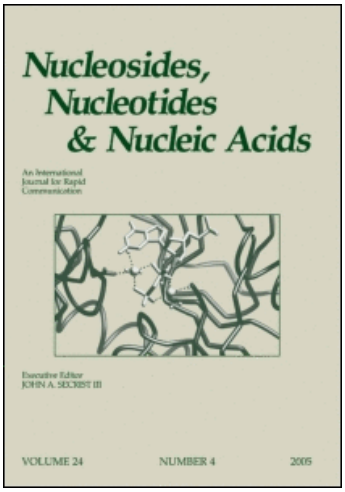


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of *N*-Substituted 1-Amino-2,3-dihydro-1*H*-imidazole-2-thione-*N*-nucleosides and *S*-Glycosylated Derivatives

Iman A. Al-Masoudi[a]; Ahmed I. Khodair[b]; Yaseen A. Al-Soud[c]; Najim A. Al-Masoudi[d]
[a] College of Veterinary, University of Basrah, Basrah, Iraq [b] Chemistry Department, Faculty of Education, Tanta University (Kafr El-Sheikh Branch), Kafr El-Sheikh, Egypt [c] College of Science, Department of Chemistry, University of Al al-Bayt, Al-Mafraq, Jordan [d] Fakultät für Chemie, Universität Konstanz, Konstanz, Germany

Online publication date: 05 December 2003

To cite this Article Al-Masoudi, Iman A. , Khodair, Ahmed I. , Al-Soud, Yaseen A. and Al-Masoudi, Najim A.(2003) 'Synthesis of *N*-Substituted 1-Amino-2,3-dihydro-1*H*-imidazole-2-thione-*N*-nucleosides and *S*-Glycosylated Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 22: 3, 299 — 307
To link to this Article: DOI: 10.1081/NCN-120021429
URL: http://dx.doi.org/10.1081/NCN-120021429

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, No. 3, pp. 299–307, 2003

Synthesis of *N*-Substituted 1-Amino-2,3-dihydro-1*H*-imidazole-2-thione-*N*-nucleosides and *S*-Glycosylated Derivatives

Iman A. Al-Masoudi,[1] Ahmed I. Khodair,[2] Yaseen A. Al-Soud,[3] and Najim A. Al-Masoudi[4,*]

[1]College of Veterinary, University of Basrah, Basrah, Iraq
[2]Chemistry Department, Faculty of Education, Tanta University (Kafr El-Sheikh Branch), Kafr El-Sheikh, Egypt
[3]College of Science, Department of Chemistry, University of Al al-Bayt, Al-Mafraq, Jordan
[4]Fakultät für Chemie, Universität Konstanz, Konstanz, Germany

ABSTRACT

Fusion of the *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thiones **1-4** with the peracylated ribose **5** in the presence of iodine afforded the *N*-nucleosides **6-9** in moderate yields. Deblocking with NaOMe/MeOH gave the free nucleosides **10-13**. Alternatively, silylation of **4** followed by ribosylation with **5** in the presence of TMSOTf as catalyst afforded **9** in moderate yield. Ribosylation of **4** with the chlorodeoxyribose derivative **15** as well as **5** in the presence of NaH in DMF afforded the thioglycosides **16** and **18**, respectively. Deblocking of **16** and **18** with NaOMe/MeOH gave the free *S*-thioglycosides **17** and **19**, respectively. Thermal rearrangement of **19** at high temperature in the presence of iodine furnished **13** in low yield. The new free nucleosides and thioglycosides were

*Correspondence: Najim A. Al-Masoudi, Fakultät für Chemie, Universität Konstanz, Postfach 5560, D-78457 Konstanz, Germany; Fax: +49 7531 34435; E-mail: NajimAl-Masoudi@uni-konstanz.de.

DOI: 10.1081/NCN-120021429
1525-7770 (Print); 1532-2335 (Online)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

inactive against HIV-1 and HIV-2 induced cytopathicity in human MT-4 lymphocyte cells.

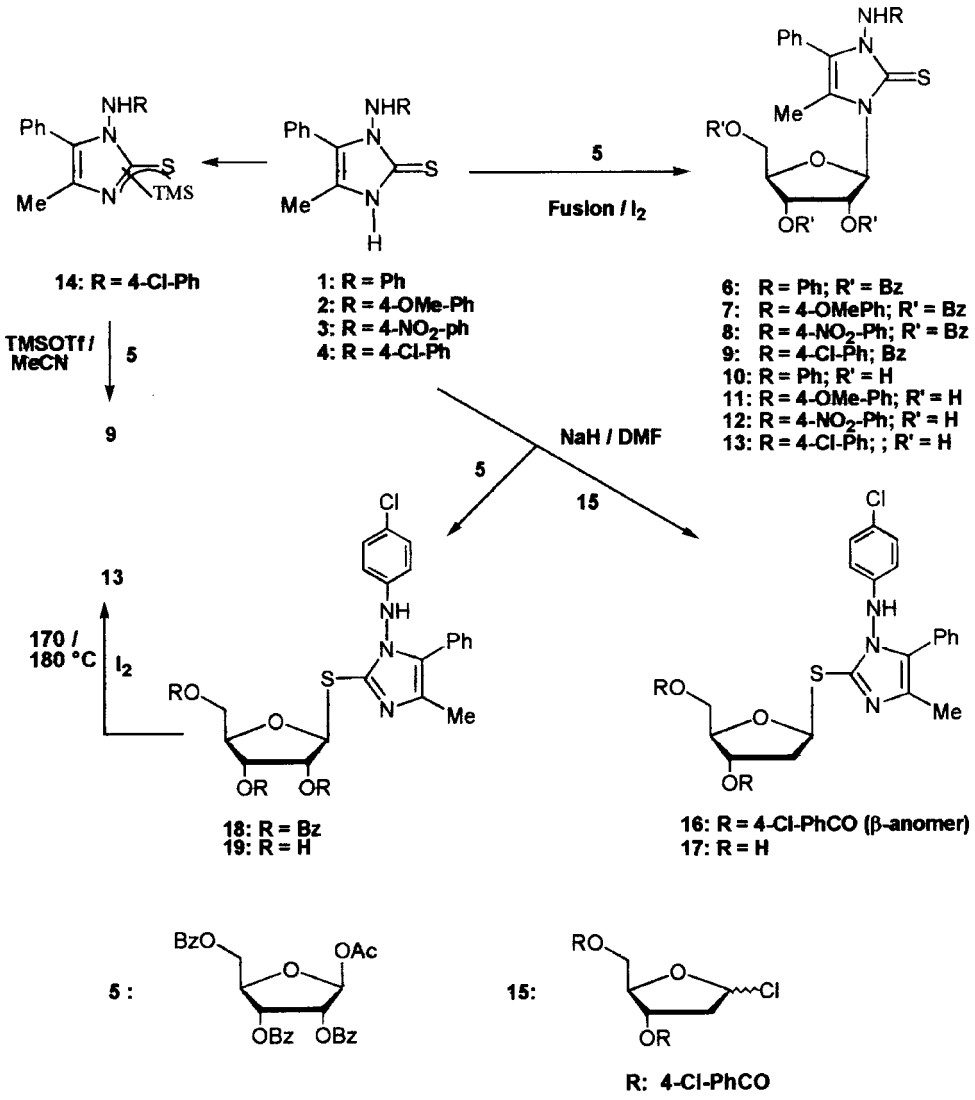
Key Words: Antiviral activity; Imidazole-2-thiones; *N*-Nucleosides; *S*-Glycosides; Ribosylation.

Various heterocycles bearing the thioureylene group are known to possess interesting biological properties.[1] For example, methimazole (1-methylimidazole-2-thione, Tapazole®) is currently used for the treatment of thyroid gland disorder.[2] Other derivatives are used for the treatment of arthritis[3,4], cardiovascular diseases[5,6], antiinflimmatory activity[7] as well as anti-HIV agents.[8] It is well known that various nucleoside analogues played an important role in the field of cancer chemotherapy and viral diseases.[9] Imbach et al.[10] have reported the first imidazole nucleosides possessing the thioureuylene group and evaluated their chemotherapeutic properties in comparison to the methimazole. These prompted us to synthesize new 2-mercapto imidazole nucleosides by ribosylation of some selected imidazole bases namely, the *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thiones.[11]

RESULTS AND DISCUSSION

The site of ribosylation of the imidazole bases[11] **1-4** were first examined by the fusion procedure, following Imbach et al. method.[10] Thus, **1-4** (1.1 equivalents) fused with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**) in the presence of iodine afforded, after chromatographic purification, the *N*-nucleosides **6-9** in 41, 45, 40 and 55% yields, respectively, with some other products which are presumably the *S*-ribosides, *N,S*-ribosides or decomposed products. 1-(4-Chlorophenylamino)-2,3-dihydro-4-methyl-5-phenyl-1*H*-imidazole-2-thione (**4**) has been selected for the Hilbert-Johnson-Birkofer procedure[12] to improve the selective *N*-ribosylation. Thus, silylation of **4** with hexamethyldisilazane (HMDS) gave the silylated product **14**, which was treated with the sugar derivative **5** in dry MeCN as solvent, and trimethylsilyl trifluoromethanesulfonate (TMSOTf)[13] as catalyst at 75°C for 3 h to give, after column chromatography, **9** in 53% yield. Deblocking of **6-9** with NaOMe/MeOH at room temperature for 16 h afforded the free nucleosides **10-13** in 73, 70, 68 and 78% yields, respectively (Sch. 1). The structures of **6-13** were characterized from their ^{1}H NMR and mass spectra. The anomeric coupling constants of **6-13** are typical for β-configurated ribofuranoses (between 5.1 and 5.5 Hz). The rotating frame nuclear overhauser effect (ROE)[14] between H-1′ and H-4′ is an additional proof for β-configuration. The proton spin systems were identified from DQF-COSY[15] and ROESY spectra, since showed a good evidance for ribosylation of **1-4** via the *N*-site of the imidazole molecule. This was confirmed by the $^3J_{C,H}$ correlation of C-2 at δ_C 162.2 and H-1′ at δ_H 6.45 of **9**. The nucleoside **9** was selected for further NMR study. The signal at δ_C 120.9, assigned to C-4, has a cross peak to δ_H 6.45 of H-1′ in the HMQC[16] spectrum. Moreover, C-2 resonated at highest field (δ_C 162.2) due to the shielding nature around (C=S) bond, and these data showed an additional proof for the *N*-glycosylation and excluded the substitution at the sulfur atom. The above

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



Scheme 1.

argument is in agreement with the spectral data obtained by Shantle et al.[11] during the N^3-methylation of N^1-substituted-4-methyl-5-phenyl-1*H*-imidazole-2-thione.

Further study was made with the 2-deoxyribose. When compound **4** was reacted with 1.1 equivalent of NaH in anhyd. DMF followed by 1.1 equivalent of chloro-deoxysugar **15** at 60°C for 2 h gave, after chromatographic separation, the thio-glycoside **16** in 35% yield. The structure of **16** was confirmed by the COSY, ROESY, HMQC and HMBC NMR experiments as well as the mass spectrum. The ^{1}H-NMR spectrum of **16** showed the anomeric ratio (α:β) to be about 1 : 3, since H-1′ (β-anomer, from HMBC experiment) appeared as a doublet of doublets at δ_H

7.07 ($J_{1',2'a} = 5.5$ Hz; $J_{1',2'b} = 3.5$ Hz). The β-configuration of **16** was further confirmed by NOE experiment.[16] Thus, irradiation of the H-1′ signal led to enhancement of the signal for H-4′ (2.8%). C-2 resonated at lower field δ_C 142.1, indicating the *S*-glycosylation and excluded the *N*-substitution, and these data again is in agreement with those of the *S*-methyl-imidazole derivative obtained by Schantle et al.[11] Similarly, treatment of **4** with the sugar derivative **5** in DMF and NaH gave, after chromatography, the thioglycoside **18** in 38% yield. Removal of the benzoyl groups of **18** with NaOMe/MeOH afforded the free thioglycoside **19** in 78% yield. The anomeric coupling constants of **18** and **19** (5.3, 4.9 Hz, respectively) are indicated for the β-configuration. The signals at δ_C 142.5 and 146.3, which attributed to C-2 of **18** and **19**, respectively, are characteristic for the site of ribosylation at the sulfur atom rather than nitrogen. Proton bearing carbon of **18** was detected by ^{1}H-^{1}H and ^{1}H-^{13}C COSY spectra as well as the HMQC spectra.[16] The assignment of the *S*-glycosylation was further studied by gradient selected HMBC[17] via the $^3J_{C,H}$ coupling between H-1′ (δ_H 6.10) and C-2 (δ_C 142.5), along with disappearance of such coupling between H-1′ and C-4. The residual sugar protons of both **18** and **19** were fully analysed (see experimental part).

When the *S*-glycoside **19** was subjected to the high temperature (170–180°C) by applying Halasa et al. method[18] in the presence of iodine as catalyst, it was rearranged into the *N*-nucleoside **13** (18% yield). The low yield of **13** is presumably due to the thermal decomposition of **19** into an unidentified products, separated by the chromatography.

The imidazole *N*-nucleosides and *S*-thioglycosides **9-13**, **16** and **19** were evaluated in vitro for their inhibitory activity of HIV-1 (III B) and HIV-2 (ROD) in human MT-4 lymphocyte cells. All compounds were inactive against both HIV-1 and HIV-2 up to 100 μg/mL. Furthermore, compounds **9-13** are under investigation for the treatment of thyroid gland disorder.

Experimental

General procedure. Melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on AC 250 and 600 MHz spectrometers, using tetramethylsilane (TMS) as internal standard, with δ: chemical shift in ppm, and coupling constants in Hz. Mass spectra were measured in glycerol as matrix, meanwhile, some molecular ions were measured with sodium ions.

Preparation of *N*-substituted 1-amino-4-methyl-5-phenyl-1*H*-imidazole-2-thione-*N*-nucleosides. *General procedure*. The desired bases **1-4** (2.21 mmol), the sugar derivative **5** (1.22 g, 2.43 mmol, 1.1 equiv.) and iodine (5.2% mole per mole of an imidazole base) was fused at 160°C for 20 min. under vacuum. After cooling, the brown residue was dissolved in $CHCl_3$ (10 mL), filtered and poured onto SiO_2 column (50 g). Elution first with $CHCl_3$, then with $CHCl_3$-MeOH (49 : 1) afforded two compounds. The first eluted compounds was were unidentified products. The second eluted compounds were characterized as the *N*-nucleosides **6-9**, mostly as foam.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methyl-5-phenyl-1-phenylamino-1*H*-imidazole-2-thione (6). From **1** (0.62 g). Yield: 0.66 g, (41%); foam. δ_H ($CDCl_3$):

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

8.89 (s, 1H, NH); 7.40–7.27 (m, 5H, C_5-*Ph*); 7.11 (dd, 1H, $J = 8.1$ Hz, NH-*Ph*); 6.72 (t, 2H, $J = 7.5$ Hz, NH-*Ph*); 6.51 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 6.48 (d, 2H, $J = 8.2$ Hz, NH-*Ph*); 5.90 (t, 1H $J_{2',3'} = 5.5$ Hz, H-2′); 5.85 (t, 1H, $J_{3',4'} = 4.2$ Hz, H-3′); 4.97 (dd, 1H, $J_{4',5''} = 3.5$ Hz, H-4′); 4.95 (dd, 1H, $J_{4',5'} = 3.0$ Hz, H-5′); 4.85 (dd, 1H, $J_{5',5''} = 12.5$ Hz, H-5″); 2.17 (s, 3H, Me). Anal. calc. for $C_{42}H_{35}SN_3O_7$ (725.8): C, 69.50; H, 4.86; N, 5.79. Found: C, 69.46; H, 4.76; N, 5.57. MS: m/z (FAB) 726 $(MH)^+$.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1-(4-methoxyphenylamino)-4-methyl-5-phenyl-1*H*-imidazole-2-thione (7). From **2** (0.67 g). Yield: 0.75 g; (45%); m.p. 80–86°C. δ_H ($CDCl_3$): 9.20 (s, 1H, NH); 7.38–7.31 (m, 5H, C_5-*Ph*); 7.17, 7.15 (2d, 2H, $J = 8.9$ Hz, NH-4-OMe*Ph*); 6.62 (d, 1H, $J_{1',2'} = 5.5$ Hz, H-1′); 6.48 (2d, 2H, $J = 8.9$ Hz, NH-4-OMe*Ph*); 5.88 (m, 2H, H-2′, H-3′); 4.99 (t, 1H, $J_{4',5''} = 2.9$ Hz, H-4′); 4.96–4.90 (m, 2H, H-5′, H-5″); 2.15 (s, 3H, Me). Anal. calc. for $C_{43}H_{38}SN_3O_8$ (756.9): C, 68.24; H, 5.06; N, 5.55. Found: C, 68.02; H, 4.98; N, 5.24. MS: m/z (FAB) 780 $(MNa)^+$.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methyl-1-(4-nitrophenylamino)-5-phenyl-1*H*-imidazole-2-thione (8). From **3** (0.72 g). Yield: 0.68 g, (40%); m.p. 110–115°C. δ_H ($CDCl_3$): 10.32 (s, 1H, NH); 7.28–7.21 (m, 5H, C_5-*Ph*); 8.11, 8.14 (2d, 2H, $J = 9.5$ Hz, NH-4-NO_2*Ph*); 6.59 (2d, 2H, $J = 9.5$ Hz, NH-4-NO_2*Ph*); 6.47 (d, 1H, $J_{1',2'} = 5.3$ Hz, H-1′); 5.82–5.77 (m, 2H, H-2′, H-3′); 4.94 (t, 1H, $J_{4',5''} = 3.5$ Hz, H-4′); 4.99 (dd, 1H $J_{4',5'} = 3.0$ Hz, H-5′); 4.96 (dd, 1H, $J_{5',5''} = 12.3$ Hz, Hz, H-5″); 2.17 (s, 3H, Me). Anal. calc. for $C_{42}H_{34}SN_4O_9$ (770.8): C, 65.45; H, 4.45; N, 7.27. Found: C, 65.33; H, 4.36; N, 7.05. MS: m/z (FAB) 793 $(MNa)^+$.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1-(4-chlorophenylamino)-4-methyl-5-phenyl-1*H*-imidazole-2-thione (9). *Method **a***. From **4** (0.70 g). Yield: 0.93 g, (55%); m.p. 85–91°C. δ_H (600 MHz, COSY, ROESY, HMQC, HMBC, $CDCl_3$): 9.17 (s, 1H, NH); 7.37–7.33 (m, 5H, C_5-*Ph*); 6.98, 6.90 (2d, 2H, $J = 8.0$ Hz, NH-4-Cl*Ph*); 6.45 (d, 1H, $J_{1',2'} = 5.2$ Hz, H-1′); 6.39, 6.30 (2d, 2H, $J = 8.0$ Hz, NH-4-Cl*Ph*); 5.85–5.80 (m, 2H, H-2′, H-3′); 4.96 (t, 1H, $J_{4',5''} = 3.3$ Hz, H-4′); 4.92 (dd, 1H $J_{4',5'} = 2.8$ Hz, H-5′); 4.87 (dd, 1H, $J_{5',5''} = 12.5$, H-5″); 2.14 (s, 3H, Me). δ_C($CDCl_3$): 66.1; 165.1, 164.6 (C=O); 162.2 (C-2); 133.4–129.0 (Ar); 126.8 (C-5); 120.9 (C-4); 114.3, 112.5 (Ph); 90.6 (C-1′); 82.0 (C-4′); 74.6 (C-3′); 70.0 (C-3′); 62.8 (C-5′); 10.8 (C_4-*Me*). Anal. calc. for $C_{42}H_{34}ClSN_3O_7$ (760.3): C, 66.35; H, 4.51; N, 5.53. Found: C, 66.25; H, 4.21; N, 5.39. MS: m/z (FAB) 760/762 $(MH)^+$.

*Method **b***. To a suspended **4** (0.80 g, 2.50 mmol) in anhyd. MeCN (25 mL) was added hexamethyldisilazane (20 mL) and the reaction mixture was heated under reflux for 16 h. After cooling, the solution was evaporated to drynress under anhyd. condition, then dissolved in MeCN (25 mL). To this, a solution of **5** (1.38 g, 2.7 mmol) in MeCN (20 mL) was added, followed by the addition of TMSOTf (1.1 mmol), dropwise and the mixture was heated at 75°C for 3 h. After cooling, a saturated aqueous solution of $NaHCO_3$ was added and the resulting mixture extracted with CH_2Cl_2 (3×30 mL). The combined organic fractions were washed with saturated NaCl solution, dried (Na_2SO_4), filtered and evaporated to dryness. The amorphous obtained was purified by flash chromatography, using MeOH, in

gradient, (0–2%) and $CHCl_3$ as eluent to give **9** (1.37 g, 72%) as amorphous compound. All the physical properties are similar to those of the authentic sample prepared in method a.

Preparation of free *N*-Nucleosides 10-13 derived from compounds (6-9). *General procedure.* A solution of the acylated nucleoside (0.80 mmol) in 0.20 M NaOMe/MeOH solution (20 mL) was stirred at room temperature for 18 h. The solution was evaporated to dryness and the residue was partitioned between water (35 mL) and ether (3 × 30 mL). The aqueous layer was evaporated to dryness and the residue was co-evaporated with EtOH (3 × 30 mL) to give a crude product. Recrystallization from EtOH afforded the desired free *N*-nucleosides.

4-Methyl-5-phenyl-1-phenylamino-3-(β-D-ribofuranosyl)-1*H*-imidazole-2-thione (10). From **6** (0.58 g). Yield: 0.24 g, (73%); m.p. 200–205°C. δ_H (DMSO-d_6): 9.00 (s, 1H, NH); 7.42–7.34 (m, 5H, C_5-*Ph*); 7.15 (dd, 1H, $J = 8.0$ Hz, NH-*Ph*); 6.81 (t, 2H, $J = 7.2$ Hz, NH-*Ph*); 6.58 (d, 2H, $J = 8.0$ Hz, NH-*Ph*); 6.51 (d, 1H, $J_{1',2'} = 5.4$ Hz, H-1′); 5.83 (t, 1H, $J = 5.9$ Hz, $C_{5'}$-OH); 5.33 (d, 1H, $J = 5.7$ Hz, $C_{2'}$-OH); 5.11 (d, 1H, $J = 3.5$ Hz, $C_{3'}$-OH); 4.18 (dd, 1H, $J_{2',3'} = 5.3$ Hz, H-2′); 4.11-3.48 (m, 4H, H-3′-H-5″); 2.23 (s, 3H, Me). Anal calc. for $C_{21}H_{23}SN_3O_4$ (413.5): C, 61.00; H, 5.61; N, 10.16. Found: C, 60.82; H, 5.53; N, 9.89. MS: m/z (FAB) 436 $(MNa)^+$.

1-(4-Methoxyphenylamino)-4-methyl-5-phenyl-3-(β-D-ribofuranosyl)-1*H*-imidazole-2-thione (11). From **7** (0.61 g). Yield: 0.25 g, (70%); m.p. 205–209°C. δ_H (DMSO-d_6): 9.31 (s, 1H, NH); 7.48–7.37 (m, 5H, C_5-*Ph*); 7.20, 7.16 (2d, 2H, $J = 9.0$ Hz, 4-OMe*Ph*); 6.63 (d, 1H, $J_{1',2'} = 5.3$ Hz, H-1′); 6.54 (2d, 2H, $J = 9.0$ Hz, NH-4-OMe*Ph*); 5.84 (t, 1H $J = 5.7$ Hz, $C_{5'}$-OH); 5.35 (d, 1H, $J = 5.5$ Hz, $C_{2'}$-OH); 5.13 (d, 1H, $J = 3.7$ Hz, $C_{3'}$-OH); 4.21 (dd, 1H, $J_{2',3'} = 5.2$ Hz, H-2′); 4.14-3.51 (m, 4H, H-3′-H-5″); 2.24 (s, 3H, Me). Anal calc. for $C_{22}H_{25}SN_3O_5$ (443.5): C, 59.58; H, 5.68; N, 9.47. Found: C, 59.27; H, 5.59; N, 9.28. MS: m/z (FAB) 466 $(MNa)^+$.

4-Methyl-1-(4-nitrophenylamino)-5-phenyl-3-(β-D-ribofuranosyl)-1*H*-imidazole-2-thione (12). From **8** (0.62 g). Yield: 0.25 g, (68%); m.p. 239–242°C. δ_H (DMSO-d_6): 10.35 (s, 1H, NH); 7.34–7.29 (m, 5H, C_5-*Ph*); 8.15, 8.19 (2d, 2H, $J = 9.5$ Hz, 4-NO_2*Ph*); 6.63 (2d, 2H, $J = 9.5$ Hz, 4-NO_2*Ph*); 6.52 (d, 1H, $J_{1',2'} = 5.2$ Hz, H-1′); 5.75 (t, 1H $J = 5.7$ Hz, $C_{5'}$-OH); 5.30 (d, 1H, $J = 5.6$ Hz, $C_{2'}$-OH); 4.98 (d, 1H, $J = 3.5$ Hz, $C_{3'}$-OH); 4.15 (dd, 1H, $J_{2',3'} = 5.2$ Hz, H-2′); 3.98-3.31 (m, 4H, H-3′-H-5″); 2.20 (s, 3H, Me). Anal calc. for $C_{21}H_{22}SN_4O_6$ (455.5): C, 55.01; H, 4.84; N, 12.22. Found: C, 54.85; H, 4.74; N, 11.82. MS: m/z (FAB) 477/479 $(MNa)^+$.

1-(4-Chlorophenylamino)-4-methyl-5-phenyl-3-(β-D-ribofuranosyl)-1*H*-imidazole-2-thione (13). *Method* **a**. From **9** (0.61 g). Yield: 0.28 g, (78%); m.p. 189–193°C. δ_H (DMSO-d_6): 9.19 (s, 1H, NH); 7.39–7.37 (m, 5H, C_5-*Ph*); 7.01, 6.95 (2d, 2H, $J = 8.0$ Hz, 4-Cl*Ph*); 6.53 (2d, 1H, $J_{1',2'} = 5.0$ Hz, H-1′); 6.42, 6.35 (2d, 2H, $J = 8.0$ Hz, 4-Cl*Ph*); 2.17 (s, 3H, Me). 5.82 (t, 1H $J = 5.9$ Hz, $C_{5'}$-OH); 5.30 (d, 1H, $J = 5.8$ Hz, $C_{2'}$-OH); 5.13 (d, 1H, $J = 3.6$ Hz, $C_{3'}$-OH); 4.13 (dd, 1H, $J_{2',3'} = 5.1$ Hz, H-2′); 4.09-3.38 (m, 4H, H-3′-H-5″); 2.23 (s, 3H, Me). Anal. calc. for $C_{21}H_{22}ClSN_3O_4$

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

(447.9): C, 55.93; H, 5.59; N, 9.32. Found: C, 55.74; H, 5.49; N, 9.16. MS: m/z (FAB) 451/453 $(MH)^+$.

Method **b**. A mixture of 19 (200 mg, 0.44 mmol) and iodine (20 mg) was heated at 170–180°C for 7 h. After cooling, the brown solid was partitioned between water (10 mL) and ether (3 × 10 mL) and the aqueous extract was evaporated to dryness. The residue was co-evaporated with EtOH (4 × 10 mL) and chromatographed on short column of silica gel ($CHCl_3$-MeOH 9 : 1, as eluent) to give **13** (35 mg, 18%), m.p., mixed m.p. and all the physical data were identical to those of the authentic sample prepared in method a.

2-(3,5-Di-*O*-4-chlorobenzoyl-2-deoxy-β-D-*erythro*pentofuranosylsulfanyl)-1-(4-chlorophenylamino)-4-methyl-5-phenyl-1*H*-imidazole (16). To a solution of **4** (0.50 g, 1.58 mmol) in DMF (10 mL) was added NaH (0.11 g, 4.76 mmol) under argon and the suspension was stirred at 60°C. After 2 h, the chloro sugar **15** (0.58 g, 1.45 mmol) was added and the solution was stirred at room temperature for 18 h. The solvent was evaporated and the residue was partitioned between $CHCl_3$ (3 × 30 mL) and water (30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. The crude residue was dissolved in $CHCl_3$ (5 mL) and poured onto SiO_2 column (50 g). Elution, in gradient, with MeOH (0–2%) and $CHCl_3$ afforded **16** (0.28 g, 25%) as amorphous, m.p. 75–81°C. δ_H (600 MHz, COSY, ROESY, HMQC, HMBC, $CDCl_3$): 9.17 (s, 1H, NH); 8.00-7.96 (m, 4H, Ar); 7.45–6.89 (m, 8H, Ar); 7.07 (dd, 1H, $J_{1',2'a} = 3.5$ Hz, $J_{1',2'b} = 5.5$ Hz, H-1′); 6.62, 6.53 (2d, 4H, $J = 8.2$ Hz, 4-Cl*Ph*); 5.67 (dt, $J_{3',4'} = 7.6$ Hz, H-3′); 4.46 (m, 1H, H-4′); 4.80 (m, 1H, H-5″); 4.58 (m 1H, H-5′); 2.90 (ddd, 1H, H-2′a); 2.70 (dt, 1H, H-2′b); 2.35 (s, 3H, Me). δ_C($CDCl_3$): 165.0, 165,2 (C = O); 142.1 (C-2); 133.2–129.0 (Ar); 126.3 (C-5); 120.0 (C-4); 114.4, 112.5 (Ph); 86.2 (C-1′); 81.0 (C-4′); 73.8 (C-3′); 64.0 (C-5′); 35.9 (C-2′); 10.9 (C_4-*Me*). Anal. calc. for $C_{35}H_{28}Cl_3SN_3O_5$ (709.1): C, 59.29; H, 3.98; N, 5.93. Found: C, 59.01; H, 5.81.; N, 5.72. MS: m/z (FAB) 708/710 $(MH)^+$.

1-(4-Chlorophenylamino)-2-(2-deoxy-β-D-*erythro*pentofuranosylsulfanyl)-4-methyl-5-phenyl-1*H*-imidazole (17). A suspension of **16** (0.40 g, 0.56 mmol) in 0.2 M NaOMe/MeOH (10 mL) was stirred at room temperature for 18 h. The solution was evaporated to dryness and the residue was partitioned between ether (3 × 30 mL) and water (20 mL). The aqueous layer was evaporated to dryness and the residued was co-evaporated with EtOH (3 × 20 mL). The residue was dissolved in MeOH (2 mL) and co-evaporated with SiO_2 (2 g), and then poured on SiO_2 column (10 g). Elution, in gradient, with MeOH (0–10%) and $CHCl_3$ gave **17** (0.21 g, 85%); m.p. 179–183°C (from EtOH). δ_C (DMSO-d_6): 9.21 (s, 1H, NH); 7.39–7.31 (m, 5H, Ph); 6.73, 6.59 (2d, 4H, $J = 8.1$ Hz; 4-Cl*Ph*); 6.61 (dd, 1H, $J_{1',2'a} = 4.2$ Hz, $J_{1',2'b} = 5.5$ Hz, H-1′); 5.15 (d, 1H, $J = 1.5$ Hz, $C_{3'}$-OH); 5.00 (t, 1H, $J = 3.5$ Hz, $C_{5'}$-OH); 4.55 (m, 1H, H-4″); 4.30 (m, 1H, H-3′); 2.48–3.52 (m, 2H, H-5′, H-5″); 2.84 (m, 1H, H-2′); 2.10 (m, 1H, H-2″); 2.37 (s, 3H, C_4-Me). δ_C (DMSO-d_6): 142.0 (C-2); 134.1-130.2 (Ar); 126.5 (C-5); 120.1 (C-4); 114.9, 112.5 (Ph); 87.3 (C-1′); 90.0 (C-4′); 70.1 (C-3′); 60.3 (C-5′); 37.1 (C-2′); 11.1 (C_4-*Me*). Anal. calc. for $C_{21}H_{22}ClSN_3O_3$ (431.9):

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

C, 58.39; H, 5.13; N, 9.73. Found: C, 58.13; H, 5.02.; N, 9.58. MS: m/z (FAB) 474/456 $(MNa)^+$.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylsulfanyl)-1-(4-chlorophenylamino)-4-methyl-5-phenyl-1*H*-imidazole (18). This compound was prepared from condensation of **4** (0.50 g, 1.58 mmol) with **5** (0.87 g, 1.74 mmol), in the similar manner of preparation of **9**. Yield: 0.34 g, (28%); m.p. 85–91°C. δ_H ($CDCl_3$): 9.20 (s, 1H, NH); 7.36–7.31 (m, 5H, C_5-*Ph*); 6.37, 6.28 (2d, 2H, $J = 8.0$ Hz, 4-Cl*Ph*); Ar); 6.10 (dd, 1H, $J_{1',2'} = 5.3$ Hz, H-1′); 6.60, 6.52 (2d, 4H, $J = 8.0$ Hz, 4-Cl*Ph*); 5.56-5.49 (m, 2H, H-2′, H-3′); 4.56 (dd, 1H, $J_{4',5''} = 3.0$ Hz, H-4′); 4.32–4.18 (m, 2H, H-5′, H-5″); 2.34 (s, 3H, Me). δ_C (DMSO-d_6): 169.2, 169.0, 168.5 (C = O); 142.5 (C-2); 133.3–128.8 (Ar); 126.4 (C-5); 120.2 (C-4); 114.5, 112.7 (Ph); 86.6 (C-1′); 80.2 (C-4′); 74.4 (C-2′); 70.5 (C-3′); 62.5 (C-5′); 11.1 (C_4-*Me*). Anal. calc. for $C_{42}H_{34}ClSN_3O_7$ (760.3): C, 66.35; H, 4.51; N, 5.53. Found: C, 66.24; H, 4.43; N, 5.35. MS: m/z (FAB) 760/762 $(MH)^+$.

1-(4-Chlorophenylamino)-4-methyl-5-phenyl-2-(β-D-ribofuranosylsulfanyl)-1*H*-imidazole (19). This compound was prepared from **18** (0.50 g, 0.66 mmol), in the similar manner of preparation of **17**. Yield: 0.23 g, (78%); m.p. 178–180°C decom. δ_H ($CDCl_3$): 9.25 (s, 1H, NH); 7.41–7.38 (m, 5H, C_5-*Ph*); 7.03, 6.98 (2d, 2H, $J = 8.0$ Hz, 4-Cl*Ph*); 5.81 (2d, 1H, $J_{1',2'} = 4.9$ Hz, H-1′); 6.46, 6.38 (2d, 2H, $J = 8.0$ Hz, NH-4-Cl*Ph*); 5.84 (t, 1H $J = 5.8$ Hz, $C_{5'}$-OH); 5.33 (d, 1H, $J = 5.7$ Hz, $C_{2'}$-OH); 5.14 (d, 1H, $J = 3.7$ Hz, $C_{3'}$-OH); 4.15 (dd, 1H, $J_{2',3'} = 5.0$ Hz, H-2′); 4.12–3.39 (m, 4H, H-3′-H-5″); 2.33 (s, 3H, Me). δ_C (DMSO-d_6): 146.3 (C-2); 134.0–129.5 (Ar); 126,8 (C-5); 120.8 (C-4); 115.2, 113.2 (Ph); 89.6 (C-1′); 84.4 (C-4′); 74.8 (C-2′); 70.9 (C-3′); 62.9 (C-5′); 11.2 (C_4-*Me*). Anal. calc. for $C_{21}H_{22}ClSN_3O_4$(447.9): C, 56.31; H, 4.95; N, 9.38. Found: C, 56.16; H, 4.87; N, 9.16. MS: m/z (FAB) 471/473 $(MNa)^+$.

REFERENCES

1. Gilman, A.G.; Murad, F. Parathyroid and Calcitonn. In *The Pharmacological Basis of Therapeutics*, 5th Ed., Goodman, L.S., Gilman, A., Eds.; Macmillan Publishing Co., Inc.: New York, N. Y. 1970, Chapter 67, p. 1501.
2. Haynes, Jr. R.C.; Murad, F. Antithyroid Drugs and Other Thyroid Inhibitors. In *Goodman and Gilman's The Pharmaceutical Basis of Therapeutics*; Gilman, A.G., Goodman, L.S., Rall, T.W., Murad, F., Eds.; Macmillan: New York, 1985, 1401.
3. Hill, T.D. 2′,2-Alkanediylbis(thio)bis(imidazoles). U.S. Patent 4,188,397 (Chem. Abstr., 1980, 92, 215444h), 1979.
4. Cherkofsky, S.C. Sharpe, T.R. Antiinflammatory imidazole compounds. Ger. Patent 2,805,166 (Chem. Abstr., 1979, 90, 23051q), 1978.
5. Kruse, L.I.; Kaiser, C.; DeWolf, W.E.; Hilbert, L.E.; Ross, S.T.; Flaim, K.E.; Sawyer, J.L. Some benzyl-substituted imidazoles, triazoles, pyridinethiones, and structural relatives as multisubstrate inhibitors of dopamine β-hydroxylase. 4. Structure-activity relationships at the copper binding site. J. Med. Chem. **1990**, *33*, 781.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

6. Kruse, L.I.; Kaiser, C.; DeWolf, W.E.; Frazee, J.S.; Ross, S.T.; Wawro, J.; Wise, M.; Flaim, K.E.; Sawyer, J.L.; Erickson, R.W.; Ezekiel, M.; Ohlstein, E.H.; Berkowitz, B.A. Multisubstrate inhibitors of dopamine β-hydroxylase. 2. Structure-activity relationships at the phenylamine binding site. J. Med. Chem. **1987**, *30*, 486–494.
7. Maeda, S.; Suzuki, M.; Iwasaki, T.; Masumoto, K.; Iwasawa, I. Synthesis of 2-mercapto-4-substituted imidazole derivatives with antiinflammatory properties. Chem. Pharm. Bull. **1984**, *32*, 2536–2541.
8. Salaski, E.J. Synthesis of imidazobenzapinthiones: A new series of HIV-1 reverse transcriptase inhibitors. Tetrahedron Lett. **1995**, *36*, 1387–1390.
9. Perigaud, C.; Gosselin, G.; Imbach, J.L. Nucleoside analogues as chemotherapeutic agents: A review. Nucleosides & Nucleotides **1992**, *11*, 903–945.
10. Gosselin, G.; Imbach, J.L.; Townsend, L.B.; Panzica, R.P. The synthesis of imidazole 2-thione nucleosides. J. Heterocyclic Chem. **1979**, *16*, 1185–1191.
11. Schantl, J.C.; Lagoja, I.M. Direct synthetic approach to *N*-substituted 1-amino-2,3-dihydro-1 *H*-imidazole-2-thiones. Heterocycles **1997**, *45*, 691–700.
12. Birkofer, L.; Ritter, A. New methoden der präparativen organischen chemie IV. Angew. Chem. **1965**, *77*, 414–426.
13. Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. Nucleosides synthesis with trimethylsilyl triflate and perchlorate as catalysts. Chem. Ber. **1981**, *114*, 1234–1255.
14. a) Bothner, A.A.; Stephensen, R.L.; Lee, J.; Warren, C.D.; Jeanloz, R.W. Structure determination of the tetrasaccharide: Transient nuclear overhauser effects in the rotating frame. J. Am. Chem. Soc. **1984**, *106*, 811–813; b) Bax, A.; Davies, D.G. Practical aspects of two-dimensional transverse NOE spectroscopy. J. Mag. Reson. **1985**, *63*, 207–213; c) Geiesinger, C.; Ernst, R.R. Frequency offset effects and their elimination in NMR rotating-frame cross relaxation spectroscopy. J. Mag. Reson. **1987**, *75*, 261-271.
15. Paintini, U.; Sørensen, O.W.; Ernst, R.R. Multi quantum filters for elucidating NMR coupling networks. J. Am. Chem. Soc. **1982**, *104*, 6800–6801.
16. a) Hurd, R.E.; John, B.K. Gradient-enhanced proton-detected heteronuclear multiple-quantum coherence spectroscopy. J. Mag. Reson. **1991**, *91*, 648–658; b) Vuister, G.W.; Boelns, R.; Kaptein, R.; Hurd, R.E.; John, B.; Van Zijil, P.C.M. Gradient-enhanced HMQC and HSQC spectroscopy. Applications to ^{15}N-Labeled Mnt Repressor. J. Am. Chem. Soc. **1991**, *113*, 9688–9690.
17. Willker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. Gradient selection in inverse heteronuclear correlation spectroscopy. Mag. Res. Chem. **1993**, *31*, 287–292.
18. Halasa, A.F.; Smith, G.E.P. Study of the Michael and Mannich reactions with benzothiazole-2-thiol. J. Org. Chem. **1971**, *36*, 636–641.

Received August 27, 2002
Accepted January 27, 2003