Synthesis of Potential Antifilarial Agents 2 [1]. Methyl 2-Substituted Purine 8-Carbamates and Related Compounds

Siya Ram†, William Evans, Dean S. Wise, Jr. and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy, and
Department of Chemistry, The University of Michigan,
Ann Arbor, MI 48109-1065

John W. McCall+

Department of Parasitology, College of Veterinary Medicine, University of Georgia,
Athens, Ga 30602

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A series of methyl 2-substituted purine 8-carbamates was prepared and evaluated for antifilarial activity. These purines were synthesized as aza congeners of benzimidazole carbamates which have shown significant anthelmintic activity to determine the effect that this modification might have on anthelmintic activity. The compounds were tested against the filarial infection, *B. pahangi*, in jirds. None of the compounds prepared in this study demonstrated antifilarial activity.

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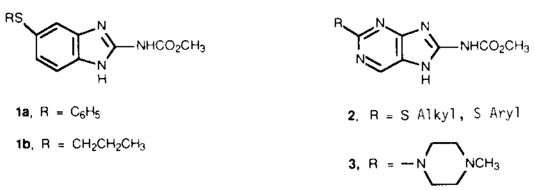
The design, synthesis and pharmacological evaluation of benzimidazole derivatives continues to be a major area of interest in the development of potential anthelmintics. In contrast, interest in purine congeners of the biologically active methyl benzimidazole carbamates as anthelmintics has been scant, even though some of the purine derivatives, which are found in the literature, have demonstrated anthelmintic activity [2,3]. No direct purine congeners of the more biologically active benzimidazole carbamates, such as fenbendazole (**1a**), or albendazole (**1b**), have been reported. In addition, to our knowledge, no purine derivatives have been evaluated for antifilarial activity. Albendazole, in addition to its general anthelmintic activity [4], has been shown to have activity against filarial infections [5]. This prompted us to prepare a series of methyl 2-substituted purine 8-carbamates having the general formulas **2** and **3**, for evaluation as potential antifilarial agents.



1a, R = C_6H_5

1b, R = $CH_2CH_2CH_3$

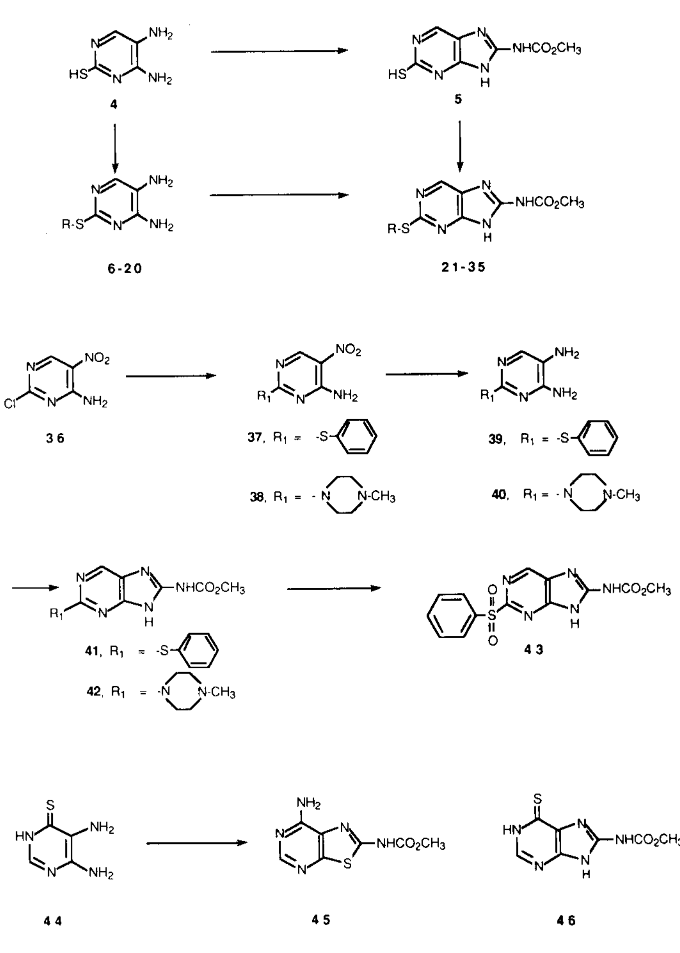
2, R = S Alkyl, S Aryl

3, R = (4-methylpiperazin-1-yl)

Chemistry.

Two approaches using 4,5-diamino-2-mercaptopyrimidine (**4**) [6,7,8] as our starting material were investigated in our effort to prepare the desired compounds. In the first method the diamine **4** was converted to methyl 2-mercaptopurine-8-carbamate (**5**) in a 42% yield by condensation with *N*-carbomethoxy-*S*-methylthiopseudourea. However, when compound **5** was subsequently treated with an alkyl halide or arylalkyl halide in *N,N'*-dimethylformamide in the presence of potassium carbonate at 50°, a complex mixture was obtained from which it was difficult to separate and purify the desired product. To circumvent this problem, an alternate approach for the synthesis of the target compounds was developed. This methodology involved the initial alkylation of the mercapto group of **4** with various alkyl or arylalkyl halides to afford the appropriately substituted 2-alkylthio or 2-arylalkylthio-4,5-di-

SCHEME -1



4, 5, 6-20, 21-35, 36, 37, R_1 = -S-Ph; 38, R_1 = 4-methylpiperazin-1-yl; 39, R_1 = -S-Ph; 40, R_1 = 4-methylpiperazin-1-yl; 41, R_1 = -S-Ph; 42, R_1 = 4-methylpiperazin-1-yl; 43; 44; 45; 46

aminopyrimidines. Subsequently these intermediates were cyclized to afford the purine ring system. Thus, 4,5-diamino-2-mercaptopyrimidine (**4**) was alkylated with one equivalent of the appropriate alkyl halide or arylalkyl halide in the presence of potassium carbonate in ethanol at reflux to give the compounds **6-20** in excellent to moderate yields. The product of the reaction was generally contaminated with approximately 2 to 4% of a dialkylated side product which was easily separated from the desired product by the use of column chromatography. To prepare 4,5-diamino-2-phenylthiopyrimidine (**39**), 4-amino-2-chloro-5-nitropyrimidine (**36**) was treated with benzenethiol in the presence of sodium ethoxide to furnish 4-amino-5-nitro-2-phenylthiopyrimidine (**37**). Chemical reduction of the nitro group of **37** with sodium dithionite under various conditions furnished only poor yields of **39**. However, catalytic hydrogenation of **37** with 5% palladium on carbon in methanol furnished **39** in 95% yield. 4,5-Diamino-2-(4-methylpiperazino)pyrimidine (**40**) was prepared by the initial treatment of **36** with 4-methylpiperazine to give 4-amino-2-(4-methylpiperazino)-5-nitropyrimidine (**38**). The subsequent reduction of **38** with hydrogen in the presence of 5% palladium on carbon gave **40** in 94% yield. The diamine **11**, which was prepared in a similar manner, was unstable and decomposed at room temperature, consequently it was used directly in the cyclization reaction without purification.

A condensation of the diamines **6-20**, **39** or **40** with *N*-carbomethoxy-*S*-methylthiopseudourea did not afford the desired purines [9]. However, a ring closure of the diamines **6-20**, **39** and **40** was accomplished in a one-pot reaction by the treatment of the diamine with methoxycar-

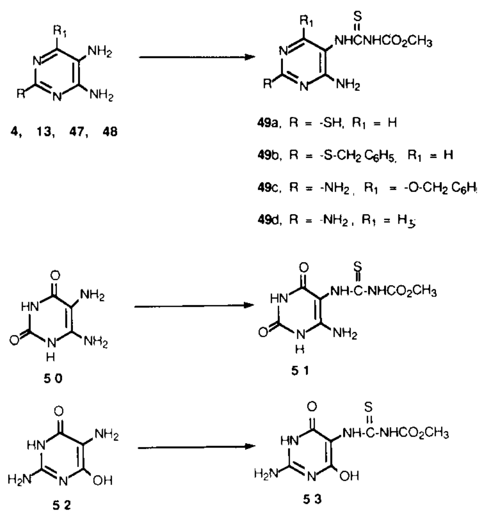
Table I

2-Alkylthio-4,5-diaminopyrimidines and Related Compounds

Compound No.	R	Yield [a] %	Mp, °C	Molecular Formula	Analysis % Calcd. (Found) C	H	N
6	$-CH_3$	58	157-161	$C_5H_8N_4S$	38.45 (38.58)	5.16 (5.11)	35.87 (35.62)
7	$-(CH_2)_2CH_3$ [b]	55	107-108	$C_7H_{12}N_4S$	45.63 (45.52)	6.57 (6.35)	30.41 (30.26)
8	$-(CH_2)_3CH_3$	81	88-89	$C_8H_{14}N_4S$	48.48 (48.25)	7.12 (7.34)	28.27 (28.58)
9 [c]	$-CH_2C\equiv N$	47	55	$C_6H_7N_5S$	---- (----)	---- (----)	---- (----)
10	$-CH_2C\equiv CH$	95	134-135	$C_7H_8N_4S$	46.65 (46.45)	4.47 (4.62)	31.09 (31.14)
11 [c]	$-CH_2CH=CHBr$	–	----	$C_7H_9BrN_4S$	---- (----)	---- (----)	---- (----)
12	$-CH_2C_3H_5$	87	114	$C_8H_{12}N_4S$	48.96 (48.96)	6.16 (6.16)	28.55 (28.55)
13	$-CH_2C_6H_5$	62	151	$C_{11}H_{12}N_4S$	56.87 (57.03)	5.21 (5.22)	24.12 (23.97)
14	$-CH_2C_6H_4$*p*-CF_3	53	153	$C_{12}H_{11}F_3N_4S$	48.00 (47.99)	3.69 (3.78)	18.66 (18.47)
15 [d]	$-CH_2C_6H_4$*p*-F	63	170-173	$C_{11}H_{11}FN_4S$	---- (----)	---- (----)	---- (----)
16	$-CH_2C_6H_4$*p*-Br	97	185-186	$C_{11}H_{11}BrN_4S$	42.45 (42.28)	3.56 (3.62)	18.00 (17.88)
17	$-CH_2C_6F_5$	76	129	$C_{11}H_7F_5N_4S$	41.00 (40.82)	2.16 (2.28)	17.39 (17.41)
18	$-CH_2COC_6H_5$	96	170-171	$C_{12}H_{12}N_4OS\cdot 0.5H_2O$	54.44 (54.65)	4.72 (4.69)	21.17 (21.26)
19	$-CH_2SC_6H_4$*p*-Cl	67	154-155	$C_{11}H_{11}ClN_4S_2$	44.21 (44.34)	3.71 (3.85)	18.75 (18.85)
20	$-(CH_2)_2OC_6H_5$	78	150-151	$C_{12}H_{14}N_4OS$	54.94 (54.84)	5.38 (5.54)	21.36 (21.15)

[a] Crystallized from ethanol, ether, hexane mixture. [b] Crystallized from ethanol. [c] Compound unstable at room temperature. [d] Crude material was used to prepare **30**.

SCHEME-2



bonyl isothiocyanate in the presence of dicyclohexylcarbodiimide (DCC) in acetonitrile [10]. Reaction of methyl 2-phenylthiopurine-8-carbamate (**41**) with 30% hydrogen peroxide in acetic acid afforded the sulfonyl derivative **43**.

Condensation of 4,5-diaminopyrimidin-6-thione (**44**) with *N*-carbomethoxy-*S*-methylthiopseudourea furnished methyl 7-aminothiazolo[5,4-*d*]pyrimidine-2-carbamate (**45**) in 26% yield instead of the desired 6-mercaptopurine derivative **46**. Treatment of the *o*-diaminopyrimidines **4, 13, 47, 48, 50** and **52** with one equivalent of methoxycarbonyl isothiocyanate in either acetonitrile or water in the absence of DCC afforded the mono-*N*-methoxycarbonylthiourea derivatives **49a-d, 51** and **53.**

Biological Activity.

All of the above purines and pyrimidines were evaluated in jirds (*Meriones ungericulatus malis*) for antifilarial activity against the adult worms of *Brugia pahangi* at a sub-

Table II

Methyl 2-Substituted Purine-8-carbamates

Compound No.	R	Yield [a] %	Mp, °C	Molecular Formula	Analysis % Calcd. (Found) C	H	N
21	$-CH_3$	29	254-258	$C_8H_9N_5O_2S \cdot HCl$	35.29 (35.00)	3.37 (3.64)	25.87 (25.52)
22	$-CH_2CH_2CH_3$	60	253-256	$C_{10}H_{13}N_5O_2S$	44.93 (44.87)	4.90 (4.97)	26.20 (26.21)
23	$-(CH_2)_3CH_3$	67	247-252	$C_{11}H_{15}N_5O_2S$	46.96 (47.07)	5.37 (5.35)	24.89 (25.04)
24	$-CH_2C \equiv N$	66	248-251	$C_9H_8N_6O_2S \cdot 0.5H_2O$	39.56 (39.74)	3.32 (3.16)	30.75 (30.88)
25	$-CH_2C \equiv CH$	62	228-229	$C_{10}H_9N_5O_2S$	45.62 (45.80)	3.45 (3.52)	26.60 (26.86)
26	$-CH_2CH=CHBr$	30	234-235	$C_{10}H_{10}BrN_5O_2S \cdot 1.5H_2O$	34.01 (34.17)	3.14 (3.14)	19.83 (19.86)
27	$-CH_2C_3H_5$	70	269-272	$C_{11}H_{13}N_5O_2S$	47.30 (47.24)	4.69 (4.77)	25.07 (24.94)
28	$-CH_2C_6H_5$	39	232-233	$C_{14}H_{13}N_5O_2S$	53.32 (53.14)	4.16 (4.22)	22.21 (22.16)
29	$-CH_2C_6H_4$*p*-CF_3	69	254-255	$C_{15}H_{12}F_3N_5O_2S$	47.00 (46.82)	3.16 (3.40)	18.27 (18.50)
30	$-CH_2C_6H_4$*p*-F	30	243-245	$C_{14}H_{12}FN_5O_2S \cdot H_2O$	48.43 (48.62)	3.96 (3.75)	20.18 (20.26)
31	$-CH_2C_6H_4$*p*-Br	37	251-252	$C_{14}H_{12}BrN_5O_2S \cdot H_2O$	40.79 (40.70)	3.42 (3.43)	16.99 (16.98)
32	$-CH_2C_6F_5$	57	255-256	$C_{14}H_8F_5N_5O_2S$	41.49 (41.79)	1.99 (2.14)	17.28 (17.46)
33	$-CH_2COC_6H_5$	58	239-240	$C_{15}H_{13}N_5O_3S$	52.47 (52.28)	3.82 (3.99)	20.40 (20.37)
34	$-CH_2SC_6H_4$*p*-Cl	65	244	$C_{14}H_{12}ClN_5O_2S_2$	44.04 (44.08)	3.17 (3.42)	18.34 (18.43)
35	$-(CH_2)_2OC_6H_5$	58	229	$C_{15}H_{15}N_5O_3S$	52.16 (52.28)	4.38 (4.50)	20.28 (20.40)

[a] Crystallized from methanol.

Table III

IR and ^{1}H NMR Parameters of Some 2-Alkylthio-4,5-diaminopyrimidines

Compound No.	IR (cm^{-1}) [a]	^{1}H NMR (δ, ppm) [b]
6	3330-3180	[c]: 2.34 (s, 3H, SCH_3), 4.03 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 6.30 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.56 (s, 1H, C_6-H)
7	3420, 3350-3280, 2960, 767	[d]: 1.08 (t, 3H, CH_3), 1.41-2.10 (m, 2H, $-CH_2$), 2.90 (t, 2H, $-SCH_2$), 3.05 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 5.32 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.86 (s, 1H, C_6-H)
8	3360-3300, 2960-2930, 2865, 758	[d]: 0.94 (t, 3H, CH_3), 1.17-2.20 (m, 4H, C-CH_2CH_2), 2.94 (t, 2H, SCH_2), 3.07 (bs, 2H, NH_2, exchangeable with deuterium oxide), 5.23 (bs, 2H, NH_2, exchangeable with deuterium oxide), 7.73 (s, 1H, C_6-H)
9	3440, 2930, 2250, 765	[d]: 3.92 (s, 2H, $-NH_2$), 4.10 (s, 2H, SCH_2), 6.07 (bs, 2H, $-NH_2$), 7.67 (s, 1H, C_6-H)
10	3358, 760	[e]: 2.07 (d, 1H, CH), 3.50 (s, 2H, $-SCH_2$), 3.77 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 5.67 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.40 (s, 1H, C_6-H)
12	3350-3320, 2920, 758	[f]: 0.14-0.77 (m, 4H, $-CH_2CH_2$), 1.13 (m, 1H, CH), 2.97 (d, 2H, $-CH_2$), 3.98 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 5.96 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.63 (s, 1H, C_6-H)
13	3360, 3300, 755, 700	[e]: 4.60 (s, 2H, NH_2, exchangeable with deuterium oxide), 4.68 (s, 2H, SCH_2), 6.67 (s, 2H, NH_2, exchangeable with deuterium oxide), 7.70 (s, 5H, Ar-H), 8.0 (s, 1H, C_6-H)
14	3350, 752, 660	[g]: 3.80 (bs, 2H, NH_2, exchangeable with deuterium oxide), 4.33 (s, 2H, SCH_2), 5.80 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.40-7.66 (m, 4H, Ar-H), 7.66 (s, 1H, C_6-H)
15	3440, 2920-2860, 752	[h]: 4.37 (d, 2H, SCH_2), 6.77-7.68 (m, 4H, Ar-H), 7.73 (s, 1H, C_6-H)
16	3300, 755, 660	[d]: 4.18 (s, 2H, SCH_2), 5.80 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.34 (s, 4H, Ar-H), 7.63 (s, 1H, C_6-H)
17	3400, 3350, 758	[d]: 3.38 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 4.53 (s, 2H, SCH_2), 6.53 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.55 (s, 1H, C_6-H)
18	3440-3418, 1678, 745, 680	[d]: 3.40 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 4.62 (bs, 2H, SCH_2), 6.53 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.10-8.57 (m, 6H, Ar-H and C_6-H)
19	3340-3330, 760, 657	[i]: 4.16 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 4.66 (s, 2H, SCH_2), 6.13 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 7.47 (s, 4H, Ar-H), 7.76 (s, 1H, C_6-H)
20	3490, 760-750, 690	[g]: 3.37 (t, 2H, SCH_2), 4.20 (t, 5H, CH_2, $-NH_2$, exchangeable with deuterium oxide), 6.04 (bs, 2H, $-NH_2$, exchangeable with deuterium oxide), 6.70-7.43 (m, 5H, Ar-H), 7.65 (s, 1H, C_6-H)

[a] Potassium bromide. [b] Signals (in parentheses) are expressed: s = singlet; d = doublet; t = triplet; m = multiplet; bs = broad singlet. [c] DMSO-d_6 + deuteriochloroform (1:2). [d] DMSO-d_6. [e] DMSO-d_6 + deuteriochloroform (1:1). [f] DMSO-d_6 + deuteriochloroform (1:4). [g] DMSO-d_6 + deuteriochloroform (1:5). [h] DMSO-d_6 + deuteriochloroform + deuterium oxide. [i] DMSO-d_6 + deuteriochloroform (2:1). [j] DMSO-d_6 + deuteriochloroform (1:3). [k] deuteriochloroform.

cutaneously administered dosage of 100 mg/kg x 5 days [11-12]. Unexpectedly, all of the compounds prepared in this study demonstrated little or no antifilarial activity at this dosage. This was surprising since both fenbendazole and albendazole have demonstrated a 100% reduction in adult worms of *B. pahangi* in jirds at a subcutaneously administered dosage of 50 mg/kg x 5 days [13]. Thus, it appears from this study that the substitution of a purine ring for the benzimidazole ring in methyl benzimidazole carbamates effects a marked negative influence on antifilarial activity.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 281 spectrophotometer and values are expressed in cm^{-1}. Proton nuclear magnetic resonance spectra were recorded on a Varian EM-360 spectrometer and chemical shift values are reported in parts per million on the δ-scale with tetramethylsilane as the internal reference. Column chromatography was performed on silica gel 60 F_{254} (70-230 mesh) using mixtures of chloroform, methanol and ethyl acetate as eluants. Analytical thin-layer chromatography was performed using glass plates coated with a 0.25 mm layer of silica gel GF_{254} (Analtech) using chloroform/methanol, (9:1) or (8:2), as the mobile phase. Compounds were detected by either visual examination under short or long-wave length UV light or by developement in an iodine atmosphere. Evaporation of solvents was carried out

Table IV

IR and ^{1}H NMR Parameters of Some Methyl 2-Substituted Purine-8-carbamates

Compound No.	IR (cm^{-1})	^{1}H NMR (δ, ppm) [b] [c]
21	2970-2960, 1720-1715	2.53 (s, 3H, SCH_3), 3.80 (s, 3H, $-OCH_3$), 8.60 (s, 1H, C_6-H)
22	2960, 2930-2750, 1710, 760	1.0 (t, 3H, $-CH_3$), 1.70 (m, 2H, $-CH_2$), 3.17 (s, 2H, CH_2), 3.80 (s, 3H, $-OCH_3$), 8.54 (s, 1H, C_6-H), 11.97 (bs, 1H, NH, exchangeable with deuterium oxide)
23	3250, 2960, 2930, 2860-2760, 1715, 755	0.9 (t, 3H, $-CH_3$), 1.20-2.0 (m, 4H, $-CH_2CH_2$), 3.14 (t, 2H, SCH_2), 3.80 (s, 3H, $-OCH_3$), 8.61 (s, 1H, C_6-H)
24	2223, 1718, 760	3.80 (s, 3H, $-OCH_3$, 4.23 (s, 2H, S-CH_2), 8.64 (s, 1H, C_6-H), 12.20 (bs, 1H, NH)
25	1720, 760	2.56 (s, 1H, C≡CH), 3.83 (s, 3H, $-OCH_3$), 4.04 (s, 2H, SCH_2), 8.73 (s, 1H, C_6-H), 12.20 (bs, 2H, NH)
26	1725, 760	3.80 (s, 3H, $-OCH_3$), 3.92 (s, 2H, S-CH_2), 6.56 (d, 2H, CH=CH), 8.57 (s, 1H, C_6-H)
27	3000-2600, 1712, 760	0.13-0.82 (m, 4H, CH_2CH_2), 1.17 (m, 1H, CH), 3.08 (d, 2H, SCH_2), 3.78 (s, 3H, $-OCH_3$), 8.53 (s, 1H, C_6-H)
28	2930, 1725, 760, 690	3.80 (s, 3H, $-OCH_3$), 4.40 (s, 2H, SCH_2), 6.83-7.70 (m, 5H, Ar-H), 8.57 (s, 1H, C_6-H), 11.90 (bs, 1H, NH, exchangeable with deuterium oxide)
29	1722, 760	3.78 (s, 3H, $-OCH_3$), 4.50 (s, 2H, SCH_2), 7.68 (s, 4H, Ar-H), 8.55 (s, 1H, C_6-H), 12.17 (bs, 1H, NH)
30	1725, 760	3.80 (s, 3H, $-OCH_3$), 4.43 (s, 2H, SCH_2), 6.83-7.90 (m, 4H, Ar-H), 8.62 (s, 1H, C_6-H), 12.0 (bs, 1H, NH)
31	1725, 760, 680	3.83 (s, 3H, $-OCH_3$), 4.42 (s, 2H, SCH_2), 7.40 (s, 4H, Ar-H), 8.40 (s, 1H, C_6-H), 12.00 (bs, 1H, NH)
32	1722, 760	3.80 (s, 3H, $-OCH_3$), 4.52 (s, 2H, SCH_2), 8.55 (s, 1H, C_6-H), 12.10 (bs, 1H, NH, exchangeable with deuterium oxide)
33	1725, 1680, 760, 680	3.80 (s, 3H, $-OCH_3$), 4.80 (s, 2H, SCH_2), 7.07-8.32 (m, 5H, Ar-H), 8.50 (s, H, C_6-H), 12.13 (bs, 1H, NH, exchangeable with deuterium oxide)
34	2900-2700, 1715, 760, 680	3.83 (s, 3H, $-OCH_3$), 4.80 (s, 2H, SCH_2), 7.44 (s, 4H, Ar-H), 8.60 (1H, C_6-H), 12.17 (bs, 1H, NH)
35	2940, 2760, 1720, 760-748, 685	3.40 (t, 2H, OCH_2), 3.79 (s, 3H, $-OCH_3$), 4.24 (t, 2H, SCH_2), 6.67-7.57 (m, 5H, Ar-H), 8.60 (s, 1H, C_6-H), 12.00 (bs, 1H, NH, exchangeable with deuterium oxide)

[a] Potassium Bromide. [b] Signals (in parentheses) are expressed: s = singlet; d = doublet; t = triplet; m = multiplet; bs = broad singlet. [c] DMSO-d_6.

under reduced pressure using a rotary evaporator and water aspirator. Microanalyses were performed by the M-H-W, Phoenix AZ.

Methyl 2-Mercaptopurine-8-carbamate (**5**).

A solution of 25% aqueous sodium hydroxide was added dropwise, to a stirred suspension of *S*-methylthiopseudourea sulfate (3.90 g, 0.14 mole) and methyl chloroformate (2.65 g, 0.028 mole) in water (5.0 ml) at 10-15°, until the *p*H of the reaction mixture reached 8.0. The *p*H of the above solution was then adjusted to 5.0 with glacial acetic acid. 4,5-Diamino-2-mercaptopyrimidine (**4**) (2.0 g, 0.014 mole) and water (40 ml) was added to the reaction mixture and the resulting mixture was stirred at 90° for 8 hours. The reaction was cooled to room temperature and the yellow precipitate which formed during the course of the reaction was collected by filtration. This solid (**5**) was purified by using a soxhlet extractor with water as the extraction solvent. The yellow colored solid was collected by filtration and dried *in vacuo* at 50°; yield 1.3 g (42%); mp >300°; ir (potassium bromide): 1750, 1140, 760 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.77 (s, 3H, $-OCH_3$), 7.90 (s, 1H, C_6-H), 12.27 (bs, 1H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_7H_7N_5O_2S$: C, 37.33; H, 3.13; N, 31.10. Found: C, 37.05; H, 3.30; N, 31.14.

General Procedure for the Synthesis of 2-Alkylthio-4,5-diaminopyrimidines **6-20**.

The appropriate alkyl halide or arylalkyl halide (0.011 mole) was added dropwise to an ice cold stirred suspension of 4,5-diamino-2-mercaptopyrimidine (0.01 mole) and potassium carbonate (0.0055 mole) in absolute ethanol (30-35 ml). The resulting reaction mixture was stirred at reflux temperature for 2-3 hours. The reaction was then cooled to room temperature and the salts (potassium bromide, potassium chloride, or potassium iodide) were removed by suction filtration. The filtrate was evaporated under reduced pressure and the resulting residue was purified by column chromatography using silica gel 60 F_{254} (70-230 mesh, 35-40 g; column size 2.5 x 30 cm). Eluting the column with chloroform or ethyl acetate furnished a disubstituted derivative, as determined by ^{1}H nmr and elemental analysis, in 2-4% yield. Further elution of the column with chloroform:methanol (9:1), or ethyl acetate:methanol (95:5) afforded the 2-alkylthio-4,5-diaminopyrimidines **6-20** in 50-97% yield. The structure of these compounds were confirmed by ir, ^{1}H nmr and analytical data.

General Procedure for the Synthesis of the Methyl Alkylthiopurine-8-carbamates **21-35**, **41** and **42**.

A solution of the appropriate diamine (0.01 mole) in acetonitrile (30 ml) was added to an ice cold stirred solution of methoxycarbonyl isothiocyanate (0.012 mole) in acetonitrile (20 ml). The resulting reaction mixture was stirred at room temperature for 20 minutes, followed by the addition of *N,N'*-dicyclohexylcarbodiimide (0.012-0.015 mole). The reaction mixture was then stirred at reflux for 4-6 hours. After cooling to room temperature the precipitate which formed during the reaction was collected by filtration, washed with toluene (50 ml), followed by ethyl ether (40 ml) and then dried under vacuum at 50° to furnish the target compounds. The products were purified either by crystallization, column chromatography over silica gel 60 F_{254}, or by trituration of the crude product with a methanol/chloroform (1:4) solution.

4-Amino-5-nitro-2-phenylthiopyrimidine (**37**).

4-Amino-2-chloro-5-nitropyrimidine (**36**, 3.80 g, 0.022 mole) was added to a solution of sodium ethoxide (1.70 g, 0.025 mole) and benzenethiol (2.76 g, 0.025 mole) in absolute ethanol (100 ml). The resulting reaction mixture was stirred at reflux temperature for 2 hours, and then it was filtered hot. On cooling the filtrate to 0°, a light yellow colored solid precipitated, which was collected by filtration. The filtrate, on further concentration, followed by cooling at 0° overnight, furnished an additional amount of compound **37**. The total yield of **37** was 3.50 g (65%), mp 170°; ir (potassium bromide) 3430, 3130-3030, 1630, 1580, 1545, 1378, 1335, 745, 700, 680 cm^{-1}; ^{1}H nmr [deuteriochloroform + DMSO-d$_6$ (20:1)]: δ 7.20-7.80 (m, 5H, Ar-H), 7.85-8.21 (m, 2H, NH$_2$, exchangeable with deuterium oxide), 8.95 (s, 1H, C$_6$-H).

Anal. Calcd. for $C_{10}H_8N_4O_2S$: C, 48.38; H, 3.25; N, 22.57. Found: C, 48.21; H, 3.48; N, 22.33.

4-Amino-2-(4-methylpiperazino)-5-nitropyrimidine (**38**).

A mixture of 4-amino-2-chloro-5-nitropyrimidine (**36**, 1.75 g, 0.01 mole) and 4-methylpiperazine (1.81 g, 0.018 mole) in absolute alcohol (30 ml) was stirred at reflux temperature for 8-10 hours. The mixture was filtered hot and the filtrate on cooling to room temperature afforded a crystalline yellow solid, which was collected by filtration, yield 2.3 g (96%), mp 184-185°; ir (potassium bromide): 3440, 3160-3000, 2940, 2858, 2820, 1635-1620, 1552, 1515, 1372, 1335, 790 cm^{-1}; ^{1}H nmr [deuteriochloroform + DMSO-d$_6$, (20:1)]: δ 2.33 (s, 3H, NCH$_3$), 2.50 (t, 4H, N(CH$_2$)$_2$), 3.93 (t, 4H, N(CH$_2$)$_2$), 7.32 (m, 2H, NH$_2$, exchangeable with deuterium oxide), 8.97 (s, 1H, C$_6$-H).

Anal. Calcd. for $C_9H_{14}N_6O_2$: C, 45.37; H, 5.92; N, 35.28. Found: C, 45.16; H, 5.93; N, 35.18.

4,5-Diamino-2-phenylthiopyrimidine (**39**).

A suspension of compound **37** (1.80 g, 0.0073 mole) in methanol (40 ml) was submitted to hydrogenation in the presence of 5% palladium on carbon (0.4 g) in a Parr apparatus at 40 psi for 2 hours. A tlc analysis [chloroform:methanol (9:1)] of the reaction mixture indicated the presence of starting material, therefore an additional amount of catalyst (0.25 g) was added and the hydrogenation continued for an additional 4 hours. At that time, a third quantity of catalyst (0.20 g) was added and the reaction mixture was further hydrogenated for 2 hours. The catalylst was removed by filtration through a Celite pad and was washed with methanol (60 ml). The combined filtrates on evaporation under reduced pressure gave a colorless solid, which was recrystallized from methanol, yield 1.45 g (92%), mp 187-188°; ir (potassium bromide) 3420, 3320, 3160, 1660, 695 cm^{-1}; ^{1}H nmr [deuteriochloroform + DMSO-d$_6$ (7:1)]: δ 3.93 (bs, 2H, NH$_2$, exchangeable with deuterium oxide), 5.93 (bs, 2H, NH$_2$, exchangeable with deuterium oxide) 7.07-7.77 (m, 6H, Ar-H, C$_6$-H).

Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.03; H, 4.62; N, 25.67. Found: C, 54.98; H, 4.65; N, 25.46.

4,5-Diamino-2-(4-methylpiperazino)pyrimidine (**40**).

Compound **40** was prepared from **38** in a manner similar to that used for the preparation of **39**. Compound **40** was recrystallized from a diethyl ether:methanol mixture in a yield of 1.5 g (94%), mp 179-180°; ir (potassium bromide) 3480-3420, 2930-2910, 2860, 1625-1650 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.37 (s, 3H, N-CH$_3$), 2.59 (t, 4H, -N(CH$_2$)$_2$), 3.57 (t, 4H, N(CH$_2$)$_2$), 4.10 (bs, 2H, NH$_2$, exchangeable with deuterium oxide), 6.26 (bs, 2H, NH$_2$, exchangeable with deuterium oxide), 7.38 (s, 1H, C$_6$-H).

Anal. Calcd. for $C_9H_{16}N_2\cdot 0.5\ H_2O$: C, 45.89; H, 7.49; N, 35.68. Found: 45.97; H, 7.12; N, 36.00.

Methyl 2-Phenylthiopurine-8-carbamate (**41**).

Compound **41** was prepared as described in the general synthesis of methyl purine 8-carbamates. Compound **41** was obtained in 62%, mp 246-247°; ir (potassium bromide) 1720, 1640, 1520, 760-742, 680, cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.78 (s, 3H, OCH$_3$), 7.23-8.0 (m, 5H, Ar-H), 8.50 (s, 1H, C$_6$-H), 12.07 (bs, 2H, NHCO and NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{13}H_{11}N_5O_2S$: C, 51.82; H, 3.68; N, 23.24. Found: C, 51.62; H, 3.87; N, 23.09.

Methyl 2-(4-Methylpiperazino)purine-8-carbamate (**42**).

Compound **42** was prepared as described in the general synthesis of methyl purine 8-carbamates. Compound **42** obtained as a colorless solid after purification by column chromatography on silica gel 60 F$_{254}$ (70-230 mesh, column size 2.5 x 25 cm) using a chloroform:methanol (4:1) mixture as eluant, yield 0.8 g (64%), mp 238-242°; ir (potassium bromide): 3400, 3300, 2930, 2740, 2690, 1725, 1652, 760 cm^{-1}.

Anal. Calcd. for $C_{12}H_{17}N_7O_2\cdot 0.25\ H_2O$: C, 48.72; H, 5.96; N, 33.15. Found: C, 48.55; H, 5.97; N, 33.13.

Methyl 2-Phenylsulfonylpurine-8-carbamate (**43**).

A 30% aqueous solution of 5% hydrogen peroxide (40 ml) was added dropwise over a period of 10 minutes to a stirred suspension of compound **41** (0.825 g, 0.0027 mole) in glacial acetic acid (45 ml) at room temperature. The mixture was stirred at room temperature for 5-6 hours. During this period the reaction mixture became clear. The solvent was removed under high vacuum at room temperature and the resulting residue was triturated with cold water (30 ml). The crystalline solid was collected by filtration and air dried to yield 0.81 g (93%) of **43**, mp 234-235°, ir (potassium bromide): 1745, 690 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.78 (s, 3H, OCH$_3$), 7.33-7.62 (m, 3H, Ar-H), 7.88-8.15 (m, 2H, Ar-H), 8.67 (s, 1H, C$_6$-H).

Anal. Calcd. for $C_{13}H_{11}N_5O_4S\cdot 1.25\ H_2O$: C, 43.88; H, 3.82; N, 19.68. Found: C, 43.73; H, 3.70; N, 19.70.

Methyl 7-Aminothiazolo[5,4-*d*]pyrimidine-2-carbamate (**45**).

Compound **45** was prepared from **44** in a manner similar to that used for the preparation of **5**. The separated solid was collected by filtration, washed with water and suspended in methanol (20 ml) followed by stirring for 15 minutes. The colorless solid was collected by filtration, air dried, yield 0.50 g (26%), mp 295-296°; ir (potassium bromide); 3470, 1725, 1640-1600, 760, 725 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.13-3.67 (m, 3H, NH$_2$, NHCO), 3.73 (s, 3H, OCH$_3$), 8.30 (s, 1H, C$_5$-H).

Anal. Calcd. for $C_7H_7N_5O_2S$: C, 37.33; H, 3.13; N, 31.10. Found: C, 37.08; H, 3.25; N, 30.93.

General Procedure for the Synthesis of 4-Amino-5-(*N'*-carbomethoxythioureido)pyrimidine Derivatives **49a-d**, **51**, and **53**.

A mixture of the appropriate 4,5-diaminopyrimidine (0.01 mole) and methoxycarbonyl isothiocyanate (0.012 mole) in acetonitrile (30 ml) was stirred at reflux for 2-24 hours. The products, which precipitated from the reaction mixture, were collected by filtration. The purification of products was carried out by resuspension of the solid in a methanol/ethyl ether mixture and stirring for 25 minutes at room temperature. The product was collected by filtration and dried under vacuum.

4-Amino-5-(N'-carbomethoxythioureido)pyrimidin-2-thione (**49a**).

Compound **49a** was obtained from 4,5-diamino-2-mercaptopyrimidine (**4**) in a yield of 81%, mp 197-198°; ir (potassium bromide) 3400, 2960, 1740, 1660-1650, 767 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.75 (s, 3H, $-OCH_3$), 7.47 (s, 1H, C_6-H), 8.08 (bs, 2H, NH_2, exchangable with deuterium oxide), 10.57 (bs, 1H, NHCO, exchangeable with deuterium oxide), 11.50 (bs, 1H, NH, exchangeable with deuterium oxide), 12.20 (bs, 1H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_7H_9N_5O_2S_2$: C, 32.42; H, 3.50; N, 27.01. Found: C, 32.22; H, 3.58; N, 26.96.

4-Amino-2-benzylthio-5-(N'-carbomethoxythioureido)pyrimidine (**49b**).

Compound **49b** was obtained from 2-benzylthio-4,5-diaminopyrimidine (**13**) in a 65% yield, mp 227°; ir (potassium bromide): 3470, 3300, 3000, 1735, 1640, 782, 742, 705, 690 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.73 (s, 3H, OCH_3), 4.33 (s, 2H, SCH_2), 6.75-7.64 (m, 7H, Ar-H and NH_2, exchangeable with deuterium oxide), 7.87 (s, 1H, C_6-H), 10.70 (s, 1-H, NHCO, exchangeable with deuterium oxide), 11.43 (s, 1H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{14}H_{15}N_5O_2S$: C, 48.12; H, 4.33; N, 20.04. Found: C, 47.95; H, 4.30; N, 19.94.

6-Benzyloxy-2,4-diamino-5-(N'-carbomethoxythioureido)pyrimidine (**49c**).

Compound **49c** was obtained from 6-benzyloxy-2,4,5-triaminopyrimidine (**47**) in a 47% yield, mp 221-223°; ir (potassium bromide) 3490, 2965, 1750, 1615, 790, 770-760, 700 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 5.31 (s, 2H, OCH_2), 6.29 (s, 4H, 2 x NH_2, exchangeable with deuterium oxide), 7.54 (s, 5H, Ar-H), 10.30 (bs, 1H, NH, exchangeable with deuterium oxide), 11.30 (s, 1H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{14}H_{16}N_6O_3S$: C, 48.27; H, 4.63; N, 24.12. Found: C, 48.19; H, 4.68; N, 24.42.

2,4-Diamino-5-(N'-carbomethoxythioureido)pyrimidine (**49d**).

Compound **49d** was obtained from 2,4,5-triaminopyrimidine (**48**) in a 87% yield, mp 228-230°; ir (potassium bromide) 3300-2960, 1745, 765, 750 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.0-8.40 (m, 5H, C_6-H and 2 x NH_2, 4H exchangeable with deuterium oxide), 11.53 (bs, 1H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_7H_{10}N_6O_2S{\cdot}0.5\ H_2SO_4$: C, 28.89; H, 3.80; N, 28.88. Found: C, 28.47; H, 3.99; N, 28.77.

4-Amino-5-(N'-carbomethoxythioureido)pyrimidin-2,6-dione (**51**).

Compound **51** was obtained from 4,5-diaminopyrimidin-2,6-dione (**50**) in a 50% yield, mp >300°; ir (potassium bromide): 3400, 1725, 1660-1620, 765 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.73 (s, 3H, OCH_3), 6.28 (s, 2H, NH_2, exchangeable with deuterium oxide), 10.07 (s, 1H, NHCO, exchangeable with deuterium oxide), 10.40 (bs, 2H, NH and -OH, exchangeable with deuterium oxide), 11.20 (bs, 1H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_7H_9N_5O_4{\cdot}0.5\ H_2O$: C, 31.31; H, 3.76; N, 26.11. Found: C, 31.50; H, 3.86; N, 26.32.

2-Amino-4,6-dihydroxy-5-(N'-carbomethoxythioureido)pyrimidine (**53**).

Compound **53** was obtained from 4,5-diamino-4,6-dihydroxypyrimidine (**52**) in a 20% yield, mp >300°; ir (potassium bromide): 3280-3150, 1725, 1640, 760 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.67 (s, 3H, $-OCH_3$), 6.85 (bs, 4H, $-NH_2$ and 2 x -NH, exchangeable with deuterium oxide), 10.10 (s, 1H, -OH, exchangeable with deuterium oxide), 11.07 (s, 1H, NHCO, exchangeable with deuterium oxide).

Anal. Calcd. for $C_7H_9N_5O_4S$: C, 32.43; H, 3.50; N, 27.02. Found: C, 32.34; H, 3.66; N, 27.29.

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† Present address: Department of Radiology, Duke University Medical Center, Durham, NC 27710.

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