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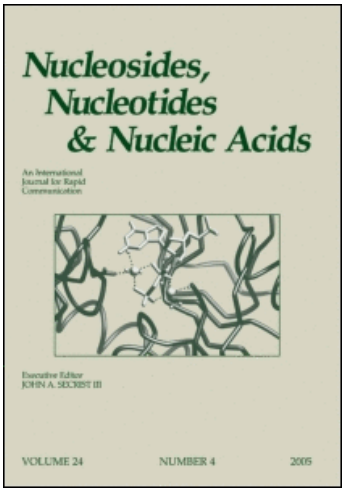


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# Synthesis and Anti-HIV Activity of 5-Fluorocytallene: N-Dimethylaminomethylene as a Facilitating Group in Acetylene → Allene Isomerization

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NUCLEOSIDES & NUCLEOTIDES, 13(8), 1779-1789 (1994)

# SYNTHESIS AND ANTI-HIV ACTIVITY OF 5-FLUOROCYTALLENE: N-DIMETHYLAMINOMETHYLENE AS A FACILITATING GROUP IN ACETYLENE → ALLENE ISOMERIZATION

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**Abstract.** The synthesis and biological activity of 5-fluorocytallene (3a) is described. 5-Fluorocytosine (4) was alkylated with 1-benzoyloxy-4-bromo-2-butyne (5) to give $N^1$-(4-benzoyloxy-2-butyn-1-yl)-5-fluorocytosine (6). Debenzoylation led to $N^1$-(4-hydroxy-2-butyn-1-yl)-5-fluorocytosine (7a). The latter compound was transformed to the $N^4$-dimethylaminomethylene derivative 8 which was isomerized *in situ* to the corresponding allene 9. Deprotection afforded 5-fluorocytallene (3a). Compound 3a suppressed the infectivity and replication of both laboratory and primary HIV-1 strains *in vitro* at nontoxic concentrations.

Several 5-fluorocytosine nucleosides derived from the corresponding 2'-deoxycytidine analogues which are active anti-HIV agents exhibit a marked anti-HIV-1 activity. Thus, compounds 1a and 1b are equally effective[1,2] as their non-fluorinated counterparts 1c and 1d. Similarly, in the oxathiolane series,

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**Dedicated to the memory of Professor Roland K. Robins**



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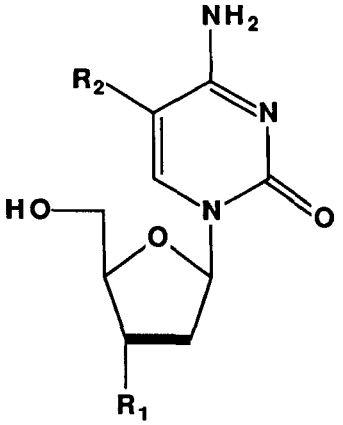
compound 2a has the same or, in some assays, even more potent anti-HIV-1 activity than the parent analogue[3,4] 2b. It was therefore of interest to investigate 5-fluorocytallene (3a), a derivative of cytallene (3b). The latter analogue is a highly active anti-HIV agent[5] comparable to 2',3'-dideoxycytidine (1c, zalcitabine, Hivid) which was recently approved[6] as a prescription drug for AIDS.

The synthesis of 5-fluorocytallene (3a) commenced with alkylation of 5-fluorocytosine (4) with 1-benzoyloxy-4-bromo-2-butyne[7] (5) according to a general procedure[8-10] using NaH in N,N-dimethylformamide (DMF) (Scheme 1). Intermediate 6 was obtained in 67 % yield. Debenzoylation of 6 with $NH_3$ in methanol afforded $N^1$-(4-hydroxy-2-butyn-1-yl)-5-fluorocytosine (7a) in 71 %



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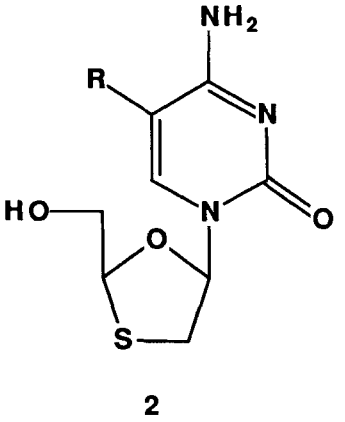
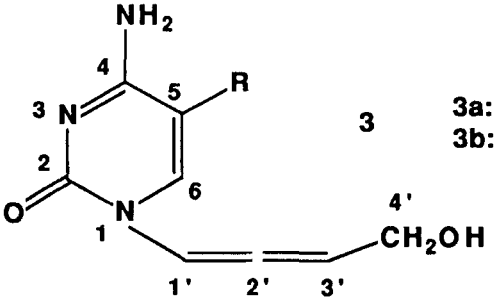


2

**1a:** $R_1$ = H, $R_2$ = F
**1b:** $R_1$ = $N_3$, $R_2$ = F
**1c:** $R_1$ = $R_2$ = H
**1d:** $R_1$ = $N_3$, $R_2$ = H

**2a:** R = F
**2b:** R = H



3

**3a:** R = F
**3b:** R = H

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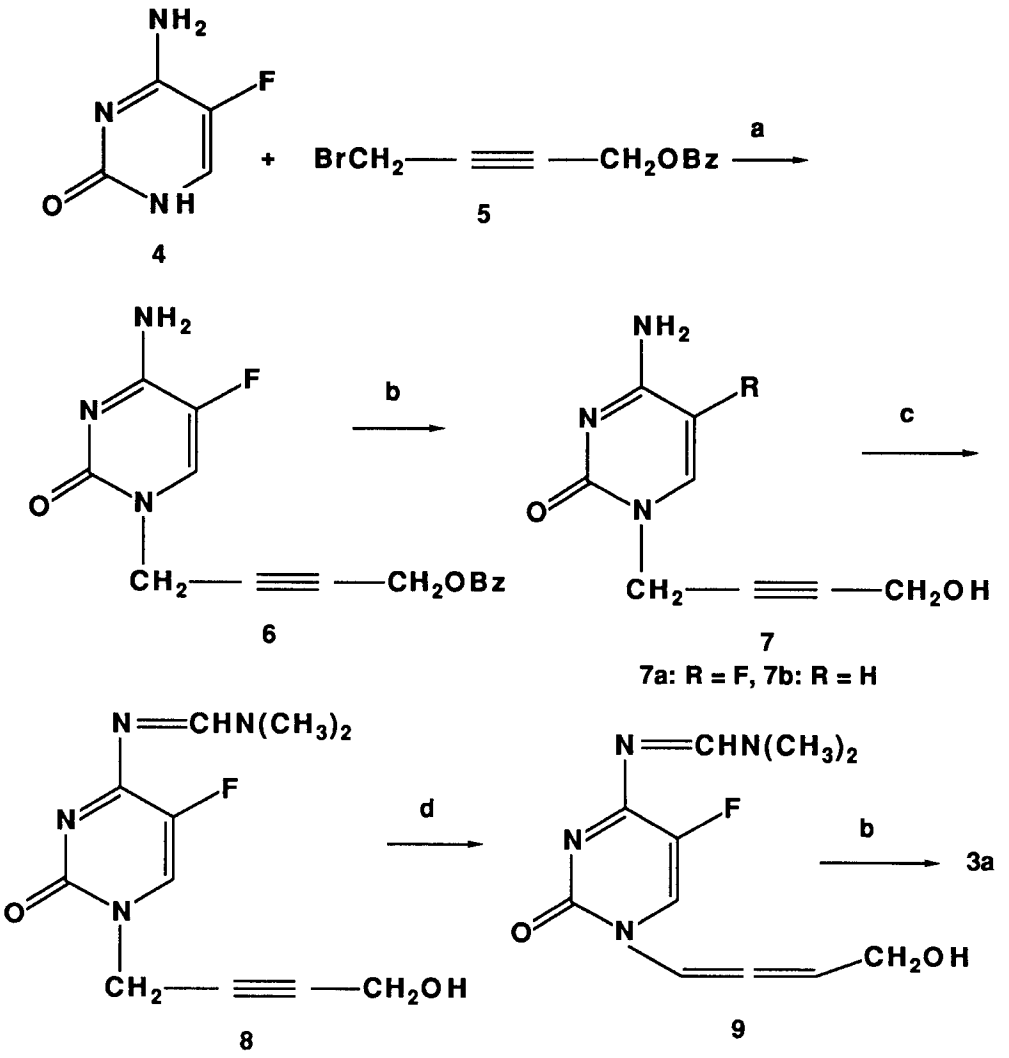


Scheme 1

yield. Isomerization of 7a with potassium tert-butoxide (tBuOK) in DMF gave a mixture of allene 3a and acetylene 7a in the ratio of ca. 1 : 1 as estimated by HPLC in water - $CH_3CN$ ( 97 : 3 ) (Table 1). It was not possible to increase the content of allene 3a by crystallization or separate 3a and 7a by chromatography on silica gel. Attempts to isomerize 7a using other strong bases met with limited

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Table 1
Base-catalyzed Isomerization of Acetylene 7a to Allene 3a

| Reagent[a] | Solvent | Temperature, °C | Reaction Time, h | Ratio[b] 7a/3a |
|---|---|---|---|---|
| $Bu_4NF$[c] | THF[c] | 25 | 24 | 66 : 34[d] |
| $NaNH_2$ | THF - DMF (2 : 1) | 25 | 24 | [e] |
| $NaNH_2$ | " | 60 | 48 | 88.5 : 11.5 |
| $Me_2NLi$ | " | 0 - 25 | 24 | [e] |
| $Me_2NLi$ | " | 60 | 48 | 80 : 20[d] |
| tBuOK | DMSO | 60 | 24 | 47 : 53[d] |
| tBuOK | DMF | 40 | 24 | 45 : 55 |
| DMAP[f] | pyridine | 60 | 24 | [e] |

[a] Ratio of reagent : 7a was 1 : 1. Compound 7a (50 µmol) in 2 mL of solvent was used unless stated otherwise.

[b] Determined by HPLC in water - $CH_3CN$ ( 97 : 3 ).

[c] 250 µmol of 7a in THF (7mL).

[d] A small amount of faster moving material, presumably compound[11] 10 was detected by TLC in $CH_2Cl_2$ - MeOH (9 : 1).

[e] No reaction.

[f] 4-(N,N-Dimethyl)aminopyridine.

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success. Thus, only isomerization with tBuOK in DMSO gave the same ratio of 7a/3a as a similar reaction in DMF. By contrast, isomerization of a substantially more basic non-fluorinated acetylene 7b furnished a mixture which contained 80 % of allene 3b. This product was readily recrystallized to give pure *cytallene*[11] (3b).

Our previous results[11] indicated that introduction of the basic $N^2$-dimethylaminomethylene function into a guanine moiety led to significant increase of the allene content in the isomerization mixture. It was therefore of interest to apply this approach for the synthesis of 5-fluorocytallene. Thus, acetylene 7a was readily converted to the respective $N^4$-dimethylaminomethylene derivative 8 using N,N-dimethylformamide dimethyl acetal in DMF[12,13]. The latter

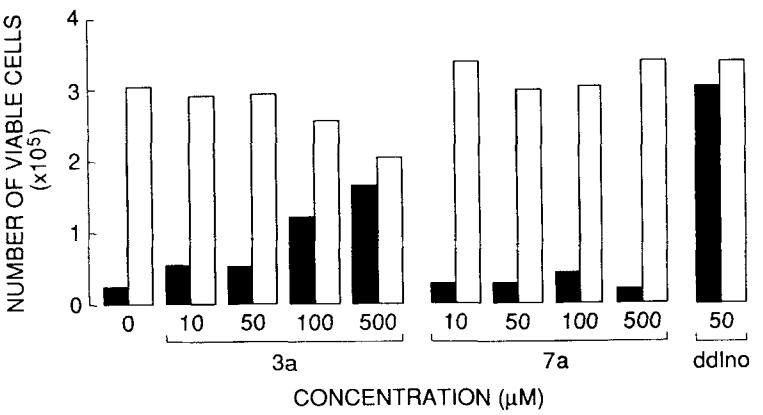


Figure 1. Inhibition of the infectivity and cytopathic effect of HIV-1 in ATH8 cells by 5-fluorocytallene (3a) and acetylene (7a). Virus-exposed cells are indicated as solid bars and virus-unexposed cells as open bars. 2',3'-Dideoxyinosine ( ddIno ) served as a positive control. For details see Experimental.

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intermediate was isomerized *in situ* using tBuOK in DMF at 40°C to give a product with a significantly improved acetylene 8/allene 9 ratio of 16 : 84 after 6 h. The " protecting " group was readily removed by treatment with $NH_3$ in methanol to give acetylene 7a/allene 3a (18 : 82) in 55 % yield. Two recrystallizations from methanol gave 99 % pure allene 3a in 12 % yield. The mixture of 3a and 7a from the mother liquors can be recycled using the procedure described above.

It is then obvious that a strongly basic N-dimethylaminomethylene group, a readily removable function, can serve as an effective facilitating group for transformation of suitable acetylenes into allenes. More acidic parent heterocycles (guanine, 5-fluorocytosine), lacking the N-dimethylaminomethylene moiety, may interfere with the carbanion formation essential for allenic isomerization.

5-Fluorocytallene (3a) was tested against HIV-1 in the ATH8 cell culture system and in the phytohemagglutinin-activated peripheral blood mononuclear ( PHA-PBM ) cell system. A moderate but significant protective effect was noted at 100 μM in the ATH8 system as shown in Figure 1. Analogue 3a also showed inhibitory activity against the replication of a primary HIV-1 strain, $HIV\text{-}1_{ERS\ 205}$ when PHA-PBM were employed as target cells (Table 2). By contrast, acetylene 7a was inactive in both test systems.

Table 2
*In Vitro* anti-HIV-1 Activity of 5-Fluorocytallene[a] (3a)

| Compound | Concentration (μM) | % HIV-1 p24 *gag* production[b] | $IC_{50}$ (μM) | $IC_{90}$ (μM) |
|---|---|---|---|---|
| 7a | 0, 4, 20, 100[c] | 100, 100, 100, 100 | >100 | >100 |
| 3a | 0, 4, 20, 100 | 100, 48.5, 7, 0 | 3.8 | 19.5 |
| AZT | 0, 0.016, 0.08, 0.4, 2 | 100, 6.6, 1.9, 1.3, 0 | 0.0055 | 0.037 |
| ddIno | 0, 0.08, 0.4, 2 | 100, 36.1, 19.4, 0 | 0.055 | 1.5 |

[a] Phytohemagglutinin-stimulated peripheral blood mononuclear (PHA-PBM) cells ($5 \times 10^5$) were preincubated with or without a test compound for 2 h, they were exposed to 200 50 % tissue culture infectious dose of a clinical strain (ERS 205 )[18] of HIV-1, and cultured for 10 days. The concentration was kept the same throughout the culture period. The p24 *gag* in the culture supernatant was quantified by radioimmunoassay (DuPont).

[b] Percent HIV-1 p24 *gag* production was calculated by the following formula: 100 x [(p24 *gag* production in the presence of test compound)/(p24 *gag* production in the absence of compound)].

[c] The listed concentrations represent the ones used for determination of the anti-HIV activity of each compound. The order of concentrations corresponds to the order of % HIV-1 p24 *gag* production values.

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The observed limited activity of 3a is difficult to explain by steric factors. The IR spectra in solid state (KBr) show a significant shift of the asymmetric vibration band of the C=C=C system toward a higher frequency ($\nu_{as}$ 1990 $cm^{-1}$) relative to that found in cytallene[11] (3b, $\nu_{as}$ 1965 $cm^{-1}$). The $\nu_{as}$ frequencies of highly electronegative fluoroallenes are at 1987 $cm^{-1}$ or above[14]. This may indicate a decrease of the electron density at the sp-hybridized $C_{2'}$ which can then possibly trigger a conformational change[15] from " anti " to " syn " (formula 11). The space-filling model studies indicate that the " anti " - " syn " barrier is lower than in nucleosides. It is then obvious that such an effect cannot take place in saturated analogues 1a, 1b and 2a. Nevertheless, the data in

Table 3

Comparison of the $^{1}H$ and $^{13}C$ NMR Chemical Shifts of Allenic System in 5-Fluorocytallene (3a) and Cytallene[a] (3b)

| Compd. | $H_{1'}$ | $H_{3'}$ | $H_{4'}$ | $C_{1'}$ | $C_{2'}$ | $C_{3'}$ | $C_{4'}$ |
|---|---|---|---|---|---|---|---|
| 3a | 7.24 | 6.14 | 4.04 | 99.88 | 194.13 | 108.02 | 59.57 |
| 3b | 7.27 | 6.12 | 4.03 | 99.32 | 193.90 | 106.83 | 59.08 |

[a] Data from ref.[11]

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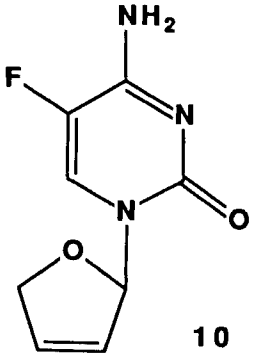
solution (NMR) give no indication of any significant change of electron density in the allenic portion of the molecule of 3a (Table 3). Therefore, more evidence must be obtained to reconcile this contradiction.

Both acetylene 7a and allene 3a were inactive against murine leukemia L1210 (clonogenic assay[16]) and P388, mouse tumors C38, M17 resistant to adriamycin, human tumor MCF-7 and fibroblast cell culture (disk-diffusion assay[16]). They were also inactive against herpes simplex virus (HSV-1, ELISA assay), human cytomegalovirus (HCMV, plaque assay), KB cells (dye-stain assay) and non-cytotoxic in human fibroblasts (visual inspection assay) at 100 μM.

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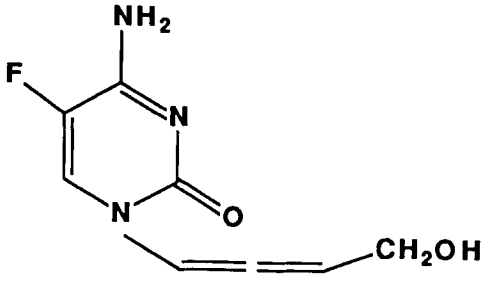


11

## Experimental Section

**General Methods.** See[11]. The NMR spectra were determined using QE 300 at 300.095 ($^{1}H$), 75.47 ($^{13}C$) and 282.314 MHz ($^{19}F$) in $CD_3SOCD_3$ unless

Fast atom bombardment mass spectra FAB-MS) were determined with 1-thioglycerol (TG) as a matrix. For high performance liquid chromatography (HPLC) Altex Ultrasphere$^{TM}$-Octyl reverse phase column (5 μ, 4.6 x 250 mm, Beckman Instruments Inc., Fullerton, California) was used with solvent systems specified in the text as eluents at a flow rate 1 mL/min. and detection at 260 nm. The concentrations of the eluted components were corrected for molar extinction coefficients of acetylene 7a ($\varepsilon_{260}$ 4,700) and allene 3a ($\varepsilon_{260}$ 5,400) at pH 7.

**N$^1$-(4-Benzoyloxy-2-butyn-1-yl)-5-fluorocytosine (6).** Sodium hydride (0.39 g, 16.1 mmol, 60% dispersion in mineral oil) was added in portions to a suspension of 5-fluorocytosine (4, 2.0 g, 15.5 mmol) in N,N-dimethylformamide (DMF, 60 mL). The mixture was stirred under $N_2$ at room temperature for 30 minutes. At first, a clear solution was obtained which then became a thick white suspension. 1-Benzoyloxy-4-bromo-2-butyne[7] (5, 4.08 g, 16.1 mmol) was added dropwise over 5 minutes. The stirring was continued for 24 hours and the reaction mixture was evaporated *in vacuo*. The crude product was preabsorbed on silica gel (3 g) and it was loaded as a slurry in dichloromethane on a column prepared from silica gel (40 g) in the same solvent. The product was eluted with $CH_2Cl_2$ - MeOH (9 : 1), the appropriate fractions were combined and evaporated to give a white solid. Compound 6 was recrystallized from methanol (3.11g, 67 %), mp. 199-200°C, $R_F$ 0.38 ($CH_2Cl_2$ - MeOH, 4 : 1). UV max (EtOH) 281 nm (ε 3,400), 230 (ε 8,800), 202 (ε 9,500). $^1$H NMR δ 7.99 (m, 3), 7.76 (m, 1), 7.69 (m, 1), 7.55 (m, 3) /$C_6H_5$, $NH_2$ and $H_6$/, 5.01 (s, 2, $H_{1'}$), 4.53 (s, 2, $H_{4'}$). $^{19}$F NMR -167.99, ($^3J_{F,H\text{-}6}$ = 6.8 Hz). Anal. Calcd for $C_{15}H_{12}FN_3O_3$: C, 59.80; H, 4.01; F, 6.31; N, 13.95. Found: C, 59.64; H, 4.22; F, 6.09; N, 13.70.

**N$^1$-(4-Hydroxy-2-butyn-1-yl)-5-fluorocytosine (7a).** A mixture of compound 6 (3.11 g, 10.3 mmol) and methanolic ammonia (25%, 170 mL) was stirred at 0°C for 1 h and then at room temperature for 15 h. The solution was concentrated to approximately 30 mL, the precipitated white solid 7a was collected by filtration, it was washed with methanol and recrystallized from 90 % ethanol (1.44 g, 71 %), mp. 234-236°C, $R_F$ 0.14 ($CH_2Cl_2$ - MeOH, 9 : 1). UV max (EtOH) 283 nm (ε 6,400), 243 (ε 7,200), 204 (ε 9,700); (pH 7) 280 nm (ε 7,400), 235 (ε 7,100), 218 (ε 7,700); $^1$H NMR δ 7.99 (d, 1, $H_6$, $^3J_{6,F}$ = 6.6 Hz), 7.51 and 7.75 (2s, 2, $NH_2$), 5.22 (t, 1, OH, $^3J_{OH,4'}$ = 5.9 Hz), 4.47 (s, 2, $H_{1'}$), 4.08 (d, 2, $H_{4'}$). $^{13}$C NMR 157.64 (d, $C_4$, $^2J_{4,F}$ = 13.0 Hz), 153.44 ($C_2$), 135.75 (d, $C_5$, $^1J_{5,F}$ = 243.1 Hz), 129.23 (d, $C_6$, $^2J_{6,F}$ = 30.9 Hz), 84.62, 78.84 ($C_{2'}$,$C_{3'}$), 48.49

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($C_{4'}$), 37.83 ($C_{1'}$); $^{19}F$ NMR -168.05 (d, $^{3}J_{F,H\text{-}6}$ = 7.6 Hz). Anal. Calcd. for $C_8H_8FN_3O_2$: C, 48.73; H, 4.09; F, 9.64; N, 21.31. Found: C, 48.68; H, 4.28; F, 9.43; N, 21.14 .

**(±)-$N^1$-(4-Hydroxy-1,2-butadien-1-yl)-5-fluorocytosine (3a).** A mixture of compound 7a (0.83 g, 4.21 mmol) and N,N-dimethylformamide dimethyl acetal (0.62 mL, 4.63 mmol) in DMF (25 mL) was stirred for 16 h at room temperature. The resultant solution was concentrated *in vacuo* and DMF was repeatedly evaporated from the residue. The crude $N^4$-dimethylaminomethylene derivative 8 was redissolved in DMF (80 mL), freshly sublimed tBuOK (0.24 g, 2.1 mmol) was added and the reaction mixture was heated at 40°C. The reaction course was followed by HPLC in water - $CH_3CN$ (9 : 1). The retention times (RT) of the $N^4$-dimethylaminomethylene acetylene 8 and allene 9 were 12.9 and 20.8 min., respectively. After 6 hours HPLC indicated approximately 80 % conversion to allene 9. Water (5 mL) was added and the resultant solution was evaporated *in vacuo*. The crude $N^4$-dimethylaminomethyleneallene 9 was stirred with methanolic ammonia (80 mL) at room temperature overnight. After evaporation, the product was absorbed on silica gel and it was loaded on a column of the same material (20 g) as a slurry in dichloromethane. The allene -acetylene mixture was eluted first with $CH_2Cl_2$ - MeOH (9 : 1) and then $CH_2Cl_2$ - MeOH (4 : 1). The appropriate fractions were combined and evaporated to give a yellow solid (0.28 g, 56 %), ratio of allene 3a/acetylene 7a was 84 : 16. Allene 3a was obtained by two recrystallizations from methanol (93 mg, 12 %), purity ≥ 99 %, mp. 170-174°C (decomp.), $R_F$ (3a) 0.38, $R_F$ (7a), 0.44 ($CH_2Cl_2$ - MeOH, 9 : 1), developed 4 times), RT (3a) 13.34 min., RT (7a) 7.34 min., (water - $CH_3CN$, 97 : 3). UV max (EtOH) 306 nm (ε 6,100), 252 (ε 5,000), 224 (ε 6,800), 204 (ε 7,000); (pH 7) 301 (ε 9,900), 225 (ε 11,100), 202 (ε 9,700); IR (KBr) 1990 $cm^{-1}$ (C=C=C); $^1H$ NMR (Varian Unity, 499.843 MHz) δ 7.95 and 7.70 (2 bs + d, 3, $NH_2$ and $H_6$, $^{3}J_{6,F}$ = 6.5 Hz), 7.24 (octet, 1, $H_{1'}$), 6.14 (apparent[17] q, 1, $H_{3'}$), 5.05 (t, 1, OH, $J_{OH,4'}$ = 6.0 Hz), 4.04 (m, 2, $H_{4'}$). $^{13}C$ NMR (125.697 MHz) 194.13 ($C_{2'}$), 157.82 (d, $C_4$, $^{2}J_{4,F}$ = 14.0 Hz), 152.38 ($C_2$), 137.10 (d, $C_5$, $^{1}J_{5,F}$ = 245.1 Hz), 125.67 (d, $C_6$, $^{2}J_{6,F}$ = 31.6 Hz), 108.02 ($C_{3'}$), 99.88 ($C_{1'}$), 59.57 ($C_{4'}$). $^{19}F$ NMR -165.50 (bd). FAB-MS 198 (M + H), 306 (M + TG + H), 395 (2 M + H), 503 (2 M + TG + H). Anal. Calcd for $C_8H_8FN_3O_2$: C, 48.73; H, 4.09; F, 9.64; N, 21.31. Found: C, 48.61; H, 4.27; F, 9.38; N, 21.08.

**Inhibition of HIV-1 Cytopathic Effect.** The assay was performed with $CD_4^+$ ATH8 cells as described[5,15]. The ATH8 cells (2 x $10^5$) were exposed to

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HIV-1/IIIB (1000 50 % tissue culture infectious dose) for 45 min., resuspended in culture medium (2 mL) containing interleukin 2 in the presence or absence of various concentrations of analogues 3a and 7a. The mixtures were incubated in culture tubes at 37°C in 5 % $CO_2$/95 % air humidified atmosphere. Virus-unexposed cells were treated similarly. On day 7 of the culture, the total viable cells were counted in a hemocytometer by trypan blue exclusion method. The data are summarized in Figure 1.

**Determination of HIV-1 *gag* Protein Production by PHA-PBM.** HIV-1 *gag* protein production by PHA-PBM was quantified as previously described[18]. Briefly, cells (5 x $10^5$/2 mL) were preincubated with tested compounds for 2 h, they were exposed to a clinical isolate of HIV-1 preparation, HIV-$1_{ERS\ 205}$, and cultured in the presence or absence of the compound. On day 3 in culture, 50 % of the culture medium was replaced with an equal amount of fresh medium. Cells were continuously exposed to the same concentrations of tested compounds. The amounts of p24 *gag* protein in culture medium were determined by radioimmunoassay (DuPont, NEN Research Products, Boston, MA ). The results are summarized in Table 2.

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