Preparation of Pyrimidine Derivatives as Potential Medicinal Agents by the Reaction of 2-Amino-4-chloro-6-methylpyrimidine with Primary and Secondary Amines

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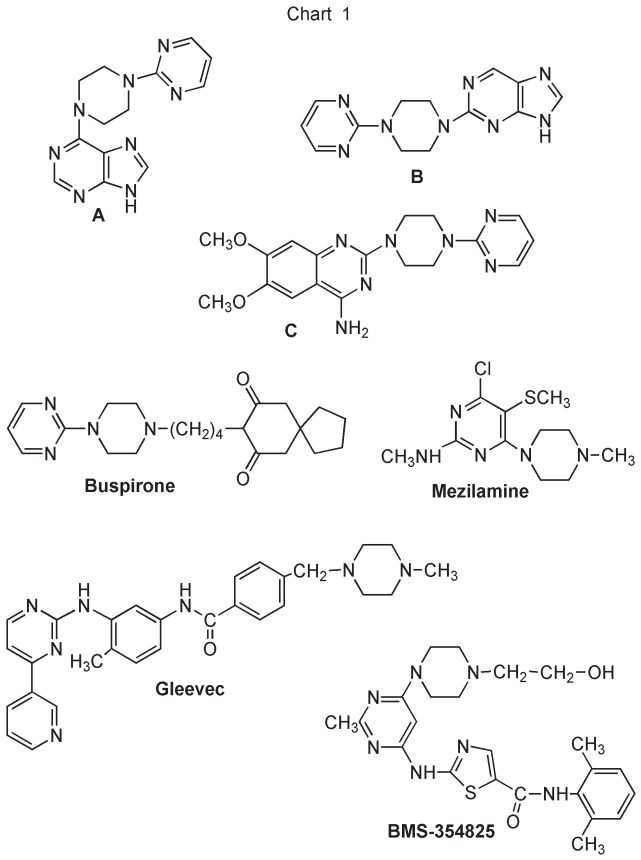
Received February 14, 2005

Thirteen derivatives of pyrimidine were prepared as potential medicinal agents by the reaction of 2-amino-4-chloro-6-methylpyrimidine with primary and secondary amines in the absence of a solvent. Six of the derivatives are piperazinylpyrimidines. The compounds prepared in this work may prove to be efficacious in the treatment of inflammation, hypertension, anxiety, depression, or cancer.

J. Heterocyclic Chem., **42**, 1289 (2005).

Several biologically active agents are given in Chart 1. The 1,4-disubstituted piperazines **A** and **B** have exhibited antiinflammatory, adrenolytic, and central nervous system depressant activity [1]. The piperazinylpyrimidine **C** has displayed excellent long lasting efficacy as an antihypertensive agent [2]. The corresponding 4-pyrimidinyl isomer, interestingly enough, was much less effective than **C**.

Chart 1

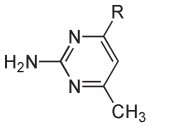


Mezilamine, a dopamine antagonist, apparently has not been evaluated as an antidepressant in humans [3]. Buspirone is used for the treatment of general anxiety disorders and depression [4]. Its mode of action is not known. It may act by reducing serotonin in the brain. Gleevec, a useful anticancer agent, inhibits the progress of chronic myeloid leukemia. The Bristol-Myers Squibb compound BMS-354825 overcomes resistance of Gleevec-resistant mutants in tissue culture and in mice [5]. BMS-354825 currently is undergoing Phase I clinical trials [5].

Six of the compounds prepared in this work (see Table 1, compounds **2** through **7**) are 1,4-disubstituted piperazines in which one of the nitrogen atoms of piperazine is bonded directly to carbon-4 (or carbon-6) of the pyrimidine ring. These six piperazinylpyrimidines have structural features similar to those present in the biologically active compounds given in Chart 1.

Table 1

2-Amino-4-methyl-6-substitutedpyrimidines



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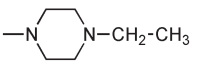
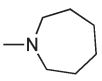
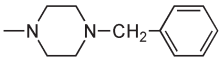
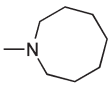
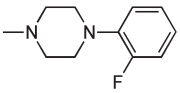
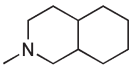
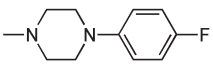
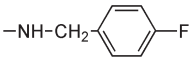
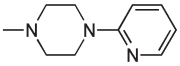
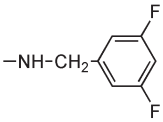
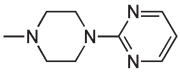
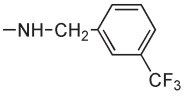
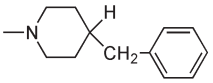
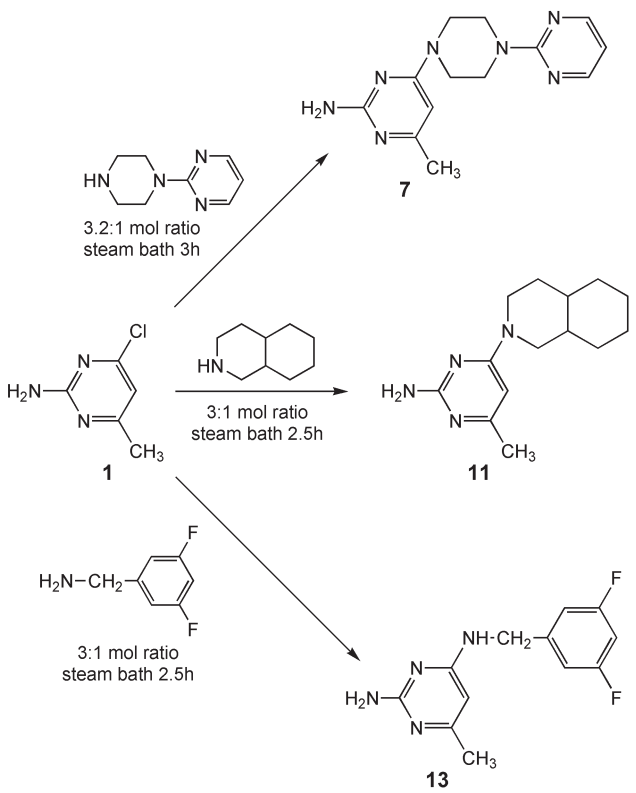
2		9	
3*		10	
4		11	
5		12	
6		13	
7		14	
8			

* See [6]

The compounds prepared in this work may prove to be efficacious in the treatment of inflammation, hypertension, anxiety, depression, or cancer. None of the compounds, however, have yet been tested for biological activity.

In this work we prepared thirteen derivatives of pyrimidine (see Table 1) by the reaction of 2-amino-4-chloro-6-methylpyrimidine (**1**) with primary and secondary amines in the absence of a solvent. In each reaction the nitrogen atom of the entering amine moiety became bonded directly to carbon-4 (or carbon-6) of the pyrimidine ring. The

Scheme 1



preparation of three of the compounds is illustrated in Scheme 1. In each reaction the 4-chlorine atom in the pyrimidine ring underwent nucleophilic substitution by a primary or secondary amine. Nucleophilic substitution of an active chlorine atom in the 2-, 4-, or 6-position of the pyrimidine ring by a primary or secondary amine is well-documented [7]. The kinetics and mechanism of this type of reaction have been studied in detail [8].

EXPERIMENTAL

The requisite 2-amino-4-chloro-6-methylpyrimidine (**1**) was prepared in two steps. Condensation of guanidine carbonate with ethyl acetoacetate in refluxing ethanol gave 2-amino-4-hydroxy-6-methylpyrimidine [9]. This 4-hydroxy compound was converted to the corresponding 4-chloro compound by refluxing the 4-hydroxy compound with an excess of phosphorus oxychloride [10,11]. Amines were purchased from Sigma Aldrich except as noted.

The general preparative procedure involved heating 2-amino-4-chloro-6-methylpyrimidine (**1**) with the amine on the steam bath for 1-3.5 h. No solvent was used. The mole ratio of amine to chloropyrimidine was 3:1. After heating the reactants, water was added. Solids were broken up and mixed with the water. Solids were collected by vacuum filtration, washed with water, and dried. The product so obtained was analyzed or, more typically, was recrystallized from the solvent pair of 95% ethanol and water and then analyzed. Compounds were dried by heating them in the air oven or by letting them stand in the desiccator over Drierite at room temperature in the dark or by both methods.

Melting points were determined on a Thomas-Hoover Unimelt apparatus. CHN analyses were determined by Schwarzkopf Microanalytical Laboratory Inc, 56-19 37th Avenue, Woodside, NY 11377. Three of the ^{1}H nmr spectra were determined by Professor Walter Boyko, Director of NMR Services at Villanova University. The other ^{1}H nmr spectra were determined by Spectral Data Services Inc, 818 Pioneer Street, Champaign, IL 61820.

4-(4-Ethylpiperazin-1-yl)-6-methylpyrimidin-2-amine (**2**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-181°) and 2.64 mL of 98% pure 1-ethylpiperazine (d 0.899), equivalent to 2.37 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 3.5 h. The mixture of dark red brown clear liquid and a small button of solid was let stand for nearly 7 days during which time the contents formed a mixture of white, tan, and brown solids. The solids were broken up and mixed well with 3x5 mL of water whereupon virtually all of the solid dissolved. Even so, the mixture was passed through a Hirsch funnel. The mini amount of solid that was collected on the funnel was washed with 5 mL water whereupon virtually all of this solid dissolved. The combined clear dark orange filtrate (20 mL) was let stand for nearly 4 days during which time fine white crystals separated. The dark orange liquid (Liquid A) above these crystals was decanted from the crystals into an evaporating dish. The damp crystals were collected, using 6x1 mL water to complete the transfer, washed with 2x2 mL water, sucked with the vacuum for 23 min, and dried at 62-63° for 3 h, white crystals, 0.204 g (13.3%), mp 112.5-117°, negative Beilstein test (no Cl). Prior to analysis this sample was let stand over Drierite for 68 h. ^{1}H nmr ($CDCl_3$): δ 1.12 (t, 3H, CH_3, ethyl), 2.21 (s, 3H, 6-CH_3, pyrimidine), 2.43 (q, 2H, CH_2, ethyl), 2.47 (ct, 4H, piperazine closest to ethyl), 3.60 (ct, 4H, piperazine closest to pyrimidine), 4.71 (bs, 2H, 2-NH_2, pyrimidine), 5.83 (s, 1H, 5-H, pyrimidine).

Anal. Calcd. for $C_{11}H_{19}N_5$: C, 59.70; H, 8.65; N, 31.65. Found: C, 60.10; H, 8.89; N, 31.66.

Liquid A was concentrated on the steam bath to 6 mL. The dark orange concentrate was cooled in ice for 84 min, let stand for nearly 7 days, and seeded with the first crop of white crystals described above. The mixture was vigorously stirred whereupon solid separated. This mixture was cooled in ice for 30 min. The solid was collected, using 2x1 mL and 1.5 mL water to complete the transfer, washed with 5 mL and 3 mL water, sucked with the vacuum for 23 min, and dried at 62° for 2 h, pure white solid,

0.337 g (22.0%), mp 112-113.5° after softening at 111-112°, negative Beilstein test (no Cl). For analysis this sample was let stand over Drierite for 67 h.

Anal. Calcd. for $C_{11}H_{19}N_5$: C, 59.70; H, 8.65; N, 31.65. Found: C, 59.89; H, 8.61; N, 31.64.

4-(4-Benzylpiperazin-1-yl)-6-methylpyrimidin-2-amine (**3**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-181°) and 3.62 mL of 98% pure 1-benzylpiperazine (Avocado Chemical Co., d 1.01), equivalent to 3.59 g (0.0204 mol) of 100% pure amine, was heated on the steam bath for 1 h and let stand overnight. To the mixture of orange mush and hard dark orange glass, 3.5 mL water were added. The mixture was heated briefly on the steam bath. The glass was broken up as much as possible. The solid was collected. This procedure was repeated with 3 mL and 2x3.5 mL water. The combined solid was washed with 2x6.5 mL water and sucked with the vacuum for 28 min, off white solid (Solid A), melted completely by 140°, negative Beilstein test (no Cl). This solid was let stand over Drierite for 3 days, 0.923 g (47.1%).

Solid A was recrystallized (charcoal) from the solvent pair of 95% ethanol and water, letting the final mixture stand for 3 days. The solid was collected, using 3x2.5 mL water to complete the transfer, washed with 2x3 mL water, and sucked with the vacuum for 138 min, off white solid (Solid B), 0.611 g (31.2%). After standing over Drierite overnight, Solid B had mp 138-141°.

Solid B was recrystallized from the solvent pair of 95% ethanol (4 mL) and water, letting the final mixture cool in ice for 38 min. The solid was collected, using 4x3 mL water to complete the transfer, washed with 2x7 mL water, sucked with the vaccum for 18 min, dried at 73-78° for 2 h, and let stand over Drierite for 45 h, off white solid (Solid C), 0.357 g (18.2%), mp 138-141°. ^{1}H nmr ($CDCl_3$): δ 2.20 (s, 3H, 4-CH_3, pyrimidine), 2.44 (ct, 4H, piperazine, closest to benzyl group), 3.52 (s, 2H, benzyl CH_2), 3.58 (ct, 4H, piperazine, closest to pyrimidine ring), 4.77 (bs, 2H, 2-NH_2, pyrimidine), 5.80 (s, 1H, 5-H, pyrimidine), 7.25-7.40 (m, 5H, benzene).

Anal. Calcd. for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71. Found: C, 67.34; H, 7.43; N, 24.70.

The combined filtrate from Solid A, consisting of pale yellow liquid and white solid, was let stand for 3 days. The solid was collected, using 2x1.5 mL water to complete the transfer, washed with 2x10 mL water, and sucked with the vacuum for 20 min, pale yellow solid (Solid D), 0.661 g (33.7%), mp 138-142°, negative Beilstein test (no Cl).

Solid D was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture stand for 15 min and cool in ice for 20 min. The solid was collected, using 2x3 mL water to complete the transfer, washed with 2x7 mL water, and sucked with the vaccum for 25 min, pale yellow solid (Solid E), 0.452 g (23.1%), mp 140-143°. Solid E was more yellowish than Solid D.

Solid E was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture cool in ice for 36 min. The solid was collected, using 2x3 mL water to complete the transfer, washed with 2 mL and 3.5 mL water, and sucked with the vacuum for 15 min, off white solid (Solid F), 32 mg (1.6%). Solid F was let stand over Drierite for 22 h, dried at 70-71° for 162 min, and let stand over Drierite for 19 h more, mp 139.5-142°.

Anal. Calcd. for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71. Found: C, 68.15; H, 7.65; N, 24.78.

After Solid F was collected, a pale yellow oil remained in the crystallization beaker. This oil solidified upon standing, forming a crusty pale yellow solid (Solid G), 0.179 g (9.1%), mp 140-142°. Solid G was dried at 69° for 1 h and then analyzed.

Anal. Calcd. for $C_{16}H_{21}N_5 \cdot {}^1/_4H_2O$: C, 66.75; H, 7.53; N, 24.33. Found: C, 66.50; H, 7.45; N, 24.07.

4-[4-(2-Fluorophenyl)piperazin-1-yl]-6-methylpyrimidin-2-amine (**4**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-178.5°) and 3.39 mL of 97% pure 1-(2-fluorophenyl)piperazine (d 1.14), equivalent to 3.74 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 1.5 h. The mixture was cooled in ice for 12 min. The mixture, consisting of semisolid and hard pale yellow glass, was treated with 3 mL and 5x5 mL water, with brief heating on the steam bath. The glass was scraped to dislodge solid. Solid was collected after each treatment with water. The combined solid was washed with 2x10 mL water, sucked with the vacuum for 10 min, and let stand over Drierite for 47 h, white solid (Solid A), 1.40 g (70.4%), mp 143-147° after softening and shrinking, negative Beilstein test (no Cl). Solid A was dried at 66-75° for 82 min, 1.37 g (68.8%).

The combined filtrate from Solid A, consisting of pale yellow liquid and white solid, was mixed with 10 mL water. The mixture was let stand for 47 h. The solid was collected, using 2x3 mL water to complete the transfer, washed with 2x7 mL water, sucked with the vacuum for 15 min, and dried at 66-68° for 22 min, off white solid (Solid B), 0.344 g (17.2%), mp 144-148° after some softening, negative Beilstein test (no Cl).

Solid A was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture cool in ice for 41 min. The solid was collected, using 2x4 mL water to complete the transfer, washed with 2x7 mL water, sucked with the vacuum for 12 min, let stand over Drierite for 70 h, and dried at 65-70° for 1 h, off white solid (Solid C), blunt end transparent needles (x100), 1.02 g (51.3%), mp 146-148.5°. ^{1}H nmr ($CDCl_3$): δ 2.23 (s, 3H, 6-CH_3, pyrimidine), 3.10 (ct, 4H, piperazine, closest to benzene), 3.73 (ct, 4H, piperazine, closest to pyrimidine), 4.73 (bs, 2H, 2-NH_2, pyrimidine), 5.90 (s, 1H, 5-H, pyrimidine), 6.90-7.10 (m, 4H, benzene).

Anal. Calcd. for $C_{15}H_{18}N_5F$: C, 62.70; H, 6.31; N, 24.37. Found: C, 62.82; H, 6.12; N, 24.38.

Solid B was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture cool in ice for 2.5 h. The solid was collected, using 3x2 mL water to complete the transfer, washed with 2x3 mL water, sucked with the vacuum for 10 min, let stand over Drierite for 44 h, and dried at 64-67° for 1.5 h, cream colored solid (Solid D), 0.237 g (11.9%), mp 145-147.5°.

Anal. Calcd. for $C_{15}H_{18}N_5F$: C, 62.70; H, 6.31; N, 24.37. Found: C, 62.89; H, 6.22; N, 24.23.

4-[4-(4-Fluorophenyl)piperazin-1-yl]-6-methylpyrimidin-2-amine (**5**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 178-181°) and 3.82 g of 98% pure 1-(4-fluorophenyl)piperazine (white solid, mp 30-33°, forming a colorless liquid upon warming on the steam bath), equivalent to 3.74 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 2 h. To the mixture of yellow brown semisolid and hard

white solid, 4x3 mL water was added with brief heating each time. The solid was broken up and collected along the way. The combined solid, still in the funnel, was dried at 62-63° for 19 h, yellowish hard solid (Solid A), 1.41 g, mp 189-192° after darkening, sintering, and shrinking, weak positive Beilstein test (some Cl present).

Solid A was recrystallized from the solvent pair of 95% ethanol (6 mL) and water (6 mL). Much solid did not dissolve in the boiling 95% ethanol. This insoluble solid was discarded. The final mixture was let stand for 28 min and cooled in ice for 37 min. The solid was collected, using 2.5 mL and 1.5 mL water to complete the transfer, washed with 2x2 mL water, sucked with the vacuum for 11 min, and dried a 62° for 2 h, pale yellow crystalline solid (Solid B), 67 mg (3.4%), mp 192-194.5° after softening and darkening at 189.5-192°, negative Beilstein test (no Cl). Just before analysis Solid B was let stand over Drierite for 18.5 h.

Anal. Calcd. for $C_{15}H_{18}N_5F$: C, 62.70; H, 6.31; N, 24.37. Found: C, 62.47; H, 6.43; N, 24.24.

The combined filtrate from Solid A, consisting of pale orange liquid and fine white solid, was let stand for 24 h. The solid was collected, using 2 mL and 1 mL water to complete the transfer, washed with 2x3 mL water, sucked with the vacuum for 10 min, and dried at 62-63° for 21 h, cream colored solid (Solid C), 157 mg (7.9%), mp 189-193.5° after shrinking and darkening, negative Beilstein test (no Cl).

Solid C was recrystallized from the solvent pair of 95% ethanol (5 mL) and enough hot water to reach the cloud point. The final mixture was let stand for 3 min and cooled in ice for 22 min. The solid was collected, using 3x1 mL water to complete the transfer, washed with 3x2 mL water, sucked with the vacuum for 15 min, and dried at 60-76° for 2 h, pale yellow crystalline solid, 49 mg (2.5%), mp 194-196° after softening at 191-194°. ^{1}H nmr ($CDCl_3$): δ 2.24 (s, 3H, 6-CH_3, pyrimidine), 3.12-3.15 (ct, 4H, piperazine), 3.72-3.75 (ct, 4H, piperazine), 4.69 (bs, 2H, 2-NH_2, pyrimidine), 5.88 (s, 1H, 5-H, pyrimidine), 6.89-6.92 (cm, 2H meta to F, phenyl), 6.92-7.01 (cm, 2H ortho to F, phenyl).

Anal. Calcd. for $C_{15}H_{18}N_5F$: C, 62.70; H, 6.31; N, 24.37. Found: C, 62.88; H, 6.26; N, 24.35.

4-Methyl-6-(4-pyridin-2-ylpiperazin-1-yl)pyrimidin-2-amine (**6**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 178-181°) and 3.16 mL of 98% pure 1-(2-pyridinyl)piperazine (d 1.072), equivalent to 3.39 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 2.5 h. The mixture of tan, yellow, white, and brown solids was let stand for 70 h. This mixture, containing hard solid, was mixed well with 7 mL of water. Solid was collected. The remaining solid was mixed with five small portions of water (13 mL total), collecting solid after each treatment with water. A small amount of solid could not be dislodged from the flask. The combined solid was washed with 6 mL water, sucked with the vacuum for 13 min, and dried at 62-63° for 1 h, cream colored solid, 1.31 g (70.1%). This product was let stand over Drierite for 46 h, mp 161-172° after softening and shrinking, negative Beilstein test (no Cl).

This product was recrystallized from the solvent pair of 95% ethanol (7 mL) and water. The filter paper was rinsed with additional hot 95% ethanol to dissolve solid. Yet, substantial solid settled out on the filter paper. This solid was discarded. The final mixture was let stand for 16 min, cooled in ice for 64 min, stirred rapidly, and cooled in ice for 12 min more. The solid was collected, using 2x2.5 mL water to complete the transfer, washed with 2x3 mL water, sucked with the vacuum for 8 min, and dried at 63-64° for 2 h, pale yellow solid (Solid A), 0.328 g (17.5%). Solid A was let stand over Drierite for 211 h, mp 173-174.5° after softening at 171.5-173°, negative Beilstein test (no Cl). ^{1}H nmr ($CDCl_3$): δ 2.23 (s, 3H, 4-CH_3, pyrimidine), 3.61-3.64 and 3.71-3.73 (each ct, 8H, piperazine), 4.86 (bs, 2H, 2-NH_2, pyrimidine), 5.86 (s, 1H, 5-H, pyrimidine), 6.64-6.66 (cm, 2H, 2x β-H, pyridine), 7.48-7.52 (td, 1H, γ-H, pyridine), 8.20-8.22 (dd, 1H, α-H, pyridine).

Anal. Calcd. for $C_{14}H_{18}N_6$: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.34; H, 6.82; N, 31.02.

The combined filtrate from Solid A was let stand for 9 days. The solid was collected, using 2x1 mL water to complete the transfer, washed with 1.5 mL water, sucked with the vacuum for 15 min, dried at 62° for 1 h, and let stand over Drierite for 67.5 h, pale yellow solid, 37 mg (2.0%), mp 168-172.5° after softening at 167-168°.

4-Methyl-6-(4-pyrimidin-2-ylpiperazin-1-yl)pyrimidin-2-amine (**7**).

A mixture of 1.00 g (0.00694 mol) 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 were added. The solids were broken up and collected, using 2 mL and 4 mL water to complete the transfer. The solids were transferred to a porcelain dish, pulverized, returned to a clean 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 2x1 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-(4-Benzylpiperidin-1-yl)-6-methylpyrimidin-2-amine (**8**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-178.5°) and 3.74 mL of 99% pure 4-benzylpiperidine (d 0.985), equivalent to 3.64 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 1.5 h. The

resulting mixture, consisting of yellow semisolid and hard orange red material, was mixed well with six small portions of water. Each time the hard solid was partially broken up and the liberated solid was collected. The combined solid was sucked with the vacuum for 20 min and let stand over Drierite for 68 h, mixture of yellow and orange solids (Solid A), 0.344 g, mp 104-117°, strong positive Beilstein test (Cl present).

The filtrate from Solid A, consisting of yellow oil and cloudy pale yellow liquid, was let stand for 69 h. The solid was collected, using 3x3.5 mL water to complete the transfer, washed with 7 mL and 9 mL water, sucked with the vacuum for 13 min, and dried at 53-56° for 88 min, 0.910 g, mp 98-115°. This solid was let stand over Drierite for 10 days, yellow solid (Solid B), 0.825 g, negative Beilstein test (no Cl).

Solid B was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture cool in ice for 1.5 h. The solid was collected, using 4x2 mL water to complete the transfer, washed with 2x2 mL water, sucked with the vacuum for 10 min, dried at 58-62° for 1 h, let stand over Drierite for 69 h, and dried at 62° for 2.5 h more, pale yellow solid, 0.489 g (24.6%), mp 138-142.5°. ^{1}H nmr ($CDCl_3$): δ 1.20 (m, 2H, 2x β-H, piperidine), 1.69 (bd, , 2H, 2x β-H, piperidine), 1.78 (m, lone H, piperidine), 2.20 (s, 3H, 6-CH_3, pyrimidine), 2.55 (d, 2H, benzyl CH_2), 2.74 (m, 2H, 2x α-H, piperidine), 4.32 (bd, 2H, 2x α-H, piperidine), 4.63 (bs, 2H, 2-NH_2, pyrimidine), 5.82 (s, 1H, 5-H, pyrimidine), 7.13-7.31 (m, 5H, phenyl).

Anal. Calcd. for $C_{17}H_{22}N_4$: C, 72.31; H, 7.82; N, 19.84. Found: C, 72.44; H, 8.05; N, 19.81.

4-Azepan-1-yl-6-methylpyrimidin-2-amine (**9**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-178.5°) and 2.34 mL of 99% pure hexamethyleneimine (d 0.880), equivalent to 2.04 g (0.0206 mol) of 100% pure amine, was heated on the steam bath for 101 min and then let stand overnight. The white and pale yellow solids were mixed with several portions of water (total 30 mL). Solid was collected after each treatment with water. The combined solid was washed with 2x3 mL water and sucked with the vacuum for 2 h, off white crystalline solid (major crop), 0.611 g (42.7%), negative Beilstein test (no Cl), mp 107-109°. An unmeasured amount of hard pale yellow solid could not be dislodged from the bottom of the flask and hence was discarded.

To the combined filtrate from the major crop, 10 mL of water were added. The mixture was let stand at room temperature overnight and cooled in ice for 11 min. The solid was collected, using 2 mL water to complete the transfer, washed with 2x2 mL water, sucked with the vacuum for 85 min, off white crystalline solid (minor crop), 0.229 g (16.0%), mp 105-107°, negative Beilstein test (no Cl).

The major crop was recrystallized from the solvent pair of 95% ethanol (20 mL) and water (20 mL), letting the final mixture stand at room temperature for 7 days. The mixture, consisting of yellow oil and clear colorless liquid, was concentrated on the steam bath to 10 mL. The concentrate was cooled in ice for 10 min and let stand for 3 days. The crusty crystalline cream colored solid was collected, using four portions of water (total 15 mL) to complete the transfer, washed with 6 mL water, sucked with the vacuum (mp 107-108°), and let stand over Drierite for 2 days, 0.414 g (29.0%).

This solid was recrystallized from the solvent pair of 95% ethanol (2.5 mL) and water, letting the final mixture stand for 2 min and cool in ice for 23 min. The crusty off white solid was collected, using 3x2 mL water to complete the transfer, washed with 2x2 mL water, sucked with the vacuum for 15 min (0.10 g, 7.0%), and let stand over Drierite for 14 min, mp 107-109°. For analysis the solid was let stand over Drierite for 23 h and dried at 57-65° for 97 min. ^{1}H nmr ($CDCl_3$): δ 1.50-1.59 (cm, 4H, 4x γ-H, hexamethyleneimine), 1.75 (bs, 4H, 4x β-H, hexamethyleneimine), 2.20 (s, 3H, 6-CH_3, pyrimidine), 3.57 (bs, 4H, 4x α-H, hexamethyleneimine), 4.70 (bs, 2H, 2-NH_2, pyrimidine), 5.73 (s, 1H, 5-H, pyrimidine).

Anal. Calcd. for $C_{11}H_{18}N_4$: C, 64.05; H, 8.80; N, 27.16. Found: C, 64.20; H, 9.09; N, 27.09.

4-Azocan-1-yl-6-methylpyrimidin-2-amine (**10**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-178.5°) and 2.62 mL of 98% pure heptamethyleneimine (d 0.896), equivalent to 2.35 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 4 h and let stand for 46 h. Water (2 mL) was added and hard solids were broken up. The solid was collected, using 5x2 mL water to complete the transfer. Large pieces of solid in the funnel were pulverized in an agate mortar and returned to the funnel. The solid in the funnel was washed with 2 mL water, sucked with the vacuum for 12 min, and dried at 61-65° for 35 min, essentially cream colored solid, 0.265 g, positive Beilstein test (Cl present).

The combined filtrate from this solid, consisting of cloudy white and golden liquids, was let stand for 9 days, giving a mixture of yellow gum, yellow crystals, and colorless liquid. The colorless liquid was decanted off and discarded. The mixture of gum and crystals was let stand for 70 h. This mixture was mixed well with 10 mL water. The solid in this mixture was collected, using 2x5 mL water to complete the transfer, washed with 2x5 mL water, sucked with the vacuum for 15 min, let stand over Drierite for 70.5 h, and dried at 62-63° for 85 min, pale yellow solid, 0.627 g (41.0%), mp 106-110° after slight softening, negative Beilstein test (no Cl).

This product was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture stand for 17 days, during which time the yellow oil in the mixture did not solidify. The mixture then was cooled briefly in ice, vigorously stirred, and seeded with solid that formed on the stirring rod. The yellow oil was transformed into solid. The mixture was cooled in ice for 10 min. The solid was collected, using 3x1 mL water to complete the transfer, washed with 2 mL and 3 mL water, sucked with the vacuum for 12 min, dried at 63° for 103 min, and let stand over Drierite for 45 h, pale yellow solid, 0.308 g (20.1%), mp 102-111.5°. ^{1}H nmr ($CDCl_3$): δ 1.47-1.57 and 1.71-1.77 (each cm, 4xβ-H, 4xγ-H, and 2xδ-H, heptamethyleneimine), 2.20 (s, 3H, 6-CH_3, pyrimidine), 3.53 (bs, 4H, 4xα-H, heptamethyleneimine), 4.79 (bs, 2H, 2-NH_2, pyrimidine), 5.71 (s, 1H, 5-H, pyrimidine).

Anal. Calcd. for $C_{12}H_{20}N_4$: C, 65.42; H, 9.15; N, 25.43. Found: C, 66.00, 65.97; H, 9.11, 9.55; N, 25.26, 25.01.

4-Methyl-6-[octahydroisoquinolin-2(1H)-yl]pyrimidin-2-amine (**11**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 178-181°) and 3.22 mL of 96% pure perhydroisoquinoline (mixture of *cis* and *trans* isomers, d 0.936), equivalent to 2.89 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 2.5 h and then let stand for 44.5 h. The mixture of tan and brown solids and hard yellow brown glass was

broken up and treated with 2x2 mL and 4 mL water with brief warming, collecting solid after each treatment with water. Then 2x4 mL water were used to complete the transfer. The solid was washed with 4.5 mL water, sucked with the vacuum for 25 min, and dried at 62° for 2 h, essentially all pale yellow solid, 0.735 g, mp 105-113°, weak positive Beilstein test (some Cl present).

This product was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture stand for 8 min. The mixture, consisting of orange oil (2 mL) and cloudy white liquid (5 mL), was cooled in ice for 78 min and then vigorously stirred, whereupon the oil solidified. The mixture was cooled in ice for 14 min. The solid was collected, using 2x2 mL and 1 mL water to complete the transfer, sucked with the vacuum for 14 min, and dried at 63° for 102 min, pale yellow solid, 0.436 g (25.5%), mp 117-120.5°, negative Beilstein test (no Cl). Prior to analysis this solid was let stand over Drierite for 67 h and dried at 62-63° for 33 min. ^{1}H nmr ($CDCl_3$): δ 1.23-1.91 (12H, octahydroisoquinoline, but not the 4x α-H), 2.19 (s, 3H, 4-CH_3, pyrimidine), [3.09-3.18 (bt), 3.19-3.22 (dd), 3.79-3.83 (dd), and 4.05 (bd): all pertain to the 4x α-H of octahydroisoquinoline], 4.74 (bs, 2H, 2-NH_2, pyrimidine), 5.8l (s, 1H, 5-H, pyrimidine).

Anal. Calcd. for $C_{14}H_{22}N_4$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.01; H, 9.27; N, 22.67.

N^4-(4-Fluorobenzyl)-6-methylpyrimidin-2,4-diamine (**12**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-178.5°) and 2.44 mL of 97% pure 4-fluorobenzylamine (d 1.10), equivalent to 2.60 g (0.0208 mol) of 100% pure amine was heated on the steam bath for 2 h, giving a tan mush. The solid was collected, using 2x2 mL and 2x3 mL water to complete the transfer, washed with 3.5 mL and 4 mL water, sucked with the vacuum for 5 min, let stand over Drierite for 20 h, and dried at 60-63° for 1 h, soft white needles (x100) (Solid A), 0.422 g, strong positive Beilstein test (Cl present).

The combined filtrate from Solid A, consisting of pale yellow oil and cloudy white liquid, was cooled in ice for 49 min. The solid that formed was collected, using 4x5 mL water to complete the transfer, washed with 2x7 mL water, sucked with the vacuum for 10 min, let stand over Drierite for 20 h, and dried at 60-63° for 1 h, soft white needles (x100) (Solid B), 0.492 g, mp 108-126°, negative Beilstein test (no Cl).

Solid B was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture cool in ice for 72 min. The solid was collected, washed with 2 mL and 3 mL water, sucked with the vacuum for 15 min, dried at 58-64° for 75 min, let stand over Drierite for 70 h, and dried at 60-61° for 1 h, soft white solid (Solid C), 36 mg (2.2%), mp 121-128°.

Anal. Calcd. for $C_{12}H_{13}N_4F$: C, 62.06; H, 5.64; N, 24.12. Found: C, 61.48; H, 5.71; N, 24.26.

What was left on the bottom of the crystallization beaker after Solid C was collected was a white and pale yellow crusty solid. This solid was broken up and collected, using 3x3 mL water to complete the transfer, washed with 2x5 mL water, sucked with the vacuum for 10 min, dried at 58-61° for 30 min, let stand over Drierite for 70 h, and dried at 60-61° for 1 h, light cream colored solid (Solid D), 0.243 g (15.1%), mp 122-127°.

Solid D was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture stand for 15 min and cool in ice for 49 min. The crusty solid was broken up, collected, using 1.5 mL and 2 mL water to complete the transfer, washed with 2 mL and 3 mL water, sucked with the vacuum for 10 min, dried at 61-62° for 16 h, let stand over Drierite for 20.5 h, and dried at 64-66° for 104 min, cream colored solid (Solid E), 0.107 g (6.6%), mp 126-129°. ^{1}H nmr ($CDCl_3$): δ 2.18 (s, 3H, 4-CH_3, pyrimidine), 4.46 (d, 2H, benzyl CH_2), 4.73 (bs, 2H, 2-NH_2, pyrimidine), 4.96 (bs, 1H, 4-NH, pyrimidine), 5.64 (s, 1H, 5-H, pyrimidine), 7.02 and 7.26 (each m, 4H, phenyl).

Anal. Calcd. for $C_{12}H_{13}N_4F$: C, 62.06; H, 5.64; N, 24.12. Found: C, 62.37; H, 5.49; N, 24.28.

N^4-(3,5-Difluorobenzyl)-6-methylpyrimidin-2,4-diamine (**13**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (soft silky white needles, mp 180°) and 2.55 mL of 96% pure 3,5-difluorobenzylamine (d 1.21), equivalent to 2.97 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 2.5 h and let stand for 18 min. The pale yellow solid and orange gel were mixed well with 2 mL water. The solid was broken up. The mixture was cooled in ice for 2 min. The solid was collected, using 6x2 mL water to complete the transfer, washed with 7 mL water, sucked with the vacuum for 30 min, and dried at 52° for 68 h, cream colored solid, 0.753 g (43.3%), mp 122.5-123.5°, negative Beilstein test (no Cl).

Anal. Calcd. for $C_{12}H_{12}N_4F_2$: C, 57.59; H, 4.83; N, 22.39. Found: C, 57.84; H, 4.65; N, 22.20.

This product was recrystallized from the solvent pair of 95% ethanol and water, letting the final mixture (8 mL) stand for 12 min. The mixture, consisting of orange oil and cloudy white liquid, was cooled in ice for 144 min whereupon the oil solidified. The white solid above crusty tan solid was collected first, using 5x1 mL water to complete the transfer. Then the tan solid was collected on the same funnel. The combined solid was washed with 2x6 mL water, sucked with the vacuum for 11 min, and dried at 52-56° for 45 h, light tan solid, 0.393 g (22.6%), mp 122-123°. ^{1}H nmr ($CDCl_3$): δ 2.13 (s, 3H, 6-CH_3, pyrimidine), 4.46 (d, 2H, benzyl CH_2), 5.25 (bs, 2H, 2-NH_2, pyrimidine), 5.59 (s, 1H, 5-H, pyrimidine), 5.75 (bs, 1H, 4-NH, pyrimidine), 6.65-6.69 (ct, 1H between the two F atoms, phenyl), 6.79-6.80 (d, 2H, phenyl).

Anal. Calcd. for $C_{12}H_{12}N_4F_2$: C, 57.59; H, 4.83; N, 22.39. Found: C, 58.10; H, 4.63; N, 22.32.

6-Methyl-N^4-[3-(trifluoromethyl)benzyl]pyrimidin-2,4-diamine (**14**).

A mixture of 1.00 g (0.00694 mol) of 2-amino-4-chloro-6-methylpyrimidine (mp 176.5-178.5°) and 3.04 mL of 98% pure 3-(trifluoromethyl)benzylamine (d 1.22), equivalent to 3.64 g (0.0208 mol) of 100% pure amine, was heated on the steam bath for 90 min, let stand for 43.5 h, and heated on the steam bath for 35 min more. The cool mixture was mixed with 6 mL water. The solid was collected, using 6x1 mL water to complete the transfer, washed with 2x2 mL water, sucked with the vacuum for 5 min, and dried at 66° for 2.5 h, off white solid, 0.178 g. This solid proved to be mostly unreacted 4-chloro compound.

The combined filtrate from this solid, consisting of cloudy white liquid and pale yellow oil, was cooled in ice for 1 h and let stand for 9 days. The lower layer of pale yellow oil was separated from the upper aqueous layer. The oil was concentrated by heating on the steam bath. The viscous concentrate was cooled in ice for 134 min, let stand for 7 days, and cooled in ice for 105 min. The concentrate now consisted of solid and yellow liquid. The solid was collected, using 4x1 mL water to complete the transfer, washed with 2x1 mL water, sucked with the vacuum for 10 min, and dried

at 65-68° for 141 min, sparkling white crusty crystals, 0.210 g (10.7%), mp 103-109°, negative Beilstein test (no Cl). Covalent F does not give a positive Beilstein test. Prior to analysis the sample was let stand over Drierite for 47 h. ^{1}H nmr ($CDCl_3$): δ 2.14 (s, 3H, 6-CH_3, pyrimidine), 4.54 (d, 2H, benzyl CH_2), 5.07 (bs, 2H, 2-NH_2, pyrimidine), 5.47 (bs, 1H, 4-NH, pyrimidine), 5.62 (s, 1H, 5-H, pyrimidine), 7.41-7.54 (m, 4H, phenyl).

Anal. Calcd. for $C_{13}H_{13}N_4F_3$: C, 55.32; H, 4.64; N, 19.85. Found: C, 55.54, 55.89; H, 4.58, 4.77; N, 19.81, 20.04.

Acknowledgement.

I thank Professor Walter Boyko, Director of NMR Services at Villanova University, for the determination of three of the ^{1}H nmr spectra and for his sagacious interpretation of most of the spectra. I thank Professor James Barnes for preparing the computer disk of the manuscript.

Dedication.

This paper is dedicated to the memory of my brother Milton Becker. In addition to being a deeply devoted husband, father, and grandfather, Milton was a superb modern impressionist artist.

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[6] Subsequent to our preparation of 4-(4-benzylpiperazin-1-yl)-6-methylpyrimidin-2-amine (**3**) carried out in 2003, we discovered that Badran and Youssef [7d,7e] had prepared **3** earlier. Badran and Youssef refluxed a mixture of 0.010 mol of 1-benzylpiperazine and 0.010 mol of 2-amino-4-chloro-6-methylpyrimidine in aqueous hydrochloric acid for 3 h. Their mol ratio of amine to the 4-chloropyrimidine was 1:1. The mp of their product was 60°. They give no yield of product. Our conditions of reaction differed from those of Badran and Youssef. We heated a mixture of 0.0204 mol of the amine and 0.00694 mol of the 4-chloropyrimidine on the steam bath for 1 h. The mol ratio of our reactants was 2.9:l. The mp of our analytically pure product was 139.5-142° which is markedly different from Badran and Youssef's mp of 60°. The ^{1}H nmr spectrum of our product confirmed its structure. Badran and Youssef give no spectral data.

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