March 2006 *Chem. Pharm. Bull.* **54**(3) 325—333 (2006) 325

Synthesis and Anti-HIV-1 and Anti-HCMV Activity of 1-Substituted 3-(3,5-Dimethylbenzyl)uracil Derivatives

Tokumi MARUYAMA,*,[a] Shigetada KOZAI,[b] Yosuke DEMIZU,[a] Myriam WITVROUW,[c]
Christophe PANNECOUQUE,[c] Jan BALZARINI,[c] Robert SNOECKS,[c] Graciella ANDREI,[c] and Erik DE CLERCQ[c]

[a] *Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University; 1314–1 Shido, Sanuki, Kagawa 769–2193, Japan:* [b] *Faculty of Pharmaceutical Sciences (Tokushima Campus), Tokushima Bunri University; Yamashiro-cho, Tokushima 770–8514, Japan: and* [c] *Rega Instituut, Katholieke Universiteit Leuven; Minderbroedersstraat 10, B-3000 Leuven, Belgium.* Received September 9, 2005; accepted November 14, 2005

3-(3,5-Dimethylbenzyl)uracil (3) was treated with alkyl halides in the presence of alkali to give 1-substituted congeners. Condensation of 3 with alcohols using the Mitsunobu reaction was also employed as an alternative method. The anti-HIV-1 activity of 1-substituted analogues of 3-(3,5-dimethylbenzyl)uracil was evaluated according to previously established procedures. It appeared that the nitrogen of the 1-cyanomethyl group is important for anti-HIV-1 activity, suggesting interaction with the amino acid residue of HIV-1 reverse transcriptase. 1-Arylmethyl derivatives also showed good anti-HIV-1 activity; and that of 2- and 4-picolyl derivatives was particularly excellent. These results were confirmed by Docking Studies using the program, Glide ligand docking jobs, which suggests hydrogen bonding between amide N–H of Lys 101 and nitrogen of the cyanomethyl and picolyl group.

Key words uracil derivative; anti-human immunodeficiency virus (HIV) activity; docking study

Human immunodeficiency virus type 1 (HIV-1) contains an important enzyme, reverse transcriptase (RT), which catalyzes the conversion of the viral genome RNA into the double-stranding DNA. Since this process is essential for viral replication, many drugs targeting this enzyme have been developed. Within the class of the anti-HIV agents which inhibit reverse transcriptase, non-nucleoside reverse transcriptase inhibitors (NNRTIs) are rapidly increasing.[1—5] It is interesting that some NNTRIs have an aromatic group at the 6 position of uracil. One compound of this type is 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT)[6] and emivirine has entered clinical phase III trials.[7] Recently, Buckheit *et al.* reported a unique and highly potent uracil derivative, 1-(3-cyclopenten-1-yl)methyl-6-(3,5-dimethylbenzoyl)-5-ethyl-2,4-pyrimidinedione (SJ-3366), which showed antiviral activity against HIV-2 as well as HIV-1.[8] Thereafter, many pyrimidine derivatives emerged as anti-HIV agents.[9,10] Against the background of these reports, we undertook a search for an anti-HIV agent by the structure–activity relationship (SAR) of the 1,3-disubstituted uracil[11]. It is demonstrated that the introduction of a cyanomethyl group onto N1 of uracil is effective for anti-HIV-1 activity. In study on N3-substituents, 3-benzyl derivatives bearing a methyl function at the *meta* position (**1b**) was proved to be a better antiviral than *ortho* (**1a**) and *para* congener (**1c**). Moreover, 1-cyanomethyl-3-(3,5-dimethylbenzyl)uracil (**2a**) showed excellent anti-HIV-1 activity. Based on this result, some 1-substituted 3-(3,5-dimethylbenzyl)uracils were also evaluated and 1-benzyl- (**2b**) and 3,5-difluorobenzyl derivatives (**2c**) were also proved to be active against HIV-1 in CEM cells (Fig. 1). 1-Benzyl derivative (**2b**) is unique since it also showed antiviral activity against HCMV as well as anti-HIV-1 activity.[11] This background prompted us to explore the antiviral activity of the 3-(3,5-dimethyl-benzyl)uracil bearing an alkyl or arylalkyl group at N1. Also reported here is Docking Studies of 1,3-disubstituted uracils with RT nevirapine binding site using the program, Glide ligand docking jobs.

Synthesis To obtain a series of 1-substituted analogues of 3-(3,5-dimethylbenzyl)uracil, 3-(3,5-dimethylbenzyl)uracil (**3b**) was prepared as follows. Thus, 1-(tetrahydrofuran-2-yl)uracil[12] was condensed with 3,5-dimethylbenzyl alcohol using the Mitsunobu reaction[13] to afford 3-(3,5-dimethylbenzyl) congener (**3a**). The product was treated with 1 M HCl to give **3b** in 69% yield. Thiation of **3b** with Lawesson's reagent[15,16] gave a 4-thio derivative (**4a**) as a main product accompanied with a small amount of the 2,4-dithiouracil (**4b**). The pyrimidines (**3b**, **4a**, **b**) were examined to introduce various alkyl groups at N1 as follows: Compound **3b** was subjected to nucleophilic substitution with allyl, ethoxymethyl, substituted benzyl or picolyl halides in the presence of K_2CO_3 in DMF to give their 1-substituted analogues **5a**, **b**, **d**—**h**, **n**—**s**. 4-Thiouracil derivatives **6a**, **b**, **d**—**h** were also obtained from **4a** using the same method as mentioned above. In case the halides were not commercially available, alcohols were employed as reagents. Thus, 2-(methylthio)ethanol, 2,2-diphenylethanol, furanyl-

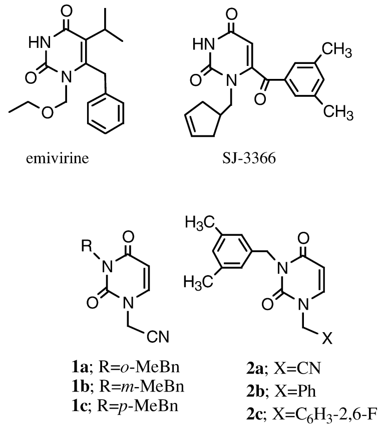
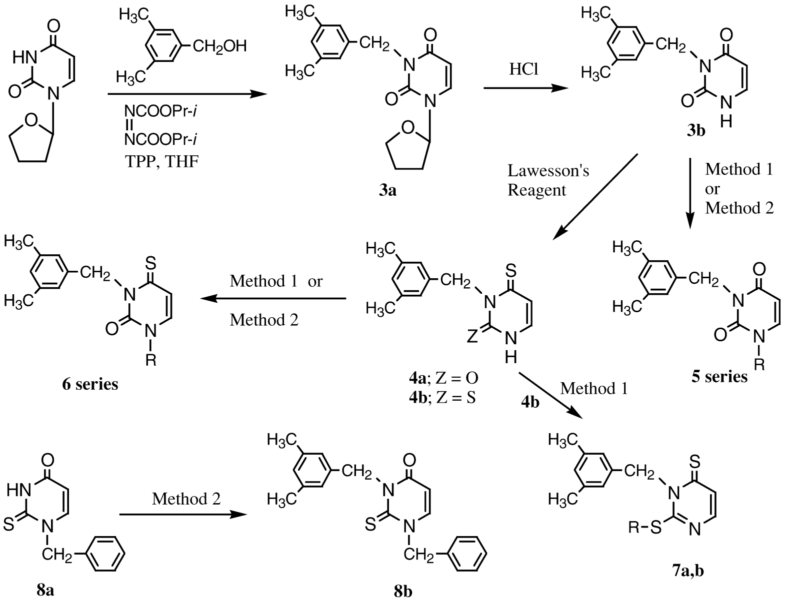


Fig. 1. Non-nucleoside Reverse Transcriptase Inhibitors

---

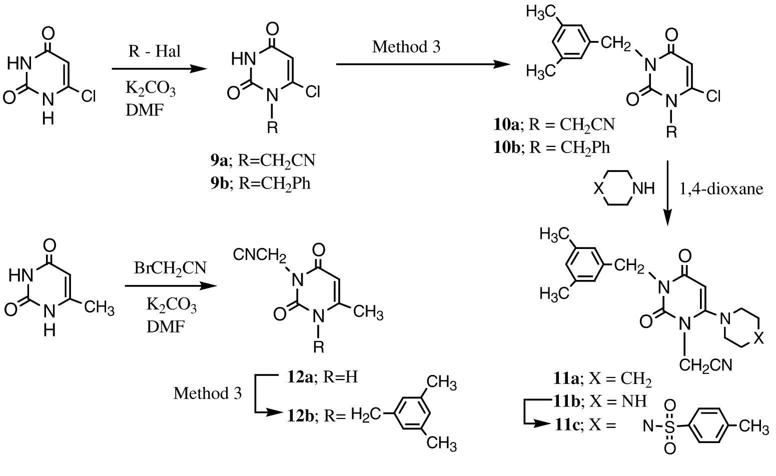
* To whom correspondence should be addressed. e-mail: maruyama@kph.bunri-u.ac.jp

methanols and thiophenemethanols were condensed with **3b** and **4a** using *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)[14] to give the 1-substituted congeners **5c**, **i**—**m** and **6c**, **i**—**m**. The alkylation onto N1 was proved by the similarity of their spectroscopic data to that of 1,3-dibenzyluracil[17,18] and the HMBC spectrum of **6k** as shown in Fig. 2. When reaction of **4b** with bromoacetonitrile was examined, however, the product was proved to be 2-cyanomethylthio-3-(3,5-dimethylbenzyl)-3,4-dihydropyrimidin-4-thione (**7a**) from the HMBC spectrum in which correlation between methylene of the cyanomethyl group was only observed with C2. A similar reaction of **4b** with benzyl bromide also gave the 2-cyanomethylthio derivative (**7b**). It has been reported that methylation of 2-thiouracil gives a 2-methylthio derivative.[19,20] This tendency was also verified in the case of 3-substituted 2,4-dithiouracil **4b**. The preference of substitution on the sulphur atom could be explained by strong nucleophilicity of the 2-sulfide anion formed by treatment of **4b** with a strong base. Thus, 1-benzylated 2-thiouracil (**8a**) was prepared by ring closure using a known method[21] and subsequent condensation of **8a** with 3,5-dimethylbenzyl alcohol as described in the section of **3a** afforded the 2-thio derivative **8b**. Next, we explored the effect of 6-substituents since introduction of a methyl group onto the 5-position of 1-benzyl-3-(3,5-dimethylbenzyl)uracil decreases its anti-HIV-1 activity.[11] Thus, 6-chlorouracil was treated with bromoacetonitrile or benzyl bromide to give the corresponding 1-alkylated congeners (**9a**, **b**). However, reaction of 6-methyluracil with bromoacetonitrile afforded 3-cyanoethyl derivative (**12a**). The electric effect of the 6-substituents accounts for this discrepancy in position on alkylation of 6-substituted uracils. The electron-withdrawing chlorine atom facilitates the dissociation of N1–H to produce an intermediary uracil-1-anion. However, the electron-donating 6-methyl group disturbs dis-



Method 1; R - Hal, K_2CO_3, DMF
Method 2; R - OH, Mitsunobu Reagent

Chart 1



Method 3; $HOCH_2C_6H_3Me_2$-3,5, azobis(*N*,*N*-dimethylfoumamide), TPP, THF

Chart 2

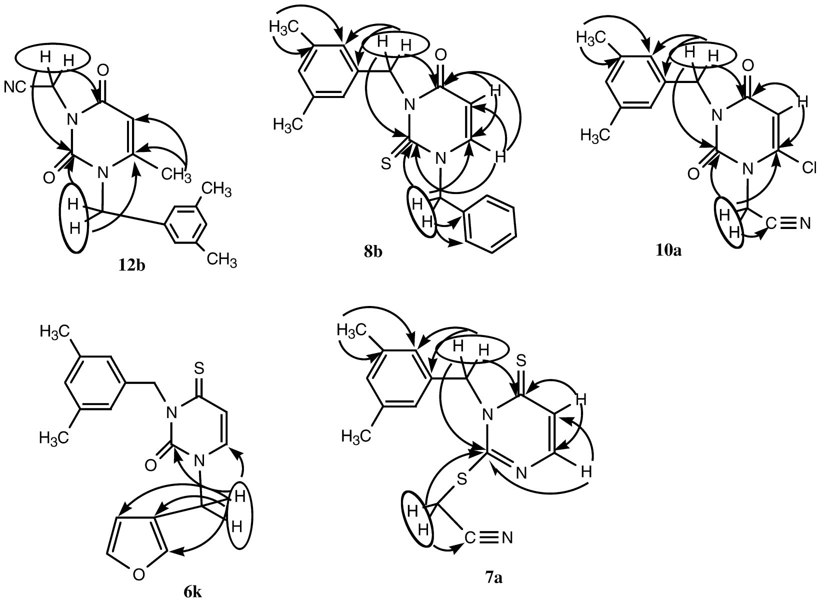


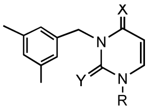
Fig. 2. HMBC Spectra of 1,3-Disubstituted Uracils and Related Compounds

sociation of N1–H and makes N3–H rather susceptible to a strong base.[22,23] Compounds **9a, b** and **12a** were converted to **10a, b** and **12b** as described in the section of **3a**. Then, 6-chloro derivative **10a** was subjected to the nucleophilic substitution with cyclic amines to give 6-substituted analogues (**11a, b**). The piperazinyl derivative (**11b**) was further reacted with tosyl chloride to give the *N*-tosyl derivative **11c**.

Structure–Activity Relationship (SAR) The antiviral effects of the 1-substituted 3-(3,5-dimethylbenzyl)uracils were assayed according to previously established procedures[24—26] and the results are presented in Table 1. In an earlier report[11] attempts were made to enhance the antiviral activity by methyl modifications in the N^3-benzyl-1-cyanomethyluracils. Methyl functions in the *ortho* (**1a**) or *para* position (**1c**) of this N-3 benzyl group proved undesirable. However, some anti-HIV activity (EC_{50} of 6.70 μM) was witnessed with the methyl function substituted in the *meta* position (**1b**) and 3-(3,5-dimethylbenzyl)-1-cyanomethyluracil (**2a**) showed powerful inhibition against HIV-1, with an EC_{50} of 0.59 μM, a CC_{50} of >464 μM, and thus, a selectivity index (SI) of >786. Therefore, the substituent at the N-3 position of uracil was fixed to the 3,5-dimethylbenzyl group. At first, the ethoxymethyl derivative (**5b**) was prepared resembling emivirine[7]. Allyl (**5a**) and 2-(methylthio)ethyl (**5c**) group were also introduced to N1 of **3b** as non-cyclic substituents. However, it appeared that the anti-HIV activity of these compounds was weak compared to that of 1-cyanomethyl derivative (**2a**). This result indicates the importance of a cyano group to adopt the binding site of HIV-1 RT.

Then, under the hypothesis that an electron-withdrawing group at N1 is essential for anti-HIV activity of **2a**, ethoxycarbonylmethyl (**5q**), 2-propanonyl (**5r**) and 2,2,2-trifluoroethyl derivatives (**5s**) were prepared. However, these compounds showed only weak activity, suggesting the role of hydrogen-receiving activity of cyano-nitrogen. Next, 1-arylmethyl-3-(3,5-dimethylbenzyl)uracils were examined since **2b** also showed good anti-HIV-1 activity (EC_{50} of 0.234 μM).[11] An introduction of chloro onto the 1-benzyl (**5d—f**) had little influence on anti-HIV-1 activity of **2b**. A bulky group such as a *tert*-butyl group (**5g**) diminishes anti-HIV-1 activity almost completely and 2,2-diphenylethyl analogue (**5i**) showed no antiviral activity. This evidence indicates that the benzyl group is sensitive to the substitution which causes high steric hindrance. Therefore, a further trial was undertaken to change the benzene to a heterocyclic aromatic ring. Thus, 1-furanylmethyl uracil such as **5j, k** showed good anti-HIV-1 activity identical to that of 1-benzyl derivative. 1-(Thiophen-2-yl)methyl derivative **5l** displayed similar activity with the 1-(furan-2-yl)methyl derivative **5j**. A trial to change 1-benzyl of **2b** to 1-picolyl was explored to know the effect of nitrogen, which forms a hydrogen bond as in cyanomethyl of **2a**. It is interesting that anti-HIV-1 activity of 1-(2-picolyl)- (**5n**) and 1-(4-picolyl) derivative (**5p**) increased ten times compared with that of **2b**. However, the antiviral activity of 1-(3-picoryl) derivative (**5o**) resembled to that of **2b**. 4-Thio modification of the uracil moiety usually enhances anti-HIV-1 activity of 1-substituted 3-(3,5-dimethylbenzyl)uracils. One exception to this rule was the relatively strong antiviral activity of the 4-chlorophenylmethyl derivative of uracil ($IC_{50}=0.211$ μM) compared to that of 4-thiouracil ($IC_{50}=1.19$ μM). Although 1-picoryl derivatives of uracil (**5n—p**) and 4-thiouracil (**6n—p**) show similar anti-HIV-1 activity, the cytotoxicity profile is different, *i.e.* CC_{50} of **5n—p** exceeded 100 μM and **6n—p** showed cytotoxicity even at 30 μM. Since 1-picolyl derivative could be dissolved in water as a salt with acid, **5n, p** are promising candidates as an anti-HIV-1 agent. Next, the effect of 6-substituents was evaluated as shown in Table 1. Although anti-HIV activity of 6-chloro congeners **10a, b** was similar to that of original compounds (**2a, b**), it appeared that this modification increased cytotoxicity. Introduction of the bulky piperidinyl (**11a**) or piperazinyl group (**11b**) to **2a** diminished their antiviral activity almost completely. Compound **12b** showed no anti-HIV-1 activity, indicating replacement of N1-cyanomethyl group, and N3-(3,5-dimethylbenzyl) group of **2a** extinguishes its anti-HIV-1 activity. Antiviral activity of compounds **5a—s**, **6a—p**, **7a, b**, **8b**, **9a**, **10a, b**, **11a—c**, **12b** was also evaluated toward HCMV, however, these com-

Table 1. Antiviral Activity of 1-Substituted 3-(3,5-Dimethylbenzyl)uracils and Their 4-Thio Congeners against HIV-1 and HCMV



Compound	R	Uracil (X=Y=O) 4-thiouracil (X=S, Y=O)	IC$_{50}$ (μM) CMV	EC$_{50}$ (μM) HIV-1(III$_B$) AD-169 strain	CC$_{50}$ (μM) CEM cells	SI
3a	Tetrahydrofuran-2-yl	X=Y=O	330	34.5	220	6
5a	$CH_2CH=CH_2$	X=Y=O	>190	1.48	155	105
5b	$CH_2OCH_2CH_3$	X=Y=O	>170	5.2	209	40
5c	$CH_2CH_2SCH_3$	X=Y=O	>160	7.39	131	18
5d	$CH_2C_6H_4Cl$-*o*	X=Y=O	21	0.211	24.0	114
5e	$CH_2C_6H_4Cl$-*m*	X=Y=O	>140	0.28	49.6	177
5f	$CH_2C_6H_4Cl$-*p*	X=Y=O	>56	0.211	44.0	209
5g	$CH_2C_6H_4C(CH_3)_3$-*p*	X=Y=O	>130	31.9	31.3	<1
5h	$CH_2COC_6H_5$	X=Y=O	110	1.89	184	97
5i	$CH_2CH(ph)_2$	X=Y=O	>5	>10	22.0	<2
5j	CH_2(furan-2-yl)	X=Y=O	>64	0.164	115	701
5k	CH_2(furan-3-yl)	X=Y=O	34	0.23	115	500
5l	CH_2(thiophen-2-yl)	X=Y=O	15	0.184	44.1	240
5m	CH_2(thiophen-3-yl)	X=Y=O	23	ND	ND	ND
5n	*a)*	X=Y=O	>160	0.040	145	3625
5o	*b)*	X=Y=O	31	0.40	279	698
5p	*c)*	X=Y=O	>160	0.053	135	2547
5q	CH_2COOEt	X=Y=O	>160	22.4	>395	>18
5r	CH_2COCH_3	X=Y=O	>570	13.7	>359	>26
5s	CH_2CF_3	X=Y=O	>640	7.75	>400	>52
6a	$CH_2CH=CH_2$	X=S, Y=O	28	0.34	77.5	228
6b	$CH_2OCH_2CH_3$	X=S, Y=O	55	1.31	97.9	75
6c	$CH_2CH_2SCH_3$	X=S, Y=O	>160	1.25	34.3	27
6d	$CH_2C_6H_4Cl$-*o*	X=S, Y=O	>54	0.067	38.8	579
6e	$CH_2C_6H_4Cl$-*m*	X=S, Y=O	>140	0.111	22.2	200
6f	$CH_2C_6H_4Cl$-*p*	X=S, Y=O	>54	1.19	27.5	23
6g	$CH_2C_6H_4C(CH_3)_3$-*p*	X=S, Y=O	>120	8.28	193	23
6h	$CH_2COC_6H_5$	X=S, Y=O	>14	0.52	36.2	70
6i	$CH_2CH(Ph)_2$	X=S, Y=O	>120	>47	>234	5
6j	CH_2(furan-2-yl)	X=S, Y=O	13	0.077	23.7	308
6k	CH_2(furan-3-yl)	X=S, Y=O	12	0.064	27.0	422
6l	CH_2(thiophen-2-yl)	X=S, Y=O	10	0.120	27.7	231
6m	CH_2(thiophen-3-yl)	X=S, Y=O	9.5	0.099	25.2	255
6n	*a)*	X=S, Y=O	30	0.041	37.9	924
6o	*b)*	X=S, Y=O	>59	0.122	13.6	111
6p	*c)*	X=S, Y=O	>15	0.041	31.4	766
7a	CH_2CN	*e)*	>1.7	0.53	12.6	24
7b	$CH_2–C_6H_5$	*e)*	4.5	0.153	21.7	142
8b	$CH_2–C_6H_5$	X=O, Y=S	12	0.0217	25.4	1171
9a	*d)*	*d)*	>270	>12.4	12.3	<1
10a	CH_2CN	6-Chlorouracil	>66	0.89	7.37	8
10b	$CH_2–C_6H_5$	6-Chlorouracil	96	0.200	34.2	171
11a	CH_2CN	6-(1-Piperidyl)uracil	99	>36.6	36.6	<1
11b	CH_2CN	6-(1-Piperazinyl)uracil	>570	>170	170	<1
11c	CH_2CN	6-(4-Tosyl-1-piperazinyl)uracil	>99	>167	>168	>1
12b	*d)*	*d)*	>710	>430	>430	1

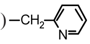
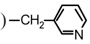
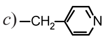
a) , *b)* , *c)* , *d)* Chart 2, *e)* Chart 1.

Table 2. Antiviral Activity of Selected 1-Substituted 3-(3,5-Dimethylbenzyl)uracils against HIV-1 and HCMV as Reported in the Literature 11

Compd.	N1-Substituent	N3-Substituent	IC$_{50}$ (μM) CMV	EC$_{50}$ (μM) HIV-1(III$_B$) AD-169 strain	CC$_{50}$ (μM) CEM cells	SI
1a	CH_2CN	$CH_2C_6H_4CH_3$-*o*	78	192	>490	>3
1a	CH_2CN	$CH_2C_6H_4CH_3$-*m*	>196	6.70	302	45
1b	CH_2CN	$CH_2C_6H_4CH_3$-*p*	78	94.8	>490	>5
2a	CH_2CN	$CH_2C_6H_4$-3,5-CH_3	>74	0.59	>464	>786
2b	$CH_2C_6H_5$	$CH_2C_6H_4$-3,5-CH_3	1.00	0.234	194	829

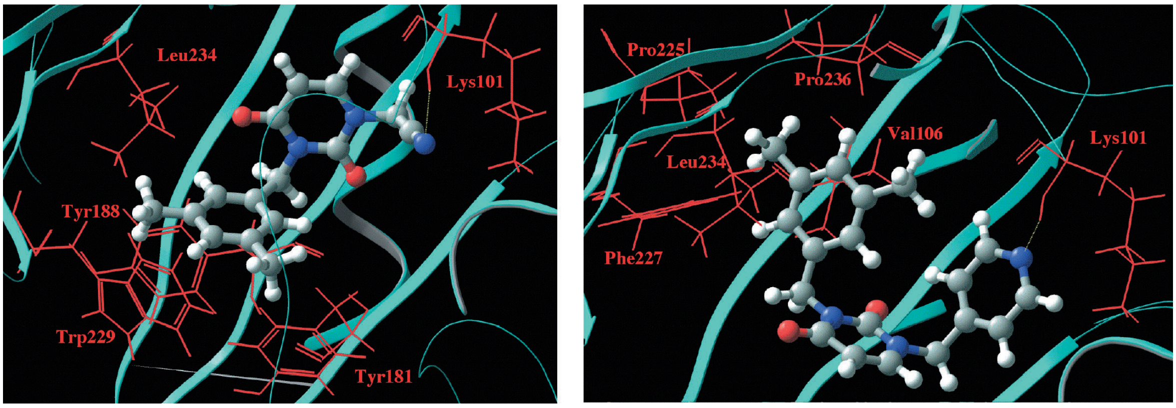


Fig. 3. Docking Structure between HIV-RT and Substrates [Left: 3-(3,5-Dimethylbenzyl)-1-cyanomethyluracil (**2a**) and Right: 3-(3,5-Dimethylbenzyl)-1-(4-picolyl)uracil (**5p**)

The backbone is represented by cyan ribbons and the side chains by red wire style. Substrates are represented by ball and stick style.

pounds displayed no strong activity.

Docking Studies of 1,3-Disubstituted Uracils X-Ray crystal structure of HIV reverse transcriptase (HIV-RT) with nevirapine was taken from PDB (1VRT)[27)] and used for docking studies. After cutting the residues of HIV-RT protein off more than 20 Å with a central focus on nevirapine, the receptor grid generation was performed to create the active site of the receptor for ligand docking. Then, 3-benzyl-1-cyanomethyluracils bearing a methyl group at the phenyl moiety (**1a**—**c**) were automatically oriented and minimized within the binding site, and docked into an active site using the program, Glide ligand docking jobs. The result was valued as G-score and E-model (these values are calculated by Glide for the combination of the posed ligand and receptor). The methyl function in the *meta* position of N-3-benzyl group **1b** was better fit than the *ortho* **1a** or *para* **1c** position. The *meta*-dimethyl (3,5-Me) analog **2a** was also better fit than the 2,5-Me or 2,4-Me position. 3,5-Me **2a** was well-adapted to the receptor by reason that the 1-cyanomethyl group $-CH_2CN$ formed hydrogen bonding interactions (H-bond) with the amide group of Lys101 residue (CN···H–N), and the phenyl moiety existed around the hydrophobic area (Tyr181, Tyr188, Trp229, and Leu234 residues) of HIV-RT (Fig. 3). The 3-dimensional shape of 3,5-Me **2a** in Fig. 3 was a good match with nevirapine complexed with HIV-RT. Next, we evaluated docking affinity of the 1-picolyl derivatives **5n**—**p** as follows. 4-Picolyl derivative (**5p**) was well-fitted to the receptor since nitrogen of the 4-picolyl formed an H-bond with the amide group of Lys101 residue (N···H–N), like the 1-cyanomethyl group of 3,5-Me **2a**. However, the phenyl moiety of **5p** existed around another hydrophobic area (Val106, Pro225, Phe227, Leu234, and Pro236 residues) of HIV-RT. All ligands **5n**—**p** were better adapted to the receptor than 3,5-Me **2a**. It has been reported that most NNRTIs are known to be engaged in the H-bond with the backbone of the amino acids Lys101 and/or Lys103.[28—34)] The docking study of **2a** and **5p** suggests the role of the H-bond for affinity with RT to some extent. However, a series of 1-benzyl and related compounds, **2b**, **5d**—**f, j**—**l**, which will not form an H-bond, still retain affinity with RT. On the contrary, the H-bond was observed when a non-active compound such as 1-cyanomethyl-3-(4-methylbenzyl)uracil (**1c**) was docked with RT. These results indicate that the H-bond is not essential for docking of 1-substituted 3-(3,5-dimethylbenzyl)uracils.

Experimental

Melting points (mp) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low-resolution mass spectra were obtained on a Shimadzu-LKB 9000B mass spectrometer in the direct-inlet mode. High-resolution mass spectra were obtained on a JMS AX-500 spectrometer in the direct-inlet mode. ^{1}H-NMR spectra were recorded on either Varian UNITY 200 (200 MHz) or Varian UNITY 600 (600 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO)-d_6) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with silica gel 60 containing fluorescent indicator F_{254} were used for thin-layer chromatography and silica gel 60 (Merck 7734, 60—200 mesh) was employed for column chromatography.

3-(3,5-Dimethylbenzyl)-1-(tetrahydropyran-2-yl)uracil (3a) To a mixture of 1-(tetrahydrofuran-2-yl)uracil (5 g, 27.4 mmol) and 3,5-dimethylbenzyl alcohol (8.2 ml, 54.8 mmol) in dry THF (150 ml) was added triphenylphosphine (14.36 g, 54.8 mmol) and DIAD (diisopropyl azodicarboxylate) (11 ml, 54.8 mmol). The solution was stirred at 50 °C for 2 h, then concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (4.2×30 cm) using 25—75% AcOEt in hexane (2 l). Evaporation of the fraction and crystallization from hexane gave white crystals (5.6 g, 68%): mp 92.5—94 °C; ^{1}H-NMR ($CDCl_3$) δ 7.29 (1H, d, J=8.1 Hz, H6), 7.08 (2H, m, two of $CH_2C_6\underline{H}_3$), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.00 (1H, dd, J=2.9, 6.2 Hz, H1′), 5.78 (1H, d, J=8.1 Hz, H5), 5.03 (2H, dd, J=13.9, 23.8 Hz, CH_2), 4.14—4.25 (1H, m, H4′a), 3.92—4.03 (1H, m, H4′b), 2.33—2.42 (1H, m, H2′a), 2.28 (6H, s, CH_3×2) 1.82—2.11 (3H, m, H2′b, H3′a, H3′b); UV λ_{max} (MeOH) nm: 265; MS m/z: 300 [M^+]; *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.09; H, 6.81; N, 9.39.

3-(3,5-Dimethylbenzyl)uracil (3b) To a solution of **3a** (4.95 g, 16.5 mmol) in 1,4-dioxane (50 ml) was added 1 M HCl (50 ml) and refluxed for 15 h, then concentrated to a small volume. The solution was neutralized at 10% NaOH. The solution was partitioned between $CHCl_3$ (50 ml×2) and water (50 ml). The organic layer was dried over $MgSO_4$ and concentrated to a small volume to give a solid. The solid was crystallized from 50% EtOH to give white crystals (2.6 g, 69%): mp 156—158 °C; ^{1}H-NMR ($CDCl_3$) δ 9.98 (1H, br s, N^1-H), 7.10 (1H, d, J=7.8 Hz, H6), 7.01 (2H, m, two of $CH_2C_6\underline{H}_3$), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.78 (1H, d, J=7.8 Hz, H5), 5.03 (2H, s, CH_2), 2.28 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 261; UV λ_{max} (NaOH) nm: 288.5; MS m/z: 230 [M^+]; *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.89; H, 6.18; N, 12.13.

Thiation of 3b to Afford 4a, b A mixture of **3b** (6.0 g, 26 mmol) and Lawesson's reagent (20.9 g, 52 mmol) in toluene (300 ml) was refluxed for 1 d, then filtered to remove the precipitation. The filtrate was concentrated to a small volume and chromatographed over a column of silica gel G (5×28 cm) using 25—75% AcOEt in hexane (3 l). The first fraction was evaporated to give 3-(3,5-dimethylbenzyl)-2,4-dithiouracil (**4b**) as yellowish crystals (0.79 g, 12%): mp 178—180 °C; ^{1}H-NMR ($CDCl_3$) δ 10.39 (1H, br s, N^1-H), 6.90 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.88 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.85 (1H, d, *J*=7.1 Hz, H6), 6.73 (1H, d, *J*=7.1 Hz, H5), 6.16 (2H, s, CH_2), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 354, 295; UV λ_{max} (0.1 M NaOH) nm: 378, 291, 265; MS *m/z*: 262 [M$^+$]; *Anal.* Calcd for $C_{13}H_{14}N_2S_2$: C, 59.51; H, 5.38; N, 10.68. Found: C, 59.20; H, 5.31; N, 10.49. From the second fraction 3-(3,5-dimethylbenzyl)-4-thiouracil (**4a**) was obtained as yellowish crystals (5.44 g, 85%): mp 156.5—157.5 °C; ^{1}H-NMR ($CDCl_3$) δ 10.21 (1H br s, N^1-H), 6.96 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.80 (1H, dd, *J*=5.8, 7.1 Hz, H6), 6.62 (1H, dd, *J*=1.6, 7.4 Hz, H5), 5.63 (2H, s, CH_2), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 328; UV λ_{max} (0.1 M NaOH) nm: 343; MS *m/z*: 246 [M$^+$]; *Anal.* Calcd for $C_{13}H_{14}N_2S_2$: C, 59.51; H, 5.38; N, 10.68. Found: C, 59.20; H, 5.31; N, 10.49.

Method 1. Reaction of 3 with Alkyl Chlorides. 1-Allyl-3-(3,5-dimethyl)benzyluracil (5a). A General Procedure for Compounds 5b, d—h, n—s and 6a, b, d—h, n—p A mixture of **3b** (230 mg, 1 mmol), allyl bromide (0.34 ml, 4 mmol) and potassium carbonate (414 mg, 3 mmol) in DMF (10 ml) was stirred at room temperature for 3 h, then acetic acid (0.5 ml) was added and concentrated to a small volume. The residue was partitioned between $CHCl_3$ (20 ml) and water (20 ml). The organic layer was dried over $MgSO_4$ and concentrated to give a solid, which was crystallized from hexane to afford white crystals (240 mg, 89%): mp 85.5—86.5 °C; ^{1}H-NMR ($CDCl_3$) 7.07—7.12 (3H, m, two of N^3-$CH_2C_6\underline{H}_3$, H6), 6.89 (1H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 5.76—5.97 (2H, m, H5, N^1-$CH_2C\underline{H}CH_2$), 5.21—5.33 (2H, m, N^1-$CH_2CHC\underline{H}_2$), 5.06 (2H, s, CH_2), 4.26 (2H, td, *J*=1.5, 5.9 Hz, N^1-CH_2), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 268; MS *m/z*: 270 [M$^+$]; *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.70; N, 10.36. Found: C, 71.00; H, 6.75; N, 10.26.

1-Allyl-3-(3,5-dimethylbenzyl)-4-thiouracil (6a) Crystallization from hexane gave light yellowish crystals (128 mg, 45%): mp 76—76.5 °C; ^{1}H-NMR ($CDCl_3$) 7.04 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.87—6.90 (2H, m, one of $CH_2C_6\underline{H}_3$, H6), 6.63 (1H, d, *J*=7.7 Hz, H5), 8.12—5.94 (1H, m, CH), 5.67 (2H, s, N^3-CH_2), 5.24—5.36 (2H, m, $C\underline{H}_2$=CH–), 4.34—4.37 (2H, m, N^1-CH_2), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 333; MS *m/z*: 286 [M$^+$]; HR-MS *m/z*: 286.1139 (M$^+$, $C_{16}H_{18}N_2OS$ requires 286.1140); *Anal.* Calcd for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78. Found: C, 67.23; H, 6.47; N, 9.91.

1-Ethoxymethyl-3-(3,5-dimethylbenzyl)uracil (5b) Reaction of **3b** (230 mg, 1 mmol) with chloromethyl ethyl ether (0.19 ml, 2 mmol) in a similar manner as described in the section of **5a** and crystallization from hexane–AcOEt gave white crystals (189 mg, 66%): mp 82—82.5 °C; ^{1}H-NMR ($CDCl_3$) 7.27 (1H, d, *J*=8.0 Hz, H6), 7.06 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.90 (1H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 5.83 (1H, d, *J*=8.0 Hz, H5), 5.16 (2H, s, CH_2), 5.06 (2H, s, CH_2), 3.59 (2H, q, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 2.28 (6H, s, $CH_3\times2$), 1.21 (3H, t, *J*=7.0 Hz, $OCH_2C\underline{H}_3$); UV λ_{max} (MeOH) nm: 260; MS *m/z*: 288 [M$^+$]; *Anal.* Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.98; N, 9.72. Found: C, 66.92; H, 7.21; N, 9.76.

1-Ethoxymethyl-3-(3,5-dimethylbenzyl)-4-thiouracil (6b) Crystallization from hexane gave light yellowish crystals (214 mg, 70%): mp 72—72.5 °C; ^{1}H-NMR ($CDCl_3$) δ 7.04 (1H, d, *J*=7.7 Hz, H6), 7.02 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.88 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.65 (1H, d, *J*=7.7 Hz, H5), 5.67 (2H, s, CH_2), 5.15 (2H, s, CH_2), 3.60 (2H, q, *J*=7.1 Hz, CH_2), 2.27 (6H, s, $CH_3\times2$), 1.22 (3H, t, *J*=7.1 Hz, CH_3); UV λ_{max} (MeOH) nm: 328; MS *m/z*: 304 [M$^+$]; HR-MS *m/z*: 304.1245 (M$^+$, $C_{16}H_{20}N_2O_2S$ requires 304.1246); *Anal.* Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.61; N, 9.20. Found: C, 63.16; H, 6.73; N, 9.37.

1-(2-Chlorobenzyl)-3-(3,5-dimethylbenzyl)uracil (5d) Reaction of **3b** (230 mg, 1 mmol) with *o*-chlorobenzyl chloride (0.25 ml, 2 mmol) in a similar manner as described in the section of **5a** and crystallization from EtOH gave white crystals (256 mg, 72%): mp 133—133.5 °C; ^{1}H-NMR ($CDCl_3$) 7.27—7.44 (4H, m, N^1-$CH_2C_6\underline{H}_4$), 7.20 (1H, d, *J*=7.9 Hz, H6), 7.06 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.90 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.76 (1H, d, *J*=7.9 Hz, H5), 5.08 (2H, s, CH_2), 5.04 (2H, s, CH_2), 2.28 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 265; MS *m/z*: 354, 356 [M$^+$]; *Anal.* Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.39; N, 7.90. Found: C, 67.97; H, 5.40; N, 7.85.

1-(2-Chlorobenzyl)-3-(3,5-dimethylbenzyl)-4-thiouracil (6d) Crystallization from EtOH gave light yellowish crystals (139 mg, 35%): mp 139.5—140 °C; ^{1}H-NMR ($CDCl_3$) 7.27—744 (4H, m, N^1-$CH_2C_6\underline{H}_4$), 7.01 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.96 (1H, d, *J*=7.4 Hz, H6), 6.88 (1H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 6.59 (1H, d, *J*=7.4 Hz, H5), 5.68 (2H, s, CH_2), 5.04 (2H, s, CH_2), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 334; MS *m/z*: 370, 372 [M$^+$]; *Anal.* Calcd for $C_{20}H_{19}ClN_2OS$: C, 64.77 H, 5.16; N, 7.55. Found: C, 64.68; H, 5.28; N, 7.67.

1-(3-Chlorobenzyl)-3-(3,5-dimethylbenzyl)uracil (5e) Reaction of **3b** (230 mg, 1 mmol) with *m*-chlorobenzyl chloride (0.25 ml, 2 mmol) in a similar manner as described in the section of **5a** and crystallization from hexane gave white crystals (207 mg, 58%): mp 122—122.5 °C; ^{1}H-NMR ($CDCl_3$) 7.29—7.33 (3H, m, N^1-$CH_2C_6\underline{H}_4$), 7.15—7.19 (1H, m, N^1-$CH_2C_6\underline{H}_4$), 7.12 (1H, d, *J*=7.8 Hz, H6), 7.06 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.90 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.79 (1H, d, *J*=7.8 Hz, H5), 5.07 (2H, s, CH_2), 4.88 (2H, s, CH_2), 2.28 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 266; MS *m/z*: 354, 356 [M$^+$]; *Anal.* Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.39; N, 7.90. Found: C, 67.45; H, 5.53; N, 7.84.

1-(3-Chlorobenzyl)-3-(3,5-dimethylbenzyl)-4-thiouracil (6e) Crystallization from EtOH gave light yellowish crystals (217 mg, 59%): mp 138.5—139.5 °C; ^{1}H-NMR ($CDCl_3$) 7.02—7.33 (4H, m, N^1-$CH_2C_6\underline{H}_4$), 7.02 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.87-6.91 (2H, m, one of N^3-$CH_2C_6\underline{H}_3$, H6), 6.61 (1H, d, *J*=7.4 Hz, H5), 5.68 (2H, s, CH_2), 4.88 (2H, s, CH_2), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 334.5; MS *m/z*: 370, 372 [M$^+$]; *Anal.* Calcd for $C_{20}H_{19}ClN_2OS$: C, 64.77 H, 5.16; N, 7.55. Found: C, 64.87; H, 5.33; N, 7.58.

1-(4-Chlorobenzyl)-3-(3,5-dimethylbenzyl)uracil (5f) Reaction of **3b** (230 mg, 1 mmol) with *p*-chlorobenzyl chloride (322 mg, 2 mmol) in a similar manner as described in the section of **5a** and crystallization from EtOH gave white crystals (220 mg, 62%): mp 119—119.5 °C; ^{1}H-NMR ($CDCl_3$) 7.20—7.37 (4H, m, N^1-$CH_2C_6\underline{H}_4$), 7.10 (1H, d, *J*=7.9 Hz, H6), 7.06 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.90 (1H, m, one of N^3-$CH_2C_6\underline{H}_3$), 5.77 (1H, d, *J*=7.9 Hz, H5), 5.07 (2H, s, CH_2), 4.88 (2H, s, CH_2), 2.28 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 266; MS *m/z*: 354, 356 [M$^+$]; *Anal.* Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.39; N, 7.90. Found: C, 67.88; H, 5.35; N, 7.89.

1-(4-Chlorobenzyl)-3-(3,5-dimethylbenzyl)-4-thiouracil (6f) Crystallization from EtOH gave light yellowish crystals (193 mg, 52%): mp 140.5—141 °C; ^{1}H-NMR ($CDCl_3$) 7.21—7.37 (4H, m, N^1-$CH_2C_6\underline{H}_4$), 7.02 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.85—6.90 (2H, m, one of N^3-$CH_2C_6\underline{H}_3$, H6), 6.60 (1H, d, *J*=7.6 Hz, H5), 5.67 (2H, s, CH_2), 4.87 (2H, s, CH_2), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 334; MS *m/z*: 370, 372 [M$^+$]; *Anal.* Calcd for $C_{20}H_{19}ClN_2OS$: C, 64.77 H, 5.16; N, 7.55. Found: C, 64.82; H, 5.31; N, 7.61.

1-(4-*tert*-Butylbenzyl)-3-(3,5-dimethylbenzyl)uracil (5g) Reaction of **3b** (230 mg, 1 mmol) with 4-(*t*-butyl)benzyl bromide (0.37 ml, 2 mmol) in a similar manner as described in the section of **5a** and crystallization from hexane gave white crystals (285 mg, 76%): mp 133—133.5 °C; ^{1}H-NMR ($CDCl_3$) 7.38 (2H, d, *J*=8.3 Hz, two of N^1-$CH_2C_6\underline{H}_4$), 7.21 (2H, d, *J*=8.3 Hz, two of N^1-$CH_2C_6\underline{H}_4$), 7.12 (1H, d, *J*=7.8 Hz, H6), 7.07 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.90 (1H, m, one of N^3-$CH_2C_6\underline{H}_3$), 5.74 (1H, d, *J*=8.1 Hz, H5), 5.07 (2H, s, CH_2), 4.88 (2H, s, CH_2), 2.28 (6H, s, $CH_3\times2$), 1.31 (9H, s, $CH_3\times3$); UV λ_{max} (MeOH) nm: 268; MS *m/z*: 376 [M$^+$]; *Anal.* Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.49; N, 7.44. Found: C, 76.75; H, 7.71; N, 7.45.

1-(4-*tert*-Butylbenzyl)-3-(3,5-dimethylbenzyl)-4-thiouracil (6g) Crystallization from EtOH gave light yellowish crystals (139 mg, 59%): mp 130—130.5 °C; ^{1}H-NMR ($CDCl_3$) 7.17—7.33 (11H, m, Ph×2, H6), 6.97 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.90 (1H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 6.27—6.34 (1H, m, H5), 5.68 (2H, s, CH_2), 4.48 (1H, dd, *J*=7.7, 8.2 Hz, CH), 4.30 (2H, d, *J*=7.7 Hz, CH_2), 2.30 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 336; MS *m/z*: 426 [M$^+$]; *Anal.* Calcd for $C_{27}H_{26}N_2OS$: C, 76.02; H, 6.14; N, 6.57. Found: C, 76.19; H, 6.24; N, 6.75.

3-(3,5-Dimethylbenzyl)-1-phenacyluracil (5h) Reaction of **3b** (230 mg, 1 mmol) with 2-chloroacetophenone (309 mg, 2 mmol) in a similar manner as described in the section of **5a** gave a foam (340 mg, 97%): ^{1}H-NMR ($CDCl_3$) δ 7.47—8.01 (5H, m, $CH_2C_6\underline{H}_5$), 7.03—7.07 (3H, m, H6, two of $CH_2C_6\underline{H}_3$), 6.88 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.84 (1H, d, *J*=7.7 Hz, H5), 5.17 (2H, s, CH_2), 5.06 (2H, s, CH_2), 2.28 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 248; MS *m/z*: 348 [M$^+$]; HR-MS *m/z*: 348.1469 (M$^+$, $C_{21}H_{20}N_2O_3$ requires 348.1674).

3-(3,5-Dimethylbenzyl)-1-phenacyl-4-thiouracil (6h) Crystallization from hexane gave light yellowish crystals (133 mg, 36%): mp 178—178.5 °C; ^{1}H-NMR ($CDCl_3$) 7.48—7.98 (5H, m, Ph), 7.02 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.88 (1H, m, one of N^3-$CH_2C_6\underline{H}_3$), 6.81 (1H, d, *J*=7.6 Hz, H6), 6.68 (1H, d, *J*=7.6 Hz, H5), 5.67 (2H, s, CH_2), 5.17 (2H, s, CH_2), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} (MeOH) nm: 246, 332; MS *m/z*: 364 [M$^+$]; *Anal.* Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.21; H, 5.52; N, 7.69. Found: C, 69.17; H, 5.66; N, 7.62.

3-(3,5-Dimethylbenzyl)-1-(2-picolyl)uracil (5n) Reaction of **3b** (230 mg, 1 mmol) with 2-picolyl chloride hydrochloride (328 mg, 2 mmol) and potassium carbonate (1.1 g, 8 mmol) in a similar manner as described in the section of **5a** and crystallization from EtOH gave white crystals (276 mg, 86%): mp 131—132 °C; ^{1}H-NMR ($CDCl_3$) 8.54—8.56 (1H, m, one of N^1-$CH_2C_5\underline{H}_4N$), 7.66—7.71 (1H, m, one of N^1-$CH_2C_5\underline{H}_4N$), 7.38—7.41 (1H, m, one of N^1-$CH_2C_5\underline{H}_4N$), 7.33 (1H, d, J=8.0 Hz, H6), 7.21—7.25 (1H, m, one of N^1-$CH_2C_5\underline{H}_4N$), 7.03 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.87 (1H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 5.78 (1H, d, J=8.0 Hz, H5), 5.04 (2H, s, CH_2), 4.98 (2H, s, CH_2), 2.26 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 268; MS *m/z*: 321 [M^+]; *Anal.* ($C_{19}H_{19}N_3O_2$) C, H, N.

3-(3,5-Dimethylbenzyl)-1-(2-picolyl)-4-thiouracil (6n) Crystallization from EtOH gave light yellowish crystals (140 mg, 42%): mp 115—115.5 °C; ^{1}H-NMR ($CDCl_3$) 8.56—8.58 (1H, m, one of N^1-$CH_2C_5\underline{H}_4N$), 7.65—7.74 (1H, m, one of N^1-$CH_2C_5\underline{H}_4N$), 7.18—7.37 (3H, m, two of N^1-$CH_2C_5\underline{H}_4N$, H6), 7.01 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.87 (2H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 6.65 (1H, d, J=7.3 Hz, H5), 5.66 (2H, s, CH_2), 4.99 (2H, s, CH_2), 2.26 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 334; MS *m/z*: 337 [M^+]; *Anal.* Calcd for $C_{19}H_{19}N_3OS$: C, 67.63; H, 5.67; N, 12.45. Found: C, 67.79; H, 5.82; N, 12.48.

3-(3,5-Dimethylbenzyl)-1-(3-picolyl)uracil (5o) Reaction of **3b** (230 mg, 1 mmol) with 3-picolyl chloride hydrochloride (243 mg, 1.5 mmol) and potassium carbonate (552 mg, 4 mmol) in a similar manner as described in the section of **5a** gave a foam (576 mg, 90%): ^{1}H-NMR ($CDCl_3$) δ 8.59—8.61 (2H, m, Py), 7.66 (1H, ddd, J=1.6, 2.2, 8.0 Hz, Py), 7.30—7.32 (1H, m, Py), 7.15 (1H, d, J=8.0 Hz, H6), 7.05 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.90 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.79 (1H, d, J=8.0 Hz, H5), 5.06 (2H, s, N^3-CH_2), 4.93 (2H, s, N^1-CH_2), 2.28 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 262—268; MS *m/z*: 321 [M^+]; HR-MS *m/z*: 321.1465 (M^+, $C_{19}H_{19}N_3O_2$ requires 321.1477).

3-(3,5-Dimethylbenzyl)-1-(3-picolyl)-4-thiouracil (6o) Crystallization from EtOH gave light yellowish crystals (149 mg, 44%): mp 122.5—123 °C; ^{1}H-NMR ($CDCl_3$) 8.62 (2H, dd, J=1.5, 4.8 Hz, two of N^1-$CH_2C_5\underline{H}_4N$), 7.66—7.70 (1H, m, one of N^1-$CH_2C_5\underline{H}_4N$), 7.30—7.33 (1H, m, one of N^1-$CH_2C_5\underline{H}_4N$), 7.03 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.90—6.96 (2H, m, one of N^3-$CH_2C_6\underline{H}_3$, H6), 6.62 (1H, d, J=8.1 Hz, H5), 5.68 (2H, s, CH_2), 4.93 (2H, s, CH_2), 2.28 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 333.5; MS *m/z*: 337 [M^+]; *Anal.* Calcd for $C_{19}H_{19}N_3OS$: C, 67.63; H, 5.67; N, 12.45. Found: C, 67.73; H, 5.82; N, 12.41.

3-(3,5-Dimethylbenzyl)-1-(4-picolyl)uracil (5p) Reaction of **3b** (230 mg, 1 mmol) with 4-picolyl chloride hydrochloride (243 mg, 1.5 mmol) and potassium carbonate (552 mg, 4 mmol) in a similar manner as described in the section of **5a** and crystallization from EtOH gave white crystals (133 mg, 35%): mp 152.5—153 °C; ^{1}H-NMR ($CDCl_3$) 8.59—8.62 (2H, m, two of N^1-$CH_2C_5\underline{H}_4N$), 7.05—7.16 (3H, m, two of N^1-$CH_2C_5\underline{H}_4N$, H6), 7.05 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.90 (1H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 5.82 (1H, d, J=7.8 Hz, H5), 5.07 (2H, s, CH_2), 4.91 (2H, s, CH_2), 2.28 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 263; MS *m/z*: 321 [M^+]; *Anal.* Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.95; N, 13.08. Found: C, 71.16; H, 6.16; N, 13.06.

3-(3,5-Dimethylbenzyl)-1-(4-picolyl)-4-thiouracil (6p) Crystallization from hexane gave light yellowish crystals (99 mg, 29%): mp 140.5—141 °C; ^{1}H-NMR ($CDCl_3$) 8.61—8.64 (2H, m, two of N^1-$CH_2C_5\underline{H}_4N$), 7.16—7.19 (2H, m, two of N^1-$CH_2C_5\underline{H}_4N$), 7.02 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.88—6.92 (2H, m, one of N^3-$CH_2C_6\underline{H}_3$, H6), 6.64 (1H, d, J=7.6 Hz, H5), 5.68 (2H, s, CH_2), 4.92 (2H, s, CH_2), 2.27 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 332; MS *m/z*: 337 [M^+]; *Anal.* Calcd for $C_{19}H_{19}N_3OS \cdot 0.2H_2O$: C, 67.63; H, 5.67; N, 12.45. Found: C, 66.84; H, 5.80; N, 12.09.

Ethyl [3-(3,5-Dimethylbenzyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimid-1-yl]acetate (5q) Reaction of **3b** (230 mg, 1 mmol) with ethyl chloroacetate (0.22 ml, 2 mmol) in a similar manner as described in the section of **5a** gave **5r** as a syrup (310 mg, 98%): ^{1}H-NMR ($CDCl_3$) δ 7.04—7.08 (3H, m, H6, two of $CH_2C_6\underline{H}_3$), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.81 (1H, d, J=8.1 Hz, H5), 5.05 (2H, s, CH_2), 4.44 (2H, s, CH_2), 4.24 (2H, dd, J=7.3, 14.3 Hz, $C\underline{H}_2CH_3$), 2.27 (6H, s, CH_3×2), 1.28 (3H, dd, J=7.0, 7.3 Hz, $CH_2C\underline{H}_3$); UV λ_{max} (MeOH) nm: 263; MS *m/z*: 316 [M^+]; HR-MS *m/z*: 316.1412 (M^+, $C_{17}H_{20}N_2O_4$ requires 316.1423).

[3-(3,5-Dimethylbenzyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimid-1-yl]-2-propanone (5r) Reaction of **3b** (230 mg, 1 mmol) with chloroacetone (0.16 ml, 2 mmol) in a similar manner as described in the section of **5a** and crystallization from hexane gave white crystals (237 mg, 83%): mp 112.5—114 °C; ^{1}H-NMR ($CDCl_3$) δ 7.02 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.95 (1H, d, J=8.1 Hz, H6), 6.88 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.80 (1H, d, J=8.1 Hz, H5), 5.04 (2H, s, CH_2), 4.52 (2H, s, CH_2), 2.28 (6H, s, CH_3×2), 2.25 (3H, s, CH_3); UV λ_{max} (MeOH) nm: 265; MS *m/z*: 286 [M^+]; *Anal.* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.25; H, 6.34; N, 9.78.

3-(3,5-Dimethylbenzyl)-1-trifluoroethyluracil (5s) Reaction of **3b** (230 mg, 1 mmol) with 2-iodo-1,1,1-trifluoroethane (0.2 ml, 2 mmol) at 80 °C overnight in a similar manner as described in the section of **5a** and crystallization from hexane gave white crystals (199 mg, 64%): mp 135.5—136.5 °C; ^{1}H-NMR ($CDCl_3$) δ 7.12 (1H, d, J=8.1 Hz, H6), 7.05 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.91 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.85 (1H, d, J=7.8 Hz, H5), 5.06 (2H, s, CH_2), 4.37 (2H, dd, J=8.3, 16.8 Hz, CH_2), 2.28 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 259; MS *m/z*: 312 [M^+]; *Anal.* Calcd for $C_{15}H_{15}F_3N_2O_2$: C, 57.69; H, 4.84; N, 8.97. Found: C, 57.79; H, 4.87; N, 8.96.

2-Cyanomethylthio-3-(3,5-dimethylbenzyl)-3,4-dihydropyrimidin-4-thione (7a) Reaction of **4b** (262 mg, 1 mmol) with bromoacetonitrile (0.14 ml, 2 mmol) in a similar manner as described in the section of **5a** and crystallization from EtOH gave light yellowish crystals (263 mg, 87%): mp 125.5—126 °C; ^{1}H-NMR ($CDCl_3$) δ 7.61 (1H, d, J=5.8 Hz, H6), 7.34 (1H, d, J=6.0 Hz, H5), 6.93 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.80 (2H, br s, two of $CH_2C_6\underline{H}_3$), 5.90 (2H, s, CH_2), 3.88 (2H, s, CH_2), 2.29 (6H, s, CH_3×2); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 187.4 (C4), 160.1 (C2), 144.8 (C8), 138.6, 132.1, 129.9 and 124.3 ($CH_2\mathit{C}_6H_3$), 126.6 (C5), 115.1 (CN), 53.4(N^3-CH_2), 21.3 (CH_3×2), 18.6 (S-CH_2), 21.3 (CH_3×2); UV λ_{max} (MeOH) nm: 295.5, 350; MS *m/z*: 301 [M^+]; *Anal.* Calcd for $C_{15}H_{15}N_3S_2$: C, 59.77; H, 5.02; N, 13.94. Found: C, 59.92; H, 5.15; N, 14.09.

2-Benzylthio-3-(3,5-dimethylbenzyl)-3,4-dihydropyrimidin-4-thione (7b) Reaction of **4b** (262 mg, 1 mmol) with benzylbromide (0.24 ml, 2 mmol) in a similar manner as described in the section of **5a** and crystallization from hexane gave light yellowish crystals (232 mg, 66%): mp 92.5—93 °C; ^{1}H-NMR ($CDCl_3$) δ 7.59 (1H, d, J=6.0 Hz, H6), 7.25—7.33 (6H, m, $CH_2C_6\underline{H}_5$, H5), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.77 (2H, br s, two of $CH_2C_6\underline{H}_3$), 5.92 (2H, s, CH_2), 4.37 (2H, s, CH_2), 2.26 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 295.5, 357; MS *m/z*: 352 [M^+]; *Anal.* Calcd for $C_{20}H_{20}N_2S_2$: C, 68.14; H, 5.71; N, 7.95. Found: C, 68.33; H, 5.63; N, 8.09.

Method 2. Mitsunobu Reaction of 3b or 4a with Alcohols. 3-(3,5-Dimethylbenzyl)-1-[(2-methylthio)ethyl]uracil (5c). A General Procedure for Compounds 5i—m, 6c, i—m To an ice-cooled mixture of **3b** (230 mg, 1 mmol) and 2-(methylthio)ethanol (0.18 ml, 2 mmol) in dry THF (20 ml) was added triphenylphosphine (524 mg, 2 mmol) and TMAD (344 mg, 2 mmol). The solution was stirred at 50 °C overnight, then concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (2.0×30 cm) using 0—50% AcOEt in hexane (1 l). Evaporation of the fraction and crystallization from hexane gave white crystals (110 mg, 36%): mp 79—79.5 °C; ^{1}H-NMR ($CDCl_3$) 7.17 (1H, d, J=7.7 Hz, H6), 7.05 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.89 (1H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 5.76 (1H, d, J=8.0 Hz, H5), 5.05 (2H, s, CH_2), 3.91 (2H, dd, J=6.2, 6.6 Hz, $CH_3SCH_2C\underline{H}_2$), 2.79 (2H, dd, J=6.2, 6.6 Hz, $CH_3SC\underline{H}_2CH_2$), 2.28 (6H, s, CH_3×2), 2.1 (3H, s, $C\underline{H}_3SCH_2CH_2$); UV λ_{max} (MeOH) nm: 268; MS *m/z*: 304 [M^+]; *Anal.* Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.61; N, 9.20. Found: C, 63.56; H, 6.83; N, 9.26.

3-(3,5-Dimethylbenzyl)-1-[(2-methylthio)ethyl]-4-thiouracil (6c) Crystallization from hexane gave light yellowish crystals (194 mg, 61%): mp 148.5—149 °C; ^{1}H-NMR ($CDCl_3$) δ 7.02 (2H, m, two of $CH_2C_6\underline{H}_3$) 6.94 (1H, d, J=7.4 Hz, H6), 6.87 (1H, m, one of $CH_2C_6\underline{H}_3$), 6.61 (1H, d, J=7.4 Hz, H5), 5.67 (2H, s, N^3-CH_2), 3.92 (2H, dd, J=6.3 6.6 Hz, CH_2), 2.80 (2H, dd, J=6.3 6.6 Hz, CH_2), 2.27 (6H, s, CH_3×2), 2.10 (3H, s, S-CH_3); UV λ_{max} (MeOH) nm: 334; MS *m/z*: 320 [M^+]; HR-MS *m/z*: 320.0995 (M^+, $C_{16}H_{20}N_2OS_2$ requires 320.1018); *Anal.* Calcd for $C_{16}H_{20}N_2OS_2$: C, 59.97; H, 6.28; N, 8.74. Found: C, 60.08; H, 6.37; N, 8.91.

3-(3,5-Dimethylbenzyl)-1-(2,2-diphenylethyl)uracil (5i) Reaction of **3b** (230 mg, 1 mmol) with 2,2-diphenylethanol (397 mg, 2 mmol) in a similar manner as described in the section of **5c** and crystallization from EtOH gave white crystals (199 mg, 70%): mp 165.5—166 °C; ^{1}H-NMR ($CDCl_3$) 7.18—7.32 (10H, m, Ph×2), 7.00 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.55 (1H, d, J=7.7 Hz, H6), 5.42 (1H, d, J=8.0 Hz, H5), 5.05 (2H, s, CH_2), 4.47 (1H, t, J=8.0 Hz, CH), 4.30 (2H, d, J=8.2 Hz, CH_2), 2.30 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 268; MS *m/z*: 410 [M^+]; *Anal.* Calcd for $C_{27}H_{26}N_2O_2 \cdot 0.2\ H_2O$: C, 78.31; H, 6.42; N, 6.77. Found: C, 78.41; H, 6.53; N, 6.79.

3-(3,5-Dimethylbenzyl)-1-(2,2-diphenylethyl)-4-thiouracil (6i) Crystallization from EtOH gave light yellowish crystals (250 mg, 59%): mp 130—130.5 °C; ^{1}H-NMR ($CDCl_3$) 7.17—7.33 (11H, m, Ph×2, H6), 6.97 (2H, br s, two of N^3-$CH_2C_6\underline{H}_3$), 6.90 (1H, br s, one of N^3-$CH_2C_6\underline{H}_3$), 6.27-6.34 (1H, m, H5), 5.68 (2H, s, CH_2), 4.48 (1H, dd, J=7.7, 8.2 Hz, CH), 4.30 (2H, d, J=7.7 Hz, CH_2), 2.30 (6H, s, CH_3×2); UV λ_{max} (MeOH) nm: 336; MS *m/z*: 426 [M^+]; *Anal.* Calcd for $C_{27}H_{26}N_2OS$: C, 76.02; H, 6.14; N, 6.57. Found: C, 76.19; H, 6.24; N, 6.75.

3-(3,5-Dimethylbenzyl)-1-[(furan-2-yl)methyl]uracil (5j) Reaction of **3b** (230 mg, 1 mmol) with furfuryl alcohol (0.17 ml, 2 mmol) in a similar manner as described in the section of **5c** gave a foam (206 mg, 66%): ^{1}H-

NMR ($CDCl_3$) δ 7.39—7.40 (1H, m, one of furanyl), 7.18 (1H, d, J=7.8 Hz, H6), 7.07 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.35—6.42 (2H, m, two of furanyl), 5.76 (1H, d, J=7.8 Hz, H5), 5.04 (2H, s, CH_2), 4.89 (2H, s, CH_2), 2.28 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 265; MS *m/z*: 310 [M^+]; HR-MS *m/z*: 310.1287 (M^+, $C_{18}H_{18}N_2O_3$ requires 310.1381).

3-(3,5-Dimethylbenzyl)-1-[(furan-2-yl)methyl]-4-thiouracil (6j) A foam (144 mg, 44%): ^{1}H-NMR ($CDCl_3$) δ 7.41—742 (1H, m, one of furanyl), 7.04 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.90 (1H, d, J=7.4 Hz, H6), 6.88 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.60 (1H, d, J=7.4 Hz, H5), 6.44 (1H, dd, J=0.8, 3.3 Hz, one of furanyl), 6.37—6.38 (1H, br s, one of furanyl), 5.66 (2H, s, CH_2), 4.89 (2H, s, CH_2), 2.27 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 332; MS *m/z*: 326 [M^+]; HR-MS *m/z*: 326.1097 (M^+, $C_{18}H_{18}N_2O_2S$ requires 326.1089).

3-(3,5-Dimethylbenzyl)-1-[(furan-3-yl)methyl]uracil (5k) Reaction of **3b** (230 mg, 1 mmol) with 3-furanylmethanol (0.17 ml, 2 mmol) in a similar manner as described in the section of **5c** gave white crystals (221 mg, 71%): mp 72.5—73 °C; ^{1}H-NMR ($CDCl_3$) δ 7.43—7.49 (2H, m, two of furanyl), 7.13 (1H, d, J=8.1 Hz, H6), 7.08 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.90 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.37—6.38 (1H, m, one of furanyl), 5.75 (1H, d, J=8.1 Hz, H5), 5.07 (2H, s, CH_2), 4.76 (2H, s, CH_2), 2.29 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 266; MS *m/z*: 310 [M^+]; *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.84; N, 9.03. Found: C, 69.77; H, 6.02; N, 8.98.

3-(3,5-Dimethylbenzyl)-1-[(furan-3-yl)methyl]-4-thiouracil (6k) Crystallization from EtOH gave light yellowish crystals (196 mg, 60%): mp 100.5—101 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.50 (1H, q, J=0.8 Hz, one of furanyl), 7.43 (1H, t, J=1.6 Hz, one of furanyl), 7.04 (2H, br s, two of $CH_2C_6\underline{H}_3$), 6.90 (1H, d, J=7.7 Hz, H6), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.59 (1H, d, J=7.7 Hz, H5), 6.37 (1H, dd, J=0.8, 1.1 Hz, one of furanyl), 5.68 (2H, s, N^3-CH_2), 4.76 (2H, s, N^1-CH_2), 2.28 (6H, s, $CH_3 \times 2$); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 190.8 (C4), 149.8 (C2), 144.3, 141.5, 119.0 and 110.0 (furanyl), 137.8, 135.5 129.3 and 125.8 ($CH_2\underline{C}_6H_3$), 134.6 (C6), 114.6 (C5), 50.4 (N^3-CH_2), 44.3 (N^1-CH_2), 21.3 ($CH_3 \times 2$); UV λ_{max} (MeOH) nm: 326; MS *m/z*: 283 [M^+]; *Anal.* Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.33; H, 5.56; N, 8.54.

3-(3,5-Dimethylbenzyl)-1-[(thiophen-2-yl)methyl]uracil (5l) Reaction of **3b** (230 mg, 1 mmol) with 2-thiophenemethanol (0.19 ml, 2 mmol) in a similar manner as described in the section of **5c** crystallization from hexane gave white crystals (175 mg, 54%): mp 79.5—80 °C; ^{1}H-NMR ($CDCl_3$) δ 7.31 (1H, dd, J=1.3, 5.1 Hz, one of $C_4\underline{H}_3S$), 7.16 (1H, d, J=7.9 Hz, H6), 7.07—7.09 (3H, m, one of $C_4\underline{H}_3S$, two of $CH_2C_6\underline{H}_3$), 6.99 (1H, dd, J=3.5, 5.1 Hz, one of $C_4\underline{H}_3S$), 6.90 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.76 (1H, d, J=7.9 Hz, H5), 5.07 (4H, br s, $CH_2 \times 2$), 2.28 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 268; MS *m/z*: 326 [M^+]; *Anal.* Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.55; N, 8.58. Found: C, 66.46; H, 5.74; N, 8.54.

3-(3,5-Dimethylbenzyl)-1-[(thiophen-2-yl)methyl]-4-thiouracil (6l) Crystallization from hexane gave light yellowish crystals (155 mg, 45%): mp 110—110.5 °C; ^{1}H-NMR ($CDCl_3$) δ 7.31—7.33 (1H, m, one of $C_4\underline{H}_3S$), 7.09—7.11 (1H, m, one of $C_4\underline{H}_3S$), 7.04 (2H, br s, two of $CH_2C_6\underline{H}_3$), 7.00 (1H, dd, J=3.6 4.9 Hz, one of $C_4\underline{H}_3S$), 6.93 (1H, d, J=7.4 Hz, H6), 6.88 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.58 (1H, d, J=7.4 Hz, H5), 5.68 (2H, s, CH_2), 5.06 (2H, s, CH_2), 2.27 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 334; MS *m/z*: 342 [M^+]; *Anal.* Calcd for $C_{18}H_{18}N_2OS_2$: C, 63.13; H, 5.29; N, 8.18. Found: C, 63.18; H, 5.27; N, 8.08.

3-(3,5-Dimethylbenzyl)-1-[(thiophen-3-yl)methyl]uracil (5m) Reaction of **3b** (230 mg, 1 mmol) with 3-thiophenemethanol (0.19 ml, 2 mmol) in a similar manner as described in the section of **5c** crystallization from hexane gave white crystals (257 mg, 85%): mp 86.5—87 °C; ^{1}H-NMR ($CDCl_3$) δ 7.34 (1H, dd, J=3.0, 4.9 Hz, one of $C_4\underline{H}_3S$), 7.23—7.25 (1H, m, one of $C_4\underline{H}_3S$), 7.11 (1H, d, J=7.7 Hz, H6), 7.06 (2H, br s, two of $CH_2C_6\underline{H}_3$), 7.22 (1H, dd, J=1.1, 4.9 Hz, one of $C_4\underline{H}_3S$), 6.89 (1H, br s, one of $CH_2C_6\underline{H}_3$), 5.74 (1H, d, J=8.0 Hz, H5), 5.07 (2H, br s, CH_2), 4.90 (2H, br s, CH_2), 2.28 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 268; MS *m/z*: 326 [M^+]; *Anal.* Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.55; N, 8.58. Found: C, 66.55; H, 5.61; N, 8.54.

3-(3,5-Dimethylbenzyl)-1-[(thiophen-3-yl)methyl]-4-thiouracil (6m) Crystallization from hexane gave light yellowish crystals (220 mg, 64%): mp 80.5—81.5 °C; ^{1}H-NMR ($CDCl_3$) δ 7.36 (1H, dd, J=3.0 4.9 Hz, one of $C_4\underline{H}_3S$), 7.27—7.28 (1H, m, one of $C_4\underline{H}_3S$), 7.02—7.04 (3H, m, two of $CH_2C_6\underline{H}_3$, one of $C_4\underline{H}_3S$), 6.88—6.90 (2H, m, one of $CH_2C_6\underline{H}_3$, H6), 6.58 (1H, d, J=7.4 Hz, H5), 5.68 (2H, s, CH_2), 4.91 (2H, s, CH_2), 2.28 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 334; MS *m/z*: 342 [M^+]; HR-MS *m/z*: 342.0861 (M^+, $C_{18}H_{18}N_3OS_2$ requires 342.0862); *Anal.* Calcd for $C_{18}H_{18}N_2OS_2$: C, 63.13; H, 5.29; N, 8.18. Found: C, 63.11; H, 5.36; N, 8.30.

6-Substituteduracils. 6-Chloro-1-cyanomethyluracil (9a) A mixture of 6-chlorouracil (440 ml, 3 mmol), bromoacetonitrile (0.28 ml, 4 mmol) and potassium carbonate (207 mg, 1.5 mmol) in DMSO (10 ml) was stirred at 70 °C for 1 h, then acetic acid (0.5 ml) was added and concentrated to a small volume. The residue was chromatographed over a column of silica gel G (2.8×33 cm) using 0—10% EtOH in $CHCl_3$ (1600 ml). Evaporation of the fraction and crystallization from H_2O–EtOH gave white crystals (273 mg, 49%): mp 225—226 °C; ^{1}H-NMR (DMSO-d_6) δ 11.90 (1H, br s, N^3-H), 6.11 (1H, s, H5), 5.04 (2H, s, N^1-CH_2); UV λ_{max} (MeOH) nm: 261; UV λ_{max} (NaOH) nm: 261; MS *m/z*: 185, 187 [M^+]; HR-MS *m/z*: 184.9992 (M^+, $C_6H_4ClN_3O_2$ requires 184.9983); *Anal.* Calcd for $C_6H_4ClN_3O_2$: C, 38.84; H, 2.17; N, 22.64. Found: C, 38.88; H, 2.31; N, 22.75.

6-Chloro-1-cyanomethyl-3-(3,5-dimethylbenzyl)uracil (10a). A General Procedure for Compound 10b To a mixture of **9a** (2.3 g, 12.6 mmol) and 3,5-dimethylbenzyl alcohol (3.8 ml, 25.3 mmol) in dry THF (100 ml) was added triphenylphosphine (6.63 g, 25.3 mmol) and TMAD (4.35 g, 25.3 mmol). The solution was stirred at 50 °C for 5 h, then concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (3.0×52 cm) using 0—50% AcOEt in hexane (2 l). Evaporation of the fraction and crystallization from mEtOH gave white crystals (2.78 g, 74%): mp 125.5—126 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.04 (2H, m, two of $CH_2C_6\underline{H}_3$), 6.92 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.07 (1H, s, H5), 5.02 (2H, s, N^3-CH_2), 4.95 (2H, s, N^1-CH_2), 2.29 (6H, s, $CH_3 \times 2$); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.7 (C4), 150.0 (C2), 143.1 (C6), 138.1, 135.3, 129.8 and 126.8 ($CH_2\underline{C}_6H_3$), 113.3 (CN), 103.9 (C5), 45.3 (N^3-CH_2), 33.7 (N^1-CH_2), 21.2 ($CH_3 \times 2$); UV λ_{max} (MeOH) nm: 261.5; MS *m/z*: 303, 305 [M^+]; HR-MS *m/z*: 303.0751 (M^+, $C_{15}H_{14}ClN_3O_2$ requires 303.0774); *Anal.* Calcd for $C_{15}H_{14}ClN_3O_2$: C, 59.31; H, 4.65; N, 13.83. Found: C, 59.38; H, 4.76; N, 13.74.

1-Benzyl-6-chloro-3-(3,5-dimethylbenzyl)uracil (10b) A syrup (358 mg, quantitative): ^{1}H-NMR ($CDCl_3$) δ 6.90—7.37 (8H, m, $CH_2C_6\underline{H}_3$, $CH_2C_6\underline{H}_5$), 5.96 (1H, s, H5), 5.27 (2H, s, CH_2), 5.05 (2H, s, CH_2), 2.28 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 269.5; MS *m/z*: 354, 356 [M^+]; HR-MS *m/z*: 354.1127 (M^+, $C_{20}H_{19}ClN_2O_2$ requires 354.1135). *Anal.* Calcd for $C_6H_4ClN_3O_2$: C, 38.84; H, 2.17; N, 22.64. Found: C, 38.88; H, 2.31; N, 22.75.

1-Benzyl-3-(3,5-dimethylbenzyl)-2-thiouracil (8b) Reaction of 1-benzyl-2-thiouracil (**8a**, 230 mg, 1 mmol) with 3,5-dimethylbenzyl alcohol (0.3 ml, 2 mmol) in a similar manner as described in the section of **10a** gave a foam (127 mg, 38%); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.28—7.39 (6H, m, H6 and $CH_2C_6\underline{H}_5$), 7.02 (2H, s, two of $CH_2C_6\underline{H}_3$), 6.88 (1H, br s, one of $CH_2C_6\underline{H}_3$), 6.01 (1H, d, J=8.0 Hz, H5), 5.71 (2H, s, N^3-CH_2), 5.54 (2H, s, N^1-CH_2), 2.28 (6H, s, $CH_3 \times 2$); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 178.4 (C2), 160.0 (C4), 142.3 (C6), 137.7, 135.6, 129.1 and 125.8 ($CH_2\underline{C}_6H_3$), 134.7, 129.1, 128.5 and 127.9 ($CH_2C_6\underline{H}_5$), 105.7 (C5), 58.9 (N^3-CH_2), 50.5 (N^1-CH_2), 21.4 ($CH_3 \times 2$); UV λ_{max} (MeOH) nm: 293 (sh), 276.5; MS *m/z*: 336 [M^+]; HR-MS *m/z*: 336.1286 (M^+, $C_{20}H_{20}N_2OS$ requires 336.1296).

1-Benzyl-3-(3,5-dimethylbenzyl)-6-(1-piperidinyl)uracil (11a). A General Procedure for Compound 11b A mixture of **10a** (152 mg, 0.5 mmol) and piperidine (0.25 ml, 2.5 mmol) in 1,4-dioxane (5 ml) was stirred at 60 °C for 4 h, then concentrated to a small volume. The residue was partitioned between $CHCl_3$ (20 ml) and water (20 ml). The organic layer was dried over $MgSO_4$, and concentrated to a small volume. The residue was chromatographed over a column of silica gel G (1.8×30 cm) using 0—50% AcOEt in hexane (1 l) to give a foam (161 mg, 91%): ^{1}H-NMR ($CDCl_3$) δ 7.09 (2H, m, $CH_2C_6\underline{H}_3$), 6.90 (1H, m, $CH_2C_6\underline{H}_3$), 5.33 (1H, s, H5), 5.02 (2H, s, CH_2), 4.69 (2H, s, CH_2), 2.92 (4H, m, four of piperidine), 2.28 (6H, s, $CH_3 \times 2$), 1.73 (6H, m, six of piperidine); UV λ_{max} (MeOH) nm: 277; MS *m/z*: 352 [M^+]; HR-MS *m/z*: 352.1904 (M^+, $C_{20}H_{24}N_4O_2$ requires 352.1900).

1-Benzyl-3-(3,5-dimethylbenzyl)-6-(1-piperazinyl)uracil (11b) Recrystallization from EtOH gave white crystals (307 mg, 87%): mp 179—180 °C; ^{1}H-NMR (DMSO-d_6) δ 6.88 (3H, br s, $CH_2C_6\underline{H}_3$), 5.32 (1H, s, H5), 4.86 (2H, s, CH_2), 4.81 (2H, s, CH_2), 2.84 (8H, s, piperazine), 2.22 (6H, s, $CH_3 \times 2$); UV λ_{max} (MeOH) nm: 275.5; MS *m/z*: 353 [M^+]; *Anal.* Calcd for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.57; H, 6.68; N, 19.81.

1-Benzyl-3-(3,5-dimethylbenzyl)-6-[4-(*p*-toluenesulfonyl)-1-piperazinyl]uracil (11c) A mixture of **11c** (177 mg, 0.5 mmol) and *p*-toluenesulfonyl chloride (330 mg, 1.7 mmol) in pyridine (5 ml) was stirred at room temperature for 30 min, then water (1 ml) was added and concentrated to a small volume. The residue was partitioned between $CHCl_3$ (20 ml) and water (20 ml). The organic layer was dried over $MgSO_4$ and concentrated to a small volume. Recrystallization of the residue from EtOH gave white crystals (247 mg, 97%): mp 215—216 °C; ^{1}H-NMR ($CDCl_3$) δ 6.90—7.69 (7H, m, $CH_2C_6\underline{H}_3$, $SO_2C_6\underline{H}_4CH_3$), 5.39 (1H, s, H5), 4.99 (2H, s, CH_2), 4.59 (2H, s, CH_2), 3.05 (8H, br s, piperazine), 2.47 (3H, s, CH_3), 2.27 (6H, s, $CH_3\times2$); UV λ_{max} ($CHCl_3$) nm: 266; MS *m/z*: 507 [M^+]; *Anal.* Calcd for $C_{26}H_{29}N_5O_4S$: C, 61.52; H, 5.76; N, 13.80. Found: C, 61.51; H, 5.73; N, 13.83.

3-Cyanomethyl-6-methyl-1-(3,5-dimethylbenzyl)uracil (12b) To a solution of 6-methyluracil (1.26 g, 10 mmol) in DMF (25 ml) was added potassium carbonate (691 mg, 5 mmol) and bromoacetonitrile (0.35 ml, 5 mmol) and stirred at 60 °C for 7 h, then acetic acid (0.5 ml) was added and concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G using 0—20% EtOH in $CHCl_3$ (2 l) to give **12a** as a solid (434 mg). To a mixture of the solid (434 mg) and 3,5-dimethylbenzyl alcohol (0.73 ml, 5 mmol) in dry THF (40 ml) was added triphenylphosphine (1.31 g, 5 mmol) and TMAD (860 mg, 5 mmol). The solution was stirred at 50 °C overnight, then concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (2.5×32 cm) using 20—80% AcOEt in hexane (2 l). Evaporation of the fraction and crystallization from EtOH gave light yellowish crystals (53 mg): mp 167—168 °C; ^1H-NMR (600 MHz, $CDCl_3$) δ 6.94 (1H, m, $CH_2C_6\underline{H}_3$), 6.76 (2H, m, $CH_2C_6\underline{H}_3$), 5.70 (1H, s, H5), 5.07 (2H, s, N^1-CH_2), 4.88 (2H, s, N^3-CH_2), 2.30 (6H, s, $CH_3\times2$), 2.23 (3H, s, C^6-CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 160.3 (C4), 153.4 (C6), 151.5 (C2), 138.9, 135.2, 129.8 and 123.9 ($CH_2\underline{C}_6H_3$), 114.5 (C=N), 101.4 (C5), 48.3 (N^1-CH_2), 28.5 (N^3-CH_2), 21.3 ($CH_3\times2$), 20.2 (C^6-CH_3); UV λ_{max} (MeOH) nm: 268.5; MS *m/z*: 283 [M^+]; *Anal.* Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.98; H, 6.11; N, 14.87.

References and Notes

1) De Clercq E., *Clin. Microbiol. Rev.*, **8**, 200—239 (1995).
2) De Clercq E., *Med. Res. Rev.*, **16**, 125—157 (1996).
3) De Clercq E., *Med. Viol.*, **6**, 97—117 (1996).
4) De Clercq E., *Nature Reviews Microbiology*, **2**, 704—720 (2004).
5) De Clercq E., *J. Med. Chem.*, **48**, 1297—1313 (2005).
6) Baba M., Tanaka H., De Clercq E., Pauwels R., Balzarini J., Schols D., Nakashima H., Perno C.-F., Walker R. T., Miyasaka T., *Biochem. Biophys. Res. Commun.*, **165**, 1375—1381 (1989).
7) Szczech G. M., Furman P., Painter G. R., Barry D. W., Borroto-esoda K., Grizzle T. B., Blum M. R., Sommadossi J.-P., Endoh R., Niwa T., Yamamoto M., Moxham C., *Antimicrob. Agents Chemther.*, **44**, 123—130 (2000).
8) Buckheit R. W., Jr., Watson K., Fliakas-Boltz V., Russell J., Loftus T. L., Osterling M. C., Turpin J. A., Pallansch L. A., White E. L., Lee J.-W., Lee S.-H., Oh J.-W., Kwon H.-S., Chung S.-G., Cho E.-H., *Antimicrob. Agents Chemother.*, **45**, 393—400 (2001).
9) Nugent R. A., Schlachter S. T., Murphy M. J., Cleek G. J., Poel T. J., Wishka D. G., Graber D. R., Yagi Y., Keiser B. J., Olmsted R. A., Kopta L. A., Swaney S. M., Poppe S. M., Morris J., Tarpley W. G., Thomas R. C., *J. Med. Chem.*, **41**, 3793—3803 (1998).
10) Mai A., Artico M., Sbardella G., Massa S., Novellino E., Greco G., Loi A. G., Tramontano E., Marongiu M. E., La Colla P., *J. Med. Chem.*, **42**, 619—627 (1999).
11) Maruyama T., Kozai S., Yamasaki T., Witvrouw M., Pannecouque M., Balzarini J., Snoeck R., Andrei G., De Clercq E., *Antiviral Chem. Chemother.*, **14**, 271—279 (2003).
12) Noell C. W., Cheng C.-C., *J. Heterocyclic Chem.*, **5**, 25—28 (1968).
13) A review of Mitsunobu reaction: Mitsunobu O., *Synthesis*, **1981**, 1—28 (1981).
14) Recently TMAD was developed as an alternative of DEAD: Tsunoda T., Otsuka J., Yamamiya Y., Ito S., *Chem. Lett.*, **1994**, 539—542 (1994).
15) Clivio P., Fourrey J.-L., Gasche J., Favre A., *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2383—2388 (1992).
16) Clivio P., Fourrey J.-L., *J. Org. Chem.*, **59**, 7273—7283 (1994).
17) Novacek A., *Coll. Czech. Chem. Comm.*, **36**, 4066—4069 (1971).
18) Ogilvie K. K., Beaucage S. L., Gillen M. F., *Tetrahedron Lett.*, **19**, 1663—1666 (1978).
19) Katritzky A. R., Baykut G., Rachwal S., Szafran M., Caster K. C., Eyler J., *J. Chem. Soc., Perkin Trans. 2*, **1989**, 1499—1506 (1989).
20) Kusturin C., Liebeskind L. S., Rahman H., Sample K., Schweitzer B., Srogl J., Neumann W. L., *Org. Lett.*, **5**, 4349—4352 (2003).
21) Winckelmann I., Larsen E. H., *Synthesis*, **1986**, 1041—1044 (1986).
22) Leistner S., Giro A. P., Wagner G., *Pharmazie*, **33**, 185—189 (1978).
23) Leistner S., Hentschel K., Wagner G., *Zeitschrift fuer Chemie*, **23**, 215—216 (1983).
24) De Clercq E., Descamps J., Verhelst G., Walker R. T., Jones A. S., Torrence P. F., Shugar D., *J. Infect. Dis.*, **141**, 563—574 (1980).
25) De Clercq E., Holy A., Rosenberg I., Sakuma T., Balzarini J., Maudgal P. C., *Nature* (London), **323**, 464—467 (1986).
26) Schols D., De Clercq E., Balzarini J., Baba M., Witvrouw M., Hosoya M., Andrei G., Snoeck R., Neyts J., Pauwels R., Nagy M., Gyorgyi-Edelenyi J., Machovich R., Horvath I., Low M., Gorog S., *Antiviral Chem. Chemother.*, **1**, 233—240 (1990).
27) Ren J., Esnouf R., Garman E., Somers D., Ross C., Kirby I., Keeling J., Darby G., Jones Y., Stuart D., *Nature Struct. Biol.*, **2**, 293—302 (1995).
28) Ren J., Milton J., Weaver K. L., Short S. A., Stuart D. I., Stammers D. K., *Structure*, **8**, 1089—1094 (2000).
29) Hopkins A. L., Ren J., Esnouf R. M., Willcox B. E., Jones E. Y., Ross C., Miyasaka T., Walker R. T., Tanaka H., Stammers D. K., Stuart D. I., *J. Med. Chem.*, **39**, 1589—1600 (1996).
30) Hsiou Y., Das K., Ding J., Clark A. D., Jr., Kleim J. P., Rösner M., Winkler I., Riess G., Hughes S. H., Arnold E., *J. Mol. Biol.*, **284**, 313—323 (1998).
31) Högberg M., Sahlberg C., Engelhardt P., Noréen R., Kangasmetsä J., Johansson N. G., Öberg B., Vrang L., Zhang H., Sahlberg B.-L., Unge T., Lövgren S., Fridborg K., Bäckbro K., *J. Med. Chem.*, **43**, 304 (2000).
32) Ren J., Esnouf R. M., Hopkins A. L., Warren J., Balzarini J., Stuart D. I., Stammers D. K., *Biochemistry*, **37**, 14394—14403 (1998).
33) Chan J. H., Hong J. S., Hunter R. N., 3rd, Orr G. F., Cowan J. R., Sherman D. B., Sparks S. M., Reitter B. E., C. Andrews W., 3rd, Hazen R. J., Clair M. St., Boone L. R., Ferris R. G., Creech K. L., Roberts G. B., Short S. A., Weaver K., Ott R. J., Ren J., Hopkins A., Stuart D. I., Stammers D. K., *J. Med. Chem.*, **44**, 1866—1882 (2001).
34) Das K., Clark A. D., Jr., Lewi P. J., Heeres J., De Jonge M. R., Koymans L. M. H., Vinkers M., Daeyaert F., Ludovici D. W., Kukla M. J., Corte B. D., Kavash R. W., Ho C. Y., Ye H., Lichtenstein M. A., Andries K., Pauwels R., de Béthune M.-P., Boyer P. L., Clark P., Hughes S. H., Janssen P. A. J., Eddy A., *J. Med. Chem.*, **47**, 2550—2560 (2004).