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# Synthesis of New MKC-442 Analogues Containing Alkenyl Chains or Reactive Functionalities at C-5

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**Summary.** In an effort to obtain more insight into the interaction between HIV-1 reverse transcriptase (RT) and MKC-442 analogues, a new series of compounds was synthesized and evaluated for inhibition of HIV-1 replication. The modifications include bulky alkenyl substituents at the C-5 position of the uracil ring. Analogues with reactive centers (aldehyde and epoxide functionalities) at C-5 were also synthesized in an attempt to develop HIV drugs with improved activity against the Y181C mutants by forming a covalent bond to the mercapto group in cysteine in the hydrophobic pocket of the mutated RT. Difficulties in the syntheses show that the epoxides are chemically reactive, whereas the aldehydes are more stable. One of the alkenyl analogues showed activity against HIV-1 in the same range as MKC-442, whereas the reactive analogues were not active against HIV with the mutation Y181C in RT.

**Keywords.** HIV-1; Non-nucleoside reverse transcriptase inhibitors; MKC-442 analogues; 5-Alkenyluracils; 5-Aldehyde or 5-epoxide substituted uracils.

## Introduction

*HEPT* (1-((2-hydroxyethoxy)-methyl)-6-(phenylthio)-thymine, **1**, Fig. 1) was originally synthesized as a nucleoside inhibitor against HIV but was acting as a non-nucleoside inhibitor by binding to a hydrophobic pocket situated approximately 10 Å away from the active site in the enzyme reverse transcriptase (RT) [1]. The binding results in a conformational change and inactivation of the enzyme [2].

MKC-442 (emivirine or coactinon, **2**, Fig. 1) is an optimized structure of *HEPT* and is currently undergoing phase III clinical trials [3]. In an attempt to optimize this lead structure we have previously introduced a vinyl group at C-5 of the uracil ring instead of the isopropyl group (**3**, Fig. 1) [4]. This compound has shown good activity against HIV-1 ($IC\text{-}50 = 0.07\ \mu M$) and was almost as active as MKC-442 ($IC\text{-}50 = 0.02\ \mu M$).

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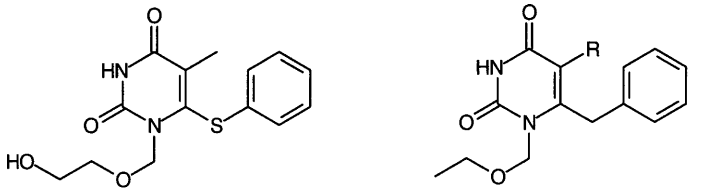



**Fig. 1.** Non-nucleoside reverse transcriptase inhibitors of HIV-1

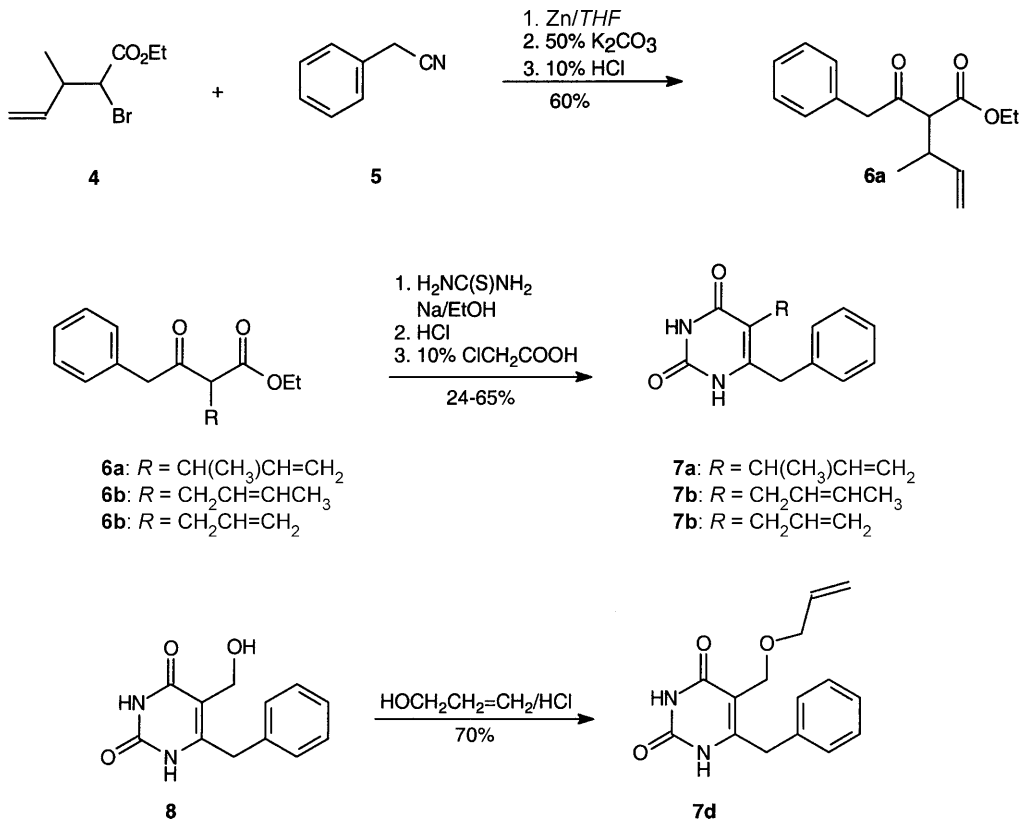
When using non-nucleoside analogues as drugs against HIV the major problem is the fast development of resistance. A very common mutation when using MKC-442 is the conversion of tyrosine at position 181 in RT to cysteine. We have previously reported the synthesis of an MKC-442 analogue with a carbaldehyde at position C-5 [4]. It was hoped that the drug would covalently bind to the hydrophobic pocket by formation of a thiohemiacetal between the carbaldehyde and the mercapto group in cysteine of the mutated virus. This carbaldehyde turned out to be inactive towards the wild-type as well as the mutant. We also have attempted to synthesize an epoxide directly attached to C-5. However, this compound turned out to be too reactive to be isolated, its ring being opened by the *m*-chloroperbenzoic acid formed during epoxidation of the corresponding alkene. In this paper we describe the introduction of the same reactive groups further away from the uracil ring. A flexible linker of adequate length between the uracil ring and the reactive groups may improve the chance of a reaction with the mercapto group in the cysteine in the mutated RT. From the available crystal structure of MKC-442 complexed with RT [5] we deduced a possible appropriate chain length of the linker. The aldehyde group can be introduced by cleavage of a double bond in the side chain at C-5, whereas the same double bond can be oxidized to give the epoxide.

In this paper we also use the intermediate compounds with allyl, 2-butenyl, 1-methyl-2-propenyl, or allyloxymethyl groups at C-5 of the uracil ring to investigate the influence of the bulkyness of the C-5 substituent on the activity against HIV-1.

## Results and Discussion

### *Chemistry*

The $\beta$-ketoester **6a** was synthesized according to the procedure described by *Danel et al.* [6] in a *Blaise* reaction. In this investigation, ethyl 2-bromo-3-methyl-4-pentenoate (**4**) [7] was reacted with Zn and phenylacetonitrile. After hydrolysis of the formed enamide the desired $\beta$-ketoester was isolated in 60% yield. Compound **6a** as well as the other $\beta$-ketoesters **6b**,**c** [8, 9] were used as starting materials for the uracil rings. These were formed by a ring closure using thiourea and NaOEt. The formed thiouracils were desulfurized using chloroacetic acid [6, 10] to give the uracils **7a**–**c** in yields of 24–65% for the two steps. As the starting $\beta$-ketoester **6b** was a mixture of the *cis* and the *trans* alkene, **7b** was also formed as a stereochemical mixture, and no attempts were made to separate the compounds.



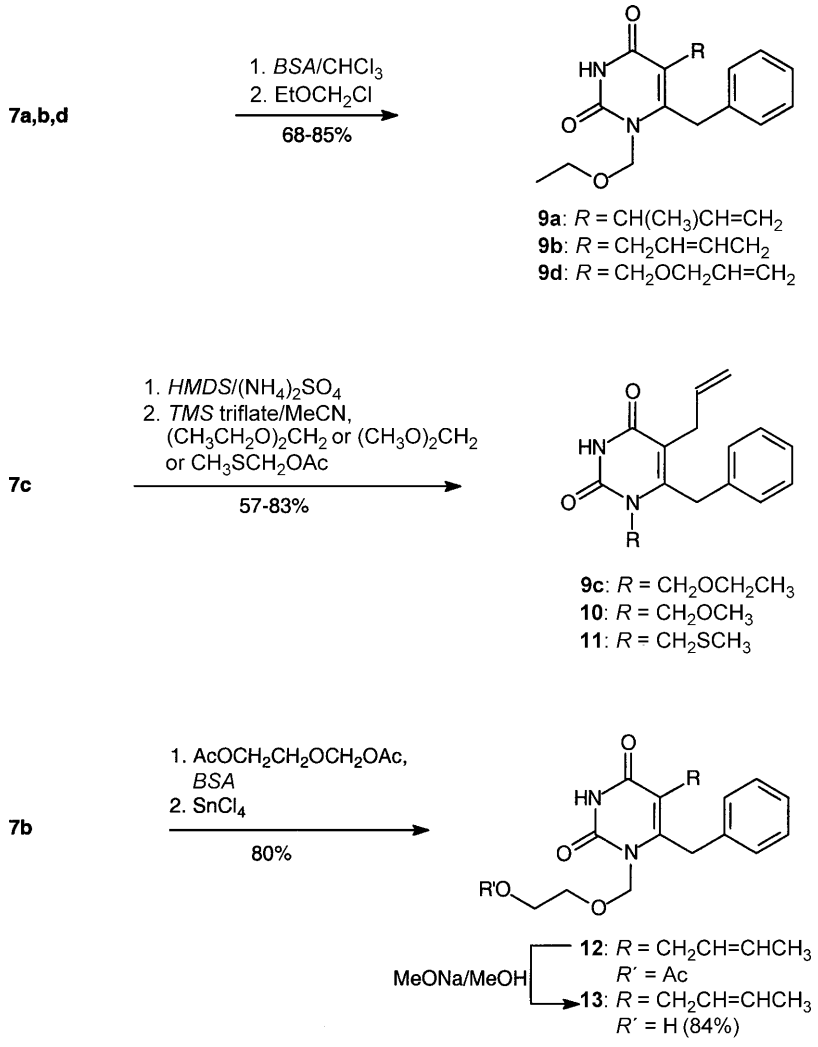

**Scheme 1**

Another uracil derivative was prepared starting from the hydroxymethylated uracil **8** which has previously been synthesized [4]. This was reacted with allyl alcohol and HCl to give the allyl ether **7d** in 70% yield [11].

The compounds **7a**, **7b**, and **7d** were alkylated at N-1 using *bis*-(trimethylsilyl)-acetamide (*BSA*) and chloromethylethyl ether [6] to give the MKC-442 analogues **9a**, **9b**, and **9d** in 68–85% yield. The C-5 allyl substituted uracil **7c** was silylated under reflux in 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) [12] and alkylated by treatment with diethoxymethane, dimethoxymethane, or methylthiomethyl acetate in the presence of trimethylsilyl trifluoromethanesulfonate (*TMS* triflate) as a *Lewis* acid catalyst [13] to give the MKC-442 analogues **9c**, **10**, and **11** in 83%, 71%, and 57% yield.

A *HEPT* analogue was synthesized starting from **7b** which was silylated using *BSA* and alkylated with 2-acetoxyethyl acetoxymethyl ether and $SnCl_4$ [14] to give **12** in 80% yield. The deprotection was carried out in sodium methoxide in methanol [14] to give the *HEPT* analogue **13** in 84% yield.

The epoxide **14b** was synthesized to test its activity against the Y181C mutant of HIV-1 RT. Compound **9b** was reacted with *m*-chloroperoxybenzoic acid (*MCPBA*) in order to epoxidize the double bond. After 4 h the desired product **14b** was isolated in 45% yield. It was tested for activity against HIV without further purification. The product could not be purified using column chromatography as



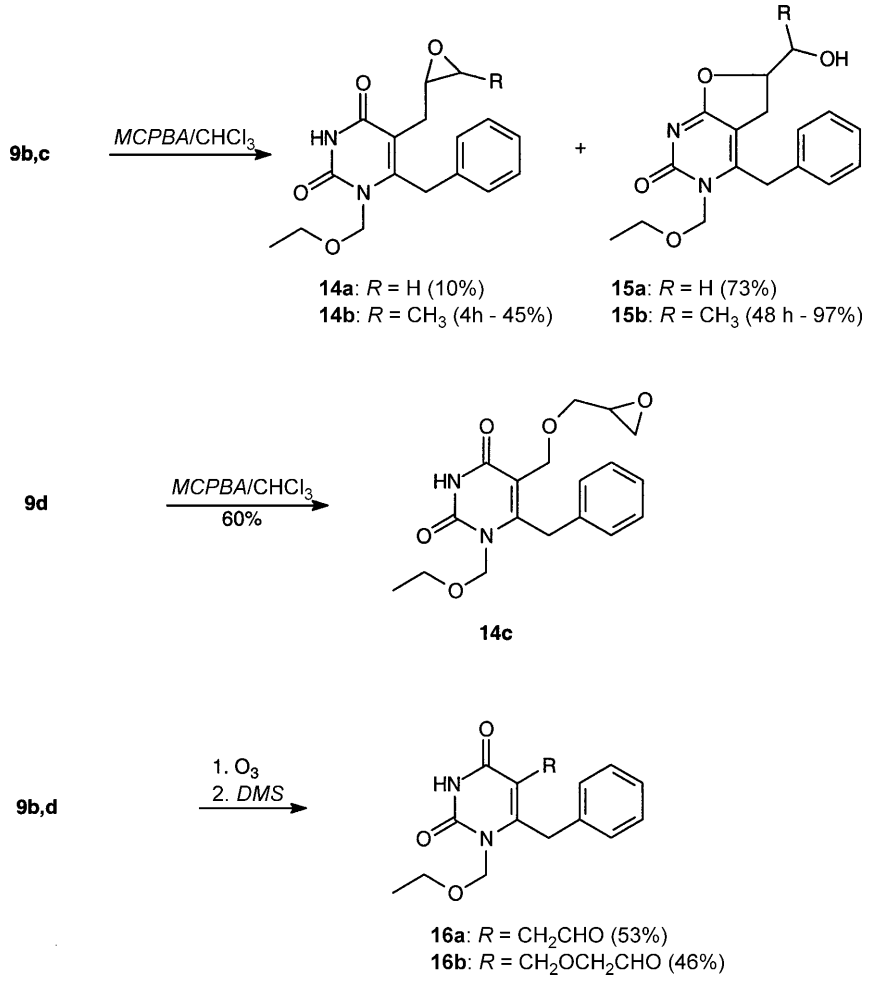

**Scheme 2**

the C-4 carbonyl reacted with the epoxide to give **15b** which was the only isolated product when the reaction time was increased to 48 h (97% yield).

The C-5 allyl substituted analogue **9c** was also reacted with *MCPBA* for 48 h, and the product was purified by column chromatography. The desired epoxide **14a** was isolated in only 10% yield, the major product being the compound where the C-4 carbonyl had reacted with the epoxide to form **15a** in 73% yield.

The C-5 allyloxymethyl substituted analogue **9d** was reacted overnight with *MCPBA* to give the corresponding epoxide **14c** which was obtained in 60% yield after column chromatography. In this case, a reaction between the C-4 carbonyl and the epoxide is unfavourable. Compounds **14** and **15** were tested for their biological activity as the racemic mixtures.

The 2-butenyl and the allyloxymethyl analogues **9b**,**d** where reacted with ozone to cleave the double bonds, and the aldehydes **16a**,**b** were isolated in 53% and 46% yield, respectively.




**Scheme 3**

*Antiviral activity*

The anti-HIV activities and cytotoxicities of the synthesized MKC-442 analogues are summarized in Table 1. The test for activity against HIV-1 was performed in MT 4 cell cultures infected with either wild type HIV-1 or the HIV-1 strain N119 that harbours a substitution of tyrosine for cysteine at position 181 (Y181C). The expression of HIV-1 was quantified by two different methods, either the HIV-1 antigen detection assay ELISA [15] or indirectly by the MTT assay [16]. As these methods give different results; the test results for MKC-442 are included as a reference using both methods. The results for compound **3** are also included for comparison.

In general, the introduction of an alkenyl group instead of an isopropyl group at C-5 did not improve the activity against HIV-1 compared to MKC-442. The most active compound is **9a** ($IC\text{-}50 = 0.04\,\mu M$) with a 1-methyl-2-propenyl side chain at C-5. This compound is almost as active as MKC-442 ($IC\text{-}50 = 0.02\,\mu M$) and slightly more active than the reference compound **3** ($IC\text{-}50 = 0.07\,\mu M$).

**Table 1.** Cytotoxicity and anti-HIV-1 activity of compound **9–16**

| | Wild type | | | Y181C mutant (N119) | | |
|---|---|---|---|---|---|---|
| | *IC-50*[a]/$\mu M$ | *CC-50*[b]/$\mu M$ | *SI*[c] | *IC-50*[a]/$\mu M$ | *CC-50*[b]/$\mu M$ | *SI*[c] |
| **9a**[f] | 0.04 | >100 | >2500 | 77 | >100 | >1 |
| **9b**[e] | 0.52 | >100 | >192 | >100 | | |
| **9c**[e] | 0.37 | >100 | >270 | 30 | >100 | >3 |
| **9d**[f] | 43 | >100 | >2 | >100 | | |
| **10**[e] | 3.7 | >100 | >27 | >100 | | |
| **11**[e] | 0.56 | >100 | >178 | >100 | | |
| **12**[e] | 42 | >100 | >2 | >100 | | |
| **13**[e] | 32 | >100 | >3 | >100 | | |
| **14a**[e] | 0.32 | >100 | >312 | 24 | >100 | >4 |
| **14b**[f] | 23 | >100 | >4 | >100 | | |
| **14c**[f] | >100 | | | >100 | | |
| **15a**[e] | >100 | | | ND[d] | – | – |
| **15b**[f] | 28 | >100 | >3 | >100 | | |
| **16a**[f] | 32 | >100 | >3 | >100 | | |
| **16b**[f] | >100 | | | >100 | | |
| **2** (MKC-442)[e] | 0.005 | 141 | 28000 | >100 | >100 | >1 |
| **2** (MKC-442)[f] | 0.02 | >100 | >5000 | 36 | | |
| **3**[f] | 0.07 | >100 | >1429 | >100 | >100 | >1 |

[a] 50% Inhibitory concentration; [b] 50% cytotoxic concentration; [c] selectivity index, *CC-50*/*IC-50* ratio; [d] not determined; [e] quantified by ELISA [15]; [f] quantified by MTT assay [16]

Interestingly, there is a slight activity against the mutated virus (Y181C). The other C-5 alkenyl substituted compounds **9b–d** show more moderate activities against HIV-1.

The compounds containing reactive epoxides (**14a–c**) or aldehydes (**16a**,**b**) in the side chains at C-5 do not show any improved activity against the wild-type virus when compared to the C-5 alkenyl substituted starting materials. Also, they do not show activity against the mutant (Y181C). The latter indicates that the covalent binding of the drug to cysteine in the RT hydrophobic pocket has not taken place or that this principle is not a sufficient prerequisite for activity against the HIV mutant Y181C.

## Experimental

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for $^1H$ and 75 MHz for $^{13}C$ with *TMS* as an internal standard. 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, USA; the found values agreed favourably 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. Solvents for chromatography were bought as HPLC grade or distilled prior to use. $CHCl_3$ was dried over 4 Å sieves. $CH_2Cl_2$ was dried by reflux over $P_2O_5$ ($5\,g \cdot dm^{-3}$) and distilled on 4 Å sieves. MeOH was dried by reflux over Mg ($5\,g \cdot dm^{-3}$) and distilled on 3 Å sieves. Pyridine was dried over KOH.

*Ethyl 2-(1-methyl-2-propenyl)-3-oxo-4-phenylbutyrate* (**6a**; $C_{16}H_{20}O_3$)

Activated Zn dust (18 g, 0.275 mol) was suspended in 125 $cm^3$ dry *THF*, and the mixture was refluxed. A few drops of ethyl 2-bromo-3-methyl-4-pentenoate (**4**) [7] were added. When the colour of the mixture turned green, 2.40 g phenylacetontrile (0.020 mol) were added in one portion; then, 4.40 g ethyl 2-bromo-3-methyl-4-pentenoate (**4**, 0.020 mol) was added dropwise over 1 h. The mixture was refluxed for 15 min, and 60 $cm^3$ 50% aq. $K_2CO_3$ were added. The mixture was stirred for 45 min to give two phases. The *THF* phase was decanted, and the $H_2O$ phase was washed with *THF*. The combined *THF* phases were reacted with 200 $cm^3$ 10% HCl at room temperature for 45 min. The mixture was evaporated *in vacuo*, and the residue was dissolved in 150 $cm^3$ $CH_2Cl_2$. The organic phase was washed with sat. aq. $NaHCO_3$ and dried ($Na_2SO_4$). The product was purified by silica gel column chromatography (20% petroleum ether (60–80°C) in $Et_2O$) to give 3.11 g **6a** (60%). It was not possible to separate the diastereoisomers.

$^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 0.94, 1.06 (3H, 2d, $J = 6.8$ Hz, CHC$H_3$), 1.17–1.26 (3H, m, $CH_2CH_3$), 2.96–3.03 (1H, m, C$H$CH$_3$), 3.50 (1H, d, $J = 9.7$ Hz, CHCO), 3.80 (2H, s, $CH_2$Ph), 4.05–4.18 (2H, q, $J = 7.1$ Hz, C$H_2$CH$_3$), 4.95–5.09 (2H, m, CH=C$H_2$), 5.57–5.77 (1H, m, C$H$=CH$_2$), 7.07–7.40 (5H, m, $H_{arom}$) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 13.99 ($CH_2CH_3$), 17.91, 17.94 ($CH_3$CH), 37.53, 37.77 (CHCH$_3$) 49.57, 49.62 ($CH_2$Ph), 61.25, 61.47 (CHCO), 63.90, 63.97 ($CH_2CH_3$), 115.23, 115.49 (CH=$CH_2$), 127.04, 127.13, 128.47, 128.57, 129.60, 129.68, 132.93, 132.99 ($C_{arom}$), 139.73, 139.77 (CH=CH$_2$) 168.16, 168.30 (COO), 201.39, 201.44 (CO) ppm; MS (EI): $m/z = 260$ ($M^+$).

*General procedure for preparation of 5,6-substituted-1H-pyrimidine-2,4-diones* **7a–c**

Na (25.1 g, 1.1 mol) was dissolved in 500 $cm^3$ absolute EtOH. Thiourea (58.23 g, 0.77 mol) was added, and the mixture was heated to reflux. The $\beta$-keto ester (**6a–c**, 0.051 mol) was added dropwise, and the mixture was refluxed for 3–6 h. EtOH was evaporated *in vacuo*, and the residue was dissolved in 400 $cm^3$ $H_2O$. The thiouracil was precipitated by neutralization with conc. HCl. The mixture was filtered, and the precipitate suspended in 500 $cm^3$ 10% aq. chloroacetic acid. The suspension was refluxed overnight and filtered after cooling. The precipitate was washed with cold EtOH and dried *in vacuo* to give **7a–c**.

*6-Benzyl-5-(1-methyl-2-propenyl)-1H-pyrimidine-2,4-dione* (**7a**; $C_{15}H_{16}N_2O_2$)

White crystals after recrystallization (EtOH/$H_2O$); yield: 24%; m.p.: 188°C (EtOH/$H_2O$); $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.31 (3H, d, $J = 7.4$ Hz, $CH_3$), 3.60–3.67 (1H, m, CH), 3.83 (2H, s, $CH_2$Ph), 4.92–4.99 (2H, m, CH=C$H_2$), 6.09–6.20 (1H, m, C$H$=CH$_2$), 7.19–7.33 (5H, m, $H_{arom}$), 9.80 (2H, s, 2 × NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 18.26 ($CH_3$), 35.13 ($CH_2$Ph), 36.25 (CH), 113.77 (CH=$CH_2$), 114.71 (C-5), 127.46, 128.62, 128.98, 134.94 ($C_{arom}$), 140.85 (CH=CH$_2$), 149.09, 151.87 (C-2, C-6), 164.22 (C-4) ppm; MS (EI): $m/z = 256$ ($M^+$).

*6-Benzyl-5-but-2-enyl-1H-pyrimidine-2,4-dione* (**7b**; $C_{15}H_{16}N_2O_2$)

White crystals after washing with $H_2O$; yield: 65%; m.p.: 181°C; $^1$H NMR (*DMSO*-$d_6$, $\delta$, 300 MHz): 1.51 (3H, d, $J = 3.6$ Hz, $CH_3$), 2.88–2.94 (2H, m, C$H_2$CH), 3.73 (2H, s, $CH_2$Ph), 5.27–5.30 (2H, m, CH=CH), 7.24–7.35 (5H, m, $H_{arom}$), 10.79 (1H, s, NH), 11.05 (1H, s, NH) ppm; $^{13}$C NMR (*DMSO*-$d_6$, $\delta$, 75 MHz): 17.58 ($CH_3$), 26.79 ($CH_2$CH), 35.03 ($CH_2$Ph), 108.60 (C-5), 125.20, 126.93 (CH=CH) 128.32, 128.48, 128.80, 136.72 ($C_{arom}$), 149.90, 151.23 (C-2, C-6), 164.77 (C-4) ppm; MS (EI): $m/z = 256$ ($M^+$).

*5-Allyl-6-benzyl-1H-pyrimidine-2,4-dione* (**7c**; $C_{14}H_{14}N_2O_2$)

White crystals after recrystallisation (EtOH); yield: 37%; m.p.: 187–189°C (EtOH); $^1$H NMR (*DMSO*-$d_6$, $\delta$, 300 MHz): 2.98 (2H, d, $J = 6.2$ Hz, C$H_2$CH=CH$_2$), 3.71 (2H, s, CH$_2$Ph), 4.87 (2H, m, CH=C$H_2$), 5.65 (1H, m, C$H$=CH$_2$), 7.18–7.32 (5H, m, H$_{arom}$), 10.80 (1H, s, NH), 11.06 (1H, s, NH) ppm; $^{13}$C NMR (*DMSO*-$d_6$, $\delta$, 7.5 MHz): 27.85 (*C*H$_2$CH=CH$_2$), 34.92 (CH$_2$Ph), 107.59 (C-5), 115.04 (CH=*C*H$_2$), 126.82–128.69 (C$_{arom}$), 135.75 (*C*H=CH$_2$), 136.60 (C$_{arom}$), 150.10, 151.10 (C-2, C-6), 164.55 (C-4) ppm; MS (EI): $m/z = 242$ (M$^+$).

*5-Allyloxymethyl-6-benzyl-1H-pyrimidine-2,4-dione* (**7d**; $C_{15}H_{16}N_2O_3$)

6-Benzyl-5-hydroxymethyl-1*H*-pyrimidine-2,4-dione [4] (**8**, 0.93 g, 4 mmol) was added to a solution of 1 cm$^3$ conc. HCl in 50 cm$^3$ allyl alcohol. The solution was heated to 100°C overnight, cooled slowly to room temperature, and left to crystallize at 5°C. The precipitate was filtered off, washed with $H_2O$ and $Et_2O$, and dried *in vacuo* to give 0.76 g **7d** (70%) as a white solid. To get an analytically pure sample it was recrystallized (EtOH/$H_2O$).

M.p.: 207–208°C (EtOH/$H_2O$); $^1$H NMR (*DMSO*-$d_6$, $\delta$, 300 MHz): 3.85 (2H, s, CH$_2$Ph), 3.96 (2H, d, $J = 5.4$ Hz, OC$H_2$CH=CH$_2$), 4.24 (2H, s, CH$_2$O), 5.15 (1H, dd, $J = 1.0$, 10.5 Hz, H$_{trans}$), 5.26 (1H, dd, $J = 1.6$, 17.3 Hz, H$_{cis}$), 5.82–5.95 (1H, m, H$_{gem}$), 7.24–7.36 (5H, m, H$_{arom}$), 11.00 (1H, br s, NH), 11.17 (1H, br s, NH) ppm; $^{13}$C NMR (*DMSO*-$d_6$, $\delta$, 75 MHz): 34.97 (CH$_2$Ph), 61.37 (CH$_2$O), 70.30 (O*C*H$_2$CH=CH$_2$), 106.76 (C-5), 116.30 (CH=*C*H$_2$), 126.71, 128.42, 128.49, 135.14 (C$_{arom}$), 136.27 (*C*H=CH$_2$), 150.84 (C-2), 153.86 (C-6), 164.26 (C-4) ppm; MS (EI): $m/z = 272$ (M$^+$).

*General procedure for the synthesis of* **9a**, **9b**, and **9d**

N,O-*Bis*-(trimethylsilyl)-acetamide (*BSA*, 3.37 g, 16.4 mmol) was dissolved in 30 cm$^3$ dry $CHCl_3$. Compounds **7a**, **7b**, or **7d** (4.69 mmol) and, after 10 min, 0.55 g chloromethyl ethyl ether (5.82 mmol) were added. The solution was stirred overnight at room temperature, quenched with 25 cm$^3$ ice cold sat. aq. $NaHCO_3$, and evaporated to near dryness under reduced pressure. The product was washed out with $Et_2O$. The combined $Et_2O$ phases were dried ($Na_2SO_4$) and evaporated under reduced pressure.

*6-Benzyl-1-ethoxymethyl-5-(1-methyl-2-propenyl)-1H-pyrimidine-2,4-dione* (**9a**; $C_{18}H_{22}N_2O_3$)

Purified by preparative TLC (3% MeOH in $CH_2Cl_2$); yield: 68%; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.18 (3H, t, $J = 7.0$ Hz, CH$_2$C$H_3$), 1.34 (3H, d, $J = 7.3$ Hz, CHC$H_3$), 3.54–3.65 (3H, m, C$H_2$CH$_3$, C$H$CH$_3$), 4.18, 4.24 (2H, 2 × d, $J = 17.5$ Hz, CH$_2$Ph), 4.88–5.20 (4H, m, CH$_2$O, CH=C$H_2$), 6.14–6.25 (1H, m, C$H$=CH$_2$), 7.10–7.37 (5H, m, H$_{arom}$), 9.43 (1H, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 15.02 (CH$_2$*C*H$_3$), 18.51 (CH*C*H$_3$), 33.54 (CH$_2$Ph), 36.42 (*C*HCH$_3$), 65.02 (*C*H$_2$CH$_3$), 72.75 (CH$_2$O), 113.87 (CH=*C*H$_2$), 118.12 (C-5), 127.20, 127.35, 129.13, 135.40 (C$_{arom}$), 140.81 (*C*H=CH$_2$), 149.59, 151.92 (C-2, C-6), 162.51 (C-4) ppm; MS (EI): $m/z = 314$ (M$^+$).

*6-Benzyl-5-but-2-enyl-1-ethoxymethyl-1H-pyrimidine-2,4-dione* (**9b**; $C_{18}H_{22}N_2O_3$)

Purified by silica gel column chromatography (1–3% MeOH in $CH_2Cl_2$); yield: 82%; oil; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.18 (3H, t, $J = 7.1$ Hz, CH$_2$C$H_3$), 1.58–1.60 (3H, m, CHC$H_3$), 3.10–3.25 (2H, m, C$H_2$CH), 3.62 (2H, q, $J = 7.0$ Hz, C$H_2$CH$_3$), 4.16 (2H, s, CH$_2$Ph), 5.13 (2H, s, CH$_2$O), 5.40–5.44 (2H, m, CH=CH) 7.09–7.36 (5H, m, H$_{arom}$), 9.97 (1H, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 14.85 (CH$_2$*C*H$_3$), 17.57 (CH*C*H$_3$), 28.15 (*C*H$_2$CH), 33.36 (CH$_2$Ph), 64.91 (*C*H$_2$CH$_3$),

72.64 ($CH_2O$), 113.81 (C-5), 126.45, 127.22, 127.25, 127.41, 129.17, 135.08 ($C_{arom}$, CH=CH), 150.33, 152.15 (C-2, C-6), 163.57 (C-4) ppm; MS (EI): $m/z = 314$ ($M^+$).

*5-Allyloxymethyl-6-benzyl-1-ethoxymethyl-1H-pyrimidine-2,4-dione* (**9d**; $C_{18}H_{22}N_2O_4$)

The product was purified by silica gel column chromatography (50% EtOAc in petroleum ether (60–80°C)); yield: 0.280 g (85%); white solid; m.p.: 99–101°C; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.17 (3H, t, $J = 7.0$ Hz, $CH_3$), 3.61 (2H, q, $J = 7.0$ Hz, $CH_2CH_3$), 4.03 (2H, dt, $J = 1.3$, 5.7 Hz, $CH_2CH{=}CH_2$), 4.30 (2H, s, $CH_2Ph$), 4.39 (2H, s, $CH_2O$), 5.41 (2H, s, $NCH_2O$), 5.17 (1H, m, $H_{trans}$), 5.25 (1H, dq, $J = 1.5$, 17.3 Hz, $H_{cis}$), 5.81–5.94 (1H, m, $H_{gem}$), 7.14–7.36 (5H, m, $H_{arom}$), 9.79 (1H, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 7.5 MHz): 14.93 ($CH_3$), 33.70 ($CH_2Ph$), 62.25 ($ArCH_2O$), 65.14 ($CH_2CH_3$), 71.67 ($OCH_2CH$), 72.66 ($NCH_2O$), 111.79 (C-5), 117.51 ($CH{=}CH_2$), 127.27, 127.49, 129.15, 134.29 ($C_{arom}$), 134.96 ($CH{=}CH_2$), 151.85 (C-2), 154.97 (C-4), 163.21 (C-6) ppm; MS (EI): $m/z = 330$ ($M^+$).

*General procedure for the synthesis of* **9c**, **10**, and **11**

Compound **7c** (3 mmol) was added to a solution of 10 mg $(NH_4)_2SO_4$ in 10 cm$^3$ *HMDS*. The solution was refluxed, and when the silylation was complete, the excess of *HMDS* was evaporated under reduced pressure to give the silylated compound as a yellow oil. This was dissolved in dry 10 cm$^3$ dry $CH_3CN$, and the solution was cooled to −35°C. *TMS* triflate (0.62 g, 2.79 mmol) was added in one portion followed by the dropwise addition of 30 mmol dialkyloxymethane or 3.5 mmol methylthiomethyl acetate. The solution was stirred for 3 h at −35°C for **9c** and **10** or allowed to warm slowly to −5°C for **11**. The reaction was quenched by addition of 10 cm$^3$ ice cold sat. aq. $NaHCO_3$ and evaporated to near dryness by co-evaporation with $2 \times 50$ cm$^3$ EtOH. For **9c** and **10**, the resulting solid was suspended in 200 cm$^3$ $Et_2O$, and the mixture was stirred for 1 h. After filtration the residue was extracted with 100 cm$^3$ $Et_2O$, and the combined organic fractions were evaporated under reduced pressure. For **11**, the resulting solid was triturated with $CHCl_3$, and the solvent was dried ($Na_2SO_4$) and evaporated *in vacuo*. The products were purified by silica gel column chromatography (25–30% EtOAc in petroleum ether (60–80°C)).

*5-Allyl-6-benzyl-1-ethoxymethyl-1H-pyrimidine-2,4-dione* (**9c**; $C_{17}H_{20}N_2O_3$)

Yield: 0.748 g (83%); m.p.: 142°C (EtOAc/petroleum ether (60–80°C)); $^1$H NMR (*DMSO*-$d_6$, $\delta$, 300 MHz): 1.00 (3H, t, $J = 7.1$ Hz, $CH_3$), 3.02 (2H, d, $J = 5.9$ Hz, $CH_2CH{=}CH_2$), 3.43 (2H, q, $J = 7.0$ Hz, $CH_2CH_3$), 4.04 (2H, s, $CH_2Ph$), 4.93 (2H, m, $CH{=}CH_2$), 5.14 (2H, s, $CH_2O$), 5.78 (1H, m, $CH{=}CH_2$), 7.13–7.33 (5H, m, $H_{arom}$), 11.50 (1H, s, NH) ppm; $^{13}$C NMR (*DMSO*-$d_6$, $\delta$, 75 MHz): 14.72 ($CH_3$), 28.78 ($CH_2CH{=}CH_2$), 33.07 ($CH_2Ph$), 63.72 ($CH_2CH_3$), 72.08 ($CH_2O$), 111.77 (C-5), 115.32 ($CH{=}CH_2$), 126.90–129.00 ($C_{arom}$), 135.42 ($CH{=}CH_2$), 135.90 ($C_{arom}$), 149.90 (C-2), 151.69 (C-6), 163.02 (C-4) ppm; MS (EI): $m/z = 300$ ($M^+$).

*5-Allyl-6-benzyl-1-methoxymethyl-1H-pyrimidine-2,4-dione* (**10**; $C_{16}H_{18}N_2O_3$)

Yield: 0.610 g (71%); m.p.: 136°C (EtOAc in petroleum ether (60–80°C)); $^1$H NMR (*DMSO*-$d_6$, $\delta$, 300 MHz): 3.03 (2H, d, $J = 5.3$ Hz, $CH_2CH{=}CH_2$), 3.22 (3H, s, $CH_3$), 4.03 (2H, s, $CH_2Ph$), 4.87–4.98 (4H, m, $CH_2O$, $CH{=}CH_2$), 5.65–5.78 (1H, m, $CH{=}CH_2$), 7.14–7.37 (5H, m, $H_{arom}$), 11.53 (1H, s, NH) ppm; $^{13}$C NMR (*DMSO*-$d_6$, $\delta$, 75 MHz): 28.76 ($CH_2CH{=}CH_2$), 33.02 ($CH_2Ph$), 55.95 ($CH_3$), 73.54 ($CH_2O$), 111.83 (C-5), 115.35 ($CH{=}CH_2$), 126.96, 127.52, 129.05 ($C_{arom}$), 135.37 ($CH{=}CH_2$), 135.82 ($C_{arom}$), 149.90 (C-2), 151.69 (C-6), 163.02 (C-4) ppm.

*5-Allyl-6-benzyl-1-methylthiomethyl-1H-pyrimidine-2,4-dione* (**11**; $C_{16}H_{18}N_2O_2S$)

Yield: 0.517 g (57%); m.p.: 110–112°C (EtOAc in petroleum ether (60–80°C)); $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.92 (3H, s, $CH_3$), 3.23 (2H, d, $J = 5.1$ Hz, C$H_2$CH=$CH_2$), 4.00 (2H, s, $CH_2$Ph), 4.97–5.03 (2H, m, CH=C$H_2$), 5.69 (2H, s, $CH_2O$), 5.70–5.90 (1H, m, C$H$=$CH_2$), 7.11–7.35 (5H, m, $H_{arom}$) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 20.38 ($CH_3$), 29.60 (*C*$H_2$CH=$CH_2$), 33.81 ($CH_2$Ph), 67.27 ($CH_2$S), 113.32 (C-5), 115.61 (CH=*C*$H_2$), 127.53, 129.27, 134.64 ($C_{arom}$), 134.88 (*C*H=$CH_2$), 149.20 (C-2), 152.87 (C-6), 169.97 (C-4) ppm.

*1-((2-Acetoxyethoxy)-methyl)-6-benzyl-5-(2-butenyl)-1H-pyrimidine-2,4-dione* (**12**; $C_{20}H_{24}N_2O_5$)

Compound **7b** (918 mg, 3.59 mmol) and 949 mg 2-acetoxyethyl acetoxymethyl ether (5.39 mmol) were dissolved in 10 cm$^3$ dry $CH_2Cl_2$. *BSA* (1.6 cm$^3$, 6.54 mmol) was added dropwise under $N_2$, and the solution was stirred overnight. Then the solution was cooled to 0°C, and 0.52 g $SnCl_4$ (2 mmol) were added. The mixture was allowed to warm to room temperature, stirred overnight, and then quenched with 25 cm$^3$ cold sat. aq. $NaHCO_3$. The product was extracted with 3 × 25 cm$^3$ $CHCl_3$. The combined organic fractions were dried ($Na_2SO_4$) and evaporated under reduced pressure to give a yellow gel which was purified on a silica gel chromatotron (5% MeOH/$CH_2Cl_2$).

Yield: 0.734 g (80%); white gel; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.56–1.59 (3H, m, CHC$H_3$), 2.05 (3H, s, $CH_3CO$), 3.12–3.16 (2H, m, C$H_2$CH), 3.79–3.83 (2H, m, $CH_2$C$H_2$), 4.14–4.20 (4H, m, $CH_2$Ph, C$H_2$C$H_2$), 5.19 (2H, s, $NCH_2O$), 5.40–5.45 (2H, m, CH=CH), 7.09–7.38 (5H, m, $H_{arom}$), 10.42 (1H, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 17.43 (CH*C*$H_3$), 20.51 ($CH_3CO$), 28.01 (*C*$H_2$CH), 33.16 ($CH_2$Ph), 62.97 (*C*$H_2$C$H_2$), 67.23 ($CH_2$*C*$H_2$), 72.79 ($NCH_2O$), 113.87 (C-5), 126.34, 127.07, 127.18, 127.27, 129.07, 134.76 ($C_{arom}$, CH=CH), 149.97, 152.22 (C-2, C-6), 163.55 (C-4), 170.78 (CO) ppm; MS (EI): $m/z = 372$ ($M^+$).

*6-Benzyl-5-(2-butenyl)-1-((2-hydroxyethoxy)-methyl)-1H-pyrimidine-2,4-dione* (**13**; $C_{18}H_{22}N_2O_4$)

1-((2-Acetoxyethoxy)-methyl)-6-benzyl-5-(2-butenyl)-1*H*-pyrimidine-2,4-dione (**12**, 0.565 g, 1.51 mmol) was dissolved in MeOH. NaOMe in 2 cm$^3$ MeOH (1 *M*, 2 mmol) was added, and the solution was stirred overnight at room temperature. Then the *pH* was adjusted to 4 by addition of 1 *M* HCl. After stirring for 20 min, sat. aq. $NaHCO_3$ was added. Unreacted starting material precipitated and was filtered off; the product was extracted with 3 × 50 cm$^3$ $CHCl_3$. The organic phase was dried ($Na_2SO_4$) and evaporated under reduced pressure.

Yield: 0.320 g (84%); white gel; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.57–1.62 (3H, m, CHC$H_3$), 3.10–3.15 (2H, m, $CH_2$), 3.69 (4H, s, $CH_2CH_2$), 4.13 (2H, s, $CH_2$Ph), 5.18 (2H, s, $NCH_2O$), 5.40–5.44 (2H, m, CH=CH), 7.10–7.37 (5H, m, $H_{arom}$), 8.02 (1H, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 17.71 (CH*C*$H_3$), 28.34 (*C*$H_2$CH), 33.65 ($CH_2$Ph), 61.59 ($CH_2OH$), 70.75 (O*C*$H_2$C$H_2$), 73.15 ($NCH_2O$), 114.00 (C-5), 126.60, 127.00 (CH=CH), 127.36, 129.19, 134.84 ($C_{arom}$), 149.99, 152.06 (C-2, C-6), 163.16 (C-4) ppm; MS (EI): $m/z = 330$ ($M^+$).

*Synthesis of compounds* **14a** *and* **15a**

5-Allyl-6-benzyl-1-ethoxymethyl-1*H*-pyrimidine-2,4-dione (**9c**, 1.25 mmol) and 0.235 g *MCPBA* (1.5 mmol) were dissolved in 20 cm$^3$ $CHCl_3$ and stirred at room temperature for 48 h. Then the mixture was diluted with 100 cm$^3$ $CHCl_3$ and washed with 10% aq. $NaHSO_3$, 10% aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, and $H_2O$. The organic phase was evaporated under reduced pressure. The product was purified by silica gel column chromatography.

*6-Benzyl-1-ethoxymethyl-5-oxiranylmethyl-1H-pyrimidine-2,4-dione*
(**14a**; $C_{17}H_{20}N_2O_4$)

Eluted from the silica gel column with EtOAc/petroleum ether (60–80°C); yield: 10%; m.p.: 122°C; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.16 (3H, t, $J = 7.0$ Hz, $CH_3$), 2.50 (2H, d, $J = 5.0$ Hz, Ar$CH_2$CH), 2.55 (2H, d, $J = 6.0$ Hz, $CH_2$CH), 3.10 (2H, q, $CH_2CH_3$), 3.64 (1H, m, CH), 4.22 (2H, m, $CH_2$Ph), 5.05 (2H, m, $NCH_2O$), 7.08–7.35 (5H, m, $H_{arom}$), 9.82 (1H, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 14.84 ($CH_3$), 28.28 (Ar$CH_2$CH), 33.81 ($CH_2$Ph), 46.81 ($CH_2$CH), 50.97 ($CH_2CHCH_2$), 65.06 ($CH_2CH_3$), 72.93 ($NCH_2O$), 110.64 (C-5), 127.39–129.63, 135.90 ($C_{arom}$), 151.99, 152.28 (C-2, C-6), 163.75 (C-4) ppm; MS (EI): $m/z = 316$ ($M^+$).

*4-Benzyl-3-ethoxymethyl-6-hydroxymethyl-5,6-dihydro-3H-furo[2,3-d]pyrimidin-2-one*
(**15a**; $C_{17}H_{20}N_2O_4$)

Eluted from the silica gel column with MeOH; yield: 73%; m.p.: 186°C; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.16 (3H, bs, $CH_3$), 2.98 (2H, d, $J = 6.4$ Hz, H-5), 3.56–3.74, 3.82–3.94 (4H, 2 m, $CH_2CH_3$, $CH_2OH$), 4.12 (2H, s, $CH_2$Ph), 4.98 (1H, bs, H-6), 5.28 (2H, s, $NCH_2O$), 7.04–7.40 (5H, m, $H_{arom}$) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 14.32 ($CH_3$), 25.81 (C-5), 34.88 ($CH_2$Ph), 62.48 ($CH_2OH$), 64.17 ($CH_2CH_3$), 72.83 ($NCH_2O$), 83.38 (C-6), 105.38 (C-4a), 126.88, 127.40, 128.64, 133.88 ($C_{arom}$), 151.27, 158.21 (C-2, C-4), 176.48 (C-7a) ppm; MS (EI): $m/z = 315$ ($M^+ - 1$).

*Synthesis of compounds* **14b** *and* **15b**

6-Benzyl-5-(*trans*-2-butenyl)-1-ethoxymethyl-1*H*-pyrimidine-2,4-dione (**9b**, 0.100 g, 0.32 mmol) was dissolved in 15 $cm^3$ dry $CH_2Cl_2$ and cooled to 0°C. *MCPBA* (0.100 g, 0.58 mmol) was added, and the solution was allowed to warm to room temperature. After 4 h or 48 h the mixture was diluted with $Et_2O$ and washed with 20% aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure.

*6-Benzyl-1-ethoxymethyl-5-(3-methyloxiranylmethyl)-1H-pyrimidine-2,4-dione*
(**14b**; $C_{18}H_{22}N_2O_4$)

After reaction with *MCPBA* for 4 h; yield: 45%; oil; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.17 (3H, t, $J = 7.1$ Hz, $CH_2CH_3$), 1.23 (3H, d, $J = 5.1$ Hz, $CHCH_3$), 2.48–2.55, 2.74–3.14 (4H, m, $CH_2CHCH$), 3.55–3.67 (2H, m, $CH_2CH_3$), 4.11–4.33 (2H, m, $CH_2$Ph), 4.99–5.43 (2H, m, $CH_2O$), 7.09–7.38 (5H, m, $H_{arom}$), 10.04 (1H, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 14.91 ($CH_2CH_3$), 17.32 ($CHCH_3$), 28.07 ($CH_2$CH), 33.85 ($CH_2$Ph), 54.67, 58.21 (CHCH), 65.03 ($CH_2CH_3$), 72.69 ($CH_2O$), 110.85 (C-5), 127.19, 129.12, 129.17, 134.96 ($C_{arom}$) 151.88, 152.00 (C-2, C-6), 163.65 (C-4) ppm; MS (EI): $m/z = 329$ ($M^+ - 1$).

*4-Benzyl-3-ethoxymethyl-6-(1-hydroxyethyl)-5,6-dihydro-3H-furo[2,3-d]pyrimidin-2-one*
(**15b**; $C_{18}H_{22}N_2O_4$)

Stirred with *MCPBA* for 48 h; yield: 97%; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.11–1.29 (6H, m, $CHCH_3$, $CH_2CH_3$), 2.84 (1H, dd, $J = 9.1$, 15.6 Hz, H-5), 3.07 (1H, dd, $J = 6.4$, 15.2 Hz, H-5), 3.63 (2H, q, $J = 7.0$ Hz, $CH_2CH_3$), 4.08 (1H, d, $J = 16.2$ Hz, CHHPh), 4.15 (1H, d, $J = 16.3$ Hz, CHHPh), 4.20–4.29 (1H, m, CHOH), 4.74–4.81 (1H, m, H-6), 5.28 (2H, s, $CH_2O$), 7.12–7.38 (5H, m, $H_{arom}$) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 14.95 ($CH_2CH_3$), 17.62 ($CHCH_3$), 24.34 (C-5), 35.55 ($CH_2$Ph), 65.08 (CHOH), 67.08 ($CH_2CH_3$), 73.62 ($CH_2O$), 86.85 (C-6), 105.84 (C-4a), 127.58, 127.97, 129.34, 134.34 ($C_{arom}$), 152.17 (C-4), 158.76 (C-2), 176.86 (C-7a) ppm.

*6-Benzyl-1-ethoxymethyl-5-oxiranylmethoxymethyl-1H-pyrimidine-2,4-dione*
(**14c**; $C_{18}H_{22}N_2O_5$)

5-Allyloxymethyl-6-benzyl-1-ethoxymethyl-1*H*-pyrimidine-2,4-dione (**9d**, 0.248 g, 0.75 mmol) was dissolved in 10 $cm^3$ $CH_2Cl_2$ and cooled to 0°C. *MCPBA* was added (0.311 g (50–90%), 0.9–1.6 mmol), and the solution was stirred overnight at room temperature under $N_2$. Then 20 $cm^3$ $Et_2O$ were added, and the organic phase was washed with $2 \times 20$ $cm^3$ sat. aq. $Na_2S_2O_3$, $2 \times 20$ $cm^3$ sat. aq. $NaHCO_3$, and $2 \times 2$ $cm^3$ brine, dried ($MgSO_4$), and evaporated under reduced pressure. The product **14c** was isolated after column chromatography (EtOAc:petroleum ether(60–80°C) = 1:1).

Yield: 0.157 g (60%); white solid; m.p.: = 99–102°C; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.18 (3H, t, $J = 7.0$ Hz, $CH_3$), 2.56 (1H, dd, $J = 2.7$ Hz, 5.0 Hz, CHC$H_2$), 2.74 (1H, t, $J = 4.6$ Hz, CHC$H_2$), 3.07–3.12 (1H, m, epoxide-CH), 3.45 (1H, dd, $J = 5.8$ Hz, 11.4 Hz, OC$H_2$CH), 3.61 (2H, q, $J = 7.0$ Hz, C$H_2$CH$_3$), 3.79 (1H, dd, $J = 3.2$ Hz, 11.6 Hz, OC$H_2$CH), 4.30 (2H, s, $CH_2$Ph), 4.42, 4.48 (2H, $2 \times$ d, $J = 11.2$ Hz, Ar$CH_2$O), 5.14 (2H, s, N$CH_2$O), 7.14–7.37 (5H, m, $H_{arom}$), 9.72 (1H, br s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 14.95 ($CH_3$), 33.72 ($CH_2$Ph), 44.24 (CH*C*$H_2$), 50.61 ($CH_2$*C*H), 63.44 (Ar$CH_2$O), 65.18 (O*C*$H_2$CH$_3$), 71.20 (O*C*$H_2$CH), 72.70 (N$CH_2$O), 111.50 (C-5), 127.31, 127.47, 129.16, 134.88 ($C_{arom}$), 151.76 (C-2), 155.18 (C-4), 163.18 (C-6) ppm; MS (EI): $m/z = 346$ ($M^+$).

*General procedure for the synthesis of* **16a** *and* **16b**

Compounds **9b** or **9d** (0.75 mmol) was dissolved in 15 $cm^3$ dry $CH_2Cl_2$ and cooled to −78°C. $O_3$ was bubbled through the solution until a blue colour appeared (*ca.* 2 min). Then $O_2$ was bubbled through until the blue colour disappeared. Dimethyl sulfide (0.28 g, 4.5 mmol) was then added at −78°C, and the solution was allowed to warm to room temperature and stirred overnight. Then the solvent was evaporated under reduced pressure.

*(6-Benzyl-1-ethoxymethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-acetaldehyde*
(**16a**; $C_{16}H_{18}N_2O_4$)

Purified by preparative TLC (EtOAc); yield: 53%; $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.17 (3H, t, $J = 7.5$ Hz, $CH_2$C$H_3$), 3.57 (2H, s, C$H_2$CHO), 3.62 (2H, q, $J = 6.7$ Hz, C$H_2$CH$_3$), 4.09 (2H, s, $CH_2$Ph), 5.17 (2H, s, N$CH_2$O), 7.10–7.36 (5H, m, $H_{arom}$), 9.64 (1H, s, CHO), 10.50 (1H, s, NH) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 14.81 ($CH_2$*C*H$_3$), 33.92 ($CH_2$Ph), 39.99 (*C*$H_2$CHO), 64.97 (*C*$H_2$CH$_3$), 72.81 (N$CH_2$O), 107.42 (C-5), 127.13, 127.33, 129.14, 134.13 ($C_{arom}$) 151.79, 152.57 (C-2, C-6), 163.36 (C-4), 197.53 (CHO) ppm; MS (EI): $m/z = 302$ ($M^+$).

*(6-Benzyl-1-ethoxymethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylmethoxy)-acetaldehyde*
(**16b**; $C_{17}H_{20}N_2O_5$)

Purified by silica gel column chromatography ($CH_2Cl_2$ – 50% $CH_2Cl_2$ in EtOAc); clear glace; yield: 0.114 g (46%); $^1$H NMR ($CDCl_3$, $\delta$, 300 MHz): 1.11 (3H, t, $J = 7.0$ Hz, $CH_3$), 3.54 (2H, q, $J = 7.0$ Hz, C$H_2$CH$_3$), 4.12 (2H, s, $CH_2$Ph), 4.30 (2H, s, Ar$CH_2$O), 4.42 (2H, s, OC$H_2$CHO), 5.08 (2H, s, N$CH_2$O), 7.07–7.29 (5H, m, $H_{arom}$), 9.55 (1H, s, CHO) ppm; $^{13}$C NMR ($CDCl_3$, $\delta$, 75 MHz): 14.96 ($CH_3$), 33.78 ($CH_2$Ph), 63.82 (Ar$CH_2$O), 65.26 (*C*$H_2$CH$_3$), 72.83 (N$CH_2$O), 75.95 (OC$H_2$CHO), 110.95 (C-5), 127.41, 129.23, 134.77 ($C_{arom}$), 151.62 (C-2), 155.76 (C-4), 163.21 (C-6), 199.82 (CHO) ppm; MS (FAB, peak matching): $m/z = 355.1271$ ($M + Na^+$; calcd.: 355.1270).

*Viruses and cells*

The HIV-1 strains HTLV-IIIB [17] and the NNRTI resistant strain N119 [18] were propagated in H9 cells [19] at 37°C, 5% $CO_2$ using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and

antibiotics (growth medium). The culture supernatant was filtered (0.45 nm), aliquoted, and stored at −80°C until use. Both HIV-1 strains were obtained from the NIH AIDS Research and Reference Program.

*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 compounds for six days in parallel with virus-infected and uninfected control cultures without compound added. Expression of HIV in the cultures was quantitated by the HIV-1 antigen detection assay ELISA [15] or indirectly quantified using the MTT assay [16]. Compounds mediating less than 30% reduction of HIV expression were considered without biological activity. Compounds were tested in parallel for cytotoxic effect in uninfected MT4 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 (*IC-50*) and the 50% cytotoxic concentration (*CC-50*) were determined by interpolation from the plots of percent inhibition *vs*. concentration of compound.

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