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The new convenient synthesis of fluorinated Penciclovir analogues 9-(4-fluoro-3-hydroxymethylbutyl) guanine (FHBG) and 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxymethylbutyl) purine (6-Fluoropenciclovir)

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Abstract

9-(4-Hydroxy-3-hydroxymethylbutyl) guanine (Penciclovir) is a potent and selective inhibitor of members of the herpes virus family. A new convenient synthesis of fluorinated Penciclovir analogues 9-(4-fluoro-3-hydroxymethylbutyl) guanine (FHBG) and 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxy-methylbutyl) purine (6-Fluoropenciclovir) were described. The structures of the products were characterized by UV, IR, ^{1}H NMR, ^{19}F NMR spectra and MS.

Keywords: Penciclovir; Anti-viral agent; PET; Fluorination reaction; Synthesis

1. Introduction

Recently, nucleoside analogues have attracted particular attention on account of extensive biological activities as anti-viral and anti-tumor agents [1,2]. It is well known that fluorine substituted compounds show remarkable differences in biological activities and pharmacological properties compared to their parent molecules. Introduction of fluorine plays a significant role in the development of new drug agents because of improving the metabolic stability or modulating the physicochemical properties or increasing binding affinity to a target protein [3,4]. Positron emission tomography (PET) has been developed to examine the intact biological systems as state-of-the-art imaging technology, and has been applied in studying in vivo mechanisms of disease present, drug pharmacokinetics, pharmacodynamics within the context of physiologically authentic environments in cellular and molecular level [5–7]. The synthesis of fluorinated nucleoside analogues has been under investigation for many years owing to interest in these compounds as potential chemotherapeutic agents. And the nucleoside analogues labeled with ^{18}F have also been applied as tracer molecules for PET imaging of Herpes Simplex Virus Type-1 thymidine kinase gene (HSV1-tk) gene expression [8]. Acyclic nucleoside analogue 9-(4-hydroxy-3-hydroxymethylbutyl) guanine (Penciclovir, **1**) is a potent and selective inhibitor of member of the herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV) and Epstein-Barr virus (EBV) [9]. Moreover, Penciclovir analogues have been used in combination with suicide enzymes in gene therapy of cancer [10]. Some new fluorinated Penciclovir analogues were prepared by incorporating fluorine in appropriate position to develop more potent anti-viral agents and apply in PET chemistry (Fig. 1). Fluorinated Penciclovir analogue 9-[(4-fluoro)-3-hydroxymethylbutyl] guanine (FHBG, **2**) showed good results in the in vitro evaluation, and the 9-(4-[^{18}F]-fluoro-3-hydroxymethylbutyl) guanine ([^{18}F]-FHBG) as one of reporter gene probes could image HSV1-tk in vivo with PET, which provided valuable information for gene therapy of cancer [11,12]. Although the synthesis of FHBG from Penciclovir was reported in the literature [13,14], the poor yield

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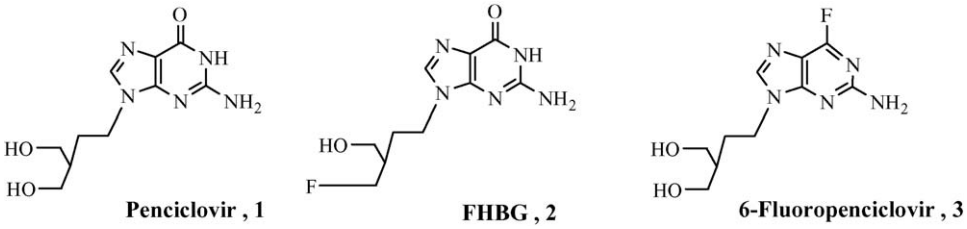


Fig. 1. Structures of Penciclovir and fluorinated Penciclovir.

needs to be improved in certain key steps. Consequently, we investigated alternate approaches and modifications that eventually resulted in an improved synthesis of FHBG starting from Penciclovir. At the same time, exploring the active site of Herpes Simplex Virus Type-1 thymidine kinase (HSV1-TK) with Penciclovir showed that 6-position of the purine ring was pertinent to activity of Penciclovir [15,16]. And the esters of 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxymethylbutyl) purine as anti-viral agents brought the encouraging results [9]. So we substituted O_6-position of the purine ring to 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxymethylbutyl) purine (6-Fluoropenciclovir, **3**) by nucleophilic fluorination reaction in alternate approaches.

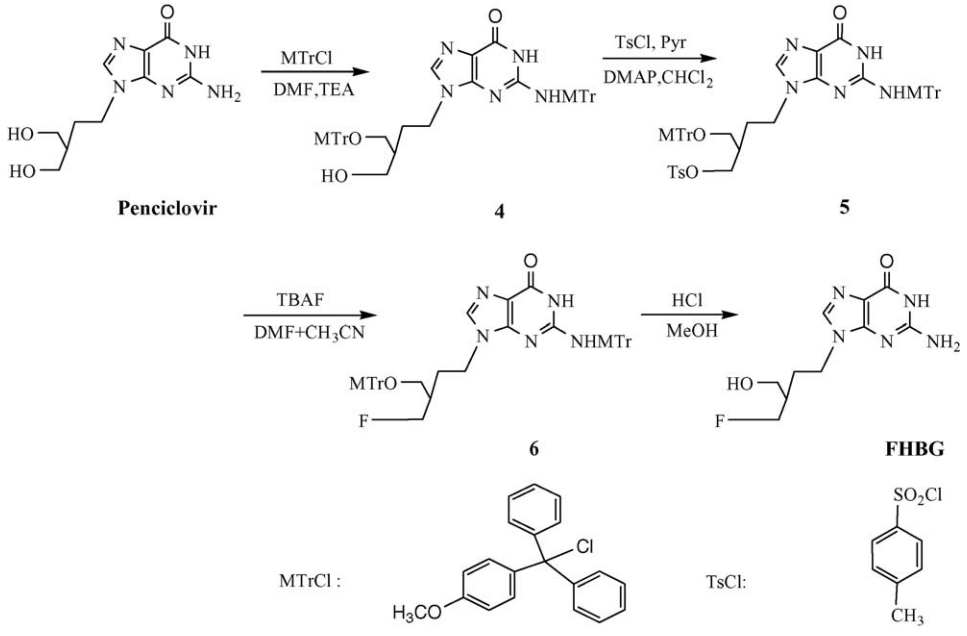
2. Results and discussion

2.1. Synthesis of FHBG

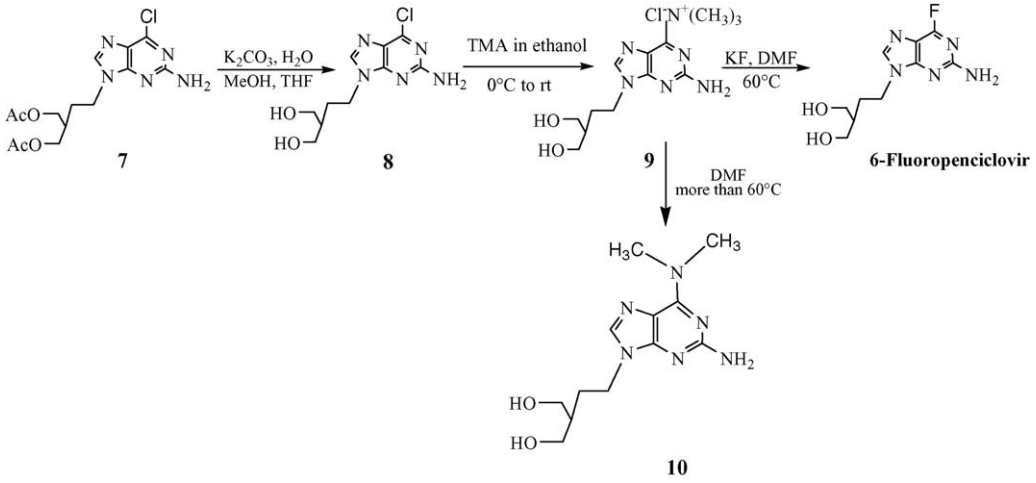
Synthesis of FHBG **2** is based on the following sequence of reactions as shown in Scheme 1. Penciclovir **1** was converted to N^2-(*p*-anisyldiphenylmethyl)-9-[(4-hydroxy)-3-*p*-anisyldiphenyl-methoxymethylbutyl] guanine **4** by treatment with monomethoxytrityl chloride and trimethylamine in DMF solution at room temperature overnight. Although higher reaction temperature could increase the rate of reaction, it brought more byproduct and decreased the yield. So the reaction temperature was decreased from 50 °C to room temperature and the reaction time was prolonged from several hours to overnight; accordingly the yield of compound **4** was increased to 54.4%, which is higher than 40% in literature [13].

Compound **4** was reacted with *p*-tosyl chloride in dry pyridine in presence of DMAP at room temperature overnight to produce the desired N^2-(*p*-anisyldiphenylmethyl)-9-[(4-tosyl)-3-*p*-anisyldiphenylmethoxy-methylbutyl] guanine **5** with high yield. The reaction of *p*-tosyl chloride dissolving in dry pyridine is exothermic, which reduce the rate of tosylation. We dissolved *p*-tosyl chloride into dry methylene chloride at 0 °C, then adding to dry pyridine solution of compound **4** dropwise, the yield was increased to 70.5%, which is higher than 35% in literature [13].

Compound **5** was reacted with tetrabutylammonium fluoride (TBAF) in mixture solution of acetonitrile and DMF to afford the N^2-(*p*-anisyldiphenylmethyl)-9-[(4-fluoro)-3-*p*-anisyldiphenylmethoxy-methylbutyl] guanine **6**. TBAF appeared to be the better fluorinating agent, perhaps due to the fact that it was more soluble in organic solvents compared to KF. Moreover, it was necessary to dry TBAF before using because hydrated TBAF varied this reaction yield [17,18]. The mixture of acetonitrile and DMF was better than only either of them as a solvent for compound **5**. This fluorination reaction was difficult



Scheme 1. Synthesis of 9-[(4-fluoro)-3-hydroxymethylbutyl] guanine.



Scheme 2. Synthesis of 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxymethylbutyl) purine.

to monitor by TLC due to the similar values of R_f in different elution system, but it could be purified by silica gel chromatography instead of known method HPLC purification.

Compound **6** was hydrolyzed in aqueous HCl to yield the desired product FHBG by removal of the monomethoxytrityl groups.

2.2. Synthesis of 6-Fluoropenciclovir

The preparation of 6-Fluoropenciclovir **3** from intermediate 2-amino-6-chloro-9-(4-acetoxy-3-acetoxy-methylbutyl) purine **7** is shown in Scheme 2.

2-Amino-6-chloro-9-(4-acetoxy-3-acetoxy-methylbutyl) purine **7** in THF was hydrolyzed to 2-amino-6-chloro-9-(4-hydroxy-3-hydroxymethylbutyl) purine **8** by using potassium carbonate in a mixed solution of water and methanol at 0 °C. This experiment should be performed under 0 °C because the chlorine being at 6-position of the purine ring was very reactive to substitution at high temperature [19].

The synthesis procedure of 2-amino-9-(4-hydroxy-3-hydroxymethylbutyl)-*N*,*N*,*N*-trimethyl-9H-purin-6-aminium chloride **9** was improved by starting from commercially available ethanolic TMA solution and Compound **8** under well defined reaction conditions and afforded a higher yield of over 90.5%.

The most widely used preparation of 6-fluoro-purine nucleoside was developed originally by nucleophilic displacement of the trimethylammonio-group [9,20,21]. The compound **9** was reacted with KF in DMF to yield 2-amino-6-fluoro-9-(4-hydroxy-3-hydroxymethylbutyl) purine **3** with the yield of 87.3%. This reaction was complicated due to the formation of byproduct 2-amino-6-dimethylamino-9-(4-hydroxy-3-hydroxymethylbutyl) purine **10** under high temperature, which could be proved by decomposition experiment of compound **9**. The temperature affected on this reaction was investigated in the synthesis of compound **3** (Fig. 2), and found that the desired compound **3** was prepared in good yield when temperature was 60 °C, but the yield of compound **3** was decreased due to formation of the compound **10** when temperature was more than 60 °C.

3. Experimental

3.1. General experimental procedures

Melting points (mp) were determined on a WRS-1A melting points apparatus and were uncorrected. ^1H and ^{19}F NMR spectra were recorded on a Bruker AC-500 (500 MHz) instrument with Me_4Si and $CFCl_3$ as internal standards in the indicated solution described below, respectively. Chemical shifts were reported in δ values in parts per million (ppm) downfield from Me_4Si ($\delta = 0$) for proton and upfield from $CFCl_3$ ($\delta = 0$) for fluorine NMR. Electron impact mass spectra (EI-MS) were obtained on MicroMass GCT CA 055 spectrometers. Infrared spectra (IR) were recorded on Avatar 370 FT-IR (Thermo Nicolet) as KBr disc. Ultraviolet spectra (UV) were recorded on Shimadzu UV-240 Spectrophotometer.

Penciclovir, 2-amino-6-chloro-9-(4-acetoxy-3-acetoxy-methylbutyl) purine were obtained as gifts from Changzhou Kony Pharmaceuticals Co. Ltd. (Changzhou, China); the other

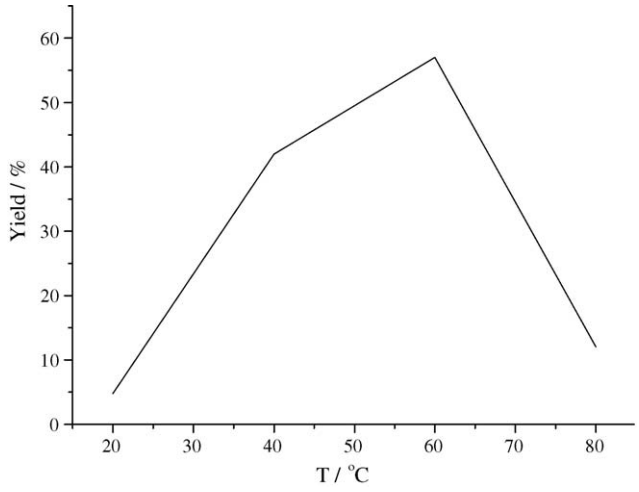


Fig. 2. The yield (%) of compound **3** under different temperatures. The yield (%) is meaning compound **3** was reacted for an hour under different temperatures.

solvents and reagents were commercially available and used as received unless otherwise specified.

Analytical thin-layer chromatography (TLC) was carried out on precoated plate (silica gel 60 F_{254}), and spots were visualized with ultraviolet light. Normal phase flash column chromatography was carried out on silica gel (200–300 mesh) with common flow of the indicated solvent system in the proportions described below.

3.2. Synthetic procedures

3.2.1. N^2-(p-Anisyldiphenylmethyl)-9-[(4-hydroxy)-3-p-anisyldiphenyl-methoxymethylbutyl] guanine (**4**)

Penciclovir (200 mg, 0.79 mmol), monomethoxytrityl chloride (600 mg, 1.94 mmol), DMAP (12 mg, cat. amount), and triethylamine (0.8 mL) were placed in a dry flask under nitrogen atmosphere. Dimethyformamide (DMF, 12 mL) was added, and the reaction mixture was stirred at room temperature overnight. TLC analysis of the product showed no starting material remained. The reaction mixture was diluted with ethyl acetate (25 mL), and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL). The combined organic phase was dried over $MgSO_4$ and evaporated to remove the solvents. After chromatography on a silica gel column using 5% MeOH in CH_2Cl_2, 340 mg of the desired product as white solid was obtained in 54.4% yield. mp 140.1–142.8 °C; UV (EtOH): λ 214, 232 and 262 nm; IR (KBr): ν 3720, 3410, 2980, 2920, 1610, 1530, 1510 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.40 (s, 1N, NH), 7.56 (s, 1N, NH), 7.45 (s, 1H, C_8H), 7.36–7.20 (m, 24H, aromatic), 6.85 (d, 2H, aromatic, J = 9 Hz), 6.75 (d, 2H, aromatic, J = 9 Hz), 4.35 (t, 1H, J = 5 Hz), 3.74 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 3.40 (t, 2H, J = 7 Hz, 1′H), 3.38–3.10 (m, 2H, CH_2OH), 2.80–2.60 (m, 2H, 5′H), 1.43 (m, 1H, 3′H), 1.23 (m, 2H, 2′H).

3.2.2. N^2-(p-Anisyldiphenylmethyl)-9-[(4-tosyl)-3-p-anisyldiphenylmethoxy-methylbutyl] guanine (**5**)

Compound **4** (570 mg, 0.714 mmol) was dissolved in dry pyridine (10 mL) and kept at 0 °C for 10 min. *p*-Tosyl chloride (1.20 g, 6.32 mmol) dissolving in CH_2Cl_2 was added to the above solution and stirred at 0 °C overnight. TLC analysis of the product showed no significant amount of starting material remained. To the reaction mixture, ethyl acetate (25 mL) was added, and washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (25 mL). The combined organic phase was dried over $MgSO_4$ and evaporated to yield the crude product. After chromatography on silica gel column using 5% MeOH in CH_2Cl_2, 479 mg of the desired product was obtained in 70.5% yield. mp 200.2–203.8 °C; UV (EtOH): λ 209, 225 and 265 nm; IR (KBr): ν 3380, 3050, 1680, 1180, 1030, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.74 (d, 2H, aromatic, J = 8 Hz), 7.35–7.05 (m, 27H, aromatic and C_8–H), 6.80 (d, 2H, aromatic, J = 8.76 Hz), 6.71 (d, 2H, aromatic, J = 8.46 Hz), 4.10–3.80 (m, 2H, 4′-CH_2OTs), 3.77 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O), 3.50–3.20 (m, 2H, 1′H), 3.10–2.80 (m, 2H, 5′H), 2.42 (s, 3H, CH_3), 1.58 (m, 1H, 3′H), 1.50–1.30 (m, 2H, 2′H).

3.2.3. N^2-(p-Anisyldiphenylmethyl)-9-[(4-fluoro)-3-p-anisyldiphenylmethoxy-methylbutyl] guanine (**6**)

Compound **5** (67 mg, 0.07 mmol), TBAF (315.2 mg, 1.0 mmol) were dissolved in mixed solution of acetonitrile (2 mL) and DMF (1 mL). The reaction was heated to 110 °C for 40 min while stirring. Solvent was removed by evaporation, and the residue was transferred to the top of a silica gel column with the aid of CH_2Cl_2. The column was eluted with 3.5% MeOH/CH_2Cl_2. 40.6 mg of the desired product yellowish solid was obtained in 72.4% yield. UV (EtOH): λ 216, 231 and 262 nm; IR (KBr): ν 3440, 2930, 1680, 1610, 1250, 1030, 825, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.41–7.10 (m, 25H, aromatic and C_8–H), 6.83 (d, 2H, aromatic, J = 8.85 Hz), 6.75 (d, 2H, aromatic, J = 8.6 Hz), 4.50–4.25 (dm, 2H, 4′H, J_{FH} = 47 Hz), 3.77 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O), 3.60–3.40 (m, 2H, 1′H), 3.10–3.00 (m, 2H, 5′H), 2.0–1.5 (m, 1H, 3′H), 1.40–0.8 (m, 2H, 2′H).

3.2.4. 9-[(4-Fluoro)-3-hydroxy-methylbutyl] guanine (**2**)

Compound **6** (77.6 mg, 0.10 mmol) was dissolved in methanol (4 mL), acidified with 1.0 mol/L HCl (0.90 mL), and heated at 110 °C for 30 min when TLC analysis showed no starting material remained. The crude mixture was neutralized with NaOH. Solvent was removed by evaporation, and transferred to the top of a silica gel column. The column was eluted with 15% MeOH/CH_2Cl_2 to afford FHBG as a white solid (21.0 mg, 85%). UV (EtOH): λ 210, 255 nm; IR (KBr): ν 3390, 3160, 2920, 1680, 1500, 1380, 1050, 783, 687 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.70 (s, 1H, C_8H), 4.45–4.35 (dd, 2H, 4′H–CH_2, J_{FH} = 47 Hz, J_{HH} = 4.7 Hz), 3.95 (t, 2H, 1′H, J_{FH} = 7.1 Hz), 3.40–3.35 (d, 2H, 5′H), 1.80–1.50 (m, 3H, 2′ & 3′H); ^{19}F NMR (DMSO-d_6): δ −227.96 (dt, J_{FH} = 47 Hz, J_{FH} = 23.5 Hz); MS *m/z* (%): 255 (M^+, 46), 204 (40), 165 (100).

3.2.5. 2-Amino-6-chloro-9-(4-hydroxy-3-hydroxymethylbutyl) purine (**8**)

Intermediate 2-amino-6-chloro-9-(4-acetoxy-3-acetoxymethylbutyl) purine (358 mg, 1.0 mmol) dissolving in THF (12 mL) was added a mixed solution of water (5 mL) and methanol (5 mL) containing potassium carbonate at 0 °C and the reaction was stirred for overnight at the same condition. When TLC analysis showed no starting material remained, solvent was removed by rotary evaporation, and the residue was transferred to the top of a silica gel column with the aid of THF and methanol. The column was eluted with 10% MeOH/CH_2Cl_2 to afford compound **8** as a white solid (212 mg, 78.4%). mp 141.6–142.0 °C; UV (EtOH): λ 223, 248 and 310 nm; IR (KBr): ν 3320, 3200, 2930, 1610, 1570, 1380, 1060 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.15 (s, 1H, C_8H), 4.05–4.15 (t, 2H, NCH_2, J = 7.3 Hz), 3.30–3.50 (m, 4H, OCH_2), 1.70–1.80 (m, 2H, CH_2CH), 1.40–1.50 (m, 1H, CH_2CH); MS *m/z* (%): 271 (M^+, 72), 240 (57), 170 (100).

3.2.6. 2-Amino-9-(4-hydroxy-3-hydroxymethylbutyl)-N,N,N-trimethyl-9H-purin-6-aminium chloride (**9**)

Ethanolic trimethylamine solution (9 mL) was cooled at 0 °C and added dropwise to a cooled solution of Compound

8 (813 mg, 3.0 mmol) in a mixture of anhydrous THF (30 mL) and DMF (10 mL) at 0 °C under nitrogen atmosphere. The resulting solution was warmed to room temperature slowly after addition of ethanolic trimethylamine and was stirred overnight. And the precipitated solid was filtered rapidly and washed with anhydrous ether (10 mL× 2). The salt was then dried at in vacuo to afford the resulting trimethylammonium chloride (896 mg, 90.5%). mp 168.1–170.5 °C; UV (EtOH): λ 225, 245, 320; IR (KBr): ν 3310, 2920, 1630, 1570, 1480, 1320, 1040 cm^{-1}; ^1H NMR (D_2O): δ 8.40 (s, 1H, C_8H), 4.20–4.30 (t, 2H, NCH_2, J = 7.42 Hz), 3.70 (s, 9H, $C(NH_3)_3$), 3.55–3.65 (m, 4H, OCH_2), 1.85–1.90 (m, 2H, CH_2CH), 1.65–1.60 (m, 1H, CH_2CH); MS *m/z* (%): 280 (M–CH_3Cl, 92), 249 (100), 191 (80).

*3.2.7. 2-Amino-6-fluoro-9-(4-hydroxy-3-hydroxymethylbutyl) purine (**3**)*

Compound **9** (165 mg, 0.5 mmol) dissolving in DMF (5 mL) was reacted with anhydrous KF (240 mg, 5 mmol) at 60 °C several hours until the TLC analysis showed no significant amount of starting material remained. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated to dryness in vacuo. The crude product was purified by column chromatography and was eluted with 10% MeOH/CH_2Cl_2. 111 mg of the desired product white solid was obtained in 87.3% yield. mp 173.5–175.4 °C; UV(EtOH): λ 306 nm; IR (KBr): ν 3320, 3310, 2930, 1660, 1570, 1410, 1220, 1030, 783, 625 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.10 (s, 1H, C_8H), 4.15–4.05 (t, 2H, 4′H–CH_2, J = 7.42), 3.45–3.30 (m, 4H, OCH_2), 1.80–1.70 (m, 2H, CH_2CH), 1.50–1.35 (m, 1H, CH_2CH); ^{19}F NMR (DMSO-d_6): δ −74.12 (s, 1F); MS *m/z* (%): 255 (M^+, 26), 224 (27), 153 (100).

*3.2.8. 2-Amino-6-dimethylamino-9-(4-hydroxy-3-hydroxymethylbutyl) purine (**10**)*

Compound **9** (165 mg, 0.5 mmol) dissolving in DMF (5 mL) was heated and stirred at 80 °C several hours until the TLC analysis showed no significant amount of starting material remained. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated to dryness in vacuo. The crude product was purified by column chromatography and eluted with 10% MeOH/CH_2Cl_2. 95.2 mg of the desired product yellow oil was obtained in 68%. IR (KBr): ν 3360, 2930, 1940, 1590, 1410, 1210, 1040, 783 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.70 (s, 1H, C_8H), 6.70 (s, 2H, NH_2), 4.58–4.52 (m, 2H, OH), 4.02–3.97 (t, 2H, 4′H–CH_2, J = 7.57 Hz), 3.55 (s, 6H, CNH_3), 3.45–3.26 (m, 4H, OCH_2), 1.70–1.65 (m, 2H, CH_2CH), 1.50–1.40 (m, 1H, CH_2CH); MS *m/z* (%): 280 (M^+, 96), 263 (40), 155 (100).

Acknowledgements

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