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### Improved Industrial Syntheses of Penciclovir and Famciclovir Using N2-Acetyl-7-Benzylguanine and a Cyclic Side Chain Precursor

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## IMPROVED INDUSTRIAL SYNTHESSES OF PENCICLOVIR AND FAMCICLOVIR USING N2-ACETYL-7-BENZYLGUANINE AND A CYCLIC SIDE CHAIN PRECURSOR

**Takayoshi Torii, Keizo Yamashita, Mitsuhiro Kojima, Yumiko Suzuki, Toyoto Hijiya, and Kunisuke Izawa** □ *AminoScience Laboratories, Ajinomoto Co., Inc., Kawasaki-ku, Kawasaki, Japan*

□ *We have established practical synthetic methods for penciclovir (PCV, **1**) and famciclovir (FCV, **2**) from N2-acetyl-7-benzylguanine (NAC7BnG, **3**) and 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (**4**)—the latter being a more easily prepared cyclic precursor of the diacetate side chain (**5**) used in the conventional process. The coupling of **4** with **3** proceeded regioselectively at the N9 position of guanine in good yield. The coupling product was then successfully transformed into the known antiviral agents in a short number of steps.*

**Keywords** Famciclovir; Industrial synthesis; Penciclovir

### INTRODUCTION

PCV (**1**) and its pro-drug FCV (**2**) are found to be potent and highly selective antiviral agents against both the herpes simplex virus (HSV) and the varicella-zoster virus (VZV) (Figure 1).<sup>[1]</sup> It has also been reported that **1** and **2** exhibit anti-hepatitis B virus (HBV) activity.<sup>[2]</sup> PCV (**1**) and FCV (**2**) are analogues of acyclovir, having an alkyl side chain at the N9 position. Boryski et al. found that the N7 isomer of diacetylacyclovir could be converted to a 1:1 mixture of the N7 and N9 isomers under acidic conditions via an oxonium ion intermediate.<sup>[3]</sup> By optimizing the reaction conditions, we eventually succeeded in obtaining an almost pure N9 isomer of acyclovir in one pot.<sup>[4]</sup> However, we could not use this same methodology to produce **1** and **2** since they do not have an oxygen atom in their side chain.<sup>[5]</sup> Accordingly, we set about establishing a new strategy for the N9 selective alkylation of guanine.

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This article is dedicated to Professor Eiko Ohtsuka on the occasion of her 70th birthday.

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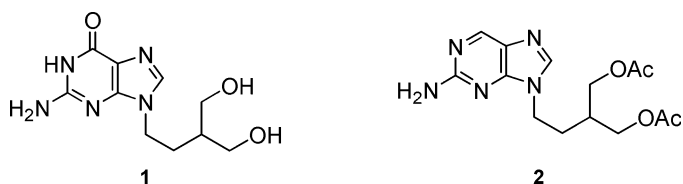


FIGURE 1 PCV (**1**) and FCV (**2**).

Normally, it is difficult to introduce an alkyl side chain at the N9 position of guanine with high regio-selectivity. In order to achieve selective N9 alkylation, 2-amino-6-halopurines are commonly used as starting materials for coupling with alkyl halide side chains.<sup>[6]</sup> However, 2-amino-6-halopurines are not ideal candidates for large scale synthesis due to their high mutagenicity. In addition, to obtain highly pure N9 compounds, N7 compounds should be eliminated from the N9/N7 mixture by means of column chromatography. To overcome these problems, we established and reported a new methodology involving the N9 selective alkylation of NAc7BnG (**3**), which can be readily prepared from guanosine.<sup>[7]</sup>

Geen et al. reported that the commercially available cyclic side chain precursor **4** was most suitable for coupling with 2-amino-6-chloropurine for the synthesis of **1** and **2**.<sup>[6f]</sup> The diacetate **5**, which is commonly used for the synthesis of **1** and **2** as the side chain precursor, can be prepared in 7 steps from ethylene glycol in 45% yield.<sup>[6c,8]</sup> On the other hand, the side chain precursor **4**<sup>[9]</sup> can be prepared from 1,2-dibromoethane in 74% yield in only 3 steps (Figure 2).<sup>[9,10]</sup> We concluded that the method using **4** as a side chain precursor would be better than the method using **5** despite the fact that it requires extra 2 steps to obtain **1** and **2** from NAc7BnG **3**. We wish to describe herein a practical synthesis of **1** and **2** using NAc7BnG **3** and the side chain precursor **4**.<sup>[11]</sup>

## RESULTS AND DISCUSSION

Firstly, we studied the coupling reaction of NAc7BnG **3** with the side chain precursor **4** (see Table 1). The coupling reaction of **3** with **4** scarcely proceeded at all using NaHCO<sub>3</sub> in DMF at room temperature under the same conditions as the coupling of 2-amino-6-chloropurine with **4** as reported by

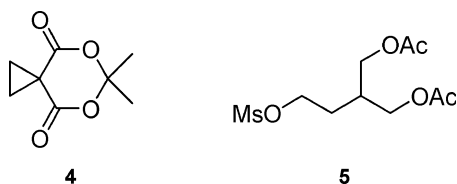
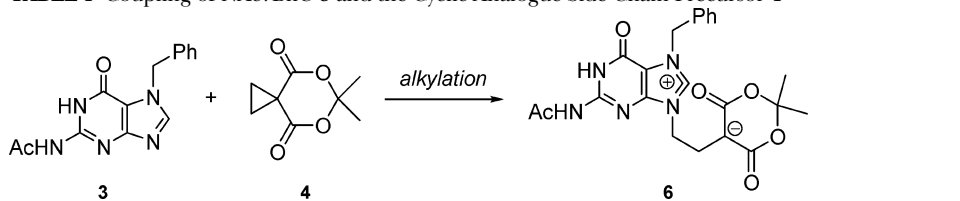


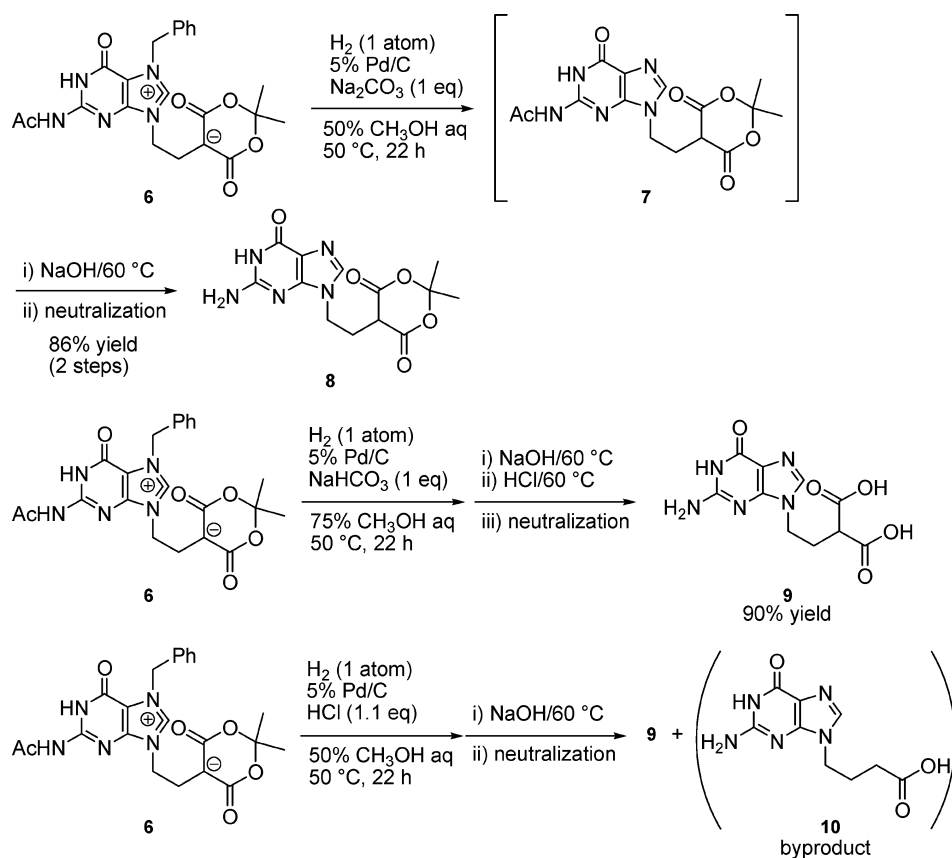
FIGURE 2 Side chain precursors **4** and **5**.

**TABLE 1** Coupling of NAc7BnG **3** and the Cyclic Analogue Side Chain Precursor **4**


| Entry | Solvent (M)                    | Temp. (°C) | <b>4</b> (eq)          | Isolated yield of crude <b>6</b> (%) | Net yield of <b>6</b> (%) <sup>a</sup> | Purity of crude <b>6</b> (wt%) <sup>b</sup> |
|-------|--------------------------------|------------|------------------------|--------------------------------------|--|---|
| 1     | DMF (0.6)                      | 60         | 1.0                    | 79                                   | 53                                     | 67  |
| 2     | NMP (1.6)                      | 60         | 1.0                    | 57                                   | 50                                     | 87  |
| 3     | DMSO (1.3)                     | 60         | 1.0                    | 45                                   | 27                                     | 60  |
| 4     | DMF (0.5)                      | 60         | 1.0                    | 49                                   | 38                                     | 78  |
| 5     | DMF (0.5)                      | 60         | 2.0                    | 92                                   | 61                                     | 66  |
| 6     | DMF (0.5)                      | 60         | 3.0                    | 135                                  | 76                                     | 56  |
| 7     | DMF (0.5)                      | 60         | 1.5 + 1.5 <sup>c</sup> | 148                                  | 86                                     | 58  |
| 8     | 5:1 DMF-H <sub>2</sub> O (1.5) | 70         | 1.2                    | 74                                   | 74                                     | 99  |

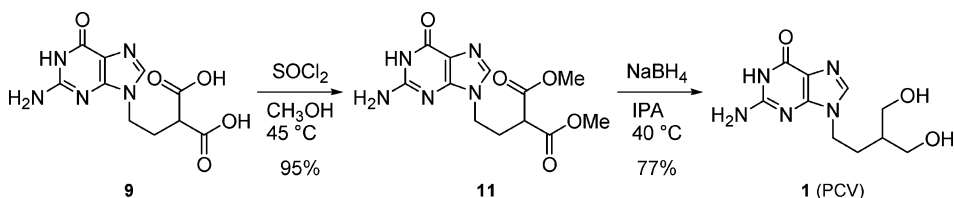
<sup>a</sup>Net yields were determined by HPLC a bsolute calibration method.<sup>b</sup>Purity of crude **6** were calculated by the isolated yield of crystals **6** and net yield of **6**.<sup>c</sup>Compound **4** was added twice.

Geen et al.<sup>[6f]</sup> On the other hand, the coupling product **6** was observed in DMF at 60°C without using a base (entry 1), which were the same conditions as the coupling of **3** with **5**.<sup>[12]</sup> It had been reported that the coupling of pyridine with **4** proceeded quantitatively at room temperature.<sup>[9]</sup> However, the coupling of **3** with **4** had to be carried out at over 60°C, probably because of the lower nucleophilicity of **3**. Although the yield of **6** was improved from 38 to 86% by adding three equivalents of **4**, it is still desirable to avoid the use of excessive amounts of **4** for reasons both of cost and environmental protection. After several unsuccessful attempts, we discovered that the yield of **6** was substantially improved to 74% by adding a small amount of water using only 1.2 equivalents of **4** (entry 8). The reason for the improvement of the yield is not clear at this point in time. After the coupling reaction, compound **6** was obtained in crystalline form in good yields by adding ethyl acetate and filtration. When an extra amount of **4** was used for the coupling reaction, the purity of **6** was only 58% (entry 7). In the case of entry 8, however, compound **6** was obtained in 99% purity by the simple purification method described above; the major impurity of the crude crystal **6** being in all probability the polymerization product of **4**. Nevertheless, we have faced severe problems such as poor filterability of **6** in the scale-up study of entry 8. The main reason for the poor filterability might be that the reaction was obliged to be carried out under highly concentrated conditions in order to maintain the yield of **6** as same level as entry 7. Therefore, we selected to use the crude crystals of **6** without further purification for the next step because the crude crystals of **6** have better physical property and the impurity

SCHEME 1 Debenzylation of **6**.

contained in the crude crystals of **6** could be removed easily at the following step.

Next, we studied the debenzylation of **6** (Scheme 1). The coupling product **6** was transformed into the debenzylated compound **7** under a hydrogen atmosphere in the presence of Pd catalyst and base. The reaction mixture changed from a slurry to a solution during the progress of the reaction. At that time, several products were observed in the reaction mixture. We considered that a part of the acetyl group of **7** at the N2 position had already undergone deprotection under these reaction conditions. Therefore, the mixture was further treated under strong basic conditions for completion of the deacetylation of **7**. After neutralization of the reaction mixture, compound **8** was obtained as crystals in 86% yield from **6**. However, we failed to isolate pure **8** when we subsequently scaled up this synthesis due to its inherently poor filterability. Therefore, the reaction mixture containing **8** was then further treated under acidic conditions at pH 3.5 to obtain the dicarboxylate **9**. Fortunately, compound **9** exhibited good filterability and was obtainable in a 90% isolated yield from **6**. Based on HMBC NMR studies,

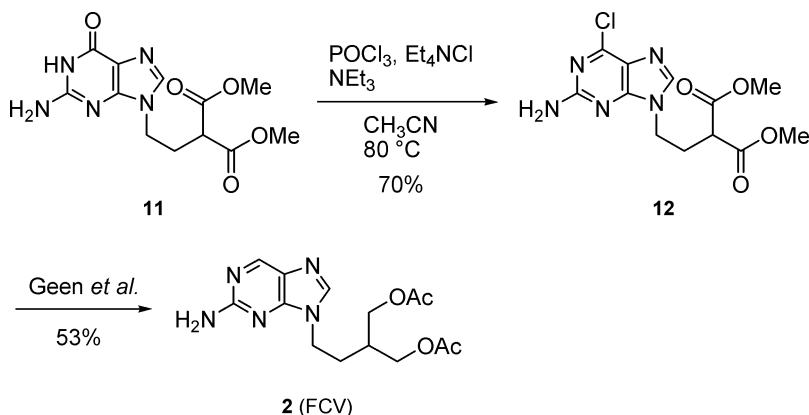


SCHEME 2 Preparation of PCV 1.

compound **9** was identified as the N9 alkylated compound. Thus, the proton signal of **9** at 4.00 ppm (H-1') showed HMBC correlation peaks with the purine base carbons only at 137.63 (C-8) and 151.48 ppm (C-4) indicating that the side chain was connected to the N9 nitrogen atom of purine base. When the coupling product **6** was debenzylated under acidic conditions aiming at the deprotection of the isopropylidene group at the same time, the decarboxylated compound **10** was produced as a byproduct. Since it was very difficult to remove **10** from **9**, we did not pursue the deprotection of **6** under acidic conditions.

The dicarboxylic acid **9** thus obtained was converted to the diester **11** in 95% yield by treating with thionyl chloride in methanol. Penciclovir **1** was obtained by the sodium borohydride reduction of **11** in 77% yield (Scheme 2). This method using NAc7BnG **3** as a starting material gave **1** in 57% overall yield and 4 isolation steps. It may thus be considered as superior to that using 2-amino-6-chlorpurine as a starting material which affords **1** in 23% yield and 4 steps.<sup>[6f]</sup> Attempts at the direct reduction of **8** did not succeed since **8** is poorly soluble in most solvents.

Next, we turned our attention to the synthesis of famciclovir **2** from **11**. The diester **11** was treated with phosphorus oxychloride in the presence of tetraethylammonium chloride and triethylamine at 80°C to give **12** in 70% yield. Compound **12** was transformed into **2** in 53% yield by the procedure described in the literature (Scheme 3).<sup>[6f]</sup> This method using NAc7BnG **3** as



SCHEME 3 Preparation of FCV 2.

a starting material gave famciclovir **2** in 27% overall yield, which might be better than the method using 2-amino-6-chloropurine as a starting material (12% yield) even though it requires extra 2 steps.<sup>[6f]</sup> It also has additional advantages in as much as it avoids the use of the mutagenic 2-amino-6-chloropurine and the need to purify intermediates by chromatographical means.

## CONCLUSION

We discovered that the cyclic side chain precursor **4** may be readily coupled with NAc7BnG **3** at the N9 position selectively. The coupling product **6** is easily and efficiently converted to known antiviral agents PCV **1** and FCV **2**. This is also a highly practical synthetic method in that it avoids the need for purification by chromatographical means.

## EXPERIMENTAL

All reagents were purchased and used without further purification. Thin-layer chromatography (TLC) was conducted on precoated TLC plates (Merck 60F254). High-performance liquid chromatography (HPLC) was performed with a Hitachi L-6000 pump and L-4000 UV detector system using a YMC-ODS-A column. Melting points were measured with the Büchi B-545. NMR spectra were obtained on a BRUKER Advance-400 MHz spectrometer. All <sup>1</sup>H-NMR spectra were measured in DMSO-*d*<sub>6</sub> solvent, and chemical shifts are reported as  $\delta$  values in parts per million relative to tetramethylsilane ( $\delta$  0.00) as an internal standard. All <sup>13</sup>C-NMR spectra were measured in DMSO-*d*<sub>6</sub> solvent, and chemical shifts are reported as  $\delta$  values in parts per million relative to DMSO-*d*<sub>6</sub> ( $\delta$  39.5) as an internal standard. Infrared (IR) spectra were recorded on an ASI React IR 1000 FT-IR spectrometer with an ATR sampling system and are reported in wavenumber (cm<sup>-1</sup>). Mass spectra (MS) and High-resolution mass spectra (HRMS) were obtained with JEOL JMS-700V (JEOL datum Ltd.).

*Crude 2-Acetyl-7-benzyl-9-[2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl]guaninium inner salt (6).*<sup>[7a]</sup> A mixture of *N*2-acetyl-7-benzylguanine (**3**) (497 mg, 1.68 mmol) and 6,6-dimethyl-5,7-dioxaspiro[2,5]octane-4,8-dione (**4**) (430 mg, 2.53 mmol) in DMF (3 ml) was stirred for 24 h at 60°C. Then to the mixture was added **4** (430 mg, 2.53 mmol), which was stirred for 21 h at 60°C. AcOEt (6 ml) was added to the mixture, filtered off and washed with AcOEt (10 ml). After drying, compound **6** (1.12 g, 58 wt%, 86%) was obtained as a pale yellowish powder.

*2-Acetyl-7-benzyl-9-[2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl]guaninium inner salt (6).* A solution of *N*2-acetyl-7-benzylguanine (**3**) (5.72 g, 20.0 mmol) in DMF (11.1 ml) and water (2.2 ml) was warmed to 70°C. Then to the mixture was added 6,6-dimethyl-5,7-dioxaspiro[2,5]octane-4,8-dione (**4**) (4.08 g, 24.0 mmol) and stirred 8 h at 70°C. DMF (6.7 ml)

and AcOEt (140 ml) were added to the mixture and stirred for 13 h at room temperature. The mixture was filtered off and washed with AcOEt (110 ml). After drying, compound **6** (6.81 g, 74%) was obtained as colorless crystals.  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.36 (6H, s,  $\text{CH}_3 \times 2$ ), 2.20 (3H, s, Ac), 2.64 (2H, t,  $J = 6.2$  Hz, H-2'), 4.22 (2H, t,  $J = 6.2$  Hz, H-1'), 5.64 (2H, s,  $\text{CH}_2$ ), 7.35–7.38 (3H, m, aryl), 7.45–7.48 (2H, m, aryl), 9.68 (1H, s, H-8);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  24.22, 24.56, 26.18, 40.73, 46.46, 51.80, 67.18, 99.52, 110.29, 128.48, 128.83, 129.10, 134.72, 140.44, 148.41, 150.80, 165.76, 174.37; IR (neat) 3080, 3000, 1737, 1704, 1565, 1410, 1248, 1206, 1187, 1135, 851, 774, 695  $\text{cm}^{-1}$ ; mp 194.5–195.4°C; MS (FAB+)  $m/z$  454 ( $\text{MH}^+$ ); HRMS (FAB+) calc for  $\text{C}_{22}\text{H}_{24}\text{N}_5\text{O}_6$  ( $\text{MH}^+$ ), 454.1727, found 454.1747.

5-[2-(Guanin-9-yl)ethyl]-2,2-dimethyl-1,3-dioxacyclohexane-4,6-dione (**8**). A mixture of **6** (2.40 g, 57 wt%, 3.0 mmol),  $\text{Na}_2\text{CO}_3$  (0.643 g, 6.0 mmol), and 5% Pd-C (0.277 g, 46.9 wt%) was stirred at 50°C in  $\text{CH}_3\text{OH}$  (10 ml) with water (10 ml) under hydrogen atmosphere of 1 atom pressure for 24 h. To the reaction mixture was added 4 M NaOH aq (2.3 ml) and  $\text{CH}_3\text{OH}$  (6 ml) and it was then filtered through Celite and the filter bed washed with 50%  $\text{CH}_3\text{OH}$  aq (10 ml). To the combined filtrates evaporated to 5.8 was added 2 M NaOH aq (1.0 ml) warmed to 60°C for 2 h. The solution was cooled to 0°C, neutralized to pH 7.0 with 2 M HCl aq., and stirred for 14 h at 0°C. The mixture was filtered off and washed with water (1 ml). After drying, compound **8** (0.836 g, 86%) was obtained as colorless crystals.  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.39 (6H, s,  $\text{CH}_3 \times 2$ ), 2.64 (2H, t,  $J = 7.3$  Hz, H-2'), 3.90 (2H, t,  $J = 7.3$  Hz, H-1'), 6.44 (2H, br,  $\text{NH}_2$ ), 7.50 (1H, s, H-8), 10.49 (1H, br, NH);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  25.73, 26.26, 42.72, 68.35, 99.20, 116.77, 137.54, 151.50, 153.60, 157.26, 165.50; IR (neat) 3330, 3176, 1686, 1644, 1553, 1403, 1260, 1196, 1111, 930, 777, 691  $\text{cm}^{-1}$ ; mp 247°C (dec.); MS (FAB-)  $m/z$  320 ( $\text{MH}^-$ ); HRMS (FAB-) calc for  $\text{C}_{13}\text{H}_{14}\text{N}_5\text{O}_5$  ( $\text{MH}^-$ ), 320.1000, found 320.0990.

2-[2-(Guanin-9-yl)ethyl]malonic acid (**9**).<sup>[1]</sup> A mixture of **6** (33.46 g, 61 wt%, 45 mmol),  $\text{NaHCO}_3$  (3.78 g, 45.0 mmol), and 5% Pd-C (4.05 g, 46.9 wt%, 0.9 mmol) was stirred at 50°C in  $\text{CH}_3\text{OH}$  (225 ml) with water (75 ml) under hydrogen atmosphere of 1 atom pressure for 19 h. The reaction mixture was then filtered through Celite, the filter bed washed with 50%  $\text{CH}_3\text{OH}$  aq (130 ml), and the combined filtrates evaporated to 70 g. To the solution was added 4 M NaOH aq (26 ml) which was warmed to 60°C for 2 h. The solution was acidified to pH 2.5 with 6 M HCl aq, water added (130 ml) and stirred for 5 h at 65°C. The solution was cooled to 0°C, its pH being controlled to 3.5 with 4M NaOH aq. It was then stirred for 3 h at 0°C and the precipitate filtered off, washed with cold 50%  $\text{CH}_3\text{OH}$  aq (18 ml) and  $\text{CH}_3\text{OH}$  (15 ml). After drying, compound **9** (11.81 g, 90%) was obtained as colorless crystals.  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  2.15–2.21 (2H, m, H-2'), 2.95 (1H, t,  $J = 6.6$  Hz, H-3'), 4.00 (2H, t,  $J = 7.4$  Hz, H-1'), 6.45 (2H, br,  $\text{NH}_2$ ), 7.63 (1H, s, H-8),



10.52 (1H, br, NH);  $^{13}\text{C}$ -NMR (100 MHz, DMSO- $d_6$ )  $\delta$  29.55, 41.63, 48.00, 116.95, 137.63, 151.48, 153.82, 157.16, 172.29; IR (neat) 3122, 2744, 1706, 1603, 1383, 1185, 839, 687  $\text{cm}^{-1}$ ; mp 258°C (dec); MS (FAB-)  $m/z$  280 ( $\text{MH}^-$ ); HRMS (FAB-) calc for  $\text{C}_{10}\text{H}_{10}\text{N}_5\text{O}_5$  ( $\text{MH}^-$ ), 280.0687, found 280.0670.

*4-(Guanin-9-yl)ethyl]butanoic acid (10)*. A mixture of **6** (2.40 g, 57 wt%, 3.0 mmol), 2 M HCl aq (1.66 ml, 3.3 mmol), and 5% Pd-C (0.277 g, 46.9 wt%) was stirred at 50°C in  $\text{CH}_3\text{OH}$  (10 ml) with water (8.34 ml) under hydrogen atmosphere of 1 atom pressure for 24 h. To the reaction mixture was added 4 M NaOH aq (3.1 ml) and  $\text{CH}_3\text{OH}$  (8 ml) and it was then filtered through Celite and the filter bed washed with 50%  $\text{CH}_3\text{OH}$  aq (10 ml). The combined filtrates were evaporated to 4.9 g, then 2 M NaOH aq (0.7 ml) added and it was warmed to 60°C for 2 h. The solution was cooled to 0°C, neutralized to pH 5.2 with 2 M HCl aq and then stirred for 14 h at 0°C. The mixture was filtered off and washed with water (1 ml). The solid (0.509 g) was purified by chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ , 4:1) to give **9** (0.396 g, 47%) and **10** (16.5 mg, 2.3%) as colorless crystals.  $^1\text{H}$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$  1.92–2.00 (2H, m, H-2'), 2.21 (2H, t,  $J = 7.4$  Hz, H-3'), 3.96 (2H, t,  $J = 7.0$  Hz, H-1'), 6.49 (2H, br,  $\text{NH}_2$ ), 7.73 (1H, s, H-8), 10.01 (1H, br, NH);  $^{13}\text{C}$ -NMR (100 MHz, DMSO- $d_6$ )  $\delta$  25.19, 31.06, 42.54, 116.57, 137.72, 151.45, 153.95, 157.00, 174.00; IR (neat) 3348, 3170, 2672, 1702, 1412, 1189, 778, 758, 695, 656  $\text{cm}^{-1}$ ; mp 275.4–277.4°C; MS (FAB-)  $m/z$  236 ( $\text{MH}^-$ ); HRMS (FAB-) calc for  $\text{C}_9\text{H}_{10}\text{N}_5\text{O}_3$  ( $\text{MH}^-$ ), 236.0789, found 236.0807.

*Dimethyl 2-[2-(guanin-9-yl)ethyl]malonate (11)*.<sup>[11]</sup> To a  $\text{CH}_3\text{OH}$  (40 ml) solution in an ice bath, thionyl chloride (6.15 ml, 80.0 mmol) was added. After adding, the mixture was warmed to rt. To the solution was added **9** (11.62 g, 40.0 mmol) and it was heated for 3.5 h at 40°C and then for 22.5 h at 45°C. After cooling to room temperature,  $\text{CH}_3\text{OH}$  (100 ml) was added and the mixture was cooled in an ice bath. The solution was neutralized with 4 M NaOH aq. (ca. 39.5 ml), heated for 0.5 h at 55°C, and then cooled to 16°C until crystals began to separate. The solid was collected on filter and washed with 50%  $\text{CH}_3\text{OH}$  aq (15 ml),  $\text{CH}_3\text{OH}$  (15 ml). The crystals were suspended in 50%  $\text{CH}_3\text{OH}$  aq (180 ml) and stirred 2 h at rt. The solid was collected on filter and washed with 50%  $\text{CH}_3\text{OH}$  aq (20 ml),  $\text{CH}_3\text{OH}$  (15 ml). After drying, compound **11** (11.74 g, 95%) was obtained as colorless crystals.  $^1\text{H}$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.35 (2H, q,  $J = 7.1$  Hz, H-2'), 3.65 (6H, s,  $\text{Ac} \times 2$ ), 3.66 (1H, t,  $J = 7.2$  Hz, H-3'), 4.16 (2H, t,  $J = 6.9$  Hz, H-1'), 7.24 (2H, br,  $\text{NH}_2$ ), 8.90 (1H, s, H-8), 11.66 (1H, br, NH);  $^{13}\text{C}$ -NMR (100 MHz, DMSO- $d_6$ )  $\delta$  27.90, 42.44, 48.47, 52.97, 109.53, 137.49, 150.37, 154.24, 155.62, 169.11; IR (neat) 3465, 3182, 2634, 1731, 1642, 1605, 1395, 1248, 1185, 1164, 911, 778, 687  $\text{cm}^{-1}$ ; mp 226°C (dec); MS (FAB+)  $m/z$  310 ( $\text{MH}^+$ ); HRMS (FAB+) calc for  $\text{C}_{12}\text{H}_{15}\text{N}_5\text{O}_5$  ( $\text{MH}^+$ ), 310.1151, found 310.1170.

*Penciclovir (1)*. To a mixture of **11** (3.25 g, 10.0 mmol) and  $\text{NaBH}_4$  (1.14 g, 30 mmol) in 2-propanol (26.5 ml), water (6.6 ml) was added over 5 min.

The solution was stirred for 2.5 h at 40°C and cooled to room temperature. The solution was quenched by 6 M HCl aq (4.5 ml) and stirred for 1.5 h at room temperature. After adding 25% NaOH aq (10 ml) and water (15 ml), the solution was evaporated until the 2-propanol was removed and it was then neutralized to pH 6.0 with 6 M HCl aq, cooled to 0°C, and stirred for 2.5 h. The precipitate was filtered off, washed with cooled water (2 ml × 2), and crude **1** (2.18 g, 7.84 mmol, 78%) was then obtained as a colorless solid. The solid was crystallized from water to afford **1** (2.09 g, 77%) as colorless crystals. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.41–1.48 (1H, m, H-3'), 1.67–1.74 (2H, m, H-2'), 3.32–3.38 (2H, m, H-4'-a), 3.39–3.46 (2H, m, H-4'-b), 4.00 (2H, t, *J* = 7.4 Hz, H-1'), 4.41 (2H, t, *J* = 5.2 Hz, OH × 24), 6.41 (2H, br, NH<sub>2</sub>), 7.68 (1H, s, H-8), 10.50 (1H, br, NH); <sup>13</sup>C-NMR (100 MHz, DMSO-d<sub>6</sub>) δ 29.15, 41.11, 41.41, 61.67, 116.94, 137.68, 151.46, 153.76, 157.17; IR (neat) 3411, 3128, 2881, 2667, 1675, 1602, 1397, 1196, 1054, 992, 781, 753 cm<sup>-1</sup>; mp 269.6–272.3°C; MS (FAB+) *m/z* 254 (MH<sup>+</sup>); HRMS (FAB+) calcd for C<sub>10</sub>H<sub>16</sub>N<sub>5</sub>O<sub>3</sub> (MH<sup>+</sup>), 254.1253, found 254.1230.

*Dimethyl 2-[2-(2-amino-6-chloropurin-9-yl)ethyl]malonate (12)*.<sup>[6f]</sup> To a mixture of **11** (0.62 g, 2.0 mmol) and tetraethylammonium chloride (0.665 g, 4.0 mmol) in CH<sub>3</sub>CN (5 ml), *N,N*-dimethylaniline (0.134 ml, 1.0 mmol), and phosphorus oxychloride (0.835 ml, 9.0 mmol) were added. The solution was stirred for 1 h at 80°C, and evaporated. The residue was diluted by CH<sub>2</sub>Cl<sub>2</sub> (9 ml). After cooling to 0°C, to the solution was added 1 M NaOH aq (5 ml) and water (1 ml); it was then stirred vigorously at 0°C, and separated. The water layer was extracted by CH<sub>2</sub>Cl<sub>2</sub> (4 ml). The combined CH<sub>2</sub>Cl<sub>2</sub> layer was washed with sat. NaHCO<sub>3</sub> aq (6 ml) and water (6 ml) and evaporated in vacuo. The residue was crystallized from CH<sub>3</sub>OH to afford **12** (0.462 g, 70%) as a pale yellowish powder. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ 2.33 (2H, q, *J* = 7.0 Hz, H-2'), 3.60 (6H, s, Ac × 2), 3.54 (1H, t, *J* = 7.2 Hz, H-3), 4.12 (2H, t, *J* = 6.8 Hz, H-1'), 6.90 (2H, br, NH<sub>2</sub>), 8.08 (1H, s, H-8); <sup>13</sup>C-NMR (100 MHz, DMSO-d<sub>6</sub>) δ 28.25, 41.30, 48.79, 52.88, 123.69, 143.47, 149.65, 154.49, 160.08, 169.12; IR (neat) 3462, 3311, 3207, 1739, 1629, 1609, 1563, 1312, 1214, 1152, 973, 913, 783, 643 cm<sup>-1</sup>; mp 140.6–142.9°C; MS (FAB+) *m/z* 328 (MH<sup>+</sup>); HRMS (FAB+) calc for C<sub>12</sub>H<sub>15</sub>ClN<sub>5</sub>O<sub>4</sub> (MH<sup>+</sup>), 328.0813, found 328.0819.

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