Purines. L.[1] Synthesis and Antileukemic Activity of the Antibiotic Guanine 7-Oxide and Its 9-Substituted Derivatives

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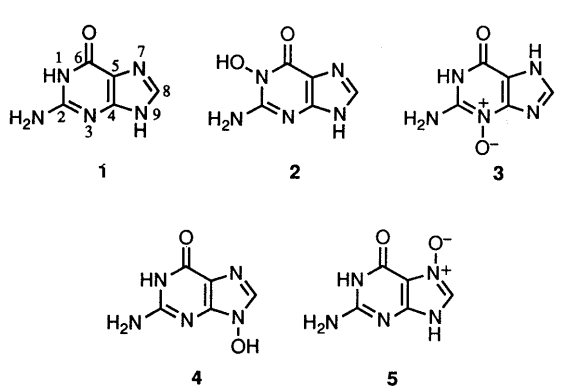
A full account is given of the first chemical synthesis of the antitumor antibiotic guanine 7-oxide (5) and its 9-substituted derivatives (24a—k and 26). Coupling of appropriate primary amines (17a—e, g—k) with phenacyl bromide (16) produced, after treatment with HCl, the corresponding *N*-substituted phenacylamine hydrochlorides (18a—e, g—k). A similar phenacylation of 4-amino-1-butanol (21) failed to give the desired compound 18f, so that 21 was heated with 2-bromomethyl-2-phenyl-1,3-dioxolane (20) at 150—155 °C for 3 h to furnish, after treatment with HCl, the amino ketal hydrochloride 22 in 40% yield. Deketalization of 22 with hot 2 N aqueous HCl afforded 18f in 96% yield. Condensations of the free bases, generated *in situ* from the hydrochlorides 18a—l and 1 N aqueous NaOH, with the chloropyrimidinone 6 were effected in aqueous EtOH at the boiling point for 20 min or at 25—30 °C for 3—24 h, giving the 6-phenacylamino-4-pyrimidinones 19a—l in 54—90% yields. On treatment with 2 N aqueous NaOH at room temperature for 10—60 min, the nitropyrimidinones 19a—k cyclized to provide the 9-substituted guanine 7-oxides 24a—k in 61—98% yields. A similar alkali-treatment of 19l failed to yield guanine 7-oxide (5). However, removal of the 9-(arylmethyl) group from 24i—k was effected with conc. H_2SO_4 at room temperature for 1—3 h in the presence of toluene, producing the target *N*-oxide 5 in 56—89% yields. In the *in vitro* bioassay of antileukemic activity against murine L5178Y cells, none of the 9-substituted guanine 7-oxides (24a—k and 26) was more effective than the parent, natural *N*-oxide 5. Within this series, however, the benzyl analogues 24g—k with or without alkoxy functions were more cytotoxic, with IC_{50}'s of 13.0—48.0 μg/ml, than the alkyl analogues 24a—f.

Keywords phenacylation primary amine; condensation chloropyrimidinone–phenacylamine; cyclization nitro–phenacylamino; deketalization; guanine 7-oxide 9-substituted; guanine 7-oxide synthesis; debenzylation; benzyl carbenium ion; tautomerism *N*-oxide–*N*-hydroxy; antitumor activity

A significant structural feature of guanine (**1**), a biologically important heterocycle, is that it bears five nitrogen atoms, four endocyclic and one exocyclic, so that four kinds of heterocyclic mono-*N*-oxide are possible in principle. Among the four possible *N*-oxides,[2] 1-hydroxyguanine (**2**),[3] guanine 3-*N*-oxide (**3**),[4,5] and 9-hydroxyguanine (**4**)[6] have been prepared by chemical synthesis. The remaining isomer, guanine 7-oxide (**5**), was not known until 1985, when three research groups,[7-9] including some of us,[9] independently reported its isolation from the culture broths of certain *Streptomyces* species, together with its observed antitumor,[7-10] antimicrobial,[9] and antiviral[11] activities. These intriguing biological activities and a blank in chemical synthesis[12] prompted us to devise a synthetic method for preparation of this antibiotic and to synthesize related compounds for evaluation of their biological activity.[13]

Prior to the present work, direct oxidation of guanine (**1**) with peroxytrifluoroacetic acid had been shown to produce the 3-*N*-oxide (**3**),[4] not the 7-*N*-oxide (**5**) as once thought.[14] The only known derivative of **5** had been 9-methylguanine 7-oxide (**24a**), which Leigh's group[15] had obtained from 2-amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone (**6**) through **8a**[16] and **13** (Chart 1). However, they had found that no reaction occurred with the unmethylated aminoacetaldehyde **12** when it was similarly treated with dilute aqueous NaOH in an attempt to prepare the 9-unsubstituted 7-oxide (**5**). In the present study, we first attempted to extend this synthetic route to include the 9-benzyl analogue **24g**, which would give the target compound **5** if debenzylation were possible while leaving the 7-oxide function intact. Thus, condensation of **6** with benzylaminoacetaldehyde dimethyl acetal (**7b**), prepared from aminoacetaldehyde dimethyl acetal and benzaldehyde in 76% yield by condensation followed by $NaBH_4$ reduction, was effected in boiling EtOH for 1 h to provide **8b** in 67% yield. However, hydrolysis of **8b** with 38% aqueous HCl at room temperature, 80 °C, or 100—110 °C gave a mixture presumed to contain the tetrahydroimidazopyrimidinone **9b** and the overhydrolyzed monocycle **10b**, and we were unable to isolate the desired aldehyde **15**. A similar difficulty in hydrolysis has also been reported for the *N*-methyl analogue **8a**.[16] In an attempt to explore an alternative route leading to the alkylaminoacetaldehyde level (types **13**—**15**), **6** was condensed with 2-(ethylamino)-ethanol in boiling EtOH for 1 h, giving **11** in 59% yield. However, oxidations of **11** with a variety of oxidizing agents,[17] such as Me_2SO and dicyclohexylcarbodiimide in the presence of H_3PO_4, Me_2SO/Ac_2O, pyridinium chlorochromate, and CrO_3–pyridine complex, were all unsuccessful in giving the ethylaminoacetaldehyde **14**. Leigh and co-workers[15] have briefly mentioned that the formyl group in **13** may be replaced by a benzoyl group for cyclization to the 7-oxide **24a**, and a similar cycliza-



1 **2** **3** **4** **5**

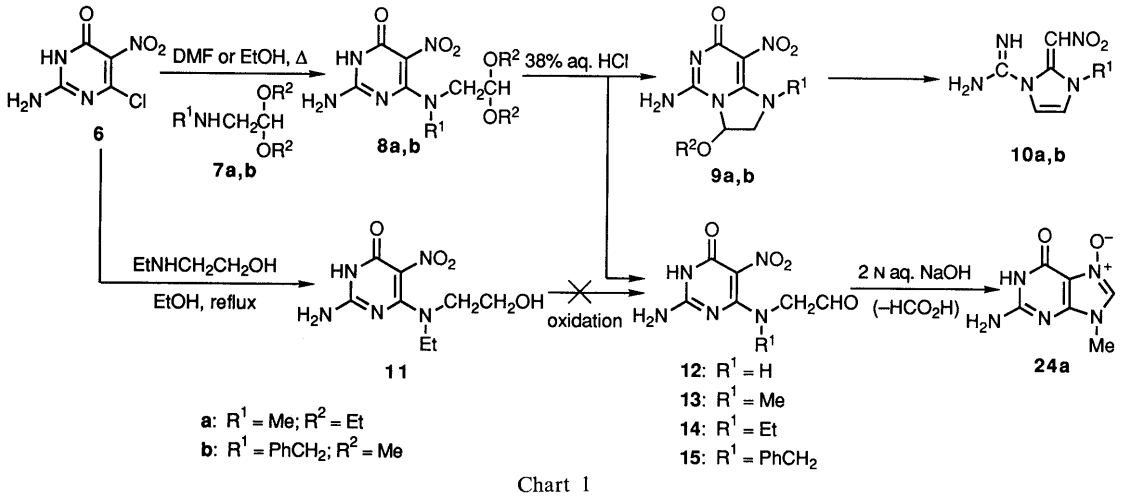


Chart 1

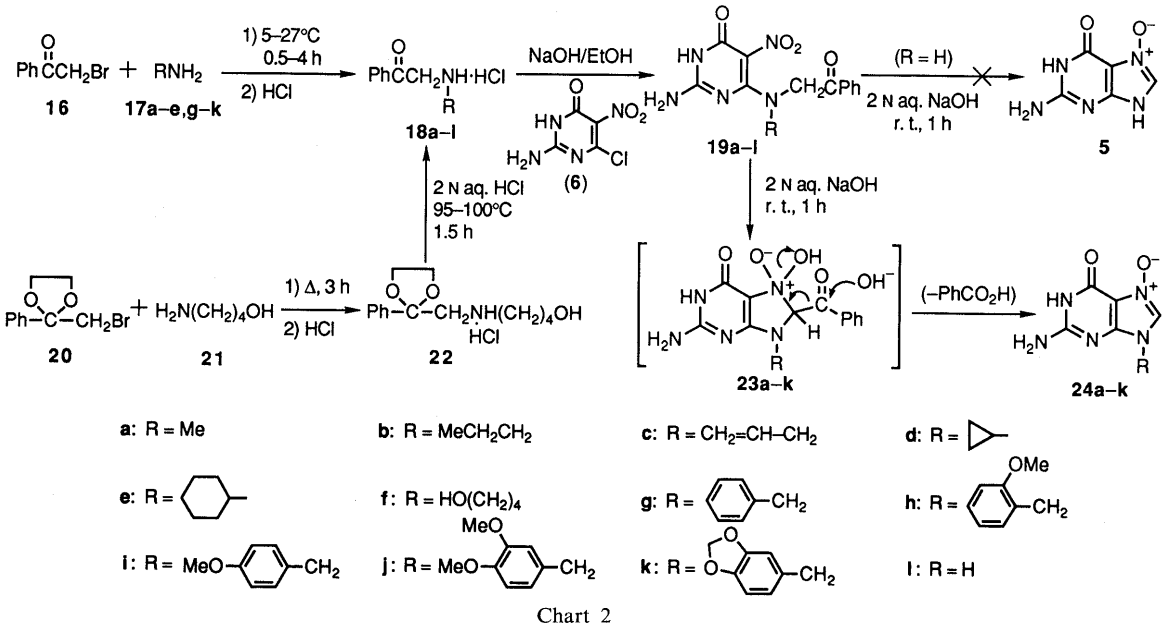


Chart 2

tion of a nitro group through nucleophilic attack by a carbanion on the NO_2 nitrogen atom has also been found to occur in related systems.[18] This led us to switch to the following phenacylamine route (Chart 2).

The starting phenacylamine hydrochlorides **18a**,[19] **18e**,[20] and **18g**[21] were prepared from phenacyl bromide (**16**) and appropriate primary amines according to the literature. Similar phenacylations of propylamine (**17b**), allylamine (**17c**), cyclopropylamine (**17d**), 2-methoxybenzylamine (**17h**), 4-methoxybenzylamine (**17i**), 3,4-dimethoxybenzylamine (**17j**), and 3,4-methylenedioxybenzylamine (**17k**) with **16** in benzene–ether or in ether at 5—27 °C for 0.5—4 h gave, after treatment with HCl, the *N*-substituted phenacylamine hydrochlorides **18b—d, h—k** in 25—52% yields. Table I summarizes the results of these coupling reactions. In an attempt to synthesize the *N*-(4-hydroxybutyl) analogue **18f**, a similar phenacylation of 4-amino-1-butanol (**21**) failed to give the desired compound, producing nonisolable unstable substances. Therefore, the ketal **20** was substituted for **16** and heated with **21** at 150—155 °C for 3 h to afford, after treatment with HCl, the amino ketal hydrochloride **22** in 40% yield. Deketalization of **22** with 2 N aqueous HCl at 95—100 °C for 1.5 h furnished **18f** in 96% yield.

Table I. Phenacylation of Primary Amines (Type **17**) with Phenacyl Bromide (**16**)

Primary amine	Reaction conditions[a]			Product[b]	
	Solvent[c]	Temp. (°C)	Time (h)	No.	Yield (%)
17b	A	5—15	1	**18b**	45
17c	A	<15	0.5	**18c**	45
17d	B	5—27[d]	4	**18d**	52
17h	B	<15	1	**18h**	25
17i	A	<15	1	**18i**	52
17j	A	<15	1	**18j**	37
17k	A	<15	1	**18k**	47

a) A primary amine and phenacyl bromide (**16**) were used in a 2:1 molar ratio. *b*) Isolated as the hydrochloride salt. *c*) The letter A stands for benzene–ether (1:2, v/v); B, ether. *d*) The inner temperature was kept at 5—10 °C during addition of the bromide **16** and then at 24—27 °C.

Condensations of the free bases, generated *in situ* from the hydrochlorides **18a—l** (2 molar eq) and 1 N aqueous NaOH (2 molar eq), with the chloropyrimidinone **6** were effected in aqueous EtOH at the boiling point for 20 min or at 25—30 °C for 3—24 h, affording the 6-(phenacylamino)-pyrimidinones **19a—l** in 54—90% yields (Table II). In the

case of **19b**, the condensation of **18b** with **6** was also tried in *N*,*N*-dimethylformamide (DMF)[22] in the presence of Et_3N at 25 °C for 12 h. However, it produced a dark brown mixture of many products, from which the desired product (**19b**) was isolated in only 34% yield. All the condensation products (**19a—l**) isolated were chromatographically pure solids, but were unstable when heated in recrystallization solvents. Although this hampered the preparation of analytical samples in most cases, support for the correctness of the assigned structures came from the proton nuclear magnetic resonance (^{1}H-NMR) spectra in Me_2SO-d_6 and the infrared (IR) spectra as well.

For cyclization of the nitropyrimidinones **19** to the *N*-oxides **24**, that of the *N*-methyl analogue **19a** was first investigated as a pilot experiment. On treatment with 2 N aqueous NaOH at room temperature for 1 h, **19a** furnished the desired 7-oxide (**24a**) and benzoic acid in 98% and 99% yields, respectively. The structure of **24a** was confirmed by a direct comparison with an authentic sample prepared by a method given in the literature[15] (Chart 1). The formation of benzoic acid in the above cyclization is explicable in terms of attack by hydroxide ion on the

TABLE II. Condensation of the Phenacylamine Derivatives (**18a—l**) with the Chloropyrimidinone **6** in Aqueous EtOH

Amine·HCl	Reaction conditions[a]		Product	
	Temp. (°C)	Time (h)	No.	Yield[b] (%)
18a	Reflux	0.33	**19a**	86
18b	30	24	**19b**	68
18c	Reflux	0.33	**19c**	66
18d	30	6	**19d**	86
18e	30	24	**19e**	71
18f	30	3	**19f**	59
18g	25	12	**19g**	81
18h	28	15	**19h**	79
18i	25	12	**19i**	54
18j	25	12	**19j**	90
18k	25	6	**19k**	66
18l[c]	30	20	**19l**	62

a) A phenacylamine derivative (in the form of the HCl salt) (type **18**), 1 N aqueous NaOH, and **6** were used in a 2:2:1 ratio. *b*) Based on the chloropyrimidinone **6** employed. *c*) A commercially available sample was used.

TABLE III. Cyclization of the Nitropyrimidinones **19a—k** to 9-Substituted Guanine 7-Oxides (**24a—k**)

Pyrimidinone	Reaction conditions[a]	Product		
	Time (min)	No.	Yield (%)	Chemical shift[b] C(8)-H singlet (δ)[c]
19a	60	**24a**[d]	98	9.03[e]
19b	60	**24b**	87	9.11[f]
19c	60	**24c**	90	9.08
19d	60	**24d**	87	9.10
19e	60	**24e**	70	9.14
19f	10	**24f**	77	9.11
19g	60[g]	**24g**	84	9.02
19h	60	**24h**	86	8.95
19i	60	**24i**	61	8.96
19j	60	**24j**	93	8.54[h]
19k	60	**24k**	68	8.97

a) Allowed to react in 2 N aqueous NaOH at room temperature. *b*) Measured in 1 N solution of D_2SO_4 in D_2O. *c*) In ppm downfield from internal sodium 3-(trimethylsilyl)propionate-*2,2,3,3*-d_4. *d*) Benzoic acid was also isolated in 99% yield. *e*) Appeared as a one-proton quartet with $J = 0.4$ Hz, owing to coupling with the N(9)-Me protons. *f*) Compound **24b** was unstable in Me_2SO-d_6 at 25 °C, turning completely into a material presumed to be 8-oxo-9-propylguanine in 48 h. *g*) Allowed to react in a 3:1 (v/v) mixture of 2 N aqueous NaOH and MeOH at room temperature. *h*) Measured in CF_3CO_2D and expressed in ppm downfield from internal Me_4Si.

TABLE IV. UV Spectra of 9-Substituted Guanine 7-Oxides (**24a—k**)

Compound	UV spectra							
	95% (v/v) aq. EtOH		H_2O (pH 1)[a]		H_2O (pH 7)[b]		H_2O (pH 13)[c]	
	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
24a	—[d]	—[d]	255	11.1	236	21.1	231	20.0
			281	7.2	270	8.1	280	8.5
24b	240	21.6	256	11.5	236	22.3	231	20.7
	274	9.2	282	7.7	270	8.6	280	8.8
24c	240	21.3	256	11.6	236	21.7	231	20.7
	275	9.5	281	7.6	270	8.8	280	9.1
24d	240	21.6	258	11.8	236	22.3	232	20.7
	274	9.8	280	8.1	270	9.3	279	9.3
24e	240	22.1	257	11.3	236	22.4	231	20.5
	274	9.4	282	7.8	270	8.6	280	9.1
24f	240	21.8	257	11.7	236	22.7	231	21.3
	274	9.3	282	7.8	270	8.9	280	9.1
24g	240	19.5	258	11.9	237	21.4	232	19.6
	274	9.2	282	8.1	270	9.4	281	9.6
24h	—[d]	—[d]	258	12.2	236	21.3	—[e]	—[e]
			279	10.6	273	11.6	279	11.8
24i	234	27.1	257	12.8	232	28.1	228	29.0
	275	11.4	280	9.2	272	10.7	280	10.9
24j	—[d]	—[d]	257	12.9	235	28.8	231	27.6
			281	11.3	277	12.2	281	12.9
24k	—[d]	—[d]	255	12.6	237	25.0	232	22.9
			285	11.9	284	12.3	285	13.4

a) Measured in 0.1 N aqueous HCl. *b*) Measured in 0.005 M phosphate buffer (pH 7). *c*) Measured in 0.1 N aqueous NaOH. *d*) Undetermined because of the poor solubility of this substance. *e*) Appeared as a rising end-absorption curve (with decreasing wavelength) in the 230 nm region.

23a, which would have formed from **19a** through cyclization between the NO_2 nitrogen atom and the phenacyl carbanion. Under similar alkaline conditions, **19b—k** also cyclized to give the 7-oxides **24b—k** in 61—93% yields. These results are summarized in Table III. The 7-oxide structures were assignable to **24b—k** on the basis of the similarities to **24a** in the mode of formation, in the chemical shift value for the C(8)-H proton (see Table III), and in the ultraviolet (UV) spectrum as shown in Table IV.

On the other hand, a parallel sequence of reactions starting with *N*-unsubstituted phenacylamine hydrochloride (**18l**) (Chart 2) did not work at the cyclization step. This failure of **19l** to produce the target *N*-oxide **5** is in general agreement with that[15] of **12** and may be explained in terms of destabilization of the phenacyl carbanion, the nucleophile for intramolecular attack on NO_2 nitrogen, by the adjacent NH group. This led us to investigate how to remove the substituent at the 9-position from a **24**-type compound without rupture of the N(7)–O bond. On treatment with 10 molar eq of conc. H_2SO_4 at 25 °C for 90 min in the presence of toluene, the 4-methoxybenzyl analogue **24i** was found to provide guanine 7-oxide (**5**) in 89% yield. Deblocking of the 3,4-dimethoxybenzyl analogue **24j** or the 3,4-methylenedioxybenzyl analogue **24k** at the 9-position was also effective under similar conditions, affording **5** in 68% or 56% yield, respectively. The identity of synthetic **5** with a natural sample was confirmed by direct comparison of the UV, IR, and ^{1}H-NMR spectra, and chromatographic behavior as well as the antimicrobial[9] and antitumor[9] activities. The above deblocking procedure was based on the previously reported specific debenzylation of 3-benzyladenine[23] and 7-alkyl-3-benzyladenines[24] that proceeds through benzyl carbenium ion formation and trapping of the cation by transbenzylation with toluene. However, application of the same procedure to the unmodified benzyl analogue **24g** or the allyl analogue **24c** failed to give the desired product (**5**). In the case of the 2-methoxybenzyl analogue **24h**, it was also ineffective, resulting in the formation of the 2-methoxy-5-sulfobenzyl analogue **26** in 69% yield, and a modification using 90% aqueous H_2SO_4 instead of conc. H_2SO_4 at 30 °C for 3 h failed to give **5**. Treatment of **24c** with potassium *tert*-butoxide in hot Me_2SO followed by alkaline permanganate oxidation, an application of the deallylation method reported by Montgomery and Thomas[25] for 9-allylpurines, also failed to yield **5**.

As regards the problem of the tautomeric forms of guanine 7-*N*-oxide in the solid state, the N(7)-oxide form (**5**) has been preferred by Kern *et al.*[7] on the basis of the X-ray crystal structure of the corresponding hydrobromide salt monohydrate. On the other hand, Kitahara *et al.*[8b] have proposed the N(7)-OH form (**25**) on the basis of the result of an X-ray analysis of a single crystal of the dihydrate of the free base grown in 15% tetrahydrofuran–2 M NH_4OH. In solution, the two forms may coexist at equilibrium (Chart 3).[9] The strong absorption band at 234 nm (ε 19400) in the UV spectrum of guanine 7-*N*-oxide in H_2O at pH 7.0 resembles those [at 232—237 nm (ε 21100—28800) (Table IV)] observed for the 9-substituted guanine 7-oxides (**24a—k**) that can serve as fixed models for the N(7)-oxide form. Since the three pK_a values of 9-unsubstituted guanine 7-*N*-oxide have been determined to be 2.6, 5.8, and 9.5,[9] the above absorption band displayed at pH 7.0 may be regarded as that arising from the anionic species. There is a certain overall similarity between the neutral species spectrum of guanine 7-*N*-oxide at pH 3.6 [λ_{max} 232 nm (ε 15900), 253 (7200), 282 (7300)] and that of 9-methylguanine 7-oxide (**24a**) at pH 5.8 [λ_{max} 236 nm (ε 21800), 269 (8200), 280 (sh) (7600)]. These facts and considerations, together with the previous deduction that the strong absorption of purine *N*-oxides in the 215—240 nm region is due to $\geq$N→O or the enol anion $\geq$N–O$^-$,[26] may suggest that the neutral species of guanine 7-*N*-oxide has a considerable proportion of the N(7)-oxide form in H_2O. However, the nonavailability of a fixed model (*e.g.*, 7-methoxyguanine) for the N(7)-OH form (**25**) in the present study renders the above discussion still inconclusive.

In view of the significant anticancer activity of guanine 7-oxide (**5**) *in vitro* and *in vivo*,[7-10] we then evaluated the above 9-substituted guanine 7-oxides (**24a—k** and **26**) for cytotoxicity to murine L5178Y leukemia cell line *in vitro*. It may be seen from Table V that as a group, the compounds in this series were less effective than the parent natural *N*-oxide **5**. Within the 9-substituted series, the benzyl analogues **24g—k** with or without alkoxy functions were more cytotoxic, with IC_{50}'s of 13.0—48.0 μg/ml, than the alkyl analogues **24a—f**. It is interesting, however, that

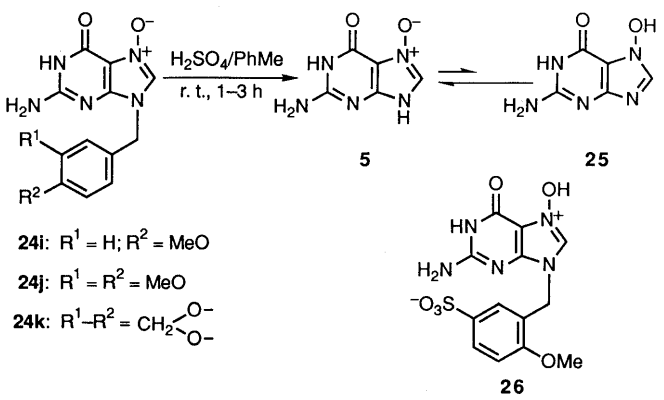


Chart 3

TABLE V. Antileukemic Activity of Guanine 7-Oxide (**5**) and 9-Substituted Derivatives (**24a—k** and **26**) toward Murine L5178Y Cells in Culture

N(7)-Oxide		% inhibition (at 50 μg/ml)	IC_{50}[a] (μg/ml)
No.	N(9)-R		
5	—	—[b]	1.10
24a	Me	15	—[b]
24b	$MeCH_2CH_2$	23	—[b]
24c	Allyl	39	—[b]
24d	Cyclopropyl	19	—[b]
24e	Cyclohexyl	21	—[b]
24f	$HO(CH_2)_4$	8	—[b]
24g	Benzyl	83	13.0
24h	2-Methoxybenzyl	61	34.0
24i	4-Methoxybenzyl	80	22.5
24j	3,4-Dimethoxybenzyl	81	48.0
24k	3,4-Methylenedioxybenzyl	76	36.0
26	2-Methoxy-5-sulfobenzyl	0	—[b]

a) IC_{50} is the concentration of a test compound required to inhibit cell growth by 50%. b) Not determined.

introduction of a sulfo group into the 5-position of the benzyl moiety in **24h** caused a loss of cytotoxicity. Jackson *et al.*[10] have reported that guanine 7-oxide (**5**) is converted within sensitive cells to guanosine 7-oxide 5′-triphosphate, and this results in inhibition of cellular protein synthesis. In this connection, the above finding that the derivatives of **5** blocked at the 9-position still have cytotoxic activity, although weaker than that of **5**, is deserving of particular mention.

In conclusion, the total synthesis of the antitumor antibiotic guanine 7-oxide (**5**) has now been realized for the first time *via* the four-step route starting from phenacyl bromide (**16**) and the chloropyrimidinone **6** and proceeding through the intermediates **18i**, **19i**, and **24i**, or **18j**, **19j**, and **24j**, or **18k**, **19k**, and **24k**. The ready availability of **5** by chemical synthesis will serve to promote studies on direct structural modifications of this antibiotic.[27,28] In addition, the syntheses of **24a—h** by parallel sequences of reactions have established a general synthetic route to 9-substituted guanine 7-oxides. Although none of the compounds in this series has been found to be superior to **5** in antileukemic activity, this would not necessarily discourage further studies of structure–activity relationships for this class of compounds.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected; boiling points are uncorrected. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates (0.25-mm thickness), Merck aluminum oxide F_{254} (type E) plates (0.25 mm), or Funakoshi Avicel SF-2020F plates, and spots were located under UV light (254 nm). High-performance liquid chromatography (HPLC) was carried out on a Waters ALC/GPC 204 liquid chromatograph equipped with a μBondapak C_{18} column [0.05 M NaH_2PO_4–Na_2HPO_4 buffer (pH 5.4), 700—1400 p.s.i., 1—1.5 ml/min], and peaks were located by using a UV absorbance detector operated at 254 nm. Spectra reported herein were recorded on a Hitachi model 320 UV spectrophotometer [on solutions in 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13)], a JASCO A-202 IR spectrophotometer, or a JEOL JNM-FX-100 NMR spectrometer at 25 °C. Internal standards used for the measurements of ^{1}H-NMR spectra were Me_4Si (for $CDCl_3$, Me_2SO-d_6, or CF_3CO_2D solutions) and sodium 3-(trimethylsilyl)propionate-*2,2,3,3-d*$_4$ (for solutions in 1 N D_2SO_4/D_2O or 1 N NaOD/D_2O). Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, dt = doublet-of-triplets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

Benzylaminoacetaldehyde Dimethyl Acetal (7b) A mixture of benzaldehyde (3.00 g, 28.3 mmol) and aminoacetaldehyde dimethyl acetal (2.98 g, 28.3 mmol) in MeOH (60 ml) was stirred at room temperature for 1 h, and then $NaBH_4$ (1.6 g, 42 mmol) was added in small portions.[29] The resulting mixture was stirred at room temperature for 12 h, neutralized by addition of 10% aqueous HCl, and concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of AcOEt and H_2O. The AcOEt extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a colorless oil (5.43 g). Vacuum distillation of the oil gave **7b** (4.20 g, 76%) as a colorless oil, bp 94—95 °C (1 mmHg) [lit. bp 147—149 °C (18 mmHg)[30]; bp 102 °C (1 mmHg)[31]]; ^{1}H-NMR ($CDCl_3$) δ: 2.68 (2H, d, J = 5 Hz, $NC\underline{H}_2CH$), 3.28 (6H, s, OMe's), 3.72 (2H, s, $C\underline{H}_2Ph$), 4.38 (1H, t, J = 5 Hz, $NCH_2C\underline{H}$), 7.14 (5H, m, Ph).

2-Amino-6-[benzyl(2,2-dimethoxyethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (8b) A stirred mixture of 2-amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone (**6**)[32] (1.00 g, 5.25 mmol) and **7b** (2.06 g, 10.6 mmol) in EtOH (30 ml) was heated under reflux for 1 h. The reaction mixture was concentrated *in vacuo* to leave a yellow oil. The oil was acidified (pH *ca.* 2) by addition of 10% aqueous HCl and then extracted with AcOEt. The AcOEt extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellow oil (1.43 g). Purification of the oil by column chromatography [silica gel, $CHCl_3$–EtOH (10 : 1, v/v)] furnished **8b** (1.23 g, 67%) as a yellow solid. Recrystallization from MeOH yielded an analytical sample as yellow needles, mp 136—138 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.38 (6H, s, OMe's), 3.54 (2H, d, J = 5 Hz, $NC\underline{H}_2CH$), 4.58 (1H, t, J = 5 Hz, $NCH_2C\underline{H}$), 4.60 (2H, s, $C\underline{H}_2Ph$), 7.15—7.4 (5H, m, Ph), 10.97 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{19}N_5O_5$: C, 51.57; H, 5.48; N, 20.05. Found: C, 51.41; H, 5.52; N, 19.91.

2-Amino-6-[ethyl(2-hydroxyethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (11) A stirred mixture of **6**[32] (1.10 g, 5.77 mmol) and 2-(ethylamino)-ethanol (1.03 g, 11.6 mmol) in EtOH (33 ml) was heated under reflux for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was triturated with H_2O (15 ml). The yellow precipitate that resulted was filtered off, washed successively with H_2O and EtOH, and recrystallized from H_2O (20 ml) to give **11**·1/4H_2O (847 mg, 59%) (dried over P_2O_5 at 2 mmHg and 60 °C for 5 h) as yellow prisms, mp 193—195 °C. Further recrystallization from H_2O and drying over P_2O_5 at 2 mmHg and 110 °C for 10 h afforded an analytical sample as yellow prisms, mp 193—195 °C; ^{1}H-NMR (Me_2SO-d_6) δ: 1.11 (3H, t, J = 7 Hz, $CH_2\underline{Me}$), 3.34 (2H, t, J = 5 Hz, $NC\underline{H}_2CH_2OH$), 3.43 (2H, q, J = 7 Hz, $C\underline{H}_2Me$), 3.55 (2H, dt, J = 5 Hz each, $NCH_2C\underline{H}_2OH$), 4.73 (1H, t, J = 5 Hz, $CH_2O\underline{H}$), 6.96 (2H, br, NH_2), 10.58 (1H, br, NH). *Anal.* Calcd for $C_8H_{13}N_5O_4$·1/4H_2O: C, 38.79; H, 5.49; N, 28.27. Found: C, 38.59; H, 5.46; N, 28.38.

Phenacylation of the Primary Amines 17a—e, g—k Leading to 2-(Substituted-amino)-1-phenylethanone Hydrochlorides (18a—e, g—k) The phenacylations of methylamine (**17a**), cyclohexylamine (**17e**), and benzylamine (**17g**) with phenacyl bromide (**16**) were effected according to the literature, giving 2-(methylamino)-1-phenylethanone hydrochloride (**18a**),[19] 2-(cyclohexylamino)-1-phenylethanone hydrochloride (**18e**),[20] and 2-(benzylamino)-1-phenylethanone hydrochloride (**18g**),[21] respectively. The other phenacylations were carried out under the reaction conditions specified in Table I in a manner similar to that described below for the phenacylation of propylamine (**17b**), and the results are summarized in Table I. The phenacylamine derivatives (**18b—d, h—k**) thus obtained were characterized as follows.

1-Phenyl-2-(propylamino)ethanone Hydrochloride (18b) A solution of phenacyl bromide (**16**) (15.92 g, 80 mmol) in a mixture of benzene (20 ml) and ether (40 ml) was added dropwise to a stirred, cooled (5—15 °C) solution of propylamine (**17b**) (9.46 g, 160 mmol) in a mixture of benzene (20 ml) and ether (40 ml). Stirring was continued at 5—15 °C for a further 1 h, and the colorless precipitate that resulted was removed by filtration and washed with benzene (2 × 10 ml). The filtrate and washings were combined and stirred under ice-cooling, and 38% aqueous HCl (10 ml) was added dropwise. The colorless crystals that deposited were filtered off, washed with acetone (2 × 10 ml), and recrystallized from H_2O (*ca.* 40 ml) to give **18b** (7.76 g, 45%) as colorless prisms, mp 193—204 °C (dec.) (sintered at 170 °C). Further recrystallization from H_2O produced an analytical sample showing unchanged melting point; IR ν_{max}^{Nujol} cm^{-1}: 2700, 2570, 2420 (NH_2^+), 1702, 1696 (COAr); ^{1}H-NMR (Me_2SO-d_6) δ: 0.93 (3H, t, J = 7.3 Hz, $CH_2CH_2\underline{Me}$), 1.4—2.0 (2H, m, $CH_2C\underline{H}_2Me$), 2.5—3.1 (2H, m, $C\underline{H}_2CH_2Me$), 4.76 (2H, s, $C\underline{H}_2COPh$), 7.3—8.1 (5H, m, COPh), 9.42 (2H, br, NH_2^+). *Anal.* Calcd for $C_{11}H_{15}NO$·HCl: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.55; H, 7.70; N, 6.60.

1-Phenyl-2-(2-propenylamino)ethanone Hydrochloride (18c) This was recrystallized successively from H_2O and from EtOH and dried over P_2O_5 at 2 mmHg and 60 °C for 12 h to give **18c**·1/4H_2O as colorless needles, mp 183—185 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 2770, 2600, 2400 (NH_2^+), 1696 (COAr); ^{1}H-NMR (Me_2SO-d_6) δ: 3.66 (2H, d, J = 6 Hz, $C\underline{H}_2CH{=}CH_2$), 4.74 (2H, s, $C\underline{H}_2COPh$), 5.2—5.6 (2H, m, $CH_2CH{=}C\underline{H}_2$), 5.7—6.2 (1H, m, $CH_2C\underline{H}{=}CH_2$), 7.3—8.1 (5H, m, COPh), 9.68 (2H, br, NH_2^+). *Anal.* Calcd for $C_{11}H_{13}NO$·HCl·1/4H_2O: C, 61.11; H, 6.76; N, 6.48. Found: C, 61.36; H, 6.59; N, 6.43.

2-(Cyclopropylamino)-1-phenylethanone Hydrochloride (18d) The salt[33a] was recrystallized from EtOH to yield **18d** as colorless prisms, mp 185—200 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 2800—2400 (NH_2^+), 1693 (COAr); ^{1}H-NMR (Me_2SO-d_6) δ: 0.6—1.2 (4H, m, cyclopropyl CH_2's), 2.6—2.9 (1H, m, cyclopropyl CH), 4.87 (2H, s, $C\underline{H}_2COPh$), 7.4—8.1 (5H, m, COPh), 9.58 (2H, br, NH_2^+). *Anal.* Calcd for $C_{11}H_{13}NO$·HCl: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.34; H, 6.82; N, 6.57.

2-[(2-Methoxybenzyl)amino]-1-phenylethanone Hydrochloride (18h) The salt[33b] was recrystallized successively from 1-propanol and from 2-propanol–acetone (1 : 1, v/v) and dried over P_2O_5 at 2 mmHg and 50 °C for 6 h, affording **18h**·H_2O as colorless prisms, mp 110—133 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 2800—2400 (NH_2^+), 1694 (COAr); ^{1}H-NMR (Me_2SO-d_6) δ: 3.77 (3H, s, OMe), 4.21 (2H, t, J = 5 Hz, $C\underline{H}_2Ar$), 4.72

(2H, t, J=5 Hz, C$\underline{H}_2$COPh), 6.9—8.1 (9H, m, aromatic protons), 9.62 (2H, br, NH_2^+). *Anal.* Calcd for $C_{16}H_{17}NO_2 \cdot HCl \cdot H_2O$: C, 62.03; H, 6.51; N, 4.52. Found: C, 61.98; H, 6.23; N, 4.56.

2-[(4-Methoxybenzyl)amino]-1-phenylethanone Hydrochloride (18i) This salt[33b] was recrystallized from EtOH to furnish colorless plates, mp 214—216 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 2730, 2610, 2420 (NH_2^+), 1712 (COAr); ^{1}H-NMR (Me_2SO-d_6) δ: 3.77 (3H, s, OMe), 4.14 (2H, s, C$\underline{H}_2$Ar), 4.73 (2H, s, C$\underline{H}_2$COPh), 6.99 [2H, d, J=8.8 Hz, C(3′)-H and C(5′)-H],[34] 7.54 [2H, d, J=8.8 Hz, C(2′)-H and C(6′)-H],[34] 7.4—8.1 (5H, m, COPh), 9.72 (2H, br, NH_2^+). *Anal.* Calcd for $C_{16}H_{17}NO_2 \cdot HCl$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.95; H, 6.22; N, 4.97.

2-[(3,4-Dimethoxybenzyl)amino]-1-phenylethanone Hydrochloride (18j) This salt[33b] was recrystallized from EtOH and dried over P_2O_5 at 2 mmHg and 60 °C for 16 h to yield **18j**·1/3H_2O as colorless prisms, mp 205—213 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 2800—2300 (NH_2^+), 1693 (COAr); ^{1}H-NMR (Me_2SO-d_6) δ: 3.77 and 3.78 (3H each, s, OMe's), 4.13 (2H, s, (C$\underline{H}_2$Ar), 4.72 (2H, s, C$\underline{H}_2$COPh), 6.9—8.1 (8H, m, aromatic protons), 9.66 (2H, br, NH_2^+). *Anal.* Calcd for $C_{17}H_{19}NO_3 \cdot HCl \cdot 1/3H_2O$: C, 62.29; H, 6.35; N, 4.27. Found: C, 62.39; H, 6.16; N, 4.14.

2-[(3,4-Methylenedioxybenzyl)amino]-1-phenylethanone Hydrochloride (18k) This salt[33b] was recrystallized from EtOH to give colorless plates, mp 207—219 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 2800—2400 (NH_2^+), 1688 (COAr); ^{1}H-NMR (Me_2SO-d_6) δ: 4.12 (2H, s, C$\underline{H}_2$Ar), 4.70 (2H, s, C$\underline{H}_2$COPh), 6.04 (2H, s, OCH_2O), 6.9—8.1 (8H, m, aromatic protons), 9.73 (2H, br, NH_2^+). *Anal.* Calcd for $C_{16}H_{15}NO_3 \cdot HCl$: C, 62.85; H, 5.27; N, 4.58. Found: C, 62.64; H, 5.19; N, 4.86.

4-[(2-Phenyl-2,2-ethylenedioxyethyl)amino]-1-butanol Hydrochloride (22) A stirred mixture of 4-amino-1-butanol (**21**) (6.86 g, 77 mmol) and 2-bromomethyl-2-phenyl-1,3-dioxolane (**20**)[35] (8.51 g, 35 mmol) was heated neat at 150—155 °C for 3 h. After cooling, the reaction mixture was poured into ice-cold H_2O (*ca.* 50 ml), and the resulting aqueous mixture was extracted with AcOEt (30 ml). The AcOEt extracts were washed with H_2O (3×30 ml), and then extracted with 10% aqueous HCl (3×15 ml). The acidic extracts were combined and concentrated to dryness *in vacuo* to leave a brown jelly. The jelly was triturated with acetone (20 ml), and the insoluble solid that resulted was filtered off, washed with a little acetone, and dried to give a first crop (3.59 g) of **22**, mp 200—204 °C (dec.). Concentration of the filtrate gave a second crop (440 mg). The total yield of **22** was 4.03 g (40%). Recrystallization of crude **22** from EtOH produced an analytical sample as colorless needles, mp 202—204 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3405 (OH), 2800—2350 (NH_2^+); ^{1}H-NMR (Me_2SO-d_6) δ: 1.2—1.9 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.7—3.1 (2H, br, CCH_2N), 3.2—3.5 (4H, m, $NC\underline{H}_2CH_2CH_2C\underline{H}_2OH$), 3.6—4.3 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.0—5.0 (1H, br, OH), 7.2—7.5 (5H, m, Ph), 8.96 (2H, br, NH_2^+). *Anal.* Calcd for $C_{14}H_{21}NO_3 \cdot HCl$: C, 58.43; H, 7.71; N, 4.87. Found: C, 58.14; H, 7.95; N, 4.79.

2-[(4-Hydroxybutyl)amino]-1-phenylethanone Hydrochloride (18f) A stirred solution of **22** (3.46 g, 12 mmol) in 2 N aqueous HCl (173 ml) was heated at 95—100 °C for 1.5 h. The reaction mixture was concentrated to dryness *in vacuo* to leave a semisolid, which was triturated with acetone (*ca.* 40 ml). The insoluble, colorless prisms that resulted were collected by filtration, washed with a little acetone, and dried to afford **18f** (2.80 g, 96%), mp 94—96 °C. Recrystallization from 2-propanol yielded an analytical sample as colorless plates, mp 94—96 °C; IR ν_{max}^{Nujol} cm^{-1}: 3420 (OH), 2800—2350 (NH_2^+), 1687 (COAr); ^{1}H-NMR (Me_2SO-d_6) δ: 1.2—2.0 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.7—3.1 (2H, m, $NC\underline{H}_2CH_2$), 3.43 (2H, t, J=6 Hz, $CH_2C\underline{H}_2OH$), 3.0—4.2 (1H, br, OH), 4.78 (2H, br s, C$\underline{H}_2$COPh), 7.3—8.1 (5H, m, COPh), 9.31 (2H, br, NH_2^+). *Anal.* Calcd for $C_{12}H_{17}NO_2 \cdot HCl$: C, 59.14; H, 7.44; N, 5.75. Found: C, 58.91; H, 7.58; N, 5.58.

Condensation of the Phenacylamine Derivatives (18a—l) with the Chloropyrimidinone 6 Leading to the Phenacylaminopyrimidinones 19a—l The condensation of 2-[(4-methoxybenzyl)amino]-1-phenylethanone hydrochloride (**18i**) with **6** will be described below in detail as a typical example.

The hydrochloride **18i** (4.59 g, 15.7 mmol) was dissolved in a stirred mixture of EtOH (47 ml) and 1 N aqueous NaOH (15.7 ml) under ice-cooling, and then **6**[32] (1.50 g, 7.87 mmol) was added in small portions. The resulting mixture was stirred at 25 °C for 12 h, concentrated *in vacuo* to *ca.* one-half its original volume, and ice-cooled. The precipitate that resulted was filtered off, washed successively with EtOH and ether, and dried to give 2-amino-6-[(4-methoxybenzyl)(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (**19i**) (1.73 g, 54%) as pale yellow prisms, mp 128—138 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3310, 3220 (NH_2 and NH), 1675 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 3.72 (3H, s, OMe), 4.70 (2H, s, C$\underline{H}_2$Ar), 4.79 (2H, s, C$\underline{H}_2$COPh), 6.87 [2H, d, J=8.5 Hz, C(3′)-H and C(5′)-H],[34] 7.00 (2H, br, NH_2), 7.27 [2H, d, J=8.5 Hz, C(2′)-H and C(6′)-H],[34] 7.4—7.9 (5H, m, COPh), 10.77 (1H, br, NH). This sample was homogeneous on TLC analysis, but was unstable when heated in recrystallization solvents.

Condensations of the other phenacylamine derivatives (**18a—h, j—l**) with **6** were conducted in a similar manner, and the products were characterized as described below. Table II summarizes the reaction conditions applied and the results obtained.

2-Amino-6-[methyl(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (19a) This was recrystallized by dissolving it in Me_2SO and adding H_2O to the resulting solution. The yellow prisms that resulted were filtered off, washed successively with H_2O, EtOH, and ether, and dried over P_2O_5 at 2 mmHg and room temperature for 24 h to give an analytical sample, mp 206—215 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 223 nm (ε unstable), 248, 278, 355; IR ν_{max}^{Nujol} cm^{-1}: 3390, 3320, 3225, 3180 (NH_2 and NH), 1703, 1678, 1655 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 2.85 (3H, s, NMe), 5.14 (2H, s, C$\underline{H}_2$COPh), 6.85 (2H, br, NH_2), 7.3—8.1 (5H, m, COPh), 10.62 (1H, br, NH). *Anal.* Calcd for $C_{13}H_{13}N_5O_4$: C, 51.49; H, 4.32; N, 23.09. Found: C, 51.36; H, 4.23; N, 22.85.

2-Amino-5-nitro-6-[(2-oxo-2-phenylethyl)propylamino]-4(3*H*)-pyrimidinone (19b) A crude sample was isolated as yellow prisms, mp 198—202 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3310, 3000 (NH_2 and NH), 1695 (sh), 1680 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 0.79 (3H, t, J=7.3 Hz, $CH_2CH_2\underline{Me}$), 1.3—1.9 (2H, m, $CH_2C\underline{H}_2Me$), 3.28 (2H, m, C$\underline{H}_2CH_2Me$), 4.98 (2H, s, C$\underline{H}_2$COPh), 6.85 (2H, br, NH_2), 7.2—8.1 (5H, m, COPh), 10.64 (1H, br, NH).

2-Amino-5-nitro-6-[(2-oxo-2-phenylethyl)-2-propenylamino]-4(3*H*)-pyrimidinone (19c) A crude sample was isolated as yellow prisms, mp 198—202 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3470, 3350, 3230 (NH_2 and NH), 1700 (sh), 1680 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 3.7—4.1 (2H, m, $NC\underline{H}_2CH{=}CH_2$), 4.90 (2H, s, C$\underline{H}_2$COPh), 4.9—5.4 (2H, m, $CH{=}C\underline{H}_2$), 5.6—6.2 (1H, m, C$\underline{H}$=CH_2), 6.95 (2H, br, NH_2), 7.2—8.1 (5H, m, COPh), 10.72 (1H, br, NH).

2-Amino-6-[cyclopropyl(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (19d) A crude sample was isolated as a yellow solid, mp 238—241 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3430, 3330, 3200 (NH_2 and NH), 1696, 1655 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 0.4—0.85 (4H, m, cyclopropyl CH_2's), 2.83 (1H, m, cyclopropyl CH), 5.20 (2H, s, C$\underline{H}_2$COPh), 6.70 (2H, br, NH_2), 7.3—8.1 (5H, m, COPh), 10.67 (1H, s, NH).

2-Amino-6-[cyclohexyl(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (19e) A crude sample was isolated as a yellow solid, mp 149—156 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3480, 3330, 3170, 3100 (NH_2 and NH), 1690 (sh) (COAr), 1670 (CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 0.8—2.0 (10H, m, cyclohexyl CH_2's), 3.73 (1H, m, cyclohexyl CH), 4.99 (2H, s, C$\underline{H}_2$COPh), 6.78 (2H, br, NH_2), 7.4—8.1 (5H, m, COPh), 10.61 (1H, br, NH).

2-Amino-6-[(4-hydroxybutyl)(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (19f) A crude sample was isolated as a yellow solid, mp 173—175 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3520 (OH), 3330, 3140 (NH_2 and NH), 1693 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 0.8—1.9 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.8—3.2 (4H, m, $NC\underline{H}_2CH_2CH_2C\underline{H}_2OH$), 4.39 (1H, t, J=5 Hz, OH), 4.98 (2H, s, C$\underline{H}_2$COPh), 6.86 (2H, br, NH_2), 7.2—8.1 (5H, m, COPh), 10.66 (1H, br, NH).

2-Amino-6-[benzyl(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (19g) A crude sample was isolated as yellow prisms, mp 140—145 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3430, 3270 (NH_2 and NH), 1702, 1692, 1670, 1655 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 4.77 (2H, s, C$\underline{H}_2$Ph), 4.81 (2H, s, C$\underline{H}_2$COPh), 7.0 (2H, br, NH_2), 6.9—8.0 (10H, m, COPh and $CH_2\underline{Ph}$), 10.80 (1H, br, NH).

2-Amino-6-[(2-methoxybenzyl)(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (19h) A crude sample was isolated as a yellow solid, mp 153—158 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3470, 3430 (NH_2 and NH), 1700 (COAr), 1675 (CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 3.70 (3H, s, OMe), 4.65 (2H, s, C$\underline{H}_2$Ar), 4.80 (2H, s, C$\underline{H}_2$COPh), 6.8—8.0 (11H, m, $CH_2\underline{Ar}$, COPh, and NH_2), 10.73 (1H, br, NH).

2-Amino-6-[(3,4-dimethoxybenzyl)(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (19j) A crude sample was isolated as yellow prisms, mp 135—141 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3490, 3390 (NH_2 and NH), 1703, 1682 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 3.71 (6H, s, OMe's), 4.67 (2H, s, C$\underline{H}_2$Ar), 4.80 (2H, s, C$\underline{H}_2$COPh), 6.7—8.0 (10H, m, $CH_2\underline{Ar}$, COPh, and NH_2), 10.76 (1H, br, NH).

2-Amino-6-[(3,4-methylenedioxybenzyl)(2-oxo-2-phenylethyl)amino]-5-nitro-4(3*H*)-pyrimidinone (19k) A crude sample was isolated as a yellow solid, mp 135—142 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3310, 3220 (NH_2 and

NH), 1674 (COAr and CONH); ^{1}H-NMR (Me_2SO-d_6) δ: 4.66 (2H, s, $C\underline{H}_2Ar$), 4.79 (2H, s, $C\underline{H}_2COPh$), 5.98 (2H, s, OCH_2O), 6.7—8.0 (10H, m, $CH_2\underline{Ar}$, COPh, and NH_2), 10.78 (1H, br, NH).

2-Amino-5-nitro-6-[(2-oxo-2-phenylethyl)amino]-4(3*H*)-pyrimidinone (19l) A crude sample was isolated as a pinkish solid, mp 282—285 °C (dec.); ^{1}H-NMR (Me_2SO-d_6) δ: 5.07 (2H, d, J=5 Hz, $NHC\underline{H}_2COPh$), 6.0—8.0 (2H, br, NH_2), 7.3—8.0 (5H, m, COPh), 9.94 (1H, t, J=5 Hz, $N\underline{H}CH_2COPh$), 10.67 (1H, br, NH).

Cyclization of the Nitropyrimidinones 19a—k to 9-Substituted Guanine 7-Oxides (24a—k) The cyclizations of **19a** and **19i** will be described below in detail as typical examples. The other cyclizations were effected in a similar manner, and the products were characterized as recorded below. Table III summarizes the reaction conditions applied and the results obtained.

9-Methylguanine 7-Oxide (24a) The methylamino analogue **19a** (200 mg, 0.659 mmol) was dissolved in 2 N aqueous NaOH (4 ml), and the resulting mixture was kept at room temperature for 1 h. The colorless crystals (presumed to be the Na salt of **24a**) that deposited were filtered off, washed with H_2O (1 ml), and then dissolved in H_2O (5 ml) with application of heat. The resulting aqueous solution was brought to pH *ca.* 5 by addition of 10% aqueous HCl, and the pale pinkish crystals that deposited were filtered off, washed successively with H_2O (3×1 ml), MeOH (2×1 ml), and ether (1 ml), and dried to afford **24a** (117 mg, 98%), mp >300 °C. Recrystallization of the crude sample by dissolving it in 1 N aqueous NaOH and adding 1 N aqueous HCl to the resulting solution (to bring it to pH *ca.* 5) and drying over P_2O_5 at 2 mmHg and 110 °C for 8 h furnished an analytical sample of **24a** as colorless prisms, mp >300 °C (lit.[15] mp >300 °C for the hemihydrate); UV (Table IV); $\lambda_{max}^{H_2O}$ (pH 5.8) 236 nm (ε 21800), 269 (8200), 280 (sh) (7600); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 3.79 [3H, d, J=0.4 Hz, N(9)-Me], 9.03 [1H, q, J=0.4 Hz, C(8)-H]. *Anal.* Calcd for $C_6H_7N_5O_2$: C, 39.78; H, 3.89; N, 38.66. Found: C, 39.52; H, 3.95; N, 38.59.

On the other hand, the aqueous filtrate and washings, obtained when the crude·Na salt was isolated from the reaction mixture, were combined and brought to pH 1 with 10% aqueous HCl. The colorless crystals that resulted were extracted with ether, and the ethereal extracts were dried over anhydrous $MgSO_4$ and concentrated to dryness *in vacuo*, leaving benzoic acid (80.0 mg, 99%) as colorless plates, mp 119—121 °C. This sample was identical (by mixture melting point test and comparison of the IR spectrum) with authentic benzoic acid.

9-(4-Methoxybenzyl)guanine 7-Oxide (24i) The 4-methoxybenzylamino analogue **19i** (1.50 g, 3.66 mmol) was dissolved in 2 N aqueous NaOH (37 ml), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was heated to 40—50 °C in order to dissolve greenish yellow crystals that had deposited and then brought to pH *ca.* 5 by addition of 10% aqueous HCl. The pale yellowish crystals that resulted were filtered off, washed successively with MeOH and ether, and dried to give **24i**·1/3H_2O (654 mg, 61%), mp >300 °C. Recrystallization from 50% (v/v) aqueous MeOH and drying over P_2O_5 at 2 mmHg and 60 °C for 12 h yielded an analytical sample of **24i**·1/3H_2O as colorless prisms, mp >300 °C; UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 3.83 (3H, s, OMe), 5.29 (2H, s, $C\underline{H}_2Ar$), 7.02 [2H, d, J=8.9 Hz, C(3′)-H and C(5′)-H],[34] 7.41 [2H, d, J=8.9 Hz, C(2′)-H and C(6′)-H],[34] 8.96 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{13}H_{13}N_5O_3\cdot1/3H_2O$: C, 53.24; H, 4.70; N, 23.88. Found: C, 53.30; H, 4.51; N, 23.70.

9-Propylguanine 7-Oxide (24b) This was recrystallized from 50% (v/v) aqueous MeOH and dried over P_2O_5 at 2 mmHg and 110 °C for 16 h, giving **24b**·1/2H_2O as almost colorless needles, mp >300 °C; UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 0.94 (3H, t, J=7 Hz, $CH_2CH_2\underline{Me}$), 1.6—2.1 (2H, m, $CH_2C\underline{H}_2Me$), 4.17 (2H, t, J=7 Hz, $C\underline{H}_2CH_2Me$), 9.11 [1H, s, C(8)-H]. *Anal.* Calcd for $C_8H_{11}N_5O_2\cdot1/2H_2O$: C, 44.03; H, 5.54; N, 32.09. Found: C, 44.09; H, 5.67; N, 31.85.

9-(2-Propenyl)guanine 7-Oxide (24c) This was recrystallized from 50% (v/v) aqueous MeOH and dried over P_2O_5 at 2 mmHg and 100 °C for 10 h to yield **24c**·3/5H_2O as colorless needles, mp >300 °C; UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 4.7—4.9 (2H, m, $NC\underline{H}_2CH=CH_2$), 5.1—5.5 (2H, m, $CH=C\underline{H}_2$), 5.8—6.3 (1H, m, $C\underline{H}=CH_2$), 9.08 [1H, s, C(8)-H]. *Anal.* Calcd for $C_8H_9N_5O_2\cdot3/5H_2O$: C, 44.08; H, 4.72; N, 32.13. Found: C, 43.83; H, 4.58; N, 31.93.

9-Cyclopropylguanine 7-Oxide (24d) This was recrystallized from 50% (v/v) aqueous MeOH and dried over P_2O_5 at 2 mmHg and room temperature for 72 h, producing **24d**·1/3H_2O as colorless needles, mp 260—290 °C (dec.); UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 0.9—1.3 (4H, m, cyclopropyl CH_2's), 3.4—3.6 (1H, m, cyclopropyl CH), 9.10 [1H, s, C(8)-H]. *Anal.* Calcd for $C_8H_9N_5O_2\cdot1/3H_2O$: C, 45.07; H, 4.57; N, 32.85. Found: C, 45.31; H, 4.34; N, 32.82.

9-Cyclohexylguanine 7-Oxide (24e) This was recrystallized from 50% (v/v) aqueous MeOH to give colorless plates, mp >300 °C; UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 1.0—2.3 (10H, m, cyclohexyl CH_2's), 4.1—4.6 (1H, m, cyclohexyl CH), 9.14 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 52.82; H, 6.20; N, 27.94.

9-(4-Hydroxybutyl)guanine 7-Oxide (24f) This was recrystallized from 50% (v/v) aqueous MeOH and dried over P_2O_5 at 2 mmHg and 100 °C for 10 h, giving **24f**·1/4H_2O as colorless plates, mp 235—247 °C (dec.); UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 1.4—1.8 and 1.8—3.2 (2H each, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 3.64 (2H, t, J=6.2 Hz) and 4.24 (2H, t, J=7.1 Hz) ($NC\underline{H}_2CH_2CH_2C\underline{H}_2OH$), 9.11 [1H, s, C(8)-H]. *Anal.* Calcd for $C_9H_{13}N_5O_3\cdot1/4H_2O$: C, 44.35; H, 5.58; N, 28.73. Found: C, 44.61; H, 5.57; N, 28.85.

9-Benzylguanine 7-Oxide (24g) This was recrystallized from 50% (v/v) aqueous MeOH to furnish almost colorless prisms, mp >300 °C; UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 5.38 (2H, s, $C\underline{H}_2Ph$), 7.45 (5H, s, $CH_2\underline{Ph}$), 9.02 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.77; H, 4.25; N, 27.06.

9-(2-Methoxybenzyl)guanine 7-Oxide (24h) For analysis, this was recrystallized and dried in a manner similar to that described above for **24a**, yielding colorless prisms, mp 265—273 °C (dec.); UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 3.85 (3H, s, OMe), 5.29 (2H, s, $C\underline{H}_2Ar$), 6.8—7.5 (4H, m, $CH_2\underline{Ar}$), 8.95 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.52; H, 4.56; N, 24.09.

9-(3,4-Dimethoxybenzyl)guanine 7-Oxide (24j) This was recrystallized from 50% (v/v) aqueous MeOH and dried over P_2O_5 at 2 mmHg and 110 °C for 12 h to provide **24j**·1/4H_2O as colorless prisms, mp 270—304 °C (dec.); UV (Table IV); ^{1}H-NMR (CF_3CO_2D) δ: 3.98 and 4.00 (3H each, s, OMe's), 5.40 (2H, s, $C\underline{H}_2Ar$), 7.12 (3H, s, $CH_2\underline{Ar}$), 8.54 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{14}H_{15}N_5O_4\cdot1/4H_2O$: C, 52.25; H, 4.85; N, 21.76. Found: C, 52.40; H, 4.73; N, 21.50.

9-(3,4-Methylenedioxybenzyl)guanine 7-Oxide (24k) This was recrystallized from 50% (v/v) aqueous MeOH and dried over P_2O_5 at 2 mmHg and 110 °C for 12 h to give **24k**·1/3H_2O as slightly pinkish needles, mp 270—283 °C (dec.); UV (Table IV); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 5.27 (2H, s, $C\underline{H}_2Ar$), 5.99 (2H, s, OCH_2O), 6.8—7.0 (3H, m, $CH_2\underline{Ar}$), 8.97 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{13}H_{11}N_5O_4\cdot1/3H_2O$: C, 50.82; H, 3.83; N, 22.79. Found: C, 51.03; H, 3.55; N, 22.57.

Guanine 7-Oxide (5) i) From **24i**: To a stirred, ice-cooled suspension of **24i**·1/3H_2O (500 mg, 1.70 mmol) in toluene (5.6 ml) was added dropwise conc. H_2SO_4 (0.93 ml, *ca.* 17 mmol), and the mixture was stirred vigorously at 25 °C for 90 min, during which time a reddish purple color was produced. The toluene layer was then decanted, and the reddish brown, oily residue was mixed with H_2O (3 ml) under ice-cooling. The resulting aqueous mixture was brought to pH *ca.* 5 by addition of 10% aqueous NaOH. The pale yellowish solid that resulted was filtered off, washed successively with benzene, H_2O, and MeOH, and dried to give **5**·1/3H_2O (264 mg, 89%), mp >300 °C. The crude sample was recrystallized by dissolving it in 2 N aqueous NH_3 and adding 1 N aqueous HCl until the resulting solution became weakly acidic, producing, after drying over P_2O_5 at 2 mmHg and room temperature for 36 h, an analytical sample of **5**·1/3H_2O as a colorless microcrystalline solid, mp >300 °C; UV $\lambda_{max}^{H_2O}$ (pH 1) 252 nm (ε 9600), 270 (sh) (7160); $\lambda_{max}^{H_2O}$ (pH 3.6) 232 (15900), 253 (7200), 282 (7300); $\lambda_{max}^{H_2O}$ (pH 7) 234 (19400), 289 (6100); $\lambda_{max}^{H_2O}$ (pH 13) 255 (sh) (5470), 286 (6430); ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 8.58 [s, C(8)-H]. *Anal.* Calcd for $C_5H_5N_5O_2\cdot1/3H_2O$: C, 34.69; H, 3.30; N, 40.45. Found: C, 34.86; H, 3.19; N, 40.32. This sample was identical (by comparison of the UV, IR, and ^{1}H-NMR spectra, TLC and HPLC behavior, and antimicrobial[9] and antitumor[9] activities) with a natural sample of **5** containing 1/3 molar eq of H_2O of crystallization. The hydrochloride salts (**5**·HCl·H_2O) [mp >300 °C; ^{1}H-NMR (1 N D_2SO_4/D_2O) δ: 8.58 [s, C(8)-H]], prepared from both samples according to the literature procedure,[7] were also identical (by comparison of the UV, IR, and ^{1}H-NMR spectra).

ii) From **24j**: To a stirred suspension of **24j**·1/4H_2O (100 mg, 0.311 mmol) in toluene (2 ml) was added dropwise conc. H_2SO_4 (0.43 ml, *ca.* 7.8 mmol), and the mixture was stirred vigorously at 26 °C for 3 h. Work-up of the reaction mixture (reddish purple) was performed in a manner similar to that described above under item (i), giving **5**·1/3H_2O (36.4 mg, 68%) as a slightly pinkish solid, mp >300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **5**·1/3H_2O.

iii) From **24k**: To a stirred suspension of **24k**·1/3H_2O (100 mg, 0.325 mmol) in toluene (2 ml) was added dropwise conc. H_2SO_4 (0.19 ml, *ca.* 3.5 mmol), and the mixture was stirred vigorously at room temperature for 1 h. The reaction mixture (reddish purple) was worked up as described above under item (i), affording **5**·1/3H_2O (31.4 mg, 56%) as a slightly brownish solid, mp >300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **5**·1/3H_2O.

9-(2-Methoxy-5-sulfobenzyl)guanine 7-Oxide (26) To a stirred suspension of **24h** (100 mg, 0.348 mmol) in toluene (2 ml) was added dropwise conc. H_2SO_4 (0.30 ml, *ca.* 5.5 mmol), and the mixture was stirred vigorously at 25 °C for 2 h. The amber reaction mixture was mixed with H_2O (1 ml) under ice-cooling, and the aqueous mixture was brought to pH *ca.* 5 by addition of 10% aqueous NaOH. The solid that deposited was filtered off, washed successively with H_2O, benzene, EtOH, and ether, and dried to give colorless prisms (88.9 mg, 69%), mp 280—293 °C (dec.). The crude product was recrystallized by dissolving it in 1 N aqueous NaOH and adding 1 N aqueous HCl until the pH of the resulting solution reached *ca.* 5. The precipitate was dried over P_2O_5 at 2 mmHg and 110 °C for 12 h, yielding **26**·1/4H_2O as colorless prisms, mp 280—293 °C (dec.); positive to a test for detection of sulfur by the sodium fusion method[36]; UV $\lambda_{max}^{H_2O}$ (pH 1) 234 nm (ε 16300), 258 (11800), 282 (9800); $\lambda_{max}^{H_2O}$ (pH 7) 234 (31600), 273 (10700); $\lambda_{max}^{H_2O}$ (pH 13) 232 (31400), 282 (11200); ^{1}H-NMR (1 N NaOD/D_2O) δ: 3.86 (3H, s, OMe), 5.20 (2H, s, C$\underline{H}_2$Ar), 7.09 [1H, d, J=8.3 Hz, C(3′)-H],[34] 7.6—7.9 [2H, m, C(4′)-H and C(6′)-H].[34,37] *Anal.* Calcd for $C_{13}H_{13}N_5O_6S$·1/4H_2O: C, 41.99; H, 3.66; N, 18.83. Found: C, 41.75; H, 3.52; N, 19.00.

Bioassay of Antileukemic Activity against Murine L5178Y Cells Murine L5178Y cells, a leukemia cell line provided by Mr. S. Shimizu (Faculty of Pharmaceutical Sciences, Kanazawa University) and maintained in successive generations, were implanted and grown in static suspension culture with Fischer's medium (Sigma) [supplemented with 10% horse serum (Whittaker M. A. Bioproducts) and 100 μg/ml kanamycin sulfate (Meiji Seika)] at 37 °C. After 2—3 d of incubation, the cells were centrifuged at 1000 rpm for 5 min, and 2×10^4 cells were resuspended in fresh medium (1 ml). The resulting suspension was added to suspensions of the test compound in fresh medium (1 ml) at various concentrations, and the cells were allowed to grow in such static suspensions at 37 °C. After 72 h of incubation, the number of cells was determined on a hemocytometer (Coulter counter, model ZBI). The cytotoxic activity of the drug was expressed as the ratio T/C (% inhibition) of mean cell number of treated groups to that of untreated control groups and as the value of IC_{50} (μg/ml), the concentration of the test compound required to inhibit cell growth by 50%. The results are summarized in Table V.

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