Preparation of Substituted *N*-Phenyl-4-aryl-2-pyrimidinamines as Mediator Release Inhibitors

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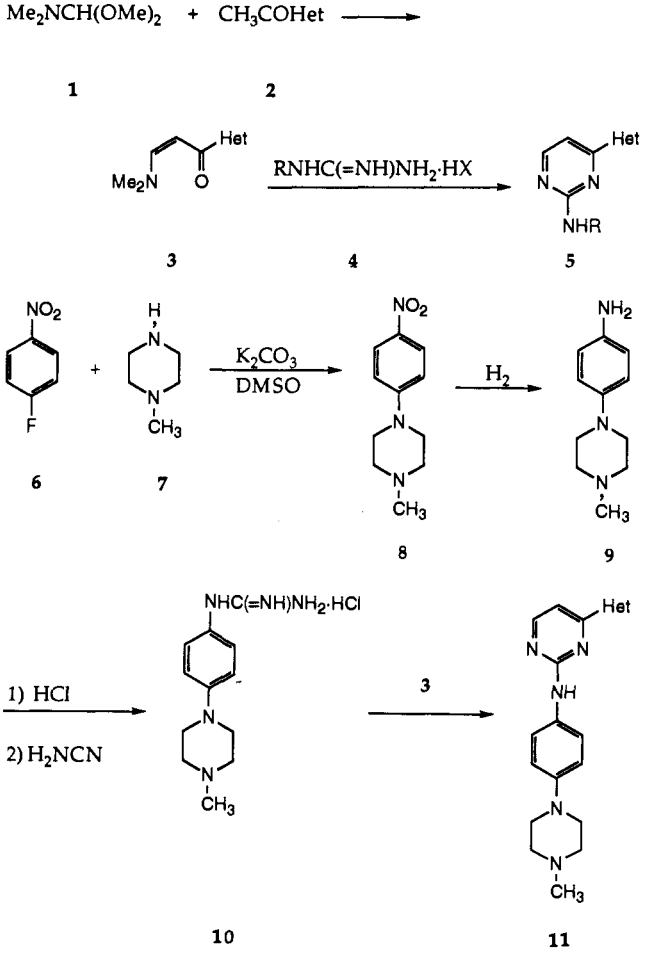
The role of immunologically released mediators, such as histamine, leukotrienes, and platelet-activating factor, is well-established for asthma and other allergic disorders. Developing therapeutic agents which would block mediator release from mast cells and other relevant cell types would provide a rational approach to asthma therapy. Using human basophil as a screen, a series of 4-aryl-2-(phenylamino)pyrimidines was found which inhibited mediator release. These compounds were prepared by condensing acetyl heterocycles with dimethylformamide dimethyl acetal to form enaminones which are cyclized with aryl guanidines to give pyrimidines. After examining a large number of analogs, *N*-[3-(1*H*-imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine (**1-27**) was chosen for toxicological evaluation.

In the currently accepted explanation for the events leading to an asthmatic attack,[1,2] antigens cross-link the E antibodies (IgE) attached to the human lung mast cells. On cross-linking, the IgE triggers the mast cell to release preformed mediators plus substances which, in turn, are converted to other mediators. The various mediators, such as histamine, leukotrienes, eosinophil chemotactic factors, and platelet-activating factor, induce the asthmatic attack. With one of the major treatments, the use of β-agonists, being increasingly questioned[3] and with death rates from asthma in industrial countries on the rise,[4] there is an urgent need for new therapy. There are a number of approaches for finding an antiasthma compound. One can search for receptor antagonists for specific mediators[5] or one can search for compounds which inhibit the release of mediators from mast cells.[6] As it is probably unlikely that one mediator causes all the symptoms of asthma,[7] the latter approach is the one we have been pursuing for a number of years.[8] Since human mast cells, the most desirable test cells, are difficult to obtain in the quantities needed for a screening program, a substitute was sought. Circulating basophils resemble mast cells in having IgE attached to their surface. On antigen challenge, the basophil releases mediators similar to those released by the mast cell. Thus, if one could find a compound which would inhibit the release of mediators from human basophils, this compound might also inhibit mediator release from human mast cells and consequently be useful as a prophylaxis for asthma and/or allergy. Human basophils, separated from leukocytes, were incubated with test compounds and challenged with anti-IgE or antigen, by the method of Lichtenstein.[9] Histamine release was measured vs controls and blanks. It was assumed that histamine release was indicative of all the mediators released. A later study, using a radioimmunoassay for leukotrienes, verified this assumption. With the basophil as a screen, 2-aminopyrimidines **5** were identified as antiasthma compounds and a synthetic program was undertaken to improve their activity.

Scheme I



Chemistry

The general method of Bredereck[10] was used for the synthesis of pyrimidines which involved reacting *N,N*-dimethylformamide dimethyl acetal (**1**), with an aromatic, generally heterocyclic, acetyl derivative **2**, to give the enaminone **3**. Reaction of **3** with a guanidine, **4**, gave pyrimidinamine **5**. At first, commercially available

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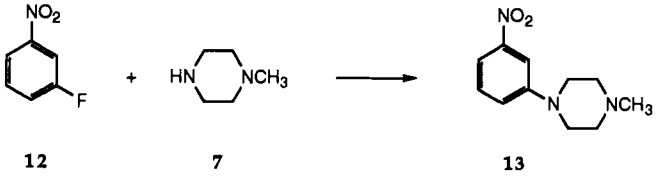
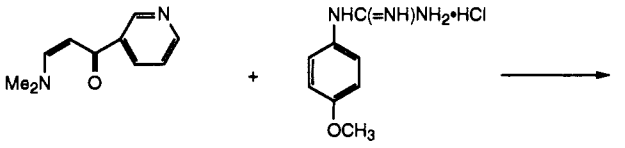
Scheme II

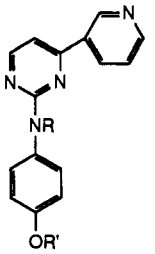


12 7 13

Scheme III



14 15



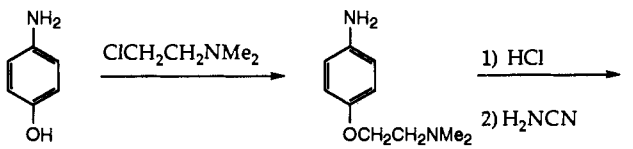
16 R = H, R' = CH_3

17 R = H, R' = H

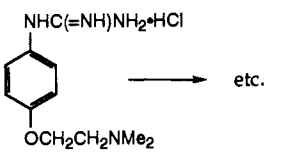
18 R = H, R' = $CH_2CH_2NEt_2$

19 R,R' = $CH_2CH_2NEt_2$

Scheme IV



20 21



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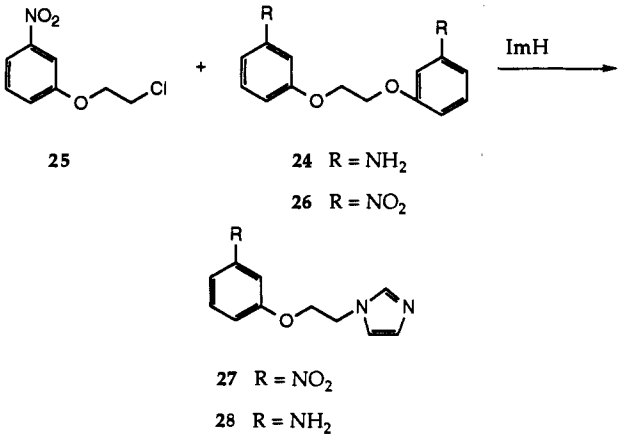
guanidines were used for preparing pyrimidines. When it was found that adding amino groups to the R substituent, when R was phenyl, increased the activity in the basophil assay, new guanidines were prepared. Some of these syntheses will be described.

4-Fluoronitrobenzene (6) reacted with *N*-methylpiperazine (7) to give 8, in good yield. Hydrogenation reduced the nitro group to amine 9, which was converted to its hydrochloride and then was fused with cyanamide to give guanidine 10 (Scheme I). If the guanidine could be obtained in crystalline form, the subsequent cyclization frequently gave 60–70% yields. In the more usual case, the guanidine 4 was a syrup and had to be used in crude form, reducing the yield of 5 to around 30%.

Since the fluoro displacement went well, and the product was readily isolated (poured into water, collected crystals), it was decided to prepare the 3-substituted compound 13 (Scheme II). While no resonance effects could be invoked here, inductive effects were sufficient to bring about a similar reaction, although higher temperatures were necessary.

Scheme V



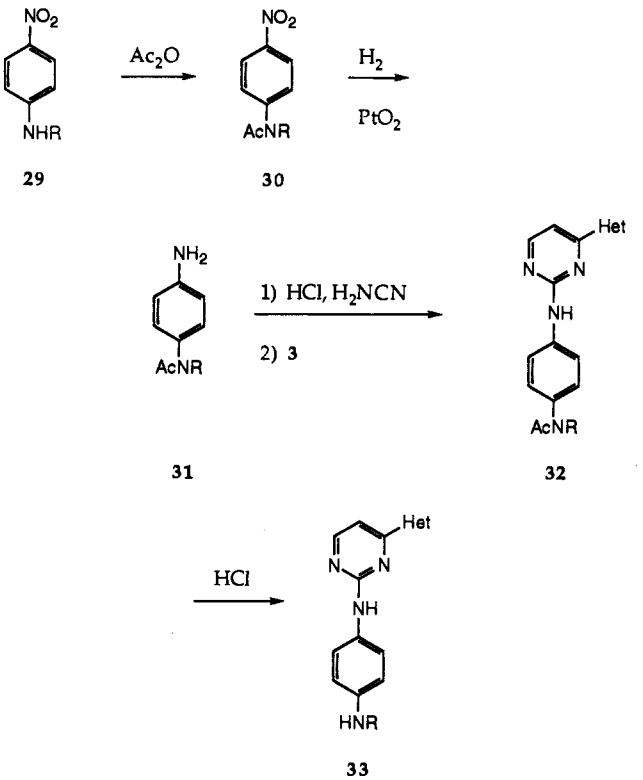
25 24 R = NH_2

26 R = NO_2

27 R = NO_2

28 R = NH_2

Scheme VI



29 30 31 32

33

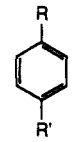
Initially aminoethers of the type 18 were prepared by coupling enaminone 14 with commercially available 15 to give 16 (Scheme III). Cleavage with 48% HBr gave 17 which could be converted by alkylation to a variety of ethers similar to 18. Unfortunately, ether formation was usually accompanied by a small amount of N-alkylated product, 19, which was a nuisance to remove. The alternative approach to making the ether first (Scheme IV), cleanly gave 21. These amines, which could be distilled and stored in the freezer, were converted to guanidines and then to pyrimidines, in much better overall yield.

Since the amino ethers, such as 18, were quite active in the basophil assay, it was decided to try to replace the amine by imidazole. Attempts to prepare 1-chloroethylimidazole from imidazole and 2-chloroethyl *p*-toluenesulfonate (23) gave only 1-vinylimidazole, while attempts to prepare 3-(2-chloroethoxy)benzenamine from 3-hydroxyaniline and 23 gave 3,3'-[1,2-ethanediylbis(oxy)]bis-[benzeneamine] (24) (^{1}H NMR). To avoid these problems,

the known compound 25 was prepared from 3-nitrophenol and 23. Some contamination of 25 by 26 was noted (^{1}H NMR) but upon conversion of 25 to 27, 26 was lost during workup. Next, hydrogenation of 27 gave 28, which was converted to the pyrimidine as previously described (Scheme V).

Amino and monomethylamino substituents were prepared by the general procedure of acylation of the appropriate nitro amine, 29, to give 30. Hydrogenation, followed by the usual pyrimidine synthesis gave 32, which upon acid hydrolysis gave 33 (Scheme VI).

Finally, 2-(4-nitrophenoxy)acetic acid (34) was converted to 35 using *N,N'*-carbonyldiimidazole and *N*-methylpiperazine and reduced with Pd black and formic acid[11] to 36.



34 R = NO_2, R' = CH_2CO_2H

35 R = NO_2, R' = CH_2CON NCH_3

36 R = NH_2, R' = CH_2CON NCH_3

Structure–Activity Relationships

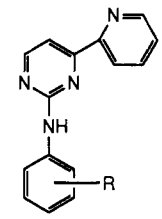
When the pyrimidines were first screened in the basophil assay, a compound was considered active if it lowered histamine release by 50% (IC_{50}) at a concentration of 48 μM. As more active compounds were found, the IC_{50} for acceptable activity was lowered to 24, 12, 6, and finally 3 μM. Results from the basophil assay largely guided the synthetic effort. Further evaluation was done in the mouse passive cutaneous anaphylaxis assay (PCA), monkey cutaneous anaphylaxis, and rat lung fragment assays.

In general, the 2-, 3-, and 4-pyridinyl, 2-furyl, and 2-thienyl groups in the pyrimidine 4-position gave the best activity. Table VIII, which lists 4-substituents other than the above five, reveals a lack of outstanding activity (basophil < 1). Examining the thiophene ring in position 4 (Tables IV and VI) reveals that 2-thienyl was generally more active than 3-thienyl; compare 4-7 to 6-4, 4-3 to 6-3, 4-6 to 6-2, 4-1 to 6-1, 4-12 to 6-6, 4-7 to 6-4, and 4-14 to 6-7. The only exception was 4-8 vs 6-5. Substituents on the thiophene ring lowered activity; compare 4-7 to 6-11 and 6-16, 4-9 to 6-12 and 6-17, 4-3 to 6-9, 4-1 to 6-8 and 6-13, and 4-12 to 6-10 and 6-15. There was some indication that substitution near the point of attachment to the pyrimidine ring decreased the activity more than remote substituents; hence, 5-methyl-2-thienyl groups were more active than 3-methyl-2-thienyl groups (6-16 vs 6-11, 6-17 vs 6-12, 6-15 vs 6-10).

In the case of a furyl group in the pyrimidine 4-position, unsubstituted 2-furyl was more potent than 5-methyl-2-furyl four times (5-17 vs 7-5, 5-6 vs 7-2, 5-14 vs 7-4, 5-1 vs 7-1) and the same once (5-10 vs 7-3). Comparing 2-furyl to 2,5-dimethyl-3-furyl showed that the unsubstituted 2-furyl was more active five times (5-17 vs 7-12, 5-10 vs 7-11, 5-6 vs 7-9, 5-14 vs 7-10, 5-4 vs 7-8) and less active twice (5-1 vs 7-6, 5-3 vs 7-7). Examining the effect of adding substituents on the pyrimidine ring led to the conclusion that activity was generally lowered. For 5-substitution, activity was lowered in two cases (5–17 vs 5–18, and 5-4 vs 5-5) and raised in one (5-1 vs 5-2). In the case of 6-substitution, nine examples showed reduced activity (1-37 vs 1-38, 1-12 vs 1-13, 2-45 vs 2-46, 3-1 vs 3-4, 3-7 vs 3-8, 3-15 vs 3-16, 3-28 vs 3-29, 3-34 vs 3-35, 3-38 vs 3-39) while two examples displayed slightly increased activity (1-1 vs 1-2, 6-13 vs 6-14).

Only two significant cases of 2-amino N-alkylation were examined. In both, activity was lost (2-15 vs 2-16 , 3-1 vs 3-3). An attempt at making a prodrug reduced the basophil activity slightly, as expectd, but did not lead to significantly longer activity when tested in the mouse PCA (3-2 vs 3-1). Eliminating the 2-amino group (1-39, 3-49) or substituting a methylene group for it (1-40, 3-50) gave little or no activity, as did replacing phenyl with cyclohexyl (3-48) or cyclopentyl (3-47).

The most significant improvement in basophil activity was produced by substituents on the phenyl ring attached to the 2-amino group. In the case where the pyrimidine



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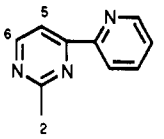
4-substituent was 2-pyridine (37), neither electron-donating nor -withdrawing substituents seemed to make any difference. However, *meta* substitution on the phenyl ring gave better activity than *ortho* or *para*, while the unsubstituted phenyl, 1-1, was inactive. Compare 1-3 and 1-18; 1-5, 1-21, and 1-34; 1-6 and 1-22; 1-7 and 1-23; 1-8 and 1-24; 1-9 and 1-25 (although 1-9 is a salt); 1-12 and 1-26; 1-15 and 1-30; 1-14 and 1-27; 1-16 and 1-31; 1-17 and 1-33; and 1-19 and 1-35. Even *m,m*-disubstitution (1-37) was more effective than *m,p*-disubstitution (1-36) while the rest of the disubstituted compounds were inactive.

In the case of 4-(3-pyridinyl)pyrimidines, the results were less clear cut. In seven cases *meta*-substituted phenyls were more active than *para* or *ortho* phenyls (2-3, 2-23, and 2-39; 2-4 and 2-27; 2-9 and 2-31; 2-12 and 2-32; 2-14 and 2-34; 2-15, 2-35, and 2-40; 2-22 and 2-38), while in five cases the *para* substitution was equal to or more active than the *meta* (2-6 and 2-28; 2-7 and 2-29; 2-8 and 2-30; 2-13 and 2-33; 2-20, 2-36, and 2-42). When available, the *ortho*-substituted compound was always the least active. In the case of the (dialkylamino)alkyl ethers, diethyl was more active than dimethyl, while diisopropyl (2-18, 2-20 and 2-21) was the least active.

Lengthening the chain (2-19 vs 2-18) of the ether had no effect. Only free bases can be compared, as salts, and even the type of salts make a difference, compare 2-1 to 2-2, and 2-24 to 2-25 and 2-26. *m,m*-Dimethyl was more active than other dimethyl substitution (2-45, 2-44). Unlike the 2-pyridinyl series, in the 3-pyridinyl case, the unsubstituted phenyl was active (2-1, 1-1).

In the 4-pyridinyl case, there were six examples of *meta*-substituted phenyls being more active than *para* ones (3-5 and 3-27, 3-20 and 3-38, 3-10 and 3-32, 3-18 and 3-36, 3-12 and 3-33, 3-9 and 3-31) and three where the *para* were slightly more active (3-7, 3-30 and 3-43; 3-15, 3-34 and 3-44; 3-25 and 3-40). In one case, *o*-phenyl substitution

Table I. 2-Pyridinylpyrimidines



	substituents[a]							
	2	6	basophil[b]	formula[c]	% yield	recryst solvent[d]	mp, °C	start mat.[e,f]
	theophylline		309 ± 55 (17)					
	Na_2 chromoglycate		1000					
1-1	NHPh		I	$C_{15}H_{12}N_4$	65	CH_2Cl_2–Me_2CO	190.5–192	comm
1-2	NHPh	Me	26.8 (1)	$C_{16}H_{14}N_4$	33	EtOH	94–98	comm[g]
1-3	NHC_6H_4-4-F		I	$C_{15}H_{11}FN_4$	64	2-PrOH	207–209	comm
1-4	NHC_6H_4-4-Cl		I	$C_{15}H_{11}ClN_4$	54	$MeOCH_2CH_2OH$	220–222	comm
1-5	NHC_6H_4-4-Me		I	$C_{16}H_{14}N_4$	51	$MeOCH_2CH_2OH$	179–181	comm
1-6	NHC_6H_4-4-Et		2.1 (1)	$C_{17}H_{16}N_4$	53	Me_2CO-hex.	148.5–149.5	comm
1-7	NHC_6H_4-4-SO_2NH_2		4.6 ± 0.1 (2)	$C_{16}H_{13}N_5O_2S$	26	$MeOCH_2CH_2OH$	274–277	amine
1-8	NHC_6H_4-4-NHAc		1.5 ± 0.8 (3)	$C_{17}H_{15}N_5O$	55	$MeOCH_2CH_2OH$	254–255	amine
1-9	NHC_6H_4-4-NH_2		1.5 ± 0.2 (4)	$C_{15}H_{13}N_5 \cdot 2HCl \cdot {}^3/_4H_2O$	77	EtOH-H_2O	285–288	1-8[h]
1-10	NHC_6H_4-4-NAcMe		1.8 ± 0.13 (4)	$C_{16}H_{17}N_5O$	38	EtOH	179–181	comm
1-11	NHC_6H_4-4-NHMe		1.4 (1)	$C_{16}H_{15}N_5 \cdot {}^1/_2H_2O$	59	EtOH	110–112	1-10[h]
1-12	NHC_6H_4-4-NMe_2		3.3 ± 1.6 (6)	$C_{17}H_{17}N_5 \cdot {}^1/_6H_2O$	31	EtOH	171–174	amine
1-13	NHC_6H_4-4-NMe_2	Me	31.9 (3)	$C_{16}H_{16}N_5 \cdot {}^1/_4H_2O$	7		145–148	amine[g]
1-14	NHC_6H_4-4-(1-Im)		1.4 ± 0.2 (3)	$C_{16}H_{14}N_6$	63	EtOH	204–206	39
1-15	NHC_6H_4-4-OMe		8.3 ± 0.3 (2)	$C_{16}H_{14}N_4O$	55	$MeOCH_2CH_2OH$	162–164	comm
1-16	NHC_6H_4-4-$OCH_2CH_2NEt_2$		>3	$C_{21}H_{25}N_5O$	9	Et_2O-hex.	106–108	amine[i]
1-17	NHC_6H_4-4-COOMe		I	$C_{17}H_{14}N_4O_2$	44	EtOAc-MeOH	231.5–233.5	amine
1-18	NHC_6H_4-3-F		1.0 ± 0.3 (5)	$C_{15}H_{11}FN_4$	44	EtOH	162–164	amine
1-19	NHC_6H_4-3-CF_3		2.9 ± 1.7 (3)	$C_{16}H_{11}F_3N_4$	49	$MeOCH_2CH_2OH$	126–128	comm
1-20	NHC_6H_4-3-CF_3		0.4 ± 0.4 (2)	$C_{16}H_{11}F_3N_4 \cdot H_2SO_4$	93	EtOH	208–211	1-19
1-21	NHC_6H_4-3-Me		0.7 ± 0.5 (5)	$C_{16}H_{14}N_4$	62		135–137	comm
1-22	NHC_6H_4-3-Et		1.4 (1)	$C_{17}H_{16}N_4$[j]	65	EtOH	101–104	amine
1-23	NHC_6H_4-3-SO_2NH_2		0.5 ± 0.3 (2)	$C_{16}H_{13}N_5O_2S$	26	$MeOCH_2CH_2OH$	223–225	amine
1-24	NHC_6H_4-3-NHAc		0.3 ± 0.2 (4)	$C_{17}H_{15}N_5O$	50	$MeOCH_2CH_2OH$	190–192	amine
1-25	NHC_6H_4-3-NH_2		0.3 ± 0.1(2)	$C_{16}H_{13}N_5$	57	$MeOCH_2CH_2OH$	153–156	1-24[h]
1-26	NHC_6H_4-3-NMe_2		0.4 ± 0.3 (2)	$C_{17}H_{17}N_5$	18	EtOH	109–111	amine
1-27	NHC_6H_4-3-(1-Im)		0.3 ± 0.1 (5)	$C_{16}H_{14}N_6$	33	EtOH	205.5–206.5	43
1-28	NHC_6H_4-3-(1-Im)			$C_{16}H_{14}N_6 \cdot HCl$	83	EtOH	232.5–234	1-27
1-29	NHC_6H_4-3-(1-Im)		0.2 ± 0.1 (11)	$C_{16}H_{14}N_6 \cdot 2HCl \cdot {}^3/_2H_2O$	100		119–126	1-27
1-30	NHC_6H_4-3-OMe		0.2 (1)	$C_{16}H_{14}N_4O$	52	EtOH	110–113	amine
1-31	NHC_6H_4-3-$OCH_2CH_2NEt_2$		1.2 ± 0.5(3)	$C_{21}H_{25}N_5O$	9	Et_2O-hex.	64–66	k
1-32	NHC_6H_4-3-(OCH_2CH_2-1-Im)		0.4 ± 0.1 (3)	$C_{20}H_{16}N_6O$	16	EtOH	149–151.5	l
1-33	NHC_6H_4-3-COOEt		3.0 ± 0.3 (3)	$C_{16}H_{16}N_4O_2 \cdot {}^1/_6H_2O$	16	EtOH	156–158	amine
1-34	NHC_6H_4-2-Me		I	$C_{16}H_{14}N_4$	55	EtOH	111–113	comm
1-35	NHC_6H_4-2-CF_3		I	$C_{16}H_{11}F_3N_4$[m]	22		106–110	comm
1-36	NHC_6H_4-3,4-Me_2		5.9 (1)	$C_{17}H_{16}N_4$	52	Me_2CO-hex.	130–133.5	comm
1-37	NHC_6H_4-3,5-Me_2		0.1 ± 0.01 (2)	$C_{17}H_{16}N_4$	47	EtOH	114–119	amine
1-38	NHC_6H_4-3,5-Me_2	Me	>24	$C_{16}H_{16}N_4$	38	EtOH	110–112	amine[g]
1-39	Ph		I	$C_{15}H_{11}N_3$	27	EtOH	70–72	comm
1-40	CH_2Ph		I	$C_{16}H_{13}N_3$	7	EtOH-H_2O	65–67	amine
1-41	NHC_6H_4-4-(4-MePip)		1.9 ± 1.5 (2)	$C_{20}H_{20}N_6$	43	EtOH	192–193	amine[n]

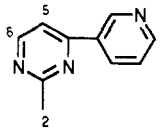
[a] Substituents in the 2-position of the pyrimidine are defined as NHPh = phenylamino, NHC_6H_4-4-(1-Im) = [[4-(1*H*-imidazol-1-yl)phenyl]amino], NMorph = 4-morpholinyl, (4-MePip) = 4-methylpiperidin-1-yl, (1-(4-Me)Im) = 4-methylimidazol-1-yl. [b] IC_{50} in μM as means ± SEM. The numbers in parentheses indicate the number of dose responses carried out. [c] The elements cited were within 0.4% of the theoretical values (except O). [d] In some cases, filtration of the hot reaction mixture to remove inorganic material, followed by cooling, caused the product to crystallize out of the reaction mixture in pure form. Hence, no recrystallization solvent is listed. [e] "Comm" means the guanidine was commercially available. "Amine" means the guanidine was prepared, without isolation, from a commercially available amine. [f] Used enaminone 3-(dimethylamino)-1-(2-pyridinyl)-2-propen-1-one (ref 16), unless otherwise noted, with method A. [g] Used enaminone 3-(dimethylamino)-1-(2-pyridinyl)-2-buten-1-one, mp 68–70 °C, method H. [h] Method B. [i] Kaye, I. A.; Burlant, W. J.; Price, L. Thiocyanation of *p*-Dialkylaminoalkoxyanilines. *J. Org. Chem.* **1951**, *16*, 1421–1426. [j] C: calcd, 73.89; found, 74.57. [k] Prepared from 3-aminophenol by method D. [l] Prepared from **42** by method I. [m] N: calcd, 17.71; found, 18.5. [n] Reference 15.

was more active than *meta* or *para* substitution (**3-6**, **3-28**, **3-42**). Since the unsubstituted phenyl (**3-1**) was very active, many substituents lowered activity. Lengthening the chain of a 4-amino ether lowered activity, as did substituting S for O (**3-25**, **3-24**, **3-26**). Replacing the dialkylamino group of **3-40** with imidazole gave a very active compound (**3-41**).

Few comparisons of phenyl substitution were available in the 4-(2-thienyl)pyrimidine series. However, there were still more cases (three: **4-6**, **4-12**; **4-5**, **4-11**; **4-2**, **4-7**) where *meta* derivatives were more active than there were in which *para* ones were more active (two: **4-3**, **4-9**; **4-4**, **4-10**). Since the unsubstituted phenyl (**4-1**) was not very active, substitution improved the activity. The imidazolylethoxy group (**4-13**) again gave the best activity of the 2-thienyl series.

When the pyrimidine 4-substituent was a 2-furyl, the unsubstituted phenyl compound **5-1** was essentially inactive. Only four valid comparisons of phenyl substitution are available. For the ethyl and imidazolyl groups, *meta* was more active than *para* (**5-3**, **5-11**; **5-8**, **5-13**). The amino ethers were equal (**5-9**, **5-15**), while the *p*-isomer of the methylpiperazinyl analog was more active (**5-7**, **5-12**). Going from one *meta* substituent to two (**5-10**, **5-17**) increased activity. Thus for the five main types of 4-heterocyclic pyridines studied (i.e., *o*-, *m*-, *p*-pyridines, thiophene, and

Table II. 3-Pyridinylpyrimidines



	substituents[a]							
	2	5	basophil	formula[b]	% yield	recryst solvent	mp, °C	start. mat.[c]
2-1	NHPh		0.9 (1)	$C_{15}H_{12}N_4$	24	CH_2Cl_2–hex.	147–148	comm
2-2	NHPh		1.3 ± 0.8 (3)	$C_{15}H_{12}N_4 \cdot H_2SO_4 \cdot H_2O$[d]	87		167–187	2-1
2-3	NHC_6H_4-4-Cl		I	$C_{15}H_{11}ClN_4$	56	$MeOCH_2CH_2OH$	183–184	comm
2-4	NHC_6H_4-4-Me		I	$C_{16}H_{14}N_4$	77	2-PrOH	135–136	comm
2-5	NHC_6H_4-4-*t*-Bu		0.6 ± 0.2 (3)	$C_{19}H_{20}N_4 \cdot {}^1/_8C_2H_6O$	8	EtOH–H_2O	130–133	amine
2-6	NHC_6H_4-4-SO_2NH_2		0.2 ± 0.1 (3)	$C_{15}H_{13}N_5O_2S \cdot {}^7/_6H_2O$	30	$MeOCH_2CH_2OH$	224–225	amine
2-7	NHC_6H_4-4-COMe		0.8 (1)	$C_{17}H_{14}N_4O$	78	$MeOCH_2CH_2OH$	181–183	amine
2-8	NHC_6H_4-4-NHAc		3.6 (1)	$C_{17}H_{15}N_5O \cdot {}^3/_4H_2O$	40	$MeOCH_2CH_2OH$	192–195	amine
2-9	NHC_6H_4-4-NH_2		2.8 ± 1.1 (4)	$C_{15}H_{13}N_5 \cdot 2HCl$	67	H_2O	296–301	2-8[e]
2-10	NHC_6H_4-4-NAcMe		0.9 ± 0.1 (3)	$C_{15}H_{17}N_5O$[f]	49	EtOH	194–197	comm
2-11	NHC_6H_4-4-NHMe		2.1 ± 0.8 (2)	$C_{16}H_{15}N_5$	53	EtOH	164–166	2-10[e]
2-12	NHC_6H_4-4-NMe_2		2.8 ± 1.8 (2)	$C_{17}H_{17}N_5$	30	EtOH	165–166	amine
2-13	NHC_6H_4-4-(4-MePip)		0.5 (2)	$C_{20}H_{22}N_6$	70	EtOH	174–175	*g*
2-14	NHC_6H_4-4-(1-Im)		1.3 ± 1.2 (4)	$C_{16}H_{14}N_6$	41	MEOH	170–172	39
2-15	NHC_6H_4-4-OMe		1.7 (1)	$C_{16}H_{14}N_4O$	60	2-PrOH	121–122	comm
2-16	$NMeC_6H_4$-4-OMe		>24	$C_{17}H_{16}N_4O$	48	Et_2O–hex.	88–90	comm
2-17	NHC_6H_4-4-OH		5.1 ± 0.7 (5)	$C_{15}H_{12}N_4O \cdot {}^1/_4H_2O$	80	EtOH	221–223	2-15[h]
2-18	NHC_6H_4-4-$OCH_2CH_2NMe_2$		0.7 ± 0.2 (3)	$C_{19}H_{21}N_5O \cdot {}^1/_4H_2O$[i]	37	$CHCl_3$–hex.	108–110	2-17[j]
2-19	NHC_6H_4-4-$OCH_2CH_2CH_2NMe_2$		0.6 ± 0.4 (2)	$C_{20}H_{21}N_5O \cdot {}^1/_{16}H_2O$	41	Et_2O–hex.	85–87	2-17[j]
2-20	NHC_6H_4-4-$OCH_2CH_2NEt_2$		0.2 ± 0.2 (3)	$C_{21}H_{25}N_5O \cdot {}^1/_4H_2O$[k]	47	Et_2O–hex.	87–89	2-17[j]
2-21	NHC_6H_4-4-$OCH_2CH_2N(iPr)_2$		4.6 (1)	$C_{23}H_{29}N_5O \cdot {}^1/_4H_2O$[l]	13	Et_2O–hex.	122–124	2-17[j]
2-22	NHC_6H_4-4-COOEt		12.4 (1)	$C_{16}H_{16}N_4O_2$	15	EtOH	197–202	amine
2-23	NHC_6H_4-3-Cl		1.5 ± 0.4 (2)	$C_{15}H_{11}ClN_4 \cdot {}^1/_4H_2O$	64	$MeOCH_2CH_2OH$	146–148	comm
2-24	NHC_6H_4-3-CF_3		I	$C_{16}H_{11}F_3N_4$	61	$CHCl_3$–hex.	181–183	comm
2-25	NHC_6H_4-3-CF_3		0.7 (1)	$C_{16}H_{11}F_3N_4 \cdot {}^7/_8HCl$	65		220–223	2-24
2-26	NHC_6H_4-3-CF_3		2.1 (2)	$C_{16}H_{11}F_3N_4 \cdot H_2SO_4 \cdot {}^1/_4H_2O$	55		196–199	2-24
2-27	NHC_6H_4-3-Me		1.5 (1)	$C_{16}H_{14}N_4$	34	$MeOCH_2CH_2OH$	103–104	comm
2-28	NHC_6H_4-3-SO_2NH_2		0.2 ± 0.9 (3)	$C_{15}H_{13}N_5O_2S$	36	$MeOCH_2CH_2OH$	278–280	amine
2-29	NHC_6H_4-3-COMe		4.1 (1)	$C_{17}H_{14}N_4O \cdot {}^1/_4H_2O$[m]	36	$CHCl_3$–hex.	166–168	amine
2-30	NHC_6H_4-3-NHAc		3.6 ± 2.7 (3)	$C_{17}H_{15}N_5$	54	$MeOCH_2CH_2OH$	239–241	comm
2-31	NHC_6H_4-3-NH_2		0.5 ± 0.1 (2)	$C_{15}H_{13}N_5 \cdot 2HCl$		EtOH–H_2O	279–284	2-30[e]
2-32	NHC_6H_4-3-NMe_2		1.8 ± 0.8 (4)	$C_{17}H_{16}N_5$	23	EtOH	123–125	amine
2-33	NHC_6H_4-3-(4-MePip)		1.2 ± 0.3 (3)	$C_{20}H_{22}N_6$	29	EtOAc,MeCOEt	132–133.5	*n*
2-34	NHC_6H_4-3-(1-Im)		0.2 ± 0.04 (3)	$C_{16}H_{14}N_6 \cdot {}^3/_4H_2O$[o]	20	MeCOEt	58–130	43
2-35	NHC_6H_4-3-OMe		0.3 (2)	$C_{16}H_{14}N_4O$	31	EtOH	126–127	amine
2-36	NHC_6H_4-3-$OCH_2CH_2NEt_2$		2.9 ± 1.3 (3)	$C_{21}H_{25}N_5O \cdot {}^1/_2CH_3OH$[p]	28	chrom	79–82	amine[q]
2-37	NHC_6H_4-3-(OCH_2CH_2-1-Im)		0.1 ± 0.04 (3)	$C_{20}H_{18}N_6O$	24	MeCOEt	135–137.5	amine[r]
2-38	NHC_6H_4-3-COOEt		10.5 ± 7.4 (5)	$C_{19}H_{16}N_4O_2 \cdot H_2O$	20	EtOH	95–103	amine
2-39	NHC_6H_4-2-Cl		I	$C_{15}H_{11}ClN_4 \cdot {}^1/_4H_2O$	54	$MeOCH_2CH_2OH$	103–104	comm
2-40	NHC_6H_4-2-OMe		9.8 ± 9.8 (2)	$C_{16}H_{14}N_4O$	77	Et_2O	99–101	amine
2-41	NHC_6H_4-2-OH		23.5 (1)	$C_{15}H_{12}N_4O$[s]	54	EtOH	166–168	2-40[h]
2-42	NHC_6H_4-2-$OCH_2CH_2NEt_2$		>6	$C_{21}H_{25}N_5O$[t]	30	chrom	gum	2-41[j]
2-43	NHC_6H_3-2,6-F_2		21.0 (2)	$C_{15}H_{10}F_2N_4 \cdot {}^1/_8H_2O$	17	EtOH	163–166	amine
2-44	NHC_6H_3-2,4-Me_2		I	$C_{17}H_{16}N_4$	43	CH_2Cl_2–hex.	113–115	comm
2-45	NHC_6H_3-3,5-Me_2		0.8 ± 0.1 (2)	$C_{17}H_{16}N_4 \cdot {}^1/_8H_2O$	52	EtOH	122–126	amine
2-46	NHC_6H_3-3,5-Me_2	Me	>24	$C_{16}H_{16}N_4$	11	EtOH	136–140	amine[u]

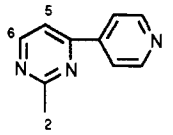
[a] See footnotes *a*, *b*, and *d* of Table I. [b] See footnote *c* of Table I. [c] Used enaminone 3-(dimethylamino)-1-(3-pyridinyl)-2-propen-1-one (ref 16) unless otherwise noted. [d] C: calcd, 49.44; found, 48.48. [e] Method B. [f] C: calcd, 67.70; found, 65.82. [g] Reference 15. [h] Method C. [i] MS M^+: calcd, 335; found, 335. [j] Method D. [k] MS M^+: calcd, 363; found, 363. [l] MS M^+: calcd, 391; found, 391. [m] MS M^+: calcd, 290; found, 290. [n] 1-Fluoro-3-nitrobenzene was converted to 1-methyl-4-(3-nitrophenyl)piperazine by method J and then to (1-piperazinyl)benzamine hydrochloride by method L. [o] MS M^+: calcd, 313; found 313. [p] MS M^+: calcd, 363, found, 363. [q] Prepared from 3-aminophenol by method D. [r] Prepared from 42 by method L. [s] MS M^+: calcd, 264; found, 264. [t] MS M^+: calcd, 363; found, 363. [u] Used enaminone 3-(dimethylamino)-2-methyl-1-(3-pyridinyl)-2-propen-1-one (Dusza, J. P.; Tomcufcik, A. S.; Albright, J. D. Eur. Pat. Appl. EP 129847; *Chem. Abstr.* 1985, *102*, 220889*m*; Aryl and Heteroaryl[7-(aryl and heteroaryl)pyrazolo[1,5-a]pyrimidin-3-yl]methanones. US 4,521,422, 1985).

furan), *meta*-substitution of the 2-anilino group usually gave the highest activity. *N*-[3-(1*H*-Imidazol-1-yl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine (**1-27**) was picked as one of the most active compounds and was evaluated in several other tests.

Since the basophil assay measured only in vitro cell histamine release inhibition and since it had been assumed that this measurement was indicative of total mediator release inhibition, it was desirable to demonstrate that at least another important mediator, leukotriene C_4 (LTC_4), was inhibited by **1-27**. Using a radioimmunoassay[12] for LTC_4 release from basophils and measuring histamine release simultaneously on a second portion of the same cells gave IC_{50} (LTC_4) = 205 ± 48 nM (n = 5) for **1-27** while IC_{50} (histamine) = 311 ± 133 nM (n = 5).

To demonstrate in vivo activity, **1-27** was tested in the mouse passive cutaneous anaphylaxis (PCA) test,[13] where an ID_{50} of ca. 50 mg/kg at times of 0.5–41 min following oral dosing was found. Compound **1-27** at doses of 400 μg/kg caused a 0.5–2 log shift (n = 4) in dose–response curves to anti-IgE in a cutaneous anaphylaxis assay in rhesus monkeys with a natural sensitivity to *Ascaris* antigen. Finally an acute LD_{50} in mice of approximately 800 mg/kg was found for **1-27**. Compound **1-27** has been chosen for further studies as a potential antiasthma agent.

Table III. 4-Pyridinylpyrimidines



	substituent[a]							
	2	6	basophil	formula[b]	% yield	recryst solvent	mp, °C	start. mat.[c]
3-1	NHPh		0.9 ± 0.4 (5)	$C_{15}H_{12}N_4$	75	EtOH	153–154	comm
3-2	N(COCOOEt)Ph		2.2 ± 1.3 (3)	$C_{19}H_{16}N_4O_3$	35	EtOH	139–140	3-1[d]
3-3	NMePh		>24	$C_{16}H_{14}N_4 \cdot {}^1/_6H_2O$	45	EtOH	105–107	amine
3-4	NHPh	Me	I	$C_{16}H_{14}N_4$	35	CH_2Cl_2–Me_2CO	207–210	comm[e]
3-5	NHC_6H_4-4-F		1.9 ± 0.5 (2)	$C_{15}H_{11}FN_4$	66	$MeOCH_2CH_2OH$	186–188	comm
3-6	NHC_6H_4-4-Me		I	$C_{16}H_{14}N_4$	68	$MeOCH_2CH_2OH$	198–199	comm
3-7	NHC_6H_4-4-Et		7.7 ± 3.5 (3)	$C_{17}H_{16}N_4$	70	CH_2Cl_2–hex.	138–140	comm
3-8	NHC_6H_4-4-Et	Me	I	$C_{16}H_{16}N_4$	29	Me_2CO–hex.	149–151	comm[e]
3-9	NHC_6H_4-4-SO_2NH_2		5.1 ± 0.3 (4)	$C_{15}H_{13}N_5O_2S$	21	$MeOCH_2CH_2OH$	225–228	amine
3-10	NHC_6H_4-4-NHAc		5.3 ± 1.4 (2)	$C_{17}H_{15}N_5O$	58	EtOH	294–296	amine
3-11	NHC_6H_4-4-NH_2		2.9 ± 0.7 (6)	$C_{15}H_{13}N_5 \cdot {}^3/_2HCl \cdot {}^3/_2H_2O$		EtOH–H_2O	292–295	3-10[f]
3-12	NHC_6H_4-4-NH_2		2.4 ± 2.1 (2)	$C_{15}H_{13}N_5 \cdot {}^1/_4H_2O$	96	EtOH	178–180[g]	3-11
3-13	NHC_6H_4-4-NAcMe		0.5 ± 0.2 (3)	$C_{16}H_{17}N_5O$		$MeOCH_2CH_2OH$	233–234	comm
3-14	NHC_6H_4-4-NHMe		*h*	$C_{16}H_{15}N_5 \cdot 2HCl$	81	EtOH	285–287	3-13[f]
3-15	NHC_6H_4-4-NMe_2		3.7 ± 1.4 (10)	$C_{17}H_{17}N_5$	9	EtOH	164–166	amine
3-16	NHC_6H_4-4-NMe_2	Me	>24	$C_{16}H_{19}N_5$[i]	14	EtOH	153–154	amine[e]
3-17	NHC_6H_4-4-(4-MePip)		0.6 (1)	$C_{20}H_{22}N_6$	73	EtOH	209–212	*j*
3-18	NHC_6H_4-4-(1-Im)		7.6 ± 2.3 (5)	$C_{16}H_{14}N_6 \cdot {}^1/_4HCON(CH_3)_2$[k]	58	DMF	248–250	39
3-19	NHC_6H_4-4-[1-(4-Me)Im]		>3	$C_{19}H_{16}N_6$	53	EtOH	244–245.5	amine[l]
3-20	NHC_6H_4-4-OMe		4.2 (1)	$C_{16}H_{14}N_4O$	73	$MeOCH_2CH_2OH$	174–175	comm
3-21	$NMeC_6H_4$-4-OMe		>24	$C_{11}H_{16}N_4O$	21	Et_2O–hex.	124–126	3-20[m]
3-22	NHC_6H_4-4-OCH_2CO(4-MePip)		0.3 ± 0.2 (3)	$C_{22}H_{24}N_6O_2$	15	EtOH–Et_2O	163–165	44
3-23	NHC_6H_4-4-OH		3.3 ± 1.3 (3)	$C_{15}H_{12}N_4O \cdot {}^1/_4EtOAc \cdot {}^1/_4H_2O$[n]	41	DMF–EtOH	249–252d	3-20[o]
3-24	NHC_6H_4-4-$O(CH_2)_3NEt_2$		1.3 ± 0.8 (4)	$C_{20}H_{23}N_5O$	27	$CHCl_3$–hex.	123–124.5	3-23[p]
3-25	NHC_6H_4-4-$OCH_2CH_2NEt_2$		0.2 ± 0.2 (2)	$C_{21}H_{25}N_5O \cdot {}^1/_8H_2O$[q]	10	Et_2O–hex.	85–87	3-23[p]
3-26	NHC_6H_4-4-$SCH_2CH_2NEt_2$		1.0 ± 0.3 (3)	$C_{21}H_{25}N_5S$[r]	13	EtOAc–hex.	84–87	amine[s]
3-27	NHC_6H_4-3-F		0.7 ± 0.1 (2)	$C_{15}H_{11}FN_4$	39	EtOH	155; 162	amine
3-28	NHC_6H_4-3-Me		8.8 ± 2.6 (3)	$C_{16}H_{14}N_4$[t]	60		157–159	comm
3-29	NHC_6H_4-3-Me	Me	I	$C_{17}H_{16}N_4$	38	CH_2Cl_2–Me_2CO	185–188.5	comm[e]
3-30	NHC_6H_4-3-Et		10.6 (1)	$C_{17}H_{16}N_4$	53	EtOH	126–128	amine
3-31	NHC_6H_4-3-SO_2NH_2		0.5 ± 0.02 (2)	$C_{15}H_{13}N_5O_2S \cdot {}^1/_6H_2O$	34	$MeOCH_2CH_2OH$	262–264	amine
3-32	NHC_6H_4-3-NHAc		2.7 ± 1.1 (3)	$C_{17}H_{17}N_5$	63	$MeOCH_2CH_2OH$	267–270	comm
3-33	NHC_6H_4-3-NH_2		1.0 ± 0.3 (3)	$C_{15}H_{13}N_5 \cdot {}^3/_6H_2O$	77	$MeOCH_2CH_2OH$	199–202	3-32[f]
3-34	NHC_6H_4-3-NMe_2		3.7 ± 2 (5)	$C_{17}H_{17}N_5$	25	EtOH	165–168	amine
3-35	NHC_6H_4-3-NMe_2	Me	>24	$C_{15}H_{19}N_5$	10	$MeOCH_2CH_2OH$	200–201	amine[e]
3-36	NHC_6H_4-3-(1-Im)		0.6 ± 0.2 (2)	$C_{18}H_{14}N_6 \cdot {}^1/_8H_2O$[u]	24	EtOH	237–239	43
3-37	NHC_6H_4-3-(1-Im)		3.9 ± 3.6 (2)	$C_{16}H_{14}N_6 \cdot {}^7/_8HCl \cdot {}^5/_8H_2O$	66	EtOH–Et_2O	259–266	3-36
3-38	NHC_6H_4-3-OMe		0.4 ± 0.3 (3)	$C_{16}H_{14}N_4O$	33	EtOH	159–160	amine
3-39	NHC_6H_4-3-OMe	Me	>24	$C_{17}H_{16}N_4O$	13	EtOH	187–189	amine[e]
3-40	NHC_6H_4-3-$OCH_2CH_2NEt_2$		0.6 ± 0.2 (2)	$C_{21}H_{25}N_5O$	33	Et_2O–hex.	104–106	amine[v]
3-41	NHC_6H_4-3-(OCH_2CH_2-1-Im)		0.2 ± 0.1 (5)	$C_{20}H_{18}N_6O \cdot {}^1/_8CH_3CN$[w]	45	CH_3CN	138–140	*x*
3-42	NHC_6H_4-2-Me		3.9 ± 0.1 (2)	$C_{16}H_{14}N_4$	62	EtOH	129–130.5	comm
3-43	NHC_6H_4-2-Et		I	$C_{17}H_{16}N_4 \cdot 2HCl$	25		228–231	amine
3-44	NHC_6H_4-2-NMe_2		36.2 (1)	$C_{17}H_{17}N_5 \cdot {}^5/_2C_4H_4O_4$[y]		Me_2CO	114–119	amine
3-45	NHC_6H_3-3-CF_3,4-(1-Im)		0.4 ± 0.2 (4)	$C_{19}H_{13}F_3N_6$	8	EtOH	239–242	*z*
3-46	$NHCH_2C_6H_3$-3,4-Me_2		I	$C_{16}H_{18}N_4$	16	EtOH	132–136	amine
3-47	NH-cyclopentyl		I	$C_{14}H_{16}N_4$	45	EtOH	122–124	comm
3-48	NH-cyclohexyl		I	$C_{15}H_{18}N_4 \cdot {}^1/_6H_2O$	9	EtOH	143–146	amine
3-49	Ph		13.9 (1)	$C_{15}H_{11}N_3 \cdot HCl$	42	EtOH	232–237	comm
3-50	CH_2Ph		I	$C_{16}H_{13}N_3 \cdot {}^5/_8C_2H_6$)	47	EtOH–H_2O	79–119	amine

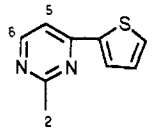
[a] See footnotes *a*, *b*, and *d* of Table I. [b] See footnote *c* of Table I. [c] The enaminone was 3-(dimethylamino)-1-(4-pyridinyl)-2-propen-1-one (ref 10) unless otherwise noted. [d] Method E. [e] Used enaminone 3-(dimethylamino)-1-(4-pyridinyl)-2-buten-1-one (footnote *u* Table II). [f] Method B. [g] Dimorphic, the second form had mp 192–193.5 °C. [h] Compound interfered with the histamine assay. [i] N: calcd, 22.93; found, 21.32. [j] Reference 15. [k] MS M^+: calcd, 314; found, 314. DMF detected in the ^1H NMR. [l] Roberts, D. A.; Campbell, S. F. Heteroarylquinolone Inotropic Agents. Eur. Pat. Appl. EP 166533 1986; *Chem. Abstr.* 1986, *105*, 115061z. [m] Method F. [n] MS M^+: calcd, 264; found, 264. [o] Method C. [p] Method D. [q] MS M^+: calcd, 363; found, 363. [r] C: calcd, 66.46; found, 65.86. S: calcd, 8.45; found, 8.90. MS M^+: calcd, 379; found, 379. [s] Buechi, J.; Enezian, J.; Enezian, G. *Congr. Sci. Pharm.* 1959, 317–328; Synthesis and Activity of Some Local Anesthetics, Derivatives of Procaine. *Chem. Abstr.* 1962, *56*, 1534*h*. Bp 113 °C/0.1 mm. [t] C: calcd, 73.26; found, 71.77. [u] MS M^+: calcd, 314; found, 314. [v] Footnote *q* of Table II. [w] MS M^+: calcd, 358; found, 358. [x] Prepared from **42** by method L. [y] Maleate. [z] Prepared from 2-fluoro-5-nitrobenzotrifluoride via method J to 1-[4-nitro-2-(trifluoromethyl)phenyl]-1H-imidazole and reduction to 4-(1H-imidazol-1-yl)-3-(trifluoromethyl)benzamine by method L.

Experimental Section

Melting points were obtained on a standardized Mel-Temp apparatus and are uncorrected. Infrared spectra were taken on a Nicolet FT-IR spectrophotometer and ultraviolet spectra on a Hewlett-Packard 4050A. A Varian FT80 was used for ^1H NMR, and spectra are given in ppm downfield from a TMS internal standard with coupling constants in hertz. For mass spectra, a Finnigan-MHT CH7 was used. Column chromatography was carried out by evaporating a MeOH solution of impure material onto a small amount of silica gel. The dried gel was placed on top of a wet (CCl_4) silica gel column. The column was eluted with $CHCl_3$ followed by 1% increments of MeOH to 10% MeOH/$CHCl_3$. TLC was carried out on silica gel plates, using MeOH/$CHCl_3$ (1:3 or 1:9).

Basophil Mediator Release. This test has been described in detail.[8b]

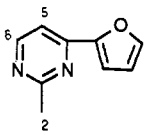
Table IV. 2-Thienylpyrimidines



	2-substituent[a]	basophil	formula[b]	% yield	recryst solvent	mp, °C	start. mat.[c]
4-1	NHPh	31.7 (1)	$C_{14}H_{11}N_3S$	66		137–139	comm
4-2	NHC_6H_4-4-Me	I	$C_{15}H_{13}N_3S$	65	$MeOCH_2CH_2OH$	179–181	comm
4-3	NHC_6H_4-4-NMe_2	0.9 ± 0.3 (4)	$C_{16}H_{16}N_4S \cdot {}^1/_6H_2O$	29	$MeOCH_2CH_2OH$	174–175	amine
4-4	NHC_6H_4-4-(4-MePip)	0.4 ± 0.3 (2)	$C_{19}H_{21}N_5S$	60	$CHCl_3$	215.5–216.5	*d*
4-5	NHC_6H_4-4-(1-Im)	4.3 ± 1.5 (3)	$C_{17}H_{13}N_5S$	62	MeOH	210.5–212	**39**
4-6	NHC_6H_4-4-OMe	3.9 (1)	$C_{15}H_{13}N_3OS$	53		158–160	comm
4-7	NHC_6H_4-3-Me	0.3 (1)	$C_{15}H_{13}N_3S$	54	EtOH	112.5–114.5	comm
4-8	NHC_6H_4-3-Et	I	$C_{16}H_{15}N_3S$	59	EtOH	114–116	amine
4-9	NHC_6H_4-3-NMe_2	2.4 ± 0.7 (2)	$C_{16}H_{16}N_4S$	37	EtOH	118–120	amine
4-10	NHC_6H_4-3-(4-MePip)	3.5 ± 0.3 (3)	$C_{19}H_{21}N_5S$	49	EtOAc	125–126.5	*e*
4-11	NHC_6H_4-3-(1-Im)	0.3 ± 0.06 (4)	$C_{17}H_{13}N_5S$	31	EtOH	183–184.5	**43**
4-12	NHC_6H_4-3-OMe	0.9 ± 0.9 (2)	$C_{15}H_{13}N_3OS$	36	EtOH	151–153	amine
4-13	NHC_6H_4-3-(OCH_2CH_2-1-Im)	0.1 ± 0.01 (3)	$C_{19}H_{17}N_5OS \cdot {}^1/_2C_2H_6O$[f]	35	EtOH	118	*g*
4-14	NHC_6H_3-3,5-Me_2	4.3 ± 1.0 (2)	$C_{16}H_{15}N_3S$	56	EtOH	152–155	amine

[a] See footnotes *a*, *b*, and *d* of Table I. [b] See footnote *c* of Table I. [c] Used enaminone 3-(dimethylamino)-1-(2-thienyl)-2-propen-1-one (Wagner, R. M.; Jutz, C. *Chem. Ber.* **1971**, *104*, 2975–2983). [d] Reference 15. [e] Footnote *u* of Table II. [f] MS M^+: calcd, 363; found, 363. [g] Prepared from **42** by method L.

Table V. 2-Furylpyrimidines



	substituent[a]							
	2	6	basophil	formula[b]	% yield	recryst solvent	mp, °C	start. mat.[c]
5-1	NHPh		32.0 (1)	$C_{14}H_{11}N_3O$	70	EtOH	144–145	comm
5-2	NHPh	Me	17.7 (1)	$C_{15}H_{13}N_3O$	45	CH_2Cl_2–hex.	141–142	comm[d]
5-3	NHC_6H_4-4-Et		I	$C_{16}H_{15}N_3O$	56	EtOH	152–155	comm
5-4	NHC_6H_4-4-NMe_2		1.9 (2)	$C_{16}H_{16}N_4O$	33	EtOH	166–167	amine
5-5	NHC_6H_4-4-NMe_2	Me	5.9 (1)	$C_{17}H_{18}N_4O$	21	EtOH	146–148	amine[d]
5-6	NHC_6H_4-4-NEt_2		8.7 (2)	$C_{16}H_{20}N_4O$	33	EtOH	132–133	amine
5-7	NHC_6H_4-4-(4-MePip)		1.8 ± 1.8 (2)	$C_{19}H_{21}N_5O$	68	EtOH	193–195	*e*
5-8	NHC_6H_4-4-(1-Im)		2.2 ± 0.9 (3)	$C_{17}H_{13}N_5O$	42	MEOH	211.5–213.5	**39**
5-9	NHC_6H_4-4-$OCH_2CH_2NEt_2$		1.3 ± 0.5 (3)	$C_{20}H_{24}N_4O_2$	21	Et_2O	114–116	amine[f]
5-10	NHC_6H_4-3-Me		2.1 ± 0.3 (9)	$C_{15}H_{13}N_3O$	56	EtOH	98–99.5	comm
5-11	NHC_6H_4-3-Et		9.7 (1)	$C_{16}H_{15}N_3O$	56	EtOH	95–98	amine
5-12	NHC_6H_4-3-(4-MePip)		5.0 ± 3.5 (3)	$C_{19}H_{21}N_5O$	36	EtOAc	134.5–136	*g*
5-13	NHC_6H_4-3-(1-Im)		0.8 ± 0.04 (2)	$C_{17}H_{13}N_5O$	26	EtOH	174–175.5	**43**
5-14	NHC_6H_4-3-OMe		0.4 ± 0.4 (3)	$C_{15}H_{13}N_3O_2$	44	EtOH	114–116	amine
5-15	NHC_6H_4-3-$OCH_2CH_2NEt_2$		1.4 ± 0.6 (2)	$C_{20}H_{24}N_4O_2$	47	chrom	gum	amine[h]
5-16	NHC_6H_4-3-(OCH_2CH_2-1-Im)		0.2 ± 0.05 (3)	$C_{19}H_{17}N_5O_2$	29	EtOH	136–137	*i*
5-17	NHC_6H_3-3,5-Me		0.7 ± 0.2 (3)	$C_{16}H_{15}N_3O$[j]	58	EtOH	126–129	amine
5-18	NHC_6H_3-3,5-Me_2	Me	>24	$C_{17}H_{17}N_3O$	42	$MeOCH_2CH_2OH$	155–158	amine[d]

[a] See footnotes *a*, *b*, and *d* of Table I. [b] See footnote *c* of Table I. [c] Used enaminone 3-(dimethylamino)-1-(2-furyl)-2-propen-1-one, (Vershchagin, L. I.; Korshunov, S. P.; Timokhin, B. V.; Kakevich, R. I. *Probl. Poluch. Poluprod. Prom-si. OrgSin.* **1967**, 223–227; Furylalkynes IX. Some transformations of Furylethynylcarbinol and its Derivatives. *Chem. Abstr.* **1968**, *68*, 21756*v*.) See also footnote *c* of Table I. [d] Used crude enaminone 3-(dimethylamino)-1-(2-furyl)-2-methyl-2-propen-1-one, method H. [e] Reference 15. [f] Footnote *i* of Table I. [g] Footnote *u* of Table II. [h] Footnote *k* of Table I. [i] Prepared from **42** by method L. [j] C: calcd, 72.43; found, 73.22.

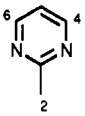
Monkey Cutaneous Anaphylaxis. Female Rhesus monkeys sensitive to *Ascaris* were anesthetized with ketamine and restrained supine. An iv line was established in a leg vein and 2 mL/kg of a 1% Evans blue dye in saline was infused through a sterile filter. Replicate serial log dilutions of −3, −4, −5, −6, and −7 of the *Ascaris* protein (Greer Laboratories, B33-8-1A4) were injected id into the right flank of the animal, 0.1 mL/spot. On occasion, anti-human IgE was injected at serial dilutions and utilized in an identical manner to *Ascaris* antigen. Twenty minutes later, the lesion areas were read as in PCA studies. Compound **1-27** at 400 μg/kg was dosed intravenously. After an additonal 5 min for absorption and distribution, a repeat of the anti-IgE injection was done on the left side and read as before. Activity was established by a reduction in lesion size at all levels of anti-human IgE.

Mouse PCA.[13] This assay has been described in detail.[8b]

In Vitro Histamine Release—Rat Lung Tissue. (a) Passive Sensitization of Lung Tissue. The lungs from male Sprague–Dawley rats were removed, cut into small portions, with care taken to remove all visible blood vessels, and finally cut into fine rectangular bits (10–15 mg) with iris scissors. The tissue was repeatedly washed in Tyrode's buffer until all visible traces of blood were removed and the washed fragments were placed in an appropriate dilution of IgE solution and incubated for 18 h at 4 °C or 3 h at 37 °C. After incubation, the tissue was washed twice in Tyrode's buffer and drained well, and ca. 15 tissue fragments (150–250 mg) were used for each sample to be assayed.

(b) **Challenge of Passivly Sensitized Lung Tissue.** Reaction tubes containing 990 μL of Tyrode's buffer alone or buffer containing the desired concentration of drug were placed in a 37 °C water bath. Three additional reaction tubes were prepared containing 1000 μL of buffer. These served as spontaneous histamine release samples. Fragments of sensitized tissue were added to each tube and allowed to incubate for 10 min. Then, 10 μL of buffer containing 40 μg of anti-IgE was added to each tube, with the exception of the spontaneous release samples,

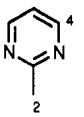
Table VI. Miscellaneous Thienylpyrimidines



	substituent[a]								
	2	4	6	basophil	formula[b]	% yield	recryst solvent	mp, °C	start. mat.
6-1	NHPh	3-thienyl		I	$C_{14}H_{11}N_3S$	44	EtOH	142–143	comm[c]
6-2	NHC_6H_4-4-OMe	3-thienyl		15.6 (1)	$C_{15}H_{13}N_3OS$	61	Me_2CO–hex.	158–160.5	comm[c]
6-3	NHC_6H_4-4-NMe_2	3-thienyl		2.1 ± 0.9 (2)	$C_{16}H_{16}N_4S$	33	EtOH	173–174	amine[c]
6-4	NHC_6H_4-3-Me	3-thienyl		3.8 (1)	$C_{15}H_{13}N_3S$	27	EtOH	104.5–105.5	comm[c]
6-5	NHC_6H_4-3-Et	3-thienyl		1.1 (1)	$C_{17}H_{16}N_2OS \cdot {}^1/_2H_2O$	60	EtOH	86–89	amine[c]
6-6	NHC_6H_4-3-OMe	3-thienyl		1.8 ± 1.2 (2)	$C_{15}H_{13}N_3OS \cdot {}^1/_4H_2O$	40	EtOH	142–145	amine[c]
6-7	NHC_6H_3-3,5-Me_2	3-thienyl		I	$C_{16}H_{15}N_3S$	56	EtOH	140–142	amine[c]
6-8	NHPh	3-Me-2-thienyl		I	$C_{15}H_{13}N_3S$	64	EtOH	137–140	comm[d]
6-9	NHC_6H_4-4-NMe_2	3-Me-2-thienyl		1.8 ± 0.5 (2)	$C_{17}H_{16}N_4S$	36	EtOH	145–148	amine[d]
6-10	NHC_6H_4-3-OMe	3-Me-2-thienyl		>24	$C_{16}H_{15}N_3OS$	40	EtOH	120–123	amine[d]
6-11	NHC_6H_4-3-Me	3-Me-2-thienyl		I	$C_{16}H_{15}N_3S$	56	EtOH	130–133	comm[d]
6-12	NHC_6H_4-3-NMe_2	3-Me-2-thienyl		I	$C_{17}H_{16}N_4S$	30	EtOH	140–142	amine[d]
6-13	NHPh	5-Me-2-thienyl		I	$C_{15}H_{13}N_3S$	54	EtOH	144–145	comm[e]
6-14	NHPh	5-Me-2-thienyl	Me	24.8 (1)	$C_{16}H_{16}N_3S$	34	EtOH	133–135	comm[f]
6-15	NHC_6H_4-3-OMe	5-Me-2-thienyl		2.3 ± 2.3 (2)	$C_{16}H_{15}N_3OS$	31	EtOH	149–151	amine[e]
6-16	NHC_6H_4-3-Me	5-Me-2-thienyl		1.4 ± 0.9 (2)	$C_{16}H_{15}N_3S \cdot {}^1/_6H_2O$	50	EtOH	114–116	comm[e]
6-17	NHC_6H_4-3-NMe_2	5-Me-2-thienyl		5.7 (1)	$C_{17}H_{13}N_4S$	33	EtOH	130–133	amine[e]

[a] See footnotes *a*, *b*, and *d* of Table I. [b] See footnote *c* of Table I. [c] Enaminone 3-(dimethylamino)-1-(3-thienyl)-2-propen-1-one. (Dusza, J. P.; Albright, J. D. Substituted Pyrazolo[1,5-a]pyrimidines and their Use as Anxiolytic Agents. US 4,281,000 1981; *Chem. Abstr.* 1981, *95*, 187293*z*.) [d] Enaminone 3-(dimethylamino)-1-(3-methyl-2-thienyl)-2-propen-1-one, mp 45–49 °C, method H. [e] Enaminone 3-(dimethylamino)-1-(5-methyl-2-thienyl)-2-propen-1-one. (Dusza, J. P.; Albright, J. D. 7-Heteroaryl[1,2,4]-triazolo[1,5-a]pyrimidines. US 4,444,774 1984; *Chem. Abstr.* 1984, *101*, 38474*z*.) [f] Enaminone 3-(dimethylamino)-1-(5-methyl-2-thienyl)-2-buten-1-one, mp 123–126 ° method H.

Table VII. Miscellaneous Furylpyrimidines



	substituents[a]							
	2	4	basophil	formula[b]	% yield	recryst solvent	mp, °C	start. mat.
7-1	NHPh	5-Me-2-furyl	I	$C_{15}H_{13}N_3O$	60	EtOH	155–156	comm[c]
7-2	NHC_6H_4-4-NEt_2	5-Me-2-furyl	28.0 (1)	$C_{19}H_{22}N_4O$	27	EtOH	118–119	amine[c]
7-3	NHC_6H_4-3-Me	5-Me-2-furyl	2.0 (1)	$C_{16}H_{15}N_3O$	51	EtOH	119–121	comm[c]
7-4	NHC_6H_4-3-OMe	5-Me-2-furyl	1.5 ± 0.4 (5)	$C_{16}H_{15}N_3O_2$	24	EtOH	95–97	amine[c]
7-5	NHC_6H_3-3,5-Me_2	5-Me-2-furyl	I	$C_{17}H_{17}N_3O$	26	EtOH	182–185	amine[c]
7-6	NHPh	2,5-Me_2-3-furyl	2.0 ± 0.2 (2)	$C_{16}H_{15}N_3O$	48	EtOH	116–118	comm[d]
7-7	NHC_6H_4-4-Et	2,5-Me_2-3-furyl	19.2 (1)	$C_{16}H_{19}N_3O \cdot {}^1/_6H_2O$	26	EtOH	93–96	comm[d]
7-8	NHC_6H_4-4-NMe_2	2,5-Me_2-3-furyl	4.9 ± 0.7 (2)	$C_{18}H_{20}N_4O \cdot {}^1/_4C_2H_6O$	24	EtOH	126–129	amine[d]
7-9	NHC_6H_4-4-NEt_2	2,5-Me_2-3-furyl	>24	$C_{20}H_{24}N_4O$	22	EtOH	133–134	amine[d]
7-10	NHC_6H_4-3-OMe	2,5-Me_2-3-furyl	5.8 ± 3.2 (2)	$C_{17}H_{17}N_3O_2$	25	EtOH	124–125	amine[d]
7-11	NHC_6H_4-3-Me	2,5-Me_2-3-furyl	28.5 (1)	$C_{17}H_{17}N_3O \cdot {}^1/_6H_2O$	45	EtOH	144–146	comm[d]
7-12	NHC_6H_3-3,5-Me_2	2,5-Me_2-3-furyl	4.1 ± 2.5 (2)	$C_{15}H_{19}N_3O$	36	EtOH	149–152	amine[d]

[a] See footnotes *a*, *b*, and *d* of Table I. [b] See footnote c of Table I. [c] Used enaminone 3-(dimethylamino)-1-(5-methyl-2-furanyl)-2-propen-1-one, mp 126–128 °C, method H. [d] Used 38.

and allowed to incubate for 60 min. Afterward, the buffer was carefully removed from each sample and 0.2 mL of 8% $HClO_4$ was added to it. After centrifuging for 15 min at 2000 rpm to remove the precipitated protein, the supernatants were decanted and assayed fluorometrically for histamine content.

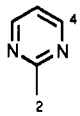
After removal of the incubation fluid, the lung fragments were resuspended in 2 mL of buffer and boiled for 10 min in capped tubes to release the remaining histamine. The tubes were then removed from the bath and allowed to cool, and a 1-mL aliquot of each sample was placed in a tube containing 0.2 mL of 8% $HClO_4$. After centrifugation at 2000 rpm for 15 min, the supernatant was decanted from the precipitated protein and analyzed for histamine[14] with the full-scale response of the histamine autoanalyzer adjusted to 400 ng of histamine; the threshold sensitivity was then approximately 25 ng.

(c) **Calculation of Results.** Calculations were made as described for the basophil test except the percent release (R) was calculated using the total histamine release from each sample rather than a mean. This was necessary since the weight of tissue varied from sample to sample, and the total histamine was proportional to that weight. For 1–27 the IC_{50} was 26.2 ± 19.8 μM (n = 2).

Method A. *N*-[4-(4-Methyl-1-piperazinyl)phenyl]-4-(2-pyridinyl)-2-pyrimidinamine (1-41). A mixture of 7.71 g (0.0250 mol) of [4-(4-methyl-1-piperazinyl)phenyl]guanidine hydrochloride,[15] 4.40 g (0.0250 mol) of 3-(dimethylamino)-1-(2-pyridinyl)-2-propen-1-one,[16] 6.90 g (0.050 mol) of K_2CO_3, and 125 mL of 2-methoxyethanol was stirred and refluxed gently. An air-cooled condenser was used to avoid having the dimethylammonium carbonate which evolved plug up the condenser. After 25 h of reflux, the solvent was permitted to evaporate, and the residue was triturated with aqueous K_2CO_3 and collected to give, on air-drying, 4.51 g of a black solid, mp 190–191 °C. The product was dissolved in 300 mL of hot EtOH and filtered through a pad of hydrous magnesium silicate, and the filtrate was boiled down to 200 mL. Cooling gave 3.76 g (43%) of yellow crystalline 1-41: mp 192–193 °C; MS (M+) 346; ^{1}H NMR (DMSO-d_6) δ 9.55 (s, 1H, 2-N*H*), 8.82 (d, 1H, J = 4.5, 6′-*H*), 8.65 (d, 1H, J = 6, 6-*H*), 8.45 (d, 1H, J = 8.5, 3′-*H*), 8.11 (m, 1H, 4′-*H*), 7.72 (d, 1H, J = 6, 5-*H*), 7.65 (d,d, 1H, J = 8.5, J = 4.5, 5′-*H*), 7.00 (d, 2H, J = 8.5, Ar*H*), 7.75 (d, 2H, J = 8.5, Ar*H*), 3.15 (m, 4H, 2(N-CH_2)), 2.55 (m, 4H, 2(N-CH_2)) 2.30 (s, 3H, CH_3). Anal. C, H, N.

Method B. N-[4-(2-Pyridinyl)-2-pyrimidinyl]-1,4-benzenediamine Dihydrochloride (1-9). After refluxing of a

Table VIII. Miscellaneous 4-Heterocyclic Pyrimidines



	substituent[a] 2	4	basophil	formula[b]	% yield	recryst solvent	mp, °C	start. mat.	eneaminone
8-1	NHC_6H_4-4-Et	2-pyrazinyl	1.9 ± 0.9 (3)	$C_{16}H_{15}N_5$	55	Me_2CO–hex.	157.5–159	comm	*c*
8-2	NHC_6H_4-3-OMe	2-benzofuranyl	2.8 ± 1.1 (4)	$C_{19}H_{15}N_3O_2$	51	$MeOCH_2CH_2OH$	132–134	amine	*d*
8-3	NHC_6H_4-4-Et	4-phenothiazinyl	I	$C_{24}H_{20}N_4S$	29	EtOH	154–164	comm	*e*
8-4	NHPh	3-indolyl	3.0 (1)	$C_{18}H_{14}N_4$	64	EtOH	188–190	comm	*f*
8-5	NHC_6H_4-3-Me	2-pyrrolyl	8.5 ± 2.6 (2)	$C_{15}H_{14}N_4$	40	EtOH	128.5–130	comm	*g*
8-6	NHPh	1-Me-2-pyrrolyl	I	$C_{15}H_{14}N_4$	63	EtOH	118–120	comm	*h*
8-7	NHC_6H_4-3-Me	3-indolyl	2.2 (1)	$C_{19}H_{16}N_4$	52	EtOH	164–167	comm	*f*
8-8	NHC_6H_4-4-Et	4-quinolyl	4.0 (1)	$C_{21}H_{16}N_4$	55	EtOH	176–178	comm	*i*
8-9	NHC_6H_4-4-OMe	1-Me-4-pyridinium	33.3 ± 18 (3)	$C_{17}H_{17}N_4IO$	73	EtOH	282–284	3-20	*j*

[a] See footnotes *a*, *b*, and *d* of Table I. [b] See footnote *c* of Table I. [c] 3-(Dimethylamino)-1-(2-pyrazinyl)-2-propen-1-one, mp 132–133 °C, method H. [d] 1-(2-Benzofuranyl)-3-(dimethylamino)-2-propen-1-one, mp 137–138.5 °C, method H. [e] 3-(Dimethylamino)-1-(2-phenothiazinyl)-2-propen-1-one, mp 240–246 °C, method H. [f] 3-(Dimethylamino)-1-(3-indolyl)-2-propen-1-one, mp 237–239 °C, method H. [g] 3-(Dimethylamino)-1-(1H-pyrrol-2-yl)-2-propen-1-one, mp 192–193 °C, method H. [h] 3-(Dimethylamino)-1-(1-methyl-1H-pyrrol-2-yl)-2-propen-1-one, mp 92.5–94.5 °C, method H. [i] 3-(Dimethylamino)-1-(4-quinolinyl)-2-propen-1-one, used crude, method H. [j] Method G.

mixture of 12.86 g (0.0421 mol) of *N*-[4-[[4-(2-pyridinyl)-2-pyrimidinyl]amino]phenyl]acetamide (1-8) and 80 mL of 6 N HCl for 30 min, the solution was cooled. A solid was collected which was recrystallized from EtOH–H_2O to give 10.84 g (77%) of 1-9, mp 285–288 °C. Anal. C, H, N, Cl.

Method C. 4-[[4-(3-Pyridinyl)-2-pyrimidinyl]amino]phenol (2-17). *N*-(4-Methoxyphenyl)-4-(3-pyridinyl)-2-pyrimidinamine (2-15) (25.0 g, 0.0899 mol) was dissolved in 60 mL of 48% HBr and refluxed 7 h. After concentrating under vacuum, the residue was dissolved in 2.5 mL of H_2O and the pH adjusted to 9 with saturated aqueous $KHCO_3$. The resulting solid was collected, washed with H_2O and Et_2O, and then dried. Recrystallization from EtOH gave 19.1 g (80%) of yellow crystals, mp 223–225 °C. A small amount was recrystallized from $CHCl_3$–EtOAc (filtered through a hydrous magnesium silicate pad) for analysis, mp 221–223 °C. Anal. C, H, N.

Method D. *N*-[4-[2-(Dimethylamino)ethoxy]phenyl]-4-(3-pyridinyl)-2-pyrimidinamine (2-18). After drying of 1.10 g (4.03 mmol) of 4-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenol (2-17) in a vacuum oven at 50 °C overnight, the phenol was dissolved in 25 mL of DMF, and 213 mg (4.43 mmol) of 50% NaH in oil was added. The mixture was stirred at room temperature, protected from moisture, until all the hydride had reacted (45 min). 2-(Dimethylamino)ethyl chloride hydrochloride (ca. 2 g) was partitioned between 1 N NaOH and Et_2O. Upon drying of the organic extract ($MgSO_4$), it was concentrated in a rotary evaporator (60 °C/13 mm) to approximately 600 mg of free amine, of which 480 mg (4.43 mM) was added to the reaction mixture. Stirring was continued overnight, whereupon the solvent was removed at 60 °C under vacuum. The residual brown gum was partitioned between EtOAc and brine. After two more extractions of the aqueous phase with EtOAc, the extracts were combined and washed with 1 N NaOH. The organic phase was dried ($MgSO_4$) and concentrated under vacuum, producing 900 mg of gum. This gum crystallized from $CHCl_3$–hexane to give 400 mg of 2-18 as beige crystals, mp 108–110 °C. A second crop of 100 mg (37%), mp 107–109 °C, was obtained upon partial evaporation of the mother liquors. Anal. C, H, N.

Method E. Oxo[phenyl[4-(4-pyridinyl)-2-pyrimidinyl]-amino]acetic Acid Ethyl Ester (3-2). To a 4.08-g (0.0164 m) portion of 2-anilino-4-(4-pyridinyl)pyrimidine (3-1) dissolved in 20 mL of 3A-sieve-dried DMF was added 0.80 g (0.0167 mol) of 50% NaH/oil with stirring, with 10 mL of DMF used as a wash. After the deep red mixture ceased effervescing, a solution of 2.23 mL (2.73 g, 0.0200 mol) of ethyl oxalyl chloride in 10 mL of DMF was cautiously added dropwise. The reaction was stirred overnight and then concentrated under vacuum. The residue was distributed between $CHCl_3$ and aqeuous $KHCO_3$, and the organic layer was separated and passed through a pad of hydrous magnesium silicate. After evaporation to dryness, the residue was recrystallized four times from EtOH to give 1.98 g of off-white, crystalline 3-2: mp 139–140 °C; yield 35%. Anal. C, N, N.

Method F. *N*-(4-Methoxyphenyl)-*N*-methyl-4-(4-pyridinyl)-2-pyrimidinamine (3-21). To a solution of 2.78 g (10.0 mmol) of 2-(4-methoxyphenyl)-4-(4-pyridinyl)pyrimidine (3-20) in 30 mL of DMF was added 0.528 g (11.0 mmol) of 50% NaH/oil, under anhydrous conditions. After the effervescence had subsided (45 min), 1.70 g (12.0 mM) of iodomethane was added and the reaction stirred at ambient temperature overnight. The solvent was removed under vacuum and the residue partitioned between $CHCl_3$ and H_2O. After separation of the organic phase, it was dried ($MgSO_4$), filtered through a pad of silica gel, and evaporated to 1.3 g of crude product. Recrystallization from Et_2O–hexane gave 0.51 g (32%) of product 3-21 as yellow crystals, mp 119–121 °C.

Method G. 4-[2-[(4-Methoxyphenyl)amino]-4-pyrimidinyl]-1-methylpyridinium Iodide (8-9).

A solution of 2.0 g (7.2 mmol) of 2-(4-methoxyphenyl)-4-(4-pyridinyl)pyrimidine (3-20) in 550 mL of EtOH and 10 mL of iodomethane was refluxed for 4 h. An additional 10 mL of iodomethane was added and the solution refluxed overnight. On standing at room temperature for several hours, product crystallized out which was collected and washed with EtOH to give 2.2 g (73%) of purple crystals: mp 282–284 °C; MS (M+) 278 ($-CH_3I$); if the amino nitrogen had been alkylated, M+ of 292 would have been found. Anal. C, H, N, I.

Method H. 3-(Dimethylamino)-1-(2,5-dimethyl-3-furanyl)-2-propen-1-one (38). 3-Acetyl-2,5-dimethylfuran (6.91 g, 0.0500 mol) and 15 mL of dimethylformamide dimethyl acetal were heated on a steam bath in an open flask, for 30 h. The residue was dissolved in CH_2Cl_2 and passed through a pad of hydrous magnesium silicate. After dilution of the filtrate with hexane, it was evaporated to about 25 mL. Cooling gave crystals which were recrystallized from heptane to give 5.09 g (53%) of enaminone 38, mp 91–95 °C. Anal. C, H, N.

Method I. [4-(1*H*-Imidazol-1-yl)phenyl]guanidine Dihydrochloride (39). To 1.59 g (0.0100 mol) of 4-(1*H*-imidazol-1-yl)benzenamine[17] (40) was added 2.5 mL of 10 N HCl, giving a new solid, and then 1.05 g (0.025 mol) of cyanamide was added followed by 1 mL of H_2O. Upon warming on a steam bath, a solution formed which, on further heating, bubbled vigorously. After 15 min, the solution was cooled to room temperature and 2.5 mL of concentrated HCl was added. Cooling to −10 °C for several days gave a precipitate which was collected and washed with ice-cold EtOH and then Et_2O, leaving 2.33 g of pinkish crystals, m 318–328 °C dec. The guanidine was boiled with 25 mL of EtOH and the insoluble (while hot) solid collected to give 2.28 g (83%) of 39 as a $2.1HCl{\cdot}0.125Et_2O$ salt: mp 318–324 °C; ^1H NMR (H_2O-d_6) δ 9.23 (s, 1H, 2-Im-*H*), 7.93 (s, 1H, Im-*H*), 7.78 (d, 2H, *J* = 8.7, Ar-*H*), 7.68 (s, 1H, Im-*H*), 7.59 (d, 2H, *J* = 8.7, Ar-H). Anal. C, H, N.

Method J. 1-(3-Nitrophenyl)-1*H*-imidazole (41). A mixture of 289.0 g (4.25 mol) of imidazole, 292 g (2.12 mol of K_2CO_3, 3 L of DMSO, and 300.0 g (2.12 mol) of 1-fluoro-3-nitrobenzene was stirred and heated for 25.5 h between 105 and 110 °C. Then

the reaction was poured into 6 L of water and cooled in the refrigerator over the weekend. After collecting the crystalline product, it was washed with 1 L of water and air-dried to give 357.6 g of solid, mp 107.5-109.5 °C. Next the solid was taken up in 2.4 L of EtOAc and the hot solution passed through a pad of hydrous magnesium silicate. Boiling the filtrate down to 1.5 L and cooling gave a precipitate which was collected and washed with 200 mL of EtOAc, to leave 151.7 g of off-white crystals, mp 107.5 °C. Evaporation of the mother liquors and recrystallization from EtOAc gave a second crop (59.7 g), mp 107–108.5 °C. Concentration again of the mother liquors followed by two recrystallizations from EtOAc gave a third crop (30.9 g), mp 108.5–110 °C; total yield = 60%; ^{1}H-NMR ($CDCl_3$) δ 8.29 (m, 2H, Ar-*H*), 7.96 (s, 1H, Im-*H*), 7.71 (m, 2H, Ar-*H*), 7.38 (s, 1H, Im-*H*), 7.28 (s, 1H, Im-*H*). Anal. C, H, Cl, N.

Method K. 1-[2-(3-Nitrophenoxy)ethyl]-1*H*-imidazole (42). To 40.64 g (0.597 mol) of imidazole in 300 mL of DMF was added 19.2 g (0.400 mol) of 1:1 NaH/oil. When the effervescence had subsided, 79.95 g (0.3965 mol) of 3-(2-chloroethoxy)-nitrobenzene[18] was added to the gray solution. After 0.5 h, the reaction turned dark orange-brown. Upon standing over the weekend, the reaction was washed with hexane to remove the immiscible oil. The reaction was then concentrated under vacuum. Water was added to the residue and the product extracted into $CHCl_3$. The organic extract was back-washed with brine and then concentrated under vacuum. Next, the residue was taken up in 200 mL of water and 100 mL of concentrated HCl and then washed (3X) with $CHCl_3$. The aqueous layer was slowly dripped onto solid K_2CO_3. More water was added, and the product was extracted into $CHCl_3$. After drying (Na_2SO_4), the solution was concentrated in vacuum to an oil, which slowly crystallized. The residue was boiled with CCl_4 and then triturated with 2-propyl acetate. Recrystallization from 2-propyl acetate (filtered through hydrous magnesium silicate) gave 30.80 g of product (42), mp 51.5–56 °C. Concentration of the mother liquors gave two additional crops (25.76 g, mp 47–52 °C; 23.39 g, 80%, mp 52–54 °C). Anal. C, H, N.

Method L. 3-(1*H*-Imidazol-1-yl)benzenamine (43). In a Parr hydrogenation bottle was placed 75.00 g of 1-(3-nitrophenyl)-1H-imidazole,[19] 0.70 g of PtO_2, and 250 mL of EtOH. The mixture was shaken in a Parr hydrogenation apparatus until no more hydrogen was taken up. This process was repeated until 241.63 g (1.2778 mol) of nitro compound had been reduced. For each batch, the catalyst was filtered off and the solvent removed under vacuum. The residues were combined to give 207.2 g of gray crystalline amine, mp 108.5–111 °C. Recrystallization of the amine from 530 mL of 2-PrOH gave 156.4 g of off-white crystals, mp 111–113 °C. Two recrystallizations of the mother liquor residues from 2-PrOH gave an additional 32.6 g (96%) of **43**: ^{1}H NMR (DMSO-d_6) δ 8.06 (s, 1H, Im-*H*), 7.55 (s, 1H, Im-*H*), 6.72 (m, 2H, Ar-*H*), 6.57 (m, 2H, Ar-*H*), 6.54 (d, 1H, Im-*H*), 5.39 (s, 2H, NH_2). Anal. C, H, N.

Method M. 1-[(4-Aminophenoxy)acetyl]-4-methylpiperazine (44). After preparation of a solution of 10.88 g (0.039 mol) of 1-methyl-4-[(4-nitrophenoxy)acetyl]piperazine[20] (12–8) in 160 mL of MeOH, 10.61 g (0.150 mol) of HCO_2Na and 6.90 mL (8.42 g, 0.156 mol) of 96% HCO_2H were added to it.[11] Next 0.827 g (7.80 mmol) of Pd black was added with stirring. The reaction mixture began to effervesce vigorously and it was cooled in a water bath. Stirring was continued for 2 h. After filtration of the reaction mixture, the filtrate was evaporated and the residual pink gum partitioned between $CHCl_3$ and saturated aqueous $KHCO_3$. The organic phase was separated, dried ($MgSO_4$), and passed through a pad of hydrous magnesium silicate. Evaporation gave 8.40 g (86%) of pink crystals, mp 80–82 °C, which gave one spot on TLC. Anal. C, H, N.

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