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# Synthesis and biological evaluation of fluorinated acyclothionucleosides

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ABSTRACT

The discovery of thio- and fluoro-nucleosides as antiviral or anticancer agents prompts us to explore the synthesis of acyclic analogues. In this paper is reported the preparation of acyclothionucleosides by the alkylation of nucleic bases with difluorothio-esters and -alcohols. Compounds structurally close to known antiviral agents were tested towards a large variety of viruses.



## 1. Introduction

The synthesis and the biological evaluation of acyclic nucleosides are still growing-up since the discovery of such compounds as antiviral agents. For example, the synthesis of acyclovir, ganciclovir or even PMEA has attracted considerable attention (Fig. 1). Their modifications have been studied to prepare new modified nucleosides with improved properties by the replacement of the oxygen atom by a carbon atom [1] or a nitrogen atom (azanucleoside) [2]. However, the insertion of a sulfur atom in their side chain was less studied [3], although this modification was successful in the discovery of antiviral agents, such as Lamivudine [4].

It is well established that the introduction of fluorine atoms onto a nucleosides enhances their biological properties. Since the last decade a number of 2′-(di)fluoronucleosides have been described [5]. The replacement of a hydrogen atom or a hydroxyl group by a fluorine atom often afforded new nucleosides with potent antiviral or anticancer properties. For example, substitution of the hydrogen atoms at the C-2′ of deoxycitidine by fluorine atoms resulted in the formation of Gemcitabine, a nucleoside with high anticancer activity [6]. These observations are also true in the case of acyclonucleosides as described for the fluoromethyl derivative of PMEA (FPMPA), which was found to be highly active against retroviruses [7].

In contrast, only few articles describe the synthesis of acyclic nucleosides in which a fluoromethylene group is introduced in the side chain of the purinic or pyrimidic bases. The most recent example, reported by Haufe, described the synthesis of constrained monofluorinated nucleoside analogues **I** (Fig. 2) [8]. These analogues have shown a low but specific activity against HSV-1 and HSV-2. To our knowledge only one paper reported the synthesis of *gem*-difluorinated carba-analogues of acyclovir **II** (Fig. 2). This latter showed an antiviral activity [9], but lower than the acyclovir.

In view of these promising results, we decided to explore the synthesis and biological studies of *gem*-difluoro-acyclothionucleosides. In this paper, are described our attempts in the preparation of acyclothionucleosides **III** and **IV** containing a difluoromethylene group in the side chain (Fig. 3). The evaluation of their biological activities towards a large variety of viruses is also reported.

## 2. Results and discussion

In connection with our scientific program concerning the synthesis of fluorosulfides, we explored the synthesis of a variety of thionucleosides from the functionnalized thioesters **1** and **2** (Fig. 3) [10]. The readily available starting material **1** was obtained according to the nucleophilic fluorination method previously described [10,11]. The careful hydrolysis of **1** at 0 °C in the presence of potassium carbonate afforded the expected alcohol **3** in 68% yield (Scheme 1). The treatment of **1** by other bases (*t*BuOK, KOH) or by working at room temperature induced a total degradation of the alcohol **3**, probably due to the formation of the corresponding unstable thiolate. Reaction of the alcohol **3** with the appropriate alkylsulfonyl chloride in the presence of triethylamine and a catalytic amount of DMAP led to products **4a** and **4b**. The mesylate **4a** was unstable at room temperature and was not isolated,

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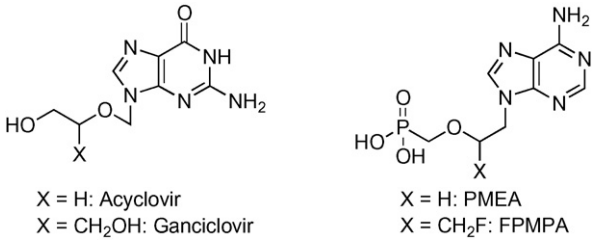



**Fig. 1.** Known antiviral agents.

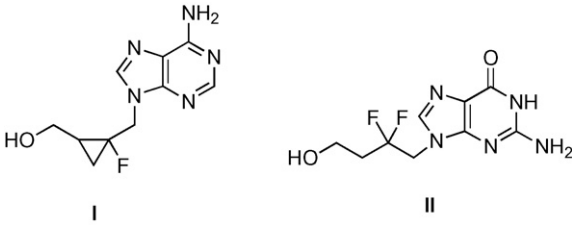



**Fig. 2.** Fluorinated acyclonucleosides.

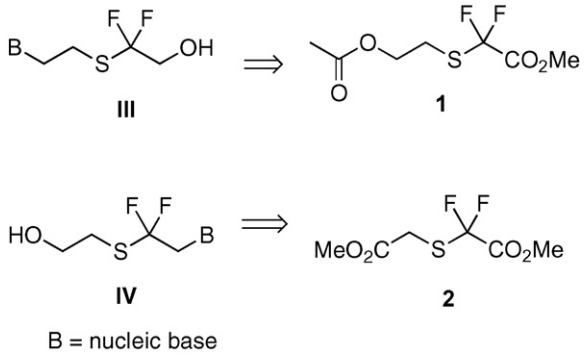
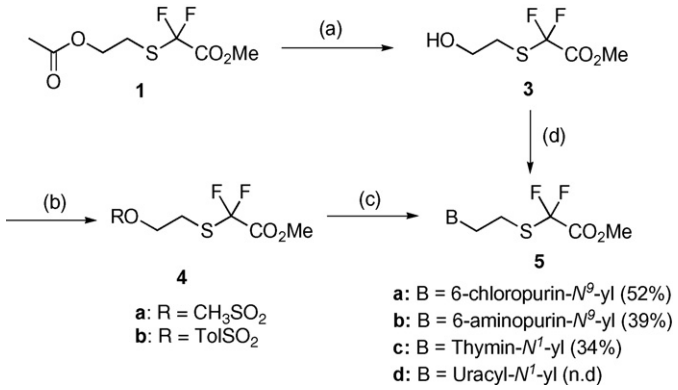



**Fig. 3.** Targeted fluorothionucleosides.

whereas the tosylate **4b** was obtained in 38% yield. The alkylation of 6-chloropurine with the tosylate **4b** in the presence of sodium hydride in THF gave the product **5a** in low yield (15%) after 48 h at 60 °C. Whatever the conditions this yield could not be improved, due to the thermal instability of **4b**.

The alkylation of the nucleic bases under milder conditions was explored to circumvent the limitation of the previous approach. We applied Mitsunobu conditions to introduce the nucleic bases. The coupling reaction was achieved directly from the alcohol **3**, and products **5a–c** were isolated in 34–52% yields (Scheme 1), depending on the nature of the nucleic base. In these reactions, the exclusive alkylation at the *N*-9 position of the purines occurred. Alkylation reactions of the 6-chloropurine or 6-aminopurine with the alcohol **3** gave the corresponding products **5a** and **5b** in 52% and 39% yield, respectively. $N^3$-Benzoylthymine and $N^3$-Benzoyluracile were also successfully alkylated when treated with **3** under Mitsunobu conditions to afford **5c** and **5d**, respectively. In this case, the exclusive alkylation at the *N*-1 position of the pyrimidines was observed, and the $N^3$-deprotection of the thymine occurred during the alkylation stage [12]. The compound **5c** was isolated in 34% yield whereas **5d** could not be separated from residual triphenylphosphine oxide [13]. As mentioned for the preparation of the alcohol **3**, this latter is highly base sensitive and some degradation occurred during the Mitsunobu reaction.



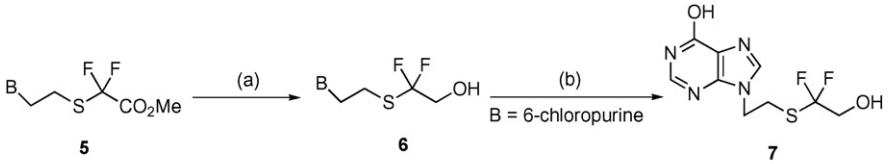

**Scheme 1.** Reagents and conditions: (a) $K_2CO_3$, MeOH, 0 °C, 1 h, 68%; (b) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 72 h, 38%; (c) 6-chloropurine, NaH, THF, 60 °C, 48 h, 15%. (d) 6-chloropurine, or 6-aminopurine, or $N^3$-Benzoylthymine or $N^3$-Benzoyluracile, DIAD, $PPh_3$, THF, rt, overnight, 34–52%.

However, attempts to introduce cytosine and guanine from the alcohol **3** under Mitsunobu conditions failed, the starting material being recovered ($^{19}$F NMR). By using protected $N^4$-acetylcytosine, no product was formed due to its low solubility in the reaction medium.

As in acyclovir, the *in situ* phosphorylation step of the terminal hydroxyl group by HSV-encoded thymidine kinase is the initial biochemical event leading to its antiherpetic activity [7], we investigated the synthesis of a series of difluorinated acyclonucleosides, possessing a terminal hydroxyl group, by reduction of **5**. The reduction of compounds **5a**, **5c–d** in the presence of sodium borohydride at room temperature afforded the corresponding alcohols **6a**, **6c–d** in good yields (Scheme 2), without any degradation of the nucleic base.

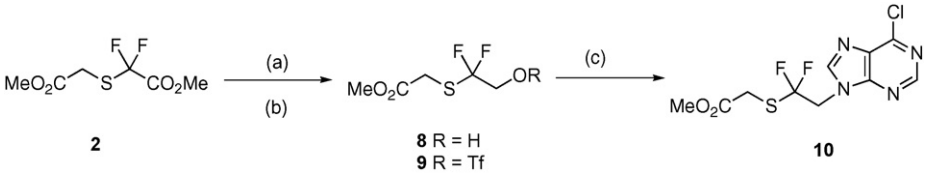
Compounds **6a** and **6c** were isolated in 89% and 77%, respectively. Derivative **6d** was not isolated due, again, to residual triphenylphosphine oxide from the previous step. Derivation of the chloropurine into the corresponding hypoxanthine derivative **7** was realized by refluxing **6a** in the presence of ethanethiol and sodium methoxide according to the literature [14].

As an additional target of this research, the synthesis of acyclonucleosides **IV** possessing a thiofluoromethylene group is in the α-position of the purine or pyrimidine base was investigated. As depicted on Scheme 3, the starting ester **2** easily prepared by




**a** B = 6-chloropurin-$N^9$-yl (89%)
**c** B = Thymin-$N^1$-yl (77%)
**d** B = Uracyl-$N^1$-yl (n.d)

**Scheme 2.** Reagents and conditions: (a) $NaBH_4$, EtOH, rt, 2 h, 77–89%. (b) $HSCH_2CH_2OH$, NaOMe, MeOH, reflux, 6 h, 32%.




**Scheme 3.** Reagents and conditions: (a) $NaBH_4$, EtOH, rt, 1 h, 71%; (b) $(CF_3SO_2)_2O$, $Et_3N$, $CH_2Cl_2$, 0 °C then rt, 3 h, quantitative; (c) 6-chloropurine, $K_2CO_3$, DMF, rt, 15 h, 16%.

Halex reaction was converted in the corresponding alcohol **8** selectively, and in good yield (71%) [10,11]. As expected, the reduction is totally regioselective and affected the carbonyl group activated by the adjacent difluoromethylene group [15,16]. Triflate **9** was prepared at 0 °C and was used without further purification due to its moisture sensitive character. However, the alkylation of the 6-chloropurine was limited by the instability of the triflate **9** in the medium. The compound **10** was obtained in low yield (<15%), and a partial degradation of **9** was observed after 15 h of stirring at room temperature [17]. Due to this limitation, no further transformation was attempted to obtain the acyclonucleosides **IV**.

Having in hand a series of acyclothionucleoside analogues **III**, the biological activity of compounds **5a**, **5c**, **6a**, **6c** and **7** were evaluated towards a large variety of virus ((HIV-1, HBV, BVDV, YFV, DENV-2, WNV) in cell culture experiments. However, none of them presented a toxicity or activity at 100 μM towards all these viruses.

## 3. Conclusion

We have synthetized acyclonucleoside analogues containing a *gem*-difluoromethylene group, in few steps from readily available fluorothioesters. Some difficulties appeared during these syntheses due to the presence of the sulfur and the fluorine atoms. In some cases the nucleic base introduction was not possible. Compounds **5a**, **5c**, **6a**, **6c** and **7**, structurally close to the known antiviral agents PMEA and acyclovir, did not exhibit any antiviral activity towards a large variety of viruses.

## 4. Experimental

### 4.1. General

All reactions were carried out under an atmosphere of dry nitrogen in flame or dried glassware with magnetic stirring. THF was dried by pressure filtration on a drier apparatus. NMR data appear in the following order: chemical shift in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), coupling constant *J* in Hz, number of protons. TMS and $CFCl_3$ are the internal standard for the $CDCl_3$ or acetone-$d^6$ solutions. The NMR were respectively recorded at 250 MHz for the $^1H$ NMR, 235 MHz for the $^{19}F$ NMR, and 100 MHz for the $^{13}C$ NMR. Flash chromatography was realized with silica gel (40–63 μm). All reagents are commercially available and used without further purification.

### 4.2. Methyl 2,2-difluoro-2-(2-acetoxyethylsulfanyl) acetate (1)

To a suspension of $ZnBr_2$ (5.00 g, 23.0 mmol) in $CH_3CN$ (45 mL) was added successively methyl 2,2-dichloro-2-(2-acetoxyethylsulfanyl)-acetate (5.90 g, 23.0 mmol), and $(HF)_3$-$NEt_3$ (14.70 mL, 92.0 mmol). After 2 h under reflux, the cooled solution was diluted by addition of $Et_2O/CH_2Cl_2$ (50 mL, 1/1) and then washed with $NH_4Cl_{sat}$ (3 mL × 10 mL) and $NaCl_{sat}$ (2 mL × 10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduce pressure. The crude product (5.5 g) was distilled under high vacuum to afford the compound **1** (b.p.: 105 °C/4.$10^{-2}$ mmHg) as a colourless liquid (80%, 4.20 g, 18.4 mmol). $^1H$ NMR ($CDCl_3$): δ 2.08 (s, 3H, $CH_3CO$), 3.13 (t, $^3J_{HH}$ = 6.5 Hz, 2H, $CH_2S$), 3.90 (s, 3H, $CH_3O$), 4.29 (t, $^3J_{HH}$ = 6.5 Hz, 2H, $CH_2O$). $^{13}C$ NMR ($CDCl_3$): δ 20.7 ($CH_3$(CO)), 27.4 ($CH_2S$), 54.0 ($CH_3O$), 62.8 ($CH_2O$), 120.3 (t, $^1J_{CF}$ = 287 Hz, $CF_2$), 162.0 (t, $^2J_{CF}$ = 33 Hz, $CO(CF_2)$), 170.7 ($CH_3CO$). $^{19}F$ NMR ($CDCl_3$, $CFCl_3$): δ −82.5 (s, $CF_2$). MS (EI), 70 eV, *m*/*z* (rel. int.): 169 [$M^{\bullet+}$−$CH_3COO$] (50), 168 (100), 109 (20), 59 (27), 43 (53). HRMS (EI+): *Not analysable*.

### 4.3. Methyl 2,2-difluoro-2-(2-hydroxy-ethylsulfanyl) acetate (3)

To a solution of methyl 2,2-difluoro-2-(2-acetoxyethylsulfanyl) acetate **1** (1.0 g, 4.42 mmol) in $CH_3OH$ (20 mL) cooled at 0 °C was added in one portion dried $K_2CO_3$ (0.61 g, 4.38 mmol). The mixture was stirred over 1 h and then quenched by addition of $HCl_{aq}$ (1N, 10 mL), and the organic layer was extracted with $CH_2Cl_2$ (2 mL × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/ethyl acetate, 6:4, $R_f$ = 0.4) to afford **3** as a colourless liquid (68%, 553 mg, 2.98 mmol). $^1H$ NMR ($CDCl_3$): δ 3.09 (t, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2S$), 3.79 (brs, 1H, O*H*), 3.88 (t, $^3J_{HH}$ = 6.0 Hz, 2H, $CH_2O$), 3.93 (s, 3H, $CH_3O$). $^{13}C$ NMR ($CDCl_3$): δ 31.0 ($CH_2S$), 54.1 ($CH_2O$), 63.3 ($CH_3O$), 120.5 (t, $^1J_{CF}$ = 285 Hz, $CF_2$), 162.3 (t, $^2J_{CF}$ = 33 Hz, *C*O). $^{19}F$ NMR ($CDCl_3$, $CFCl_3$): δ −82.1 (s, $CF_2$). HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_5H_9F_2O_3S$ 187.0240, found 187.0228.

### 4.4. Methyl 2-[2-(6-chloropurin-9-yl)-ethylsulfanyl)]2,2-difluoroacetate (5a)

To a suspension of $PPh_3$ (423 mg, 1.61 mmol) and 6-chloropurine (183 mg, 1.18 mmol) in THF (2 mL) under $N_2$, was added a solution of methyl 2,2-difluoro-2-(2-hydroxy-ethylsulfanyl) acetate **3** (200 mg, 1.07 mmol) in THF (1 mL). To this cooled mixture (0 °C) was slowly added DIAD (0.423 mL, 2.14 mmol). The mixture was stirred at rt overnight and the solvent was evaporated under reduce pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate, 6:4, $R_f$ = 0.2) to afford the compound **5a** (m.p. = 130 °C) as a white solid (52%, 180 mg, 0.56 mmol). $^1H$ NMR ($CDCl_3$): δ 3.45 (t, $^3J_{HH}$ = 6.5 Hz, 2H, $CH_2S$), 3.95 (s, 3H, $CH_3O$), 4.62 (t, $^3J_{HH}$ = 6.5 Hz, 2 H, $CH_2N$), 8.20 (s, 1H), 8.77 (s, 1H). $^{13}C$ NMR ($CDCl_3$): δ 28.4 ($CH_2S$), 44.6 ($CH_2N$), 54.4 ($CH_3O$), 120.4 (t, $^1J_{CF}$ = 288 Hz, $CF_2$), 131.8 ($C_{ar}$), 145.6 (CH), 151.3 ($C_{ar}$), 151.7 (CCl), 152.1 (CH), 161.6 (t, $^2J_{CF}$ = 33 Hz, *C*O). $^{19}F$ NMR ($CDCl_3$, $CFCl_3$): δ −81,5 (s, $CF_2$). HRMS (EI+) *m*/*z* $[M]^+$ calcd for $C_{10}H_9ClF_2N_4O_2S$ 322.0103, found 322.0109.

### 4.5. Methyl 2-[(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-ethylsulfanyl]-2,2-difluoroacetate (5c)

To a suspension of $PPh_3$ (634 mg, 2.42 mmol) and $N^3$-benzoylthymine (408 mg, 1.77 mmol) in THF (3 mL) under $N_2$,

was added a solution of methyl 2,2-difluoro-2-(2-hydroxyethylsulfanyl) acetate **3** (300 mg, 1.61 mmol) in THF (1.5 mL). To this cooled mixture (0 °C) was slowly added DIAD (0.639 mL, 3.22 mmol). The mixture was stirred at rt overnight and the solvent was evaporated under reduce pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate, 4:6, $R_f$ = 0.3) to afford the compound **5c** (m.p. = 123 °C) as a white solid (34%, 161 mg, 0.55 mmol). $^1$H NMR ($CDCl_3$): $\delta$ 1.91 (s, 3H, C$H_3$), 3.14 (t, $^3J_{HH}$ = 7.5 Hz, 2H, C$H_2$S), 3.90 (s, 3H, C$H_3$O), 4.22 (t, $^3J_{HH}$ = 7.5 Hz, 2H, C$H_2$N), 7.08 (brs, 1 H, C*H*), 10.3 (brs, 1H, N*H*). $^{13}$C NMR ($CDCl_3$): $\delta$ = 12.9 (*C*H$_3$), 26.1 (t, $^3J_{CF}$ = 3.0 Hz, *C*H$_2$S), 40.2 (*C*H$_2$N), 54.1 (*C*H$_3$O), 110.2 (*C*(CH$_3$)), 120.5 (t, $^1J_{CF}$ = 287 Hz, *C*F$_2$), 135.2 (*C*H), 153.1 (*C*O), 162.2 (t, $^2J_{CF}$ = 33 Hz, *C*O), 163.9 (*C*O). $^{19}$F NMR ($CDCl_3$, $CFCl_3$): $\delta$ −82.5 (s, C$F_2$). MS (EI), 70 eV, *m*/*z* (rel. int.): 295 [M+1] (10), 294 [M$^{\bullet+}$] (16), 185 (100), 153 (20), 110 (32), 55 (13). HRMS (EI+) *m*/*z* [M$^+$] calcd for $C_{10}H_{12}F_2N_2O_4S$ 294.0485, found 294.0475.

### 4.6. 2-[2-(6-chloropurin-9-yl)-ethylsulfanyl)]2,2-difluoroethanol (6a)

To a solution of **5a** (170 mg, 0.53 mmol) in EtOH (6 mL) at 0 °C, was added in one portion $NaBH_4$ (40 mg, 1.06 mmol). The mixture was stirred at rt over 2 h, and was quenched by addition of $HCl_{aq}$ (5 mL, 1 N). The mixture was extracted with $CH_2Cl_2$ (5 mL × 10 mL), and the organic layer was dried ($MgSO_4$) then concentrated under vaccum. The crude product was recrystallized in $Et_2O/CH_2Cl_2$ (1:1) to afford **6a** (m.p. = 200 °C) as a white powder (89%, 138 mg, 0.47 mmol). $^1$H NMR (acetone-$d^6$): $\delta$ 3.53 (t, $^3J_{HH}$ = 6.8 Hz, 2H, C$H_2$S), 3.94 (dt, $^3J_{HH}$ = 6.9 Hz, $^3J_{HF}$ = 12.0 Hz, 2H, C$H_2$CF$_2$), 4.74 (t, $^3J_{HH}$ = 6.8 Hz, 2H, C$H_2$N), 5.07 (t, $^3J_{HH}$ = 6.9 Hz, 1H, O*H*), 8.60 (s, 1H), 8.77 (s, 1H). $^{13}$C NMR (acetone-$d^6$): $\delta$ 27.2 (t, $^3J_{CF}$ = 3.3 Hz, *C*H$_2$S), 44.8 (*C*H$_2$-N), 65.3 (t, $^2J_{CF}$ = 29.3 Hz, *C*H$_2$(CF$_2$)), 130.5 (t, $^1J_{CF}$ = 278.5 Hz, *C*F$_2$), 131.9 ($C_{ar}$), 147.3 (*C*H), 150.2 ($C_{ar}$), 151.9 (*C*H), 152.7 ($C_{ar}$). $^{19}$F (acetone-$d^6$, $CFCl_3$): $\delta$ −82.4 (t, $^3J_{HF}$ = 12.0 Hz, C$F_2$). MS (IE), 70 eV, *m*/*z* (rel. int.): 295 [M+1] (11), 294 [M$^{\bullet+}$] (3), 215 (40), 213 (100), 155 (12). Anal. Calcd for $C_9H_9ClF_2N_4OS$: C, 36.68; H, 3.08; S, 10.88. Found C, 36.38; H, 3.22; S, 10.86.

### 4.7. 2-[(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-ethylsulfanyl]-2,2-difluoro-ethanol (6c)

To a solution of **5c** (150 mg, 0.51 mmol) in EtOH (6 mL) at 0 °C, was added in one portion $NaBH_4$ (40 mg, 1.06 mmol). The mixture was stirred at rt over 2 h, and was quenched by addition of $HCl_{aq}$ (5 mL, 1 N). The mixture was extracted with $CH_2Cl_2$ (5 mL × 10 mL), and the organic layer was dried ($MgSO_4$) then concentrated under vaccum. The crude product was recrystallized in $CHCl_3$ to afford **6c** (m.p. = 188 °C) as a white powder (77%, 105 mg, 0.39 mmol). $^1$H NMR (acetone-$d^6$): $\delta$ 1.83 (s, 3H, C$H_3$), 3.06 (t, $^3J_{HH}$ = 7.4 Hz, 2H, C$H_2$S), 3.92 (dt, $^3J_{HH}$ = 7.0 Hz, $^3J_{HF}$ = 12.5 Hz, 2H, C$H_2$CF$_2$), 4.14 (t, $^3J_{HH}$ = 7.4 Hz, 2H, C$H_2$N), 4.93 (t, $^3J_{HH}$ = 7.0 Hz, 1H, O*H*), 7.31 (brs, 1H, C*H*), 9.78 (brs, 1H, N*H*). $^{13}$C NMR (acetone-$d^6$): $\delta$ 12.3 (*C*H$_3$), 25.2 (*C*H$_2$S), 40.5 (*C*H$_2$N), 65.1 (t, $^3J_{CH}$ = 29.8 Hz, *C*H$_2$CF$_2$), 108.6 (*C*CH$_3$), 130.4 (t, $^1J_{CF}$ = 277.4 Hz, *C*F$_2$), 136.0 (*C*H), 151.6 (*C*O), 164.1 (*C*O). $^{19}$F (acetone-$d^6$, $CFCl_3$): $\delta$ -93.9 (t, $^3J_{FH}$ = 12.5 Hz, C$F_2$). MS (EI), 70 eV, *m*/*z* (rel. int.): 266 [M$^{\bullet+}$] (5), 140 (20), 127 (100), 126 (37), 110 (45), 83 (23). Anal. Calcd for $C_9H_{12}F_2N_2O_3S$: C 40.60; H 4.54; S 12.04. Found C 40.33; H 4.73; S 12.57.

### 4.8. 9-[2-(1,1-difluoro-2-hydro-ethylsulfanyl)-ethyl]-9H-purin-6-ol (7)

To a solution of **6a** (100 mg, 0.34 mmol) in $CH_3OH$ (15 mL) was successively added EtSH (0.114 mL, 1.63 mmol) and then a 1 M solution of $CH_3ONa$ in $CH_3OH$ (1.5 mL, 1.5 mmol). The stirred mixture was refluxed over 8 h. To the cooled mixture was added $CH_3CO_2H$ (15 mL), and the solvents were removed under high vacuum. The crude product (140 mg) was purified by flash column chromatography ($CH_2Cl_2/CH_3OH$, 9:1, $R_f$ = 0.3) to afford **7** (m.p. = 254 °C) as a white powder (32%, 30 mg, 0.11 mmol). $^1$H NMR (DMSO-$d^6$): $\delta$ 3.30 (t, $^3J_{HH}$ = 6.7 Hz, 2H, C$H_2$S), 3.76 (t, $^3J_{HF}$ = 12.9 Hz, 2H, C$H_2$CF$_2$), 4.38 (t, $^3J_{HH}$ = 6.7 Hz, 2 H, C$H_2$N), 8.05 (s, 1H), 8.08 (s, 1H). $^{13}$C NMR (DMSO-$d^6$): $\delta$ 27.2 (*C*H$_2$S), 43.8 (*C*H$_2$N), 64.3 (t, $^2J_{CF}$ = 28.6 Hz, *C*H$_2$(CF$_2$)), 124.1, 130.4 (t, $^1J_{CF}$ = 279.1 Hz, *C*F$_2$), 140.6 (*C*H$_{ar}$), 145.9 (*C*H$_{ar}$), 148.6, 156.9 (*C*–OH). $^{19}$F NMR (DMSO-$d^6$, $CFCl_3$): $\delta$ −81.44 (t, $^3J_{HF}$ = 12.9 Hz, C$F_2$). MS (IE), 70 eV, *m*/*z* (rel. int.): 276 [M$^{\bullet+}$] (12), 195 (100), 149 (21), 136 (33), 115 (29), 82 (29). HRMS (EI+) *m*/*z* [M]$^+$ calcd for $C_9H_{10}F_2N_4O_2S$ 276.0493, found 276.0486.

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## References

[1] (a) J. Chen, T. Sambaiah, B. Illarionov, M. Fischer, A. Bacher, M. Cushman, J. Org. Chem. 69 (2004) 6996–7003;
(b) C. Bacchelli, R. Condom, N. Patino, A.M. Aubertin, Nucleosides Nucleotides Nucleic Acids 19 (2000) 567–584.
[2] M. Koszytkowska-Stawinska, W. Sas, Tetrahedron Lett. 45 (2004) 5437–5440.
[3] (a) C.U. Kim, B.Y. Luh, P.F. Misco, J.J. Bronson, M.J.M. Hitchcock, I. Ghazzouli, J.C. Martin, J. Med. Chem. 33 (1990) 1207–1213;
(b) D. Villemin, F. Thibault-Starzyk, Synth. Commun. 23 (1993) 1053–1059.
[4] M. Yokoyama, Synthesis 12 (2000) 1637–1655.
[5] K.W. Pankiewicz, Carbohydr. Res. 327 (2000) 87–105.
[6] (a) W. Plunkett, P. Huang, V. Ganghi, V. Nucleosides, Nucleosides Nucleotides Nucleic Acids 16 (1997) 1261–1270;
(b) L.P. Kotra, Y. Xiang, M.G. Newton, R.F. Schinazi, Y.C. Cheng, C.K. Chu, J. Med. Chem. 40 (1997) 3635–3644;
(c) W. Plunkett, P. Huang, V. Gandhi, Anti-Cancer Drugs Des. 6 (1995) 7;
(d) P. Pourquier, J.C. Gioffre, G. Kohlhagen, F. Goldwasser, L.W. Hertel, S. Yu, R.T. Pon, W.H. Gmeiner, Y. Pommier, Clin. Cancer Res. 8 (2002) 2499–2500.
[7] E. De Clercq, Nucleosides Nucleotides Nucleic Acids 13 (1994) 1271–1295.
[8] T.C. Rosen, E. De Clercq, J. Balzarini, G. Haufe, Org. Biomol. Chem. 2 (2004) 229–237.
[9] P.J. Casara, M.T. Kenny, K.C. Jund, Tetrahedron Lett. 32 (1991) 3823–3828.
[10] (a) S. Gouault, C. Guérin, L. Lemoucheux, T. Lequeux, J.C. Pommelet, Tetrahedron Lett. 44 (2003) 5061–5064;
(b) S. Gouault, J.C. Pommelet, T. Lequeux, Synlett (2002) 996–998.
[11] (a) C. Jouen, S. Lemaître, T. Lequeux, J.C. Pommelet, Tetrahedron 54 (1998) 10801–10810;
(b) C. Jouen, J.C. Pommelet, Tetrahedron 53 (1997) 12565–12574.
[12] K. Yamada, S. Sakata, Y. Yoshimura, J. Org. Chem. 63 (1998) 6891–6899.
[13] The reaction products were not separated by flash chromatography on silica gel.
[14] H.R. Moon, H.O. Kim, S.K. Lee, W.J. Choi, M.W. Chun, L.S. Jeong, Bioorg. Med. Chem. 10 (2002) 1499–1507.
[15] T. Kitazume, T. Yamazaki, Experimental Methods in Organic Fluorine Chemisry, Kodansha, Tokyo, 1998.
[16] M. Miyauchi, E. Nakayama, K. Watanabe, K. Fujimoto, J. Ide, Sankyo Kenkyusho Nempo (Annu. Rep. Sankyo Res. Lab.) 38 (1986) 41–54.
[17] N.A. Fokina, A.M. Kornilov, V.P. Kukhar, J. Fluorine Chem. 111 (2001) 69–76.