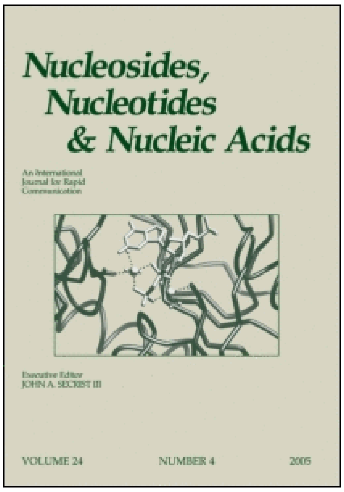

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# Synthesis and Studies of 3′-*C*-Trifluoromethyl-β-D-ribonucleosides Bearing the Five Naturally Occurring Nucleic Acid Bases[#]

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## ABSTRACT

3′-*C*-Trifluoromethyl-β-D-ribonucleoside derivatives bearing the five naturally occurring nucleic acid bases have been synthesized. All these derivatives were prepared by glycosylation reactions of purine and pyrimidine bases with a suitable peracylated 3-*C*-trifluoromethyl ribofuranose precursor. After deprotection, the resulting title nucleoside analogues were tested for their inhibitory properties against the replication of HIV, HBV and several RNA viruses. However, none of these compounds showed significant antiviral activity.

*Key Words:* 3′-*C*-Trifluoromethyl-β-D-ribonucleosides; Antiviral agents.

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[#] In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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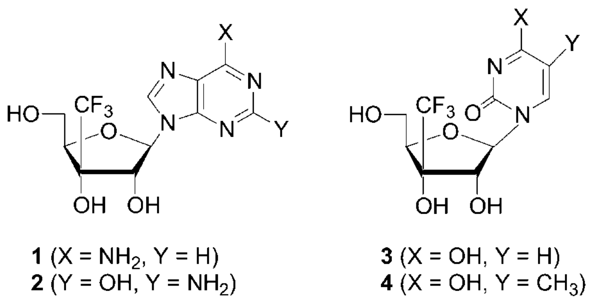
## INTRODUCTION

Nucleoside analogues represent one of the main classes of therapeutic agents for the treatment of viral affections. To date, numerous nucleoside derivatives have been approved by the FDA for the treatment of various viral diseases including Herpes viruses, Human Immunodeficiency Virus (HIV) and Hepatitis B virus (HBV) infections.[1] The mechanism of action of those compounds is based upon the intracellular phosphorylation to their 5′-triphosphate form which can interact with virus-specific polymerases, acting as inhibitors or chain terminator of viral nucleic acid synthesis. In order to discover new nucleoside derivatives endowed with potent antiviral activity, modifications of the base and/or the sugar moiety of natural nucleosides can be attempted. As a part of our ongoing research program on trifluoromethyl nucleoside analogues,[2–5] we have synthesized 3′-*C*-trifluoromethyl-β-D-ribonucleoside derivatives bearing the five naturally occurring nucleic acid bases (**1**–**5**) (Chart 1). Compounds **1**, **3** and **4** have been previously reported.[6] Nevertheless, we decided to undertake the synthesis of these 3′-*C*-$CF_3$-ribonucleosides of adenine (**1**), uracil (**3**) and thymine (**4**) as well as the synthesis of the hitherto unknown derivatives of guanine (**2**) and cytosine (**5**) in order to perform the antiviral evaluation of the whole series against HIV, HBV and several RNA viruses.

## RESULTS AND DISCUSSION

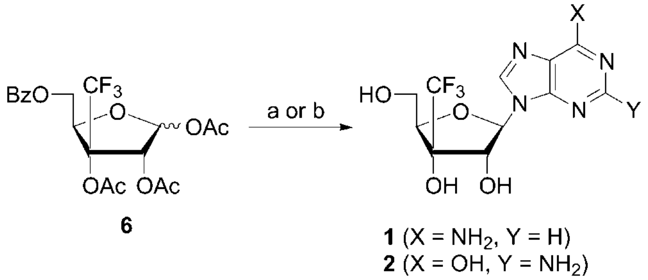
The synthesis began with the preparation of an appropriate trifluoromethyl sugar precursor, namely, 1,2,3-tri-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranose (**6**) that was obtained from commercially available D-xylose following a procedure previously described in the literature.[6] The syntheses of the purine derivatives (**1**, **2**) are depicted in Sch. 1. A glycosylation reaction with adenine and **6** in acetonitrile using stannic [tin(IV)] chloride as a catalyst afforded 9-(2,3-di-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranosyl)adenine in 45%. Total deprotection of the latter with methanolic ammonia provided crystalline nucleoside **1**. For the preparation of the guanosine analogue **2**, a condensation reaction of



**1** (X = $NH_2$, Y = H)
**2** (Y = OH, Y = $NH_2$)

**3** (X = OH, Y = H)
**4** (X = OH, Y = $CH_3$)
**5** (X = $NH_2$, Y = H)

*Chart 1.*

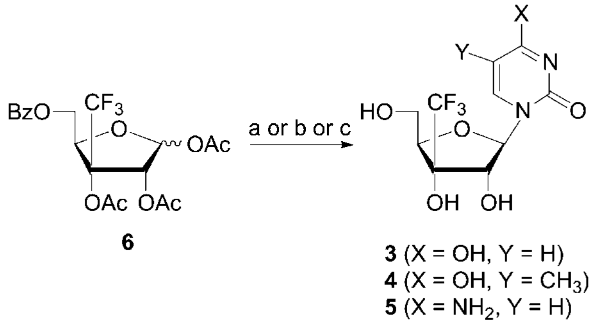


***Scheme 1.*** *Reagents and conditions*: a) 1) Adenine, $SnCl_4$, $CH_3CN$, r.t.; 2) $MeOH/NH_3$, r.t.; b) 1) silylated 2-amino-6-chloropurine, TMSOTf, toluene, reflux; 2) $HS(CH_2)_2OH$, MeONa, MeOH, reflux.

silylated 2-amino-6-chloropurine with **6** was carried out under Vorbrüggen conditions using trimethylsilyl trifluoromethane sulfonate (TMSOTf) as a catalyst in refluxing toluene to afford the protected intermediate 2-amino-6-chloro purine 3′-*C*-trifluoromethyl 9-β-D-riboside. After purification, the latter was directly treated with 2-mercaptoethanol and sodium methanolate in refluxing methanol[7] to provide the target nucleoside **2** in 30% overall yield.

The syntheses of the 3′-*C*-trifluoromethyl β-D-ribonucleoside pyrimidine derivatives are depicted in Sch. 2. Briefly, glycosylation reactions with uracil or thymine and sugar **6**, under Vorbrüggen conditions, using TMSOTf as a catalyst in anhydrous acetonitrile at 50°C afforded 1-(2,3-di-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranosyl) nucleosides of uracil and thymine which were directly deprotected using methanolic ammonia to give compounds **3** and **4**.

The cytosine derivative **5** was obtained from the protected 3′-*C*-CF3 ribonucleoside of uracil by using the nitrophenylation-ammonolysis procedure.[8]



***Scheme 2.*** *Reagents and conditions*: a) 1) silylated uracil, TMSOTf, $CH_3CN$, r.t.; 2) $MeOH/NH_3$; b) 1) silylated thymine, TMSOTf, $CH_3CN$, r.t.; 2) $MeOH/NH_3$, r.t.; c) 1) silylated uracil, TMSOTf, $CH_3CN$, r.t.; 2) 1-methylpyrrolidine, $CH_3CN$, $(CF_3CO)_2O$, 0°C; 3) 4-nitrophenol, 0°C; 4) concd aq $NH_3$/dioxane, 55°C; 5) $MeOH/NH_3$, r.t.

## BIOLOGICAL RESULTS

The title nucleosides **1**–**5** were tested for their effects on the replication of HIV, HBV and several RNA viruses (including yellow fever virus and bovine viral diarrhea virus) in cell culture experiments. However, none of these compounds showed marked antiviral effects or detectable alteration of host-cell morphology at the highest concentration tested (generally 100 μM), with the exception of 3′-*C*-CF3 adenosine (**1**) [MT-4 cells ($CC_{50} = 66\,\mu M$)].

## CONCLUSION

The syntheses of 3′-*C*-trifluoromethyl-β-D-ribonucleosides bearing the five naturally occurring acid bases were undertaken with the hope to discover new nucleoside derivatives endowed with antiviral effects. However, none of the target compounds exhibited significant antiviral activity. Several factors could be responsible for the inactivity of these nucleoside derivatives. Their inability to enter cells or to serve as substrates for intracellular enzymes catalysing phosphorylation, as well as a lack of inhibition of viral polymerases by their triphosphate forms, would all account for their antiviral inactivity. Further research would be needed to support these hypotheses, but since no significant antiviral activity emerged both from previously reported work[6] and from the present data, it does not seem worthwhile to pursue additional studies on 3′-*C*-trifluoromethyl-β-D-ribonucleoside analogues.

## EXPERIMENTAL SECTION

Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are uncorrected. UV spectra were recorded on an Uvikon 931 (Kontron) spectrophotometer. $^1H$ NMR spectra were recorded at 400 MHz, $^{13}C$ NMR spectra at 100 MHz and $^{19}F$ NMR at 235 MHz in $(CD_3)_2SO$ at ambient temperature with a Brüker DRX 400. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual solvent peak, $(CD_3)CD_2HSO$ being set at $\delta$-$_H$ 2.49 and $\delta$-$_C$ 39.5 relative to tetramethylsilane (TMS). $^{19}F$ chemical shifts are reported using trichlorofluoromethane as external reference. Deuterium exchange and COSY experiments were performed in order to confirm proton assignments. Coupling constants, *J*, are reported in Hertz. 2D $^1H$-$^{13}C$ heteronuclear COSY were recorded for the attribution of $^{13}C$ signals. FAB mass spectra were recorded in the positive-ion or negative-ion mode on a JEOL SX 102. The matrix was a mixture (50:50, v/v) of glycerol and thioglycerol (G-T), or 3-nitrobenzyl alcohol (NBA). Specific rotations were measured on a Perkin-Elmer Model 241 spectropolarimeter (path length 1 cm), and are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). Thin layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 $F_{254}$ (Merck, Art. 5554), visualization of products being accomplished by UV absorbency followed by charring with 5% ethanolic sulfuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385). All moisture-sensitive reactions were carried out under rigorous anhydrous conditions and under an argon atmosphere using oven-dried glassware. Solvents were dried and distilled prior to use and solids were dried over $P_2O_5$ under reduced pressure.

**9-(3-*C*-Trifluoromethyl-β-D-ribofuranosyl)adenine (1).** Stannic chloride (0.4 mL, 3.41 mmol) was added cautiously to a stirred suspension of adenine (0.25 g, 1.85 mmol) and 1,2,3-tri-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranose **6** (0.7 g, 1.56 mmol) in dry acetonitrile (14 mL) at room temperature. After 72 h, pyridine (6 mL) was added to the resultant solution. The white precipitate was filtered and washed with chloroform (3×50 mL). The combined filtrates were washed with a solution of saturated sodium hydrogen carbonate (3×100 mL), water (3×100 mL), dried over sodium sulfate and evaporated. Silica gel column chromatography of the residue using a stepwise gradient of methanol (1–2%) in dichloromethane afforded 9-(2,3-di-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranosyl)adenine (367 mg, 45%) as a white foam. A solution of 9-(2,3-di-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranosyl)adenine (0.367 mg, 0.7 mmol) in methanolic ammonia (previously saturated at −10°C and tightly stoppered) (20 mL) was stirred for 14 h at room temperature, then evaporate to dryness. Crystallisation in MeOH gave compound **1** (160 mg, 64%). Melting point = 247°C (mp > 250°C lit.[6]). $[\alpha]_D^{20}$-15 ($c = 1.02$, DMSO). UV (Ethanol 95) $\lambda_{max}$ 258 nm, (ε 14800). NMR $^1H$ (DMSO-$d_6$, 400 MHz) δ 8.41 (1H, s, H-8), 8.15 (1H, s, H-2), 7.35 (2H, br s, $NH_2$), 6.58 (1H, br s, OH), 6.16 (1H, br s, OH), 5.89 (1H, d, $J_{1'\text{-}2'} = 7.8$ Hz, H-1′), 5.34 (1H, br s, OH), 5.14 (1H, d, H-2′), 4.06 (1H, t, $J_{4'\text{-}5',5''} = 4.2$ Hz, H-4′), 3.68 (2H, m, H-5′ and H-5″). NMR $^{13}C$ (DMSO-$d_6$, 100 MHz) δ 157 (C-6), 153.5 (C-2), 150.4 (C-4), 141.1 (C-8), 127 (q, $^1J_{C\text{-}F} = 279$ Hz, $CF_3$), 120.1 (C-5), 86.9 (C-1′), 86.5 (C-4′), 78.7 (q, $^2J_{C\text{-}F} = 28.8$ Hz, C-3′), 72.5 (C-2′), 61 (C-5′). NMR $^{19}F$ (DMSO-$d_6$, 235 MHz) δ −73.8 (s, $CF_3$). SM FAB$^+$ (GT) m/z 336 $(M + H)^+$, 136 $(BH_2)^+$. FAB$^-$ (GT) m/z 334 $(M - H)^-$, 134 $(B)^-$. Anal. Calcd. for $C_{11}H_{12}F_3N_5O_4.0.6\ H_2O$ : C, 38.18, H, 3.84, N, 20.24, F, 16.47. Found : C, 38.28, H, 3.71, N, 20.05, F, 16.41.

**9-(3-*C*-Trifluoromethyl-β-D-ribofuranosyl)guanine (2).** To a suspension of 2-amino-6-chloropurine (0.42 g, 2.48 mmol) in anhydrous toluene (10 mL) was added *N*,*O*-bis(trimethylsilyl) acetamide (2.2 mL, 9 mmol). The suspension was refluxed for 2 hours, then 1,2,3-tri-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-D-ribofuranose (**6**) (1 g, 2.23 mmol), previously dissolved in anhydrous toluene (10 mL), and TMSOTf (0.52 mL, 2.7 mmol) were added. The reaction was refluxed for 4 hours then diluted with ethyl acetate (30 mL) and washed with a saturated sodium hydrogen carbonate solution (2 × 30 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified using a silica gel column chromatography [eluent:ethyl acetate/petroleum ether (1/1)] to afford 2-amino-6-chloro-9-(2,3-di-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranosyl)purine (0.50 g, 40%) as a white foam. To a solution of 2-amino-6-chloro-9-(2,3-di-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranosyl)purine (0.85 g, 1.53 mmol) in methanol (128 mL) were added 2-mercaptoethanol (0.43 mL, 6.13 mmol) and sodium methylate (0.33 g, 6.12 mmol). The reaction was refluxed for 12 hours, then neutralised with a 1N chlorhydric acid solution. After evaporation under reduced pressure the crude product was subjected to silica gel column chromatography using a stepwise gradient of methanol (10–50%) in dichloromethane to afford 9-(3-*C*-trifluoromethyl-β-D-ribofuranosyl)guanine (0.4 g, 74%) which was crystallised from water after filtration over Millex HV filter. Melting point > 350°C. $[\alpha]_D^{20} + 4$ ($c = 1.01$, DMSO). UV (Ethanol 95) $\lambda_{max}$ 252 nm, (ε 9500). NMR $^1$H (DMSO-$d_6$, 400 MHz) δ 10.75 (1H, br s, N-H), 8.07 (1H, s, H-8), 6.56 (3H, br s, $NH_2 + OH$), 6.25 (1H, br s, OH), 5.78 (1H, d, $J_{1'-2'} = 7.8$ Hz, H-1′), 5.19 (1H, t, $J = 4.8$ Hz, OH-5′), 4.93 (1H, d, H-2′), 4.04 (1H, m, H-4′), 3.69 (2H, m, H-5′ and H-5″). NMR $^{13}$C (DMSO-$d_6$, 100 MHz) δ 157.6 (C-6), 154.7 (C-2), 152.7 (C-4), 136.6 (C-8), 125.6 (q, $^1J_{C\text{-}F} = 284.5$ Hz, $CF_3$), 117.5 (C-5), 86.1 (C-4′), 85.4 (C-1′), 78.6 (q, $^2J_{C\text{-}F} = 28.4$ Hz, C-3′), 73 (C-2′), 60.8 (C-5′). NMR $^{19}$F (DMSO-$d_6$, 235 MHz) δ −73.9 (s, $CF_3$). Anal. Calcd. for $C_{11}H_{12}F_3N_5O_5$.0.9 $H_2O$ : C, 35.96, H, 3.79, N, 19.06, F, 15.51. Found : C, 36.09, H, 3.57, N, 18.71, F, 15.27.

**1-(3-*C*-Trifluoromethyl-β-D-ribofuranosyl)uracil (3).** The preparation of compound **3** was achieved following a protocol already reported in the literature.[6] Melting point = 267–268°C (mp > 250°C lit.[6]). $[\alpha]_D^{20} + 3$ ($c = 1.05$, DMSO). UV (Ethanol 95) $\lambda_{max}$ 258 nm, (ε 10900). NMR $^1$H (DMSO-$d_6$, 400 MHz) δ 11.57 (1H, br s, N-H), 8.11 (1H, d, $J_{6\text{-}5} = 8.1$ Hz, H-6), 6.69 (1H, br s, OH), 6.29 (1H, br s, OH), 6.05 (1H, d, $J_{1'-2'} = 7.8$ Hz, H-1′), 5.87 (1H, d, H-5), 5.34 (1H, br s, OH-5′), 4.55 (1H, d, H-2′), 4.12 (1H, m, H-4′), 3.78 (2H, m, H-5′ and H-5″). NMR $^{13}$C (DMSO-$d_6$, 100 MHz) δ 163.8 (C-4), 151.8 (C-2), 141.8 (C-6), 125.5 (q, $^1J_{C\text{-}F} =$ 280 Hz, $CF_3$), 103.4 (C-5), 86.4 (C-1′), 85.6 (C-4′), 78.6 (q, $^2J_{C\text{-}F} = 28.6$ Hz, C-3′), 72.6 (C-2′), 60.6 (C-5′). NMR $^{19}$F (DMSO-$d_6$, 235 MHz) δ −74.1 (s, $CF_3$). SM FAB$^+$ (GT) m/z 313 $(M + H)^+$, 201 $(S)^+$, 113 $(BH_2)^+$. FAB$^-$ (GT) m/z 311 $(M - H)^-$, 111 $(B)^-$. Anal. Calcd. for $C_{10}H_{11}F_3N_2O_6$ : C, 38.47, H, 3.55, N, 8.97. Found: C, 38.82, H, 3.65, N, 9.00.

**1-(3-*C*-Trifluoromethyl-β-D-ribofuranosyl)thymine (4).** The preparation of compound **4** was achieved following a protocol already reported in the literature.[6] $[\alpha]_D^{20} + 1$ ($c = 1.00$, DMSO). UV (Ethanol 95) $\lambda_{max}$ 263 nm, (ε 10300). NMR $^1$H (DMSO-$d_6$, 400 MHz) δ 11.00 (1H, br s, N-H), 7.84 (1H, d, $J_{6\text{-}CH3} = 0.8$ Hz, H-6), 6.30 (1H, br s, OH), 5.94 (1H, d, $J_{1'-2'} = 8$ Hz, H-1′), 5.30 (1H, br s, OH), 4.47 (1H, d, H-2′), 4.00 (1H, m, H-4′), 3.68 (2H, m, H-5′ and H-5″), 1.86 (3H, s, $CH_3$). NMR $^{13}$C (DMSO-$d_6$, 100 MHz) δ 164.6 (C-4), 152.0 (C-2), 137.1 (C-6), 125.6 (q, $^1J_{C\text{-}F} = 285$ Hz, $CF_3$), 110.9 (C-5), 86.1 (C-1′), 85.5 (C-4′), 78.5 (q, $^2J_{C\text{-}F} = 28.9$ Hz, C-3′), 72.3 (C-2′), 60.6 (C-5′), 13.0 ($CH_3$). NMR $^{19}$F (DMSO-$d_6$, 235 MHz) δ −74.0 (s, $CF_3$). SM FAB$^+$ (GT) m/z 327 $(M + H)^+$, 127 $(BH_2)^+$. FAB$^-$ (GT) m/z 325 $(M - H)^-$, 125 $(B)^-$. Anal. Calcd. for $C_{11}H_{13}F_3N_2O_6$.0.9 $H_2O$ : C, 38.58, H, 4.36, N, 8.18,.F 16,64. Found : C, 38.69, H, 4.22, N, 8.10, F 16.60.

**1-(3-*C*-Trifluoromethyl-β-D-ribofuranosyl)cytosine (5).** A solution of 1-(2,3-di-*O*-acetyl-5-*O*-benzoyl-3-*C*-trifluoromethyl-β-D-ribofuranosyl)uracil[6] (0.804 g, 1.61 mmol) and 1-methyl-pyrrolidine (1.6 mL, 15.38 mmol) in anhydrous acetonitrile (8 mL) was cooled to 0°C. Trifluoroacetic anhydride (0.57 mL, 4.03 mmol) was then added. After 45 minutes at 0°C, 4-nitrophenol (0.67 g, 4.82 mmol) was added to the

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solution. After stirring for 18 hours at 0°C, the solution was then poured into a solution of saturated sodium hydrogen carbonate (50 mL), and the resultant mixture was extracted with dichloromethane (3×50 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was dissolved in dioxane (8 mL) and concentrated aqueous ammonia (1.6 mL, *d* 0.89), and stirred at 55°C for 12 hours. The resulting yellow solution was concentrated under reduced pressure and directly treated with methanolic ammonia (previously saturated at −10°C and tightly stoppered) (32 mL) for 12 hours at room temperature. After evaporation to dryness under reduced pressure, the residue was subjected to silica gel column chromatography, with a stepwise gradient of methanol (10–20%) in dichloromethane to afford the title compound **5** (0.13 g, 26%). An analytical sample of **5** was obtained as its chlorhydrate salt. Melting point = 240°C. $[\alpha]_D^{20} + 13$ ($c = 1.00$, DMSO). UV (Ethanol 95) $\lambda_{max}$ 272 nm, ($\varepsilon$ 9000). NMR $^1$H (DMSO-$d_6$, 400 MHz) $\delta$ 9.93 and 8.82 (3H, 2 x br s, $NH_3^+$), 8.24 (1H, d, $J_{6\text{-}5} = 7.8$ Hz, H-6), 6.62 (1H, br s, OH), 6.21 (2H, m, H-5 and OH), 5.86 (1H, d, $J_{1'\text{-}2'} = 7.5$ Hz, H-1′), 4.36 (1H, d, H-2′), 3.99 (1H, m, H-4′), 3.58 (2H, m, H-5′ and H-5″). NMR $^{13}$C (DMSO-$d_6$, 100 MHz) $\delta$ 160.3 (C-4), 148.5 (C-2), 145.5 (C-6), 125.3 (q, $^1J_{C\text{-}F} = 284$ Hz, $CF_3$), 95.9 (C-5), 87.5 (C-1′), 86.1 (C-4′), 78.6 (q, $^2J_{C\text{-}F} = 29$ Hz, C-3′), 73.6 (C-2′), 60.4 (C-5′). NMR $^{19}$F (DMSO-$d_6$, 235 MHz) $\delta$ −74.0 (s, $CF_3$). Anal. Calcd. for $C_{10}H_{13}ClF_3N_3O_5.1.3\ H_2O$ : C, 32.37, H, 4.24, N, 11.32. Found: C, 32.28, H, 3.90, N, 11.25.

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