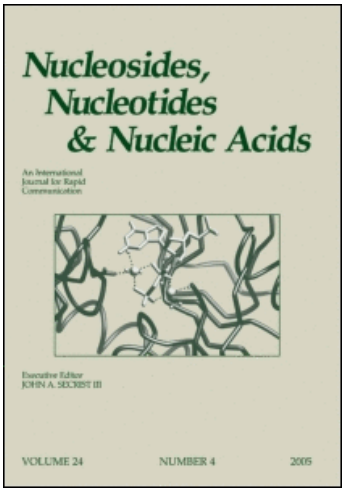

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis of new Thiazolidinone Nucleoside Analogues

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Abstract: The synthesis of new thiazolididone nucleoside analogues is described. Among the different proposed synthetic pathways, the condensation of various nucleic bases using TMSOTf and Et_3N as coupling reagents on a key sulfoxide thiazolidinone intermediate led to the desired compounds in a one-pot procedure. Analytical data and NMR studies confirmed the proposed structure assignment for these compounds.

The search for more effective anti-HIV therapies includes discovering new drugs with different mechanisms of action (1,2,3) and improving those drugs already shown to be efficacious, particularly nucleosides. Nucleoside analogues have long been known as antiviral agents because of their ability to interfere with DNA synthesis by inhibiting DNA polymerases (4). Large numbers of analogues have been synthesized and tested, but very few have been approved for clinical testing either for lack of activity or for excessive toxicity. Much efforts have been devoted to compounds that lack the 3'-hydroxyl substituent of the natural nucleosides because they can act as chain terminators after their incorporation into the DNA chain. The nucleoside analogues that have been studied most thoroughly as potential anti-HIV drugs include various 2',3'-dideoxyribose (5) , 2',3'-didehydro-2',3'-dideoxyribose (6) and 3'-substituted-2',3'-dideoxyribose (7) derivatives of thymine, uracil, 5-alkyluracil, 5-halouracil, cytosine, adenine and guanine. More recently, other analogues with modified ribose moieties including compounds in which a methylene group replaces $O_{4'}$ (8) or where $C_{3'}$ is substituted by oxygen or sulfur, have been described. One of them 3TC (β(-) 2',3'-dideoxy-3'-thiacytidine) (9,10,11) has been approved by FDA for an open-label

compassionate use protocol. 3TC is the first example of nucleoside which shows that both β-enantiomers have very close antiretroviral activity, but the (-) enantiomer appears to be 100 times less cytotoxic than the (+) enantiomer (12). The anti-HIV and anti-HBV properties of these analogues with modified ribose moieties prompted us to investigate the synthetic feasability of new heteronucleosides where the ribose ring has been replaced by a 1,3-thiazolidin-4-one moiety (FIG. 1).

To our knowledge such thiazolidinone ring which can mimic the ribose ring has never been used in nucleoside chemistry. The synthesis of thiazolidinone nucleoside analogues required the formation of the intermediate 2-benzoyloxymethyl-1,3-thiazolidin-4-one (**3**). Formation of this compound was accomplished through the sequence described by Surrey et al. (13) shown on scheme 1: starting from mercaptoacetic acid (**1**), benzoyloxyacetaldehyde (**2**) (14) and ammonium carbonate, 2-benzoyloxymethyl-1,3-thiazolidin-4-one (**3**) was obtained in 47% yield.

It is important to note that every compound obtained (**3**-**16β**) is an ± enantiomers mixture.

The first step was to introduce a leaving group like acetoxy at 5-position of the thiazolidinone ring. This was achieved through the following sequences (SCHEME 2). After N-acetylation of **3** using acetic anhydride (92% yield), the resulting N-acetylated intermediate **4** was treated with 3-chloroperbenzoic acid (mCPBA) in CH_2Cl_2 at room temperature and led to the sulfoxide **5** which was easily isolated in 91% yield.

Compound **5** was then submitted to the Pummerer rearrangement under different experimental conditions (14-17). We found that refluxing compound **5** for 24 h in acetic anhydride led to the mixture of diastereoisomers **6** in 73% yield. It should be underlined that the use of sodium acetate as recommended in some cases (15,16) is detrimental to the formation of the desired 5-acetoxy-thiazolidinone **6**. Separation of the diastereoisomers mixture was achieved by flash-chromatography and the two diastereoisomers **6a** and **6b** were isolated. Assignment of cis/trans configuration of these two diastereoisomers was based on NOEDIFF experiments that upon irradiation of H-5 in **6a** and **6b**, enhancement of H-2 peak, suggesting cis orientation, was observed in **6b**,while no enhancement was observed in **6a**, indicating trans configuration.

Glycosylation with N^4-acetylcytosine was attempted under different conditions (18,19). When the silylated nucleic base was condensed with **6** using different catalysts as $TiCl_4$, $SnCl_4$ or TMSOTf (20), no coupling products were observed.

These results led us to use the one-pot procedure already described by O'Neil et al. (21). Sulfoxide **5** was added to a mixture of 1 eq of N-acetylcytosine, 3 eq of TMSOTf and 3 eq of Et_3N in dry toluene at room temperature, the desired product **7** was obtained in low yield (SCHEME 3). Unfortunately removal of the protecting group

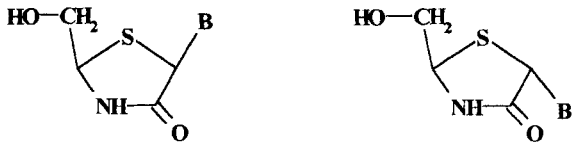
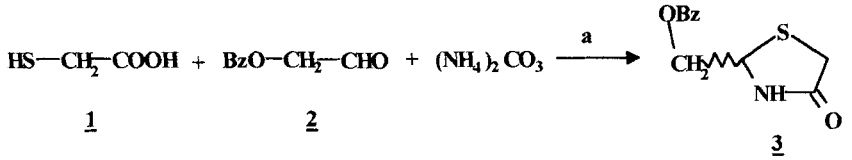
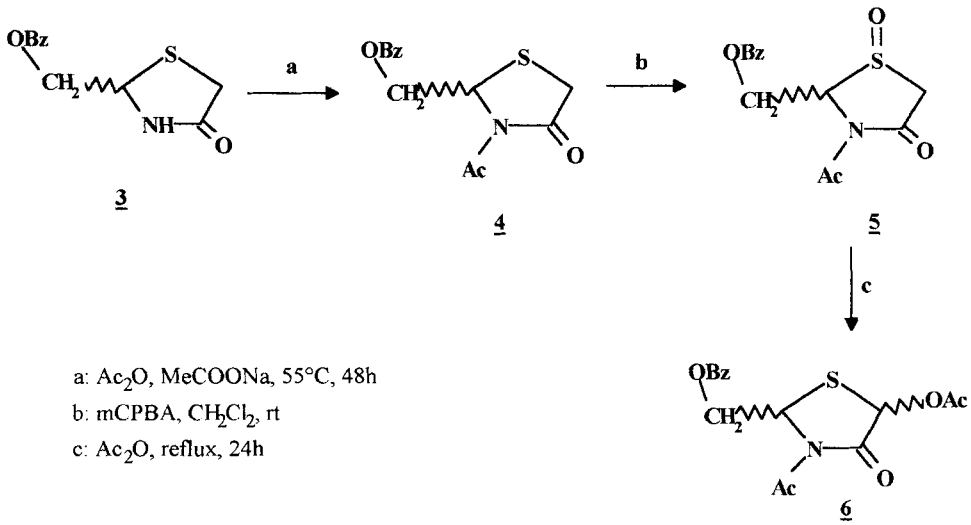


FIG.1



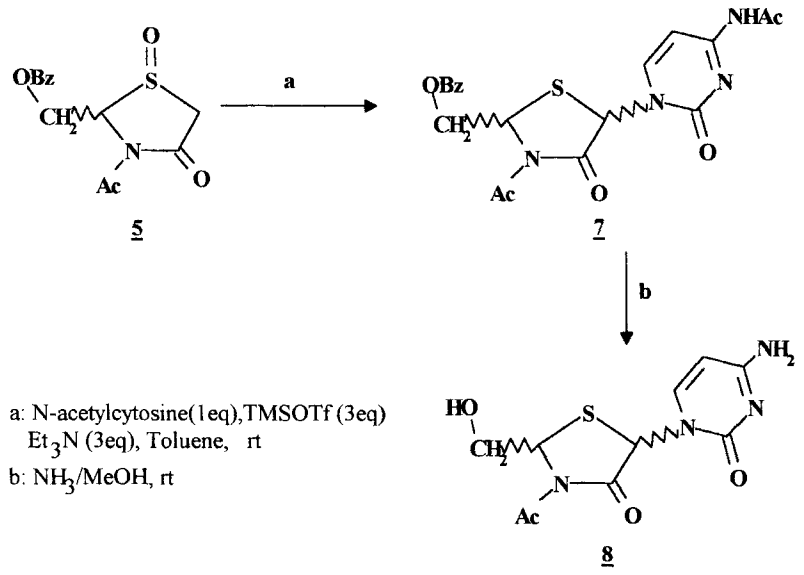
a: Toluene, reflux, overnight

SCHEME 1



a: Ac_2O, MeCOONa, 55°C, 48h
b: mCPBA, CH_2Cl_2, rt
c: Ac_2O, reflux, 24h

SCHEME 2

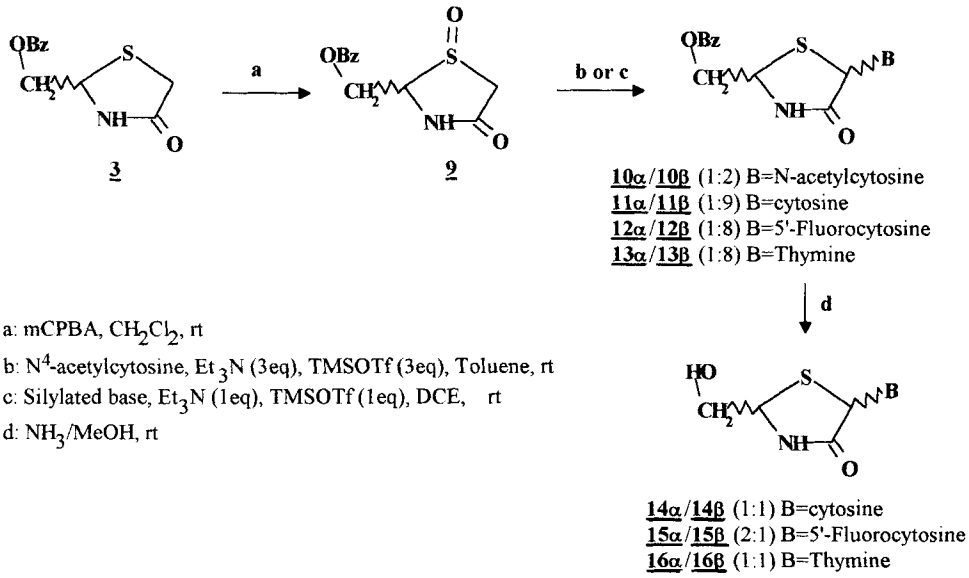


SCHEME 3

using NH_3/MeOH conditions (19) led to compound **8** (SCHEME 3) and not to the expected fully deprotected compounds **14α** and **14β** (shown on SCHEME 4).

To overcome the difficulties encountered during the deprotective step, we investigated a new strategy which can be summerized as follows: to the 1-oxide-2-benzoyloxymethyl-1,3-thiazolidin-4-one (**9**) was condensed the N-acetylcytosine using 3 eq of TMSOTf and 3 eq of Et_3N as coupling catalyst (method b). The 2-benzoyloxymethyl-5-(N^4-acetylcytosin-1-yl)-1,3-thiazolidin-4-one (**10**) was obtained in 20% yield as a mixture of diastereoisomers α/β (1:2 ratio). After deprotection using NH_3/MeOH compounds **14α** and **14β** were isolated as a mixture of diastereoisomers α/β (1:1 ratio) in quantitative yield (SCHEME 4).

Finally in order to improve the synthesis in terms of yield we adopted the following sequence. Under anhydrous conditions to a mixture of various silylated bases and 1 eq of sulfoxide **9** dissolved in dry 1,2-dichloroethane (DCE) were added successively 1 eq of Et_3N and 1 eq of TMSOTf (method c) as suggested by Dardaine et al. (22). The corresponding coupling products **11**, **12**, **13** were obtained in 30 to 40% yield as α/β mixtures. Deprotection of these products using methanolic ammonia solution led to the desired nucleoside analogues **14-16** in quantitative yield as a mixture of α/β diastereoisomers (SCHEME 4).



SCHEME 4

The anomeric mixtures **10-13** were not separated into theirs α and β forms because of an epimerisation described subsequently. The configuration and the assignment of NMR signals were determinated by NOESY experiments on these anomeric mixtures. This sequence showed interactions between H-2 and H-5, H-5 and Phenyl, H-5' and CH_2, H-6' and CH_2 indicating the β anomeric configuration (**10β-13β**) while no interaction between H-2 and H-5 and interactions between H-5 and CH_2, H-2 and H-5' suggest the α anomeric configuration (**10α-13α**).

It is interesting to note that during the deprotective step in a saturated solution of ammonia in methanol as well as in a methanolic solution of NaOH 1% (23), epimerisation of the mixture of diastereoisomers **11-13** was observed. This latter could be explained through a ring opening mechanism involving the carbon 2 and the sulfur atom as suggested by Baldwin et al. (24). Separation of the diastereoisomers mixtures into the α forms and β forms was then achieved on deprotected diastereoisomers **14-16** by HPLC technique using a Merck Lichrospher RP-18 (10μm, 25x250 mm) and CH_3CN/H_2O gradients as a mobile phase. In these conditions of HPLC separation, the β anomers (**14β-16β**) were the first eluted and then the most polar compounds. Likewise, the determination of the anomeric configuration of mixtures **14-16** was based on NOESY experiments. This sequence showed interactions between H-2 and H-5, H-5'

and CH_2 indicating the β anomers (**14β-16β**) while interactions between H-5 and CH_2 and the absence of interaction between H-2 and H-5 indicate the α anomers (**14α-16α**).

Structural assignments for the compounds were based on elemental analysis and spectroscopic data. ^1H, ^{13}C NMR, M.S. and U.V. spectra are described in the experimental part. ^{13}C NMR signal assignments were confirmed by DEPT sequence. Biological evaluation of these new series of nucleosides will be published elsewhere.

Experimental section

All the reagents and solvents were of commercial quality from freshly opened containers and purchased from Aldrich Chimica Company. Reagent quality solvents were used without further purification. TLC Merck-F_{254nm} aluminium plates and preparative layer Merck-F_{254nm} plates were purchased from Merck Co. Darmstadt. Preparative flash column chromatographies (25) were performed using silica gel Merck G60 230-240 mesh. ^1H and ^{13}C NMR spectra were obtained using a Bruker AMX 200 or Bruker AMX 400. Chemical shifts (δ) are given in parts per million (ppm) downfield from the internal TMS reference. U.V. spectra were obtained on a KONTRON Uvikon 900 spectrometer. FAB+ mass spectra were obtained on a JEOL DX-100 mass spectrometer at the Laboratoire de Mesures Physiques-RMN, USTL, Montpellier, France. Microanalysis was performed by the Service de Microanalyses du CNRS at Lyon Vernaison-France.

All compounds gave C,H,N within ±0.3% of theoretical values.

2-benzoyloxymethyl-1,3-thiazolidin-4-one (3)

To a solution of 3.1 g of 2-benzoyloxyacetaldehyde (19mmol, 1eq) in 80 mL toluene were added 1.43 mL of mercaptoacetic acid (21mmol, 1.1eq) and 1.1 g of ammonium carbonate (11mmol, 0.6eq). The solution was refluxed overnight and the water formed was removed through a Dean-Stark apparatus. The solution was cooled to room temperature and washed with a 5% $NaHCO_3$ aqueous solution (25 mL). Subsequently the mixture was extracted with EtOAc (3x20 mL). The combined EtOAc extracts were washed with saturated brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The desired product **3** was purified by flash chromatography (EtOAc/Toluene 1:9), recrystallized in toluene and obtained in 47% yield (2.1 g) as a white solid. m.p.=167°C. Rf (EtOAc/Toluene 1:1)=0.3. ^1H NMR ($CDCl_3$) δ: 3.55 (m,2H,CH_2-5), 4.30 (dd,J=11.5Hz,J=7.8Hz,1H,C2-CH_{2a}), 4.50 (dd,J=11.5Hz,J=3.7Hz, 1H,C2-CH_{2b}), 4.90 (dd,J=7.7Hz,J=3.6Hz,1H,H-2), 6.80 (bs,1H,NH), 7.42-8.06 (m,5H,arom); ^{13}C NMR ($CDCl_3$) δ: 31.0 (C-5), 54.7 (C-2), 68.6 (CH_2-O), 128.6-133.5

(arom), 167.0 (CO-NH),172.0 (CO-O); MS (FAB+): 238 $(M+H)^+$; UV (MeOH) λ: 230.0nm, 273.0nm.

2-benzoyloxymethyl-3-acetyl-1,3-thiazolidin-4-one (4)

A solution of 0.07 g of **3** (0.3mmol) in 25 mL of acetic anhydride was heated at 55°C for two days. The resulting mixture was washed with a 5% $NaHCO_3$ aqueous solution (20mL) and extracted with EtOAc (3x15 mL). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated under *vacuum*. After purification by flash chromatography (EtOAc/Toluene 1:2), compound **4** was isolated as a colored solid in 92% yield (0.076g). m.p.=74°C. Rf (EtOAc/Toluene 1:2)=0.7. ^1H NMR ($CDCl_3$) δ: 2.55 (s,3H,CH_3), 3.55 (d,J=16.8Hz,1H,H-5a), 3.95 (d,J=16.7Hz,1H,H-5b), 4.57 (dd,J=11.7Hz,J=3.2Hz,1H,C2-CH_{2a}), 4.75 (dd,J=11.7Hz, J=3.9Hz,1H,C2-CH_{2b}), 5.68 (dd,J=3.3Hz,J=3.8Hz,1H,H-2), 7.42-8.00 (m,5H,arom); ^{13}C NMR ($CDCl_3$) δ: 24.8 (CH_3), 34.4 (C-5), 58.3 (C-2), 66.5 (CH_2-O), 128.6-133.4 (arom), 166.1 (CO-N-Ac), 167.4 (CO-CH_3), 170.3 (CO-O); MS (FAB+): 280 $(M+H)^+$; UV (MeOH) λ: 237.0nm, 273.0nm.

1-oxide-2-benzoyloxymethyl-3-acetyl-1,3-thiazolidin-4-one (5)

At 0°C to a solution of **4** (0.07 g, 0.25mmol, 1eq) in 20 mL of CH_2Cl_2 was added dropwise a solution of 0.065 g of 3-chloroperbenzoic acid (0.30mmol, 1.2eq) in 10 mL of CH_2Cl_2. The reaction mixture was stirred at 0°C for 20 min and 7h at room temperature. After addition of a 5% $NaHCO_3$ aqueous solution (25 mL), the solution was extracted with EtOAc (3x20 mL). The combined EtOAc extracts were dried over Na_2SO_4. The desired compound **5** after purification by flash chromatography (EtOAc/Toluene 1:1) was isolated as a white solid and obtained in 91% yield (0.067 g). m.p.=91°C. Rf (EtOAc/Toluene 1:1)=0.18. ^1H NMR ($CDCl_3$) δ: 2.64 (s,3H,CH_3), 3.65 (d,J=17.6Hz,1H,H-5a), 4.00 (d,J=17.6Hz,1H,H-5b), 4.75 (dd,J=12.7Hz,J=2.9Hz,1H,C2-CH_{2a}), 4.85 (dd,J=12.7Hz,J=4.3Hz,C2-CH_{2b}), 5.52 (dd,J=2.9Hz,J=4.2Hz,1H,H-2), 7.44-7.91 (m,5H,arom); ^{13}C NMR ($CDCl_3$) δ: 24.3 (CH_3), 55.4 (C-5), 59.6 (C-2), 60.5 (CH_2-O), 127.7-133.2 (arom), 164.9-170.8 (CO); MS (FAB+): 296 $(M+H)^+$; UV (MeOH) λ: 230.0nm, 273.0nm.

2-benzoyloxymethyl-3-acetyl-5-acetoxy-1,3-thiazolidin-4-one (6)

Under nitrogen atmosphere 0.080 g of compound **5** (0.27mmol) in 25 mL of acetic anhydride was refluxed for 24 h. After solvent evaporation, the residue was washed with 5% $NaHCO_3$ aqueous solution (20 mL), extracted with EtOAc (2x25 mL) and dried over Na_2SO_4. The two diastereoisomers **6** (trans/cis) in 1 to 3 ratio were purified

and separated by flash chromatography (EtOAc/Toluene 5:95) to provide 0.017 g of **6a** (trans-isomers) and 0.050 g of **6b** (cis-isomers). Yield 73%. 6a (trans-isomers): Rf(Toluene)=0.43; ^{1}H NMR ($CDCl_3$) δ: 2.27 (s,3H,C$\underline{H}_3$-COO), 2.53 (s,3H,C$\underline{H}_3$-CO-N), 4.50 (dd,J=11.8Hz,J=2.6Hz,1H,C2-C$\underline{H}_{2a}$), 4.70 (dd,J=11.7Hz, J=3.6Hz,1H,C2-C$\underline{H}_{2b}$), 5.67 (dd,J=2.6Hz,J=3.7Hz,1H,H-2), 6.42 (s,1H,H-5), 7.42-7.99 (m,5H,arom); ^{13}C NMR ($CDCl_3$) δ: 21.0 (C$\underline{H}_3$-CO-O), 26.0 (C$\underline{H}$3-CO-N), 58.1 (C-2), 67.0 (C$\underline{H}_2$-O), 75.2 (C-5), 128.0-135.0 (arom), 166.0-170.0 (C$\underline{O}$); MS(FAB+): 338 $(M+H)^+$; 6b(cis-isomers): Rf(Toluene)=0.41; ^{1}H NMR ($CDCl_3$) δ: 2.27 (s,3H,C$\underline{H}_3$-COO), 2.53 (s,3H,C$\underline{H}_3$-CO-N), 4.57 (dd,J=8.2Hz,J=3.6Hz,1H,C2-C$\underline{H}_{2a}$), 4.65 (dd,J=8.2Hz,J=3.8Hz,1H,C2-C$\underline{H}_{2b}$), 5.60 (dd,J=3.6Hz,J=3.8Hz,1H,H-2), 6.25 (s,1H,H-5), 7.42-7.99 (m,5H,arom); ^{13}C NMR ($CDCl_3$) δ: 21.0 (C$\underline{H}_3$-CO-O), 26.0 (C$\underline{H}$3-CO-N), 58.0 (C-2), 67.0 (C$\underline{H}_2$-O), 75.0 (C-5), 128.0-135.0 (arom), 166.0-170.0 (C$\underline{O}$); MS (FAB+): 338 $(M+H)^+$; UV (MeOH) λ: 237.0nm, 274.0nm.

2-benzoyloxymethyl-3-acetyl-5-(N^4-acetylcytosin-1-yl)-1,3-thiazolidin-4-one (7)

To a suspension of 0.104 g of N-acetylcytosine (0.68mmol, 1eq) in 15 mL of dry toluene at 0°C were added slowly 0.393 mL of TMSOTf (2.03mmol, 3eq) and 0.283 mL of Et_3N (2.03mmol, 3eq) under vigourous stirring and nitrogen atmosphere. After 20 min was added at 0°C a suspension of 0.2 g of sulfoxide **5** (0.68mmol, 1eq) in 5mL of dry toluene. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduce pressure and the resulting residue was dissolved in EtOAc (15mL) and washed with a 5% $NaHCO_3$ aqueous solution (2x10mL). The mixture was extracted with EtOAc (3x10mL). The combined EtOAc extracts were dried over Na_2SO_4 and then filtered and concentrated. After purification by preparative layer chromatography (EtOAc/Toluene/MeOH 6:3:1), 0.04g of **7** were obtained as a white solid (yield 13%). m.p.=168°C. Rf(EtOAc/Toluene 65/35)=0.2. ^{1}H NMR ($CDCl_3$) δ: 2.25 (s,3H,C$\underline{H}_3$-CO-N4'), 2.60 (s,3H,C$\underline{H}_3$-CO-N), 4.60 (dd,J=11.8Hz,J=2.8Hz,1H,C2-C$\underline{H}_{2a}$), 4.80 (dd,J=11.7Hz,J=3.7Hz,1H,C2-C$\underline{H}_{2b}$), 5.80 (dd,J=2.9Hz,J=3.6Hz,1H,H-2), 6.60 (s,1H,H-5), 7.30-8.10 (m,7H,arom+2H cyt.); ^{13}C NMR ($CDCl_3$): 24.0 (C$\underline{H}_3$), 62.0 (C-5), 64.0 (C-2), 68.0 (C$\underline{H}_2$-O), 100.0 (C-5'), 128.0-134.0 (arom), 147.0 (C-6'), 155.0 (C$\underline{O}$-2'), 164.0 (C-4'), 166.0-171.0 (C$\underline{O}$); MS (FAB+): 431 $(M+H)^+$; UV (MeOH) λ: 208.6nm, 234.5nm, 252.6nm.

2-benzoyloxymethyl-3-acetyl-5-(cytosin-1-yl)-1,3-thiazolidin-4-one (8)

0.040 g of compound **7** were dissolved in a solution of NH_3/MeOH and stirred at room temperature overnight. After removing the solvent, the solid was washed with a solution of EtOAc/Et_2O (1:1) (3×10 mL). Compound **8** was obtained in quantitative

yield as a colored solid (0.026 g).Rf(EtOAc/Toluene/MeOH 65/30/5)=0.07. ^{1}H NMR (DMSO-d^6) δ: 2.50 (s,3H,C<u>H</u>$_3$-N), 3.60 (m,2H,C2-C<u>H</u>$_2$), 4.75 (m,1H,H-2), 6.10 (d,J=7.1Hz,1H,H-5'), 6.30 (s,1H,H-5), 7.80 (d,J=7.1Hz,1H,H-6'), 8.25 (bs,2H,N<u>H</u>$_2$); MS (FAB+): 285 (M+H)$^+$; UV (MeOH) λ: 214.4nm, 241.4nm, 269.0nm.

1-oxide-2-benzoyloxymethyl-1,3-thiazolidin-4-one (<u>9</u>)

At 0°C to a solution of 0.070 g (0.29mmol, 1eq) of **<u>3</u>** in 20 mL of CH_2Cl_2 was added dropwise a solution of 0.061 g (0.35mmol, 1.2eq) of mCPBA in 10 mL of CH_2Cl_2 . The reaction mixture was stirred at 0°C for 20 min, then 7 h at room temperature and finally hydrolyzed with a 5% $NaHCO_3$ aqueous solution (15 mL). The mixture was extracted with EtOAc (3x5 mL). The combined extracts were dried over Na_2SO_4 . A flash chromatography (EtOAc/Toluene 3:1) provided 0.067g of **<u>9</u>** as a white foam in 90% yield. Rf(EtOAc/Toluene 1:1)=0.1. ^{1}H NMR ($CDCl_3$) δ: 3.45 (d,J=13.6Hz,1H,H-5b), 3.80 (d,J=13.6Hz,1H,H-5a), 4.75 (t,J=5Hz,1H,H-2), 4.90 (d,J=5Hz,2H,C2-C<u>H</u>$_2$), 6.90 (bs,1H,N<u>H</u>), 7.44-8.05 (m,5H,arom); ^{13}C NMR ($CDCl_3$) δ: 29.0 (<u>C</u>-2), 62.0 (<u>C</u>-5), 68.0 (<u>C</u>H$_2$-O), 128.0-134.0 (arom), 168.1 (<u>C</u>O-NH), 172.2 (<u>C</u>O-O); MS (FAB+): 254 (M+H)$^+$; UV (MeOH) λ: 203.0nm, 230.5nm, 274.7nm.

2-benzoyloxymethyl-5-(N^4-acetylcytosin-1-yl)-1,3-thiazolidin-4-one (<u>10α</u>/<u>10β</u>)

At 0°C, to a suspension of 0.121g (0.79mmol, 1eq) of N-acetylcytosine in 15 mL of anhydrous toluene were slowly added 0.46 mL (2.37mmol, 3eq) of TMSOTf and 0.330 mL (2.37 mmol, 3eq) of Et_3N under vigourous stirring and nitrogen atmosphere. After 20 min, was added a suspension of 0.2 g (0.79mmol, 1eq) of **<u>5</u>** in anhydrous toluene (5 mL). The reaction mixture was stirred overnight at room temperature. After solvent evaporation, the residue was dissolved in EtOAc (10 mL) and was washed with H_2O (10 mL). The resulting emulsion was centrifuged and a white precipitate of 0.06 g of **<u>10</u>** <u>α</u>/<u>10β</u> was obtained in 20% yield. mp=206°C. Rf(EtOAc/MeOH 1:1)=0.24. ^{1}H NMR (CD_3OD-d_4) δ: 2.20 (s,3H,C<u>H</u>$_3$-CO-N4' α), 2.50 (s,3H,C<u>H</u>$_3$-CO-N4' β), 4.48 (d,J=5.1Hz,2H,C2-C<u>H</u>$_2$ β), 4.55 (dd,J=11.5Hz,J=4.4Hz,1H,C2-C<u>H</u>$_{2a}$ α), 4.55 (dd, J=11.5Hz,J=6.2Hz,1H,C2-C<u>H</u>$_{2b}$α), 5.15 (dd,J=4.5Hz,J=6.1Hz,1H,H-2α), 5.35 (t, J=5.0Hz,1H,H-2β), 5.85 (d,J=7.5Hz,1H,H-5'α), 6.05 (d,J=7.5Hz,1H,H-5'β), 6.40 (s,1H,H-5α), 6.45 (d,1H,H-5β), 7.45-8.10 (m,12H,arom+2H-6'); ^{13}C NMR (DMSO-d_6) δ: 12.0 (<u>C</u>H$_3$), 25.0 (<u>C</u>H$_3$), 47.0 (<u>C</u>H$_2$),60.0 (S-<u>C</u>H-CO), 64.0 (C-2), 68.0 (<u>C</u>H$_2$), 90.0 and 94.0 (C5'), 127.0-134.0 (arom), 146.0 and 149.0 (C6'), 159.0 (<u>C</u>O-2'), 163.0-164.0 (C4'), 167.0-172.0 (<u>C</u>O); MS (FAB+): 389 (M+H)$^+$;UV (MeOH) λ: 214.4nm, 241.4nm, 269nm.

2-benzoyloxymethyl-5-(cytosin-1-yl)-1,3-thiazolidin-4-one (11α/11β)

Under anhydrous conditions 0.3 g (1.2mmol, 1eq) of sulfoxide **9** was dissolved in anhydrous DCE (10 mL). After silylation using trimethylsilylchloride (TMSCl) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS), 0.158 g (1.4 mmol, 1.2 eq) of cytosine dissolved in dry DCE (5 mL) was added to the solution. To the reaction mixture were added slowly 0.264 mL (1.2mmol, 1eq) of TMSOTf and 0.164 mL (1.2mmol, 1eq) of Et_3N. The solution was stirred under nitrogen atmosphere during 48 h. After removing the solvent, the solid was dissolved in EtOAc (15 mL) and washed with H_2O (15 mL). The resulting emulsion was centrifuged and a white solid was obtained and dried. The desired product was obtained as 0.15 g of a white solid in 36.5% yield (α/β:1/9). mp=194°C. Rf(EtOAc/MeOH 1:1)=0.6. **11α isomers**:^{1}H NMR (DMSO-d_6) δ: 4.47 (dd,J=11Hz,J=4.9Hz,1H,C2-CH_{2a}), 4.64 (dd,J=11Hz,J=7.2Hz,1H,C2-CH_{2b}), 5.00 (dd,J=5.0Hz,J=7.1Hz,1H,H-2), 5.75 (d, J=7.3Hz,1H,H-5'), 6.10 (s,1H,H-5), 7.35 (bs,2H,NH_2), 7.50-8.10 (m,5H,Arom), 7.60 (d,J=7.3Hz,1H,H-6'), 9.50 (s,1H,NH-3); **11β isomers**: ^{1}H NMR (DMSO-d_6) δ: 4.35 (d,J=5.2Hz,2H,CH_2), 5.20 (t,J=5.2Hz,1H,H-2), 5.80 (d,J=7.4Hz,1H,H-5'), 6.20 (s,1H,H-5), 7.30 (bs,2H,NH_2), 7.50-8.10 (m,12H,10Harom), 7.65 (d,J=7.4Hz,1H,H-6'), 9.40 (s,1H,NH-3); **11α/11β mixtures**: ^{13}C NMR (DMSO-d_6) δ: 53.0 (S-CH-CO), 55.0 ($2CH_2$), 64.0-63.0 (S-CH-NH), 92.0 (C-5'), 134.0-128.0 (arom), 147.0-145.0 (C-6'), 155.0 (CO-2'), 166.0-165.0 (C-4'), 172.0-170.0 (CO); MS (FAB+): 347 $(M+H)^+$; UV (MeOH) λ: 211.5nm, 230.5nm, 271.8nm.

2-benzoyloxymethyl-5-(5-fluorocytosin-1-yl)-1,3-thiazolidin-4-one (12α/12β)

After silylation using trimethylsilylchloride (TMSCl) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS), 0.152 g (1.19mmol, 1.2eq) of 5-fluorocytosine in anhydrous DCE (5 mL) was added to a solution of 0.25 g (0.99mmol, 1eq) of sulfoxide **9** in DCE (10 mL) under anhydrous conditions. To the reaction mixture were added slowly 0.192 mL (0.99mmol, 1eq) of TMSOTf and 0.138 mL (0.99mmol, 1eq) of Et_3N. The resulting solution was stirred at room temperature under nitrogen during 48 h. The solvent was removed and the residue was dissolved in 20 mL of EtOAc. The solution was washed with distilled water (1×20 mL). The resulting emulsion was centrifuged. A white solid was obtained and dried under reduced pressure. The desired product was obtained as 0.108 g of a white solid in 30% yield (α/β:1/8). mp=245°C. Rf(EtOAc/MeOH 1:1)=0.8. **12α isomers**:^{1}H NMR (DMSO-d_6) δ: 4.60 (m,2H,C2-CH_2), 5.05 (m,1H,H-2), 6.10 (s,1H,H-5), 7.50-8.10 (m,6H,Arom+H-6'), 9.50 (s,1H,NH-3); **12β isomers**: ^{1}H NMR (DMSO-d_6) δ: 4.42 (d,J=5.1Hz,2H,C2-CH_2), 5.25 (t,J=5.0Hz,1H,H-2), 6.15 (s,1H,H-5), 7.50-8.10 (m,6H,5Harom+H-6'), 9.45 (s,1H,NH-3); **12α/12β mixtures**: ^{13}C NMR (DMSO-d_6) δ: 53.0 (S-CH-CO), 57.0 (O-CH_2), 64.0-63.0 (S-CH-

NH), 134.0-128.0 (arom+C-5'), 140.0 (C-6'), 151.0 (CO-2'), 157.0 (C-4'), 171.0-169.0 (CO); MS (FAB+): 365 $(M+H)^+$; UV (MeOH) λ: 208.6nm, 239.6nm, 271.0nm.

2-benzoyloxymethyl-5-(thymin-1-yl)-1,3-thiazolidin-4-one (13α/13β)

To a solution of 0.2 g (0.79mmol, 1eq) of sulfoxide **9** in dry DCE (10 mL) was added a solution of 0.12 g (0.95mmol, 1.2eq) of thymine, after silylation using trimethylsilylchloride (TMSCl) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS), in DCE under anhydrous conditions and vigourous stirring. Then 0.153 mL (0.79mmol, 1eq) of TMSOTf and 0.110 mL (0.79mmol, 1eq) of Et_3N were slowly added under nitrogen and vigourous stirring. The solution was stirred during 48 h at room temperature. After solvent removing, the residue was dissolved in EtOAc (20 mL). The resulting emulsion was centrifuged and the product was dried under reduced pressure to obtain 0.085 g of a white solid in 30% yield (α/β:1/8). mp=257°C. Rf(EtOAc/MeOH 1:1)=0.9. **13α** isomers: ^1H NMR (DMSO-d_6) δ: 1.70 (s,3H,CH_3), 4.60 (m,J=7.8Hz,2H,C2-CH_2), 5.10 (m,1H,H-2), 6.25 (s,1H,H-5), 7.50-8.10 (m,6H,Arom+H-6'), 9.50 (s,1H,NH-3); **13β** isomers: ^1H NMR (DMSO-d_6) δ: 1.80(s,3H,CH_3); 4.40 (d,J=5.0Hz,2H,C2-CH_2), 5.25 (t,J=5.1Hz,1H,H-2), 6.35 (s,1H,H-5), 7.50-8.10 (m,6H,5Harom+H-6'), 9.60 (s,1H,NH-3); **13α/13β** mixtures: ^{13}C NMR (DMSO-d_6) δ: 12.0 (CH_3), 45.0 (S-CH-CO), 54.0 (S-CH-NH), 67.0 (O-CH_2), 110.0 (C-5'), 134.0-128.0 (arom), 150.0 (CO-2'), 161.0 (C-6'), 165.0 (C-4'), 172.0-170.0 (CO); MS (FAB+): 362 $(M+H)^+$; UV (MeOH) λ: 207.0nm, 267.4nm.

2-hydroxymethyl-5-(cytosine-1-yl)-1,3-thiazolidin-4-one (14α/14β)

The compound **10** or **11** (0.06 g) was dissolved in a methanolic solution saturated in ammonia. The suspension was stirred at room temperature overnight. After removing the solvent, the solid was washed with a solution of EtOAc/Et_2O (1:1) (3×10 mL) and dried under reduced pressure. The products **14** were obtained as a white solid in quantitative yield (0.041 g, **14α/14β** 1:1). mp=174°C. Rf(EtOAc/MeOH 1:1)=0.41. **14α** isomers ^1H (DMSO-d_6) δ: 3.60 (dd,J=11.3hz,J=5.2Hz,1H,C2-CH_{2a}), 3.65 (dd,J=11.3hz,J=4.4Hz,1H,C2-CH_{2b}) 4.70 (dd,J=4.5Hz,J=5.2Hz,1H,H-2), 6.05 (d,J=7.5Hz,1H,H-5'), 6.15 (s,1H,H-5), 7.80 (d,J=7.5Hz,1H,H-6'), 8.20 (bs,2H,NH_2), 9.10 (bs,1H,NH-3); MS (FAB+): 243 $(M+H)^+$; **14β** isomers ^1H (DMSO-d_6) δ: 3.45 (dd,J=11.0Hz,J=5.9Hz,1H,C2-CH_{2a}), 3.60 (dd,J=11.0Hz,J=4.4Hz,1H,C2-CH_{2b}), 4.85 (t,J=4.4Hz,J=5.8Hz,1H,H-2), 6.00 (d,J=7.6Hz,1H,H-5'), 6.25 (s,1H,H-5), 7.80 (d,J=7.6Hz,1H,H-6'), 8.25 (bs,2H,NH_2), 9.20 (s,1H,NH-3); MS (FAB+): 243 $(M+H)^+$; **14α/14β** isomers ^{13}C (DMSO-d_6) δ: 58.0-55.0 (S-CH-NH and S-CH-CO), 66.0-64.0 (O-

CH_2), 90.0 (C-5'),144.0 (C-6'), 153.0 (CO-2'), 155.0 (CO-2'), 165.0 (C-4'), 171.0-169.0 (CO); UV (MeOH) λ:211.0nm, 226.0nm, 272.4nm.

2-hydroxymethyl-5-(fluoro-5-cytosin-1-yl)-1,3-thiazolidin-4-one (15α/15β)

Compound **12** (0.100 g) was dissolved in NH_3/MeOH and stirred overnight at room temperature. The solvent was removed and the solid was washed with EtOAc/Et_2O (1:1) (3×10 mL) and dried under reduced pressure.The product was obtained as a white solid in quantitative yield (0.070 g, **15α/15β**: 2/1). mp=185°C. Rf(EtOAc/MeOH 1:1)=0.68. **15α** isomers ^1H (DMSO-d_6) δ: 3.40 (m,J=11Hz,J=3.9Hz,J=5.0Hz,1H,C2-CH_{2a}), 3.60 (m,J=11.0Hz,J=4.5Hz,J=4.7Hz,1H,C2-CH_{2b}), 4.70 (dd,J=3.9Hz,J=4.5Hz, 1H,H-2), 5.45 (dd,J=4.7Hz,J=5.0Hz,1H,OH), 6.25 (s,1H,H-5), 7.95 (bs,2H,NH_2), 8.05 (d,J=6.8Hz,1H,H6'), 9.10 (bs,1H,NH-3); MS (FAB+): 261 $(M+H)^+$; **15β** isomers ^1H (DMSO-d_6) δ: 3.40 (dd,J=5.6Hz,J=4.5Hz,2H,C2-CH_2), 4.85 (t,J=4.5Hz,1H,H-2), 5.25 (t,J=5.6Hz,1H,OH), 6.05 (s,1H,H-5), 7.70 (bs,2H,NH_2), 7.90 (d,J=6.8Hz,1H,H-6'), 9.0 (bs,1H,NH-3); MS (FAB+): 261 $(M+H)^+$; **15α/15β** isomers ^{13}C (DMSO-d_6) δ: 54.0 (S-CH-CO), 58.0-56.0 (S-CH-NH), 64.0-63.0 (CH_2-O), 134.0-132.0 (C-5'), 141.0-139.0 (C-6'), 150.0 (CO-2'), 157.0 (C-4'), 170.0-168.0 (CO); UV (MeOH) λ: 215.0nm, 239.0nm, 279.8nm.

2-hydroxymethyl-5-(thymin-1-yl)-1,3-thiazolidin-4-one (16α/16β)

A suspension of compound **13** (0.080 g) in NH_3/MeOH solution was stirred overnight at room temperature. The product was obtained as a white solid in quantitative yield (0.056 g, **16α/16β**:1/1) after solvent removal and 3 washes with EtOAc/Et_2O (1:1) (3×10 mL). mp=149°C. Rf(EtOAc/MeOH 1:1)=0.78.

16α isomers ^1H (DMSO-d_6) δ: 1.85 (s,3H,CH_3), 3.60 (m,2H,C2-CH_2), 4.75 (m,1H,H-2), 5.35 (m,1H,OH), 6.35 (s,1H,H-5), 7.20 (bs,1H,NH-3'), 7.50 (s,1H,H-6'), 9.30 (bs,1H,NH-3); MS (FAB+): 258 $(M+H)^+$; **16β** isomers ^1H (DMSO-d_6) δ: 1.85 (s,3H,CH_3), 3.40 (m,2H,C2-CH_2), 4.90 (m,1H,H-2), 5.45 (m,1H,OH), 6.25 (s,1H,H-5), 7.20 (s,1H,NH-3'),7.70 (s,1H,H-6'), 9.20 (bs,1H,NH-3); MS (FAB+): 258 $(M+H)^+$; **16α /16β**isomers ^{13}C (DMSO-d_6) δ: 12.0 (CH_3), 53.0-49.0 (S-CH-NH and S-CH-CO), 68.0-67.0 (O-CH_2), 170.0 (CO),110.0 (C-5'),150.0-149.0 (C-2'), 164.0-163.0 (C-6'), 167.0 (C-4'). UV (MeOH) λ: 214.9nm, 267.0nm.

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