Synthesis of Novel N-1 (Allyloxymethyl) Analogues of 6-Benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442, Emivirine) with Improved Activity Against HIV-1 and Its Mutants

Nasser R. El-Brollosy,[†] Per T. Jørgensen,[†] Berit Dahan,[†] Anne Marie Boel,[†] Erik B. Pedersen,*[,†] and Claus Nielsen[‡]

Nucleic Acid Center,[§] Department of Chemistry, University of Southern Denmark, Campusvej 55, DK-5230 Odense M Denmark and Retrovirus Laboratory, Department of Virology, State Serum Institute, Artillerivej 5, DK-2300 Copenhagen, Denmark

Received May 30, 2002

This paper reports the synthesis and the antiviral activities of a series of 6-arylmethyl-1-(allyloxymethyl)-5-alkyluracil derivatives, which can be viewed as analogues of the anti-HIV-1 drug emivirine (formerly MKC-442) from which they differ in the replacement of the ethoxymethyl group with variously allyloxymethyl moieties. The most active compounds N-1 allyloxymethyl- and N-1 3-methylbut-2-enyl substituted 5-ethyl-6-(3,5-dimethylbenzyl)uracils (**12** and **13**) showed activity against HIV-1 wild-type in the picomolar range with selective index of greater than 5×10^6 and activity in the submicromolar range against the clinically important Y181C and K103N mutant strains known to be resistant to emivirine. Structure−activity relationship studies established a correlation between the anti-HIV-1 activity and the substitution pattern of the N-1 allyloxymethyl group.

Introduction

The reverse transcriptase (RT) of the human immunodeficiency virus type 1 (HIV-1) is a key target for inhibition of HIV-1 replication.[1,2] In recent years, much effort has been put into the design and synthesis of HIV-1 non-nucleoside RT inhibitors (NNRTIs, reviewed in ref 3). Among the representatives of the NNRTIs, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT, **1**)[4] constitutes an important inhibitor and has been extensively studied for many years. Although HEPT did not show very high activity against HIV-1, it was considered an interesting lead compound for the synthesis of new analogues, among them the 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil[5] (emivirine, formerly MKC-442, **2**) and the corresponding 1-benzyloxymethyl analogue[6] (TNK-651, **3**). Both compounds showed high activity against HIV-1, and MKC-442 was chosen as a candidate for clinical trials with AIDS patients.[7] However, Triangle Pharmaceuticals halted development of emivirine in January 2002 when a comparative study showed emivirine to be less potent than other antiretrovirals.[8] A serious disadvantage of HEPT analogues, like almost all NNRTIs, is development of drugs resistance mediated by mutations of residues that line the NNRTI binding pocket of the viral RT and reduce drug binding. However, further interest in the HEPT class has been augmented by the finding that GCA-186[9] (Figure 1, **4**), which has 3,5-dimethyl substituents on its phenyl ring (only difference to MKC-442), was better able to tolerate the presence of Y181C or K103N mutations than did emivirine itself. The above-mentioned single-point mutations give high-level resistance for many NNRTI including the FDA (U.S. Food and Drug Administration) approved drugs (nevirapine,[10] delavirdine,[11] and efavirenz[12]). No resistance data for TNK-651 are available.

According to structure−activity relationships (SAR), studies of several crystal structures of the RT complex with inhibitors, such as HEPT,[13] MKC-442,[6] TNK-651,[6] and GCA-186,[9] indicate that the optimal C-5 and C-6 substituents of the uracil ring with respect to HIV-1 inhibition are already found. The only site where new important modifications may be tried is the N-1 position of the uracil.[14] The substituent at N-1 may have larger volume (e.g., TNK-651) and length, and even bulky N-1 substituents may be accommodated because of the flexibility of the Pro236 loop region.[9,14]

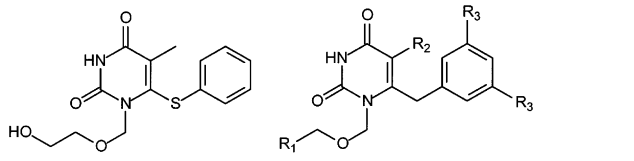
The rationale of the present study was that the susceptibility of MKC-442 analogues to drug-resistant mutations might be reduced by improving the binding of the inhibitors by exploiting the possibility of additional π-stacking to the NNRTI binding site. Inspection of the above-mentioned crystal structure reveals the presence of several aromatic amino acid residues in the NNRTI pocket, especially Tyr318 appears attractive, situated in a close distance (3.8 Å) to the N-1 ethoxymethyl group of MKC-442. This paper reports the synthesis and the antiviral activities of a series of 6-arylmethyl-1-(allyloxymethyl)-5-alkyluracil derivatives (**8**−**21**) designed by the above criterion, the new compounds being viewed as a hybrid between MKC-442 and TNK-651. It is a further object of the present paper to expand our understanding of the structure−activity relationship among non-nucleoside HEPT analogues.

Chemistry

The synthesis of the newly designed products was straightforward and is described in Scheme 1. The acetals **6** were prepared according to the method of Nazaretyan et al.[15] by refluxing the appropriate alcohol

* To whom correspondence should be addressed. Phone: +4566502555. Fax: +4566158780. E-mail: EBP@Chem.sdu.dk.
[†] University of Southern Denmark.
[‡] State Serum Institute.
[§] A research center funded by The Danish National Research Foundation for studies on nucleic acid.

10.1021/jm020949r CCC: $22.00
Published on Web 11/23/2002

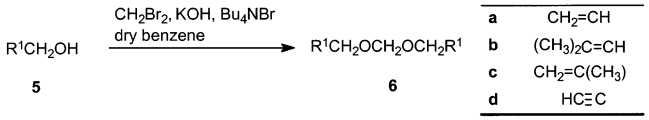


1 HEPT

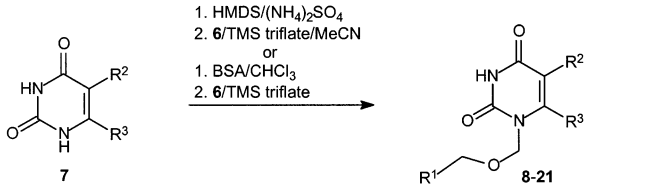
2 MKC-442 (R_1 = methyl, R_2 = isopropyl, R_3 = H)
3 TNK-651 (R_1 = phenyl, R_2 = isopropyl, R_3 = H)
4 GCA-186 (R_1 = R_3 = methyl, R_2 = isopropyl)

Figure 1. Chemical structure of HEPT, MKC-442, TNK-651, and GCA-186.

Scheme 1



5,6	R^1
a	CH_2=CH
b	$(CH_3)_2$C=CH
c	CH_2=C(CH_3)
d	HC≡C



7	R^2	R^3
a	*i*-Pr	$PhCH_2$
b	Et	3,5-$Me_2C_6H_3CH_2$
c	Et	1-Naphthylmethyl
d	*i*-Pr	3,5-$Me_2C_6H_3CH_2$

5, dibromomethane, and tetrabutylammonium bromide in benzene to afford the acetals **6** after distillation. It is important to distill the product to remove tetrabutylammonium bromide from the product to avoid difficulties in chromatographic work up of the products in the subsequent condensation reaction. The required 5,6-disubstituted uracils **7** were easily synthesized according to the method of ours[16] from the corresponding 3-oxo estes prepared by reaction of the appropriate arylacetonitrile with ethyl 2-bromobutyrate or ethyl 2-bromo-3-methylbutyrate. The so-formed ethyl 2-alkyl-4-aryl-3-oxo ester was condensed with thiourea to furnish the corresponding 2-thiouracil, which in boiling aqueous chloroacetic acid afforded 5-alkyl-6-(arylmethyl)uracils **7a**−**d** by exchanging sulfur with oxygen. The substituted uracils **7a**−**d** was silylated at reflux in 1,1,1,3,3,3-hexamethyldisilazane (HMDS)[17] and alkylated by treatment with bis(allyloxy)methane **6a**−**c** in the presence of trimethylsilyl trifluoromethanesulfonate (TMS triflate) as a Lewis acid catalyst[18] to give the MKC-442 analogues **8**−**10** and **12**−**14** in 10−77% yield. For compounds **11** and **15**−**21,** the method was modified by silylation in situ of **7a**−**d** using *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) and alkylated at the N-1 position with bis(propargyloxy)methane (**6d**) (for compounds **7a, b**) or bis(allyloxy)methane **6a**−**c** (for compounds **7c**, **d**), respectively, in the presence of TMS triflate to give **11** and **15**−**21** in 58−73% yield.

The compounds were identified by comparison of similar NMR data.[5,16] N-1 Substitution was proved by the NOE enhancement in the benzyl protons when 1-CH_2 was irradiated. The N-3 regioisomer was not observed.

Biological Results and Discussion

The novel MKC-442 derivatives synthesized in this study were evaluated for cytotoxicity and inhibitory activity against two different HIV-1 strains induced cytopathogenicity in MT-4 cells, and the results are listed in Table 1 along with the results from MKC-442 and the three currently available NNRTIs for the treatment of AIDS, nevirapine, delavirdine, and efavirenz, which are included in the table for comparison.

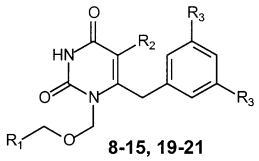
The majority of the synthesized compounds and the reference compounds have similar antiviral activities against wild-type HIV-1 IIIB (a T-cell-tropic strain) and HIV-1 HxB2 (a molecular clone) in MT-4 cells. In contrast, compounds **12** and **13** were significantly strain dependent, showing a 200- and 15-fold, respectively, increment against the molecular clone than against the HIV-1 IIIB strain (Table 1). The factors responsible for the improved inhibitory profile of these compounds remain to be elucidated. One explanation could be that HxB2 is a more pure strain having a lower content of mutated virus; however, one would expect to see the same trend of all the tested compounds, but this is not the case in our study.

All the present compounds can be divided into three groups according to the substitution pattern at C-5 and C-6 position of the uracil ring. (i) series a: the first-generation derivatives (MKC-442 analogues); compounds **8**−**11** (C-5 = isopropyl and C-6 = benzyl), (ii) series b: compounds **12**−**18** (C-5 = ethyl, and C-6 = 3,5-dimethylbenzyl or 1-naphthylmethyl), and (iii) series c: the second-generation inhibitors (GCA-186 analogues); compounds **19**−**21** (C-5 = isopropyl and C-6 = 3,5-dimethylbenzyl).

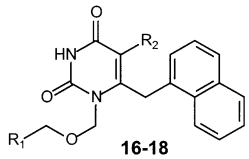
As seen from examination of the results listed in Table 1, structural variation in the three series have resulted in a wide range of biological activity ranging in ED_{50} values from 1 to 0.00002 μM against wild-type HIV-1. When comparing trends among the series of compounds, we found that greater or equal activity is obtained from series a through series c. The majority of the novel compounds were noncytotoxic for MT-4 cells at doses as high as 100 μM (highest concentration tested), and the rest of the compounds showed CD_{50} values comparative to delavirdine.

Compound **8** (the most active compound in the series a) substituted at R_1 by a rigidify vinyl group was in our study 5 times more potent than MKC-442 (4 nM versus 20 nM). The factors responsible for the significant activity of compound **8** remain to be elucidated but suggest either π-stacking to Tyr318 or a repositioning of Pro236. Increasing the bulkiness around the double bound of **8** with methyl moieties to **9** and **10** leads to significant drop in activity compared to **8** (8- and 70-fold, respectively). However, compound **9** was still equipotent to the lead compound MKC-442 and efavirenz, and compound **10** was equipotent to nevirapine. The

Table 1. Anti-HIV-1 Activity of Novel Emivirine Analogues (Compounds **8**−**21**).[a] MKC-442 (6-Benzyl-1-ethoxymethyl-5-isopropyluracil), Nevirapine (Viramune), Delavirdine (Rescriptor), and Efavirenz (Sustiva) Are Used for Comparison



8-15, 19-21



16-18

				ED$_{50}$ (μM) for HIV-1 IIIB strain[b]					ED$_{50}$ (μM) for HIV-1 HxB2 strain[b]				
compd	R_1	R_2	R_3	wild type	Y181C	Y181C + K103N	CD$_{50}$ (μM)[c]	SI[d]	wild type	Y181C	K103N	CD$_{50}$ (μM)[c]	SI[d]
Series a													
8	CH_2═CH	*i*-Pr	H	0.004	100	>100	>100	25 000	0.00 3	3.3	0.9	>100	> 33 333
9	$(CH_3)_2C$═CH	*i*-Pr	H	0.03	>100	>100	32	1067	0.03	> 100	3.8	34	1122
10	CH_2═$C(CH_3)$	*i*-Pr	H	0.28	>100	>100	40	142	0.05	> 100	> 10 0	>100	> 2000
11	HC≡C	*i*-Pr	H	0.007	>100	>100	>100	> 14 285	NT[e]	NT[e]	NT[e]	NT[e]	
Series b													
12	CH_2═CH	Et	CH_3	0.004	0.32	10	100	25 000	0.00 0 02	0.07	0.0 2	>100	> 5 00 0000
13	$(CH_3)_2C$═CH	Et	CH_3	0.0003	0.34	>100	36	120 000	0.00 0 02	0.45	0.0 9	61	3 03 3333
14	CH_2═$C(CH_3)$	Et	CH_3	0.0025	0.36	28	>100	> 40 000	0.00 8	4.0	2.2	>100	> 12 500
15	HC≡C	Et	CH_3	0.003	>100	3	>100	> 33 333	NT[e]	NT[e]	NT[e]	NT[e]	
16	CH_2═CH	Et		1	NT[e]	NT[e]	32	32	NT[e]	NT[e]	NT[e]	NT[e]	
17	$(CH_3)_2C$═CH	Et		0.3	NT[e]	NT[e]	>100	>333	NT[e]	NT[e]	NT[e]	NT[e]	
18	CH_2═$C(CH_3)$	Et		1	NT[e]	NT[e]	35	35	NT[e]	NT[e]	NT[e]	NT[e]	
Series c													
19	CH_2═CH	*i*-Pr	CH_3	0.0002	>100	>100	30	150 000	NT[e]	NT[e]	NT[e]	NT[e]	
20	$(CH_3)_2C$═CH	*i*-Pr	CH_3	0.0002	19	28	>100	> 500 000	NT[e]	NT[e]	NT[e]	NT[e]	
21	CH_2═$C(CH_3)$	*i*-Pr	CH_3	0.00015	15	26	>100	> 667 000	NT[e]	NT[e]	NT[e]	NT[e]	
MKC-442	CH_3	*i*-Pr	H	0.02	44	>100	>100	> 5000	0.01	3.8	2.1	>100	> 10 000
nevirapine (Viramune)				0.38	>100	>100	>100	>263	0.57	22	4.3	>100	> 175
delavirdine (Rescriptor)				0.06	>100	>100	42	700	0.19	4.5	3.0	>42	> 221
efavirenz (Sustiva)				0.01	0.3	2.7	>100	> 10 000	0.04	0.04	0.3 5	>100	> 250 0

[a] All data represent mean values for three separate experiments. [b] Effective concentration of compound required to achieve 50% inhibition of HIV-1 multiplication in MT-4-infected cells. [c] Cytotoxic doses of compound required to reduce the viability of normal uninfected MT-4 cells by 50%. The symbol (>) indicates that the CD$_{50}$ was not reached at the highest concentration tested. [d] Selectivity index: ratio CD$_{50}$/ED$_{50}$ see the Experimental Section for description of assay. [e] NT: not tested.

detrimental effect of the bulkiness of compounds **9** and especially with **10** could be due to a steric clash with adjacent residues and thus to weakened interaction with the NNRTI pocket. To confirm the above-mentioned findings, we found it interesting to synthesize the corresponding ethynyl compound **11** to verify our hypotheses. Indeed, the present of an ethynyl group restored the activity to a level comparable to that of compound **8**. Furthermore, **8** and **11** had larger selectivity indices (SIs, ratios of CD$_{50}$ to ED$_{50}$) than MKC-442 (25 000 and >14 000, respectively, versus >5000).

Encouraged by the promising results for compounds **8** and **11**, we next investigated the influence of the substituent at C-5 and C-6 for the activity against HIV-1. It is known from the literature that the corresponding MKC-442 analogue with the same substitution at C-5 and C-6 as in the series b are equipotent to MKC-442 itself.[5] In our study compounds, **12** and **15** followed the trend of MKC-442 with similar activities as their benzyl counterparts (**8** and **11**). Surprisingly, compound **12** and **13** was significantly (100-fold) more potent against HIV-1 replication compared to the corresponding benzyl analogues **9** and **10**. Compound **13** showed the highest activity and selectivity (0.3 nM, SI 120 000) in the series b, 67 times more active as MKC-442; however, compound **12** was equipotent to compound **13** when tested against wild-type HIV-1 HxB2 strain, with ED$_{50}$ = 20 pM and SI > 5 000 000. In contrast to the observation made in series a, bulky substituent at R_1 seems to be essential for high activity in the series b.

According to molecular modeling study on MKC-442, it was postulated by Hopkins et al.[6] that replacement of the 6-benzyl group with a naphthylmethyl might be favorable. To confirm the above-mentioned findings from molecular modeling, we synthesized the closely related 1-naphthylmethyl derivatives **16**−**18**. The effect was rather dramatic as can be seen by comparing **12**−**14** with a decrease in activity against HIV of about 3 powers, thus demonstrating that the naphthylmethyl group is unfavorably positioned to make interactions with the π-clouds of the aromatic chain of Tyr181 and Tyr188. However, compound **17** showed similar activity and SI as nevirapine.

Like previous data reported in the HEPT series,[5,9] introduction of an isopropy group at C-5 and a 3,5-dimethylbenzyl substituent at C-6 (e.g., AGC-186) does potentiate the antiviral activity. Thus, compounds **19**, **20**, and **21** were about 20-, 150-, and 1900-fold more active against HIV-1 than their unsubstituted benzyl counterparts **8**−**10** (series a versus c). Furthermore, **19**−**21** had very large selectivity indices which were 150 000, >500 000, and >667 000, respectively. The results in series a and b suggested that the substitution pattern of the vinyl group at R_1 is an important criterion for activity, which surprisingly is not the case in series c.

Antiviral Activity of the MKC-442 Analogues against HIV-1 Mutations. The novel MKC-442 derivatives were tested in cell culture for their ability to inhibit the multiplication of HIV-1 strains carrying the Y181C, K103N, and Y181C + K103N mutations. The

Y181C mutation is associated with high-level resistance to MKC-442, nevirapine, and delavirdine but remain susceptible to efavirenz. The K103N mutant confers resistance to MKC-442, nevirapine, delavirdine, and efavirenz.

As seen from examination of the results listed in Table 1, only compounds **12**−**14** showed activity against the drug-resistant strain Y181C with activity in the submicromolar range. The Y181C mutation provides a 2200-fold reduced sensitivity to MKC-442, but compound **12** and **14** are only 80- and 114-fold less potent toward this mutant, respectively, and compound **13** shows a greater loss of potency (1100-fold). Surprisingly, compound **15** was inactive against Y181C despite the structural similarity with compound **12**. Additionally, compound **12** was also significantly more potent (20 nM) against the K103N mutant than MKC-442 (105-fold) and efavirenz (18-fold).

Unfortunately, none of the analogues in series c showed any inhibition to the above-mentioned mutants despite the structural similarity to GCA-186 which has showed greater resilience to Y181C and K103N mutants than MKC-442 itself.[9]

Surprisingly, the concentration of compound **12** required to inhibit any of the viruses with single mutations in type HIV-1 HxB2 strain was comparable to or less than the concentration of MKC-442, nevirapine, delavirdine, and efavirenz required to inhibit the wild-type HIV-1 HxB2 strain.

Conclusion

In summary, we have described the synthesis and structure−activity relationship of a new series N-1 allyloxymethyl analogues of MKC-442. The most active compounds **12** and **13** showed activity against wild-type HIV-1 HxB2 strain in the picomolar range with selective index of greater than 5 000 000. These compounds are among the most active NNRTIs ever described in the literature. Both compounds showed greater inhibitory effect than MKC-442 to the clinically important Y181 and K103N mutant strains.

On the basis of the promising anti-HIV-1-data, the next step will consist in optimizing the N-1 allyoxymethyl linker of the new MKC-442 analogues. These experiments are currently in progress.

Experimental Section

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). EI mass spectra were recorded on a Finnigan Mat SSQ 710, FAB mass spectra on a Kratos MS50RF instrument. Melting points were determined on a Büchi melting point apparatus. Elemental analyses were performed at Atlantic Microlab, Inc., Atlanta, Georgia; found values agreed favorably with the calculated ones. The progress of reactions was monitored by TLC (analytical silica gel plates 60 F_{254}). Merck silica gel (0.040−0.063 mm) was used for column chromatography.

Acetals 6a−d. General Procedure. A mixture of KOH (38.8 g, 692 mmol), alcohol 5 (691 mmol), dibromomethane (60.1 g, 24.2 mL, 346 mmol), and tetrabutylammonium bromide (12.0 g, 37 mmol) in anhydrous benzene (200 mL) was heated under reflux for 4 h. The reaction mixture was left to cool to room temperature, and H_2O (200 mL) was added and extracted with ether (2 × 100 mL). The ether phase was dried ($MgSO_4$) and evaporated under reduced pressure. The acetals **6a−d** were isolated by distillation.

Bis(allyloxy)methane (6a). Yield 25.9 g containing 5% benzene (55%); bp 115−125 °C/760 mmHg; lit.[15] 138−139 °C/680 mmHg; ^{1}H NMR ($CDCl_3$): δ 5.92 (m, 2H, 2 × CH=), 5.23 (m, 4H, 2 × =CH_2), 4.72 (s, 2H, OCH_2O), 4.09 (dd, 4H, J = 5.6 and 1.5 Hz, 2 × OCH_2CH=); ^{13}C NMR ($CDCl_3$): δ 134.41 (CH=), 117.02 (CH_2=), 93.74 (OCH_2O), 68.26 (OCH_2CH=).

Bis(3-methyl-2-butenyloxy)methane (6b). Yield 27.84 g (44%); bp 112−114 °C/23 mmHg; ^{1}H NMR ($CDCl_3$): δ 5.38 (t, 2H, J = 7.0 Hz, 2 × CH=), 4.69 (s, 2H, OCH_2O), 4.07 (d, 4H, J = 7.0 Hz, 2 × OCH_2CH=), 1.76 (s, 6H, 2 × CH_3), 1.69 (s, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$): δ 137.37 ($(CH_3)_2C$), 120.54 (CH=), 93.59 (OCH_2O), 63.69 (OCH_2CH=), 25.69 (2 × CH_3), 17.85 (2 × CH_3); MS m/z 184 (M^+). Anal. ($C_{11}H_{20}O_2$) H; C: calcd 71.70; found, C, 71.11.

Bis(2-methyl-2-propenyloxy)methane (6c). Yield 20.29 g (38%); bp 68−70 °C/18 mmHg; ^{1}H NMR ($CDCl_3$): δ 5.00 (s, 2H, 2 × CHH=), 4.91 (s, 2H, 2 × CHH=), 4.74 (s, 2H, OCH_2O), 4.01 (s, 4H, 2 × OCH_2C), 1.77 (s, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$): δ 141.75 (CH_2=C), 112.10 (CH_2=C), 93.53 (OCH_2O), 71.18 (OCH_2C), 19.52 (2 × CH_3); MS m/z 156 (M^+).

Bis(propargyloxy)methane (6d). Yield 17.1 g (40%); bp 110−115 °C/35 mmHg; lit.[15] 85−87 °C/30 mmHg; ^{1}H NMR ($CDCl_3$): δ 4.86 (s, 2H, OCH_2O), 4.09 (s, 4H, 2 × OCH_2C), 2.45 (s, 2H, 2 × CH); ^{13}C NMR ($CDCl_3$): δ 91.94 (OCH_2O), 78.97 (C≡), 74.49 (OCH_2C≡) 54.54 (HC≡).

Acyclic Uracil Derivatives 8−10, 12−14. General Procedure. A mixture of compound 7 (3 mmol), 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (30 mL) and $(NH_4)_2SO_4$ (10 mg) was heated under reflux overnight. The mixture was concentrated at room temperature under reduced pressure to obtain the silylated base as translucent oil or as a pale yellow solid. The resulting residue was dissolved in anhydrous CH_3CN (10 mL) and cooled to −40 °C. Trimethylsilyl trifluoromethanesulfonate (TMS triflate) (3 mmol) was added in one portion followed by the dropwise addition of the appropriate acetal **6a−c** (3 mmol). When the reaction was finished (TLC analysis), the mixture was quenched with ice-cold saturated solution of $NaHCO_3$ (20 mL) and evaporated to near dryness by coevaporation with ethanol (2 × 50 mL). The resulting solid was suspended in Et_2O (200 mL), and the mixture was stirred for 1 h. After filtration, the residue was extracted with Et_2O (100 mL) and the combined organic fractions were evaporated under reduced pressure to give **8−10** and **12−14** after silica column chromatography (10 → 25% EtOAc in petroleum ether).

1-(Allyloxymethyl)-6-benzyl-5-isopropyluracil (8). Yield 518 mg (55%); mp 98−100 °C; ^{1}H NMR (DMSO-d_6): δ 1.13 (d, 6H, J = 6.8 Hz, CH(CH_3)$_2$) 2.78 (sep, 1H, J = 6.9 Hz, CH(CH_3)$_2$), 4.02 (dd, 2H, J = 5.5, 1.4 Hz, OCH_2CH=), 4.14 (s, 2H, CH_2Ph), 5.08 (s, 2H, NCH_2O), 5.19 (m, 2H, =CH_2), 5.82 (m, 1H, CH=), 7.17−7.38 (m, 5H, aryl), 11.36 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 20.04 (CH(CH_3)$_2$), 27.41 (CH(CH_3)$_2$), 33.00 (CH_2Ph), 69.19 (OCH_2CH=), 72.20 (OCH_2N), 116.96 (C5), 118.18 (CH_2=), 126.76, 127.39, 128.93, 134.34, 136.38 (aryl, CH=), 148.15 (C2), 151.61 (C6), 162.42 (C4); MS m/z 314 (M^+). Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

6-Benzyl-5-isopropyl-1-(3-methylbut-2-enyloxymethyl) uracil (9). Yield 100 mg (10%); ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 6H, J = 7.1 Hz, CH(CH_3)$_2$), 1.65, 1.73 (2 × s, 6H, C=C(CH_3)$_2$), 2.88 (sep, 1H, J = 6.8 Hz, CH(CH_3)$_2$), 4.09 (d, 2H, J = 6.9 Hz, OCH_2CH), 4.19 (s, 2H, CH_2Ph), 5.13 (s, 2H, NCH_2O), 5.30 (t, 1H, J = 7.0 Hz, OCH_2CH=), 7.17−7.38 (m, 5H, aryl), 11.36 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 18.02, 25.79 (C=C(CH_3)$_2$), 20.39 (CH(CH_3)$_2$), 28.29 (CH(CH_3)$_2$), 33.35 (CH_2Ph), 65.99 (OCH_2CH=), 72.66 (OCH_2N), 119.69 (C5), 119.99 (OCH_2CH=), 127.24, 129.14, 135.37 (aryl), 138.33, ((CH_3)$_2C$=), 148.55 (C6), 151.81 (C2), 162.38 (C4).

6-Benzyl-5-isopropyl-1-(2-methylallyloxymethyl)-uracil (10). Yield 760 mg (77%); mp 108−110 °C; ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 6H, J = 7.1 Hz, CH(CH_3)$_2$), 1.72 (s, 3H, CH_2=CCH_3), 2.88 (sep, 1H, J = 6.9 Hz, CH(CH_3)$_2$), 4.04 (s, 2H, OCH_2C), 4.21 (s, 2H, CH_2Ph), 4.89, 4.96 (2 × s, 2H,

CH_2=C), 5.16 (s, 2H, NCH_2O), 7.12 (d, 2H, J = 7.3 Hz, aryl), 7.26−7.39 (m, 3H, aryl), 11.36 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 19.45 (CH_2=CCH_3), 20.39 (CH(CH_3)$_2$), 28.30 (*C*H(CH_3)$_2$), 33.46 (CH_2Ph), 72.85 (OCH_2N), 73.54 (CCH_2O), 112.51 (CH_2=), 119.80 (C5), 127.23, 129.20, 135.32 (aryl), 141.26, (CH_2*C*=), 148.45 (C6), 151.97 (C2), 162.50 (C4); MS *m*/*z* 328 (M^+). Anal. ($C_{19}H_{24}N_2O_3$·0.25H_2O) C, H, N.

1-(Allyloxymethyl)-6-(3,5-dimethylbenzyl)-5-ethyluracil (12). Yield 514 mg (55%); mp 115−116 °C; ^{1}H NMR (DMSO-d_6): δ 0.91 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.24 (s, 6H, 2 × CH_3), 2.30 (q, 2H, J = 7.2 Hz, CH_2CH_3), 4.01 (s, 2H, OCH_2-CH=), 4.03 (s, 2H, CH_2Ph), 5.04 (s, 2H, NCH_2O), 5.17 (m, 2H, =CH_2), 5.84 (m, 1H, CH=), 6.78−6.88 (m, 3H, aryl), 11.47 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.46 (CH_2CH_3), 18.48 (CH_2-CH_3), 20.75 (2 × CH_3), 32.78 (CH_2Ph), 69.26 (OCH_2CH=), 72.00 (OCH_2N), 115.58 (C5), 116.90 (CH_2=), 138.10, 135.98, 134.40, 128.39, 125.04 (aryl, CH=), 148.47 (C2), 151.67 (C6), 163.16 (C4); MS *m*/*z* 328 (M^+). Anal. ($C_{19}H_{24}N_2O_3$·0.25H_2O) C, H, N.

6-(3,5-Dimethylbenzyl)-5-ethyl-1-(3-methylbut-2-enyloxymethyl)uracil (13). Yield 310 mg (29%); mp 136−138 °C; ^{1}H NMR ($CDCl_3$): δ 1.08 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.66, 1.74 (2 × s, 6H, C=C(CH_3)$_2$), 2.28 (s, 6H, 2 × CH_3), 2.48 (q, 2H, J = 7.4 Hz, CH_2CH_3), 4.09 (m, 4H, CH_2Ph, OCH_2CH=), 5.13 (s, 2H, NCH_2O), 5.31 (t, 1H, J = 7.0 Hz, OCH_2CH=), 6.70 (s, 2H, aryl), 6.90 (s, 1H, aryl), 9.68 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.76 (CH_2CH_3), 19.10 (CH_2CH_3), 18.02, 25.77 (2 × =CCH_3), 21.23 (2 × CH_3), 33.19 (CH_2Ph), 65.99 (OCH_2CH=), 72.54 (OCH_2N), 116.74 (C5), 120.03 (OCH_2CH=), 124.99, 128.88, (aryl), 134.94, ((CH_3)$_2$*C*=), 138.23, 138.79 (aryl), 149.22 (C2), 151.93 (C6), 163.50 (C4); MS *m*/*z* 356 (M^+). Anal. ($C_{21}H_{28}N_2O_3$·0.1H_2O) C, H, N.

6-(3,5-Dimethylbenzyl)-5-ethyl-1-(2-methylallyloxymethyl)uracil (14). Yield 120 mg (13%); mp 142−144 °C; ^{1}H NMR ($CDCl_3$): δ 1.08 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.73 (s, 3H, CH_2=CCH_3), 2.29 (s, 6H, 2 × CH_3), 2.51 (q, 2H, J = 7.4 Hz, CH_2CH_3), 4.03, 4.10 (2 × s, 4H, CH_2Ph, OCH_2C), 4.90, 4.98 (2 × s, 2H, CH_2=C), 5.16 (s, 2H, NCH_2O), 6.71 (s, 2H, aryl), 6.91 (s, 1H, aryl), 9.58 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.74 (CH_2CH_3), 19.12 (CH_2CH_3), 19.45 (CH_2=CCH_3), 21.25 (2 × CH_3), 33.22 (CH_2Ph), 72.74 (OCH_2N), 73.56 (OCH_2CH=), 112.47 (CH_2=C), 116.81 (C5), 124.99, 128.94, (aryl), 134.89, 138.87 (aryl), 141.29 (CH_2*C*=), 149.34, (C2), 151.96 (C6), 164.91 (C4); MS *m*/*z* 342 (M^+). Anal. ($C_{20}H_{26}N_2O_3$·0.1H_2O) C, H, N.

Acyclic Uracil Derivatives 11, 15−21. General Procedure. The appropriate uracil **7** (1 mmol) was stirred in dry CH_3CN (15 mL) under N_2, and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (0.87 mL, 3.5 mmol) was added. The mixture became clear after stirring at room temperature for 10 min. The reaction mixture was cooled to −50 °C and TMS triflate (0.18 mL, 1 mmol) was added followed by dropwise addition of the appropriate acetal (2 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched with ice-cold saturated solution of $NaHCO_3$ (5 mL), and evaporated under reduced pressure. The residue was extracted with Et_2O (3 × 50 mL), and the combined organic fractions were dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel with $CHCl_3$ to afford the product.

6-Benzyl-5-isopropyl-1-(prop-2-ynyloxymethyl)uracil (11). Yield 180 mg (58%); mp 103−104 °C; ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 6H, J = 6.9 Hz, CH(CH_3)$_2$), 2.44 (t, 1H, J = 2.3 Hz, ≡CH), 2.85 (sep, 1H, J = 6.9 Hz, C*H*(CH_3)$_2$), 4.18 (s, 2H, CH_2-Ph), 4.29 (d, 2H, J = 2.3 Hz, OCH_2C≡), 5.21 (s, 2H, NCH_2O), 7.11−7.37 (m, 5H, aryl), 9.34 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 20.40 (CH(*C*H$_3$)$_2$), 28.32 (*C*H(CH_3)$_2$), 33.48 (CH_2Ph), 57.18 (OCH_2C≡), 72.64 (OCH_2N), 74.72 (H*C*≡C), 79.05 (HC≡*C*),-119.98 (C5), 127.25, 127.29, 129.21, 135.15 (aryl), 148.25 (C6), 151.97 (C2), 162.31 (C4); HRMS-MALDI (M + H^+) calcd for $C_{18}H_{21}N_2O_3$, 313.1547; found, 313.1552.

6-(3,5-Dimethylbenzyl)-5-ethyl-1-(prop-2-ynyloxymethyl)uracil (15). Yield 195 mg (60%); mp 154−156 °C; ^{1}H NMR ($CDCl_3$): δ 1.06 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.28 (s, 6H, 2 × CH_3), 2.44 (t, 1H, J = 2.5 Hz, =CH), 2.45 (q, 2H, J = 7.4 Hz, CH_2CH_3), 4.07 (s, 2H, CH_2Ph), 4.28 (d, 2H, J = 2.4 Hz, OCH_2C≡), 5.20 (s, 2H, OCH_2N), 6.71 (s, 2H, aryl), 6.90 (s, 1H, aryl), 9.49 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.78 (CH_2CH_3), 19.14 (CH_2CH_3), 21.25 (2 × CH_3), 33.25 (CH_2Ph), 57.22 (OCH_2C≡), 72.56 (OCH_2N), 74.64 (H*C*≡C), 79.11 (HC≡*C*), 116.97 (C5), 125.01, 129.00, 134.74, 138.89 (aryl), 149.16 (C6), 152.01 (C2), 163.32 (C4). HRMS-MALDI (M + Na^+), calcd for $C_{19}H_{22}N_2O_3Na$, 349.1523; found, 349.1521.

1-Allyloxymethyl-5-ethyl-6-(naphthalen-1-ylmethyl)uracil (16). Yield 253 mg (72%); mp 119−123 °C; ^{1}H NMR (DMSO-d_6): δ 0.90 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.27 (q, 2H, J = 7.4 Hz, CH_2CH_3), 3.97 (dd, 2H, J = 4.3, 1.4 Hz, OCH_2-CH=), 4.52 (s, 2H, CH_2Naph), 4.96 (s, 2H, NCH_2O), 5.12 (m, 2H, =CH_2), 5.76 (m, 1H, CH=), 7.11−8.21 (m, 7H, Naph), 11.54 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.49 (CH_2CH_3), 18.50 (CH_2CH_3), 30.19 (CH_2Naph), 69.24 (OCH_2CH=), 72.21 (OCH_2N), 116.13 (C5), 116.96 (CH_2=), 123.12, 123.68, 125.84, 126,26, 126.71, 127.49, 128.79, 130.96, 131.95, 133.44, 134.27 (Naph, CH=), 148.50 (C2), 151.72 (C6), 163.11 (C4); MS *m*/*z* 350 (M^+). Anal. ($C_{21}H_{22}N_2O_3$·0.5 H_2O) C, H, N.

5-Ethyl-1-(3-methylbut-2-enyloxymethyl)-6-(naphthalen-1-ylmethyl)uracil (17). Yield 276 mg (73%); mp 179−181 °C; ^{1}H NMR ($CDCl_3$): δ 1.03 (t, 3H, J = 7.3 Hz, CH_2CH_3), 1.62, 1.65 (2 × s, 6H, C=C(CH_3)$_2$), 2.39 (q, 2H, J = 7.3 Hz, CH_2CH_3), 4.06 (d, 2H, J = 6.9 Hz, OCH_2CH), 4.55 (s, 2H, CH_2-Naph), 5.04 (s, 2H, NCH_2O), 5.23 (t, 1H, J = 7.0 Hz, OCH_2CH=), 7.02−8.08 (m, 7H, Naph), 9.84 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.73 (CH_2CH_3), 18.00 (CH_3), 19.10 (CH_2CH_3), 25.64 (CH_3), 30.41 (CH_2Naph), 66.07 (OCH_2CH=), 72.70 (OCH_2N), 117.36 (C5), 119.96 (OCH_2CH=), 122.57, 123.42, 125.53, 126.19, 126.70, 127.98, 128.96, 131.03, 131.21, 133.80 (Naph), 138.13, ((CH_3)$_2$*C*=), 149.29 (C6), 151.92 (C2), 163.33 (C4); MS *m*/*z* 378 (M^+). Anal. ($C_{23}H_{26}N_2O_3$·0.75 H_2O) C, H, N.

5-Ethyl-1-(2-methylallyloxymethyl)-6-(naphthalen-1-ylmethyl)uracil (18). Yield 258 mg (71%); mp121−123 °C; ^{1}H NMR ($CDCl_3$): δ 1.04 (t, 3H, J = 7.3 Hz, CH_2CH_3), 1.70 (s, 3H, CH_2=CCH_3), 2.40 (q, 2H, J = 7.3 Hz, CH_2CH_3), 4.01 (s, 2H, OCH_2C), 4.57 (s, 2H, CH_2Naph), 4.86, 4.94 (2 × s, 2H, CH_2=C), 5.07 (s, 2H, NCH_2O), 7.03−8.08 (m, 7H, Naph), 9.84 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.73 (CH_2CH_3), 19.13 (CH_2-CH_3), 19.41 (CH_2=CCH_3), 30.31 (CH_2Naph), 72.94 (OCH_2N), 73.54 (OCH_2CH=), 112.43 (CH_2=C), 117.46 (C5), 122.49, 123.49, 125.56, 126.23, 126.74, 128.06, 129.01, 130.92, 131.22, 133.84 (Naph), 141.18 (CH_2*C*=), 149.25, (C6), 152.00 (C2), 163.37 (C4); MS *m*/*z* 364 (M^+). Anal. ($C_{22}H_{24}N_2O_3$·0.25 H_2O) C, H, N.

1-(Allyloxymethyl)-6-(3,5-dimethylbenzyl)-5-isopropyluracil (19). Yield 245 mg (72%); mp 104−105 °C; ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 6H, J = 6.7 Hz, CH(CH_3)$_2$), 2.29 (s, 6H, 2 × CH_3), 2.82 (sep, 1H, J = 6.7 Hz, C*H*(CH_3)$_2$), 4.11−4.14 (m, 4H, OCH_2CH, CH_2Ph), 5.16 (s, 2H, NCH_2O), 5.21−5.33 (m, 2H, =CH_2) 5.81−5.92 (m, 1H, CH=) 6.71 (s, 2H, aryl), 6.90 (s, 1H, aryl), 9.47 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 20.41 (CH-(*C*H$_3$)$_2$), 21.26 (2 × CH_3), 28.34 (*C*H(CH_3)$_2$), 33.35 (CH_2Ph), 70.52 (OCH_2CH=), 72.72 (OCH_2N), 117.66 (CH_2=), 119.68 (C5), 125.01, 128.84, 133.69, 138.83 (aryl), 135.01 (CH=), 148.72 (C6), 152.04 (C2), 162.53 (C4); MS *m*/*z* 342 (M^+). Anal. ($C_{20}H_{26}N_2O_3$) C, H, N.

6-(3,5-Dimethylbenzyl)-5-isopropyl-1-(3-methylbut-2-enyloxymethyl)uracil (20). Yield 240 mg (65%); mp 133−134 °C; ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 6H, J = 6.9 Hz, CH(CH_3)$_2$), 1.66, 1.74 (2 × s, 6H, C=C(CH_3)$_2$), 2.28 (s, 6H, 2 × CH_3), 2.84 (sep, 1H, J = 6.9 Hz, C*H*(CH_3)$_2$), 4.09−4.10 (m, 4H, OCH_2CH, CH_2Ph), 5.14 (br.s, 2H, NCH_2O), 5.31 (t, 1H, J = 6.4 Hz, OCH_2CH=), 6.70 (s, 2H, aryl), 6.89 (s, 1H, aryl), 9.47 (s, 1H, NH). ^{13}C NMR ($CDCl_3$); δ 18.03, 25.80 (C=C(*C*H$_3$)$_2$) 20.41 (CH-(*C*H$_3$)$_2$), 21.25 (2 × CH_3), 28.30 (*C*H(CH_3)$_2$), 33.27 (CH_2Ph), 65.99 (OCH_2CH=), 72.67 (OCH_2N), 119.57 (C5), 120.06 (OCH_2CH=), 125.00, 128.78, 135.08, 138.75 (aryl), 138.23 ((CH_3)$_2$*C*=), 148.80 (C6), 151.94 (C2), 162.51 (C4); MS *m*/*z* 370 (M^+). Anal. ($C_{22}H_{30}N_2O_3$·0.5 H_2O) C, H, N.

6-(3,5-Dimethylbenzyl)-5-isopropyl-1-(2-methylallyloxymethyl)uracil (21). Yield 356 mg (67%); mp 137−139 °C; ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 6H, J = 6.9 Hz, CH(CH_3)$_2$), 1.73

(s, 3H, CH_2=CCH_3), 2.29 (s, 6H, 2 × CH_3), 2.83 (sep, 1H, J = 6.9 Hz, CH(CH_3)$_2$), 4.04 (s, 2H, OCH_2C), 4.13 (s, 2H, CH_2Ph), 4.89, 4.97 (2 × s, 2H, CH_2=C), 5.17 (s, 2H, NCH_2O), 6.71 (s, 2H, aryl), 6.90 (s, 1H, aryl), 9.64 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 19.45 (CH_2=CCH_3) 20.39 (CH(CH_3)$_2$), 21.24 (2 × CH_3), 28.30 (CH(CH_3)$_2$), 33.28 (CH_2Ph), 72.88 (OCH_2N), 73.51 (CCH_2O), 112.42 (CH_2=), 119.65 (C5), 124.99, 128.81, 135.02, 138.78 (aryl), 141.31 (CH_3C=), 148.71 (C6), 152.06 (C2), 162.63 (C4); MS m/z 356 (M^+). Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

Virus and Cells. The inhibitory activity against HIV-1 infection was evaluated using MT-4 cells[20] as target cells and the HIV-1 strain HTLV−IIIB[21] as infectious virus. The virus was propagated in H9 cells[20] at 37 °C, 5% CO_2 using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and antibiotics (growth medium). Culture supernatant was filtered (0.45 nm), aliquotted, and stored at −80 °C until use.

Inhibition of HIV-1 Replication. Compounds were examined for possible antiviral activity against both strains of HIV-1 using MT4 cells as target cells. MT4 cells were incubated with virus (0.005 MOI) and growth medium containing the test dilutions of compound for 6 days in parallel with virus-infected and uninfected control cultures without compound added. Expression of HIV in the cultures was indirectly quantified using the MTT assay.[21] Compounds mediating less than 30% reduction of HIV expression were considered without biological activity. Compounds were tested in parallel for cytotoxic effect in uninfected MT-4 cultures containing the test dilutions of compound as described above. A 30% inhibition of cell growth relative to control cultures was considered significant. The 50% inhibitory concentration (EC_{50}) and the 50% cytotoxic concentration (CC_{50}) were determined by interpolation from the plots of percent inhibition versus concentration of compound. The test for activity against HIV-1 was performed in MT-4 cell cultures infected with either wild-type HIV-1 (strain IIIB[21] and strain HxB2[22]) or NNRTI resistant HIV-1 (strain N119,[23] strain A17,[23b,24] strain ARP1013, and strain ARP1010 were obtained from J. P. Kleim through the Centralised Facility for AIDS Reagents,U.K.).

References

(1) Mitsuya, H.; Yarchoan, R.; Broder, S. Molecular targets for AIDS therapy. *Science* **1990**, *249*, 1533−1544.

(2) De Clercq, E. Targets and strategies for the antiviral chemotherapy of AIDS. *Trends Pharmacol. Sci.* **1990**, *11*, 198−205.

(3) Pedersen, O. S.; Pedersen, E. B. Non-nucleoside reverse transcriptase inhibitors: the NNRTI boom. *Antiviral Chem. Chemother.* **1999**, *10*, 285−314.

(4) Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R. T.; Balzarini, J.; De Clercq, E. A novel lead for specific anti-HIV-1 agents: 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine. *J. Med. Chem.* **1989**, *32*, 2507−2509.

(5) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Inouye, N.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. Synthesis and antiviral activity of 6-benzyl analogues of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) as potent and selective anti-HIV-1 agents. *J. Med. Chem.* **1995**, *38*, 2860−2865.

(6) Hopkins, A. L.; Ren, J.; Esnouf, R. M.; Willcox, B. E.; Jones, E. Y.; Ross, C.; Miyasaka, T.; Walker, R. T.; Tanaka, H.; Stammers, D. K.; Stuart, D. I. Complexes of HIV-1 reverse transcriptase with inhibitors of the HEPT series reveal conformational changes relevant to the design of potent non-nucleoside inhibitors. *J. Med. Chem.* **1996**, *39*, 1589−1600.

(7) Baba, M.; Tanaka, H.; Miyasaka, T.; Yuasa, S.; Ubasawa, M.; Walker, R. T.; De Clercq, E. HEPT derivatives: 6-Benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442). *Nucleosides Nucleotides* **1995**, *14*, 575−583.

(8) Press statement from Triangle Pharmaceuticals Inc. 17 January 2002, http://www.tripharm.com/static/news/drug.html.

(9) Hopkins, A. L.; Ren, J.; Tanaka, H.; Baba, M.; Okamato, M.; Stuart, D. I.; Stammers, D. K. Design of MKC-442 (emivirine) analogues with improved activity against drug-resistant HIV mutants. *J. Med. Chem.* **1999**, *42*, 4500−4505.

(10) Grob, P. M.; Wu, J. C.; Cohen, K. A.; Ingraham, R. H.; Shih, C. K.; Hargrave, K. D.; McTague, T. L.; Merluzzi, V. J. Nonnucleoside inhibitors of HIV-1 reverse transcriptase: Nevirapine as a prototype drug. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 145−152.

(11) Romero, D. L.; Olmsted, R. A.; Poel, T. J.; Morge, R. A.; Biles, C.; Keiser, B. J.; Kopta, L. A.; Friis, J. M.; Hosley, J. D.; Stefanski, K. J.; Wishka, D. G.; Evans, D. B.; Morris, J.; Stehle, R. G.; Sharma, S. K.; Yagi, Y.; Voorman, R. L.; Adams, W. J.; Tarpley, W. G.; Thomas, R. C. Targeting delavirdine/atevirdine resistant HIV-1: Identification of (alkylamino)piperidine-containing bis(heteroaryl)piperazines as broad spectrum HIV-1 reverse transcriptase inhibitors. *J. Med. Chem.* **1996**, *39*, 3769−3789.

(12) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. L-743,726 (DMP-266): a novel, highly potent nonnucleoside inhibitor of the human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602−2605.

(13) Ren, J. S.; Esnouf, R.; Garman, E.; Jones, Y.; Somers, D.; Ross, C.; Kirby, I.; Keeling, J.; Darby, G.; Stuart, D.; Stammers, D. High-resolution structure of HIV-1 RT: insights from four RT-inhibitor complexes. *Nat. Struct. Biol.* **1995**, *2*, 293−302.

(14) Kireev, D. B.; Chrétien, J. J.; Grierson, D. S.; Monneret, C. A 3D QSAR study of a series of HEPT analogues: The influence of conformational mobility on HIV-1 reverse transcriptase inhibition. *J. Med. Chem.* **1997**, *40*, 4257−4264.

(15) Nazaretyan, A. Kh.; Torosyan, G. O.; Babayan, A. T. Quarternary ammonium salts in alkylation reactions (synthesis of formaldehyde acetals). *J. Appl. Chem. USSR* **1985**, *58*, 2396−2400.

(16) (a) Danel, K.; Larsen, E.; Pedersen, E. B. Easy synthesis of 5,6-disubstituted acyclouridine derivatives. *Sythesis* **1995**, *8*, 934−936. (b) Danel, K.; Larsen, E.; Pedersen, E. B.; Vestergaard, B. F.; Nielsen, C. Synthesis and potent anti-HIV-1 activity of novel 6-benzyluracil analogues of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine. *J. Med. Chem.* **1996**, *39*, 2427−2431. (c) Danel, K.; Nielsen, C.; Pedersen, E. B. Anti-HIV active Naphthyl analogues of HEPT and DABO. *Acta Chem. Scand.* **1997**, *51*, 426−430.

(17) Wittenburg, E. A new synthesis of nucleosides. *Z. Chem.* **1964**, *4*, 303−304.

(18) Vorbrüggen, H.; Krolikiewiecz, K.; Bennua, B. Nucleoside synthesis with trimethylsilyl triflate and perchlorate as catalysts. *Chem. Ber.* **1981**, *114*, 1234−1255.

(19) Harada, S.; Koyanagi, Y.; Yamamoto, N. Infection of HTLV−III/LAV in HTLV−I-carrying cells MT-2 and MT-4 and application in a plaque assay. *Science* **1985**, *229*, 563−566.

(20) Popovic, M.; Sarngadharan, M. G.; Read, E.; Gallo, R. C. Detection, isolation and continuous production of cytophathic retroviruses (HTLV−III) from patients with AIDS and pre-AIDS. *Science* **1984**, *224*, 497−500.

(21) Mosmann, T. Rapid colorimetic assay for cellular growth and survival. Application to proliferation and cytotoxicity assays. *J. Immunol. Methods* **1983**, *65*, 55−63.

(22) Shaw, G. M.; Hahn, B. H.; Arya, S. K.; Groopman, J. E.; Gallo, R. C.; Wong-Staal, F. Molecular characterization of human T-cell leukemia (lymphotropic) virus type III in the acquired immune deficiency syndrome. *Science* **1984**, *226*, 1165−1171.

(23) (a) Richman, D.; Shih, C. K.; Lowy, I.; Rose, J.; Prodanovich, P.; Goff, S.; Griffin, J. Human immunodeficiency virus type 1 mutants resistant to nonnucleoside inhibitors of reverse transcriptase arise in tissue culture. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 11241−11245. (b) Hara, H.; Fujihashi, T.; Sakata, T.; Kaji, A.; Kaji, H. Tetrahydronaphthalene lignan compounds as potent anti-HIV type 1 agents. *AIDS Res. Hum. Retroviruses* **1997**, *13*, 6695−705.

(24) Nunberg, J. H.; Schleif, W. A.; Boots, E. J.; O'Brien, J. A.; Quintero, J. C.; Hoffman, J. M.; Emini, E, A.; Goldman, M. E. Viral resistance to human immunodeficiency virus type 1-specific pyridinone reverse transcriptase inhibitors. *J. Virol.* **1991**, *65*, 4887−4892.

JM020949R