halogen, or hydrogen;

R^2 is hydrazino or hydrazono;

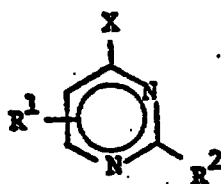
alk is C_{1-6} alkylene, either straight chain or branched; and

Z is selected from the group consisting of hydrogen, phenyl, indolyl, thienyl, benzothenyl, benzofuranyl, and benzimidazolyl;

said process comprising:

(a) coupling an X-substituted pyrimidine of Formula IV

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(IV)

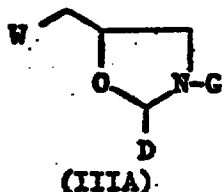
wherein

X is hydroxyl or halogen, and
R¹ and R² are as defined above,

with (1) a suitable W-substituted propanol or incipient propanol
compound III which can be either IIIA, IIIB, IIIC, or IIID,

wherein

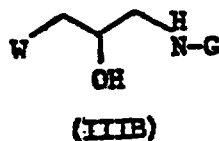
IIIA is



(IIIA)

in which the group D is hydrogen or phenyl; G is the radical
[-alk-Z] wherein alk is C₁₋₆ alkylene and Z is hydrogen, phenyl,
indole, thienyl, benzothienyl, benzofuranyl, or benzimidazolyl;
and W is halogen when X is hydroxyl and W is hydroxyl when X is
halogen;

IIIB is



(IIIB)

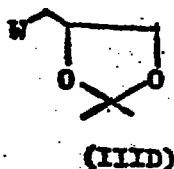
in which W and G are as defined above;

IIIC is



in which W is as defined above; and

IIID is



in which W is as defined above;

and then

(b) if IIIA was used in step (a), subjecting the coupled intermediate product formed in step (a) above to hydrolysis, so as to form I;

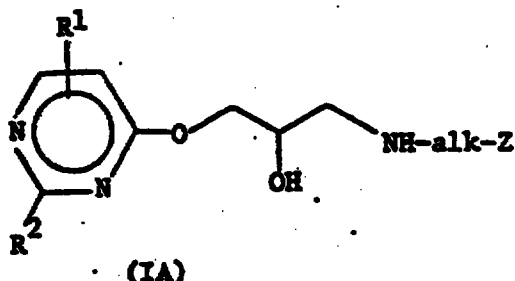
or if IIIC was used in step (a), subjecting the coupled intermediate product formed in step (a) to an amination with H_2NG , where G is as defined above, so as to form I;

or if IIID was used in step (a), subjecting the coupled intermediate product formed in step (a) to hydrolysis, activation of the terminal hydroxy, and aminolysis of H_2NG (where G is as defined above), so as to form I.



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25. A process for preparing a compound of formula I, IA,



wherein

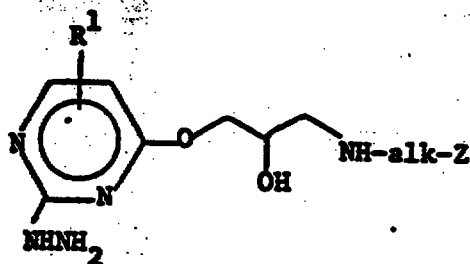
R^1 is C_{1-6} alkyl, amino, C_{1-4} acylamino, cyano, halogen, or hydrogen;

R^2 is either hydrazino or hydrazono (wherein hydrazono is $[-NHN=\overset{R^a}{\underset{R^b}{C}}]$, wherein R^a and R^b are either the same or different and are C_{1-3} alkyl or phenyl moieties;

alk is C_{1-6} alkylene; and

Z is selected from the group of hydrogen, phenyl, indolyl, thienyl, benzothienyl, benzofuranyl, and benzimidazolyl;

said process comprising a modification of the process of claim 24 wherein, in the X-substituted pyrimidine of Formula IV, R^2 is not hydrazino or hydrazono but instead is amino, acylamino, cyano, halogen, hydrogen or phenyl; and said process including also the following: (a) (if a compound with R^2 = hydrazino is desired) subjecting the initially formed analog of the desired compound I to the additional step of being treated with hydrazine so as to produce the desired 2-hydrazino compound of formula I



; or

(I: $R^2 = \text{NHNH}_2$)

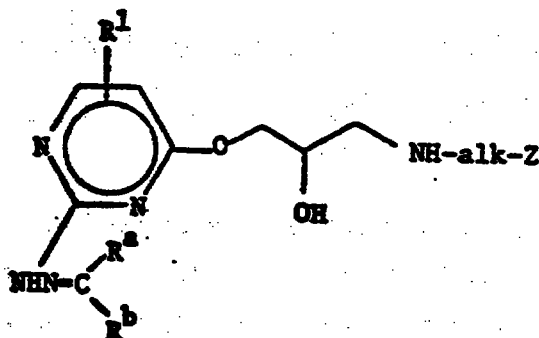
(b) (if a compound with $R^2 = \text{hydrazone}$ is desired) subjecting the initially formed analog of the desired compound I to the additional steps of step (a) recited above plus the step of treating the product of step (a) with a carbonyl compound

VII



(VII)

wherein R^a and R^b are as defined above under acidic conditions so as to obtain the desired compound of the following formula





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26. A process according to claim 24 or 25, substantially as described in any of the foregoing Examples 14, 15, 20, 21, 23 to 25, 28 to 32 and 36 to 44.

27. A compound of Formula I or salt thereof as specified in claim 1 prepared by a process according to claim 24, 25 or 26.

28. A pharmaceutical composition comprising a compound of Formula I or salt thereof according to any of claims 1 to 21 and 27, together with a pharmaceutically acceptable excipient, vehicle, carrier or diluent therefor.

to the public, and the public
has the right to know the
truth about the government
and its actions, and to
be informed of the truth
about the government's
actions.