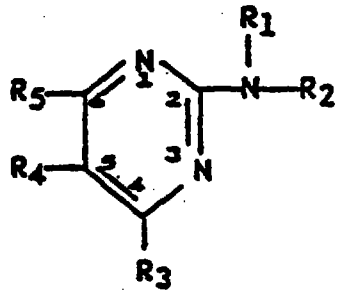
This Sheet Has Been Replaced

Title: 4,5,6-Substituted-N-(substituted--phenyl)-2-pyrimidinamines

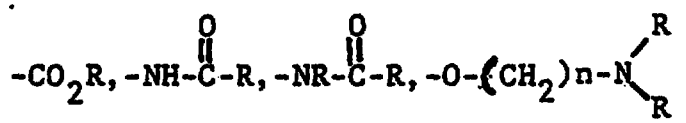
BRIEF SUMMARY OF THE INVENTION

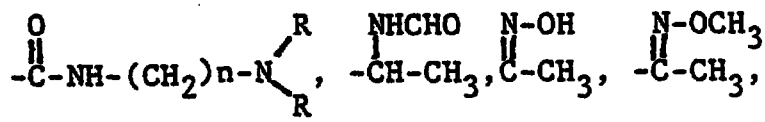
This invention relates to new organic compounds and; more particularly, is concerned with novel 4,5,6-substituted-N-(substituted-phenyl)-2-pyrimidinamines having anti-asthmatic activity which may be represented by the following structural formula:

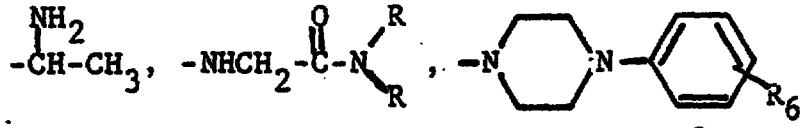


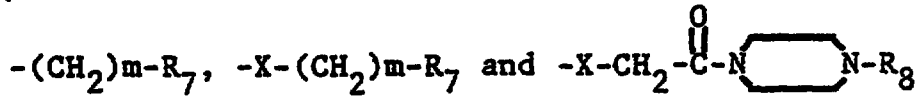
wherein R_1 is hydrogen, alkyl(C_1-C_3), $-COCO_2C_2H_5$ or N,N--dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1-C_6), alkoxy(C_1-C_3),

chloro, bromo, iodo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl-(C_1-C_3)amino, dialkyl(C_1-C_3)amino, alkyl-(C_1-C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfamilamido, N,N-dialkyl(C_1-C_3)sulfamilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formula:









wherein R is alkyl(C_1-C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl(C_1-C_3), alkoxy(C_1-C_3), chloro, bromo, iodo or trifluoromethyl, R_7 is 1H-imidazol-1-yl or morpholino and R_8 is alkyl(C_1-C_3), phenyl or monosubstituted phenyl wherein the substituents are alkyl(C_1-C_3), halogen or trifluoromethyl; R_3 is 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyridinyl methyl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl; R_4 is hydrogen or alkyl(C_1-C_3); and R_5 is hydrogen or alkyl(C_1-C_3); and the pharmacologically acceptable acid-addition salts thereof.

This Sheet Has Been Replaced



This Sheet Has Been Replaced

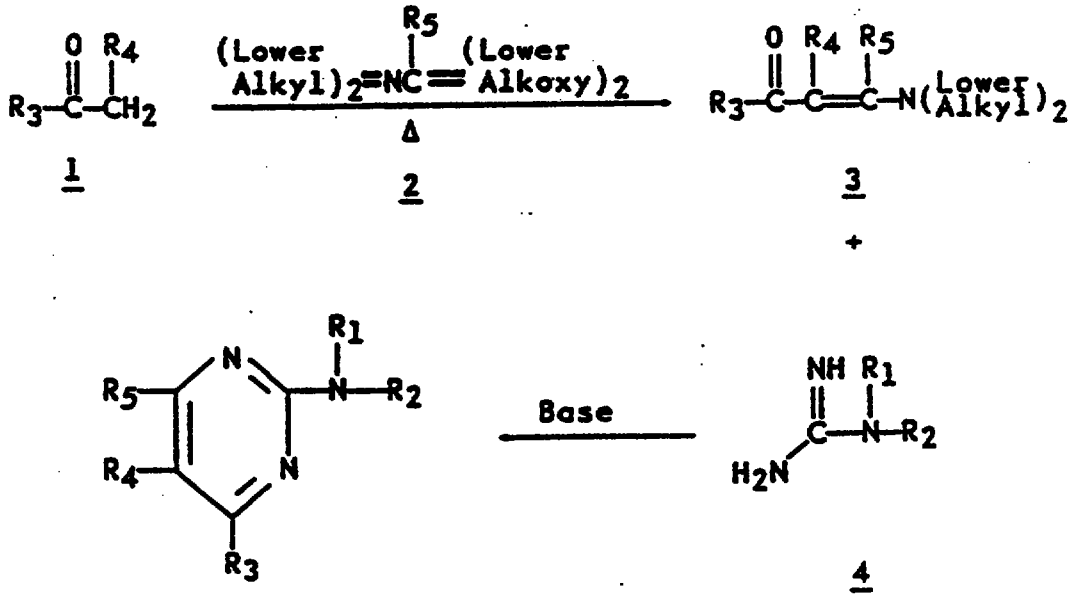
The present invention also icludes novel compositions of matter containing the above-defined compounds which are useful for treating asthma, allergic diseases, inflammation and diabetes in mammals. The invention also comprises processes of preparing the compounds within the scope of the above formula.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of the present invention are obtainable as crystalline materials having characteristic melting points and absorption spectra. They are in general sparingly soluble in organic solvents such as lower alkanols, chloroform, tetrahydrofuran, N,N-dimethylformamide, dichloromethane, acetone and the like, but are generally insoluble in water.

The novel 4,5,6-substituted-2-pyrimidinamines of the present invention in general may be prepared as set forth in the following reaction schemes.

Scheme I

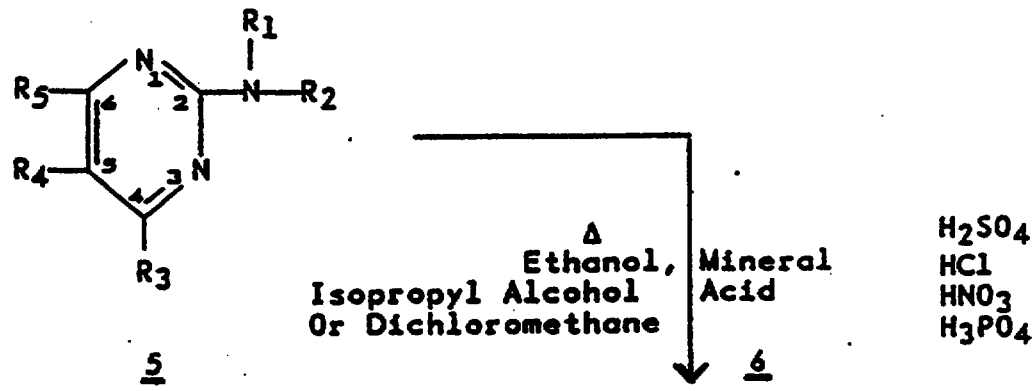


wherein R_1, R_2, R_3, R_4 and R_5 are as hereinabove defined.

In accordance with Scheme I, a heteroaryl (R_3) alkanoyl (R_4) compound 1, e.g 2-acetylpyridine, 2-acetyl-

furan, 3-acetylthiophene, 2-acetyl-6-methylpyridine, 2-propionyl pyridine or 3-propionyl pyridine and the like, is reacted with a di(lower alkyl)-formamide or acetamide di(lower alkyl) acetal 2, e.g; N,N-dimethylformamide dimethylacetal or N,N-dimethylacetamide dimethylacetal at an elevated temperature in the range of about 50°C. to about 150°C. for from about 4 to 24 hours to produce the 3-di(lower alkyl)aminoacrylophenone 3. The acrylophenone 3 is then reacted with an appropriately substituted phenylguanidine $(R_1)(R_2)$, 4 as the base or as the carbonate, sulfate, nitrate, hydrochloride or dihydrochloride salt in an inert solvent such as absolute ethanol, n-propanol, isopropyl alcohol or 2-methoxyethanol and the like, by heating at the reflux temperature for from 6-48 hours. The product 5 is separated by the partial evaporation of the solvent, then cooling and collected and recrystallized in a conventional manner from solvents such as n-propyl alcohol, isopropyl alcohol, absolute ethyl alcohol or 2-methoxyethanol and the like and combinations of solvents such as chloroform/hexane, dichoromethane/-hexane or isopropyl alcohol/ethylene glycol monomethyl ether and the like.

Scheme II



wherein R_1, R_2, R_3, R_4 and R_5 are as hereinabove defind.

In accordance with Scheme II, when the 4,5,6-substituted- 2-pyrimidinamine product 5 is dissolved by heating in a solvent such as absolute ethanol, isopropyl alcohol or dichloromethane, then stirred at room temperature and reacted with a mineral acid such as sulfuric acid, hydrochloric acid, nitric acid or phosphoric acid and the like, dissolved in absolute ethanol or isopropyl alcohol and the like, the 4,5,6-substituted-2-pyrimidinamine acid addition salt 6 is precipitated on standing for 30 minutes and chilling for several hours.

Alternatively, acid addition salts may be formed with organic acidds such as citric acid or maleic acid and the like by dissolving the desired 4,5,6-substituted-2-pyrimidinamine in hot, absolute ethanol or 2-methoxyethanol in the presence of the organic acid. Cooling provides the desired compounds as solids.

The novel compounds of the present invention are highly active as antiasthmatic and antiallergic agents as will be demonstrated hereinbelow.

The bronchospasm of allergic asthma is a consequence of the release of mediators, such as histamine and slow-reacting substances from masts cells. The role of mediator release in the induction of an asthmatic attack has been fully reviewed and documented; see Kaliner, M. and Austen, K. F., Bronchial Asthma Mechanisms and Therepautics, E. B. Weiss, Editor, Little, Brown and Company, Boston, 163, (1976); Lichtenstein, L. M., Asthma-Physiology, Immunopharmacology and Treatment, Second International Symposium, L. M. Lichtenstein and K. F. Austen, Editors, Academic Press, New York, 51, (1979); and Bell, S. C., et al., Annual Reports in Medicinal Chemistry, 14, 51, H. J. Hess, Editor, Academic Press, New York, (1979).

The novel compounds of this invention have been tested by the procedure of Lichtenstein, L. M. and Osler, A. G., J. Exp. Med., 120, 507-530 (1964), which evaluates

the ability of compounds to inhibit mediator (histamine) release from immunologically stimulated human basophils.

Reagents

10X Concentrated Tris Buffer

Dissolve 140.3 g of sodium chloride, 7.45 g of Trizma-Tris Pre-Set, Reagent Grade, pH 7.6, at 25°C (Sigma Chemical Co.) in sufficient water to give a final volume of 2 liters.

Human Albumin

(Sigma Chemical Co.) (30 mg/ml)

Calcium and Magnesium Stocks

Made to 0.075 M 0.5 M respectively, with calcium chloride dihydrate and magnesium chloride hexahydrate.

Tris-A Buffer

A 10 ml portion of 10X Tris Buffer and 1.0 ml of human albumin are diluted to 100 ml with water.

Tris ACM Buffer

A 10 ml portion of 10X Tris Buffer, 1.0 ml of human albumin, 0.8 ml of calcium stock and 0.2 ml of magnesium stock are diluted to 100 ml with water.

Rabbit Antihuman IgE

Behring Diagnostics (Generally used at 10 µg protein/ml final concentration).

House Dust Mite Extract (Dermatophagoides Farinae)

Strength 1:100 (w:v) allergenic extract, Hollister-Stier Labs. Generally this is diluted 1:1000 to 1:10,000 (considering the vial as stock).

Other Allergens

Interdermal solutions or intramuscular preparations for hyposensitization, Hollister-Steir Labs. The final concentration used is on the order of 1 PNU/ml.

Separation of Leukocytes from Human Blood and Challenge

Eighty milliliters of blood is withdrawn from subjects with known histamine release to anti-IgE, ragweed antigen or other specific allergen, using four 20 ml heparinized tubes. This 80 ml of blood is mixed with

20 ml of saline containing 0.6 g of dextrose and 1.2 g of dextran. The blood is allowed to sediment at room temperature in two 50 ml polycarbonate centrifuge tubes until a sharp interface develops between the red cells and plasma (60-90 minutes). The plasma (top) layer from each tube is withdrawn by pipet and transferred to respective 50 ml polycarbonate tubes. The plasma is centrifuged for 8 minutes at 110X G at 4°C. The supernatant is carefully poured off as completely as possible and the cell button is resuspended in 2-3 ml of Tris-A buffer using a siliconized Pasteur pipet. The resuspension is accomplished by drawing the liquid gently in an out of the pipet, with the tip below the liquid until an even suspension of cells is obtained. Sufficient Tris-A buffer is then added to bring the volume in the tube to about 45 ml and the tube is centrifuged at 110X G for 8 minutes at 4°C. The supernatant is poured off and the cell button is resuspended and centrifuged as described above. The supernatant is poured off and the cell button is suspended in 2-3 ml of Tris-ACM buffer to make the final volume sufficient to allow addition to the reaction tubes.

Reaction tubes containing anti-IgE or antigens, either alone or with test compound in a total volume of 0.2 ml are prepared and placed in a 37°C bath. The cells are warmed to 37°C and frequently swirled to ensure an even suspension, while 1.0 ml aliquots are added to each reaction tube. The tubes are then incubated for 60 minutes at 37°C, vortexing the tubes gently every 15 minutes to keep the cells evenly suspended. When the reaction is complete, the tubes are centrifuged at 4°C for 10 minutes at 1500 rpm to sediment the cells. One ml aliquots of supernatant are transferred to 12 mm by 75 mm polyethylene tubes and 0.2 ml of 8% perchloric acid is added to each tube. Blanks and totals are included in each test. The blanks have cells and all reagents except antigen or anti-IgE. The totals contain 0.24 ml of 8% perchloric acid, one ml of cells and 0.2 ml of buffer. All samples are

then centrifuged to remove the precipitate protein.

Assay of Released Histamine by the Automated Fluorometric Method

This automated method has been described by Siraganian, R. P., in Anal. Biochem., 57, 383 (1974) and J. Immunol. Methods, 7, 283 (1975) and is based on the manual method of Shore, P. A., et al., J. Pharmacol. Exp. Ther., 217, 182 (1959).

The automated system consists of the following Technicon Autoanalyzer II components: Sampler IV, Dual-Speed Proportioning Pump III, Fluoronephelometer with a narrow pass primary filter 7-60 and a secondary filter 3-74, Recorder, and Digital Printer. The manifold used is the one described by Siraganian vide supra, with the following modifications: the dialyzer is omitted; all pumping tubes pass through a single proportioning pump with large capacity and twice the volume of sample is taken for anaylsis.

The automated chemistry consists of the following steps: Extraction from alkaline saline into butanol, back extraction into dilute hydrochloric acid by addition of heptane, reaction of histamine with o-phthaldialdehyde (OPT) at high pH and conversion of the OPT adduct to a stable fluorophore with phosphoric acid. The reaction product is then passed through the fluorometer. The full scale response is adjusted to 50 ng histamine base with a threshold sensitivity of approximately 0.5 ng.

Calculation of the Results of Histamine Release Tests

The instrument blank (wash) is substracted from the ng histamine of each sample. Then the ng histamine of each sample is divided by the mean of the three totals (cells lysed with perchloric acid) to obtain percent release.

Control samples contain antigen but no test compound. Blank (or spontaneous release) samples contain neither antigen nor test compound. The mean of the blanks

(three replicates) is subtracted from the percent release for controls and test compounds.

The means for control and test compound groups are computed and the result for a test compound is computed as percent of control by the formula:

$$100 \times \frac{\text{\% Histamine Release with Test Compound}}{\text{\% Histamine Release in Controls}}$$

Values obtained at different concentrations of test compound are used to calculate an IC_{50} (the concentration in μM which causes a 50% inhibition of histamine release) by linear regression. A compound is considered active if the IC_{50} is $\leq$48 μM.

The results of this test on typical compounds of this invention appear in Table I.

TABLE I

Inhibition of Histamine Release from Immunologically Stimulated Human Basophils

Compound	IC_{50} (μM)
4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine	17.7
4-(4-Pyridinyl)-N-[(3-trifluoromethyl)phenyl]-2-pyrimidinamine	32.0
N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	1.4
N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine	0.9
N-(4-Acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	0.8
N-(4-Fluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	<48
N-(4-Methoxyphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	8.3
N-(4-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	1.0
N-(4-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	1.9
N-(4-Bromophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	2.3
4-(3-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, hydrochloride	0.7
4-(2-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	2.9
N-(4-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine	3.9

TABLE I (continued)

Compound	IC_{50} (μM)
N-(4-Ethylphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-2-pyrimidinamine	<48
N-Phenyl-4-(2-thienyl)-2-pyrimidinamine	31.7
N-(3-Chloro-4-methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	9.3
N-(3-Methylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	0.7
N-(3-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	9.4
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine	0.9
N-(3-Methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	1.5
N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	7.7
N-(4-Ethylphenyl)-5-methyl-4-(4-pyridinyl)-2-pyrimidinamine	<48
N-(4-Ethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	<48
N-(4-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	2.1
N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidinamine	0.3
4-(2-Furanyl)-N-phenyl-2-pyrimidinamine	48
4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	3.5
N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	13.4

TABLE I (continued)

Compound	IC_{50} (μM)
N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	19.1
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	<24
N-(4-Ethylphenyl)-4-pyrazinyl-2-pyrimidinamine	2.8
N-(3-Methylphenyl)-4-pyrazinyl-2-pyrimidinamine	5.4
N-(2-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	3.9
N-(3-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	10.6
N-(2,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	47.1
N-(2,3-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	20.2
N-(3-Methylphenyl)-4-(3-thienyl)-2-pyrimidinamine	3.8
N-(2,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	<48
N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	4.4
N-1-Naphthalenyl-4-(4-pyridinyl)-2-pyrimidinamine	31.3
N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	1.0
N-1-Naphthalenyl-4-(2-pyridinyl-2-pyrimidinamine	3.0
N-(2,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	24.0

TABLE I (continued)

Compound	IC_{50} (μM)
4-(4-Pyridinyl)-N-(2,4,6-trimethylphenyl)-2-pyrimidinamine	10.5
4-(2-Furanyl)-N-(4-methoxyphenyl)-2-pyrimidinamine	<48
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	<24
4-(2-Furanyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	<48
N-(4-Fluorophenyl)-4-(2-furanyl)-2-pyrimidinamine	13.3
N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine	2.2
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-1,2,3-propanetricarboxylate (2:1)	3.5
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, (Z)-2-butenedioate (1:1)	1.0
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, sulfate	3.0
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dinitrate	1.2
N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, pyridine-1-oxide	17.7
N-(3,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	5.9
N-(4-Methoxyphenyl)-4-(3-thienyl)-2-pyrimidinamine	15.6
N-(3-Ethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	9.7
4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamine	3.0

TABLE I (continued)

Compound	IC_{50}(μM)
N-(2-Methoxy-5-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	6.9
N-(3-Methylphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-2-pyrimidinamine	9.4
N-(3-Ethylphenyl)-4-(2-thienyl)-2-pyrimidinamine	48.0
N-(3-Ethylphenyl)-4-(3-thienyl)-2-pyrimidinamine	1.1
4-(1H-Indol-2-yl)-N-(3-methylphenyl)-2-pyrimidinamine	2.2
4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, methyl ester	27.5
N-(3-Methylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine	10.9
N-Phenyl-4-(-4-quinolinyl)-2-pyrimidinamine	3.0
N-(4-Ethylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine	4.0
4-(2-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	3.0
N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidinamine, sulfate	3.0
4-(2-Furanyl)-N-[3-(methylphenyl)]-2-pyrimidinamine, sulfate	3.0
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, phosphate	3.3
N-(3,5-Dimethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	0.7
N-(3,5-Dimethylphenyl)-4-(2-thienyl)-2-pyrimidinamine	4.3

TABLE I (continued)

Compound	IC_{50} (μM)
N-(2,4-Difluorophenyl)-4-(4-pridinyl)-2-pyrimidinamine	<48
N-(2,4-Difluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	<48
N-(3-Methylphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	1.4
N-(2,6-Difluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	2.9
4-(4-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	<48
N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	<48
N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	3.0
4-(3-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	2.6
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride	3.0
N-[4-(1,1-Dimethylethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.7
N-(2,6-Difluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	22.0
N-(4-Ethylphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	36.3
N-[(3,4-Dimethylphenyl)methyl]-4-(2-pyridinyl-2-pyrimidinamine	39.8
N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	3.0
N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	3.0

TABLE I (continued)

Compound	IC_{50}(μM)
N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine	11.1
4-(5-Methyl-2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	2.0
4-Methyl-6-(5-methyl-2-thienyl)-N-phenyl-2-pyrimidinamine	24.8
N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	3.8
N-(3-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	0.4
N-(3-Methoxyphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	0.2
N-[4-(Dimethylamino)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	2.7
N-(3-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	0.3
N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	0.8
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, ethyl ester	12.4
N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	3.7
4-(2,5-Dimethyl-3-furanyl)-N-phenyl-2-pyrimidinamine	2.0
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl)benzenediamine, trihydrochloride	0.4
4-(2,5-Dimethyl-3-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	28.5
4-(2,5-Dimethyl-3-furanyl)-N-(3,5-dimethylphenyl-2-pyrimidinamine	4.1

TABLE I (continued)

Compound	IC_{50}(μM)
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	4.4
4-(2,5-Dimethyl-3-furanyl)-N-(4-ethylphenyl)--2-pyrimidinamine	19.2
N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	1.7
3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid, ethyl ester	3.0
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	0.5
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol	5.1
3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid, ethyl ester	20.3
N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	3.2
N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	0.6
N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.8
N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.5
N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	2.7
N'-[4-(2-Furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	1.9
N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,4-benzendiamine	0.6
N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	4.9

TABLE I (continued)

Compound	IC_{50} (μM)
N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	1.8
N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, phosphate	0.3
N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	1.5
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	3.5
N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	37.7
N-[4-[3-Dimethylamino)propoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.5
N-[4-[2-Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.2
N-[4-[2-Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, hydrochloride	0.5
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid	7.6
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	0.5
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, trihydrochloride	1.0
N-(3,5-Dimethylphenyl)-4-(2-furanyl)-5-methyl-2-pyrimidinamine	<24
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	0.5
N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	6.1

TABLE I (continued)

Compound	IC_{50}(μM)
4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine, sulfate	5.0
N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	5.6
4-Methyl-N-phenyl-6-(2-pyridinyl)-2-pyrimidinamine	26.8
4-[[4-(4-(Pyridinyl)-2-pyrimidinyl]amino]-phenol	3.3
N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	1.5
N-[4-[2-(Dimethylamino)ethoxy]phenyl]N',N'-dimethyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine	9.1
N-[4-[3-Dimethylamino)propoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	1.3
N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.2
4-[2-[(4-Methoxyphenyl)amino]-4-pyrimidinyl]-1-methylpyridinium, iodide	33.3
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl)]-1,3-benzenediamine, sulfate	1.0
N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	2.4
N,N-Dimethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]-1,3-benzenediamine	1.6
N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,3-benzenediamine	<24
N-[2-(Diethylamino)ethyl]-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide	0.8

TABLE I (continued)

Compound	IC_{50}(μM)
4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-phenoxy]acetic acid, ethyl ester	5.8
N,N-Diethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.1
N,N-Dimethyl-N'-[4-methyl-6-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	31.8
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	12.3
N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, hydrochloride	3.0
N,N-Diethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.7
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	1.3
1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]ethanone, oxime	11.4
1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]ethanone, O-methyloxime	5.1
N,N-Diethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	10.1
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	1.8
4-(2-Furanyl)-N-[4-(1H-imidazol-1-yl)phenyl]-2-pyrimidinamine	2.2
N-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-benzamide	4.6
N,N-Dimethyl-N'-[4-(5-methyl-2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	5.7

TABLE I (continued)

Compound	IC_{50}(μM)
N,N-Dimethyl-N'-[4-(3-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	2.1
N-[1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]phenyl]ethyl]formamide	0.4
N-[4-[1-Aminoethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, trihydrochloride	0.8
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzenesulfonamide	0.2
N-(3-Chlorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	3.1
N-(3-Chlorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	1.5
N-(3-Methoxyphenyl)-4-(3-thienyl)-2-pyrimidinamine	1.7
N-Methyl-N-[4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	1.1
N-Methyl-N-[4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	0.1
N-Methyl-N-[4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	0.6
[4-(2-Furanyl)-N-(3-methoxyphenyl)-2-pyrimidinamine	0.3
4-(2-Benzofuranyl)-N-(3-methoxyphenyl)-2-pyrimidinamine	1.2
Oxo[phenyl[4-(4-pyridinyl)-2-pyrimidinyl]-amino]acetic acid, ethyl ester	2.1
N-[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	5.3

TABLE I (continued)

Compound	IC_{50}(μM)
N,N-Dimethyl-N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-1,3-benzenediamine	40
N-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	3.6
4-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-benzenesulfonamide	4.5
N-[4-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	1.5
N-(3-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine	0.9
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	1.5
N-(3-Methoxyphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	2.3
N-(3-Chlorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	1.3
4-(2-Furanyl)-N-[4-(4-methyl-1-piperazinyl)-phenyl]-2-pyrimidinamine	1.8
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.6
N-(3-Methoxyphenyl)-4-(2,5-dimethyl-3-furanyl)-2-pyrimidinamine	5.8
N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	1.0
N-(3-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	0.7
N-(3-Fluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	3.3
N-(3-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	0.9
1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]ethanone	4.1

TABLE I (continued)

Compound	IC_{50} (μM)
N-Methyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	2.1
N-[4-(1-Methylethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	1.1
N-Methyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.4
N-(3-Ethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	1.7
N-(3-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	1.4
3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]benzenesulfonamide	0.7
3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzenesulfonamide	0.2
N-[4-(1,1-Dimethylethyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	4.6
N,N-Diethyl-N'-[4-(2-furanyl)-2-pyrimidinyl]-1,4-benzenediamine	3.4
3-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-benzenesulfonamide	0.5
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,2-benzenediamine, fumarate	36.2
2-[1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethylidene]hydrazinecarboxamide	8.1
N-[4-[2-[bis(1,1-Dimethylethyl)amino]ethoxy]-phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	4.6
α-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]benzenemethanol	4.5
N-[1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]phenyl]ethyl]formamide	4.6
N-[3-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	2.1

TABLE I (continued)

Compound	IC_{50} (μM)
N-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	5.0
N-[4-(3-Pyridinyl)-2-pyrimidinyl]-1,3-benzene-diamine, dihydrochloride	0.4
N,N-Diethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]1,4-benzenediamine	28.0
N-(3-Methoxyphenyl)-4-(5-methyl-2-furanyl)-2-pyrimidinamine	1.2
N-[3-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]acetamide	0.3
N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyri-dinyl)-2-pyrimidinamine	0.1
N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,3-benzene-diamine	1.0
N-[2-Methyl-4-[[4-(4-pyridinyl)-2-pyrimi-dinyl]amino]phenyl]acetamide	1.2
2-Methyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	0.9
N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,3-benzene-diamine	0.2
N-[4-[[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]-amino]phenyl]acetamide	0.3
N-[3-(1-Aminoethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, trihydrochloride	5.1
N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	2.8
N-(2-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimi-dinamine	9.8
N-[4-[[4-(2-Thienyl)-2-pyrimidinyl]amino]-phenyl]acetamide	0.2
N-[2-Methyl-4-[4-(3-pyridinyl)-2-pyrimidinyl]-phenyl]acetamide	1.8
N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-diethyl-1,4-benzenediamine	6.2

TABLE I (continued)

Compound	IC_{50} (μM)
N-[4-[[4-(2-Furanyl)-2-pyrimidinyl]amino]-phenyl]acetamide	0.7
N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)-phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.4
N-[3-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	0.1
2-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenol	23.5
4-(2-Furanyl)-N-[3-(1H-imidazol-1-yl)phenyl]-2-pyrimidinamine	0.8
N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(2-furanyl)-2-pyrimidinamine	1.3
N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)-phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	1.6
N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(2-thienyl)-2-pyrimidinamine	0.6
N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.7
N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	2.4
N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	0.4
N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	0.2

The ability of these compounds to inhibit lipoxygenase activity in terms of the suppression of the release and biosynthesis of leukotriene B4(LTB4) and 5-hydroxy-eicosatetraenoic acid (5-HETE) was measured as follows.

In this assay $3x10^7$ peritoneal neutrophils derived from guinea pigs were incubated at 37°C in

Dulbeccos buffer containing 50mM tris buffer (pH 7.4). Five minutes before the addition of 100 μM arachidonic acid and 20 μM calcium ionophore (A23187), control vehicle or the test compounds were added to the neutrophils at a concentration of 10 μg/ml.

Three minutes after the addition of arachidonic acid and calcium ionophore the total lipid was partitioned into chloroform after adjusting the pH to 3 with citric acid and the addition of equal parts of methanol and chloroform.

The 5-HETE and LTB4 were resolved by HPLC using a 5 μM 4x25 cm octadecyl silica column (IBM Instruments) with 70-80% methanol in water adjusted to pH 3.0 with acetic acid. As the mobile phase was pumped at 1.0 ml/-minute, LTB4 and 5-HETE were detected by absorbance at 270 and 236 nm, respectively.

LTB4 and 5-HETE were quantitated by comparison with the control and the results were expressed as a percent of control. The lower the percentage, the more active the compound.

The results of this test on representative compounds of this invention appear in Table II.

TABLE II

Inhibition of Neutrophil Lipoxygenase from Immunologically Stimulated Guinea Pig Neutrophiles

Compound	% Inhibition	
	LTB4	5-HETE
4-(3-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine	58.1	
N-(4-Acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine		37.0
N-(4-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine		45.0
N-(4-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine		45.0
N-(4-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine		53.0
4-(3-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine		58.0
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine		58.0
N-(3-Methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine		40.0
N-[4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	33.9	41.0
N-(4-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	29.5	41.0
4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	7.4	3.0
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	48.0	

TABLE II (continued)

Compound	% Inhibition	
	LTB4	5-HETE
N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	53.4	54.0
N-(3-Methylphenyl)-4-pyrazinyl-2-pyrimidinamine		50.0
N-(3-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	36.4	28.7
N-(2,3-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	58.4	
N-Phenyl-4-(3-thienyl)-2-pyrimidinamine		56.0
N-(3-Methylphenyl)-4-(3-thienyl)-2-pyrimidinamine		48.0
N-(4-Ethylphenyl)-4-(3-thienyl)-2-pyrimidinamine		56.0
N-(2,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine		54.0
N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	53.1	54.0
N-(2-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	17.4	21.0
N-(2,5-Dimethoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	43.2	47.0
N-(2,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	37.0	43.0
N-(2-Methoxy-5-methylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine		54.0

TABLE II (continued)

Compound	% Inhibition	
	LTB4	5-HETE
4-(4-Pyridinyl)-N-(2,4,6-trimethylphenyl)-2-pyrimidinamine	53.6	
4-(2-Furanyl)-N-(4-methoxyphenyl)-2-pyrimidinamine		44.0
4-(2-Furanyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine	45.0	49.0
N-(4-Fluorophenyl)-4-(2-furanyl)-2-pyrimidinamine	33.0	
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-1,2,3-propanetricarboxylate (2:1)	58.0	
N-[(3,4-Dimethylphenyl)methyl]-4-(4-pyridinyl)-2-pyrimidinamine	24.0	36.0
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, sulfate	56.0	
4-(2-Benzofuranyl)-N-(3-methylphenyl)-2-pyrimidinamine	46.1	
N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine		19.0
N-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine		19.0
N-(3,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	17.3	35.0
N-(4-Fluorophenyl)-4-(3-thienyl)-2-pyrimidinamine	51.6	
4-(10H-Phenothiazin-2-yl)-N-phenyl-2-pyrimidinamine		48.0

TABLE II (continued)

Compound	% Inhibition	
	LTB4	5-HETE
4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamine	41.2	39.0
N-(2-Methoxy-5-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	44.7	37.0
N-(3-Methylphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-2-pyrimidinamine		60.0
4-(1-Methyl-1H-pyrrol-2-yl)-N-phenyl-2-pyrimidinamine		57.0
N-(4-Ethylphenyl)-4-(1H-indol-3-yl)-2-pyrimidinamine	56.5	
N-[1,1'-Biphenyl]-4-yl-(4-pyridinyl)-2-pyrimidinamine	37.1	45.0
4-[[4-(4-Pyridinyl)-2-pyrimidinyl]-amino]-benzoic acid, methyl ester	45.2	47.0
N-(3-Methylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine	16.0	
N-Phenyl-4-(4-quinolinyl)-2-pyrimidinamine	46.4	57.0
N-(4-Ethylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine		58.0
N-(3,5-Dimethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	56.1	
N-[4-(1,1-Dimethylethyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	47.8	54.0
N-Methyl-N-phenyl-4-(2-pyridinyl)-2-pyrimidinamine	58.1	54.0

TABLE II (continued)

Compound	% Inhibition	
	LTB4	5-HETE
N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine	55.4	
N-(4-Ethylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine	32.6	54.0
4-(3-Pyridinyl)-N-[3-(trifluoromethyl)-phenyl]-2-pyrimidinamine sulfate	37.3	49.0
N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride	48.0	43.0
4-(3-Methyl-2-thienyl)-N-phenyl-2-pyrimidinamine		59.0
4-(5-Methyl-2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	59.6	
4-Methyl-6-(5-methyl-2-thienyl)-N-phenyl-2-pyrimidinamine	42.3	52.0
N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	16.6	12.4
N-(3-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	31.2	50.0
N-[4-(Dimethylamino)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	20.1	17.2
N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	50.7	56.0
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, ethyl ester	35.8	47.0
N,N-Dimethyl-N-'[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	43.4	34.0

TABLE II (continued)

Compound	% Inhibition	
	LTB4	5-HETE
4-(2,5-Dimethyl-3-furanyl)-N-phenyl-2-pyrimidinamine	46.9	56.0
N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	40.7	37.0
N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	37.6	39.0
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenol		30.0
3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-benzoic acid, ethyl ester	36.1	50.0
N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	50.0	
N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	34.1	
N'[4-(2-Furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	16.9	16.9
N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	49.8	17.8
N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	21.6	17.0
N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	16.4	13.6
N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	46.8	42.0
N,N-Dimethy-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	51.1	

TABLE II (continued)

Compound	% Inhibition	
	LTB4	5-HETE
N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	1.6	10.0
N-(3,5-Dimethylphenyl)-4-methyl-6-(3-pyridinyl)-2-pyrimidinamine	32.7	40.0
N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzendiamine	3.6	
4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine, sulfate	52.4	
N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	22.9	30.0
4-Methyl-N-phenyl-6-(2-pyridinyl)-2-pyrimidinamine	30.3	42.0
4-[[4-(4-Pyridinyl)-2-pyrimidinyl]-amino]-phenol		36.0
N-(4-Methoxyphenyl)-N-methyl-4-(4-pyridinyl-2-pyrimidinamine	57.4	
N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	39.6	50.0
N,N-Dimethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]-1,3-benzenediamine	31.1	37.7
N-Methyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	24.1	53.6
N-[1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]phenyl]ethyl]formamide	34.0	
N-[4-[[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]amino]phenyl]acetamide	51.0	46.0
N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-diethyl-1,4-benzenediamine	51.0	45.0
N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	20.0	16.0

TABLE II (continued)

Compound	% Inhibition	
	LTB4	5-HETE
N-[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	47.0	28.0
N-[3-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	50.0	51.0
N-[3-(1H-Imidazolyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	50.0	39.0
N-[4-(2-Furanyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride		54.0
N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine		19.0
4-[[4-(2-Furanyl)-2-pyrimidinyl]amino]-benzenesulfonamide	47.0	

The novel compounds of the present invention are effective as antiasthmatic agents in mammals when administered in amounts ranging from about 0.1 mg to about 100 mg/kg of body weight per day. A preferred dosage regimen for optimum results would be from about 0.1 mg to about 25 mg/kg of body weight per day, and such dosage units are employed that a total of from about 7 mg to about 1.8 g of the active compound for a subject of about 70 kg of body weight are adminstered in a 24 hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage is that these active compounds may be adminstered in any convenient manner such as by the oral, aerosol, intravenous, intramuscular, or subcutaneous routes.

The active compounds may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be compressed into tablets or they may be incorporated directly with the food of the diet. For oral therapeutic administration, these active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 200 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts used. In addition, these active compounds may be incorporated into sustained-release preparations and formulations.

Compositions according to the present invention having the desired clarity, stability and adaptability for parenteral use are obtained by dissolving from 0.10% to 10.0% by weight of active compound in a vehicle consisting of a polyhydric aliphatic alcohol or mixtures thereof. Especially satisfactory are glycerin, propylene glycol, and polyethylene glycols. The polyethylene glycols consist of a mixture of non-volatile, normally liquid, polyethylene glycols which are soluble in both water and organic liquids and which have molecular weights of from about 200 to 1500. Although various mixtures of the aforementioned non-volatile polyethylene glycols may be employed, it is preferred to use a mixture having an average molecular weight of from about 200 to about 400.

In addition to the active compound, the parenteral solutions may also contain various preservatives which may be used to prevent bacterial and fungal contamination. The preservatives which may be used for these purposes are, for example, myristyl-gamma-picolinium chloride, benzalkonium chloride, phenethyl alcohol, p-chlorophenyl-alpha-glycerol ether, methyl and propyl parabens, and thimerosal. As a practical matter, it is also convenient to employ antioxidants. Suitable antioxidants include, for example, sodium bisulfite, sodium metabisulfite, and sodium formaldehyde sulfoxylate. Generally, from about 0.05% to about 0.2% concentrations of antioxidant are employed.

These compounds may also be administered by inhalation using conventional Aerosol® formulations.

The invention will be described in greater detail in conjunction with the following specific examples.

Example 1

4-(3-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine

A 7.04 g amount of 3-dimethylamino-1-(3-pyridinyl)-2-propen-1-one (U. S. Patent 4,281,000) and 18.72 g of [3-(trifluoromethyl)phenyl]guanidine carbonate in 500 ml of n-propanol was heated at reflux temperature for 16 hours. The solvent was evaporated to near dryness, then water was added and the precipitate which formed was collected by filtration, then recrystallized from hexane to give 5.55 g of the desired product, mp 170-171°C.

Example 2

N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine

A mixture of 14.4 g of 3-dimethylamino-1-(3-pyridinyl)-2-propen-1-one and 16.1 g of 4-methoxyphenyl guanidine carbonate in 200 ml of isopropanol was heated at reflux for 20 hours. The reaction mixture was cooled, the crude product was collected by filtration and washed with water. The material was recrystallized from isopropanol

to give the desired product as light yellow crystals, mp 121-122°C.

Example 3

N-(4-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine

A 14.4 g amount of 3-dimethylamino-1-(4-pyridinyl)-2-propen-1-one (U. S. Patent 4,281,000) and 16.1 g of 4-methoxyphenylguanidine carbonate in 200 ml of isopropanol was heated at reflux for 24 hours. The solvent was evaporated to 1/3 volume, then the mixture was cooled in an ice-bath to crystallize the crude product. The product was collected by filtration and washed with water, then with isopropanol. The material was recrystallized from isopropanol/ethylene glycol monomethyl ether to give 16.7 g of the desired product as yellow crystals, mp 174-175°C.

Example 4

N-(4-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine

A mixture of 10.9 g of 3-dimethylamino-1-(2-thienyl)-2-propen-1-one (U. S. Patent 4,374,988) and 11.8 g of 4-methoxyphenylguanidine carbonate in 150 ml of isopropanol was heated at reflux for 48 hours. The solution was cooled, then filtered, giving 9.0 g of the desired product as yellow crystals, mp 158-160°C.

Example 5

4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid, methyl ester

A solution of 10.0 g of 4-guanidinobenzoic acid, hydrochloride in 310 ml of methanol was mixed with 6.0 ml (9.68 g) of thionyl chloride at 0°C for 15 minutes, then stirred for one hour at room temperature and then heated at reflux for 16 hours. The solvent ws removed in vacuo and the solid was washed with ether and air dried to give 11.4 g of white crystals (A).

The above procedure was repeated using 20.0 g of 4-guanidinobenzoic acid, 11.9 ml (19.4 g) of thionyl chloride and 600 ml of methanol to give 22.6 g of white crystals (B).

The products (A) and (B) were combined and recrystallized from absolute ethanol. The product was washed with cold absolute ethanol and air dried giving 26.2 g of p-guanidinobenzoic acid, methyl ester, hydrochloride as white crystals, mp 137-138.5°C (dec.).

A 9.15 g amount of the above compound was partially dissolved in 100 ml of methanol (stored over 4A molecular sieves) and 2.15 g of sodium methoxide was added. The mixture was stirred briefly, then 7.0 g of 3-dimethylamino-1-(4-pyridinyl)-2-propen-1-one was added and the mixture was heated under argon with stirring for 21.5 hours. The reaction mixture was cooled in an ice bath, then filtered and washed with cold methanol. The residue was dissolved in a mixture of dichloromethane and methanol and filtered to remove sodium chloride. The filtrate was concentrated on a steam bath until crystal formation. The mixture was allowed to stand at room temperature for 16 hours then was filtered. The precipitate was washed with ice cold methanol then dried and gave 5.8 g of the desired product, mp 194.5-196.5°C.

Example 6

3-Dimethylamino-1-(3-indolyl)-2-propen-1-one

A mixture of 3.18 g of 3-acetylindole and 5.17 ml. (4.36 g) of tert-butoxybis(dimethylamino)methane was heated on a steam bath for 4 hours. The cooled reaction mixture was triturated with n-hexanes and gave a semi-solid. The solvent was removed in vacuo and the material was triturated with dichloromethane giving 3.08 g of the desired compound as a tan crystalline solid, mp 239-245°C.

Example 7

3-Dimethylamino-1-(5-methyl-2-thienyl)-2-propen-1-one

A mixture of 56.08 g of 2-acetyl-5-methylthiophene and 250 ml of N,N-dimethylformamide dimethylacetal was heated on a steam bath under an air condenser for 16 hours. The mixture was cooled in an ice bath and filtered giving 66.82 g of the desired compound, mp 118-121°C.

Example 8

3-(Dimethylamino)-1-(5-methyl-2-furanyl)-2-propen-1-one

A mixture of 37.24 g of 2-acetyl-5-methylfuran and 150 ml of N,N-dimethylformamide dimethylacetal was heated on a steam bath under an air condenser for 16.5 hours. The solvent was removed in vacuo and the residue taken up in dichloromethane and passed through a short column of magnesium silicate. The filtrate was evaporated on a steam bath with the addition of n-hexanes to a volume of 100-150 ml. Cooling with scratching gave 28.31 g of the desired compound, mp 123-125°C.

Example 9

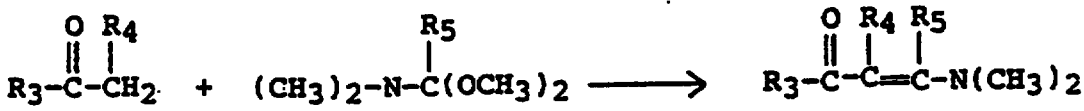
3-(Dimethylamino)-1-(1H-pyrrol-2-yl)-(E)-2-propen-1-one

A mixture of 39.6 g of 2-acetylpyrrole and 104 ml (87.7 g) of tert-butoxy bis(dimethylamino)methane was heated on a steam bath for 20 minutes. The reaction was allowed to subside, then heating was continued for 6 hours. The mixture solidified then was slurried in hexane with chilling. The crude product was collected, washed with hexane and dried. The solid was dissolved in chloroform containing 5% methanol and filtered through magnesium silicate. The eluent was evaporated in vacuo and the residue was recrystallized from dichloromethane/hexane containing a small amount of methanol. The solid was collected, washed with hexane then dried in vacuo giving 25.1 g of the desired compound as yellow crystals, mp 192-193°C (dec.).

The following 3-(dimethylamino)acrylophenone intermediate compounds listed in Table III were prepared in a similar manner to the procedures described in Examples 6-8 and by those described in U. S. Patents 4,281,000, 4,374,988 and in Case 29,240, Serial number 672,753, filed on November 19, 1984.

TABLE III

3-(Dimethylamino)acrylophenone Intermediates



Ex.	R_3	R_4	R_5	MP°C
10	2-Furanyl	H	H	84-86
11	2-pyridinyl	H	H	127-130
12	2-furanyl	CH_3	H	Oil
13	4-pyridinyl	CH_3	H	106-108
14	4-methyl-3-pyridinyl	H	H	116-118
15	4-methyl-3-pyridinyl	H	CH_3	119-120
16	2-pyrazinyl	H	H	132-133
17	3-thienyl	H	H	89-90
18	4-quinolinyl	H	H	
19	3-methyl-2-thienyl	H	H	45-49
20	1-methyl-1H-pyrrol-2-yl	H	H	94-95
21	5-methyl-2-thienyl	H	CH_3	123-126
22	2,5-dimethyl-3-furanyl	H	H	91-95
23	2-pyridinyl	H	CH_3	68-70

This Sheet Has Been Replaced



TABLE III (continued)

Ex.	R_3	R_4	R_5	MP°C
24	2-thienyl	H	CH_3	97-99
25	4-pyridinyl	H	CH_3	88-89
26	3-pyridinyl	H	CH_3	62-64
27	3-pyridinyl	CH_3	H	76-78
28	3-methyl-2-pyridinyl	H	H	97-98
29	2-benzofuranyl	H	H	137.0-138.5
30	3-pyridinyl	H	H	97-99
31	2-phenothiazine	H	H	

Examples 32-251

4,5,6-Substituted-2-pyrimidinamines

The following 4,5,6-substituted-2-pyridinamine final products listed in Table IV were obtained by reacting a 3-(dimethylamino)acrylophenone from Table III and an appropriately substituted phenylguanidine base, carbonate, sulfate, nitrate or hydrochloride salt in an inert solvent such as absolute ethanol, n-propanol, isopropanol, 2-methoxyethanol, or n-butanol and the like, with or without a base such as sodium hydroxide, potassium hydroxide or potassium carbonate and the like by heating at the reflux temperature for from 6-90 hours, then recovering the product in a conventional manner with recrystallization from solvents such as n-propanol, isopropanol, absolute ethanol and the like.

TABLE IV

2-Amino-4,5,6-substituted Pyrimidinamines

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
32	Ex. 12	Phenylguanidine carbonate	4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine	141-142
33	Ex. 3	[3-(Trifluoromethyl)-phenyl]guanidine carbonate	4-(4-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	198-200
34	Ex. 1	Phenylguanidine carbonate	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine	147-148
35	Ex. 1	(4-Acetylphenyl)guanidine	N-(4-Acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	181-183
36	Ex. 1	(4-Fluorophenyl)guanidine carbonate	N-(4-Fluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	167-169
37	Ex. 11	(4-Methoxyphenyl)guanidine carbonate	N(4-Methoxyphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	162-164
38	Ex. 3	(4-Fluorophenyl)guanidine carbonate	N-(4-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	186-188

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
39	Ex. 1	(4-Bromophenyl)guanidine carbonate	N-(4-Bromophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	174-175
40	Ex. 4	(4-Fluorophenyl)quanidine carbonate	N-(4-Fluorophenyl)-4-(2-thienyl)-2-pyrimidinamine	176-178
41	Ex. 11	[3-(Trifluoromethyl)-phenyl]guanidine carbonate	4-(2-Pyridinyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	161-162
42	Ex. 4	Phenylguanidine carbonate	N-Phenyl-4-(2-thienyl)-2-pyrimidinamine	137-139
43	Ex. 1	3-Chloro-4-methylphenylguanidine carbonate	N-(3-Chloro-4-methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	140-145
44	Ex. 11	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	135-137
45	Ex. 3	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	157-159

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
46	Ex. 3	Phenylguanidine carbonate	N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine	153-154
47	Ex. 1	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	102-103
48	Ex. 3	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	138-140
49	Ex. 13	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-5-methyl-4-(4-pyridinyl)-2-pyrimidinamine	132-133
50	Ex. 3	3,4-Dichlorophenylguanidine carbonate	N-(3,4-Dichlorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	214-216
51	Ex. 1	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	120-122.5
52	Ex. 11	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	148.5-149.5

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
53	Ex. 4	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidinamine	112.5-114.5
54	Ex. 10	Phenylguanidine carbonate	4-(2-Furanyl)-N-phenyl-2-pyrimidinamine	144-145
55	Ex. 10	3-Methylphenylguanidine carbonate	4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	98-99.5
56	Ex. 14	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	154-155
57	Ex. 15	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-6-methyl-4-(6-methyl-3-pyridinyl)-2-pyrimidinamine	118-120
58	Ex. 16	4-Ethylphenylguanidine carbonate	N(4-Ethylphenyl)-4-pyrazinyl-2-pyrimidinamine	157.5-159
59	Ex. 16	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(4-pyrazinyl)-2-pyrimidinamine	112.5-117

This Sheet Has Been Replaced

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
60	Ex. 3	2-Methylphenylguanidine carbonate	N-(2-Methylphenyl)-4-pyrazinyl)-2-pyrimidinamine	129-130.5
61	Ex. 3	3-Ethylphenylquanidine sulfate	N-(3-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	126-128
62	Ex. 3	2,5-Dimethylphenylguanidine carbonate	N-(2,5-Dimethylphenyl)-4-(4-pyridinyl-2-pyrimidinamine	131-134
63	Ex. 3	2,3-Dimethylhenylguanidine carbonate	N-(2,3-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	121-123
64	Ex. 17	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(3-thienyl)-2-pyrimidinamine	104.5-105.5
65	Ex. 11	2,5-Dimethylphenylguanidine carbonate	N-(2,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	139-142
66	Ex. 3	3,5-Dimethylphenylguanidine carbonate	N-(3,5-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	183-185

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
67	Ex. 3	1-Naphthylguanidine nitrate	N-1-Naphthalenyl-4-(4-pyridinyl)-2-pyrimidinamine	174-176
68	Ex. 11	3,5-Dimethylphenylguanidine hydrochloride	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	114-119
69	Ex. 11	1-Naphthylguanidine nitrate	N-1-Naphthalenyl-4-(2-pyridinyl)-2-pyrimidinamine	135-138
70	Ex. 3	2,4-Dimethylphenylguanidine carbonate	N-(2,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	116-118
71	Ex. 3	2,4,6-Trimethylphenylguanidine carbonate	4-(4-Pyridinyl)-N-(2,4,6-trimethylphenyl)-2-pyrimidinamine	142-144
72	Ex. 10	4-Methoxyphenylguanidine carbonate	4-(2-Furanyl)-N-(4-methoxyphenyl)-2-pyrimidinamine	155-158.5
73	Ex. 10	[3-(Trifluoromethyl)-phenyl]guanidine carbonate	4-(2-Furanyl)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	150-154

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
74	Ex. 10	4-Fluorophenylguanidine carbonate	N-(4-Fluorophenyl)-4-(2-furanyl)-2-pyrimidinamine	150-152
75	Ex. 11	N-Cyclopentylguanidine sulfate	N-Cyclopentyl-4-(2-pyridinyl)-2-pyrimidinamine	106-109
76	Ex. 11	3,4-Dimethylphenylguanidine carbonate	N-(3,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	130-133.5
77	Ex. 17	4-Methoxyphenylguanidine carbonate	N-(4-Methoxyphenyl)-4-(3-thienyl)-2-pyrimidinamine	158-160.5
78	Ex. 10	3-Ethylphenylguanidine sulfate	N-(3-Ethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	95-98
79	Ex. 6	Phenylguanidine carbonate	4-(1H-Indol-3-yl)-N-phenyl-2-pyrimidinamine	188-190
80	Ex. 3	2-Methoxy-5-methylphenylguanidine carbonate	N-(2-Methoxy-5-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	96-98.5

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
81	Ex. 20	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-2-pyrimidinamine	117-120
82	Ex. 20	4-Ethylphenylquanidine carbonate	N-(4-Ethylphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-2-pyrimidinamine	89-91
83	Ex. 20	Phenylguanidine carbonate	4-(1-Methyl-1H-pyrrol-2-yl)-N-phenyl-2-pyrimidinamine	118-120
84	Ex. 4	3-Ethylphenylguanidine sulfate	N-(3-Ethylphenyl)-4-(2-thienyl)-2-pyrimidinamine	114-116
85	Ex. 17	3-Ethylphenylguanidine sulfate	N-(3-Ethylphenyl)-4-(3-thienyl)-2-pyrimidinamine	86-89
86	Ex. 6	3-Methylphenylguanidine carbonate	4-(1H-Indol-2-yl)-N-(3-methylphenyl)-2-pyrimidinamine	164-167
87	Ex. 18	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine	196-198

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
88	Ex. 18	Phenylguanidine carbonate	N-Phenyl-4-(4-quinolinyl)-2-pyrimidinamine	182-184
89	Ex. 18	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(4-quinolinyl)-2-pyrimidinamine	176-178
90	Ex. 10	3,5-Dimethylphenylguanidine hydrochloride	N-(3,5-Dimethylphenyl)-4-(2-furanyl)-2-pyrimidinamine	126-129
91	Ex. 4	3,5-Dimethylphenylguanidine hydrochloride	N-(3,5-Dimethylphenyl)-4-(2-thienyl)-2-pyrimidinamine	152-155
92	Ex. 3	N-Methyl-N-phenylguanidine hydrochloride	N-Methyl-N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine	105-107
93	Ex. 3	2,4-Difluorophenylguanidine hydrochloride	N-(2,4-Difluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	172-174
94	Ex. 1	2,4-Difluorophenylguanidine hydrochloride	N-(2,4-Difluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	163-165

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
95	Ex. 7	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	114-116
96	Ex. 3	2,6-Difluorophenylguanidine hydrochloride	N-(2,6-Difluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	174-176
97	Ex. 9	Phenylguanidine carbonate	N-Phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine	154-157
98	Ex. 1	4-Tert-butylphenylguanidine sulfate	N-[4-(1,1-Dimethylethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	130-133
99	Ex. 1	2,6-Difluorophenylguanidine hydrochloride	N-(2,6-Difluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	163-166
100	Ex. 7	3,5-Dimethylhenylguanidine hydrochloride	N-(3,5-Dimethylphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	133-135
101	Ex. 7	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	123-125

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
102	Ex. 11	3,4-Dimethylphenylguanidine hydrochloride	N-[(3,4-Dimethylphenyl)methyl]-4-(2-pyridinyl)-2-pyrimidinamine	158-160
103	Ex. 7	3,5-Dimethylphenylguanidine hydrochloride	N-(3,5-Dimethylphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamine	151-155
104	Ex. 9	3-Methylphenylguanidine carbonate	N-(3-Methylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine	129-130
105	Ex. 8	3-Methylphenylguanidine carbonate	4-(5-Methyl-2-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	119-121
106	Ex. 21	Phenylguanidine carbonate	4-Methyl-6-(5-methyl-2-thienyl)-N-phenyl-2-pyrimidinamine	133-135
107	Ex. 3	4-(Dimethylamino)phenylguanidine dihydrochloride	N-[4-(Dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	164-166
108	Ex. 3	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	159-160

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
109	Ex. 11	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	110-113
110	Ex. 11	4-(Dimethylamino)phenylguanidine dihydrochloride	N-[4-(Dimethylamino)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	171-174
111	Ex. 1	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	126-127
112	Ex. 1	3,5-Dimethylphenylguanidine hydrochloride	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	125-128
113	Ex. 1	4-(Ethoxycarbonyl)phenylguanidine hydrochloride	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]benzoic acid, ethyl ester	197-202
114	Ex. 1	4-(Dimethylamino)phenylguanidine dihydrochloride	N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	165-166
115	Ex. 22	Phenylguanidine carbonate	4-(2,5-Dimethyl-3-furanyl)-N-phenyl-2-pyrimidinamine	116-118

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
116	Ex. 17	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(3-thienyl)-2-pyrimidinamine	151-152.5
117	Ex. 22	3-Methylphenylguanidine carbonate	4-(2,5-Dimethyl-3-furanyl)-N-(3-methylphenyl)-2-pyrimidinamine	144-146
118	Ex. 22	3,5-Dimethylphenylguanidine hydrochloride	4-(2,5-Dimethyl-3-furanyl)-N-(3,5-dimethylphenyl)-2-pyrimidinamine	149-152
119	Ex. 22	4-Ethylphenylguanidine carbonate	4-(2,5-Dimethyl-3-furanyl)-N-(4-ethylphenyl)-2-pyrimidinamine	93-96
120	Ex. 1	3-Dimethylaminophenylguanidine dihydrochloride	N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	123-125
121	Ex. 11	3-(Ethoxycarbonyl)phenylguanidine hydrochloride	3-[[4-(2-Pyridinyl)-2-pyrimidinyl]-amino]benzoic acid, ethyl ester	156-158
122	Ex. 11	3-(Dimethylamino)phenylguanidine dihydrochloride	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	109-111

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
123	Ex. 1	3-(Ethoxycarbonyl)phenylguanidine hydrochloride	3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid, ethyl ester	95-103
124	Ex. 10	4-(Dimethylamino)phenylguanidine dihydrochloride	N'-[4-(2-Furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	166-167
125	Ex. 4	4-(Dimethylamino)phenylguanidine dihydrochloride	N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	174-175
126	Ex. 22	4-(Dimethylamino)phenylguanidine dihydrochloride	N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	126-129
127	Ex. 19	4-(Dimethylamino)phenylguanidine dihydrochloride	N,N-Dimethyl-N'-[4-(3-methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	145-148
128	Ex. 3	3-(Dimethylamino)phenylguanidine dihydrochloride	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	165-168
129	Ex. 12	3,5-Dimethylphenylguanidine	N-(3,5-Dimethylphenyl)-4-(2-furanyl)-5-methyl-2-pyrimidinamine	155-158

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
130	Ex. 12	4-(Dimethylamino)phenyl-guanidine dihydrochloride	N'-[4-(2-Furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	146-148
131	Ex. 29	4-(Dimethylamino)phenyl-guanidine dihydrochloride	N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-dimethyl-1,4-benzenediamine	175-178
132	Ex. 11	2-Guanidinobenzimidazole	N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1H-benzimidazol-2-amine	276-279.5
132	Ex. 23	Phenylguanidine carbonate	4-Methyl-N-phenyl-6-(2-pyridinyl)-2-pyrimidinamine	94-98
134	Ex. 4	3-(Dimethylamino)phenyl-guanidine dihydrochloride	N,N-Dimethyl-N'-[4-(2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	118-120
135	Ex. 8	3-(Dimethylamino)phenyl-guanidine dihydrochloride	N,N-Dimethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]-1,3-benzenediamine	126-129
136	Ex. 22	3-(Dimethylamino)phenyl-guanidine dihydrochloride	N'-[4-(2,5-Dimethyl-3-furanyl)-2-pyrimidinyl]-N,N-dimethyl-1,3-benzenediamine	153-155

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
137	Ex. 3	4-Aminoacetylphenylguanidine hydrochloride	N-[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	294-296
138	Ex. 3	4-(Diethylamino)phenylguanidine dihydrochloride	N,N-Diethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	126-128
139	Ex. 1	4-(Diethylamino)phenylguanidine dihydrochloride	N,N-Diethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	100-104
140	Ex. 17	Phenylguanidine carbonate	N-Phenyl-4-(3-thienyl)-2-pyrimidinamine	142-143
141	Ex. 11	4-Fluorophenylguanidine carbonate	N-(4-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	207-209
142	Ex. 11	4-Chlorophenylguanidine carbonate	N-(4-Chlorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	220-222
143	Ex. 3	4-Methylphenylguanidine carbonate	N-(4-Methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	197.5-198.5

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
144	Ex. 31	N-[3-(Trifluoromethyl)-phenyl]guanidine carbonate	4-(2-Phenothiazine)-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	240-243
145	Ex. 31	4-Methoxyphenylguanidine carbonate	N-(4-Methoxyphenyl)-4-(2-phenothiazine)-2-pyrimidinamine	220-225
146	Ex. 31	3,4-Dichlorophenylguanidine carbonate	N-(3,4-Dichlorophenyl)-4-(2-phenothiazine)-2-pyrimidinamine	235-238
147	Ex. 11	2,4-Dimethylphenylguanidine carbonate	N-(2,4-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	111.5-113.5
148	Ex. 3	2-Methoxyphenylguanidine carbonate	N-(2-Methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	112-117
149	Ex. 3	2,5-Dimethoxyphenylguanidine carbonate	N-(2,5-Dimethoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	151.5-155.0
150	Ex. 11	2-Methoxy-5-methylphenylguanidine carbonate	N-(2-Methoxy-5-methylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	117-118.5

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MPºC
151	Ex. 3	3,4-Dimethylphenylguanidine hydrochloride	N-[(3,4-Dimethylphenyl)methyl]-4-(4-pyridinyl)-2-pyrimidinamine	132-136
152	Ex. 29	3-Methylphenylguanidine carbonate	4-(2-Benzofuranyl)-N-(3-methylphenyl)-2-pyrimidinamine	143-144
153	Ex. 3	3,4-Dimethylphenylguanidine carbonate	N-(3,4-Dimethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	169-171.5
154	Ex. 17	4-Fluorophenylguanidine carbonate	N-(4-Fluorophenyl)-4-(3-thienyl)-2-pyrimidinamine	185-187
155	Ex. 31	Phenylguanidine carbonate	4-(10H-Phenothiazin-2-yl)-N-phenyl-2-pyrimidinamine	218-220
156	Ex. 6	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(1H-indol-3-yl)-2-pyrimidinamine	209-210
157	Ex. 3	1,1'-Biphenylguanidine hydrochloride	N-[1,1'-Biphenyl]-4-yl-4-(4-pyridinyl)-2-pyrimidinamine	203-205

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
158	Ex. 3	[4-(1,1-Dimethylethyl)-phenyl]guanidine sulfate	N-[4-(1,1-Dimethylethyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	181-183
159	Ex. 11	N-Methyl-N-phenylguanidine hydrochloride	N-Methyl-N-phenyl-4-(2-pyridinyl)-2-pyrimidinamine	88-91
160	Ex. 9	4-Ethylphenylguanidine carbonate	N-(4-Ethylphenyl)-4-(1H-pyrrol-2-yl)-2-pyrimidinamine	131-133
161	Ex. 19	Phenylguanidine carbonate	4-(3-Methyl-2-thienyl)-N-phenyl-2-pyrimidinamine	137-140
162	Ex. 25	4-Dimethylaminophenylguanidine dihydrochloride	N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	153-154
163	Ex. 26	3,5-Dimethylphenylguanidine hydrochloride	N-(3,5-Dimethylphenyl)-4-methyl-6-(3-pyridinyl)-2-pyrimidinamine	136-140
164	Ex. 12	N-[3-(Trifluoromethyl)-phenyl]guanidine carbonate	4-(2-Furanyl)-5-methyl-N-[3-(trifluoromethyl)phenyl]-2-pyrimidinamine	169-171

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
165	Ex. 23	N-(3,5-Dimethylphenyl)-guanidine	N-(3,5-Dimethylphenyl)-4-methyl-6-(2-pyridinyl)-2-pyrimidinamine	110-112
166	Ex. 10	2-Guanidinobenzimidazole	N-[4-(2-Furanyl)-2-pyrimidinyl]-1H-benzimidazol-2-amine	306.5-308
167	Ex. 23	N-[4-(Dimethylamino)-phenyl]guanidine dihydrochloride	N,N-Dimethyl-N'-[4-methyl-6-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	145-148
168	Ex. 3	4-(1-Imidazolyl)phenyl-guanidine dihydrochloride	N-[4-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	>320
169	Ex. 30	4-(1-Imidazolyl)phenyl-guanidine dihydrochloride	N-[4-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	134-174 (Dec.)
170	Ex. 11	N-[4-Diethylamino)phenyl]guanidine dihydrochloride	N,N-Diethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	138-139
171	Ex. 11	4-(1-Imidazolyl)phenyl-guanidine dihydrochloride	N-[4-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	204-206

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
172	Ex. 10	4-(1-Imidazolyl)phenylguanidine dihydrochloride	4-(2-Furanyl)-N-[4-(1H-imidazol-1-yl)phenyl]-2-pyrimidinamine	211-212.5
173	Ex. 12	N-[3-Dimethylamino)phenyl]guanidine dihydrochloride	N,N-Dimethyl-N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-1,3-benzenediamine	154-156
174	Ex. 21	N-[3-Dimethylamino)phenyl]guanidine dihydrochloride	N,N-Dimethyl-N'-[4-(5-methyl-2-thienyl)-2-pyrimidinyl]-1,3-benzenediamine	130-133
175	Ex. 17	N-[4-(Dimethylamino)-phenyl]guanidine dihydrochloride	N,N-Dimethyl-N'-[4-(3-thienyl)-2-pyrimidinyl]-1,4-benzenediamine	173-174
176	Ex. 13	N-[3-(Dimethylamino)phenyl]guanidine dihydrochloride	N,N-Dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	200-201
177	Ex. 4	4-(1-Imidazolyl)phenylguanidine hydrochloride	N-[4-(1H-Imidazol-1-yl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	179-189 (Dec.)
178	Ex. 19	N-(3-Methoxyphenyl)guanidine hydrochloride	N-(3-Methoxyphenyl)-4-(3-methyl-2-thienyl)-2-pyrimidinamine	120-123

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
179	Ex. 30	N-[4-(Acetylamino)phenyl]guanidine hydrochloride	N-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	192-195
180	Ex. 30	N-(4-Benzenesulfonamido)-guanidine hydrochloride	4-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]benzenesulfonamide	224-225
181	Ex. 3	N-(3-Chlorophenyl)guanidine carbonate	N-(3-Chlorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	160-161
182	Ex. 30	N-(3-Chlorophenyl)guanidine carbonate	N-(3-Chlorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	146-148
183	Ex. 17	N-(3-Methoxyphenyl)guanidine hydrochloride	N-(3-Methoxyphenyl)-4-(3-thienyl)-2-pyrimidinamine	142-145
184	Ex. 4	N-(3-Methoxyphenyl)guanidine hydrochloride	N-(3-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine	151-153
185	Ex. 30	N-Methyl-N-acetylphenylguanidine hydrochloride	N-Methyl-N-[4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	194-197

This Sheet Has Been Replaced

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
186	Ex. 3	N-Methyl-N-acetylphenylguanidine hydrochloride	N-Methyl-N-[4-[[4-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	233-234
187	Ex. 11	N-Methyl-N-acetylphenylguanidine hydrochloride	N-Methyl-N-[4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	179-181
188	Ex. 10	N-(3-Methoxyphenyl)guanidine hydrochloride	4-(2-Furanyl)-N-(3-methoxyphenyl)-2-pyrimidinamine	114-116
189	Ex. 29	N-(3-Methoxyphenyl)guanidine hydrochloride	4-(2-Benzofuranyl)-N-(3-methoxyphenyl)-2-pyrimidinamine	137
190	Ex. 9	N-(Ethylphenyl)guanidine carbonate	N-(4-Ethylphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-2-pyrimidinamine	89-91
191	Ex. 3	N-Acetylphenylguanidine hydrochloride	N-[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	294-296
192	Ex. 10	N,N-Dimethylphenylguanidine dihydrochloride	N,N-Dimethyl-N'-[4-(2-furanyl)-5-methyl-2-pyrimidinyl]-1,3-benzenediamine	154-156

This Sheet Has Been Replaced

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
193	Ex. 30	N-Acetylphenylguanidine hydrochloride	N-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	192-195
194	Ex. 11	Sulfonylaminophenylguanidine hydrochloride	4-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]benzenesulfonamide	274-277
195	Ex. 11	N-Acetylphenylguanidine hydrochloride	N-[4-[[4-(2-Pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	254-255
196	Ex. 4	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(2-thienyl)-2-pyrimidinamine	151-153
197	Ex. 30	4-(4-Methylpiperazin-1-yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-1-piperazinyl)-phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	174-175
198	Ex. 7	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(5-methyl-2-thienyl)-2-pyrimidinamine	149-151
199	Ex. 11	3-Chlorophenylguanidine hydrochloride	N-(3-Chlorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	164-165

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
200	Ex. 10	4-(4-Methylpiperazin-1-yl)phenylguanidine dihydrochloride	4-(2-Furanyl)-N-[4-(4-methyl-1-piperazinyl)phenyl]-2-pyrimidinamine	193-195
201	Ex. 4	4-(4-Methylpiperazin-1-yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-1-piperazinyl)-phenyl]-4-(2-thienyl)-2-pyrimidinamine	215.5-216.5
202	Ex. 11	4-(4-Methylpiperazin-1-yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-1-piperazinyl)-phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	192-193

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
203	Ex. 13	4-(4-Methylpiperazin-1-yl)phenylguanidine dihydrochloride	N-[4-(4-Methyl-1-piperazinyl)-phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	207-209
204	Ex. 22	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(2,5-dimethyl-3-furanyl)-2-pyrimidinamine	124-125
205	Ex. 13	3-Fluorophenylguanidine hydrochloride	N-(3-Fluorophenyl)-4-(4-pyridinyl)-2-pyrimidinamine	162
206	Ex. 30	3-Fluorophenylguanidine hydrochloride	N-(3-Fluorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	147-150
207	Ex. 11	3-Fluorophenylguanidine hydrochloride	N-(3-Fluorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	162-164
208	Ex. 10	4-Acetylphenylguanidine	1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone	166-168

TABLE IV. (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
209	Ex. 30	1-(Methylethyl)phenyl-guanidine hydrochloride	N-[4-(1-Methylethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	124-125
210	Ex. 30	3-Ethylphenylguanidine hydrochloride	N-(3-Ethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	80-88
211	Ex. 11	3-Ethylphenylguanidine hydrochloride	N-(3-Ethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine	101-104
212	Ex. 11	3-Benzenesulfonamido-guanidine hydrochloride	3-[[4-(2-Pyridinyl)-2-pyrimidinyl]-amino]benzenesulfonamide	223-225
213	Ex. 30	3-Benzenesulfonamido-guanidine hydrochloride	3-[[4-(3-Pyridinyl)-2-pyrimidinyl]-amino]benzenesulfonamide	278-280
214	Ex. 24	4-(1,1-Dimethylethyl)-phenylguanidine hydro-chloride	N-[4-(1,1-Dimethylethyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	150-154
215	Ex. 10	4-(Diethylamino)phenyl-guanidine hydrochloride	N,N-Diethyl-N'-[4-(2-furanyl)-2-pyrimidinyl]-1,4-benzenediamine	132-133

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
216	Ex. 13	4-Benzenesulfonamido-guanidine hydrochloride	3-[[4-(4-Pyridinyl)-2-pyrimidinyl]-amino]benzenesulfonamide	262-264
217	Ex. 13	4-Acetylaminophenyl-guanidine hydrochloride	N-[3-[[4-(4-Pyridinyl)-2-pyrimi-dinyl]amino]phenyl]acetamide	267-270
218	Ex. 30	4-Acetylaminophenyl-guanidine hydrochloride	N-[3-[[4-(3-Pyridinyl)-2-pyrimi-dinyl]amino]phenyl]acetamide	239-241
219	Ex. 11	3-Acetylaminophenyl-guanidine hydrochloride	N-[3-[[4-(2-Pyridinyl)-2-pyrimi-dinyl]amino]phenyl]acetamide	190-192
220	Ex. 13	3-(1H-Imidazol-1-yl)-phenylguanidine di-hydrochloride	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	232-234
221	Ex. 13	4-Acetylamino-3-methyl-phenylguanidine hydro-chloride	N-[2-Methyl-4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	230-235
222	Ex. 21	4-Acetylaminophenyl-guanidine hydrochloride	N-[4-[[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]amino]phenyl]acetamide	227-230

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
223	Ex. 30	3-[2-(Diethylaminoethoxy)phenyl]guanidine dihydrochloride	N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	79-82
224	Ex. 30	2-Methoxyphenylguanidine carbonate	N-(2-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine	99-101
225	Ex. 24	4-Acetylaminophenylguanidine hydrochloride	N-[4-[[4-(2-Thienyl)-2-pyrimidinyl]amino]phenyl]acetamide	201-203
226	Ex. 30	4-Acetylamino-3-methylphenylguanidine hydrochloride	N-[2-Methyl-4-[4-(3-pyridinyl)-2-pyrimidinyl]phenyl]acetamide	233-235
227	Ex. 29	4-Diethylaminophenylguanidine hydrochloride	N'-[4-(2-Benzofuranyl)-2-pyrimidinyl]-N,N-diethyl-1,4-benzenediamine	134-136
228	Ex. 12	4-Acetylaminophenylguanidine hydrochloride	N-[4-[[4-(2-Furanyl)-2-pyrimidinyl]amino]phenyl]acetamide	230-232

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
229	Ex. 13	4-(Imidazol-1-yl)-3-(trifluoromethyl)phenylguanidine dihydrochloride	N-[4-(1H-Imidazol-1-yl)-3-(trifluoromethyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	238-239
230	Ex. 11	4-Acetylamino-3-methylphenylguanidine hydrochloride	N-[2-Methyl-4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide	232-234
231	Ex. 30	3-(1-Imidazolyl)phenylguanidine dihydrochloride	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	137-144
232	Ex. 24	3-(1-Imidazolyl)phenylguanidine dihydrochloride	N-[3-(1H-Imidazolyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	183-184.5
233	Ex. 10	3-(1-Imidazolyl)phenylguanidine dihydrochloride	4-(2-Furanyl)-N-[3-(1H-imidazol-1-yl)phenyl]-2-pyrimidinamine	160-168

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
234	Ex. 10	3-(Diethylamino)ethoxy-phenylguanidine dihydro-chloride	N-[3-[2-(Diethylamino)ethoxy]phen-yl]-4-(2-furanyl)-2-pyrimidinamine	
235	Ex. 10	3-Methylphenylguanidine hydrochloride	4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine, hydrochloride	195-199
236	Ex. 11	4-(1-Imidazolyl)-3-(tri-fluoromethyl)phenyl-guanidine dihydro-chloride	N-[4-(1H-Imidazol-1-yl)-3-(tri-fluoromethyl)phenyl]-4-(2-pyridin-yl)-2-pyrimidinamine	216-218
237	Ex. 24	3-(Diethylamino)ethoxy-phenylguanidine di-hydrochloride	N-[3-[2-(Diethylamino)ethoxy]phen-yl]-4-(2-thienyl)-2-pyrimidinamine	
238	Ex. 10	4-Benzenesulfonamido-guanidine hydrochloride	4-[[4-(2-Furanyl)-2-pyrimidinyl]-amino]benzenesulfonamide	255-257
239	Ex. 21	4-Benzenesulfonamido-guanidine hydrochloride	4-[[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]amino]benzenesul-fonamide	241-245

This Sheet Has Been Replaced

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
240	Ex. 17	N-Methylacetylamino-phenylguanidine hydro-chloride	N-Methyl-N-[4-[[4-(3-thienyl)-2-pyrimidinyl]amino]phenyl]acetamide	150-153
241	Ex. 13	3-[4-Methyl-1-piperazinyl]phenylguanidine hydrochloride	N-[3-(4-Methyl-1-piperazinyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	150-151.5
242	Ex. 10	3-[4-Methyl-1-piperazinyl]phenylguanidine hydrochloride	4-(2-Furanyl)-N-[3-(4-methyl-1-piperazinyl)phenyl]-2-pyrimidinamine	134.5-136
243	Ex. 24	3-[4-Methyl-1-piperazinyl]phenylguanidine hydrochloride	N-[3-(4-Methyl-1-piperazinyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	125-126.5
244	Ex. 13	2-Dimethylaminophenyl-guanidine dihydro-chloride	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,2-benzenediamine	114-119

This Sheet Has Been Replaced

TABLE IV (continued)

Ex.	Acrylophenone Source	Phenylguanidine Precursor	Product	MP°C
245	Ex. 13	3-(Diethylamino)ethoxyphenylguanidine dihydrochloride	N-[3-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	100-103
246	Ex. 24	3-(Diethylamino)ethoxyphenylguanidine dihydrochloride	N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(2-thienyl)-2-pyrimidinamine	
247	Ex. 24	3-(Dimethylamino)ethoxyphenylguanidine dihydrochloride	N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(2-thienyl)-2-pyrimidinamine	96-98
248	Ex. 17	3-(Dimethylamino)ethoxyphenylguanidine dihydrochloride	N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-thienyl)-2-pyrimidinamine	83-85
249	Ex. 21	4-Diethylaminophenylguanidine hydrochloride	N,N-Diethyl-N'-[4-(5-methyl-2-furanyl)-2-pyrimidinyl]-1,4-benzenediamine	118-119
250	Ex. 21	3-Methoxyphenylguanidine hydrochloride	N-(3-Methoxyphenyl)-4-(5-methyl-2-furanyl)-2-pyrimidinamine	
251	Ex. 13	3-(1H-Imidazol-1-yl)-phenylguanidine dihydrochloride	N-[3-(1H-Imidazol-1-yl)phenyl]-4--(4-pyridinyl)-2-pyrimidinamine	232-239

Example 252

1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]pnenyl]-ethanone, oxime

A 2.03 mg portion of N-(4-acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was mixed with 210 ml of absolute ethanol and 1.26 g of hydroxylamine hydrochloride. An 18.2 ml portion of 1N sodium hydroxide was added, the mixture was heated at reflux for 2 hours and then evaporated to 1/4 volume. This was cooled, the solid collected, washed with ethanol and water and dried, giving 1.9 g of the desired product as cream colored crystals, mp 239-241°C.

Example 253

1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenyl]-ethanone, O-methyloxime

The procedure of Example 252 was repeated using methoxyamine hydrochloride, giving 1.78 g of the desired product as yellow crystals, mp 163-167°C.

Example 254

N-[1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]ethyl]formamide

A mixture of 7.25 g of N-(4-acetylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, 100 ml of formamide and 31 ml. of 98% formic acid was refluxed with stirring overnight. The solvents were then boiled off for 1/2 hour, the reaction cooled and poured into one liter of water. This was extracted with 725 ml of chloroform. The chloroform extract was back washed with 150 ml of water, then dried, filtered and evaporated to a foam. The foam was partitioned between chloroform and water. An equal volume of saturated potassium bicarbonate was added. The organic phase was separated, dried, filtered and evaporated to a foam. This foam was chromatographed on silica gel topped with a thin layer of hydrous magnesium silicate and eluted with chloroform (first four fractions), then with 2% methanol in chloroform (last two fractions). The sixth

(final) fraction was evaporated and then crystallized from chloroform-hexane, giving 1.05 g of the desired product as cream colored crystals, mp 118-121°C.

Example 255

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

A 1.10 g portion of dry 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 25 ml of dimethylformamide. A 213 mg portion of sodium hydride (50% in oil) was added, the reaction was sealed and stirred for 45 minutes. A 480 mg portion of 2-dimethylaminoethyl chloride in 2 ml of dimethylformamide was added and the sealed mixture was stirred overnight. The solvent was removed at 60°C and the residue partitioned between 25 ml of water and 50 ml of ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The organic phases were combined, washed with 1N sodium hydroxide, dried, filtered and evaporated. The residue was taken up in 20 ml of chloroform, boiled down to 1/3 volume and hexane added to turbidity. The mixture was allowed to stand overnight, giving 400 mg of the desired product as beige crystals, mp 108-110°C.

Example 256

N-[4-[3-(Dimethylamino)propoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

A 5.46 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was reacted with 3-dimethylaminopropyl chloride by the procedure of Example 255, giving 2.9 g of the desired product, mp 85-87°C.

Example 257

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

The procedure of Example 256 was repeated using 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol, giving 300 mg of the desired product as yellow crystals, mp 85-87°C.

Example 258

N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

The procedured of Example 255 was repeated, using 2-diethylaminoethyl chloride, giving 3.45 g of the desired product as yellow crystals, mp 87-89°C.

Example 259

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

The procedure of Example 255 was repeated using 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol, giving 1.6 g of the desired product as yellow crystals, mp 120-122°C.

Example 260

N-[4-[2-(Dimethylamino)ethoxy]phenyl]-N',N'-dimethyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine

The procedure of Example 259 was repeated. Subsequent crops of crystals gave 0.4 g of the desired product, mp 87-91°C.

Example 261

N-[4-[3-(Dimethylamino)propoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine

A 2.78 g portion of 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol and 2.35 g of 3-dimethylamino-propyl chloride were reacted as described in Example 255, giving 850 mg of the desired product, mp 123-124.5°C.

Example 262

[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenoxy]-acetic acid, ethyl ester

A mixture of 5.58 g of 4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenol was reacted with ethyl bromo acetate as described in Example 255, giving 1.8 g of the desired product as yellow crystals, mp 109-111°C.

Example 263

N-(4-Methoxyphenyl)-N-methyl-4-(3-pyridinyl)-2-pyrimidinamine

A 2.78 g portion of N-(4-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was dissolved in 30 ml of dimethylformamide. A 528 mg portion of sodium hydride (50% in oil) was added, the reaction sealed and stirred for 45 minutes. A solution of 1.70 g of methyl iodide in 2 ml of dimethylformamide was added, the sealed mixture was stirred overnight and the solvent removed. The residue was partitioned between water and chloroform. The organic phase was dried, filtered and evaporated. The residue was crystallized from ether-hexane giving 1.4 g of the desired product as yellow crystals, mp 88-90°C.

Example 264

N-(4-Methoxyphenyl)-N-methyl-4-(4-pyridinyl)-2-pyrimidinamine

The procedure of Example 263 was repeated using N-(4-methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, giving 510 mg of the desired product as yellow crystals, mp 124-126°C.

Example 265

N-[2-(Diethylamino)ethyl]-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide

A 1.55 ml portion of diethylethylenediamine was added to a solution of 0.01 mole of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid chloride in 50 ml of 1,2-dimethoxyethane. A 10 ml portion of triethylamine was added and the mixture was stirred for 2 hours. The solid was collected, washed with water and recrystallized from absolute ethanol, giving 1.22 g of the desired product, mp 148-150°C.

Example 266

N-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide

A 5.85 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid in 30 ml of thionyl chloride was refluxed on a steam bath for one hour, then evaporated to dryness. The residue was boiled with dimethoxyethane, then cooled and the solid recovered and washed with ether, giving 6.90 g of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzoic acid chloride.

A 6.03 g portion of the above acid chloride was suspended in 25 ml of ethanol and 10 ml of 25% aqueous methyl amine was added. The resulting solid was collected, taken up in hot 2-methoxyethanol, cooled and the solid collected, giving 3.35 g of the desired product, mp 254-257°C.

Example 267

4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]benzoic acid

To a solution of 19.89 g of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid, ethyl ester in 200 ml of 3A ethanol was added 12.5 ml of 10N sodium hydroxide. This mixture was refluxed on a steam bath for 3 hours and then allowed to evaporate. The residue was taken up in water and treated with 10.4 ml of concentrated hydrochloric acid. The resulting solid was collected and dried, giving 18.11 g of the desired product, mp 311-317°C.

Example 268

[4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenoxy]-acetic acid

An 800 mg portion of [4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenoxy]acetic acid, ethyl ester was dissolved in 100 ml of ethanol and 10.7 ml of 1N sodium hydroxide was added. The mixture was stirred for 2 hours, the solvent removed and the residue dissolved in 5 ml of water. The pH was adjusted to 7.0 with 1N hydrochloric acid and the solid collected, washed with water and dried.

The solid was recrystallized from dimethylformamide-ethanol, giving 600 mg of the desired product as yellow crystals, mp 308-310°C.

Example 269

4-[2-[(4-Methoxyphenyl)amino]-4-pyrimidinyl]-1-methylpyridinium iodide

A 2.0 g portion of N-(4-methoxyphenyl)-4-(4-pyridinyl-2-pyrimidinamine was dissolved in 550 ml of absolute ethanol and filtered. To this was added 10 ml of iodomethane. The reaction was heated on a steam bath for 4 hours. Another 10 ml of iodomethane was added and refluxing was continued overnight. The mixture was cooled, the solid collected, washed with ethanol and dried, giving 2.2 g of the desired product as purple crystals, mp 282-284°C.

Example 270

4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol

A 25.0 g portion of N-(4-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine was dissolved in 200 ml of 48% hydrobromic acid and stirred overnight under an argon atmosphere. The mixture was then heated on a steam bath for 7 hours, cooled overnight and evaporated at 60°C. The residue was basified with 200 ml of saturated potassium bicarbonate solution and stirred for 1.5 hours. The solid was collected, washed with water, dried and recrystallized from hot absolute ethanol, giving 19.1 g of the desired product, mp 223-225°C.

Example 271

4-[[4-(4-Pyridinyl)-2-pyrimidinyl]amino]phenol

The procedure of Example 270 was repeated using N-(4-methoxyphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, giving 3.0 g of the desired product as yellow crystals, mp 268-270°C.

Example 272

N-[4-(2-Propenyloxy)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

A 2.73 g portion of dry 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 50 ml of dry dimethylformamide. A 528 mg portion of sodium hydride (50% in oil) was added, the reaction was sealed and stirred for 45 minutes. A solution of 1.33 g of allyl bromide in 10 ml of dimethylformamide was added, the sealed mixture was stirred overnight and then evaporated at 80°C. The residue was partitioned between water and chloroform. The organic phase was separated, dried and filtered. The filtrate was evaporated and the residue crystallized from chloroform-hexane, giving 1.7 g of the desired product as yellow crystals, mp 105-108°C.

Example 273

N-(4-Ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine, pyridine-1-oxide

A mixture of 2.76 g of N-(4-ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine and 3.45 g of m-chloroperbenzoic acid in 100 ml of dichloromethane was stirred at room temperature for 20 hours. The mixture was washed three times with an aqueous saturated solution of sodium bicarbonate and a small amount of saturated saline. The organic layer was dried over magnesium sulfate, filtered through diatomaceous earth, then evaporated in vacuo to give a gelatenous solid. The solid was slurried with 50 ml of dichloromethane and filtered. The solid was washed with a small amount of dichloromethane and air dried to give 500 mg of the product. Recrystallization from absolute methanol gave 460 mg of the desired product, mp 223-225°C.

Example 274

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dihydrochloride

A 2.0 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 70 ml of dichloromethane with warming. The solution was cooled to room temperature, then hydrogen chloride gas was bubbled in to give a brick red precipitate. The mixture became very thick and more dichloromethane was added. The precipitate was collected, air dried, then dried in vacuo and gave 2.63 g of the desired product as red-orange crystals, mp 259-262°C.

Example 275

N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, hydrochloride

A 2.85 g amount of N-[4-[[4-(4-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide was added to a mixture of 10 ml of concentrated hydrochloric acid and 10 ml of water. The reaction mixture was heated at reflux for 90 minutes, then evaporated in vacuo to obtain a solid. The solid was recrystallized from 3A ethanol/water and gave 2.31 g of the desired product as a yellow crystalline solid, mp 292-295°C.

Additional hydrochloride salts listed in Examples 276 to 287 in Table V were obtained from the corresponding base compound by following procedures similar to those described in Examples 274 and 275 and employing various other solvents such as isopropyl alcohol, ethanol, ether and the like.

TABLE V

Ex	Compound	MP°C
276	4-(3-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]pyrimidinamine, hydrochloride	220-223
277	N,N-Dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	239-245
278	N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, hydrochloride	115-150 (dec)
279	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-(pyrimidinyl)]-1,3-benzenediamine, dihydrochloride	204-213
280	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, trihydrochloride	202-205
281	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	178-184
282	N,N-Dimethyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	229-234
283	N,N-Dimethy-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride	232-235
284	N-[4-(1-Aminoethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine, trihydrochloride	
285	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine, hydrochloride	232.5-234
286	N-[3-(1H-Imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine, hydrochloride	259-266
287	4-(2-Furanyl)-N-[3-(4-methyl-1-piperazinyl)phenyl]-2-pyrimidinamine, hydrochloride	259-263

Example 288

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, sulfate

A 2.48 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 120 ml of absolute ethanol with heating, then a solution of 1.02 g of concentrated sulfuric acid in 25 ml of ethanol was added dropwise with stirring. The mixture turned orange then a yellow precipitate formed. The mixture was chilled, the preciptate

was collected, by filtration, washed with cold ethanol then with ether, and air dried to give 2.73 g of yellow-orange crystals.

The preceding compound was dissolved in a small amount of water, then a saturated aqueous solution of sodium bicarbonate was added to pH 8.0 to yield a light yellow precipitate. The precipitate was collected, washed with water and dried in vacuo. A 2.25 g portion this material was recrystallized from about 200 ml of absolute methanol in the cold. The product was collected, washed with absolute ethanol and dried in vacuo to give 1.75 g of the desired product as orange cyrstals, mp 233-235°C.

Additional sulfate salts which were prepared from the corresponding base compound in the manner described hereinabove are listed as Examples 289 to 300 in Table VI.

TABLE VI

Ex	Compound	MP°C
289	4-(2-Pyridinyl)-N-[3-trifluoromethyl)-phenyl]-2-pyrimidinamine, sulfate	208-211
290	N-(3-Methylphenyl)-4-(2-thienyl)-2-pyrimidinamine, sulfate	207.5-210
291	4-(2-Furanyl)-N-(3-methylphenyl)-2-pyrimidinamine sulfate	187-193
292	4-(4-Pyridinyl)-N-[3-(trifluoromethyl)phenyl)]-2-pyrimidinamine, sulfate	250-253
293	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	103-123
294	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine, sulfate	167-187
295	4-(3-Pyridinyl)-N-[3-trifluoromethyl)phenyl]-2-pyrimidinamine, sulfate	196-199

TABLE VI (continued)

Ex	Compound	MP°C
296	N-(3,5-Dimethylphenyl)-[4-(3-pyridinyl)-2-pyrimidinamine, sulfate	209-214
297	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, sulfate	216-218
298	N-(3,5-Dimethylphenyl)-4-methyl-6-(5-methyl-2-thienyl)-2-pyrimidinamine, sulfate	232-234
299	4-(2-Furanyl)-5-methyl-N-phenyl-2-pyrimidinamine, sulfate	140-144
300	N,N-Dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, sulfate	204-211

Example 301

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, phosphate

A 2.0 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 100 ml of ethanol with heating. The solution was allowed to cool to room temperature, then a solution of 2.07 g of phosphoric acid in 25 ml of ethanol was added with stirring. The mixture was chilled for several hours, then the precipitate which formed was collected by filtration, washed twice with cold ethanol and dried in vacuo for 16 hours to give 3.43 g of the desired product as orange crystals, mp 210.5-212.5°C.

Additional phosphate salts which were prepared from the corresponding base compound in the manner described hereinabove are listed as Examples 302 to 305 in Table VII.

TABLE VII

Ex	Compound	MP°C
302	N-(3,5-Dimethylphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	190-192
303	N-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine, phosphate	185-188
304	N-Phenyl-4-(3-pyridinyl)-2-pyrimidinamine phosphate	176-179
305	N-(3,5-Dimethylphenyl)-4-(2-pyridinyl)-2-pyrimidinamine, phosphate	199-202

Example 306

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, (Z)-2-butenedioate (1:1)

A mixture of 4.97 g of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine and 2.55 g of maleic acid was dissolved in hot 2-methoxyethanol. Cooling gave 4.15 g of the desired product as an orange crystalline solid, mp 211-214°C.

Example 307

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, dinitrate

A 2.0 g amount of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine was dissolved in 100 ml of ethanol with heating. The solution was allowed to cool to room temperature, then a solution of 1.5 ml of concentrated nitric acid in 25 ml of ethanol was added with stirring to give a red-orange precipitate. The mixture was allowed to stand 30 minutes at room temperature, then was chilled for several hours. The solid was collected, washed with cold absolute ethanol and air dried to give 2.80 g of the desired product as red-orange crystals, mp 167-169°C (dec.).

Example 308

N-Phenyl-4-(4-pyridinyl)-2-pyrimidinamine, compound with 2-hydroxy-1,2,3-propanetricarboxylate (2:1)

A mixture of 4.97 g of N-phenyl-4-(4-pyridinyl)-2-pyrimidinamine and 4.62 g of citric acid was dissolved in hot absolute ethanol. Cooling gave 6.14 g of the product of the example as a yellow cystalline solid, mp 155-157°C.

Example 309

Oxo[phenyl[4-(4-pytridinyl)-2-pyrimidinyl]amino]-acetic acid, ethyl ester

A 4.08 g portion of 2-phenylamino-4-(4-pyridinyl)-pyrimidine was dissolved in 20 ml of dimethylformamide. A 5 g portion of 50% sodium hydride in oil was added using 10 ml of dimethylformamide as a wash. When bubbling ceased, a solution of 2.23 ml of ethyl oxalyl chloride in 10 ml of dimethylformamide was added dropwise. Chloroform and aqueous 10% potassium bicarbonate were added. The organic layer was separated, dried, filtered and evaporated giving the desired product.

Example 310

N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride

A 12.86 g portion of N-[4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide in a mixture of 40 ml of water and 40 ml of concentrated hydrochloric acid was refluxed for 30 minutes and then cooled. The solid was collected and dried, giving 10.84 g of the desired product, mp 285-288°C.

Following the procedure of this Example, and using as starting materials the products of the indicated examples, the products of Examples 311-322 in Table VIII were derived.

This Sheet Has Been Replaced



TABLE VIII

Ex.	Starting Material	Product	MP°C
311	Ex. 185	N-Methyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	164-166
312	Ex. 187	N-Methyl-N'-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	110-112
313	Ex. 218	N-[4-(3-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine, dihydrochloride	279-284
314	Ex. 217	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	199-202
315	Ex. 221	2-Methyl-N-[4-(4-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	297-304
316	Ex. 219	N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine	153-156
317	Ex. 182	N-[3-(1-Aminomethyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	230(dec.)
318	Ex. 222	N-[4-(5-Methyl-2-thienyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	284-287
319	Ex. 228	N-[4-(2-Furanyl)-2-pyrimidinyl]-1,4-benzenediamine, dihydrochloride	261-266
320	Ex. 226	2-Methyl-N-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	176-178
321	Ex. 230	2-Methyl-N-[4-(2-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	196-198
322	Ex. 191	N-[4-(4-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	192-193.5

Example 323

2-[1-[4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]ethylidene]hydrazinecarboxamide

A 2.9 g portion of 1-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone was mixed with 1.23 g of semicarbazide hydrochloride in 200 ml of absolute ethanol and 1.10 ml of 10N sodium hydroxide was added. This mixture was refluxed overnight, then cooled to room temperature and the solid collected and washed with ethanol, water and ethanol. The solid was recrystallized from dimethylsulfoxide/ethanol, giving 2.9 g of the desired product, mp 256-258°C.

Example 324

N-[4-[2-[bis(1-Methylethyl)amino]ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine

A 2.64 g portion of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol was dissolved in 60 ml of dimethylformamide by warming on a steam bath and then cooled. A 2.0 g portion of diisopropylaminoethyl chloride hydrochloride was added and dissolved with stirring. A 20 ml portion of 5N sodium hydroxide was added dropwise over 5 minutes, then 5 ml of water was added and the mixture was stirred for 20 hours. The mixture was then heated on a steam bath for 30 minutes, allowed to stand 48 hours and then evaporated. The residual gum was purified by flash dry column chromatography on silica gel eluting fractions 1-3 with methanol and fractions 4-6 with 1% methanol in chloroform. Fractions 4-6 were combined and evaporated, giving 500 mg of the desired product.

Example 325

α-Methyl-4-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]benzenemethanol

A 1.45 g portion of 1-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone was dissolved with stirring in 220 ml of ethanol. A 125 mg portion of sodium borohydride was added and stirring continued for 3 hours. A 63 mg portion of sodium borohydride was added and

stirring continued overnight. A 2 ml portion of glacial acetic acid was added and the mixture evaporated. The solid was triturated with water, dried and recrystallized from 30 ml of ethanol giving 710 mg of the desired product, mp 145-147°C.

Example 326

N-[1-[3-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]-phenyl]ethyl]formamide

A mixture of 2.9 g of 1-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]ethanone, 40 ml of formamide and 13 ml of concentrated formic acid was refluxed for 15 hours, then cooled and evaporated. The residue was partitioned between unsaturated aqueous potassium bicarbonate and chloroform. The organic phase was separated, dried, filtered and evaporated. The residue was chormatographed on silica gel, eluting 125 ml fractions, fractions 1-4 with chloroform and fractions 5-7 with 2% methanol in chloroform. Fractions 5-7 were combined and evaporated, giving 1.25 g of the desired product as a yellow foam.

Example 327

2-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol

A mixture of 35 g of N-(2-methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine in 200 ml of 47% aqueous hydrobromic acid was refluxed for 7 hours and then evaporated. The residue was mixed with saturated aqueous potassium bicarbonate and allowed to stand overnight, then filtered. The filtrate was concentrated, giving 3.5 g of the desired compound, mp 166-169°C.

Example 328

N-[3-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine

A solution of 250 ml of 2-acetylpyridine and 500 ml of N,N-dimethylformamide dimethyl acetal was heated on a steam bath for 6 hours. After concentrating the reaction solution under vacuum, 1 liter of hexane was added to the part crystalline residue. The product was collected as small crystalline particles which were washed with an additional liter of hexane. Air drying was followed by drying at 45°C under vacuum, leaving 350.7 g of 3-dimethylamino-1-(2-pyridinyl)-2-propen-1-one.

A mixture of 289.0 g of imidazole, 292 g of potassium carbonate, 3 liters of dimethyl sulfoxide, and 300.0 g of 1-fluoro-3-nitrobenzene was stirred and heated for 25.5 hours between 105-110°C. Then the reaction was poured into 6 liters of water and cooled in the refrigerator over the weekend. The crystalline product was collected and washed with 1 liter of water. Air drying gave 357.6 g of solid. The solid was taken up in 2.4 liters of ethyl acetate and the hot solution passed through hydrous magnesium silicate. After boiling the filtrate down to 1.5 liters, it was cooled to give a precipitate which was collected and washed with 200 ml of ethylacetate, to leave 151.7 g of off-white crystals. After evaporating the mother liquor to dryness, the residue was recrystallized from 350 ml of ethyl acetate to give 59.7 g more product. The mother liquor from the second fraction was evaporated and the residual material recrystallized twice from ethyl acetate to give 30.9 g more product. Total product, 242.3 g of 1-(3-nitrophenyl)-1H-imidazole.

In a Parr hydrogenation bottle was placed 75.00 g of 1-(3-nitrophenyl)-1H-imidazole, 0.70 g platinum oxide, and 250 ml of ethanol. Shaking of this mixture in a Parr

hydrogenation apparatus was continued until no more hydrogen was taken up. This process was repeated with 76.33 g of the imidazole, 1.0 g of platinum oxide and 250 ml of ethanol and again with 90.4 g of the imidazole, 1.0 g of platinum oxide and 240 ml of ethanol, until a total of 241.63 g had been reduced. For each batch the catalyst was filtered off and the solvent was removed under vacuum; and then the residues were combined to give 207.2 g of gray crystalline amine. Next the amine was recrystallized from 530 ml of 2-propanol. After collecting the product, it was washed with 200 ml of 2-propanol, and dried, under vacuum, to give 156.4 g of 3-(1H-imidazol-1-yl)benzamine.

A solution of 43.3 g of hydrogen chloride in 290 ml of ethanol was added to 189.0 g of 3-(1H-imidazol-1-yl)benzamine in a 2 liter Erlenmeyer flask. Then 104.7 g of cyanamid was added. The mixture was cautiously warmed in a water bath to an internal temperature of 83°C over 25 minutes. When no exotherm had been noted, the flask was placed inside the steam bath and heated for 2 hours. A final temperature of 97°C was achieved. The resulting brown syrup which was [3-(1H-imidazol-1-yl)phenyl]guanidine, monohydrochloride, was used in the next reaction without further purification.

A mixture of 164 g of potassium carbonate, 209.1 g of 3-dimethylamino-1-(2-pyridyl)-2-propen-1-one, 1.187 mole of crude [3-(1H-imidazol-1-yl)phenyl]guanidine monohydrochloride, and 1 liter of methoxyethanol was stirred and heated under very gentle reflux. A dry-ice condenser filled with water was used to prevent plugging by the dimethylammonium carbonate which is given off by the reaction. The reaction was stopped after 26.5 hours and permitted to stand overnight. A heavy precipitate had formed which was collected as A and washed with 100 ml of ether. The filtrate was concentrated under vacuum as B. Both A and B were triturated with 1.5 liters of water. Then A was washed with 300-400 ml of ethanol, followed by 100 ml of ether to leave, on drying, 172.9 g of gray solid,

mp 200-202°C. Recrystallization of B from 150 ml of 2-propanol gave a black solid, C. Next, a classical fractional recrystallization was carried out using methoxyethanol as the solvent. In the final stages, a large amount of charcoal was added to remove color. In this fashion two main fractions were obtained D, 79.0 g of yellow crystals, mp 204.5-205.5°C, and E, 18.05 g of yellow crystals, mp 204-204.5°C. The yield of D plus E was 26% of the desired product.

EXAMPLE 329

1-(2-Chloroethoxy)-3-nitrobenzene

A mixture of 6.96g. of m - nitrophenol, 100 ml. of 2-butanone, 6.9 g. of potassium carbonate, and 11.74 g. of 2 chloroethyl-tosylate was stirred and heated under reflux for 24 hours. After cooling to room temperature, the salts were filtered off and the filtrate concentrated under vacuum. The residue crystallized on seeding and was recrystallized from carbon tetrachloride to give 8.3 g. of product, m.p. 54.5° - 57° C.

EXAMPLE 330

1-[2-(3-Nitrophenoxy)ethyl]-1H-imidazole

After dissolving 3.74 g. of imidazole in 60 ml. of dry N,N-dimethylformamide, 1.78 g. of 50% sodium hydride in oil was added. When the effervescence had stopped (circa 1 hr.),7.35 g. of 1-(2-chloroethoxy)-3-nitrobenzene was added. After stirring overnight, the reaction was concentrated under vacuum. Water was added to the residue and the product was extracted into chloroform. The product was extracted out of the chloroform layer with dilute hydrochloric acid. Next, the aqueous acid layer was neutralized with potassium carbonate and the oily product extracted into chloroform. Upon drying the chloroform extract with sodium sulfate, it was concentrated under vacuum to an oil which

crystallized on standing. Recrystallization from isopropyl acetate gave 6.12 g. of product as the monohydrate, m.p. 52.5°-55.5° C.

EXAMPLE 331

3-[2-(1H-Imidazol-1-yl)ethoxy]benzamine

Using a Parr hydrogenator, 5.00 g. of 1-[2-(3-nitrophenoxy)ethyl]-1H-imidozole in 100 ml. of ethanol and 0.2 g. of platinum oxide was hydrogenated until the hydrogen uptake stopped. The catalyst was filtered off and the filtrate concentrated under vacuum. Several recrystallizations from isopropyl acetate gave 2.8 g. of amine, m.p. 74°-76.5° C.

EXAMPLE 332

[3-[2-(1H-Imidazol-1-yl)ethoxy]phenyl]-guanidine Dihydrochloride

To a solution of 1.7 g. of hydrogen chloride in 50 ml. of ethanol was added 4.70 g. of 3-[2-(1H-imidazol-1-yl)ethoxy]benzamine in 10 ml. of ethanol. After concentration under vacuum a foam was obtained which gradually crystallized. Next 1.95 g. of cyanamid and 20 ml. of ethanol were added and the mixture heated cautiously, first in a water bath, then directly in a steam bath for a total of 5 hours. A light brown oily guanidine resulted, which was used without purification.

EXAMPLE 333

3-[2-(4-Morpholinyl)ethoxy]-benzenamine

N-[2-Chloroethyl)morpholine hydrochloride, 80 g., was partitioned between 5N sodium hydroxide and methylene chloride. After drying the organic layer over magnesium sulfate, the solvent was removed under reduced pressure to leave 65 g. of free amine.

To 36.01 g. of m-aminophenol dissolved in 325 ml. of N,N-dimethylformamide, 16.3 g. of 50% sodium hydride in oil was added. The reaction was stirred for 1 hour, until the effervescence stopped; then 57 g. of N-(2-chloroethyl)

morpholine, from above, was added. After stirring overnight, the mixture was heated on a steam bath for 1/2 hr., then concentrated under vacuum. The residue was taken up in 300 ml.of 2N hydrochloric acid and washed twice with ether. After basifying with 10N sodium hydroxide, the product was extracted into ether, dried (magnesium sulfate), filtered through hydrous magnesium silicate and evaporated to a brown oil. Distillation gave 34.0 g. of a golden oil, b.p. 165°-180° C./0.45mm.

EXAMPLE 334

[3-[2-(4-Morpholinyl)ethoxy]phenyl] guanidine monohydrochloride

Prepared from 3-[2-(4-morpholinyl)ethoxy]-benza--mine by the method of Example 332

EXAMPLE 335

1-(Bromoacetyl)-4-methylpiperazine monohydrochloride

A solution of 10.0 g. of 1-methyepiperazine in 150 ml of chloroform was cooled in a water bath while 17.3 g. of bromoacetyl chloride in 150 ml. of chloroform was added dropwise, with stirring, over 1/2 hour. A calcium chloride tube protected the reaction from moisture. After stirring overnight, the precipitate was collected and washed with chloroform. The crude product was dried under vacuum at 50° and used as such.

EXAMPLE 336

1-[(4-Aminophenoxy)acetyl]-4-methylpiperazine

Prepared from p-aminophenol and 1-(bromoacetyl)-4-methylpiperazine by the method of Example 333 to give a product of m.p. 71°-73° C.

EXAMPLE 337

1-[[4-[(Aminoiminomethyl)amino]phenoxy]acetyl]-4-methylpiperazine Dihydrochloride

Prepared from 1-[(4-aminophenoxy)acetyl]-4-methylpiperazine by the method of Example 332.

TABLE IX

Ex.	Acryloyl Source	Phenylguanidine precurser	Product	Mp°C.
338	Ex. 11	[3-[2-(1H-Imidazol-1-yl)-ethoxy]-phenyl]guanidine dihydrochloride	N-[3-[2-(1H--Imidazol-1-yl)-ethoxy]phenyl--4-(2-pyridinyl)-2-pyrimidinamine	149-151.5
339	Ex. 13	[3-[2-(4-morpholinyl)-ethoxy]-phenyl]guanidine monohydrochloride	N-[3-[2-(4-morpholinyl)-ethoxy]phenyl]--4-(4-pyridinyl)--2-pyrimidinamine	179-181
340	Ex. 24	[3-[2-(4-morpholinyl)ethoxy]-phenyl]guanidine monohydrochloride	N-[3-[2-(4-morpholinyl)ethoxy]-phenyl]-4-(2-thienyl)-2-pyrimidinamine	134-136
341	Ex. 10	[3-[2-(4-morpholinyl)ethoxy]-phenyl]guanidine monohydrochloride	4-(2-furanyl)-N-[3-[2-(4-morpholinyl)ethoxy]-phenyl]-2-pyrimidinamine	88-90
342	Ex. 24	1-[[4-[(Aminoiminomethyl)amino]-phenoxy]acetyl]-4-methyl piperazine dihydrochloride	1-Methyl-4-[[4--(2-thienyl)-2-pyrimidinyl]-phenoxy]acetyl)-piperazine	173-175

This Sheet Has Been Replaced

TABLE IX (continued)

Ex.	Acryloyl Source	Phenylguanidine precurser	Product	Mp°C.
343	Ex. 24	(4-chlorophenyl) guanidine carbonate	N-(4-chlorophenyl) -4-(2-thienyl)-2-pyrimidinamine	185-186
344	Ex. 26	[2-[bis(1-methyl-ethyl)amino[ethoxy [guanidine hydro-chloride	N-[2-[2-[bis(1--methylethyl) amino]ethoxy] phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	54-57

The disease diabetes mellitus is characterized by metabolic defects in the production and utilization of glucose which results in the failure to maintain appropriate blood sugar levels. The result of this defect is elevated blood glucose or hyperglycemia. Research on the treatment of diabetes has centered on attempts to normalize fasting and postprandial blood glucose levels. Treatments have included parenteral administration of exogenous insulin, oral administration of drugs and dietary therapies.

Two major forms of diabetes mellitus are now recognized. Type I diabetes, or insulin-dependent diabetes, is a result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes, often occurs in the face of normal, or even elevated, levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin.

The compounds of the present invention and the pharmacologically active acid-addition salts thereof, effectively lower blood glucose levels when administered orally to genetic strains of hyperglycemic mice which are animal models

of type II diabetes. The exact mechanism by which they act is not known and the invention should not be construed as limited to any particular mechanism of action. As effective hypoglycemic agents, these compounds are useful for the treatment of hyperglycemia in type II diabetes.

The compounds of this invention were tested for hypoglycemic activity according to the following procedure.

Obese mice [C57 Bl/6J (ob/ob)], their lean littermates (ob/$\pm$ or +/+) and diabetic mice [C57 Bl/Ks (db/db)] and their non-diabetic littermates (db/+ or +/+) were obtained from Jackson Laboratories, Bar Harbor, Maine. Obese mice were 8 weeks of age and diabetic mice were 9 weeks of age at the start of the test.

The test compounds were dissolved in methanol, mixed with powdered Purina rodent chow on a weight of compound to weight of chow basis and thoroughly dried.

Groups of 4 control mice received vehicle (methanol) treated chow.

Groups of 4 test mice were fed ad libitum for one month and food consumption was measured daily (on week days) by weighing the food bins before and after the addition of fresh chow. Thus a 40 g mouse fed the test compound at a concentration of 0.02% of the diet would receive a dose of 20 mg/kg/day if it ate 4 g of chow per day.

Blood samples were collected before the first treatment and once at the end of each week of treatment by retro-orbital puncture using the end of each week of treatment by retro-orbital puncture using heparinized capillary tubes. Plasma was separated by centrifugation in a Beckman microfuge for 5 minutes. Plasma glucose concentrations were determined with the Beckman Glucose Analyzer which uses a glucose oxidase method.

The results of this test on representative compounds of this invention appear in Table X.

This Sheet Has Been Replaced



TABLE X

Effect of Test Compounds on Blood Glucose

COMPOUND	Type of Mice	Dose % (W/W)	Blood Glucose Levels in mg/100ml Days 0	5	7	14	21	28
N-(4-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	219	137				
	ob/ob	0.1	210		118	80		
	ob/ob	0.025	209		223	166		
N-(4-Chlorophenyl)-4-(2-thienyl)-2-pyrimidinanine	ob/ob	0.1	212	160				
	ob/ob	0.025	220		148	134		
N-(4-ethylphenyl) -4-(4-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	216	181				
	ob/ob	0.1	223	164				
4-(2-furanyl)-N-phenyl-2-pyrimidinamine	ob/ob	0.1	214	166				

Table X Cont'd.

COMPOUND	Type of Mice	Dose % (W/W)	Blood Glucose Levels in mg/100ml Days 0	5	7	14	21	28
N-[4-(1,1-Dimethylethyl) phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	208	114	175			
	ob/ob	0.1	214	169	155			
	ob/ob	0.1	218	124				
	ob/ob	0.1	229	118				
	ob/ob	0.1	225		120	116	131	135
	ob/ob	0.05	214		139	143	180	188
	ob/ob	0.01	214		163	138	181	162
	db/db	0.1	426		390	174	281	207
	db/db	0.05	429		314	293	250	270
	db/db	0.01	431		335	407	400	499
N-[4-(Dimethylamino)phenyl] -4-(4-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	240	138				
	ob/ob	0.1	230	147				
N-[4-[3-(Dimethylamino)propoxy] phenyl]-4-(3-pyridinyl) -2-pyrimidinamine	ob/ob	0.1	215	234				
N-[4-[2-(diethylamino)ethoxy] phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	220	191				

Table X Cont'd

COMPOUND	Type of Mice	Dose % (W/W)	Blood Glucose Levels in mg/100ml Days 0	5	7	14	21	28
N'-[4-(2-Benzofurnayl)-2-pyrimidinyl)-N,N-dimethyl-1,4-benzenediamine	ob/ob	0.1	229	153				
	ob/ob	0.1	202	147				
	ob/ob	0.1	223	144				
N-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	218	151	167			
	ob/ob	0.1	228	144				
	ob/ob	0.1	225	134				
	ob/ob	0.1	232		148	128	155	140
	ob/ob	0.05	230		158	198	196	163
	ob/ob	0.01	236		163	252	175	177
	db/db	0.1	369		410	403	328	222
	db/db	0.05	400		277	404	329	250
	db/db	0.01	368		393	321	494	336
N-[4-(1H-Imidazol-1-yl)phenyl]4-(4-pyridinyl)-2-pyrimidinamine	db/db	0.1	424		397	233		
	ob/ob	0.1	219	128				
	ob/ob	0.025	210		200	148		
	ob/ob	0.1	211		105	140		
	ob/ob	0.1	222		119	132		
	ob/ob	0.01	219		158	159		
	ob/ob	0.025	222		157	175		
N,N-Diethyl-N^1-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine	ob/ob	0.1	223	138				
	ob/ob	0.1	210	163				
	ob/ob	0.1	216	153				

This Sheet Has Been Replaced

Table X Cont'd

COMPOUND	Type of Mice	Dose % (W/W)	Blood Glucose Levels in mg/100ml Days 0	5	7	14	21	28
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	225	128				
	ob/ob	0.025	208		159	171		
	ob/ob	0.1	218		127	131		
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	217	171				
	ob/ob	0.1	223	167				
	ob/ob	0.1	234	141				
4-(2-Furnayl)-N-[4-(1H-imidazol-1-yl)phenyl]-2-pyrimidinamine	ob/ob	0.1	227	137				
	ob/ob	0.025	215		164	244		
	ob/ob	0.1	214		140	160		
N-[4-(1H-Imidazol-1-yl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	ob/ob	0.1	221		109	116		
	ob/ob	0.025	221		147	171		
	ob/ob	0.01	217		212	161		
	ob/ob	0.1	224	125				
	ob/ob	0.1	203	131				
	ob/ob	0.1	231	126				
	ob/ob	0.1	218	134				
	ob/ob	0.025	218		175	185		
	ob/ob	0.1	220		135	117		
	db/db	0.1	423		492	349		

This Sheet Has Been Replaced

Table X Cont'd

COMPOUND	Type of Mice	Dose & (W/W)	Blood Glucose Levels in mg/100ml Days 0	5	7	14	21	28
4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino] benzenesulfonamide	ob/ob	0.1	219	122				
	ob/ob	0.1	240	147				
	ob/ob	0.1	216	185				
	ob/ob	0.1	229	142				
	ob/ob	0.1	228	211				
N-(3-Chlorophenyl)-4-(4-pyrindinyl)-2-pyrimidinamine	ob/ob	0.1	220	127				
	ob/ob	0.1	237	163				
	ob/ob	0.1	216	135				
	ob/ob	0.1	205	157				
	ob/ob	0.025	210		157	135		
	ob/ob	0.1	212		173	129		
N-(3-Chlorophenyl)-4-(3-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	205	135				
	ob/ob	0.025	221		205	131		
	ob/ob	0.1	244		211	138		
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	212	236				
N-(3-Chlorophenyl)-4-(2-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	207	204				

Table X Cont'd

COMPOUND	Type of Mice	Dose & (W/W)	Blood Glucose Levels in mg/100ml Days 0	5	7	14	21	28
4-(2-Furnayl)-N-[4-(4-methyl-1-piperazinyl)phenyl]-2-pyrimidinamine	ob/ob ob/ob ob/ob	0.1 0.025 0.1	203 210 229	149	179 163	130 141		
4-(2-Furanyl)-N-(3-methoxyphenyl)-2-pyrimidinamine	ob/ob ob/ob ob/ob ob/ob	0.1 0.1 0.1 0.1	221 239 217 219	132 113 162 209				
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-thienyl)-2-pyrimidinamine	ob/ob	0.1	203	188				
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	204	210				

This Sheet Has Been Replaced

Table X Cont'd

COMPOUND	Type of Mice	Dose & (W/W)	Blood Glucose Levels in mg/100ml Days 0	5	14	21	28
N-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	204		118	124	178	161
	ob/ob	0.025	210		157	200	152	202
	ob/ob	0.01	210		130	192	178	147
	db/db	0.1	406		273	140	178	279
	ob/ob	0.1	221	125				
	ob/ob	0.1	233	131				
	ob/ob	0.1	226	117				
	ob/ob	0.1	215	138				
	ob/ob	0.025	231		154	134		
	ob/ob	0.1	223		171	137		
N-[3-(1H-Imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	225	173				
N-[4-[2-(Diethylamino)ethoxy]phenyl]-4-(2-thienyl)-2-pyrimidinamine	ob/ob	0.1	228	154				
	ob/ob	0.1	215	137				
N-[2-[2-[Bis(1-methylethyl)amino]ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine	ob/ob	0.1	228	153				

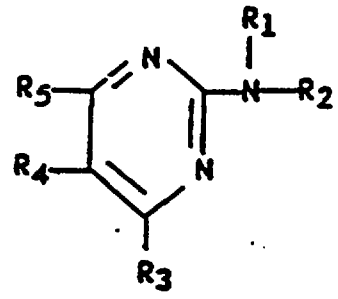
This Sheet Has Been Replaced

30,242-00

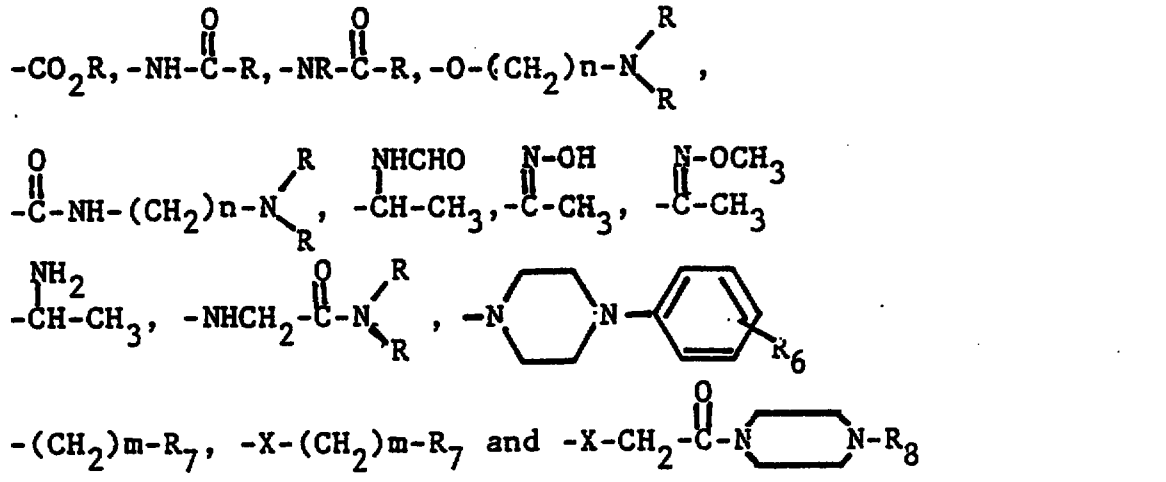
CLAIMS

We Claim:

1. A compound selected from the group consisting of those of the formula:



wherein R_1 is hydrogen, alkyl(C_1-C_3), $-COCO_2C_2H_5$ or N,N-dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1-C_6), alkoxy(C_1-C_3), chloro, bromo, iodo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl(C_1-C_3)amino, dialkyl(C_1-C_3)amino, alkyl-(C_1-C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfanilamido, N,N-dialkyl(C_1-C_3)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formulae:



wherein R is alkyl(C_1-C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl(C_1-C_3), alkoxy (C_1-C_3),chloro, bromo, iodo or trifluoromethyl, R_7 is 1H-

-imidazol-1-yl or morpholino and R_8 is alkyl(C_1-C_3), phenyl or monosubstituted phenyl wherein the substituents are alkyl (C_1-C_3), halogen or trifluoromethyl; R_3 is 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 4-methyl-3--pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3--furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno--thiazinyl, 4-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyri--dinyl methyl iodide, dimethylaminophenyl or N-acetyl-N--methylaminophenyl; R_4 is hydrogen or alkyl(C_1-C_3); and R_5 is hydrogen or alkyl(C_1-C_3); and the pharmacologically acceptable acid-addition salts thereof.

2. The compound according to Claim 1; N-[3-(1H--imidazol-1-yl)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.

3. The compound according to Claim 1; N-[3-(1H--imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine.

4. The compound according to Claim 1; N,N--dimethyl-N'-[4-methyl-6-(4-pyridinyl)-2-pyrimidinyl]--1,4-benzenediamine.

5. The compound according to Claim 1; N'-[4--(2-furanyl)-5-methyl-2-pyrimidinyl]-N,N-dimethyl-1,4--benzenediamine.

6. The compound according to Claim 1; N-[4--(dimethylamino)phenyl]-4-(4-pyridinyl)-2-pyrimidinamine.

7. The compound according to Claim 1; 4-(2--furanyl)-N-(3-methylphenyl)-2-pyrimidinamine.

8. The compound according to Claim 1; N,N--dimethyl-N'-[4-(4-pyridinyl)-2-pyrimidinyl]-1,3-benzene-diamine, sulfate.

9. The compound according to Claim 1; N-[4--[2-(diethylamino)ethoxy]phenyl]-4-(4-pyridinyl)-2-pyrimi-dinamine.

10. The compound according to Claim 1; 4-(1H--indol-3-yl)-N-phenyl-2-pyrimidinamine.

This Sheet Has Been Replaced

* C L M S *

11. The compound according to Claim 1; N-(4-ethylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.

12. The compound according to Claim 1; N,N-dimethyl-N'-[4-(3-pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine, trihydrochloride.

13. The compound according to Claim 1; N-[4-(1H-imidazol-1-yl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.

14. The compound according to Claim 1; N-[4-(4-methyl-1-piperazinyl)phenyl]-4-(3-pyridinyl)-2-pyrimidinamine.

15. The compound according to Claim 1; N-(3-methylphenyl)-4-(4-pyridinyl)-2-pyrimidinamine.

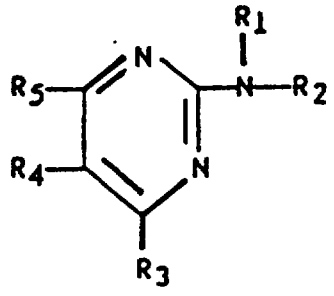
16. A method of treating asthma and/or allergic diseases in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

17. A method of treating inflammation in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

18. A method of treating diabetes in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

19. A composition of matter in dosage unit form comprising from about 5 mg to about 1500 mg of a compound of Claim 1 in association with a pharmaceutically acceptable carrier.

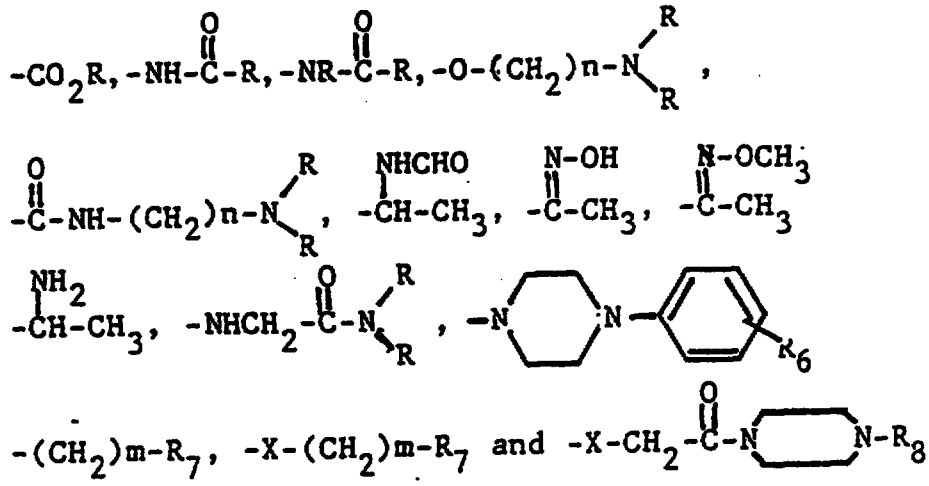
20. A process for producing a compound of the formula:



wherein R_1 is hydrogen, alkyl(C_1-C_3), $-COCO_2C_2H_5$ or N,N-

This Sheet Has Been Replaced

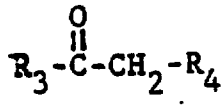
dimethylaminoethyl; R_2 is mono- or poly-substituted phenyl wherein the substituents are alkyl(C_1-C_6), alkoxy(C_1-C_3), chloro, bromo, iodo, trifluoromethyl, hydroxy, phenyl, amino, monoalkyl(C_1-C_3)amino, dialkyl(C_1-C_3)amino, alkyl-(C_1-C_3)keto, propenyloxy, carboxyl, oxyacetic acid, oxyacetic acid ethyl ester, sulfanilamido, N,N-dialkyl(C_1-C_3)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or moieties of the formula:



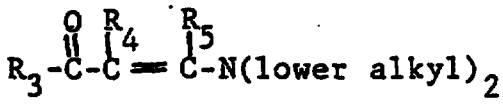
wherein R is alkyl(C_1-C_3), X is oxygen (-O-) or sulfur (-S-), m is 1-3, n is 2 or 3, R_6 is hydrogen, alkyl(C_1-C_3), alkoxy (C_1-C_3),chloro, bromo, iodo or trifluoromethyl, R_7 is 1H--imidazol-1-yl or morpholino and R_8 is alkyl(C_1-C_3), phenyl or monosubstituted phenyl wherein the substituents are alkyl (C_1-C_3), halogen or trifluoromethyl; R_3 is 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 4-methyl-3--pyridinyl, 2-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3--furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno--thiazinyl, 4-pyrazinyl, 2-benzofuranyl, 2-(pyridine-N-oxide), 3-(pyridine-N-oxide), 4-(pyridine-N-oxide), 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 4-pyri--dinyl methyl iodide, dimethylaminophenyl or N-acetyl-N--methylaminophenyl; R_4 is hydrogen or alkyl(C_1-C_3); and R_5

This Sheet Has Been Replaced

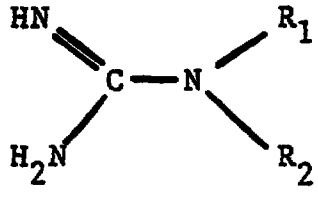
is hydrogen or alkyl(C_1-C_3) which comprises condensing an alkanoyl-heteroaryl derivative of the formula:



wherein R_3 and R_4 are as hereinbefore defined with an N,N-di(lower alkyl)formamide or acetamide di(lower alkyl)-acetal at 50°-150° C. for 4-24 hours to provide a 3-di-(lower alkyl)amino acrylophenone of the formula:



which is then cyclized with a substituted phenylguanidine of the formula:



wherein R_1 and R_2 are as hereinbefore defined in an inert organic solvent at the reflux temperature for 6-48 hours.

This Sheet Has Been Replaced