Pyrimidine Thioethers: A Novel Class of HIV-1 Reverse Transcriptase Inhibitors with Activity Against BHAP-Resistant HIV

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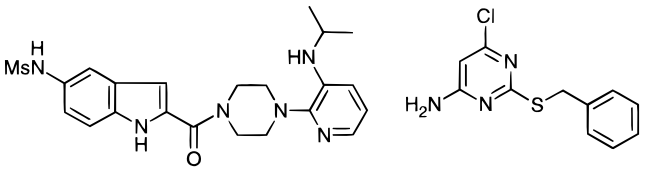
A series of pyrimidine thioethers was synthesized and evaluated for inhibitory properties against wild-type HIV-1 reverse transcriptase (RT) and an RT carrying the resistance-conferring mutation P236L. Modifications of both the pyrimidine and the functionality attached through the thioether yielded several analogues, which demonstrated activity against both enzyme types, with IC_{50} values as low as 190 nM against wild-type and 66 nM against P236L RT. Evaluation of a select number of pyrimidine thioethers in cell culture showed that these compounds have excellent activity against HIV-1_{IIIB}-WT and retain good activity against a laboratory-derived HIV-1_{MF} delavirdine-resistant variant.

Introduction

The reverse transcriptase (RT) of the human immunodeficiency virus type 1 (HIV-1) is a proven target for inhibition of HIV-1 replication.[1−3] Several HIV-1 nonnucleoside RT inhibitors (NNRTIs), including Pharmacia & Upjohn's BHAP, delavirdine (DLV) (**1**),[4,5] Boehringer Ingelheim's nevirapine,[6] and Merck's L-697,661,[7] have demonstrated potent inhibition of HIV-1 replication in cell culture. Recently, both delavirdine (Rescriptor tablets) and nevirapine (Viramune) have been approved for therapeutic intervention in HIV-1-infected individuals.

The dynamics of HIV-1 infection,[8,9] in combination with the high error rate arising from a lack of a proofreading function during reverse transcription of the HIV RNA genome, leads to the generation of a quasispecies from which variants are selected by drug treatment. Numerous RT mutations have been identified (singly or in combination) following selection of resistant virus either in cell culture or in the clinic. For example, nevirapine[10] and L-697,661[11] both select for highly resistant virus which expresses a mutant RT with a tyrosine-to-cysteine substitution at amino acid 181 (Y181C). This substitution in RT confers broad cross-resistance to most NNRTIs currently in development. In contrast, the BHAPs, such as DLV, preferentially select in vitro for a proline to leucine modification at amino acid 236 (P236L).[12] Previous work had shown that rather than imparting cross-resistance, the P236L mutation generates an RT which retained sensitivity or was actually sensitized to the inhibitory action of the other NNRTIs.[12,13] Selection of variants with distinct resistance profiles (e.g., P236L) that retain sensitivity to other NNRTIs would suggest that treatment with one NNRTI could be effectively followed with others.

Earlier we reported that the pyrimidine thioether **2** was a good inhibitor of HIV-1 RT.[14] This class of compounds was identified from our efforts to discover and develop NNRTIs effective against DLV-resistant RT and virus. Further evaluation revealed that the P236L RT mutation increased the sensitivity of this mutant enzyme to the inhibitory effects of **2**, compared to wild-type RT. This report focuses on preliminary investigations aimed at improving the activity of pyrimidine thioethers versus P236L RT, through modification of the pyrimidine ring substitution and variation of the substitution on the C-2 sulfide.



1, delavirdine mesylate **2**

Chemistry

Initially we investigated changes in the aryl group on the right-hand side of the molecule. Following the described procedure for the synthesis of **2**,[15] 4-aminothiouracil (**3**) was treated with NaOH in aqueous EtOH at room temperature and then with 2-(bromomethyl)naphthalene to give **4** (R = 2-naphthyl). This was reacted with 1.5 equiv of $POCl_3$ and 1 equiv of 2-picoline at reflux to give **5** (R = 2-naphthyl) (Scheme 1, method A). We prepared many analogues in this manner, without isolation of the intermediate aminohydroxypyrimidine, using the appropriate alkyl or benzyl halides.

However, we sought an alternative route that would avoid the use of $POCl_3$ after the right-hand pieces were attached and enable the synthesis of pyrimidines with reactive or acid-sensitive side chains. Thus, **40** was converted to **41** (Scheme 1) by alkylation with *p*-methoxybenzyl chloride, treatment with $POCl_3$/2-picoline, and ammonolysis with NH_4OH in CH_3CN.[16] Removal of the protecting group was accomplished by treating **41** with an excess of CH_3SO_3H in CH_2Cl_2, and the product was isolated by careful precipitation with

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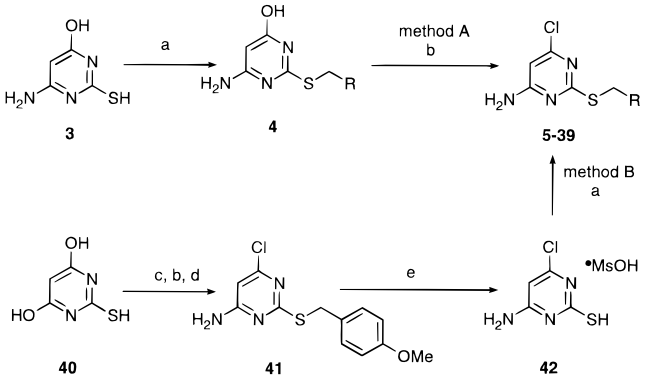
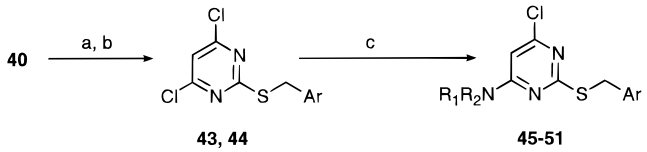
Scheme 1[a]



[a] Reagents: (a) RCH_2Br, NaOH, EtOH, H_2O; (b) $POCl_3$, 2-picoline; (c) 4-methoxybenzyl bromide, NaOH, EtOH, H_2O; (d) NH_4OH, CH_3CN; (e) MsOH.

Scheme 2[a]



[a] Reagents: (a) $ArCH_2Br$, NaOH, EtOH, H_2O; (b) $POCl_3$, 2-picoline; (c) R_1R_2NH, CH_2Cl_2, Et_3N.

Et_2O to give **42**. This was treated with the appropriate alkylating agent in the presence of aqueous NaOH/EtOH (method B).

To study the substitution of the pyrimidine ring, we converted **40** to **43** and **44** by alkylation with benzyl bromide or 2-(bromomethyl)naphthalene, respectively, followed by $POCl_3$/2-picoline (Scheme 2). These intermediates were treated with amines to give the desired pyrimidines **45**−**51**. The acetamido analogue of **5** was prepared through transacylation from EtOAc to give **52**. **2** was converted to **54** with pyrrolidine at reflux for 60 h. **53** and **55**−**57** were prepared by standard methods.

Direct substitution of the chloro moiety by carbon was not possible, so **60**, **64**, and **67** were assembled from the appropriate β-keto esters. The 4-CF_3 group was introduced from the commercially available β-keto ester, which was transformed to the uracil analogue **58** (Scheme 3). This was converted to the chloride **59** with $POCl_3$/2-picoline and then to the amine **60**, by treatment with NH_3/MeOH. Other functionality, however, was not obtained quite as easily.

The 4-cyanopyrimidine **64** was synthesized (Scheme 4) beginning with the β-keto ester by first conversion to the acetal **61**, which was then hydrolyzed and converted to the oxime **62**. This was never isolated but rather treated immediately with $POCl_3$/2-picoline resulting in chlorination of the pyrimidine ring and simultaneous dehydration of the oxime to the nitrile **63**. Finally, treatment with NH_4OH/THF gave **64**.

The 4-ethoxycarbonyl derivative **67** was synthesized (Scheme 5) from thioorotic acid, **65**, by alkylation with 2-(bromomethyl)naphthalene, conversion to the ethyl ester, and then chlorination to give **66**. Attempts to directly convert **66** to **67**, using NH_4OH in various organic solvents or anhydrous NH_3/MeOH, were unsuccessful, so **66** was first transformed to the azide and then reduced with $SnCl_2$ to give **67** in 62% yield for both steps.

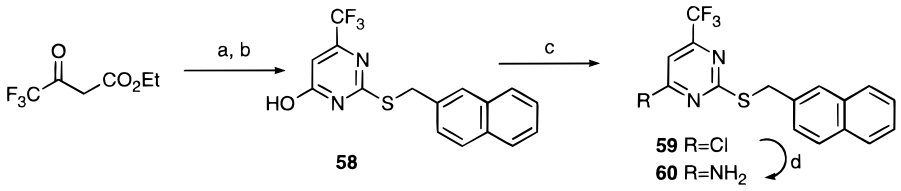
To investigate the importance of the thioether linker, we prepared various analogues in which the sulfur was replaced with oxygen, nitrogen, and carbon (Scheme 6). 4-Amino-2,6-dichloropyrimidine, **68**, was treated with appropriate alkoxides to prepare the ether derivatives (**69**−**72**). 2-Amino-4,6-dichloropyrimidine, **73**, was alkylated with (bromomethyl)naphthalene and then heated with NH_3/MeOH at 100 °C in a sealed tube to give the substituted amine **74**. To create an alkyl chain to the aromatic group, **75** was treated with Ms-Cl, followed by KCN to give the nitrile **76**.[17] **76** was transformed to an imido ether with HCl/EtOH and then to the amidine **77**. Finally, this was converted to **78** via reaction with ethyl cyanoacetate and then treatment with $POCl_3$. The thioethers **5** and **33** were also oxidized to sulfones **79** and **80** and to a sulfoxide, **81**.

Results and Discussion

Replacement of the phenyl moiety of lead structure **2** by diverse alkyl and aryl groups led to the series of compounds shown in Table 1. As indicated, the 2- and 1-naphthyl analogues, **5** and **6**, exhibited good inhibition against both enzymes (relative to **2**). Saturation of the phenyl ring of **2** led to the less potent cyclohexyl analogue **7**, which showed only modest activity against the wild-type enzyme but no detectable activity versus P236L. The nonyl derivative **8** showed no activity. Introduction of an acid, ester, or amide residue on a short alkyl chain, as in **9**, **10**, or **11**, also gave inactive compounds. Increasing the distance between the sulfur and the phenyl of **2** by a single carbon (**12**) eliminated activity, while deletion of the methylene linker of **2** yielded an inactive compound (data not shown). However, a rigid olefin residue, as in **13**, improved the inhibition versus the P236L enzyme to levels better than those of **5**. This suggests that the enzyme pocket can accommodate a large, but flat, hydrophobic group at this position. An analogue of **13**, which is ring-constrained (**14**), shows dramatically reduced activity against both enzymes. Taken together, **14** and **15** can be seen as analogues of **5** and **6** in which the A-ring is partially saturated. Although **15** shows good activity versus P236L RT, its activity against wild-type is greatly reduced. Saturation of the B-ring and introduction of added bulk in the form of four methyl groups, such as in **16**, gave an inactive compound. Replacing the B-ring of **5** with a dioxolane to give the piperonyl derivatives **17** and **18** significantly improved activity against both enzymes. The introduction of a single chlorine onto the parent ring system, **18**, gave a compound with IC_{50} values < 100 nM against both enzymes.

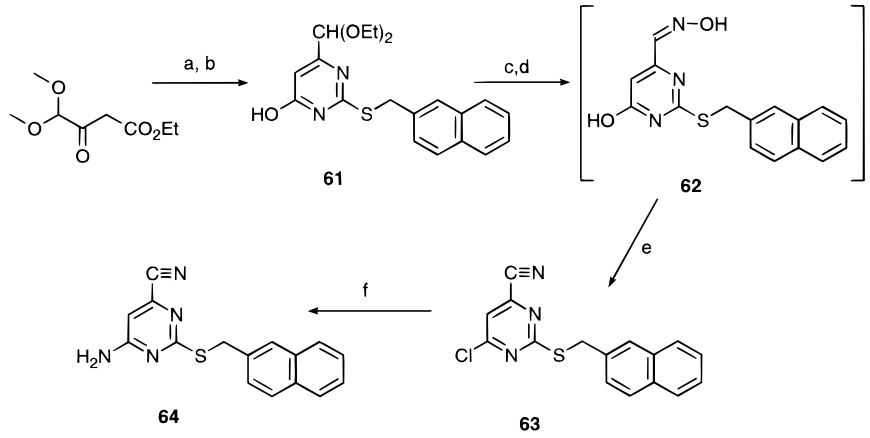
Having identified the naphthalene moiety as a suitable replacement for phenyl, we next explored the effects of varying substitution on the pyrimidine ring. As can be seen from Table 2, replacement of the amino group of **2** or **5** with various groups (**43**−**53**) led to significantly reduced levels of activity against both enzymes. Initial analogues (**4**, **54**, **55**) in which the chlorine was replaced were similarly inactive. Replacing either the primary amino or chloro groups of **5** with a simple proton provided **56** and **57**, which demonstrated less activity than **5** but essentially equivalent activity as **2**. In contrast, the 4-(trifluoromethyl)pyrimidine **60** was slightly less potent than **5** demonstrating that the

Scheme 3[a]



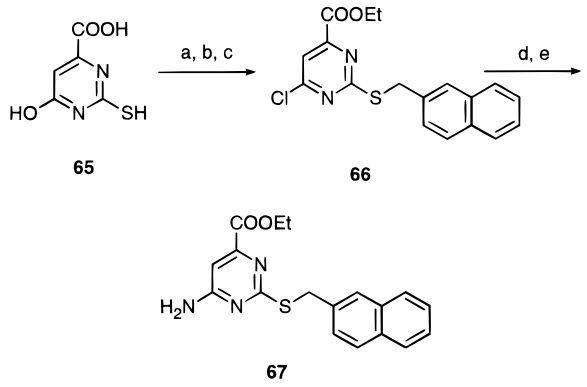
[a] Reagents: (a) thiourea; (b) 2-(bromomethyl)naphthalene, NaOH, EtOH, H_2O; (c) $POCl_3$, 2-picoline; (d) NH_3/MeOH.

Scheme 4[a]



[a] Reagents: (a) thiourea; (b) 2-(bromomethyl)naphthalene, NaOH, EtOH, H_2O; (c) 50% HOAc; (d) NH_2OH·HCl, NaOAc; (e) $POCl_3$, 2-picoline; (f) NH_4OH, THF.

Scheme 5[a]

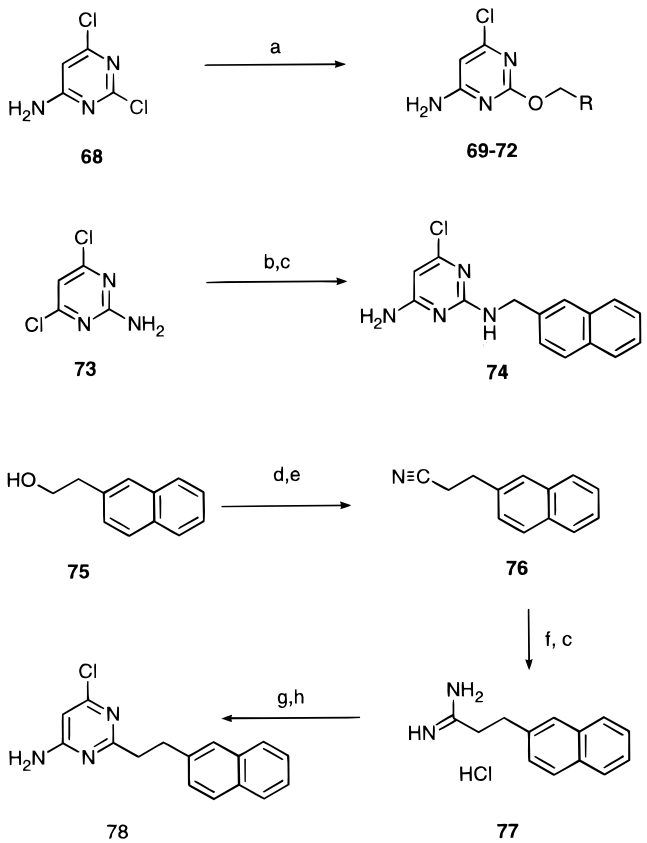


[a] Reagents: (a) 2-(bromomethyl)naphthalene, NaOH, EtOH, H_2O; (b) EtOH, CDI, DMF; (c) $POCl_3$, 2-picoline; (d) NaN_3, DMF; (e) $SnCl_2$, EtOH.

trifluoromethyl moiety is a conservative replacement for chlorine. Other electron-withdrawing groups were not as good. The 4-cyanopyrimidine **64** was less active than **60**, while the 4-ethoxycarbonyl **67** was inactive. These results suggest that the optimal RT activity depends on a delicate balance between a small electron-withdrawing group at C-4 and a primary amine at C-6 on the pyrimidine.

Derivatives, which modify the thioether linkage by replacing the sulfur with other heteroatoms or a methylene group, are presented in Table 3. Introduction of an ether bridge led to analogues (**69**−**72**) with reduced activity against wild-type RT relative to the corresponding sulfur-containing derivative, although activity versus P236L is still observed. Derivatives with amino (**74**) or methylene (**78**) in place of the sulfur are essentially inactive. Oxidation of the sulfur diminished the activity

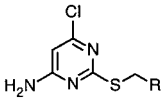
Scheme 6[a]

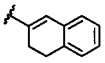
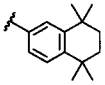
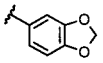
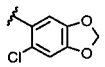


[a] Reagents: (a) RCH_2OH, 50% NaH; (b) 2-naphthyl-CH_2Br, NaOH, EtOH, H_2O; (c) NH_3/MeOH; (d) MsCl, Et_3N; (e) KCN, DMF; (f) HCl, EtOH; (g) EtO_2CCH_2CN, NaOMe, MeOH; (h) $POCl_3$, 2-picoline.

of the molecules, as **79**−**81** showed slight suppression of the P236L enzyme, but only at higher doses.

Table 1. Inhibition of HIV-1 Reverse Transcriptase: Effects of Thiol Substitution on HIV-1 Reverse Transcriptase Inhibition



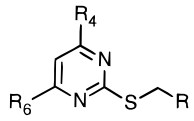
no.	R	method	% inhibition at 10μM[a] wild type	P236L
1	NA		(0.17)	(3.57)
2	Ph	A	(6.66)	(1.47)
5	2-naphthyl	A	87 (0.46)	96 (0.15)
6	1-naphthyl	A	89	96
7	cyclohexyl	A	37	13
8	n-C_8H_{16}	A	0	0
9	CO_2H	B	0	0
10	CH_2CO_2Et	B	11	7
11	$CONEt_2$	B	14	14
12	$PhCH_2$	A	33	12
13	(E)-PhCH=CH-	A	96 (0.19)	98 (0.066)
14		B	71	87
15		B	47 (16)	88 (0.6)
16		A	7	23
17		B	82	95
18		A	98 (0.085)	99 (0.016)

[a] Numbers in parentheses are IC_{50} values determined at eight drug concentrations.

Realizing that the activity could best be adjusted by modification of the aryl piece of the molecule, the dramatic activity of **13** led to the synthesis of additional olefinic analogues. As shown in Table 4, replacing the phenyl of **13** with methyl **19** gave good inhibition against P236L and wild-type, although not as good as **13**. This is the smallest molecule to show inhibition, but the results suggested that increasing the steric bulk might also increase the activity. The methyl ester **20** had activity comparable to that of the original lead **2**. Converting this to tertiary amides **21** and **22** gave more potent compounds, but the secondary amide **23** was significantly less active. This suggests the placement of the amide within a highly lipophilic pocket of the enzyme, which is disrupted in the secondary amide either through the presence of the hydrogen-bonding proton or through poor geometry.

The improvement in activity seen with **5** and **22**, which is likely due to an increase in lipophilicity, led to a study of substituted phenyl derivatives of **2**. Systematic introduction of a methyl group to each position of the phenyl ring of **2** was investigated as an initial approach toward locating sites for improving activity. As shown in Table 5, this strategy identified the 3-position as potency enhancing (**24**−**26**). Additional derivatives at the 3-position, compounds **30**−**36,** were uniformly potent against P236L but could not be differentiated. **37** showed significant suppression of both wild-type and P236L enzymes, but at a level that did not match that seen with **25**.

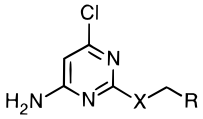
Table 2. Effects of Pyrimidine Substitution on HIV-1 Reverse Transcriptase Inhibition



no.	R_4	R_6	R[c]	% inhibition at 10 μM[a,b] wild-type	P236L
1	NA	NA	NA	(0.17)	(3.57)
2	Cl	NH_2	Ph	(6.66)	(1.47)
5	Cl	NH_2	Nap	87 (0.46)	96 (0.15)
43	Cl	Cl	Ph	19	25
44	Cl	Cl	Nap	0	23
45	Cl	PrNH	Ph	14	30
46	Cl	$HO(CH_2)_3NH$	Ph	17	3
47	Cl	cyclohexylamino	Ph	26	6
48	Cl	NH_2−NH	Ph	ND	31
49	Cl	pyrrolidino	Ph	35	41
50	Cl	piperidino	Ph	47	47
51	Cl	1-imidazolyl	Nap	12	17
52	Cl	AcNH	Nap	30	53
53	Cl	Ph	Nap	ND	5
54	pyrrolidino	NH_2	Ph	3	0
4	OH	NH_2	Nap	10	4
55	Me	NH_2	Ph	0	4
56	Cl	H	Nap	61	86
57	H	NH_2	Nap	50	71
60	CF_3	NH_2	Nap	94 (0.29)	94 (0.43)
64	CN	NH_2	Nap	84	93
67	CO_2Et	NH_2	Nap	17	24

[a] See legend to Table 1. [b] ND, not determined; NA, not applicable. [c] Ph, phenyl; Nap, 2-naphthyl.

Table 3. Effect of Altering the Heteroatom Linkage on HIV-1 Reverse Transcriptase Inhibition

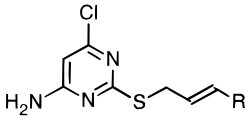


no.	X	R	% inhibition at 10 μM[a,b] wild-type	P236L
2	S	Ph	(6.66)	(1.47)
5	S	2-naphthyl	87 (0.46)	96 (0.15)
69	O	Ph	1	44
70	O	3-methylphenyl	25	72
71	O	1-naphthyl	2	67
72	O	2-naphthyl	63	80
74	NH	2-naphthyl	9	17
78	CH_2	2-naphthyl	ND	12
79	SO	2-naphthyl	45	75
80	SO	3-bromophenyl	ND	40
81	SO_2	3-bromophenyl	ND	14

[a,b] See legend to Table 2.

Seven compounds that demonstrated the most potent in vitro inhibitory activities against WT and P236L RTIs (IC_{50} range: 0.06−0.47 and 0.05−0.16 μM, respectively) were next evaluated for antiviral activity in cell culture.[18] As shown in Table 6, all seven compounds displayed submicromolar IC_{90} values against WT HIV-1 (HIV-1_{IIIB}). The tertiary amide compounds **21** and **22** showed potencies similar to that of DLV. Although the in vitro enzyme assay results indicated that the P236L substitution sensitized RT to each of the seven compounds compared to WT-RT, only **21** and **22** had submicromolar IC_{90} values against the laboratory-

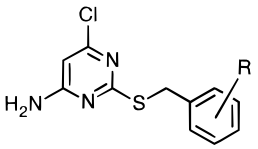
Table 4. Olefinic Pyrimidine Derivatives



			% inhibition at 10 μM[a,b]	
no.	R	method	wild-type	P236L
1			(0.17)	(3.57)
2			(6.66)	(1.47)
13	Ph	A	(0.19)	(0.066)
19	Me	A	5	47
20	CO_2Me	B	78 (5.25)	93 (0.93)
21	$CONMe_2$	B	99 (0.20)	99 (0.07)
22	$CONEt_2$	B	98 (0.05)	99 (0.03)
23	CONHEt	B	40	55

[a,b] See legend to Table 2.

Table 5. Effects of Aryl Substitution on HIV-1 Reverse Transcriptase Inhibition



			% inhibition at 10 μM[a,b]	
no.	R	method	wild-type	P236L
2	H	A	(6.66)	(1.47)
24	4-Me	A	3	5
25	3-Me	A	96 (0.28)	98 (0.045)
26	2-Me	A	2	0
27	4-Ph	A	8	20
28	4-tBu	A	37	56
29	4-CO_2Me	A	6	15
30	3-CO_2Me	A	93 (0.33)	94 (0.23)
31	3-CF_3	A	80	91
32	3-MeO	A	70 (0.98)	97 (0.16)
33	3-I	A	ND	89
34	3-Br	A	94 (0.76)	97 (0.14)
35	3-Cl	A	ND	65
36	3-F	A	ND	79
37	3,4-Cl_2	A	80 (0.49)	94 (0.062)
38	3,5-Br_2	A	ND	73
39	3,5-Cl_2	A	ND	65
41	4-MeO	A	25	63

[a,b] See legend to Table 2.

Table 6. HIV-1 Reverse Transcriptase and Antiviral Activities of Selected Compounds

	HIV-1 RT IC_{50} (μM)[a]		IC_{90} (μM)[b]	
compd	WT	P236L	HIV-1-WT	HIV-1MF-DLV^r
delavirdine	0.26	18	0.03	53.58
5	0.47	0.15	0.22	2.76
13	0.19	0.07	0.15	5.05
21	0.20	0.07	0.09	0.74
22	0.06	0.05	0.02	0.11
25	0.28	0.05	0.11	1.76
32	ND	0.16	0.27	3.21
34	ND	0.14	0.35	4.52

[a] ND, not determined. [b] IC_{90}, concentration of drug that inhibited p24 production by 90% in infected MT4 cells. Cell culture assays were performed as previously described.[18]

derived DLV-resistant variant of HIV-1_{MF}-DLV^r. Thus, the in vitro IC_{50} for this set of compounds against the P236L RT did not strictly correlate with their respective antiviral activities measured in cell culture infection experiments.

Conclusion

The pyrimidine thioethers constitute a novel series of NNRTIs that display potent RT inhibitory activity in vitro. Beginning with **2**, our efforts have led to the identification of pyrimidine thioether derivatives with IC_{50} values against WT RT comparable to that of DLV and, importantly, with potent activity against DLV-resistant RT. Further evaluation identified two compounds, **21** and **22**, with marked activity versus WT and DLV-resistant HIV-1 replication in cell culture. We have continued our studies on this novel class of NNRTIs, focusing on enhancing potency, broadening the spectrum of antiviral activity to encompass additional strains of drug-resistant HIV-1, including those expressing the Y181C mutation, and improving pharmacokinetic performance. Positive results in all these parameters will be reported in a subsequent manuscript.

Experimental Section

Materials and Methods. Mass spectra, infrared spectra, and combustion analysis were obtained by the Physical and Analytical Chemistry Unit of Pharmacia & Upjohn. ^{1}H NMR spectra were obtained at 300 MHz on a Bruker AM 300 or at 400 MHz on a Bruker ARX 400 spectrometer using tetramethylsilane as an internal standard unless stated otherwise. Melting points were measured on a Thomas/Hoover apparatus and are uncorrected. Thin-layer chromatography was conducted on Analtech GF silica gel plates. Column chromatography was conducted at medium pressure using silica gel (E. Merck, 70−230 mesh).

6-Amino-2-[(1-naphthalenylmethyl)thio]-4(1*H*)-pyrimidinone (4). Compound **3** (2.1 g, 15 mmol) was slurried in EtOH (15 mL) at 50 °C, then treated with 3.25 N NaOH (4.75 mL, 15.5 mmol), and stirred for 30 min. 2-(Chloromethyl)-naphthalene (3.43 g, 15.5 mmol) was added slowly over 5 min. After the mixture stirred for 15 min, H_2O (10 mL) was added to the resulting slurry, and the reaction was allowed to stir for 30 min. After cooling to room temperature, the solid was collected, washed with 2 × H_2O and 1 × EtOH, and then dried overnight to give pure **4**: 3.19 g (11.2 mmol, 75%); mp 247−250 °C (DMF/H_2O); ^{1}H NMR (DMSO) δ 7.99 (s, 1 H), 7.85−7.88 (m, 3 H), 7.48−7.58 (m, 3 H), 6.59 (s, 2 H), 4.93 (s, 1 H), 4.49 (s, 2 H); MS (EI) *m*/*z* 283 (M^+). Anal. ($C_{15}H_{13}N_3OS$) C, H, N.

General Procedure for the Synthesis of 2-(Substituted thio)chloroaminopyrimidine Derivatives. Method A. 6-Chloro-2-[(2-naphthalenylmethyl)thio]-4-pyrimidinamine (5). Compound **4** (2.47 g, 9.10 mmol) was added to $POCl_3$ (9 mL) and 2-picoline (1.40 mL, 13.6 mmol) and then stirred at reflux overnight. The thick, gummy reaction mixture was then poured onto ice and neutralized with NH_4-OH. This mixture was heated to boiling with stirring for 60 min, during which time a solid formed. If needed, additional NH_4OH was added to keep the pH > 7. The solid was filtered and washed with H_2O. The crude was chromatographed (hexane/EtOAc, 3:1) and then recrystallized from heptane to give **5** as a white solid: 1.03 g (3.46 mmol, 38%); mp 98−100 °C; ^{1}H NMR δ 7.89 (s, 1 H), 7.78−7.80 (m, 3 H), 7.44−7.54 (m, 3 H), 6.14 (s, 1 H), 4.97 (s, 2 H), 4.51 (s, 2 H); IR 1647, 1635, 1565, 1534 cm^{-1}; MS (EI) *m*/*z* 301 (M^+). Anal. ($C_{15}H_{12}ClN_3S$) C, H, N.

6-Chloro-2-[(1-naphthalenylmethyl)thio]-4-pyrimidinamine (6): 17%; mp 114−116 °C (heptane); ^{1}H NMR δ 8.11−8.13 (d, J = 8.0 Hz, 1 H), 7.84−7.87 (d, J = 9.4 Hz, 1 H), 7.76−7.79 (d, J = 8.2 Hz, 1 H); IR 1653, 1566, 1532 cm^{-1}; MS (EI) *m*/*z* 301 (M^+). Anal. ($C_{15}H_{12}ClN_3S$) C, H, N.

6-Chloro-2-[(2-cyclohexylmethyl)thio]-4-pyrimidinamine (7): 15%; mp 142−143 °C (EtOAc); ^{1}H NMR δ 6.13 (s, 1 H), 4.90 (s, 2 H), 3.00 (d, J = 6.7 Hz, 2 H), 1.87 (m, 2 H), 1.65 (m, 4 H), 1.23 (m, 3 H), 1.00 (m, 2 H); IR 1646, 1564, 1532 cm^{-1}; MS (EI) *m*/*z* 257 (M^+). Anal. ($C_{11}H_{16}ClN_3S$) C, H, N.

6-Chloro-2-[(1-nonyl)thio]-4-pyrimidinamine (8): 12%; mp 97 °C (heptane); ^{1}H NMR δ 7.26 (s, 2 H), 6.15 (s, 1 H), 3.00 (m, 2 H), 1.6 (m, 2 H), 1.25 (m, 12 H), 0.85 (m, 3 H); IR 1648, 1564, 1533 cm^{-1}; MS (EI) *m/z* 287 (M$^+$). Anal. ($C_{13}H_{22}ClN_3S$) C, H, N.

6-Chloro-2-[[1-(2-phenyl)ethyl]thio]-4-pyrimidinamine (12): 16%; mp 127−128 °C; ^{1}H NMR δ 7.25−7.35 (m, 5 H), 6.16 (s, 1 H), 4.9 (s, 2 H), 3.29−3.31 (m, 2 H), 3.04 (m, 2 H); IR 1642, 1571, 1533 cm^{-1}; MS (EI) *m/z* 265 (M$^+$). Anal. ($C_{12}H_{12}ClN_3S$) C, H, N.

6-Chloro-2-[(3-phenyl-2-propenyl)thio]-4-pyrimidinamine (13): 23%; mp 117−119 °C (heptane); ^{1}H NMR δ 7.37 (m, 2 H), 7.32−7.22 (m, 4 H), 6.65 (d, J = 15.7 Hz, 1 H), 6.31 (dt, J = 14.8, 7.2 Hz, 1 H), 6.17 (s, 1 H), 4.97 (s, 2 H), 3.94 (d, J = 7.2 Hz, 2 H), 1.64 (d, J = 6.6 Hz, 3 H); IR 1621, 1564, 1524 cm^{-1}; MS (EI) *m/z* 277 (M$^+$). Anal. ($C_{13}H_{12}ClN_3S$) C, H, N.

6-Chloro-2-[[(1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphth-6-yl)methyl]thio]-4-pyrimidinamine (16): 13%; mp 133−135 °C (EtOAc); ^{1}H NMR δ 7.34−7.35 (m, 1 H), 7.23−7.25 (m, 1 H), 7.14−7.17 (m, 1 H), 6.16 (s, 1 H), 5.03 (s, 2 H), 4.3 (s, 2 H); IR 1645, 1567, cm^{-1}; MS (EI) *m/z* 361 (M$^+$). Anal. ($C_{19}H_{24}ClN_3S$) C, H, N.

6-Chloro-2-[[(6-chloro-1,3-benzodioxol-5-yl)methyl]thio]-4-pyrimidinamine (18): 21%; mp 157−158 °C (toluene); ^{1}H NMR (DMSO) δ 7.42 (brd s, 2 H), 7.22 (s, 1 H), 7.09 (s, 1 H), 6.19 (s, 1 H), 6.06 (s, 1 H), 4.27 (s, 2 H); IR 1634, 1564, 1532 cm^{-1}; MS (EI) *m/z* 331 (M$^+$). Anal. ($C_{12}H_9Cl_2N_3O_2S$) C, H, N.

6-Chloro-2-[(1-but-2-enyl)thio]-4-pyrimidinamine (19): 11%; mp 67−69 °C (EtOAc); ^{1}H NMR δ 7.30 (s, 2H), 6.16 (s, 1 H), 5.70 (m, 1 H), 5.56 (m, 1 H), 3.64 (d, J = 6.9 Hz, 2 H), 1.64 (d, J = 6.6 Hz, 3 H); IR 1641, 1572, 1533 cm^{-1}; MS (EI) *m/z* 215 (M$^+$). Anal. ($C_8H_{10}ClN_3S$) C, H, N.

6-Chloro-2-[[(4-methylphenyl)methyl]thio]-4-pyrimidinamine (24): 28%; mp 95−96 °C; ^{1}H NMR δ 7.35 (d, J = 8.0 Hz, 2 H), 7.13−7.16 (d, J = 7.9 Hz, 2 H), 6.25 (s, 1 H), 5.09 (s, 2 H), 4.40 (s, 2 H), 2.32 (s, 3 H); IR 1644, 1574, 1535 cm^{-1}; MS (EI) *m/z* 265 (M$^+$). Anal. ($C_{12}H_{12}ClN_3S$) C, H, N.

6-Chloro-2-[[(3-methylphenyl)methyl]thio]-4-pyrimidinamine (25): 29%; mp 97−98 °C (hexane/EtOAc); ^{1}H NMR δ 7.19−7.26 (m, 3 H), 7.07 (m, 1 H), 6.15 (s, 1 H), 4.98 (s, 2 H), 4.32 (s, 2 H), 2.33 (s, 3 H); IR 1629, 1532, 1526 cm^{-1}; MS (EI) *m/z* 265 (M$^+$). Anal. ($C_{12}H_{12}N_3ClS$) C, H, N.

6-Chloro-2-[[(2-methylphenyl)methyl]thio]-4-pyrimidinamine (26): 22%; mp 129−130 °C; ^{1}H NMR δ 7.45−7.48 (m, 1 H), 7.15−7.19 (m, 3 H), 6.21 (s, 1 H), 5.04 (s, 2 H), 4.37 (s, 2 H), 2.38 (s, 3 H); IR 1623, 1566, 1531 cm^{-1}; MS (EI) *m/z* 265 (M$^+$). Anal. ($C_{12}H_{12}ClN_3S$) C, H, N.

6-Chloro-2-[[(1,1′-biphenyl-4-yl)methyl]thio]-4-pyrimidinamine (27): 9%; mp 162−163 °C (MtBE); ^{1}H NMR δ 7.31−7.59 (m, 9 H), 6.16 (s, 1 H), 4.95 (s, 2 H), 4.39 (s, 2 H); IR 1684, 1572, 1540 cm^{-1}; MS (EI) *m/z* 327 (M$^+$). Anal. ($C_{17}H_{14}ClN_3S$) C, H, N.

6-Chloro-2-[[[4-(1,1-dimethylethyl)phenyl]methyl]thio]-4-pyrimidinamine (28): 46%; mp 124−125 °C (Et_2O/hexane); ^{1}H NMR δ 7.33 (s, 4 H), 6.16 (s, 1 H), 5.05 (s, 2 H), 4.33 (s, 2 H), 1.30 (s, 9 H); IR 1646, 1623, 1572 cm^{-1}; MS (EI) *m/z* 307 (M$^+$). Anal. ($C_{15}H_{18}ClN_3S$) C, H, N.

6-Chloro-2-[[(4-carbomethoxyphenyl)methyl]thio]-4-pyrimidinamine (29): 19%; mp 202−203 °C; ^{1}H NMR δ 7.97 (d, J = 8.3 Hz, 2 H), 7.48−7.51 (d, J = 8.2 Hz, 2 H), 6.16 (s, 1 H), 4.9 (s, 2 H), 4.37 (s, 2 H), 1.58 (s, 3 H); IR 1715, 1653, 1609, 1575, 1538 cm^{-1}; MS (EI) *m/z* 309 (M$^+$). Anal. ($C_{13}H_{12}ClN_3O_2S$) C, H, N.

6-Chloro-2-[[(3-carbomethoxyphenyl)methyl]thio]-4-pyrimidinamine (30): 21%; mp 169−170 °C (EtOAc); ^{1}H NMR δ 7.68−7.98 (d, J = 8.4 Hz, 2 H), 7.48−7.51 (d, J = 8.2 Hz, 2 H), 6.16 (s, 1 H), 4.92 (s, 2 H), 4.37 (s, 2 H), 3.90 (s, 3 H); IR 1715, 1652, 1572, 1534 cm^{-1}; MS (EI) *m/z* 309 (M$^+$). Anal. ($C_{13}H_{12}ClN_3O_2S$) C, H, N.

6-Chloro-2-[[[3-(trifluoromethyl)phenyl]methyl]thio]-4-pyrimidinamine (31): 19%; mp 95−96 °C; ^{1}H NMR δ 7.72 (s, 1 H), 7.60 (m, 1 H), 7.42−7.4 8 (m, 2H), 6.17 (s, 1 H), 5.02 (s, 2 H), 4.36 (s, 2 H); IR 1658, 1585, 1566, 1537 cm^{-1}; MS (EI) *m/z* 319 (M$^+$). Anal. ($C_{12}H_9ClF_3N_3S$) C, H, N.

6-Chloro-2-[[(3-methoxyphenyl)methyl]thio]-4-pyrimidinamine (32): 26%; mp 99 °C (hexane/EtOAc); ^{1}H NMR δ 7.19−7.24 (m, 1 H), 6.99−7.00 (m, 2 H), 6.78−6.81 (m, 1 H), 6.16 (s, 1 H), 5.03 (s, 2 H), 4.33 (s, 2 H), 3.80 (s, 3 H); IR 1651, 1641, 1564, 1533 cm^{-1}; MS (EI) *m/z* 281 (M$^+$). Anal. ($C_{12}H_{12}ClN_3OS$) C, H, N.

6-Chloro-2-[[(3-iodophenyl)methyl]thio]-4-pyrimidinamine (33): 31%; mp 108 °C (hexane/EtOAc); ^{1}H NMR δ 7.80 (s, 1 H), 7.55−7.58 (d, J = 8.0 Hz, 1 H), 7.37−7.39 (d, J = 8.0 Hz, 1 H), 7.00−7.05 (t, J = 7.8 Hz, 1 H), 6.16 (s, 1 H), 5.13 (s, 2 H), 4.25 (s, 2 H); IR 1628, 1564, 1531 cm^{-1}; MS (EI) *m/z* 377 (M$^+$). Anal. ($C_{11}H_9ClIN_3S$) C, H, N.

6-Chloro-2-[[(3-bromophenyl)methyl]thio]-4-pyrimidinamine (34): 24%; mp 91−92 °C (hexane/EtOAc); ^{1}H NMR δ 7.58−7.59 (m, 1 H), 7.33−7.39 (m, 2 H), 7.14−7.19 (m, 1 H), 6.21 (s, 1 H), 5.28 (s, 2 H), 4.29 (s, 2 H); IR 1658, 1585, 1569, 1537 cm^{-1}; MS (EI) *m/z* 329 (M$^+$). Anal. ($C_{11}H_9BrClN_3S$) C, H, N.

6-Chloro-2-[[(3-chlorophenyl)methyl]thio]-4-pyrimidinamine (35): 27%; mp 103−104 °C; ^{1}H NMR δ 7.57−7.58 (m, 1 H), 7.30−7.36 (m, 2 H), 7.11−7.17 (m, 1 H), 6.19 (s, 1 H), 5.24 (s, 2 H), 4.25 (s, 2 H); IR 1635, 1617, 1566, 1532 cm^{-1}; MS (EI) *m/z* 285 (M$^+$). Anal. ($C_{11}H_9Cl_2N_3S$) C, H, N.

6-Chloro-2-[[(3-fluorophenyl)methyl]thio]-4-pyrimidinamine (36): 30%; mp 97−98 °C; ^{1}H NMR δ 7.12−7.25 (m, 3 H), 6.93 (m, 1 H), 6.18 (s, 1 H), 5.20 (s, 2 H), 4.33 (s, 2 H); IR 1633, 1590, 1563, 1532 cm^{-1}; MS (EI) *m/z* 269 (M$^+$). Anal. ($C_{11}H_9ClFN_3$) C, H, N.

6-Chloro-2-[[(3,4-dichlorophenyl)methyl]thio]-4-pyrimidinamine (37): 31%; mp 171 °C; ^{1}H NMR δ 7.54−7.55 (m, 1 H), 7.35−7.38 (m, 1 H), 7.24−7.28 (m, 1 H), 6.20 (s, 1 H), 5.19 (s, 2 H), 4.26 (s, 2 H); IR 1639, 1571, 1532 cm^{-1}; MS (EI) *m/z* 319 (M$^+$). Anal. ($C_{11}H_8Cl_3N_3S$) C, H, N.

6-Chloro-2-[[(3,5-dibromophenyl)methyl]thio]-4-pyrimidinamine (38): 30%; mp 184−185 °C; ^{1}H NMR δ 7.62−7.63 (m, 1 H), 7.53 (s, 1 H), 7.48 (m, 1 H), 6.19 (s, 1 H), 5.13 (s, 2 H), 4.36 (s, 2 H); IR 1638, 1563, 1532 cm^{-1}; MS (EI) *m/z* 407 (M$^+$). Anal. ($C_{11}H_8Br_2ClN_3S$) C, H, N.

6-Chloro-2-[[(3,5-dichlorophenyl)methyl]thio]-4-pyrimidinamine (39): 35%; mp 166−167 °C; ^{1}H NMR δ 7.32 (m, 2 H), 7.23 (s, 1 H), 6.19 (s, 1 H), 5.11 (s, 2 H), 4.25 (s, 2 H); IR 1639, 1563, 1532 cm^{-1}; MS (EI) *m/z* 319 (M$^+$). Anal. ($C_{11}H_8Cl_3N_3S$) C, H, N.

6-Chloro-2-[[(4-methoxyphenyl)methyl]thio]-4-pyrimidinamine (41). To a solution of 4,6-dihydroxy-2-mercaptopyrimidine (**40**) (40.0 g, 0.278 mol) in 95% EtOH (360 mL) at 22 °C was added 3 N NaOH (97.3 mL, 0.292 mol) followed by H_2O (360 mL). The stirred solution was treated dropwise with 4-methoxybenzyl chloride (45.5 g, 0.292 mol) over a 5-min period. The reaction mixture was heated at 60 °C for 1.5 h, stirred at ambient temperature for another 1.5 h, and cooled in ice bath at 0 °C for 4 h, and the white solid precipitate was collected. Overnight drying in the vacuum oven at 100 °C yielded 55.56 g (0.210 mol, 76%) of 4,6-dihydroxy-2-[(4-methoxybenzyl)thio]pyrimidine, sufficiently pure for subsequent reactions: mp 207−208 °C; ^{1}H NMR (DMSO) δ 11.71 (brd s, 2 H), 7.29 (d, J = 8.7 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 2 H), 5.10 (s, 1 H), 4.26 (s, 2 H), 3.67 (s, 3 H); IR 3032, 1641, 1611 cm^{-1}; MS (EI) *m/z* 264 (M$^+$). Anal. ($C_{12}H_{12}N_2O_3S$) C, H, N.

To the above (27.93 g, 0.106 mol) was added 2-picoline (16.46 g, 0.177 mol) followed by $POCl_3$ (243 g, 1.59 mol), and the contents were heated to reflux for 8 h. The excess $POCl_3$ was removed in vacuo and the thick black slurry poured onto crushed ice (500 mL). The mixture was stirred at 22 °C to allow decomposition of the remaining $POCl_3$, then EtOAc was added, and the contents were stirred overnight. The aqueous layer was extracted with 3 × EtOAc; then the combined organics were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed (hexane/EtOAc, 98:2) to yield 4,6-dichloro-2-[(4-methoxybenzyl)thio]pyrimidine (20.41 g, 0.0677 mol, 64%): mp 39−42 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 2 H), 7.01 (s, 1 H), 6.84 (d, J = 8.7 Hz, 2

H), 4.33 (s, 2 H), 3.78 (s, 3 H); MS (EI) *m/z* 300 (M^+). Anal. ($C_{12}H_{10}Cl_2N_2OS$) C, H, N.

A solution of the above dichloride (19.55 g, 0.0649 mol) in warm CH_3CN (391 mL) was treated with concentrated NH_4OH (391 mL) and then heated to 75 °C for 9 h and at 40 °C overnight. The contents were cooled to room temperature, filtered, and concentrated in vacuo. The white solid was extracted with EtOAc, and the organic layer was washed with a mixture of H_2O (50 mL) and saturated NaCl (75 mL). The combined aqueous layers were extracted with EtOAc and the combined organics dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in refluxing Et_2O plus minimum amount of EtOAc, diluted with hexane, and placed in the refrigerator to give **41** as a crystalline product (15.0 g, 0.053 mol, 82%): mp 118.5−119.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 8.7 Hz, 2 H), 6.07 (s, 1 H), 4.93 (br s, 2 H), 4.23 (s, 2 H), 3.72 (s, 3 H); IR 3421, 3302, 3279, 1640, 1619 cm^{-1}; MS (EI) *m/z* 281 (M^+). Anal. ($C_{12}H_{12}ClN_3OS$) C, H, S; N: calcd, 14.95; found, 14.41.

4-Amino-6-chloro-2(1*H*)-pyrimidinethione,Monomethanesulfonate (42). A suspension of **41** (60.0 g, 0.1993 mol) in CH_2Cl_2 (675 mL) at 22 °C was treated with MsOH (153 g, 1.595 mol). After stirring at room temperature until TLC indicated consumption of starting materials (3.5 h), the wine-red reaction mixture was diluted dropwise with Et_2O with periodic seeding during the initial addition phase until a suspended solid began to form in generous amount. The rate of addition was then gradually accelerated until a total of 3 L had been added over a period of several hours. When allowed to stir overnight, the suspended product seems to form a more granular solid of higher purity than if collected immediately after the addition of Et_2O. The yellow solid was collected at room temperature on a filter and washed with Et_2O. The crude product was suspended in refluxing CH_2Cl_2 (480 mL) to which was added MeOH in portions until nearly all material dissolved (ca. 270 mL). The hot mixture was filtered and the warm filtrate diluted, initially dropwise, with Et_2O with periodic seeding until a significant amount of white suspended solid was noted. Then the addition of Et_2O was accelerated until a total of 3 L was added over a period of 3 h. The pale-yellow solid was collected at room temperature, washed with Et_2O, and dried in a vacuum oven at 50 °C to obtain 49.2 g (0.191 mol, 96%) of analytically pure **42**: mp 166.5−167 °C; ^{1}H NMR (DMSO) δ 6.34 (s, 1 H), 2.46 (s, 3 H); IR 3146, 1704, 1677, 1669 cm^{-1}; MS (EI) *m/z* 161 (M^+). Anal. ($C_5H_8ClN_3O_3S_2$) C, H, N.

General Procedure for the Synthesis of 2-(Substituted thio)chloroaminopyrimidine Derivatives. Method B. (*E*)-4-[(4-Amino-6-chloro-2-pyrimidinyl)thio]-2-butenoic Acid Methyl Ester (20). Compound **42** (300 mg, 1.16 mmol) was dissolved in 3.25 M NaOH (2 mL) and EtOH (1 mL) and then treated with methyl 4-bromocrotonate (0.16 mL, 1.40 mmol). After 30 min, the solid was dissolved in CH_2Cl_2 (50 mL) and water (50 mL). The organic phase was washed with H_2O (30 mL) and saturated NaCl (30 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography (hexane/EtOAc, 75:25) to give **20** as white granules: 119 mg (0.46 mmol, 40%); mp 146−149 °C (hexane/EtOAc); ^{1}H NMR δ 7.08−6.97 (m, 1 H), 6.17 (s, 1 H), 6.04−6.01 (m, 1 H), 5.02 (br s, 2 H), 3.85 (dd, J = 7.1, 1.3 Hz, 2 H), 3.73 (s, 3 H); IR 1649, 1572, 1531 cm^{-1}; MS (EI) *m/z* 259 (M^+). Anal. ($C_9H_{10}N_3ClSO_2$) C, H, N.

2-[(4-Amino-6-chloro-2-pyrimidinyl)thio]acetic acid (9): 69%; mp 173−176 °C (hexane/EtOAc); ^{1}H NMR (DMSO) δ 12.65 (s, 1 H), 7.29 (s, 2 H), 6.17 (s, 1 H), 3.85 (s, 1 H); IR 1726, 1663, 1576, 1529 cm^{-1}; MS (EI) *m/z* 219 (M^+). Anal. ($C_6H_6ClN_3O_2S$) C, H, N.

3-[(4-Amino-6-chloro-2-pyrimidinyl)thio]propanoic acid methyl ester (10): 23%; mp 112−114 °C; ^{1}H NMR δ 6.17 (s, 1 H), 5.28 (br s, 2 H), 3.71 (s, 3 H), 3.32 (t, J = 7.1 Hz, 2 H), 2.80 (t, J = 7.1 Hz, 2 H); IR 1719, 1651, 1574, 1532 cm^{-1}; MS (EI) *m/z* 247 (M^+). Anal. ($C_8H_{10}N_3ClO_2S$) C, H, N.

***N*,*N*-Diethyl-2-[(4-amino-6-chloro-2-pyrimidinyl)thio]-acetamide (11):** 78%; mp 156−157 °C; ^{1}H NMR (DMSO) δ 7.25 (br s, 2 H), 6.17 (s, 1 H), 4.00 (s, 2 H), 3.40 (q, J = 7.0 Hz, 2 H), 3.26 (q, J = 7.0 Hz, 2 H), 1.17 (t, J = 7.0 Hz, 3 H), 1.00 (t, J = 7.0 Hz, 3 H); IR 1654, 1621, 1573, 1531 cm^{-1}; MS (EI) *m/z* 274 (M^+). Anal. ($C_{10}H_{15}N_4ClOS$) C, H, N.

6-Chloro-2-[[(3,4-dihydro-2-naphthalenyl)methyl]thio]-4-pyrimidinamine (14): 52%; mp 104−105 °C; ^{1}H NMR δ 7.18−7.06 (m, 3 H), 7.04−7.02 (m, 1 H), 6.55 (s, 1 H), 6.13 (s, 1 H), 5.31 (br s, 2 H), 4.00 (s, 2 H), 2.85 (t, J = 8.0 Hz, 2 H), 2.42 (t, J = 8.2 Hz, 2 H); IR 1645, 1573, 1513 cm^{-1}; MS (EI) *m/z* 303 (M^+). Anal. ($C_{15}H_{14}N_3ClS$) C, H, N.

6-Chloro-2-[[(3,4-dihydro-1-naphthalenyl)methyl]thio]-4-pyrimidinamine (15): 78%; mp 127−130 °C; ^{1}H NMR δ 7.35 (d, J = 7.2 Hz, 1 H), 7.21−7.12 (m, 3 H), 6.22 (t, J = 4.6 Hz, 1 H), 6.14 (s, 1 H), 5.01 (br s, 2 H), 4.23 (s, 2 H), 2.76 (t, J = 7.2 Hz, 2 H), 2.33−2.28 (m, 2 H); IR 1643, 1532 cm^{-1}; MS (EI) *m/z* 303 (M^+). Anal. ($C_{15}H_{14}N_3ClS$) C, H, N.

2-[[(1,3-Benzodioxol-5-yl)methyl]thio]-6-chloro-4-pyrimidinamine (17): 59%; mp 148−150 °C; ^{1}H NMR (DMSO) δ 7.32 (br s, 2 H), 6.98 (d, J = 1.6 Hz, 1 H), 6.89 (dd, J = 8.0, 1,7 Hz, 1 H), 6.81 (d, J = 7.9 Hz, 1 H), 6.18 (s, 1 H), 5.97 (s, 2 H), 4.21 (s, 2 H); IR 1640, 1570, 1532, 1500 cm^{-1}; MS (EI) *m/z* 295 (M^+). Anal. ($C_{12}H_{10}ClN_3O_2S$) C, H, N.

(*E*)-*N*,*N*-Dimethyl-4-[(4-amino-6-chloro-2-pyrimidinyl)-thio]-2-butenamide (21): 53%; mp 173−176 °C (hexane/EtOAc); ^{1}H NMR (DMSO) δ 7.34 (br s, 2 H), 6.68−6.57 (m, 2 H), 6.19 (s, 1 H), 3.82−3.80 (m, 2 H), 3.01 (s, 3 H), 2.84 (s, 3 H), 2.80 (t, J = 7.1 Hz, 2 H); IR 1661, 1575, 1530 cm^{-1}; MS (EI) *m/z* 272 (M^+). Anal. ($C_{10}H_{13}ClN_4OS$) C, H, N.

(*E*)-*N*,*N*-Diethyl-4-[(4-amino-6-chloro-2-pyrimidinyl)-thio]-2-butenamide (22): 45%; mp 143−145 °C (hexane/EtOAc); ^{1}H NMR (DMSO) δ 7.34 (br s, 2 H), 6.65−6.56 (m, 2 H), 6.19 (s, 1 H), 3.81 (d, J = 6.1 Hz, 2 H), 3.35−3.27 (m, 4 H), 1.08−0.99 (m, 6 H); IR 1660, 1605, 1574, 1530 cm^{-1}; MS (EI) *m/z* 300 (M^+). Anal. ($C_{12}H_{17}N_4ClOS$) C, H, N.

(*E*)-*N*-Ethyl-4-[(4-amino-6-chloro-2-pyrimidinyl)thio]-2-butenamide (23): 11%; mp 160−161 °C (hexane/EtOAc); ^{1}H NMR (DMSO) δ 7.98 (m, 1 H), 7.31 (br s, 2 H), 6.62 (dt, J = 15.2, 6.8 Hz, 1 H), 6.19 (s, 1 H), 6.07 (d, J = 15.2 Hz, 1 H), 3.79 (d, J = 6.9 Hz, 2 H), 3.19−3.07 (m, 2 H), 1.01 (t, J = 7.2 Hz, 3 H); IR 1663, 1644, 1614, 1578, 1558, 1524 cm^{-1}; MS (EI) *m/z* 327 (M^+). Anal. ($C_{10}H_{13}ClN_4OS$) C, H, N.

General Procedure for the Synthesis of Dichloropyrimidines. 4,6-Dichloro-2-[(phenylmethyl)thio]pyrimidine (43). Thiobarbituric acid (5.22 g, 36.2 mmol) in EtOH (52 mL) was treated with 3.25 M NaOH (11.1 mL, 36.2 mmol) and then heated to reflux for 30 min. Bn-Br (4.3 mL, 36 mmol) was added, and reflux continued for an additional 2 h. The resultant white solid was collected, washed with cold H_2O and EtOH, and then dried to yield 2-[(phenylmethyl)thio]barbituric acid as a white solid: 6.5 g (27 mmol, 77%); mp > 320 °C; ^{1}H NMR (DMSO-d_6) δ 7.45−7.36 (m, 2 H), 7.34−7.21 (m, 3 H), 5.18 (s, 1 H), 4.38 (s, 2 H).

The crude (5.95 g, 25.4 mmol) was treated with $POCl_3$ (26 mL) and heated to reflux for 2 h; then excess $POCl_3$ was removed in vacuo. The hot residue was poured onto ice, the pH was adjusted to 7 with NaOH, and then the aqueous phase was extracted 3 × EtOAc. The organics were washed with 3 × NaOH and 2 × saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo. The crude was chromatographed (toluene/hexane, 1:1) to give **43** as an irritating yellow oil: 5.0 g (18 mmol, 73%); ^{1}H NMR δ 7.45−7.41 (m, 2 H), 7.35−7.23 (m, 3 H), 7.03 (s, 1 H), 4.38 (s, 2 H); IR 1539, 1530 cm^{-1}; MS (EI) *m/z* 272 (M^+).

4,6-Dichloro-2-[(2-naphthalenylmethyl)thio]pyrimidine (44): 54%; mp 113−114 °C; ^{1}H NMR δ 7.92 (s, 1 H), 7.80 (m, 3 H), 7.52 (m, 1 H), 7.48−7.45 (m, 2 H), 7.03 (s, 1 H), 4.54 (s, 2 H); IR 1542, 1532 cm^{-1}; MS (EI) *m/z* 322 (M^+). Anal. ($C_{15}H_{10}N_2Cl_2S$) C, H, N.

General Procedure for the Synthesis of (Substituted amino)pyrimidines. 6-Chloro-2-[(phenylmethyl)thio]-*N*-propyl-4-pyrimidinamine (45). Compound **43** (0.23 g, 0.87 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with Et_3N (0.18 mL, 1.3 mmol) and *n*-propylamine (0.14 mL, 1.7 mmol). The mixture was stirred at room temperature for 20 h, then washed with 2 × saturated $NaHCO_3$, dried with $MgSO_4$, and

concentrated in vacuo. The residue was chromatographed (hexane/EtOAc, 10:1) to give **45** as a colorless oil, 0.23 g (0.79 mmol, 91%), which solidified upon standing: mp 67−68 °C; ^{1}H NMR δ 7.42−7.40 (m, 2 H), 7.32−7.20 (m, 3 H), 6.03 (s, 1 H), 5.04 (brd s, 1 H), 4.35 (s, 2 H), 3.23 (m, 2 H), 1.61 (hex, 2 H), 0.97 (t, J = 7.4 Hz, 3H); IR 1574, 1538 cm^{-1}; MS (EI) m/z 293 (M^+). Anal. ($C_{14}H_{16}ClN_3S$) C, H, N.

6-Chloro-2-[(phenylmethyl)thio]-*N*-(3-hydroxypropyl)-4-pyrimidinamine (46): 87%; mp 103−104 °C; ^{1}H NMR δ 7.43−7.41 (m, 2H), 7.32−7.22 (m, 3H), 6.06 (s, 1H), 5.34 (brd s, 1H), 4.36 (s, 2H), 3.73 (t, 2H), 3.50 (brd s, 2H), 1.81 (m, 2H); IR 1608, 1601, 1572 cm^{-1}; MS (EI) m/z 309 (M^+). Anal. ($C_{14}H_{16}ClN_3OS$) C, H, N.

6-Chloro-2-[(phenylmethyl)thio]-*N*-cyclohexyl-4-pyrimidinamine (47): 82%; ^{1}H NMR δ 7.43−7.40 (m, 2H), 7.32−7.20 (m, 3 H), 6.00 (s, 1 H), 4.96 (brd s, 1 H), 4.34 (s, 2 H), 3.75−3.19 (brd, 1 H), 1.99−1.93 (m, 2 H), 1.83−1.60 (m, 3 H), 1.43−1.15 (m, 5 H); IR 1567, 1537 cm^{-1}; MS (EI) m/z 333 (M^+). Anal. ($C_{17}H_{20}ClN_3S$) C, H, N.

6-Chloro-2-[(phenylmethyl)thio]-4(1*H*)-pyrimidinone hydrazone (48): 29%; mp 136−138 °C (EtOH/H_2O); ^{1}H NMR δ 7.41−7.39 (m, 2 H), 7.32−7.23 (m, 3 H), 6.56 (m, 1 H), 6.48 (brd s, 1 H), 4.34 (s, 2 H), 3.21 (m, 1 H); IR 1652, 1575, 1551 cm^{-1}; MS (EI) m/z 236 (M^+). Anal. ($C_{11}H_{11}ClN_4S$) C, H, N.

4-Chloro-2-[(phenylmethyl)thio]-6-(1-pyrrolidinyl)pyrimidine (49): 43%; mp 80−81 °C (cyclohexane);^{1}H NMR δ 7.43−7.40 (m, 2 H), 7.31−7.22 (m, 3 H), 5.99 (s, 1 H), 4.36 (s, 2 H), 3.60 (m, 2 H), 3.28 (m, 2 H), 2.10−1.87 (m, 4 H); IR 1585, 1580, 1540 cm^{-1}; MS (EI) m/z 305 (M^+). Anal. ($C_{15}H_{16}N_3ClS$) C, H, N.

4-Chloro-2-[(phenylmethyl)thio]-6-piperidinylpyrimidine (50): 64%; mp 85−86 °C (cyclohexane);^{1}H NMR δ 7.42−7.40 (m, 2 H), 7.32−7.20 (m, 3 H), 6.18 (s, 1 H), 4.34 (s, 2 H), 3.57 (m, 4 H), 1.70−1.64 (m, 2 H), 1.62−1.54 (m, 4 H); IR 1572, 1533 cm^{-1}; MS (EI) m/z 319 (M^+). Anal. ($C_{16}H_{18}ClN_3S$) C, H, N.

4-Chloro-6-imidazolyl-2-[(naphthalenylmethyl)thio]-pyrimidine (51): 34%; mp 115−117 °C; ^{1}H NMR δ 8.45 (s, 1 H), 7.92 (s, 1 H), 7.83−7.79 (m, 3 H), 7.57−7.53 (m, 2 H), 7.49−7.44 (m, 2 H), 7.22 (s, 1 H), 6.99 (s, 1 H), 4.58 (s, 2 H); IR 1560, 1544, 1520, 1508 cm^{-1}; MS (EI) m/z 352 (M^+). Anal. ($C_{18}H_{13}ClN_4S\cdot0.25H_2O$) C, H, N.

***N*-[6-Chloro-2-[(2-naphthalenylmethyl)thio]-4-pyrimidinyl]acetamide (52).** Compound **5** (0.30 g, 1.0 mmol) was dissolved in EtOAc (5 mL) and treated with NaOMe (25% in MeOH, 0.23 mL, 1.0 mmol). After stirring for 3 h, the reaction was quenched with 1 M HCl, washed with H_2O and saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo to give **52** as white crystals: 123 mg (0.358 mmol, 36%); mp 179−180 °C (EtOAc); ^{1}H NMR 7.87 (s, 2 H), 7.80 (m, 3 H), 7.55−7.45 (m, 3 H), 4.52 (s, 2 H), 2.21 (s, 3 H); IR 1696, 1582, 1552, 1511 cm^{-1}; MS (EI) m/z 343 (M^+). Anal. ($C_{17}H_{14}ClN_3OS$) C, H, N.

6-Chloro-2-[(2-naphthalenylmethyl)thio]-4-phenylpyrimidine (53). 4-Chloro-2-[(naphthalenylmethyl)thio]-6-phenylpyrimidine[19] (0.34 g, 1.0 mmol) and $POCl_3$ (3 mL) were heated at reflux for 2 h; then excess $POCl_3$ was distilled. The residue was poured onto ice, extracted with EtOAc, washed with saturated $NaHCO_3$ and saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo to yield **53**: 129 mg (0.356 mmol, 36%); mp 93−94 °C (toluene/hexane); ^{1}H NMR (DMSO) δ 8.23 (m, 1 H), 8.03 (s, 1 H), 8.00 (s, 1 H), 7.90 (m, 2 H), 7.85 (m, 1 H), 7.7−7.45 (m, 6 H), 4.69 (s, 2 H); IR 1599, 1548, 1522 cm^{-1}; MS (EI) m/z 358 (M^+). Anal. ($C_{21}H_{15}ClN_2S$) C, H, N.

2-[(Phenylmethyl)thio]-6-pyrrolidino-4-pyrimidinamine (54). Compound **2** (0.20 g, 0.80 mmol) in THF (1.6 mL) was treated with pyrrolidine (0.20 mL, 2.4 mmol) and heated to reflux for 60 h. The mixture was cooled and concentrated with a stream of nitrogen; then the residue was dissolved in CH_2Cl_2 and washed 3 × H_2O. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The brown residue was chromatographed (hexane/EtOAc, 2:1) to yield **54** as tan needles: 0.11 g (0.37 mmol, 47%); mp 143−144 °C (toluene/heptane); ^{1}H NMR δ 7.40 (d, 2 H), 7.29−7.20 (m, 3 H), 5.08 (s, 1 H), 4.41 (brd s, 2 H), 4.37 (s, 2 H), 3.41 (m, 4 H), 1.95 (m, 4 H); IR 1633, 1584, 1545 cm^{-1}; MS (EI) m/z 286 (M^+). Anal. ($C_{15}H_{18}N_4S$) C, H, N.

6-Methyl-2-[(phenylmethyl)thio]-4-pyrimidinamine (55). 2-(Benzylthio)-4-chloro-6-methylpyrimidine[20] (0.50 g, 2.0 mmol) was dissolved in NH_3/MeOH (2 mL) and then heated in a sealed vial to 100 °C for 24 h. The mixture was cooled and concentrated with a stream of N_2; then the residue was dissolved in EtOAc and washed 3 × H_2O. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The brown residue was chromatographed (hexane/EtOAc, 3:1) to yield **55**: 152 mg (0.657 mmol, 33%); mp 107−108 °C; ^{1}H NMR δ 7.40 (m, 2 H), 7.27 (m, 3 H), 6.05 (s, 1 H), 5.07 (brd s, 2 H), 4.37 (s, 2 H), 2.31 (s, 3 H); IR 1626, 1587, 1583, 1537 cm^{-1}; MS (EI) m/z 231 (M^+). Anal. ($C_{12}H_{13}N_3S$) C, H, N.

4-Chloro-2-[(2-naphthalenylmethyl)thio]pyrimidine (56). 2-Thiouracil (2.56 g, 20.0 mmol) suspended in H_2O (20 mL) was treated with NaOH (0.88 g, 20 mmol) and then stirred until dissolved. The reaction was diluted with EtOH (20 mL), treated with 2-(bromomethyl)naphthalene (4.6 g, 21 mmol), and then heated at reflux for 3 h. The reaction was cooled and the precipitate collected. The hydroxypyrimidine (3.48 g, 12.9 mmol) was heated in $POCl_3$ (16 mL) overnight at reflux. Excess reagent was removed at reduced pressure and the residue poured onto ice. The product was extracted with EtOAc, washed with saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo. The brown residue was chromatographed (hexane/EtOAc, 9:1) to yield **56**: 2.97 g (10.4 mmol, 52%); mp 76−77 °C; ^{1}H NMR (DMSO-d_6) δ 8.64 (d, J = 5.3 Hz, 1 H), 7.97 (s, 1 H), 7.88 (m, 3 H), 7.6−7.45 (m, 3 H), 7.43 (d, J = 5.2 Hz, 1 H) 4.59 (s, 2 H); IR 1545, 1532 cm^{-1}; MS (EI) m/z 286 (M^+). Anal. ($C_{15}H_{11}ClN_2S$) C, H, N.

2-[(2-Naphthalenylmethyl)thio]-4-pyrimidinamine (57). 2-Thiocytosine (505 mg, 3.97 mmol) was dissolved in EtOH (1.3 mL) and 3.25 M NaOH (1.3 mL, 4.2 mmol) and stirred for 20 min. 2-(Bromomethyl)naphthalene (877 mg, 3.97 mmol) was added, and the reaction was heated to reflux for 30 min. After cooling, the reaction was concentrated in vacuo, and the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ and saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo. The crude was chromatographed (hexane/EtOAc, 9:1) to yield **57**: 0.24 g (0.91 mmol, 23%); mp 115−116 °C (cyclohexane);^{1}H NMR (DMSO) δ 7.93 (m, 2 H), 7.85 (m, 3 H), 7.55 (m, 1 H), 7.48 (m, 2 H), 7.00 (brd s, 2 H), 6.16 (d, J = 5.8 Hz, 1 H), 4.46 (s, 2 H); IR 1649, 1638, 1611, 1577, 1542 cm^{-1}; MS (EI) m/z 267 (M^+). Anal. ($C_{15}H_{13}N_3S$) C, H, N.

2-[(Phenylmethyl)thio]-6-(trifluoromethyl)-4-pyrimidinol (58). Ethyl trifluoroacetoacetate (8.84 g, 48.0 mmol) and thiourea (3.8 g, 50 mmol) were combined in absolute EtOH (50 mL), treated with 25% NaOMe/MeOH (12.0 mL, 52.5 mmol), and then heated to reflux. After 4 h, the reaction was concentrated nearly to dryness, acidified with 1 N HCl (53 mL), and filtered. The solid was washed with water and dried. Crude solid (1.47 g, 7.50 mmol) was dissolved in EtOH (2.5 mL) and 3.25 N NaOH (2.3 mL, 7.5 mmol), treated with a solution of 2-(bromomethyl)naphthalene (1.65 g, 7.50 mmol) in EtOH (5 mL), and then refluxed for 1 h. The cooled reaction mixture was filtered and the crude product purified by recrystallization from EtOH to yield **58**: 1.55 g (4.62 mmol, 10%); mp 211−212 °C; ^{1}H NMR (DMSO) δ 7.94 (s, 1 H), 7.86 (d, J = 8.4 Hz, 2 H), 7.80 (m, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.50 (m, 2 H), 6.61 (s, 1 H), 4.56 (s, 2 H); IR 1676, 1553, 1419 cm^{-1}; MS (EI) m/z 336 (M^+). Anal. ($C_{16}H_{11}F_3N_2OS$) C, H, N.

4-Chloro-2-[(2-naphthalenylmethyl)thio]-6-(trifluoromethyl)pyrimidine (59). Compound **58** (1.47 g, 4.37 mmol) and $POCl_3$ (5 mL) were heated to reflux for 2 h, and the excess $POCl_3$ was distilled. The residue was poured onto ice and extracted 3 × EtOAc. The organics were then washed with H_2O and saturated NaCl, dried with $MgSO_4$, and then concentrated in vacuo. The crude product was then purified by recrystallization from hexane: 910 mg (2.56 mmol, 58%); mp 65−66 °C; ^{1}H NMR δ 7.95 (s, 1 H), 7.81 (d, J = 8.7 Hz, 2 H), 7.81(s, 1 H), 7.54 (m, 1 H), 7.47 (m, 2 H), 7.27 (s, 1 H), 4.57 (s,

2 H); IR 1564, 1552, 1541 cm^{-1}; MS (EI) *m/z* 354 (M^+). Anal. ($C_{16}H_{10}ClF_3N_2S$) C, H, N.

2-[(2-Naphthalenylmethyl)thio]-6-(trifluoromethyl)-4-pyrimidinamine (60). Compound **59** (733 mg, 2.06 mmol) was treated with NH_3/MeOH (6 mL) at 0 °C for 1 h, then warmed to room temperature, and stirred for 2.5 h. The reaction was concentrated, and the crude products were purified by chromatography (hexane/EtOAc, 6:1, 1:1) to give **60**: 70 mg (0.21 mmol, 10%); mp 144−145 °C; ^1H NMR δ 7.91 (s, 1 H), 7.77 (m, 3 H), 7.53 (dd, J = 1.7, 8.5 Hz, 1 H), 7.44 (m, 2 H), 6.41 (s, 1 H), 5.14 (s, 2 H), 4.52 (s, 2 H); IR 1642, 1547 cm^{-1}; MS (EI) *m/z* 335 (M^+). Anal. ($C_{16}H_{12}F_3N_3S$) C, H, N.

6-(Diethoxymethyl)-2-[(2-naphthalenylmethyl)thio]-4-pyrimidinol (61). Ethyl diethoxyacetate (10.4 mL, 60.0 mmol) and EtOAc (9.0 mL, 90 mmol) were heated to 80−90 °C and then treated with Na (1.44 g, 60 mmol) in small portions. After 2 h, EtOAc (9.0 mL, 90 mmol) and Na (1.44 g, 60 mmol) were added, and heating was maintained for an additional 3 h. The red oily mass was poured onto water (15 mL), acidified with 10% HCl, and extracted 3 × methyl *tert*-butyl ether. The organics were washed with 3 × saturated $NaHCO_3$ and saturated NaCl, dried with $MgSO_4$, and then concentrated in vacuo. The crude product was dried overnight in the vacuum oven at 70 °C to remove any ethyl acetoacetate that may have been produced. The crude keto ester was treated with thiourea (4.57 g, 60 mmol), EtOH (45 mL), and 25% NaOMe (13 mL, 57 mmol) and heated to reflux for 4 h. The reaction was diluted with water (50 mL), treated with 2-(bromomethyl)naphthalene (12.0 g, 54.3 mmol), and then stirred warm for 1 h. The white solid was diluted with H_2O, filtered, and then recrystallized from EtOAc to give **61**: 11.2 g (30.1 mmol, 50%); mp 163−164 °C; ^1H NMR (DMSO) δ 7.95 (s, 1 H), 7.85 (m, 3 H), 7.58 (dd, J = 1.7, 8.4 Hz, 1 H), 7.48 (m, 2 H), 6.14 (s, 1 H), 5.21 (s, 1 H), 4.56 (s, 2 H), 3.58 (m, 4 H), 1.13 (t, J = 7.1 Hz, 6 H); IR 1664, 1549 cm^{-1}; MS (EI) *m/z* 370 (M^+);

6-Chloro-2-[(2-naphthalenylmethyl)thio]-4-pyrimidinecarbonitrile (63). Compound **61** (1.85 g, 5.0 mmol) and 50% HOAc (20 mL) were refluxed for 2 h and then taken to dryness under a stream of nitrogen. The crude aldehyde was suspended in hot EtOH (25 mL), treated with NaOAc (2.8 g) and then with a solution of NH_2OH·HCl (1.85 g) in H_2O (25 mL), and then refluxed for 1 h. The crude product, **62**, was isolated by filtration: 1.204 g (3.87 mmol, 77%).

62 (720 mg, 2.31 mmol), $POCl_3$ (3 mL), and 2-picoline (0.5 mL) were heated to reflux for 2 h, then poured onto ice, and extracted 2 × EtOAc. The organics were washed with 2 × saturated $NaHCO_3$, dried with $MgSO_4$, and then concentrated in vacuo. The crude product was purified by chromatography (hexane/EtOAc, 95:5) to give **63**: 322 mg (1.03 mmol, 45%); mp 120−121 °C; ^1H NMR δ 7.93 (s, 1 H), 7.82 (d, J = 4.3 Hz, 3 H), 7.50 (m, 3 H), 7.27 (s, 1 H), 4.55 (s, 2 H); IR 1551, 1527, 1509 cm^{-1}; MS (EI) *m/z* 311 (M^+). Anal. ($C_{16}H_{10}ClN_3S$) C, H, N.

6-Amino-2-[(2-naphthalenylmethyl)thio]-4-pyrimidinecarbonitrile (64). Compound **63** (0.30 g, 0.96 mmol) was treated with 1:1 THF/NH_4OH (10 mL) and stirred at room temperature for 6 h. The reaction was diluted with EtOAc, washed with water and saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by recrystallization from toluene: 155 mg (0.530 mmol, 55%); mp 154−155 °C; ^1H NMR δ 7.89 (s, 1 H), 7.80 (m, 3 H), 7.48 (m, 3 H), 6.45 (s, 1 H), 5.15 (s, 2 H), 4.51 (s, 2 H); IR 3168 (b), 1650, 1642, 1581, 1534 cm^{-1}; MS (EI) *m/z* 292 (M^+). Anal. ($C_{16}H_{12}N_4S$) C, H, N.

6-Chloro-2-[(2-naphthalenylmethyl)thio]-4-pyrimidinecarboxylic Acid Ethyl Ester (66). Thioorotic acid, **65** (1.72 g, 10.0 mmol), was suspended in 80% EtOH (20 mL) and then treated with NaOH (0.88 g, 22 mmol) and H_2O (10 mL). The suspension was stirred for 5 min, then 2-(bromomethyl)-naphthalene (2.2 g, 10 mmol) was added, and the reaction was heated to reflux for 2 h. While still warm, the reaction was quenched with 1 N HCl (11 mL) to give a white precipitate. After cooling, the solid was collected, washed with water, and then dried: 3.03 g (9.70 mmol, 97%); ^1H NMR (DMSO) δ 8.10 (s, 1 H), 7.83 (m, 3 H), 7.60 (dd, J = 1.8, 8.5 Hz, 1 H), 7.48 (m, 2 H), 6.63 (s, 1 H), 4.59 (s, 2 H).

The crude acid (2.50 g, 8.00 mmol) and CDI (1.9 g, 12 mmol) were stirred in DMF (30 mL) for 30 min. EtOH (8 mL) was added, and the mixture stirred for 1.5 h. The reaction was poured onto H_2O (200 mL) and stirred for 20 min; then the product was collected by filtration and dried: 2.37 g (7.05 mmol, 88%); ^1H NMR (DMSO) δ 8.06 (s, 1 H), 7.83 (m, 3 H), 7.63 (d, J = 8.4 Hz, 1 H), 7.48 (m, 2 H), 6.65 (s, 1 H), 4.58 (s, 2 H), 4.36 (q, J = 7.1 Hz, 2 H), 1.35 (t, J = 7.1 Hz, 3 H).

The crude ester (2.32 g, 6.81 mmol), $POCl_3$ (7 mL), and 2-picoline (0.7 mL) were stirred at room temperature for 3 h and then poured onto ice. The precipitate was collected and stirred with NH_4OH for 15 min. The tan solid was collected and recrystallized from MeOH to give **66**: 1.72 g (4.79 mmol, 70%) mp 95−96 °C; ^1H NMR δ 8.00 (s, 1 H), 7.81 (m, 3 H), 7.61 (s, 1 H), 7.59 (m, 1 H), 7.46 (m, 2 H), 4.59 (s, 2 H), 4.49 (q, J = 7.1 Hz, 2 H), 1.45 (t, J = 7.1 Hz, 3 H); IR 1729, 1540 cm^{-1}; MS (EI) *m/z* 358 (M^+). Anal. ($C_{18}H_{15}ClN_2O_2S$) C, H, N.

6-Amino-2-[(2-naphthalenylmethyl)thio]-4-pyrimidinecarboxylic Acid Ethyl Ester (67). **66** (1.11 g, 3.08 mmol) in DMF (9 mL) was treated with NaN_3 (0.60 g, 9.23 mmol) and stirred for 24 h. The yellow solution was concentrated in vacuo to dryness and then diluted with EtOAc. The solution was filtered through Celite, washed with H_2O and saturated NaCl, dried with $MgSO_4$, and then concentrated in vacuo to yield crude azide: 1.20 g. The crude azide in EtOAc (45 mL) and EtOH (20 mL) was treated with $SnCl_2$ (3.8 g, 17 mmol). After 15 min, the reaction was poured onto ice/saturated $NaHCO_3$, and the resulting tin salts were filtered through Celite. The filtrate was extracted 2 × EtOAc, and the organics were washed with saturated NaCl, dried with $MgSO_4$, and then concentrated in vacuo. The crude product was then purified by trituration with methyl *tert*-butyl ether to yield **67**: 646 mg (1.90 mmol, 62% for 2 steps); mp 188−189 °C; ^1H NMR (DMSO) δ 8.22 (s, 1 H), 8.02 (s, 1 H), 7.83 (m, 3 H), 7.60 (dd, J = 1.1, 8.3 Hz, 1 H), 7.48 (m, 2 H), 7.27 (s, 2 H), 6.76 (s, 1 H), 4.47 (s, 2 H), 4.32 (q, J = 7.1 Hz, 2 H), 1.31 (t, J = 7.1 Hz, 3 H); IR 1703, 1648, 1593, 1540 cm^{-1}; MS (EI) *m/z* 339 (M^+). Anal. ($C_{18}H_{17}N_3O_2S$) C, H, N.

6-Chloro-2-[(phenylmethyl)oxy]-4-pyrimidinamine (69). NaH (50% in oil, 61 mg, 1.2 mmol) and THF (3.6 mL) were slurried together and cooled to 0 °C. BnOH (0.12 mL, 1.2 mmol) was added and the solution warmed to 22 °C for 30 min. The reaction mixture was recooled to 0 °C and **68** (198 mg, 1.2 mmol) added. The solution was stirred for 18 h at 22 °C, then quenched with saturated NH_4Cl, and concentrated in vacuo. The residue was dissolved in EtOAc, washed with 2 × saturated $NaHCO_3$ and 1 × saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed (hexane/EtOAc, 4:1) to yield **69**: 101 mg (0.430 mmol, 36%); mp 114−115 °C; ^1H NMR δ 7.45 (m, 2 H), 7.34 (m, 3 H), 6.15 (s, 1 H), 5.36 (s, 2 H), 5.00 (brd s, 2 H); IR 1642, 1632, 1583, 1551 cm^{-1}; MS (EI) *m/z* 235 (M^+). Anal. ($C_{11}H_{10}ClN_3O$) C, H, N.

6-Chloro-2-[[(3-methylphenyl)methyl]oxy]-4-pyrimidinamine (70): 45%; mp 85−87 °C; ^1H NMR δ 7.27−7.23 (m, 3 H), 7.16−7.11 (m, 1 H), 6.18 (s, 1 H), 5.48 (brd s, 2 H), 5.33 (s, 2 H), 2.35 (s, 3 H); IR 1641, 1586, 1552 cm^{-1}; MS (EI) *m/z* 249 (M^+). Anal. ($C_{12}H_{12}ClN_3O$) C, H, N.

6-Chloro-2-[(1-naphthalenylmethyl)oxy]-4-pyrimidinamine (71): 19%; mp 160−161 °C; ^1H NMR δ 8.11 (d, J = 7.8 Hz, 1 H), 7.89−7.82 (m, 2 H), 7.65 (d, J = 7.0 Hz, 1 H), 7.55−7.42 (m, 3 H), 6.14 (s, 1 H), 5.82 (s, 2 H), 5.01 (brd s, 2 H); IR 1582, 1550, 1511 cm^{-1}; MS (EI) *m/z* 285 (M^+). Anal. ($C_{15}H_{12}N_3ClO$) C, H, N.

6-Chloro-2-[(2-naphthalenylmethyl)oxy]-4-pyrimidinamine (72): 11%; mp 130−131 °C (heptane/toluene); ^1H NMR δ 7.92 (s, 1 H), 7.85−7.82 (m, 3 H), 7.56−7.46 (m, 3 H), 6.15 (s, 1 H), 5.52 (s, 2 H), 5.01 (brd s, 2 H); IR 1632, 1578, 1545 cm^{-1}; MS (EI) *m/z* 285 (M^+). Anal. ($C_{15}H_{12}N_3ClO$) C, H, N.

6-Chloro-2-[(2-naphthalenylmethyl)amino]-4-pyrimidinamine (74). Compound **73** (0.25 g, 1.5 mmol) was

dissolved in CH_2Cl_2 (4 mL), cooled to 0 °C, and treated with NaH (50% in oil, 72 mg, 1.5 mmol). After stirring for 30 min at 0 °C, 2-(bromomethyl)naphthalene (0.49 g, 2.2 mmol) was added and the mixture stirred at room temperature for 72 h and then at reflux for 10 h. The mixture was cooled, diluted with CH_2Cl_2, and quenched with saturated NH_4Cl. The organic layer was washed with 2 × H_2O, dried with $MgSO_4$, and concentrated to an orange solid. The material was chromatographed (hexane/EtOAc, 15:1) to give a dichloropyrimidine as a fluffy white solid: 191 mg (0.630 mmol, 42%); mp 155−156 °C (heptane).

This pyrimidine (97 mg, 0.32 mmol) was added to saturated NH_3 in MeOH (4 mL), and the resultant solution was heated to 110 °C for 24 h in a sealed vial. After cooling to room temperature, the solvent was removed in a stream of N_2 and the residue partitioned between EtOAc and H_2O. The organic portion was washed with 2 × H_2O and 1 × saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (EtOAc/hexane, 1:1) to give **74** as a white solid: 76 mg (0.27 mmol, 83%); mp 134−135 °C; ^{1}H NMR δ 7.83−7.74 (m, 5 H), 7.48−7.41 (m, 3 H), 5.84 (s, 1 H), 4.75 (brd s, 2 H), 4.73 (s, 2 H); IR 1646, 1622, 1594, 1572, 1528 cm^{-1}; MS (EI) *m*/*z* 284 (M^+). Anal. ($C_{15}H_{13}N_4Cl$) C, H, N.

6-Chloro-2-[2-(2-naphthyl)ethyl]-4-pyrimidinamine (78). 2-Naphthylethanol (7.8 g, 45 mmol) and Et_3N (6.6 mL, 47 mmol) in THF (75 mL) at 0 °C were treated dropwise with MsCl (3.6 mL, 47 mmol), then warmed to 22 °C, and stirred for 3 h. The reaction was diluted with EtOAc, washed with 2 × 1 M HCl, 1 × H_2O, 2 × saturated $NaHCO_3$, and 1 × saturated NaCl, dried with Na_2SO_4, and concentrated in vacuo to give the mesylate as a slightly pink solid: 11.8 g (45.0 mmol, 100%); ^{1}H NMR δ 7.83−7.79 (m, 3 H), 7.70 (s, 1 H), 7.51−7.44 (m, 2 H), 7.35 (m, 1 H), 4.51 (t, J = 6.9 Hz, 2 H), 3.22 (t, J = 6.8 Hz, 2 H), 2.83 (s, 3 H).

The crude mesylate (11.8 g, 45.0 mmol) and KCN (11.7 g, 0.18 mol) in DMF (67 mL) were heated to 60−70 °C for 15 h. After cooling, the reaction was poured into H_2O (500 mL), which was then extracted with 4 × 75 mL of MtBE. The combined organic layers were washed with H_2O and saturated NaCl, dried with $MgSO_4$, and concentrated in vacuo to give the nitrile **76**: 5.38 g (29.7 mmol, 66%); mp 76−77 °C (heptane/toluene); ^{1}H NMR δ 7.84−7.79 (m, 3 H), 7.69 (s, 1 H), 7.52−7.44 (m, 2 H), 7.36−7.33 (m, 1 H), 3.13 (t, J = 7.4 Hz, 2 H), 2.71 (t, J = 7.4 Hz, 2 H).

Into a −78 °C solution of **76** (2.04 g, 11.2 mmol) in absolute EtOH (40 mL) and CH_2Cl_2 (150 mL) was bubbled HCl for 20 min. When the addition was complete, the reaction was warmed to −20 °C and maintained for 2 h. The mixture was concentrated in vacuo to give the crude imido ester HCl: 1.52 g (5.80 mmol, 51%); ^{1}H NMR δ 7.90−7.86 (m, 4 H), 7.78 (s, 1 H), 7.54−7.44 (m, 3 H), 4.41 (q, J = 7.0 Hz, 2H), 3.16−3.05 (m, 4 H), 1.29 (t, J = 7.0 Hz, 3 H).

To a solution of NH_3/MeOH (3.9 M, 25 mL, 97 mmol) at 0 °C was added the imido ester·HCl salt (1.27 g, 4.8 mmol) in several portions. The solution was stirred at 0 °C for 20 min and then at 22 °C for 1 h. The reaction mixture was concentrated in vacuo, then resuspended in 1:1 EtOH/$CHCl_3$ (30 mL), cooled, and filtered. The resultant solid was dried under vacuum to provide **77** as a white powder which was used without further purification: ^{1}H NMR δ 7.78−7.74 (m, 3 H), 7.67 (s, 1 H), 7.45−7.34 (m, 3 H), 3.14 (t, J = 7.1 Hz, 2 H), 2.81 (t, 2 H).

Compound **77** (1.08 g, 4.60 mmol) and ethyl cyanoacetate (0.52 g, 4.6 mmol) in MeOH (5 mL) were treated with a solution of NaOMe (25% in MeOH, 1.1 mL, 4.8 mmol) and then heated at reflux for 24 h. After cooling, the mixture was filtered, and the solids were washed with 2 × cold MeOH and H_2O: 0.43 g (1.6 mmol, 35%). The hydroxypyrimidine (0.379 g, 1.43 mmol) was treated with $POCl_3$ (1.2 mL, 13 mmol) and 2-picoline (0.14 mL, 1.4 mmol) and then heated to reflux for 22 h. After cooling, the reaction was quenched on ice and heated to reflux for 30 min. The reaction was cooled, adjusted to pH 10 with concentrated NH_4OH, and again heated to reflux for 1 h. After cooling, the residue was dissolved in EtOAc, washed with 3 × saturated $NaHCO_3$ and 1 × saturated NaCl, dried with $MgSO_4$, and then concentrated in vacuo. The resultant oil was chromatographed (hexane/EtOAc, 4:1) to give **78** as a waxy solid: 95 mg (0.33 mmol, 23%); ^{1}H NMR δ 7.81−7.75 (m, 4 H), 7.68 (s, 1 H), 7.47−7.36 (m, 3 H), 6.29 (s, 1 H), 5.25 (s, 2 H), 3.27−3.2 (m, 2 H), 3.13−3.08 (m, 2 H); IR 1632, 1572, 1544, 1508 cm^{-1}; MS (EI) *m*/*z* 283 (M^+). Anal. ($C_{16}H_{14}ClN_3$) C, H, N.

6-Chloro-2-[(2-naphthalenylmethyl)sulfinyl]-4-pyrimidinamine (79). Compound **5** (30 mg, 0.10 mmol) was dissolved in MeOH (1 mL) and treated dropwise with a solution of SeO_2 (11 mg, 0.1 mmol) and 30% H_2O_2 (1 drop) in MeOH (1 mL). After 1 h, 30% H_2O_2 (1 drop) was added, and stirring continued for 30 min. The reaction was diluted with H_2O and filtered. The white precipitate was washed with acetone and air-dried to give **79**: 15 mg (0.047 mmol, 47%); mp 222−223 °C; ^{1}H NMR (DMSO) δ 7.87 (m, 4 H), 7.73 (s, 2 H), 7.53 (m, 2 H), 7.25 (d, J = 8.4 Hz, 1 H), 6.50 (s, 1 H), 4.53 (d, J = 12.8 Hz, 1 H), 4.37 (d, J = 12.8 Hz, 1 H); IR 1612, 1574, 1518 cm^{-1}; MS (EI) *m*/*z* 318 (M^+). Anal. ($C_{15}H_{12}ClN_3OS$) C, H, N.

6-Chloro-2-[[(3-bromophenyl)methyl]sulfinyl]-4-pyrimidinamine (80). Compound **34** (0.16 mg, 0.50 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C, treated with 50% mCPBA (0.17 mg, 0.50 mmol), and stirred overnight at room temperature. The solid was collected and washed with MtBE to give **80**: 77 mg (0.22 mmol, 44%); mp 216−217 °C (acetonitrile); ^{1}H NMR (DMSO) δ 7.49 (d, J = 7.5 Hz, 1 H), 7.32 (m, 1 H), 7.27 (t, J = 7.7 Hz, 1 H), 7. 12 (d, J = 7.6 Hz, 1 H), 6.48 (s, 1 H), 4.38 (d, J = 12.8 Hz, 1 H), 4.21 (d, J = 12.8 Hz, 1 H); IR 1646, 1633, 1576, 1520 cm^{-1}; MS (EI) *m*/*z* 345 (M^+). Anal. ($C_{11}H_9BrClN_3OS$) C, H, N.

6-Chloro-2-[[(3-bromophenyl)methyl]sulfonyl]-4-pyrimidinamine (81). Compound **34** (0.66 g, 2.0 mmol) was dissolved in HOAc (5 mL), treated with 30% H_2O_2 (1 mL), and stirred for 72 h at room temperature. The reaction was diluted with EtOAc, washed 1 × H_2O, 3 × saturated $NaHCO_3$, and 1 × saturated NaCl, then dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (EtOAc/hexane, 1:1), then dissolved in acetone, and knocked out with H_2O: 286 mg (0.790 mmol, 39%); mp 191−192 °C; ^{1}H NMR (DMSO) δ 8.19 (s, 1 H), 7.95 (s, 1 H), 7.56 (m, 2 H), 7.33 (m, 2 H), 6.45 (s, 1 H), 4.87 (s, 2 H); IR 1648, 1639, 1576, 1515 cm^{-1}; MS (EI) *m*/*z* 361 (M^+). Anal. ($C_{11}H_9BrClN_3O_2S$) C, H, N.

HIV RT Assay. The standard reaction mixture for the RT assay contained 2 mM dithiothreitol, 60 mM NaCl, 10 mM $MgCl_2$, 50 μM Tris-HCl (pH 8.3), 0.05% Nonidet P-40, 50 μM thymidine triphosphate with 12 μCi/mL [*methyl*-^{3}H]thymidine 5′-triphosphate (Amersham), 200 nM template:primer (poly(rA)$_{600}$:oligo(dT)$_{10}$; from Pharmacia), and 4 homodimers and was obtained as previously described.[11,21,22] The assay was carried out at 28 °C for 10 min in a total volume of 100 μL. The enzyme reaction was terminated by addition of 100 μL of trichloroacetic acid (10%, v/v). The acid-precipitated materials, recovered on glass fiber filters by Micro96 Harvester (SKATRON), were analyzed for radioactivity.

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