Nonnucleoside HIV-1 Reverse-Transcriptase Inhibitors, Part 5.[1] Synthesis and Anti-HIV-1 Activity of Novel 6-Naphthylthio HEPT Analogues

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As part of a series of studies to discover new HIV reverse-transcriptase inhibitors, various novel 6α- and 6β-naphthylthio 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio) thymine (HEPT) derivatives were synthesized, and *in vitro* anti-HIV-1 activity was evaluated. The results revealed that most of 6α-naphthylthio HEPT derivatives (7a—w) showed good activity [for 7e, IC_{50} value of 0.048 μM and selectivity index (SI) value of 735; for 7h, IC_{50} value of 0.057 μM and SI value of 579; for 7k, IC_{50} value of 0.063 μM and SI value of 565], 6β-naphthylthio HEPT derivatives (8a—f) showed low activity, but the introduction of α nitro group to the C-1 position of the 6β-naphthyl ring in the 6β-naphthylthio series (11a—c) resulted in a dramatic increase in anti-HIV-1 activity.

Key words nonnucleoside reverse-transcriptase inhibitor; 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio) thymine (HEPT) analogue; HIV-1; mutation

As a key component in combination therapy for acquired immunodeficiency syndrome (AIDS), nonnucleoside reverse-transcriptase inhibitors (NNRTIs) play an essential role in suppressing HIV-1 replication.[2] Unlike nucleoside reverse-transcriptase inhibitors (NRTIs),[3] NNRTIs generally show low toxicity since they do not bind to cellular polymerases, but interact with a specific allosteric site adjacent to the polymerase site of HIV-1 RT and thus lead to a noncompetitive mechanism.[4,5] Many efforts have been made to develop NNRTIs for the treatment of AIDS in the past two decades, and more than 30 structurally different classes of NNRTIs have been identified to have high anti-HIV activity,[6,7] from among which the three drugs nevirapine, delavirdine, and efavirenz are currently approved by the US FDA for clinical use.[8] However, their clinical use is limited by the rapid development of drug-resistant viral strains.[9] Therefore research interest in the NNRTI field is now focused on looking for novel NNRTIs with the ability to inhibit both wild type HIV-1 and clinically resistant mutants.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio) thymine (HEPT, **1**) analogues are an attractive class of NNRTIs, some of which have been found to show high activity against mutant HIV-1 strains,[10,11] such as GCA-186 (**2a**), TNK6123 (**2b**), *etc*. Very recently, based on the crystal structure of HEPT analogues complexed with RT[4] and our 3D-QSAR studies of HEPT analogues, we have designed and synthesized a series of 6-naphthylmethyl HEPT analogues (**3**) with high anti-HIV-1 activity and moderate activity against the Y181C+K103N mutant.[12,13] In continuation of the above research and to investigate thoroughly the structure–activity relationship at *N*-1 and C-6 of HEPT derivatives, we initiated the present study of the synthesis and biological evaluation of 6-naphthylthio-substituted HEPT analogues.

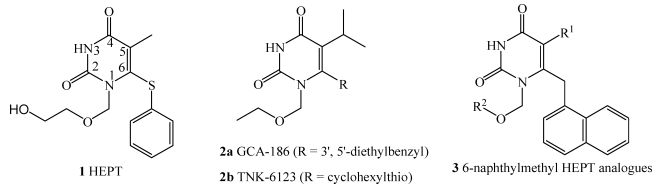

Fig. 1

Chemistry

The synthetic route to 6-naphthylthio HEPT analogues (**7a**—**w**, **8a**—**f**) is depicted in Chart 1. The 6-chlorouracil derivatives **5a**—**e** were known to be readily available from barbituric acid derivatives **4a**—**e**[14]; the intermediates **6a**—**w** were prepared by silylation and *N*-1 alkylation of **5a**—**e** under three different conditions[15—17]: 1) compounds **6a**—**p** were prepared in 74—97% yields by silylation of **5a**—**e** with *N*,*O*-bis-(trimethylsilyl)-acetamide (BSA) in CH_2Cl_2, followed by *N*-1 alkylation with various alkyloxy chloromethyl ethers using tetrabutylammonium iodide as a catalyst; 2) **6q**—**v** were prepared in 36—58% yields by silylation of **5b**, **c** with BSA in CH_3CN and *in situ N*-1 alkylation with different acetals using TMS triflate as a catalyst; 3) **6w** was prepared in 54% yield by *N*-1 alkylation of **5c** with 2-acetoxyethyl acetoxymethyl ether in the presence of $SnCl_4$ as a catalyst. Subsequently, the target 5-alkyl-1-alkyloxymethyl-6α-naphthanethiouracils (**7a**—**v**) and 6β-isomers (**8a**—**f**) were obtained by sulfenylation of **6a**—**v** using two methods: 1) **7a**—**v** were prepared by sulfenylation of **6a**—**v** with α-naphthanethiol in C_2H_5OH and 1 M ethanolic NaOH solution in 59—96% yields. 2) Owing to the unpleasant smell from α and β-naphthanethiol, the above sulfenylation method was modified with a one-pot reduction-sulfenylation.[18] Thus 1-alkoxymethyl-5-alkyl-6-chlorouracils (**6a**—**f**, **w**) were reacted with dinaphthyl disulfides and $NaBH_4$ using CH_3OH as a solvent to afford the target compounds **7w** and **8a**—**f** in 69—90% yields.

The synthesis of 6-(1-substituted 2-naphthylthio) HEPT derivatives (**11a**—**c**, **12a**—**c**, **13**) is shown in Chart 2. 5-Ethyl-6-chlorouracil **5b** was transferred to the thioether **9** following the route to **8a**—**f** shown in Chart 1. The nitration of

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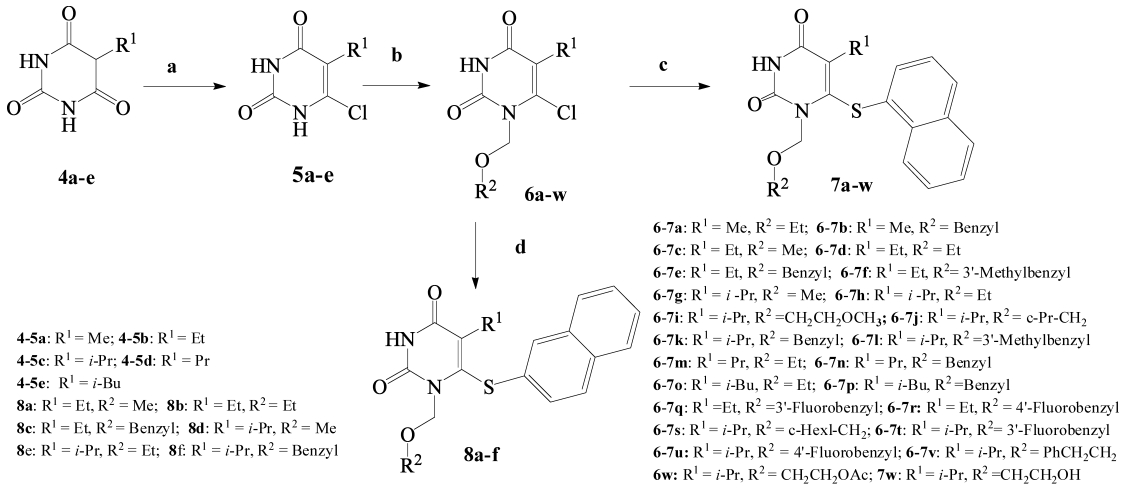
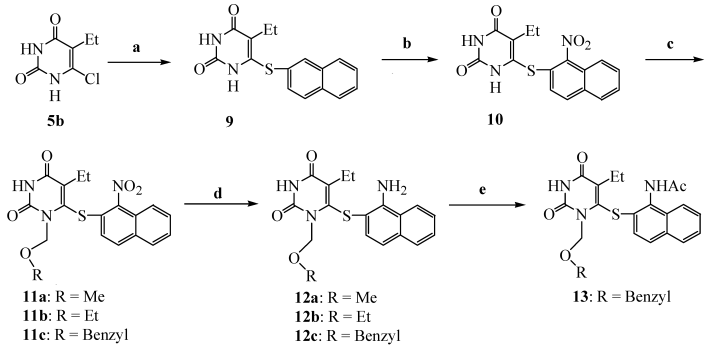


Reagents: (a) $POCl_3$; (b) (1) BSA / CH_2Cl_2, (2) Bu_4NI / R^2OCH_2Cl; R^2OCH_2Cl / TMS triflate or $AcOCH_2CH_2OCH_2Cl$ / $SnCl_4$; (c) α-naphthanethiol, NaOH / ethanol or α-dinaphthane disulfides, $NaBH_4$ / CH_3OH; (d) β-dinaphthane disulfides, $NaBH_4$ / CH_3OH

Chart 1. Synthesis of 6-Naphthylthio HEPT Analogues (**7a**—**w**)

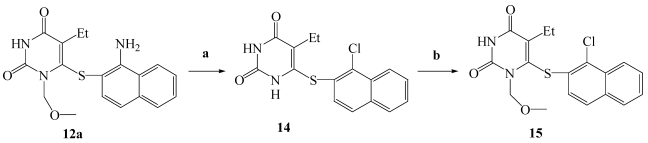


Reagents: (a) β-dinaphthane disulfides, $NaBH_4$ / CH_3OH; (b) HNO_3 / H_2SO_4; (c) (1) BSA / CH_2Cl_2, (2) Bu_4NBr / R_1OCH_2Cl; (d) $Na_2S_2O_3$; (e) AcCl, TEA / CH_2Cl_2.

Chart 2. Synthesis of 6-(1-Substituted-2-naphthylthio) HEPT Analogues

9 with concentrated HNO_3/H_2SO_4 provided the crude 6-(1-nitro-2-naphthylthio) ethyluracil **10**, without separation, which was directly subjected to the next *N*-1 alkylation with various alkyl chloromethyl ethers to afford 6-(1-nitro-2-naphthylthio) HEPT derivatives **11a**—**c** in 22—37% yields. The structures of **11a**—**c** were elucidated based on ^{1}H-NMR spectra, in which four doublets and two quadruplets in the naphthyl region were observed, and no singlet was present in the naphthyl region. This clearly indicated that the nitro substituent should be located at the C-1 position of the 2-naphthyl ring. Further reduction of the nitro groups in **11a**—**c** with $Na_2S_2O_3$ in CH_3OH/CH_2Cl_2 formed 6-(1-amine-2-naphthylthio) HEPT derivatives **12a**—**c** in 51—65% yields. Acylation of **12c** with acetyl chloride in the presence of Et_3N in CH_2Cl_2 provided 6-(1-acetylamine-2-naphthylthio) HEPT derivative **13** in 32% yield.

The synthesis of 6-(1-chloro-2-naphthylthio) HEPT derivative **15** is shown in Chart 3. Compound **12a** was reacted with $NaNO_2$/CuCl/concentrated HCl *via* Sandmeryer's reaction/dealkylation to provide **14** in 39% yield. Realkylation of **14** with methyloxy chloromethyl ether in CH_2Cl_2 produced the target compound **15** in 64% yield.



Reagents: (a) $NaNO_2$ / CuCl, HCl (36%); (b) BSA / CH_2Cl_2, Bu_4NI / $MeOCH_2Cl$.

Chart 3. Synthesis of 6-(1-Chloro-2-naphthylthio) HEPT Analogues (**15**)

Results and Discussion

The target compounds **7a**—**w**, **8a**—**f**, **11a**—**c**, **12a**—**c**, **13**, and **15** together with HEPT and 2,3-dideoxy inosine (DDI) were examined for their activity against wild-type HIV-1 in MT-4 cells, and some were also selected for testing against the NNRTI-resistant strain S0561945 with Y181C+K103N mutations. The results are listed in Table 1.

Most of the 6α-naphthylthio series **7a**—**w** showed high activity against wild-type HIV-1. In particular, 1-benzyloxymethyl-5-ethyl-6-(1-naphthylthio)uracil **7e** was the most potent, with an IC_{50} value of 0.048 μM and selectivity index (SI) of 735, followed by 1-ethoxymethyl-5-isopropyl-6-(1-naphthylthio)uracil **7h** with an IC_{50} value of 0.057 μM and SI of 579. Compared with GCA-186 (**2a**) and TNK6123 (**2b**), **7e** was still 48- and 16-fold less potent against wild-type

Table 1. Inhibition of HIV-1 Replication in MT-4 by 6-Naphthylthio Substituted HEPT Analogues

Compd.	IC_{50} [a] (μM)	CC_{50} [b] (μM)	SI [c]	S0561845 (μM)	Compd.	IC_{50} (μM)	CC_{50} (μM)	SI	S0561845 (μM)
7a	0.46	39.6	87	37.4	**7u**	0.067	30.23	451	ND
7b	0.18	52.5	286	33.4	**7v**	2.77	31.40	11	ND
7c	0.50	38.78	78	ND [d]	**7w**	0.23	77.07	340	ND
7d	0.15	38.4	250	39.3	**8a**	22.02	210.09	9.5	212.6
7e	0.048	34.28	735	8.54	**8b**	3.37	42.19	13	42.19
7f	0.21	28.73	137	ND	**8c**	0.65	154.50	238	ND
7g	0.51	38.40	75	ND	**8d**	4.69	59.58	13	ND
7h	0.057	33.20	579	338	**8e**	2.65	36.30	14	34.73
7i	0.65	35.58	54	ND	**8f**	0.83	187.34	228	289.4
7j	0.38	32.75	85	ND	**11a**	0.47	50.13	107	49.87
7k	0.063	35.30	565	34.72	**11b**	0.099	43.89	446	46.63
7l	0.25	29.60	118	ND	**11c**	0.065	34.19	466	34.34
7m	1.86	37.11	20	ND	**12a**	25.99	180.48	7	198.04
7n	0.83	32.57	39	ND	**12b**	7.06	195.23	28	42.32
7o	7.37	36.12	5	ND	**12c**	3.65	>37.88	>10	>57.7
7p	2.96	32.51	11	ND	**13c**	8.78	155.47	18	>26.74
7q	0.21	31.47	150	ND	**15**	22.66	192.90	8.5	205.32
7r	0.092	30.96	326	28.67	HEPT	5.06	405.37	79	500
7s	12.53	171.92	14	ND	DDI	5.37	529	98	7.15
7t	0.11	32.82	327	30.67					

a) Inhibitory concentration of compound achieving 50% inhibition of HIV-1 multiplication in MT-4 infected cells. *b*) Cytotoxic concentration of compound required to reduce the viability of normal uninfected MT-4 cells by 50%. *c*) Selectivity index: ratio CC_{50}/IC_{50}. *d*) ND=not tested.

HIV-1.

The 6β-naphthylthio series **8a**—**f** generally showed low activity, and their results were in full agreement with those of our reported 6α- and 6β-naphthylmethyl HEPT analogues.[12] However, the corresponding 6β-1-nitro-naphthylthio series **11a**—**c** showed remarkable activity against wild-type HIV-1 and were, respectively, 47-, 34-, and 10-fold more active than their corresponding unsubstituted 6β-naphthylthio compounds **8a**—**c**. However, no increase in activity was observed for compounds **12a**—**c** with α-amino, **15** with α-chloro, and **13** with α-acetamino substituents. Based on a molecular modeling study, we deduced that this difference in antiviral activity might be due to the following reasons: 1) the α-nitro group in **11a**—**c** could reduce the electron density of the 6β-naphthyl ring, thereby enhancing the π–π stacking interaction between the 6β-naphthyl ring and the phenyl group of Tyr181, 188 in RT; however, the α-amino substituent at an equivalent position could decrease this action, and thus the 6β-1-nitro-naphthylthio series **11a**—**c** contributed more to the potency against HIV-1 than the 6β-1-amino-naphthylthio series **12a**—**c**. 2) Concerning the lower activity of 6β-1-chloro-naphthylthio analogue **15** than that of its 6β-1-nitro-naphthylthio counterpart **11a**, we suggest there might be an H-bond interaction between the α-nitro group and phenolic group of Tyr181, but this viewpoint needs to be further validated by theoretical calculations.

We also investigated the structure–activity relationships of the *N*-1 side chain in the 6α-naphthylthio series. When the C-5 substituent was an isopropyl group (for **7g**—**l**, **s**—**w**), the 1-ethoxy derivative **7h** proved to be the most active, followed by 1-benzyloxy derivative **7k** and 1-(4-fluorobenzyloxy) derivative **7u**; the others such as 1-(3-fluorobenzyloxy) derivative **7t**, 1-hydroxyethoxy derivative **7w**, *etc.*, had much less potency than the above three compounds. When the C-5 substituent was an ethyl group (for **7c**—**f**, **q**—**r**), the 1-benzyloxy derivative **7e** was found to be the most potent, followed by 1-(4-fluorobenzyloxy) derivative **7r**. The 1-ethoxy derivative **7d** was found to be less potent, with an IC_{50} value of 0.15 μM.

Some target compounds were also examined for activity against the NNRTI-resistant strain S0561945 with Y181C+K103N mutations. Only compound **7e** was found to show good activity against the resistant strain, with an IC_{50} value of 8.54 μM. However, that was 178-fold less than its activity against the wild-type strain, and therefore compound **7e** was still sensitive to the Y181C+K103N mutation.

Conclusion

The present paper describe the synthesis and structure–activity relationships of a new series of 6α- and 6β-naphthylthio analogues of HEPT. Of these, **7e** in particular showed the greatest activity against both wild-type HIV-1 MT-4 strain and the Y181C+K103N mutant strain; significant effects on structural modification were obtained by the introduction of α nitro group to the C-1 position of the 6β-naphthyl ring.

Experimental

Melting points (mp) were measured on a WRS-1B digital melting point apparatus. IR spectra were recorded on an Avvatar 360 FT-IR instrument. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker DMX500 (500 MHz) or JEOL EX-400 (400 MHz) spectrometers. Chemical shifts (δ) were expressed in ppm with the protonated solvent as a reference. Mass spectra (MS) were recorded on MAT95 and for the electronic impacts (EI) at 70 eV. Column chromatography was performed with silica gel G (300—400 mesh), and TLC was performed on plates coated with silica gel GF_{254}. Solvents were purified using standard procedures.[19]

Anti-HIV-1 Activity Assays The activity of the compounds against HIV-1 ($HTLV\text{-}III_B$ strain) and the Y181C+K103N mutant strain was based on the inhibition of virus-induced cytopathologic effects in MT-4 cells using the MTT method.[20] Briefly, virus stocks were titrated in MT-4 cells and expressed as the 50% cell culture infective dose ($CCID_{50}$). MT-4 cells were suspended in culture medium at 1×10^5 cells/ml and infected with HIV at a multiplicity of infection of 0.02. Immediately after viral infection, 100 μl of the cell suspension was placed in each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. The test compounds were dissolved in DMSO at 50 mM or higher. After 4-d incubation at 37 °C, the number of viable cells was determined using the 3-(4,5-di-

methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. Compounds were tested in parallel for cytotoxic effects in uninfected MT-4 cells.

General Procedure for the Synthesis of 5-Alkyl-1-alkoxymethyl-6-chlorouracils 6a—p To a stirred suspension of 5-alkyl-6-chlorouracil **5a**—**e** (2.0 mmol) in CH_2Cl_2 (8 ml) at room temperature under a nitrogen atmosphere BSA (4.4 mmol) was added dropwise *via* a syringe, and after stirring for an additional 30 min, the mixture became clear. *n*-Bu_4NI (7 mg, 0.02 mmol) was added in one portion, the mixture was cooled to 0 °C, alkyl chloromethyl ether (3.0 mmol) was added dropwise, and then stirring was continued for an additional 2 h at 0 °C. The mixture was poured into cold saturated $NaHCO_3$ solution (20 ml) and stirred for 30 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (20 ml×2). The combined organic phases were washed with brine (30 ml×2), dried over Na_2SO_4, and evaporated *in vacuo* to dryness to afford a yellow solid, which was purified by column chromatography on silica gel with the eluent of EtOAc and petroleum ether (60—90 °C, 1 : 2) to afford pure **6a—p**.

6a: White powder, 87% yield, mp 152—155 °C; **6b**: yellow powder, 79% yield, mp 145—147 °C; **6c**: white powder, 93% yield, mp 135—157 °C; **6d**: white powder, 86% yield, mp 124—126 °C; **6e**: yellow powder, 81% yield, mp 117—118 °C; **6f**: yellow powder, 83% yield, mp 104—106 °C; **6g**: white powder, 97% yield, mp 138—139 °C; **6h**: white powder, 92% yield, mp 93—94 °C; **6i**: white powder, 93% yield, mp 91—93 °C; **6j**: white powder, 85% yield, mp 84—86 °C; **6k**: yellow powder, 91% yield, mp 142—143 °C; **6l**: yellow powder, 75% yield, mp 111—114 °C; **6m**: white powder, 87% yield, mp 127—129 °C; **6n**: yellow powder, 74% yield, mp 130—131 °C; **6o**: white powder, 91% yield, mp 101—103 °C; **6p**: yellow powder, 92% yield, mp 95—97 °C.

General Procedure for the Synthesis of 5-Alkyl-1-alkoxymethyl-6-chlorouracils (6q—v) To a stirred solution of 5-alkyl-6-chlorouracil **5b**, **c** (2 mmol) in anhydrous CH_3CN (30 ml), BSA (6.0 mmol, 1.56 ml) was added dropwise under a nitrogen atmosphere *via* a syringe. After stirring at room temperature for 30 min, the mixture was cooled to −50 °C and trimethylsilyltrifluoromethansulfonate (TMS triflate) (0.36 ml, 2 mmol) was added, followed by dropwise addition of bis(2-alkenyloxy)methane (4 mmol). The reaction mixture was then stirred at room temperature for 3—4 h. Cold saturated $NaHCO_3$ solution (10 ml) was added, and the solvent was evaporated under reduced pressure at room temperature. The residue was extracted with EtOAc (3×30 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The product was chromatographed on silica gel using the eluent of EtOAc and petroleum ether (60—90 °C, 1 : 3) to afford pure **6q**—**v**.

6q: White solid, 44% yield, mp 108—110 °C; **6r**: white solid, 36% yield, mp 113—114 °C; **6s**: yellow solid, 58% yield, mp 42—44 °C; **6t**: white solid, 48% yield, mp 94—96 °C; **6u**: white solid, 40% yield, mp 103—105 °C; **6v**: yellow solid, 58% yield, mp 67—69 °C.

1-[(2-Acetoxyethoxy)methyl]-5-isopropyl-6-chlorouracils (6w) To a stirred mixture of 5-iospropyl-6-chlorouracil **5c** (0.376 g, 2.0 mmol) and 2-acetoxyethyl acetoxymethyl ether (0.54 g, 3.0 mmol) in CH_2Cl_2 (5 ml), BSA (1.2 ml, 4.8 mmol) was added dropwise. After stirring at room temperature for 0.5 h, the resulting clear solution was cooled to 0 °C, $SnCl_4$ (0.04 ml, 0.4 mmol) was added, and the mixture left to stir at room temperature overnight, then poured into cold saturated $NaHCO_3$ solution (50 ml) and extracted with CH_2Cl_2 (20 ml×3), The combined organic phases were washed with brine (50 ml), dried over Na_2SO_4, and evaporated *in vacuo* to dryness to afford a yellow solid. The crude product was purified by column chromatography on silica gel with a mixture of EtOAc and petroleum ether (60—90 °C, 1 : 2) as eluent to afford **6w** in 54% yield. mp 121—123 °C, ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.27 (6H, d, J=7.0 Hz), 2.10 (s, 3H), 3.23 (1H, m), 3.83 (2H, t, J=6.6 Hz), 4.23 (2H, t, J=6.6 Hz), 5.54 (2H, s), 8.87 (1H, s).

General Procedure for the Preparation of HEPT Analogues 7a—v To a stirred solution of 5-alkyl-1-alkoxymethyl-6-chlorouracils (**6q**—**v**) (1.0 mmol) in anhydrous EtOH (4 ml) was added ethanloic NaOH solution 0.5 M (2.0 ml) and 1-naphthanethiol (0.16 g, 1.0 mmol), and stirring was continued at room temperature overnight. The solvent was evaporated under reduced pressure, the residue was suspended in water (5 ml), acidified to pH 5—6 with HCl 1 M, and extracted with CH_2Cl_2 (10 ml×3). The combined organic phases were washed with brine (30 ml), dried over Na_2SO_4, and evaporated *in vacuo* to dryness. The crude product was purified by column chromatography on silica gel with a mixture of EtOAc and petroleum ether (60—90 °C, 1 : 2) as eluent to afford the product.

1-Ethoxymethyl-5-methyl-6-(1-naphthylthio)uracil (7a) Synthesized from **6a** as a white powder in 78% yield, mp 229—232 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.95 (3H, t, J=6.9 Hz), 1.77 (3H, s), 3.44 (2H, q, J=6.9 Hz), 5.40 (2H, s), 7.44—8.18 (7H, m), 11.50 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.8, 14.9, 64.8, 74.8, 119.9, 123.6, 125.9, 126.0, 126.8, 127.1, 128.1, 128.9, 130.1, 131.1, 134.1, 146.7, 151.3, 162.5. IR (KBr) cm^{-1}: 3422, 3032, 1701, 1664, 1105. MS *m*/*z* (%): 342 (56), 283 (42), 128 (45), 57 (100).

1-[(Benzyloxy)methyl]-5-methyl-6-(1-naphthylthio)uracil (7b) Synthesized from **6b** as a white solid in 83% yield, mp 158—159 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.93 (3H, s), 4.63 (2H, s), 5.63 (2H, s), 7.22—7.29 (5H, m), 7.35—8.20 (7H, m), 8.80 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.7, 71.5, 74.9, 120.0, 123.5, 125.9, 126.0, 126.8, 127.1, 127.6, 127.8, 128.0, 128.3, 128.9, 129.9, 131.0, 134.0, 137.2, 146.4, 151.3, 162.5. IR (KBr) cm^{-1}: 3157, 3031, 1697, 1669, 1585, 1081. MS *m*/*z* (%): 404 (8), 283 (15), 217 (30), 91(100).

1-Methoxymethyl]-5-ethyl-6-(1-naphthylthio)uracil (7c) Synthesized from **6c** as a white solid in 72% yield, mp 131—133 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, t, J=7.3 Hz), 2.41 (2H, q, J=7.3 Hz), 3.91 (3H, s), 4.51 (2H, s), 6.89—7.97 (7H, m), 9.29 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 13.6, 22.2, 56.4, 76.2, 123.5, 125.8, 125.8, 127.0, 127.4, 127.8, 127.9, 129.4, 130.4, 131.4, 134.1, 144.1, 151.8, 161.5. IR (KBr) cm^{-1}: 3025, 1711, 1676, 1567, 1075. MS *m*/*z* (%): 342 (42), 297 (100), 254 (34), 159 (56), 115 (68).

1-Ethoxymethyl-5-ethyl-6-(1-naphthylthio)uracil (7d) Synthesized from **6d** as a white powder in 96% yield, mp 166—168 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.77 (3H, t, J=7.3 Hz), 0.88 (3H, t, J=7.0 Hz), 2.45 (2H, q, J=7.3 Hz), 3.39 (2H, q, J=7.0 Hz), 5.29 (2H, s), 7.38—8.18 (7H, m), 11.80 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.2, 14.8, 22.1, 64.8, 74.8, 123.4, 125.0, 125.9, 126.6, 126.7, 127.0, 127.7, 128.8, 130.7, 130.9, 134.0, 145.1, 151.6, 162.2; IR (KBr) cm^{-1}: 3026, 1712, 1649, 1579, 1069. MS *m*/*z* (%): 356 (56), 297 (100), 254 (31), 115 (74).

1-[(Benzyloxy)methyl]-5-ethyl-6-(1-naphthylthio)uracil (7e) Synthesized from **6e** as a white solid in 79% yield, mp 162—166 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.95 (3H, t, J=7.4 Hz), 2.63 (2H, q, J=7.3 Hz), 4.58 (2H, s), 5.47 (2H, s), 7.15—7.21 (5H, m), 7.25—8.31 (7H, m), 8.48 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.3, 22.1, 71.7, 75.0, 123.4, 125.1, 125.9, 126.7, 126.8, 127.1, 127.5, 127.7, 127.8, 128.3, 128.9, 130.7, 134.1, 137.3, 145.0, 151.4, 161.8. IR (KBr) cm^{-1}: 3034, 1718, 1656, 1581, 1061. MS *m*/*z* (%): 418 (6), 297(15), 217 (30), 91(100).

1-[3-Methyl(benzyloxy)methyl]-5-ethyl-6-(1-naphthylthio)uracil (7f) Synthesized from **6f** as a white solid in 71% yield, mp 172—175 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.76 (3H, t, J=7.3 Hz), 2.38 (3H, s), 2.63 (2H, q, J=7.3 Hz), 4.45 (2H, s), 5.39 (2H, s), 6.89—7.18 (5H, m), 7.35—8.14 (7H, m), 11.78 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 13.4, 22.2, 31.8, 71.4, 75.1, 123.3, 124.6, 124.9, 125.7, 126.7, 127.1, 127.6, 128.0, 128.1, 128.5, 128.9, 128.9, 130.6, 131.2, 134.1, 137.6, 144.8, 151.4, 161.5. IR (KBr) cm^{-1}: 3054, 1713, 1669, 1575, 1073. MS *m*/*z* (%): 432 (13), 297 (55), 217 (30), 105 (100).

1-Methoxymethyl-5-isopropyl-6-(1-naphthylthio)uracil (7g) Synthesized from **6g** as a white solid in 86% yield, mp 171—173 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.98 (6H, d, J=7.0 Hz), 3.30 (1H, q, J=7.0 Hz), 3.35 (3H, s), 5.31 (2H, s), 7.39—8.17 (7H, m), 11.67 (1H, s). ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 20.2 (d), 31.4, 56.3, 76.2, 123.3, 125.9, 126.7, 127.2, 127.6, 127.7, 127.7, 129.3, 130.3, 131.5, 134.0, 144.1, 151.4, 161.6. IR (KBr) cm^{-1}: 3173, 3031, 1713, 1686, 1560, 1090. MS *m*/*z* (%): 356 (3.7), 311 (11.9), 159 (3.9), 115 (12.8), 45 (100).

1-Ethoxymethyl-5-isopropyl-6-(1-naphthylthio)uracil (7h) Synthesized from **6h** as a white solid in 85% yield, mp 182—183 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.06 (3H, t, J=7.0 Hz), 1.13 (6H, d, J=7.0 Hz), 3.45 (1H, q, J=7.0 Hz), 3.52 (2H, q, J=7.0 Hz), 5.46 (2H, s), 7.19—8.30 (7H, m), 8.57 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.9, 20.0 (d), 31.7, 64.8, 75.0, 123.4, 125.1, 125.8, 126.8, 127.0, 127.7, 128.9, 129.0, 130.7, 131.3, 134.1, 145.0, 151.4, 161.2. IR (KBr) cm^{-1}: 3037, 1700, 1672, 1561, 1084. MS *m*/*z* (%): 370 (6), 254 (32), 159 (52), 115 (100).

1-[(2-Methoxyethyloxy)methyl]-5-isopropyl-6-(2-naphthylthio)uracil (7i) Synthesized from **6i** as a white solid in 90% yield, mp 122—123 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.14 (6H, d, J=7.0 Hz), 3.25 (3H, s), 3.38 (2H, t, J=4.6 Hz), 3.45 (1H, m), 3.69 (2H, t, J=4.6 Hz), 5.54 (2H, s), 7.18—8.22 (7H, m), 9.50 (1H, br s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.0 (d), 31.7, 58.9, 68.9, 71.6, 75.2, 123.4, 125.0, 125.8, 126.8, 127.0, 127.6, 128.8, 129.1, 130.6, 131.3, 134.0, 144.9, 151.6, 161.3. IR (KBr) cm^{-1}: 3160, 3036, 1705, 1686, 1566, 1083. MS *m*/*z* (%): 400 (32.9), 311 (40.7), 297 (10.8), 89 (100), 59 (87.2).

1-[(Cyclopropylmethoxy)methyl]-5-isopropyl-6-(1-naphthylthio)uracil (7j) Synthesized from **6j** as a white solid in 82% yield, mp 150 °C (dec.). ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.05 (2H, t, J=4.4, 4.8 Hz), 0.34 (2H, d,

J=1.5, 6.6 Hz), 0.80 (1H, m), 1.06 (6H, d, J=6.9 Hz), 3.25 (2H, d, J=6.9 Hz), 3.36 (1H, m), 5.40 (2H, s), 7.42—8.17 (7H, m), 11.65 (1H, s). ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 3.2 (d), 10.7, 20.1 (d), 31.5, 73.1, 74.8, 123.3, 126.1, 126.7, 127.2, 127.4, 127.6, 127.7, 129.2, 130.3, 131.6, 133.9, 144.3, 151.3, 161.6. IR (KBr) cm^{-1}: 3018, 1710, 1642, 1589, 1086. MS *m/z* (%): 396 (16), 297 (24), 159 (22), 55 (100).

1-[(Benzyloxy)methyl]-5-isopropyl-6-(1-naphthylthio)uracil (7k) Synthesized from **6k** as a white solid in 81% yield, mp 146—147 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.12 (6H, d, J=7.0 Hz), 3.44 (1H, m), 4.60 (2H, s), 5.53 (2H, s), 7.15—7.22 (5H, m), 7.27—8.20 (7H, m), 8.21 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.0 (d), 31.7, 71.7, 75.1, 123.4, 125.1, 125.9, 126.8, 127.0, 127.5, 127.7, 127.7, 127.8, 128.3, 128.4, 128.8, 129.2, 130.6, 131.1, 134.1, 137.4, 144.7, 151.4, 161.1. IR (KBr) cm^{-1}: 3037, 1718, 1662, 1561, 1074. MS *m/z* (%): 432 (18), 311 (53), 217 (22), 91 (100).

1-[(3-Methyl-phenylmethyloxy)methyl]-5-isopropyl-1-naphthylthio)uracil (7l) Synthesized from **6l** as a white solid in 88% yield, mp 137—141 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.11 (6H, d, J=7.0 Hz), 2.29 (3H, s), 2.46 (1H, m), 4.56 (2H, s), 5.53 (2H, s), 7.02—7.17 (5H, m), 7.35—8.21 (7H, m), 8.48 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.00 (d), 21.3, 31.7, 71.7, 75.1, 123.4, 124.7, 125.0, 125.9, 126.8, 127.0, 127.7, 128.3, 128.3, 128.5, 128.8, 129.1, 130.6, 131.1, 134.0, 137.9, 144.7, 151.4, 161.1. IR (KBr) cm^{-1}: 3053, 1711, 1663, 1588, 1068. MS *m/z* (%): 446 (14.4), 311 (54.2), 231 (50.2), 115 (10.3), 105 (100).

1-Ethoxymethyl-5-propyl-6-(1-naphthylthio)uracil (7m) Synthesized from **6m** as a white solid in 83% yield, mp 155—156 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.77 (3H, t, J=7.2 Hz), 1.04 (3H, t, J=7.0 Hz), 1.37 (2H, m), 2.59 (2H, t, J=7.7 Hz), 3.50 (2H, q, J=7.0 Hz), 5.40 (2H, s), 7.19—8.26 (7H, m), 9.25 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.0, 14.9, 22.3, 30.4, 64.8, 74.9, 123.5, 125.3, 125.4, 125.9, 126.8, 127.1, 127.8, 128.9, 130.8, 130.9, 134.1, 145.6, 151.7, 162.4. IR (KBr) cm^{-1}: 3047, 1700, 1671, 1580, 1097. MS *m/z* (%): 370 (48), 311 (100), 283 (44), 115 (38).

1-[(Benzyloxy)methyl]-5-propyl-6-(1-naphthylthio)uracil (7n) Synthesized from **6n** as a white solid in 75% yield, mp 104—107 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.80 (3H, t, J=7.3 Hz), 1.36 (2H, m), 2.56 (2H, t, J=7.8 Hz), 4.58 (2H, s), 5.47 (2H, s), 7.16—7.20 (5H, m), 7.32—8.23 (7H, m), 9.27 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.1, 21.9, 30.4, 70.7, 75.0, 123.4, 124.1, 126.0, 126.7, 127.2, 127.6, 127.7 (d), 127.8 (d), 128.4 (d), 129.2, 130.4, 131.1, 138.0, 144.5, 151.5, 162.4. IR (KBr) cm^{-1}: 3009, 1711, 1640, 1561, 1065. MS *m/z* (%): 432 (13.9), 311 (33.1), 217 (47.7), 115 (11.5), 91 (100).

1-Ethoxymethyl-5-isobutyl-6-(1-naphthylthio)uracil (7o) Synthesized from **6o** as a white solid in 89% yield, mp 148—150 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.90 (6H, d, J=6.6 Hz), 1.00 (3H, t, J=7.0 Hz), 1.98 (1H, m), 2.56 (2H, d, J=7.3 Hz), 3.47 (2H, q, J=7.0 Hz), 5.35 (2H, s), 7.13—8.24 (7H, m), 9.03 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.9, 22.3 (d), 28.7, 36.5, 64.8, 75.0, 123.4, 124.8, 124.9, 126.9, 125.9, 126.8, 127.0, 127.7, 128.8, 130.6, 134.1, 145.9, 151.7, 162.5. IR (KBr) cm^{-1}: 3031, 1714, 1663, 1577, 1100. MS *m/z* (%): 384 (75.4), 311 (73.3), 283 (92.1), 115 (52.8), 59 (100).

1-[(Benzyloxy)methyl]-5-isobutyl-6-(1-naphthylthio)uracil (7p) Synthesized from **6p** as a white solid in 91% yield, mp 129—130 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.91 (6H, d, J=6.6 Hz), 1.96 (1H, m), 2.54 (2H, d, J=7.3 Hz), 4.55 (2H, s), 5.59 (2H, s), 7.10—7.22 (5H, m), 7.33—8.20 (7H, m), 8.81 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.4 (d), 28.8, 36.6, 71.7, 75.1, 123.5, 124.9, 125.0, 127.0, 126.9, 127.1, 127.5, 127.7, 127.7, 128.0, 128.3, 128.5, 128.9, 130.5, 130.6, 134.1, 137.4, 145.6, 151.7, 162.5. IR (KBr) cm^{-1}: 3031, 1712, 1649, 1560, 1074. MS *m/z* (%): 446 (11.7), 325 (24.0), 217 (15.4), 115 (9.0), 91 (100).

1-[(3-Fluorobenzyloxy)methyl]-5-ethyl-6-(1-naphthylthio)uracil (7q) Synthesized from **6q** as a white solid in 82% yield, mp 134—136 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.98 (3H, t, J=7.3 Hz), 2.68 (2H, q, J=7.8 Hz), 4.55 (2H, s), 5.48 (2H, s), 6.85—7.23 (4H, m), 7.34—8.22 (7H, m,), 9.14 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 22.3, 71.0, 75.2, 114.4, 122.9, 123.5, 125.1, 126.0, 126.7, 126.9, 127.0, 127.3, 128.0, 129.0, 129.9, 130.8, 134.2, 138.5, 140.1, 144.9, 151.5, 161.8. IR (KBr) cm^{-1}: 3036, 1719, 1663, 1546, 1065. MS *m/z* (%): 436 (7.8), 297 (20.6), 235 (16.8), 115 (26.2), 109 (100).

1-[(4-Fluorobenzyloxy)methyl]-5-ethyl-6-(1-naphthylthio)uracil (7r) Synthesized from **6r** as a white solid in 73% yield, mp 184—185 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.97 (3H, t, J=7.7 Hz), 2.66 (2H, q, J=7.6 Hz), 4.50 (2H, s), 5.46 (2H, s), 6.88—7.17 (4H, m), 7.28—8.21 (7H, m), 9.70 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 22.3, 70.9, 74.9, 115.2, 123.5, 125.0, 126.1, 126.1, 127.1, 127.2, 127.5, 127.9, 128.8, 129.0, 129.4, 129.5, 130.8, 133.1, 134.2, 145.0, 151.6, 161.2. IR (KBr) cm^{-1}: 3175, 1709, 1682, 1588, 1517, 1061. MS *m/z* (%): 436 (2.9), 297 (12.6), 235 (28.7), 109 (100).

1-[(Cyclohexylmethoxy)methyl]-5-isopropyl-6-(1-naphthylthio)uracil (7s) Synthesized from **6s** as a white solid in 76% yield, mp 149—153 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (6H, d, J=6.9 Hz), 1.15 (6H, m), 1.76 (6H, m), 3.39 (1H, m), 3.45 (2H, d, J=7.4 Hz), 5.45 (2H, s), 7.20—8.23 (7H, m), 8.45 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.1 (d), 30.2, 25.8 (d), 26.7, 29.6 (d), 40.6, 68.9, 71.9, 123.6, 125.7, 125.9, 126.9, 127.6, 127.8, 128.5, 129.3, 129.9, 131.6, 133.7, 144.6, 151.5, 161.2. IR (KBr) cm^{-1}: 3363, 1725, 1663, 1562, 1089. MS *m/z* (%): 438 (3.0), 311 (7.4), 189 (23.4), 97 (37.1), 55 (100).

1-[(3-Fluorobenzyloxy)methyl]-5-isopropyl-6-(1-naphthylthio)uracil (7t) Synthesized from **6t** as a white solid in 67% yield, mp 145—147 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.16 (6H, d, J=7.3 Hz), 3.49 (1H, m), 4.56 (2H, s), 5.54 (2H, s), 6.87—7.20 (4H, m), 7.28—8.22 (7H, m), 9.70 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.2 (d), 31.9, 71.0, 75.1, 114.5, 122.1, 122.3, 123.1, 123.5, 125.1, 126.0, 127.0, 127.2, 127.9, 129.0, 129.3, 130.1, 131.1, 133.2, 134.2, 144.7, 151.7, 161.3. IR (KBr) cm^{-1}: 3044, 1706, 1664, 1560, 1085. MS *m/z* (%): 450 (4.0), 311 (21.7), 297 (9.7), 235 (12.3), 109 (100).

1-[(4-Fluorobenzyloxy)methyl]-5-isopropyl-6-(1-naphthylthio)uracil (7u) Synthesized from **6u** as a white solid in 73% yield, mp 177—181 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12 (6H, d, J=7.3 Hz), 3.45 (1H, m), 4.51 (2H, s), 5.50 (2H, s), 6.90—7.21 (4H, m), 7.30—8.19 (7H, m), 9.68 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.1 (d), 31.9, 70.9, 75.0, 115.5, 123.5, 125.2, 126.2, 127.0, 127.2, 127.9, 128.5, 128.8, 128.8, 128.9, 129.0, 129.4, 129.5, 131.2, 136.7, 144.7, 151.6, 161.3. IR (KBr) cm^{-1}: 3044, 1715, 1659, 1563, 1084. MS *m/z* (%): 450 (1.9), 311 (12.2), 235 (11.4), 115 (8.1), 109 (100).

1-[(2-Phenylethoxy)methyl]-5-isopropyl-6-(1-naphthylthio)uracil (7v) Synthesized from **6v** as a white solid in 59% yield, mp 157—161 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.14 (6H, d, J=7.0 Hz), 2.66 (2H, t, J=7.6 Hz), 3.42 (1H, m), 3.67 (2H, t, J=7.6 Hz), 5.44 (2H, s), 7.08—7.25 (5H, m), 7.31—8.22 (7H, m), 8.42 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.1 (d), 31.8, 47.2, 56.9, 75.1, 123.2, 124.9, 125.3, 125.8, 126.0, 126.5, 127.3, 127.5, 127.8, 128.5, 128.6, 128.9, 129.3, 130.1, 131.1, 137.1, 144.7, 151.5, 161.2. IR (KBr) cm^{-1}: 3369, 1701, 1676, 1497, 1077. MS *m/z* (%): 446 (3.2), 312 (18.0), 297 (14.8), 115 (14.9), 105 (100).

General Procedure for the Preparation of HEPT Analogues (7w, 8a—f, 9) To a stirring solution of 6-chlorouracil **6** (2.0 mmol), diaryl disulfide (1.1 mmol) in CH_3OH (5 ml) and $NaBH_4$ (79 mg, 2.0 mmol) were added at 0 °C in portions under a nitrogen atmosphere. The resulting mixture was warmed to room temperature and stirring continued for about 12 h. Evaporation of the solvent *in vacuo* gave a pale solid, which was dissolved in H_2O (5 ml), and the mixture was adjusted to pH 6 with aqueous HCl 1 M, and extracted with CH_2Cl_2 (10 ml×2). The combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to dryness. The residue was washed with petroleum ether (60—90 °C), and the crude products were chromatographed with a solution of EtOAc and petroleum ether (60—90 °C, 1 : 3) as eluent or recrystallized from EtOAc to give the pure product (**7w**, or **8a**—**f**, **9**).

1-(Hydroxyethoxymethyl)-6-(α-naphthalenethio)-5-isopropyluracil (7w) Synthesized from **6w** as a white solid in 69% yield, mp 184—187 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.97 (6H, d, J=6.9 Hz), 3.31 (1H, m), 3.47 (2H, t, J=6.6 Hz), 4.01 (2H, t, J=6.6 Hz), 4.4 (1H, br s) 5.41 (2H, s), 7.40—8.17 (7H, m), 11.64 (1H, s). ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 20.1, 31.4, 60.4, 70.8, 75.3, 123.3, 125.9, 126.7, 127.2, 127.5, 127.6, 127.6, 129.2, 130.3, 131.6, 133.9, 144.2, 151.4, 161.6. IR (KBr) cm^{-1}: 3485, 3065, 2960, 1693, 1425, 1406, 1113. MS *m/z* (%): 386 (M^+, 5), 318 (43), 115 (100).

1-Methoxymethyl-5-ethyl-6-(2-naphthylthio)uracil (8a) Synthesized from **6c** as a white solid in 78% yield, mp 139—145 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H, t, J=7.3 Hz), 2.73 (2H, q, J=7.3 Hz), 3.36 (3H, s), 5.45 (2H, s), 7.26—7.81 (7H, m), 9.12 (1H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.2, 22.2, 56.3, 74.7, 124.4, 125.9, 126.4, 126.6, 126.7, 127.2, 127.9, 129.7, 130.8, 132.0, 133.6, 144.9, 151.4, 162.3. IR (KBr) cm^{-1}: 3023, 1701, 1686, 1582, 1074. MS *m/z* (%): 342 (6), 254 (14), 159 (34), 115 (100).

1-Ethoxymethyl-5-ethyl-6-(2-naphthylthio)uracil (8b) Synthesized from **6d** as a white crystals in 86% yield, mp 141—142 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.00 (3H, t, J=7.4 Hz), 1.06 (3H, t, J=7.0 Hz), 2.70 (2H, q, J=7.4 Hz), 3.56 (2H, q, J=7.0 Hz), 5.48 (2H, s), 7.27—7.81 (7H, m), 8.57 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.3, 14.9, 22.1, 64.9, 74.8, 124.9, 125.8, 126.5, 126.5 (d), 127.2, 127.8, 129.6, 130.8, 132.1,

133.8, 144.9, 151.4, 162.1. IR (KBr) cm^{-1}: 3024, 2976, 1718, 1697, 1449, 1419, 1101. MS *m/z* (%): 356 (M^+, 12), 318 (36), 297 (22), 159 (51), 115 (100).

1-[(Benzyloxy)methyl]-5-ethyl-6-(2-naphthylthio)uracil (8c) Synthesized from **6e** as a white solid in 85% yield, mp 120—123 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz), 2.68 (2H, q, J=7.3 Hz), 4.62 (2H, s), 5.51 (2H, s), 7.18—7.26 (5H, m), 7.33—8.07 (7H, m), 9.06 (1H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.2, 22.5, 71.8, 75.7, 124.8, 125.8, 126.0, 126.2, 126.7, 126.7, 127.3, 127.7 (d), 127.9, 128.4, 128.6, 130.0, 132.4, 133.4, 137.2, 142.9, 151.7, 161.9. IR (KBr) cm^{-1}: 3030, 1702, 1671, 1583, 1066. MS *m/z* (%): 418 (12), 297(35), 217 (41), 91 (100).

1-Methoxymethyl-5-isopropyl-6-(2-naphthylthio)uracil (8d) Synthesized from **6g** as a white solid in 73% yield, mp 166—170 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.18 (6H, d, J=6.9 Hz), 3.38 (3H, s), 3.56 (1H, m), 5.50 (2H, s), 7.28—7.82 (7H, m), 9.01 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.1 (d), 31.8, 57.1, 76.9, 125.1, 126.1, 126.7, 127.3, 127.3, 128.0, 129.0, 129.8, 131.1, 132.2, 133.9, 144.8, 151.3, 161.3. IR (KBr) cm^{-1}: 3015, 1709, 1647, 1560, 1095. MS *m/z* (%): 356 (6), 311 (22), 159 (32), 115 (57), 45 (100).

1-Ethoxymethyl-5-isopropyl-6-(2-naphthylthio)uracil (8e) Synthesized from **6h** as a yellow solid in 83% yield, mp 181 °C (dec.). ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.93 (3H, t, J=7.0 Hz), 1.01 (6H, d, J=7.0 Hz), 3.36 (1H, q, J=7.0 Hz), 3.50 (2H, q, J=7.0 Hz), 5.42 (2H, s), 7.43—7.97 (7H, m), 11.66 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.9, 20.0 (d), 31.7, 64.8, 74.9, 125.0, 126.0, 126.5, 127.2 (d), 127.8, 128.8, 129.5, 131.2, 132.1, 133.8, 144.8, 151.4, 161.4. IR (KBr) cm^{-1}: 3162, 2970, 1717, 1647, 1584, 1413, 1087. MS *m/z* (%): 370 (6), 283 (38), 254 (32), 159 (55), 115 (100).

1-[(Benzyloxy)methyl]-5-isopropyl-6-(2-naphthylthio)uracil (8f) Synthesized from **6k** as a white solid in 77% yield, mp 166—167 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.96 (6H, d, J=6.9 Hz), 3.37 (1H, m), 4.56 (2H, s), 5.53 (2H, s), 7.16—7.22 (5H, m), 7.41—7.90 (7H, m), 11.62 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.0 (d), 31.7, 71.7, 75.0, 125.0, 126.1, 126.5, 127.2 (d), 127.6 (d), 127.8 (d), 128.3 (d), 128.9, 129.6, 131.0, 132.1, 133.8, 137.3, 144.5, 151.3, 161.1. IR (KBr) cm^{-1}: 3035, 1719, 1654, 1563, 1077. MS *m/z* (%): 432 (8), 311 (28), 217 (32), 91 (100).

5-Ethyl-6-(2-naphthanethio)uracil (9) Synthesized from **5b** as a white solid in 90% yield, mp 256—258 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 0.96 (3H, t, J=7.3 Hz), 2.30 (2H, q, J=7.4 Hz), 7.41—8.14 (7H, m), 11.32 (1H, s), 11.82 (1H, s). ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 14.2, 20.3, 118.8, 127.1, 127.3, 127.8, 128.0, 128.1, 128.7, 129.5, 130.5, 132.6, 133.8, 143.7, 151.2, 163.6. IR (KBr) cm^{-1}: 3155, 3018, 2962, 1710, 1655, 1589, 1469, 1421, 1196. MS *m/z* (%): 318 (M^+, 36), 115 (100).

5-Ethyl-6-(1-nitro-2-naphthylthio)uracil (10) To a stirred mixture of 5-ethyl-6-(2-naphthanethio)uracil **9** (2.98 g, 10 mmol) and concentrated H_2SO_4 (20 ml), a mixture of concentrated H_2SO_4 (4.3 ml) and fumed HNO_3 (0.48 ml, 11 mmol) was added dropwise at about −5 °C, stirring was continued at 0 to −5 °C for an additional 1 h. The mixture was poured onto crushed ice (120 g), filtered, and washed successively with H_2O (30 ml×3) and EtOH (25 ml×2). The resulting yellow solid was dried *in vacuo* and subjected to the next step without further purification (3.2 g, 93%).

1-Methoxymethyl-5-ethyl-6-(1-nitro-2-naphthylthio)uracil (11a) Synthesized from crude **10** (3.43 g, 10.0 mmol) and methyl chloromethyl ether (1.61 g, 20 mmol) in a similar manner to the preparation of **6a**—**p** as a yellow powder (1.43 g, 37%), but the chromatography was performed with a mixture of EtOAc and petroleum ether (60—90 °C, 1 : 1) as eluent. mp 179—186 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.02 (3H, t, J=7.3 Hz), 2.70 (2H, q, J=7.3 Hz), 3.34 (3H, s), 5.47 (2H, s), 7.39 (1H, dd, J=6.8, 9.2 Hz), 7.56 (1H, dd, J=7.8, 8.3 Hz), 7.70 (1H, d, J=6.8 Hz), 7.91 (1H, d, J=8.2 Hz), 8.23 (1H, d, J=7.8 Hz), 8.38 (1H, d, J=9.2 Hz), 9.29 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.4, 22.3, 56.4, 74.9, 123.7, 124.9, 125.9, 126.4, 126.7, 127.2, 128.1, 128.4, 133.9, 134.9, 143.3, 145.7, 151.4, 162.2. IR (KBr) cm^{-1}: 3031, 1704, 1687, 1653, 1587, 1072. MS *m/z* (%): 387 (11.6), 325 (13.6), 216 (8.8), 114 (8.1), 45 (100).

1-Ethoxymethyl-5-ethyl-6-(1-nitro-2-naphthylthio)uracil (11b) Synthesized from crude **10** (0.68 g, 2.0 mmol) and ethyl chloromethyl ether (0.39 g, 4.0 mmol, 0.38 ml) in a similar manner to the preparation of **11a** as a yellow powder (0.19 g, 24), mp 65—69 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H, t, J=7.3 Hz), 1.02 (3H, t, J=7.0 Hz), 2.68 (2H, q, J=7.3 Hz), 3.55 (2H, q, J=7.0 Hz), 5.49 (2H, s), 7.40 (1H, dd, J=6.8, 9.1 Hz), 7.61 (1H, dd, J=7.7, 8.3 Hz), 7.72 (1H, d, J=6.8 Hz), 7.94 (1H, d, J=8.3 Hz), 8.25 (1H, d, J=7.7 Hz), 8.37 (1H, d, J=9.1 Hz), 9.25 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.4, 15.1, 22.3, 65.1, 75.1, 123.7, 124.9, 125.9, 126.4, 126.7, 127.2, 128.1, 128.4, 133.8, 134.8, 143.3, 145.7, 151.6, 162.2. IR (KBr) cm^{-1}: 3178, 1701, 1685, 1649, 1588, 1069. MS *m/z* (%): 401 (8.0), 342 (10.9), 171 (10.8), 149 (24.5), 115 (9.4), 59 (100).

1-[(Benzyloxy)methyl]-5-ethyl-6-(1-nitro-2-naphthylthio)uracil (11c) Synthesized from crude **10** (0.68 g, 2.0 mmol) and benzyl chloromethyl ether (0.47 g, 3.0 mmol) in a similar manner to the preparation of **11a** as a yellow powder (0.21 g, 22%). mp 156—157 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.02 (3H, t, J=7.3 Hz), 2.68 (2H, q, J=7.3 Hz), 4.56 (2H, s), 5.57 (2H, s), 7.07—7.18 (5H, m), 7.46 (1H, dd, J=6.9, 9.2 Hz), 7.55 (1H, dd, J=7.8, 8.2 Hz), 7.64 (1H, d, J=6.9 Hz), 7.93 (1H, d, J=8.2 Hz), 8.20 (1H, d, J=7.8 Hz), 8.48 (1H, d, J=9.2 Hz), 9.41 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.6, 22.3, 71.7, 75.1, 123.7, 124.4, 125.0, 125.5, 125.6, 127.5, 127.6, 127.6, 127.9, 128.0, 128.3, 128.3, 133.7, 133.9, 134.9, 137.1, 143.5, 146.5, 151.4, 161.9. IR (KBr) cm^{-1}: 3029, 1701, 1677, 1655, 1589, 1522, 1068. MS *m/z* (%): 463 (1.3), 357 (3.2), 262 (19.5), 91 (100), 92 (9.0).

1-Methoxymethyl-5-ethyl-6-(1-amino-2-naphthylthio)uracil (12a) To a stirred mixture of $Na_2S_2O_3$ (4.6 g, 29 mmol), CH_3OH (25 ml) and H_2O (10 ml), a solution of 1-methoxymethyl-5-ethyl-6-(1-nitro-2-naphthylthio)-uracil **11a** (1.2 g, 3.1 mmol) in CH_2Cl_2 (15 ml) was added at 0 °C. Stirring was continued for an additional 1 h. The solid was separated by filtration and washed with CH_2Cl_2 (20 ml×3), the filtrate was diluted with H_2O (30 ml), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (30 ml×2). The combined organic phases were washed with brine (50 ml×2), dried over Na_2SO_4, evaporated, and chromatographed on silica gel with a mixture of EtOAc and petroleum ether (60—90 °C, 1 : 1) as eluent to afford **12a** as a yellow solid (0.59 g, 53 %). mp 161—164 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.94 (3H, t, J=7.3 Hz), 2.64 (2H, q, J=7.3 Hz), 3.29 (3H, s), 4.05 (2H, br s), 5.37 (2H, s), 6.74 (1H, dd, J=0.9, 6.9 Hz), 7.13—7.22 (3H, m), 7.67—7.68 (2H, m), 9.10 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.4, 22.3, 56.4, 74.4, 111.2, 118.9, 120.4, 124.3, 125.2, 126.3, 127.3, 129.4, 130.4, 133.4, 141.5, 145.3, 151.4, 162.2. IR (KBr) cm^{-1}: 3465, 3230, 1719, 1682, 1568, 1078. MS *m/z* (%): 357 (35.5), 312 (14.0), 269 (16.2), 57 (43.6), 45 (100).

1-Ethoxymethyl-5-ethyl-6-(1-amino-2-naphthylthio)uracil (12b) Synthesized from **11b** (0.27 g, 0.67 mmol) and $Na_2S_2O_3$ (1.0 g, 6.7 mmol) in a similar manner to the preparation of **12a** as a yellow powder (0.16 g, 65%). mp: 169—173 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99 (3H, t, J=7.4 Hz), 1.10 (3H, t, J=6.9 Hz), 2.71 (2H, q, J=7.3 Hz), 3.57 (2H, q, J=6.9 Hz), 4.25 (2H, br), 5.49 (2H, s), 6.82 (1H, dd, J=1.4, 6.4 Hz), 7.19—7.32 (3H, m), 7.73—7.76 (2H, m), 9.30 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 15.0, 22.3, 65.1, 75.1, 111.2, 118.9, 120.3, 124.2, 125.1, 126.3, 127.3, 129.3, 130.4, 133.3, 141.7, 145.5, 151.4, 162.2. IR (KBr) cm^{-1}: 3397, 1701, 1671, 1567, 1096. MS *m/z* (%): 371 (64.6), 312 (34.9), 269 (25.9), 130 (46.1), 59 (100).

1-[(Benzyloxy)methyl]-5-ethyl-6-(1-amino-2-naphthylthio)uracil (12c) Synthesized from **11c** (0.40 g, 0.87 mmol) and $Na_2S_2O_3$ (1.4 g, 8.7 mmol) in a similar manner to the preparation of **12a** as a yellow powder (0.19 g, 51%). mp 147—151 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 2.64 (2H, q, J=7.3 Hz), 4.13 (2H, br s), 4.58 (2H, s), 5.53 (2H, s), 6.74—7.17 (4H, m), 7.22—7.71 (6H, m), 9.81 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 22.2, 71.8, 74.9, 110.5, 118.3, 122.3, 123.0, 123.7, 126.6, 127.7 (d), 127.9, 128.0, 128.1, 128.4 (d), 130.7, 134.9, 137.4, 142.4, 151.5, 161.1. IR (KBr) cm^{-1}: 3230, 1719, 1650, 1578, 1561, 1090. MS *m/z* (%): 433 (14.2), 297 (7.9), 235 (17.6), 109 (68.3), 91 (100).

1-[(Benzyloxy)methyl]-5-ethyl-6-(1-acetamino-2-naphthylthio)uracil (13) A mixture of **12c** (0.13 g, 0.3 mmol), CH_2Cl_2 (2 ml), and Et_3N (1 ml) was stirred at −5 °C. Then a solution of AcCl (0.05 ml, 0.5 mmol) and CH_2Cl_2 (1 ml) was added dropwise and stirred at room temperature for 2 h. H_2O (5 ml) was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (10 ml×2). The combined organic phases were washed with brine (20 ml), dried over Na_2SO_4, evaporated, and chromatographed on silica gel with a mixture of EtOAc and petroleum ether (60—90 °C, 1 : 1) as eluent to afford **13** as yellow foam (45 mg, 0.1 mmol), in 32% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.09 (3H, t, J=7.3 Hz), 2.58 (3H, s), 2.67 (2H, q, J=7.3 Hz), 4.61 (2H, s), 5.54 (2H, s), 7.09—7.23 (5H, m), 7.34—7.83 (6H, m), 8.50 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8, 19.9, 30.7, 71.5, 75.1, 115.4, 119.7, 122.1, 122.9, 123.9, 127.0, 127.9, 128.1, 128.9, 129.0, 129.1 (d), 130.0, 131.0, 134.7, 138.8, 141.9, 146.8, 151.5, 161.0. IR (KBr) cm^{-1}: 3203, 1721, 1701, 1656, 1546, 1490, 1080. MS *m/z* (%): 475 (6.1), 311 (29.9), 159 (6.9), 217 (30), 115 (16.7), 109 (100).

5-Ethyl-6-(1-chloro-2-naphthylthio)uracil (14) A mixture of 1-methoxymethyl-5-ethyl-6-(1-amino-2-naphthylthio)uracil **12a** (0.50 g, 1.4 mmol), concentrated HCl (3.5 ml), and H_2O (3.5 ml) was stirred at −5 °C, a

solution of $NaNO_2$ (0.5 g, 7.2 mmol) and H_2O (5 ml) was added dropwise until KI-starch paper became blue. Then the resulting mixture was added to the stirred solution of CuCl (0.8 g, 8.1 mmol) in concentrated HCl (36%, 2.5 ml) at 0 °C, and the reaction mixture was stirred for 1 h. The mixture was poured onto crushed ice (10 g), the precipitate was collected by filtration, washed with H_2O (4 ml×3) and EtOH (3 ml×2), dried *in vacuo* to afford **14** as green solid, recrystallization from EtOH/DMF (1 : 1) afforded pure **14** as a pale powder (0.18 g, 39%), mp 223—227 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.97 (3H, t, J=7.3 Hz), 2.39 (2H, q, J=7.3 Hz), 7.53—8.17 (6H, m), 11.26 (1H, br s); 11.87 (1H, br s).

1-Methoxymethyl-5-ethyl-6-(1-chloro-2-naphthylthio)uracil (15) Following the route to **11a**—**c**, this compound was synthesized from 5-ethyl-6-(1-chloro-2-naphthylthio)uracil **14** (0.17 g, 0.52 mmol) and methyl chloromethyl ether as a pale powder (0.12 g, 64%). mp 187—190 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, t, J=7.3 Hz), 2.67 (2H, q, J=7.3 Hz), 3.39 (3H, s), 5.47 (2H, s), 7.31—8.15 (6H, m), 9.09 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.2, 22.4, 56.8, 75.2, 123.5, 124.4, 125.1, 125.8, 126.8, 127.6, 128.0, 129.4, 131.3, 132.8, 134.1, 145.1, 151.6, 162.6. IR (KBr) cm^{-1}: 3019, 1703, 1670, 1581, 1071. MS *m*/*z* (%): 376 (9), 331 (13), 288 (17), 193 (23), 45 (100).

References

1) For Part 4, see: He Y. P., Kuang Y. Y., Chen F. E., De Clercq E., Balzarini J., Pannecouque C., *Monatshefte für Chemie*, in press, (2005).
2) De Clercq E., *Antiviral Res.*, **38**, 153—179 (1998).
3) Yarchoan H., Mitsuya R., Thomas R. V., Pluda J. M., Hartman N. R., Perno C. F., Marczyk K. S., Allain J. P., Johns D. G., Broder S., *Science*, **245**, 412—415 (1989).
4) Ren J. S., Esnouf R., Garman E., Jones Y., Somers D., Ross C., Kirby I., Keeling J., Darby G., Stuart D., Stammers D., *Nature Struct. Biol.*, **2**, 293—302 (1995).
5) Hopkins A. L., Ren J., Esnouf R. M., Willcox B. E., Jones E. Y., Ross C., Miyasaka T., Walker R. T., Tanaka H., Stammers K. D., Stuart D. I., *J. Med. Chem.*, **39**, 1589—1600 (1996).
6) Pedersen O. S., Pedersen E. B., *Antivir. Chem. Chemothe.*, **10**, 285—312 (1999).
7) Hajos G., Riedl Z., Molnar J., Szabo D., *Drug Future*, **25**, 47—62 (2000).
8) Pomerantz R. J., Horn D. L., *Nat. Med.*, **9**, 867—873 (2003).
9) De Clercq E., *J. Med. Chem.*, **38**, 2491—2517 (1995).
10) Hopkins A. L., Ren J., Tanaka H., Stammers D. K., *J. Med. Chem.*, **42**, 4500—4505 (1999).
11) Tanaka H., Takashima H., Ubasawa M., Baba M., Walker R. T., De Clercq E., Miyasaka T., *J. Med. Chem.*, **35**, 4713—4719 (1992).
12) Meng G., Chen F. E., De Clercq E., Balzarini J., Pannecouque C., *Chem. Pharm. Bull.*, **51**, 779—789 (2003).
13) Meng G., Doctoral dissertation, Fudan University, China, 2003.
14) Koroniak H., Jankowski A., Krasnowski M., *Org. Prep. Proced. Int.*, **25**, 563—568 (1993).
15) Lee N., Kim Y.-W., Kim K. H., Kim D.-K., *J. Heterocyclic. Chem.*, **34**, 659—663 (1996).
16) El-Brollosy N. R., Jorgensen P. T., Dahan B., Boel A. M., Pedersen E. B., Nielsen C., *J. Med. Chem.*, **45**, 5721—5726 (2002).
17) Rosowaky A., Kim S.-H., Wick M., *J. Med. Chem.*, **24**, 1177—1181 (1981).
18) Sun G. F., Kuang Y. Y., Wang S. X., Chen F. E., *Synth. Commun.*, **34**, 2229—2235 (2004).
19) Leonard J., Lygo B., Procter G., "Advanced Practical Organic Chemistry," 2nd ed., The Alden Press, Osney Mead, Oxford, 1995.
20) Pauwels R., Balzarini J., Baba M., Snoeck R., De Clercq E., *J. Virol. Methods*, **20**, 309—322 (1988).