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Synthesis of Carbon-14 Labelled 2-Amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine (SK 1875), a Potential Prodrug of Penciclovir

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SUMMARY

The synthesis of ^{14}C-2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxy-but-1-yl)purine from [1-^{14}C] diethyl malonate is described. The overall radiochemical yield of the product in a nine-step sequence was 16.1%, and the compound's radiochemical purity was 98.5%.

Key words: 2-amino-9-(3-hydroxy[^{14}C]methyl-4-isopropoxycarbonyloxybut-1-yl)purine, SK 1875 [^{14}C], antiviral agent, radiosynthesis

INTRODUCTION

An acyclonucleoside 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (penciclovir) is a potent and highly selective inhibitor of the replication of herpesviruses including herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) in cell cultures and in animals,[1-4] and of hepatitis B virus (HBV) and duck hepatitis B virus (DHBV) in cell cultures.[5,6] The antiviral spectrum of penciclovir against human herpesviruses is similar to that of 9-(2-hydroxyethoxy-methyl)guanine (acyclovir), and both compounds have comparable potency against these viruses.[7] The advantage of penciclovir over acyclovir is that its antiviral activity in cell culture is more persistent than that of acyclovir because penciclovir triphosphate is much more stable than acyclovir triphosphate within infected cells.[2,8]

However, like other acyclic nucleoside analogs such as acyclovir,[9] ganciclovir,[10] and buciclovir,[11] penciclovir has poor oral bioavailability in mice and rats.[12,13] To overcome this inadequacy, 2-amino-9-(4-acetoxy-3-acetoxymethylbut-1-yl)purine (famciclovir), the diacetyl 6-deoxy analog of penciclovir, has been developed as a prodrug of penciclovir.[12]

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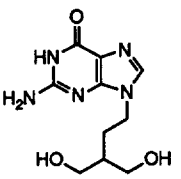
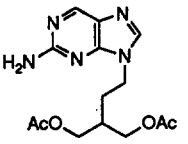


Penciclovir



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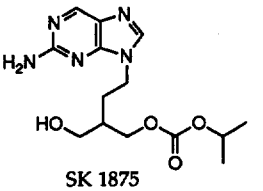


SK 1875

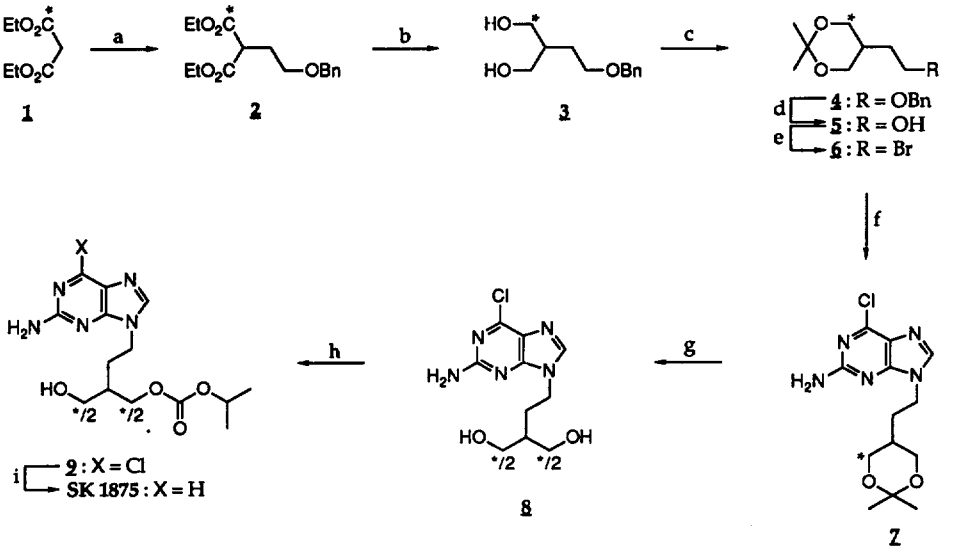
In mice, rats, and humans, famciclovir is orally well absorbed and then extensively converted to penciclovir by the enzymatic removal of two *O*-acetyl groups, followed by oxidation at the 6-position of the purine ring by xanthine oxidase.[12–14] In the U.S., famciclovir has recently been approved by the FDA for the treatment of herpes zoster (shingles) and acute recurrent genital herpes. Famciclovir has been reported to inhibit DHBV replication in chronically infected ducks,[15] to control HBV replication effectively in liver transplant patients,[16,17] and to inhibit HBV replication in a double-blind, placebo-controlled, single-center clinical trial in patients with chronic HBV infection.[18] A large, multicenter trial of famciclovir against chronic HBV infection is currently in progress.

As part of our ongoing program to develop antiviral prodrugs, we have recently prepared the amino acid esters of penciclovir[19] and a series of 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxybut-1-yl)purines[20] as potential prodrugs of penciclovir. Among them, 2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine (SK 1875) showed suitable physicochemical properties such as high solubility and stability in aqueous solution and oral penciclovir bioavailability comparable to famciclovir in mice and rats.[20] To facilitate the pharmacokinetic and metabolic studies of this new prodrug, SK 1875, we required the ^{14}C-labelled compound. Since it was anticipated that SK 1875 would undergo similar metabolic pathways as famciclovir, we decided to label the α-carbon to the oxygen atom of the acyclic moiety. In this report, we describe the synthesis of ^{14}C-2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine from [1-^{14}C] diethyl malonate.

RESULTS AND DISCUSSION

^{14}C-2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine was synthesized in nine steps from [1-^{14}C] diethyl malonate as shown in Scheme 1. Enolization of [1-^{14}C] diethyl malonate **1** with NaH in THF at 0 °C and treatment of the resulting enolate solution with 2-benzyloxyethyl bromide gave the alkylated diethyl malonate **2** in 90% yield. Reduction of the diester **2** with $LiAlH_4$ in ether at room temperature proceeded smoothly to afford the corresponding diol **3** in 90% yield, and the diol **3** was converted to the acetonide-protected compound **4** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid in a quantitative yield of 99% after chromatographic purification on silica gel. Compound **4** was debenzylated under catalytic hydrogenation condition (1 atom of H_2, 10% Pd/C,

Scheme 1[a]



*: position of label

[a](a) NaH, THF, 0 °C, 30 min; 2-benzyloxyethyl bromide, reflux, 9 h; (b) $LiAlH_4$, Et_2O, rt, overnight; (c) 2,2-dimethoxypropane, *p*-TsOH, THF, rt, overnight; (d) H_2 (1 atm), 10% Pd/C, THF, rt, overnight; (e) CBr_4, PPh_3, DMF, 0 °C, 2 h; (f) 2-amino-6-chloropurine, K_2CO_3, DMF, rt, overnight; (g) $AcOH/H_2O$ (4/1), rt, 2 h; (h) isopropyl chloroformate, pyridine, 0 °C, 2 h; (i) ammonium formate, 10% Pd/C, MeOH, reflux, 1 h.

THF, rt) to give the desired alcohol **5** in a high yield of 95%, and the resulting alcohol **5** was transformed into the bromide **6** in 85% yield using CBr_4 and PPh_3 in DMF. Alkylation of 2-amino-6-chloropurine with the bromide **6** was carried out in anhydrous DMF at room temperature using anhydrous K_2CO_3. The desired N-9 alkylated product **7** was obtained in high yield (85%) after purification on silica gel. The acetonide group of compound **7** was removed quantitatively by using $AcOH/H_2O$ (4:1) at room temperature, and the resulting crude diol **8** was subsequently treated with isopropyl chloroformate in pyridine at 0 °C to produce the mono isopropyl carbonate derivative **9** in an affordable yield of 45%. Finally, the chloro atom of the purine ring of compound **9** was removed under a catalytic hydrogen transfer hydrogenation condition using ammonium formate and a catalytic amount of 10% Pd/C in refluxing MeOH to afford the target compound, ^{14}C-2-amino-9-(3-hydroxymethyl-4-isopropoxycarbonyloxybut-1-yl)purine in 65% yield after purification on silica gel. The overall radiochemical yield of

SK 1875 from [1-^{14}C] diethyl malonate in a nine-step sequence was 16.1%, and the radiochemical purity was 98.5%.

EXPERIMENTAL

[1-^{14}C] Diethyl malonate was synthesized from potassium [^{14}C] cyanide [NEN, Boston, MA]. All solvents and reagents were of analytical grade and were used without further purification. Radioactivity was measured by a Tri-carb 2100TR liquid scintillation counter (Packard) using Lumagel Safe (LUMAC, LSC B.V.) as a liquid scintillation cocktail. High Performance Liquid Chromatography (HPLC) was performed using a Model 510 (Waters) pump equipped with a 484-tunable absorbance detector (Waters). Radiochemical purity (RCP) was determined either by an automatic TLC-linear analyser Tracemaster 20 (EG&G Berthold) or by a HPLC radioactivity monitor LB 506C-1 (EG&G Berthold) equipped with a pump, LB 5035 (EG&G Berthold) and with optiflow safe (EG&G Berthold) as the liquid scintillation cocktail. The HPLC was run on a C_{18} μ-Bondapak column (Millipore-Waters). All reactions were monitored by TLC (silica gel $60F_{254}$ plate, Merck), and ultraviolet light, iodine tank, automatic TLC-linear analyser Tracemaster 20, and X-ray film (Konica) were used in TLC visualization. For column chromatography we employed silica gel 60 (230~400 mesh; ASTM, Merck). All labelled materials were identified by chromatographic comparison with the corresponding authentic unlabelled samples. ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer; the chemical shifts are reported in parts per million (ppm) relative to TMS in $CDCl_3$ or DMSO-d_6. Electron impact mass spectra (EI-MS) were obtained on a VG Quattro mass spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Unlabelled samples, prepared by the same synthetic procedure, were used for mass spectra and elemental analyses.

Diethyl [2-(benzyloxy)ethyl] [1-^{14}C] malonate (2). To a stirred suspension of NaH (64 mg, 2.66 mmol) in anhydrous THF (15 mL) at 0 °C was added dropwise diethyl [1-^{14}C] malonate **1** (388 mg, 2.42 mmol; 1,614 MBq), and stirring was continued for 30 min at 0 °C under nitrogen. To the resulting enolate solution was slowly added 2-benzyloxyethyl bromide (572 mg, 2.66 mmol) at 0 °C, and the mixture was refluxed for 9 h. Extractive work-up ($H_2O/CHCl_3$), followed by flash column chromatography (silica gel, 20% Et_2O/hexanes) afforded the diester **2** (641 mg, 2.18 mmol, 90%; 1,453 MBq) as a colorless oil, which had a specific activity of 667 MBq/mmol: TLC RCP >98%, R_f = 0.35, silica gel, 30% Et_2O/hexanes; ^{1}H NMR ($CDCl_3$/TMS) δ 1.24 (t, J = 7.2 Hz, 6 H, 2 CH_3), 2.22 (q, J = 6.0 Hz, 2 H, $CHCH_2CH_2$), 3.53 (t, J = 6.0 Hz, 2 H, OCH_2), 3.59 (t, J = 6.0 Hz, 1 H, $CHCH_2$), 4.12–4.23 (m, 4 H, 2 OCH_2CH_3), 4.48 (s, 2 H, OCH_2Ph), 7.25–7.33 (m, 5 H, ArH). EI-MS m/z 203 ($M^+ - C_7H_7$).

4-Benzyl-2-(hydroxymethyl)-[1-^{14}C]-1,4-butanediol (3). To a stirred suspension of $LiAlH_4$ (165 mg, 4.36 mmol) in anhydrous Et_2O (5 mL) in an ice-water bath was added dropwise a solution of diester **2** (641 mg, 2.18 mmol; 1,453 MBq) in anhydrous Et_2O (5 mL); the mixture was warmed to room temperature immediately. The reaction mixture

was then stirred at room temperature under nitrogen overnight; it was then carefully quenched by adding $Na_2SO_4 \cdot 10H_2O$. After further stirring for 2 h, the resulting white precipitates were filtered off, and the filtered inorganic salt was washed thoroughly with hot THF. The combined filtrate was concentrated *in vacuo*, and the resulting residue was purified by flash column chromatography (silica gel, 3% MeOH/$CHCl_3$) to afford the diol **3** (412 mg, 1.96 mmol, 90%; 1,308 MBq) as a colorless oil, which had a specific activity of 667 MBq/mmol: TLC RCP >97%, R_f = 0.23, silica gel, 5% MeOH/$CHCl_3$; ^1H NMR ($CDCl_3$/TMS) δ 1.70 (q, *J* = 6.0 Hz, 2 H, CH_2CH_2CH), 1.83–1.92 (m, 1 H, CH), 2.62 (t, *J* = 5.7 Hz, 2 H, 2 OH), 3.58 (t, *J* = 5.7 Hz, 2 H, OCH_2CH_2), 3.64–3.78 (m, 4 H, 2 $HOCH_2CH$), 4.52 (s, 2 H, OCH_2Ph), 7.25–7.35 (m, 5 H, ArH). EI-MS *m* / *z* 192 ($M^+ - H_2O$).

5-[2-(Benzyloxy)ethyl]-2,2-dimethyl-[4-^{14}C]-1,3-dioxane (4). A mixture of diol **3** (412 mg, 1.96 mmol; 1,308 MBq) with 2,2-dimethoxypropane (612 mg, 5.88 mmol), and a catalytic amount of *p*-toluenesulfonic acid (11.2 mg, 0.59 mmol) in anhydrous THF (10 mL) was stirred overnight at room temperature and then neutralized to pH 7 with triethylamine. The reaction mixture was filtered through a silica gel pad, which was pretreated with triethylamine, and the filtrate was concentrated *in vacuo* to give an oily acetonide **4** (486 mg, 1.94 mmol, 99%; 1,295 MBq), which had a specific activity of 668 MBq/mmol: TLC RCP >96%, R_f = 0.79, silica gel, 5% MeOH/$CHCl_3$; ^1H NMR ($CDCl_3$/TMS) δ 1.41 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.55 (q, *J* = 6.3 Hz, 2 H, CH_2CH_2CH), 1.95–2.17 (m, 1 H, CH), 3.50 (t, *J* = 6.3 Hz, 2 H, OCH_2CH_2), 3.62 (dd, *J* = 12.0 Hz, *J* = 8.7 Hz, 2 H, OCH_{ax}), 3.90 (dd, *J* = 12.0 Hz, *J* = 4.5 Hz, 2 H, OCH_{eq}), 4.48 (s, 2 H, OCH_2Ph), 7.26–7.32 (m, 5 H, ArH). EI-MS *m* / *z* 250 (M^+).

2,2-Dimethyl-5-(2-hydroxyethyl)-[4-^{14}C]-1,3-dioxane (5). A solution of benzyl ether **4** (486 mg, 1.94 mmol; 1,295 MBq) in THF (10 mL) was stirred overnight in a H_2 atmosphere (a balloon) in the presence of 10% Pd/C (50 mg) at room temperature. The resulting mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness *in vacuo* to afford the alcohol **5** (295 mg, 1.85 mmol, 95%; 1,230 MBq) as a colorless oil, which had a specific activity of 665 MBq/mmol: TLC RCP >80%, R_f = 0.25, silica gel, 5% MeOH/$CHCl_3$; ^1H NMR ($CDCl_3$/TMS) δ 1.42 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.55 (q, *J* = 6.6 Hz, 2 H, CH_2CH_2CH), 1.84 (br s, 1 H, OH), 1.91–2.01 (m, 1 H, CH), 3.64 (dd, *J* = 12.0 Hz, *J* = 8.1 Hz, 2 H, OCH_{ax}), 3.66–3.72 (m, 2 H, $HOCH_2CH_2$), 3.91 (dd, *J* = 12.0 Hz, *J* = 4.5 Hz, 2 H, OCH_{eq}). EI-MS *m* / *z* 142 ($M^+ - H_2O$).

5-(2-Bromoethyl)-2,2-dimethyl-[4-^{14}C]-1,3-dioxane (6). To a solution of alcohol **5** (295 mg, 1.85 mmol; 1,230 MBq) and CBr_4 (1.84 g, 5.55 mmol) in anhydrous DMF (20 mL) at 0 °C was added Ph_3P (1.45 g, 5.55 mmol) in one portion, and the mixture was stirred for 2 h at 0 °C. The reaction mixture was partitioned between hexanes and H_2O, and the aqueous layer was extracted once with Et_2O. The combined organic layer was washed with H_2O, saturated $NaHCO_3$, and saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a yellowish residue. The crude residue was purified by flash column chromatography (silica gel, 10% Et_2O/hexanes) to afford the bromide **6** (359 mg, 1.57 mmol, 85%; 1,046 MBq) as a colorless oil, which had a specific activity of

666 MBq/mmol: TLC RCP >97%, R_f = 0.25, silica gel, 20% Et_2O/hexanes; ^1H NMR ($CDCl_3$/TMS) δ 1.41 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.90–1.99 (m, 3 H, $CHCH_2CH_2$), 3.43 (t, J = 6.6 Hz, 2 H, $BrCH_2CH_2$), 3.61 (dd, J = 12.0 Hz, J = 6.6 Hz, 2 H, OCH_{ax}), 3.96 (dd, J = 12.0 Hz, J = 3.9 Hz, 2 H, OCH_{eq}). Anal. Calcd for $C_8H_{15}BrO_2$: C, 43.07; H, 6.78. Found: C, 42.83; H, 6.95.

2-Amino-6-chloro-9-[2-(2,2-dimethyl-[4-^{14}C]-1,3-dioxan-5-yl)ethyl]purine (7). A mixture of 2-amino-6-chloropurine (400 mg, 2.36 mmol) with bromide **6** (350 mg, 1.57 mmol; 1,046 MBq), and anhydrous K_2CO_3 in anhydrous DMF (20 mL) was stirred overnight at room temperature under nitrogen, and the mixture was filtered. The filtrate was evaporated to dryness *in vacuo*, and the resulting residue was purified by flash column chromatography (silica gel, 75% EtOAc/hexanes) to afford the N-9 alkylated product **7** (416 mg, 1.33 mmol, 85%; 889 MBq) as a white solid, which had a specific activity of 668 MBq/mmol: TLC RCP >98%, R_f = 0.66, silica gel, 20% MeOH/$CHCl_3$; ^1H NMR (DMSO-d_6) δ 1.27 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.52–1.63 (m, 1 H, CH), 1.71–1.79 (m, 2 H, $CHCH_2CH_2$), 3.54 (dd, J = 11.7 Hz, J = 8.7 Hz, 2 H, OCH_{ax}), 3.79 (dd, J = 11.7 Hz, J = 4.2 Hz, 2 H, OCH_{eq}), 4.07 (t, J = 7.2 Hz, 2 H, NCH_2), 6.90 (br s, 2 H, NH_2), 8.17 (s, 1 H, H-8). Anal. Calcd for $C_{13}H_{18}ClN_5O_2$: C, 50.08; H, 5.82; N, 22.46. Found: C, 50.29; H, 5.97; N, 22.27.

2-Amino-6-chloro-9-(4-hydroxy-3-hydroxy[^{14}C]methylbut-1-yl)purine (8). Acetonide **7** (416 mg, 1.33 mmol; 889 MBq) was dissolved in AcOH/H_2O (4/1, 20 mL), and the solution was stirred at room temperature for 2 h. All solvents were removed completely under reduce pressure to give the diol **8** (362 mg, 1.33 mmol, 100%; 889 MBq) as a white solid, which had a specific activity of 668 MBq/mmol: TLC RCP >98%, R_f = 0.33, silica gel, 20% MeOH/$CHCl_3$; ^1H NMR (DMSO-d_6) δ 1.38–1.52 (m, 1 H, CH), 1.74–1.81 (m, 2 H, $CHCH_2CH_2$), 3.32–3.46 (m, 4 H, 2 OCH_2), 4.12 (t, J = 7.2 Hz, 2 H, NCH_2), 4.41 (br s, 2 H, 2 OH), 6.88 (br s, 2 H, NH_2), 8.14 (s, 1 H, H-8). Anal. Calcd for $C_{10}H_{14}ClN_5O_2$: C, 44.21; H, 5.19; N, 25.78. Found: C, 44.39; H, 5.36; N, 25.65.

2-Amino-6-chloro-9-(3-hydroxy[^{14}C]methyl-4-isopropoxycarbonyloxybut-1-yl)purine (9). To a stirred solution of diol **8** (362 mg, 1.33 mmol; 889 MBq) in anhydrous pyridine (30 mL) at 0 °C was added dropwise isopropyl chloroformate (2.66 mL, 2.66 mmol, 1.0 M solution in toluene), and the mixture was stirred at 0 °C for 2 h under nitrogen. The reaction was quenched with MeOH, and the reaction mixture was evaporated to dryness *in vacuo*. The resulting yellow residue was purified by flash column chromatography (silica gel, 4% MeOH/$CHCl_3$) to afford the mono-carbonate **9** (219 mg, 0.60 mmol, 45%; 400 MBq) as a white solid, which had a specific activity of 667 MBq/mmol: TLC RCP >98.5%, R_f = 0.27, silica gel, 10% MeOH/$CHCl_3$; ^1H NMR (DMSO-d_6) δ 1.20 (d, J = 6.0 Hz, 6 H, $CH(CH_3)_2$), 1.65–1.88 (m, 3 H, $CHCH_2CH_2$), 3.41(t, J = 5.1 Hz, 2 H, CH_2OH), 4.00–4.10 (m, 2 H, OCH_2), 4.12 (t, J = 7.2 Hz, 2 H, NCH_2), 4.65 (t, J = 5.1 Hz, 1 H, OH), 4.72 (septet, J = 6.0 Hz, 1 H, $CH(CH_3)_2$), 6.88 (br s, 2 H, NH_2), 8.14 (s, 1 H, H-8). Anal. Calcd for $C_{14}H_{20}ClN_5O_4$: C, 47.00; H, 5.63; N, 19.57. Found: C, 47.11; H, 5.67; N, 19.42.

2-Amino-9-(3-hydroxy[^{14}C]methyl-4-isopropoxycarbonyloxybut-1-yl)purine (SK 1875). A mixture of carbonate **9** (219 mg, 0.60 mmol; 400 MBq) with ammonium

formate (190 mg, 3.01 mmol), and 10% Pd/C (20 mg) in MeOH was refluxed for 1 h, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, 5% MeOH/$CHCl_3$) to afford the 6-deoxycarbonate **(SK 1875)** (126 mg, 0.39 mmol, 65%; 260 MBq) as a white solid, which had a specific activity of 667 MBq/mmol: radio-HPLC RCP 98.5%, Column μ-Bondapak C_{18} (3.9 x 150 mm), Eluent CH_3CN/5 mM KH_2PO_4 in H_2O (13/87, v/v), Flow rate 1.0 mL/min, Detector UV 248 nm, Retention time 20.75 min; ^1H NMR (DMSO-d_6) δ 1.20 (d, J = 6.0 Hz, 6 H, $CH(CH_3)_2$), 1.65–1.91 (m, 3 H, $CHCH_2CH_2$), 3.41(t, J = 5.1 Hz, 2 H, CH_2OH), 4.01–4.10 (m, 2 H, OCH_2), 4.12 (t, J = 6.9 Hz, 2 H, NCH_2), 4.66 (t, J = 5.1 Hz, 1 H, OH), 4.72 (septet, J = 6.0 Hz, 1 H, $CH(CH_3)_2$), 6.46 (br s, 2 H, NH_2), 8.07 (s, 1 H, H-8), 8.55 (s, 1 H, H-6). Anal. Calcd for $C_{14}H_{21}N_5O_4$: C, 52.00; H, 6.55; N, 21.66. Found: C, 52.20; H, 6.64; N, 22.06.

REFERENCES

1. Harnden, M. R., Jarvest, R. L., Bacon, T. H., and Boyd, M. R. – J. Med. Chem. 30: 1636 (1987).
2. Boyd, M. R., Bacon, T. H., Sutton, D., and Cole, M. – Antimicrob. Agents Chemother. 31: 1238 (1987).
3. Boyd, M. R., Bacon, T. H., and Sutton, D. – Antimicrob. Agents Chemother. 32: 358 (1988).
4. Sutton, D., and Boyd, M. R. – Antimicrob. Agents Chemother. 37: 642 (1993).
5. Korba, B. E., and Boyd, M. R. – Antimicrob. Agents Chemother. 40: 1282 (1996).
6. Jacobson, M. A., de Miranda, P., Cederberg, D. M., Burnett, T., Cobb, E., Brodie, H. R., and Mills, J. – Antimicrob. Agents Chemother. 31: 1251 (1987).
7. Boyd, M. R., Safrin, S., and Kern, E. R. – Antiviral Chem. Chemother. 4 (Suppl. 1): 3 (1993).
8. Bacon, T. H., and Schinazi, R. F. – Antiviral Chem. Chemother. 4 (Suppl. 1): 25 (1993).
9. de Miranda, P., Krasny, H. C., Page, D. A., and Elion, G. B. – J. Pharmacol. Exp. Ther. 219: 309 (1981).
10. Jacobson, M. A., de Miranda, P., Cederberg, D. M., Burnette, T., Cobb, E., Brodie, H, R., and Mills, J. – Antimicrob. Agents Chemother. 31: 1251 (1987).
11. Larsson, A., Stenberg, K.. Ericson, A.-C., Haglund, U., Yisak, W.-A., Johansson, N. G., Öberg, B., and Datema, R. – Antimicrob. Agents Chemother. 30: 598 (1986).
12. Harnden, M. R., Jarvest, R. L., Boyd, M. R., Sutton, D., and Vere Hodge, R. A. – J. Med. Chem. 32: 1738 (1989).
13. Vere Hodge, R. A., Sutton, D., Boyd, M. R., Harnden, M. R., and Jarvest, R. L. – Antimicrob. Agents Chemother. 33: 1765 (1989).
14. Pue, M. A.,.and Benet, L. Z. – Antiviral Chem. Chemother. 4 (Suppl. 1): 47 (1993).
15. Tsiquaye, K. N., Slomka, M. J., and Maung, M. – J. Med. Virol. 42: 306 (1994).
16. Krüger, M., Tillmann, H. L, Trautwein, C., Bode, U., Oldhafer, K., Böker, K. H. W.,

Pichlmayr, R., and Manns, M. P. – In Proceedings of the American Association for the Study of Liver Disease: 45th Annual Meeting p. 134 (1994).

17. Böker, K. H. W., Ringe, B., Krüger, M., Pichlmayr, R., and Manns, M. P. – Transplantation 57: 1706 (1994).
18. Main, J., Brown, J. L., Karayiannis, P., Georgiou, P., Boyd, M., Prince, W., and Thomas H. – J. Hepatol. 21 (Suppl. 1): S32 (1994).
19. Kim, D.-K., Lee, N., Im, G.-J., Kim, Y.-W., Chang, K., Kim, H.-T., Cho, Y.-B., Choi, W.-S., Jung, I., and Kim, K. H. – Bioorg. Med. Chem. Lett. 6: 1849 (1996).
20. Kim, D.-K., Lee, N., Kim, Y.-W., Chang, K., Kim, J.-S., Im, G.-J., Choi, W.-S., Jung, I.. Kim, T.-S., Hwang, Y.-Y., Min, D.-S., Um, K. A., Choi, Y.-B., and Kim, K. H. – J. Med. Chem. 41: 3435 (1998).

