GLYCOSYLATION OF 1-AMINOIMIDAZOLE-2(3*H*)-THIONES

Irene M. LAGOJA[1], Arthur VAN AERSCHOT[2], Chris HENDRIX[3] and Piet HERDEWIJN[4,*]

Laboratory of Medicinal Chemistry, Rega Institute, Minderbroedersstraat 10, B-3000 Leuven, Belgium; e-mail: [1] irene.lagoja@rega.kuleuven.ac.be, [2] arthur.vanaerschot@rega.kuleuven.ac.be, [3] chris.hendrix@rega.kuleuven.ac.be, [4] piet.herdewijn@rega.kuleuven.ac.be

Received March 9, 2000
Accepted april 18, 2000

The selectivity of the glycosylation of 1-aminoimidazole-2(3*H*)-thiones can be controlled. Depending on the chosen conditions, either the kinetically favored *S*-glycosides or the thermodynamically more stable *N*-glycosylated compounds are obtained in only one anomeric configuration (β-anomer).

Key words: 1-Aminoimidazole-2(3*H*)-thiones; Nucleosides; Glycosylations; Glycosidations; Ribosides; Imidazoles.

AICA-riboside[1] (1-(β-D-ribofuranosyl)-5-amino-4-imidazolecarboxamide) is an example of an open ring purine nucleoside showing potent antiviral activity. EICAR (ref.[2]) (5-alkynyl-1-β-D-ribofuranosylimidazole-4-carboxamide), likewise an imidazole derivative, shows a strong antileucemia activity. These results stimulated us to investigate the synthesis and biological activity of other imidazole based nucleosides.

The sugar-base condensation reaction is one of the key reactions in nucleoside chemistry. The reaction with most impact in this area is the condensation developed by Vorbrüggen[3]. This reaction of a silylated nucleobase and an acylated carbohydrate is performed in the presence of a Lewis acid. With ribofuranoses, high stereoselectivity (β-isomer) and regioselectivity (N^9-isomer of purines and N^1-isomers of pyrimidines) are achieved. This reaction, however, has been used less often for heterocycles with thioamide functionality, where less regioselectivity is expected.

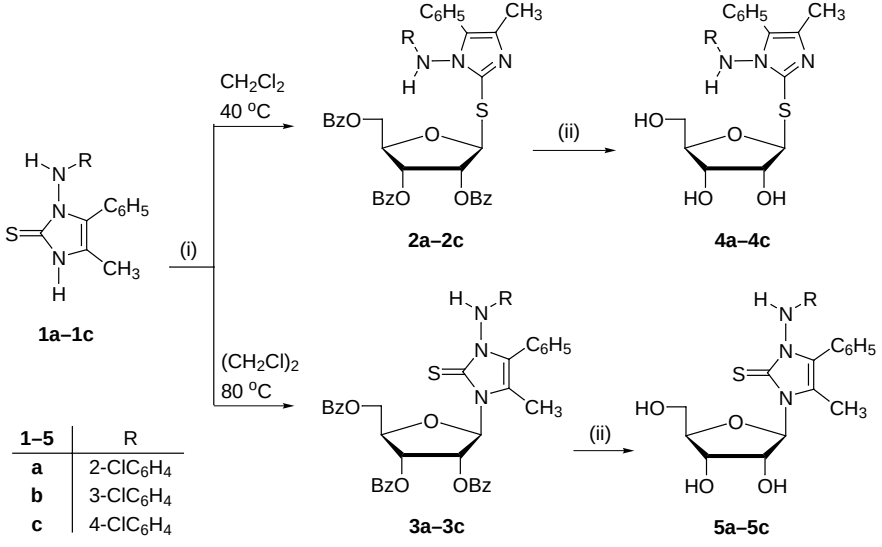
Thiouracil is a classic example. Studies of glycosylation of thiouracil showed that it is possible to direct the reaction to both α- and β-nucleosides[4] as well as to *N*- or *S*-glycosylated thiouracil[5]. With aminothiadiazolinethione, only the β-*N*-ribofuranoside could be obtained[6], following both condensation and fusion procedures[7]. In the present paper we investi-

gate the selectivity of glycosylation of 1-aminoimidazole-2(3*H*)-thiones using Vorbrüggen's condensation.

The chosen 1-aminoimidazole-2(3*H*)-thiones not only offer the advantages of straightforward syntheses[8] but also possess two reactive centers – the thioamide and thiohydrazide functions. We demonstrate that, by controlling the reaction conditions, preferentially either the *N*- or *S*-glycosylated heterocycles can be obtained in a stereoselective way.

RESULTS AND DISCUSSION

The starting heterocycle, 1-aminoimidazole-2(3*H*)-thione, was synthesized by a [3+2] cycloaddition of an azoalkene intermediate with thiocyanic acid[8]. The coupling of 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose with 1-aminoimidazole-2(3*H*)-thiones **1a**–**1c** was investigated using the method of Vorbrüggen[1] with 2 equivalents of trimethylsilyltrifluoromethanesulfonate as Lewis acid. The silylation of 1-aminoimidazole-2(3*H*)-thiones **1a**–**1c** was carried out *in situ*. Depending on the solvent and reaction temperature, the glycosylation could lead either to the formation of the kinetically favored *S*-glycoside **2a**–**2c** or the thermodynamically more stable *N*-glycosylated products **3a**–**3c** (Scheme 1).



1–5	R
a	2-ClC$_6$H$_4$
b	3-ClC$_6$H$_4$
c	4-ClC$_6$H$_4$

(i) 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose / *N*,*O*-bis(trimethylsilyl)acetamide (BSA) / trimethylsilyltrifluoromrthanesulfonate (TMSOTf); (ii) NH_3/MeOH, r.t.

SCHEME 1

Using low temperatures (40 °C, dichloromethane) the 1-(chloroanilino)-4-methyl-5-phenyl-2-[(β-D-ribofuranosyl)sulfanyl]imidazole derivatives **2a**–**2c** were obtained. Carrying out the reaction at higher temperatures (80 °C, 1,2-dichloroethane) the 1-(chloroanilino)-4-methyl-5-phenyl-3-(β-D-ribofuranosyl)imidazole-2(3*H*)-thione derivatives **3a**–**3c** were obtained as major products. Under both conditions, the nucleosides **2a**–**2c** and **3a**–**3c** were formed exclusively in only one anomeric configuration. Deprotection of tribenzoates **2a**–**2c** and **3a**–**3c** making use of NH_3–MeOH afforded the free nucleosides **4a**–**4c** and **5a**–**5c** in high yields.

The β-configuration of the blocked (**2a**–**2c**, **3a**–**3c**) and deblocked (**4a**–**4c**, **5a**–**5c**) nucleosides is deduced from the appearance of the anomeric proton as a doublet having a *J* value around 6 Hz (whereas the coupling constant in the range 3–4 Hz would be characteristic of the α-anomers[9]). The β-anomer was expected because of the neighboring group participation of the 2-*O*-benzoyl group in the condensation. The glycosylation site was determined using NMR spectroscopy. The ^{1}H NMR spectra for the β-*N*-isomers **3a**–**3c**, **5a**–**5c** are characterized by a more deshielded anomeric proton resonance (δ 6.45–6.48) in comparison to the β-*S*-isomers **2a**–**2c**, **4a**–**4c** (δ 5.43–5.46). In the ^{13}C NMR, chemical shifts of the 4-methyl group (δ ≈ 10 ppm) as well as the resonance signals of the imidazole ring carbons (δ ≈ 120, 127, 162; 5-C, 4-C, 2-C) are almost the same for the 1-aminoimidazole-2(3*H*)-thiones **1a**–**1c** and the *N*-glycosylated derivatives **3a**–**3c**, **5a**–**5c**. In the *S*-glycosylated imidazole derivatives **2a**–**2c**, **4a**–**4c**, the 4-methyl group (δ ≈ 14) shows a downfield shift of 4 ppm. Similar observations were reported for the *N*-, *O*- and *S*-methylated thiouracil[10]. The chemical shifts of the imidazole ring in the (ribofuranosylsulfanyl)imidazolines **2a**–**2c**, **4a**–**4c** (δ ≈ 129, 132, 135; 5-C, 4-C, 2-C) are comparable with those of 2-(methylsulfanyl)imidazole derivatives[6].

The UV spectra of compounds **1a**–**1c** and **5a**–**5c** show two major absorption bands (λ_{max} = 235 nm, λ_{max} = 283 nm) similar to those of diphenylamine[11] indicating the aromatic character of the imidazole-2(3*H*)-thione system. Differences of the absorption at 235 nm are due to the variations in the substitution pattern of the *N*-phenyl moiety. The π–π* transitions of the N–C(=S)–N chromophore probably give rise to absorptions at about 283 nm, as this is the only absorption band showing a significant shift when comparing to the *S*-glycosylated derivatives **4a**–**4c** and **7b** (λ_{max} = 274 nm).

In the condensation reaction with thiouracil[3], initially the *S*-glycoside is formed, which subsequently rearranges *in situ* to the N^1-nucleoside. The products formed by glycosylation of 1-aminoimidazole-2(3*H*)-thiones **1a**–**1c** are in accordance with these results. The glycosylation of 1-amino-

imidazole-2(3*H*)-thiones **1a**–**1c** apparently occurs in two distinct steps: (i) a rapid glycosylation to form the *S*-glycoside and (ii) a slower rearrangement to the more stable *N*-nucleoside. This is in agreement with the observation that at lower temperatures, thus under kinetic conditions, *S*-glycosides **2a**–**2c** could be isolated as main products, whereas under thermodynamic conditions, the more stable *N*-glycosides **3a**–**3c** were obtained (Table I).

The relatively high amount of the N-isomer obtained upon glycosylation of **1a**, is probably due to higher steric hindrance by the chlorine atom in *ortho* position in the *N*-phenyl moiety.

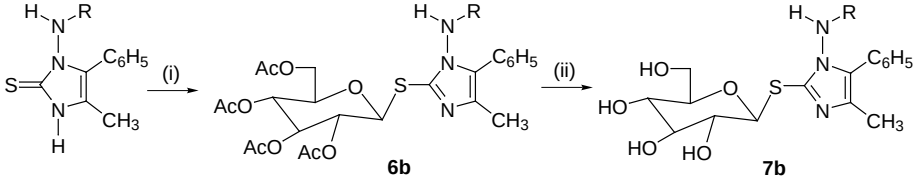
As exemplified by compound **2c** the conversion possibility from *S*- to *N*-glycosides has been proved. For this purpose the silylated 1-(4-chloroanilino)-4-methyl-5-phenyl-2-[(2,3,5-tri-*O*-benzoyl-β-D-ribofuran-osyl)sulfanyl]imidazole (**2c**) was treated with trimethylsilyltrifluoromethanesulfonate as Lewis acid. After heating the reaction mixture in 1,2-dichloroethane for three hours, the complete transformation to 1-(4-chloroanilino)-4-methyl-5-phenyl-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-2(3*H*)-thione (**3c**) could be observed on TLC (R_F (CH_2Cl_2–MeOH 99 : 1) **2c**: 0.56; **3c**: 0.86). The spectroscopic data of the isolated transglycosylation product also were identical with those of the previously prepared **3c**.

The isomers of the blocked nucleosides could be easily separated by column chromatography. The benzoyl protecting groups of **2a**–**2c**, **3a**–**3c** were cleaved by treatment with methanolic ammonia and the free ribose adducts were purified by column chromatography.

TABLE I
The *N*-/*S*-glycosylation product ratio at 40 and 80 °C after isolation by column chromatography (reaction time 4 h)

Solvent	Temperature, °C	Imidazole	*N*/*S*-glycosylation ratio
CH_2Cl_2	40	**1a**	1 : 3
CH_2Cl_2	40	**1b**	1 : 10
CH_2Cl_2	40	**1c**	1 : 13
$ClCH_2CH_2Cl$	80	**1a**	1 : 0
$ClCH_2CH_2Cl$	80	**1b**	6 : 1
$ClCH_2CH_2Cl$	80	**1c**	9 : 1

As already described with thiohydantoin[12], glucosylation of **1b**, even at elevated temperature, yielded only the *S*-glucosyl derivative **6b**. In this case, penta-*O*-acetylglucose was used for the coupling reaction, but deprotection was also carried out with methanolic ammonia yielding **7b** (Scheme 2). These results, likewise, can be explained by steric hindrance.



1b R = 3-ClC$_6$H$_4$

(i) penta-*O*-acetyl-D-glucose / *N,O*-bis(trimethylsilyl)acetamide (BSA) / trimethylsilyltrifluoromethanesulfonate (TMSOTf), $(CHCl)_2$, 80 °C; (ii) NH_3/MeOH, r.t.

SCHEME 2

In the ^{1}H NMR the coupling constant of the anomeric proton of **7b** (δ 4.87–4.92, J = 9 Hz) is also in accordance with the values reported in literature[13] for the β-anomer. In contrast to the results reported with thiouracil derivatives[3], the *S*-nucleosides **4a**–**4c** and **7b** proved stable compounds. They can be purified on silica gel and stored at room temperature without decomposition. These compounds are not destroyed under alkaline reaction conditions and the described formation of disulfides[14] could not be observed.

CONCLUSIONS

The glycosylation of 1-aminoimidazole-2(3*H*)-thiones **1a**–**1c** has been studied and the results were found to be in accordance with those described for thiouracil. Control of the reaction temperature allows access to either the kinetically favored *S*-ribosylimidazole derivatives **4a**–**4c** or the thermodynamically more stable *N*-ribosylimidazole adducts **5a**–**5c**. Upon glucosylation of **1b**, exclusively the *S*-glucosyl product could be obtained, even at elevated temperatures, which can be explained by steric hindrance.

The compounds **4a**–**4c**, **5a**–**5c** and **7b** have been evaluated for their activity against DNA viruses, RNA viruses and against HIV-1 and HIV-2. No specific antiviral activity was observed.

EXPERIMENTAL

NMR spectra were recorded on a Varian, Gemini 200 spectrometer (^{1}H at 200 MHz, ^{13}C at 50 MHz). Chemical shifts are given in ppm (δ-scale). All NH/OH protons were assigned by exchange with D_2O. In AA′BB′ systems, the determination of *J* (in Hz) is based on the assumption of an AB quartet[15]. Mass spectra were recorded on a Kratos Concept 1H mass spectrometer (MS, LSIMS; *m*/*z* (%)). Samples were dissolved in glycerol (Gly)/thioglycerol (Thgly)/3-nitrobenzyl alcohol and secondary ions were accelerated at 6 kV. Scans were performed at 10 s/decade). Exact mass measurements were performed on a quadrupole-time of flight mass spectrometer (Q-Tof-2, Micromass, Manchester, U.K.) equipped with a standard electrospray ionization (ESI) interface. Samples were infused in a 2-propanol–water (1 : 1) mixture at 3 ml/min. UV was carried out on a Philips PU 8740 UV/VIS spectrometer (MeOH, λ_{max}, nm (log ε)). TLC was carried out on TLC aluminium sheets (Merck, Silica gel 60 F_{254}) and silica (200–425 mesh) was used for column chromatography. Melting points were determined with a Büchi-SMP – 20 capillary melting point apparatus. For glycosylations, dry (molecular sieves) analytical grade dichloromethane and 1,2-dichloroethane were used. Solvents for column chromatography were used without any further purification.

Syntheses of 1-Aminoimidazole-2(3*H*)-thiones **1a**–**1c**. General Procedure

The 1-aminoimidazole-2(3*H*)-thione **1c** was prepared as described in literature[8]. Compounds **1a** and **1b** were obtained using the same procedure.

1-(2-Chloroanilino)-4-methyl-5-phenylimidazole-2(3H)-thione (**1a**). Yield 88%; m.p. 220–221 °C dec. (methanol). R_F 0.54 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR (DMSO-d_6): 2.15 (3 H, s, 4-Me); 6.08 (1 H, d, *J* = 8, 6-H, N-Ar); 6.72 (1 H, dd, J^1 = 8, J^2 = 8.8, 4-H, N-Ar); 7.04 (1 H, dd, J^1 = 8, J^2 = 8.8, 5-H, N-Ar); 7.23 (1 H, d, *J* = 8, 3-H, N-Ar); 7.30–7.48 (5 H, m, 5-Ph); 8.76 (1 H, s, 1-NNH); 12.55 (1 H, s, 3-NH). ^{13}C NMR (DMSO-d_6): 10.1 (4-Me); 127.7, 128.1, 128.5, 129.1 (1-C, 4-CH, 2,6-CH, 3,5-CH, 5-Ph); 113.2, 117.3, 120.4, 127.8, 129.1, 142.8 (6-CH, 2-C, 4-CH, 5-CH, 3-CH, 1-C, 2-ClC_6H_4); 120.0, 126.7, 161.9 (4-C, 5-C, 2-C, imidazole). UV (λ_{max} (log ε)): 207 (4.45), 232 (4.06), 281 (4.24). MS (LSIMS; Gly, TFA; *m*/*z* (%)): 316 (100) $[M + H]^+$, 190 (48) $[M–ClC_6H_4N]^+$, 131 (60) $[C_9H_9N]^+$. Exact mass ($C_{16}H_{15}ClN_3S$) calculated: 316.0675 $[M + H]^+$; found: 316.0660. For $C_{16}H_{14}ClN_3S$ (315.8) calculated: 60.85% C, 4.47% H; found: 60.81% C, 4.65% H.

1-(3-Chloroanilino)-4-methyl-5-phenylimidazole-2(3H)-thione (**1b**). Yield 85%; m.p. 215–217 °C dec. (methanol). R_F 0.55 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR (DMSO-d_6): 2.15 (3 H, s, 4-Me); 6.37 (1 H, d, *J* = 8.4, 6-H, N-Ar); 6.42 (1 H, s, 2-H, N-Ar); 6.72 (1 H, d, *J* = 8, 4-H, N-Ar); 7.12 (1 H, dd, J^1 = 8, J^2 = 8.4, 5-H, N-Ar); 7.34–7.38 (5 H, m, 5-Ph); 9.30 (1 H, s, 1-NNH); 12.55 (1 H, s, 3-NH). ^{13}C NMR (DMSO-d_6): 10.1 (4-Me); 127.6, 128.2, 128.6, 129.0 (1-C, 4-CH, 2,6-CH, 3,5-CH, 5-Ph); 111.2, 111.9, 119.1, 130.8, 133.6, 148.9 (6-CH, 2-CH, 4-CH, 5-CH, 3-C, 1-C, 3-ClC_6H_4); 120.2, 126.6, 161.8 (4-C, 5-C, 2-C, imidazole). UV (λ_{max} (log ε)): 207 (4.45), 237 (4.00), 283 (4.11). MS (LSIMS; Thgly, NaOAc; *m*/*z* (%)): 360 (16) $[M – H + 2 Na]^+$, 338 (44) $[M + Na]^+$, 316 (66) $[M + 1]^+$, 190 (69) $[M – ClC_6H_4N]^+$, 131 (100) $[C_9H_9N]^+$. Exact mass ($C_{16}H_{15}ClN_3S$) calculated: 316.0675 $[M+H]^+$; found: 316.0703. For $C_{16}H_{14}ClN_3S$ (315.8) calculated: 60.85% C, 4.47% H; found: 60.38% C, 4.44% H.

Glycosylation of 1-Aminoimidazole-2(3*H*)-thiones **1a**–**1c**. General Procedure

To a suspension of 1-aminoimidazole-2(3*H*)-thiones **1a**–**1c** (0.5 g, 1.58 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose (0.8 g, 1.6 mmol) in dichloromethane (20 ml; method *A*) or dichloroethane (20 ml; method *B*), *N*,*O*-bis(trimethylsilyl)acetamide (0.8 ml, 3.2 mmol) was added. The mixture was stirred under nitrogen at ambient temperature for 20 min giving a clear, slightly yellow solution. After addition of trimethylsilyltrifluoromethanesulfonate (0.57 ml, 3.2 mmol) under nitrogen, the reaction mixture was heated under reflux for 4 h. The resulting yellow mixture was cooled to ambient temperature and washed with saturated aqueous $NaHCO_3$ (2 × 100 ml) and brine (1 × 50 ml). After drying over anhydrous Na_2SO_4, the solvent was evaporated and the obtained oil was purified by column chromatography (silica gel, 15 × 3 cm, CH_2Cl_2–MeOH 99 : 1) to yield the glycosylated imidazole derivatives **2a**–**2c** and **3a**–**3c**. Depending on the reaction temperature, either the *S*- (method *A*) **2a**–**2c** or the *N*-glycosylated imidazole derivatives **3a**–**3c** (method *B*) could be obtained as the major products.

*1-(2-Chloroanilino)-4-methyl-5-phenyl-2-[(2,3,5-tri-O-benzoyl-*β*-D-ribofuranosyl)sulfanyl]imidazole* (**2a**). Yield 1.01 g (84%) (method *A*). R_F 0.56 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR ($CDCl_3$): 2.30 (3 H, s, 4-Me); 4.58–4.71 (3 H, m, 2 × H-5′ + H-4′); 5.74–5.81 (3 H, m, H-3′, H-4′, H-5′); 6.14 (1 H, d, J = 8, 6-H, N-Ar); 6.81 (1 H, dd, J^1 = 8, J^2 = 8.8, 4-H, N-Ar); 7.03 (1 H, dd, J^1 = 8, J^2 = 8.8, 5-H, N-Ar); 7.16 (1 H, d, J = 8, 3-H, N-Ar); 7.30–7.79 (14 H, m, 5-Ph + 3 × 3,4,5-H, Bz); 7.88–8.02 (6 H, m, 3 × 2,6-H, Bz); 7.87 (1 H, s, 1-NNH). ^{13}C NMR ($CDCl_3$): 14.0 (4-Me); 64.4, 72.0, 74.7, 81.2, 87.7 (5-CH_2, 3, 2, 4, 1-CH, ribose); 113.6, 118.7, 121.9, 142.9 (6-CH, 2-C, 4-CH, 1-C, N-Ar); 127.9–133.5 (5-Ph + 3,5-CH, N-Ar + 3 × Bz + 5-C, imidazole); 132.0, 135.8 (4-C, 2-C, imidazole); 165.2, 165.3, 166.2 (3 × C=O). MS (LSIMS; Thgly, NBA; *m*/*z* (%)): 760 (5) $[M + H]^+$, 445 (28) [tribenzoylribose]$^+$, 201 (27), 105 (100) $[C_6H_5CO]^+$.

*1-(3-Chloroanilino)-4-methyl-5-phenyl-2-[(2,3,5-tri-O-benzoyl-*β*-D-ribofuranosyl)sulfanyl]imidazole* (**2b**). Yield 0.80 g (66%) (method *A*). R_F 0.56 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR ($CDCl_3$): 2.30 (3 H, s, 4-Me); 4.58–4.70 (3 H, m, 2 × H-5′ + H-4′); 5.72–5.76 (3 H, m, H-3′, H-4′, H-5′); 6.30 (1 H, d, J = 8.4, 6-H, N-Ar); 6.51 (1 H, s, 2-H, 3-ClC_6H_4); 6.78 (1 H, d, J = 8, 4-H, N-Ar); 7.03 (1 H, dd, J^1 = 8, J^2 = 8.4, 5-H, N-Ar); 7.31–7.57 (14 H, m, 5-Ph + 3 × 3,4,5-H, Bz); 7.67 (1 H, s, 1-NNH); 7.87–8.05 (6 H, m, 3 × 2,6-H, Bz). ^{13}C NMR ($CDCl_3$): 14.1 (4-Me); 64.3, 72.0, 74.6, 81.6, 88.8 (5-CH_2, 3, 2, 4, 1-CH ribose); 111.2, 113.3, 121.6, 135.2, 148.3 (6-CH, 2-CH, 4-CH, 3-C, 1-C, N-Ar); 128.4–133.6 (5-Ph + 5-CH, N-Ar + 3 × Bz + 5-C, imidazole); 132.4, 135.8 (4-C, 2-C, imidazole); 165.2, 165.4, 166.2 (3 × C=O). MS (LSIMS; Thgly, NBA; *m*/*z* (%)): 760 (2) $[M + H]^+$, 445 (18) [tribenzoylribose]$^+$, 201 (30), 105 (100) $[C_6H_5CO]^+$.

*1-(4-Chloroanilino)-4-methyl-5-phenyl-2-[(2,3,5-tri-O-benzoyl-*β*-D-ribofuranosyl)sulfanyl]imidazole* (**2c**). Yield 0.80 g (66%) (method *A*). R_F 0.56 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR ($CDCl_3$): 2.29 (3 H, s, 4-Me); 4.56–4.70 (3 H, m, 2 × H-5′ + H-4′); 5.72–5.75 (3 H, m, H-3′, H-4′, H-5′); 6.37 (2 H, d, J = 8.8, 2,6-H, N-Ar); 7.05–7.09 (2 H, d, J = 8.8, 3,5-H, N-Ar); 7.30–7.57 (14 H, m, 5-Ph + 3 × 3,4,5-H, Bz); 7.88–8.04 (6 H, m, 3 × 2,6-H, Bz); 7.60 (1 H, s, 1-NNH). ^{13}C NMR ($CDCl_3$): 14.1 (4-Me); 64.3, 72.0, 74.6, 81.6, 88.3 (5-CH_2, 3, 2, 4, 1-CH, ribose); 114.4, 126.5, 145.7 (2,6-CH, 4-C, 1-C, N-Ar); 128.0–133.7 (5-Ph + 3,5-CH, N-Ar + 3 × Bz + 5-C, imidazole); 132.2, 135.9 (4-C, 2-C, imidazole); 165.2, 165.4, 166.3 (3 × C=O). MS (LSIMS; Thgly, NBA; *m*/*z* (%)): 760 (4) $[M + H]^+$, 445 (27) [tribenzoylribose]$^+$, 201 (29), 105 (100) $[C_6H_5CO]^+$.

*1-(2-Chloroanilino)-4-methyl-5-phenyl-3-(2,3,5-tri-O-benzoyl-*β*-D-ribofuranosyl)imidazole-2(3H)-thione* (**3a**). Yield 0.76 g (64%) (method *B*). R_F 0.84 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR ($CDCl_3$): 2.37 (3 H, s, 4-Me); 4.73–4.83 (2 H, m, 2 × H-5′); 4.93–4.98 (1 H, m, H-4′); 6.13–6.26 (2 H,

m, H-2′, H-3′); 6.40 (1 H, d, J = 8, 6-H, N-Ar); 6.86 (1 H, dd, J^1 = 8, J^2 = 8.8, 4-H, N-Ar); 7.00 (1 H, dd, J^1 = 8, J^2 = 8.8, 5-H, N-Ar); 7.07 (1 H, d, J = 8, 3-H, N-Ar); 7.24–7.62 (16 H, m, 5-Ph + 3 × 3,4,5-H, Bz, 1-NNH, H-1′); 7.97–8.16 (m, 6 H, 3 × 2,6-H, Bz). ^{13}C NMR ($CDCl_3$): 10.2 (4-Me); 63.4, 70.1, 72.3, 79.5, 88.6 (5-CH_2, 3, 2, 4, 1-CH, ribose); 114.2, 120.1, 122.2, 142.0 (6-CH, 2-C, 4-CH, 1-C, N-Ar); 127.5–133.7 (5-Ph + 3,5-CH, N-Ar + 3 × Bz); 120.8, 126.2, 164.8 (4-C, 5-C, 2-C, imidazole); 165.3, 165.6, 166.1 (3 × C=O). MS (LSIMS; Gly, NaOAc; m/z (%)): 782 (2) $[M + Na]^+$, 105 (100) $[C_6H_5CO]^+$, 77 (6) $[C_6H_5]^+$.

*1-(3-Chloroanilino)-4-methyl-5-phenyl-3-(2,3,5-tri-O-benzoyl-*β*-D-ribofuranosyl)imidazole-2(3H)-thione* (**3b**). Yield 0.97 g (81%) (method *B*). R_F 0.83 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR ($CDCl_3$): 2.35 (3 H, s, 4-Me); 4.66–4.77 (2 H, m, 2 × H-5′); 4.87–4.93 (1 H, m, H-4′); 6.04–6.20 (2 H, m, H-2′, H-3′); 6.47 (1 H, d, J = 8.4, 6-H); 6.67 (1 H, s, 2-H, N-Ar); 6.84–7.08 (3 H, m, 4,5-H, N-Ar, H-1′); 7.33–7.60 (15 H, m, 5-Ph + 3 × 3,4,5-H, Bz, 1-NNH); 7.93–8.11 (6 H, m, 3 × 2,6-H, Bz). ^{13}C NMR ($CDCl_3$): 10.3 (4-Me); 63.5, 70.2, 72.4, 79.6, 88.7 (5-CH_2, 3, 2, 4, 1-CH, ribose); 112.8, 115.0, 122.4, 135.0, 147.3 (6-CH, 2-CH, 4-CH, 3-C, 1-C, N-Ar); 128.5–133.7 (5-Ph + 5-CH, N-Ar + 3 × Bz); 120.9, 126.5, 164.6 (4-C, 5-C, 2-C, imidazole); 165.5, 165.6, 166.3 (3 × C=O). MS (LSIMS; Thgly, NBA; m/z (%)): 760 (25) $[M + H]^+$, 105 (70) $[C_6H_5CO]^+$, 69 (100).

*1-(4-Chloroanilino)-4-methyl-5-phenyl-3-(2,3,5-tri-O-benzoyl-*β*-D-ribofuranosyl)imidazole-2(3H)-thione* (**3c**). Yield 0.99 g (82%) (method *B*). R_F 0.83 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR ($CDCl_3$): 2.34 (3 H, s, 4-Me); 4.69–4.85 (2 H, m, 2 × H-5′); 4.88–4.93 (1 H, m, H-4′); 6.06–6.23 (2 H, m, H-2′, H-3′); 6.52 (2 H, d, J = 8.8, 2,6-H, N-Ar); 7.02, 7.06 (3 H, m, 3,5-H, N-Ar, H-1′); 7.33–7.60 (15 H, m, 5-Ph + 3 × 3,4,5-H, Bz, 1-NNH); 7.91–8.10 (6 H, m, 3 × 2,6-H, Bz). ^{13}C NMR ($CDCl_3$): 10.1 (4-Me); 63.4, 70.2, 72.3, 79.5, 88.6 (5-CH_2, 3, 2, 4, 1-CH, ribose); 115.9, 126.9, 144.6 (2,6-CH, 4-C, 1-C, N-Ar); 128.4–133.6 (5-Ph + 3,5-CH, N-Ar + 3 × Bz); 120.7, 126.4, 164.4 (4-C, 5-C, 2-C, imidazole); 165.3, 165.6, 166.1 (3 × C=O). MS (LSIMS; Thgly, NBA; m/z (%)): 760 (4) $[M + H]^+$, 221 (30), 105 (100) $[C_6H_5CO]^+$.

Deprotection of the Benzoylated Ribosides **2a**–**2c** and **3a**–**3c**. General Procedure

A solution of the protected sugar adduct **2a**–**2c** and **3a**–**3c** (0.6 g, 0.79 mmol) in saturated NH_3–MeOH (20 ml) was stirred at 20 °C overnight. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (silica, 10 × 2 cm, CH_2Cl_2–MeOH 99 : 1 to 1 : 1) yielding the pure free ribosides **4a**–**4c** and **5a**–**5c**, respectively.

*1-(2-Chloroanilino)-4-methyl-5-phenyl-2-[(*β*-D-ribofuranosyl)sulfanyl]imidazole* (**4a**). Yield 0.34 g (96%). R_F 0.55 (CH_2Cl_2–MeOH 9 : 1). ^{1}H NMR (DMSO-d_6): 2.24 (3 H, s, 4-Me); 3.50 (2 H, m, 2 × H-5′); 3.80 (1 H, m, H-4′); 4.05 (2 H, m, H-2′ + H-3′); 5.02 (2 H, ex, 2 × OH); 5.43 (2 H, m, d after exchange, J = 6, OH + H-1′); 5.89 (1 H, d, J = 8, 6-H, N-Ar); 6.73 (1 H, dd, J^1 = 8, J^2 = 8.8, 4-H, N-Ar); 7.05 (1 H, dd, J^1 = 8, J^2 = 8.8, 5-H, N-Ar); 7.24 (1 H, d, J = 8, 3-H, N-Ar); 7.30–7.47 (5 H, m, 5-Ph); 9.19 (1 H, s, 1-NNH). ^{13}C NMR (DMSO-d_6): 14.1 (4-Me); 61.3, 70.2, 75.4, 85.3, 89.1 (5-CH_2, 3, 2, 4, 1-CH, ribose); 112.4, 116.7, 120.8, 128.1, 129.6, 142.9 (6-CH, 2-C, 4-CH, 5-CH, 3-CH, 1-C, N-Ar); 127.7, 128.2, 128.5, 130.1 (4-CH, 2,6-CH, 3,5-CH, 1-C, 5-Ph); 129.2, 134.2, 140.0 (5-C, 4-C, 2-C, imidazole). UV (λ_{max} (log ε)): 206 (4.58), 234 (4.28), 275 (4.26). MS (LSIMS; Thgly; m/z (%)): 448 (28) $[M + 1]^+$, 316 (66) 196 [imidazole – $C_6H_4ClN]^+$, 131 (64) $[C_9H_9N]^+$, 55 (100). Exact mass ($C_{21}H_{23}ClN_3O_4S$) calculated: 448.1098 $[M + H]^+$; found: 448.1093. For $C_{21}H_{22}ClN_3O_4S$ (447.9) calculated: 56.31% C, 4.95% H; found: 55.90% C, 5.00% H.

*1-(3-Chloroanilino)-4-methyl-5-phenyl-2-[(*β-*D-ribofuranosyl)sulfanyl]imidazole* (**4b**). Yield 0.33 g (95%). R_F 0.55 (CH_2Cl_2–MeOH 9 : 1). ^{1}H NMR (DMSO-d_6): 2.23 (3 H, s, 4-Me); 3.50 (2 H, m, 2 × H-5′); 3.82 (1 H, m, H-4′); 4.05 (2 H, m, H-2′ + H-3′); 5.01 (2 H, ex, 2 × OH); 5.46 (2 H, m, d after exchange, J = 6, OH + H-1′); 6.25 (1 H, d, J = 8.4, 6-H, N-Ar); 6.33 (1 H, s, 2-H, N-Ar); 6.74 (1 H, d, J = 8, 4-H, N-Ar); 7.17 (1 H, dd, J^1 = 8, J^2 = 8.4, 5-H, N-Ar); 7.27–7.37 (5 H, m, 5-Ph); 9.58 (1 H, s, 1-NNH). ^{13}C NMR (DMSO-d_6): 14.2 (4-Me); 61.2, 70.3, 75.4, 85.3, 89.3 (5-CH_2, 3, 2, 4, 1-CH, ribose); 110.4, 111.2, 119.6, 131.1, 134.0, 148.9 (6-CH, 2-CH, 4-CH, 3-C, 1-C, N-Ar); 127.8, 128.6, 128.9, 130.0 (4-CH, 2,6-CH, 3,5-CH, 1-C, 5-Ph); 129.4, 134.3, 139.8 (5-C, 4-C, 2-C, imidazole). UV (λ_{max} (log ε)): 207 (4.60), 237 (4.37), 274 (4.34). MS (LSIMS; Thgly; *m*/*z* (%)): 448 (24) $[M + H]^+$, 316 (66), 190 (79) [imidazole – $C_6H_4ClN]^+$, 131 (100) $[C_9H_9N]^+$. Exact mass ($C_{21}H_{23}ClN_3O_4S$) calculated: 448.1098 $[M + H]^+$; found: 448.1093. For $C_{21}H_{22}ClN_3O_4S$ (447.9) calculated: 56.31% C, 4.95% H; found: 56.26% C, 5.12% H.

*1-(4-Chloroanilino)-4-methyl-5-phenyl-2-[(*β-*D-ribofuranosyl)sulfanyl]imidazole* (**4c**). Yield 0.33 g (95%). R_F 0.55 (CH_2Cl_2–MeOH 9 : 1). ^{1}H NMR (DMSO-d_6): 2.22 (3 H, s, 4-Me); 3.50 (2 H, m, 2 × H-5′); 3.83 (1 H, m, H-4′); 4.04 (2 H, m, H-2′ + H-3′); 5.02 (2 H, ex, 2 × OH); 5.46 (2 H, m, d after exchange, J = 6, OH + H-1′); 6.32 (2 H, d, J = 8.8, AA′BB′, 2,6-H, N-Ar); 7.14 (2 H, d, J = 8.8, AA′BB′, 3,5-H, N-Ar); 7.34–7.37 (5 H, m, 5-Ph); 9.44 (1 H, s, 1-NNH). ^{13}C NMR (DMSO-d_6): 14.1 (4-Me); 61.3, 70.3, 75.4, 85.3, 89.2 (5-CH_2, 3, 2, 4, 1-CH, ribose); 113.4, 123.4, 129.2, 146.1 (2,6-CH, 4-C, 3,5-CH, 1-C, N-Ar); 127.8, 128.6, 128.9, 130.1 (4-CH, 2,6-CH, 3,5-CH, 1-C, 5-Ph); 129.0, 134.2, 139.8 (5-C, 4-C, 2-C, imidazole). UV (λ_{max}, (log ε)): 205 (4.46), 241 (4.40), 274 (4.26). MS (LSIMS; Thgly; *m*/*z* (%)): 448 (34) $[M + H]^+$, 316 (62), 190 (100) [imidazole – $C_6H_4NCl]^+$, 131 (64) $[C_9H_9N]^+$. Exact mass ($C_{21}H_{23}ClN_3O_4S$) calculated: 448.1098 $[M + H]^+$; found: 448.190. For $C_{21}H_{22}ClN_3O_4S$ (447.9) calculated: 56.31% C, 4.95% H; found: 56.19% C, 5.15% H.

*1-(2-Chloroanilino)-4-methyl-5-phenyl-3-(*β-*D-ribofuranosyl)imidazole-2(3H)-thione* (**5a**). Yield 0.33 g (94%). R_F 0.56 (CH_2Cl_2–MeOH 9 : 1). ^{1}H NMR (DMSO-d_6): 2.29 (3 H, s, 4-Me); 3.51–3.76 (3 H, m, 2 × H-5′ + H-4′); 4.06 (1 H, m, H-3′); 4.50 (1 H, m, H-2′); 6.45 (1 H, d, J = 6, H-1′); 4.91 (1 H, t, J = 6, 5′-OH); 5.13 (1 H, d, J = 6, OH); 5.25 (1 H, d, J = 6, OH); 6.10 (1 H, d, J = 8, 6-H, N-Ar); 6.74 (1 H, dd, J^1 = 8, J^2 = 8.8, 4-H, N-Ar); 7.06 (1 H, dd, J^1 = 8, J^2 = 8.8, 5-H, N-Ar); 7.23 (1 H, d, J = 8, 3-H, N-Ar); 7.34–7.48 (5 H, m, 5-Ph); 8.79 (1-NNH). ^{13}C NMR (DMSO-d_6): 10.3 (4-Me); 61.0, 68.9, 71.5, 84.4, 91.1 (5-CH_2, 3, 2, 4, 1-CH, ribose); 113.3, 117.5, 120.6, 127.9, 129.6, 142.5 (6-CH, 2-C, 4-CH, 5-CH, 3-CH, 1-C, N-Ar); 127.7, 128.5, 128.8, 130.0 (1-C, 4-CH, 2,6-CH, 3,5-CH, 5-Ph); 121.3, 127.0, 165.1 (4-C, 5-C, 2-C, imidazole). UV (λ_{max} (log ε)): 205 (4.46), 232 (4.07), 284 (4.21). MS (LSIMS; Gly, TFA; *m*/*z* (%)): 448 (100) $[M + H]^+$, 316 (57), 280 (60), 190 (95) [imidazole – $C_6H_4NCl]^+$, 131 (62) $[C_9H_9N]^+$. Exact mass ($C_{21}H_{23}ClN_3O_4S$) calculated: 448.1098 $[M + H]^+$; found: 448.1107. For $C_{21}H_{22}ClN_3O_4S$ (447.9) calculated: 56.31% C, 4.95% H; found: 56.25% C, 5.06% H.

*1-(3-Chloroanilino)-4-methyl-5-phenyl-3-(*β-*D-ribofuranosyl)imidazole-2(3H)-thione* (**5b**). Yield 0.34 g (96%). R_F 0.56 (CH_2Cl_2–MeOH 9 : 1). ^{1}H NMR (DMSO-d_6): 2.29 (3 H, s, 4-Me); 3.50–3.77 (3 H, m, 2 × H-5′ + H-4′); 4.07 (1 H, m, H-3′); 4.52 (1 H, m, H-2′); 6.45 (1 H, d, J = 6, H-1′); 4.91 (1 H, t, J = 6, 5′-OH); 5.13 (1 H, OH); 5.31 (1 H, OH); 6.36 (1 H, d, J = 8.4, 6-H, N-Ar); 6.44 (1 H, s, 2-H, N-Ar); 6.74 (1 H, d, J = 8, 4-H, N-Ar); 7.14 (1 H, dd, J^1 = 8, J^2 = 8.4, 5-H, N-Ar); 7.33–7.39 (5 H, m, 5-Ph); 9.34 (1 H, s, 1-NNH). ^{13}C NMR (DMSO-d_6): 10.3 (4-Me); 61.0, 68.9, 71.4, 84.3, 91.0 (5-CH_2, 3, 2, 4, 1-CH, ribose); 111.2, 112.1, 119.3, 130.8, 133.6, 148.6 (6-CH, 2-CH, 4-CH, 5-CH, 3-C, 1-C, N-Ar); 127.9, 128.6, 128.8, 130.0 (1-C, 4-CH, 2,6-CH, 3,5-CH, 5-Ph); 121.5, 126.9, 165.0 (4-C, 5-C, 2-C, imidazole). UV (λ_{max} (log ε)):

206 (4.56), 235 (4.19), 283 (4.27). MS (LSIMS; Thgly; *m/z* (%)): 448 (13) $[M + H]^+$, 316 (36), 189 (57) [imidazole – $C_6H_4ClN]^+$, 131 (64) $[C_9H_9N]^+$, 55 (100). Exact mass ($C_{21}H_{23}ClN_3O_4S$) calculated: 448.1098 $[M + H]^+$; found: 448.1107. For $C_{21}H_{22}ClN_3O_4S$ (447.9) calculated: 56.31% C, 4.95% H; found: 55.96% C, 5.19% H.

1-(4-Chloroanilino)-4-methyl-5-phenyl-3-(β-D-ribofuranosyl)imidazole-2(3H)-thione (**5c**). Yield 0.33 g (95%). R_F 0.56 (CH_2Cl_2–MeOH 9 : 1). ^{1}H NMR (DMSO-d_6): 2.28 (3 H, s, 4-Me); 3.50–3.72 (3 H, m, 2 × H-5′ + H-4′); 4.06 (1 H, m, H-3′); 4.50 (1 H, m, H-2′); 6.44 (1 H, d, J = 6, H-1′); 4.90 (1 H, t, J = 6, 5′-OH); 5.20 (1 H, OH); 5.30 (1 H, OH); 6.43 (2 H, d, J = 8.8, AA′BB′, 2,6-H, N-Ar); 7.14 (2 H, d, J = 8.8, AA′BB′, 3,5-H, N-Ar); 7.34–7.39 (5 H, m); 9.22 (1 H, s, 1-NNH). ^{13}C NMR (DMSO-d_6): 10.3 (4-Me); 61.0, 68.9, 71.4, 84.3, 91.1 (5-CH_2, 3, 2, 4, 1-CH, ribose); 114.2, 123.2, 128.8, 146.0 (2,6-CH, 4-C, 3,5-CH, 1-C, N-Ar); 127.9, 128.6, 128.8, 129.9 (1-C, 4-CH, 2,6-CH, 3,5-CH, 5-Ph); 121.4, 127.0, 165.0 (4-C, 5-C, 2-C, imidazole). UV (λ_{max} (log ε)): 204 (4.36), 238 (4.20), 283 (4.21). MS (LSIMS; Thgly; *m/z* (%)): 448 (15) $[M + H]^+$, 316 (36), 190 (53) [imidazole – $C_6H_4ClN]^+$, 55 (100). Exact mass ($C_{21}H_{23}ClN_3O_4S$) calculated: 448.1098 $[M + H]^+$; found: 448.1191. For $C_{21}H_{22}ClN_3O_4S$ (447.9) calculated: 56.31% C, 4.95% H; found: 56.17% C, 5.26% H.

1-(3-Chlorophenylamino)-4-methyl-5-phenyl-2-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)]-sulfanylimidazole (**6b**)

This compound was obtained by glucosylation of **1c** (0.5 g, 1.58 mmol) with penta-*O*-acetyl-D-glucose (0.62 g, 1.6 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (0.8 ml, 3.2 mmol) and trimethylsilyltrifluoromethanesulfonate (0.57 ml, 3.2 mmol) in 1,2-dichloroethane (reflux 2 h). Yield 0.65 g (65%). R_F 0.2 (CH_2Cl_2–MeOH 99 : 1). ^{1}H NMR ($CDCl_3$): 2.39 (3 H, s, 4-Me); 1.89, 2.00, 2.04, 2.09 (4 × 3 H, 4 × CH_3, Ac); 3.71 (1 H, m, H-6′); 4.10–4.38 (2 H, m, H-6′ + H-5′); 4.83–5.10 (3 H, m, H-3′, H-2′, H-4′); 5.10 (1 H, d, J = 9, H-1′); 6.27 (1 H, d, J = 8.4, 6-H, N-Ar); 6.47 (1 H, s, 2-H, N-Ar); 6.86 (1 H, d, J = 8, 4-H, N-Ar); 7.12 (1 H, dd, J^1 = 8, J^2 = 8.4, 5-H, N-Ar); 7.32–7.35 (5 H, m); 7.81 (1 H, s, 1-NNH). ^{13}C NMR ($CDCl_3$): 14.0 (4-Me); 20.1, 20.3, 20.4, 20.8 (4 × CH_3, Ac); 61.2, 67.8, 69.4, 73.3, 75.8, 86.3 (6-CH_2, 4, 2, 3, 5, 1-CH, glucose); 111.0, 113.1, 121.4, 130.4, 135.1, 148.4 (6-CH, 2-CH, 4-CH, 5-CH, 3-C, 1-C, N-Ar); 128.0, 128.1, 128.3, 129.1 (1-C, 4-CH, 2,6-CH, 3,5-CH, 5-Ph); 129.1, 132.3, 135.4 (5-C, 4-C, 2-C, imidazole); 169.4, 169.8, 169.9, 170.7 (4 × C=O, Ac). MS (LSIMS; Thgly, NaOAc; *m/z* (%)): 646 (16) $[M + H]^+$, 316 (11) [imidazole + $H]^+$, 169 (100), 109 (76).

1-(3-Chloroanilino)-2[(β-D-glucopyranosyl)sulfanyl]-4-methyl-5-phenylimidazole (**7b**)

Compound **7b** was obtained by deprotection of **6b** (0.56 g, 0.87 mmol) with NH_3–MeOH. After removal of the solvent, the resulting precipitate was recrystallized from $CHCl_3$. Yield 0.40 g (93%); m.p. 150–152 °C ($CHCl_3$). R_F 0.52 (CH_2Cl_2–MeOH 9 : 1). ^{1}H NMR (DMSO-d_6): 2.23 (3 H, s, 4-Me); 3.09 (1 H, m, H-4′); 3.12 (1 H, m, H-2′); 3.17 (1 H, m, H-3′); 3.18 (1 H, m, H-5′); 3.44, 3.77 (2 H, m, 2 × H-6′); 4.87 (1 H, d, J = 9, H-1′); 4.74, 5.45, 6.32, 6.72 (4 × s, 4 × OH); 6.26 (1 H, d, J = 8.4, 6-H, N-Ar); 6.31 (1 H, s, 2-H, N-Ar); 6.74 (1 H, d, J = 8, 4-H, N-Ar); 7.17 (1 H, dd, J^1 = 8, J^2 = 8.4, 5-H, N-Ar); 7.35–7.37 (5 H, m, 5-Ph); 9.36 (1 H, s, 1-NNH). ^{13}C NMR (DMSO-d_6): 14.2 (4-Me); 61.0, 69.9, 72.9, 78.0, 80.9, 87.3 (6-CH_2, 4, 2, 3, 5, 1-CH, glucose); 111.6, 114.4, 119.6, 131.1, 133.6, 148.9 (6-CH, 2-CH, 4-CH, 5-CH, 3-C, 1-C, N-Ar); 127.8, 128.5, 128.9, 130.4 (4-CH, 2,6-CH, 3,5-CH, 1-C, 5-Ph); 129.1, 134.1, 138.9 (5-C, 4-C, 2-C, imidazole). UV (λ_{max} (log ε)): 205 (4.46), 238 (4.11), 272 (4.14). MS (LSIMS; Thgly, NaOAc; *m/z* (%)): 500 (100) $[M + Na]^+$, 478 (5) $[M + H]^+$, 316 (18) [imidazole + $H]^+$,

131 (50) $[C_9H_9N]^+$. Exact mass ($C_{22}H_{25}ClN_3O_5S$) calculated: 478.1203 $[M + H]^+$; found: 478.1191. For $C_{22}H_{24}ClN_3O_5S \cdot 0.5H_2O$ (478.0) calculated: 54.26% C, 5.17% H; found: 54.20% C, 5.22% H.

Elemental analyses were obtained from the Microanalytical Labor, Fakultät für Chemie, Universität Konstanz. Dr A. Van Aerschot is a research associate of the Flemish Fund of Scientific Research. Authors thank Dr J. Rozenski for exact mass analysis and Prof. E. De Clercq and Dr C. Pannecouque for antiviral screening.

REFERENCES

1. a) Cook P. D., Robins R. K.: *J. Am. Chem. Soc.* **1976**, *78*, 1492; b) Yamazaki A., Okutsu M.: *J. Heterocycl. Chem.* **1978**, *15*, 3353; c) Kalman T., Houston D.: *Nucleosides Nucleotides* **1989**, *8*, 899; d) Wall M., Benkovic S. J.: *J. Med. Chem.* **1999**, *42*, 3421.
2. Matsuda A., Sasaki T., Ueda T.: *Chem. Pharm. Bull.* **1988**, *36*, 2730.
3. a) Niedballa U., Vorbrüggen H.: *J. Org. Chem.* **1974**, *39*, 3654; b) Vorbrüggen H., Krolikiewicz K., Bennua B.: *Chem. Ber.* **1981**, *114*, 1234; c) Vorbrüggen H., Höfle G.: *Chem. Ber.* **1981**, *114*, 1256; d) Vorbrüggen H., Bennua B.: *Chem. Ber.* **1981**, *114*, 1279.
4. a) Bretner M., Kulikowski T., Dzik J. M., Balinska M., Rode W., Shugar D.: *J. Med. Chem.* **1993**, *36*, 3611; b) Budešínský Z., Šmejkal F., Budešínský M.: *Collect. Czech. Chem. Commun.* **1982**, *47*, 2145; c) Dinan F. J., Chodkowski J., Barren J. B., Robinson D. M., Reinhardt D. V.: *J. Org. Chem.* **1982**, *47*, 1769.
5. Kuimelis R. G., Nambiar K. P.: *Nucleosides Nucleotides* **1993**, *12*, 737.
6. Ding Y., Zhang Y.-Y., Zhang J., Chen Y.-Q.: *Biochem. Med. Chem. Lett.* **1997**, *13*, 1607.
7. a) T. Ueda in: *Chemistry of Nucleosides and Nucleotides* (L. B. Townsend, Ed.), Vol. 1, p. 2. Plenum Press, New York–London 1988; b) Robins R. K., Meyer R. B., Jr. in: *Chemistry of Nucleosides and Nucleotides* (L. B. Townsend, Ed.), Vol. 1, p. 130. Plenum Press, New York–London 1988.
8. Schantl J. G., Lagoja I. M.: *Heterocycles* **1997**, *45*, 691.
9. Townsend L. B. in: *Synthetic Procedures in Nucleic Acid Chemistry* (W. W. Zorbach and R. S. Tipson, Eds), Vol. 2, p. 267. Wiley–Interscience, New York 1973; and references therein.
10. Still I. W. J., Plavac N., Mc Kinnon D. M., Cauhan M. S.: *Can. J. Chem.* **1978**, 56, 725.
11. Diphenylamine (ethanol, λ_{max} (log ε)): 237 (3.72), 286 (4.38); Scheibe G., Gadner H. H.: *UV Atlas of Organic Compounds*, p. D11/19. Butterworth, London and Verlag Chemie, Weinheim 1967.
12. Al Obaid A. M., El-Subbagh H. I., Khodair A. I., El-Mazar M. M. M.: *Anti-Cancer Drugs* **1996**, *7*, 873.
13. Böhringer M., Roth H.-J., Hunziker J., Göbel M., Krishnan R., Ginger A., Schweizer B., Schreiber J., Leumann C., Eschenmoser A.: *Helv. Chim. Acta* **1992**, *75*, 1416.
14. Kalman T. I., Bardos T. J.: *J. Am. Chem. Soc.* **1967**, *89*, 1171.
15. Becker E. D.: *High Resolution NMR, Theory and Chemical Application*, p. 169. Academic Press, New York 1969.