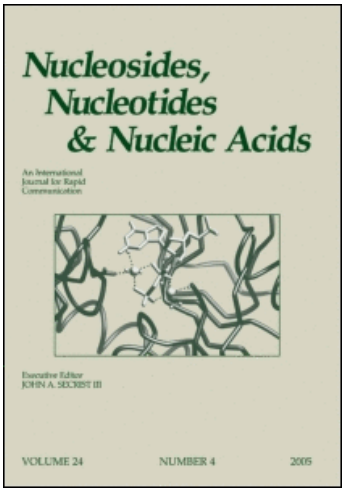

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Revisit to the Reaction of *O*-Phenylene Diamine with Thiosemicarbazide to Give Benzimidazole-2-Thione Rather than Benzotriazine-2-Thione and its Glycosylation

El Sayed H. El Ashry[ab]; Aly A. Aly[c]; Mohamed R. Aouad[bd]; Mohammed R. Amer[a]
[a] International Center for Chemical and Biological Science, H. E. J. Research Institute of Chemistry, University of Karachi, Karachi, Pakistan [b] Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt [c] Chemistry Department, Faculty of Science, Benha University, Benha, Egypt [d] Chemistry Department, Faculty of Science, University of Science and Technology, Oran, Oran, Algeria

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REVISIT TO THE REACTION OF *O*-PHENYLENE DIAMINE WITH THIOSEMICARBAZIDE TO GIVE BENZIMIDAZOLE-2-THIONE RATHER THAN BENZOTRIAZINE-2-THIONE AND ITS GLYCOSYLATION

El Sayed H. El Ashry,[1,2] Aly A. Aly,[3] Mohamed R. Aouad,[2,4] and Mohammed R. Amer[1]

[1]*International Center for Chemical and Biological Science, H. E. J. Research Institute of Chemistry, University of Karachi, Karachi, Pakistan*
[2]*Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt*
[3]*Chemistry Department, Faculty of Science, Benha University, Benha, Egypt*
[4]*Chemistry Department, Faculty of Science, University of Science and Technology, Oran, Oran, Algeria*

□ *Reaction of* o*-phenylene diamine with thiosemicarbazide did not give benzotriazine-2-thione* ***2*** *as reported, although the product was found to be benzimidazole-2-thione* ***3****. Glycosylation of* ***3*** *with acetobromo sugars* ***4a-4b*** *gave the respective thioglycosides* ***7a-7d*** *in addition to minor products of the nucleosides* ***8a*** *and* ***8b****, in the case of the gluco- and galacto-analogs, respectively. The regioselectivity of glycosylation reaction has been investigated.*

Keywords Imidazole-thione; benzotriazine-thione; thioglycosides; glycosyl-imidazole; thiosemicarbazide

INTRODUCTION

Nature is a driving force toward the discovery of many reactions; thus, many existing carbohydrates in biological systems or, more generally, in nature are found as polysaccharides or glycoconjugates, in which monosaccharides are linked via *O*- or *N*-glycosidic bonds.[1–4] The formation of such bonds is a challenge in modern synthetic organic chemistry and, therefore, there is still a strong demand for developing a simple and stereoselective glycosylation procedure. One of these methods is the use of thioglycosides

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Address correspondence to El Sayed H. El Ashry, Chemistry Department, Faculty of Science, Alexandria University, Alexandria 31213, Egypt. E-mail: eelashry60@hotmail.com

as precursors, which makes them an important class of carbohydrate derivative.[3] Thioglycosides have found their importance in enzyme inhibition studies due to their chemical and enzymatic stability, which is being greater than the corresponding *O*-glycoside-analogues.[3,4] They have also been found to be useful as inducers and ligands for affinity chromatrography of carbohydrate-processing enzymes and proteins.[3]

Thioglycosides, as well, have been used as donors with excellent chemoselectivity in glycosylation processes in addition of being good acceptors.[4] Among these glycosyl donors are the glycosylthio heterocycles that can have heterocycles or be transformed into heterocycles with different functionalities in addition to their stability under variety of reaction conditions.

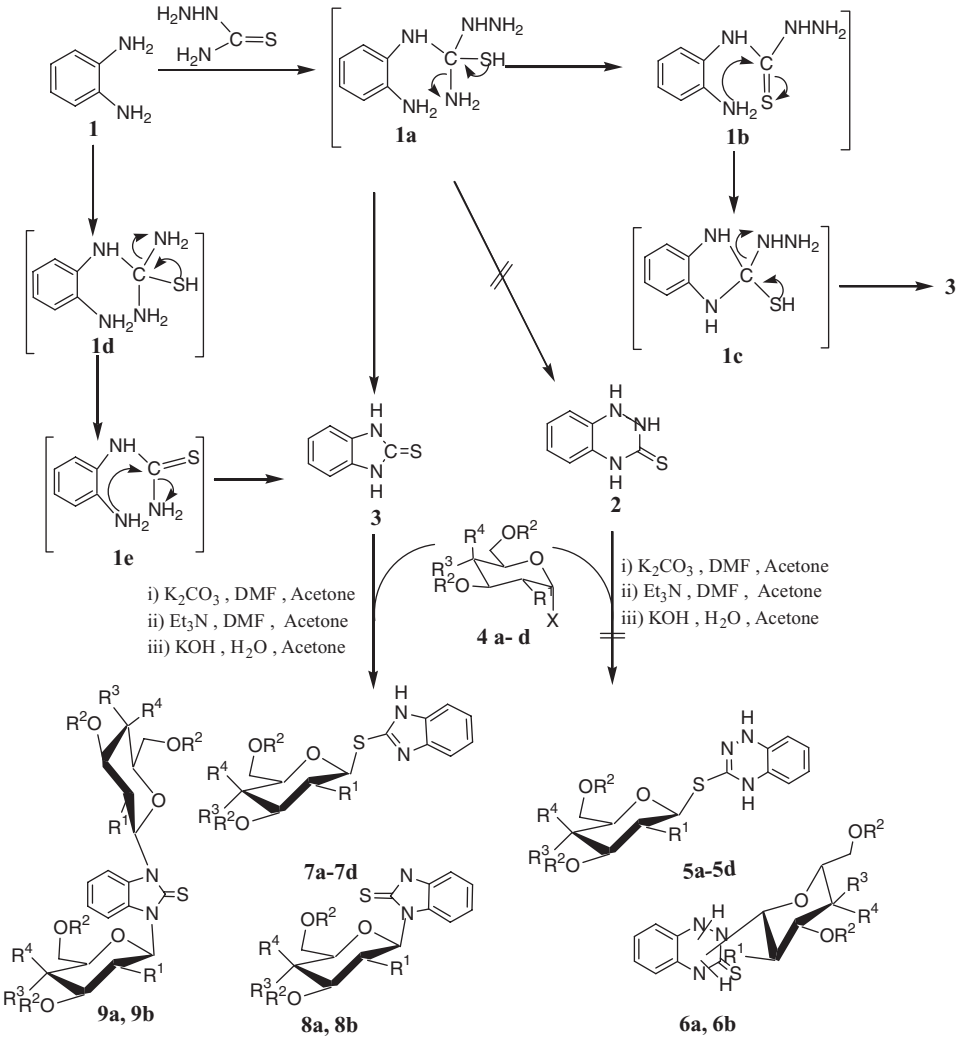
We have reviewed this topic,[3] which prompted us to synthesize the thioglycosides of 3-thioxo-1,2-dihydro-1,2,4-benzotriazine **2** as a continuation of our work on the synthesis of glycosylthio heterocycles.[5] The later heterocycle **2** was prepared in literature[6] by fusion of *o*-phenylene diamine **1** with thiosemicarbazide. It was reported in various publications[6–11] that its alkylation can be simply achieved to give the respective thioalkyl derivatives, in addition to preparing a number of its bridgehead nitrogen heterocycles. However, after the work in the present investigation, we reached to the conclusion that the structure **3** should be assigned to the product rather than **2.** Another recent report[12] reached to the same conclusion, although its details were not available to us. In the present article, we report our finding regarding the structure of **3** in addition to its glycosylation that led to the respective *S*- and *N*-glycosides.

RESULTS AND DISCUSSION

The reaction of *o*-phenylene diamine **1** with thiosemicarbazide gave a product that has the same characteristics as that reported in literature.[6] Its structure was first given as the benzotriazine **2,** but considering the contradictory report of Bakavoli,[12] it became necessary to confirm the structure of the reported heterocycle **2**. Our results led to the conclusion that the structure of the product has the imidazole thione **3** instead of **2**. Thus, it was identical with the imidazolethione **3** prepared from the reaction of **1** with thiourea,[13] or with carbon disulphide. It became interesting to find whether the product **3** was formed from **2** possibly under the severe conditions of fusion or not. Thus, the fusion of **1** with thiosemicarbazide was attempted under mild conditions and for shorter time, but in all cases the product was found to have structure **3** and not **2**. A possible mechanism of the reaction of thiosemicarbazide with **1** could be through two subsequent nucleophilic attacks of the two amino groups of **1** on the C=S which gave intermediate **1a** and then **1c** via **1b**, which lose hydrazine moiety to give **3**. Similarly the thiourea precedes through **1d** and then **1e**, which lose ammonia instead of

hydrazine to give **3.** Consequently, we can confirm that the product formed has the structure **3** and not **2** (Scheme 1).

Surprisingly, the alkylation of **2** was reported to give the corresponding *S*-alkylated derivatives although the given spectral data lack one NH proton in their ^{1}H-NMR and lack 15 amu in their mass spectra. Consequently the reported alkylated derivatives have to be revised considering their structures as imidazole derivatives.



a: X = Br , R^1 =R^3= OAc , R^2 = Ac , R^4 = H
b: X = Br , R^1 =R^4= OAc , R^2 = Ac , R^3 = H
c: X = Br , R^1 = R^3= OBz , R^2 = Bz , R^4 = H
d: X = Cl , R^1 = NHAc , R^2 = Ac , R^3 = OAc , R^4 = H

SCHEME 1 Reaction of o-phenylene diamin with thiosemicarbazine and glycosylation of the product.

When **3** was reacted with the acetylated glucosyl bromide **4a** and acetylated galactosyl bromide **4b** as well as benzoylated glucosyl bromide **4c** and 2-*N*-acetyl-amino glucosyl chloride **4d**, the resulting products were found to be dependent on the used acid scavengers. In presence of K_2CO_3 in acetone, the respective thioglycosides **7a** and **7b**, but not **5a** and **5b**, were obtained and were accompanied by minor products **8a** and **8b**, but not **6a** and **6b**. On the other hand, **7c** and **7d** were not accompanied by minor products. When triethylamine or potassium hydroxide were used as the scavengers, the products were only of the thioglycoside type **7a–7d.** The ^{1}H-NMR and ^{13}C-NMR spectra in each of the resulting thioglycosides confirmed the presence of one glycosyl moiety in addition to four aromatic protons, seven carbons, and only one NH proton instead of the expected two NH protons in case of benzothiazine-derived thio glycosides. Moreover, their mass spectra indicated that their molecular weights were less than the expected molecular weights for **5a–5d**, **6a**, and **6b**; all the spectra are missing 15 amu. These data could agree with the structures **7a**[14]**–7d**, 8a,[14] and **8b**, respectively. Their structures were unequivocally confirmed by the glycosylation of **3** with **4a-4d** under the same reaction conditions. The reaction of **3** with acetobromoglucose was studied[14] by using sodium ethoxide and gave **7a**, whereas in the presence of mercuric chloride, the respective N-glucoside **8a** and *N,N*-bisglucoside **9a** were the products. Compounds **7a** and **8a** have the same physical constants as that isolated under our condition.

In conclusion, the reaction of *o*-phenylene diamine **1** with thiosemicarbazide gave benzimidazole-2-thione **3** rather than benzotriazine-2-thione **2.** When the benzimidazole-2-thione **3** was reacted with aceto halo sugars **4a-d**, it gave thioglycosides having one sugar moiety mainly on the sulfur and a minor product on the *N* depending on the acid scavenger. Thus, using triethylamine in DMF/acetone or KOH in water/acetone gave only a single product whereas using K_2CO_3 in DMF/acetone afforded an additional product in case of the glucosyl and galactosyl halides. It should be noted that benzimidazole conjugates have potential biological activity.[15]

EXPERIMENTAL

Melting points were determined with a melt-temp apparatus (SMP10) in open capillaries and are uncorrected. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} with detection by ultraviolet (UV) light absorption. ^{1}H NMR spectra were recorded on avane Bruker NMR spectrometer at 300 or 500 MHz, whereas the ^{13}C NMR was done on the same instrument at 75 or 100 MHz, respectively, with TMS as internal standard. Mass spectra were recorded on a Finnigan (MAT312) and Jeol (JMS.600H), HRMS were recorded with Thermo Finnegan (MAT 95XP). Solvents were purified by simple distillation.

Reaction of o-Phenylene Diamine with Thiosemicarbazide

A mixture *o*-phenylene diamine (5.4 g, 0.05 mol) and thiosemicarbazide (4.6 g, 0.05 mol) was heated in an oil bath at 180–190°C till melting and then solidified after 1h. The reaction mixture was cooled and recrystallized from ethanol to give brown powder, Yield 69%, m.p. 299°C (lit.[6] m.p. 290°C). Similarly Reaction of *o*-phenylene diamine with thiourea gave the same product, m.p. 299°C, (lit.[13] m.p. 303–304°C).

Reaction of *o*-Phenylene Diamine with Carbon Disulphide

o-Phenylene diamine (22 g, 0.02 mol) was added to a solution of potassium hydroxide (12 g, 0.022 mol) in water (30 mL) ethanol (200 mL) and carbon disulfide (17 g, 0.022 mol). The mixture was heated under reflux for 3 hours and then charcoal was added followed by filtration. The stirred filtrate was heated to 60–70°C, then warm water (70°C, 250 mL), and acetic acid (45 mL) were added. After cooling, the benzimidazole-2-thione **3** was obtained as white crystals, yield 57%. It was recrystallized from ethanol, m.p. 299°C (lit.[13] 303–304°C), TLC, $\mathbf{R}_f$ 0.57 (6:4, n-hexane: EtOAc); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H = 7.07–7.14 (m, 4H, Ar), 12.48 (s, 2H, 2 NH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 168.1(C = S), 132.2 (C-8, C-9), 122.2 (C-5, C-6), 109.3 (C-4, C-7); MS-EI: *m/z* (%) = 150 (100) [M^+], 123 (13.7), 106 (13.4), 91(10.6); HMRS-EI (M^+), *m/z*: Calcd for $C_7H_6N_2S$: 150.0236. Found 150.0252.

Glycosylation of Benzimidazole-2-thione 3

General Procedure

Method A. A mixture of compound **3** (0.15 g, 1.0 mmol) and potassium carbonate (0.2 g, 1.5 mmol) in dry acetone (25 mL) and DMF (10 drops) was stirred for 1 hour, then the glycosyl halide **4a-4d** (1.2 mmol) was added. Stirring was continued for overnight and the mixture was filtered and washed with acetone. Acetone was evaporated under reduced pressure and the product was subjected to column chromatography to give **7** and **8**.

Method B. A mixture of compound **3** (0.15 g, 1.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) in dry acetone (25 mL) and DMF (10 drops) was processed as above.

Method C. A mixture of compound **3** (1.5 g, 0.01 mol) and potassium hydroxide (0.56 g, 0.01 mol) in water (15 mL) was treated with the glycosyl halide **4 a–d** (0.012 mol) in acetone (30 mL). The reaction mixture was stirred at room temperature until the reaction was judged complete by TLC using n-hexane/ethyl acetate (6:4). Then, it was processed as above.

2- (2′, 3′, 4′, 6′-Tetra-*O*-acetyl-β-D-glucopyranosyl-thio) benzimidazole (7a)

It was eluted with n-hexane:EtOAc (6:4) to give colorless crystals; TLC, $\mathbf{R}_f$ 0.42 (1:1 n-hexane/EtOAc); Yield method a) 58%, b) 59%, c) 66%, m.p. 142°C (lit.[14] m.p. 144–146°C); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 1.89, 1.94, 1.97, 1.98 (4s, 12H, 4 CH_3CO), 3.98–4.19 (m, 3H, H-5′, H-6′, H-6″), 4.96–5.08 (2dd, 2H, $J_{2'\ 1'}$ = 10.2 Hz, $J_{4',3'}$ = 10.2 Hz, H-2′, H-4′), 5.42 (t, 1H, $J_{3',2'} = J_{3',4'}$ = 10.2 Hz, H-3′), 5.78 (d, 1H, $J_{1',2'}$ = 10.2 Hz, H-1′), 7.15- 7.17 (m, 2H, ArH), 7.41 (d, 1H, J = 7.0 Hz, ArH), 7.56 (d, 1H, J = 7.0 Hz, ArH), 12.62 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6): δ_C = 171.2, 169.9, 169.6, 169.4 (4 CH_3CO), 143.6 (C-S), 123.5, 122.7 (C-9, C-8), 119.4 (C-5), 110.7 (C-6), 95.5 (C-7), 90.1 (C-4), 83.4 (C-1′), 76.5 (C-5′), 73.5 (3′), 70.0 (2′), 67.9 (C-4′), 61.7 (C-6′), 20.8, 20.7, 20.6, 20.5 (4 CH_3CO); MS-EI: m/z (%) = 480 (7.0) [M^+], 331 (46), 169 (100), 150 (74.9), 109 (94.4); HRMS-EI (M^+): m/z: Calcd for $C_{21}H_{24}N_2O_9S$: 480.1203. Found 480.1205.

2-(2′, 3′, 4′, 6′-Tetra-*O*-acetyl-β-D-galactopyranosyl-thio) benzimidazole (7b)

It was eluted with n-hexane:EtOAc (6:4) to give colorless crystals, TLC, $\mathbf{R}_f$ 0.30 (1:1 n-hexane/EtOAc); Yield method a) 56%, b) 58%, c) 62%, m.p. 106°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.96, 2.05, 2.08, 2.09 (4s, 12H, 4 CH_3CO), 3.98- 4.02 (m, 1H, H-5′), 4.12 (dd, 1H, $J_{6',5'}$ = 4.6 Hz, $J_{6',6''}$ = 11.7 Hz, H-6′), 4.31 (dd, 1H, $J_{6'',5'}$ = 4.6 Hz, $J_{6'',6'}$ = 11.7 Hz, H-6″), 5.07 (dd, 1H, $J_{2',1'} = J_{2',3'}$ = 9.9 Hz, H-2′), 5.09 (d, 1H, $J_{4',3'}$ = 4.6 Hz, H-4′), 5.30 (dd, 1H, $J_{3',2'}$ = 9.9 Hz, $J_{3',4'}$ = 4.6 Hz, H-3′), 5.45 (d, 1H, $J_{1',2'}$ = 9.9 Hz, H-1′), 7.22- 7.27 (m, 2H, ArH), 7.39–7.42 (m, 1H, ArH), 7.71–7.74 (m, 1H, ArH), 9.97 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6): δ_C = 170.7, 169.9, 169.8, 169.7(4 CH_3CO), 144.5 (C-S), 143.4, 134.8 (C-8, C-9), 123.4, 122.5 (C-5, C-6), 11 9.3 (C-7), 110.4 (C-4), 84.0 (C-1′), 75.4 (C-5′), 71.5 (C-3′), 67.4 (C-2′), 67.2 (C-4′), 62.0 (C-6′), 20.7, 20.6, 20.5, 20.4 (4 CH_3CO); MS (EI): m/z (%) = 480 (13.3) [M^+], 361 (26.3), 331 (100), 169 (100), 150 (92.4); HRMS-EI (M^+): m/z: Calcd for $C_{21}H_{24}N_2O_9S$: 480.1203; Found 480.1205.

2-(2′, 3′, 4′, 6′-Tetra-*O*-benzoyl-β-D-glucopyranosyl-thio) benzimidazole (7c)

It was eluted with n-hexane:EtOAc (7:3) to give white crystals, TLC, $\mathbf{R}_f$ 0.60 (6:4 n-hexane/EtOAc); Yield method a) 59%, b) 68%, c) 60%, m.p. 100°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H = 4.43–4.52 (m, 2 H, H-5′, H-6′), 4.65–4.68 (m, 1H, H-6″), 5.68–5.72 (dd, 2H, $J_{4',\ 3'}$ = 9.3 Hz, $J_{2',\ 1'}$ = 10.1 Hz, H-2′, H-4′), 6.16 (t, 1H, $J_{\ 3',\ 2'} = J_{\ 3',\ 4'}$ = 9.3 Hz, H-3′), 6.26 (d, 1H,

$J_{1',2'}$ = 10.1 Hz, H-1′), 7.16–7.18 (m, 2H, ArH), 7.34–7.42 (m, 8 H, ArH), 7.45 (t, 2H, J = 7.7 Hz, ArH), 7.52–7.60 (m, 2H, ArH), 7.71(d, 2H, J = 7.4 Hz, ArH), 7.82 (dd, 8H, J = 7.6 Hz, J = 7.5 Hz, ArH), 12.63 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6): δ_C = 165.3, 164.9, 164.7, 164.6 (4 Ph*C*O), 145.4 (C-S), 143.5, 135.2 (C-8, C-9), 133.8, 133.7, 133.6, 133.3, 129.21, 129.2, 129.1, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3 (Ar), 122.2, 121.5(C-5, C-6), 117.9 (C-7), 110.8 (C-4), 82.6 (C-1′), 75.0 (C-5′), 73.9 (C-3′), 70.9 (C-2′), 68.9 (C-4′), 62.7 (C-6′); MS (EI): m/z (%) = 728 (0.4) [M^+], 606 (13), 334 (90.4), 321(47.3), 150 (47.4), 105 (100); HRMS-ESI: m/z Calcd for $C_{41}H_{33}N_2O_9S$ (M^++H) 729.1907, Found 729.1901.

2-(2′-Acetamido-2′-deoxy-3′, 4′, 6′-tri-*O*-acetyl-β-D-glucopyranosyl-thio)benzimidazole (7d)

It was eluted with n-hexane:EtOAc (2:8) to give white crystals, TLC, $\mathbf{R}_f$ 0.50 (9.5:0.5 CH_2Cl_2/MeOH); Yield method a) 71%, b) 53%, c) 51%, m.p. 185°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 1.78, 1.85, 1.93, 1.97 (4s, 12H, 3 CH_3CO, NHCOCH_3), 3.93–3.97 (m, 2H, H-5′, H-6′), 4.10 (ddd, 1H, $J_{2',1'}$ = 10.7 Hz, $J_{2',3'}$ = 9.6 Hz, $J_{2',NH}$ = 9.8 Hz, H-2′), 4.18 (dd, 1H, $J_{6',5'}$ = 4.9 Hz, $J_{6',6'}$ = 12.4 Hz, H-6′′), 4.90 (t, 1H, $J_{4',3'} = J_{4',5'}$ = 9.6 Hz, H-4′), 5.19 (t, 1H, $J_{3',2'} = J_{3',4'}$ = 9.6 Hz, H-3′), 5.66 (d, 1H, $J_{1',2'}$ = 10.7 Hz, H-1′), 7.10–7.15 (m, 2H, ArH), 7.46 (d, 2H, ArH), 8.24 (d, 1H, $J_{NH,2'}$ = 9.8 Hz, D_2O exchangeable, NHAc), 12.52 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6): δ_C = 169.9, 169.5, 169.4, 169.3 (4 CH_3CO), 146.4 (C-S), 142.0, 134.5 (C-8, C-9), 122.2, 121.9 (C-5, C-6), 117.7 (C-7), 110.6 (C-4), 83.6 (C-1′), 74.9 (C-5′), 73.2 C-3′), 68.4 (C-4′), 61.7 (C-6′), 52.0 (C-2′), 22.6, 20.4, 20.3, 20.3 (4 CH_3CO); MS-FAB: m/z = 479 [M^++1], HRMS-ESI: m/z Calcd for $C_{21}H_{26}N_3O_8S$ (M^++H) 480.1441, Found 480.1435.

1-*N*-(2′, 3′, 4′, 6′-Tetra-*O*-acetyl-β-D-glucopyranosyl) benzimidazole-2-thione (8a)

It was eluted with n-hexane:EtOAc (6:4) to give colorless crystals, TLC, $\mathbf{R}_f$ 0.73 (6:4 n-hexane/EtOAc); Yield method a) 35%, m.p. 213–215°C (lit.[13] m.p. 214–217°C); MS-FAB: m/z = 481 [M^++1]. HRMS-ESIMS: m/z Calcd for $C_{21}H_{25}N_2O_9S$ (M^++H) 481.1281, Found 481.1275.

1-*N*-(2′, 3′, 4′, 6′-Tetra-*O*-acetyl-β-D-galactopyranosyl) benzimidazole-2-thione (8b)

It was eluted with n-hexane:EtOAc (6:4) to give colorless crystals, TLC, $\mathbf{R}_f$ 0.64 (6:4, n-hexane/EtOAc); Yield method a) 30%, m.p. 110°C; MS-FAB:

m/z = 481[M^++1]. HRMS-ESIMS: m/z Calcd for $C_{21}H_{25}N_2O_9S$ (M^++H) 481.1281, Found 481.1275.

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