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Synthesis, structural studies and antiretroviral evaluation of $3'$-aza-$4'$-thia-$2',3'$-dideoxynucleosides (thiazolidine-nucleoside analogues)

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Summary — Starting with the concept that heterocyclic pseudo-ribose rings could confer potent antiviral activity to nucleoside analogues, we synthesized $3'$-aza-$4'$-thia-$2',3'$-dideoxynucleosides. The synthesis of such analogues required the preparation of *N*-protected-1,3-thiazolidines adequately disubstituted in 2- and 5-positions. Introduction of nucleobases on these sugar-like thiazolidines was achieved through coupling reactions using tin(IV) chloride as a catalyst. The *N*-protecting group (*N*-fluorenylmethoxycarbonyl, *N*-acetyl and *N*-tosyl) of the thiazolidine ring is crucial for final deprotection of $3'$-aza-$4'$-thia-$2',3'$-dideoxynucleosides. None of these compounds were found active on HIV-infected MT-4 cells.

thiazolidine / nucleoside / anti-HIV activity

Résumé — Synthèse, études structurales et évaluation antirétrovirale de $3'$-aza-$4'$-thia-$2',3'$-didésoxynucléosides (analogues nucléosidiques de type thiazolidine). *Considérant que des hétérocycles mimant le cycle ribose pouvaient conférer à des analogues nucléosidiques des propriétés antivirales (HIV, HBV), un certain nombre de $3'$-aza-$4'$-thia-$2',3'$-didésoxynucléosides ont été synthétisés. L'obtention de cette nouvelle classe d'analogues nucléosidiques a nécessité la mise au point de synthèse de 1,3-thiazolidine adéquatement disubstituées en position 2 et 5. Le couplage des bases nucléiques sur les pseudo-sucres de type thiazolidine a été réalisé à l'aide du chlorure d'étain(IV) comme catalyseur. Les déprotections donnant accès aux composés finaux $3'$-aza-$4'$-thia-$2',3'$-didésoxynucléosides ont nécessité l'utilisation du groupement protecteur* N*-fluorénylméthoxycarbonyl (N-Fmoc). Les groupements protecteurs* N*-acétyl et* N*-tosyl se sont avérés inadéquates lors de cette déprotection. Ces nouveaux composés nucléosidiques de type thiazolidine n'ont montré aucune activité antirétrovirale sur HIV.*

thiazolidine / nucléoside / activité anti-HIV

Introduction

A number of targets have been identified for possible strategies for the inhibition of the replication of human immunodeficiency virus (HIV), the causative agent of AIDS [1] and of these, the most successfully exploited so far is the virally encoded reverse transcriptase (RT). $2',3'$-Dideoxynucleosides such as AZT, ddC (**1**), ddI, d_4T represent one class of compounds which block HIV replication in vitro [2] by inhibition of the HIV-1 RT, after intracellular conversion to their triphosphate derivatives. Recent developments have suggested that more fundamental modifications or changes in the pentofuranosyl moiety are compatible with anti-HIV activity. These nucleoside analogues, containing a modified sugar moiety, have received considerable interest [3, 4]. As a result, replacement of the furanose ring by other five-membered rings, such as 1,3-oxathiolane **2**–**4** [3, 5], 1,3-dioxolane **5** [3, 4], isomeric tetrahydrofuran **6** [6], tetrahydrothiophene **7** and **8** [7, 8], pyrrolidine **9**, **10** [9, 10] and isoxazolidine [11] has been already described (table I). Some of these compounds are selective anti-HIV agents (**1**–**6**). Compounds **1** and **2** are currently under clinical trials and present original properties. In contrast to 'classical' nucleoside analogues (AZT, ddA, d_4T, d_4C), in which the biological activity resides mainly or exclusively in the D-natural enantiomeric form [12, 13], some L-(−)-enantiomers (unnatural) of **1** (β-L-ddC and β-L-FddC), **2** ($3TC^{TM}$) and **3** (FTC) are more potent or equipotent [14–16] and less cytotoxic than the corresponding D-(+)-enantiomers [17]. Compounds such as **1**, **2** and **3** (L- and D-enantiomers) are also inhibitors of the in vitro replication of hepatitis B virus (HBV) [14, 18].

In order to study the influence of the ribose ring structure on the anti-HIV activity, we have undertaken a program of synthesis of new heteronucleosides in which the furanose ring has been replaced by a

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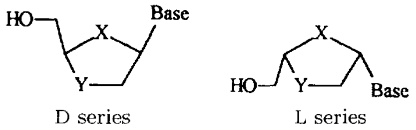
* Correspondence and reprints

Table I. Nucleoside analogues containing modified sugar moiety.



Compound	*X*	*Y*	*Base*	*Reference*
1	O	CH_2	Cytosine	2
2	O	S	Cytosine	3
3	O	S	5-Fluorocytosine	3
4	S	O	Adenine	5
5	O	O	Thymine	3, 4
6	CH_2	O	Adenine	6
7	CH_2	S	Cytosine	7
8	S	CH_2	Thymine	8
9	CH_2	NH	Thymine	9
10	NAc	CH_2	Thymine	10
11	S	NAc	Cytosine	this work
12	S	NTs	Cytosine	this work
13	S	NH	Cytosine	this work

1,3-thiazolidine ring (**11–13**). Recently, we reported that the synthesis of *N*-protected-2,5-disubstituted-1,3-thiazolidines could represent sugar substitutes for the development of this new class of nucleosides analogues [19]. We describe here syntheses and structural studies of thiazolidine nucleosides, as well as their antiviral properties.

Results and discussion

The synthesis of these nucleoside analogues required adequately substituted and protected thiazolidines. In nucleoside chemistry, the acetyloxy substituent is the most commonly used leaving group in the Vorbrüggen-type reaction [20]. Only a few other examples employing aroyl or acyloxy leaving groups have been described. Retrosynthetic analysis suggests that compounds **14** (R = H; R′ = OBz), **15** (R = H; R′ = OAc), **16** (R = Ac; R′ = OBz), **17** (R = Ac; R′ = OAc), **18** (R = Ts; R′ = OBz) and **37** (R = Fmoc; R′ = OBz) (fig 1) can serve as key intermediates for the synthesis of five-membered-ring nucleoside analogues.

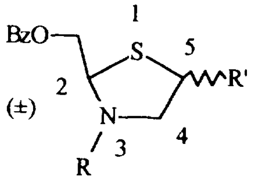


Fig 1. Thiazolidine-sugar derivatives suitable for synthesis of nucleoside analogues.

Unfortunately, the thiazolidines **14–18** were obtained in low yield starting from the same intermediate **19** (R = H; R′ = H) which was functionalized at the C-5 position through standard Pummerer reaction or benzoylhydroxylation using dibenzoyl peroxide as previously described [19].

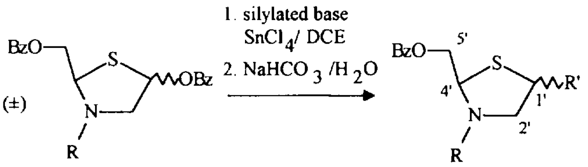
The *N*-unsubstituted compounds **14** and **15** appear to be very useful intermediates for the direct synthesis of thiazolidine-nucleosides. Unfortunately, standard coupling reactions with silylated bases using various Lewis acids, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf), tin tetrachloride ($SnCl_4$) or titanium tetrachloride ($TiCl_4$) as coupling catalyst failed. Because the cytosine derivatives exhibit, in general, more potent anti-HIV and anti-HBV activities than the other analogues [4e], they were chosen as representative candidates of this thiazolidine-nucleoside class. The lack of the *N*-protecting group seems to be detrimental to the reaction under the tested experimental conditions. In order to overcome this problem, we used *N*-acetyl compound **17** as a substrate for the coupling with silylated cytosine. Only a very low yield of a racemic mixture of 1-[2-(benzoyloxymethyl)-3-acetyl-1,3-thiazolidin-5-yl]cytosine, **20** and **21** was obtained. Therefore, an alternative synthetic route was attempted. The synthesis of compound **21** was achieved by coupling the persilylated N^4-acetylcytosine with derivative **16** in the presence of the catalyst tin(IV) chloride ($SnCl_4$ 1 M solution in CH_2Cl_2). The reaction was performed in 1,2-dichloroethane (DCE) at reflux for 48 h (table II, entry 1).

The α/β configuration of both racemic isomers **20** and **21** separated by silica-gel chromatography, was assigned on the basis of ^1H NMR studies. A 5% NOE enhancement was observed between protons H(1′) and H(4′) in the case of racemic β-isomer **21** and not in the case of racemic α-isomer **20**. In the case of *N*-acetylated compounds, NMR spectra recorded at 20 °C exhibited hindered internal rotation about the *N*-acetyl bond. This means that twin peaks corresponding to the two rotational conformers (*Z*/*E*) can be detected on the NMR time scale (see table IV) [21]. This phenomenon was already observed in the NMR spectra of *N*-acetylated thiazolidine and acetamido-azasugar [22] such as *N*-acetyl-4-azanucleoside **10** [10]. The observed chemical shifts and coupling-constant values assigned to the thiazolidine protons for each diastereomer **20** and **21** are reported in tables III and IV.

Table II (entries 2–4) presents the formation of protected 3′-aza-4′-thianucleosides of 5-fluorocytosine, thymine and adenine. It is important to note that every compound **20–27** is a mixture of ± enantiomers. They were obtained through the coupling reaction of different purine and pyrimidine bases with the compound **16**, using similar experimental conditions as for the synthesis of compounds **20** and **21**. Anomeric configuration assignments of other 1,3-thiazolidinyl nucleosides were based on the comparison of the ^1H NMR patterns to those of **20** and **21** as well as the chemical shifts of characteristic protons in the NMR data, shown in table III. The H-1′ of the β isomers were downfield relative to the H-1′-α signals. The 1′- and 4′-proton patterns and chemical shifts characterized each α and β isomer.

The α and β isomers were obtained in yields between 35 and 55%. The β/α ratio depends on the heterocyclic base structure. In the case of N^4-acetylcytosine and N^4-benzoyl-5-fluorocytosine derivatives, the β/α ratio is about 1:3. This is in contrast to the cases of thymine and N^6-benzoyladenine derivatives, where the ratio is 5:1 and 2:1 respectively, in favor of the desired

Table II. Formation of racemic *N*-protected 3′-aza-4′-thianucleosides.



Entry	*Substrate*	*R*	*R′*	*α (yield)*	*β (yield)*
1	**16**	Ac	N^4-Acetylcytosine	**20** (40)	**21** (15)
2	**16**	Ac	N^4-bz-5-fluorocytosine	**22** (36)	**23** (10)
3	**16**	Ac	Thymine	**24** (6)	**25** (30)
4	**16**	Ac	N^6-Benzoyladenine	**26** (14)	**27** (25)
5	**18**	Ts	N^4-Acetylcytosine	**34** (22)	**35** (29)
6	**37**	Fmoc	Cytosine	**38** (42)	**40** (18)
7	**37**	Fmoc	6-Chloropurine	**39** (11)	**41** (16)

Table III. Characteristic ^{1}H NMR chemical shifts in ppm for thiazolidinyl-nucleosides.

Compound	*H-1′*	*H-2′*	*H-2″*	*H-4′*	*H-5′*
20[a]	6.36 (d) 6.41 (d)	4.27 (d) 5.08 (d)	3.69 (dd) 4.05 (dd)	5.70 (dd) 6.30 (yet)	4.64 4.39
21[a]	6.41 (d) 6.44 (d)	4.25 (d) 5.15 (d)	3.62 4.10 (dd)	5.75 (dd) 6.08	4.52 (dd) 4.68 (dd)
28[b]	6.08(d) 6.20 (d)	4.08 (d) 4.53 (d)	3.50-3.60 3.86 (dd)	5.51	3.50–3.60
29[b]	6.18	4.56 (d) 3.29–4.10	3.29–4.10 5.43(ψt)	5.32 (dd)	3.29–4.10
22[a]	6.32	4.22 (d) 5.06 (d)	3.68 (dd) 4.05 (dd)	5.74 (dd) 6.32	4.32–4.62
23[a]	6.41 (ψ t)	4.20 (d) 5.18	3.52 6.06	5.72	4.62–4.74
30[c]	6.04 (d) 6.10 (d)	4.09 (d) 4.56 (d)	3.60 3.93	5.54 (ψ t) 5.72 (ψ t)	3.60
31[c]	6.14	4.42 (d) 4.46 (d)	3.31 (dd) 3.60–3.82	5.32 (ψ t) 5.45 (ψ t)	3.60–3.82
24[a]	6.34–6.40	4.14 (d) 4.99 (d)	3.66 (dd) 4.01 (dd)	5.70 (dd) 6.30 (ψ t)	4.30–4.60
25[a]	6.93	4.14–4.58 4.95 (d)	3.65 (dd) 4.14–4.58	5.76 (dd) 6.30 (ψ t)	4.14–4.58
32[b]	6.64 (d) 7.27 (d)	4.26 (d) 4.55 (d)	3.42–3.56 3.92 (dd)	5.40 (dd) 5.65 (dd)	3.42–3.56
26[a]	6.35	4.49 (d) 5.32 (d)	3.78 (dd) 4.13 (dd)	5.84 (dd) 6.40 (ψ t)	4.38–4.68
27[a]	7.11 (d) 7.23 (d)	4.47 (d) 5.49 (d)	3.91 (dd) 4.25 (dd)	5.75 (dd) 6.47 (ψ t)	4.54–4.74
33[d]	7.15	4.10 (d) 4.89 (d)	3.10–3.47	5.24 (dd) 5.66 (ψ t)	3.10–3.47
34/35[a]	5.95 (ψ t) 6.26 (d)	4.43 (dd) 4.60 (d)	3.57 (dd) 3.92 (dd)	5.40 (ψ t) 5.92 (dd)	4.24 (dd) 4.46 (dd) 4.51 (dd) 4.74 (dd)
12a[b]	5.94 (d)	4.11 (d)	3.91 (dd)	5.82 (ψ t)	3.44–3.72
12b[b]	5.53 (ψ t)	4.20 (d)	3.55 (dd)	5.17 (ψ t)	3.63–3.77

[a] $CDCl_3$; [b] DMSO-d_6; [c] D_2O; [d] CD_3OD; [e] ψ means pseudo.

Table IV. Characteristic ^1H–^1H coupling constant values in hertz.

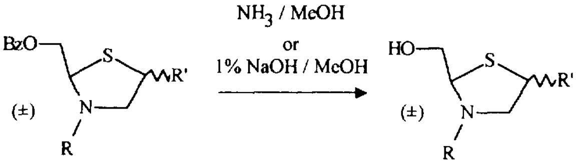
Compound	$J_{H1'-H2'}$	$J_{H1'-H2''}$	$J_{H2'-H2''}$	$J_{H4'-H5'}$	$J_{H4'-H5''}$
20[a]	0	4.0	−13.2	5.0	8.5
	0	5.1	−14.0	5.5	5.7
21[a]	0	4.2	−13.0	5.5	6.3
	0	5.1	−14.0	–	–
28[b]	0	4.6	−13.6	nd	nd
	0	4.5	−13.2	–	–
29[b]	0	nd	−13.3	4.0	10.2
	–	–	–	5.0	5.2
22[a]	0	5.5	−13.2	4.7	8.6
	–	4.2	−14.1	–	–
30[c]	0	4.8	−13.3	6.0	5.0
	0	4.3	−13.7	–	–
31[c]	0	5.2	−12.4	5.0	5.5
	–	–	−11.2	4.2	4.3
24[a]	0	6.7	−14.0	5.0	8.3
	0	4.2	−13.5	5.7	7.0
25[a]	0	7.6	−13.6	4.9	8.5
	–	–	–	5.7	5.8
32[b]	0	8.0	−12.6	5.0	8.0
	0	7.6	−13.5	4.6	6.4
26[a]	0	5.0	−13.0	4.7	8.4
	0	3.9	−13.6	5.7	5.5
27[a]	0	4.1	−13.2	4.3	8.5
	0	4.3	−13.9	6.1	5.8
34/35[a]	6.7	6.3	−13.5	6.1	6.3
	0	4.6	−13.9	4.9	7.6
12a[b]	0	4.0	−13.3	6.9	7.4
12b[b]	7.1	7.3	−13.5	5.1	5.3

[a] $CDCl_3$; [b] DMSO-d_6; [c] D_2O; [d] CD_3OD; [e] ψ means pseudo.

β-isomers. Predominant α-isomer was also obtained during the synthesis of 2′,3′-dideoxy-4′-thiopyrimidine nucleoside analogues [8]. This was probably due to the presence of the sulfur atom.

When compounds **20–27** were treated with saturated methanolic ammonia solution at room temperature for deprotection, only partially deprotected nucleosides **28–33** were isolated (table V, entries 1–6).

Table V. Deprotected racemic 3′-aza-4′-thianucleosides.



Entry	*Substrate*	*Product*	*R*	*R′*
1	**20**	**28** (α)	Ac	Cytosine
2	**21**	**29** (β)	Ac	Cytosine
3	**22**	**30** (α)	Ac	5-Fluorocytosine
4	**23**	**31** (β)	Ac	5-Fluorocytosine
5	**25**	**32** (β)	Ac	Thymine
6	**27**	**33** (β)	Ac	Adenine
7	**34/35**	**12a** (α) **12b** (β)	Ts	Cytosine
8	**38**	**13a** (α)	H	Cytosine
9	**40**	**13b** (β)	H	Cytosine

Other standard *N*-deacetylation procedures were also tested in the cases of compounds **28** and **29**. Acidic [23a] (1.2 N HCl aqueous solution) or basic (1.0 N NaOH aqueous solution or 1.0 N KOH methanolic solution) media led to decomposition products; the use of hydrazine [23b] (35% w in water) or triethyloxonium tetrafluoroborate [23c] (Et_3OBF_4 1 M solution in CH_2Cl_2) followed by basic hydrolysis left the starting materials **28** and **29** unchanged. Similar observations have been already reported in the deprotection of *N*-acetylated-1,3-thiazolidine-4-carboxylic acid and related compounds [24]. *N*-Tosyl analogues have also been synthesized in order to study the influence of the *N*-protecting group on the α/β ratio and on the anti-HIV activity. Considering this, a racemic mixture of N^4-acetyl-1-[2-(benzoyloxymethyl)-3-tosyl-1,3-thiazolidin-5-yl]cytosine **34** and **35** was obtained by condensation of *N*-tosyl sugar **18** with silylated N^4-acetylcytosine in a 51% overall yield (table II, entry 5). It should be underlined that in this case, the separation of isomers was not possible using standard column-chromatography techniques. Based on a ^1H NMR study, the α/β ratio was about 1:1. Treatment of a mixture of compounds **34** and **35** with saturated methanolic ammonia solution at room temperature afforded partially deprotected nucleoside analogues α-anomer **12a** and β-anomer **12b**, which were successfully separated by chromatography on a silica-gel column (table V, entry 7).

Since fully deprotected azathianucleosides could not be obtained through the synthetic routes described above, we investigated another kind of *N*-protected-2,5-disubstituted-1,3-thiazolidine as starting synthon. The fluorenylmethoxycarbonyl (Fmoc) group is known to be extensively employed in peptide chemistry to protect amino groups. Its excellent acid stability and its facile removal led us to synthesize the corresponding *N*-Fmoc-2-benzoyloxymethyl-1,3-thiazolidine. Starting from compound **19** and 9-fluorenylmethyl chloroformate (Fmoc-Cl) [25] in the presence of $NaHCO_3$ in a dioxane/water (5:1) mixture we were able to form racemic *N*-Fmoc-2-benzoyloxymethyl-1,3-thiazolidine **36** (95% yield). Benzoylhydroxylation of compound **36** using excess dibenzoyl peroxide [26] afforded *N*-Fmoc-2-benzoyloxymethyl-5-benzoyloxy-1,3-thiazolidine **37** in a 32% yield. Condensation of silylated cytosine and 6-chloropurine on the thiazolidine derivative **37** in the presence of $SnCl_4$ gave the corresponding protected α-isomers **38**, **39** and β-isomers **40**, **41** in low yields after chromatographic separation (table II, entries 6 and 7). When each isolated isomer was deprotected using 1% sodium or potassium hydroxide in methanol [27], the cytosine derivatives **38** and **40** led in one step to 3′-aza-4′-thia-2′,3′-dideoxycytidines (ATC) **13a** and **13b** (table V, entries 8 and 9). In contrast, the purine analogues **39** and **41** decomposed under these conditions.

From these results, it can be concluded that the first synthesis of an azathianucleoside analogue has been achieved through the use of *N*-Fmoc-

2-benzoyloxymethyl-5-benzoyloxy- 1,3-thiazolidine coupling modified sugar **37**. The type of N-protecting group on the thiazolidine ring represents a key parameter in the synthesis of such compounds. Only N-Fmoc derivatives appear to be suitable for a final deprotection step. Other N-protecting groups like acetyl and tosyl required removal conditions which led to partially deprotected nucleoside analogues or to ring decomposition products. It should also be underlined that various α/β ratio were obtained depending on the structure of the N-protecting group.

All the new synthesized azathianucleoside congeners were tested for their antiviral potential. Evaluation was performed through syncitia formation in infected MT-4 cells [28]. No anti-HIV activity was found for compounds **12a**, **12b**, **13a**, **13b** or **20**–**35** at concentrations below 100 μM and their anti-HBV evaluation is in progress.

Experimental section

General

Nuclear magnetic resonance spectra were recorded with a Bruker AMX-200 or AMX-400 (^{1}H NMR; ^{13}C NMR). Chemical shift values were expressed in δ values (part per million) relative to TMS as internal standard. Elemental analyses were determined by the Service central d'analyse CNRS, Vernaison–Lyon, France and gave combustion values for C, H, N, S within ±0.4% of the theoretical values. FAB$^+$ mass spectra were obtained on a Jeol DX-100 mass spectrometer (Laboratoire de mesures physiques-RMN, Dr Astier, USTL, Montpellier, France) using a cesium ion source. Infrared spectra were obtained using a Perkin-Elmer 1605 FTIR spectrophotometer; values in cm^{-1}. UV spectra were recorded with a Kontron UVIKON-930; values in nm. Melting points were determined using Mel-Temp II, Laboratory Devices, in sealed tubes and are uncorrected. Preparative flash column chromatography was performed using Merck G60 230-240 silica gel. Analytical thin-layer chromatography was performed on 60F$_{254}$ silica gel aluminium plates of 0.2 mm thickness (Merck, Darmstadt). All reagents were of commercial quality from freshly opened containers. Compounds **16** and **18** were prepared by a known procedure [19].

- *Acylation of heterocyclic bases*

N^4-Benzoyl-5-fluorocytosine and N^6-benzoyladenine were obtained as previously described [29].

- *General silylation and coupling procedure*

The bases were routinely silylated by heating at reflux temperature with excess 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (20–30 mL HMDS was used for 1 mmol heterocyclic base) for 15–20 h under a nitrogen atmosphere. In cases where the base did not dissolve promptly after 1–2 h, 5.0 equiv of trimethylchlorosilane (TMSCl) was added to accelerate the silylation. The homogeneous solution was cooled to room temperature and evaporated in vacuo. The residue, assumed to be the completely silylated heterocyclic base, was used immediately for the next step. The following manipulations were performed in a glovebox with exclusion of moisture. The silylated base (1.5 equiv) was dissolved in anhydrous dichloroethane (10 mL/mmol of sugar), $SnCl_4$ added (1M solution in CH_2Cl_2 1.4 equiv) and complexation allowed at 25 °C for 30 min. To this solution was added the required thiazolidine (1.0 equiv) in anhydrous dichloroethane (10 mL/mmol of sugar). The homogeneous solution was heated for several hours, cooled, and poured into cold saturated aqueous $NaHCO_3$ solution. After stirring for 30 min, the tin salts were removed by filtration through a Celite pad and washed with dichloromethane (1 × 20 mL). The filtrate was recovered, the aqueous phase was extracted with dichloromethane (1 × 30 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and brine (1 × 50 mL) before drying (Na_2SO_4) and removal of the solvent under reduced pressure. In this way, the following nucleoside analogues were prepared.

- N^4*-Acetyl-1-(2-benzoyloxymethyl-3-acetyl-1,3-thiazolidin-5-yl)cytosine* **20** *and* **21**

N^4-Acetylcytosine (0.18 g, 1.17 mmol), 2-benzoyloxymethyl-3-acetyl-5-benzoyloxy-1,3-thiazolidine **16** (0.30 g, 0.78 mmol) and $SnCl_4$, 1 M solution in CH_2Cl_2 (1.09 mL, 1.09 mmol) yielded, after flash column chromatography ($MeOH/CHCl_3$, 1–5%), two products:

α-Isomer **20** (0.13 g, 40%) was triturated with diethyl ether to give a white solid mp = 217–218 °C; R_f [$MeOH/CHCl_3$, 5%] = 0.23.

UV (EtOH, 95%): λ_{max} = 208, 233, 303.

FTIR (KBr): 1 724 (C=O ester), 1 662 (C=O amide), 1 268 (C–O ester).

^{1}H NMR (table III) and ^{13}C NMR show two conformers (E/Z) in 2:5 ratio.

^{13}C NMR ($CDCl_3$) δ: 22.4 (CH_3), 24.9 (CH_3), 56.4 (C-2′), 60.0 (C-1′), 61.6 (C-4′), 64.8 (C-5′), 65.5 (C-5′), 96.8 (C-5), 128, 129 and 133 (C arom), 144.7 (C-6), 155.3 (C-2), 162.6 (C-4), 165.9 (C=O), 170.1 (C=O).

MS (FAB$^+$) m/z: 417 (M + H$^+$).

Anal calc for $C_{19}H_{20}N_4O_5S$: C, 54.79; H, 4.84; N, 13.45; S, 7.70. Found: C, 54.44; H, 5.11; N, 13.27; S, 7.71.

β-Isomer **21** (0.05 g, 15%) was triturated with diethyl ether to give a white solid mp = 127–128 °C; R_f [$MeOH/CHCl_3$: 5%] = 0.17.

UV (EtOH, 95%): λ_{max} = 208, 230, 303.

FTIR (KBr): 1 720 (C=O ester), 1 664 (C=O amide), 1 268 (C–O ester).

^{1}H NMR (table III) and ^{13}C NMR show two conformers (E/Z) in 5:6 ratio.

^{13}C NMR ($CDCl_3$) δ: 22.5 (CH_3), 24.8 (CH_3), 54.0 (C-2′), 56.2 (C-2′), 59.4 (C-1′), 62.1 (C-4′), 63.0 (C-4′), 65.5 (C-5′), 65.7 (C-5′), 97.5 (C-5), 128, 129 and 133 (C arom), 144.7 (C-6), 155.6 (C-2), 162.7 (C-4), 166.0 (C=O), 168.5 (C=O), 168.8 (C=O), 170.8 (C=O).

Anal calc for $C_{19}H_{20}N_4O_5S$: C, 54.79; H, 4.84; N, 13.45; S, 7.70. Found: C, 55.18; H, 5.13; N, 13.12; S, 7.89.

- N^4*-Benzoyl-1-(2-benzoyloxymethyl-3-acetyl-1,3-thiazolidin-5-yl)-5-fluorocytosine* **22** *and* **23**

N^4-Benzoyl-5-fluorocytosine (0.11 g, 0.48 mmol), the thiazolidine **16** (0.15 g, 0.39 mmol) and $SnCl_4$ 1 M solution in CH_2Cl_2 (0.47 mL, 0.47 mmol) yielded after column chromatography ($MeOH/CHCl_3$, 1%) two products:

α-Isomer **22** (0.07 g, 36%) was triturated with diethyl ether to give a white solid mp = 170–172 °C; R_f [$MeOH/CHCl_3$, 5%] = 0.24.

UV ($CHCl_3$): λ_{max} = 239, 269, 332.

FTIR (KBr): 1 725 (C=O ester), 1 673 (C=O amide), 1 270 (C–O ester).

^{1}H NMR (table III) and ^{13}C NMR show two conformers (E/Z) in 3:4 ratio.

^{13}C NMR ($CDCl_3$) δ: 22.5 (CH_3), 56.3 (C-2′), 58.7 (C-2′), 60.2 (C-1′), 61.7 (C-4′), 62.7, 64.0 and 64.5 (C-5′), 64.9 (C-5′), 128, 129 and 133.3 (C arom), 133.0 and 133.5

(C-6, $^2J_{CF}$ = 22 Hz), 135.7 and 139.0 (C-5, J_{CF} = −166 Hz), 141.7 and 142.1 (C-4, $^2J_{CF}$ = 18 Hz), 147.2 (C-2), 166.0 (C=O), 166.1 (C=O), 168.4 (C=O).

Anal calc for $C_{24}H_{21}FN_4O_5S$: C, 58.05; H, 4.26. Found: C, 58.02; H, 4.39.

β-Isomer **23** (0.02 g, 10%) foam; R_f [MeOH/CHCl$_3$, 5%] = 0.16.

UV (CHCl$_3$): λ_{max} = 239, 269, 332.

FTIR (KBr): 1 725 (C=O ester), 1 673 (C=O amide), 1 270 (C–O ester).

^{1}H NMR (table III) shows two conformers (*E*/*Z*) in 1:1 ratio.

Anal calc for $C_{24}H_{21}FN_4O_5S$: C, 58.05; H, 4.26. Found: C, 58.13; H, 4.66.

• *1-(2-Benzoyloxymethyl-3-acetyl-1,3-thiazolidin-5-yl)thymine* **24** *and* **25**

Thymine (0.10 g, 0.81 mmol), the thiazolidine **16** (0.16 g, 0.79 mmol) and SnCl$_4$ 1 M solution in CH$_2$Cl$_2$ (0.79 mL, 0.79 mmol) produced an oily residue which was purified by column chromatography (MeOH/CHCl$_3$, 1–4%) to yield two products:

α-Isomer **24** (0.01 g, 6%) as a foam; R_f [MeOH/CHCl$_3$, 5%] = 0.40.

UV (EtOH, 95%): λ_{max} = 208, 223, 267.

FTIR (KBr): 1 713 (C=O ester), 1 660 (C=O amide), 1 266 (C–O ester).

^{1}H NMR (table III) shows two conformers (*E*/*Z*) in 3:4 ratio.

Anal calc for $C_{18}H_{19}N_3O_5S$: C, 55.51; H, 4.92; N, 10.79. Found: C, 55.12; H, 4.72; N, 10.43.

β-Isomer **25** (0.05 g, 30%) was triturated with diethyl ether to give a white solid; mp = 208–210 °C; R_f [MeOH/CHCl$_3$, 5%] = 0.24.

UV (MeOH): λ_{max} = 208, 225, 269.

FTIR (KBr): 1 713 (C=O ester), 1 648 (C=O amide), 1 278 (C–O ester).

^{1}H NMR (table III) shows two conformers (*E*/*Z*) in 4:7 ratio.

Anal calc for $C_{18}H_{19}N_3O_5S$: C, 55.51; H, 4.92; N, 10.79; S, 8.23. Found: C, 55.74; H, 5.14; N, 10.34; S, 8.12.

• N^6*-Benzoyl-9-(2-benzoyloxymethyl-3-acetyl-1,3-thiazolidin-5-yl)adenine* **26** *and* **27**

N^6-Benzoyladenine (0.17 g, 0.70 mmol), the thiazolidine **16** (0.21 g, 0.55 mmol) and SnCl$_4$ 1 M solution in CH$_2$Cl$_2$ (0.83 mL, 0.83 mmol) yielded after column chromatography (MeOH/CH$_2$Cl$_2$, 2%) two products:

α-Isomer **26** (0.04 g, 14%) was triturated with diethyl ether to give a white solid; mp = 97–100 °C; R_f [MeOH/CH$_2$Cl$_2$, 10%] = 0.57.

UV (EtOH 95%): λ_{max} = 203, 227, 282.

FTIR (KBr): 1 720 (C=O ester), 1 640 (C=O amide), 1 268 (C–O ester).

^{1}H NMR (table III) and ^{13}C NMR show two conformers (*E*/*Z*) in 3:5 ratio.

^{13}C NMR (CDCl$_3$) δ: 21.8 (CH$_3$ *E*), 22.3 (CH$_3$ *Z*), 51.4 (C-2′ *E*), 56.2 (C-2′ *Z*), 60.0 (C-1′ *E*), 60.4 (C-1′ *Z*), 60.8 (C-4′ *Z*), 61.9 (C-4′ *E*), 64.8 (C-5′), 65.3 (C-5′), 123.5 (C-5), 127, 128, 129, 132 and 133 (C arom), 140.5 (C-4), 141.3 (C-8), 143.1 (C-6), 152.9 (C-2), 164.4 (C=O), 166.0 (C=O), 168.7 (C=O).

MS (FAB$^+$) *m*/*z*: 503 (M + H$^+$).

Anal calc for $C_{25}H_{22}N_6O_4S$: C, 59.75; H, 4.41; N, 16.72. Found: C, 60.10; H, 4.28; N, 16.44.

β-Isomer **27** (0.07 g, 25%) was triturated with diethyl ether to give a white solid; mp = 122–126 °C; R_f [MeOH/CH$_2$Cl$_2$: 10%] = 0.31.

UV (EtOH, 95%): λ_{max} = 203, 228, 278.

FTIR (KBr): 1 722 (C=O ester), 1 640 (C=O amide), 1 273 (C–O ester).

^{1}H NMR (table IV) and ^{13}C NMR show two conformers (*E*/*Z*) in 1:1 ratio.

^{13}C NMR (CDCl$_3$) δ: 21.6 (CH$_3$ *E*), 22.3 (CH$_3$ *Z*), 51.2 (C-2′ *E*), 57.8 (C-2′ *Z*), 60.1 (C-1′ *E*), 61.4 (C-1′ *Z*), 64.1 (C-4′ *Z*), 64.5 (C-4′ *E*), 64.7 (C-5′), 65.3 (C-5′), 128, 129, 132 and 133 (C arom), 136.8 (C-5), 142.2 (C-8), 143.5 (C-4), 150.8 (C-6), 151.2 (C-2), 166.0 (C=O), 168.6 (C=O).

MS (FAB$^+$) *m*/*z*: 503 (M + H$^+$).

Anal calc for $C_{25}H_{22}N_6O_4S$: C, 59.75; H, 4.41; N, 16.72. Found: C, 59.99; H, 4.62; N, 16.84.

• N^4*-Acetyl-1-(2-benzoyloxymethyl-3-tosyl-1,3-thiazolidin-5-yl)cytosine* **34** *and* **35**

N^4-Acetylcytosine (0.04 g, 0.26 mmol), the thiazolidine **18** (0.08 g, 0.16 mmol) and SnCl$_4$ 1 M solution in CH$_2$Cl$_2$ (0.20 mL, 0.20 mmol) yielded after column chromatography (MeOH/CHCl$_3$, 1–5%) a mixture of α and β isomers as a white solid (0.04 g, 51%); R_f [MeOH/CHCl$_3$, 10%] = 0.51. ^{1}H NMR (table III).

Anal calc for $C_{24}H_{24}N_4O_6S_2$: C, 54.53; H, 4.57; N, 10.60. Found: C, 54.80; H, 4.58; N, 10.72.

Partial deprotection of nucleoside analogues

The fully protected nucleosides were dissolved in anhydrous methanol previously saturated with ammonia, and stirred at room temperature for several hours. The methanolic ammonia was evaporated in vacuo, the residue taken up in water (10 mL H$_2$O for 1 mmol of nucleoside) and extracted twice with ether and chloroform to remove benzamide and methyl benzoate as well as other material. The aqueous phase was then either lyophilized or evaporated for crystallization from other solvents or evaporated for purification by column chromatography. The following compounds were obtained in yields ⩾80%.

• *1-(2-Hydroxymethyl-3-tosyl-1,3-thiazolidin-5-yl)-cytosine* **12a** *and* **12b**

A mixture of protected nucleoside analogues **34/35** (0.03 g, 0.06 mmol) was submitted to deprotection conditions as previously described. Column chromatography (MeOH/CHCl$_3$, 5–7%) yielded two products as white solids:

α-Isomer **12a** (0.01 g, 39%); mp = 124–126 °C (MeOH/CHCl$_3$); R_f [MeOH/CHCl$_3$: 15%] = 0.15.

UV λ_{max}: (H$_2$O, pH 7) 274, (pH 11) 275, (pH 2) 279.

FTIR (KBr): 1 648 (C=O), 1 343 (SO), 1 161 (SO).

^{1}H NMR (table III).

MS (FAB$^+$) *m*/*z*: 383 (M + H$^+$).

Anal calc for $C_{15}H_{18}N_4O_4S_2$: C, 47.10; H, 4.74; N, 14.65. Found: C, 47.22; H, 4.38; N, 14.55.

β-Isomer **12b** (0.01 g, 39%); mp = 128–129 °C (MeOH/CHCl$_3$); R_f [MeOH/CHCl$_3$, 15%] = 0.17.

UV λ_{max}: (H$_2$O, pH 7) 274, (pH 11) 274, (pH 2) 280.

FTIR (KBr): 1 646 (C=O), 1 341 (SO), 1 160 (SO).

^{1}H NMR (table III).

MS (FAB$^+$) *m*/*z*: 383 (M + H$^+$).

Anal calc for $C_{15}H_{18}N_4O_4S_2$: C, 47.10; H, 4.74; N, 14.65. Found: C, 46.95; H, 4.34; N, 14.33.

• *1-(2-Hydroxymethyl-3-acetyl-1,3-thiazolidin-5-yl)-cytosine* **28** *and* **29**

α-Isomer **28** was obtained as a white solid; mp = 195–200 °C (MeOH/$CHCl_3$); R_f [MeOH/$CHCl_3$, 25%] = 0.15.

UV λ_{max}: (H_2O, pH 7) 274, (pH 11) 273, (pH 2) 282.

FTIR (KBr): 1 654 (C=O amide).

^{1}H NMR (table III).

MS (FAB^+) m/z: 271 (M + H^+).

Anal calc for $C_{10}H_{14}N_4O_3S$: C, 44.43; H, 5.22; N, 20.72. Found: C, 44.32; H, 5.18; N, 20.59.

β-Isomer **29** was obtained as a white solid; mp = 72 °C (MeOH/$CHCl_3$); R_f [MeOH/$CHCl_3$, 25%] = 0.13.

UV λ_{max}: (H_2O, pH 7) 274, (pH 11) 274, (pH 2) 281.

FTIR (KBr): 1 654 (C=O amide).

^{1}H NMR (table III) shows two conformers (E/Z) in 5:8 ratio.

MS (FAB^+) m/z: 271 (M + H^+).

Anal calc for $C_{10}H_{14}N_4O_3S$: C, 44.43; H, 5.22; N, 20.72. Found: C, 44.65; H, 5.45; N, 20.74.

• *1-(2-Hydroxymethyl-3-acetyl-1,3-thiazolidin-5-yl)-5-fluorocytosine* **30** *and* **31**

α-Isomer **30** was obtained as a white solid; mp = 114–117 °C (dec) (MeOH/$CHCl_3$); R_f [MeOH/$CHCl_3$, 25%] = 0.21.

UV λ_{max}: (H_2O, pH 7) 283, (pH 11) 283, (pH 2) 284.

FTIR (KBr): 1 654 (C=O amide).

^{1}H NMR (table III) shows two conformers (E/Z) in 1:1 ratio.

MS (FAB^+) m/z: 289 (M + H^+).

Anal calc for $C_{10}H_{13}FN_4O_3S$: C, 41.66; H, 4.54; N, 19.43. Found: C, 41.28; H, 4.32; N, 19.26.

β-Isomer **31** was obtained as a white solid; mp = 114 °C (dec) (MeOH/$CHCl_3$); R_f [MeOH/$CHCl_3$, 25%] = 0.21.

UV λ_{max}: (H_2O pH 7) 279, (pH 11) 287, (pH 2) 282.

FTIR (KBr): 1 654 (C=O amide).

^{1}H NMR (table III) shows two conformers (E/Z) in 7:4 ratio.

MS (FAB^+) m/z: 289 (M + H^+).

Anal calc for $C_{10}H_{13}FN_4O_3S$: C, 41.66; H, 4.54; N, 19.43. Found: C, 41.62; H, 4.48; N, 19.79.

• *1-(2-Hydroxymethyl-3-acetyl-1,3-thiazolidin-5-yl)-thymine* **32**

β-Isomer **32** was obtained as a white solid; mp = 70 °C (MeOH/$CHCl_3$); R_f [MeOH/$CHCl_3$, 10%] = 0.25.

UV λ_{max}: (H_2O, pH 7) 269, (pH 11) 272, (pH 2) 277.

FTIR (KBr): 1 718, 1 654 (C=O amide).

^{1}H NMR (table III) shows two conformers (E/Z) in 1:1 ratio.

MS (FAB^+) m/z: 286 (M + H^+).

Anal calc for $C_{11}H_{15}N_3O_4S$: C, 46.30; H, 5.30; N, 14.72. Found: C, 45.98 ;H, 5.01; N, 14.81.

• N^9-*(2-Hydroxymethyl-3-acetyl-1,3-thiazolidin-5-yl)adenine* **33**

β-Isomer **33** was obtained as a foam; R_f [MeOH/$CHCl_3$, 10%] = 0.25.

^{1}H NMR (table III) shows two conformers (E/Z) in 2:1 ratio.

UV λ_{max}: (EtOH, 95%) 281, (EtOH 0.01 N HCl) 285.

Anal calc for $C_{11}H_{14}N_6O_2S$: C, 44.88; H, 4.79; N, 28.55. Found: C, 45.11; H, 4.92; N, 28.18.

• *2-Benzoyloxymethyl-3-(9-fluorenylmethoxy-carbonyl)-1,3-thiazolidine* **36**

2-Benzoyloxymethyl-1,3-thiazolidine **19** (0.516 g, 2.31 mmol) was dissolved in 30 mL dioxane/water (5:1) solution containing sodium bicarbonate (0.194 g, 2.31 mmol), and 9-fluorenylmethyl chloroformate (0.598 g, 2.31 mmol) was added. The mixture was stirred for 5 h at room temperature. After evaporation of the solvents under reduced pressure, CH_2Cl_2 (40 mL) and 5% $NaHCO_3$ aqueous solution (50 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (10 mL). Organic phases were washed with 5% $NaHCO_3$ aqueous solution (2 × 50 mL) and brine (55 mL), dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography using a gradient of EtOAc/hexane (10–17%) yielded 95% of **36** (0.985 g, 2.21 mmol) as a foam. R_f [EtOAc/toluene, 10%] = 0.51.

^{1}H NMR ($CDCl_3$) δ: 3.00 (m, 2H, H-4), 3.65 (m, 2H, H-5), 4.35–4.60 (m, 6H, H-9′ and H-10′), 5.30 (br s, 1H, H-2), 7.33–8.08 (m, 26H, H arom).

^{13}C NMR ($CDCl_3$) δ: 31.7 (C-5), 48.0 (C-9′), 49.6 (C-4), 60.1 (C-2), 66.1 (C2-*C*), 68.0 (C-10′), 118.6 (C-4′, C-5′), 123.3 (C-1′, C-8′), 125.5, 126.1, 126.8, 128.0, 131.4 (C-2′, C-3′, C-6′, C-7′, C arom), 139.2, 139.3 (C-4′a, C-4′b), 141.6 (C-9′a, C-9′b), 151.6 (C-12′), 163.2 (CO).

MS (FAB^+) m/z: 446 (M + H^+).

Anal calc for $C_{26}H_{23}NO_4S$: C, 70.09; H, 5.20. Found: C, 70.28; H, 5.34.

• *2-Benzoyloxymethyl-3-(9-fluorenylmethoxy-carbonyl)-5-benzoyloxy-1,3-thiazolidine* **37**

Compound **36** (0.967 g, 2.17 mmol) dissolved in dry benzene (70 mL) was refluxed for 1 day and excess dibenzoyl peroxide (1.04 g, 4.28 mmol) was added portionwise. After evaporation of the solvent, CH_2Cl_2 (50 mL) and 5% $NaHCO_3$ aqueous solution (50 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (10 mL). Organic phases were washed with 5% $NaHCO_3$ aqueous solution (50 mL), brine (55 mL), dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography using EtOAc/hexane (1%) yielded a mixture of *cis/trans* isomers of **37** in 32% yield (0.393 g, 0.69 mmol) as a yellow foam which crystallized on standing mp = 50–58 °C; R_f [EtOAc/toluene, 5%] = 0.35. ^{1}H NMR shows two isomers (A/B) in 4:3 ratio.

UV λ_{max}: (EtOH, 95%) 300, 265, 227, 210.

FTIR (KBr): 1 719, 1 266.

^{1}H NMR ($CDCl_3$) δ: 3.71 (dd, 4H, H-4a A, J = 2.8 and 13.1 Hz), 3.75 (dd, 3H, H-4a B, J = 1.5 and −13.3 Hz), 4.15–4.64 (m, 35H, H-10′, H-9′, C2-CH_2 A and B forms), 4.77 (d, 3H, H-4b B, J = −13.3 Hz), 4.94 (d, 4H, H-4b A, J = −13.1 Hz), 5.73 (pseudo t, 4H, H-2 A, J = 5.8 and 6.1 Hz), 5.99 (pseudo t, 3H, H-2 B, J = 5.81 and 5.85 Hz), 6.42 (d, 4H, H-5 A, J = 2.8 Hz), 6.49 (d, 3H, H-5, J = 1.5 Hz), 7.22–8.07 (m, 126H, H arom).

^{13}C NMR ($CDCl_3$) δ: 46.9 (C-9′), 53.4 (C-4), 60.0 (C-2), 60.9 (C-2), 65.1 (C2-*C*), 66.5 (C2-*C*), 67.9 (C-10′), 68.2 (C-10′), 80.3 (C-5), 80.9 (C-5), 119.9 (C-4′, C-5′), 124.7 (C-1′, C-8′), 127 (C-2′, C-3′, C-6′, C-7′), 128, 129, 133 (C arom), 141.2 (C-4′a, C-4′b), 143.5 (C-9′a, C-9′b), 154 (C-12′), 165.4 (CO), 165.6 (CO), 165.8 (CO), 166.0 (CO).

Anal calc for $C_{33}H_{27}NO_6S$: C, 70.04; H, 4.81. Found: C, 70.32; H, 4.92.

• *1-[2-Benzoyloxymethyl-3-(9-fluorenylmethoxy-carbonyl)-1,3-thiazolidin-5-yl]cytosine* **38** *and* **40**

Using the general coupling procedure as described above, cytosine (0.18 g, 1.69 mmol), 2-benzoyloxymethyl-3-(9-fluorenylmethoxycarbonyl) - 5 - benzoyloxy - 1,3 - thiazolidine **37**

(0.543 g, 0.97 mmol) and $SnCl_4$ 1 M solution in CH_2Cl_2 (1.36 mL, 1.36 mmol) yielded after column chromatography ($MeOH/CHCl_3$, 1–8%) two products:

α-Isomer **38** (0.227 g, 42%) mp = 120–123 °C; R_f [$MeOH/CHCl_3$, 10%] = 0.25.

UV (EtOH): λ_{max} = 217, 265, 300; (EtOH/0.01 N HCl, pH 3.5) 211, 266, 298.

FTIR (KBr): 1 719, 1 642, 1 266.

^{1}H NMR ($CDCl_3$) δ: 3.70 (m, 1H, H-2′a), 3.98–4.36 (m, 6H, H-2′b, H-9″, H-10″, H-5′), 5.63 (pseudo t, 1H, H-4″, *J* = 7.75 and 8.31 Hz), 6.25 (dd, 1H, H-1′, *J* = 2.5 and 11.1 Hz), 7.28–7.86 (m, 17H, H-6, H-5, H arom, NH_2).

^{13}C NMR ($CDCl_3$) δ: 47.4 (C-9″), 54.5 (C-2′), 61.0 (C-4′), 62.9 (C-1′), 65.6 (C-5′), 68.5 (C-10″), 96.0 (C-5), 120.6 (C-4″, C-5″), 125.1 (C-1″,C-8″), 127.7, 128.4 (C-2″, C-3″, C-6″, C-7″), 129.1, 129.8, 130.2, 134.1 (C arom), 140.8, 141.3 (C-6), 141.7 (C-4″a, C-4″b), 143.7 (C-9″a, C-9″b), 154.0 (C-4), 154.6 (C-12″), 157.0 (C=O), 166.3 (C-2).

Anal calc for $C_{30}H_{26}N_4O_5S$: C, 64.96; H, 4.72; N, 10.10. Found: C, 65.15; H, 4.33; N, 10.22.

β-Isomer **40** (0.100 g, 18%) mp = 112–114 °C; R_f [$MeOH/CHCl_3$, 10%] = 0.22.

^{1}H NMR ($CDCl_3$) δ: 3.48 (dd, 1H, H-4′a, *J* = 6.8 and −12.6 Hz), 4.21 (t, 1H, H-9″, *J* = 6.2 Hz), 4.43–4.60 (m, 4H, H-10″, C2′-CH_2), 4.70 (dd, 1H, H-4′b, *J* = 7.1 and −12.6 Hz), 5.68 (d, 1H, H-2′, *J* = 7.4 Hz), 6.48 (pseudo t, 1H, H-5′, *J* = 6.8 and 7.1 Hz), 7.33–8.17 (m, 17H, H-6, H-5, H arom, NH_2).

^{13}C NMR ($CDCl_3$) δ: 46.9 (C-9″), 53.5 (C-4′), 61.8 (C-2′), 62.1 (C-5′), 66.0 (C2′-*C*), 68.2 (C-10″), 95.6 (C-5), 120, 124, 127, 128 (C-4″, C-5″, C-1″, C-8″, C-2″, C-3″, C-6″, C-7″), 129, 130, 133 (C arom), 141.2 (C-6), 143.2 (C-4″a, C-4″b), 143.8 (C-9″a, C-9″b), 152.3 (C-4), 153.6 (C-12″), 156 (C=O), 166.2 (C-2).

Anal calc for $C_{30}H_{26}N_4O_5S$: C, 64.96; H, 4.72; N, 10.10. Found: C, 64.99; H, 4.84; N, 10.31.

• N^9-*[2-Benzoyloxymethyl-3-(9-fluorenylmethoxycarbonyl)-1,3-thiazolidin-5-yl]-6-chloropurine* **39** *and* **41**

6-Chloropurine (0.103 g, 0.66 mmol), the 2-benzoyloxymethyl-3-(9-fluorenylmethoxycarbonyl)-5-benzoyloxy-1,3-thiazolidine **37** (0.322 g, 0.57 mmol) and $SnCl_4$ 1 M solution in CH_2Cl_2 (0.66 mL, 0.66 mmol) yielded after separation by column chromatography (EtOAc/toluene, 15–22%) two products which crystallized on standing:

α-Isomer **39** (0.04 g, 11%) as a white solid, mp = 68 °C.

UV (MeOH): λ_{max} = 213, 265, 300.

FTIR (KBr): 2 919, 2 848, 1 719, 1 595, 1 537, 1 443, 1 266, 1 114, 708.

^{1}H NMR ($CDCl_3$) δ: 3.88–4.61 (m, 7H, H-4′, H-9″, H-10″, C2′-CH_2), 5.60 (br s, 1H, H-2′), 6.31 (br s, 1H, H-5′), 7.27–8.10 (m, 13H, H arom), 8.47 (s, 1H, H-2), 8.85 (s, 1H, H-8).

Anal calc for $C_{31}H_{24}ClN_5O_4S$: C, 62.25; H, 4.04; N, 11.71. Found: C, 62.34; H, 3.97; N, 11.82.

β-Isomer **41** (0.056 g, 16%) as a white solid, mp = 74–77 °C.

UV (MeOH): λ_{max} = 213, 266, 299.

FTIR (KBr): 1 719, 1 595.

^{1}H NMR ($CDCl_3$) δ: 3.92 (m, 1H, H-4′a), 4.14–4.40 (m, 3H, H-9″, H-10″), 4.56–4.89 (m, 3H, H-4′b, C2′-CH_2), 5.44 (br s, 1H, H-2′), 6.61 (d, 1H, H-5′, *J* = 3.6 Hz), 7.29–8.37 (m, 13H, H arom), 8.51 (s, 1H, H-2), 8.97 (s, 1H, H-8).

Anal calc for $C_{31}H_{24}ClN_5O_4S$: C, 62.25; H, 4.04; N, 11.71. Found: C, 62.18; H, 3.99; N, 11.59.

• *1-[2-Hydroxymethyl-1,3-thiazolidin-5-yl]cytosine* **13a** *and* **13b**

Each protected nucleoside was stirred in 1% sodium hydroxide in anhydrous methanol (1 mL), for half an hour at room temperature. After evaporation, the residue was taken up in water and extracted twice with ether and chloroform to remove non-polar materials. The aqueous layer was applied to a column containing 1 g of Dowex 50X8-100 (H^+ form) and the resin was washed with water (about 15 mL) until the eluent showed pH 5, then with 0.5 M NH_4OH (20 mL) until no further UV active material was seen in the eluent. The basic eluent was evaporated to dryness and a white hygroscopic solid was obtained. One equivalent of 0.01 N HCl was added, then the solution was lyophilized and yielded a slightly brown solid.

α-Isomer **13a** ^{1}H NMR ($CDCl_3$) δ: 3.08–3.57 (m, 5H, H-4′ C2′-CH_2 and OH), 4.99 (pseudo t, 1H, H-2′, *J* = 6.0 and 6.2 Hz), 5.68 (d, 1H, H-5, *J* = 7.3 Hz), 6.20 (br s, 1H, H-5′), 7.11 (br s, 3H, D_2O exchangeable, NH and NH_2), 8.09 (d, 1H, H-6, *J* = 7.3 Hz).

FTIR (KBr): 3 365, 3 213, 2 931, 1 654, 1 490, 1 396, 1 278, 790.

UV λ_{max}: (H_2O pH 7) 273, (pH 12) 273, (pH 2) 278.

MS (FAB^+) *m/z*: 229 (M + H^+).

Anal calc for $C_8H_{13}ClN_4O_2S$: C, 36.29; H, 4.94; N, 21.16. Found: C, 36.40; H, 5.08; N, 21.64.

β-Isomer **13b** mp = 133–136 °C (dec).

^{1}H NMR ($CDCl_3$) δ: 3.10–3.52 (m, 3H, H-4′ and OH), 3.81 (m, 2H, C2′-CH_2), 4.62 (br s, 1H, H-2′), 5.71 (d, 1H, H-5, *J* = 7.3 Hz), 6.20 (br s, 1H, H-5′), 7.11 (br s, 3H, D_2O exchangeable, NH and NH_2), 8.09 (d, 1H, H-6, *J* = 7.3 Hz).

FTIR (KBr): 1 648.

UV λ_{max}: (H_2O, pH 7) 273, (pH 12) 273, (pH 2) 278.

MS (FAB^+) *m/z*: 229 (M + H^+).

Anal calc for $C_8H_{13}ClN_4O_2S \cdot 1.0\ H_2O$: C, 33.97; H, 5.34; N, 19.81. Found: C, 34.40; H, 5.18; N, 20.01.

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