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# Nonnucleoside HIV-1 Reverse Transcriptase Inhibitors, Part 4[1]. Synthesis and Anti-HIV Activity of *N*-1-*β*-Carbonyl-6-naphthylmethyl Analogues of *HEPT*

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**Summary.** A series of 6-naphthylmethyl substituted *HEPT* analogues bearing a *β*-carbonyl and a terminal phenyl ring or ester groups on the *N*-1 side chain of uracil were synthesized, and the *in vitro* anti-HIV activity was evaluated. Most of these *HEPT*s were considerably less potent and selective or inactive, only a few compounds showed moderate or high activity against HIV-1. The results demonstrated that the anti-HIV-1 activity of 6-naphthylmethyl substituted *HEPT* analogues was diminished or eliminated when the *β*-oxygen of *N*-1 side chain was replaced by a carbonyl group.

**Keywords.** Nonnucleoside reverse transcriptase inhibitors; *HEPT*; Uracil-6-naphthylmethyl analogues; Anti-HIV-1 activity.

## Introduction

Key targets in the search of potent drugs useful for AIDS therapy have been identified in the life cycle of HIV-1. The HIV reverse transcriptase (RT), as a key enzyme responsible for the proviral DNA synthesis, was one of the most attractive targets for the development of anti-HIV-1 agents [2]. To date, a number of inhibitors of HIV RT have been developed [3]. Among the representatives of the nonnucleoside reverse transcriptase inhibitors (*NNRTIs*), 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)thymine (*HEPT*) [4] (**1**, Fig. 1) constitutes an important inhibitor and has been extensively studied for many years.

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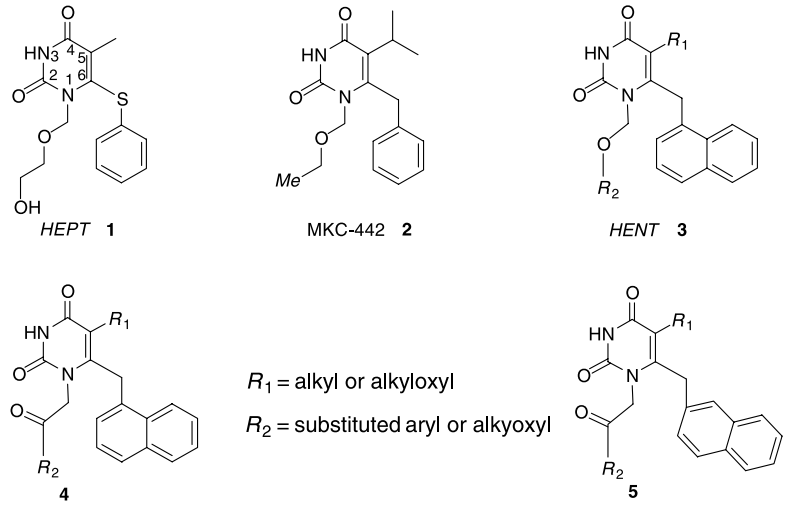



**Fig. 1.** Structures of *HEPTs*

Several crystal structures of HIV-1 RT complexed with *HEPT* analogues, *e.g.*, *HEPT*, *MKC-442* (**2**, Fig. 1), have been determined which provide important structural information about the *NNRTIs* binding site and can be utilized for structure-based rational drug design [5]. Very recent, based on *Hopkin*'s postulation and 3D-QSAR studies of *HEPT* analogues (*HENTs*) [6], our group had successfully designed and synthesized a series of 6-naphthylmethyl substituted *HEPT* analogues (*HENTs*) (**3**, Fig. 1) as high potent HIV-1 inhibitors [1a]. To further explore these analogues, a conventional 3D-QSAR model for them has been derived [7]. The picture which emerges from these studies shows that the *N*-1-substitutent of the uracil is situated in a large and flexible hydrophobic pocket of the RT, which allows for steric, electrostatic, hydrogen bonding, and hydrophobicity interaction. Thus, new important structural modifications in this site were investigated.

Although many syntheses and structure-activity relationship studies have been established that minor structural modifications of the *N*-1 side chain can induce drastic differences in the biological activity of the *HEPT* system, the interaction between this substituent and the RT still remains uncertain [8]. A part of our ongoing program is to further explore the effects of different substitutents on the anti-HIV-1 activity of *HEPT* derivatives and, in particular, to determine the role that the $\beta$-oxygen of the *N*-1 side chain may play in this interaction. According to the interaction model of the enzyme-inhibitor complex, the *N*-1 side chain of the *HENTs* is adjacent to residue *Tyr*318, some enhancement of potency was attributed to the favorable hydrogen bond interaction between the $\beta$-oxygen of the *N*-1 side chain and the main chain NH of *Tyr*318 residue. We postulate the substitution of the $\beta$-oxygen with a carbonyl group, may be beneficial to the hydrogen bond interaction between the RT and the inhibitors. Combined with the finding that some space of the binding pocket of RT around the *N*-1 side chain of these *HEPTs* remains unexploited, a series of 5-(alkyl or alkyloxyl)-6-(1-naphthylmethyl)-1-(aryl or alkyoxyl-carbonylmethyl)uracils (**4**, Fig. 1) were designed. Although in

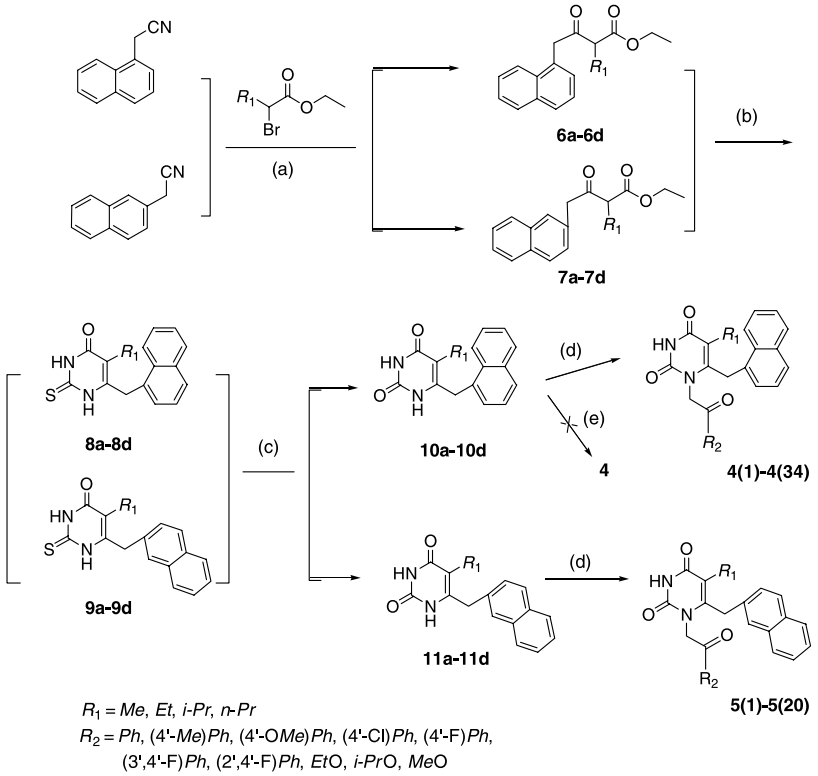
our previous observation, most of the 6-(2-naphthylmethyl) substituted *HEPT* analogues are less potent, for the need of the SAR studies, this compound **5** series was also synthesized in this present work.

## Results and Discussion

### *Chemistry*

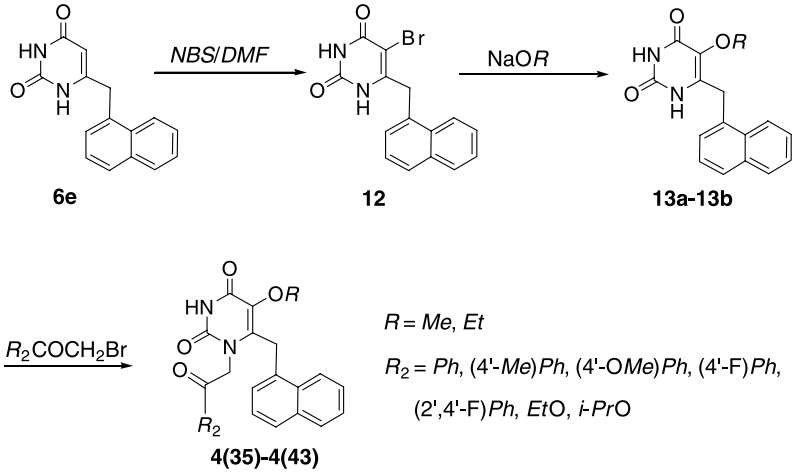
The synthesis of the 5-alkyl-6-(1-naphthylmethyl)uracil derivatives **4(1)**–**4(34)** is outlined in Scheme 1. The key intermediates uracils **10** were prepared from commercially available 1-naphthylacetonitrile and ethyl 2-bromoalkanoates following our procedure described previously [1a]. Alkylation of **10** with $R_2COCH_2Br$ in the presence of $K_2CO_3$ in anhydrous *DMF* afforded the desired target compounds **4(1)**–**4(34)** in poor yields of 8–34%.

With the aim to increase the yield of target compounds, and decrease *N*-3-substituted and disubstituted uracils by-products formation, we turned our attention to transform **8** into **4** using *Danel*'s method [9]. The silylation of **10**




**Reagents and conditions** (a) Zn, *THF*, then 10% aq. HCl; (b) NaO*Et*, $NH_2CSNH_2$; (c) 10% aq. $ClCH_2COOH$, reflux; (d) $R_2COCH_2Br$, $K_2CO_3$, *DMF*, 14-24 h, rt; (e) *i*, *HMDS*/$(NH_4)_2SO_4$, *ii*, $R_2COCH_2Br/(NH_4)_2SO_4$, *iii*, $NaHCO_3$ or *i*, *BAS*, $CH_2Cl_2$, *ii*, $R_2COCH_2Br$, $K_2CO_3$, $Bu_4NI$, *iii*, $NaHCO_3$, *Et*OH

**Scheme 1**




**Scheme 2**

was carried out by silylating reagents such as *HMDS*/$(NH_4)_2SO_4$ [10], *N*,*O*-bis(trimethylsilyl)acetamide (*BSA*) [11], or $(CH_3)_3SiCl/Et_3N$ [12] in almost quantitative yield. But when the 2,4-di-*O*-(trimethylsilyl)ethers were further condensed with various $R_2COCH_2Br$, none of the desired products were obtained. This is probably due to the steric hindrance of the 6-naphthylmethyl and 2-*O*-silyloxy groups.

The synthesis of 5-alkyl-6-(2-naphthylmethyl)uracil derivatives **5(1)–5(20)** is similar to that of their related 5-alkyl-6-(1-naphthylmethyl)uracil derivatives, except for the 2-naphthylacetonitrile which was adopted as the raw material instead of 1-naphthylacetonitrile.

The syntheses of 5-alkoxyl substituted *HEPT* analogues **4(35)–4(43)** were presented in Scheme 2. Treatment of compound **6e** with *N*-bromosuccinimide (*NBS*) in anhydrous *DMF* at 70°C for 3 h gave the bromouracil **12** in 96% yield, which reacted with NaO*Me* or NaO*Et* to yield the alkoxyuracil **13a** and **13b** in 76 and 68%, respectively. The *N*-alkylation of **13a** and **13b** with various as for $R_2COCH_2Br$ under the same reaction conditions as for the preparation of **4(1)–4(34)** afforded the target compounds **4(35)–4(43)** in 8–37% yields.

All structures of target compounds synthesized were determined by $^1H$ NMR spectra and MS. *N*-1 substitution was proved by the *NO*E enhancement in one of the protons when methylene at *C*-1 position was irradiated.

## *Antiviral Activity*

All of the novel *HEPT* analogues were evaluated for their cytotoxicity and anti-HIV-1 activity in MT-4 cells infected with the wild-type HIV-1 strain IIIB in comparison with *HEPT*. As can be seen from the $IC_{50}$ and $CC_{50}$ values in Table 1, the compounds bearing a simple methyl or propyl group at the *C*-5 position are uniformly inactive, and the 5-alkoxyl compounds **4(35)** and **4(38)** also showed weak activity. Only the 5-ethyl and 5-isopropyl derivatives showed a

**Table 1.** Anti-HIV-1 activity in MT-4 cells of compounds **4(1)–4(43)** and **5(1)–5(20)**[a]

| Compd | $R_1$ | $R_2$ | $IC_{50}(\mu M)$[b] | $CC_{50}(\mu M)$[c] | SI[d] |
|---|---|---|---|---|---|
| **4(1)** | *Me* | *Ph* | NA[e] | 49.82 | – |
| **4(2)** | *Me* | (4′-$CH_3$)*Ph* | NA | 398.2 | – |
| **4(3)** | *Me* | (4′-$CH_3O$)*Ph* | NA | 128.29 | – |
| **4(4)** | *Me* | (4′-Cl)*Ph* | NA | 33.66 | – |
| **4(5)** | *Me* | (4′-F)*Ph* | NA | 49.93 | – |
| **4(6)** | *Me* | (3′,4′-F)*Ph* | $\geq$45.95 | 194.12 | $\leq$4.22 |
| **4(7)** | *Me* | $C_2H_5O$ | NA | 182.87 | – |
| **4(8)** | *Me* | *i-Pr*O | NA | 42.70 | – |
| **4(9)** | *Me* | $OCH_3$ | 20.95 | 216.92 | 10 |
| **4(10)** | *Et* | *Ph* | NA | 34.27 | – |
| **4(11)** | *Et* | (4′-$CH_3$)*Ph* | NA | 34.05 | – |
| **4(12)** | *Et* | (4′-$CH_3O$)*Ph* | NA | 35.12 | – |
| **4(13)** | *Et* | (4′-Cl)*Ph* | NA | 29.86 | – |
| **4(14)** | *Et* | (4′-F)*Ph* | 4.35 | 32.66 | 8 |
| **4(15)** | *Et* | (3′,4′-F)*Ph* | NA | 31.18 | – |
| **4(16)** | *Et* | (2′,4′-F)*Ph* | 3.68 | 57.54 | 16 |
| **4(17)** | *Et* | $C_2H_5O$ | – | – | – |
| **4(18)** | *Et* | *i-Pr*O | NA | 48.16 | – |
| **4(19)** | *Et* | $OCH_3$ | 2.47 | 174.80 | 71 |
| **4(20)** | *i-Pr* | *Ph* | 7.08 | 30.78 | 4 |
| **4(21)** | *i-Pr* | (4′-$CH_3$)*Ph* | NA | 32.93 | – |
| **4(22)** | *i-Pr* | (4′-$CH_3O$)*Ph* | NA | 32.58 | – |
| **4(23)** | *i-Pr* | (4′-Cl)*Ph* | 10.16 | 27.74 | 3 |
| **4(24)** | *i-Pr* | (4′-F)*Ph* | 3.14 | 33.68 | 11 |
| **4(25)** | *i-Pr* | (3′,4′-F)*Ph* | NA | 32.3 | – |
| **4(26)** | *i-Pr* | (2′,4′-F)*Ph* | 3.21 | 211.83 | 66 |
| **4(27)** | *i-Pr* | $C_2H_5O$ | 4.18 | 36.79 | 9 |
| **4(28)** | *i-Pr* | *i-Pr*O | NA | 35.71 | – |
| **4(29)** | *i-Pr* | $OCH_3$ | 0.38 | 117.89 | 310 |
| **4(30)** | *n-Pr* | (4′-$CH_3$)*Ph* | NA | 34.11 | – |
| **4(31)** | *n-Pr* | (4′-$CH_3O$)*Ph* | NA | 35.52 | – |
| **4(32)** | *n-Pr* | (4′-Cl)*Ph* | NA | 30.43 | – |
| **4(33)** | *n-Pr* | (2′,4′-F)*Ph* | NA | 43.97 | – |
| **4(34)** | *n-Pr* | $C_2H_5O$ | NA | 42.71 | – |
| **4(35)** | O*Me* | *Ph* | 24.89 | 139.84 | 6 |
| **4(36)** | O*Me* | (4′-$CH_3O$)*Ph* | NA | 145.51 | – |
| **4(37)** | O*Me* | (4′-F)*Ph* | NA | 189.71 | – |
| **4(38)** | O*Me* | (2′,4′-F)*Ph* | 13.57 | 133.26 | 10 |
| **4(39)** | O*Me* | $C_2H_5O$ | NA | 184.78 | – |
| **4(40)** | O*Me* | *i-Pr*O | NA | 188.04 | – |
| **4(41)** | O*Et* | *Ph* | NA | 85.19 | – |
| **4(42)** | O*Et* | (4′-$CH_3O$)*Ph* | NA | 132.59 | – |
| **4(43)** | O*Et* | (2′,4′-F)*Ph* | NA | 91.11 | – |
| **5(1)** | *Me* | $C_2H_5O$ | NA | 116.48 | – |
| **5(2)** | *Et* | *Ph* | NA | >314.08 | – |
| **5(3)** | *Et* | (4′-$CH_3$)*Ph* | NA | >303.4 | – |

(*continued*)

**Table 1** (*continued*)

| Compd | $R_1$ | $R_2$ | $IC_{50}(\mu M)$[b] | $CC_{50}(\mu M)$[c] | SI[d] |
|---|---|---|---|---|---|
| **5(4)** | *Et* | (4′-Cl)*Ph* | NA | 167.43 | – |
| **5(5)** | *Et* | (4′-F)*Ph* | NA | ≥269.23 | – |
| **5(6)** | *Et* | (3′,4′-F)*Ph* | NA | 278.8 | – |
| **5(7)** | *Et* | (2′,4′-F)*Ph* | NA | 259.22 | – |
| **5(8)** | *Et* | $C_2H_5O$ | NA | >341.53 | – |
| **5(9)** | *Et* | *i-Pr*O | NA | >328.95 | – |
| **5(10)** | *Et* | *Me*O | NA | ≥318.18 | – |
| **5(11)** | *i-Pr* | *Ph* | NA | >303.4 | – |
| **5(12)** | *i-Pr* | (4′-$CH_3$)*Ph* | NA | >293.43 | – |
| **5(13)** | *i-Pr* | (4′-$CH_3O$)*Ph* | NA | 134.16 | – |
| **5(14)** | *i-Pr* | (4′-Cl)*Ph* | NA | 175.11 | – |
| **5(15)** | *i-Pr* | (4′-F)*Ph* | NA | >290.69 | – |
| **5(16)** | *i-Pr* | (3′,4′-F)*Ph* | NA | >279.02 | – |
| **5(17)** | *i-Pr* | (2′,4′-F)*Ph* | NA | 229.13 | – |
| **5(18)** | *i-Pr* | $C_2H_5O$ | NA | 57.63 | – |
| **5(19)** | *i-Pr* | *i-Pr*O | NA | 317.26 | – |
| **5(20)** | *i-Pr* | *Me*O | – | – | – |
| **1** | | | 5.06 | 405.37 | 80 |
| **3(1)** | *Et* | *Ph*$CH_2$ | 0.017 | 32.56 | 1915 |
| **3(2)** | *i-Pr* | *Ph*$CH_2$ | 0.021 | 29.87 | 1422 |

[a] All data represent mean values for three separate experiments; [b] concentration required to protect the cell against viral cytopathogenicity by 50% in MT-4 cells; [c] concentration that reduces the MT-4 cell viability by 50%; [d] selectivity index: ratio $CC_{50}/IC_{50}$, a higher SI means a more selective compound; [e] NA: no activity

moderate activity against HIV-1 compared with *HEPT*, *e.g.*, 5-ethyl-1-(methoxycarbonylmethyl)-6-(1-naphthyl-methyl)uracil (**4(19)**) and 1-[(2′,4′-difluorophenyl)carbonylmethyl]-5-isopropyl-6-(1-naphthyl-methyl)uracil (**4(26)**) were more active than *HEPT*. Compound **4(29)** exhibited potent inhibitor activity against HIV-1 replication with $IC_{50}$ value of 0.38 $\mu M$, which was almost 14-fold higher than that of *HEPT*. However, all 2-naphthylmethyl substituted *HEPT* derivatives were found to be inactive, which was consistent with our previous findings [1a, 6] that the substitution position of the methyl group with the thymine skeleton is very important for these compounds to exert the anti-HIV-1 activity.

By comparing the structures and activity relationship of these new compounds with that of our previous 6-naphthylmethyl substituted *HENTs* such as compounds **3(1)** and **3(2)**, the present results demonstrated that replacement of the $\beta$-oxygen of the *N*-1 side chain by an carbonyl group diminished, or eliminated the anti-HIV-1 activity of the compounds. To analyse the exact reason for the decline in inhibitory potencies of our series and deeply explore the SAR of the *N*-1 side chain of *HEPTs*, further molecular modeling and quantitative structure-activity relationship (QSAR) studies have been undertaken, and the results will be reported elsewhere.

**Table 2.** Physical properties and spectral data of compounds **4(1)–4(43)** and **5(1)–5(20)**

| Compd | Formula | Yield (%) | Mp (°C) | EI-MS ($m/z$) | $^1$H NMR (*DMSO*-$d_6$, *J*: Hz) |
|---|---|---|---|---|---|
| **4(1)** | $C_{24}H_{20}N_2O_3$ | 16 | 221.9–223.5 | 384 ($M^+$) | 1.81 (s, 3H, $CH_3$), 4.34 (s, 2H, $CH_2$), 5.14 (s, 2H, $NCH_2$), 7.14–7.89 (m, 12H, *Ph*), 11.59 (s, 1H, NH) |
| **4(2)** | $C_{20}H_{26}N_2O_5$ | 22 | 246.7–247 | 398 ($M^+$) | 1.81 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 4.31 (s, 2H, $CH_2$), 5.09 (s, 2H, $NCH_2$), 7.12–8.03 (m, 11H, *Ph*), 11.58 (s, 1H, NH) |
| **4(3)** | $C_{20}H_{26}N_2O_5$ | 25 | 150.0–150.7 | 414 ($M^+$) | 1.81 (s, 3H, $CH_3$), 3.82 (s, 3H, $OCH_3$), 4.29 (s, 2H, $CH_2$), 5.07 (s, 2H, $NCH_2$), 6.91–8.02 (m, 11H, *Ph*), 11.57 (s, 1H, NH) |
| **4(4)** | $C_{24}H_{19}ClN_2O_3$ | 11 | 254.7–256.8 | 418 ($M^+$) | 1.81 (s, 3H, $CH_3$), 4.35 (s, 2H, $CH_2$), 5.13 (s, 2H, $NCH_2$), 7.11–8.12 (m, 11H, *Ph*), 11.60 (s, 1H, NH) |
| **4(5)** | $C_{24}H_{19}FN_2O_3$ | 19 | 230.5–231.0 | 402 ($M^+$) | 1.81 (s, 3H, $CH_3$), 4.34 (s, 2H, $CH_2$), 5.13 (s, 2H, $NCH_2$), 7.11–7.90 (m, 7H, 4H, $Ph_{2,3,5,6}$), 11.58 (s, 1H, NH) |
| **4(6)** | $C_{24}H_{18}F_2N_2O_3$ | 12 | 236.9–237.8 | 420 ($M^+$) | 1.83 (s, 3H, $CH_3$), 4.37 (s, 2H, $CH_2$), 4.94 (s, 2H, $NCH_2$), 7.12–8.09 (m, 10H, *Ph*), 11.59 (s, 1H, NH) |
| **4(7)** | $C_{20}H_{20}N_2O_4$ | 17 | 196.3–198.7 | 352 ($M^+$) | 1.02 (t, 3H, $J=7.1$, $CH_3$), 1.83 (s, 3H, $CH_3$), 3.93 (q, 2H, $J=7.1$, $OCH_2$), 4.29 (s, 2H, $CH_2$), 4.39 (s, 2H, $NCH_2$), 7.10–8.17 (m, 7H, *Ph*), 11.61 (s, 1H, NH) |
| **4(8)** | $C_{21}H_{22}N_2O_4$ | 11 | 218.1–218.2 | 366 ($M^+$) | 1.02 (t, 3H, $J=7.1$, $CH_3$), 1.83 (s, 3H, $CH_3$), 3.93 (q, 2H, $J=7.1$, $OCH_2$), 4.29 (s, 2H, $CH_2$), 4.39 (s, 2H, $NCH_2$), 7.10–8.17 (m, 7H, *Ph*), 11.61 (s, 1H, NH) |
| **4(9)** | $C_{19}H_{18}N_2O_4$ | 9 | 238.2–239.5 | 338 ($M^+$) | 1.81 (s, 3H, $CH_3$), 3.50 (s, 3H, $OCH_3$), 4.30 (s, 2H, $CH_2$), 4.40 (s, 2H, $NCH_2$), 7.09–8.16 (m, 7H, *Ph*), 11.6 (s, 1H, NH) |
| **4(10)** | $C_{25}H_{22}N_2O_3$ | 23 | 237.2–237.6 | 389 ($M^+$) | 0.89 (t, 3H, $J=7.5$, $CH_3$), 2.29 (q, 2H, $J=7.5$, $CH_2$), 4.33 (s, 2H, $CH_2$), 5.08 (s, 2H, $NCH_2$), 7.12–8.05 (m, 12H, *Ph*), 11.59 (s, 1H, NH) |
| **4(11)** | $C_{26}H_{24}N_2O_3$ | 13 | 216.2–216.8 | 412 ($M^+$) | 0.90 (t, 3H, $J=7.35$, $CH_3$), 2.28 (q, 2H, $J=7.35$, $CH_2$), 2.30 (s, 3H, $CH_3$), 4.30 (s, 2H, $CH_2$), 5.04 (s, 2H, $NCH_2$), 7.12–8.04 (m, 11H, *Ph*), 11.55 (s, 1H, NH) |
| **4(12)** | $C_{26}H_{24}N_2O_4$ | 18 | 228.0–228.5 | 428 ($M^+$) | 0.88 (t, 3H, $J=7.40$, $CH_3$), 2.29 (q, 2H, $J=7.40$, $CH_2$), 3.79 (s, 3H, $OCH_3$), 4.26 (s, 2H, $CH_2$), 5.00 (s, 2H, $NCH_2$), 6.88–8.02 (m, 11H, *Ph*), 11.54 (s, 1H, NH) |
| **4(13)** | $C_{25}H_{21}ClN_2O_3$ | 15 | 272.5–274.6 | 432 ($M^+$) | 0.90 (t, 3H, $J=7.30$, $CH_3$), 2.31 (q, 2H, $J=7.30$, $CH_2$), 4.34 (s, 2H, $CH_2$), 5.08 (s, 2H, $NCH_2$), 7.11–8.06 (m, 11H, *Ph*), 11.56 (s, 1H, NH) |

(*continued*)

**Table 2** (*continued*)

| Compd | Formula | Yield (%) | Mp (°C) | EI-MS ($m/z$) | $^1$H NMR (*DMSO*-$d_6$, *J*: Hz) |
|---|---|---|---|---|---|
| **4(14)** | $C_{25}H_{21}FN_2O_3$ | 21 | 240.0–250.0 | 416 ($M^+$) | 0.91 (t, 3H, $J = 7.30$, $CH_3$), 2.30 (q, 2H, $J = 7.30$, $CH_2$), 4.34 (s, 2H, $CH_2$), 5.09 (s, 2H, $NCH_2$), 7.12–8.07 (m, 11H, *Ph*), 11.59 (s, 1H, NH) |
| **4(15)** | $C_{25}H_{20}F_2N_2O_3$ | 12 | 200.0–200.5 | 434 ($M^+$) | 0.91 (t, 3H, $J = 7.35$, $CH_3$), 2.30 (q, 2H, $J = 7.40$, $CH_2$), 4.35 (s, 2H, $CH_2$), 5.10 (s, 2H, $NCH_2$), 7.08–8.10 (m, 10H, *Ph*), 11.59 (s, 1H, NH) |
| **4(16)** | $C_{25}H_{20}F_2N_2O_3$ | 16 | 236.1–237.8 | 434 ($M^+$) | 0.90 (t, 3H, $J = 7.25$, $CH_3$), 2.32 (q, 2H, $J = 7.25$, $CH_2$), 4.37 (s, 2H, $CH_2$), 4.90 (s, 2H, $NCH_2$), 7.12–8.11 (m, 10H, *Ph*),11.58 (s, 1H, NH) |
| **4(17)** | $C_{21}H_{22}N_2O_4$ | 23 | 169.4–172.9 | 366 ($M^+$) | 0.91 (t, 3H, $J = 7.30$, $CH_3$), 1.01 (t, 3H, $J = 7.05$, $CH_3$), 2.31 (q, 2H, $J = 7.30$, $CH_2$), 3.92 (q, 2H, $J = 7.05$, $OCH_2$), 4.24 (s, 2H, $CH_2$), 4.38 (s, 2H, $NCH_2$), 7.10–8.19 (m, 7H, *Ph*), 11.60 (s, 1H, NH) |
| **4(18)** | $C_{22}H_{24}N_2O_4$ | 16 | 200.3–200.8 | 380 ($M^+$) | 0.91 (t, 3H, $J = 7.35$, $CH_3$), 1.01 (d, 6H, $J = 6.25$, $2CH_3$), 2.32 (q, 2H, $J = 7.35$, $CH_2$), 4.20 (s, 2H, $CH_2$), 4.36 (s, 2H, $NCH_2$), 4.76 (m, 1H, $J = 6.25$, OCH), 7.10–8.18 (m, 7H, *Ph*), 11.59 (s, 1H, NH) |
| **4(19)** | $C_{20}H_{20}N_2O_4$ | 12 | 150.3–151.4 | 352 ($M^+$) | 0.89 (t, 3H, $J = 7.35$, $CH_3$), 2.29 (q, 2H, $J = 7.35$, $CH_2$), 3.49 (s, 3H, $OCH_3$), 4.25 (s, 2H, $CH_2$), 4.39 (s, 2H, $NCH_2$), 7.08–8.20 (m, 7H, *Ph*), 11.60 (s, 1H, NH) |
| **4(20)** | $C_{26}H_{24}N_2O_3$ | 34 | 234.7–235.4 | 412 ($M^+$) | 1.17 (d, 6H, $J = 6.8$, $2CH_3$), 2.70 (m, 1H, $J = 6.75$, CH), 4.35 (s, 2H, $CH_2$), 5.13 (s, 2H, $NCH_2$), 7.13–8.06 (m, 12H, *Ph*), 11.47 (s, 1H, NH) |
| **4(21)** | $C_{27}H_{26}N_2O_3$ | 16 | 237.6–238.2 | 426 ($M^+$) | 1.17 (d, 6H, $J = 6.85$, $2CH_3$), 2.31 (s, 3H, $CH_3$), 2.70 (m, 1H, $J = 6.85$, CH), 4.30 (s, 2H, $CH_2$), 5.08 (s, 2H, $NCH_2$), 7.13–8.04 (m, 11H, *Ph*), 11.45 (s, 1H, NH) |
| **4(22)** | $C_{27}H_{26}N_2O_4$ | 13 | 163.5–163.9 | 442 ($M^+$) | 1.17 (d, 6H, $J = 6.85$, $2CH_3$), 2.70 (m, 1H, $J = 6.85$, CH), 3.78 (s, 3H, $OCH_3$), 4.28 (s, 2H, $CH_2$), 5.06 (s, 2H, $NCH_2$), 6.90–7.90 (m, 11H, *Ph*), 11.45 (s, 1H, NH) |
| **4(23)** | $C_{26}H_{23}ClN_2O_3$ | 16 | 243.5–246.3 | 446 ($M^+$) | 1.16 (d, 6H, $J = 6.85$, $2CH_3$), 2.70 (m, 1H, $J = 6.85$, CH), 4.34 (s, 2H, $CH_2$), 5.13 (s, 2H, $NCH_2$), 7.11–8.07 (m, 11H, *Ph*), 11.47 (s, 1H, NH) |
| **4(24)** | $C_{26}H_{23}FN_2O_3$ | 29 | 240.9–241.4 | 430 ($M^+$) | 1.16 (d, 6H, $J = 6.75$, $2CH_3$), 2.70 (m, 1H, $J = 6.75$, CH), 4.33 (s, 2H, $CH_2$), 5.12 (s, 2H, $NCH_2$), 7.11–8.06 (m, 11H, *Ph*), 11.46 (s, 1H, NH) |
| **4(25)** | $C_{26}H_{22}F_2N_2O_3$ | 16 | 219.3–220.5 | 448 ($M^+$) | 1.16 (d, 6H, $J = 6.85$, $2CH_3$), 2.70 (m, 1H, $J = 6.85$, CH), 4.34 (s, 2H, $CH_2$), 5.13 (s, 2H, $NCH_2$), 7.09–8.08 (m, 10H, *Ph*), 11.47 (s, 1H, NH) |
| **4(26)** | $C_{26}H_{22}F_2N_2O_3$ | 23 | 277.5–278.8 | 448 ($M^+$) | 1.16 (d, 6H, $J = 6.65$, $2CH_3$), 2.70 (m, 1H, $J = 6.65$, CH), 4.36 (s, 2H, $CH_2$), 4.94 (s, 2H, $NCH_2$), 7.12–8.09 (m, 10H, *Ph*), 11.46 (s, 1H, NH) |

(*continued*)

**Table 2** (*continued*)

| Compd | Formula | Yield (%) | Mp (°C) | EI-MS ($m/z$) | $^1$H NMR (*DMSO*-$d_6$, *J*: Hz) |
|---|---|---|---|---|---|
| **4(27)** | $C_{22}H_{24}N_2O_4$ | 28 | 159.1–160.8 | 380 ($M^+$) | 1.00 (t, 3H, $J=7.1$, $CH_3$), 1.17 (d, 6H, $J=6.90$, $2CH_3$), 2.74 (q, 1H, $J=6.9$, CH), 3.92 (q, 2H, $J=7.1$, $OCH_2$), 4.37 (s, 2H, $CH_2$), 4.43 (s, 2H, $NCH_2$), 7.09–8.17 (m, 7H, *Ph*), 11.47 (s, 1H, NH) |
| **4(28)** | $C_{23}H_{26}N_2O_4$ | 11 | 149.9–150.4 | 394 ($M^+$) | 1.01 (d, 6H, $J=6.20$, $2CH_3$), 1.17 (d, 6H, $J=6.75$, $2CH_3$), 2.75 (m, 1H, $J=6.75$, CH), 4.24 (s, 2H, $CH_2$), 4.36 (s, 2H, $NCH_2$), 4.77 (m, 1H, $J=6.20$, OCH), 7.10–8.16 (m, 7H, *Ph*), 11.48 (s, 1H, NH) |
| **4(29)** | $C_{21}H_{22}N_2O_4$ | 10 | 226.0–226.3 | 366 ($M^+$) | 1.17 (d, 6H, $J=6.85$, $2CH_3$), 2.72 (m, 1H, $J=6.75$, CH), 3.51 (s, 3H, $OCH_3$), 4.29 (s, 2H, $CH_2$), 4.38 (s, 2H, $NCH_2$), 7.09–8.17 (m, 7H), 11.48 (s, 1H, NH) |
| **4(30)** | $C_{27}H_{26}N_2O_3$ | 24 | 218.9–219.9 | 426 ($M^+$) | 0.78 (t, 3H, $J=7.35$, $CH_3$), 1.32 (m, 2H, $J=$ 7.5, $CH_2$), 2.26 (t, 2H, $J=7.6$, $CH_2$), 2.31 (s, 3H, $CH_3$), 4.29 (s, 2H, $CH_2$), 5.03 (s, 2H, $NCH_2$), 7.12–8.05 (m, 11H, *Ph*), 11.53 (s, 1H, NH) |
| **4(31)** | $C_{27}H_{26}N_2O_4$ | 18 | 226.0–227.1 | 442 ($M^+$) | 0.78 (t, 3H, $J=7.30$, $CH_3$), 1.32 (m, 2H, $J=$ 7.30, $CH_2$), 2.27 (t, 2H, $J=7.35$, $CH_2$), 3.78 (s, 3H, $OCH_3$), 4.28 (s, 2H, $CH_2$), 5.00 (s, 2H, $NCH_2$), 6.89–8.03 (m, 11H, *Ph*), 11.53 (s, 1H, NH) |
| **4(32)** | $C_{26}H_{23}ClN_2O_3$ | 27 | 225.2–225.9 | 446 ($M^+$) | 0.78 (t, 3H, $J=7.38$, $CH_3$), 1.34 (m, 2H, $J=7.38$, $CH_2$), 2.27 (t, 2H, $J=7.35$, $CH_2$), 4.34 (s, 2H, $CH_2$), 5.07 (s, 2H, $NCH_2$), 7.10–8.05 (m, 11H, *Ph*), 11.58 (s, 1H, NH) |
| **4(33)** | $C_{26}H_{22}F_2N_2O_3$ | 26 | 160.7–162.9 | 448 ($M^+$) | 0.78 (t, 3H, $J=7.35$, $CH_3$), 1.34 (m, 2H, $J=7.35$, $CH_2$), 2.29 (t, 2H, $J=7.40$, $CH_2$), 4.36 (s, 2H, $CH_2$), 5.17 (s, 2H, $NCH_2$), 7.11–8.11 (m, 10H, *Ph*), 11.57 (s, 1H, NH) |
| **4(34)** | $C_{22}H_{24}N_2O_4$ | 12 | 134.8–135.5 | 380 ($M^+$) | 0.77 (t, 3H, $J=7.30$, $CH_3$), 1.00 (t, 3H, $J=7.20$, $CH_3$), 1.33 (m, 2H, $J=7.50$, $CH_2$), 2.28 (t, 2H, $J=7.50$, $CH_2$), 3.91 (q, 2H, $J=7.15$, $OCH_2$), 4.37 (s, 2H, $CH_2$), 4.54 (s, 2H, $NCH_2$), 7.09–8.19 (m, 7H, *Ph*), 11.58 (s, 1H, NH) |
| **4(35)** | $C_{24}H_{20}N_2O_4$ | 19 | 173.3–174.3 | 400 ($M^+$) | 3.41 (s, 3H, $OCH_3$), 5.18 (d, 1H, $J=18.15$, NCH), 5.41 (d, 1H, $J=18.05$, NCH), 5.49 (s, 1H, CH), 5.68 (s, 1H, CH), 7.26–7.89 (m, 12H, *Ph*), 8.67 (s, 1H, NH) |
| **4(36)** | $C_{25}H_{22}N_2O_5$ | 12 | 229.2–230.5 | 430 ($M^+$) | 3.25 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 5.28 (dd, 2H, $J=4.5$, $NCH_2$), 5.17 (s, 1H, CH), 5.95 (s, 1H, CH), 7.01–7.99 (m, 11H, *Ph*), 11.56 (s, 1H, NH) |
| **4(37)** | $C_{24}H_{19}FN_2O_4N$ | 37 | 232.9–233.3 | 418 ($M^+$) | 3.25 (s, 3H, $OCH_3$), 5.20 (s, 1H, CH), 6.04 (s, 1H, CH), 5.33 (d, 2H, $J=18.6$, $NCH_2$), 7.30–8.02 (m, 11H, *Ph*), 11.60 (s, 1H, NH) |
| **4(38)** | $C_{24}H_{18}F_2N_2O_4$ | 8 | 233.4–234.2 | 436 ($M^+$) | 3.29 (s, 3H, $OCH_3$), 5.12 (s, 2H, $NCH_2$), 5.28 (s, 1H, CH), 6.11 (s, 1H, 11CH), 7.22– 8.08 (m, 11H, *Ph*), 11.60 (s, 1H, NH) |

(*continued*)

**Table 2** (*continued*)

| Compd | Formula | Yield (%) | Mp (°C) | EI-MS ($m/z$) | $^1$H NMR (*DMSO*-$d_6$, *J*: Hz) |
|---|---|---|---|---|---|
| **4(39)** | $C_{20}H_{20}N_2O_5$ | 10 | 166.1–166.8 | 368 ($M^+$) | 1.08 (t, 3H, $J = 7.11$, $CH_3$), 4.00 (m, 2H, $OCH_2$), 4.55 (dd, 2H, $J = 13.6$, $NCH_2$), 5.20 (s, 1H, CH), 6.07 (s, 2H, $CH_2$), 7.50–8.08 (m, 7H, *Ph*), 11.61 (s, 1H, NH) |
| **4(40)** | $C_{21}H_{22}N_2O_5$ | 11 | 181.4–183.8 | 382 ($M^+$) | 1.04 (d, 3H, $J = 6.2$, $CH_3$), 1.15 (d, 3H, $J = 6.2$, $CH_3$), 3.38 (s, 3H, $OCH_3$), 4.44 (dd, 2H, $J = 17.8$, $NCH_2$), 4.81 (m, 1H, $J = 6.2$, CH) 5.19 (s, 1H, CH), 6.03 (s, 1H, CH), 7.52–8.07 (m, 7H, *Ph*), 11.61 (s, 1H, NH) |
| **4(41)** | $C_{25}H_{22}N_2O_4$ | 22 | 227.8–229.0 | 414 ($M^+$) | 1.25 (t, 3H, $J = 7.2$, $CH_3$), 3.59 (m, $J = 7.1$, $OCH_2$), 5.19 (d, 1H, $J = 16.8$, NCH), 5.59 (d, 1H, $J = 16.8$, NCH), 5.68 (s, 1H, CH), 5.73 (s, 1H, CH), 7.26–7.89 (m, 12H, *Ph*), 8.67 (s, 1H, NH) |
| **4(42)** | $C_{26}H_{24}N_2O_5$ | 19 | 209.2–210.4 | 444 ($M^+$) | 0.99 (t, 3H, $J = 6.9$, $CH_3$), 3.49 (m, 2H, $J = 7.1$, $OCH_2$), 3.84 (s, 3H, $OCH_3$), 5.30 (s, $NCH_2$), 5.18 (s, 1H, CH), 6.03 (s, 1H, CH), 7.02–7.99 (m, 11H, *Ph*), 11.55 (s, 1H, NH) |
| **4(43)** | $C_{25}H_{20}F_2N_2O_4$ | 19 | 228.8–228.9 | 450 ($M^+$) | 1.06 (t, $J = 6.99$, $CH_3$), 3.60 (m, $J = 7.0$, $OCH_2$), 5.14 (s, 2H, $NCH_2$), 5.30 (s, 1H, CH), 6.18 (s, 1H, CH), 7.22–8.08 (m, 10H, *Ph*), 11.60 (s, 1H, NH) |
| **5(1)** | $C_{20}H_{20}N_2O_4$ | 9 | 205.4–205.8 | 352 ($M^+$) | 0.94 (t, 3H, $J = 7.05$, $CH_3$), 1.96 (s, 3H, $CH_3$), 3.73 (q, 2H, $J = 7.05$, $OCH_2$), 4.18 (s, 2H, $CH_2$), 4.45 (s, 2H, $NCH_2$), 7.35–7.89 (m, 7H, *Ph*), 11.56 (s, 1H, NH) |
| **5(2)** | $C_{25}H_{22}N_2O_3$ | 9 | 242.9–245.3 | 398 ($M^+$) | 0.97 (t, 3H, $J = 7.44$, $CH_3$), 2.41 (q, 2H, $J = 7.45$, $CH_2$), 4.11 (s, 2H, $CH_2$), 5.21 (s, 2H, $NCH_2$), 7.72–7.83 (m, 12H, *Ph*), 11.54 (s, 1H, NH) |
| **5(3)** | $C_{26}H_{24}N_2O_3$ | 13 | 243.0–243.5 | 412 ($M^+$) | 0.97 (t, 3H, $J = 7.25$, $CH_3$), 2.34 (s, 3H, $CH_3$), 2.43 (q, 2H, $J = 7.35$, $CH_2$), 4.08 (s, 2H, $CH_2$), 5.17 (s, 2H, $NCH_2$), 7.23–7.83 (m, 11H, *Ph*), 11.55 (s, 1H, NH) |
| **5(4)** | $C_{25}H_{21}ClN_2O_3$ | 12 | 233.1–233.6 | 432 ($M^+$) | 0.98 (t, 3H, $J = 7.30$, $CH_3$), 2.43 (q, 2H, $J = 7.35$, $CH_2$), 4.13 (s, 2H, $CH_2$), 5.21 (s, 2H, $NCH_2$), 7.44–7.75 (m, 11H, *Ph*), 11.53 (s, 1H, NH) |
| **5(5)** | $C_{25}H_{21}FN_2O_3$ | 13 | 215.7–217.9 | 416 ($M^+$) | 0.98 (t, 3H, $J = 7.35$, $CH_3$), 2.43 (q, 2H, $J = 7.40$, $CH_2$), 4.12 (s, 2H, $CH_2$), 5.21 (s, 2H, $NCH_2$), 7.21–7.84 (m, 11H, *Ph*), 11.53 (s, 1H, NH) |
| **5(6)** | $C_{25}H_{20}F_2N_2O_3$ | 5 | 232.0–232.8 | 434 ($M^+$) | 0.99 (t, 3H, $J = 7.25$, $CH_3$), 2.45 (q, 2H, $J = 7.25$, $CH_2$), 4.14 (s, 2H, $CH_2$), 5.24 (s, 2H, $NCH_2$), 7.24–7.81 (m, 10H, *Ph*),11.53 (s, 1H, NH) |
| **5(7)** | $C_{25}H_{20}F_2N_2O_3$ | 7 | 230.6–230.8 | 434 ($M^+$) | 0.98 (t, 3H, $J = 7.35$, $CH_3$), 2.45 (q, 2H, $J = 7.35$, $CH_2$), 4.16 (s, 2H, $CH_2$), 5.03 (s, 2H, $NCH_2$), 7.32–7.83 (m, 10H, *Ph*), 11.53 (s, 1H, NH) |

(*continued*)

**Table 2** (*continued*)

| Compd | Formula | Yield (%) | Mp (°C) | EI-MS ($m/z$) | $^1$H NMR (*DMSO*-$d_6$, *J*: Hz) |
|---|---|---|---|---|---|
| **5(8)** | $C_{21}H_{22}N_2O_4$ | 8 | 186.2–186.6 | 366 ($M^+$) | 0.92 (t, 3H, $J = 7.05$, $CH_3$), 0.96 (t, 3H, $J = 7.35$, $CH_3$), 2.43 (q, 2H, $J = 7.35$, $CH_2$), 3.73 (q, 2H, $J = 7.10$, $OCH_2$), 4.18 (s, 2H, $CH_2$), 4.40 (s, 2H, $NCH_2$), 7.36–7.90 (m, 7H), 11.55 (s, 1H, NH) |
| **5(9)** | $C_{22}H_{24}N_2O_4$ | 12 | 194.0–194.9 | 380 ($M^+$) | 0.92 (d, 6H, $J = 6.2$, $2CH_3$), 0.96 (t, 3H, $J = 7.25$, $CH_3$), 2.42 (q, 2H, $J = 7.25$, $CH_2$), 4.17 (s, 2H, $CH_2$), 4.36 (s, 2H, $NCH_2$), 4.55 (m, 1H, $J = 6.25$, OCH), 7.36–7.9 (m, 7H), 11.53 (s, 1H, NH) |
| **5(10)** | $C_{20}H_{20}N_2O_4$ | 12 | 209.8–210.9 | 352 ($M^+$) | 0.96 (t, 3H, $J = 7.40$, $CH_3$), 2.42 (q, 2H, $J = 7.35$, $CH_2$), 3.31 (s, 3H, $OCH_3$), 4.18 (s, 2H, $CH_2$), 4.40 (s, 2H, $NCH_2$), 7.36–7.90 (m, 7H, *Ph*), 11.55 (s, 1H, NH) |
| **5(11)** | $C_{26}H_{24}N_2O_3$ | 8 | 251.2–254.2 | 412 ($M^+$) | 1.22 (d, 6H, $J = 6.85$, $2CH_3$), 2.92 (m, 1H, $J = 6.85$, CH), 4.12 (s, 2H, $CH_2$), 5.25 (s, 2H, $NCH_2$), 7.31–7.85 (m, 12H, *Ph*), 11.42 (s, 1H, NH) |
| **5(12)** | $C_{27}H_{26}N_2O_3$ | 9 | 255.4–255.5 | 426 ($M^+$) | 1.22 (d, 6H, $J = 6.85$, $2CH_3$), 2.34 (s, 3H, $CH_3$), 2.91 (m, 1H, $J = 6.85$, CH), 4.09 (s, 2H, $CH_2$), 5.20 (s, 2H, $NCH_2$), 7.24–7.84 (m, 11H, *Ph*), 11.41 (s, 1H, NH) |
| **5(13)** | $C_{27}H_{26}N_2O_4$ | 16 | 242.2–245.9 | 442 ($M^+$) | 1.22 (d, 6H, $J = 6.90$, $2CH_3$), 2.91 (m, 1H, $J = 6.90$, CH), 3.81 (s, 3H, $OCH_3$), 4.07 (s, 2H, $CH_2$), 5.18 (s, 2H, $NCH_2$), 6.95–7.84 (m, 11H, *Ph*) |
| **5(14)** | $C_{26}H_{23}ClN_2O_3$ | 4 | 259.8–260.1 | 446 ($M^+$) | 1.22 (d, 6H, $J = 6.90$, $2CH_3$), 2.91 (m, 1H, $J = 6.90$, CH), 4.13 (s, 2H, $CH_2$), 5.24 (s, 2H, $NCH_2$), 7.44–7.82 (m, 7H, *Ph*), 11.44 (s, 1H, NH) |
| **5(15)** | $C_{26}H_{23}FN_2O_3$ | 7 | 223.1–224.5 | 430 ($M^+$) | 1.22 (d, 6H, $J = 6.75$, $2CH_3$), 2.93 (m, 1H, $J = 6.75$, CH), 4.13 (s, 2H, $CH_2$), 5.24 (s, 2H, $NCH_2$), 7.25–7.87 (m, 11H, *Ph*), 11.42 (s, 1H, NH) |
| **5(16)** | $C_{26}H_{22}F_2N_2O_3$ | 18 | 210.1–210.7 | 448 ($M^+$) | 1.23 (d, 6H, $J = 6.85$, $2CH_3$), 2.96 (m, 1H, $J = 6.90$, CH), 4.15 (s, 2H, $CH_2$), 5.27 (s, 2H, $NCH_2$), 7.25–7.83 (m, 13H, *Ph*–$H_{2,5,6}$), 11.43 (s, 1H, NH) |
| **5(17)** | $C_{26}H_{22}F_2N_2O_3$ | 11 | 214.3–214.9 | 448 ($M^+$) | 1.23 (d, 6H, $J = 6.85$, $2CH_3$), 2.96 (m, 1H, $J = 6.80$, CH), 5.06 (s, 2H, $CH_2$), 5.75 (s, 2H, $NCH_2$), 7.06–7.84 (m, 13H, *Ph*–$H_{3,5,6}$), 11.43 (s, 1H, NH) |
| **5(18)** | $C_{22}H_{24}N_2O_4$ | 17 | 188.3–189.0 | 380 ($M^+$) | 0.94 (t, 3H, $J = 7.2$,$CH_3$), 1.22 (d, 6H, $J = 6.85$, $2CH_3$), 2.94 (m, 1H, $J = 6.80$, CH), 3.78 (q, 2H, $J = 7.1$, $OCH_2$), 4.19 (s, 2H, $CH_2$), 4.43 (s, 2H, $NCH_2$), 7.36–7.91 (m, 7H, *Ph*), 11.49 (s, 1H, NH) |
| **5(19)** | $C_{23}H_{26}N_2O_4$ | 15 | 193.5–193.9 | 394 ($M^+$) | 0.94 (d, 6H, $J = 6.25$, $2CH_3$), 1.21 (d, 6H, $J = 6.85$, $2CH_3$), 2.96 (m, 1H, $J = 6.85$, CH), 4.17 (s, 2H, $CH_2$), 4.40 (s, 2H, $NCH_2$), 4.60 (m, 1H, J = 6.25, OCH), 7.36–7.91 (m, 7H, *Ph*), 11.44 (s, 1H, NH) |
| **5(20)** | $C_{21}H_{22}N_2O_4$ | 8 | 226.0–226.3 | 366 ($M^+$) | 1.17 (d, 6H, $J = 6.85$, $2CH_3$), 2.72 (m, 1H, $J = 6.75$, CH), 3.51 (s, 3H, $OCH_3$), 4.29 (s, 2H, $CH_2$), 4.38 (s, 2H, $NCH_2$), 7.09–8.17 (m, 7H, *Ph*), 11.48 (s, 1H, NH) |

## Experimental

Melting points were determined on a WRS-1 digital melting point instrument and uncorrected. $^1$H NMR spectra were obtained on a Bruker DMX 500 MHz spectrometer in *DMSO*-$d_6$ as solvent. Chemical shifts are recorded in $\delta$ (ppm) units relative to the internal reference tetramethylsilane (*TMS*). Mass spectra were obtained on a HP 5989A spectrometer. Analytical TLC was performed with silica gel $GF_{254}$ plates. Reagents and solvents were purified and dried by standard methods prior to use.

*General Procedure for Preparation of Derivatives **4(1)–4(34)***

To a suspension of the uracil **(10a–10d)** (2 mol) and $K_2CO_3$ (0.55 g, 4 mmol) in anhydrous *DMF* (10 $cm^3$) was added $BrCH_2CO$*R* (2.2 mmol) and the mixture was vigorously stirred for 12–24 h at room temperature until the starting material was consumed according to TLC detection (*Et*O*Ac*:PE 2:1). The reaction mixture was poured into cold $H_2O$ (60 mL), and extracted with $CH_2Cl_2$($3 \times 50$ mL). The combined organic layers were washed with brine ($3 \times 50$ $cm^3$), dried ($Na_2SO_4$), and evaporated *in vacuo* to give crude compounds, which were chromatographed on silica gel with ethyl acetate/petroleum ether (bp 60–90°C)/$CH_2Cl_2$ as eluents to give pure **4(1)–4(34)**.

*Typical Procedure for the Preparation of **5(1)–5(20)***

Under the same reaction conditions as used for the preparation of **4(1)–4(34)**, except that **11a–11c** were used as the starting material instead of **10a–10d**.

*Typical Procedure for the Preparation of **13a** and **13b***

*5-Bromo-6-(1-naphthylmethyl)uracil* (**12**)

A mixture of 6-(1-methyl)uracil (**6e**, 5.54 g, 22 mmol) and *N*-bromosuccinimide (4.06 g, 24.2 mmol) in anhydrous *DMF* (30 $cm^3$) was stirred at 70°C for 3 h. The reaction mixture was cooled to room temperature, and poured into cold $H_2O$ (70 $cm^3$). The solid was filtered and washed with $H_2O$ to give **12** (0.69 g, 96%), mp 197–199°C; MS (EI): $m/z = 330$ ($M^+$); $^1$H NMR (*DMSO*-$d_6$, 500 MHz): $\delta = 4.36$ (s, 2H, $CH_2$), 7.18–8.11 (m, 7H), 11.44 (s, 1H, $N_1$-H), 11.61 (s, 1H, $N_3$-H) ppm.

*5-Methoxy-6-(1-naphthylmethyl)uracil* (**13a**)

Metal sodium (0.138 g, 6 mmol) was dissolved in 25 $cm^3$ abs. *Me*OH, then **12** (0.99 g, 3 mmol) was added in one portion, and the mixture was refluxed with stirring for 12 h. The solvent was evaporated *in vacuo*. The residue was dissolved in $H_2O$ (30 $cm^3$), and neutralized with 1 *M* aq. HCl. The solid was filtered off and washed with $H_2O$ to give **13a** (0.694 g, 76%), mp 214.4–214.9°C; MS (EI): $m/z = 282$ ($M^+$); $^1$H NMR (*DMSO*-$d_6$, 500 MHz): $\delta = 3.41$ (s, 1H, OMe), 5.49 (s, 1H, CH), 5.68 (s, 1H, CH), 7.54–8.13 (m, 7H), 10.80 (s, 1H, $N_1$-H), 11.10 (s, 1H, $N_3$-H) ppm.

*5-Ethoxy-6-(1-naphthylmethyl)uracil* (**13b**)

Under the same reaction conditions the preparation of **13a**, but as for *Et*OH was used as solvent instead of *Me*OH. Yield 68%, mp 201.0–202.1°C; MS (EI): $m/z = 296$ ($M^+$); $^1$H NMR (500 MHz): $\delta = 1.19$ (t, 3H, $J = 7.7$ Hz, Me), 3.64 (m, 2H, $J = 7.7$ Hz, $OCH_2$), 5.40 (s, 1H, CH), 5.83 (s, 1H, CH), 7.52–8.13 (m, 7H), 10.97 (s, 1H, $N_1$-H), 11.10 (s, 1H, $N_3$-H) ppm.

*Typical Procedure for the Preparation of **4(35)–4(43)***

Under the same reaction conditions as used for the preparation of **4(1)–4(34)**, except that **13a** and **13b** were used as raw material instead of **10**.

*Anti-HIV Assays*

Compounds were evaluated for possible antiviral activity against both strains of HIV-1 and HIV-2 using MT-4 cells as target cells. As previously described [1], MT-4 cells were incubated with virus and growth medium containing the test dilutions of compound for seven days. Uninfected control and virus infected cultures without compound added were grown in parallel. Expression of HIV in the cultures was quantified indirectly using the MTT assay [13]. The inhibitory concentration of compounds was expressed as the concentration that caused 50% inhibition of viral cytopathoxicity ($IC_{50}$) without direct toxicity to the cells. Cytotoxicity of the compounds was evaluated in parallel with their anti-viral activity. The cytotoxic concentration ($CC_{50}$) of compounds was monitored based on the growth of noninfected cells by trypan blue exclusion method and corresponded to the concentration required to cause 50% cell death.

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