Preparation of Derivatives of 1-(2-Pyrimidinyl)piperazine as Potential Antianxiety, Antidepressant, and Antipsychotic Agents

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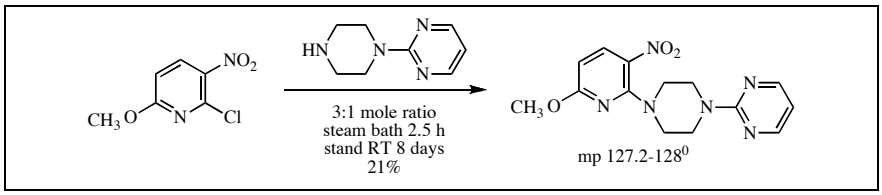

This paper describes the preparation of twenty-eight derivatives of 1-(2-pyrimidinyl)piperazine as potential antianxiety, antidepressant, and antipsychotic agents. In twenty-six of the preparations a chloro nitrogen heterocycle was caused to react with an excess of 1-(2-pyrimidinyl)piperazine in the absence of solvent. A specific example is given above.

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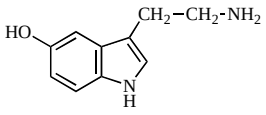
INTRODUCTION

Serotonin, released from nerve terminals in virtually all regions of the brain, plays a direct role in normal functions of the central nervous system and in mental



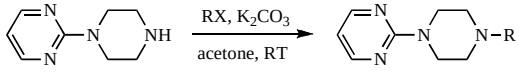
serotonin
5-hydroxytryptamine
5-HT

diseases such as anxiety, depression, psychosis, obsessive compulsive disorders, aggression, and eating disorders.

The role of serotonin receptors in the brain is being actively studied with respect to normal and abnormal functions of the brain. Fourteen different serotonin receptors are known. Serotonin receptor dysfunction is implicated in many neuropsychiatric disorders [1-9].

Greengard and coworkers [9] have determined that the protein p11 binds to the serotonin receptor 5-HT_{1B}. Low levels of p11 in mice and in humans are associated with depression. When the workers provided the mice with antidepressants, the p11 levels increased. In other experiments, administration of p11 alleviated depression symptoms. Also, they found that high levels of p11 increase the number of receptors on the surface of neurons, enhancing serotonin signaling.

In 1994 Makrosz and coworkers [10] reported the preparation of the seven alkyl derivatives of 1-(2-pyrimidinyl)piperazine indicated below. These workers



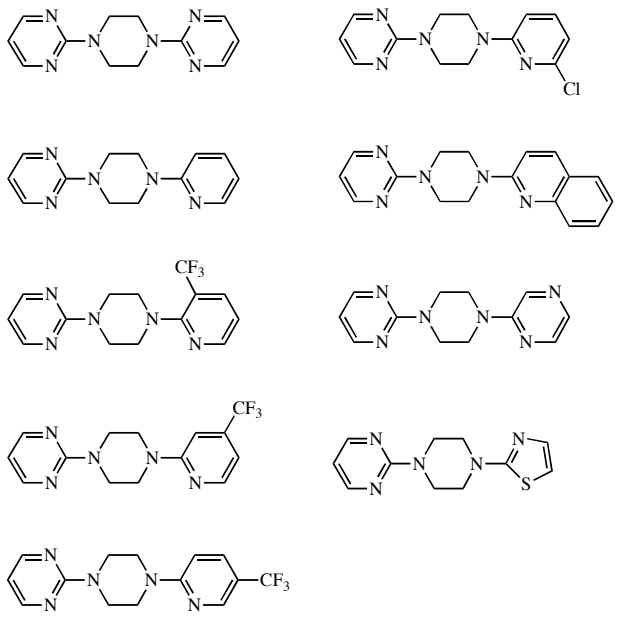
1-(2-pyrimidinyl)piperazine

where R = CH_3-, C_2H_5-, n-C_3H_7-, n-C_4H_9-, n-C_5H_{11}-, n-C_6H_{13}-, n-C_8H_{17}-

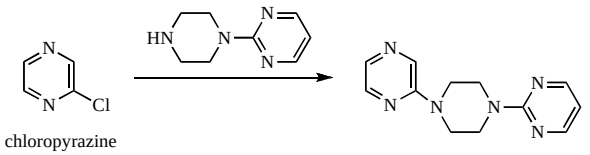
studied the affinity of these derivatives for the serotonin receptor sites on neurons in the rat brain.

In 1990 and 1991 Matsumoto and coworkers [11,12] reported the preparation of nine derivatives of 1-(2-pyrimidinyl)piperazine (see Table 1). To

Table 1



prepare these derivatives Matsumoto and coworkers caused a chloro nitrogen heterocycle, such as chloropyrazine, to react with 1-(2-pyrimidinyl)-piperazine in the presence of triethylamine in tetrahydrofuran at 100° under high pressure for four days. No biological testing of the nine compounds is reported in the two papers.



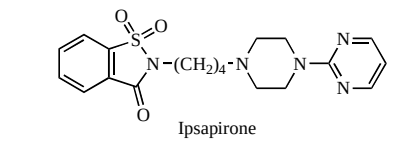
chloropyrazine

Arranz and coworkers [13] and Vega and coworkers [14] have prepared seven compounds that are structurally related to each other and to the anxiolytic drug ipsapirone (see Table 2). Each compound contains the 1-(2-pyrimidinyl)piperazinyl moiety and a sulfone ring. These seven compounds have not yet been evaluated as possible antianxiety and antidepressant drugs [14].

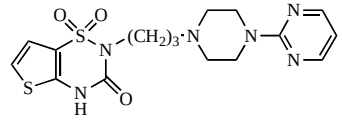
Compounds **A** and **B** have exhibited antiinflammatory, adrenolytic, and central nervous system depressant activity [15]. The substituted quinazoline **C** has displayed excellent long lasting efficacy as an antihypertensive agent [16]. The 4-pyrimidinyl isomer of **C**, interestingly enough, was much less active than **C** [16]. Compounds **A**, **B**, and **C** contain the 1-(2-pyrimidinyl)piperazinyl moiety.

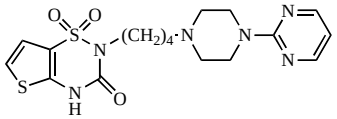
The structural formulas of buspirone, gepirone, ipsapirone, tandospirone, and zalospirone are given in Table 3. These five compounds, collectively called azapirones, have been extensively evaluated in animals and in man [17]. The azapirones have antianxiety and antidepressant properties. Structurally the azapirones have in common the 1-(2-pyrimidinyl)piperazinyl moiety. 1-(2-Pyrimidinyl)piperazine itself is a metabolic breakdown product—a metabolite—of the azapirones. Indeed, the 1-(2-pyrimidinyl)piperazine formed *in vivo* is considered to be partly responsible for the efficacy of the azapirones in the treatment of depression. Pinder believes that the efficacy of antidepressants could be improved by the use of combination therapy [18].

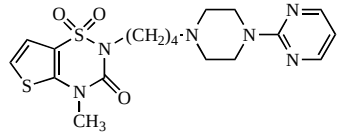
Table 2

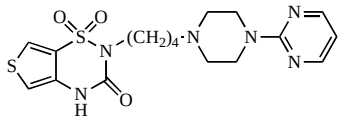


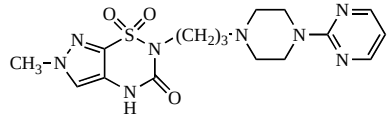
Ipsapirone

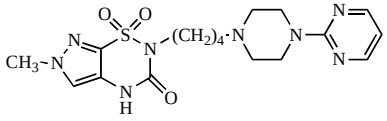


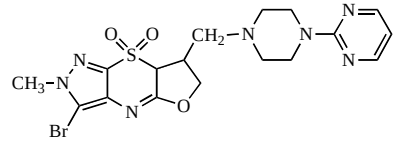












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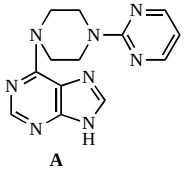
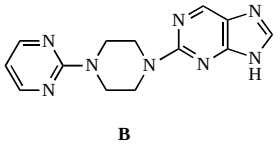


A



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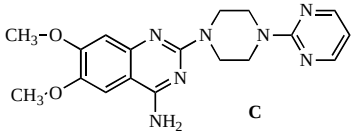
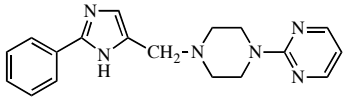


C

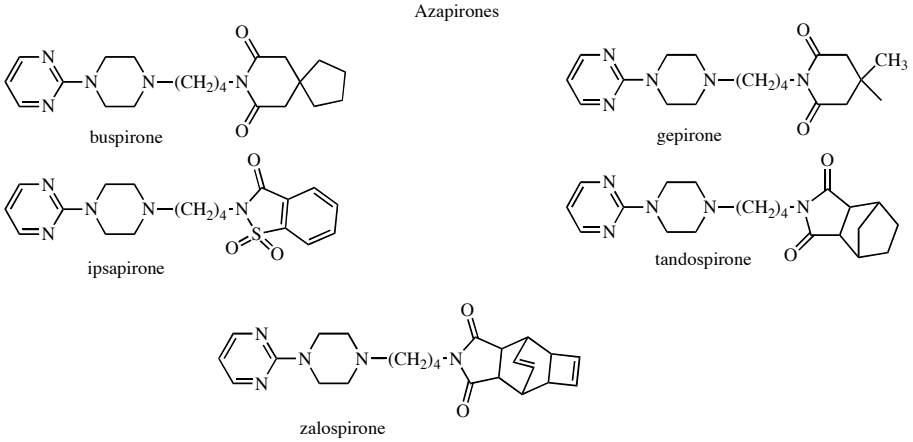
The most notable azapirone is buspirone, also called buspar. Buspirone is manufactured by Bristol-Myers Squibb. This drug was first marketed in June 1985. It is used to treat general anxiety disorders and depression. Adverse reactions of buspirone are light headedness, nausea, and headaches.



NGD94-1

Table 3

Azapirones



The compound called NGD94-1, prepared by Thurkauf and coworkers [19], has exhibited antipsychotic activity in a model system in rats. This activity has prompted evaluation of this compound as a possible treatment for schizophrenia [19-21]. NGD94-1 is a derivative of 1-(2-pyrimidinyl)piperazine.

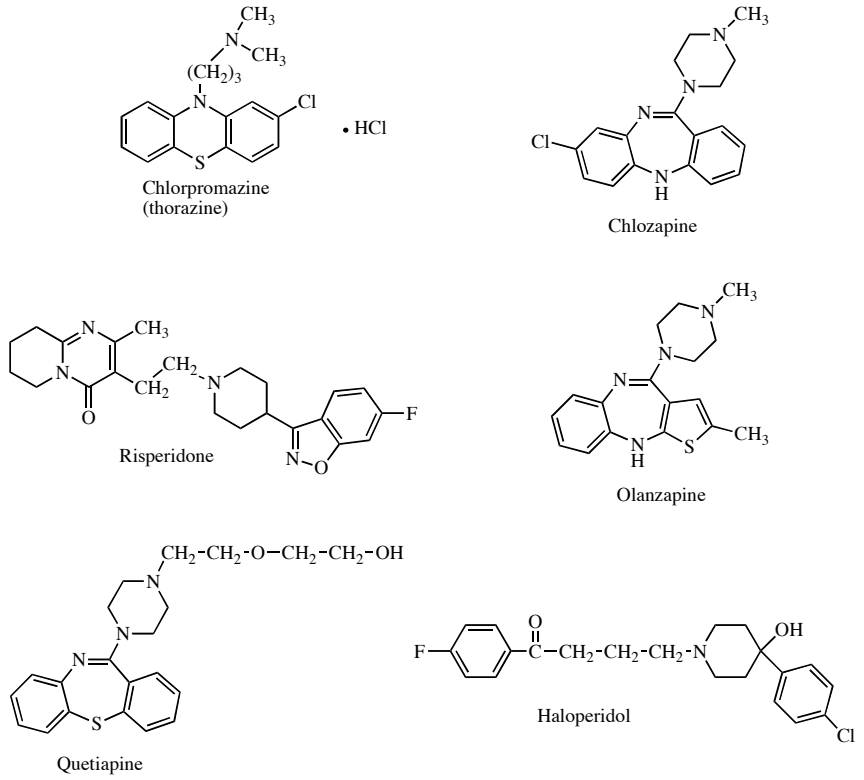
Chlorpromazine (also called thorazine) is the oldest antipsychotic drug prescribed by doctors. At least five other drugs are commonly being prescribed. These drugs are given in Table 4. Structurally, clozapine, olanzapine, and quetiapine are 1,4-disubstituted piperazine compounds. Risperidone contains a condensed pyrimidine ring and a benzoisoxazole moiety.

RESULTS AND DISCUSSION

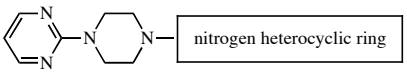
These considerations have prompted us to prepare derivatives of 1-(2-pyrimidinyl)piperazine as potential

Table 4

Antipsychotic Drugs



antianxiety, antidepressant, and antipsychotic agents. We report herein the preparation of twenty-eight derivatives of 1-(2-pyrimidinyl)piperazine (see Table 5).



In twenty-six of these derivatives one of the nitrogen atoms in the piperazine ring is bonded directly to a carbon atom in a nitrogen heterocyclic ring. The nitrogen heterocyclic rings found in these derivatives are pyrimidine, uracil, purine, theophylline, quinazoline, pyridine, pyrazine, quinoxaline, pyridazine, imidazole, tetrazole, and benzoxazole. Two of the derivatives (**11** and **12**) contain two 1-(2-pyrimidinyl)piperazinyl moieties; the rest contain one. In two other derivatives (**27** and **28**) the 1-(2-pyrimidinyl)piperazinyl moiety is bonded directly to a carbon atom in a substituted benzene ring.

The preparation of two of the derivatives (**2** and **17**) by the reaction of 1-(2-pyrimidinyl)piperazine with a chloro nitrogen heterocycle is illustrated in Scheme 1. The preparation of another derivative (**15**) is illustrated in the graphic in the abstract.

Table 5

Derivatives of 1-(2-Pyrimidinyl)piperazine

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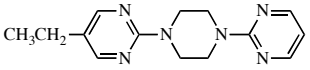

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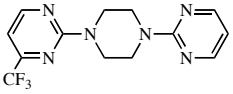

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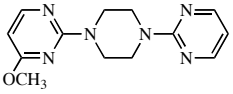

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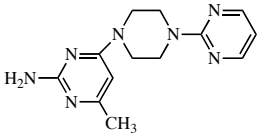

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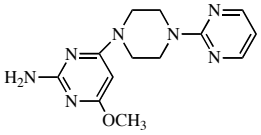

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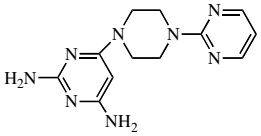

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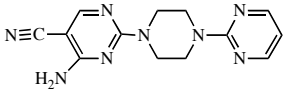

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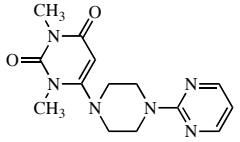

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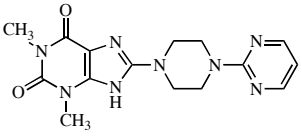

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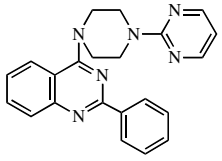

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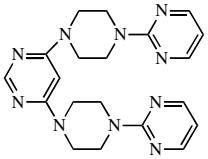

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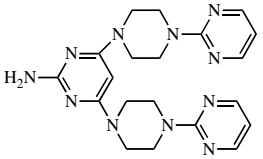

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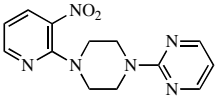

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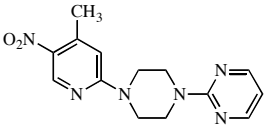

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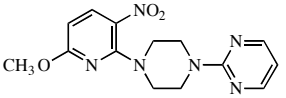

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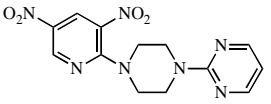

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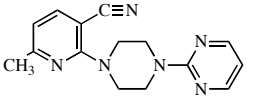

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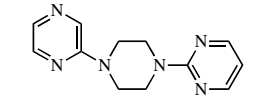

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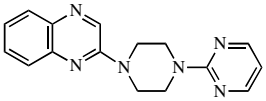

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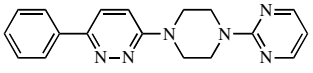

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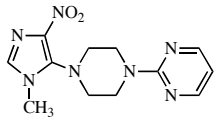

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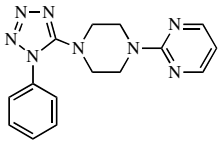

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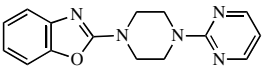

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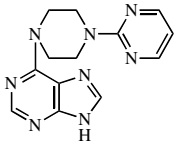

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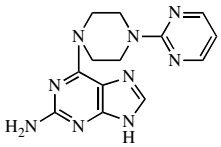

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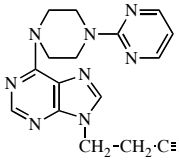

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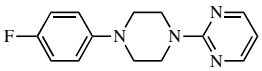

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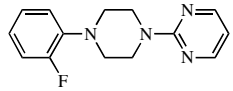
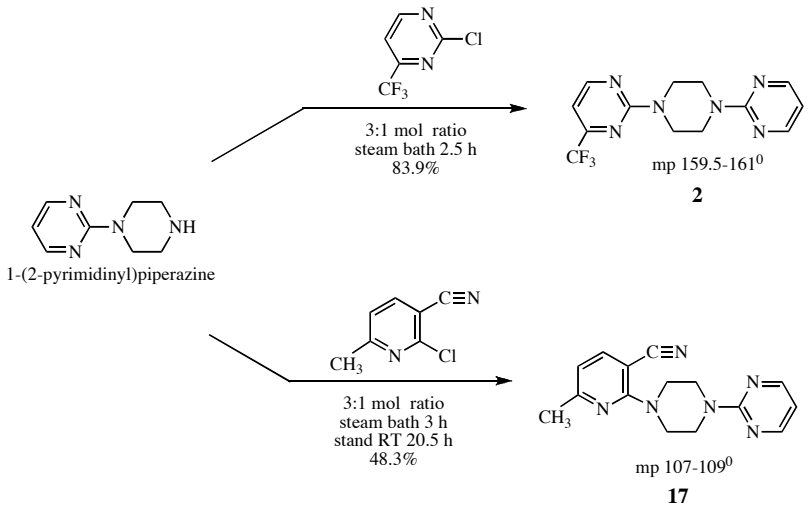


* see [22]

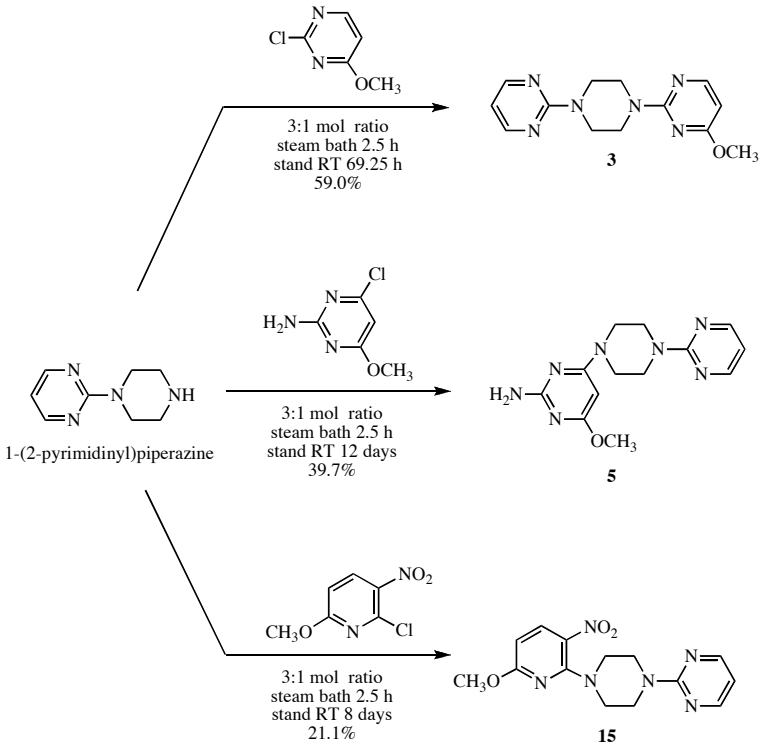
Scheme 1

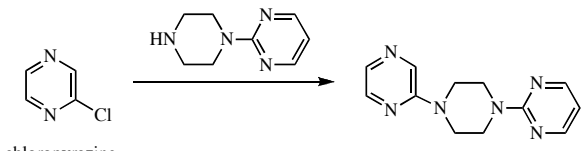


A few of the derivatives prepared in this work deserve additional comment. Three of the starting compounds contain both an active chlorine atom and an active methoxy group (see Scheme 2). We found that only the chlorine atom was displaced by 1-(2-pyrimidinyl)-piperazine, giving the products **3**, **5**, and **15**. In the pyridine starting compound, the chlorine atom is made much more reactive than the methoxy group by the adjacent nitro substituent.

Subsequent to our preparation of the pyrazine derivative **18** carried out in 2005 we discovered that Matsumoto and coworkers [12] had prepared **18** in 1991 by heating a mixture of 1-(2-pyrimidinyl)piperazine (6 mmol), chloropyrazine (7 mmol), triethylamine (10 mmol), and an unspecified amount of tetrahydrofuran at 100° under high pressure

Scheme 2





18

for four days. Their mol ratio of chloropyrazine to 1-(2-pyrimidinyl)piperazine was 0.9:1. Their yield of product (mp 117-118°) was 31%. Our conditions of reaction differed markedly from those of Matsumoto and coworkers. We heated a mixture of 0.0261 mol of 1-(2-pyrimidinyl)piperazine and 0.00870 mol of chloropyrazine on the steam bath for 3.5 h. Our mol ratio of amine to chloropyrazine was 3:1. Our yield of analytically pure product (mp 105.5-106°) was 42.6%. The ^{1}H nmr spectrum of our product confirmed its structure. Matsumoto and coworkers give no spectral data for their product.

We obtained an 8% yield of the theophylline derivative **9**. In duplicate CHN analyses the found %C and %H values were acceptable but the found %N values were low. No ^{1}H nmr spectrum could be obtained on **9** because the compound was insoluble in a number of deuterated solvents. The mp of **9** was greater than 292°. The infrared spectrum of **9** showed a medium band at 3138-3164 cm^{-1} indicating the presence of the N-H group in the imidazole moiety and showed strong bands at 1651 cm^{-1} and 1707 cm^{-1}, each indicating a lactam carbonyl group.

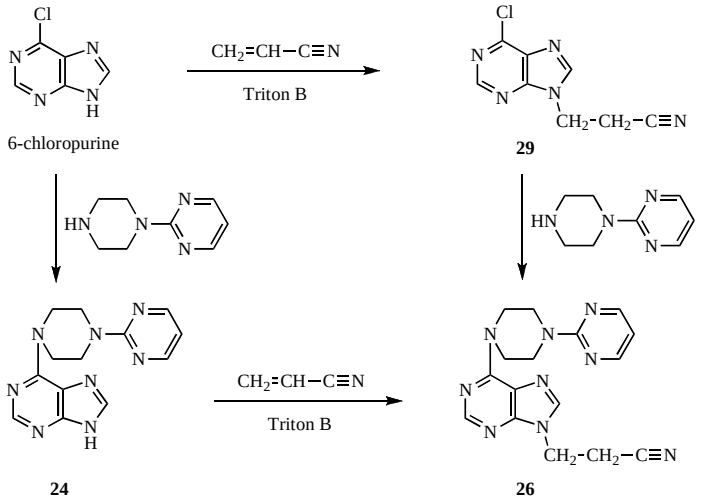
In early 1961 we prepared **29** by cyanoethylation of 6-chloropurine with an excess of acrylonitrile in the presence of Triton B as catalyst [23] (see Scheme 3). Our mol ratio of acrylonitrile to 6-chloropurine was 14:1 in one experiment and 19:1 in another experiment. The reactants were refluxed (acrylonitrile has a normal boiling point of 77°) for 1 h in one experiment and 2 h in another experiment [24].

Subsequently in 1965 Baker and Tanna [25] reported the preparation of **29** by the reaction of 6-chloropurine with acrylonitrile in dimethylformamide as solvent using potassium carbonate, not Triton B, as catalyst. They stirred the reaction mixture at room temperature for 4 h and then let the mixture stand at room temperature for 70 h. In l985 Rosemeyer and Seela [26] prepared **29** using the method of Baker and Tanna. Baker and Tanna [25] and Rosemeyer and Seela [26] provided spectral evidence that cyanoethylation of 6-chloropurine occurred at N-9, and not at N-7, of the purine ring.

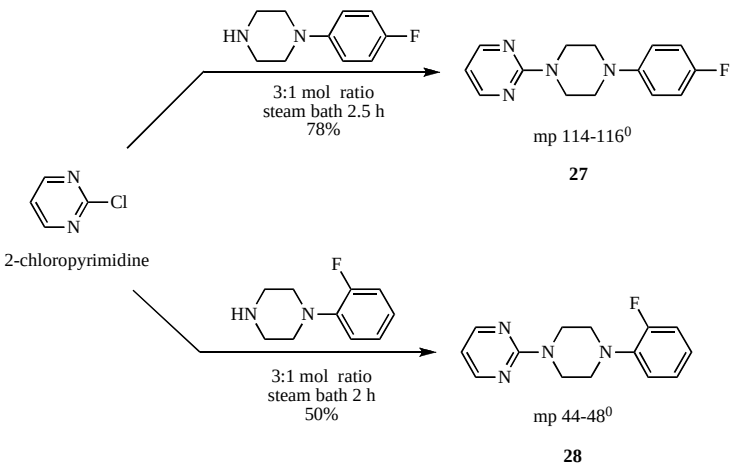
Recently we prepared **26** by heating **29** with an excess of 1-(2-pyrimidinyl)piperazine. We also prepared **26** by first reacting 6-chloropurine with an excess of 1-(2-pyrimidinyl)piperazine [27] to give **24** and then reacting **24** with an excess of acrylonitrile in the presence of Triton B as catalyst [28]. The ^{1}H nmr spectrum of **26** prepared from **29** was identical to the ^{1}H nmr spectrum of **26** prepared from **24**.

Two derivatives of 1-(2-pyrimidinyl)piperazine, namely **27** and **28**, were prepared by a reaction that did not use 1-(2-pyrimidinyl)piperazine as a reactant. The preparation of these derivatives is illustrated in Scheme 4 [29].

Scheme 3

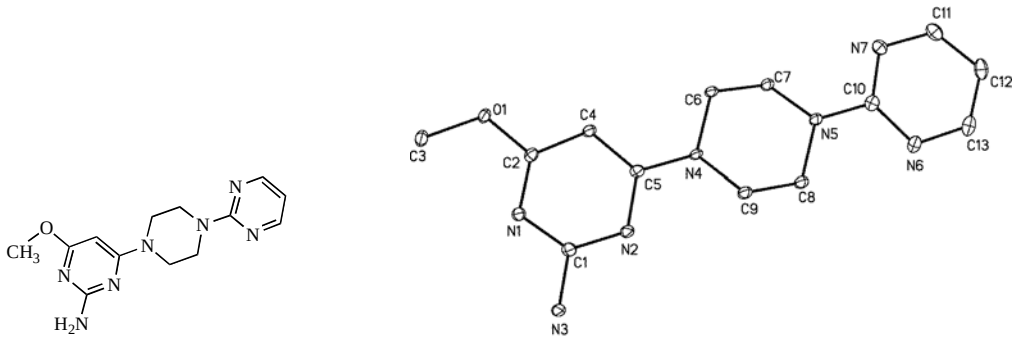


Scheme 4

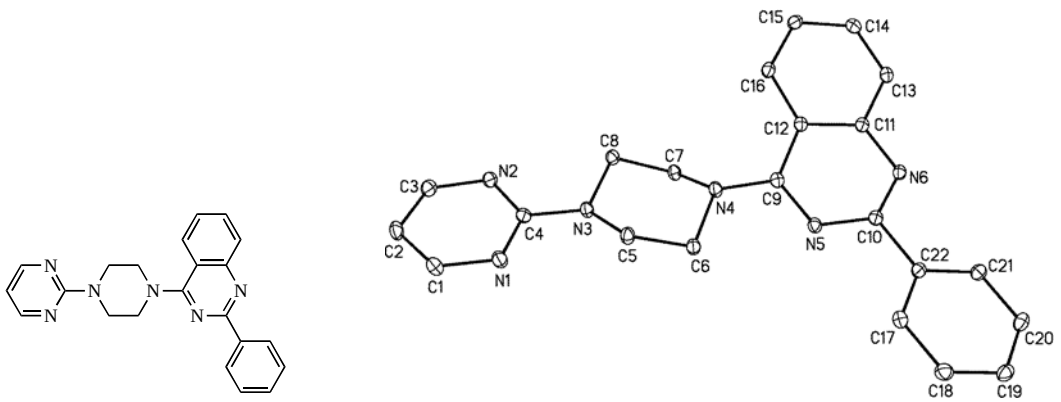


Single crystal x-ray diffraction analysis, an exciting analytical method, was used to prove and describe the structures of compounds **5**, **10**, and **21**. Each X-ray structure and its companion structural formula are illustrated below.

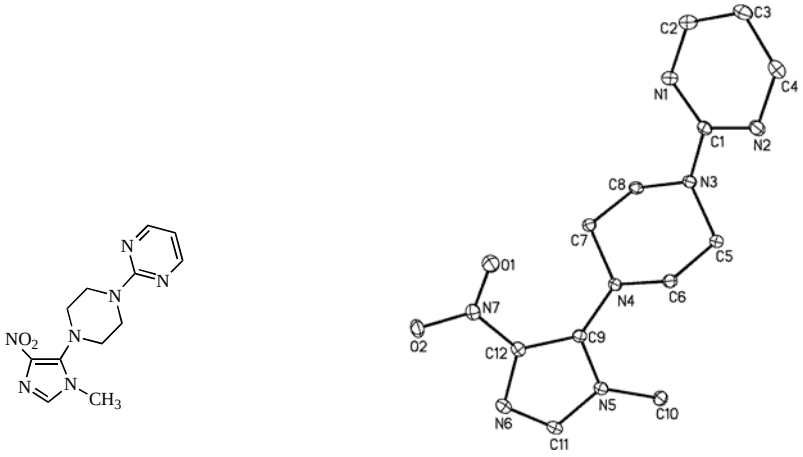
The potential efficacy of the compounds prepared in this work might be manifested on three levels: (a) the parent compound itself might be efficacious; (b) the 1-(2-pyrimidinyl)piperazine metabolite formed from the parent compound might be efficacious; (c) the compound that is formed after severance of the 1-(2-pyrimidinyl)-piperazinyl moiety from the parent compound might be efficacious. None of the compounds prepared in this work have yet been tested for biological activity.



5



10



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The following table describes X-ray diffraction parameters for compounds **5**, **10**, and **21**:

	5	**10**	**21**
Empirical Formula	$C_{26}H_{34}N_{14}O_2$	$C_{22}H_{20}N_6$	$C_{12}H_{15}N_7O_2$
Formula Weight	574.67	368.44	289.31
Color, habit	colorless, rods	colorless, rods	yellow, blades
Crystal System	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/n$	$P2_12_12_1$	$P2_1/c$
A, Å	17.783(3)	7.7499(9)	11.392(2)
b, Å	6.7547(13)	13.4983(16)	7.7360(17)
c, Å	23.883(5)	17.334(2)	14.680(3)
α, deg	90	90	90
β, deg	107.211(2)	90	93.482(2)
γ, deg	90	90	90
V (Å^3)	2740.4(9)	1813.3(4)	1291.3(5)
Z	4	4	4
Temperature (K)	100	100	100
Density$_{calc}$, (g cm^{-3})	1.393	1.350	1.488
2θ range, deg	1.69-28.19	1.91-28.41	1.79-28.40
GOF (F^2)	1.043	1.030	1.038
μ(Mo, Kα), mm^{-1}	0.096	0.085	0.108
R(F)/Rw(F)	0.0621/0.2136	0.0370/0.0986	0.0400/0.1048

EXPERIMENTAL

All chemicals, except as noted, were purchased from Sigma Aldrich Company. In almost all reactions the mole ratio of 1-(2-pyrimidinyl)piperazine to the chloro nitrogen heterocycle was 3:1. No solvent was used in the reactions.

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. CHN analyses were determined by Schwarzkopf Microanalytical Laboratory Inc, 56-19 37th Avenue, Woodside, NY 11377. ^{1}H nmr spectra were determined and interpreted by Spectral Data Services Inc, 818 Pioneer Street, Champaign, IL 61820. Infrared spectra were determined at Villanova University using a Perkin-Elmer Spectrum One FT-IR/Attenuated Total Reflectance Accessory.

5-Ethyl-2-(4-pyrimidin-2-yl-piperazin-1-yl)pyrimidine (1). A mixture of 0.880 mL of 97% pure 2-chloro-5-ethylpyrimidine (d 1.17), equivalent to 0.999 g (0.00699 mol) of 100% pure compound, and 3.03 mL of 98% pure 1-(2-pyrimidinyl)-piperazine (Acros Fisher, d 1.16), equivalent to 3.44 g (0.0210 mol) of 100% pure amine, was heated on the steam bath for 3 h. The mixture, consisting mostly of light brown solid, was let stand for 67.5 h. The hard waxy solid was broken up and mixed with 2x10 mL water, collecting solid after each treatment with water. Larger pieces of solid in the funnel were removed, pulverized, and returned to the funnel. The solid was washed with 2x5 mL water, sucked with the vacuum for 10 min, dried at 65° for 2.75 h, and let stand over Drierite for 68 h, tan solid, 1.97 g (100%), mp 99-100.5° after softening at 98.5-99°, negative Beilstein test (no Cl). ^{1}H nmr ($CDCl_3$): δ 1.20 (t, 3H, ethyl CH_3), 2.48 (q, 2H, ethyl CH_2), 3.90 (q, 8H, piperazine), 6.51 (t, 1H, 5-H, monosubstituted pyrimidine), 8.21 (s, 2H, 4-H & 6-H, disubstituted pyrimidine), 8.33 (d, 2H, 4-H & 6-H, monosubstituted pyrimidine). *Anal.* Calcd. for $C_{14}H_{18}N_6$: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.12; H, 6.91; N, 31.05.

2-(4-Pyrimidin-2-yl-piperazin-1-yl)-4-(trifluoromethyl)-pyrimidine (2). A mixture of 1.05 g of 99% pure 2-chloro-4-(trifluoromethyl)pyrimidine (d 1.51), equivalent to 1.04 g (0.00568 mol) of 100% pure compound, and 2.60 mL of 98%

pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 2.96 g (0.0180 mol) of 100% pure amine, was heated on the steam bath for 2.5 h. The cool mixture of white and orange solids was mixed well with 14 mL water. The solid was collected, using 6 mL and 5x4 mL water to complete the transfer, washed with 2x8 mL water, sucked with the vacuum for 12 min, and dried at 70-71° for 67 h, white solid, 1.31 g (74.4%), mp 158-159.5°, negative Beilstein test (no Cl).

Anal. Calcd. for $C_{13}H_{13}N_6F_3$: C, 50.32; H, 4.22; N, 27.09. Found: C, 50.98; H, 3.98; N, 27.25.

The combined filtrate, consisting of colorless liquid and solid, was let stand for 69 h. The solid was collected, using 5 mL water to complete the transfer, washed with 4 mL water, sucked with the vacuum for 13 min, and dried at 70-72° for 69 h, white solid, 0.167 g (9.5%), mp 159.5-161°, negative Beilstein test (no Cl). ^{1}H nmr ($CDCl_3$): δ 3.91-3.98 (cm, 8H, piperazine), 6.53 (t, 1H, 5-H, monosubstituted pyrimidine), 6.79 (d, 1H, 5-H, disubstituted pyrimidine), 8.34 (d, 2H, 4-H & 6-H, monosubstituted pyrimidine), 8.52 (d, 1H, 6-H, disubstituted pyrimidine). *Anal.* Calcd. for $C_{13}H_{13}N_6F_3$: C, 50.32; H, 4.22; N, 27.09. Found: C, 50.66; H, 4.08; N, 27.20.

4-Methoxy-2-(4-pyrimidin-2-yl-piperazin-1-yl)pyrimidine (3). An intimate mixture of 1.02 g of 98% pure 2-chloro-4-methoxypyrimidine (mp 54-57°), equivalent to 1.00 g (0.00690 mol) of 100% pure compound, and 2.98 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 3.39 g (0.0207 mol) of 100% pure amine, was heated on the steam bath for 2.5 h and let stand for 69.25 h. To the mixture, 15 mL water was added. Finely divided solid was collected. Hard solid left in the reaction flask was broken up and collected in the same funnel, using 2x10 mL and 2x5mL water to complete the transfer. Large pieces of hard solid were removed from the funnel, pulverized, and returned to the funnel. The solids were washed with 2x10 mL water, sucked with the vacuum for 45 min, and dried at 72-73° for 93.5 h, off white solid (Solid A), 1.45 g (77.1%), mp 94-96° after softening at 93-94°, negative Beilstein test (no Cl).

Solid A was recrystallized from the solvent pair of 95% ethanol (12 mL) and enough hot water to impart cloudiness to the mixture. The mixture (19 mL) was let stand for 4 min and cooled in ice for 106 min. The solid that formed was collected, using 4x5 mL water to complete the transfer, and dried at 72° for 45.5 h, white solid (Solid B), 1.11 g (59.0%), mp 93-95.5°. ^{1}H nmr ($CDCl_3$): δ 3.90 (s, 8H, piperazine), 3.91 (s, 3H, CH_3-O), 6.01 (d, 1H, 5-H, disubstituted pyrimidine), 6.51 (t, 1H, 5-H, monosubstituted pyrimidine), 8.08 (d, 1H, 6-H, disubstituted pyrimidine), 8.33 (d, 2H, 4-H & 6-H, monosubstituted pyrimidine). *Anal.* Calcd. for $C_{13}H_{16}N_6O$: C, 57.34; H, 5.92; N, 30.86. Found: C, 57.83, 57.17; H, 6.23, 5.54; N, 30.68, 29.97.

4-Methyl-6-(4-pyrimidin-2-yl-piperazin-1-yl)pyrimidin-2-amine (4). A mixture of 1.00 g (0.00694) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-178.5°) and 3.68 g of 98% pure 1-(2-pyrimidinyl)piperazine (Acros Fisher), equivalent to 3.61 g (0.0220 mol) of 100% pure amine, was heated on the steam bath for 185 min. To the cool hard mixture of white, tan, and brown solids, 3 mL water was added. The solids were broken up and collected, using 2 mL and 4 mL water to complete the transfer. The solids were removed from the funnel, pulverized, returned to the funnel, washed with 2x6 mL water, sucked with the vacuum for 10 min, let stand over Drierite for 164.5 h, and dried at 65-66° for 1 h, 1.59 g, mp 184-188.5° after softening at 177-184°, strong positive Beilstein test (Cl present).

This solid was recrystallized from the solvent pair of 95% ethanol (9 mL) and water. The solid that did not dissolve in the boiling 95% ethanol was discarded. The final mixture was let stand for 18 min and cooled in ice for 80 min. The solid was collected, using 4x3 mL water to complete the transfer, washed with 2x6 mL water, sucked with the vacuum for 17 min (pasty solid), and dried at 67-68° for 75 min, crusty cream colored solid, 0.412 g (21.9%), mp 187.5-188.5° after softening at 186-187.5°, negative Beilstein test (no Cl).

This product was recrystallized from the solvent pair of 95% ethanol (5 mL) and water (7 mL), letting the final mixture cool in ice for 43 min. The solid was collected, using 2 mL water to complete the transfer, washed with 2 mL and 3 mL water, sucked with the vacuum for 30 min (pasty solid), dried at 67-68° for 2 h, let stand over Drierite for 91 h, and dried at 67° for 161 min, cream colored solid, mp 188-189° after softening at 187-188°. ^{1}H nmr ($CDCl_3$): δ 2.23 (s, 3H, 4-CH_3, trisubstituted pyrimidine), 3.68 (ct, 4H, piperazine), 3.89 (ct, 4H, piperazine), 4.82 (bs, 2H, 2-NH_2, trisubstituted pyrimidine), 5.87 (s, 1H, 5-H, trisubstituted pyrimidine), 6.54 (t, 1H, 5-H, monosubstituted pyrimidine), 8.34 (d, 2H, 4-H & 6-H, monosubstituted pyrimidine). *Anal.* Calcd. for $C_{13}H_{17}N_7$: C, 57.55; H, 6.32; N, 36.14. Found: C, 57.68; H, 6.51; N, 35.99.

4-Methoxy-6-(4-pyrimidin-2-yl-piperazin-1-yl)pyrimidin-2-ylamine (5). An intimate mixture of 95% pure 2-amino-4-chloro-6-methoxypyrimidine (mp 168-171°), equivalent to 1.00 g (0.00625 mol) of 100% pure compound, and 2.71 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 3.08 g (0.0188 mol) of 100% pure amine, was heated on the steam bath for 2.5 h and let stand for 12 days. To the solid, 6 mL water was added. Some of the solid was broken up and collected. To the hard button of solid left in the flask, 4 mL water was added and hard solid was partially broken up. More solid was collected on the same funnel. The button of solid and another piece of solid were removed from the flask, pulverized, and transferred to the same funnel. The solid was washed with 2x10 mL water, sucked with the vaccum for 43 min, and dried at 71-72° for 45.75 h, cream colored solid (Solid A), 1.45 g (81%), mp 176.5-181° after shrinking some at 175-176.5°, negative Beilstein test (no Cl). The CHN analysis was poor. *Anal.* Calcd. for $C_{13}H_{17}N_7O$: C, 54.34; H, 5.96; N, 34.12. Found: C, 52.18; H, 5.49; N, 32.14.

A 0.3077 g sample of Solid A was recrystallized from 30 mL of 95% ethanol, letting the hot nearly colorless filtrate stand for 71.5 h. The crystals that formed were collected, using 4x2 mL 95% ethanol to complete the transfer, sucked with the vacuum for 17 min, and dried at 72° for 7 days, short fine sparkling pale yellow needles (Solid B), 0.158 g (8.83%), mp 183-184.5°. *Anal.* Calcd. for $C_{13}H_{17}N_7O$: C, 54.34; H, 5.96; N, 34.12. Found: C, 54.70; H, 5.20; N, 34.15.

The rest of Solid A was recrystallized from 68 mL of 95% ethanol, letting the hot filtrate stand for 22.75 h. The crystals that formed were collected, using 6x2 mL 95% ethanol to complete the transfer, sucked with the vacuum for 34 min, and dried at 72-73° for 6 days, short fine sparkling pale yellow needles (Solid C), 0.554 g (30.9%), mp 183-184.5°. ^{1}H nmr ($CDCl_3$): δ 3.63 (cm, 4H, piperazine), 3.84 (s, 3H, 4-OCH_3, trisubstituted pyrimidine), 3.89 (cm, 4H, piperazine), 4.72 (bs, 2H, 2-NH_2, trisubstituted pyrimidine), 5.35 (s, 1H, 5-H, trisubstituted pyrimidine), 6.52 (t, 1H, 5-H, monosubstituted pyrimidine), 8.33 (d, 2H, 4-H & 6-H, monosubstituted pyrimidine). The structure of **5** was proved by single crystal X-ray diffraction analysis. *Anal.* Calcd. for $C_{13}H_{17}N_7O$: C, 54.34;

H, 5.96; N, 34.12. Found: C, 54.68; H, 5.40; N, 34.14. Solid B plus Solid C constituted a yield of 0.712 g (39.7%) of once recrystallized product, mp 183-184.5°.

6-(4-Pyrimidin-2-yl-piperazin-1-yl)pyrimidine-2,4-diamine (6). A mixture of 1.02 g of 98% pure 4-chloro-2,6-diamino-pyrimidine, equivalent to 1.00 g (0.00709 mol) of 100% pure compound, and 3.10 g of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 3.60 g (0.0220 mol) of 100% pure amine, was heated on the steam bath for 7 h. The mixture of viscous brownish orange liquid and white solid was let stand for 23.5 h. To this mixture, 6 mL water was added. The hard white solid was broken up. Virtually all of the solid was scooped out of the mixture, put on filter paper to absorb liquid, pulverized, and let stand over Drierite for an unmeasured period of time. This solid (Solid A) did not melt up to 230° and gave a persistent positive Beilstein test (Cl present).

The pale orange cloudy liquid remaining in the 25 mL round bottom reaction flask contained a small amount of white particles. To this mixture, 11 mL water was added. The mixture was let stand for 20.5 h. The solid that separated was collected, using 5x2 mL water to complete the transfer, washed with 9 mL water, sucked with the vacuum for 1.5 h, and dried at 75-83° for 68 h, soft cottony solid (Solid B) that was pale yellow on the surface and white underneath the surface, 0.312 g (15.9%), mp 187-189.5° after softening at 186-187°, negative Beilstein test (no Cl). The CHN analysis on Solid B was poor. *Anal.* Calcd. for $C_{12}H_{16}N_8$: C, 52.93; H, 5.92; N, 41.15. Found: C, 53.67; H, 6.07; N, 39.90.

Solid B was recrystallized from the solvent pair of 95% ethanol (3 mL) and water (3 mL), letting the final mixture stand for 29 min, cool in ice for 23 min, and stand for 20 h. The impressive needles that formed were collected, using 5x1.5 mL water to complete the transfer, washed with 3x3 mL water, sucked with the vacuum for 32 min, let stand over Drierite for 69.5 h, and dried at 60-63° for 2.5 h, cream colored needles (Solid C), 0.125 g (6.4%), mp 189.5-191.5° after softening at 188-189° and after some darkening over several degrees before 188°. The found %C and %N were unacceptable. *Anal.* Calcd. for $C_{12}H_{16}N_8$: C, 52.93; H, 5.92; N, 41.15. Found: C, 53.41; H, 6.08; N, 40.39.

The combined filtrate from Solid C consisted of cloudy colorless liquid and solid. This solid was collected, using 1 mL water to complete the transfer, washed with 2x1 mL water, sucked with the vacuum for 10 min, let stand over Drierite for 68.5 h, and dried at 60-63° for 2.5 h, off white solid (Solid D), 21 mg (1.1%), mp 190-191.5° after softening at 189-190° and after some darkening over several degrees before 189°. ^{1}H nmr ($CDCl_3$): δ 3.60-3.63 (cm, 4H, piperazine), 3.87-3.90 (cm, 4H, piperazine), 4.40 and 4.57 (each bs, each 2H, 2-NH_2 & 4-NH_2, trisubstituted pyrimidine), 5.17 (s, 1H, 5-H, trisubstituted pyrimidine), 6.52 (t, 1H, 5-H, monosubstituted pyrimidine), 8.33 (d, 2H, 4-H & 6-H, monosubstituted pyrimidine). *Anal.* Calcd. for $C_{12}H_{16}N_8$: C, 52.93; H, 5.92; N, 41.15. Found: C, 53.34; H, 5.87; N, 40.87.

4-Amino-2-(4-pyrimidin-2-yl-piperazin-1-yl)pyrimidine-5-carbonitrile (7). An intimate mixture of 1.03 g of 97% pure 4-amino-2-chloropyrimidine-5-carbonitrile (mp 200° dec), equivalent to 1.00 g (0.00645 mol) of 100% pure compound, and 2.79 mL of 98% pure 1-(2- pyrimidinyl)piperazine (mp 29-36°, solid was melted on the steam bath; and used some liquid amine from another container, d 1.16), equivalent to 3.18 g (0.0194 mol) of 100% pure amine, was heated on the steam bath for 2.5 h and let stand for 69.5 h. The mixture of white and yellow solids was mixed with 15 mL water. Large pieces of solid were broken up. The solid was collected, using 2x5 mL water to complete the transfer, washed with 10 mL water, sucked with the vacuum for 62 min, and dried at 72-73° for 45 h, cream colored solid (Solid A), 1.72 g (94.0%), negative Beilstein test (no Cl). On taking a mp the sample did not melt by 270° but underwent darkening. When a sample was ignited on the flat end of a metal spatula, the sample melted completely to a black liquid that burned with a flame and disappeared completely upon strong heating. Thus the melting point of the sample was greater than 270°. ir: 2214 cm^{-1} medium (C≡N). ^{1}H nmr (D_2O/HCl): δ 3.23 (bs, 8H, piperazine), 4.65 (s, 1H, HDO), 6.22 (t, 1H, 5-H, monosubstituted pyrimidine), 7.55 (s, 1H, 4-H, trisubstituted pyrimidine), 7.74 (d, 2H, 4-H & 6-H, monosubstituted pyrimidine). The found %N was low. *Anal*: Calcd. for $C_{13}H_{14}N_8$: C, 55.31; H, 5.00; N, 39.69. Found: C, 54.89, 55.11; H, 4.92, 4.92; N, 38.82, 39.02.

A mixture of 0.1220 g of Solid A and 25 mL of 95% ethanol was heated on the steam bath with stirring for several minutes. The solid in the milky mixture was collected, sucked with the vacuum for 2 h, and dried at 72° for 70.75 h, cream colored solid (Solid C), 0.0765 g (61.9% recovery). *Anal.* Calcd. for $C_{13}H_{14}N_8$: C, 55.31; H, 5.00; N, 39.69. Found: C, 55.63, 55.36; H, 4.82, 5.05; N, 39.66, 39.78.

1,3-Dimethyl-6-(4-pyrimidin-2-yl-piperazin-1yl)-1*H*-pyrimidine-2,4-dione (8). A mixture of 1.04 g of 99% pure 6-chloro-1,3-dimethyluracil (Acros Fisher, mp 109-113°), equivalent to 1.03 g (0.00589 mol) of 100% pure compound, and 2.50 mL of 98% pure 1-(2-pyrimidinyl)piperazine (solid melted on the steam bath, d 1.16), equivalent to 2.84 g (0.0177 mol) of 100% pure amine, was heated on the steam bath for 3 h 9 min and let stand for 45 h. To the mixture of viscous orange liquid and dirty yellow solid, 7 mL water were added. The mixture was heated for 30 s. Hard solid was partially broken up. The remaining button of solid was removed from the reaction flask, pulverized, and returned to the flask. The solids in the flask were collected, using 3x3 mL water to complete the transfer, washed with 2x3.5 mL and 4.5 mL water, and dried at 63-65° for 46 h, light cream colored solid (Solid A), 0.905 g (50.8%), mp 199-203° after softening at 197.5-199°, negative Beilstein test (no Cl). ir: 1640 cm^{-1} (strong), 1692 cm^{-1} (strong) (each, lactam carbonyl). ^{1}H nmr ($CDCl_3$): δ 3.01 (cm, 4H, piperazine), 3.33 (s, 3H, CH_3-N, uracil), 3.46 (s, 3H, CH_3-N, uracil), 3.98 (bs, 4H, piperazine), 5.27 (s, 1H, 5-H, uracil), 6.58 (t, 1H, 5-H, monosubstituted pyrimidine), 8.34 (d, 2H, 4-H & 6-H, monosubstituted pyrimidine). *Anal.* Calcd. for $C_{14}H_{18}N_6O_2$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.64, 56.19; H, 5.89, 5.87: N, 27.25, 27.73.

The remaining Solid A (0.672 g) was recrystallized from 50 mL of 95% ethanol, letting the filtrate (45 mL) stand for 71.5 h. During this time the volume of the filtrate spontaneously reduced to 40 mL. The crystals that separated were collected, using 3x3.5 mL 95% ethanol to complete the transfer, washed with 4 mL 95% ethanol, sucked with the vacuum for 18 min, and dried at 72° for 47.5 h, impressive light cream colored crystals, 0.466 g (26.1%), mp 203-205° after a little softening at 201-203°. *Anal.* Calcd. for $C_{14}H_{18}N_6O_2$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.52; H, 5.49; N, 27.63.

1,3-Dimethyl-8-(4-pyrimidin-2-yl-piperazin-1-yl)-3,9-dihydropurine-2,6-dione (9). A mixture of 1.02 g of 98% pure 8-chlorotheophylline (mp 290° dec), equivalent to 1.00 g

(0.00465 mol) of 100% pure compound, and 3.00 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 3.41 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 5.5 h and let stand for 43.5 h. The mixture of liquid and solid was mixed with 10 mL water. Large pieces of solid were broken up. The solid was collected, using 2x2 mL water to complete the transfer, washed with 2x5 mL water, sucked with the vacuum for 47 min, and dried at 67-78° for 70 h, white solid, 0.132 g (8.3%), mp > 292°, negative Beilstein test (no Cl). On ignition on a metal surface, the sample melted rapidly, produced no smoky flame, and disappeared completely. ir: 3138-3164 cm^{-1} (medium) (NH, imidazole moiety), 1651 cm^{-1} (strong), 1707 cm^{-1} (strong) (each, lactam carbonyl). No ^1H nmr spectrum could be obtained because the product was insoluble in a number of deuterated solvents. The duplicate %N values were low. *Anal.* Calcd. for $C_{15}H_{18}N_8O_2$: C, 52.62; H, 5.30; N, 32.73. Found: C, 52.86, 52.42; H, 5.46, 5.33; N, 32.16, 31.78.

2-Phenyl-4-(4-pyrimidin-2-yl-piperazin-1-yl)quinazoline (10). A mixture of 1.00 g of 97% pure 4-chloro-2-phenyl-quinazoline, equivalent to 0.970 g (0.00402 mol) of 100% pure compound, and 4.40 mL of 98% pure 1-(2-pyrimidinyl)-piperazine (d 1.16), equivalent to 5.00 g (0.0305 mol) of 100% pure amine, was heated on the steam bath for 3 h and let stand for 20 min. The mixture was mixed well with 2x10 mL and 2x4 mL water, collecting solid after each treatment with water. Large pieces of solid were broken up during these treatments. The solid was washed with 2x5 mL water, sucked with the vacuum for 10 min, and dried at 67-68° for 18.5 h, off white solid with slight pinkish coloration, 1.49 g (100%), mp 162-164.5° after softening at 160-162°, negative Beilstein test (no Cl). ^1H nmr ($CDCl_3$): δ 3.91-3.94 and 4.07-4.09 (each t, 8H, piperazine), 6.52 (t, 1H, 5-H, pyrimidine), 7.41-7.51 (cm, 4H, 2xmeta-H, each benzene ring), 7.71-7.75 (t, 1H, para-H, monosubstituted benzene), 7.93 and 7.99 (each d, 2H, 2xortho-H of benzene ring at the fusion with pyrimidine ring), 8.34 (d, 2H, 4-H & 6-H, pyrimidine), 8.57 (cd, 2H, 2x ortho-H, monosubstituted benzene). The structure of **10** was proved by single crystal x-ray diffraction analysis. *Anal.* Calcd. for $C_{22}H_{20}N_6$: C, 71.72; H, 5.47; N, 22.81. Found: C, 71.58; H, 5.54; N, 23.00.

4,6-Bis-(4-pyrimidin-2-yl-piperazin-1-yl)pyrimidine (11). A mixture of 1.03 g of 97% pure 4,6-dichloropyrimidine, equivalent to 1.00 g (0.00671 mol) of 100% pure compound, and 5.81 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 6.61 g (0.0403 mol) of 100% pure amine, was heated from room temperature to 120° over 15 min. Thereafter the mixture was heated for 195 min. During this time the temperature of the reaction mixture varied from 92° to 118° over 72 min (37% of the heating time) and from 120° to 157° over 123 min (63% of the heating time). Then 10 mL water was added. The hard solid was broken up, collected, using 3x5 mL water to complete the transfer, washed with 2x10 mL water, sucked with the vacuum for 10 min, and dried at 69-71° for 67 h, tan solid, 2.36 g (87.1%), mp 216-221° melted completely to a clear dark brown liquid after darkening and slight shrinking over many degrees before 216°, negative Beilstein test (no Cl). ^1H nmr ($CDCl_3$): δ 3.70-3.72 and 3.93-3.95 (each cm, 16H, both piperazine rings), 5.65 (s, 1H, 5-H, disubstituted pyrimidine), 6.53 (t, 2H, 5-H, each monosubstitured pyrimidine ring), 8.30 (s, 1H, 2-H, disubsubstituted pyrimidine), 8.35 (d, 4H, 4-H & 6-H, each monosubstituted pyrimidine ring). *Anal.* Calcd. for $C_{20}H_{24}N_{10} \bullet ¼ H_2O$: C, 58.74; H 6.04; N, 34.25. Found: C, 58.55; H, 5.87; N, 34.27.

This product was recrystallized from the solvent pair of 95% ethanol and water with unusual results. Not all of the solid dissolved in the hot 95% ethanol. This insoluble solid was discarded. The final mixture was let stand for 19 h. No solid separated. To the solution, 15 mL water were added. The resulting solution was let stand for 3 h and then cooled in ice for 5 min with vigorous stirring and scratching. No solid separated. The solution (100 mL) was concentrated on the steam bath to 35 mL. The concentrate, consisting of liquid and solid, was cooled in ice for 10 min and let stand for 20 h. The solid was collected, using 2x3 mL water to complete the transfer, washed with 3 mL and 4 mL water, sucked with the vacuum for 10 min, and dried at 64-66° for 3 h, brown solid, 0.159 g, mp 157.5-180° melted completely to a clear dark orange liquid after gradually softening, shrinking, and sintering. Apparently the solid decomposed during recrystallization and concentration. The combined filtrate from this solid was discarded.

4,6-Bis-(4-pyrimidin-2-yl-piperazin-1-yl)pyrimidin-2-yl-amine (12). A mixture of 1.01 g of 99% pure 2-amino-4,6-dichloropyrimidine, equivalent to 1.00 g (0.00609 mol) of 100% pure compound, and 5.27 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 5.99 g (0.0365 mol) of 100% pure amine, was heated to 120° over 12 min. Thereafter, the total heating time was 3.5 h (210 min). About 80% of this time (about 167 min) the temperature was kept at 120-161° and about 20% of this time (about 43 min) the temperature was kept at 107-119°. The resulting mixture of yellow and brown solids was let stand for 66 h. To this mixture, 20 mL water was added. Large pieces of hard solid in the reaction flask were broken up. Larger pieces of solid were removed from the flask, pulverized, and collected. All solids remaining in the flask were collected, using 54 mL water in seven portions to complete the transfer. The solids were sucked with the vacuum (pasty solid), dried at 68-77° for 46 h, and let stand over Drierite for 24 h, dark tan solid, 2.46 g (96.5%), mp 180-184° after softening over many degrees before 180°, weak fleeting positive Beilstein test (a little Cl present).

A small portion of this solid was recrystallized from the solvent pair of 95% ethanol and water. Not all of the solid dissolved in the hot 95% ethanol. This insoluble solid was discarded. The final mixture was let stand for 7 days.

The solid that formed was collected, washed with 3 mL water, sucked with the vacuum for 10 min, and dried at 69-71° for 3 days, pale yellow crispy solid, mp 177.5-184° after shrinking, darkening, and softening at 172-177.5°, negative Beilstein test (no Cl). Prior to analysis the sample was let stand over Drierite for 7 days. ^1H nmr ($CDCl_3$): δ about 1.70 (vbs, water), 3.66-3.68 and 3.90-3.93 (each cm, 16H, both piperazine rings), about 4.80 (vbs, 2H, 2-NH_2, trisubstituted pyrimidine), 5.20 (s, 1H, 5-H, trisubstituted pyrimidine), 6.53 (t, 2H, 5-H, both monosubstituted pyrimidine rings), 8.34 (d, 4H, 4-H & 6-H, both monosubstituted pyrimidine rings). *Anal.* Calcd. for $C_{20}H_{25}N_{11} \bullet ¾ H_2O$: C, 55.48; H, 6.17; N, 35.58. Found: C, 55.54; H, 6.40; N, 35.29.

2-[4-(3-Nitropyridin-2-yl)piperazin-1-yl]pyrimidine (13). A mixture of 1.01 g of 99% pure 2-chloro-3-nitropyridine (mp 101-104°), equivalent to 1.00 g (0.00629 mol) of 100% pure compound, and 2.72 g of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 3.10 g (0.0189 mol) of 100% pure amine, was heated on the steam bath for 2.25 h and let stand for 21.25 h. To the mixture of orange brown viscous liquid and orange brown solid, 10 mL water were added. The mixture, now

yellow, was heated briefly on the steam bath. Hard solid was partially broken up. The solids were mixed well with the water and collected, using 2x5.5 mL and 2x4.5 mL water to complete the transfer. Large pieces of hard solid were removed from the funnel, pulverized, and returned to the funnel. The solid was washed with 2x7 mL water, sucked with the vacuum for 15 min, and dried at 36-41° for 46.25 h, orange solid (Solid A), 1.35 g (75.0%), mp 55.5-64° after softening at 54-55.5°, negative Beilstein test (no Cl). The found %N was low. *Anal.* Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.36. Found: C, 54.16; H, 5.11; N, 28.29.

Solid A was recrystallized from the solvent pair of 95% ethanol (10 mL) and enough water to reach the cloud point. The final mixture was let stand for 15 min and cooled in ice for 25 min. The solid and gummy material that separated was collected, using 10 mL water to complete the transfer, and sucked with the vacuum for 10 min. The contents in the funnel, now all solid, was put in a 20 mL beaker. The beaker was sealed. In this way the solid was let stand for 69 h. Then the crusty solid was pulverized and dried at 36-37° for 23.15 h, dark orange solid (Solid B), 0.569 g (31.6%), mp 66.5-73° after softening at 64.5-66.5°. ^{1}H nmr ($CDCl_3$): δ 3.57 (ct, 4H, piperazine), 3.74 (ct, 4H, piperazine), 6.53 (t, 1H, 5-H, pyrimidine), 6.79 (dd, 1H, β-H, pyridine), 8.17 (d, 1H, α-H or γ-H, pyridine), 8.34 (d, 2H, 4-H & 6-H, pyrimidine), 8.36 (d, 1H, α-H or γ-H, pyridine). The found %N was low. *Anal.* Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.36. Found: C, 54.67; H, 4.94; N, 28.48.

Solid B was recrystallized from 95% ethanol (5 mL). The hot ethanolic solution was filtered. Orange solid (Solid C, see below) separated almost immediately from the filtrate. This mixture was let stand for 6 min. The clear orange liquid (Liquid A) above Solid C was decanted into a 20 mL beaker. Shortly thereafter orange solid (Solid D) separated from Liquid A. Liquid A was let stand for 84 min. The solid (Solid D) in Liquid A was collected, using 5 mL and 3 mL methanol to complete the transfer, washed with 3 mL methanol, sucked with the vacuum for 7 min, and dried at 38-40° for 69.75 h, dark orange crystals (Solid D), 69 mg (3.8%), mp 73-75° after softening at 72-73°. Prior to analysis Solid D was let stand over Drierite for 49 h. *Anal.* Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.36. Found: C, 54.85; H, 5.07; N, 29.44.

Solid C (see above) was collected, using 2x2 mL water to complete the transfer, washed with 3 mL water, sucked with the vacuum for 32 min, and dried at 38-40° for 70.5 h, dark orange crystals (Solid C), 85 mg (4.7%), mp 72-75.5° after softening at 69-72° and shrinking slightly. Prior to analysis Solid C was let stand over Drierite for 49 h. *Anal.* Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.36. Found: 54.75, H, 4.86; N, 29.36.

The combined filtrate from Solid D, consisting of liquid and solid, was let stand for 70.5 h. The solid was collected, washed with 2.5 mL hexane, sucked with the vacuum for 25 min, and dried at 46-47° for 45 h, orange solid (Solid E), 9 mg (0.5%), mp 72-73°. Prior to analysis Solid E was let stand over Drierite for 2 h. *Anal.* Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.36. Found: C, 54.69; H, 4.89; N, 29.36.

2-[4-(4-Methyl-5-nitropyridin-2-yl)piperazin-1-yl]pyrimidine (14). A mixture of 1.03 g of 97% pure 2-chloro-4-methyl-5-nitropyridine (mp 37-39°), equivalent to 1.00 g (0.00578 mol) of 100% pure compound, and 2.50 mL of 98% pure 1-(2-pyrimidinyl)piperazine (solid was melted on the steam bath, d 1.16), equivalent to 2.84 g (0.0173 mol) of 100% pure amine, was heated on the steam bath for 3 h and let stand for 20.75 h. To the hard yellow solid, 15 mL water was added. The solid was broken up, mixed well with the water, collected, using 4x3.5 mL water to complete the transfer, washed with 6.5 mL water, sucked with the vacuum for 10 min, and dried at 64-72° for 4 days, yellow solid, 1.68 g (97.1%), mp 211.5-213° after some darkening, sintering, and shrinking at 208.5-211.5°, negative Beilstein test (no Cl). ^{1}H nmr ($CDCl_3$): δ 2.64 (s, 3H, γ-CH_3, pyridine), 3.85 (ct, 4H, piperazine), 3.97 (ct, 4H, piperazine), 6.41 (s, 1H, β-H, pyridine), 6.57 (t, 1H, 5-H, pyrimidine), 8.36 (d, 2H, 4-H & 6-H, pyrimidine), 9.01 (s, 1H, α-H, pyridine). *Anal.* Calcd. for $C_{14}H_{16}N_6O_2$: C, 55.99; H, 5.37; N, 27.98. Found: C, 56.50, 56.10; H, 5.34, 5.28; N, 27.84, 27.62.

2-[4-(6-Methoxy-3-nitropyridin-2-yl)piperazin-1-yl]pyrimidine (15). An intimate mixture of 1.02 g of 98% pure 2-chloro-6-methoxy-3-nitropyridine (mp 78-80°), equivalent to 1.00 g (0.00532 mol) of 100% pure compound, and 2.30 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 2.62 g (0.0160 mol) of 100% pure amine, was heated on the steam bath for 2.5 h and let stand for 8 days. To the mixture, 10 mL water was added. Solid was broken up as much as possible and collected. Another 10 mL water was added. The mixture was heated briefly on the steam bath. More solid was broken up and collected on the same funnel, using 6 mL and 4.5 mL water to complete the transfer. Some of the solid seemed slightly gummy. A button of hard solid and other solid were removed from the funnel, pulverized, and returned to the funnel. The solid was sucked with the vacuum for 30 min and let stand over Drierite for 2 days (Solid A), strong positive Beilstein test (Cl present).

Solid A was recrystallized from 75 mL of 95% ethanol. A small amount of Solid A did not dissolve in the hot 95% ethanol. The hot filtrate (60 mL) was let stand for 69.5 h. Only the loose crystals were collected, sucked with the vacuum for 45 min, and dried at 71-73° for 5 days, impressive mats of bright yellow needles (Solid B), 0.355 g (21.1%), mp 127.2-128° melted completely to an opaque yellow liquid after softening and shrinking slightly at 126-127.2°, negative Beilstein test (no Cl).

Solid B was recrystallized from 28 mL of 95% ethanol, letting the filtrate stand for 102 min. Only the loose crystals were collected, washed with 5 mL 95% ethanol, sucked with the vacuum for 20 min, and dried at 71-72° for 46 h, mats of bright yellow needles (Solid C), 0.153 g (9.11%), mp 127.2-128° melted completely to a clear yellow liquid after softening at 126.5-127.2°. ^{1}H nmr ($CDCl_3$): δ 3.61 (ct, 4H, piperazine), 3.96 (s, 3H, CH_3O), 3.99 (ct, 4H, piperazine), 6.18 (d, 1H, β-H, pyridine), 6.54 (t, 1H, 5-H, pyrimidine), 8.25 (d, 1H, γ-H, pyridine), 8.34 (d, 2H, 4-H & 6-H, pyrimidine). *Anal.* Calcd. for $C_{14}H_{16}N_6O_3$: C, 53.16; H, 5.10; N, 26.57. Found: C, 53.12; H, 5.21; N, 26.60.

2-[4-(3,5-Dinitropyridin-2-yl)piperazin-1-yl]pyrimidine (16). A mixture of 1.01 g of 99% pure 2-chloro-3,5-dinitropyridine (mp 64-66°), equivalent to 1.00 g (0.00490 mol) of 100% pure compound, and 2.12 mL of 98% pure 1-(2-pyrimidinyl)-piperazine (d 1.16), equivalent to 2.41 g (0.0147 mol) of 100% pure amine, was heated on the steam bath for 2.25 h and let stand for 21.5 h. To the orange brown and yellow solids, 10 mL water was added. The hard solid was broken up and collected, using 3x5 mL water to complete the transfer. Large pieces of hard solid in the funnel were removed, pulverized, and returned to the funnel. The solid was washed with 2x9 mL water, sucked with the vacuum for 20 min, and dried at 63-68° for 23 h, dark mustard colored solid, 1.50 g (92.6%), mp 171.5-173° after softening, shrinking, and darkening at 168-171.5°, negative Beilstein test (no Cl). ^{1}H nmr ($CDCl_3$): δ 3.77 (ct, 4H,

piperazine), 4.05 (ct, 4H, piperazine), 6.59 (t, 1H, 5-H, pyrimidine), 8.36 (d, 2H, 4-H & 6-H, pyrimidine), 8.95 (d, 1H, α-H or γ-H, pyridine), 9.15 (d, 1H, α-H or γ-H, pyridine). *Anal.* Calcd. for $C_{13}H_{13}N_7O_4$: C, 47.13; H, 3.96; N, 29.60. Found: C, 47.58, 47.61; H, 3.87, 3.99: N, 29.11, 29.33.

A 50 mg sample of the analytical compound described immediately above was dissolved in 17 mL boiling 95% ethanol and the yellow solution was filtered. The filtrate (11 mL) was let stand for 67 min. The crystals that formed were collected and dried at 70-71° for 45 h, golden yellow crystals, 15 mg (0.92%), mp 170-171° after softening at 168-170°. *Anal.* Calcd. for $C_{13}H_{13}N_7O_4$: C, 47.13; H, 3.96; N, 29.60. Found: C, 47.34; H, 3.03; N, 29.73.

6-Methyl-2-(4-pyrimidin-2-yl-piperazin-1-yl)nicotinonitrile (17). An intimate mixture of 1.02 g of 98% pure 2-chloro-6-methyl-3-pyridinecarbonitrile (mp 114-116°), equivalent to 1.00 g (0.00654 mol) of 100% pure compound, and 2.82 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 3.21 g (0.0196 mol) of 100% pure amine, was heated on the steam bath for 3 h and let stand for 25.5 h. To the mixture of soft pink and hard white solids, 10 mL water was added. Hard solid was broken up. Then 5 mL water was added. Large pieces of solid were removed from the reaction flask, pulverized, and returned to the flask. The solid was collected, using 5 mL and 2x2.5 mL water to complete the transfer, washed with 2x8 mL water, sucked with the vacuum for 62 min, and dried at 72° for 45.75 h, chalky poorly wettable light tan solid (Solid A), 1.26 g (68.9%), mp 105-111°, negative Beilstein test (no Cl).

Solid A was recrystallized from the solvent pair of 95% ethanol (20 mL) and water (7 mL), letting the final mixture stand for 105 min. The solid that formed was collected, using 6 mL and 2x4 mL water to complete the transfer, washed with 7 mL and 8 mL water, sucked with the vacuum for 14 min, and dried at 71-72° for 21.75 h, light tan crystalline solid (Solid B), 0.884 g (48.3%), mp 107-109° after softening at 105-107°. ir: 2212 cm^{-1} medium (C≡N). ^1H nmr ($CDCl_3$): δ 2.43 (s, 3H, α-CH_3, pyridine), 3.81 (m, 4H, piperazine), 3.98 (m, 4H, piperazine), 6.53 (t, 1H, 5-H, pyrimidine), 6.63 (d, 1H, β-H, pyridine), 7.67 (d, 1H, γ-H, pyridine), 8.34 (d, 2H, 4-H & 6-H, pyrimidine). The found %N in the first two CHN analyses was low. Thereafter, Solid B was let stand over Drierite at room temperature in the dark for 24 days and then subjected to a third CHN analysis. *Anal.* Calcd. for $C_{15}H_{16}N_6$: C, 64.27; H, 5.75; N, 29.98. Found: C, 64.40, 64.27, 64.89; H, 5.92, 5.70, 5.81; N, 29.50, 29.45, 29.73.

4-Pyrimidin-2-yl-3,4,5,6-tetrahydro-2*H*-[1,2´]bipyrazinyl (18). A mixture of 0.797 mL of 98% pure chloropyrazine (d 1.28), equivalent to 1.00 g (0.00870 mol) of 100% pure compound, and 3.77 mL of 98% pure 1-(2-pyrimidinyl)-piperazine (solid was melted on the steam bath, d 1.16), equivalent to 4.28 g (0.0261 mol) of 100% pure amine, was heated on the steam bath for 3.5 h and let stand for 69 h. To the yellow and pink crystalline solids, 10 mL water was added. Solids were broken up, collected, using 3x3 mL water to complete the transfer, washed with 3 mL and 2x4 mL water, sucked with the vacuum for 10 min, and dried at 61-62° for 22 h, white solid (Solid A), 0.799 g (37.7%), mp 102.5-105° after softening at 101-102.5°, negative Beilstein test (no Cl). Prior to analysis Solid A was let stand over Drierite for 26 h. *Anal.* Calcd. for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.62; H, 5.89; N, 34.40.

The solid in the combined filtrate from Solid A was collected, using 2x2.5 mL water to complete the transfer, washed with 2x2.5 mL water, sucked with the vacuum for 8 min, and dried at 62° for 20.75 h, white solid (Solid B), 0.103 g (4.9%), mp 105.5-106° after softening at 104-105.5°, negative Beilstein test (no Cl). Prior to analysis Solid B was let stand over Drierite for 26 h. ^1H nmr ($CDCl_3$): δ 3.69-3.71 (ct, 4H, piperazine), 3.96-3.99 (ct, 4H, piperazine), 6.54 (t, 1H, 5-H, pyrimidine), 7.88 (d, 1H, 6-H, pyrazine), 8.09 (dd, 1H, 5-H, pyrazine), 8.19 (d, 1H, 3-H, pyrazine), 8.35 (d, 2H, 4-H & 6-H, pyrimidine). *Anal.* Calcd. for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.47; H, 5.80; N, 34.68.

2-(4-Pyrimidin-2-yl-piperazin-1-yl)quinoxaline (19). A mixture of 1.02 g of 98% pure 2-chloroquinoxaline (mp 47-50°), equivalent to 1.00 g (0.00606 mol) of 100% pure compound, and 2.62 mL of 98% pure 1-(2-pyrimidinyl)piperazine (heated on the steam bath to melt solid, d 1.16), equivalent to 2.98 g (0.0182 mol) of 100% pure amine, was heated on the steam bath for 3.5 h and let stand for 7 days. To the mixture of orange and yellow solids, 10 mL water was added. Hard solid was partially broken up. The liberated fine solid was collected. A large button of hard solid in the reaction flask was broken up. To this mixture 7 mL water were added and more fine-solid was collected. Larger pieces of solid remaining in the reaction flask were removed, pulverized, and returned to the flask. The solid in the flask was mixed with 10 mL water and collected, using 3.5 mL and 2 mL water to complete the transfer. The solid was washed with 6 mL and 7.5 mL water, sucked with the vacuum for 15 min, let stand over Drierite for 15 days, and dried at 63-70° for 138 min, yellow solid, 1.25 g (70.6%), mp 178-181°, negative Beilstein test (no Cl). Prior to analysis the compound was let stand over Drierite for 46 h. ^1H nmr ($CDCl_3$): δ 3.89 (ct, 4H, piperazine), 4.02 (ct, 4H, piperazine), 6.55 (t, 1H, 5-H, pyrimidine), 7.41 and 7.60 (each t, 2H, both meta-H, benzene ring), 7.72 and 7.90 (each d, 2H, both ortho-H, benzene ring), 8.36 (d, 2H, 4-H & 6-H, pyrimidine), 8.63 (s, lone H, pyrazine moiety). *Anal.* Calcd. for $C_{16}H_{16}N_6$: C, 65.74; H, 5.52: N, 28.75. Found: C, 65.96; H, 5.28; N, 28.34.

3-Phenyl-6-(4-pyrimidin-2-yl-piperazin-1-yl)pyridazine (20). A mixture of 1.02 g of 98% pure 3-chloro-6-phenylpyridazine (mp 154-161°), equivalent to 1.00 g (0.00524 mol) of 100% pure compound), and 4.10 mL of 98% pure 1-(2-pyrimidinyl)piperazine (mp 31-33°, mostly solid, warmed on the steam bath to give a clear pale yellow liquid, d 1.16), equivalent to 4.67 g (0.0284 mol) of 100% pure amine, was heated on the steam bath for 3.5 h and let stand for 44 h. To the light brown and pinkish hard solids, 20 mL water was added. This mixture was heated on the steam bath for 30 s. The hard solid was broken up, collected, using three portions of water (7 mL total) to complete the transfer, washed with 7 mL and 9 mL water, sucked with the vacuum for 17 min, and dried at 61-63° for 70.5 h, white solid (Solid A), 1.49 g, mp 178-197° after gradually softening, negative Beilstein test (no Cl).

When an attempt was made to recrystallize Solid A from the solvent pair of 95% ethanol and water, only a small part of Solid A dissolved in 15 mL of boiling 95% ethanol. The liquid part of this hot mixture was filtered by gravity. The clear colorless filtrate gave rise to flocculent solid. This mixture was heated on the steam bath. An unmeasured volume of 95% ethanol was added. The flocculent solid disappeared, giving a colorless solution. To this hot solution, 5 mL of hot water was added. The resulting solution (18 mL) was let stand for 5 days. The solid that formed was collected, using 3x2 mL water to complete the transfer, washed with 2x3 mL water, sucked with the vacuum

for 10 min, dried at 64-65° for 4 h, and let stand over Drierite for 12 days, white solid (Solid B), 47 mg (2.8%), mp 132-144°.

Another attempt was made to recrystallize the remaining Solid A (most of the original Solid A) from the solvent pair of 95% ethanol and water. Again only a small part of Solid A dissolved in the hot 95% ethanol. The liquid portion of the mixture was filtered by gravity. The filtrate gave rise to flocculent solid. The mixture was heated on the steam bath. An unmeasured volume of hot 95% ethanol was added to the hot filtrate. The flocculent solid disappeared. To the hot colorless solution, 8 mL hot water was added. The resulting solution (52 mL) was let stand for 5 days. The crystals that formed were collected, using 2 mL water to complete the transfer, washed with 3 mL water, sucked with the vacuum for 23 min, dried at 64-65° for 4 h, and let stand over Drierite for 12 days, impressive well formed transparent long thin needles with blunt ends (Solid C), 61 mg (3.6%), mp 194.5-196°. ^{1}H nmr ($CDCl_3$): δ 3.81-3.84 (ct, 4H, piperazine), 4.00-4.03 (ct, 4H, piperazine), 6.54 (t, 1H, 5-H, pyrimidine), 7.03 (d, 1H, 4-H, pyridazine), 7.40 (ct, 1H, para-H, phenyl), 7.45 (ct, 2H, 2xmeta-H, phenyl), 7.68 (d, 1H, 5-H, pyridazine), 8.04 (d, 2H, 2xortho-H, phenyl), 8.35 (d, 2H, 4-H & 6-H, pyrimidine). *Anal.* Calcd. for $C_{18}H_{18}N_6$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.11; H, 5.69; N, 26.54. No further work was carried out on the alcohol insoluble portion (the major portion) of Solid A left from the two recrystallizations.

2-[4-(3-Methyl-5-nitro-3*H*-imidazol-4-yl)piperazin-1-yl]-pyrimidine (21). A mixture of 1.02 g of 98% pure 5-chloro-1-methyl-4-nitro-1*H*-imidazole (mp 148-150°), equivalent to 1.00 g (0.00617 mol) of 100% pure compound, and 2.66 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 3.03 g (0.0185 mol) of 100% pure amine, was heated on the steam bath for 2.5 h and let stand for 20.5 h. To the mixture, 10 mL water was added. Hard solid was broken up and mixed well with the water. The solid was collected, using 2x3 mL water to complete the transfer. Nearly all of the solid was finely divided and yellow. A small amount of solid was hard and darker. Most of the hard darker solid was removed from the funnel, pulverized, and returned to the funnel. The solid was washed with 2x7 mL water, sucked with the vacuum for 20 min, and dried at 64-78° for 45.5 h, yellow solid (Solid A), 1.32 g (68.0%), mp 153-156.5° after some softening and shrinking over several degrees prior to 153°, negative Beilstein test (no Cl). The found %N was low. *Anal.* Calcd. for $C_{12}H_{15}N_7O_2$: C, 49.82; H, 5.23; N, 33.89. Found: C, 49.93; H, 5.18; N, 33.10.

Solid A was recrystallized from the solvent pair of 95% ethanol (30 mL) and enough water to reach the cloud point. The mixture (28 mL) was let stand for 46 h. The crystals were collected, using 2x3 mL water to complete the transfer, washed with 2x5.5 mL water, sucked with the vacuum for 1 h, and dried at 62-65° for 71.75 h, impressive long thin sparkling needles (Solid B), 0.592 g (30.5%), mp 159-162° after softening at 157-159°. ^{1}H nmr ($CDCl_3$): δ 3.24 (ct, 4H, piperazine), 3.65 (s, 3H, 3-CH_3, imidazole), 4.00 (bs, 4H, piperazine), 6.55 (t, 1H, 5-H, pyrimidine), 7.30 (s, 1H, α-H, imidazole), 8.34 (d, 2H, 4-H & 6-H, pyrimidine). The found %N was low. *Anal.* Calcd. for $C_{12}H_{15}N_7O_2$: C, 49.82; H, 5.23; N, 33.89. Found: C, 49.76; H, 5.42; N, 33.14.

Solid B was recrystallized from 10 mL 95% ethanol. The hot filtrate was let stand for 28 min. The crystals were collected, sucked with the vacuum for 16 min, and dried at 63-66° for 45.5 h, sparkling short fine yellow needles (Solid C), 0.148 g (7.63%), mp 133-136° after softening at 131-133°. The low mp was surprising. The found %C and %N were both low. *Anal.* Calcd. for $C_{12}H_{15}N_7O_2$: C,49.82; H, 5.23; N, 33.89. Found: C, 49.31; H, 5.32; N, 33.31.

Solid C was let stand over Drierite for 16 days and dried at 74-78° for 69.5 h (Solid D), mp 162-163° melted completely to a clear yellow liquid. The structure of **21** was proved by single crystal x-ray diffraction analysis. *Anal.* Calcd. for $C_{12}H_{15}N_7O_2$: C, 49.82; H, 5.23; N, 33.89. Found: C, 49.67; H, 5.47: N, 33.62.

2-[4-(1-Phenyl-1*H*-tetrazol-5-yl)piperazin-1-yl]pyrimidine (22). An intimate mixture of 1.03 g of 97% pure 5-chloro-1-phenyl-1*H*-tetrazole (mp 122-124°), equivalent to 1.00 g (0.00552 mol) of 100% pure compound, and 2.40 mL of 98% pure 1-(2-pyrimidinyl)piperazine (mp 29-36°, melted on the steam bath, d 1.16), equivalent to 2.72 g (0.0166 mol) of 100% pure amine, was heated on the steam bath for 2.25 h and let stand for 70 h. To the mixture of tan and white solids, 5 mL water was added. Hard solid was broken up. The solid was collected, using 3 mL and 2 mL water to complete the transfer. Large pieces of solid were removed from the funnel, pulverized, and returned to the funnel. The solid was washed with 2x6 mL water, sucked with the vacuum for 10 min, let stand over Drierite for 9 days, dried at 73-78° for 68 h, and let stand over Drierite for 48.5 h, cream colored chalky solid (Solid A), 1.38 g (81.2%), mp formed a dark yellow brown melt by 178°, gave a fleeting faintly green color in the Beilstein test.

Solid A was recrystallized from the solvent pair of 95% ethanol (25 mL) and water (18 mL). The hot mixture was let stand for 40 min, cooled in ice for 85 min, and let stand for 9 days. The crystals that formed were collected, using 4.5 mL water to complete the transfer, washed with 4 mL water, sucked with the vacuum for 34 min, dried at 66-68° for 47.5 h, and let stand over Drierite for 5 days, slightly cream colored nacreous poorly wettable crystals (Solid B), 0.394 g (23.2%), mp 159-171° after softening at 145-159°, negative Beilstein test (no Cl). For the duplicate CHN analysis, Solid B was let stand over Drierite for 20 days more. ^{1}H nmr ($CDCl_3$): δ 3.33 (ct, 4H, piperazine), 3.88 (ct, 4H, piperazine), 6.54 (t, 1H, 5-H, pyrimidine), 7.53-7.66 (m, 5H, phenyl), 8.31 (d, 2H, 4-H & 6-H, pyrimidine). *Anal.* Calcd. for $C_{15}H_{16}N_8$: C, 58.43; H, 5.23; N, 36.34. Found: C, 58.51, 58.35; H, 5.41, 5.08; N, 35.81, 35.21.

Solid B was recrystallized from the solvent pair of 95% ethanol (10 mL) and water (2 mL). The hot mixture was let stand for 70 min. The crystals that formed were collected, using 5 mL water to complete the transfer, washed with 5 mL water, sucked with the vacuum for 17 min, and dried at 72-74° for 68 h, white crystals (Solid C), 0.111 g (6.5%), mp 172.5-174° after softening at 170-172.5°. The sample of Solid C used for the duplicate CHN analysis had stood over Drierite for 3 days prior to analysis. *Anal.* Calcd. for $C_{15}H_{16}N_8$: C, 58.43; H, 5.23; N, 36.34. Found: C, 59.15, 58.59; H, 5.25, 5.18; N, 36.49, 36.23.

2-(4-Pyrimidin-2-yl-piperazin-1-yl)benzoxazole (23). A 25 mL round bottomed flask was charged with 0.913 g of 99% pure 2-chlorobenzoxazole (bp 95-96°/20 mm Hg, mp 7°, d 1.32), equivalent to 0.904 g (0.00587 mol) of 100% pure compound. To this 2-chloro compound, 2.80 mL of 98% pure 1-(2-pyrimidinyl)piperazine (mp 29-36°, melted on the steam bath, d 1.16), equivalent to 3.19 g (0.0195 mol) of 100% pure amine, were added. An immediate reaction occurred, giving dense white fumes and white solid. This mixture of solid and liquid was shaken briefly, heated on the steam bath for 2 h, and let stand for 45.5 h. To this mixture, 10 mL water was added. Large

pieces of solid were broken up. The solid was collected, using 5.5 mL, 4.5 mL, and 3.0 mL water to complete the transfer, washed with 7.5 mL water, sucked with the vacuum for 45 min, and dried at 72-73° for 44.75 h, light tan solid (Solid A), 1.54 g (93.3%), mp 176-181° melted completely to a slightly opaque colorless liquid after softening at 174-176°, negative Beilstein test (no Cl).

Solid A was recrystallized from the solvent pair of 95% ethanol and water, letting the final solution (61 mL) stand for 45 min. The solid that formed was collected, using 10 mL water to complete the transfer, washed with 10 mL water, sucked with the vacuum for 15 min, and dried at 72° for 119.5 h, soft white crystalline solid (Solid B), 0.774 g (46.9%), mp 179-181° melted completely to a clear colorless liquid after softening at 178-179°. ^{1}H nmr ($CDCl_3$): δ 3.78 (m, 4H, piperazine), 3.99 (m, 4H, piperazine), 6.55 (t, 1H, 5-H, pyrimidine), 7.04 (t, 1H, H of benzene ring meta to fusion point), 7.19 (t, 1H, H of benzene ring meta to fusion point), 7.28 (d, 1H, H of benzene ring ortho to fusion point), 7.39 (d, 1H, H of benzene ring ortho to fusion point), 8.34 (d, 2H, 4-H & 6-H, pyrimidine). *Anal.* Calcd. for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.90. Found: C, 64.78, 64.40; H, 5.18, 4.99; N, 25.33, 24.90.

6-(4-Pyrimidin-2-yl-piperazin-1-yl)-9*H*-purine (24). An intimate mixture of 1.92 g of 99% pure 6-chloropurine (mp > 300°), equivalent to 1.90 g (0.0123 mol) of 100% pure compound, and 5.37 mL of 98% pure 1-(2-pyrimidinyl)-piperazine (d 1.16), equivalent to 6.05 g (0.0369 mol) of 100% pure amine, was heated on the steam bath for 3.5 h, let stand for 67 h, heated on the steam bath for 4 h more, and let stand for 45 h. The mixture was mixed with 20 mL water. Solid was broken up and collected, using 3 mL and 3x3.5 mL water to complete the transfer. Larger pieces of solid in the funnel were put back into the reaction flask and mixed with 3x3.5 mL water, each time breaking up solid. The solid was collected on the same funnel. The solid was sucked with the vacuum for 2 h and dried at 70-71° for 44 h, greenish gray solid (Solid A), 2.79 g (80.4%). On taking a melting point Solid A did not melt and did not undergo any change up to 200° when the determination was stopped. On ignition on the flat end of a metal spatula, Solid A melted completely, produced a few streaks of flame, and left no residue. In the Beilstein test Solid A produced a fleeting green color.

Solid A was insoluble in cold and hot 95% ethanol, insoluble in cold and hot hexane, insoluble in cold and hot water, insoluble in cold and hot 2-propanol, and insoluble in cold but soluble in hot dimethylformamide. Solid A was recrystallized in small portions.

A 0.1909 g sample of Solid A was recrystallized from the solvent pair of 95% ethanol and water. A significant amount of Solid A did not dissolve in 40 mL of hot 95% ethanol. The mixture was filtered by gravity. The hot clear pale olive filtrate (37 mL) was let stand for 47 min and cooled in ice for 22 min. To the cold solution 40 mL water were added. The cloudy mixture was cooled in ice for 89 min and let stand for 92 h. The mixture was filtered by gravity to remove a small amount of greenish grey flocculent solid. The filtrate (65 mL), consisting of clear and nearly colorless liquid, was concentrated by heating on the steam bath for 38 min. The concentrate, consisting of crystals and pale yellow liquid, was transferred to a 50 mL beaker, using 1 mL water to complete the transfer. The mixture was cooled in ice for 51 min. The crystals were collected, using 2 mL water to complete the transfer, sucked with the vacuum for 25 min, and dried at 70-71° for 46 h, pale yellow solid (Solid B), 0.122 g (63.9% recovery), fleeting green color in the Beilstein test. ^{1}H nmr (DMSO-d_6): δ 3.89 (ct, 4H, piperazine), 4.32 (bs, 4H, piperazine), 6.67 (t, 1H, 5-H, pyrimidine), 8.17 (s, 1H, 2-H or 8-H, purine), 8.26 (s, 1H, 2-H or 8-H, purine), 8.41 (d, 2H, 4-H & 6-H, pyrimidine), 13.1 (bs, 1H, 9-H, purine). *Anal.* Calcd. for $C_{13}H_{14}N_8$: C, 55.31; H, 5.00; N, 39.69. Found: C, 55.32; H, 4.94; N, 39.34.

A 0.4000 g sample of Solid A was recrystallized from the solvent pair of 95% ethanol and water. Not all of the sample dissolved in 40 mL of boiling 95% ethanol. The mixture was filtered by gravity. The filtrate (33 mL), clear and pale olive, was let stand for 40 min and cooled in ice for 113 min. The solid that formed was collected, sucked with the vacuum for 37 min (pasty solid), and dried at 71° for 44 h, pale greenish yellow solid (Solid C), 92 mg (23% recovery), fleeting green color in the Beilstein test.

A 0.4000 g sample of Solid A was recrystallized from 20 mL dimethylformamide. Not all of the sample dissolved in the hot solvent. The recrystallized solid (Solid D), light grey, was dried at 71° for 140 min, 0.103 g (25.7% recovery).

A 0.5032 g sample of Solid A was recrystallized from the solvent pair of 95% ethanol and water. Four 20 mL portions of hot 95% ethanol were used to dissolve most of the solid. The ethanolic filtrate was concentrated to 30 mL. To this concentrate, 28 mL of hot water was added. The resulting mixture was let stand for 69 h. The solid that formed was collected, using 1 mL water to complete the transfer, sucked with the vacuum for 50 min, and dried at 71° for 48 h, pale greenish yellow solid (Solid E), 0.156 g (31.0% recovery).

Concentration of the combined filtrate from Solid E, gave, after drying at 71-72° for 46.5 h, pale greenish yellow solid (Solid F), 17 mg (3.3% recovery).

The five recrystallized products (B-F) were combined to give Solid G (0.394 g). Solid G was used in the cyanoethylation reaction, giving **26**.

6-(4-Pyrimidin-2-yl-piperazin-1-yl)-9*H*-purin-2-ylamine (25). An intimate mixture of 1.01 g of 99% pure 2-amino-6-chloropurine (mp >300°), equivalent to 1.00 g (0.00588 mol) of 100% pure compound, and 5.08 mL of 98% pure 1-(2-pyrimidinyl)piperazine (mp 29-36°, solid melted on the steam bath, d 1.16), equivalent to 5.78 g (0.0352 mol) of 100% pure amine, was heated on the steam bath for 2.25 h, let stand for 68 h, and heated on the steam bath for 3.75 h more. The soft solid, mostly light tan was let stand for 45 h. The solid was mixed with 20 mL water. The pasty solid was collected, using 2.5 mL water to complete the transfer, sucked with the vacuum for 65 min, and dried at 72° for 7 days, cream colored solid (Solid A), l.64 g (93.3%), mp 269.5-277° after gradually darkening to a black solid.

Solid A was recrystallized from the solvent pair of 95% ethanol (105 mL) and water (25 mL). A significant amount of solid A did not dissolve in the hot 95% ethanol. The final hot solution was let stand for 10 days. A minor amount of tan solid ringed the glassware above the main mixture. This tan solid was not disturbed when the product was collected. The main product was collected, using 7 mL and 3 mL water to complete the transfer, washed with 5 mL water, sucked with the vacuum for 50 min, and dried at 72° for 45.25 h, soft white solid (Solid B), 0.460 g (26.3%), negative Beilstein test (no Cl). When solid B was ignited on the flat end of a metal spatula, the sample melted rapidly and the liquid evaporated completed. ^{1}H nmr (DMSO-

d_6): δ 3.84 (ct, 4H, piperazine), 4.22 (bs, 4H, piperazine), 5.80 (bs, 2H, 2-NH_2, purine), 6.66 (t, 1H. 5-H, pyrimidine), 7.73 (s, 1H, 8-H, purine), 8.40 (d, 2H, 4-H & 6-H, pyrimidine), 12.23 (bs, 1H, 9-H, purine). *Anal.* Calcd. for $C_{13}H_{15}N_9$: C, 52.52; H, 5.09: N, 42.40. Found: C, 52.49, 52.83; H, 5.00, 5.15; N, 41.76, 42.19.

3-(6-Chloropurin-9-yl)propionitrile (29). An intimate mixture of 0.500 g (0.00323 mol) of 6-chloropurine (Francis Earle Laboratories), 3.00 mL of acrylonitrile (Eastman Kodak, d 0.811), equivalent to 2.43 g (0.0458 mol) of the compound, and seven small drops of 40% Triton B #1 was refluxed for 1 h and cooled in ice for 30 min. The solid that precipitated was collected, using several small portions of water to complete the transfer, washed with two small portions of water, and let stand over calcium chloride for 28.5 h, pale yellow finely divided solid (Solid A), mp 147-152.5°.

The solid in the combined yellow filtrate from Solid A was collected, using a few small portions of water to complete the transfer, washed with two small portions of water, and let stand over calcium chloride for 28.5 h, straw colored solid (Solid B), mp 145-146.5° after some shrinking prior to 145°.

The combined filtrate from Solid B was cooled in the refrigerator for 3 months. The solid was collected, washed once with water, and dried at 80° for 23 h, pale yellow solid (Solid C), 57 mg (8.5%), mp 145-152° after some shrinking prior to 145°.

Solids A and B were combined to give Solid D, 0.323 g (48.1%), small rod shaped crystals (x100) for the most part. Solid D was soluble in hot water, soluble in cold absolute ethanol, and insoluble in cold but soluble in hot benzene. Solid D was recrystallized (charcoal) from the solvent pair of benzene (40 mL) and cyclohexane (35 mL), allowing the final hot mixture to stand for 23.5 h. The crystals that separated were collected, washed with two portions of benzene, and dried at 80° for 14 h, small faintly pale yellow needles (Solid E), 0.228 g (34.0%), mp 149.5-151.5°.

Solid E was recrystallized (tiny amount of charcoal) from the solvent pair of benzene (30 mL) and cyclohexane. The hot benzene solution was filtered through two pieces of quantitative filter paper. The filtrate was heated briefly and filtered through clean quantitative filter paper and clean funnel. Hot cyclohexane (unmeasured volume) was added to the filtrate. Much solid separated. The mixture was heated on the steam bath. Several milliters of warm benzene were added in order to cause virtually all of the solid to dissolve. To this mixture several milliters of warm cyclohexane were added. The mixture was heated on the steam bath. The hot mixture (75 mL) was let stand for 162 min. The crystals that separated were collected, using two generous portions of cyclohexane to complete the transfer, washed with four generous portions of cyclohexane, and dried at 80° for 15 h, small fine white needles with a faint yellow tint (Solid F), 0.109 g (16.2%), mp 149-150.5°, positive Beilstein test (Cl present). ir: 2250 cm^{-1} weak (C≡N). ^{1}H nmr ($CDCl_3$): δ 3.09 (t, 2H, CH_2-C≡N), 4.16 (t, 2H, CH_2-N), 8.24 (s, 1H, 2-H or 8-H, purine), 8.78 (s, 1H, 2-H or 8-H, purine). *Anal.* Calcd. for $C_8H_6N_5Cl$: C, 46.28; H, 2.91; N, 33.73. Found: C, 46.54, 46.62; H, 3.12, 3.09; N, 33.58.

3-[6-(4-Pyrimidin-2-yl-piperazin-1-yl)purin-9-yl]propionitrile (26) from 3-(6-Chloropurin-9-yl)propionitrile (29) and 1-(2-Pyrimidinyl)piperazine. An intimate mixture of 1.00 g (0.00481 mol) of dry 3-(6-chloropurin-9-yl)propionitrile and 4.58 mL of 98% pure 1-(2-pyrimidinyl)piperazine (d 1.16), equivalent to 5.20 g (0.0317 mol) of 100% pure amine, was heated on the steam bath for 3 h, let stand for 19 h, and heated on the steam bath for 2.5 h more. To the cool mixture 6.5 mL water were added. The mixture was stirred well. Large pieces of solid were broken up. The mixture was cooled in ice for 5 min. The solid was collected, using 5x1 mL water to complete the transfer, washed with 4.5 mL and 7 mL water, sucked with the vacuum for 13 min, and dried at 64-65° for 118 h, chalky cream colored poorly wettable solid (Solid A), 0.997 g (61.9%), mp 175-177°, positive Beilstein test (Cl present), insoluble in cold but soluble in boiling 95% ethanol, and insoluble in cold and hot water.

Solid A was recrystallized from the solvent pair of 95% ethanol and water. An appreciable amount of Solid A did not dissolve in the 57 mL of hot 95% ethanol. The hot mixture was filtered by gravity, giving a clear colorless filtrate (40 mL). Hot water (20 mL) was added to the filtrate. The mixture was let stand for 69 h. The solid in the mixture was collected, using 3.5 mL and 4 mL water to complete the transfer, washed with 3.5 mL water, sucked with the vacuum for 17 min, and dried at 62-76° for 47 h, white solid with a faint yellow color (Solid B), 0.349 g (21.7%), mp 175-176° after softening with a little darkening at 173-175°, gave a fleeting green color in the Beilstein test. ^{1}H nmr ($CDCl_3$): δ 3.03 (t, 2H, CH_2-C≡N), 4.01 (ct, 4H, piperazine), 4.40 (bs) and 4.48 (m) (4H, piperazine), 4.48 (t, 2H, N-CH_2), 6.54 (t, 1H, 5-H, pyrimidine), 7.86 (s, 1H, 2-H or 8-H, purine), 8.35 (d, 2H, 4-H & 6-H, pyrimidine), 8.36 (s, 1H, 2-H or 8-H, purine). The CHN analysis was poor. *Anal.* Calcd. for $C_{16}H_{17}N_9$: C, 57.30; H, 5.11; N, 37.59. Found: C, 58.14; H, 5.12; N, 35.42.

The combined filtrate (63 mL) from Solid B, consisting of cloudy white liquid and a tiny amount of solid, was concentrated to 13 mL by heating on the steam bath for 56 min. The concentrate, consisting of colorless liquid and much solid, was put in a 20 mL beaker and let stand for 93.5 h. The solid was collected, using 3.5 mL water to complete the transfer, washed with 6.5 mL water, sucked with the vacuum for 1 h, and dried at 69-74° for 74 h, white solid (Solid C), 65 mg (4.0%), mp 174.5-176° after softening at172-174.5°, fleeting positive Beilstein test. Solids B and C were combined to give Solid D.

Solid D was recrystallized from the solvent pair of 95% ethanol (22 mL) and water (12 mL), letting the final hot mixture stand for 45.5 h. The solid that formed was collected, using 1.5 mL and 5 mL water to complete the transfer, washed with 5.5 mL water, sucked with the vacuum for 1.5 h, and dried at 73° for 70.5 h, white solid (Solid E), 0.146 g (9.07%), mp 174.5-177° after softening at 173-174.5°, fleeting positive Beilstein test. The CHN analysis was poor. *Anal.* Calcd. for $C_{16}H_{17}N_9$: C, 57.30; H, 5.11; N, 37.59. Found: C, 58.06; H, 5.16; N, 35.90.

The combined filtrate from Solid E was let stand for 5 days. The solid in the filtrate was collected, using 2 mL water to complete the transfer, sucked with the vacuum for 2 h, and dried at 73° for 45.5 h, pure white solid (Solid F), 66 mg (4.1%), mp 176-178° after softening at 175-176°, fleeting positive Beilstein test. ir: 2251 cm^{-1} weak (C≡N). The found %C was unacceptable. *Anal.* Calcd. for $C_{16}H_{17}N_9$: C, 57.30; H, 5.11; N, 37.59. Found: C, 57.84, 58.01; H, 5.05, 5.30; N, 37.18, 37.28.

Solid E was recrystallized from the solvent pair of 95% ethanol (10 mL) and enough hot water to reach the cloud point. The hot mixture (15 mL) was let stand for 23 min, cooled in ice for 15 min, and let stand for 46.5 h. The solid that formed was collected, using 2x2.5 mL water to complete the transfer,

washed with 3 mL water, sucked with the vacuum for 2 h, and dried at 71-73° for 68.5 h, pure white solid (Solid G), 57 mg (3.6%), mp 174.5-177.5° after softening and shrinking at 174-174.5°. ^{1}H nmr ($CDCl_3$): δ 3.03 (t, 2H, CH_2-C≡N), 3.99 (ct, 4H, piperazine), 4.40 (bs, 4H, piperazine), 4.49 (t, 2H, N-CH_2), 6.54 (t, 1H, 5-H, pyrimidine), 7.85 (s, 1H, 2-H or 8-H, purine), 8.35 (d, 2H, 4-H & 6-H, pyrimidine), 8.36 (s, 1H, 2-H or 8-H, purine). *Anal.* Calcd. For $C_{16}H_{17}N_9$: C, 57.30; H, 5.11; N, 37.59. Found: C, 57.67; H, 5.03; N, 37.43. The ^{1}H nmr spectrum of this product was identical to the ^{1}H nmr spectrum of the product formed from the cyanoethylation of 6-(4-pyrimidin-2-yl-piperazin-1-yl)-9*H*-purine (**24**).

3-[6-(4-Pyrimidin-2-yl-piperazin-1-yl)purin-9-yl]propionitrile (26) from the Cyanoethylation of 6-(4-Pyrimidin-2-yl-piperazin-1-yl)-9*H*-purine (24). An intimate mixture of 0.394 g (0.00140 mol) of 6-(4-pyrimidin-2-yl-piperazin-1-yl)-9*H*-purine (composite of five once recrystallized products), 1.76 mL of 99% pure acrylonitrile (d 0.806), equivalent to 1.41 g (0.0266 mol) of 100% pure compound, and 7 small drops of 40% in water Triton B was heated on the steam bath for 1.5 h and cooled in ice for 5 min. To the dark brown viscous syrup, 10 mL water was added. The mixture was cooled in ice for 55 min and transferred to a 50 mL beaker. The mixture, consisting of pale yellow liquid and brown gum on the bottom of the beaker, was let stand for 68.5 h. The pale yellow solid in the mixture was collected, taking care to collect only the pale yellow solid. However, a tiny amount of finely divided brown particles also was collected. The solid was sucked with the vacuum for 65 min (tan pasty solid) and dried at 71° for 46 h. The solid now was brown, 0.213 g (45.4%). The solid was let stand over Drierite for 48 h and then pulverized. The solid now was powdery and pale dull orange (Solid A), mp 155-170° after softening and shrinking at 146-154°.

Solid A was recrystallized from the solvent pair of 95% ethanol (10 mL) and water (14 mL). The final hot mixture was let stand for 70 h. The solid that formed was collected, using 3 mL and 1.5 mL water to complete the transfer, sucked with the vacuum for 67 min, and dried at 71-72° for 45 h, pale yellow solid (Solid B), 84 mg (18%), mp 169-173° after some shrinking and softening at 164-169°. ir: 2248 cm^{-1} weak (C≡N). ^{1}H nmr ($CDCl_3$): δ 3.03 (t, 2H, CH_2-C≡N), 3.99 (ct, 4H, piperazine), 4.40 (bs, 4H, piperazine), 4.48 (t, 2H, N-CH_2), 6.54 (t, 1H, 5-H, pyrimidine), 7.86 (s, 1H, 2-H or 8-H, purine), 8.35 (d, 2H, 4-H & 6-H, pyrimidine), 8.36 (s, 1H, 2-H or 8-H, purine). *Anal.* Calcd. for $C_{16}H_{17}N_9$: C, 57.30; H, 5.11; N, 37.59. Found: C, 57.21; H, 5.25; N, 37.26. The ^{1}H nmr spectrum of this product was identical to the ^{1}H nmr spectrum of the product formed from the reaction of 1-(2-pyrimidinyl)piperazine with 3-(6-chloro-purin-9-yl)propionitrile (**29**).

2-[4-(4-Fluorophenyl)piperazin-1-yl]pyrimidine (27). A mixture of 1.02 g of 98% pure 2-chloropyrimidine (Acros Fisher), equivalent to 1.00 g (0.00870 mol) of 100% pure 2-chloropyrimidine, and 4.66 g of 98% pure 1-(4-fluoro-phenyl)piperazine (mp 30-33°, formed a colorless liquid upon warming), equivalent to 4.57 g (0.0254 mol) of 100% pure amine, was heated on the steam bath for 2.5 h and let stand for 15 min, giving a butterscotch colored mush and hard dark brown solid. This mixture was mixed with 4x5 mL water, each time partially breaking up hard solid and collecting the liberated solid. The solid in the funnel was washed with 10 mL water, sucked with the vacuum for 20 min and dried at 63-66° for 20 h, light tan solid (Solid A), 1.74 g (77.7%), mp 114-116°, negative Beilstein test (no Cl). *Anal.* Calcd. for $C_{14}H_{15}N_4F$: C, 65.10; H, 5.85; N, 21.69. Found: C, 65.05; H, 5.75: N, 21.69.

Solid A was recrystallized from the solvent pair of 95% ethanol and water. When the hot 95% ethanolic solution was filtered by gravity, much solid settled out on the filter paper. The solid was carefully scraped from the filter paper and returned to the initial 20 mL beaker. More 95% ethanol was used to dissolve this solid. The hot ethanolic solution was filtered again. The same thing happened and the same procedure was followed. During the third filtration, virtually no solid settled out on the filter paper. The final solution (15 mL, clear and pale yellow) was let stand for 18 min and cooled in ice for 1.5 h. The solid that formed was collected, using 2x1 mL water to complete the transfer, washed with 8 mL water, sucked with the vacuum for 10 min, and dried at 59-61° for 44 h, fine silky white needles (Solid B), 0.467 g (20.8%), mp 116-117° after softening at 115-116°. ^{1}H nmr ($CDCl_3$): δ 3.16 (ct, 4H, piperazine), 3.98 (ct, 4H, piperazine), 6.51 (t, 1H, 5-H, pyrimidine), 6.90-7.00 (m, 4H, phenyl), 8.33 (d, 2H, 4-H & 6-H, pyrimidine). *Anal.* Calcd. for $C_{14}H_{15}N_4F$: C, 65.10; H, 5.85; N, 21.69. Found: C, 65.01; H, 5.73; N, 21.54.

The combined filtrate from Solid B, consisting of solid and pale yellow liquid, was let stand for 46 h. The solid was collected, using 1 mL water to complete the transfer, washed with 3 mL water, sucked with the vacuum for 8 min, and dried at 62° for 23 h, fluffy cream colored solid, 35 mg (1.6%), mp 114-115.5°.

2-[4-(2-Fluorophenyl)piperazin-1-yl]pyrimidine (28). A mixture of 1.00 g of 98% pure 2-chloropyrimidine (Acros Fisher), equivalent to 0.980 g (0.00852 mol) of 100% pure compound, and 4.25 mL of 97% pure 1-(2-fluorophenyl)piperazine (d 1.14), equivalent to 4.70 g (0.0261 mol) of 100% pure amine, was heated on the steam bath for 2 h and cooled in ice for 3 min. The solid was collected, using 15 mL water to complete the transfer, washed with 2 mL water, sucked with the vacuum for 3 min, and let stand over Drierite for 21 h, pinkish solid (Solid A), 0.491 g, strong positive Beilstein test (Cl present).

The combined filtrate from Solid A, consisting of pinkish gummy solid and cloudy liquid, was put in a 25 mL flask, using 2 mL water to complete the transfer. The mixture was let stand for 21.5 h. The solid was collected, using 2x2 mL water to complete the transfer, washed with 2x5 mL water, sucked with the vacuum for 8 min, and let stand over Drierite for 4 days, light pink crystalline solid (Solid B), 1.13 g (50.4%), mp 44-46°, negative Beilstein test (no Cl).

The combined filtrate from Solid B was let stand for 4 days. The solid was collected, using 1.5 mL water to complete the transfer, sucked with the vacuum for 14 min, and let stand over Drierite for 7 days, dark pinkish crystalline solid (Solid C), mp 40-43°.

Solid B was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture stand for 2 min and cool in ice for 50 min. The mixture was transferred to a 25 mL flask, using 3x1 mL water to complete the transfer. The mixture was let stand for 47 h. The hard solid in the mixture was broken up, collected, using 5x2 mL water to complete the transfer, washed with 2x3 mL water, sucked with the vacuum for 20 min, and let stand over Drierite for 5 days, light pinkish crystalline solid (Solid D), 0.787 g (35.1%), mp 41-44°. ^{1}H nmr ($CDCl_3$): δ 3.15 (ct, 4H, piperazine), 4.00 (ct, 4H, piperazine), 6.51 (t, 1H, 5-H, pyrimidine), 6.96 and 7.06 (each cm, 4H, phenyl), 8.34 (d, 2H, 4-H & 6-H, pyrimidine). *Anal.* Calcd. for $C_{14}H_{15}N_4F$: C, 65.10; H, 5.85; N, 21.69. Found: C, 65.29; H, 5.84; N, 21.62.

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Dedication. This paper is dedicated to the memory of my friend Judy Ostro. I met Judy when she was a twenty-eight year old widow. Her husband had died of cancer. Struggling with adverse emotional aspects of her past, Judy nevertheless raised two fine daughters who have borne seventeen grandchildren, eight of whom Judy knew during her lifetime. One month before her forty-eighth birthday Judy lost her battle with acute leukemia. Judy was an *Ayshes Chayil*—a woman of valour.

REFERENCES AND NOTES

[1] Saudour, F.; Amara, D.A.; Dierich, A.; LeMeur, M.; Ramboz, S.; Segu, L.; Buhot, M-C.; Hen, R. *Science*, *New Series* **1994**, *265*, 1875.

[2] Duman, R. S.; Heninger, G. R.; Nestler, E. J. *Archives of General Psychiatry* **1997**, *57*, 597.

[3] Uphouse, L. *Neuroscience and Biochemical Reviews* **1997**, *21*, 679.

[4] Meltzer, H. Y. *Neuropsychopharmacology* **1999**, *21*, 106 S.

[5] Barnes, N. M.; Sharp, T. *Neuropharmacology* **1999**, *38*, 1083.

[6] Moret, C.; Briley, M. *Eur. J. Pharmacology* **2000**, *404*, 1.

[7] Gingrich, J. A.; Hen, R. *Psychopharmacology (Berlin)* **2001**, *155*, 1.

[8] Manji, H. K.; Drevets, W. C.; Charney, D. S. *Nature Medicine* **2001**, *7*, 541.

[9] Svenningssen, P.; Chergui, K.; Rachleff, I.; Flagjolet, M.; Zhana, X.; El Yacoubi, M.; Vaugeois, J. M.; Nomikos, G. S.; Greengard, P. *Science* **2006**, *311*, 77.

[10] Mokrosz, J. M.; Strekowski, L.; Buszynska, B.; Harden, D. B.; Mokrosz, M. J.; Bajarski, A. J. *Pharmazie* **1994**, *49*, 801.

[11] Matsumoto, K.; Hashimoto, S.; Minatogawa, H.; Munakata, M.; Otani, S. *Chemistry Express* **1990**, *5*, 473.

[12] Matsumoto, K.; Hashimoto,S.; Toda, M.; Hashimoto, M.; Otani, S. *Chemistry Express* **1991**, *6*, 775.

[13] Arranz, M. E.; Diaz, J. A.; Vega, S.; Campos-Toimil, M.; Orallo, F.; Cardelus, I.; Llenas, J.; Fernandez, A. G. *Eur. J. Med. Chem.* **2000**, *35*, 751.

[14] Vega, S.; Arranz, M. E.; Aran, V. J. *J. Heterocyclic Chem.* **2005**, *42*, 763.

[15] Regnier, G.; Canevari, R.; Le Douarec, J. C.; Laubie, M. *Chimica Therapeutica* **1972**, *7*, 192.

[16] Campbell, S. F.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 1794.

[17a] Goldberg, H. L.; Finnerty, R. J. *Am. J. Psychiatry* **1979**, *136*, 1184. [b] Rickels, K. *J. Clinical Psychiatry* **1981**, *42*, 40. [c] Gammans, R. E.; Mayol, R. F.; LaBudde, J. A.; Gasten, G. P. *Federation Proc.* **1982**, *41*, 1335, abstract no. 6223. [d] Riblet, L. A.; Taylor, D. P.; Eison, M. S.; Stanton, H. C. *J. Clinical Psychiatry* **1982**, *43*, 11. [e] Newton, R. E.; Casten, G. P.; Alms, D. R.; Benes, C. O.; Marunycz, J. D. *J. Clinical Psychiatry* **1982**, *43*, 100. [f] Feighner, J. P.; Meredith, C. H.; Hendrickson, G. A. *J. Clinical Psychiatry* **1982**, *43*, 103. [g] Caccia, S.; Conti,I.; Vigano, G.; Garattini, S. *Pharmacology* **1986**, *33*, 46. [h] Schweizer, E. E.; Amsterdam, J.; Rickels, K.; Kaplan, M.; Droba, M. *Psychopharmacology Bulletin* **1986**, *22*, 183. [i] Gammans, R. E.; Mayol, R. F.; LaBudde, J. A. *The American Journal of Medicine* **1986**, *80* (suppl.3B), 41. [j] Dischino, D. D.; Covington, R. R.; Combs, C. M.; Gammans, R. E. *J. Labelled Compounds and Pharmaceuticals* **1987**, *25*, 359. [k] Amsterdam, J. D.; Berwish, N.; Potter, L.; Rickels, K. *Current Therapeutic Research* **1987**, *41*, 185. [l] Bianchi, G.; Caccia, S.; Della Vedova, F.; Garattini, S. *Eur. J. Pharmacol.* **1988**, *151*, 365. [m] Cott, J. M.; Kurtz, N. M.; Robinson, D. S.; Lancaster, S. P.; Copp, J. E. *Psychopharmacology Bull.* **1988**, *24*, 164. [n] Jajoo, H. K.; Mayol, R. F.; LaBudde, J. A.; Blair, I. A. *Drug Metabolism and Disposition* **1989**, *17*, 634. [o] Taylor, D. P. *Ann. NY Academy of Sciences* **1990**, *600*, 545. [p] Rausch, J. L.; Ruegg, R.; Moeller, F. G. *Psychopharmacology Bull.* **1990**, *26*, 169. [q] Heller, A. H.; Beneke, M.; Kuemmel, B.; Spencer, D.; Kurtz, N. M. *Psychopharmacology Bull.* **1990**, *26*, 219. [r] Robinson, D. S.; Rickels, K.; Feighner, J.; Fabre Jr, L. F.; Gammans, R. E.; Shrotriya, R. C.; Alms, D. R.; Andary, J. J.; Messina, M. E. *J. Clinical Psychopharmacology* **1990**, *10* (3 suppl.), 67S-76S. [s] Jenkins, S. W.; Robinson, D. S.; Fabre Jr, L. F.; Andary, J. J.; Messina, M. E.; Reich, L. A. *J. Clinical Psychopharmacology* **1990**, *10* (3 suppl.), 77S-85S. [t] Rickels, K.; Amsterdam, J. D.; Clary, C.; Puzzuoli, G.; Schweizer, E. E. *J. Clin. Psychiatry* **1991**, *52*, 34. [u] Pinder, R. M.; Weiringa, J. H. *Medical Research Reviews* **1993**, *13*, 259. [v] Kerns, E. H.; Volk, K. J.; Hail, M. E.; Whitney, J. L.; Rourick, R. A.; Klohr, S. E.; Leel, M. S. Paper originally presented at The 1996 International Symposia on Laboratory Atomation and Robotics (ISLAR 96). [w] Barradell, L. B.; Fitton, A. *CNS Drugs* **1996**, *5*, 147. [x] Fulton, B.; Brogden, R. N. *CNS Drugs* **1997**, *7*, 68.

[18] Pinder, R. M. *Psychopharmacology: Recent Advances and Future Prospects* **1986**, pp. 44-62.

[19] Thurkauf, A.; Yuan, J.; Chen, X.; He, X. S.; Wasley, J. W. F.; Hutchinson, A.; Woodruff, K. H.; Meade, R.; Hoffman, D. C.; Donovan, H.; Jones-Hertzog, D. K. *J. Med. Chem.* **1997**, *40*. 1.

[20] Tallman, J. F.; Primos, R. J.; Brodbeck, R.; Cornfield, L.; Meade, R.; Woodruff, K.; Ross, P.; Thurkauf, A.; Gallagher, J. *J. of Pharmacology and Experimental Therapeutics* **1997**, *282*, 1011.

[21] Schaus, J. M.; Bymaster, F. B. *Annual Reports in Medicinal Chemistry* **1998**, *33*, 1.

[22] We had prepared **4** earlier. The preparation of **4** is described in the paper by I. Becker *J. Heterocyclic Chem.* **2005**, *42*, 1289. The same preparative details are given in this paper.

[23] I. Becker, PhD Dissertation, Temple University, Phila., PA, 1961, pp 105-107. Our experimental procedure was patterned after that described by Whitmore, F. C.; Mosher, H. S.; Adams, R. R.; Taylor, R. B.; Chapin, E. C.; Weisel, C.; Yanko, W. *J. Am. Chem. Soc.* **1944**, *66*, 725 and after procedures given by Bruson, H. A. *Cyanoethylation* in *Organic Reactions* Adams, R., ed., John Wiley and Sons, Inc, NY, 1949, Vol. 5, pages 109ff.

[24] The structure of **29** was confirmed by a positive Beilstein test (Cl present), by CHN analyses, by an ir spectrum that indicated the presence of an aliphatic C≡N group in the molecule, and by a ^{1}H nmr spectrum.

[25] Baker, B. R.; Tanna, P. M. *J. Org. Chem.* **1965**, *30*, 2857.

[26] Rosemeyer, H.; Seela, F. *Heterocycles* **1985**, *23*, 2669.

[27] The preparation of **24** had been reported earlier by Regnier, G.; Canevari, R.; LeDouarec, J-C.; Laubie, M. *Chimie Therapeutique* **1972**, *7*, 192. But specific experimental details for the preparation of **24** are not given in this paper. Instead, details are given for the preparation of a compound of analogous structure. Apparently, then, they prepared **24** by refluxing a mixture of 1-(2-pyrimidinyl)piperazine and 6-chloropurine (2:1 mol ratio) in dimethylformamide (normal bp 153°) for 7 h. Their product, recrystallized from dimethylformamide, had mp greater than 350°. They give no spectral data for their product.

Our preparation of **24** differed significantly from that of Regnier and coworkers. In our preparation a mixture of 6.05 g (0.0369 mol) of 1-(2-pyrimidinyl)piperazine and 1.90 g (0.0123 mol) of 6-chloropurine (3:1 mol ratio of amine to 6-chloropurine) was heated on the steam bath for 3.5 h, let stand for 67 h, heated on the steam bath for 4 h more, and let stand for 45 h. Our crude product gave a negative Beilstein test (no Cl). It was recrystallized from the solvent pair of 95% ethanol and water. Our once recrystallized product gave an acceptable CHN analysis, and gave a ^{1}H nmr spectrum that confirmed its structure.

[28] Our product **26**, prepared by cyanoethylation of **24**, gave an acceptable CHN analysis, gave an ir spectrum that indicated the presence of an aliphatic C≡N group in the molecule, and gave a ^{1}H nmr spectrum that confirmed its structure.

[29] SciFinder lists no references for either **27** or **28** but does list five commercial sources for **27** and one commercial source for **28**.