Synthesis of 2,8-Disubstituted Imidazo[1,5-*a*]pyrimidines with Potent Antitumor Activity

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Seventeen 1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidine derivatives bearing electron-withdrawing substituents were designed and synthesized by novel ring closure as potential antitumor agents. They were screened for their activities against mouse leukemia L1210 and human oral epidermoid carcinoma KB cell lines, and relationships of structure and antitumor activity in vitro are discussed. It was found that 8-thiocarbamoyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**8c**) exhibited activity comparable to that of 5-fluorouracil against both L1210 and KB cells. The existence of both 2-thioxo and 8-substituent with a thioxo group in the molecule is crucial for the cytotoxicity against L1210 and KB cells. A novel procedure for introduction of a double bond between C-3 and C-4 in **8c** was developed. Introduction of the 3,4-double bond increased the activity against L1210, but against KB cells the activity decreased by 4-fold. Cytotoxicity of compounds **8c** and 8-thiocarbamoyl-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**11c**) against human solid tumor and leukemia cell lines was further evaluated. The saturation of the 3,4-double bond led to a significant increase in cytotoxicity against tumor cell lines tested.

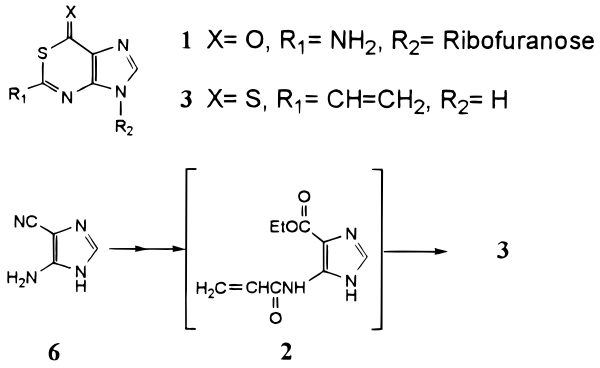
Introduction

Previously, we described the synthesis of a variety of 5-substituted imidazo[1,5-*a*]thiazin-7(3*H*)-ones, e.g., the base moiety of 6-thiaoxanosine (**1**), as potential antiviral and anticancer agents.[1,2] During our attempts to synthesize the base moiety of 5-vinyl-7-thione analogue of **1**, namely, 5-ethenylimidazo[4,5-*d*][1,3]thiazin-7(3*H*)-thione (**3**), via **2** by the known cyclization procedure (Chart 1), we unexpectedly discovered an interesting ring-closure reaction which led to the synthesis of imidazo[1,5-*a*]pyrimidin-2(1*H*)-ones. Thus, when ethyl 5-aminoimidazole-4-carboxylate (**4**) was acylated with acryloyl chloride, we obtained 8-ethoxycarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-one (**7a**; Scheme 1) instead of 5-acryloylamino derivative **2**. Thiation of **7a** with Lawesson's reagent afforded monothiated derivative **7b** and dithiated derivative **7c**, respectively, and **7c** was found to be more active against L1210 and KB cells than **7a** and **7b**. We, therefore, synthesized derivatives of imidazo[1,5-*a*]pyrimidines by exploitation of our new ring-closure reaction in search of more potent derivatives and for structure−activity relationship studies. We also describe a novel synthetic procedure for the 1,2-dihydroimidazo[1,5-*a*]pyrimidine ring system.

Chemistry

Acylation of 5-amino-4-ethoxycarbonyl-, 5-amino-4-carbamoyl-, and 5-amino-4-cyanoimidazoles (**4**−**6**, respectively) with aliphatic or aromatic acyl chloride in the presence of base usually gives rise to the corresponding 4-substituted 5-acylaminoimidazoles. However, when **4** was treated with acryloyl chloride in acetonitrile at 80 °C for 3 h in the presence of triethylamine, we obtained a crystalline product which was analyzed correctly for the desired 5-acryloylaminoimidazole (**2**) in 56% yield. The ^{1}H NMR spectrum of this product, however, showed the lack of vinyl protons but the presence of two-proton triplets at δ 2.75 and 4.23. There is one deuterium-exchangeable (NH, δ 9.83) and one aromatic (δ 7.46) proton in the molecule. Moreover, this compound exhibited the correlation among methylene protons at δ 4.23 and three carbons at δ 132.48 (C-6), 136.30 (C-8a), and δ 162.23 (C-2) in ^{1}H−^{13}C heteronuclear multiple bond connectivity. These data are fully consistent *only* with the 8-ethoxycarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-one structure (**7a**; Scheme 1). A plausible mechanism for the

Chart 1



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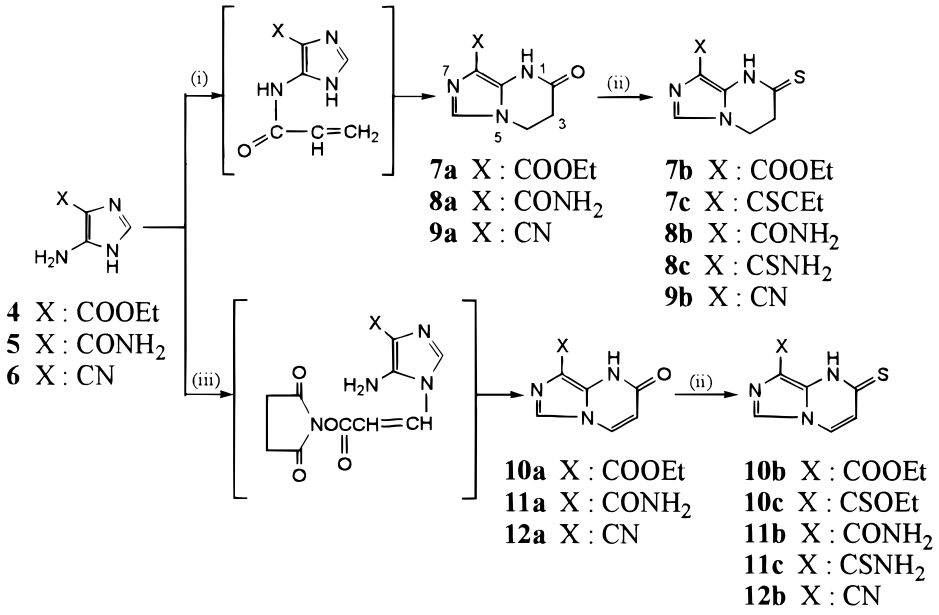
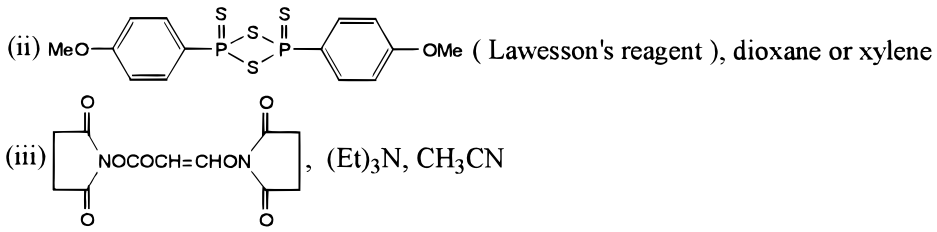
Scheme 1[a]

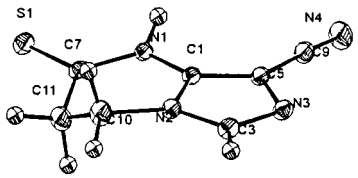


[a] Reagent : (i) CH_2=CHCOCl, $(Et_3)N$ or imidazole or K_2CO_3, CH_3CN

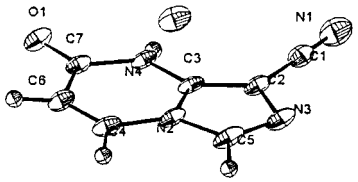


formation of **7a** from **4** would be intramolecular Michael addition which occurred between the initially formed enone and the imidazole nitrogen. A similar treatment of **5** and **6** afforded **8a** and **9a**, respectively.

Thiation of **7a** with Lawesson's reagent in xylene at 130 °C for 16 h produced mono- and dithiated products **7b** and **7c** in 24% and 66% yields, respectively. The structural determination of the dithio compound as 8-ethoxythiocarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]-pyrimidin-2(1*H*)-thione (**7c**) rests upon spectral data (^{1}H NMR, ^{13}C NMR, and MS) as well as elemental analyses. Selective thiation at C-2 was accomplished by reducing the reaction time to 30 min (yield of **7b** was 74%). Reaction of **8a** with the same reagent in dioxane at 100 °C for 1 h afforded dithio derivative **8c** in 77% yield. When the reaction was carried out at lower temperature (70 °C), the sole thiated product was 2-thioxo derivative **8b** which was isolated in 28% yield. The isomeric 2-oxo-8-thioamide **8d** was obtained in 87% yield from **9a** by treatment with H_2S. These experiments clearly showed that a cyclic amide carbonyl is more readily thiated than an exocyclic amide carbonyl group. In a similar treatment of **9a** in dioxane at 100 °C for 1 h, 2-thio derivative **9b** (55%) was obtained along with the dithio product **8c** (29%). Prolonged heating (3 h) caused complete conversion of **9a** into **8c**. Formation of the thioamide from the cyano group occurred more rapidly in dioxane than in xylene probably due to the abundance of moisture in the former. Thus, we developed a method for a one-step synthesis of the active compound **8c** from **9a**.



9b



12a

Figure 1. ORTEP drawing of **9b** and **12a** and the crystallographic numbering scheme.

The structures of these thiated products **7b**, **8b**−**d,** and **9b** were established by spectral (^{1}H NMR, ^{13}C NMR, and MS) as well as elemental analyses. Surprisingly, no geminal couplings, anticipated for the methylene protons in **7b**−**9b**, were observed. The X-ray crystallographic analysis of **9b** firmly confirmed the 1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidine structure (Figure 1).

For the synthesis of 1,2-dihydro compounds **10a**, **11a,** and **12a**, acylation of **4**−**6** with propiolic acid with various coupling reagents including DMC and DCC failed to obtain the desired products in satisfactory yields. However, we found that these products can be

Table 1. Physical Properties of Imidazo[1,5-*a*]pyrimidine Derivatives

compound	C-8	C-2	mp(℃)	yield(%)	formula[b]
7a	EtOC(O)	O	157 - 158	56	$C_9H_{11}N_3O_3$
7b	EtOC(O)	S	213 - 215	74	$C_9H_{11}N_3O_2S$
7c	EtOC(S)	S	166 - 168	66	$C_9H_{11}N_3OS_2$
8a	$H_2NC(O)$	O	269 - 271	47	$C_7H_8N_4O_2$ 1/2 H_2O
8b	$H_2NC(O)$	S	268 - 272[a]	28	$C_7H_8N_4OS$
8c	$H_2NC(S)$	S	258 - 262[a]	77	$C_7H_8N_4S_2$
8d	$H_2NC(S)$	O	242 - 243	87	$C_7H_8N_4OS$ 1/9H_2O
9a	NC	O	292 - 293	40	$C_7H_6N_4O$
9b	NC	S	223 - 225[a]	55	$C_7H_6N_4S$
10a	EtOC(O)	O	235 - 236	46	$C_9H_9N_3O_3$
10b	EtOC(O)	S	231 - 234[a]	44	$C_9H_9N_3O_2S$
10c	EtOC(S)	S	153 – 155[a]	49	$C_9H_9N_3OS_2$·1/9H_2O
11a	$H_2NC(O)$	O	260 – 261	59	$C_7H_6N_4O_2$ 3/5H_2O
11b	$H_2NC(O)$	S	238 – 242[a]	34	$C_7H_6N_4OS$·1/4H_2O
11c	$H_2NC(S)$	S	278 – 280[a]	73	$C_7H_8N_4S_2$
12a	NC	O	> 300	71	$C_7H_4N_4O$
12b	NC	S	243 – 248[a]	40	$C_7H_4N_4S$·1/10H_2O

[a] Decomposed. [b] Analyses of all new compounds for C, H, N, and S agree with calculated values in the range of ±0.4%.

synthesized in 46−71% yields by the reaction of **4**−**6** with *N*-succinimidyl 3-succinimidoxypropenoate (**13**; Scheme 1). Reagent **13** was prepared in 73% yield by treatment of propiolic acid with *N*,*N*′-disuccinimidyl carbonate in acetonitrile in the presence of pyridine. The structure of **12a** and the geometry around the double bond, in particular, were further confirmed by X-ray crystallography (Figure 1).

Thiation of **10a**, **11a,** and **12a** gave the corresponding mono- and dithiated products **10b**, **11b**, **12b, 10c**, and **11c**, respectively in 34−73% yields depending upon the reaction conditions.

Cytotoxicity and Discussion

All newly synthesized compounds were screened for their cytotoxicity against mouse leukemia L1210 cells and human oral epidermoid carcinoma KB cells by the method of Carmichael et al.,[3] and the results are summarized in Table 2. These results clearly showed that the sulfur-free compounds **7a**−**12a** are totally inactive against both cell lines. Introduction of one sulfur atom to the molecules **7a**−**12a** exerted a slight cytotoxicity only against L1210 cells. Addition of the second sulfur atom to the molecules dramatically increased the cytotoxicity of the compounds against both cell lines. Thus, compounds **8c** and **11c** exhibited potent activity against these cell lines. Against L1210, **11c** was found to show the most potent activity (IC_{50}, 0.31 μM) among the new compounds tested. The 3,4-saturated analogue **8c** exhibited activity as potent as 5FU against both L1210 cells (IC_{50}, 0.61 μM) and KB cells (IC_{50}, 3.2 μM).

The activity of three compounds (**7c**, **8c,** and **11c**) that were found to be quite cytotoxic to both L1210 and KB cell lines was further evaluated against human solid tumor and leukemic cell lines (Table 3). In general, saturation of the 3,4-double bond in the imidazo[1,5-*a*]-pyrimidine ring system led to a significant increase in cytotoxicity against human solid tumor cell lines. This effect was found most dramatically in the case of KATO III cell line. Whereas the unsaturated derivative **11c** exhibited no cytotoxicity even at 100 μM concentration against this cell line, the 3,4-saturated compound **8c** became very active (IC_{50}, 4.7 μM). The increase in activity was more than 20-fold. The influence of the 3,4-double bond on the activity against leukemic cells was not so apparent as both thioamide derivatives **8c** and **11c** showed similar activity against most of the five leukemic cell lines tested (Table 3).

The role of sulfur on cytotoxic effect is remarkable (Table 2). Compounds without sulfur (**7a**−**12a)** did not exhibit cytotoxicity. Monothio substitution at C-2 (**7b**−**12b** and **8d**) made these compounds active against L1210 cells; **9b**, **11b,** and **12b** became cytotoxic even against KB cells. A dramatic increase in cytotoxicity by introduction of an additional sulfur (**7c**, **8c,** and **11c**) implies that the existence of both the 2- and 8-thioxo groups in these heterocyclic compounds is decisively important for potent cytotoxicity against these cell lines.

It is also to be noted that the function of the 3,4-double bond is significant for cytotoxicity. As is apparent from the X-ray structure (Figure 1), the double bond makes the six-membered ring flattened and restricts conformational flexibility compared to the 3,4-saturated structure. It is most likely that the conformational flexibility of the six-membered ring moiety is a significant factor to be active against solid tumor cells.

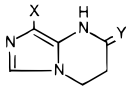
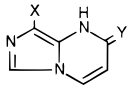
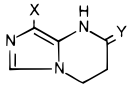
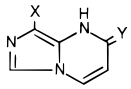
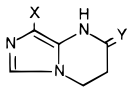
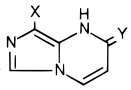
Conclusion

In this paper we described novel ring closure reactions which led to the synthesis of derivatives containing the rarely studied imidazo[1,5-*a*]pyrimidine ring system: there are only four publications available dealing with the chemistry of this ring system.[4−7] Among a total of 17 compounds that we prepared, two of them, 8-thiocarbamoyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**8c**) and 8-thiocarbamoyl-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**11c**), showed potent cytotoxicity. Thus, cytotoxicity of **8c** against both mouse leukemia L1210 (IC_{50}, 0.61 μM) and human solid tumor KB (IC_{50}, 3.2 μM) cells was found to be as potent as that of 5-FU (IC_{50}, 0.61 and 2.3 μM, respectively). Compound **11c**, on the other hand, exhibited exceptional potency against L1210 (IC_{50}, 0.31 μM), while its activity against KB cells was somewhat low (IC_{50}, 12.8 μM). The presence of two sulfur atoms in the molecule is essential for potent cytotoxicity, and in general, 3,4-saturated derivatives are more potent against solid tumors than the unsaturated counterparts, while both are active against leukemic cell lines. Compounds **8c** and **11c** may serve as useful lead compounds for the search of more powerful antineoplastic agents.

Experimental Section

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^1H and ^{13}C NMR were recorded on JEOL JNL-GX270 (270 M Hz) and EX400 (400 MHz) spectrometers with Me_4Si as the internal standard. Spectra were taken in DMSO-d_6, and the chemical shifts are reported in parts per million (δ). Resonance patterns are reported with the following notations: b (broad), s (singlet), d (doublet), t (triplet), and q (quartet). Mass spectra were run

Table 2. Growth Inhibitory Effect of Imidazo[1,5-*a*]pyrimidine Derivatives on Murine Leukemia L1210 and Human Oral Epidermoid Carcinoma KB Cells[a]

class	substituent		compound	$IC_{50}(\mu M)$[b]	
				L1210	KB
sulfur-free compound 	X=COOEt	Y=O	**7a**	>100	>100
	$X=CONH_2$	Y=O	**8a**	>100	>100
	X=CN	Y=O	**9a**	>100	>100
	X-COOEt	Y=O	**10a**	>100	>100
	$X=CONH_2$	Y=O	**11a**	>100	>100
	X=CN	Y=O	**12a**	>100	>100
monosulfurous compound 	X=COOEt	Y=S	**7b**	62 ± 9	>100
	$X=CONH_2$	Y=S	**8b**	38 ± 11	>100
	$X=CSNH_2$	Y=O	**8d**	37 ± 8	>100
	X=CN	Y=S	**9b**	40 ± 14	35 ± 15
	X=COOEt	Y=S	**10b**	72 ± 12	>100
	$X=CONH_2$	Y=S	**11b**	49 ± 5	88 ± 17
	X=CN	Y=S	**12b**	ND[d]	35 ± 16
disulfurous compound 	X=CSOEt	Y=S	**7c**	5.4 ± 2.1	6.2 ± 1.5
	$X=CSNH_2$	Y=S	**8c**	0.61 ± 0.32	3.2 ± 2.1
	X=CSOEt	Y=S	**10c**	4.2 ± 1.9	84 ± 15
	$X=CSNH_2$	Y=S	**11c**	0.31 ± 0.14	13 ± 5
reference			**5FU**[c]	0.62 ± 0.28	2.3 ± 1.2

[a] The tetrazolium-based semiautomated colorimetric assay (MTT assay), developed by Carmichael,[3] was modified and used for the in vitro assay. Each tumor cell (2×10^3/well) was incubated in the presence or absence of compound for 72 h. Then, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide was added. After incubation for 4 h more, the resulting MTT-formazan was dissolved in DMSO and the OD (540 nm) was measured. Percent inhibition was calculated as follows: % inhibition = [1 − OD of sample well/OD of control well] × 100. [b] IC_{50} (μM) was given as the concentration at 50% inhibition of cell growth. [c] 5-Fluorouracil. [d] ND, not determined.

on a JEOL JMS-DX303 spectrometer. Flash chromatography was performed on Merck Kieselgel 60 (70−230 mesh) and a Yamazen Ultra Pack ODS-A-40B column.

8-Ethoxycarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-one (**7a**). To a solution of **4** (780 mg, 5 mmol) and Et_3N (1.1 mL) in dry MeCN (25 mL) was added dropwise a solution of acryloyl chloride (0.61 mL, 7.5 mmol) in dry MeCN (2 mL) at room temperature. The mixture was kept at 50 °C for 16 h and then concentrated in vacuo, and the residue was chromatographed (MeOH−$CHCl_3$, 5:98.5 v/v) to give pure **7a** (580 mg, 56%): ^{1}H NMR (DMSO-d_6) δ 1.26 (t, 3H, CH_3CH_2), 2.75 (t, 2H, H-3), 4.22 (q, 2H, CH_3CH_2), 4.23 (t, 2H, H-4), 7.46 (s, 1H, H-6), 9.83 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 14.43, 30.10, 38.81, 59.10, 112.52, 136.30, 162.10, 166.47; EIMS *m*/*z* 209 (M^+). Anal. ($C_9H_{11}N_3O_3$) C, H, N.

8-Ethoxycarbonyl-1,2,3,4-tetrahydro[1,5-*a*]pyrimidine-2(1*H*)-thion (**7b**) and **8-Ethoxythiocarbonyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione** (**7c**). A mixture of **7a** (92 mg, 0.44 mmol) and Lawesson's reagent (355 mg, 0.88 mmol) in dry xylene (15 mL) was heated at 130 °C for 16 h. After concentration of the mixture in vacuo, the residue was chromatographed (MeOH−$CHCl_3$, 1.4:98.6 v/v) to separate **7b** (24 mg, 24%) and **7c** (70 mg, 66%).

7b: ^{1}H NMR (DMSO-d_6) δ 1.28 (t, 3H, C*H*$_3$CH$_2$), 3.21 (t, 2H, H-3), 4.16 (t, 2H, H-4), 4.25 (q, 2H, CH$_3$C*H*$_2$), 7.60 (s, 1H, H-6), 11.46 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 14.52, 38.89, 39.30, 59.84, 116.64, 133.87, 162.12. 197.01; EIMS *m*/*z* 225 (M^+). Anal. ($C_9H_{11}N_3O_2S$) C, H, N, S.

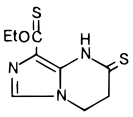
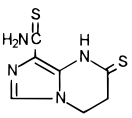
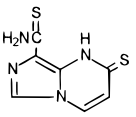
7c: ^{1}H NMR (DMSO-d_6) δ 1.40 (t, 3H, C*H*$_3$CH$_2$), 3.28 (t, 2H, H-3), 4.21 (t, 2H, H-4), 4.64 (q, 2H, CH$_3$C*H*$_2$), 7.62 (s, 1H, H-6), 11.71 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 13.70, 38.42, 38.84, 66.24, 121.69, 133.13, 136.02, 197.31, 201.09; EIMS *m*/*z* 241 (M^+). Anal. ($C_9H_{11}N_3OS_2$) C, H, N, S.

8-Carbamoyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-one (**8a**). To a solution of **5** (406 mg, 2.5 mmol) and imidazole (590 mg, 8.7 mmol) in dry DMF (15 mL) was added dropwise a solution of acryloyl chloride (0.5 mL, 6.3 mmol) in dry DMF (3 mL) at room temperature. The mixture was heated at 80 °C for 3 h and then concentrated in vacuo. The residue was chromatographed (MeOH−$CHCl_3$, 8:92 v/v) to give pure **8a** (213 mg, 47%): ^{1}H NMR (DMSO-d_6) δ 2.76 (t, 2H, H-3), 4.24 (t, 2H, H-4), 6.99 (bs, 2H, NH_2), 7.40 (s, 1H, H-6), 9.12 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 38.66, 45.21, 114.79, 130.61, 135.59, 164.94, 165.41; EIMS *m*/*z* 180 (M^+). Anal. ($C_9H_8N_4O_2 \cdot {}^1/_2H_2O$) C, H, N.

8-Carbamoyl-1,2,3,4-tetrahydro[1,5-*a*]pyrimidin-2(1*H*)-thione (**8b**). A mixture of **8a** (90 mg, 0.5 mmol) and Lawesson's reagent (212 mg, 0.3 mmol) in dry dioxane (8 mL) was heated at 70 °C for 1 h. After concentration of the mixture in vacuo, the residue was chromatographed (MeOH−$CHCl_3$, 4:96 v/v) to give **8b** (27 mg, 28%): ^{1}H NMR (DMSO-d_6) δ 3.22 (t, 2H, H-3), 4.17 (t, 2H, H-4), 7.29 (bs, 1H, NH), 7.38 (bs, 1H, NH), 7.54 (s, 1H, H-6), 10.09 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 38.78, 39.70, 115.76, 132.07, 164.83, 195.19; EIMS *m*/*z* 196 (M^+). Anal. ($C_7H_8N_4OS$).

8-Thiocarbamoyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**8c**). A mixture of **8a** (246 mg, 1.52 mmol) and Lawesson's reagent (140 mg, 1.14 mmol) in dioxane (20 mL) was heated at 100 °C for 1 h. After concentration of the mixture in vacuo, the residue was chromatographed (MeOH−$CHCl_3$, 1:19 v/v) to give **8c** (248 mg, 77%): ^{1}H NMR (DMSO-d_6) δ 3.25 (t, 2H, H-3), 4.21 (t, 2H, H-4), 7.63 (s, 1H,

Table 3. Effects of **7c**, **8c**, **11c**, and 6MP on the Growth of Various Human Tumors in Vitro[a]

cell line	origin	IC_{50} (μM)		
				
		7c	**8c**	**11c**
SW-480	colon adenocarcinoma	49.8 ± 4.9	5.7 ± 6.5	57.1 ± 10.0
DLD-1	colon adenocarcinoma	16.6 ± 6.0	6.6 ± 5.2	30.5 ± 5.9
MKN-28	stomach adenocarcinoma	15.8 ± 6.9	4.5 ± 0.1	28.1 ± 9.8
MKN-45	stomach adenocarcinoma	19.9 ± 8.8	9.9 ± 9.1	>100
KATO-III	stomach adenocarcinoma	18.3 ± 6.1	4.7 ± 0.9	>100
PC-9	lung adenocarcinoma	12.4 ± 6.9	4.3 ± 8.6	20.5 ± 6.4
Lu-65	lung large cell carcinoma	14.1 ± 9.3	3.8 ± 1.1	4.6 ± 7.4
MCF-7	breast adenocarcinoma	15.8 ± 9.6	5.2 ± 8.1	16.2 ± 7.5
MDA-MB-435	breast adenocarcinoma	45.6 ± 5.8	12.3 ± 10.8	57.1 ± 11.6
PANC-1	pancreas adenocarcinoma	78.8 ± 4.2	12.3 ± 10.2	>100
K562	chronic myelogenous leukemia	13.3 ± 9.5	4.1 ± 1.9	17.1 ± 9.5
CCRF-CEM	acute lymphatic leukemia	10.0 ± 8.3	3.6 ± 1.7	4.2 ± 0.7
MOLT-4	acute lymphatic leukemia	10.0 ± 8.7	3.2 ± 1.5	2.3 ± 1.1
HL-660	promyelocytic leukemia	5.4 ± 6.6	2.8 ± 0.5	2.5 ± 1.5
Daudi	Burkitt's lymphoma	3.3 ± 1.0	1.1 ± 0.6	0.81 ± 0.51

H-6), 9.10 (bs, 1H, NH), 9.43 (bs, 1H, NH), 12.23 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 38.17, 38.90, 131.91, 133.88, 186.96, 195.84; EIMS *m/z* 212 (M^+). Anal. ($C_7H_8N_4S_2$) C, H, N, S.

8-Thiocarbamoyl-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-one (**8d**). A solution of **9a** (640 mg, 4.0 mmol) and KOH (2.4 g) in MeOH (100 mL) was chilled to 0 °C, and H_2S was bubbled in for 1 h. The mixture was heated in a steel bomb at 100 °C for 1 h and then poured onto crushed ice. The solution was neutralized with dilute AcOH to pH 4, and the pale-yellow precipitates were filtered to afford 417 mg of **8d**. An additional crop of **8d** was obtained from the filtrate upon concentration to give the total yield of 734 mg (87%): ^{1}H NMR (DMSO-d_6) δ 2.81 (t, 2H, H-3), 4.27 (t, 2H, H-4), 7.51 (s, 1H, H-6), 8.88 (bs, 1H, NH), 9.18 (bs, 1H, NH), 10.40 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 29.46, 38.88, 118.45, 130.76, 136.63, 165.71, 187.18; EIMS *m/z* 196 (M^+). Anal. ($C_7H_8N_4OS\cdot 1/4H_2O$) C, H, N, S.

8-Cyano-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-one (**9a**). To a solution of **6** (540 mg, 5.0 mmol) and imidazole (612 mg, 9.0 mmol) in dry MeCN (15 mL) was added dropwise a solution of acryloyl chloride (0.61 mL, 7.5 mmol) in dry MeCN (3 mL) at 80 °C. The mixture was stirred at 80 °C for 3 h and then concentrated in vacuo. The residue was chromatographed (MeOH−$CHCl_3$, 6:94 v/v) to give **9a** (320 mg, 40%): ^{1}H NMR (DMSO-d_6) δ 2.72 (t, 2H, H-3), 4.22 (t, 2H, H-4), 7.55 (s, 1H, H-6), 11.50 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 29.92, 39.08, 92.79, 114.88, 133.72, 138.79, 166.73; EIMS *m/z* 162 (M^+). Anal. ($C_7H_6N_4O$) C, H, N.

8-Cyano-1,2,3,4-tetrahydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**9b**). A mixture of **9a** (246 mg, 1.52 mmol) and Lawesson's reagent (460 mg, 1.14 mmol) in dioxane (20 mL) was heated at 100 °C for 1 h. After concentration of the mixture in vacuo, the residue was triturated with $CHCl_3$ to crystallize **9b** (150 mg, 55%): ^{1}H NMR (DMSO-d_6) δ 3.17 (t, 2H, H-3), 4.15 (t, 2H, H-4), 7.67 (s, 1H, H-6), 13.49 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 38.86, 39.28, 93.98, 114.54, 134.80, 135.99, 197.58; EIMS *m/z* 178 (M^+). Anal. ($C_7H_6N_4S$) C, H, N, S.

8-Ethoxycarbonyl-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-one (**10a**). A solution of **4** (388 mg, 2.5 mmol), **13** (790 mg, 2.8 mmol, vide infra), and Et_3N (2 mL) in dry MeCN (25 mL) was heated at 50 °C for 16 h. After concentration in vacuo, the residue was treated with MeOH (20 mL) and the mixture was stirred at 60 °C for 30 min. The insoluble materials were filtered, and the filtrate was concentrated and chromatographed (MeOH−$CHCl_3$, 4:96 v/v) to give **10a** (238 mg, 46%): ^{1}H NMR (DMSO-d_6) δ 1.28 (t, 3H, CH_3CH_2), 4.28 (q, 2H, CH_3CH_2), 6.11 (d, 1H, H-3, J = 7.81 Hz), 7.91 (s, 1H, H-6), 8.39 (d, 1H, H-4, J = 7.81 Hz), 11.18 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 14.41, 59.21, 108.78, 110.18, 128.45, 134.76, 135.81, 158.99, 161.59; EIMS *m/z* 207 (M^+). Anal. ($C_9H_9N_3O_3$) C, H, N.

8-Ethoxycarbonyl-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**10b**). A mixture of **10a** (181 mg, 0.87 mmol) and Lawesson's reagent (211 mg, 0.52 mmol) in dry xylene (10 mL) was heated at 130 °C for 1 h. After concentration of the mixture in vacuo, the residue was chromatographed (MeOH−$CHCl_3$, 1:99 v/v) to give **10b** (92 mg, 44%): ^{1}H NMR (DMSO-d_6) δ 1.31 (t, 3H, CH_3CH_2), 4.32 (q, 2H, CH_3CH_2), 6.74 (d, 1H, H-3, J = 7.69 Hz), 8.05 (s, 1H, H-6), 8.27 (d, 1H, H-4, J = 7.15 Hz); ^{13}C NMR (DMSO-d_6) δ 14.28, 59.75, 110.48, 118.47, 127.98, 128.97, 133.99, 161.52, 182.86; EIMS *m/z* 223 (M^+). Anal. ($C_9H_9N_3O_2S$) C, H, N, S.

8-Ethoxythiocarbonyl-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**10c**). A mixture of **10a** (120 mg, 0.87 mmol) and Lawesson's reagent (469 mg, 1.16 mmol) in dry xylene (16 mL) was heated at 130 °C for 16 h. After concentration of the mixture in vacuo, the residue was chromatographed using $CHCl_3$ as an eluent to give **10c** (68 mg, 49%): ^{1}H NMR (DMSO-d_6) δ 1.42 (t, 3H, CH_3CH_2), 4.69 (q, 2H, CH_3CH_2), 6.87 (d, 1H, H-3, J = 7.15 Hz), 8.03 (s, 1H, H-6), 8.35 (d, 1H, H-4, J = 7.81 Hz), 12.45 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 13.62, 66.32, 118.98, 128.65, 128.87, 135.50, 182.73, 200.23; EIMS *m/z* 239 (M^+). Anal. ($C_9H_9N_3OS_2\cdot 1/9H_2O$) C, H, N, S.

8-Carbamoyl-1,2-dihydroxyimidazo[1,5-*a*]pyrimidin-2(1*H*)-one (**11a**). A solution of **5** (163 mg, 1.0 mmol), **13** (316 mg, 1.1 mmol), and Et_3N (0.8 mL) in dry MeCN (25 mL) was heated at 50 °C for 16 h. After cooling, the crystalline product **11b** was filtered, washed with H_2O, and dried (238 mg, 46%): ^{1}H NMR (DMSO-d_6) δ 6.05 (d, 1H, H-3, J = 8.25 Hz), 7.16 (bs, 2H, NH_2), 8.36 (s, 1H, H-6), 8.38 (d, 1H, H-4, J = 7.69 Hz),

10.36 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 108.50, 112.84, 126.83, 133.46, 134.71, 158.26, 164.57; EIMS *m*/*z* 160 (M^+). Anal. ($C_7H_6N_4O_2 \cdot 3/5H_2O$) C, H, N.

8-Carbamoyl-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2-(1*H*)-thione (**11b**). A mixture of **11a** (45 mg, 0.25 mmol) and Lawesson's reagent (46 mg, 0.11 mmol) in dry dioxane (8 mL) was heated under reflux for 45 min. After concentration of the mixture in vacuo, **11b** (17 mg, 35%) was separated by medium-pressure liquid chromatography (MeCN−2% aqueous AcOH, 35:65 v/v): ^{1}H NMR (DMSO-d_6) δ 6.70 (d, 1H, H-3, J = 7.32 Hz), 7.44 (bs, 1H, NH), 7.58 (bs, 1H, NH), 8.03 (s, 1H, H-6), 8.28 (d, 1H, H-4, J = 7.81 Hz), 11.39 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 113.05, 117.74, 127.39, 128.76, 132.20, 164.61, 181.69; EIMS *m*/*z* 194 (M^+). Anal. ($C_7H_6N_4OS \cdot {}^1/_4H_2O$) C,H, N, S.

8-Thiocarbamoyl-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**11c**). A mixture of **11a** (89 mg, 0.5 mmol) and Lawesson's reagent (303 mg, 0.75 mmol) in dioxane (8 mL) was refluxed for 2 h. After cooling, the crystals deposited were filtered and washed with EtOH to give **11c** (77 mg, 73%): ^{1}H NMR (DMSO-d_6) δ 6.79 (d, 1H, H-3), 8.09 (s, 1H, H-6), 8.32 (d, 1H, H-4), 9.22 (bs, 1H, NH), 9.51 (bs, 1H, NH), 12.93 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 116.07, 118.23, 128.76, 134.18, 181.76, 186.35; EIMS *m*/*z* 210 (M^+). Anal. ($C_7H_6N_4S_2$) C, H, N, S.

8-Cyano-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-one (**12a**). A solution of **6** (700 mg, 6.5 mmol), **13** (2.2 g, 7.8 mmol), and Et_3N (4 mL) in dry MeCN (50 mL) was heated at 50 °C for 16 h. After concentration in vacuo, the residue was crystallized from H_2O to give **12a** (735 mg, 71%): ^{1}H NMR (DMSO-d_6) δ 6.11 (d, 1H, H-3, J = 6.05 Hz), 7.98 (s, 1H, H-6), 8.40 (d, 1H, H-4, J = 7.15 Hz), 12 88 (bs, 1H, 1-NH); ^{13}C NMR (DMSO-d_6) δ 90.65, 109.01, 114.48, 129.26, 134.65, 138.55, 159.31; EIMS *m*/*z* 160 (M^+). Anal. ($C_7H_4N_4O$) C, H, N.

8-Cyano-1,2-dihydroimidazo[1,5-*a*]pyrimidin-2(1*H*)-thione (**12b**). A mixture of **12a** (160 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol) in dry dioxane (10 mL) was heated under reflux for 1 h. After concentration of the mixture in vacuo, **12b** (71 mg, 40%) was separated by medium-pressure liquid chromatography (MeCN−2% aqueous AcOH, 35:65 v/v): mp 243−248 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.41 (d, 1H, H-3, J = 7.32 Hz), 8.45 (s, 1H, H-6), 8.89 (d, 1H, H-4, J = 7.82 Hz); ^{13}C NMR (DMSO-d_6) δ 90.98, 114.10, 119.22, 127.69, 129.95, 136.24, 183.45; EIMS *m*/*z* 176 (M^+). Anal. ($C_7H_4N_4S \cdot {}^1/_{10}H_2O$) C, H, N, S.

***N*-Succinimidyl 3-Succinimidoxypropenoate** (**13**). A mixture of propiolic acid (1.47 g, 21 mmol), *N*,*N*′-disuccinimidyl carbonate (5.38 g, 21 mmol), and pyridine (1.6 mL) in dry MeCN (100 mL) was stirred at room temperature for 16 h. The colorless crystals precipitated were collected by filtration and washed with H_2O to give **13** (4.3 g, 73%): ^{1}H NMR (DMSO-d_6) δ 2.73 (s, 4H, CH2), 2.83 (s, 4H, CH2), 6.29 (d, 1H, −CH═, J = 12.2 Hz), 8.28 (d, 1H, −CH═, J = 12.2 Hz); EIMS *m*/*z* 282 (M^+).

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Supporting Information Available: ORTEP drawings of **9b** and **12a**, crystal data and refinement parameters, coordinates, anisotropic temperature factors, distances, and angles. This information is available free of charge via the Internet at http://pubs.acs.org.

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