# Notes

# Synthesis and Cytotoxic Activity of 6-Vinyl- and 6-Ethynyluridine and 8-Vinyland 8-Ethynyladenosine

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It is well-known that the introduction of vinyl and ethynyl moieties into nucleosides is of crucial importance for cytostatic, antiviral, or other biological activities. In this study 6- and 8-vinyland -ethynyluridine and -adenosine were prepared by a general procedure involving the palladium-catalyzed cross-coupling of trimethylsilylacetylene or vinyltributyltin. The introduction of a vinyl group at C-6 of uridine or an ethynyl group at C-8 of adenosine resulted in nucleoside derivatives showing cytostatic activity against several murine and/or human tumor cell lines. Interestingly, 8-vinyladenosine had pronounced selective inhibitory effects on human (Molt/4F and MT-4) versus murine (L1210 and FM3A) tumor cell lines.

### Introduction

As reported by a number of authors, the introduction of alkyl, alkenyl and/or alkynyl groups into natural purine and pyrimidine nucleosides is of great interest in view of their potential biological activities.<sup>1</sup> In particular, modifications of the C-8 position in purine nucleosides and the C-6 position of pyrimidine nucleosides are of significant interest for their influence on the conformation of the glycosidic bond (i.e., selectivity on adenosine receptors<sup>2</sup>). Robins and Samano<sup>3</sup> have recently reported on the synthesis of 2'-deoxynucleoside-2'-spirocyclopropanes as mechanistic probes for ribonucleotide reductase (RR).<sup>4</sup> They have demonstrated that biomimetic radical reactions yield, through the spirocyclopropyl ring opening, 5,6-dihydro-6,2'-ethano-2',3'-unsaturated cyclouridine (1) and 8,2'-ethano-2',3'unsaturated cycloadenosine (2). Moreover, Chatto-



padhyaya et al. have reported the intramolecular cyclization of olefins as a means for trapping carbon radicals at the 2'- and 3'-carbons of nucleosides,<sup>5</sup> and Tanaka et al. have recently demonstrated the usefulness of 6-(bromovinyl)uracil derivatives in radical-mediated cyclizations.<sup>6</sup> Taking these considerations into account,

we envisaged compounds 5, 9 and 13, 14 as possible candidates for antitumor/antiviral agents.7 The following considerations guided our approach: (a) potential antitumor/antiviral activities may be obtained by introduction of alkenyl and alkynyl groups at an opportune position of the nucleosidic base;<sup>8</sup> (b) a suitable function that could trap the incipient radical formed at position 2' or 3' of a ribonucleoside may serve as a probe for the proposed mechanism of action of ribonucleotide reductase; (c) alkynyl and vinyl moieties are known to be highly reactive with respect of the radical species; (d) the potential formation of cyclonucleosides, through addition to the unsaturated functionality (vinyl or ethynyl) of the incipient radical on the glycosylic portion. may account for the biological activity.<sup>5</sup>

# Chemistry

Initially, we were attracted by the possibility to obtain 5<sup>9</sup> starting from compounds 4a and/or 4b (Scheme 1). A logical approach prompted us to study the oxidation of 4a with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) whereas treatment with bases of 4b could reasonably afford deprotection of the (triisopropylphenyl)sulfonyl group (TPS) with concomitant elimination of hydrobromic acid. Compound 4a has been already reported by Bichofberger,<sup>10</sup> and 4b was simply prepared through reaction of the protected 5-bromouridine with triisopropylbenzenesulfonyl chloride (TPS-Cl). All attempts to achieve 5 as mentioned above were unsatisfactory: oxidation of 4a afforded only traces of the target compound, the cleavage of the glycosylic bond being the principal reaction. However, better results, even not satisfactory, were obtained when 4b was first deprotected with tetrabutylammonium fluoride (TBAF) in THF solution and in situ treated with tetrabutylammonium hydroxide: very limited amounts (16%) of the expected compound 5, with concomitant disappearance of starting material, could be recovered.

In order to produce higher amounts of compound 5, we planned a different strategy (Scheme 2): based on

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#### Scheme 1<sup>a</sup>



<sup>a</sup> (i) Vinylmagnesium bromide, THF, 0 °C; (ii) (1) TBAF, THF, (2) Bu<sub>4</sub>NOH, H<sub>2</sub>O.

Scheme 2<sup>a</sup>



<sup>a</sup> (i) Tributylvinylstannane, (Ph<sub>3</sub>P)<sub>4</sub>Pd, DMF; (ii) (trimethylsilyl)acetylene, (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, Et<sub>3</sub>N; (iii) CF<sub>3</sub>CO<sub>2</sub>H/H<sub>2</sub>O 50%; (iv) NH<sub>4</sub>F, MeOH, 70 °C.

the study of Tanaka and co-workers<sup>11</sup> on the position 6 of pyrimidine bases, we envisaged the key intermediate  $6^{11}$  as a suitable candidate. This compound is amenable of conversion to both the desired derivatives 7 and 8 through a coupling reaction with a suitable source of alkynyl or alkenyl functions. The ethynyl derivative 8 was prepared in 68% yield, by a methodology developed previously<sup>12</sup> and involving the coupling of **6** and (trimethylsilyl)acetylene with (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>. For the introduction of the vinyl moiety, the palladium-catalyzed cross-coupling reaction with organotin reagents is known to be a valuable approach,<sup>13</sup> and applications of this procedure for the alkylation of purine and pyrimidine nucleosides have been recently reported.<sup>8,14,15</sup> Either tetraalkyltin or alkyltributyltin reagents were employed on a suitable halide precursor to give the corresponding alkyl nucleoside. We used vinyltributyltin in DMF in the presence of catalytic amount of  $(Ph_3P)_4Pd$  to obtain in almost quantitative yield the expected 7.<sup>16</sup> Deprotection of 7 and 8 at both 5'-O-tert-butyldimethylsilyl (TBDMS) and 2',3'-O-isopropylidene groups was performed with 50% aqueous trifluoroacetic acid to give 5 and  $9^{17}$  (with concurrent removal of the trimethylsily) group) in good yield (Scheme 2). Moreover compound **5** has also been prepared from 6- ethynyluridine (9) by direct hydrogenation on Pd-BaSO<sub>4</sub> catalyst. However, overreduction, formation of side products, and difficulties in the monitoring of the reduction led to very limited yields (20%).

The above-described approach was extended to protected 8-iodoadenosine  $(10)^{15}$  to give in 85 and 63% yields 11 and 12, respectively (Scheme 2). Difficulties in the deprotection step have been encountered; however, the use of NH<sub>4</sub>F in methanol<sup>18</sup> instead of the standard TBAF procedure gave the final compounds 13 and 14 in 50 and 77% yield, respectively. These difficulties in the deprotection of silylated-vinyl adenosine have also been encountered by Van Aerschot et al.<sup>8</sup> and overcome through a tranisent silylation step. The NH<sub>4</sub>F/methanol deprotection avoided the conjugate addition reaction that occurs by the use of TBAF.

Finally, extension of our procedure to the preparation of the cytidine analogs of compounds **5** and **9** failed. Surprisingly, we did not succeed in converting 6-iodo-4-(1,2,4-triazol-1-yl)-5'-O-(tert-butyldimethylsilyl)-2',3'isopropylideneuridine,<sup>19,20</sup> into the expected coupling products.

# **Results and Discussion**

6- and 8-vinyl- and -ethynyluridine and -adenosine have been prepared, starting from the corresponding iodo-substituted intermediates. Our methodology further extend the chemistry developed for the function-

Table 1. Inhibitory Effects of Nucleoside Derivatives 5, 9, 13, and 14 on the Proliferation of Murine Leukemia L1210, Murine Mammary Carcinoma FM3A, and Human T-Lymphoblast Molt/4F and MT-4 Cells

	$\mathrm{IC}_{50}~(\mu\mathrm{M})^a$			
compd	L1210	FM3A	Molt/4F	MT4
5	$21 \pm 0.7$	24	$14 \pm 0.12$	11
9	>372	>372	>372	$286 \pm 78$
13	$190 \pm 38$	145	$6.5\pm0.1$	$15\pm5$
14	$54 \pm 24$	27	$25\pm0.1$	$22 \pm 7$

 $^a$  50% inhibitory concentration, or compound concentration required to inhibit tumor cell proliferation by 50%.

alization of position 6 on uridine and position 8 on adenosine and allows a general procedure for the preparation of either 6- and 8-vinyl- or -ethynyluridine and -adenosine based on a palladium-catalyzed crosscoupling strategy. Whereas 6-ethynyluridine (9) was devoid of any marked cytostatic activity against murine (L1210 and FM3A) and human (Molt/4F and MT-4) cells [50% inhibitory concentration (IC<sub>50</sub>)  $\geq$  286  $\mu$ M (Table 1)], its 6-vinyl-substituted counterpart (5) inhibited tumor cell proliferation with an IC<sub>50</sub> of  $12-24 \mu M$ against the four tumor cell lines investigated. Whereas 8-ethynyladenosine (14) inhibited the proliferation of all four cell lines (IC<sub>50</sub> 22-54  $\mu$ M), 8-vinyladenosine (13) was poorly cytostatic against the murine tumor cells (L1210 and FM3A), but had a more pronounced inhibitory effect on human Molt/4F and MT-4 cell proliferation (IC\_{50}: 6.5–15  $\mu M).$  These data may be suggestive of differences in the metabolism of 8-vinyladenosine in human *versus* murine tumor cell lines.

Thus, the introduction of a vinyl moiety at the C-6 of uridine, or a vinyl or ethynyl group at the C-8 of adenosine, which induce the opposite conformation of the glycosidic bond if compared to the natural nucleosides, made these nucleosides markedly more cytostatic than the natural ones. The pronounced cytostatic activity of 8-vinyladenosine (13) together with its previously reported antiviral activity (i.e., herpes simplex virus type 1, vaccinia virus, and respiratory syncytial virus)<sup>8</sup> make this compound particularly interesting. Moreover, in constrast with the trend observed in the 5-vinyl- and 5-ethynyl-substituted 2'-deoxyuridine series,<sup>21</sup> 6 vinyluridine is a potent cytostatic compound, whereas the 6-ethynyl derivative is inactive.

#### **Experimental Part**

**Chemistry.** Melting points were obtained in open capillary tubes and are uncorrected. Reaction courses were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F254 Merck plates with detection under 254-nm UV lamp and/or by spraying the plates with 10% H<sub>2</sub>SO<sub>4</sub>/MeOH and heating. Nuclear magnetic resonance (<sup>1</sup>H NMR, <sup>13</sup>C NMR) spectra were determined in DMSO-d<sub>6</sub> or CDCl<sub>3</sub> solution with a Bruker AC-200 spectrometer, and peak positions are given in parts per million downfield from tetramethylsilane as internal standard. Ultraviolet spectra were recorded on a JASCO 510 spectrometer. Column chromatography was performed with Merck 60-200-mesh silica gel. Room temperature varied between 22 and 25 °C. All drying operations were performed over anhydrous magnesium sulfate. Microanalysis were in agreement with calculated values within ±0.4%.

**Starting Materials.** Starting compounds **3a**,<sup>10</sup> **6**,<sup>11</sup> and **10**<sup>15</sup> were prepared as reported.

4-O-[(Triisopropylphenyl)sulfonyl]-5-bromo-2',3',5'-tris-O-(tert-butyldimethylsilyl)uridine (3b). Compound 3b was prepared following and adapting the procedure described on the parent uridine derivative.<sup>10</sup> Chromatography (EtOAc/ Hexane, 1:9) gave a foam (yield 87%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.08 (s, 1H, H6), 7.21 (s, 2H, Ar), 5.96 (d, J = 2.2 Hz, 1H, H1'), 4.29 (m, 5H, H2', H3', H4', and 2 × CH-isop), 3.70 (m, 2H, H5'), 2.90 (m, 1H, CH-isop), 1.31 (d, J = 7 Hz, 12H, Me-isop), 1.29 (d, J = 7 Hz, 6H, Me-isop), 0.88–0.94 (3 s, 27H, tBu), 0.10–0.02 (m, 18H, SiMe).

4-O-[(Triisopropylphenyl)sulfonyl]-5-bromo-6-vinyl-5,6-dihydro-2',3',5'-tris-O-(tert-butyldimethylsilyl)uridine (4b). Compound 3b (0.50 g, 0.53 mmol) was dissolved in anhydrous THF (5 mL) under positive argon pressure, and vinylmagnesium bromide 1.0 M in THF (2.5 mL, 2.5 mmol) was added at 0 °C. After 1 h at 0 °C, TLC indicated complete reaction and the mixture was then diluted with Et<sub>2</sub>O (20 mL), treated with saturated NH<sub>4</sub>Cl (20 mL), and washed with H<sub>2</sub>O (50 mL). The organic layer was dried and evaporated to give a crude residue (1.1 g), which was purified by chromatography (EtOAc/hexane, 9:1, in the presence of traces of  $Et_3N$ ) to give 4b as an oil (0.49 g, yield 96%). The resulting compound was stable only if stored in solution (CH<sub>2</sub>Cl<sub>2</sub>) below -17 °C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.23 (s, 2H, Ar), 6.39 (s, 1H, NH), 5.99–5.83 (m, 1H, vinyl), 5.90 (d, J = 6.5 Hz, 1H, H1'), 5.37 (d, J = 17Hz, 1H, vinyl), 5.22 (d, J = 10 Hz, vinyl), 4.64 (d, J = 4 Hz, 1H, H6) 4.19-3.93 (m, 5H, H2', H3', H4', and  $2 \times$  CH-isop), 3.70 (m, 2H, H5'), 2.90 (M, 1h, CH-isop), 1.31 (d, J = 7 Hz,12H, 2 × Me-isop), 1.29 (d, J = 7 Hz, 6H, Me-isop), 0.88–0.94 (3s, 27H, tBu), 0.10-0.02 (m, 18H, SiMe).

Preparation of 6- and 8-Vinyl-Protected Uridine (7) and Adenosine (11). General Procedure. In a typical experiment in a 100 mL two-necked flask, halide (6 and 10) (0.95 mmol) was dissolved in dry DMF (20 mL), and (Ph<sub>3</sub>P)<sub>4</sub>-Pd (0.054 g, 0.0475 mmol) and tributylvinylstannane (1 mL, 4.76 mmol) were added. The mixture was stirred at 90 °C for 1.5 h under positive argon pressure (TLC, EtOAc/hexane, 3:7). When the reaction was complete, the solvent was evaporated, and the brown residue was dissolved in EtOAc (50 mL), washed with saturated NH<sub>4</sub>Cl (1 × 20 mL), dried, and evaporated. The resulting brown oil was purified by chromatography (EtOAc/hexane, 3:7, in presence of traces of Et<sub>3</sub>N).

7: yield 95%; foam; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.1 (sbr, 1H, NH), 6.68 (dd, J = 10 Hz, J = 17 Hz, 1H, vinyl), 5.88 (d, J = 17 Hz, 1H, vinyl), 5.78 (s, 1H, H5), 5.75 (d, J = 2.2 Hz, 1H, H1'), 5.67 (d, J = 10 Hz, 1H, vinyl), 5.19 (dd, J = 2.2 Hz, J = 6.4 Hz, 1H, H2'), 4.84 (dd, J = 6.4 Hz, J = 4.4 Hz, 1H, H3'), 4.15 (m, 1H, H4'), 3.80 (m, 2H, H5'), 1.55 (s, 3H, Me-isop), 1.34 (s, 3H, Meisop), 0.9 (s, 9H, tBu), 0.05 (s, 6H, SiMe).

11: yield 85%; mp 184–186 °C (EtOH/H<sub>2</sub>O); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.28 (s, 1H, H2), 6.98 (dd, J = 12, Hz, J = 18 Hz, 1H, vinyl), 6.47 (dd, J = 2 Hz, J = 18 Hz, 1H, vinyl), 5.99 (d, J = 6 Hz, 1H, H1'), 5.95 (s, 2H, NH<sub>2</sub>), 5.70 (dd, J = 2 Hz, J = 12 Hz, 1H, vinyl), 5.29 (dd, J = 6.2 Hz, J = 4.6 Hz, 1H, H2'), 4.50 (dd, J = 2.4 Hz, J = 4.6 Hz, 1H, H3'), 4.07 (m, 2H, H4', H5'), 3.78 (dd, J = 6.4 Hz, J = 13.6 Hz, 1H, H5'), 0.97–0.75 (3s, 27H, tBu), 0.16–0.02 (m, 18H, SiMe).

Preparation of 6- and 8-(Trimethylsilyl)ethynyl-Protected Uridine (8) and Adenosine (12). General Procedure. In a typical experiment in a 100 mL two-necked flask, freshly distilled dry  $Et_3N$  (40 mL) was vigorously purged with nitrogen for 30 min, and halide (6 and 10) (0.92 mmol) was added followed by (trimethylsilyl)acetylene (0.426 mL, 3.01 mmol), (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (0.015 g, 0.0213 mmol), and CuI (0.01 g, 0.0526 mmol). This suspension was stirred at room temperature for 1 h and then at 80 °C for 2 h under positive argon pressure (TLC, EtOAc/hexane, 3:7). When the reaction was complete, the solvent was evaporated, and the brown residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), washed with 2% disodium EDTA/H<sub>2</sub>O (2  $\times$  50 mL) and H<sub>2</sub>O (2  $\times$  50 mL), dried, and evaporated. The resulting brown oil was purified by column chromatography (EtOAc/hexane, 3:7, in presence of traces of Et<sub>a</sub>N).

8: yield 68%; yellow syrup; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.77 (br, 1H, NH), 6.33 (d, J = 1.5 Hz, 1H, H1'), 5.94 (d, J = 2.2 Hz, 1H, H5), 5.19 (dd, J = 1.6 Hz, J = 6.6 Hz, 1H, H2'), 4.80 (dd, J = 4 Hz, J = 6.6 Hz, 1H, H3'), 4.17 (m, 1H, H4'), 3.82 (m, 2H, H5'), 1.53 (s, 3H, Me-isop), 1.35 (s, 3H, Me-isop), 0.88 (s, 9H, tBu), 0.29 (s, 9H, SiMe<sub>3</sub>), 0.04 (s, 6H, SiMe<sub>2</sub>).

12: yield 63%; yellow solid mp 85-87 °C (EtOH/H<sub>2</sub>O); <sup>1</sup>H NMR ( $CDCl_3$ )  $\delta$  8.29 (s, 1H, H2), 6.15 (d, J = 6.8 Hz, 1H, H1'), 6.01 (s, 2H, NH<sub>2</sub>), 5.38 (dd, J = 4.4 Hz, J = 7 Hz, 1H, H2'), 4.45 (d, J = 4.2 Hz, 1H, H3'), 4.18–4.07 (m, 2H, H4', H5')  $3.77 \,(dd, J = 4.4 \,Hz, J = 9 \,Hz, 1H, H5'), 0.97 - 0.78 \,(3s, 27H, J)$ tBu), 0.29-0.07 (m, 27H, SiMe).

**General Procedures for Deprotection.** Preparation of 6-Vinyl- (5) and 6-Ethynyluridine (9). The protected compound (1 mmol) was dissolved at 0 °C in aqueous trifluoroacetic acid (TFA) (20 mL), and the mixture was stirred overnight at room temperature. After evaporation the crude residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH, 9:1).

5:9 yield 88%; mp 203-205 °C (MeOH/Et<sub>2</sub>O); UV (H<sub>2</sub>O)  $\lambda_{max}$ 276 ( $\epsilon$  4260),  $\lambda_{min}$  238 ( $\epsilon$  460),  $\lambda_{max}$  212 ( $\epsilon$  2420); <sup>1</sup>H NMR  $(DMSO-d_6) \delta 11.40 (sbr, 1H, NH), 6.79 (dd, J = 11 Hz, J = 17)$ Hz, 1H, vinyl), 5.91 (d, J = 17 Hz, 1H, vinyl), 5.75 (s, 1H, H5), 5.69 (d, J = 2.2 Hz, 1H, H1'), 5.60 (d, J = 11 Hz, 1H, vinyl), 5.23 (d, J = 5.6 Hz, 1H, OH2'), 4.97 (d, J = 6.2 Hz, 1H, OH3'), 4.80 (t, J = 5.6 Hz, 1H, OH5'), 4.40 (m, 1H, H2'), 4.01 (m, 1H, H2')H3'), 3.69-3.43 (m, 3H, H4' and H5'). Anal. (C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>) C, H, N.

9: yield 73%; mp 216 °C (MeOH/Et<sub>2</sub>O), (lit.<sup>17</sup> mp 217-219 °C). Anal. (C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub>) C, H, N.

Preparation of 8-Vinyl- (13) and 8-Ethynyladenosine (14). The protected compound (1 mmol) was dissolved at room temperature in MeOH (20 mL), and NH<sub>4</sub>F<sup>18</sup> (5 mmol) was added. The mixture was refluxed at 60-70 °C until complete conversion to deprotected compound (TLC, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1). After evaporation, the crude residue was purified by column chromatography.

13: yield 50%; mp 241 °C (MeOH/Et<sub>2</sub>O) (lit.<sup>8</sup> mp 245 °C dec); UV (H<sub>2</sub>O)  $\lambda_{max}$  228 ( $\epsilon$  25 700),  $\lambda_{min}$  253 ( $\epsilon$  5900),  $\lambda_{max}$  288 ( $\epsilon$ 13 400); <sup>1</sup>H NMR (DMSO- $d_6$ )  $\delta$  8.11 (s, 1H, H2), 7.44 (s, 2H, NH<sub>2</sub>), 7.10 (dd, J = 11 Hz, J = 17 Hz, 1H, vinyl), 6.35 (dd, J= 2 Hz, J = 17 Hz, 1H, vinyl), 5.96 (d, J = 7 Hz, 1H, H1'), 5.77–5.67 (m, 2H, OH5' and vinyl), 5.38 (d, J = 7 Hz, 1H, OH2'), 5.22 (d, J = 4.6 Hz, 1H, OH3'), 4.81 (m, 1H, H2'), 4.12 (m, 1H, H3'), 3.99 (m, 1H, H4'), 3.56 (m, 2H, H5'). Anal.  $(C_{12}H_{15}N_5O_4)$  C, H, N.

14: yield 77%; mp 232-234 °C (MeOH/Et<sub>2</sub>O); UV (H<sub>2</sub>O)  $\lambda_{max}$ 228 ( $\epsilon$  20 000),  $\lambda_{\min}$  247 ( $\epsilon$  3900),  $\lambda_{\max}$  292 ( $\epsilon$  17 000); <sup>1</sup>H NMR  $(\text{CDCl}_3) \delta 8.18 \text{ (s, 1H, H2), 7.70 (s, 2H, NH}_2), 5.96 \text{ (d, } J = 7$ Hz, 1H, H1'), 5.57 (m, 1H, OH5'), 5.48 (d, J = 7 Hz, 1H, OH2 '), 5.25 (d, J = 4.4 Hz, 1H, OH3'). Anal. (C<sub>12</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>) C, H, Ń.

Biology. (a) Cells. Murine leukaemia L1210, murine mammary carcinoma FM3A, human T-lymphoblast Molt/4F, and human T-lymphocyte MT-4 cells were cultivated in Eagle's minimal essential medium (Gibco BRL, Paisley, Scotland) (L1210, FM3A) or RPMI-1640 medium (Gibco BRL) (Molt/4F, MT-4), supplemented with 10% fetal calf serum (Gibco BRL), 2 mM L-glutamine (Gibco BRL), and 0.075% NaHCO<sub>3</sub>. Cells were subcultivated twice a week.

(b) Inhibition of Tumor Cell Proliferation. All assays were performed in flat-bottomed 96-well microplates (Falcon) as previously described.<sup>22,23</sup> Briefly, the cells were suspended in growth medium and added to the microplate wells at a density of 5  $\times$  10<sup>4</sup> L1210 or FM3A cells/well (200  $\mu$ L) or 6.25  $\times$  10<sup>4</sup> Molt/4 or MT-4 cells/well in the presence of varying concentrations of the test compounds. The cells were then allowed to proliferate for 48 (L1210 and FM3A), 72 (Molt/4), or 120 h (MT-4) at 37  $^\circ$ C in a humidified, CO<sub>2</sub>-controlled atmosphere. At the end of the incubation period, the L1210, FM3A, and Molt/4F cells were counted in a Coulter counter (Coulter Electronics Ltd., Harpenden, Herts, U.K.). MT-4 cell cultures were stained by trypan blue to count the number of viable cells under the microscope. The IC<sub>50</sub> was defined as the concentration of compound that reduced the number of viable cells by 50%. All values shown in Table 1 for L1210, Molt/4F, and MT-4 cells are means of at least two or three independent experiments; the data shown for FM3A cells are derived from one single experiment.

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(s, 1H, triazole), 8.13 (s, 1H, triazole), 7.67 (s, 1H, H5), 6.30 (s, 1H, H1'), 5.20 (d, J = 6.4 Hz, 1H, H2'), 4.90 (dd, J = 6.4 Hz, J = 4.4 Hz, 1H, H3'), 4.25 (m, 1H, H4'), 3.90 (m, 2H, H5'), 1.55 (s, 3H, Me-isop), 1.34 (s, 3H, Me-isop), 0.9 (s, 9H, tBu), 0.05 (s, 6H, SiMe).

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