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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Abstract: In an effort to make HSV-tk gene reporter probes 8-FPCV and 8-FGCV labeled with fluorine-18, via the nucleophilic 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 prodrug-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-[^{18}F]fluoropenciclovir ([^{18}F]FPCV, **3**), 9-(4-[^{18}F]fluoro-3-hydroxymethylbutyl)guanine ([^{18}F]FHBG, **5**) and 8-[^{18}F]fluoroganciclovir ([^{18}F]FGCV, **4**), 9-{(3-[^{18}F]fluoro-1-hydroxy-2-propoxy)methyl}guanine ([^{18}F]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 [^{18}F]FPCV and [^{18}F]FGCV were labeled with fluorine-18 at 8-position of guanine ring of PCV and GCV; [^{18}F]FHBG and [^{18}F]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 [^{18}F]FPCV, [^{18}F]FHBG and [^{18}F]FGCV, [^{18}F]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 [^{18}F]FHBG and [^{18}F]FHPG starting from very starting materials 1,3-dibenzyloxy-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 [^{18}F]FPCV and [^{18}F]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 [^{18}F]FHBG and [^{18}F]FHPG appear often in the literature, however, only a few papers reported the synthesis of [^{18}F]FPCV and [^{18}F]FGCV, and PET imaging study using these two tracers. The key problem is the difficulty in the synthetic methodology of [^{18}F]FPCV and [^{18}F]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 [^{18}F]FPCV and [^{18}F]FGCV.

To circumvent this problem, we investigated the synthesis of [^{18}F]FPCV and [^{18}F]FGCV through the alternative approach by the nucleophilic substitution reaction of a precursor having a leaving group at 8-position of the

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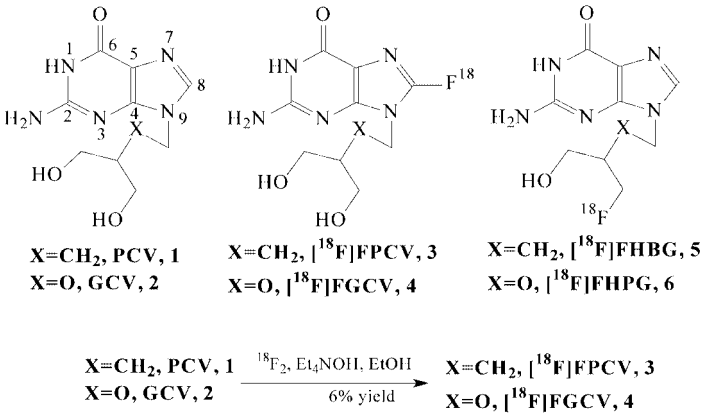
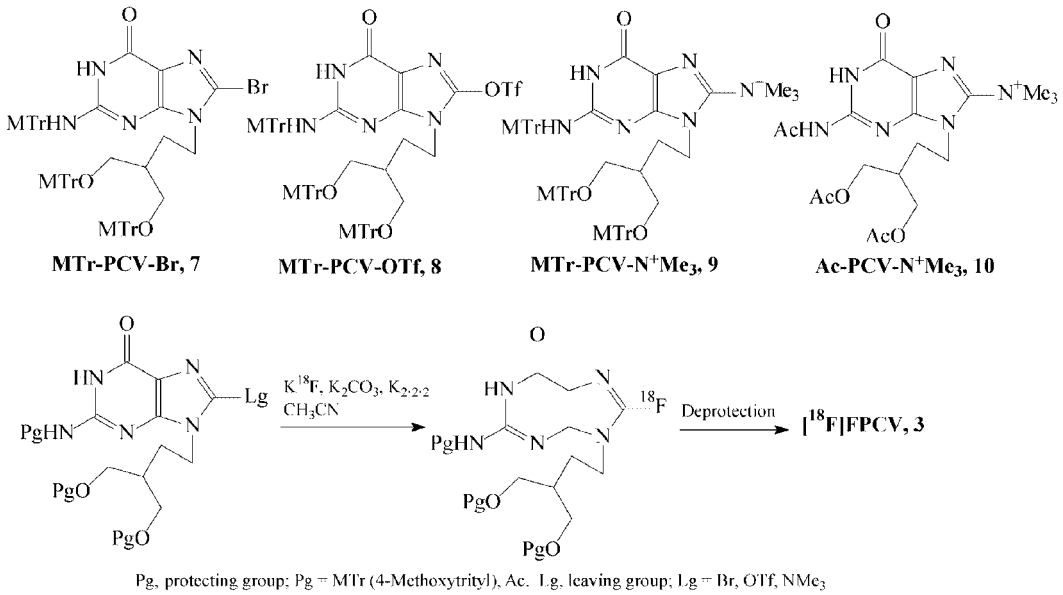


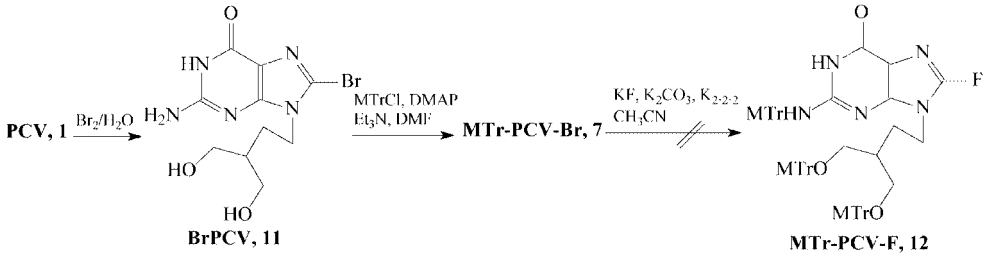
Scheme 1

guanosine with potassium [^{18}F]fluoride (K^{18}F)/Kryptofix 2.2.2 ($K_{2.2.2}$). K^{18}F is used to produce 2-[^{18}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.[38] Since K^{18}F is available to most cyclotrons, we designed several possible precursors as shown in Scheme 2, which might lead to the synthesis of [^{18}F]FPCV by a nucleophilic substitution reaction with K^{18}F.

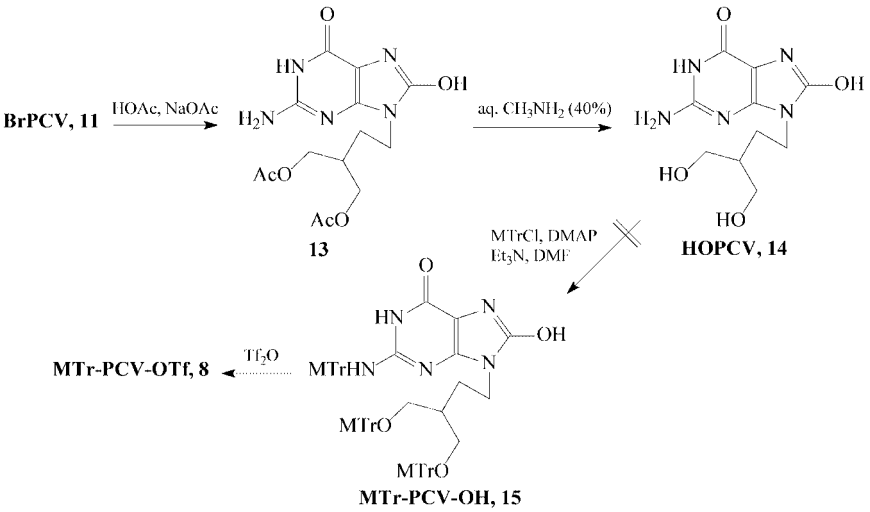
The precursor N^2-(*p*-anisyldiphenylmethyl)-8-bromo-9-[(4-*p*-anisyldiphenylmethoxy)-3-*p*-anisyldiphenylmethoxymethylbutyl]guanine (MTr–PCV–Br, **7**) was synthesized as shown in Scheme 3. PCV, **1** was reacted with dilute bromine water solution[39] at room temperature to afford 8-bromopenciclovir (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



Scheme 2



Scheme 3



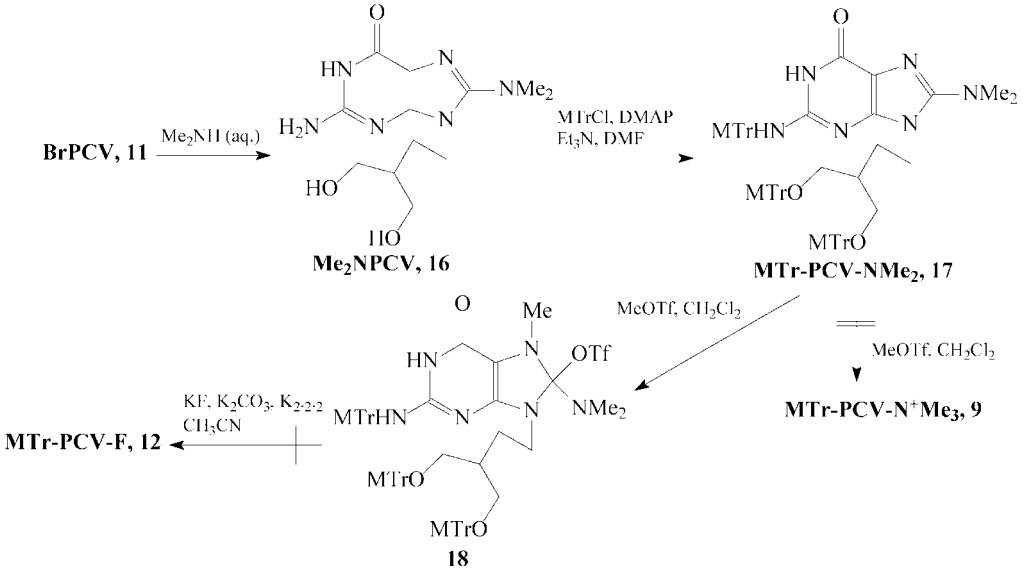
Scheme 4

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_3CN 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.

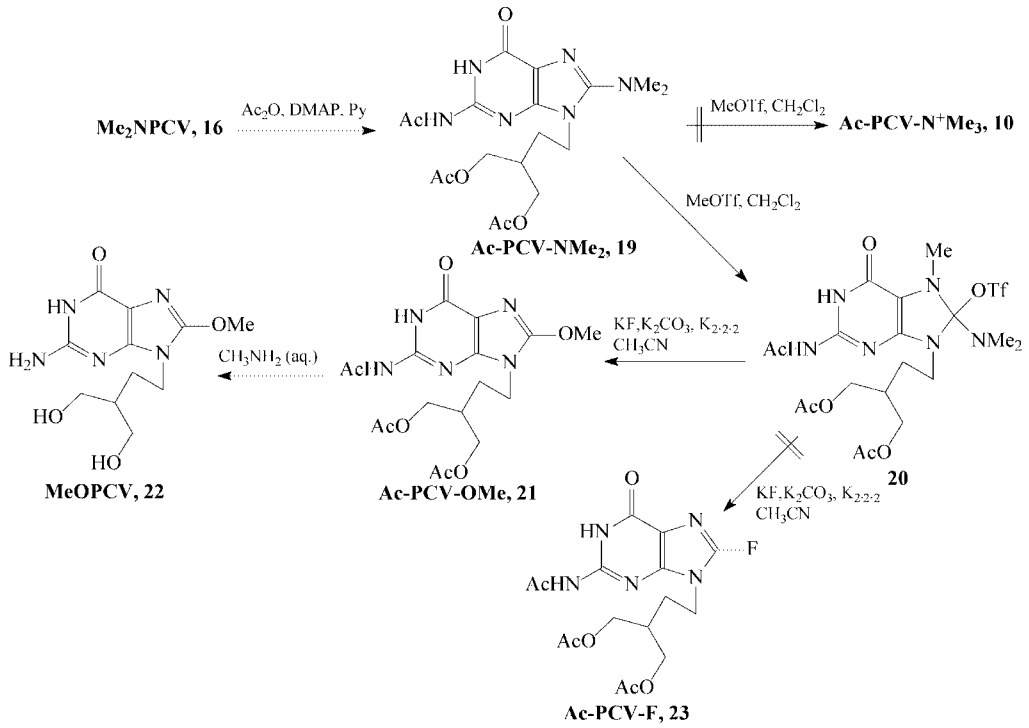
The effort to prepare another possible precursor MTr–PCV–OTf, **8** was designed in Scheme 4. **11** was reacted with HOAc–NaOAc[40] to give 8-hydroxy-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine (**13**) in 88% yield. Two acetyl groups of **13** were easily removed by aqueous CH_3NH_2 solution[41] to 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_2O).

Finally, we attempted to construct a PCV quaternized methylamine salt MTr–PCV–N^+Me_3, **9** (Scheme 5) as a possible precursor for the synthesis of FPCV. **11** was reacted with aqueous $(CH_3)_2NH$ solution[42,43] to provide Me_2NPCV, **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[44] gave a possible intermediate N^2-(*p*-anisyldiphenylmethyl)-7-methyl-8-dimethylamino-9-[(4-*p*-anisyldiphenylmethoxy)-3-*p*-anisyldiphenylmethoxymethylbutyl]guanine-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^+Me_3, **10** (Scheme 6) was also at-



Scheme 5

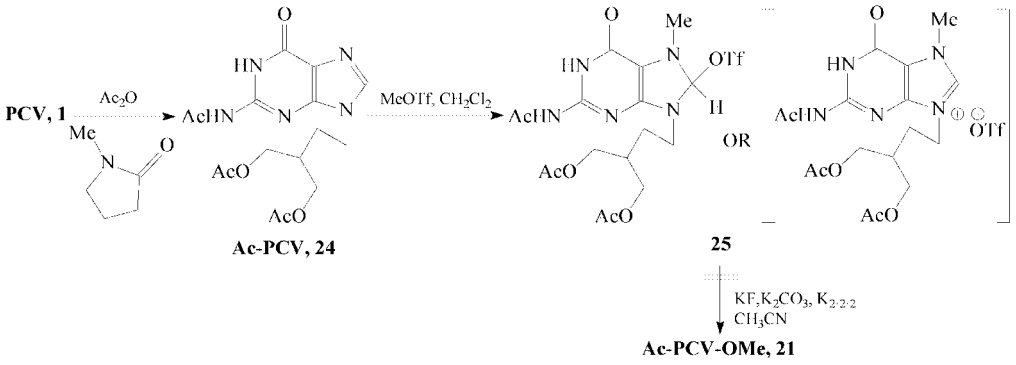


Scheme 6

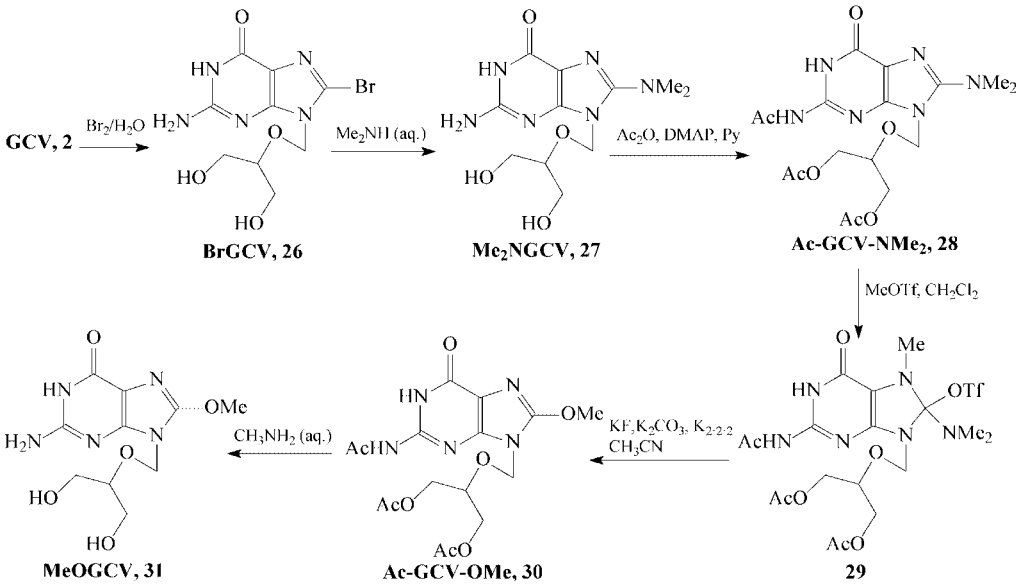
tempted. The protection of all of the hydroxyl and 2-amino groups of **16** by Ac_2O gave Ac–PCV–NMe_2, **19** in 74% yield. Similarly, the reaction of **19** with methyl triflate gave a possible intermediate N^2-acetyl-7-methyl-8-dimethylamino-9-[4-acetoxy-3-(acetoxymethyl)butyl]-guanine-8-triflate (**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-CH_3 and 8-NMe_2. 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/$K_{2.2.2}$ 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 CH_3NH_2 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 Ac_2O to afford Ac–PCV, **24** in 55% yield. The reaction of **24** with methyl triflate gave a possible intermediate N^2-acetyl-7-methyl-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine-8-triflate (**25**) in nearly quantitative yield. The subsequent reaction of **25** with KF/$K_{2.2.2}$ 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[39] at room temperature to afford 8-bromoganciclovir (BrGCV, **26**) in 62% yield. **26** was reacted



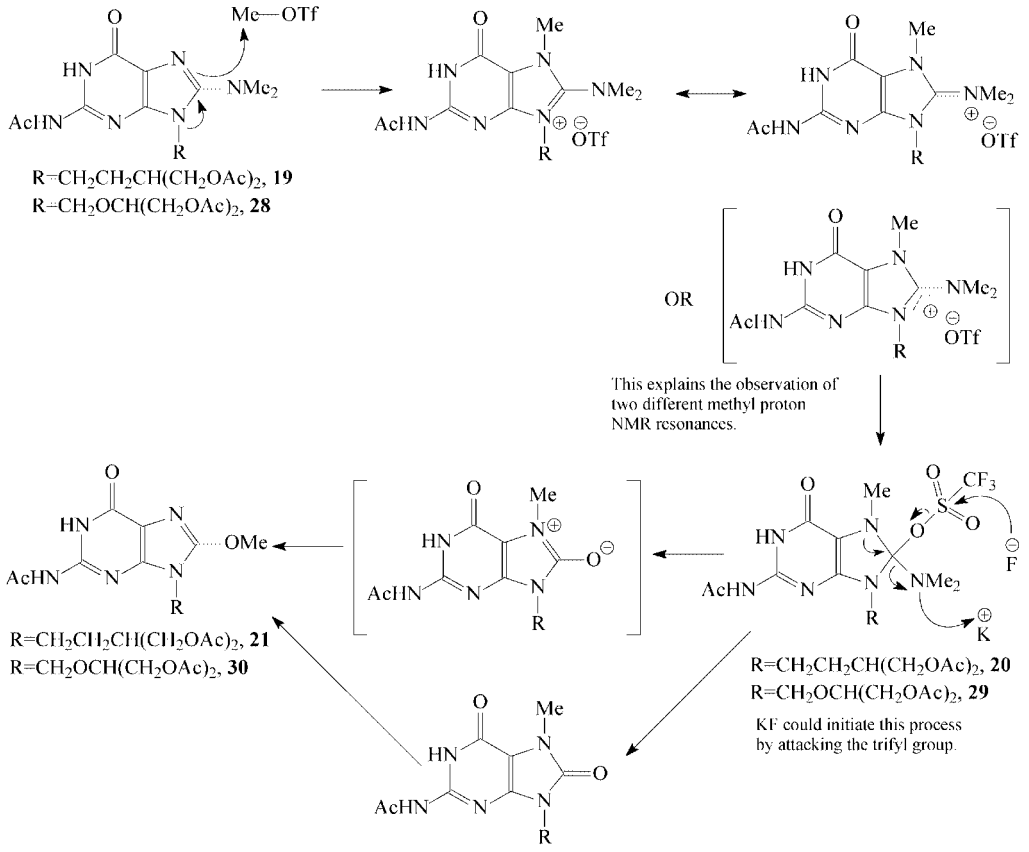
Scheme 7



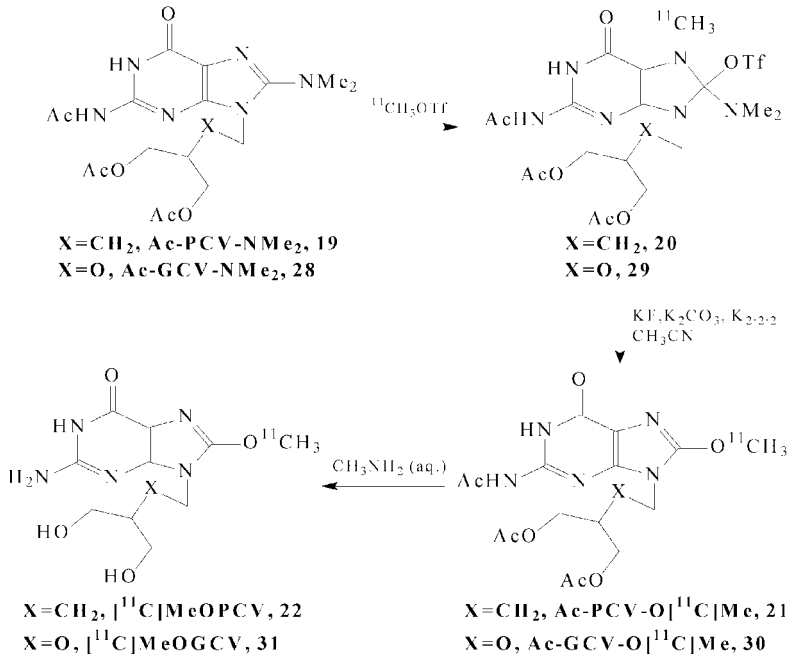
Scheme 8

with aqueous $(CH_3)_2NH_2$ solution to provide Me_2NGCV, **27** in 94% yield. The protection of all of the hydroxyl and 2-amino groups of **27** by Ac_2O 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/$K_{2.2.2}$ afforded Ac-GCV-OMe, **30** in 48% yield. **30** was easily deprotected by aqueous CH_3NH_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/$K_{2.2.2}$ was speculated in Scheme 9. 8-Dimethylaminoguanine derivative (**19** or **28**)



Scheme 9



Scheme 10

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 trifyl 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}C]methyl triflate[45–48] to produce 8-[^{11}C]methoxy-PCV and 8-[^{11}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/$K_{2.2.2}$ 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 (δ) relative to internal standard TMS (δ = 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 × 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 N_2 maintained by a direct line from a 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, 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 × 5 mL) and acetone (5 mL), and dried under vacuum to give an off-white solid **11** (1.09 g, 76%); mp 236–238 ºC; R_f 0.21 (CH_3CN–H_2O, 95:5).

^{1}H NMR (DMSO-d_6): δ = 10.68 (s, 1 H, 1-NH), 6.57 (s, 2 H, 2-NH_2), 4.43 (s, 2 H, OH), 3.97 (t, J = 7.35 Hz, 2 H, 1′-CH_2), 3.20–3.55 (m, 4 H, 4′-CH_2), 1.56–1.76 (m, 2 H, 2′-CH_2), 1.35–1.56 (m, 1 H, 3′-CH).

LRMS (CI, CH_4): m/z (%) = 252.1 (100), 331.0 (41) [M$^+$].

HRMS (CI, CH_4): *m*/*z* calcd for $C_{10}H_{14}BrN_5O_3$: 331.0280; found: 331.0280

N^2-(*p*-Anisyldiphenylmethyl)-8-bromo-9-[(4-*p*-anisyldiphenylmethoxy)-3-*p*-anisyldiphenylmethoxymethylbutyl]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 Et_3N (0.4 mL, 2.87 mmol) was stirred at 50–60 ºC 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 solid residue was dissolved in small amount of CH_2Cl_2, transferred to the top of a silica gel column and eluted with 2.5% MeOH–CH_2Cl_2 to give **7** (0.23 g, 67%); mp >135 ºC (dec.); R_f 0.33 (4% MeOH–CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 6.60–7.45 (m, 42 H, aromatic), 3.75 (s, 6 H, 9-OCH_3), 3.67 (s, 3 H, 2-OCH_3), 3.56 (br s, 2 H, 1′-CH_2), 3.00–3.20 (m, 4 H, 4′-CH_2), 1.70–1.84 (m, 1 H, 3′-CH), 1.40–1.53 (m, 2 H, 2′-CH_2).

LRMS (EI): *m*/*z* (%) = 273 (100), 1148 (1.9) $[M + H]^+$.

HRMS (FAB): *m*/*z* calcd for $C_{70}H_{63}BrN_5O_6$: 1148.3962; found: 1148.3925.

8-Hydroxy-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine (13); Typical Procedure

The mixture of **11** (0.050 g, 0.15 mmol), NaOEt (0.070 g, 0.85 mmol) and AcOH (5 mL) was heated to reflux (160 ºC) for 4 h. After cooling, solvent was removed at reduced pressure. MeOH was added to dissolve the solid residue, and then silica gel was added to absorb the MeOH solution. MeOH was then stripped, and the dry silica gel was transferred to the top of a silica gel column and eluted with CH_2Cl_2–MeOH (15:1–6:1) to afford **13** (0.047 g, 88%); mp 65 ºC (dec.); R_f 0.18 (CH_2Cl_2–MeOH, 15:1).

^{1}H NMR (DMSO-d_6): δ = 10.68 (br s, 1 H, 8-OH), 10.54 (s, 1 H, 1-NH), 6.46 (s, 2 H, 2-NH_2), 3.91–4.09 (m, 4 H, 4′-CH_2), 3.65 (t, *J* = 7.35 Hz, 2 H, 1′-CH_2), 1.98 (s, 6 H, 4′-CH_3CO_2), 1.85–2.00 (m, 1 H, 3′-CH), 1.60–1.72 (m, 2 H, 2′-CH_2).

LRMS (CI, CH_4): *m*/*z* (%) = 353.1 (100) $[M^+]$.

HRMS (CI, CH_4): *m*/*z* calcd for $C_{14}H_{19}N_5O_6$: 353.1335; found: 353.1329.

8-Hydroxy-9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (HOPCV, 14); Typical Procedure

13 (0.030 g, 0.085 mmol) was dissolved in aq CH_3NH_2 solution (40%, 5 mL). The solution was heated at 75 ºC for 2 h. After cooling to r.t., the reaction mixture was evaporated to dryness. The colorless solid was washed with cold water, and dried under vacuum to give a white solid **14** (0.019 g, 81%); mp 285 °C (dec.).

^{1}H NMR (DMSO-d_6): δ = 10.49 (br s, 2 H, 1-NH, 8-OH, D_2O exchangeable), 6.45 (s, 2 H, 2-NH_2, D_2O exchangeable), 4.35 (br s, 2 H, OH, D_2O exchangeable), 3.64 (t, *J* = 6.25 Hz, 2 H, 1′-CH_2), 3.20–3.50 (m, 4 H, 4′-CH_2), 1.50–1.68 (m, 2 H, 2′-CH_2), 1.38–1.50 (m, 1 H, 3′-CH).

LRMS (EI): *m*/*z* (%) = 167.0 (100), 269.1 (42) $[M^+]$.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{15}N_5O_4$: 269.1124; found: 269.1121.

8-Dimethylamino-9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (Me_2NPCV, 16); Typical Procedure

A solution of **11** (0.10 g, 0.30 mmol) in $(CH_3)_2NH$ (40% aq solution, 5 mL) was heated at 130 °C for 48 h until TLC showed that the starting material was gone. Volatiles were evaporated to dryness. The residue was dissolved in hot water, filtered, concentrated to a small volume, and then cooled down at 4 °C for recrystallization. A white solid was filtered off and dried under vacuum to give **16** (0.071 g). The filtrate was absorbed on silica gel, dried under vacuum, transferred on the top of a silica gel column, and eluted with CH_3CN–H_2O (12:1) to give **16** (0.014 g, 95%); mp 250 °C; R_f 0.24 (CH_3CN–H_2O, 9:1).

^{1}H NMR (DMSO-d_6): δ = 10.35 (s, 1 H, 1-NH), 6.29 (s, 2 H, 2-NH_2), 4.41 (t, *J* = 5.15 Hz, 2 H, OH), 3.88 (t, *J* = 7.36 Hz, 2 H, 1′-CH_2), 3.25–3.50 (m, 4 H, 4′-CH_2), 2.72 (s, 6 H, 8-NCH_3), 1.62–1.75 (m, 2 H, 2′-CH_2), 1.36–1.49 (m, 1 H, 3′-CH).

LRMS (EI): *m*/*z* (%) = 296.2 (100) $[M^+]$ (100).

HRMS (EI): *m*/*z* (%) calcd for $C_{12}H_{20}N_6O_3$: 296.1597; found: 296.1593.

N^2-(*p*-Anisyldiphenylmethyl)-8-dimethylamino-9-[(4-*p*-anisyldiphenylmethoxy)-3-*p*-anisyldiphenylmethoxymethylbutyl]-guanine (MTr-PCV-NMe_2, 17); Typial Procedure

16 (0.19 g, 0.64 mmol), MTrCl (0.79 g, 2.56 mmol) and DMAP (0.019 g, 0.16 mmol) were dissolved in anhyd DMF (20 mL) and Et_3N (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 $MgSO_4$, 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–CH_2Cl_2 to give **17** (0.37 g, 52%); mp 140 °C (dec.); R_f 0.30 (5% MeOH–CH_2Cl_2).

^{1}H NMR (DMSO-d_6): δ = 10.35 (s, 1 H, 1-NH, D_2O exchangeable), 7.48 (s, 1 H, 2-NH, D_2O exchangeable), 6.60–7.35 (m, 42 H, aromatic), 3.73 (s, 6 H, 4′-OCH_3), 3.60 (s, 3 H, 2′-OCH_3), 3.12–3.26 (m, 2 H, 1′-CH_2), 2.62–2.89 (m, 4 H, 4′-CH_2), 2.49 (s, 6 H, 8-NCH_3), 1.56–1.72 (m, 1 H, 3′-CH), 1.00–1.18 (m, 2 H, 2′-CH_2).

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

HRMS (FAB): *m*/*z* calcd for $C_{72}H_{69}N_6O_6$: 1113.5278; found: 1113.5230.

N^2-(*p*-Anisyldiphenylmethyl)-7-methyl-8-dimethylamino-9-[(4-*p*-anisyldiphenylmethoxy)-3-*p*-anisyldiphenylmethoxymethylbutyl]guanine-8-triflate (18); Typical Procedure

17 (0.050 g, 0.045 mmol) was dissolved in anhyd CH_2Cl_2 (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.); R_f 0.38 (7% MeOH–CH_2Cl_2).

^{1}H NMR (DMSO-d_6): δ = 11.13 (s, 1 H, 1-NH, D_2O exchangeable), 7.98 (s, 1 H, 2-NH, D_2O exchangeable), 6.59–7.38 (m, 42 H, aromatic), 3.73 (s, 6 H, OCH_3), 3.64 (s, 3 H, 7-CH_3), 3.59 (s, 3 H, OCH_3), 3.26–3.43 (m, 2 H, 1′-CH_2), 2.93 (s, 6 H, 8-NCH_3), 2.60–2.96 (m, 4 H, 4′-CH_2), 1.78–1.94 (m, 1 H, 3′-CH), 1.04–1.29 (m, 2 H, 2′-CH_2).

N^2-Acetyl-8-dimethylamino-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine (19); Typical Procedure

The solution of **16** (0.050 g, 0.17 mmol), DMAP (0.0040 g, 0.33 mmol) and Ac_2O (0.2 mL, 2.12 mmol) in pyridine (5 mL) was refluxed under N_2 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 CH_2Cl_2, and transferred to the top of a silica gel column and eluted with CH_2Cl_2–MeOH (20:1) to afford **19** (0.053 g, 74%); mp 155–157 °C; R_f 0.32 (CH_2Cl_2–MeOH, 15:1).

^{1}H NMR (DMSO-d_6): δ = 11.95 (br s, 1 H, NH, D_2O exchangeable), 11.59 (br s, 1 H, NH, D_2O exchangeable), 3.93–4.09 (m, 6 H, 1′-

CH_2 and 4′-CH_2), 2.79 (s, 6 H, 8-NCH_3), 2.16 (s, 3 H, 2-CH_3CON), 1.98 (s, 6 H, CH_3CO_2), 1.74–1.91 (m, 3 H, 2′-CH_2 and 3′-CH).

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

HRMS (EI): *m*/*z* calcd for $C_{18}H_{26}N_6O_6$: 422.1914; found; 422.1924.

N^2-Acetyl-7-methyl-8-dimethylamino-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine-8-triflate (20); Typical Procedure

To the cold solution of **19** (0.050 g, 0.12 mmol) in anhyd CH_2Cl_2 (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%); R_f 0.18 (CH_2Cl_2–MeOH, 15:1).

^{1}H NMR (DMSO-d_6): δ = 12.47 (s, 1 H, NH, D_2O exchangeable), 11.97 (s, 1 H, NH, D_2O exchangeable), 4.15 (t, *J* = 7.36 Hz, 2 H, 1-CH_2), 4.03 (d, *J* = 5.14 Hz, 4 H, 4′-CH_2), 3.85 (s, 3 H, 7-CH_3), 3.15 (s, 6 H, 8-NCH_3), 2.21 (s, 3 H, 2-CH_3CON), 2.01 (s, 6 H, CH_3CO_2), 1.94–2.06 (m, 1 H, 3′-CH), 1.74–1.88 (m, 2 H, 2′-CH_2).

N^2-Acetyl-8-methoxy-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine (Ac–PCV–OMe, 21); Typical Procedure

To a 10 mL V-vial containing anhyd KF (0.36 g, 6.20 mmol) and $K_{2.2.2}$ (0.36 g, 0.96 mmol) was added a solution of **20** (0.21 g, 0.36 mmol) in anhyd CH_3CN (8 mL). Under N_2 flow the mixture was heated to 110 °C to remove any moisture in the system by azeotroping. The second portion of anhyd CH_3CN (8 mL) was added to accomplish the azeotroping. When the mixture was nearly anhydrous, the third portion of CH_3CN (8 mL) was added. The V-vial was sealed and heated at 125 °C overnight. After removal of solvent, the residue was dissolved in EtOAc, and washed with water, dried over MgSO4, and evaporated under vacuum. The resulting residue was dissolved in a small amount of CH_2Cl_2, and transferred to the top of a silica gel column and eluted with CH_2Cl_2–MeOH (40:1) to give a white solid **21** (0.044 g, 30%); mp 105–107 °C; R_f 0.13 (CH_2Cl_2–MeOH, 40:1).

^{1}H NMR ($CDCl_3$): δ = 11.92 (s, 1 H, 1-NH), 9.68 (s, 1 H, 2-NH), 4.06–4.25 (m, 4 H, 4′-CH_2), 3.83 (t, *J* = 6.27 Hz, 2 H, 1′-CH_2), 3.56 (s, 3 H, 8-OCH_3), 2.27 (s, 3 H, 2-CH_3CON), 2.03 (s, 6 H, CH_3CO_2), 1.94–2.00 (m, 1 H, 3′-CH), 1.72–1.78 (m, 2 H, 2′-CH_2).

^{13}C NMR ($CDCl_3$): δ = 172.22 (s), 171.49 (s), 152.36 (s), 150.24 (s), 146.90 (s), 144.74 (s), 104.70 (s), 63.94 (t), 37.77 (t), 34.70 (d), 29.07 (q), 27.90 (t), 24.23 (q), 21.11 (q).

LRMS (EI): *m*/*z* (%) = 409.2 (100) [M^+].

HRMS (EI): *m*/*z* calcd for $C_{17}H_{23}N_5O_7$: 409.1598; found: 409.1611.

8-Methoxy-9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (MeOPCV, 22); Typical Procedure

The solution of **21** (0.030 g, 0.073 mmol) in aq CH_3NH_2 solution (40%, 5 mL) was heated at 75 °C for 2 h until TLC showed that 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 CH_2Cl_2–MeOH (15:1), then with CH_3CN–H_2O (9:1) to give **22** (0.016 g, 77%); mp 250 °C (dec.); R_f 0.30 (CH_3CN–H_2O, 9:1).

^{1}H NMR (DMSO-d_6): δ = 10.80 (br s, 1 H, 1-NH, D_2O exchangeable), 6.52 (s, 2 H, 2-NH_2, D_2O exchangeable), 4.35 (br s, 2 H, OH, D_2O exchangeable), 3.67 (t, *J* = 6.62 Hz, 2 H, 1′-CH_2), 3.25–3.45 (m, 4 H, 4′-CH_2), 3.30 (s, 3 H, 8-OCH_3), 1.50–1.60 (m, 2 H, 2′-CH_2), 1.36–1.47 (m, 1 H, 3′-CH).

LRMS (EI): *m*/*z* (%) = 181 (100), 283 (17) [M^+].

HRMS (EI): *m*/*z* calcd for $C_{11}H_{17}N_5O_4$: 283.1281; found: 283.1288.

N^2-Acetyl-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine (Ac-PCV, 24); Typical Procedure

The mixture of PCV, **1** (0.10 g, 0.40 mmol), Ac_2O (0.2 mL, 2.12 mmol) and 1-methylpyrrolidone (5 mL) was heated to 150 ºC for 5 h. The volatiles were removed under vacuum. To the residue was added MeOH to dissolve it, and then was added silica gel to absorb the solution. The silica gel was dried under vacuum, transferred to the top of a silica gel column, and eluted with CH_2Cl_2–MeOH (15:1–10:1) to afford a white solid **25** (0.082 g, 55%); R_f 0.42 (CH_2Cl_2–MeOH, 15:1).

^{1}H NMR (DMSO-d_6): δ = 11.47–12.29 (br s, 2 H, 1-NH and 2-NH), 8.01 (s, 1 H, 8-CH), 4.13 (t, *J* = 7.00 Hz, 2 H, 1′-CH_2), 4.00 (d, *J* = 5.15 Hz, 4 H, 4′-CH_2), 2.17 (s, 3 H, 2-CH_3CON), 1.98 (s, 6 H, 4′-CH_3CO_2), 1.78–1.95 (m, 3 H, 2′-CH_2, 3′-CH).

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

HRMS (EI): *m*/*z* calcd for $C_{16}H_{21}N_5O_6$: 379.1492; found: 379.1501.

N^2-Acetyl-7-methyl-9-[4-acetoxy-3-(acetoxymethyl)butyl]guanine-8-triflate (25); Typical Procedure

Compound **24** (0.068 g, 0.18 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL). Under an ice-salt bath methyl triflate (25 μL, 0.22 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 **25** (0.097 g, ca 100%); R_f 0.20 (CH_2Cl_2–MeOH, 15:1).

^{1}H NMR (DMSO-d_6): δ = 12.57 (s, 1 H, 1-NH), 12.12 (s, 1 H, 2-NH), 9.48 (s, 1 H, 8-CH), 4.31 (t, *J* = 7.35 Hz, 2 H, 1′-CH_2), 4.07 (s, 3 H, 7-CH_3), 4.04 (d, *J* = 5.14 Hz, 4 H, 4′-CH_2), 2.22 (s, 3 H, 2-CH_3CON), 2.01 (s, 6 H, CH_3CO_2), 1.84–2.11 (m, 3 H, 2′-CH_2 and 3′-CH).

8-Bromo-9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (BrGCV, 26); Typical Procedure

GCV, **2** (0.53 g, 2.08 mmol) was suspended in water (20 mL). Under vigorous stirring, Br_2 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 × 5 mL) and acetone (5 mL), and dried under vacuum to give an off-white solid **26** (0.43 g, 62%); mp >300 °C.

^{1}H NMR (DMSO-d_6): δ = 10.72 (s, 1 H, 1-NH), 6.62 (br s, 2 H, 2-NH_2), 5.38 (s, 2 H, 1′-CH_2), 4.18 (br s, 2 H, OH), 3.50–3.65 (m, 1 H, 3′-CH), 3.20–3.50 (m, 4 H, 4′-CH_2).

8-Dimethylamino-9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (Me_2NGCV, 27); Typical Procedure

A solution of **26** (0.20 g, 0.60 mmol) in $(CH_3)_2NH$ (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 12:1 CH_3CN–H_2O to give a white solid **27** (0.17 g, 94%); mp >225 °C (dec.), R_f 0.28 (CH_3CN–H_2O, 9:1).

^{1}H NMR (DMSO-d_6): δ = 10.46 (s, 1 H, 1-NH, D_2O exchangeable), 6.33 (s, 2 H, 2-NH_2, D_2O exchangeable), 5.26 (s, 2 H, 1′-CH_2), 4.57 (t, *J* = 5.88 Hz, 2 H, OH, D_2O exchangeable), 3.65–3.74 (m, 1 H, 3′-CH), 3.30–3.54 (m, 4 H, 4′-CH_2), 2.82 (s, 6 H, 8-NCH_3).

LRMS (EI): *m*/*z* (%) = 194.1 (100), 298.1 (23) [M^+].

HRMS (EI): *m*/*z* calcd for $C_{11}H_{18}N_6O_4$: 298.1390; found: 298.1380.

***N*²-Acetyl-8-dimethylamino-9-[(1,3-diacetoxy-2-propoxy)methyl]guanine (Ac-GCV-NMe$_2$, 28); Typical Procedure**

The solution of **27** (0.20 g, 0.67 mmol), DMAP (0.016 g, 0.13 mmol) and Ac_2O (0.8 mL, 8.48 mmol) in anhyd pyridine (15 mL) was refluxed under N_2 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 CH_2Cl_2, and transferred to top of a silica gel column and eluted with CH_2Cl_2–MeOH (30:1) to afford **28** (0.229 g, 81%); mp 90 °C (dec.); R_f 0.18 (CH_2Cl_2–MeOH, 25:1).

^{1}H NMR (DMSO-d_6): δ = 12.00 (s, 1 H, NH), 11.55 (s, 1 H, NH), 5.36 (s, 2 H, 1′-CH_2), 3.98–4.22 (m, 5 H, 3′-CH and 4′-CH_2), 2.89 (s, 6 H, 8-NCH_3), 2.18 (s, 3 H, 2-CH_3CON), 1.91 (s, 6 H, CH_3CO_2).

LRMS (EI): *m*/*z* (%) = 236 (100), 424 (27) [M^+].

HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}N_6O_7$: 424.1706; found: 424.1713.

***N*²-Acetyl-7-methyl-8-dimethylamino-9-[(1,3-diacetoxy-2-propoxy)methyl]guanine-8-triflate (29); Typical Procedure**

To the cold solution of **28** (0.15 g, 0.35 mmol) in anhyd CH_2Cl_2 (20 mL) was added methyl triflate (48 μL, 0.42 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 **29** (0.21 g, ca 100%); R_f 0.20 (CH_2Cl_2–MeOH, 15:1).

^{1}H NMR (DMSO-d_6): δ = 12.49 (s, 1 H, NH), 11.90 (s, 1 H, NH), 5.52 (s, 2 H, 1′-CH_2), 4.00–4.30 (m, 5 H, 3′-CH and 4′-CH_2), 3.86 (s, 3 H, 7-CH_3), 3.24 (s, 6 H, 8-NCH_3), 2.23 (s, 3 H, 2-CH_3CON), 1.99 (s, 6 H, CH_3CO_2).

***N*²-Acetyl-8-methoxy-9-[(1,3-diacetoxy-2-propoxy)methyl]guanine (Ac-GCV-OMe, 30); Typical Procedure**

To a 10 mL V-vial containing anhyd KF (0.36 g, 6.20 mmol) and $K_{2.2.2}$ (0.36 g, 0.96 mmol) was added a solution of **29** (0.18 g, 0.31 mmol) in anhyd CH_3CN (8 mL). Under N_2 flow the mixture was heated to 110 °C to remove any moisture in the system by azeotroping. The second portion of CH_3CN (8 mL) was added to accomplish the azeotroping. When the mixture was nearly anhyd, the third portion of CH_3CN (8 mL) was added. The V-vial was sealed and heated at 125 °C for 6.5 h. After removal of solvent, the residue was dissolved in CH_2Cl_2, and transferred to the top of a silica gel column and eluted with CH_2Cl_2–MeOH (40:1) to give a white solid **30** (0.060 g, 48%); R_f 0.22 (CH_2Cl_2–MeOH, 25:1).

^{1}H NMR ($CDCl_3$): δ = 11.95 (s, 1 H, 1-NH), 9.16 (s, 1 H, 2-NH), 5.32 (s, 2 H, 1′-CH_2), 4.12–4.24 (m, 5 H, 3′-CH and 4′-CH_2), 3.61 (s, 3 H, 8-OCH_3), 2.30 (s, 3 H, 2-CH_3CON), 2.04 (s, 6 H, CH_3CO_2).

LRMS (EI): *m*/*z* (%) = 181 (100), 411 (20) [M^+].

HRMS (EI): *m*/*z* calcd for $C_{16}H_{21}N_5O_8$: 411.1390; found: 411.1392.

8-Methoxy-9-[(1,3-dihydroxyl-2-propoxy)methyl]guanine (MeOGCV, 31); Typical Procedure

The solution of **30** (0.060 g, 0.15 mmol) in aq CH_3NH_2 solution (40%, 5 mL) was heated at 75 °C for 2 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 CH_2Cl_2–MeOH (15:1), then with CH_3CN–H_2O (9:1) to give a white solid **31** (0.036 g, 87%); mp 267 °C, R_f 0.38 (CH_3CN–H_2O, 9:1).

^{1}H NMR (DMSO-d_6): δ = 10.87 (s, 1 H, 1-NH, D_2O exchangeable), 6.54 (s, 2 H, 2-NH_2, D_2O exchangeable), 5.12 (s, 2 H, 1′-CH_2), 4.52 (t, *J* = 5.15 Hz, 2 H, OH, D_2O exchangeable), 3.55–3.66 (m, 1 H, 3′-CH), 3.32 (s, 3 H, 8-OCH_3), 3.23–3.44 (m, 4 H, 4′-CH_2).

LRMS (FAB): *m*/*z* (%) = 176 (100), 308 (18) [M + Na^+].

HRMS (FAB): *m*/*z* calcd for $C_{10}H_{15}N_5NaO_5$: 308.0971; found: 308.0971.

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