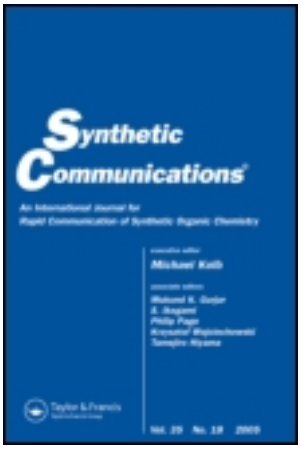

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Synthesis of 1-[(2-Hydroxyethoxy)Methyl]-6-(5,6,7,8-Tetrahydronaphthylmethyl-1) Thymine as Novel Inhibitor against Drug-Resistant HIV Mutants

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Abstract: Synthesis of two new 1-[(2-hydroxyethoxy)methyl]-6-(5,6,7,8-tetrahydronaphthylmethyl-1)thymine derivatives **10a**–**b**, as potent inhibitors against a mutant type of HIV, starting from thymine, is described. In the preparation of the corresponding **10a**–**b** from compounds **9a**–**b**, the three-step reaction via deprotection, hydrogenolysis, and hydrogenation was carried out in a one-pot procedure.

Keywords: HEPT, HEPT analogues, HIV-1 RT inhibitors

INTRODUCTION

As is well known, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT, **1**, Fig. 1) is a lead compound for designing anti-HIV reverse transcriptase inhibitors because of its relatively high anti-HIV reverse transcriptase activity.[1] As early as 1990, Baba et al. reported that when the 6-phenylthio group of **1** was replaced by a 6-cyclohexylthio group, the activity of its analogue (HEPT-H, **2**) against a drug-resistant HIV mutant was increased notably.[2] TNK-6123 (**3**) with a C-6 thiocyclohexyl group has more flexibility in adapting to the mutated drug-binding site.[3] The studies of structure–activity relationship showed that the two aromatic rings in the skeleton of these derivatives are very important for binding between the ligand and the

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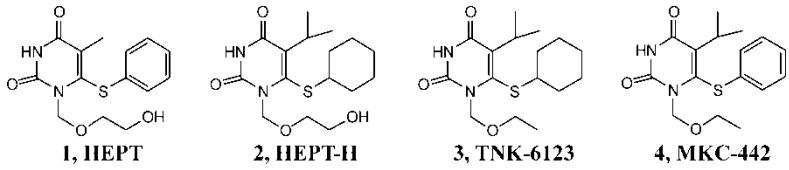


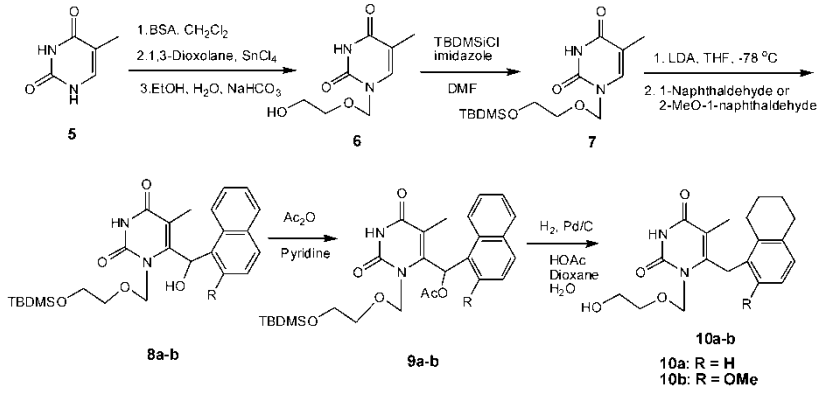
Figure 1. Chemical structures of HEPT and its analogues.

reverse transcriptas (RT) active binding pocket (MKC-442, **4**).[4] The suggestions described by Hopkin et al. disclosed the substitution with a 1-naphthylmethyl group at the C-6 position of the HEPT and its analogs would benefit the enhancement of the biological activity,[5] which was also confirmed by our recent research results.[6]

To further explore the structure–activity relationship of this series of compounds against both wild and mutant types of HIV-1, in this paper we report the synthesis of two new 1-[(2-hydroxyethoxy)methyl]-6-(5,6,7,8-tetrahydronaphthylmethyl-1)thymine derivatives.

RESULTS AND DISCUSSION

The synthetic route to target molecules **10a–b** is outlined in Scheme 1. Compound **6** was prepared starting from thymine in a one-pot procedure via silylation, *N*-1-alkylation, and deprotection in 28% yield. Protection on 2-hydroxy group of *N*-1 side chain with tertbutyl dimethyl chlorosilane (TBDMSiCl) in the presence of imidazole in DMF at room temperature for 14 h gave compound **7** in a 93% yield. We treated **7** with LDA in THF at



Scheme 1. The synthetic route to target compounds **10a–b**.

−78°C for 1 h, and the resulting *C*-6-lithiated species were allowed to react with the 1-naphthaldehyde derivatives to give 6-(arylhydroxymethyl)thymine derivatives **8a,b** in 32% and 51% yields, respectively. Acetylation of **8a** or **8b** with Ac_2O in pyridine gave the acetates **9a,b** in good yield. Finally, the transformation of **9a**,**b** into the corresponding compounds **10a**,**b** was accomplished in a one-pot procedure via the deprotection, hydrogenolysis, and hydrogenation upon treatment of 10% Pd/C under 1 atm of H_2 at 60°C for 15 h in an HOAc, H_2O, and dioxane mixed solvent. The target compounds **10a** and **10b** were obtained in 76% and 68% isolated yield, respectively. The merits of this one-pot procedure are clean reaction, highly regioselectivity, mild conditions, feasible workup, and good yield.

The structures of these new compounds **8a–b, 9a–b**, and **10a–b** were identified by IR, ^{1}H NMR, ^{13}C NMR and MS spectra. The difference of chemical shift and the peak form between the ^{1}H NMR of **7** and **8** indicates that the rotation of the N-C bond on the *N*-1-side chain was hindered by the introduction of 1-naphthylhydroxymethyl to C-6 position of thymine (Fig. 2). This made the two protons on *N*-1-CH_2O have different chemical environments. Therefore, the single peak of CH_2 was split into double–double peaks, resulting in an AB system. The ^{1}H-^{1}H COSY spectrum of **8b** indicates that there is a correlation between the protons of methylene group and the hydroxyl group, which leads to the single peak splitting into double peaks.

It can also be supposed from the difference between the ^{1}H NMR spectrum of **8a** and **8b** that there should exist an intramolecule hydrogen bond between the hydroxyl group on the C-6 methelene and the 2-methoxy group on naphthyl ring (Fig. 2, **8b**). This six-member ring may enhance the chemical environmental difference between two protons, which could account for the transformation from the AB system of the two protons on *N*-1-CH_2O of **8a** to the AX system of **8b**.

In summary, we have developed a facile and convenient method for the synthesis of the 1-[(2-hydroxyethoxy)methyl]-6-(5,6,7,8-tetrahydronaphthylmethyl-1)thymine derivatives **10a–b**. This method will be useful in the synthesis of the novel 5,6,7,8-tetrahydronaphthylmethyl-1 substituted HEPT analogs as potent HIV-1 RT inhibitors against a drug-resistant mutant. The

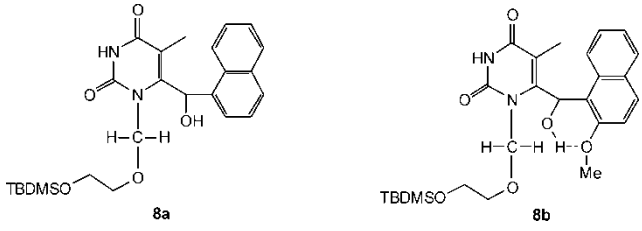


Figure 2. Chemical structures of compounds **8a–b**.

evaluation of in vitro anti-HIV-1 activity of two compounds **10a–b** against both wild and mutant types is in progress.

EXPERIMENTAL

Melting points were measured on a WRS-1B digital melting point instrument and are uncorrected. IR spectra were recorded on a Nicolet FT-IR 360 spectrometer as KBr pellets. ^{1}H NMR spectra were obtained on a Bruker DMX 500 MHz spectrometer. Chemical shifts were reported in ppm units from TMS as an internal standard. ^{13}C NMR spectra were run on a Bruker DMX 125 MHz spectrometer. Mass spectra were obtained on a HP 5989A spectrometer by direct inlet at 70 eV. Column chromatography was performed with silica gel G. Analytical TLC was performed with silica-gel G plates. Reagents and solvents were used without further purification with the exception of THF (distilled over sodium and benzophenone). All air-sensitive reactions were run under an atmosphere of nitrogen. All glassware was oven-dried prior to use. The reactions under N_2 were carried out using Schlenk techniques.

1-[(2-Hydroxyethoxy)methyl]-thymine (6). To a suspension of thymine **5** (2.52 g, 20 mmol) in CH_2Cl_2 (50 mL) was added *N, O*-bis(trimethylsilyl) acetamide (BSA, 11 mL, 44 mmol) under a nitrogen atmosphere, and the reaction mixture was stirred at rt for 3 h. 1, 3-Dioxolane (1.7 mL, 24 mmol) and anhydrous $SnCl_4$ (2.8 mL, 24 mmol) were added to the mixture. The mixture was continued for an additional 17 h under reflux, then cooled and poured into the mixture of $MeOH/H_2O$ (50 mL, 1:1, *V*/*V*) containing $NaHCO_3$ (11 g). After stirring for 2 h at rt, the resulting mixture was filtered off, and the filter cake was washed with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4. After the evaporation of solvent in vacuo, the residue was crystallized from EtOAc/EtOH (1:1, *V*/*V*) to afford pure **6** (1.12 g, 28%) as white crystals. Mp 136–138°C (lit.[7] mp 150–152°C). IR (KBr): $\nu = 3442$ (NH), 3057 (Me), 1701 (C═O), 1686 (C═O), 1412 (O-H, br), 1142 (C-O), 1054 (C-OH) cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 1.77$ (s, 3H, CH_3), 3.23–3.49 (m, 4H, CH_2CH_2), 4.65 (br s, 1H, O*H*), 5.06 (s, 2H, NCH_2), 7.57 (s, 1H, C*H*), 11.3 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): $\delta = 12.3$, 60.5, 71.0, 76.8, 109.6, 141.0, 151.6, 164.7. EI-MS: m/z (%): M^+ 201 (13.31), 200 (7.10), 278 (83.71), 139 (24.89), 126 (100.0), 96 (23.61), 83 (10.81).

1-[(2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy)methyl]thymine (7). A mixture of **6** (4.5 mmol), anhydrous DMF (15 mL), imidazole (368 mg, 5.4 mmol), and *tert*-butyldimethylsilyl chloride (TBDMSiCl) (815 mg, 5.4 mmol) was stirred at rt for 14 h. The precipitate was collected by filtration

and washed with sat. aq. $NaHCO_3$ (3 × 75 mL) and H_2O (3 × 75 mL), and dried in vacuo to give the crude product, which was recrystallized from hexane to afford pure **7** (6.57 g, 93%) as white crystals. Mp 132–134°C (lit.[7] mp 137–138°C). IR (KBr): $\nu = 3427$ (NH), 3036 (Me), 1698 (C═O), 1657 (C═O), 1101 (C-OH) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.06$ (s, 6H, 2 × CH_3), 0.89 (s, 9H, 3 × CH_3), 1.93 (s, 3H, CH_3), 3.63–3.77 (m, 4H, CH_2CH_2), 5.18 (s, 2H, NCH_2), 7.15 (s, 1H, C*H*), 8.30 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): $\delta = 5.3$, 5.4, 12.3, 18.3, 25.8, 25.9, 62.4, 70.9, 73.3, 111.5, 138.9, 151.1, 163.9. EI-MS: m/z (%): M^+ 314 (0.25), 257 (14.97), 237 (1.08), 139 (100.00), 126 (0.91), 96 (54.85), 83 (0.60).

General Procedure for the Preparation of 1-[[2-[(*tert*-butyldimethyl-silyl)oxy]ethoxy]methyl]-6-(1-hydroxy-1-naphthylmethyl-1)thymine Derivatives 8a–b

To a solution of LDA (4.29 mmol) in THF (6.3 mL) was added **7** (1.58 mmol) dissolved in THF (6.3 mL) at −78°C under a nitrogen atmosphere. After stirring for 1 h, 1-naphthaldehyde or 2-methoxy-1-naphthaldehde (3.16 mmol) in THF (5 mL) was added at the same temperature over a period of 2 h, then quenched with AcOH (0.42 mL) and allowed to warm to rt. The reaction mixture was evaporated under reduced pressure to dryness. The residue was purified by chromatography ($CHCl_3$ as eluate), and crystallized from appropriate solvent to give pure **8a–b**.

1-[(2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy)ethyl]-6-(1-hydroxy-1-naphthylmethyl-1)thymine (8a): White crystals (EtOAc), yield: 32%, mp 196–198°C. IR (KBr): $\nu = 3413$ (NH), 3068 (Me), 1703 (C═O), 1685 (C═O), 1092 (C-OH), 1092 (Si-O, br) cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = -0.14$ (s, 3H, CH_3), 0.10 (s, 3H, CH_3), 0.73 (s, 9H, 3 × CH_3), 1.66 (s, 3H, CH_3), 3.48–3.53 (m, 4H, CH_2CH_2), 5.06 (br s, 1H, O*H*), 5.36 (d, 1H, $J = 10$ Hz, C*H*), 6.52–6.60(dd, 2H, AB, $J = 10.0$, 5.0 Hz, NCH_2), 7.45–8.07 (m, 7H, Ar-*H*), 11.53 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6): $\delta = (-5.1, -5.0, 11.2, 18.3, 26.1, 62.5, 68.1, 70.6, 73.6, 110.8, 124.1–134.0, 151.4, 152.0, 164.4.$ EI-MS: m/z (%): 413 ($M^+ - 57$, 1.13), 295 (28.04), 277 (11.62), 265 (39.62), 141 (100.00); HRMS: m/z calcd. for $C_{25}H_{34}N_2O_5Si$: 470.2237; Found: 470.2233.

1-[(2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy)ethyl]-6-[1-hydroxy-1-(2-methoxynaphthyl)methyl-l]thymine (8b): White crystals (EtOH), yield: 51%, mp 142–144°C. IR (KBr): $\nu = 3475$ (NH), 3019 (Me), 1703 (C═O), 1654 (C═O), 1088 (C-OH), 1073 (Si-O, br) cm^{-1}. ^1H NMR (DMSO-d_6): δ (−0.03 (s, 3H, CH_3), −0.003 (s, 3H, CH_3), 0.80 (s, 9H, 3 × CH_3), 1.76 (s, 3H, CH_3), 3.34–3.62 (m, 4H, CH_2CH_2), 3.71 (s, 3H, OCH_3), 4.98

(s, 1H, O*H*), 5.47 (d, 1H, $J = 10$ Hz, C*H*), 6.28–6.61 (dd, AX, 2H, $J = 10.0$, 5.0 Hz, NCH_2), 7.39–8.41 (m, 6H, Ar-*H*), 11.38 (s, 1H, N*H*); ^{1}H-^{1}H COSY (DMSO-d_6): 4.98 (s, 1H, O*H*) correlates with 5.47 (d, 1H, $J = 10$ Hz, C*H*). ^{13}C NMR (DMSO-d_6): $\delta = -4.90$, -4.88, 10.9, 18.4, 26.3, 57.0, 62.8, 66.9, 70.7, 74.2, 108.3, 115.3-152.2, 153.9, 155.2, 164.5. EI-MS: m/z (%): 501 (0.50), 443 ($M^+ - 57$, 0.63), 295 (15.90), 277 (11.62), 263 (29.55), 171 (100.00); HRMS: m/z calcd. for $C_{26}H_{36}N_2O_6Si$: 500.2343; Found: 500.2335.

General Procedure for the Preparation of 1-[[2-[(tert-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(1-acetoxy-1-naphthylmethy-1)thymine Derivatives 9a–b[8]

To a solution of **8a** or **8b** (0.5 mmol) in pyridine (20 mL) added was acetic anhydride (1 mL), and the mixture was stirred at rt for 12 h. The mixture was poured into sat. aq. $NaHCO_3$ (30 mL), and extracted with EtOAc (3×30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3×30 mL) and H_2O (3×30 mL), dried over $MgSO_4$. The solvent was concentrated in vacuo. The residue was purified by chromatography on silica gel ($CHCl_3$/hexane, 8:2, *V*/*V*), and recrystallized from EtOAc.

1-[(2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy)methyl]-6-(1-acetoxy-1-naphthylmethyl-1)thymine (9a): White crystals, yield: 94%, mp 160–162°C. IR (KBr): $\nu = 3421$ (NH), 3031 (Me), 2928 (Me), 1747 (C=O), 1710 (C=O), 1666 (C=O), 1075 (Si-O, br) cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = -0.12$ (d, 6H, $2 \times$ CH_3), 0.76 (s, 9H, $3 \times$ CH_3), 2.04 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.28–3.61 (m, 4H CH_2CH_2), 5.21–5.59 (m, 2H, NCH_2), 7.26 (s, 1H, C*H*), 7.35–7.94 (m, 7H, Ar-*H*), 8.79 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ (-5.2, -5.1, 11.8, 18.2, 20.6, 26.1, 62.1, 70.1, 70.2, 74.0, 111.5, 123.1–134.2, 147.1, 151.8, 164.0, 170.4. EI-MS: m/z (%): 512 (1.46), 455 (M^+-57, 0.38), 337 (34.98), 295 (8.69), 277 (100.00), 265 (24.71), 206 (15.96), 189 (22.57), 141 (36.99); HRMS: m/z calcd. for $C_{27}H_{36}N_2O_6Si$: 512.2343; Found: 512.2333.

1-[(2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy)methyl]-6-[1-acetoxy-1-(2-methoxynaphthyl)methyl-1]thymine (9b): White crystals, yield: 72%, mp 141–143°C. IR (KBr): $\nu = 3478$ (NH), 3028 (Me), 2855 (Me), 1747 (C=O), 1706 (C=O), 1622 (C=O), 1077 (Si-O) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 0.00$ (d, 6H, $2 \times$ CH_3), 0.82 (s, 9H, $3 \times$ CH_3), 1.62 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.74–3.80 (m, 4H, CH_2CH_2), 5.28–5.61 (m, 2H, NCH_2), 7.23 (s, 1H, C*H*), 7.43–7.95 (m, 6H, Ar-*H*), 8.53 (br s, 1H, N*H*); ^{13}C NMR (DMSO-d_6): $\delta = 5.4$, 10.6, 18.2, 21.0, 25.8, 56.4, 62.7, 66.8, 71.9, 76.13, 108.7, 113.9–150.7, 152.1, 156.1, 163.9, 170.4. EI-MS: m/z (%): 542 (0.09), 485 ($M^+ - 57$, 1.00), 367 (43.54), 325 (10.25), 307 (28.58),

295 (6.21), 236 (3.70), 171 (100.00); HRMS: m/z calcd. for $C_{28}H_{38}N_2O_7Si$: 542.2448; Found: 542.2436.

General Procedure for the Preparation of 1-[(2-hydroxyethoxy) methyl]-6-(5,6,7,8-tetrahydronaphthylmethyl-1)thymine Derivatives 10a–b

A mixture of **9a** or **9b** (1 mmol), 10% Pd/C (50 mg) and AcOH/H_2O/dioxane (20 mL, 2:1:2, *V*/*V*/*V*) was stirred at 60°C for 15 h under hydrogen (1 atm). The catalyst was removed by filtration, and washed with EtOH (2 × 10 mL). The filtrate was concentrated in vacuo and recrystallized from an appropriate solvent to give the target molecules **10a** or **10b**.

1-[(2-Hydroxyethoxy)methyl]-6-(5,6,7,8-tetrahydronaphthylmethyl-1) thymine (10a): White crystals (EtOH), yield: 76%, mp 197–199°C. IR (KBr): $\nu = 3413$ (NH), 2928 (Me), 1708 (C═O), 1672 (C═O) cm^{-1}, 1459 (O-H, d), 1159 (C-O), 1063 (C-OH). ^{1}H NMR (DMSO-d_6): $\delta = 1.72$ (m, 4H, -CH_2CH_2-), 1.82 (s, 3H, CH_3), 2.66–2.76 (m, 4H, 2 × CH_2), 3.42–3.47 (m, 4H, OCH_2CH_2O), 3.92 (s, 2H, CH_2), 4.62 (d, 1H, O*H*), 4.93 (s, 2H, NCH_2), 6.64–7.03 (m, 3H, Ar-*H*), 11.46 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6): $\delta = 10.8$, 22.7, 23.3, 26.1, 30.1, 31.2, 60.5, 70.9, 73.2, 110.2, 123.2–137.8, 149.9, 152.0, 163.8. EI-MS: m/z (%): 345 (37.36), 283 (84.37), 270 (100.00), 255 (54.02), 210 (15.13), 140 (18.46), 131 (63.42), 115 (15.78); HRMS: m/z calcd. for $C_{19}H_{24}N_2O_4$: 344.1736; Found: 344.1745.

1-[(2-Hydroxyethoxy)methyl]-6-(2-methoxy-5,6,7,8-tetrahydronaphthyl-methyl-1)thymine (10b): White crystals (AcOEt), yield: 68%, mp 189–191°C. IR (KBr): $\nu = 3530$ (OH), 3153 (NH), 2941 (Me), 2942 (Me), 1697 (C═O), 1652 (C═O) cm^{-1}, 1400 (OH, d), 1092 (C═O), 1063 (OH). ^{1}H NMR (DMSO-d_6): δ (1.53 (s, 3H, CH_3), 1.64–1.74 (m, 4H, –CH_2CH_2–), 2.61–2.68 (m, 4H, 2 × CH_2), 3.47–3.49 (m, 4H, OCH_2CH_2O), 3.58 (s, 3H, CH_3), 3.93 (s, 2H, CH_2), 4.63 (d, 1H, O*H*), 5.30 (s, 2H, NCH_2), 6.77–6.97 (m, 3H, Ar-*H*), 11.30 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): $\delta = 10.3$, 22.7, 23.3, 26.8, 27.7, 29.5, 56.1, 60.5, 70.6, 73.3, 110.2, 123.2-137.8, 149.9, 152.0, 163.8. EI-MS: m/z (%): 375 (17.17), 313 (52.94), 268 (100.00), 240 (12.03), 225 (23.93), 161 (20.15), 115 (7.16); HRMS: m/z calcd. for $C_{20}H_{26}N_2O_5$: 374.1842; Found: 374.1856.

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