Synthesis and Anti-HIV-1 Activity of Novel 2,3-Dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones

Krzysztof Danel,[†] Erik B. Pedersen,*[,†] and Claus Nielsen[‡]

Department of Chemistry, Odense University, DK-5230 Odense M, Denmark, and Retrovirus Laboratory, Department of Virology, Statens Seruminstitut, DK-2300 Copenhagen, Denmark

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Appropriately substituted 2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones **9**−**12** and **18** were considered as annulated analogues of HEPT (1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine), and some of these compounds were also found active against HIV-1, the most active one being 2,3-dihydro-5-[(3,5-dimethylphenyl)methyl]-3-ethoxy-6-ethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**10b**). S-Alkylation of 5-alkyl-6-(arylmethyl)-2-thiouracils **1**−**4** was performed with 2-bromoacetaldehyde acetals to furnish the *S*-[bis(alkoxy)ethyl] derivatives **5**−**8** and with allyl bromide to furnish *S*-allyl derivatives **17**. The target compounds **9**−**12** were obtained by an N^1 regioselective intramolecular cyclization reaction of silylated **5**−**8** using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as the catalyst. Treatment of the *S*-allyl derivatives **17** with bromine in dry methylene chloride afforded the 3-(bromomethyl) derivatives **18**.

Reverse transcriptase (RT), being the pivot in the human immunodeficiency virus (HIV) replication,[1] is still one of the most attractive targets for the development of new antiretroviral agents.[2−4] Among the non-nucleoside inhibitors of RT, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) has been considered an interesting lead compound for the synthesis of new compounds with activity against HIV,[5,6] e.g. MKC-442 (Figure 1).[7] Unlike AZT (Zidovudine) and its congeners, their biological mechanism appears to be a noncompetitive one due to the interaction at an allosteric site of the reverse transcriptase.[8] Unfortunately, these compounds also lead to the emergence of virus-drug resistance.[9] That is why the irreversible inhibition of the reverse transcriptase would be a very attractive perspective.

Previously, we reported[6c] the synthesis and activity against HIV-1 for a series of S-DABOs derivatives which are 2-alkylthio analogues of dihydroalkoxybenzyloxopyrimidines (DABO).[10] In this paper we describe an easy and fast method for the synthesis of new thiazolo[3,2-*a*]pyrimidines, which could be considered as hybrids between S-DABOs and HEPT analogues. Although thiazolo[3,2-*a*]pyrimidines have been well studied as immunomodulators,[11] anticancer agents,[12,13] analgesics,[14,15] psychotropes,[12,16] and, more recently, as anti-inflammatory and positive inotropic agents,[17] they have not yet been explored as possible anti-HIV-1 agents.

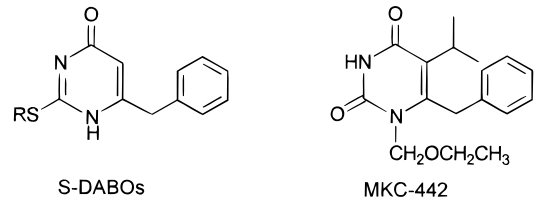
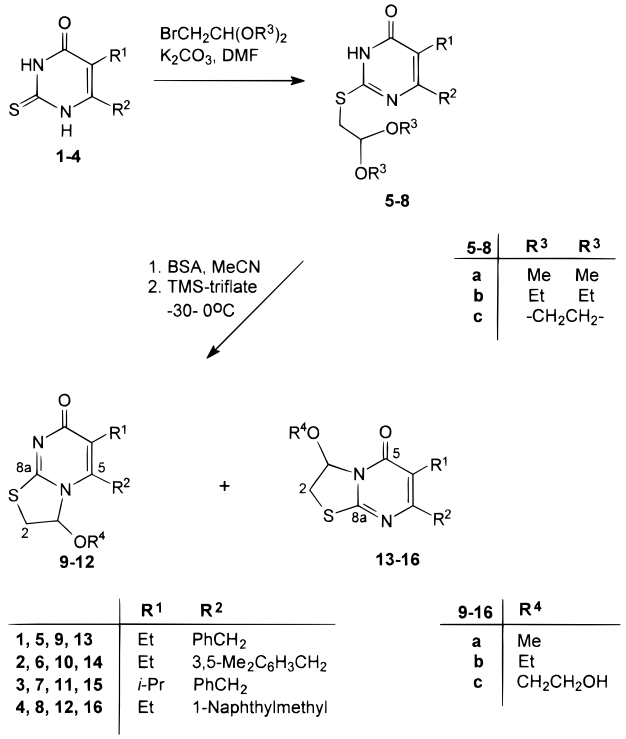


Figure 1.

Scheme 1



5-8	R^3	R^3
a	Me	Me
b	Et	Et
c	-CH_2CH_2-	

	R^1	R^2
1, 5, 9, 13	Et	$PhCH_2$
2, 6, 10, 14	Et	3,5-$Me_2C_6H_3CH_2$
3, 7, 11, 15	*i*-Pr	$PhCH_2$
4, 8, 12, 16	Et	1-Naphthylmethyl

9-16	R^4
a	Me
b	Et
c	CH_2CH_2OH

Chemistry

Our general strategy for the synthesis of nonnucleoside analogues was based on intramolecular condensation of silylated S-DABOs (Scheme 1).

The required thiouracils **1**−**4** were easily synthesized from the appropriate *β*-oxo esters by treatment with thiourea.[6] Thus the obtained thiopyrimidines **1**−**4** were nearly quantatitavely S-alkylated with the appropriate 2-bromoacetaldehyde acetals in the presence of anhydrous potassium carbonate. The products **5**−**8** could be

[†] Odense University.
[‡] Statens Seruminstitut.
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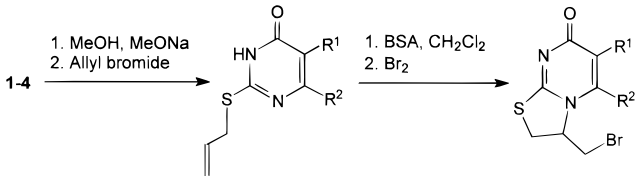
used as raw materials in subsequent reactions without further purification. The report of Bormann and Troxler[18] showed that base-catalyzed reaction of thiouracil with bromoacetaldehyde diethyl acetal gave nearly equal amounts of the S-alkylated thiouracil and its N^1 and N^3 cyclized products. We were interested in obtaining the N^1 cyclized regioisomer as the main products. Therefore, the 4-oxo group of the pyrimidines **5**−**8** was protected by treatment with *N*,*O*-bis(trimethylsilyl)-acetamide (BSA). The intramolecular cyclization was carried out by a modification of the method of Niedballa and Vorbrüggen using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as the catalyst.[19] As a result, the N^1 regioisomers were isolated as the main products in 10−50% yield whereas the N^3 regioisomers were isolated in minor yields (4−9%) after chromatographic purification. The observed regioselectivity is in agreement with the Vorbrüggen-type glycosylation of 2-thiouracil showing N^1 more nucleophilic than N^3.[20] The reactivity of **5**−**8** decreased in the following order (R^3): methyl, ethyl, and ethylene. Very low yields were sometimes obtained for R^3 = ethylene. The reaction was easily followed on TLC, and the N^1- and the N^3-alkylated products could always be identified by their R_f values ($R_f^{N-3} > R_f^{N-1}$). Thiazolo[3,2-*a*]pyrimidines **9**−**12** were obtained in a state of purity after recrystallization or chromatographic purification. Compound **12b** was easily distinguished from its corresponding regioisomer **16b** by ^{1}H nuclear Overhauser effects (NOE). Only for **12b** an NOE in 3-H (3%) could be observed on irradiation of the methylene group of the arylmethyl substituent. Also, comparison of the spectroscopic data of the new compounds with those of Bormann and Troxler[18] together with those of the HEPT[6a,b] and xanthine analogues[21] confirmed the above structures. The characteristic features one can use for identification are the NMR shifts of H-3 protons at lower fields in **13**−**16** than in **9**−**12** and the splitting of the CH_2 protons in the arylmethyl group into two doublets in case of the N^1 regioisomers due to creation of a chiral center in the proximity of these protons.

It is well proved that the sterical factors[5,22,23] might influence the activity of HEPT analogues. It could be explanable in terms of better hydrophobic interactions of the aromatic system at the modulatory site of the reverse transcriptase. The presence of a good leaving group such as bromine in close proximity to the amino acid residues (Tyr181-OH)[23] would also be a very attractive goal to achieve with possible alkylation at that place. That could disturb the catalytic site of reverse transcriptase more drastically, eventually leading to irreversible inhibition of the enzyme. The synthesis of alkylating compounds in the thiazolo[3,2-*a*]pyrimidines series was achieved in two-step reaction as delineated in Scheme 2. The exocyclic bromomethyl group in **18** is believed to have the same lability of bromine in alkylation reactions as the one found for 2-(bromomethyl)-1,3-dioxalanes.[24]

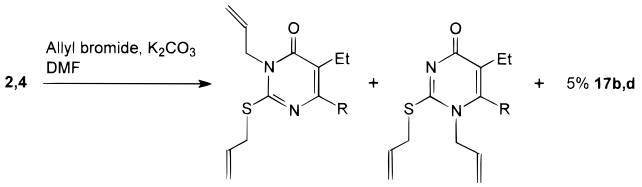
Alkylation of **2**, **4** with allyl bromide (1:1) in the presence of K_2CO_3 in DMF gave a mixture of N^3,S- and S,N^1-bis(alkylated) products, **19b**,**d** and **20b**,**d** (Scheme 3). The mono-S-alkylated derivative **17b**,**d** was observed in a low yield (5%). The structure of bis-

Scheme 2



17,18	R^1	R^2
a	Et	$PhCH_2$
b	Et	3,5-$Me_2C_6H_3CH_2$
c	*i*-Pr	$PhCH_2$
d	Et	1-Naphthylmethyl

Scheme 3



19, 20	R
a	3,5-$Me_2C_6H_3CH_2$
b	1-Naphthylmethyl

(alkylated) products (**19b**,**d** and **20b**,**d**) was assigned on the basis of data of similar compounds.[25]

When anhydrous methanol and sodium methoxide were used, only the S-alkylated product was obtained. We noticed that usage of excess allyl bromide led to better yields. Thus, when allyl bromide was used in the ratio 5:1 for **3**, we obtained **17c** nearly quantatitavely. The ratio 1:1 led to 55% yield of the S-alkylated derivative. The crude 2-allylthiouracils **17a**−**d** were treated with bromine in methylene chloride after silylation with BSA to avoid the N-3 regioisomer formation. Thus electrophilic attack of secondary carbocation at the N^1 provided the corresponding thiazolo[3,2-*a*]pyrimidines in moderate yields after column purification. All of the synthesized bromine analogues were properly substituted at N^1, which can be easily seen on the basis of the splitting of the CH_2Ar in the ^{1}H NMR spectrum. The N^3 products were not observed.

Results of the Anti-HIV Assay and Discussion

Table 1 shows those of the newly synthesized compounds which showed antiviral activity against HIV-1 in MT-4 cells. All other compounds were either inactive against HIV-1 at 100 μM (**9c**, **11a**,**c**, **12a**,**c**, **13b**,**c**, **14c**, **18a**, and **19b**) or toxic to the MT-4 cells at 100 μM (**5a**−**c**, **7b**,**c**, **8b**,**c**, **12b**, **14a**,**b**, **15a**−**c**, **16a**,**c**, **18c**,**d**, and **20a**,**b**) or at 10 μM (**19a**), but without showing any antiviral activity against HIV-1 at subtoxic concentrations.

The target compounds **9**−**12** share some structural features with compounds belonging to the HEPT class and are considered as their annulated analogues. As in the HEPT series, the two methyl groups at the 3- and 5-positions of the benzyl substituent play an important role in the biological activity.[26,27] Thus the 3,5-dimethylbenzyl derivatives **10a**−**c** showed higher

Table 1. Antiviral Activity against HIV-1 in MT-4 Cells

compd	ED_{50},[a] μM	CD_{50},[b] μM	SI[c]
6b	21	>100	>5
6c	3	37	12
7a	4	32	8
8a	32	>100	>3
9a	36	>100	>3
9b	46	>100	>2
10a	3	>100	>33
10b	0.7	>100	>140
10c	19	>100	>5
11b	100	>100	>1
17a	1.5	>100	>67
17b	2	68	34
17c	1.5	>100	>67
18b	2.8	46	16
AZT	0.04	52	1300
MKC-442	0.005	141	28000

[a] Effective dose of compound, achieving 50% inhibition of HIV-1 antigen production in MT-4 cultures. [b] Cytotoxic dose of compound, required to reduce the proliferation of normal uninfected MT-4 cells by 50%. [c] Selectivity index: ratio CD_{50}/ED_{50}. ED_{50} and CD_{50} are expressed as the mean values of three independent determinations.

activity than their benzyl (**9**) or 1-naphthylmethyl (**12**) counterparts, the latter being devoid of any activity at 100 μM. Compounds **10a**−**c** are only moderately active when compared with 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442), which is the HEPT analogue chosen as the candidate for clinical trials with AIDS patients.[28] It should be noticed that compounds **10a**−**c** are lacking the 3-NH of the pyrimidine which is a prerequisite for the hydrogen bond to the carbonyl of Lys101 of RT in RT-HEPT complexes.[23] However, hydrogen bonding of the nonnucleoside inhibitor in the hydrophobic pocket of RT could still be possible if N-3 protonation of **10** is assumed. Compound **18b**, showing similar antiviral activity, is also a 2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one like compounds **9**−**12**, the only difference being replacement the 3-alkoxy with bromomethyl.

The activity of compounds **6b**,**c**, **7a**, **8a**, and **17a**−**c** against HIV-1 is to be expected since these compounds are merely new S-DABO derivatives. Their activity against HIV-1 is of comparable magnitude to those previously reported for S-DABOs.[10]

Experimental Section

NMR spectra were recorded on a Bruker AC-250 FT NMR spectrometer at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C with TMS as an internal standard. Mass spectra were recorded on a Varian MAT 311A spectrometer. The progress of the reaction was monitored by TLC analytical silica gel plates 60 F_{254}. Merck silica gel (0.040−0.063 mm) was used for column chromatography and Merck silica gel (0.063−0.200 mm) for preparative thin-layer chromatography (PTLC). Extracts were dried over Na_2SO_4, and the solvents were removed under reduced pressure. Solvents were reagent grade and, when necessary, purified and dried by standards methods. Elemental analyses were performed by the Microanalytical Laboratory at the Research Institute for Pharmacy and Biochemistry in Prague, Czech Republic.

General Procedure for the Preparation 5−8. To a mixture of thiouracil[6] (**1**−**4**) (4 mmol) and anhydrous potassium carbonate (4 mmol) in DMF (10 mL) was added the appropriate 2-bromoacetaldehyde acetal (4.5 mmol). The mixture was stirred at 65 °C for 3 h. The reaction was monitored by TLC with MeOH/$CHCl_3$. After cooling to room temperature, the mixture was filtered and the solid residue washed with a small amount of DMF. The solvent was removed in vacuo and the oily residue coevaporated with toluene (2 × 10 mL). EtOAc/petroleum ether (bp 60−80 °C) (1:1) was added. A precipitate could result (K_2CO_3) and was filtered off. The filtrate was evaporated to dryness, and the residue started to crystallize on standing. Thus obtained crude products **5**−**8** were used without further purification for the next step.

6-Benzyl-2-[(2,2-dimethoxyethyl)thio]-5-ethylpyrimidin-4(1*H*)-one (5a): prepared from **1**;[6a] mp 115−117 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.4 Hz, CH_3), 2.43 (q, 2H, J = 7.4 Hz, CH_2), 3.19 (d, 2H, J = 5.3 Hz, SCH_2), 3.23 (s, 6H, 2 × CH_3), 3.83 (s, 2H, CH_2Ph), 4.40 (t, 1H, J = 5.3 Hz, CH), 7.14−7.26 (m, 5H, H_{arom}), 8.82 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 18.8 (CH_2), 32.5 (CH_2Ph), 40.2 (SCH_2), 53.9 (OCH_3), 103.4 (CH), 121.0 (C-5), 126.0, 128.1, 128.8, 139.0 (Ph), 159.8 (C-6), 161.2 (C-4), 168.9 (C-2). Anal. ($C_{17}H_{22}N_2O_3S\cdot0.5H_2O$) C, H, N.

6-Benzyl-2-[(2,2-diethoxyethyl)thio]-5-ethylpyrimidin-4(1*H*)-one (5b): prepared from **1**; mp 95−96 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.2 Hz, CH_3), 1.10 (t, 6H, J = 7.0 Hz, CH_3), 2.45 (q, 2H, J = 7.2 Hz, CH_2), 3.19 (d, 2H, J = 5.2 Hz, SCH_2), 3.38−3.57 (m, 4H, 2 × CH_2), 3.83 (s, 2H, CH_2Ph), 4.53 (t, 1H, J = 5.2 Hz, CH), 7.14−7.25 (m, 5H, H_{arom}), 9.62 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.4 (CH_3), 15.1 (CH_3), 18.9 (CH_2), 33.6 (CH_2Ph), 40.2 (SCH_2), 62.5 (OCH_2), 101.8 (CH), 120.7 (C-5), 125.9, 128.1, 128.9, 139.1 (Ph), 161.0 (C-6), 161.2 (C-4), 169.6 (C-2). Anal. ($C_{19}H_{26}N_2O_3S$) C, H, N.

6-Benzyl-2-[(1,3-dioxolan-2-yl)thio]-5-ethylpyrimidin-4(1*H*)-one (5c): prepared from **1**; mp 127−130 °C; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, J = 7.3 Hz, CH_3), 2.35 (q, 2H, J = 7.3 Hz, CH_2), 3.15 (d, 2H, J = 4.3 Hz, SCH_2), 3.60−3.78 (m, 6H, 2 × CH_2, CH_2Ph), 4.90 (t, 1H, J = 4.4 Hz, CH), 7.10−7.39 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 18.9 (CH_2), 33.3 (CH_2Ph), 40.2 (SCH_2), 65.0 (OCH_2), 102.7 (CH), 120.0 (C-5), 125.8, 128.0, 129.0, 139.3 (Ph), 161.3 (C-6), 161.4 (C-4), 171.2 (C-2). Anal. ($C_{17}H_{20}N_2O_3S\cdot0.5H_2O$) C, H, N.

2-[(2,2-Dimethoxyethyl)thio]-6-[(3,5-dimethylphenyl)-methyl]-5-ethylpyrimidin-4(1*H*)-one (6a): prepared from **2**; mp 132−133 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.4 Hz, CH_3), 2.27 (s, 6H, CH_3), 2.45 (q, 2H, J = 7.4 Hz, CH_2), 3.31 (d, 2H, J = 5.5 Hz, SCH_2), 3.32 (s, 6H, 2 × CH_3), 3.83 (s, 2H, CH_2Ph), 4.48 (t, 1H, J = 5.5 Hz, CH), 6.83 (s, 3H, H_{arom}), 12.78 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.2 (CH_3), 18.7 (CH_2), 21.2 (2 × CH_3), 32.5 (CH_2Ph), 40.2 (SCH_2), 54.0 (OCH_2), 103.1 (CH), 122.5 (C-5), 126.7, 128.0, 137.8, 138.0 (Ar), 156.1 (C-6), 161.6 (C-4), 165.1 (C-2). Anal. ($C_{19}H_{26}N_2O_3S\cdot0.25H_2O$) C, H, N.

2-[(2,2-Diethoxyethyl)thio]-6-[(3,5-dimethylphenyl)-methyl]-5-ethylpyrimidin-4(1*H*)-one (6b): prepared from **2**; mp 119−121 °C; ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.4 Hz, CH_3), 1.19 (t, 6H, J = 7.0 Hz, CH_3), 2.27 (s, 6H, CH_3), 2.58 (q, 2H, J = 7.4 Hz, CH_2), 3.29 (d, 2H, J = 5.4 Hz, SCH_2), 3.42−3.67 (m, 4H, 2 × CH_2), 3.82 (s, 2H, CH_2Ph), 4.61 (t, 1H, J = 5.5 Hz, CH), 6.83 (s, 3H, H_{arom}), 12.71 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.1 (CH_3), 15.1 (CH_3), 18.7 (CH_2), 21.2 (2 × CH_3), 33.6 (CH_2Ph), 40.1 (SCH_2), 62.6 (OCH_2), 101.3 (CH), 122.6 (C-5), 126.5, 127.9, 137.8, 138.0 (Ar), 156.3 (C-6), 161.6 (C-4), 165.0 (C-2). Anal. ($C_{21}H_{30}N_2O_3S$) C, H, N.

6-[(3,5-Dimethylphenyl)methyl]-2-[(1,3-dioxolan-2-yl)-thio]-5-ethylpyrimidin-4(1*H*)-one (6c): prepared from **2**; mp 154−156 °C; purified by column chromatography (0−50% EtOAc/petroleum ether (bp 60−80 °C)); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H, J = 7.4 Hz, CH_3), 2.27 (s, 6H, CH_3), 2.57 (q, 2H, J = 7.4 Hz, CH_2), 3.38 (d, 2H, J = 4.3 Hz, SCH_2), 3.81 (s, 2H, CH_2-Ph), 3.83−4.02 (m, 4H, 2 × CH_2), 5.11 (t, 1H, J = 4.4 Hz, CH), 6.83 (s, 1H, H_{arom}), 6.86 (s, 2H, H_{arom}), 12.39 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.1 (CH_3), 18.8 (CH_2), 21.2 (2 × CH_3), 33.6 (CH_2Ph), 40.2 (SCH_2), 65.3 (OCH_2), 102.1 (CH), 122.5 (C-5), 126.8, 128.0, 137.8, 138.0 (Ar), 155.8 (C-6), 161.6 (C-4), 164.8 (C-2).

6-Benzyl-2-[(2,2-dimethoxyethyl)thio]-5-isopropylpyrimidin-4(1*H*)-one (7a): prepared from **3**;[6b] mp 106−107 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 6H, J = 6.9 Hz, CH_3), 3.05 (heptet, 1H, J = 6.9 Hz, CH), 3.19 (d, 2H, J = 5.1 Hz, SCH_2), 3.22 (s, 6H, 2 × CH_3), 3.89 (s, 2H, CH_2Ph), 4.40 (t, 1H, J = 4.4 Hz,

CH), 7.14−7.26 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 20.1 (CH_3), 27.2 (CH), 32.4 (CH_2Ph), 40.8 (SCH_2), 54.0 (OCH_2), 103.5 (CH), 123.7 (C-5), 125.9, 128.1, 128.6, 139.3 (Ph), 160.2 (C-6), 161.0 (C-4), 169.3 (C-2). Anal. ($C_{18}H_{24}N_2O_3S$) C, H, N.

6-Benzyl-2-[(2,2-diethoxyethyl)thio]-5-isopropylpyrimidin-4(1*H*)-one (7b): prepared from **3**; as an oil; ^1H NMR ($CDCl_3$) δ 1.19 (t, 6H, J = 7.1 Hz, CH_3), 1.27 (d, 6H, J = 6.9 Hz, CH_3), 3.10 (heptet, 1H, J = 6.9 Hz, CH), 3.28 (d, 2H, J = 5.4 Hz, SCH_2), 3.45−3.65 (m, 4H, 2 × CH_2), 3.93 (s, 2H, CH_2-Ph), 4.58 (t, 1H, J = 5.5 Hz, CH), 7.18−7.30 (m, 5H, H_{arom}), 12.64 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 19.6 (CH_3), 27.9 (CH), 33.5 (CH_2Ph), 40.8 (SCH_2), 62.7 (OCH_2), 101.4 (CH), 125.3 (C-5), 126.2, 128.3, 128.5, 138.4 (Ph), 156.4 (C-6), 160.9 (C-4), 164.2 (C-2). Anal. ($C_{20}H_{28}N_2O_3S$) C, H, N.

6-Benzyl-2-[(1,3-dioxolan-2-yl)thio]-5-isopropylpyrimidin-4(1*H*)-one (7c): prepared from **3**; precipitated from the crude mixture with $CHCl_3$/petroleum ether (bp 60−80 °C); ^1H NMR (DMSO-d_6) δ 1.11 (d, 6H, J = 6.8 Hz, CH_3), 2.93 (heptet, 1H, J = 6.9 Hz, CH), 3.13 (d, 2H, J = 4.8 Hz, SCH_2), 3.69 (s, 2H, CH_2Ph), 3.74−3.93 (m, 4H, 2 × CH_2), 4.96 (t, 1H, J = 4.7 Hz, CH), 7.14−7.26 (m, 5H, H_{arom}); ^{13}C NMR (DMSO-d_6) δ 20.1 (CH_3), 27.2 (CH), 32.5 (CH_2Ph), 40.9 (SCH_2), 64.3 (OCH_2), 103.2 (CH), 120.5 (C-5), 125.4, 127.9, 128.3, 140.6 (Ph), 158.1 (C-6), 163.1 (C-4), 171.9 (C-2). Anal. ($C_{18}H_{22}N_2O_3S\cdot0.25H_2O$) C, H, N.

2-[(2,2-Dimethoxyethyl)thio]-5-ethyl-6-(1-naphthylmethyl)pyrimidin-4(1*H*)-one (8a): prepared from **4**;[6c] ^1H NMR ($CDCl_3$) δ 1.11 (t, 3H, J = 7.4 Hz, CH_3), 2.63 (q, 2H, J = 7.4 Hz, CH_2), 3.06 (d, 2H, J = 5.5 Hz, SCH_2), 3.14 (s, 6H, 2 × CH_3), 4.24 (t, 1H, J = 5.4 Hz, CH), 4.35 (s, 2H, $CH_2C_{10}H_7$), 7.11−8.08 (m, 7H, H_{arom}), 12.81 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 18.8 (CH_2), 32.3 ($CH_2C_{10}H_7$), 37.4 (SCH_2), 53.9 (OCH_3), 102.7 (CH), 123.0 (C-5), 123.8, 125.3, 125.5, 126.0, 126.5, 127.1, 128.6, 132.2, 133.7, 134.3 (Ar), 156.3 (C-6), 161.3 (C-4), 165.0 (C-2).

2-[(2,2-Diethoxyethyl)thio]-5-ethyl-6-(1-naphthylmethyl)pyrimidin-4(1*H*)-one (8b): prepared from **4**; mp 128−130 °C; ^1H NMR (DMSO-d_6) δ 0.92−1.02 (m, 9H, 3 × CH_3), 2.51 (q, 2H, J = 7.4 Hz, CH_2), 2.99 (d, 2H, J = 5.4 Hz, SCH_2), 3.15−3.35 (m, 4H, 2 × CH_2), 4.34 (s, 2H, $CH_2C_{10}H_7$), 4.34 (t, 1H, J = 4.4 Hz, CH), 7.21−8.16 (m, 7H, H_{arom}), 12.57 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 12.9 (CH_3), 14.9 (CH_3), 18.2 (CH_2), 32.4 ($CH_2C_{10}H_7$), 36.6 (SCH_2), 61.5 (OCH_3), 100.3 (CH), 123.9 (C-5), 125.3, 125.5, 125.8, 126.2, 126.7, 128.3, 131.8, 132.2, 134.6 (Ar), 158.7 (C-6), 161.0 (C-4), 168.3 (C-2). Anal. ($C_{23}H_{28}N_2O_3S$) C, H, N.

2-[(1,3-Dioxolan-2-yl)thio]-5-ethyl-6-(1-naphthylmethyl)pyrimidin-4(1*H*)-one (8c): prepared from **4**; mp 155−157 °C; ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.4 Hz, CH_3), 2.62 (q, 2H, J = 7.4 Hz, CH_2), 3.12 (d, 2H, J = 4.3.4 Hz, SCH_2), 3.70−3.89 (m, 4H, 2 × CH_2), 4.35 (s, 2H, $CH_2C_{10}H_7$), 4.79 (t, 1H, J = 4.4 Hz, CH), 7.21−8.07 (m, 7H, H_{arom}), 12.41 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 18.9 (CH_2), 33.4 ($CH_2C_{10}H_7$), 37.5 (SCH_2), 65.2 (OCH_3), 101.7 (CH), 123.1 (C-5), 124.0, 125.4, 125.5, 126.0, 126.8, 127.1, 128.6, 132.3, 133.8, 134.3 (Ar), 155.8 (C-6), 161.2 (C-4), 164.7 (C-2). Anal. ($C_{21}H_{22}N_2O_3S\cdot0.5H_2O$) C, H, N.

General Procedure for 9−12 and 13−16. The crude **5**−**8** (4 mmol) was dissolved in dry MeCN (10 mL) under Ar. *N*,*O*-Bis(trimethylsilyl)acetamide (0.89 g, 4.4 mmol, 1.08 mL) was added. The mixture was cooled to −40 °C, and TMS triflate (0.89 g, 4 mmol, 0.77 mL) was added dropwise. The mixture was allowed to warm to room temperature slowly (typically overnight). Cold saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with saturated aqueous NaCl, dried, and evaporated in vacuo. Compounds **9**−**12** were in some cases isolated by crystallization, and isomeric compounds **13**−**16** in the mother liquor were purified by PTLC. In all other cases the typical procedure was to isolate **9**−**12** by column chromatography and to purify the fraction of **13**−**16** from the column chromatography by subsequent PTLC. The yields are overall yields based on compounds **1**−**4**.

5-Benzyl-2,3-dihydro-6-ethyl-3-methoxy-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (9a): oil which started to crystallize; column chromatography (0−2% MeOH/CH_2Cl_2); R_f = 0.16 (5% MeOH/CH_2Cl_2); yield 551 mg (46%); mp 152−154 °C; ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.52−2.68 (m, 2H, CH_2CH_3), 3.21 (d, 1H, J = 12.8 Hz, 2-H), 3.33 (s, 3H, OCH_3), 3.38 (dd, 1H, J = 12.8, 5.9 Hz, 2-H), 3.95 (d, 1H, J = 16.9 Hz, 5-C*H*H), 4.27 (d, 1H, J = 16.9 Hz, 5-CH*H*), 5.45 (d, 1H, J = 5.5 Hz, 3-H), 7.12−7.39 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 19.6 (CH_2), 29.6 (5-CH_2), 33.4 (C-2), 53.2 (OCH_3), 90.1 (C-3), 123.1, 127.4, 129.3, 135.0 (C-6, Ph), 144.4 (C-5), 166.5 (C-7), 169.2 (C-8_a). Anal. Calcd ($C_{16}H_{18}N_2O_2S$): C, 63.55; H, 6.00; N, 9.26. Found: C, 63.04; H, 6.01; N, 8.90.

5-Benzyl-2,3-dihydro-3-ethoxy-6-ethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (9b): column chromatography (0−2% MeOH/CH_2Cl_2); R_f = 0.21 (5% MeOH/CH_2Cl_2); yield 447 mg (35%); mp 167−170 °C; ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.19 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.49−2.60 (m, 2H, CH_2CH_3), 3.19 (d, 1H, J = 12.6 Hz, 2-H), 3.38 (dd, 1H, J = 12.7, 5.9 Hz, 2-H), 3.51−3.57 (m, 2H, OCH_2CH_3), 4.00 (d, 1H, J = 16.9 Hz, 5-C*H*H), 4.26 (d, 1H, J = 16.9 Hz, 5-CH*H*), 5.60 (d, 1H, J = 5.6 Hz, 3-H), 7.11−7.39 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.2, 14.8 (2 × CH_3), 19.6 (CH_2), 30.3 (5-CH_2), 33.4 (C-2), 61.9 (OCH_2), 89.4 (C-3), 123.1, 127.3, 129.2, 135.0 (C-6, Ph), 144.4 (C-5), 166.5 (C-7), 169.3 (C-8_a). Anal. ($C_{17}H_{20}N_2O_2S$) C, H, N.

5-Benzyl-2,3-dihydro-6-ethyl-3-(2-hydroxyethoxy)-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (9c): R_f = 0.09 (8% MeOH/CH_2Cl_2); yield 127 mg (10%); mp 140−141 °C (EtOH/EtOAc,); ^1H NMR (DMSO-d_6) δ 0.86 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.34 (q, 2H, J = 7.3 Hz, CH_2CH_3), 3.38−3.51 (m, 5H, 2-H and OCH_2-CH_2), 3.58 (dd, 1H, J = 12.9, 5.0 Hz, 2-H), 4.09 (d, 1H, J = 17.2 Hz, 5-C*H*H), 4.21 (d, 1H, J = 17.1 Hz, 5-CH*H*), 4.81 (t, 1H, J = 5.1 Hz, OH), 5.81 (d, 1H, J = 4.6 Hz, 3-H), 7.19−7.39 (m, 5H, H_{arom}); ^{13}C NMR (DMSO-d_6) δ 12.7 (CH_3), 19.0 (CH_2), 30.3 (5-CH_2), 33.0 (C-2), 59.7, 68.6 (OCH_2CH_2), 90.2 (C-3), 121.4, 126.7, 127.5, 128.7, 136.0 (C-6, Ph), 145.3 (C-5), 166.3 (C-7), 168.2 (C-8_a). Anal. ($C_{17}H_{20}N_2O_3S$) C, H, N.

2,3-Dihydro-5-[(3,5-dimethylphenyl)methyl]-6-ethyl-3-methoxy-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (10a): precipitated with EtOAc/petroleum ether (bp 60−80 °C) from the crude mixture; R_f = 0.21 (8% MeOH/CH_2Cl_2); yield 662 mg (50%); mp 151−153 °C; ^1H NMR ($CDCl_3$) δ 1.11 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.29 (s, 6H, 2 × CH_3), 2.44−2.67 (m, 2H, CH_2CH_3), 3.20 (d, 1H, J = 12.9 Hz, 2-H), 3.35 (s, 3H, OCH_3), 3.38 (dd, 1H, J = 12.9, 6.0 Hz, 2-H), 3.85 (d, 1H, J = 16.8 Hz, 5-C*H*H), 4.19 (d, 1H, J = 16.7 Hz, 5-CH*H*), 5.56 (d, 1H, J = 5.8 Hz, 3-H), 6.71 (s, 2H, H_{arom}), 6.91 (s, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 19.6 (CH_2), 21.2 (2 × CH_3), 29.6 (5-CH_2), 33.2 (C-2), 53.1 (OCH_2), 90.0 (C-3), 123.0, 125.1, 129.1, 134.8, 139.0 (C-6, Ar), 144.7 (C-5), 166.5 (C-7), 169.3 (C-8_a). Anal. ($C_{18}H_{22}N_2O_2S\cdot0.25H_2O$) C, H, N.

2,3-Dihydro-5-[(3,5-dimethylphenyl)methyl]-3-ethoxy-6-ethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (10b): precipitated with EtOAc/petroleum ether (bp 60−80 °C); R_f = 0.24 (8% MeOH/CH_2Cl_2); yield 403 mg (29%); mp 155−157 °C; ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.22 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.29 (s, 6H, 2 × CH_3), 2.34−2.65 (m, 2H, CH_2CH_3), 3.18 (d, 1H, J = 12.7 Hz, 2-H), 3.38 (dd, 1H, J = 12.7, 5.9 Hz, 2-H), 3.45−3.62 (m, 2H, OCH_2), 3.86 (d, 1H, J = 16.8 Hz, 5-C*H*H), 4.18 (d, 1H, J = 16.8 Hz, 5-CH*H*), 5.60 (d, 1H, J = 5.6 Hz, 3-H), 6.71 (s, 2H, H_{arom}), 6.91 (s, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.9 (2 × CH_3), 19.6 (CH_2), 21.2 (2 × CH_3), 30.3 (5-CH_2), 33.2 (C-2), 61.8 (OCH_2), 89.2 (C-3), 123.0, 125.1, 129.1, 134.8, 139.0 (C-6, Ar), 144.7 (C-5), 166.5 (C-7), 169.4 (C-8_a). Anal. ($C_{19}H_{24}N_2O_2S$) C, H, N.

2,3-Dihydro-5-[(3,5-dimethylphenyl)methyl]-6-ethyl-3-(2-hydroxyethoxy)-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (10c): R_f = 0.12 (8% MeOH/CH_2Cl_2); yield 350 mg (27%); mp 203−205 °C (EtOH/H_2O); ^1H NMR (DMSO-d_6) δ 0.89 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.24 (s, 6H, 2 × CH_3), 2.28−2.49 (m, 2H, CH_2CH_3), 3.44−3.49 (m, 5H, 2-H and OCH_2CH_2), 3.58 (dd, 1H, J = 12.9, 5.1 Hz, 2-H), 3.99 (d, 1H, J = 17.1 Hz, 5-C*H*H), 4.12 (d, 1H, J = 17.0 Hz, 5-CH*H*), 4.82 (t, 1H, J = 5.1 Hz, OH),

5.78 (d, 1H, J = 4.7 Hz, 3-H), 6.79 (s, 2H, H_{arom}), 6.88 (s, 1H, H_{arom}); ^{13}C NMR (DMSO-d_6) δ 12.7 (CH_3), 19.0 (CH_2), 20.8 (2 × CH_3), 30.3 (5-CH_2), 32.8 (C-2), 59.7, 68.7 (OCH_2CH_2), 90.2 (C-3), 121.4, 125.1, 128.2, 135.8, 137.8 (C-6, Ar), 145.3 (C-5), 166.3 (C-7), 168.2 (C-8_a). Anal. ($C_{19}H_{24}N_2O_3S$) C, H, N.

5-Benzyl-2,3-dihydro-6-isopropyl-3-methoxy-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (11a): column chromatography (0−2% MeOH/CH_2Cl_2); R_f = 0.29 (5% MeOH/CH_2Cl_2); yield 382 mg (45%) as a white foam; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3H, J = 7.0 Hz, CHMe_2), 1.33 (d, 3H, J = 7.0 Hz, CHMe_2), 3.01 (heptet, 1H, J = 7.0 Hz, CHMe$_2$), 3.21 (d, 1H, J = 12.8 Hz, 2-H), 3.33 (s, 3H, OCH_3), 3.38 (dd, 1H, J = 12.8, 5.9 Hz, 2-H), 3.93 (d, 1H, J = 17.2 Hz, 5-CHH), 4.32 (d, 1H, J = 17.2 Hz, 5-CHH), 5.56 (d, 1H, J = 5.6 Hz, 3-H), 7.11−7.40 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 19.7, 20.0 (2 × CH_3), 27.9 (CH), 29.7 (5-CH_2), 33.3 (C-2), 53.3 (OCH_3), 90.2 (3-C), 125.7, 127.3, 129.3, 135.1 (C-6, Ph), 143.9 (C-5), 166.0 (C-7), 168.4 (C-8_a). Anal. Calcd ($C_{17}H_{20}N_2O_2S$·0.75H_2O): C, 61.89; H, 6.57; N, 8.49. Found: C, 61.90; H, 6.16; N, 8.12.

5-Benzyl-2,3-dihydro-3-ethoxy-6-isopropyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (11b): an oil which started to crystallize; column chromatography (0−2% MeOH/CH_2Cl_2); R_f = 0.23 (5% MeOH/CH_2Cl_2); yield 357 mg (40%); mp 140−142 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.31 (d, 3H, J = 7.0 Hz, CHMe_2), 1.33 (d, 3H, J = 7.0 Hz, CHMe_2), 3.00 (heptet, 1H, J = 7.0 Hz, CHMe$_2$), 3.18 (d, 1H, J = 12.6 Hz, 2-H), 3.38 (dd, 1H, J = 12.6, 5.7 Hz, 2-H), 3.46−3.57 (m, 2H, OCH_2), 3.94 (d, 1H, J = 17.2 Hz, 5-CHH), 4.32 (d, 1H, J = 17.2 Hz, 5-CHH), 5.60 (d, 1H, J = 5.6 Hz, 3-H), 7.11−7.40 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 14.9 (CH_3), 19.7, 20.2 (2 × CH_3), 27.9 (CH), 30.4 (5-CH_2), 33.3 (C-2), 62.0 (OCH_2), 89.5 (3-C), 125.6, 127.3, 129.3, 135.2 (C-6, Ph), 143.8 (C-5), 165.9 (C-7), 168.5 (C-8_a). Anal. ($C_{18}H_{22}N_2O_2S$·0.75H_2O) C, H, N.

5-Benzyl-2,3-dihydro-3-(2-hydroxyethoxy)-6-isopropyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (11c): R_f = 0.07 (8% MeOH/CH_2Cl_2); yield 126 mg (14%); mp 158−160 °C; (EtOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 1.09 (d, 3H, J = 6.8 Hz, CHMe_2), 1.33 (d, 3H, J = 6.8 Hz, CHMe_2), 2.84 (heptet, 1H, J = 6.9 Hz, CHMe$_2$), 3.41−3.54 (m, 5H, 2-H and OCH_2CH_2), 3.58 (dd, 1H, J = 12.7, 5.0 Hz, 2-H), 4.08 (d, 1H, J = 17.4 Hz, 5-CHH), 4.32 (d, 1H, J = 17.3 Hz, 5-CHH), 5.86 (d, 1H, J = 4.7 Hz, 3-H), 7.18−7.39 (m, 5H, H_{arom}); ^{13}C NMR (DMSO-d_6) δ 19.1, 19.4 (2 × CH_3), 27.3 (CH), 30.3 (5-CH_2), 33.0 (C-2), 59.7, 68.7 (OCH_2CH_2), 90.4 (C-3), 123.7, 126.5, 127.5, 128.7, 136.2 (C-6, Ph), 145.0 (C-5), 165.7 (C-7), 167.5 (C-8_a). Anal. ($C_{18}H_{22}N_2O_3S$) C, H, N.

2,3-Dihydro-6-ethyl-3-methoxy-5-(1-naphthylmethyl)-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (12a): PTLC (2% MeOH/$CHCl_3$); yield 256 mg (38%); mp 174−178 °C ($CHCl_3$/toluene); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.47−2.59 (m, 2H, CH_2CH_3), 3.13 (d, 1H, J = 12.9 Hz, 2-H), 3.26 (s, 3H, OCH_3), 3.34 (dd, 1H, J = 12.9, 5.9 Hz, 2-H), 4.45 (d, 1H, J = 17.4 Hz, 5-CHH), 4.55 (d, 1H, J = 17.4 Hz, 5-CHH), 5.32 (d, 1H, J = 5.7 Hz, 3-H), 7.02−8.10 (m, 7H, $H_{naphthyl}$); ^{13}C NMR ($CDCl_3$) δ 13.4 (CH_3), 19.6 (CH_2), 29.7 (5-CH_2), 30.0 (C-2), 53.5 (OCH_3), 90.4 (C-3), 122.1−133.9 (C-6, Ar), 144.4 (C-5), 166.5 (C-7), 169.2 (C-8_a). Anal. ($C_{20}H_{20}N_2O_2S$) C, H, N.

2,3-Dihydro-3-ethoxy-6-ethyl-5-(1-naphthylmethyl)-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (12b): PTLC (3% MeOH/CH_2Cl_2); R_f = 0.24 (5% MeOH/CH_2Cl_2); yield 151 mg (21%) as a yellow foam; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.14 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.41−2.56 (m, 2H, CH_2CH_3), 3.14 (d, 1H, J = 12.8 Hz, 2-H), 3.26−3.49 (m, 3H, 2-H, OCH_2), 4.46 (d, 1H, J = 17.5 Hz, 5-CHH), 4.54 (d, 1H, J = 17.5 Hz, 5-CHH), 5.45 (d, 1H, J = 5.5 Hz, 3-H), 7.02−8.10 (m, 7H, $H_{naphthyl}$); ^{13}C NMR ($CDCl_3$) δ 13.1, 14.7 (2 × CH_3), 19.4 (CH_2), 30.0 (5-CH_2), 30.3 (SCH_2), 62.3 (OCH_2), 89.7 (NCH), 121.9−133.5 (C-6, Ar), 144.5 (C-5), 166.5 (C-7), 169.2 (C-8_a). Anal. ($C_{21}H_{22}N_2O_2S$·0.25H_2O) C, H, N.

2,3-Dihydro-6-ethyl-3-(2-hydroxyethoxy)-5-(1-naphthylmethyl)-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (12c): precipitated by adding EtOAc to the crude mixture; R_f = 0.14 (8% MeOH/CH_2Cl_2); yield 230 mg (30%); mp 226−228 °C; ^{1}H NMR (DMSO-d_6) δ 0.90 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.30 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.27−3.43 (m, 5H, OCH_2CH_2, 2-H), 3.56 (dd, 1H, J = 12.9, 5.2 Hz, 2-H), 4.56 (s, 2H, 5-CH_2), 4.67 (br s, 1H, OH), 5.65 (d, 1H, J = 5.1 Hz, 3-H), 7.05−8.25 (m, 7H, $H_{naphthyl}$); ^{13}C NMR (DMSO-d_6) δ 12.5 (CH_3), 18.8 (CH_2), 30.0 (5-CH_2), 30.3 (C-2), 59.5, 68.6 (OCH_2CH_2OH), 90.3 (C-3), 122.0−133.1 (C-6, Ar), 144.8 (C-5), 166.1 (C-7), 167.9 (C-8_a). Anal. ($C_{21}H_{22}N_2O_3S$·0.25H_2O) C, H, N.

7-Benzyl-2,3-dihydro-6-ethyl-3-methoxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (13a): PTLC (2% MeOH/CH_2Cl_2); R_f = 0.58 (5% MeOH/CH_2Cl_2); yield 47 mg (4%) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.56 (q, 2H, J = 7.4 Hz, CH_2CH_3), 3.23 (d, 1H, J = 12.2 Hz, 2-H), 3.57 (dd, 1H, J = 12.0, 5.5 Hz, 2-H), 3.57 (s, 3H, OCH_3), 3.88 (s, 2H, 7-CH_2), 6.13 (d, 1H, J = 5.2 Hz, 3-H), 7.19−7.31 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 19.1 (CH_2), 33.6 (7-CH_2), 40.3 (C-2), 58.4 (OCH_3), 89.1 (C-3), 122.1, 126.4, 128.4, 128.7, 137.8 (C-6, Ar), 160.3, 161.2, 161.8 (C-5, C-7, C-8_a); EI MS m/z 302 (M^+).

7-Benzyl-2,3-dihydro-3-ethoxy-6-ethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (13b): PTLC (2% MeOH/CH_2Cl_2); R_f = 0.57 (5% MeOH/CH_2Cl_2); yield 96 mg (8%) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.21 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.56 (q, 2H, J = 7.4 Hz, CH_2CH$_3$), 3.19 (d, 1H, J = 12.1 Hz, 2-H), 3.55 (dd, 1H, J = 12.0, 5.5 Hz, 2-H), 3.79−3.85 (m, 2H, OCH_2CH$_3$), 3.87 (s, 2H, 7-CH_2), 6.18 (d, 1H, J = 5.4 Hz, 3-H), 7.16−7.27 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 12.8, 15.0 (2 × CH_3), 19.0 (CH_2), 34.0 (7-CH_2), 40.2 (C-2), 66.6 (OCH_2), 87.8 (C-3), 121.9, 126.3, 128.2, 128.5, 137.7 (C-6, Ph), 160.2, 161.0, 161.5 (C-5, C-7, C-8_a); EI MS m/z 316 (M^+).

7-Benzyl-2,3-dihydro-6-ethyl-3-(2-hydroxyethoxy)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (13c): PTLC (3% MeOH/CH_2Cl_2); R_f = 0.26 (8% MeOH/CH_2Cl_2); yield 38 mg (4%); ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.55 (q, 2H, J = 5.6 Hz, CH_2CH$_3$), 3.25 (d, 1H, J = 12.3 Hz, 2-H), 3.54 (dd, 1H, J = 12.3, 5.5 Hz, 2-H), 3.71−3.86 (m, 5H, OCH_2CH_2OH), 3.87 (s, 2H, 7-CH_2), 6.26 (d, 1H, J = 5.4 Hz, 3-H), 7.18−7.30 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3), 18.9 (CH_2), 33.3 (7-CH_2), 40.2 (C-2), 61.7, 71.7 (OCH_2CH_2OH), 88.7 (C-3), 121.9, 126.3, 128.3, 128.5, 137.6 (C-6, Ph), 160.2, 161.5, 161.7 (C-5, C-7, C-8_a); EI MS m/z 332 (M^+).

2,3-Dihydro-7-[(3,5-dimethylphenyl)methyl]-6-ethyl-3-methoxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (14a): column chromatography (0−2% MeOH/CH_2Cl_2); R_f = 0.68 (8% MeOH/CH_2Cl_2); yield 94 mg (7%); ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.26 (s, 6H, 2 × CH_3), 2.58 (q, 2H, J = 7.5 Hz, CH_2CH$_3$), 3.22 (d, 1H, J = 12.2 Hz, 2-H), 3.52−3.60 (m, 4H, 2-H, OCH_3), 3.80 (s, 2H, 7-CH_2), 6.12 (d, 1H, J = 5.3 Hz, 3-H), 6.84 (s, 1H, H_{arom}), 6.85 (s, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 19.1 (CH_2), 21.2 (2 × CH_3), 33.6 (7-CH_2), 40.2 (C-2), 58.3 (OCH_3), 89.2 (C-3), 122.0, 126.4, 128.1, 137.5, 137.8 (C-6, Ph), 160.1, 161.3, 161.7 (C-5, C-7, C-8_a); EI MS m/z 330 (M^+).

2,3-Dihydro-7-[(3,5-dimethylphenyl)methyl]-3-ethoxy-6-ethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (14b): column chromatography (0−2% MeOH/CH_2Cl_2); R_f = 0.73 (8% MeOH/CH_2Cl_2); yield 90 mg (7%); ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.21 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.27 (s, 6H, 2 × CH_3), 2.58 (q, 2H, J = 7.4 Hz, CH_2CH$_3$), 3.20 (d, 1H, J = 12.1 Hz, 2-H), 3.56 (dd, 1H, J = 12.1, 5.4 Hz, 2-H), 3.79 (s, 2H, 7-CH_2), 3.82−3.86 (m, 2H, OCH_2), 6.19 (d, 1H, J = 5.3 Hz, 3-H), 6.83 (s, 1H, H_{arom}), 6.86 (s, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 12.8, 15.0 (2 × CH_3), 19.0 (CH_2), 21.0 (2 × CH_3), 34.0 (7-CH_2), 40.1 (C-2), 66.6 (OCH_2), 87.8 (C-3), 121.8, 126.3, 128.0, 137.5, 137.7 (C-6, Ph), 160.1, 161.2, 161.6 (C-5, C-7, C-8_a); EI MS m/z 344 (M^+).

2,3-Dihydro-7-[(3,5-dimethylphenyl)methyl]-6-ethyl-3-(2-hydroxyethoxy)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (14c): column chromatography (0−2% MeOH/CH_2Cl_2); R_f = 0.33 (8% MeOH/CH_2Cl_2); yield 74 mg (6%); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.27 (s, 6H, 2 × CH_3), 2.52−2.62 (m, 2H, CH_2CH$_3$), 3.26 (d, 1H, J = 12.3 Hz, 2-H), 3.56 (dd, 1H, J = 12.3, 5.5 Hz, 2-H), 3.73−3.87 (m, 5H, OCH_2-CH_2OH), 3.80 (s, 2H, 7-CH_2), 6.29 (d, 1H, J = 5.3 Hz, 3-H), 6.85 (s, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 12.8 (CH_3), 19.0 (CH_2),

21.0 (2 × CH_3), 33.3 (7-CH_2), 40.1 (C-2), 61.8, 71.5 (OCH_2CH_2), 88.6 (C-3), 121.9, 126.3, 128.0, 137.3, 137.8 (C-6, Ph), 160.1, 161.8, 161.9 (C-5, C-7, C-8_a); EI MS *m*/*z* 360 (M^+).

7-Benzyl-2,3-dihydro-6-isopropyl-3-methoxy-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (15a): PTLC (2% MeOH/CH_2Cl_2); R_f = 0.59 (5% MeOH/CH_2Cl_2); yield 50 mg (6%); ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, *J* = 7.0 Hz, CH*Me*$_2$), 1.26 (d, 3H, *J* = 7.0 Hz, CH*Me*$_2$), 3.08 (heptet, 1H, *J* = 7.0 Hz, C*H*Me$_2$), 3.22 (d, 1H, *J* = 12.2 Hz, 2-H), 3.56 (dd, 1H, *J* = 12.0, 5.5 Hz, 2-H), 3.56 (s, 3H, OCH_3), 3.91 (s, 2H, 7-CH_2), 6.12 (d, 1H, *J* = 5.2 Hz, 3-H), 7.16−7.31 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) 19.5, 19.6 (2 × CH_3), 28.1 (CH), 33.6 (7-CH_2), 41.0 (C-2), 58.3 (OCH_3), 89.0 (C-3), 124.8, 126.3, 128.4, 128.5, 138.1 (C-6, Ph), 160.3, 160.8, 160.8 (C-5, C-7, C-8_a); EI MS *m*/*z* 316 (M^+).

7-Benzyl-2,3-dihydro-3-ethoxy-6-isopropyl-5*H*-thiazolo-[3,2-*a*]pyrimidin-5-one (15b): PTLC (2% MeOH/CH_2Cl_2); R_f = 0.72 (5% MeOH/CH_2Cl_2); yield 48 mg (5%); ^{1}H NMR ($CDCl_3$) δ 1.19−1.27 (m, 9H, CH*Me*$_2$ and CH_2CH_3), 3.08 (heptet, 1H, *J* = 7.0 Hz, C*H*Me$_2$), 3.21 (d, 1H, *J* = 12.1 Hz, 2-H), 3.58 (dd, 1H, *J* = 12.0, 5.5 Hz, 2-H), 3.78−3.90 (m, 2H, OCH_2CH_3), 3.91 (s, 2H, 7-CH_2), 6.19 (d, 1H, *J* = 5.1 Hz, 3-H), 7.16−7.31 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3), 19.5, 19.6 (2 × CH_3), 28.1 (CH), 34.8 (7-CH_2), 41.0 (C-2), 66.8 (OCH_2), 87.8 (C-3), 124.7, 126.3, 128.4, 128.5, 138.1 (C-6, Ph), 160.3, 160.7, 160.8 (C-5, C-7, C-8_a); EI MS *m*/*z* 330 (M^+).

7-Benzyl-2,3-dihydro-3-(2-hydroxyethoxy)-6-isopropyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (15c): PTLC (4% MeOH/CH_2Cl_2); R_f = 0.30 (8% MeOH/CH_2Cl_2); yield 38 mg (4%); ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 3H, *J* = 6.9 Hz, CH*Me*$_2$), 1.25 (d, 3H, *J* = 6.9 Hz, CH*Me*$_2$), 3.09 (heptet, 1H, *J* = 6.9 Hz, C*H*Me$_2$), 3.27 (d, 1H, *J* = 12.3 Hz, 2-H), 3.57 (dd, 1H, *J* = 12.2, 5.5 Hz, 2-H), 3.74−3.89 (m, 5H, OCH_2CH_2OH), 3.92 (s, 2H, 7-CH_2), 6.28 (d, 1H, *J* = 5.4 Hz, 3-H), 7.16−7.31 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 19.4, 19.5 (2 × CH_3), 28.0 (CH), 33.2 (7-CH_2), 40.1 (C-2), 61.8, 71.6 (OCH_2CH_2OH), 88.5 (C-3), 124.7, 126.3, 128.3, 128.4, 137.8 (C-6, Ph), 160.1, 161.0, 161.3 (C-5, C-7, C-8_a); EI MS *m*/*z* 346 (M^+).

2,3-Dihydro-6-ethyl-3-methoxy-7-(1-naphthylmethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (16a): PTLC (2% MeOH/$CHCl_3$); R_f = 0.40 (2% MeOH/$CHCl_3$); yield 60 mg (9%); ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.55 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 3.18 (d, 1H, *J* = 12.3 Hz, 2-H), 3.49−3.58 (m, 4H, OCH_3, 2-H), 4.33 (s, 2H, 7-CH_2), 6.13 (d, 1H, *J* = 5.4 Hz, 3-H), 7.14−8.10 (m, 7H, $H_{naphthyl}$); ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 19.2 (CH_2), 33.6 (7-CH_2), 37.5 (C-2), 58.4 (OCH_3), 89.3 (C-3), 123.1−133.7 (C-6, Ar), 160.4, 161.0, 161.7 (C-5, C-7, C-8_a); EI MS *m*/*z* 352 (M^+).

2,3-Dihydro-3-ethoxy-6-ethyl-7-(1-naphthylmethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (16b): PTLC (3% MeOH/CH_2Cl_2); R_f = 0.72 (5% MeOH/CH_2Cl_2); yield 56 mg (8%); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 1.23 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 2.53 (q, 2H, *J* = 7.4 Hz, CH_2CH_3), 3.21 (d, 1H, *J* = 12.0 Hz, 2-H), 3.56 (dd, 1H, *J* = 12.1, 5.4 Hz, 2-H), 3.80−3.93 (m, 2H, OCH_2CH_3), 4.33 (s, 2H, 7-CH_2), 6.22 (d, 1H, *J* = 5.4 Hz, 3-H), 7.14−8.11 (m, 7H, $H_{naphthyl}$); ^{13}C NMR ($CDCl_3$) δ 12.9, 15.2 (2 × CH_3), 19.2 (CH_2), 34.2 (7-CH_2), 37.5 (C-2), 62.3 (OCH_2), 88.0 (C-3), 123.1−133.7 (C-6, Ar), 160.5, 161.0, 161.7 (C-5, C-7, C-8_a); EI MS *m*/*z* 366 (M^+).

2,3-Dihydro-6-ethyl-3-(2-hydroxyethoxy)-7-(1-naphthylmethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (16c): PTLC (50% EtOAc/petroleum ether (60−80 °C)); R_f = 0.42 (8% MeOH/CH_2Cl_2); yield 50 mg (7%); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 2.46−2.62 (m, 2H, CH_2CH_3), 3.25 (d, 1H, *J* = 12.4 Hz, 2-H), 3.54 (dd, 1H, *J* = 12.3, 5.5 Hz, 2-H), 3.62−3.92 (m, 5H, OCH_2CH_2OH), 4.33 (s, 2H, 7-CH_2), 6.30 (d, 1H, *J* = 5.3 Hz, 3-H), 7.13−8.09 (m, 7H, $H_{naphthyl}$); ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3), 19.1 (CH_2), 33.3 (7-CH_2), 37.5 (C-2), 61.9, 71.7 (OCH_2CH_2OH), 88.8 (C-3), 123.0−133.7 (C-6, Ar), 160.4, 161.6, 161.8 (C-5, C-7, C-8_a); EI MS *m*/*z* 382 (M^+).

General Procedure for Preparation 17a−d. Compound **1**−**4** (2 mmol) was dissolved in anhydrous methanol (6 mL), and MeONa (118 mg, 2.2 mmol) was added followed by addition of allyl bromide (4.4 mmol). A white precipitate could occur. After completion of the reaction according to TLC analysis, water was added (10 mL). The precipitate was filtered off, dried, and recrystallized from EtOAc/petroleum ether (bp 60−80 °C) (**17a**,**c**). In the case of **17b** and **17d** the mixture was extracted with Et_2O.

2-(Allylthio)-6-benzyl-5-ethylpyrimidin-4(3*H*)-one (17a): R_f = 0.40 (30% EtOAc/petroleum ether (bp 60−80 °C); yield 314 mg (55%); mp 136−138 °C (EtOAc/petroleum ether (bp 60−80 °C); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 2.59 (q, 2H, *J* = 7.4 Hz, CH_2CH_3), 3.74 (d, 2H, *J* = 7.0 Hz, SC*H*$_2$), 3.91 (s, 2H, 6-CH_2), 5.03 (dd, 1H, *J* = 10.1, 1.3 Hz, CH=C*H*$_2$), 5.18 (dd, 1H, *J* = 17.0, 1.3 Hz, CH=C*H*$_2$), 5.81 (ddt, 1H, *J* = 17.0, 10.1, 7.0 Hz, C*H*=CH$_2$), 7.19−7.28 (m, 5H, H_{arom}), 12.65 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.1 (CH_3), 18.7 (CH_2), 33.2 (6-CH_2), 40.4 (SCH_2), 118.3 (CH=*C*H$_2$), 122.4 (C-5), 126. 4, 128.3, 129.0, 132.9 (Ph), 138.3 (*C*H=CH$_2$), 156.0 (C-6), 161.7 (C-4), 165.2 (C-2). Anal. ($C_{16}H_{18}N_2OS$) C, H, N.

2-(Allylthio)-6-[(3,5-dimethylphenyl)methyl]-5-ethylpyrimidin-4(3*H*)-one (17b): column chromatography (0−10% EtOAc/petroleum ether (bp 60−80 °C); R_f = 0.15 (20% EtOAc/petroleum ether (bp 60−80 °C); yield 319 mg (51%); mp 146−149 °C; ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 2.27 (s, 6H, 2 × CH_3), 2.59 (q, 2H, *J* = 7.4 Hz, CH_2CH_3), 3.76 (d, 2H, *J* = 6.9 Hz, SC*H*$_2$), 3.83 (s, 2H, 6-CH_2), 5.05 (dd, 1H, *J* = 10.0, 1.0 Hz, CH=C*H*$_2$), 5.17 (dd, 1H, *J* = 17.0, 1.3 Hz, CH=C*H*$_2$), 5.83 (ddt, 1H, *J* = 16.9, 10.0, 6.9 Hz, C*H*=CH$_2$), 6.84 (s, 1H, H_{arom}), 6.86 (s, 2H, H_{arom}), 12.60 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.2 (CH_3), 18.8 (CH_2), 21.2 (2 × CH_3), 33.2 (6-CH_2), 40.3 (SCH_2), 118.2 (CH=*C*H$_2$), 122.3 (C-5), 126.8, 128.0, 133.0, 137.8 (Ph), 138.1 (*C*H=CH$_2$), 156.0 (C-6), 161.8 (C-4), 165.2 (C-2).

2-(Allylthio)-6-benzyl-5-isopropylpyrimidin-4(3*H*)-one (17c): R_f = 0.49 (30% EtOAc/petroleum ether (bp 60−80 °C); yield 593 mg (99%); mp 123−125 °C (EtOAc/petroleum ether (bp 60−80 °C); ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 6H, *J* = 6.9 Hz, CH*Me*), 3.09 (heptet, 1H, *J* = 6.9 Hz, C*H*Me$_2$), 3.75 (d, 2H, *J* = 6.9 Hz, SC*H*$_2$), 3.94 (s, 2H, 6-CH_2), 5.05 (dd, 1H, *J* = 10.0, 0.9 Hz, CH=C*H*$_2$), 5.18 (dd, 1H, *J* = 16.9, 1.3 Hz, CH=C*H*$_2$), 5.83 (ddt, 1H, *J* = 16.9, 10.0, 6.9 Hz, C*H*=CH$_2$), 7.16−7.30 (m, 5H, H_{arom}), 12.81 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 19.6 (2 × CH_3), 27.9 (CH), 33.0 (6-CH_2), 40.9 (SCH_2), 118.1 (CH=*C*H$_2$), 125.0 (C-5), 126.2, 128.3, 128.7, 132.9 (Ph), 138.5 (*C*H=CH$_2$), 156.0 (C-6), 161.2 (C-4), 164.6 (C-2). Anal. Calcd ($C_{17}H_{20}N_2OS\cdot0.25H_2O$): C, 66.96; H, 6.61; N, 9.18. Found: C, 66.82; H, 6.79; N, 8.72.

2-(Allylthio)-5-ethyl-6-(1-naphthylmethyl)pyrimidin-4(3*H*)-one (17d): column chromatography (0−10% EtOAc/petroleum ether (bp 60−80 °C)); yield 337 mg (50%); mp 162−165 °C; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 2.64 (q, 2H, *J* = 7.4 Hz, CH_2CH_3), 3.43 (d, 2H, *J* = 6.9 Hz, SC*H*$_2$), 4.37 (s, 2H, 6-CH_2), 4.84 (dd, 1H, *J* = 10.0, 1.0 Hz, CH=C*H*$_2$), 4.91 (dd, 1H, *J* = 17.0, 1.3 Hz, CH=C*H*$_2$), 5.51 (ddt, 1H, *J* = 17.0, 10.0, 6.9 Hz, C*H*=CH$_2$), 7.23−8.08 (m, 7H, $H_{naphthyl}$), 12.65 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 18.8 (CH_2), 33.0 (6-CH_2), 37.5 (SCH_2), 117.9 (CH=*C*H$_2$), 122.7−133.8 (C-5, Ar), 134.4 (*C*H=CH$_2$), 156.0 (C-6), 161.5 (C-4), 165.1 (C-2).

Procedure for Preparation of 18a−d. Compound **17** (0.78 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL). To the clear solution was added equimolar amount of *N*,*O*-bis(trimethylsilyl)acetamide (160 mg, 0.20 mL) followed by dropwise addition of dry bromine (250 mg, 2 mmol) dissolved in CH_2Cl_2 (5 mL). After completion of the reaction according to TLC analysis and evaporation of the solvent, the oily residue was chromatographed on a silica gel column with 0.5−1% MeOH/CH_3Cl to afford product **18**.

5-Benzyl-3-(bromomethyl)-2,3-dihydro-6-ethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (18a): R_f = 0.25 (5% MeOH/CH_2Cl_2); yield 210 mg (73%); mp 78−80 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 2.52−2.63 (m, 2H, CH_2CH_3), 3.11 (m, 1H, C*H*HBr), 3.34 (d, 1H, *J* = 11.9 Hz, 2-H), 3.46 (m, 1H, 2-H), 3.64 (t, 1H, *J* = 10.7 Hz, CH*H*Br), 3.85 (d, 1H, *J* = 16.8 Hz, 5-C*H*H), 4.23 (d, 1H, *J* = 16.8 Hz, 5-CH*H*), 4.64−4.72 (m, 1H, 3-H), 7.14−7.43 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 19.8 (CH_2), 28.2 (*C*H$_2$Br), 30.4, 34.7 (5-

CH_2, C-2), 63.9 (C-3), 123.6 (C-6), 127.4, 127.8, 129.5, 134.3 (Ph), 143.9 (C-5), 165.1, 169.0 (C-7, C-8a).

3-(Bromomethyl)-2,3-dihydro-5-[(3,5-dimethylphenyl)methyl]-6-ethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (18b): R_f = 0.30 (5% MeOH/CH_2Cl_2); yield 180 mg (59%) as a foam; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.31 (s, 6H, 2 × CH_3), 2.52−2.65 (m, 2H, CH_2CH_3), 3.11 (m, 1H, C*H*HBr), 3.35 (d, 1H, J = 11.9 Hz, 2-H), 3.47 (m, 1H, 2-H), 3.59 (t, 1H, J = 10.6 Hz, CH*H*Br), 3.83 (d, 1H, J = 16.6 Hz, 5-C*H*H), 4.06 (d, 1H, J = 16.7 Hz, 5-CH*H*), 4.68−4.75 (m, 1H, 3-H), 6.74 (m, 2H, H_{arom}), 6.95 (s, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 19.9 (CH_2), 21.2 (2 × CH_3), 28.2 (CH_2Br), 30.4, 34.6 (5-CH_2, C-2), 63.8 (C-3), 123.4 (C-6), 125.2, 129.5, 134.1 139.3 (Ph), 144.3 (C-5), 165.1, 169.2 (C-7, C-8a); EI MS *m*/*z* 392 (M^+).

5-Benzyl-3-(bromomethyl)-2,3-dihydro-6-isopropyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (18c): R_f = 0.24 (5% MeOH/CH_2Cl_2); yield 222 mg (38%) as a white foam; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3H, J = 6.9 Hz, CH*Me*), 1.36 (d, 3H, J = 6.9 Hz, CH*Me*), 3.00 (heptet, 1H, J = 6.9 Hz, C*H*Me$_2$), 3.18 (m, 1H, C*H*HBr), 3.34 (d, 1H, J = 11.9 Hz, 2-H), 3.47 (m, 1H, 2-H), 3.65 (t, 1H, J = 10.6 Hz, CH*H*Br), 3.83 (d, 1H, J = 17.1 Hz, 5-C*H*H), 4.32 (d, 1H, J = 17.1 Hz, 5-CH*H*), 4.70−4.77 (m, 1H, 3-H), 7.14−7.44 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 19.4, 20.2 (2 × CH_3), 28.1 (CH), 28.4 (CH_2Br), 30.4, 34.5 (5-CH_2, C-2), 63.9 (C-3), 126.1 (C-6), 127.3, 127.7, 129.4, 134.4 (Ph), 143.4 (C-5), 164.6, 168.2 (C-7, C-8a).

3-(Bromomethyl)-2,3-dihydro-6-ethyl-5-(1-naphthylmethyl)-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (18d): yield 56 mg (20%); mp >275 °C dec (EtOH/EtOAc); ^{1}H NMR (DMSO-d_6) δ 0.91 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.31−2.49 (m, 2H, CH_2-CH_3), 3.50 (d, 1H, J = 12.1 Hz, 2-H), 3.73−3.85 (m, 3H, 2-H and CH_2Br), 4.56 (d, 1H, J = 18.0 Hz, 5-C*H*H), 4.74 (d, 1H, J = 18.1 Hz, 5-CH*H*), 5.03 (m, 1H, 3-H), 7.14−8.00 (m, 7H, $H_{naphthyl}$); ^{13}C NMR (DMSO-d_6) δ 12.5 (CH_3), 19.2 (CH_2), 31.3, 31.5, 31.7 (CH_2Br, 5-CH_2, C-2), 64.1 (C-3), 123.3−133.4 (C-6, Ar), 147.4 (C-5), 165.6, 167.0 (C-7, C-8a).

Preparation of Bis(alkylated) Derivatives 19a,b and 20a,b. Two millimoles of **2** or **4** was dissolved in DMF (2 mL). To the solution anhydrous was added K_2CO_3 (276 mg, 2 mmol) followed by allyl bromide (242 mg, 0.17 mL, 2 mmol). The mixture was stirred overnight. The mixture was filtered, the residue was washed with a small amount of DMF, and the combined organic fractions were evaporated to dryness. Column chromatography with 4% EtOAc/petroleum ether (bp 60−80 °C) afforded two fractions.

3-Allyl-2-(allylthio)-6-[(3,5-dimethylphenyl)methyl]-5-ethylpyrimidin-4(3*H*)-one (19a): R_f = 0.30 (15% EtOAc/petroleum ether (bp 60−80 °C); yield 358 mg (51%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.4 Hz, CH_3), 2.27 (s, 6H, CH_3), 2.60 (q, 2H, J = 7.4 Hz, CH_2), 3.74 (d, 2H, J = 7.0 Hz, SCH_2), 3.79 (s, 2H, CH_2Ph), 4.61 (d, 2H, J = 5.7 Hz, NCH_2), 5.04−5.28 (m, 4H, CH=CH_2), 5.75−5.94 (m, 2H, C*H*=CH_2), 6.84 (s, 1H, H_{phenyl}), 6.88 (s, 2H, H_{phenyl}); ^{13}C NMR ($CDCl_3$) δ 13.1 (CH_3), 19.4 (CH_2), 21.2 (2 × CH_3), 34.8 (CH_2), 40.0 (SCH_2), 46.5 (NCH_2), 118.2 (CH=CH_2), 118.7 (CH=CH_2), 121.3 (C-5), 126.9, 127.9 (Ar), 130.6 (*C*H=CH_2), 132.8 (*C*H=CH_2), 137.7, 138.1 (Ar), 156.6 (C-6), 158.6 (C-4), 162.4 (C-2); EI MS *m*/*z* 353 (M^+). Anal. Calcd ($C_{21}H_{26}N_2OS$): C, 71.15; H, 7.39; N, 7.90. Found: C, 71.55; H, 7.77; N, 7.38.

3-Allyl-2-(allylthio)-5-ethyl-6-(1-naphthylmethyl)pyrimidin-4(3*H*)-one (19b): R_f = 0.34 (20% EtOAc/petroleum ether (bp 60−80 °C)); yield 356 mg (47%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, J = 7.4 Hz, CH_3), 2.66 (q, 2H, J = 7.4 Hz, CH_2), 3.30 (d, 2H, J = 6.9 Hz, SCH_2), 4.33 (s, 2H, $CH_2C_{10}H_7$), 4.59 (dd, 2H, J = 5.7, 1.4 Hz, NCH_2), 4.80−4.94 (m, 2H, CH=CH_2), 5.18−5.32 (m, 2H, CH=CH_2), 5.38−5.48 (m, 1H, C*H*=CH_2), 5.78−5.93 (m, 1H, C*H*=CH_2), 7.23−8.05 (m, 7H, $H_{naphthyl}$); ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3), 19.4 (CH_2), 34.3 (CH_2), 37.2 (SCH_2), 46.5 (NCH_2), 117.9 (CH=CH_2), 118.7 (CH=CH_2), 121.7 (C-5), 124.2, 125.3 (Ar), 125.4, 125.8, 127.0, 127.1, 128.6 (Ar), 130.5 (*C*H=CH_2), 132.5 (*C*H=CH_2), 133.7, 134.5 (Ar), 156.8 (C-6), 158.3 (C-4), 162.3 (C-2); EI MS *m*/*z* 376 (M^+). Anal. ($C_{23}H_{24}N_2OS$) C, H, N.

1-Allyl-2-(allylthio)-6-[(3,5-dimethylphenyl)methyl]-5-ethylpyrimidin-4(1*H*)-one (20a): R_f = 0.64 (15% EtOAc/petroleum ether (bp 60−80 °C)); yield 263 mg (37%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, J = 7.4 Hz, CH_3), 2.25 (s, 6H, 2 × CH_3), 2.58 (q, 2H, J = 7.4 Hz, CH_2), 3.77 (dd, 2H, J = 7.9, 1.1 Hz, SCH_2), 3.94 (s, 2H, CH_2Ph), 4.87 (dt, 2H, J = 6.9, 1.5 Hz, NCH_2), 5.06 (ddd, 1H, J = 10.3, 1.4, 0.7 Hz, CH=CH_2), 5.20 (m, 1H, CH=CH_2), 5.24 (m, 1H, CH=CH_2), 5.35 (m, 1H, CH=CH_2), 5.90−6.11 (m, 2H, C*H*=CH_2), 6.81 (s, 1H, H_{phenyl}), 6.84 (s, 2H, H_{phenyl}); ^{13}C NMR ($CDCl_3$) δ 13.2 (CH_3), 18.2 (CH_2), 21.2 (2 × CH_3), 33.7 (CH_2), 40.3 (SCH_2), 66.9 (NCH_2), 116.7 (C-5), 117.0 (CH=*C*H_2), 117.4 (CH=*C*H_2), 126.6, 127.9 (Ar), 132.8 (*C*H=CH_2), 134.4 (*C*H=CH_2), 137.7, 138.2 (Ar), 166.1 (C-6), 166.3 (C-4), 167.0 (C-2); EI MS *m*/*z* 354 (M^+). Anal. Calcd ($C_{21}H_{26}N_2OS$): C, 71.15; H, 7.39; N, 7.90. Found: C, 71.19; H, 7.60; N, 7.43.

1-Allyl-2-(allylthio)-5-ethyl-6-(1-naphthylmethyl)pyrimidin-4(1*H*)-one (20b): R_f = 0.60 (20% EtOAc/petroleum ether (bp 60−80 °C)); yield 272 mg (36%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, J = 7.4 Hz, CH_3), 2.56 (q, 2H, J = 7.4 Hz, CH_2), 3.58 (d, 2H, J = 6.8 Hz, SCH_2), 4.47 (s, 2H, $CH_2C_{10}H_7$), 4.87 (dd, 2H, J = 6.3, 1.4 Hz, NCH_2), 4.95 (m, 1H, CH=CH_2), 5.12 (m, 1H, CH=CH_2), 5.25 (m, 1H, CH=CH_2), 5.36 (m, 1H, CH=CH_2), 5.71−5.87 (m, 1H, C*H*=CH_2), 5.99−6.12 (m, 1H, C*H*=CH_2), 7.01−8.13 (m, 7H, $H_{naphthyl}$); ^{13}C NMR ($CDCl_3$) δ 13.1 (CH_3), 18.3 (CH_2), 33.6 (CH_2), 37.6 (SCH_2), 67.0 (NCH_2), 116.9 (C-5), 117.3 (CH=*C*H_2), 117.5 (CH=*C*H_2), 123.9, 125.3, 125.5, 125.9, 126.4, 127.1, 128.6 (Ar), 132.2 (*C*H=CH_2), 132.8 (*C*H=CH_2), 133.7, 134.2, 134.5 (Ar), 165.6 (C-6), 166.5 (C-4), 167.0 (C-2); EI MS *m*/*z* 376 (M^+). Anal. ($C_{23}H_{24}N_2OS$) C, H, N.

Virus and Cells. The HIV-1 strain HTLV−IIIB[29] was propagated in H9 cells[30] 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 HIV-1 using MT-4 cells as target cells. For screening studies, MT-4 cells were incubated with virus (0.005 MOI) for 2 h, washed, and thereafter added in a proportion of 1:10 to uninfected cells, which had been preincubated in growth medium containing the test compound for 2 h. Cultures were maintained with the test compound for 6 days in parallel with virus-infected control cultures without compound added. Expression of HIV in the culture medium was quantitated by HIV-1 antigen detection ELISA.[31] Compounds mediating less than 30% reduction of antigen expression were considered without biological activity. Compounds mediating a reduction of 30% or more were examined for cytotoxic effect using concentration-dependent inhibition of MT-4 cell proliferation as measure of cytotoxicity using the MTT assay as previously described.[32] A 30% inhibition of cell growth relative to control cultures was considered significant.

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