Synthesis of 8-Methoxypenciclovir and 8-Methoxyganciclovir through Methyl Triflate, a New Potential Approach to Label Penciclovir and Ganciclovir with Carbon-11

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Received 4 August 2003; revised 15 September 2003

Abstract: In an effort to make HSV-tk gene reporter probes 8-FPCV and 8-FGCV labeled with fluorine-18, via the nucelophilic substitution reaction of PCV and GCV quaternized methylamine salt precursors with KF/Kryptofix 2.2.2, a new and unusual reaction through methyl triflate was discovered. Subsequently, new compounds 8- MeOPCV and 8-MeOGCV were synthesized from PCV and GCV in six steps with 12% and 20% overall chemical yield, respectively, and a novel potential approach to label PCV and GCV with carbon-11 has been proposed.

Key words: gene reporter probes, herpes simplex virus thymidine kinase (HSV-tk), positron emission tomography (PET), 8-methoxypenciclovir, 8-methoxyganciclovir

Gene transfer technology has shown significant potential in treating several common cancers using a variety of viral and non-viral vectors.1–7 Among these, herpes simplex virus thymidine kinase (HSV-tk) has been used as a key drug-converting enzyme for a number of anticancer gene therapy approaches.8,9 The enzyme has a broad substrate specificity and can convert less toxic penciclovir (PCV, 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine, 1) or ganciclovir (GCV, 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine, 2) into toxic compounds that result in cell death.10 Imaging of HSV-tk expression is reliant on the use of enzyme imaging agents, fluorinated (fluorine-18) prodrugs such as fluorinated PCV and GCV analogs 8-[18F]fluoropenciclovir ([18F]FPCV, 3), 9-(4-[18F]fluorohydroxymethylbutyl)guanine ([18F]FHBG, 5) and 8-[18F]fluoroganciclovir ([18F]FGCV, 4), 9-[3-[18F]fluoro-1-hydroxy-2-propoxy)methyl]guanine ([18F]FHPG, 6), coupled with biomedical imaging technique positron emission tomography (PET).11–33 Considerable efforts have been devoted to the synthesis of these gene reporter probes and numerous improved synthesis were reported in the literature,11,12,25,29,30 in which [18F]FPCV and [18F]FGCV were labeled with fluorine-18 at 8-position of guanine ring of PCV and GCV; [18F]FHBG and [18F]FHPG were labeled with fluorine-18 at the side chain of PCV and GCV. The potential importance of these compounds as gene therapy imaging tools is great, and broader research investigation to fully explore and validate their utility is important. However, the limited commercial availability, complicated synthetic procedure and high costs of starting materials PCV and GCV can present an obstacle to more widespread evaluation of these intriguing agents. Wishing to study these compounds in this laboratory, we decided to make our own material by following the literature methods. Although several papers dealing with the synthesis of [18F]FPCV, [18F]FHBG and [18F]FGCV, [18F]FHPG from PCV and GCV have appeared, there are gaps in synthetic detail among them, and certain key steps gave poor yields or were difficult to repeat in our hands. Consequently, we investigated alternate approaches and modifications to make radiolabeled PCV and GCV analogs. In our previous works, we have reported an improved total synthesis of [18F]FHBG and [18F]FHPG starting from very starting materials 1,3-dibenzoyloxy-2-propanol and guanine, and triethyl-1,1,2-ethanetricarboxylate and 2-amino-6-chloropurine.34–36 In this ongoing study, we devoted our effort to make [18F]FPCV and [18F]FGCV. However, a new and unexpected reaction resulted in the synthesis of new compounds 8-methoxypenciclovir (8-MeOPCV) and 8-methoxyganciclovir (8-MeOGCV) from PCV and GCV, respectively, and the discovery of a novel potential approach to label PCV and GCV with carbon-11.

HSV-tk reporter probes [18F]FHBG and [18F]FHPG appear often in the literature, however, only a few papers reported the synthesis of [18F]FPCV and [18F]FGCV, and PET imaging study using these two tracers. The key problem is the difficulty in the synthetic methodology of [18F]FPCV and [18F]FGCV (Scheme 1), which limited their utility. The current method for labeling 8-position of a guanosine with fluorine-18 is an approach by the electrophilic reaction of the guanosine with elemental fluorine-18 gas,37 which is produced by a cyclotron equipped with a special gas target. Since fluorine gas is the most reactive chemical that can even ignite metal, the gas target and the system cost very high. Therefore fluorine-18 gas target is not available to most cyclotrons. This restrains the availability and research work of radiotracers [18F]FPCV and [18F]FGCV.

To circumvent this problem, we investigated the synthesis of [18F]FPCV and [18F]FGCV through the alternative approach by the nucelophilic substitution reaction of a precursor having a leaving group at 8-position of the
guanosine with potassium $[^{18}\text{F}]$fluoride (K$^{18}\text{F}$/Kryptofix 2.2.2 ($K_{2.2.2}$)). K$^{18}\text{F}$ is used to produce 2-$[^{18}\text{F}]$fluoro-2-deoxy-D-glucose (FDG), which is the only PET imaging agent used clinically at this point in time and is available to all PET imaging centers. Since K$^{18}\text{F}$ is available to most cyclotrons, we designed several possible precursors as shown in Scheme 2, which might lead to the synthesis of $[^{18}\text{F}]$FPCV by a nucleophilic substitution reaction with K$^{18}\text{F}$.

The precursor $N^2$-(p-anisyldiphenylmethyl)-8-bromo-9-[(4-p-anisyldiphenylmethoxy)-3-p-anisyldiphenylmethoxyethylbutyl]guanine (MTr–PCV–Br, 7) was synthesized as shown in Scheme 3. PCV, 1 was reacted with dilute bromine water solution at room temperature to afford 8-bromopenciclovir (BrPCV, 11) in 76% yield. The protection of all of the hydroxyl and 2-amino groups of BrPCV with 4-methoxytrityl chloride gave the precursor 7 in 67% yield. The selection of crowd methoxytrityl group as protecting group was based on its easily leaving...
under mild acidic condition. The mixture of 7 and anhydrous KF and phase transfer catalyst K$_2$2.2 or 18-crown-6 in anhydrous CH$_3$CN or DMF or DMSO was heated at elevated temperature for up to 2 days. No halogen exchange reaction occurred, and only starting material was isolated from the reaction mixture. Thus it was unable to make MTr–PCV–F, 12 through this approach.

The effort to prepare another possible precursor MTr–PCV–OTf, 8 was designed in Scheme 4. 11 was reacted with HOAc–NaOAc to give 8-hydroxy-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine (13) in 88% yield. Two acetyl groups of 13 were easily removed by aqueous CH$_3$NH$_2$ solution to afford 8-hydroxypenciclovir (HOPCV, 14) in 81% yield. 14 could not selectively block aliphatic hydroxyl and 2-amino groups, thus it was unable to prepare MTr–PCV–OH, 15. Subsequently, it is difficult to synthesize MTr–PCV–OTf, 8, because 8-OTf group could only be introduced by the reaction of 8-OH group with triflic anhydride (Tf$_2$O).

Finally, we attempted to construct a PCV quaternized methylamine salt MTr–PCV–N$^+\text{Me}_3$, 9 (Scheme 5) as a possible precursor for the synthesis of FPCV. 11 was reacted with aqueous (CH$_3$)$_2$NH solution to provide MTr–PCV–NMe$_2$, 16 in 95% yield. The protection of all of the hydroxyl and 2-amino groups of 16 by 4-methoxytrityl chloride gave the MTr–PCV–NMe$_2$, 17 in 52% yield. The reaction of 17 with methyl triflate gave a possible intermediate N$^2$-(p-anisylidiphenylmethyl)-7-methyl-8-dimethylamino-9-[(4-p-anisylidiphenylmethoxy)-3-p-anisylidiphenylmethoxymethylbutyl]guanino-8-triflate (18) in 98% yield, rather than quaternary ammonium salt 9, the product anticipated to arise via the methylation of compound 17, since the $^1$H NMR spectrum of 18 showed discrete single peaks of 7-CH$_3$ and 8-NMe$_2$. The subsequent reaction of 18 with KF/K$_2$2.2 failed to give 12, and only the starting material was recovered.

The construction of a similar PCV quaternized methylamine salt Ac–PCV–N$^+\text{Me}_3$, 10 (Scheme 6) was also at-
tempted. The protection of all of the hydroxyl and 2-amino groups of 16 by Ac₂O gave Ac–PCV–NMe₂, 19 in 74% yield. Similarly, the reaction of 19 with methyl triflate gave a possible intermediate N²-acetyl-7-methyl-8-dimethylamino-9-[4-acetoxy-3-(acetoxymethyl)butyl]-guanine-8-triflate (20) in nearly quantitative yield, rather than quaternary ammonium salt 10. Likewise, the ¹H NMR spectrum of 20 observed two different methyl proton NMR resonances of 7-CH₃ and 8-NMe₂. The compound 20 was fairly stable when it was heated, but it was decomposed after it was stored for a few days. The subsequent reaction of 20 with KF/K₂.2.2 failed to afford Ac–PCV–F, 23, the product anticipated to arise via the nucleophilic substitution reaction. Instead, an unusual reaction through methyl triflate was discovered, and there was obtained an unexpected product Ac–PCV–OMe, 21 in 30% yield. 21 was easily deprotected by aqueous CH₃NH₂ solution to give 8-methoxypenciclovir (MeOPCV, 22) in 77% yield.

To further study the existence of the intermediate of PCV analogs reacted with methyl triflate and the unexpected reaction led to synthesis of MeOPCV, another synthetic approach was designed as shown in Scheme 7. PCV, 1 was reacted with Ac₂O to afford Ac–PCV, 24 in 55% yield. The reaction of 24 with methyl triflate gave a possible intermediate N²-acetyl-7-methyl-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine-8-triflate (25) in nearly quantitative yield. The subsequent reaction of 25 with KF/K₂.2.2 failed to provide 21. Therefore, we can conclude that 8-dimethylamino group is necessary for the unexpected reaction.

In view of the novelty of the synthesis of MeOPCV, we investigated the utility of the unexpected reaction for the synthesis of 8-methoxyganciclovir (MeOGCV, 31) as shown in Scheme 8. GCV, 2 was reacted with dilute bromine water solution at room temperature to afford 8-bromoganciclovir (BrGCV, 26) in 62% yield. 26 was reacted

Scheme 6

Scheme 7
with aqueous (CH$_3$)$_2$NH$_2$ solution to provide Me$_2$NGCV, 27 in 94% yield. The protection of all of the hydroxyl and 2-amino groups of 27 by Ac$_2$O gave the Ac–GCV–NMe$_2$, 28 in 81% yield. The reaction of 28 with methyl triflate gave a possible intermediate N$^2$-acetyl-7-methyl-8-dimethylamino-9-[(1,3-diacetoxy-2-propoxy)methyl]guanine-8-triflate (29) in nearly quantitative yield. The reaction of 29 with KF/K$_2$CO$_3$ afforded Ac-GCV-OMe, 30 in 48% yield. 30 was easily deprotected by aqueous CH$_3$NH$_2$ solution to give MeOGCV, 31 in 87% yield.

The mechanism for the possible pathway to the observed 8-methoxy derivatives of guanines via sequential treatment of MeOTf and KF/K$_2$CO$_3$ was speculated in Scheme 9. 8-Dimethylaminoguanine derivative (19 or 28)
reacted with MeOTf through several ylide transition structures or iminium (urea) species as intermediates to form one of the possible intermediates (20 or 29). Then base KF attacked the trityl group in the intermediate through another ylide transition structure or iminium (urea) species intermediate to give 8-methoxyguanine derivative (21 or 30), or directly to give an unstable iminium (urea) species intermediate, which quickly isomerized to compound 21 or 30. This mechanism speculation is supported by the evidence of the observation of two different methyl proton NMR resonances of the possible intermediates 18, 20, 25 and 29. Since the 8-methoxy group in MeOPCV and MeOGCV was introduced through methyl triflate, this might be a new potential methodology to label PCV and GCV with \([11 \text{C}]\)methyl triflate 45–48 to produce 8-[11 \text{C}]methoxy-PCV and 8-[11 \text{C}]methoxy-GCV. A potential approach to label PCV and GCV with carbon-11 has been proposed as shown in Scheme 10.

In summary, MeOPCV was synthesized from PCV in six steps with 12% overall chemical yield, and MeOGCV was synthesized from GCV in six steps with 20% overall chemical yield, a new and unusual reaction through methyl triflate to introduce methoxyl group to C-8 position of the guanine derivatives PCV and GCV was discovered, which provides a novel potential synthetic access to carbon-11 labeled PCV and GCV analogs. The possible mechanism of the unexpected reaction was suggested. More extensive investigation will be required to determine the details of the mechanism, the roles of methyl triflate and KF/K2.2.2 involved in the reaction, and the adducts of methyl triflate with PCV and GCV derivatives.

All commercial reagents and solvents were used without further purification unless otherwise specified. Melting points were determined on a MEL-TEMP II capillary tube apparatus and were uncorrected. \(^1\)H NMR spectra were recorded on a Bruker QE 300 MHz NMR spectrometer using TMS as an internal standard. Chemical shift data for the proton resonances were reported in ppm (\(\delta\)) relative to internal standard TMS (\(\delta=0.0\)). The low-resolution mass spectra were obtained using a Bruker Biflex III MALDI-Tof mass spectrometer, and the high-resolution mass measurements were obtained using a Kratos MS80 mass spectrometer, in the Department of Chemistry at Indiana University. Chromatographic solvent proportions are expressed on a v/v basis. TLC was run using Analtech silica gel GF uniplates (5 \(\times\) 10 cm\(^2\)). Plates were visualized by UV light. Normal phase flash chromatography was carried out on EM Science silica gel 60 (230–400 mesh) with a forced flow of the indicated solvent system in the proportions described below. All moisture-sensitive reactions were performed under a positive pressure of \(\text{N}_2\) maintained by a direct line from a \(\text{N}_2\) source.

The starting materials PCV and GCV were synthesized in our previous work. 34–36 8-Bromo-9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (BrPCV, 11; Typical Procedure) PCV, 1 (1.00 g, 3.95 mmol) was suspended in water (50 mL). Under vigorous stirring, \(\text{Br}_2\) water solution (0.20 M, 30 mL, 5.86 mmol) was added dropwise in a period of 30 min using a syringe. The mixture became homogeneous, and later precipitate formed. After addition the mixture was stirred at r.t. for another 30 min. The solid was filtered, washed with water (2 \(\times\) 5 mL) and acetone (5 mL), and dried under vacuum to give an off-white solid 11 (1.09 g, 76%); mp 236–238 °C; \(R_f\) 0.21 (CH\(_3\)CN–H\(_2\)O, 95:5).

\(^1\)H NMR (DMSO-\(d_6\); \(\delta=10.68\) (s, 1 H, 1-NH), 6.57 (s, 2 H, 2-\(\text{NH}_2\)), 4.43 (s, 2 H, \(\text{OH}\)), 3.97 (t, \(J=7.35\) Hz, 2 H, 1'-\(\text{CH}_2\)), 3.20–3.55 (m, 4 H, 4'-\(\text{CH}_2\)), 1.56–1.76 (m, 2 H, 2'-\(\text{CH}_2\)), 1.35–1.56 (m, 1 H, 3'-\(\text{CH}\)).

LRMS (CI, CH\(_3\)I): \(m/z\) (%): 252.1 (100), 331.0 (41) [M\(^+\)].
HRMS (CI, CH₄): m/z calc'd for C₁₀H₁₄BrN₂O₂: 331.0280; found: 331.0280

N²-(p-Anisylidinophenylmethyl)-8-bromo-9-[(4-p-anisylidinophenylmethoxy)-3-p-anisylidinophenylmethylbutyl]guanine (MTr-PCV-Br, 7); Typical Procedure
The mixture of 11 (0.10 g, 0.30 mmol), 4-methoxytrityl chloride (MTrCl, 0.40 g, 1.30 mmol), DMAP (0.010 g, 0.082 mmol), DMF (10 mL), and Et₂N (0.4 mL, 2.87 mmol) was stirred at 50–60 °C for 3 h. After cooling to r.t., the mixture was diluted with EtOAc and washed with water. The aq layer was extracted with another portion of EtOAc. The combined organic layer was washed once with brine, and dried to give a yellowish solid. The residue was dissolved in small amount of CH₂Cl₂, transferred to the top of a silica gel column and eluted with 2.5% MeOH–CH₂Cl₂ to give 7 (0.23 g, 67%); mp >135 °C (dec.); Rf 0.18 (CH₂Cl₂–MeOH, 15:1).

1H NMR (CDCl₃): δ = 6.60–7.45 (m, 42 H, aromatic), 3.75 (s, 6 H, 9-OCH₃), 3.67 (br s, 3 H, 2-OCH₃), 3.56 (br s, 2 H, 1′-CH₃). 13C NMR (CDCl₃): δ = 114.8 (100), 111.3 (0.1) [M + H]⁺.

HRMS (CI, CH₄): m/z (%) = 353.1 (100) [M⁺].

HRMS (CI, CH₄): m/z calc'd for C₁₄H₁₉N₅O₆: 353.1335; found: 353.1329.

N²-(p-Anisylidinophenylmethyl)-8-dimethylamino-9-[(4-p-anisylidinophenylmethoxy)-3-p-anisylidinophenylmethylbutyl]guanine (MTr-PCV-NMe₂, 17); Typical Procedure
MTrCl (0.79 g, 2.56 mmol) and DMAP (0.019 g, 0.16 mmol) were dissolved in anhyd DMF (20 mL) and Et₂N (0.8 mL, 5.74 mmol). The mixture was stirred at 50–60 °C for 3 h. After cooling to r.t., the mixture was diluted with EtOAc and washed with brine. The aq layer was extracted with another portion of EtOAc. The combined organic layer was washed with brine, dried over MgSO₄, and evaporated under vacuum. The brown liquid residue was transferred to the top of a silica gel column and eluted with 2.5–3.0% MeOH–CH₂Cl₂ to give 17 (0.37 g, 52%); mp 140 °C (dec.); Rf 0.30 (5% MeOH–CH₂Cl₂).

1H NMR (DMSO-d₆): δ = 10.35 (s, 1 H, 1-NH, D₂O exchangeable), 7.48 (s, 1 H, 2-NH, D₂O exchangeable), 6.60–7.35 (m, 42 H, aromatic), 3.73 (s, 6 H, 4'-OCH₃), 3.60 (s, 3 H, 3'-OCH₃), 3.12–3.26 (m, 2 H, 1'-CH₂), 2.62–2.89 (m, 4 H, 4'-CH₂), 2.49 (s, 6 H, 8-NCH₃), 1.56–1.72 (m, 1 H, 3'-CH), 1.00–1.18 (m, 2 H, 2'-CH₂).

HRMS (EI): m/z (%) = 273.0 (100), 1113.5 (0.1) [M + H]⁺.

HRMS (EB): m/z (%) = 296.2 (100) [M⁺].

HRMS (FAB): m/z (%) calc'd for C₁₄H₁₉N₅O₆: 296.1572; found: 296.1539.

N²-(p-Anisylidinophenylmethyl)-7-methyl-8-dimethylamino-9-[(4-p-anisylidinophenylmethoxy)-3-p-anisylidinophenylmethylbutyl]guanine-triflate (18); Typical Procedure
MTrCl (0.050 g, 0.17 mmol) was dissolved in anhyd CH₂Cl₂ (10 mL). Under an ice-salt bath methyl triflate (6 µL, 0.053 mmol) was added. The solution was stirred and allowed to warm to r.t slowly overnight. The solvent was removed under vacuum, and the residue was dried under vacuum overnight to give a brown solid 18 (0.056 g, 98%); mp 100 °C (dec.); Rf 0.38 (7% MeOH–CH₂Cl₂).

1H NMR (DMSO-d₆): δ = 11.13 (s, 1 H, 1-NH, D₂O exchangeable), 7.98 (s, 1 H, 2-NH, D₂O exchangeable), 6.59–7.38 (m, 42 H, aromatic), 3.73 (s, 6 H, 4'-OCH₃), 3.64 (s, 3 H, 3'-OCH₃), 3.59 (s, 3 H, OCH₃), 3.26–3.43 (m, 2 H, 1'-CH₂), 2.93 (s, 6 H, 8-NCH₃), 2.60–2.96 (m, 4 H, 4'-CH₂), 1.78–1.94 (m, 1 H, 3'-CH), 1.04–1.29 (m, 2 H, 2'-CH₂).

N²-Acetyl-8-dimethylamino-9-[(4-acetoxy-3-acetoxymethyl)butyl]guanine (19); Typical Procedure
The solution of 16 (0.050 g, 0.17 mmol), DMAP (0.004 g, 0.33 mmol) and Ac₂O (0.2 mL, 2.12 mmol) in pyridine (5 mL) was refluxed under N₂ for 1 h until TLC showed that the starting material was gone. After cooling to r.t., water (0.5 mL) was added and the mixture was stirred for 15 min. After evaporation of volatiles, the brown residue was dissolved in a small amount of CH₂Cl₂, and transferred to the top of a silica gel column and eluted with CH₂Cl₂–MeOH (20:1) to afford 19 (0.053 g, 74%); mp 155–157 °C; Rf 0.32 (CH₂Cl₂–MeOH, 15:1).

1H NMR (DMSO-d₆): δ = 11.95 (br s, 1 H, NH, D₂O exchangeable), 11.59 (br s, 1 H, NH, D₂O exchangeable), 3.93–4.09 (m, 6 H, 1'-CH₂).
CH₃ and 4°CH₂), 2.79 (s, 6 H, 8-NCH₃), 2.16 (s, 3 H, 2'-CH₃), 1.98 (s, 6 H, CH₂CO₂), 1.74−1.91 (m, 3 H, 2'-CH₃ and 3'-CH).

LRMS (EI): m/z (%) = 422.2 (100) [M⁺].

HRMS (EI): m/z calc for C₁₆H₂₃N₅O₇: 422.1914; found: 422.1924.

N₂-Acetyl-7-methyl-8-dimethylamino-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine-8-triflate (20); Typical Procedure

To a cold solution of 19 (0.050 g, 0.12 mmol) in anhyd CH₂Cl₂ (10 mL) was added methyl triflate (16 μL, 0.14 mmol) dropwise under an ice-salt bath. The solution was stirred and allowed to warm up to r.t. slowly overnight. Volatiles were removed under vacuum to give a brown solid 20 (0.069 g, ca 100%); Rₛ 0.18 (CH₂Cl₂–MeOH, 15:1).

1H NMR (CDMSO-d₆): δ = 12.47 (s, 1 H, NH, D₂O exchangeable), 11.97 (s, 1 H, NH, D₂O exchangeable), 4.15 (t, J = 7.36 Hz, 2 H, 1'-CH₂), 3.04 (d, J = 5.14 Hz, 4 H, 4°-CH₂), 3.85 (s, 3 H, 7-CH₃), 3.15 (s, 6 H, 8-NCH₃), 2.21 (s, 3 H, 2-CH₃CON), 2.01 (s, 6 H, CH₂CO₂), 1.94−2.06 (m, 1 H, 3'-CH₂), 1.74−1.88 (m, 2 H, 2'-CH₂).

LRMS (EI): m/z (%) = 278.1 (100), 379.2 (71) [M⁺].

HRMS (EI): m/z calc for C₁₇H₂₄N₆O₇: 379.1492; found: 379.1501.

8-Bromo-9-(1,3-dihydroxy-2-propoxy)methylguanine (BrGCV, 26); Typical Procedure

GCV, 2 (0.53 g, 2.08 mmol) was suspended in water (20 mL). Under vigorous stirring, Br₂ water solution (0.20 M, 16 mL, 3.12 mmol) was added dropwise in a period of 30 min using a syringe. The mixture became homogeneous, and later precipitate formed. After addition the mixture was stirred at r.t. for another 30 min. The solid was filtered, washed with water (2 x 5 mL) and acetone (5 mL), and dried under vacuum to give an off-white solid 26 (0.43 g, 62%); mp >300 °C.

1H NMR (CDCl₃): δ = 12.57 (s, 1 H, 1-NH), 12.12 (s, 1 H, 2-NH), 9.48 (s, 1 H, 8-CH₂), 4.31 (t, J = 7.35 Hz, 2 H, 1'-CH₂), 4.07 (s, 3 H, 7-CH₃), 4.04 (d, J = 5.14 Hz, 4 H, 4°-CH₂), 2.22 (s, 3 H, 2'-CH₂CON), 2.01 (s, 6 H, CH₂CO₂), 1.84−2.11 (m, 11 H, 2'-CH₂ and 3'-CH₂).

LRMS (EI): m/z (%) = 278.1 (100), 379.2 (71) [M⁺].

HRMS (EI): m/z calc for C₁₇H₂₄N₆O₇: 379.1492; found: 379.1501.

8-Dimethylamino-9-(1,3-dihydroxy-2-propoxy)methylguanine (MeNGCV, 27); Typical Procedure

A solution of 26 (0.20 g, 0.60 mmol) in (CH₂)₅NH (40% aq solution, 10 mL) was heated at 130 °C for 48 h until TLC showed that the starting material was gone. After cooling to r.t., silica gel was added to absorb the solution, dried under vacuum, and transferred to the top of a silica gel column and eluted with CH₃CN–H₂O to give a white solid 27 (0.17 g, 94%); mp >225 °C (dec.). Rₛ 0.28 (CH₃CN–H₂O, 9:1).

1H NMR (CDCl₃): δ = 10.46 (s, 1 H, 1-NH), 6.62 (br s, 2 H, 2'-NH), 5.38 (s, 2 H, 1'-CH₂), 4.18 (br s, 2 H, OH), 3.50−3.65 (m, 1 H, 3'-CH₂), 3.20−3.30 (m, 4 H, 4°-CH₂).

LRMS (EI): m/z (%) = 294.1 (100), 298.1 (23) [M⁺].

HRMS (EI): m/z calc for C₁₇H₂₄N₆O₇: 298.1390; found: 298.1380.
N2-Acetyl-8-dimethylamino-9-[(1,3-diacteox-2-propoxy)methyl]guanine (Ac-GCV-OMe, 30); Typical Procedure

The solution of 27 (0.20 g, 0.67 mmol), DMAP (0.016 g, 0.13 mmol) and Ac2O (0.8 mL, 8.48 mmol) in anhyd pyridine (15 mL) was refluxed under N2 for 2 h until TLC showed that the starting material was gone. After cooling to r.t., water (3 mL) was added and the mixture was stirred for 15 min. After evaporation of volatiles, the brown residue was dissolved in a small amount of CH2Cl2 and transferred to top of a silica gel column and eluted with CH2Cl2–MeOH (30:1) to afford 28 (0.229 g, 81%); mp 90 °C (dec.); Rf 0.18 (CH2Cl2–MeOH, 25:1).

\( \text{HRMS (FAB): } m/z \text{ calcd for C}_{17} \text{H}_{24} \text{N}_{6} \text{O}_{7} : 424.1713; \text{ found: 424.1713.} \)

References


