Nonnucleoside HIV-1 Reverse Transcriptase Inhibitors: Part I. Synthesis and Structure–Activity Relationship of 1-Alkoxymethyl-5-alkyl-6-naphthylmethyl Uracils as HEPT Analogues

Ge MENG,[a] Fen-Er CHEN,*[,a] Erik DE CLERCQ,[b] Jan BALZARINI,[b] and Christophe PANNECOUQUE[b]

[a] *Department of Chemistry, Fudan University; 220 Handan Road, Shanghai 200433, P. R. China: and* [b] *Rega Institute for Medical Research, Katholieke Universiteit Leuven; 10 Minderbroedersstraat, B-3000 Leuven, Belgium.*

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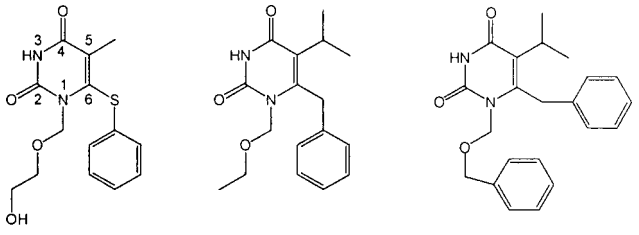
1-Alkoxymethyl-5-alkyl-6-naphthylmethyl uracils, which are novel 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) analogues, were synthesized for evaluation as selective and potent nonnucleoside human immunodeficiency virus (HIV)-1 reverse transcriptase inhibitors. The anti-HIV-1 activity of these compounds was assayed *in vitro* using HIV-1 infected MT-4 and CEM bioassays. The EC_{50}, CC_{50} and SI were recorded and calculated. The appropriate position, especially in the 1-position of the naphthyl ring, led to dramatic increases in potency, in both MT-4 and CEM cellular assays. The most important compounds in this series, 1-ethoxymethyl-5-isopropyl-6-(1-naphthylmethyl)thymine 8l (IC_{50}=17 nM, CC_{50}=38332 nM, SI=2229) and 1-benzyloxymethyl-5-ethyl-6-(1-naphthylmethyl)thymine 8n (IC_{50}=17 nM, CC_{50}=32560 nM, SI=1889) were significantly more potent than HEPT (EC_{50}=7.0 μM, CD_{50}=740 μM) in the anti-HIV-1 *in vitro* cellular assay.

Key words HIV-1 reverse transcriptase inhibitor; 1-alkoxymethyl-5-alkyl-6-naphthylmethyl uracil; structure–activity relationship

Despite major advances in pharmaceutical and surgical treatment, AIDS (Aquired Immune Deficiency Syndrome), caused by human immunodeficiency virus (HIV), a RNA dependent retrovirus,[1,2] remains one of the major causes of death in the world[3,4] Inhibition of reverse transcriptase (RT), the HIV-encoded polymerase which directs both RNA and DNA synthesis, has been proven to be one of the most effective ways to block viral multiplication.[5] It is already well known that there are two main active binding sites in HIV-1 RT, which are proximal but distinct. One is the nucleoside binding site (NBP), another is the nonnucleoside binding pocket (NNBP).[6] Several classes of compounds have been identified as being highly specific RT inhibitors, which included either substrate analogues such as AZT, DDC and DDI, which are currently used as nucleoside reverse transcriptase inhibitors (NRTIs) in AIDS therapy, or nonsubstrate analogues (NNRTIs) such as tetrahydroimidazo[4,5,1-jk]-[1,4]benzodiazpin-2(1H4)-one (TIBO), 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)thymine (HEPT, **1**) (Fig. 1), nevirapine, delavirdine and efavirenz, which are called nonnucleoside reverse transcriptase inhibitors (NNRTIs),[7] among which HEPT and it analogs (MKC-442, **2** and TNK-651, **3**) (Fig. 1) are the most potent class of compounds showing activity against mutant HIV virus strains and having relatively less drug resistance and lower side-effects compared with NRTIs and other NNRTI.[8]



1 HEPT **2** MKC-442 **3** TNK-651

Fig. 1. Structures of HEPT and Typical Analogs

The unique structure of HEPT as well as its highly anti HIV-1 specific activity has induced many kinds of structural modifications on the skeleton of thymine.[9] Tanaka, H. *et al.* have synthesized 6-substituted derivatives of HEPT[10] and found that a ring structure at the 6-position of the pyrimidine moiety is an important determinant for the anti-HIV activity.

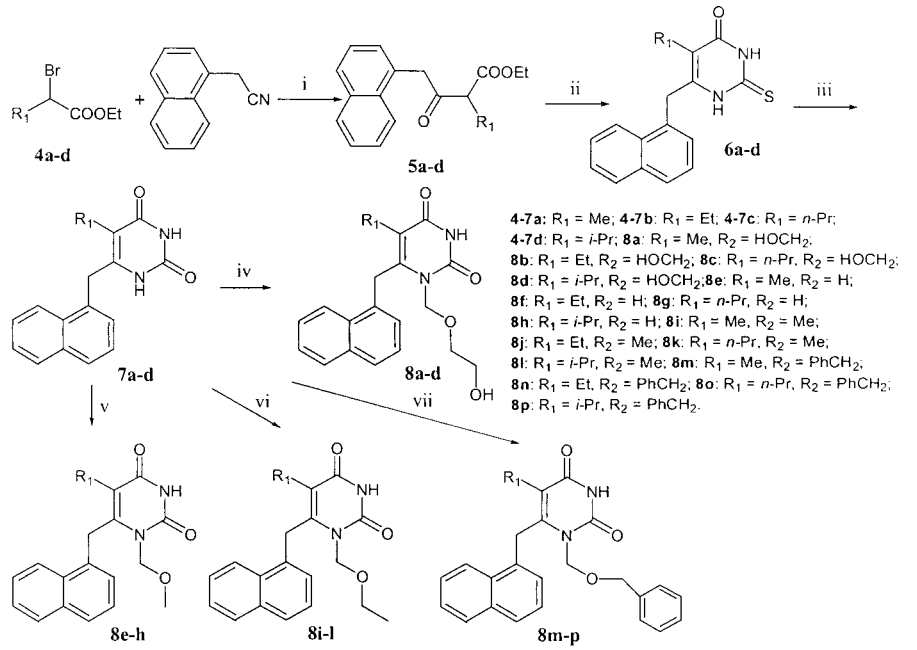
In a recent study on the structure of the HIV-1 RT complexed with HEPT analogs, it was found that the roof of the active binding pocket of RT has a particularly hydrophobic surface (Tyr181, Tyr188, Phe 227 and Trp229), and that significant nearby volume remains unexploited. It was also postulated that the replacement of the 6-phenylthio group with a 6-naphthylmethyl group might be favorable for the hydrophobic interaction between enzyme and inhibitor.[11—13] When a 6-naphthylmethyl substituted HEPT analog was docked into the active pocket of a RT crystal structure, more negative binding energy and better accommodation were observed.[14]

Our recent 3D-QSAR (CoMFA) studies of HEPT analogs also showed that a suitable length of N-side chain is crucial for the anti-HIV-RT activity.[15] The triggering effect of 5-alkyl on the interaction with the active binding site has been shown by previous relative QSAR.[16,17] The present paper describes the synthesis of 1-alkoxymethyl-5-alkyl-6-naphthyl methyl uracils as HEPT analogs and evaluates their SARs with regards to their *in vitro* biological activities in two HIV-1 infected cells lines and the binding affinity for the HIV-RT-NNBP. The typical synthetic routes for these compounds are listed in Charts 1 and 2.

Chemistry

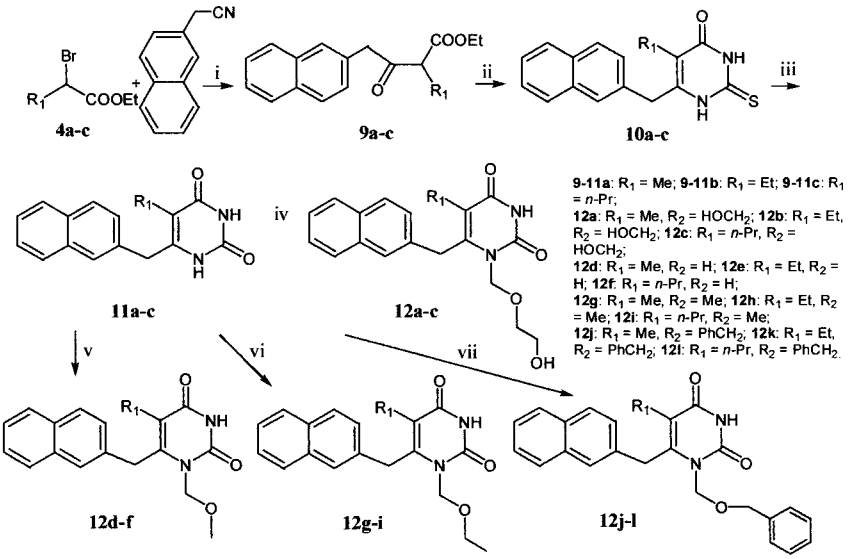
1-Alkoxymethyl-5-alkyl-6-naphthylmethyl uracils were prepared by the procedure outlined in Charts 1 and Chart 2. The synthesis method of the β-series compounds is similar to that of their α-counterparts except for the different raw material.

* To whom correspondence should be addressed. e-mail: rfchen@fudan.edu.cn



Reagents and conditions: i, Zn, THF then HCl, ii, NaOEt, NH_2CSNH_2, iii, $ClCH_2COOH$ or H_2O_2, iv, BSA/CH_2Cl_2, Dioxolane/$SnCl_4$, $MeOH/NaHCO_3$, v, BSA/CH_2Cl_2, $MeOCH_2Cl/Bu_4NI$, $EtOH/NaHCO_3$; vi, $HMDS/(NH_4)_2SO_4$, $EtOCH_2Cl$/TMF triflate, $NaHCO_3$, vii, BSA/CH_2Cl_2, $PhCH_2OCH_2Cl/K_2CO_3$ (anhydrous), $NaHCO_3/H_2O$

Chart 1. Synthesis of α-Series Target Compounds **8a**—**p**



Reagents and conditions i-vii are almost the same as the conditions stated in Chart 1.

Chart 2. Synthesis of β-Series Target Compounds **12a**—**l**

Ethyl 2-alkyl-3-oxo-4-(1-naphthyl)butyrates **5a**—**d** were prepared upon reaction of 1-naphthylacetonitrile with activated zinc dust and ethyl 2-bromoalkanoates **4a**—**d**[18] using an improved method of the Blaise Reaction[19,20] described previously.[21,22] The so formed 3-oxo esters **5a**—**d** were converted into a 5-alkyl-6-(1-naphthylmethyl)-2-thiouracil **6a**—**d** by reaction with thiourea in the presence of NaOEt.[23] **6a**—**d** were refluxed with chloroacetic acid or H_2O_2 overnight to afford 5-alkyl-6-(1-naphthylmethyl)uracils **7a**—**d** (Chart 1).[24] With the aim of avoiding the desulfuration of **6a**—**c**, we turned our attention to the transformation of **5a**—**d** into **7a**—**d**, the procedures, commonly used for the preparation of uracils, were tested. **5a** was reacted with urea in the presence of NaOEt in refluxing anhydrous ethanol for 24 h. Only the desirable **7a** was isolated in a 4% yield, even under microwave irradiation.

The silylation of 5-alkyl-6-(1-naphthylmethyl)uracils **7a**—**d** was achieved with silylating reagents such as *N*,*O*-bis-(trimethylsilyl)acetamide (BSA),[25] $HMDS/(NH_4)_2SO_4$[26,27] or $(CH_3)_3SiCl/Et_3N$[28] in almost quantitative yield.[29,30] Among all these silylating agents tested, BSA is the best choice. The condensation reaction of the *O*-silylated ethers with 1,3-dioxolane (1 : 1.2 mole ratio) was accomplished using $SnCl_4$ as a Lewis acid catalyst[31] followed by deprotection of the TMS groups with $NaHCO_3/MeOH/H_2O$ to give the desired 1-[(2-hydroxyethoxy)methyl]-5-alkyl-6-(1-naphthylmethyl)uracils

8a—**d**, respectively. The *O*-silylated ethers were condensed with various alkylating agents such as chloromethyl methyl ether, chloromethyl ethyl ether or benzyl chloromethyl ether (1 : 1.2 mole ratio) catalyzed by tetrabutylammonium iodide (Bu_4NI), subsequent cleavage of O-TMS ethers with $NaHCO_3/EtOH/H_2O$ to afford the expected 1-alkyoxymethyl-5-alkyl-6-(1-naphthylmethyl)uracils **8a**—**p** in 18—44% yields (Table 1). For the reaction of **8a**—**k**, trimethylsilyltrifluoromethane sulfonate (TMS Triflate)[32] was used in place of Bu_4NI. The yield was increased notably, and as in the case of **8l**, the yield was up to 54%. It was also found that when the mole ratio of **7a**, **7b** to chloromethyl methyl ether was 1 : 2.4, the N^1,N^3-bisalkylated derivatives **13a** and **13b** were formed in 32% and 38% isolated yield, respectively. It is worth mentioning that none of the N^1,N^3-bisalkylated product was detected if **7c** or **7d** was the substrate. Interestingly, when chloromethyl methyl ether was substituted with benzyl chloromethyl ether, no bisalkylation product was found, which may due to the steric hindrance effect of the bulky benzyl group.

The structures of the target compounds could be verified from the mass spectral, ^1H-, ^{13}C-NMR, and ^1H–^1H NOESY data, and are firmly supported by a single crystal X-ray structure determination for compound **8f** (Fig. 4, Tables 1, 2).

Bioassay Results

Substituted HEPT analogues were screened for inhibition of HIV replication in MT-4 cells and CEM cells, and their bioassay data are shown in Tables 1 and 2. 1-Ethoxymethyl-5-isopropyl-6-(1-naphthylmethyl)thymine **8l** and 1-benzyloxymethyl-5-ethyl-6-(1-naphthylmethyl)thymine **8n** were the most promising compounds. They exhibited extremely potent inhibitory activity against HIV-1 replication, with an EC_{50} value of 17 nM, (0.0061 μg/ml), CC_{50} value of 38332 nM, and SI value of 2229 for **8l**, and an EC_{50} value of 17 nM, (0.0069 μg/ml), CC_{50} value of 325600 nM, and SI value of 1889 for **8n**, which were much better than those of HEPT (EC_{50}=7.0 μM, CD_{50}=740 μM).

Table 1. Anti-HIV-1 Activity of 6-Naphthylmethyl Substituted HEPT Analogs in MT-4 and CEM Cells

Compd.	IC_{50} (μM) MT-4	CC_{50} (μM) MT-4	SI MT-4	EC_{50} (μM) CEM	CEM (μM) CEM	SI CEM
8a	0.500	204.973	401	0.559	124.948	224
8b	0.649	190.903	289	0.762	124.521	163
8c	4.780	189.503	40	6.247	108.373	17
8d	0.076	53.236	708	0.111	58.396	524
8e	1.451	183.084	127	2.483	127.043	51
8f	0.213	111.307	377	0.494	106.433	216
8g	N	188.075	<1	>59.143	127.749	2
8h	0.065	42.199	664	0.130	52.046	400
8i	0.225	43.314	193	0.167	50.286	302
8j	0.041	77.389	1930	0.104	88.419	854
8k	0.795	39.838	50	0.275	33.790	123
8l	0.017	38.333	2229	0.060	32.086	538
8m	0.041	32.914	800	0.075	41.692	555
8n	0.017	32.560	1889	0.042	20.391	480
8o	0.234	30.710	131	0.220	20.667	94
8p	0.021	29.865	1404	0.048	19.266	399
12a	N	142.793	<1	>58.799	99.370	2
12b	45.601	181.727	4	>56.472	121.132	2
12d	15.606	173.604	11	25.795	120.594	5
12e	≥8.268	97.764	≤12	>12.340	92.859	8
12f	N	71.711	<1	>59.143	54.412	1
12g	3.270	158.354	48	4.412	97.178	22
12h	3.194	82.209	26	5.116	69.493	14
12j	4.066	34.079	8	3.444	24.264	7
12k	1.449	34.160	24	3.324	22.215	7
12l	6.688	31.773	5	>9.657	18.977	2
HEPT				7.0		

N: means not active. Biological activity data is currently being obtained.

Results and Discussion

Previous structure–activity relationship (SAR) of HEPT and its analogues shows that the length of the N-1 side chain is also crucial for the antiviral activity. The triggering effect of the 5-substituted group also helps to improve the binding affinity between the active binding site and the inhibitors,[33] and thus enhance biological activity.[34,35]

The 1-ethyloxymethyl was initially selected because of its suitable length, which resembles that of the MKC-442 side chain. The 1-benzyloxymethyl was chosen because TNK-651 has the same side chain at its *N*-1 position. The 1-hydroxyethyloxymethyl group is the same as that of HEPT. The variations of the substituted position from α- to β- of naphthylmethyl showed markedly reduced activity. This demonstrated that the naphthylmethyl aromatic plane needs to protrude in a certain direction for anti-HIV-1 RT inhibitory activity.

Based on its efficacy and safety profile, MKC-442 was advanced into clinical trials. Our focus was subsequently directed toward the further structural modification of the basic skeleton of this candidate. A substantial amount of work was done on the SAR, incorporating various 1-side chains and 5-alkyl groups. A driving force for this change was a concern with the ubiquitous presence of the two aromatic planes—the thymine and 6-benzyl group in the ligands for HIV-1 RT receptors. Within the chemical program, particular emphasis was placed on the incorporation of basic functionalities, which would aid in the binding affinity between the ligands and the receptor.

This paper highlights the *in vivo* SARs of a selected group of compounds, which incorporate a naphthylmethyl group as a replacement of the benzyl or phenythio group, resulting in an exceptionally potent series of novel HIV-1 RT inhibitors. This could be seen from the biological data compared with some other HEPT analogs reported in the literature. In the present study, based on the reported SAR, we focused our attention on the variation of the alkoxymethyl substituent at the *N*-1 position of the lead structure **2** (Chart 2, Table 1), the alkyl group at the 5-position, and alternation of the substitution position of 6-naphthylmethyl.

Generally speaking, variation of the 1-position group between hydroxyethoxymethyl, methoxymethyl, ethoxymethyl and benzoxymethyl often result in changes in anti-HIV-1 activity. The anti-HIV-1 activity increases as the 5-position substitution of the thymine ring is changed from Me, *n*-Pr, Et, and *i*-Pr, among which *i*-Pr is the most potent group in enhancing the biological activity. Sometimes an *n*-Pr substitution results in the decrease or complete loss of anti-HIV-1 activity. It is worthwhile to mention that compounds **9a** and **9b** had no activity in either of the two cell culture lines.

Since it was observed the α-series compounds are much more potent than the β-series, further analysis was conducted in detail into the SAR of the α-series compounds. Two

graphs in Fig. 2 present the activity expressed by μM for these compounds.

From Fig. 2, we can see clearly that the anti-HIV-1 activity in MT-4 cells fluctuated as the 5-alkyl group changed from methyl, ethyl, *i*-propyl to *n*-propyl, and increased as the *N*-1 side chain changed from $HOCH_2CH_2OCH_2$, CH_3OCH_2 to $CH_3CH_2OCH_2$, $PhCH_2OCH_2$, except for the only one without activity (**8g**), whose IC_{50} is shown in Fig. 2. as the point above the highest point. The two most potent compounds are **8l** and **8n** (EC_{50}=17 nM), with the ethyl and *i*-propyl substituted at the 5-position, ethoxymethyl and benzoxymethyl substituted at the *N*-1 position. The only compound (**8g**) without any effect in the HIV-1 infected MT-4 cells is the one with *n*-propyl at the 5-position and the methoxymethyl group at the *N*-1 side chain. This is in agreement with our former QSAR (CoMFA) model. A suitable length on the side chain on the *N*-1 is very crucial for the anti-HIV-1 activity. The *i*-propyl group is the most potent one in triggering the aromatic planes to adopt the conformation suitable for the combination between the drug ligand and the HIV-1 RT-NNBP, while an *n*-propyl group is less effective at improving the activity against HIV-1.

The similar fluctuations in the two graphs in Fig. 2 also indicated that these compounds show almost the same response in both cell lines. The compound with the lowest activity on HIV-1 infected cells is **8g**.

Apart from the above research, we have also done some work on the QSAR, which will be discussed here.

Based on the activity in MT-cells, we drew a Hansch QSAR equation as follow (Eq. 1).

$$\text{Log } 1/EC_{50} = -156.752 + 1.473I + 0.0103V_m - 3.653\text{C Log}P - 646.545O_2 + 359.767O_4 - 2.650\text{Dipole} \quad (1)$$

$$n=21,\ R=0.963,\ F(16,2)=29.645,\ p<0.001,\ s=0.32$$

I means indication variable, when naphthyl substitution is at the α-position, I=1, when naphthyl substitution is at the β-position, I=0; V_m means the volume of the molecule; C Log *P* means the calculated value of the lipid/water partition coefficient; O_2 means the charge distribution on the 2-O atom; O_4 means the charge distribution on the 4-O atom; Dipole means the dipole of the compounds. From Equation, we can see that the activity is related to the substitution position, molecular volume, partition coefficient, and the dipole of the compound.

In order to evaluate the binding affinity of different isomers with the HIV-1 RT, docking was conducted with a DOCK module and binding free energy (ΔG) was calculated (Fig. 3).

The different binding conformations and binding free energy of different of isomers were analyzed from the docking result. Generally speaking, the binding free energies of α-isomers are much more negative than those of their β-counterparts. The naphthyl planes of β-isomers are much more distorted than those of α-isomers, and the aromatic property decreased a lot in these β-isomers after binding with the HIV-1 RT NNBP. Thereafter we can conclude that the aromatic property of the small molecules could be the main sourse of the biological activity. It could be also deduced by computation that the activity also has a certain relation with ΔG.

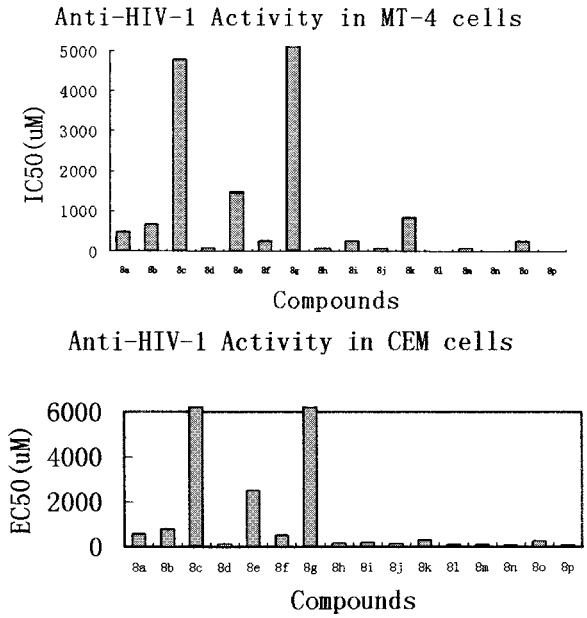
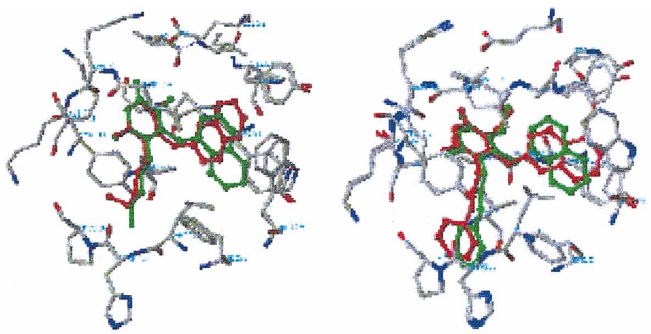


Fig. 2. Anti-HIV-1 Activity in MT-4 and CEM Cells of **8a**—**p**



8a (green) and **12a** (red) **8n** (green) and **12k** (red)

Fig. 3. Binding Conformation of Different Isomers in RT NNBP

Conclusion

The SAR Summary: 1. Changing the 1-position group between ethoxymethyl, methoxymethyl, benzoxymethyl, and hydroxyethoxymethyl, often results in variation of the anti-HIV-1 activity.

2. The anti-HIV-1 activity increases as the group at the 5-position of the thymine ring is changed from Me, *n*-Pr, Et, *i*-Pr. These conclusions agree with previous SAR findings.

3. When the naphthyl substitution position is changed from the α-position to the β-position, the bioactivity is decreased or completely lost, which means that the α-series compounds showed much higher activity that the β-series compounds.

4. *N*-1, *N*-3-Bisalkylating HEPT analogs have almost no activity against any HIV-1 infected cells, which is in agreement with previous findings.

It has been demonstrated that the benzyl group of the HEPT analog MKC-442 can be replaced by a naphthylmethyl group ring system to provide a novel and highly potent class of HIV-1 RT inhibitors. The substitution position of the naphthylmethyl group with the thymine skeleton is very important for anti-HIV activity. The α-series compound showed much higher activity that the β-series compound.

In conclusion, the 6-(1-naphthylmethyl)substituted HEPT analogues behave as typical nonnucleoside reverse transcriptase inhibitors (NNRTIs) against HIV-1.

Experimental

Melting points were measured on a WRS-1 digital melting point instrument. IR spectra were recorded on a Nicolet FT-IR 360 spectrometer as KBr pellets. ^{1}H-NMR spectra were obtained on a Bruker DMX 500 MHz spectrometer in DMSO-d_6 as solvent. Chemical shifts were reported in ppm units from TMS as an internal standard. ^{13}C-NMR spectra were run on a Bruker DMX 500 MHz spectrometer using DMSO-d_6 as solvent. 2D-NOESY spectra were performed on a Bruker DMX 500 MHz, and X-crystallography was recorded on Bruker Smart APEX X-ray apparatus. Mass spectra were obtained on a HP 5989A spectrometer by direct inlet at 70 eV. Column chromatography was performed with silica gel G. Analytical TLC was performed with silica gel G plates. Reagents and solvents were all AR grade and used without further purification with the exception of THF (distilled over sodium/benzophenone), CH_2Cl_2 (distilled over anhydrous Na_2SO_4), MeCN (distilled over P_2O_5, and dried over anhydrous K_2CO_3) and 1,3-dioxolane (distilled over anhydrous Na_2SO_4). All air-sensitive reactions were run under an atmosphere of nitrogen. All glassware was oven-dried prior to use. The reactions under N_2 were carried out using Schlenk techniques.

Cell Lines, Virus and Cell Cultures The CEM cell line and the MT-4 cell line were cultured in RPMI/10 %FCS, and the medium replaced twice a week. The laboratory-adapted strain HIVLAV B stock was prepared from the supernatant of infected CEM cells line, and aliquots were kept frozen at −80 °C until use.

Anti-HIV-1 Activity Assays Anti-HIV-1 activity was monitored by the efficiency of drug compounds to inhibit the cytopathogenicity of HIV in MT-4 cells by the following method.[36,37] Briefly, 3×10^5 MT-4 cells were first pre-incubated with 100 μl of various concentrations of drug compounds dissolved in DMSO or in H_2O and then diluted in phosphate buffer saline solution for 1 h at 37 °C. Then 100 μl of an appropriate virus dilution was added to the mixture, and the cells incubated for 1 h at 37 °C. After three washes, the cells were re-suspended in culture medium in the presence or absence of drug compounds. Cultures were then continued for 7 d at 37 °C under a 5% CO_2 atmosphere, and the medium was replaced on day 3 post-infection with culture medium supplemented or without drug compounds. Each culture condition was carried out in duplicate. Viral cytopathogenicity was followed each day with an inverted optical microscope. Typically, the virus dilution used in this assay (multiplicity of infection of 1.1 CCID/cell) led to cytopathogenicity on day 5 post-infection. The inhibitory concentration of drug compounds was expressed as the concentration that caused 50% inhibition of viral cytopathogenicity (EC_{50}) without direct toxicity for the cells. The cytotoxic concentration (CC_{50}) of the drug compounds was monitored based on the growth of noninfected cells by trypan blue exclusion and corresponded to the concentration required to cause 50% cell death. It should be emphasized that when compounds required the addition of DMSO to be solubilized in water, the concentration in the volume of DMSO used was always less than 10% with respect to water (the final concentration of DMSO in MT-4 cell incubation medium being less than 2%). Since DMSO could affect the antiviral activity of the tested drugs,[38] antiviral assays in which solutions containing equal concentrations of DMSO in water were used. Moreover, the final DMSO concentration (1/1000) was well below the concentration which affected the in vitro HIV-1 infection of T-cells.

Chemical Syntheses Ethyl 2-bromoalkanoates **4a**—**d** were prepared by esterification of 2-bromoalkanoic acids with ethanol according to the reported methods.[39] **4a**: R=Me, Yield: 80%, bp 49 °C/15 mmHg (lit. bp 66 °C/27 mmHg); **4b**: R=Et, Yield: 66%, bp 174—178 °C (lit. bp 176—178 °C); **4c**: R=*n*-Pr, Yield: 86%, bp 189—191 °C (lit. bp 190—192 °C,[40] 93—96 °C/26 mmHg, 84—86 °C/16 mmHg, 84—85 °C/10 mmHg[41]); **4d**: R=*i*-Pr, Yield: 88%, bp 186—188 °C (lit. bp 185—187 °C). 1-Naphthylacetonitrile was prepared according to the literature.[42—44]

General Procedure A for Ethyl 2-Alkyl-3-oxo-4-(1-naphthyl)butyrates 5a—d Activated zinc dust (zinc powder washed sequentially with 3 N aq. HCl, water, EtOH, Et_2O, and dried *in vacuo*; 32 g, 492 mol) was suspended in dry THF (200 ml) and refluxed under a nitrogen atmosphere. A few drops of ethyl 2-bromoalkanoate **4a**—**d** were added to initiate the reaction. After the appearance of a green color (*ca.* 1 h), 1-naphthylacetonitrile (17 g, 102 mmol) was added in one portion followed by the dropwise addition of ethyl 2-bromoalkanoates **4a**—**d** (403 mmol) over 1 h. The reaction mixture was refluxed for an additional 10 min, diluted with THF (750 ml), and quenched with aq K_2CO_3 (50%, 113 ml). Rapid stirring for 45 min gave two distinct layers. The THF layer was decanted, the residue washed with THF (2×200 ml) and the combined THF fractions were treated with aq. HCl (10%, 100 ml) at room temperature for 45 min. The mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (600 ml), and washed with sat. aq. $NaHCO_3$ (500 ml). The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give an oily red residue (37 ml, 36 g). This product can be used without further purification for the synthesis of compound **6** by knowing the content (34.65—47.47%) of ethyl 2-alkyl-3-oxo-4-(1-naphthyl)butyrates **5a**—**d** in the oily residue, which is determined by GC-MS. Further purification of compounds **5a**—**d** could be achieved by chromatography.

5a: R=Me; Yield: 45%; [silica gel G, 300 g; petroleum ether (bp 60—90 °C); petroleum ether (bp 60—90 °C)/Et_2O, 6 : 1] to give a clear yellowish oil; **5b**: R=Et; Yield: 60%; [silica gel G, 300 g; petroleum ether (bp 60—90 °C); petroleum ether (bp 60—90 °C)/Et_2O, 5 : 1] to give a clear yellowish oil; **5c**: R=*n*-Pr; Yield: 51%; [silica gel G, 300 g; petroleum ether (bp 60—90 °C); petroleum ether (bp 60—90 °C)/Et_2O, 5 : 2] to give a clear yellowish oil, **5d**: R=*i*-Pr; Yield: 45%; [silica gel G, 300 g; petroleum ether (bp 60—90 °C); petroleum ether (bp 60—90 °C)/Et_2O, 5 : 2] to give a clear yellowish oil.

General Procedure B for 5-Alkyl-6-(1-naphthylmethyl)-2-thiouracils 6a—d Sodium (20 g) was dissolved in anhydrous EtOH (40 ml), and then thiourea (48 g, 631 mmol) and the red oily residue (10 ml, the content of compound 2 is *ca.* 12.5 mmol) were added to the clear solution. The reaction mixture was refluxed for 6.5 h and monitored by TLC, evaporated *in vacuo* at 40—50 °C until nearly dry, and the residues dissolved in H_2O (400 ml). The 2-thiothymines were precipitated by addition of conc. aq. HCl (70 ml) and subsequent acidification to pH 4 with glacial AcOH to give a yellowish precipitate, which was sequentially washed with cold EtOH and cold Et_2O to obtain compounds **6a**—**d** as a white crystal or powder. This product can also be used without further purification for the synthesis of compound **7**. Compounds **6a**—**d** can be further purified by recrystallization from suitable solvent to give a white crystal.

5-Methyl-6-(1-naphthylmethyl)-2-thiouracil (6a) According to general procedure B, the product was obtained as a white fine crystallized powder, mp 228—231 °C (EA); Yield: 95%; FT-IR (KBr): ν=3141 (NH), 3051 (NH), 2949 (Me), 1670 (C=O), 1176 (C=S) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.70 (s, 3H, Me), 4.32 (s, 2H, CH_2), 7.07—8.12 (m, 7H, naphthyl), 12.30 (s, 1H, N-1H), 12.51 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=10.2 (Me), 32.7 (CH_2), 113.1 (C-5), 123.9—133.9 (10C, naphthyl), 149.6 (C-6), 162.4 (C-2), 174.7 (C-4); EI-MS: *m*/*z* (%)=282 (4.12), 192 (32.39), 160 (57.19), 141 (1.68), 128 (51.60); HR-MS: *m*/*z* Calcd for $C_{16}H_{14}N_2OS$: 282.0827. Found: 282.0839. *Anal.* Calcd for $C_{16}H_{14}N_2OS$ (282.4): C, 68.06; H, 5.00; N, 9.92; S, 11.36. Found: C, 68.16; H, 5.10; N, 9.98; S, 11.47.

5-Ethyl-6-(1-naphthylmethyl)-2-thiouracil (6b) According to general procedure B, the product was obtained as a white needle crystal, mp 188—191 °C (95% EtOH); Yield: 61%; FT-IR (KBr): ν=3423 (NH), 2959 (Me), 2887 (CH_2), 1676 (C=O), 1187 (C=S) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.82 (t, 3H, *J*=7.35, Me), 2.19 (q, 2H, *J*=7.35 Hz, CH_2), 4.32 (s, 2H, CH_2), 7.08—8.14 (m, 7H, naphthyl), 12.28 (s, 1H, N-1H), 12.50 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=13.5 (Me), 18.3 (CH_2), 32.3 (CH_2), 118.9 (C-5), 123.9—133.8 (10C, naphthyl), 149.3 (C-6), 161.9 (C-2), 174.9 (C-4); EI-MS: *m*/*z* (%)=296 (100), 281 (23.8), 267 (24.53), 141 (26.37), 128 (14.34); HR-MS: *m*/*z* Calcd for $C_{17}H_{16}N_2OS$: 296.0983. Found: 296.0971. *Anal.* Calcd for $C_{17}H_{16}N_2OS$ (296.4): C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.97; H, 5.49; N, 9.55; S, 10.95.

5-*n*-Propyl-6-(1-naphthylmethyl)-2-thiouracil (6c) According to general procedure B, the product was obtained as a white powder; mp 170—173 °C (anhydrous EtOH); yield 85%; FT-IR (KBr): ν=3625 (NH), 3051 (Me), 2958 (CH_2), 2866 (CH), 1773 (C=O), 1630 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.70 (t, 3H, *J*=7.3 Hz, Me), 1.22 (m, 2H, *J*=7.6 Hz, CH_2), 2.14 (t, 2H, *J*=7.7 Hz, CH_2), 4.31 (s, 2H, CH_2), 7.08—8.14 (m, 7H, naphthyl), 12.29 (s, 1H, N-1H), 12.49 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=14.2 (Me), 21.8 (CH_2), 26.7 (CH_2), 32.3 (CH_2), 117.4 (C-5), 123.8—133.7 (10C, naphthyl), 149.6 (C-6), 162.0 (C-2), 174.8 (C-4); EI-MS: *m*/*z* (%)=210 (87.14), 295 (9.42), 281 (59.64), 264 (10.61), 141 (28.40), 128 (12.41); HR-MS: *m*/*z* Calcd for $C_{18}H_{18}N_2OS$: 310.1140. Found: 310.1157. *Anal.* Calcd for $C_{18}H_{18}N_2OS$ (310.1): C, 69.65; H, 5.84; N, 9.02; S, 10.33. Found: C, 69.50; H, 5.95; N, 9.13; S, 10.22.

5-Isopropyl-6-(1-naphthylmethyl)-2-thiouracil (6d) According to general procedure B, the product was obtained as a white cubic crystal; mp 228—232 °C (EA with EtOH); Yield: 80%; FT-IR (KBr): ν=3403 (NH), 2952 (Me), 1665 (C=O), 1163 (C=S) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.07 (d, 6H, *J*=6.9 Hz, 2Me), 2.61 (m, 1H, *J*=6.9 Hz, CH), 4.33 (s, 2H, CH_2),

7.07—8.12 (m, 7H, naphthyl), 12.21 (s, 1H, N-1H), 12.40 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=20.1 (2Me), 27.2 (CH), 32.6 (CH_2), 121.3 (C-5), 123.8—133.8 (10C, naphthyl), 148.8 (C-6), 161.1 (C-2), 174.8 (C-4); EI-MS: *m/z* (%)=310 (100), 295 (73.09), 267 (14.36), 141 (34.09), 128 (14.41); HR-MS: *m/z* Calcd for $C_{18}H_{18}N_2OS$: 310.1140. Found: 310.1151. *Anal.* Calcd for $C_{18}H_{18}N_2OS$ (310.4): C, 69.65; H, 5.84; N, 9.02; S, 10.33. Found: C, 69.60; H, 5.90; N, 9.13; S, 10.20.

General Procedure C for 5-Alkyl-6-(1-naphthylmethyl)uracils 7a—d The 6-(1-naphthylmethyl)-5-alkyl-2-thiouracils (**6a**—**d**) (3.35 g, 12 mmol) were suspended in 10% aq chloroacetic acid (500 ml) and the solution was refluxed for 24 h to 48 h, till the TLC showed that no raw material was found. After cooling to room temperature, the precipitate was filtered off, sequentially washed with cold EtOH and cold Et_2O, and then dried *in vacuo* to give compound **7a**—**d** as a white powder. This product can also be used without further purification for the synthesis of compound **8**. Compounds **7a**—**d** were purified by recrystallization with a suitable solvent to give a white crystal.

5-Methyl-6-(1-naphthylmethyl)uracil (7a) According to general procedure C, the product was obtained as a white cubic crystal, mp 266—268 °C (abs. EtOH); Yield: 67%; FT-IR (KBr): ν=3417 (NH), 2829 (Me), 1737 (C=O), 1660 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.65 (s, 3H, Me), 4.22 (s, 2H, CH_2naphthyl), 7.12—8.12 (m, 7H, naphthyl), 10.76 (s, 1H, N-1H), 11.11 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=9.9 (Me), 33.1 (CH_2), 106.8 (C-5), 123.7—133.8 (10C, naphthyl), 148.9 (C-6), 151.4 (C-2), 165.3 (C-4); EI-MS: *m/z* (%)=266 (100), 251 (34.50), 141 (36.89), 128 (82.98); HR-MS: *m/z* Calcd for $C_{16}H_{14}N_2O_2$: 266.1055. Found: 266.1051. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$ (280.3): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.22; N, 1.44.

5-Ethyl-6-(1-naphthylmethyl)uracil (7b) According to general procedure C, the product was obtained as a white crystal, mp 206—209 °C (95% EtOH); Yield: 71%; FT-IR (KBr): ν=3407 (NH), 2967 (Me), 1721 (C=O), 1648 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.80 (t, 3 H, *J*=7.35 Hz, Me), 2.15 (q, 2H, *J*=7.35, CH_2), 4.22 (s, 2H, CH_2naphthyl), 7.14—8.14 (m, 7H, naphthyl), 10.73 (s, 1H, N-1H), 11.08 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=13.9 (Me), 18.1 (CH_2), 32.7 (CH_2), 112.9 (C-5), 123.7—133.8 (10C, naphthyl), 148.6 (C-6), 151.4 (C-2), 164.9 (C-4); EI-MS: *m/z* (%)=280 (100), 265 (56.75), 251 (18.89), 141 (66.42), 128 (63.90); HR-MS: *m/z* Calcd for $C_{17}H_{16}N_2O_2$: 280.1212. Found: 280.1201. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$ (280.3): C, 74.84; H, 5.75; N, 9.99. Found: C, 74.80; H, 5.60; N, 9.83.

5-*n*-Propyl-6-(1-naphthylmethyl)uracil (7c) According to general procedure C, the product was obtained as a white crystal, mp 211—214 °C (EtOH); Yield 94%; FT-IR (KBr): ν=3394 (NH), 2940 (Me), 1707 (C=O), 1648 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.70 (t, 3H, *J*=7.3 Hz, Me), 1.21 (m, 2H, *J*=7.6 Hz, CH_2), 2.10 (t, 2H, *J*=7.7 Hz, CH_2), 4.22 (s, 2H, CH_2naphthyl), 7.14—8.14 (m, 7H, naphthyl), 10.75 (s, 1H, N-1H), 11.09 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=14.2 (Me), 22.3 (CH_2), 26.7 (CH_2), 32.8 (CH_2), 111.5 (C-5), 123.8—133.8 (10C, naphthyl), 149.0 (C-6), 151.4 (C-2), 165.1 (C-4); EI-MS: *m/z* (%)=294 (63.39), 279 (5.1), 265 (100), 141 (52.46), 128 (22.03); HR-MS: *m/z* Calcd for $C_{18}H_{18}N_2O_2$: 294.1368. Found: 294.1349. *Anal.* Calcd for $C_{18}H_{18}N_2O_2$ (294.3): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.28; H, 6.18; N, 9.32.

5-Isopropyl-6-(1-naphthylmethyl)uracil (7d) According to general procedure C, the product was obtained as a white cubic crystal, mp 199—203 °C (EA); Yield: 97%; FT-IR (KBr): ν=3394 (NH), 2961 (Me), 2870 (Me), 1708 (C=O), 1647 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.06 (d, 6 H, *J*=7.7 Hz, 2Me), 2.50 (m, 1H, *J*=7.7 Hz, CH), 4.23 (s, 2H, CH_2naphthyl), 7.12—8.13 (m, 7H, naphthyl), 10.70 (s, 1H, N-1H), 10.99 (s, 1H, N-3H); ^{13}C- NMR (500 MHz): δ=20.6 (2Me), 27.0 (CH), 33.2 (CH_2), 115.7 (C-5), 123.8—133.8 (10C, naphthyl), 148.2 (C-6), 151.6 (C-2), 164.3 (C-4); EI-MS: *m/z* (%)=294 (74.62), 279 (100), 141 (56.01), 128 (24.37); HR-MS: *m/z* Calcd for $C_{18}H_{18}N_2O_2$: 294.1368. Found: 294.1346. *Anal.* Calcd for $C_{18}H_{18}N_2O_2$ (294.3): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.23; H, 6.14; N, 9.35.

General Procedure D for 1-[(2-Hydroxyethoxy)methyl]-5-alkyl-6-(1-naphthylmethyl)uracil 8a—d *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 5.5 ml, 22 mmol) was added under a nitrogen atmosphere to 5-alkyl-6-(1-naphthylmethyl) uracils **7a**—**d** (10 mmol) suspended in CH_2Cl_2 (25 ml), and the mixture was stirred at room temperature for 3 h. To this was further gently added 1,3-dioxolane (0.85 ml, 12 mmol) and tin tetrachloride (1.4 ml, 12 mmol) by keeping the nitrogen pressure positive. The resulting mixture was then refluxed for 17 h and the reaction mixture thus obtained was poured into a mixture of methanol and water (25 ml, 1 : 1) containing sodium bicarbonate (5.5 g). After stirring for 2 h, the resulting mixture was filtered through sellaite and the filter cake was washed with CH_2Cl_2 (25 ml). The filtrate was separated into two distinct layers, the organic layer was separated, and the inorganic layer was washed with CH_2Cl_2 (3×25 ml). The organic fraction was combined and dried over anhydrous Na_2SO_4 overnight. The clear organic solution thus obtained was filtered and the filtrate was concentrated *in vacuo* to the appearance of a white precipitate. This residue was stored in a refrigerator overnight and was filtered and the filter cake was washed with a small amount of CH_2Cl_2 (5 ml) to give the desired target molecules 1-[(2-hydroxyethoxy)methyl]-5-alkyl-6-(1-naphthylmethyl)uracils **8a**—**d**. Column chromatography (25% EtOAc in cyclohexane) gave a white foam, which was recrystallized from a suitable solvent to give **8a**—**d** as a white crystal.

1-[(2-Hydroxyethoxy)methyl]-5-methyl-6-(1-naphthylmethyl)uracil (8a) According to general procedure D, the product was obtained as a white crystal, mp 197—199 °C (EtOAc); Yield 18%; FT-IR (KBr): ν=3414 (NH), 1701 (C=O), 1685 (C=O), 1066 (C–OH) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.78 (s, 3H, Me), 3.42 (m, 4H, *J*≈4.62 Hz, CH_2CH_2), 4.52 (s, 2H, CH_2naphthyl), 4.98 (s, 2H, NCH_2), 7.11—8.18 (m, 10H, naphthyl), 11.55 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=10.8 (Me), 31.2 (CH_2naphthyl), 60.4 (OCH_2), 70.9 (OCH_2), 73.3 (NCH_2), 110.5 (C-5), 123.5—133.9 (10C, naphthyl), 149.4 (C-6), 152.0 (C-2), 163.8 (C-4); EI-MS: *m/z* (%)=340 (1.52), 278 (83.71), 266 (100.0), 251 (49.30), 206 (28.53), 178 (17.21), 141 (18.82), 128 (33.93); HR-MS: *m/z* Calcd for $C_{19}H_{20}N_2O_4$: 340.1423. Found: 340.1429. *Anal.* Calcd for $C_{19}H_{20}N_2O_4$ (340.1): C, 60.25; H, 5.92; N, 8.23. Found: C, 60.19; H, 5.83; N, 8.18.

1-[(2-Hydroxyethoxy)methyl]-5-ethyl-6-(1-naphthylmethyl)uracil (8b) According to general procedure D, the product was obtained as a white crystal, mp 173—175 °C (EtOAc); Yield 37%; FT-IR (KBr): ν=3406 (NH), 1713 (C=O), 1665 (C=O), 1104 (C–O), 1059 (C–OH) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.89 (t, 3H, *J*=7.3 Hz, Me), 2.26 (q, 2H, *J*=7.3 Hz, CH_2), 3.42 (m, 4H, *J*≈4.74 Hz, CH_2CH_2), 4.51 (s, 2H, CH_2naphthyl), 4.95 (s, 2H, NCH_2), 7.10—8.20 (m, 7H, naphthyl), 11.52 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.1 (Me), 19.1 (CH_2), 30.7 (CH_2naphthyl), 60.4 (OCH_2), 71.0 (OCH_2), 73.3 (NCH_2), 116.5 (C-5), 123.5—133.9 (10C, naphthyl), 149.0 (C-6), 152.1 (C-2), 163.5 (C-4); DEPT (45): 13.9 (Me), 18.8 (CH_2), 30.5 (CH_2naphthyl), 60.1 (OCH_2), 70.7 (OCH_2), 73.0 (NCH_2), 123.3—128.9 (7C, naphthyl); EI-MS: *m/z* (%)=354 (1.30), 292 (76.39), 280 (100.0), 265 (41.09), 251 (26.36), 151 (19.73), 141 (48.48), 128 (36.42), 115 (18.33); HR-MS: *m/z* Calcd for $C_{20}H_{22}N_2O_4$: 354.1580. Found: 354.1590. *Anal.* Calcd for $C_{20}H_{22}N_2O_4$ (354.2): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.69; H, 6.20; N, 7.85.

1-[(2-Hydroxyethoxy)methyl]-5-*n*-propyl-6-(1-naphthylmethyl)uracil (8c) According to general procedure D, the product was obtained as a white powder, mp 158—159 °C (EtOAc); Yield 9%; FT-IR (KBr): ν=3425 (NH), 1711 (C=O), 1666 (C=O), 1105 (C–O), 1060 (C–OH) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.76 (t, 3H, *J*=6.9 Hz, Me), 1.32 (q, 2H, *J*=6.9 Hz, CH_2), 2.22 (t, 2H, *J*=7.1 Hz, CH_2), 3.39—3.43 (m, 4H, *J*≈4.74 Hz, CH_2CH_2), 4.51 (s, 2H, CH_2naphthyl), 4.94 (s, 2H, NCH_2), 7.10—8.20 (m, 7H, naphthyl), 11.53 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=13.8 (Me), 21.9 (CH_2), 27.1 (CH_2), 30.2 (CH_2naphthyl), 59.8 (OCH_2), 70.4 (OCH_2), 72.6 (NCH_2), 114.6 (C-5), 123.0—133.3 (10C, naphthyl), 148.7 (C-6), 151.5 (C-2), 163.1 (C-4); EI-MS: *m/z* (%)=368 (4.82), 306 (51.48), 294 (100.0), 277 (39.95), 265 (81.61), 141 (38.04), 128 (14.82), 115 (14.07); HR-MS: *m/z* Calcd for $C_{21}H_{24}N_2O_4$: 368.1736. Found: 368.1744. *Anal.* Calcd for $C_{21}H_{24}N_2O_4$ (368.2): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.44; H, 6.75; N, 7.56.

1-[(2-Hydroxyethoxy)methyl]-5-isopropyl-6-(1-naphthylmethyl)uracil (8d) According to general procedure D, the product was obtained as a white crystal, mp 191—193 °C (EtOAc); Yield 31%; FT-IR (KBr): ν=3477 (NH), 1693 (C=O), 1609 (C=O), 1109 (C–O), 1070 (C–OH) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.14 (d, 6H, *J*=6.9 Hz, 2Me), 2.50 (m, 1H, *J*=7.1 Hz, CH), 3.42 (m, 4H, *J*≈4.74 Hz, CH_2CH_2), 4.52 (s, 2H, CH_2naphthyl), 4.98 (s, 2H, NCH_2), 7.12—8.18 (m, 7H, naphthyl), 11.41 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=20.9 (2Me), 28.4 (CH), 31.3 (CH_2naphthyl), 60.6 (OCH_2), 71.1 (OCH_2), 73.7 (NCH_2), 119.3 (C-5), 123.8—134.1 (10C, naphthyl), 149.0 (C-6), 152.3 (C-2), 163.1 (C-4); EI-MS: *m/z* (%)=368 (0.55), 306 (78.03), 291 (100.0), 279 (14.40), 141 (24.24), 128 (5.69), 115 (8.63); HR-MS: *m/z* Calcd for $C_{21}H_{24}N_2O_4$: 368.1736. Found: 368.1748. *Anal.* Calcd for $C_{21}H_{24}N_2O_4$ (368.4): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.47; H, 6.73; N, 7.51.

General Procedure E for 1-Methoxymethyl-5-alkyl-6-(1-naphthylmethyl)uracils 8e—h When the silylation of 5-Alkyl-6-(1-naphthylmethyl)uracils (25 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (11.19 g, 55 mmol, 13.6 ml) in CH_2Cl_2 (30 ml) was completed using the above

method, Bu_4NI (93 mg, 0.25 mmol) and chloromethyl methyl ether (2.84 g, 30.0 mmol, 2.8 ml) were added to the above solution. The mixture was heated to reflux for 2 h and allowed to cool to room temperature. When the reaction was finished (TLC analysis), the reaction mixture was poured into a saturated $NaHCO_3$ solution (10 ml), EtOH (5 ml) and ice (5 ml), and stirred for an additional 1 h. The organic phase was washed with brine (15 ml), dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was crystallized from EtOH or EtOAc to give the target compounds. Column chromatography (25% EtOAc in cyclohexane) gave a white foam, which was recrystallized with a suitable solvent to give **8e**—**h** as a white crystal.

1-Methoxymethyl-5-methyl-6-(1-naphthylmethyl)uracil (8e) According to general procedure E, the product was obtained as a white crystal, mp 188—189 °C (EtOAc); Yield 42%; FT-IR (KBr): ν=3176 (NH), 3048 (NH), 1701 (C=O), 1676 (C=O), 1081 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.78 (s, 3H, Me), 3.22 (s, 3H, OMe), 4.46 (s, 2H, CH_2naphthyl), 4.91 (s, 2H, NCH_2), 7.11—8.16 (m, 7H, naphthyl.), 11.54 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=10.8 (Me), 31.1 (CH_2naphthyl), 56.5 (OCH_3), 74.3 (NCH_2), 110.6 (C-5), 123.4—133.9 (10C, naphthyl), 149.2 (C-6), 152.1 (C-2), 163.8 (C-4); EI-MS: *m/z* (%)=310 (1.54), 278 (97.53), 263 (5.73), 141 (18.28), 128 (6.20), 115 (15.04); HR-MS: *m/z* Calcd for $C_{18}H_{18}N_2O_3$: 310.1317. Found: 310.1311. *Anal.* Calcd for $C_{18}H_{18}N_2O_3$ (310.1): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.56; H, 5.77; N, 9.12.

1-Methoxymethyl-5-ethyl-6-(1-naphthylmethyl)uracil (8f) According to general procedure E, the product was obtained as a white crystal, mp 169—170 °C (EtOAc); Yield 37%; FT-IR (KBr): ν=3147 (NH), 3091 (NH), 1705 (C=O), 1650 (C=O), 1083 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.91 (t, 3H, J=7.35 Hz, Me), 2.27 (q, 2H, J=7.35 Hz, CH_2), 3.22 (s, 3H, Me), 4.48 (s, 2H, CH_2naphthyl), 4.88 (s, 2H, NCH_2), 7.11—8.20 (m, 7H, naphthyl), 11.55 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.0 (Me), 19.1 (CH_2), 30.6 (CH_2naphthyl), 56.6 (OCH_3), 74.3 (NCH_2), 116.6 (C-5), 123.5—133.9 (10C, naphthyl), 148.8 (C-6), 152.2 (C-2), 163.4 (C-4); EI-MS: *m/z* (%)=324 (2.53), 292 (100.0), 277 (51.29), 234 (12.75), 141 (18.41), 128 (5.33); HR-MS: *m/z* Calcd for $C_{19}H_{20}N_2O_3$: 324.1474. Found: 324.1477. *Anal.* Calcd for $C_{19}H_{20}N_2O_3$ (324.1): C, 70.35; H, 6.21; N, 8.64. Found: C, 70.28; H, 6.18; N, 8.66.

1-Methoxymethyl-5-*n*-propyl-6-(1-naphthylmethyl)uracil (8g) According to general procedure E, the product was obtained as a white crystal, mp 150—152 °C (EtOAc); Yield 46%; FT-IR (KBr): ν=3157 (NH), 3017 (NH), 2959 (Me), 2872 (CH_2), 2826 (CH_2), 1708 (C=O), 1648 (C=O), 1083 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.77 (t, 3H, J=7.35 Hz, Me), 1.33 (m, 2H, J=7.35 Hz, CH_2), 2.22 (t, 2H, J=7.35 Hz, CH_2), 3.21 (s, 3H, Me), 4.48 (s, 2H, CH_2naphthyl), 4.87 (s, 2H, NCH_2), 7.11—8.19 (m, 7H, naphthyl), 11.53 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.3 (Me), 22.5 (CH_2), 27.6 (CH_2), 30.7 (CH_2naphthyl), 56.6 (OMe), 74.3 (NCH_2), 115.3 (C-5), 123.5—133.9 (10C, naphthyl), 149.1 (C-6), 152.1 (C-2), 163.6 (C-4); EI-MS: *m/z* (%)=338 (12.20), 306 (62.56), 277 (100.0), 234 (18.73), 171 (18.60), 141 (20.87); HR-MS: *m/z* Calcd for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1638. *Anal.* Calcd for $C_{20}H_{22}N_2O_3$ (338.2): C, 70.99; H, 6.55; N, 8.82. Found: C, 70.88; H, 6.39; N, 8.88.

1-Methoxymethyl-5-isopropyl-6-(1-naphthylmethyl)uracil (8h) According to general procedure E, the product was obtained as a white crystal, mp 171—172 °C (EtOAc); Yield 39%; FT-IR (KBr): ν=3180 (NH), 3042 (NH), 1705 (C=O), 1667 (C=O), 1077 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.16 (d, 6H, J=7.35 Hz, 2Me), 2.65 (m, 1H, J=7.35 Hz, CH), 3.24 (s, 3H, Me), 4.51 (s, 2H, CH_2naphthyl), 4.93 (s, 2H, NCH_2), 7.13—8.19 (m, 7H, naphthyl), 11.46 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=20.6 (2Me), 28.1 (CH), 31.0 (CH_2naphthyl), 56.6 (OMe), 74.5 (NCH_2), 119.1 (C-5), 123.5—133.8 (10C, naphthyl), 148.4 (C-6), 152.1 (C-2), 162.7 (C-4); EI-MS: *m/z* (%)=338 (4.47), 306 (75.79), 291 (100.0), 248 (16.46), 171 (19.88), 141 (24.04); HR-MS: *m/z* Calcd for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1622. *Anal.* Calcd for $C_{20}H_{22}N_2O_3$ (338.4): C, 70.99; H, 6.55; N, 8.82. Found: C, 70.79; H, 6.33; N, 8.84.

General Procedure F for 1-Ethoxymethyl-5-alkyl-6-(1-naphthylmethyl)uracils 8i—l 5-Alkyl-6-(1-naphthylmethyl)uracils (3 mmol) were silylated with 1,1,1,3,3,3-hexamethyl disilazane (HMDS) (5 ml) in the presence of $(NH_4)_2SO_4$ (10 mg). When the silylation was complete, the excess of HMDS was evaporated *in vacuo* to yield translucent yellow oil, which was dissolved in anhydr. MeCN (10 ml) and cooled to −35 °C. Trimethylsilyl trifluoromethanesulfonate (TMS triflate) (0.26 g, 2.79 mmol) was added in one portion, followed by the dropwise addition of chloromethyl ethyl ether (0.34 g, 0.34 ml, 3.6 mmol). After this, the mixture was stirred for 3 h at −35 °C. When the reaction was finished (TLC analysis), the mixture was quenched with ice cold sat. $NaHCO_3$ (10 ml) and evaporated to near dryness by coevaporation with ethanol (2×50 ml). The resulting solid was suspended in Et_2O (200 ml) and the mixture stirred for 1 h. After filtration the residue was extracted with Et_2O (100 ml) and the combined organic fraction was evaporated to furnish the crude products, 1-ethoxymethyl-5-alkyl-6-(1-naphthylmethyl)uracils **8i**—**l**. Column chromatography (10→25%) EtOAc in petroleum ether gave a white foam, which was recrystallized from a suitable solvent to give **8i**—**l** as a white crystal or powder.

1-Ethoxymethyl-5-methyl-6-(1-naphthylmethyl)uracil (8i) According to general procedure F, the product was obtained as a white crystal, mp 192—194 °C (EtOAc/EtOH); Yield 37%; FT-IR (KBr): ν=3423 (NH), 1707 (C=O), 1645 (C=O), 1108 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.18 (t, 3H, J≈7.2 Hz, Me), 1.97 (s, 3H, Me), 3.59 (q, 2H, J≈7.1 Hz, OCH_2), 4.55 (s, 2H, CH_2, CH_2naphthyl), 5.05 (s, 2H, NCH_2), 7.00—8.07 (m, 7H, naphthyl), 8.6 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=10.7 (Me), 15.0 (Me), 31.0 (CH_2naphthyl), 65.1 (OCH_2), 73.1 (NCH_2), 111.5 (C-5), 122.5—134.0 (10C, naphthyl), 149.8 (C-6), 152.8 (C-2), 163.6 (C-4); EI-MS: *m/z* (%)=324 (0.76), 278 (100.0), 141 (15.07), 128 (11.07); HR-MS: *m/z* Calcd for $C_{19}H_{20}N_2O_3$: 324.1474. Found: 324.1484. *Anal.* Calcd for $C_{19}H_{20}N_2O_3$ (324.4): C, 70.35; H, 6.21; N, 8.64. Found: C, 70.22; H, 6.11; N, 8.39.

1-Ethoxymethyl-5-ethyl-6-(1-naphthylmethyl)uracil (8j) According to general procedure F, the product was obtained as a white crystal, mp 176—178 °C (EtOAc); Yield 24%; FT-IR (KBr): ν=3158 (NH), 3023 (NH), 1707 (C=O), 1648 (C=O), 1087 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.90 (t, 3H, J=7.3 Hz, Me), 0.98 (t, 3H, J=7.0 Hz, Me), 2.26 (q, 2H, J=7.3 Hz, CH_2), 3.43 (q, 2H, J=7.0 Hz, OCH_2), 4.50 (s, 2H, CH_2naphthyl), 4.93 (s, 2H, NCH_2), 7.10—8.20 (m, 7H, naphthyl), 11.52 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.1 (Me), 15.2 (Me), 19.1 (CH_2), 30.8 (CH_2naphthyl), 64.3 (OCH_2), 72.8 (NCH_2), 116.5 (C-5), 123.5—133.9 (10C, naphthyl), 149.0 (C-6), 152.1 (C-2), 163.5 (C-4); DEPT (45): 13.9 (Me), 15.0 (Me), 18.8 (CH_2), 30.5 (CH_2naphthyl), 64.0 (OCH_2), 72.5 (NCH_2), 123.3—128.9 (7C, naphthyl); EI-MS: *m/z* (%)=338 (0.78), 292 (100.0), 277 (52.34), 141 (15.37), 128 (6.42); HR-MS: *m/z* Calcd for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1638. *Anal.* Calcd for $C_{20}H_{22}N_2O_3$ (338.2): C, 70.99; H, 6.55; N, 8.28. Found: C, 70.87; H, 6.64; N, 8.34.

1-Ethoxymethyl-5-*n*-propyl-6-(1-naphthylmethyl)uracil (8k) According to general procedure F, the product was obtained as a white crystal, mp 158—159 °C (EtOAc); Yield 40%; FT-IR (KBr): ν=3163 (NH), 3041 (NH), 2960 (Me), 2869 (CH_2), 2820 (CH_2), 1674 (C=O), 1616 (C=O), 1088 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.76 (t, 3H, J=7.0 Hz, Me), 0.98 (t, 3H, J=7.0 Hz, Me), 1.33 (m, 2H, J=7.35 Hz, CH_2), 2.22 (m, 2H, J=7.35 Hz, CH_2), 3.40 (q, 2H, J=7.0 Hz, CH_2Me), 4.50 (s, 2H, CH_2naphthyl), 4.93 (s, 2H, NCH_2), 7.10—8.19 (m, 7H, naphthyl), 11.54 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=114.2 (Me), 15.1 (Me), 22.4 (CH_2), 27.6 (CH_2), 30.7 (CH_2naphthyl), 64.2 (OCH_2), 72.7 (NCH_2), 115.2 (C-5), 123.4—133.8 (10C, naphthyl), 149.2 (C-6), 152.0 (C-2), 163.6 (C-4); EI-MS: *m/z* (%)=352 (1.29), 306 (72.05), 291 (100.0), 141 (33.00), 115 (15.19), 128 (7.40); HR-MS: *m/z* Calcd for $C_{21}H_{24}N_2O_3$: 352.1787. Found: 352.1797. *Anal.* Calcd for $C_{21}H_{24}N_2O_3$ (352.2): C, 71.57; H, 6.86; N, 7.95. Found: C, 71.35; H, 6.68; N, 7.81.

1-Ethoxymethyl-5-isopropyl-6-(1-naphthylmethyl)uracil (8l) According to general procedure F, the product was obtained as a white crystal, mp 165—166 °C (EtOAc); Yield 44% or 54%;[45] FT-IR (KBr): ν=3164 (NH), 3042 (NH), 1701 (C=O), 1670 (C=O), 1077 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.98 (t, 3H, J=7.0 Hz, Me), 1.14 (d, 6H, J=7.35 Hz, 2Me), 2.65 (m, 1H, J=7.35 Hz, CH), 3.43 (q, 2H, J=7.0 Hz, CH_2Me), 4.51 (s, 2H, CH_2naphthyl), 4.93 (s, 2H, NCH_2), 7.12—8.17 (m, 7H, naphthyl), 11.40 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=15.2 (Me), 20.6 (2Me), 28.1 (CH), 31.0 (CH_2naphthyl), 64.2 (OCH_2), 72.9 (NCH_2), 119.0 (C-5), 123.5—133.8 (10C, naphthyl), 148.5 (C-6), 152.0 (C-2), 162.7 (C-4); EI-MS: *m/z* (%)=352 (1.29), 306 (72.05), 291 (100.0), 141 (33.00), 115 (15.19), 128 (7.40); HR-MS: *m/z* Calcd for $C_{21}H_{24}N_2O_3$: 352.1787. Found: 352.1773. *Anal.* Calcd for $C_{21}H_{24}N_2O_3$ (352.2): C, 71.57; H, 6.86; N, 7.95. Found: C, 71.31; H, 6.78; N, 7.78.

General Procedure G for 1-[(Benzyloxy)methyl]-5-alkyl-6-(1-naphthylmethyl)uracils 8m—p Silylated 5-alkyl-6-(1-naphthylmenthyl)uracils **4a**—**d** (2 mmol) were obtained by one of the above methods. A solution of benzyl chloromethyl ether (0.47 g, 0.45 mL, 3 mmol) in anhydrous CH_2Cl_2 (10 ml) was added to the above clear solution, and then anhydrous powdered potassium carbonate (21.0 mg) was also added. The reaction mixture was stirred at 20—25 °C for 3 h and worked up as above to give the target molecules **8m**—**p**. Column chromatography cyclohexane : EtOAc (2 : 1) gave a white foam, which was recrystallized with EtOAc to give **8m**—**p** as a white crystal or powder.

1-[(Benzyloxy)methyl]-5-methyl-6-(1-naphthylmethyl)uracil (8m) According to general procedure G, the product was obtained as a white crystal,

mp 177—179 °C (EtOAc); Yield 33%; FT-IR (KBr): ν=3435 (NH), 1701 (C=O), 1671 (C=O), 1068 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.76 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 4.52 (2s, 2H, CH_2naphthyl, 2H, CH_2Ph), 5.07 (s, 2H, OCH_2), 7.11—8.15 (m, 7H, naphthyl), 7.19—7.25 (m, 5H, Ph), 11.55 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=10.8 (Me), 31.0 (CH_2naphthyl), 70.7 (OCH_2), 73.1 (NCH_2), 110.6 (C-5), 123.4—137.9 (6C, Ph; 10C, naphthyl,), 149.2 (C-6), 152.0 (C-2), 163.8 (C-4); EI-MS: *m/z* (%)=387 (2.91), 357 (8.54), 278 (57.17), 265 (33.62), 217 (33.83), 141 (14.81), 91 (100.00); HR-MS: *m/z* Calcd for $C_{24}H_{22}N_2O_3$: 386.1630. Found: 386.1644. *Anal.* Calcd for $C_{24}H_{22}N_2O_3$ (352.2): C, 74.59; H, 5.74; N, 7.25. Found: C, 74.39; H, 5.79; N, 7.22.

1-[(Benzyloxy)methyl]-5-ethyl-6-(1-naphthylmethyl)uracil (8n) According to general procedure G, the product was obtained as a white powder, mp 177—179 °C (EtOAc); Yield 24%; FT-IR (KBr): ν=3448 (NH_2), 1713 (C=O), 1655 (C=O), 1070 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.89 (t, 3H, *J*=7.35 Hz, Me), 2.24 (q, 2H, *J*=7.35 Hz, CH_2), 4.51 (2s, 2H, OCH_2Ph; 2H, CH_2naphthyl), 5.03 (s, 2H, NCH_2), 7.10—8.18 (m, 7H, naphthyl), 7.19—7.25 (m, 5H, Ph), 11.50 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.0 (Me), 19.0 (CH_2), 30.7 (CH_2naphthyl), 70.9 (OCH_2), 73.0 (NCH_2), 116.5 (C-5), 123.4—137.9 (6C, Ph; 10C, naphthyl), 148.7 (C-6), 152.0 (C-2), 163.3 (C-4); EI-MS: *m/z* (%)=292 (63.44), 250 (6.35), 236 (12.65), 217 (39.71), 141 (18.30), 91 (100.00); HR-MS: *m/z* Calcd for $C_{25}H_{24}N_2O_3$: 400.1787. Found: 400.1791. *Anal.* Calcd for $C_{25}H_{24}N_2O_3$ (400.2): C, 74.98; H, 6.04; N, 7.00. Found: C, 74.83; H, 6.18; N, 7.20.

1-[(Benzyloxy)methyl]-5-*n*-propyl-6-(1-naphthylmethyl)uracil (8o) According to general procedure G, the product was obtained as a white lump, mp 130—133 °C (EtOH); Yield 18%; FT-IR (KBr): ν=3152 (NH), 3029 (NH), 2959 (Me), 2869 (CH_2), 2832 (CH_2), 1704 (C=O), 1658 (C=O), 1065 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.13 (d, 6H, *J*=7.35 Hz, 2Me), 2.65 (m, 1H, *J*=7.35 Hz, CH), 4.53 (2 s, 2H, OCH_2Ph; 2H, CH_2naphthyl), 4.93 (s, 2H, NCH_2), 7.12—8.17 (m, 7H, naphthyl), 7.19—7.24 (m, 5H, Ph), 11.40 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=20.7 (2Me), 28.2 (CH), 31.1 (CH_2naphthyl), 70.9 (OCH_2), 73.3 (NCH_2), 119.1 (C-5), 123.4—137.9 (6C, Ph; 10C, naphthyl,), 148.4 (C-6), 152.1 (C-2), 162.8 (C-4); EI-MS: *m/z* (%)=414 (1.79), 306 (51.05), 293 (30.77), 277 (19.64), 217 (26.49), 141 (15.24), 91 (100.00); HR-MS: *m/z* Calcd for $C_{26}H_{26}N_2O_3$: 414.1943. Found: 414.1955. *Anal.* Calcd for $C_{26}H_{26}N_2O_3$ (400.2): C, 75.34; H, 6.32; N, 6.76. Found: C, 75.26; H, 6.22; N, 6.66.

1-[(Benzyloxy)methyl]-5-isopropyl-6-(1-naphthylmethyl)uracil (8p) According to general procedure G, the product was obtained as a white crystal, mp 146—148 °C (EtOAc); Yield 18%; FT-IR (KBr): ν=3160 (NH), 3044 (NH), 1710 (C=O), 1676 (C=O), 1072 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.13 (d, 6H, *J*=7.35 Hz, 2Me), 2.65 (m, 1H, *J*=7.35 Hz, CH), 4.53 (2 s, 2H, OCH_2Ph; 2H, CH_2naphthyl), 4.93 (s, 2H, NCH_2), 7.12—8.17 (m, 7H, naphthyl), 7.19—7.24 (m, 5H, Ph), 11.40 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=20.7 (2Me), 28.2 (CH), 31.1 (CH_2naphthyl), 70.9 (OCH_2), 73.3 (NCH_2), 119.1 (C-5), 123.4—137.9 (6C, Ph; 10C, naphthyl,), 148.4 (C-6), 152.1 (C-2), 162.8 (C-4); EI-MS: *m/z* (%)=306 (66.62), 293 (48.53), 250 (19.46), 217 (37.25), 141 (20.88), 91 (100.00); HR-MS: *m/z* Calcd for $C_{26}H_{26}N_2O_3$: 414.1943. Found: 414.1955. *Anal.* Calcd for $C_{26}H_{26}N_2O_3$ (400.2): C, 75.34; H, 6.32; N, 6.76. Found: C, 75.44; H, 6.19; N, 6.52.

General Procedure H for Ethyl 2-Alkyl-3-oxo-4-(2-naphthyl)butyrates 9a—c Almost the same as general procedure A, except that 2-naphthylacetonitrile was used instead of 1-naphthylacetonitrile. The final crude products were tested by GC-MS to determine the contents and calculate the final yields. **9a**: R=Me; Yield: 48%; **9b**: R=Et; Yield: 62%; **9c**: R=*n*-Pr; Yield: 55%. These products can also be used without further purification for the synthesis of compound **10** by knowing the content (41.47—56.68%) of ethyl 2-alkyl-3-oxo-4-(2-naphthyl) butyrates **9a**—**c** in the oily residue, which is determined by GC-MS.

General Procedure I for 5-Alkyl-6-(2-naphthylmethyl)-2-thiouracils 10a—c Almost the same as the general procedure B, except that **9a**—**c** were used as the raw materials instead of **6a**—**d**. These products can also be used without further purification for the synthesis of compound **11**. Compounds **10a**—**c** can be further purified by recrystallization from a suitable solvent to give white crystals.

5-Methyl-6-(2-naphthylmethyl)-2-thiouracil (10a) According to general procedure I, the product was obtained as a white fine crystallized fine white plates, mp 225—227 °C (absolute EtOH); Yield: 89%; FT-IR (KBr): ν=3160 (NH), 3051 (NH), 2949 (Me), 1649 (C=O), 1229 (C=S) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.82 (s, 3H, Me), 4.02 (s, 2H, naphthylCH_2), 7.39—7.90 (m, 7H, naphthyl), 12.33 (s, 1H, N-1H), 12.44 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=10.4 (Me), 35.6 (CH_2), 112.1 (C-5), 126.3—134.9 (naphthyl), 149.9 (C-6), 162.5 (C-2), 174.6 (C-4); EI-MS: *m/z* (%)=282 (100.00), 267 (11.51), 194 (17.90), 165 (21.30), 141 (77.73), 128 (59.09); HR-MS: *m/z* Calcd for $C_{16}H_{14}N_2OS$: 282.0827. Found: 282.0839. *Anal.* Calcd for $C_{16}H_{14}N_2OS$ (282.4): C, 68.06; H, 5.00; N, 9.92; S, 11.36. Found: C, 68.16; H, 5.10; N, 9.98; S, 11.47.

5-Ethyl-6-(2-naphthylmethyl)-2-thiouracil (10b) According to general procedure I, the product was obtained as white plate crystals, mp 198—201 °C (anhydrous EtOH); Yield: 86%; FT-IR (KBr): ν=3162 (NH), 3052 (NH), 2958 (Me), 2865 (CH_2), 1655 (C=O), 1163 (C=S) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.82 (t, 3H, *J*=7.35 Hz, Me), 2.30 (q, 2H, *J*=7.35 Hz, CH_2), 4.03 (s, 2H, naphthylCH_2), 7.38—7.90 (m, 7H, naphthyl), 12.30 (s, 1H, N-1H), 12.43 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=13.3 (Me), 18.2 (CH_2), 35.2 (CH_2), 117.9 (C-5), 126.3—128.6 (naphthyl), 149.4 (C-6), 162.0 (C-2), 174.7 (C-4); EI-MS: *m/z* (%)=296 (100.00), 281 (26.15), 267 (7.26), 141 (76.70), 128 (41.17); HR-MS: *m/z* Calcd for $C_{17}H_{16}N_2OS$: 296.0983. Found: 296.0971. *Anal.* Calcd for $C_{17}H_{16}N_2OS$ (296.4): C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.97; H, 5.49; N, 9.55; S, 10.95.

5-*n*-Propyl-6-(2-naphthylmethyl)-2-thiouracil (10c) According to general procedure I, the product was obtained as a white crystal; mp 177—179 °C (EtOH); Yield 80%; FT-IR (KBr): ν=3198 (NH), 3064 (NH), 2954 (Me), 2869 (CH_2), 1657 (C=O), 1567 (C=S) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.78 (t, 3H, *J*=7.3 Hz, Me), 1.22 (m, 2H, *J*=7.6 Hz, CH_2), 2.26 (t, 2H, *J*=7.7 Hz, CH_2), 4.02 (s, 2H, naphthylCH_2), 7.38—7.91 (m, 7H, naphthyl), 12.31 (s, 1H, N-1H), 12.44 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=14.6 (Me), 22.2 (CH_2), 27.2 (CH_2), 35.7 (CH_2), 116.9 (C-5), 126.7—135.2 (10C, naphthyl), 150.2 (C-6), 162.5 (C-2), 175.1 (C-4); EI-MS: *m/z* (%)=310 (100.00), 295 (11.01), 281 (73.38), 141 (35.76), 128 (9.12); HR-MS: *m/z* Calcd for $C_{18}H_{18}N_2OS$: 310.1140. Found: 310.1151. *Anal.* Calcd for $C_{18}H_{18}N_2OS$ (310.1): C, 69.65; H, 5.84; N, 9.02. Found: C, 69.59; H, 5.73; N, 9.15.

General Procedure J for 5-Alkyl-6-(2-naphthylmethyl)uracils 11a—c The 6-(2-naphthylmethyl)-5-alkyl-2-thio uracils (**10a**—**c**) (3.35 g, 12 mmol) were suspended in 10% aq. chloroacetic acid (500 ml) and the solution was refluxed for 48 h, till the TLC showed that no raw material remained. After cooling to room temperature, the precipitate was filtered off, sequentially washed with cold EtOH and cold Et_2O, and finally dried *in vacuo* to give compounds **11a**—**c** as white powders. This product also can be used without further purification for the synthesis of compound **12**. Compounds **11a**—**c** were purified by recrystallization with a suitable solvent to give white crystals.

5-Methyl-6-(2-naphthylmethyl)uracil (11a) According to general procedure J, the product was obtained as white crystal plates, mp 236—238 °C (EA); Yield: 87%; FT-IR (KBr): ν=3111 (NH), 3001 (NH), 2830 (Me), 1727 (C=O), 1656 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.79 (s, 3H, Me), 3.92 (s, 2H, CH_2naphthyl), 7.41—7.90 (m, 7H, naphthyl), 10.86 (s, 1H, N-1H), 11.07 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=10.2 (Me), 36.0 (CH_2), 105.8 (C-5), 126.2—134.6 (10C, naphthyl), 149.3 (C-6), 151.4 (C-2), 165.5 (C-4); EI-MS: *m/z* (%)=266 (100), 251 (13.69), 141 (47.98), 128 (91.52); HR-MS: *m/z* Calcd for $C_{16}H_{14}N_2O_2$: 266.1055. Found: 266.1051. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$ (280.3): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.22; N, 1.44.

5-Ethyl-6-(2-naphthylmethyl)uracil (11b) According to general procedure C, the product was obtained as white plate crystals, mp 241—243 °C (EtOH/H_2O : 3/1); Yield: 92%; FT-IR (KBr): ν=3105 (NH), 2968 (Me), 2818 (CH_2), 1708 (C=O), 1647 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.82 (t, 3 H, *J*=7.35 Hz, Me), 2.27 (q, 2H, *J*=7.35 Hz, CH_2), 3.93 (s, 2H, CH_2naphthyl), 7.41—7.90 (m, 7H, naphthyl), 10.80 (s, 1H, N-1H), 11.05 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=14.0 (Me), 18.1 (CH_2), 35.6 (CH_2), 112.0 (C-5), 126.2—135.0 (10C, naphthyl), 149.0 (C-6), 151.4 (C-2), 165.0 (C-4); EI-MS: *m/z* (%)=280 (100), 265 (53.68), 251 (3.40), 141 (43.06), 128 (32.39); HR-MS: *m/z* Calcd for $C_{17}H_{16}N_2O_2$: 280.1212. Found: 280.1201. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$ (280.3): C, 74.84; H, 5.75; N, 9.99. Found: C, 74.80; H, 5.60; N, 9.83.

5-*n*-Propyl-6-(1-naphthylmethyl)uracil (11c) According to general procedure C, the product was obtained as a white crystal, mp 200—201 °C (EtOH); Yield 90%; FT-IR (KBr): ν=3200 (NH), 3195 (NH), 2958 (Me), 2839 (CH_2), 1724 (C=O), 1662 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.780 (t, 3H, *J*=7.3 Hz, Me), 1.23 (m, 2H, *J*=7.6 Hz, CH_2), 2.23 (t, 2H, *J*=7.7 Hz, CH_2), 4.03 (s, 2H, naphthylCH_2), 7.40—7.90 (m, 7H, naphthyl), 10.81 (s, 1H, N-1H), 11.03 (s, 1H, N-3H); ^{13}C-NMR (500 MHz): δ=14.2 (Me), 22.3 (CH_2), 26.8 (CH_2), 35.8 (CH_2), 110.7 (C-5), 126.2—135.0 (10C, naphthyl), 149.3 (C-6), 151.4 (C-2), 165.2 (C-4); EI-MS: *m/z* (%)=294 (81.13), 279 (5.21), 265 (100), 141 (61.466), 128 (18.01); HR-MS: *m/z* Calcd for $C_{18}H_{18}N_2O_2$: 294.1368. Found: 294.1349. *Anal.* Calcd for

$C_{18}H_{18}N_2O_2$ (294.3): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.28; H, 6.18; N, 9.32.

The β series target molecules **12a—l** were prepared according to the synthesis methods of their corresponding α series counterparts.

1-[(2-Hydroxyethoxy)methyl]-5-methyl-6-(2-naphthylmethyl)uracil (12a) According to general procedure D, the product was obtain as a white crystal, mp 177—179 °C (EtOH); Yield 4%; FT-IR (KBr): ν=3412 (NH), 3057 (Me), 2936 (CH_2), 1712 (C=O), 1639 (C=O), 1072 (C–OH) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.85 (s, 3H, Me), 3.45—3.54 (m, 4H, J≈4.62 Hz, CH_2CH_2), 3.96 (s, 2H, CH_2naphthyl), 4.61 (s, 1H, OH), 5.26 (s, 2H, NCH_2), 7.43—7.89 (m, 10H, naphthyl), 11.20 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=11.0 (Me), 34.1 (CH_2naphthyl), 60.4 (OCH_2), 70.7 (OCH_2), 73.0 (NCH_2), 110.1 (C-5), 125.6—133.7 (10C, naphthyl), 149.1 (C-6), 152.0 (C-2), 163.9 (C-4); EI-MS: m/z (%)=340 (2.96), 310 (33.22), 279 (53.13), 267 (100.0), 250 (14.31), 179 (11.12), 141 (26.64), 128 (17.82); HR-MS: m/z Calcd for $C_{19}H_{20}N_2O_4$: 340.1423. Found: 340.1430. *Anal.* Calcd for $C_{19}H_{20}N_2O_4$ (340.1): C, 60.25; H, 5.92; N, 8.23. Found: C, 60.29; H, 5.81; N, 8.13.

1-[(2-Hydroxyethoxy)methyl]-5-ethyl-6-(2-naphthylmethyl)uracil (12b) According to general procedure D, the product was obtain as a white powder, mp 136—138 °C (EtOAc); Yield 37%; FT-IR (KBr): ν=3382 (NH), 3153 (NH), 2933 (Me), 2872 (CH_2), 1710 (C=O), 1668 (C=O), 1105 (C–O), 1062 (C–OH) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.91 (t, 3H, J=7.3 Hz, Me), 2.35 (q, 2H, J=7.3 Hz, CH_2), 3.44—3.51 (m, 4H, J≈4.74 Hz, CH_2CH_2), 4.29 (s, 2H, CH_2naphthyl), 4.67 (s, 1H, OH), 5.07 (s, 2H, NCH_2), 7.40—7.92 (m, 7H, naphthyl), 11.51 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=13.1 (Me), 18.1 (CH_2), 32.6 (CH_2naphthyl), 59.5 (OCH_2), 69.8 (OCH_2), 72.1 (NCH_2), 115.1 (C-5), 124.7—133.4 (10C, naphthyl), 147.7 (C-6), 151.1 (C-2), 162.6 (C-4); EI-MS: m/z (%)=354 (4.88), 292 (43.07), 280 (100.0), 265 (38.28), 141 (33.71), 128 (18.61), 115 (13.16); HR-MS: m/z Calcd for $C_{20}H_{22}N_2O_4$: 354.1580. Found: 354.1592. *Anal.* Calcd for $C_{20}H_{22}N_2O_4$ (354.2): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.15; N, 7.96.

1-Methoxymethyl-5-methyl-6-(2-naphthylmethyl)uracil (12d) According to general procedure E, the product was obtained as a white crystal, mp 147—149 °C (EtOAc); Yield 27%; FT-IR (KBr): ν=3172 (NH), 3050 (NH), 2938 (Me), 2829 (Me), 1692 (C=O), 1626 (C=O), 1070 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.86 (s, 3H, Me), 3.27 (s, 3H, OMe), 4.25 (s, 2H, CH_2naphthyl), 5.04 (s, 2H, NCH_2), 7.48—7.92 (m, 7H, naphthyl.), 11.52 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=11.1 (Me), 34.2 (CH_2naphthyl), 56.4 (OCH_3), 74.2 (NCH_2), 110.3 (C-5), 125.6—133.8 (10C, naphthyl), 149.1 (C-6), 152.1 (C-2), 163.9 (C-4); EI-MS: m/z (%)=310 (11.59), 278 (100.00), 263 (6.67), 141 (15.2), 128 (4.14), 115 (12.55); HR-MS: m/z Calcd for $C_{18}H_{18}N_2O_3$: 310.1317. Found: 310.1309. *Anal.* Calcd for $C_{18}H_{18}N_2O_3$ (310.1): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.49; H, 5.73; N, 9.05.

1-Methoxymethyl-5-ethyl-6-(2-naphthylmethyl)uracil (12e) According to general procedure E, the product was obtained as a white crystal, mp 130—132° C (EtOAc); Yield 35%; FT-IR (KBr): ν=3160 (NH), 3026 (NH), 2973 (Me), 2824 (CH_2), 1710 (C=O), 1649 (C=O), 1082 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.90 (t, 3H, J=7.35 Hz, Me), 2.33 (q, 2H, J=7.35 Hz, CH_2), 3.25 (s, 3H, Me), 4.24 (s, 2H, CH_2naphthyl), 5.00 (s, 2H, NCH_2), 7.39—7.92 (m, 7H, naphthyl), 11.51 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.1 (Me), 19.1 (CH_2), 33.6 (CH_2naphthyl), 56.5 (OCH_3), 74.2 (NCH_2), 116.3 (C-5), 125.7—134.4 (10C, naphthyl), 148.6 (C-6), 152.2 (C-2), 163.6 (C-4); EI-MS: m/z (%)=324 (12.06), 292 (100.00), 277 (36.93), 234 (10.06), 141 (18.75), 128 (3.85); HR-MS: m/z Calcd for $C_{19}H_{20}N_2O_3$: 324.1474. Found: 324.1481. *Anal.* Calcd for $C_{19}H_{20}N_2O_3$ (324.1): C, 70.35; H, 6.21; N, 8.64. Found: C, 70.37; H, 6.28; N, 8.61.

1-Methoxymethyl-5-*n*-propyl-6-(2-naphthylmethyl)uracil (12f) According to general procedure E, the product was obtained as a white crystal, mp 67—70 °C (EtOAc); Yield 15%; FT-IR (KBr): ν=3175 (NH), 3048 (NH), 2960 (Me), 1675 (C=O), 1621 (C=O), 1076 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.82 (t, 3H, J=7.35 Hz, Me), 1.34 (m, 2H, J=7.35 Hz, CH_2), 2.32 (t, 2H, J=7.35 Hz, CH_2), 3.28 (s, 3H, Me), 4.27 (s, 2H, CH_2naphthyl), 5.03 (s, 2H, NCH_2), 7.40—7.93 (m, 7H, naphthyl), 11.57 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.3 (Me), 22.5 (CH_2), 27.7 (CH_2), 33.8 (CH_2naphthyl), 56.5 (OMe), 74.2 (NCH_2), 115.0 (C-5), 125.8—134.4 (10C, naphthyl), 149.0 (C-6), 152.2 (C-2), 163.8 (C-4); EI-MS: m/z (%)=338 (8.80), 306 (33.21), 291 (5.29), 306 (33.21), 171 (11.72), 141 (17.86); HR-MS: m/z Calcd for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1639. *Anal.* Calcd for $C_{20}H_{22}N_2O_3$ (338.2): C, 70.99; H, 6.55; N, 8.82. Found: C, 70.83; H, 6.59; N, 8.86.

1-Ethoxymethyl-5-methyl-6-(2-naphthylmethyl)uracil (12g) According to general procedure F, the product was obtained as a white crystal, mp 134—136 °C (EtOAc); Yield 36%; FT-IR (KBr): ν=3176 (NH), 3049 (NH), 2972 (Me), 2813 (CH_2), 1674 (C=O), 1626 (C=O), 1108 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.02 (t, 3H, J≈7.2 Hz, Me), 1.86 (s, 3H, Me), 3.49 (q, 2H, J≈7.1 Hz, OCH_2), 4.27 (s, 2H, CH_2naphthyl), 5.09 (s, 2H, NCH_2), 7.38—7.91 (m, 7H, naphthyl), 11.5 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=11.0 (Me), 15.2 (Me), 34.2 (CH_2naphthyl), 64.1 (OCH_2), 72.7 (NCH_2), 110.2 (C-5), 125.6—133.8 (10C, naphthyl), 149.2 (C-6), 152.0 (C-2), 164.0 (C-4); EI-MS: m/z (%)=324 (6.76), 278 (100.0), 141 (16.57), 128 (11.60); HR-MS: m/z Calcd for $C_{19}H_{20}N_2O_3$: 324.1474. Found: 324.1469. *Anal.* Calcd for $C_{19}H_{20}N_2O_3$ (324.4): C, 70.35; H, 6.21; N, 8.64. Found: C, 70.29; H, 6.17; N, 8.37.

1-Ethoxymethyl-5-ethyl-6-(2-naphthylmethyl)uracil (12h) According to general procedure F, the product was obtained as a white lump, mp 120—122 °C (EtOAc); Yield 37%; FT-IR (KBr): ν=3201 (NH), 3053 (NH), 2976 (Me), 2935 (Me), 1677 (C=O), 1618 (C=O), 1080 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.91 (t, 3H, J=7.3 Hz, Me), 1.02 (t, 3H, J=7.0 Hz, Me), 2.34 (q, 2H, J=7.3 Hz, CH_2), 3.48 (q, 2H, J=7.0 Hz, OCH_2), 4.27 (s, 2H, CH_2naphthyl), 5.06 (s, 2H, NCH_2), 7.10—8.20 (m, 7H, naphthyl), 11.52 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.1 (Me), 15.2 (Me), 19.1 (CH_2), 33.7 (CH_2naphthyl), 64.2 (OCH_2), 72.7 (NCH_2), 116.2 (C-5), 125.7—134.4 (10C, naphthyl), 148.7 (C-6), 152.1 (C-2), 163.6 (C-4); EI-MS: m/z (%)=338 (0.78), 292 (100.0), 277 (52.34), 141 (15.37), 128 (6.42); HR-MS: m/z Calcd for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1638. *Anal.* Calcd for $C_{20}H_{22}N_2O_3$ (338.2): C, 70.99; H, 6.55; N, 8.28. Found: C, 70.87; H, 6.64; N, 8.34.

1-[(Benzyloxy)methyl]-5-methyl-6-(2-naphthylmethyl)uracil (12j) According to general procedure G, the product was obtained as a yellow needle-like crystal, mp 101—104 °C (EtOH); Yield 35%; FT-IR (KBr): ν=3159 (NH), 3025 (Me), 1708 (C=O), 1665 (C=O), 1068 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.85 (s, 3H, CH_3), 4.25 (s, 2H, CH_2naphthyl), 4.55 (s, 2H, CH_2Ph), 5.16 (s, 2H, OCH_2), 7.23—7.31 (m, 5H, Ph), 7.31—7.88 (m, 7H, naphthyl), 11.52 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=11.1 (Me), 34.2 (CH_2naphthyl), 70.6 (OCH_2), 72.8 (NCH_2), 110.3 (C-5), 125.7—137.9 (6C, Ph; 10C, naphthyl), 149.1 (C-6), 152.0 (C-2), 164.0 (C-4); EI-MS: m/z (%)=387 (0.54), 357 (0.62), 278 (35.65), 265 (36.22), 217 (29.39), 141 (12.94), 91 (100.00); HR-MS: m/z Calcd for $C_{24}H_{22}N_2O_3$: 386.1630. Found: 386.1649. *Anal.* Calcd for $C_{24}H_{22}N_2O_3$ (352.2): C, 74.59; H, 5.74; N, 7.25. Found: C, 74.37; H, 5.73; N, 7.28.

1-[(Benzyloxy)methyl]-5-ethyl-6-(2-naphthylmethyl)uracil (12k) According to general procedure G, the product was obtained as a white powder, mp 135—137 °C (EtOAc/Cylohexane); Yield 60%; FT-IR (KBr): ν=3421 (NH), 3199 (NH), 2969 (Me), 2936 (CH_2), 1697 (C=O), 1676 (C=O), 1050 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.90 (t, 3H, J=7.35 Hz, Me), 2.32 (q, 2H, J=7.35 Hz, CH_2), 4.25 (s, 2H, CH_2naphthyl), 4.54 (s, 2H, OCH_2Ph), 5.13 (s, 2H, NCH_2), 7.23—7.33 (m, 5H, Ph), 7.33—7.89 (m, 7H, naphthyl), 11.50 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.1 (Me), 19.1 (CH_2), 33.6 (CH_2naphthyl), 70.8 (OCH_2), 72.8 (NCH_2), 116.2 (C-5), 125.7—140.1 (6C, Ph; 10C, naphthyl), 148.5 (C-6), 152.0 (C-2), 163.5 (C-4); EI-MS: m/z (%)=400 (1.54), 292 (34.33), 279 (34.02), 236 (6.96), 217 (29.34), 141 (14.71), 91 (100.00); HR-MS: m/z Calcd for $C_{25}H_{24}N_2O_3$: 400.1787. Found: 400.1799. *Anal.* Calcd for $C_{25}H_{24}N_2O_3$ (400.2): C, 74.98; H, 6.04; N, 7.00. Found: C, 74.89; H, 6.11; N, 7.06.

1-[(Benzyloxy)methyl]-5-*n*-propyl-6-(2-naphthylmethyl)uracil (12l) According to general procedure G, the product was obtained as a white powder, mp 120—123 °C (EtOAc); Yield 42%; FT-IR (KBr): ν=3164 (NH), 3032 (NH), 2968 (Me), 1691 (C=O), 1619 (C=O), 1061 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.81 (t, 3H, J=7.35 Hz, Me), 1.32 (q, 2H, J=7.35 Hz, CH_2), 2.29 (t, 2H, J=7.35 Hz, CH_2), 4.25 (s, 2H, CH_2naphthyl), 4.54 (s, 2H, OCH_2Ph); 5.12 (s, 2H, NCH_2), 7.23—7.29 (m, 5H, Ph), 7.29—7.89 (m, 7H, naphthyl), 11.50 (s, 1H, NH); ^{13}C-NMR (500 MHz): δ=14.3 (Me), 22.5 (CH_2), 27.7 (CH_2naphthyl), 70.8 (OCH_2), 72.8 (NCH_2), 114.9 (C-5), 125.7—138.0 (6C, Ph; 10C, naphthyl), 148.8 (C-6), 152.0 (C-2), 163.7 (C-4); EI-MS: m/z (%)=414 (1.15), 308 (15.34), 293 (21.28), 250 (4.72), 217 (16.33), 141 (16.38), 91 (100.00); HR-MS: m/z Calcd for $C_{26}H_{26}N_2O_3$: 414.1943. Found: 414.1949. *Anal.* Calcd for $C_{25}H_{24}N_2O_3$ (414.2): C, 75.34; H, 6.32; N, 6.76. Found: C, 75.27; H, 6.37; N, 6.79.

General Procedure K for *N*1,*N*3-Bis-alkoxymethylation Products 13a—c According to general procedure E, 5-alkyl-6-(1-naphthylmethyl)uracils (25 mmol) and chloromethyl methyl ether (5.68 g, 60.0 mmol, 5.6 ml) (mole ratio=1 : 2.4) were used for the *N*-1, *N*-3 bisalkylation. Column chromatography (25% EtOAc in cyclohexane) gave a white foam, which was recrystallized with a suitable solvent to give **13a**—**c** as white crystals.

1-Methoxymethyl-3-methoxymethyl-5-methyl-6-(1-naphthylmethyl)-

uracil (13a) According to general procedure K,[46] the product was obtained as a white crystal, mp 101—103 °C (EtOAc); Yield 32%; FT-IR (KBr): ν=1702 (C=O), 1655 (C=O), 1105 (C–O), 1083 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.83 (s, 3H, Me), 3.24 (s, 3H, OMe), 3.35 (s, 3H, OMe), 4.52 (s, 2H, CH_2naphthyl), 4.98 (s, 2H, N-1CH_2), 5.31 (s, 2H, N-3CH_2), 7.15—8.17 (m, 7H, naphthyl); ^{13}C-NMR (500 MHz): δ=11.4 (Me), 31.3 (CH_2naphthyl), 56.7 (N1-OCH_3), 57.5 (N3-OCH_3), 72.7 (N-1CH_2), 75.4 (N-3CH_2), 110.0 (C-5), 123.5—133.9 (10C, naphthyl), 148.8 (C-6), 152.5 (C-2), 162.9 (C-4); EI-MS: *m/z* (%)=354 (2.12), 322 (18.68), 290 (100.0), 279 (55.04), 250 (26.15) 234 (33.95), 221 (32.33), 141 (23.21); HR-MS: *m/z* Calcd for $C_{20}H_{22}N_2O_4$: 354.1580. Found: 354.1588. *Anal.* Calcd for $C_{20}H_{22}N_2O_4$ (354.4): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.19; N, 7.81.

1-Methoxymethyl-3-methoxymethyl-5-ethyl-6-(1-naphthylmethyl)-uracil (13b) According to general procedure K, the product was obtained as a white crystal, mp 98—100 °C (EtOAc); Yield 38%; FT-IR (KBr): ν=1707 (C=O), 1655 (C=O), 1182 (C–O), 1084 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=0.93 (t, 3H, J=7.39 Hz, Me), 2.31 (q, 2H, J=7.39 Hz, CH_2), 3.23 (s, 3H, OMe), 3.36 (s, 3H, OMe), 4.52 (s, 2H, CH_2naphthyl), 4.95 (s, 2H, N-1CH_2), 5.31 (s, 2H, N-3CH_2), 7.14—8.20 (m, 7H, naphthyl.); ^{13}C-NMR (500 MHz): δ=13.9 (Me), 19.6 (CH_2), 30.8 (CH_2naphthyl), 56.7 (N1-OCH_3), 57.5 (N3-OCH_3), 72.6 (N-1CH_2), 75.3 (N-3CH_2), 115.8 (C-5), 123.5—133.8 (10C, naphthyl), 148.4 (C-6), 152.5 (C-2), 162.4 (C-4); EI-MS: *m/z* (%)=368 (2.40), 336 (20.01), 304 (100.0), 293 (51.55), 264 (21.74), 248 (32.76), 235 (42.50), 141 (33.98); HR-MS: *m/z* Calcd for $C_{21}H_{24}N_2O_4$: 368.1763. Found: 368.1793. *Anal.* Calcd for $C_{21}H_{24}N_2O_4$ (400.2): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.40; H, 6.37; N, 7.53.

1-Ethoxymethyl-3-ethoxymethyl-5-methyl-6-(2-naphthylmethyl)uracil (13c) According to general procedure K, the product was obtained as a white crystal, mp 99—101 °C (EtOAc); Yield 38%; FT-IR (KBr): ν=1696 (C=O), 1659 (C=O), 1114 (C–O), 1081 (C–O) cm^{-1}; ^{1}H-NMR (500 MHz): δ=1.02 (t, 3H, J=7.39 Hz, Me), 1.12 (t, 3H, J=7.39 Hz, Me), 1.91 (s, 3H, Me), 3.51 (q, 2H, CH_2), 3.59 (q, 2H, CH_2), 4.30 (s, 2H, CH_2naphthyl), 5.16 (s, 2H, N-1CH_2), 5.32 (s, 2H, N-3CH_2), 7.39—7.92 (m, 7H, naphthyl.); ^{13}C-NMR (500 MHz): δ=11.7 (Me), 15.2 (Me), 15.5 (Me), 34.3 (CH_2naphthyl), 64.3 (N1-OCH_2), 65.2 (N3-OCH_2), 71.1 (N-1CH_2), 73.8 (N-3CH_2), 109.6 (C-5), 125.7—133.7 (10C, naphthyl), 148.8 (C-6), 152.4 (C-2), 163.0 (C-4); EI-MS: *m/z* (%)=382 (25.03), 336 (31.35), 304 (100.0), 292 (82.40), 279 (100.00), 262 (23.97), 250 (42.81), 235 (30.57), 179 (21.73), 141 (41.70); HR-MS: *m/z* Calcd for $C_{22}H_{26}N_2O_4$: 382.1893. Found: 382.1885. *Anal.* Calcd for $C_{22}H_{26}N_2O_4$ (382.2): C, 60.09; H, 6.85; N, 7.32. Found: C, 60.13; H, 6.75; N, 7.29.

X-Ray Crystal Structure Analysis of 8f Crystals of **8f** suitable for X-ray analysis were obtained by recrystallization from EtOAc (Fig. 4). $C_{19}H_{20}N_2O_3$, MW=324.15; translucent block; crystal size [mm]: 0.25×0.20×0.15; space group $P2_1/n$; monoclinic; Z=4; $a/b/c$ [Å]=10.325(4)/14.813(5)/11.295(4); β [°]=110.709(5); V=1616.0(10) Å^3; $\rho_{calcd.}$=1.333 g·cm^{-3}; F(000)=688; μ=0.091 mm^{-1}; T=293(2) K; ω-scan: 4.60°<2θ<54.42°; 7908 reflections collected, 3583 independent, 2193 observed; R ($I>2\sigma_1$): $R1$=0.0595, w$R2$=0.1203; R (all data): $R1$=0.1100, w$R2$=0.1377; Goof=1.014. For structure solution and refinement, the programs SHELXS97 were used. For structure refinement, full-matrix least-squares on F^2 (SHELXL97) were used. The H atoms were calculated geometrically and a riding model was applied during the refinement process. Absorption corrections were used by semi-empirical method from equivalents and multi-scans.

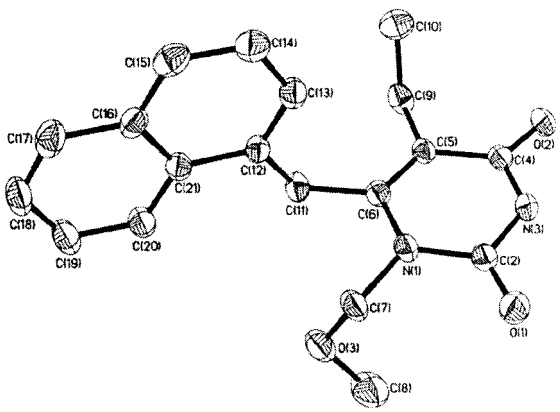


Fig. 4. Molecular Structure of **8f** Obtained by X-Ray Diffraction

Selected bond lengths [Å], bond angles [°] and torsion angles [°]: C(6)–C(11) 1.499(3), C(11)–C(12) 1.517(4), N(1)–C(7) 1.479(3), C(5)–C(6)–C(11) 123.8(2), C(6)–C(11)–C(12) 113.86(19), C(6)–N(1)–C(7) 121.14(19), C(2)–N(1)–C(7) 116.46(19), N(1)–C(7)–O(3)–C(8) 67.9(3), C(5)–C(6)–C(11)–(12) 103.4(3), N(1)–C(6)–C(11)–C(12) 74.8(3), C(6)–C(11)–C(12)–C(13) 30.6(3), C(6)–C(11)–C(12)–C(21) 153.3(3).

Supporting Information Available Atomic coordinates and further crystallographic details have been deposited at the Cambridge Crystallographic Data Center, deposition number CCDC 176680, and copies of this data can be obtained by application to CCDC, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK (fax: +441223-336033; E-mail: deposit@ccdc.cam.ac).

Molecular Modeling The construction of molecular models and the interpolation with previously developed CoMFA models and dock calculations were performed using SYBYL software on a SGI workstation. The details of conformational analysis, structure optimization, and CoMFA alignment have been reported previously.[15,34]

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