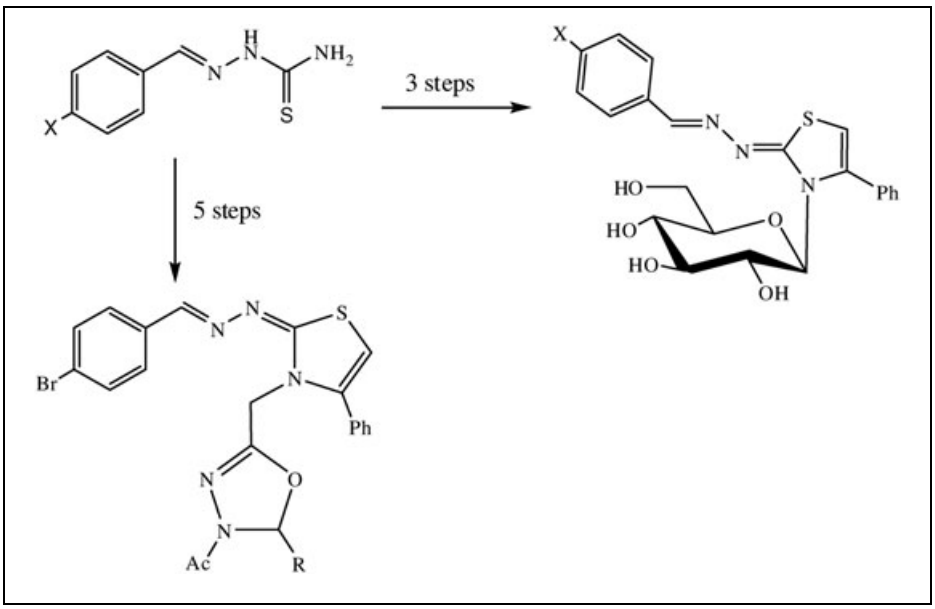
Synthesis and Antimicrobial Activity of New Thiazole Derivatives and Their Glucoside and Acyclic Nucleoside Analogs

Omar M. Ali,[a] Wael A. El-Sayed,[b] Heba A. El-Sayed,[a] and Adel A.-H. Abdel-Rahman[a]*

[a]Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt
[b]Department of Photochemistry, National Research Centre, Cairo, Egypt
*E-mail: adelnassar63@hotmail.com

Received December 14, 2010
DOI 10.1002/jhet.900
Published online 29 October 2012 in Wiley Online Library (wileyonlinelibrary.com).



New thiazole derivatives were synthesized. The *N*-substituted acyclic nucleoside analogs and the substituted glucosides were also prepared. The synthesized compounds were tested for their antimicrobial activity against *Candida albicans*, *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis*. The obtained results indicated that most of the tested compounds exhibited low to high moderate activities whereas few compounds were found to exhibit little or no activity against the tested microorganisms.

J. Hetercycl Chem., **49**, 1026 (2012).

INTRODUCTION

Thiadiazoles exhibit a broad spectrum of biological effectiveness such as antiparkinsonism [1], hypoglycaemic [2], antihistaminic [3], anticancer [4], anti-inflammatory [5], antiasthmatic [6], and antihypertensive [7] activities. Further, there has been considerable interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals and exhibiting a broad spectrum of biological activities [8–10]. Numerous structurally diverse metabolites incorporating thiazole structural moiety, having antitumor, antifungal, and enzyme-inhibiting activities, have been produced by Cyanobacteria [11]. *Lyngbya majuscula* is a source of many thiazole peptides such as pseudodysidenin, nordysidenin, and barbamide [12]. Natural and synthetic thiazole chemistries as well as their biological applications have been extensively reviewed [13]. Thiazoles with carbohydrate structure core have been recognized as potent and increasingly important antimetabolite agents [14–16]. Thiopeptides, called the amythiamicins, were isolated from a strain of *Amycolatopsis* sp. [17]. Promothiocins A and B, isolated from a *Streptomyces* sp. SF2741, with thiazole structural core, are potent antibiotics, which inhibit protein synthesis in bacteria [18,19]. Cystothiazoles, bisthiazole, and β-methoxyacrylate structures are thiazole alkaloids isolated from myxobacterium *Cystobacter fusus* strain AJ-13278 [20,21]. Gunieamides A and B, thiazole-containing depsipeptides, were isolated from a Papua Guinea collection of the marine cyanobacterium *L. majuscule* [22]. Novel lead compounds containing thiazolyl moiety attached to pyrazolyl ring systems [23,24] have been shown to possess pronounced dual anti-inflammatory and antimicrobial activities. Furthermore, nucleoside analogs are structurally, metabolically, and pharmacodynamically related agents that have diverse

biological actions and therapeutic effects including antiviral [25,26] and antitumor [27–29] activities. The above facts and our interest [26,30–34] in the attachment of carbohydrate moieties to newly synthesized heterocycles searching for new biologically active leads promoted us to synthesize new substituted thiazoles glucosides and their acyclic analogous and evaluate their antimicrobial activity.

RESULTS AND DISCUSSION

2-(4-Bromobenzylidene)hydrazinecarbothioamide (**1**) was prepared from substituted benzaldehyde and thiosemicarbazide following the reported procedure [35]. The thioamide derivative **1** was allowed to react with phenacyl bromide in ethanol at reflux temperature to afford the thiazole derivative **2** in 81% yield. The structure of **2** was confirmed by ^{1}H-NMR and mass spectra, which agreed with the assigned structure. Thus, the ^{1}H-NMR spectrum showed two singlets at δ 6.93 and 8.34 for H-5-thiazole and C*H*═N, respectively, in addition to the aromatic proton at δ 7.29–7.87 ppm. Its mass spectrum revealed the presence of the molecular ion peak at *m/z* 357/359 ([M^+], 80%) corresponding to the molecular formula $C_{16}H_{12}BrN_3S$, which was in agreement with the assigned structure. Reaction of **2** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**) in acetone and potassium hydroxide afforded the *N*-glucoside derivative **4** in 80% yield. Its ^{1}H-NMR spectrum revealed the presence of the *O*-acetyl-methyl groups at δ 1.86–2.02 ppm, the signals of the sugar protons at δ 3.39–4.22 ppm, and the anomeric proton as a doublet at δ 5.74 ppm. Deacetylation of **4** using methanolic ammonia solution afforded the deprotected derivative **5**. Its IR spectrum showed the characteristic absorption band at ν 3428 cm^{-1} corresponding to the hydroxyl groups (Scheme 1).

Alkylation of **2** with ethylchloroacetate in alkaline medium afforded the corresponding ethyl ester derivative **6** in 89% yield. Treatment of **6** with hydrazine hydrate in ethanol at reflux temperature gave the corresponding hydrazide **7** in 86% yield. The structures of **6** and **7** were confirmed by IR, ^{1}H-NMR, and mass spectra, which agreed with the assigned structures. When the hydrazide **7** was allowed to react with D-mannose, D-galactose, and D-xylose in an aqueous ethanolic solution with a catalytic amount of acetic acid, the corresponding sugar {2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole} acetylhydrazones **8a–c** were obtained in 74–79% yields. The structures of these compounds were confirmed by analytical and spectral data. The IR spectra of **8a–c** showed the presence of characteristic absorption bands corresponding to the hydroxy groups in the region ν 3311–3410 cm^{-1}. The ^{1}H-NMR spectra showed signals of the sugar chain protons at δ 3.25–4.12 ppm, the C-1 methine proton as a doublet in the range δ 7.44–7.53 ppm in addition to the aromatic protons in the region δ 7.20–7.41 ppm, whereas the two singlets in the range δ 6.81–6.87 and 8.30–8.40 ppm are corresponding to H-5-thiazole and C*H*═N, respectively. Treatment of the sugar hydrazones **8a–c** with acetic anhydride in pyridine at room temperature gave the corresponding per-*O*-acetyl derivatives **9a–c** in 78–83% yields. The IR spectra of **9a–c** showed characteristic absorption bands at ν 1739–1750 cm^{-1} corresponding to the carbonyl ester groups, while the ^{1}H-NMR spectra of **9a**,**b** showed the signals of the *O*-acetyl-methyl protons at δ 1.95–2.16 ppm. The rest of the sugar protons appeared in the range δ 4.03–5.50 ppm. The reaction of sugar arylhydrazones with boiling acetic anhydride is well known to give either the corresponding per-*O,N*-acetyl derivatives or the respective per-*O,N*-acetyl-1,3,4-oxadiazolin derivatives [25], [36–38]. However, reaction of the sugar hydrazones **8a–c** with acetic anhydride at 100°C gave the sugar-substituted 1,3,4-oxadiazoline derivatives **10a–c** in 75–78% yields. The IR spectra of **10a–c** showed characteristic absorption bands at 1618–1683 cm^{-1} and 1735–1748 cm^{-1} corresponding to the carbonyl amide and the carbonyl ester groups, respectively, indicating the presence of an *N*-acetyl group in addition to the *O*-acetyl groups. The ^{1}H-NMR spectra of **10a**,**b** showed signals of the *O*- and *N*-acetyl-methyl protons as singlets in the range δ 1.95–2.39 ppm. The rest of the sugar chain protons appeared in the range δ 3.98–5.37 ppm in addition to the aromatic protons as multiplets in the region δ 7.25–7.39 ppm (Scheme 2).

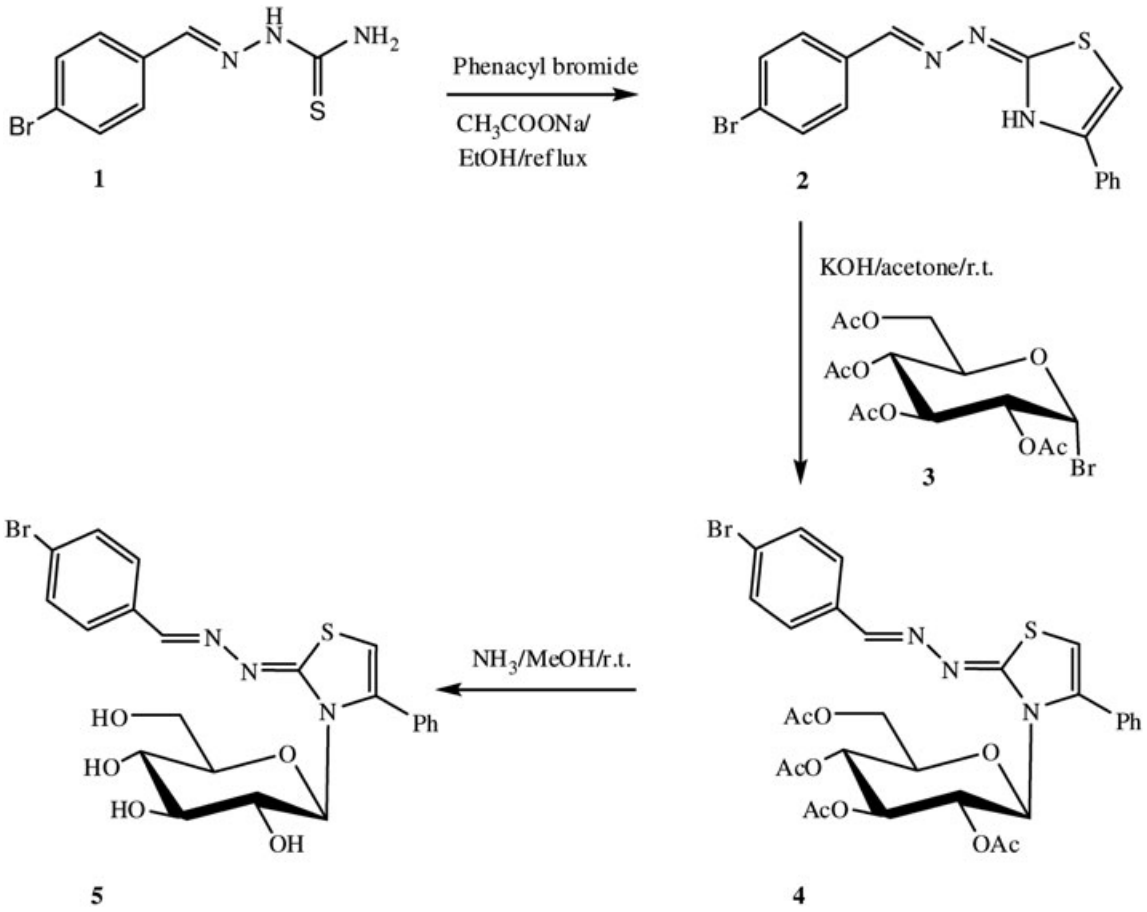
ANTIMICROBIAL ACTIVITY

The synthesized compounds were evaluated for their antimicrobial activity against *Escherichia coli* NRRL B-210 (Gram-negative bacteria), *Bacillus subtilis* NRRL B-543 and *Staphylococcus aureus* (Gram-positive bacteria), and *Candida albicans* NRRL Y-477 (Fungi). The minimal inhibitory concentrations (MICs) of the tested compounds were determined by the dilution method [39,40].

The MIC values of the tested compounds are presented in Table 1 and were found to be in accordance with the results obtained in the primary screening.

The result revealed that compounds showed varying degrees of inhibition against the tested microorganisms. In general, compounds **7**, **8a**, and **8c** displayed the highest activity against *Bacillus subtilis* followed by compounds **5**, **8b**, **9b**, **9c**, and **10b**. Compounds **8a** and **8b** displayed the highest inhibition activity against *Staphylococcus aureus* with MIC value of 75 μg/mL, whereas compounds **5**, **8a**, **8c**, **9c**, and **10a** revealed the highest activity against *Escherichia coli*. The antifungal activity of compounds **5**, **8b**, and **10a–c** showed the highest activity against *Candida albicans*.

Scheme 1. Synthesis of 3-(β-D-glucopyranosyl-2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole.



In conclusion, new 2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole and its *N*-substituted acyclic nucleoside analogs as well as the substituted glucosides were prepared and studied for their antimicrobial activity. Substitution at the free *N*-3 in the thiazole moiety afforded compounds with increased inhibtion activities with respect to the four microorganisms.

EXPERIMENTAL

Melting points were determined with a Kofler block apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 1720 FTIR spectrometer for KBr disc. NMR spectra were recorded on a varian Gemini 200 NMR Spectrometer at 300 MHz for ^{1}H-NMR with TMS as a standard. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F 245. Elemental analyses were performed at the Microanalytical data centre at Faculty of science, Cairo University, Egypt.

2-[(4-Bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole (2). A mixture of 2-(4-bromobenzylidene)hydrazinecarbothioamide (**1**) [35] (0.51 g, 2 mmol) in absolute ethanol (20 mL), phenacyl bromide (0.40 g, 2 mmol), and anhydrous sodium acetate (0.20 g, 2 mmol) was heated under reflux for 3h. The solvent was concentrated under reduced pressure and left to cool for overnight. The separated solid product was filtered off and recrystallized from ethanol to afford **2** 0.57 g, (81%), m.p. 210–212°C.

^{1}H-NMR (DMSO-d_6) δ 6.93 (s, 1H, H-5-thiazole), 7.29–7.87 (m, 10H, Ar-H, NH), 8.34 (s, 1H, C*H*═N); MS *m/z* (%) = 357/359 (M^+, 80). Anal. Calcd. for $C_{16}H_{12}BrN_3S$ (358.26): C, 53.64; H, 3.38; N, 11.73. Found: C, 53.55; H, 3.25; N, 11.53.

3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-2-[(4-bromobenzylid-ene)hydrazono]-4-phenyl-2,3-dihydrothiazole (4). 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**; 4.11 g, 10 mmol) in acetone (15 mL) was added to a solution of **2** (3.58 g, 10 mmol) in an aqueous potassium hydroxide [(0.57 g, 10 mmol) in distilled water (1 mL)]. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure at 40°C, and the residue was washed with distilled water to remove the formed potassium bromide. The product was dried and recrystallized from ethanol to give **4** 5.50 g, (80%), m.p. 128–130°C; IR (KBr): ν 1592 (C═N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.86, 2.02 (2s, 12H, 4*x*CH_3), 4.07–4.19 (m, 2H, H-6′), 5.04 (m, 1H, H-4′), 5.07 (m, 1H, H-5′), 5.20 (m, 1H, H-2′), 5.52 (m, 1H, H-3′), 5.74 (d, 1H, *J* = 9.8 Hz, H-1′), 6.90 (s, 1H, H-5-thiazole), 7.17–8.43 (m, 9H, Ar-H), 8.31(s, 1H, C*H*═CN); MS *m/z* (%) = 687/689 (M^+, 33). Anal. Calcd. for $C_{30}H_{30}BrN_3O_9S$ (688.53): C, 52.33; H, 4.39; N, 6.10. Found: C, 52.17; H, 4.22; N, 5.93.

Scheme 2. Synthesis of sugar acetylhydrazones and acyclic *C*-nucleosides.

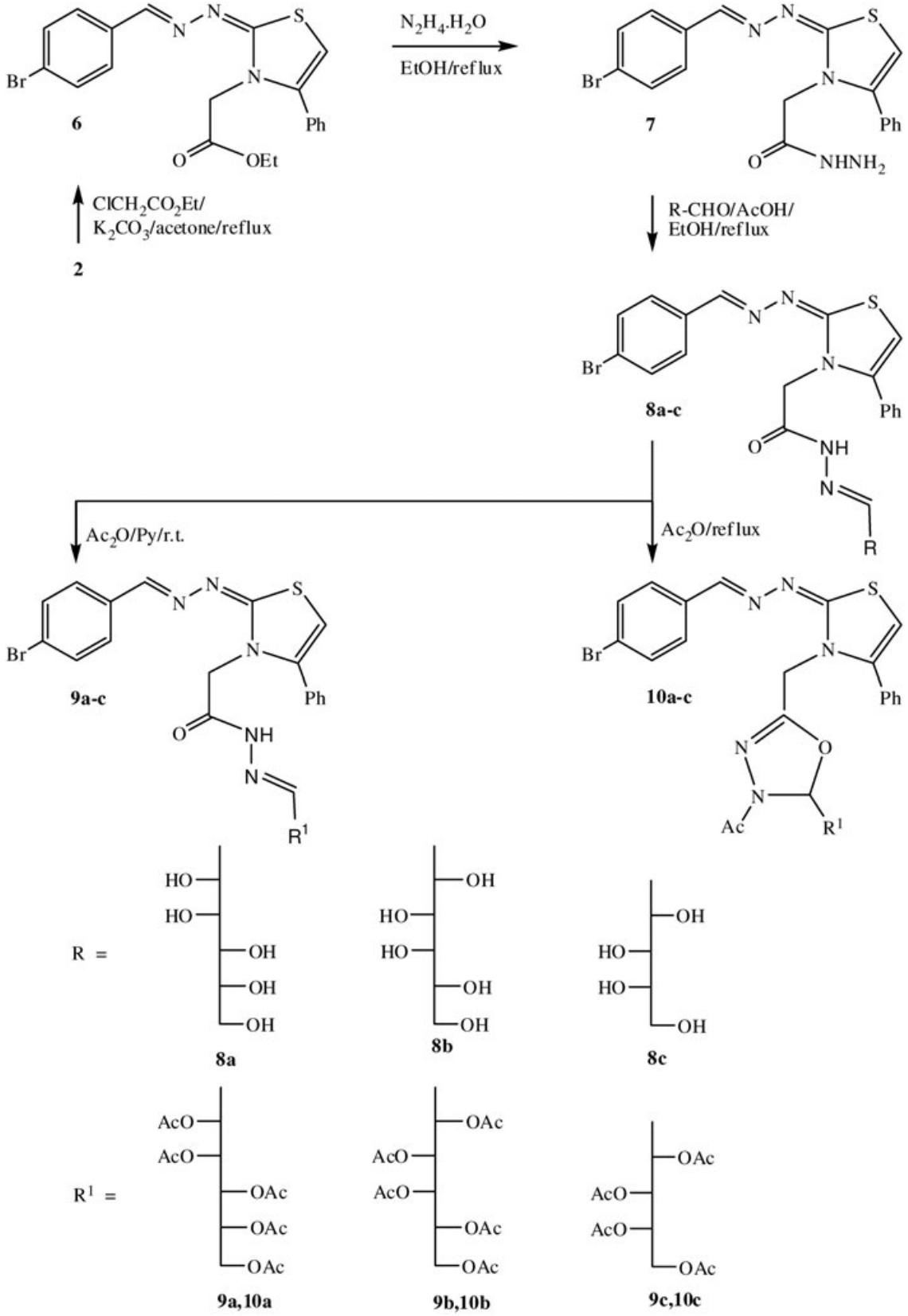


Table 1

Minimum inhibitory concentrations (MIC-μg/mL) of the title compounds negative control DMSO, no activity.

Compound	*Bacillus subtilis*	*Escherichia coli*	*Staphylococcus aureus*	*Candida albicans*
2	225	100	500	225
4	500	225	475	50
5	100	75	100	75
6	250	500	225	125
7	75	225	125	100
8a	100	75	75	100
8b	50	100	75	75
8c	75	75	100	100
9a	250	250	100	225
9b	100	250	100	150
9c	100	75	100	125
10a	75	75	75	75
10b	75	100	225	75
10c	75	225	250	75
Penicillin	31	45	34	40

3-(β-D-Glucopyranosyl-2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole (5). A solution of **4** (6.88 g, 10 mmol) in methanolic ammonia solution was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in absolute ethanol (10 mL) and left overnight to give the deprotected product **5** as a brownish solid 3.95 g, (76%), m.p. 152–154°C, IR (KBr): ν 1605 (C═N), 3428 cm^{-1} (OH), ^{1}H-NMR (DMSO-d_6) δ 3.25–3.60 (m, 2H, H-6′), 4.30–4.90 (m, 8H, H-2′, H-3′, H-4′, H-5′, 4*x*OH), 6.20 (d, 1H, *J* = 8.0 Hz, H-1′), 6.83 (s, H-5 thiazole), 7.15–7.78 (m, 9H, Ar-H), 8.28 (s, 1H, C*H*═N); MS *m/z* (%) = 519/521 (M^+, 25). Anal. Calcd. for $C_{22}H_{22}BrN_3O_5S$ (520.40): C, 50.78; H, 4.26; N, 8.07. Found: C, 50.66; H, 4.17; N, 7.93.

3-Carbethoxymethyl-2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole (6). Ethyl chloroacetate (1.22 g, 10 mmol) was added to a solution of **2** (3.58 g, 10 mmol) in anhydrous acetone (20 mL) and anhydrous potassium carbonate (0.99 g, 10 mmol). The reaction mixture was heated under reflux for 12 h, poured on crushed-ice, filtered-off, and recrystallized from ethanol to give **6** 3.95 g, (89%), m.p. 190–192°C; IR (KBr): ν 1605 (C═N), 1736 (C═O), 3423 cm^{-1} (NH); MS *m/z* (%) = 443/445 (M^+, 20). Anal. Calcd. for $C_{20}H_{18}BrN_3O_2S$ (444.34): C, 54.06; H, 4.08; N, 9.46. Found: C, 53.90; H, 3.89; N, 9.29.

3-Acetylhydrazine-2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole (7). A solution of the ethyl ester derivative **6** (4.44 g, 10 mmol) in ethanol (20 mL) and hydrazine hydrate (10 mL) was refluxed for 4 h. The solvent was removed under reduced pressure, and the remaining precipitate was collected, dried, and recrystallized from ethanol to afford **7** 3.70 g, (86%), m.p. 258–260°C, IR (KBr): ν 1753 (C═O), 3427 cm^{-1} (NH); ^{1}H-NMR (DMSO-d_6) δ: 2.51 (s, 2H, NH_2), 4.63 (s, 2H, CH_2), 6.88 (s, 1H, H-5-thiazole), 7.16-7.47 (m, 9H, Ar-H), 8.40 (bs, 2H, C*H*═N, NH); MS *m/z* (%) = 429/431 (M^+, 17). Anal. Calcd. for $C_{18}H_{16}BrN_5OS$ (430.32): C, 50.24; H, 3.75; N, 16.27. Found: C, 50.11; H, 3.60; N, 16.09.

Sugar {2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole}acetylhydrazones 8a–c. Hydrazide derivative **7** (4.30 g, 10 mmol) in ethanol (10 mL) was added to a well-stirred solution of the respective monosaccharides (10 mmol) in water (2 mL) and glacial acetic acid (1 mL). The mixture was heated under reflux, and the resulting solution was concentrated under reduced pressure and left to cool. The formed precipitate was filtered off, washed with water and cold ethanol, dried, and recrystallized from ethanol to afford the corresponding sugar hydrazones **8a–c** in 74–79 yields.

D-(+)-Mannose {2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole}acetylhydrazone (8a). White powder 4.67 g, (79%), m.p. 235–237°C, ^{1}H-NMR (DMSO-d_6) δ 3.27–4.09 (m, 6H, H-2′, H-3′, H-4′, H-5′, H-6′), 4.50 (bs, 3H, 3*x*OH), 4.64 (s, 2H, CH_2), 4.78 (bs, 2H, 2*x*OH), 6.82 (s, 1H, H-5-thiazole), 7.20–7.38 (m, 9H, Ar-H), 7.48 (d, 1H, *J* = 2.5 Hz, H-1′), 8.30 (s, 1H, C*H*═N), 11.08 (bs, 1H, NH); MS *m/z* (%) = 591/593 (M^+, 6). Anal. Calcd. for $C_{24}H_{26}BrN_5O_6S$ (592.46): C, 48.65; H, 4.42; N, 11.82. Found: C, 48.50; H, 4.22; N, 11.67.

D-(+)-Galactose {2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole}acetylhydrazone (8b). White powder 4.38 g, (74%), m.p. 210–212°C; IR (KBr): ν 1678 (C═N), 3070 (NH), 3311 cm^{-1} (OH); ^{1}H-NMR (DMSO-d_6) δ 3.25–3.90 (m, 5H, H-3′, H-4′, H-5′, H-6′), 4.12 (m, 1H, H-2′), 4.40 (bs, 1H, OH), 4.60 (bs, 2H, 2*x*OH), 4.65 (s, 2H, CH_2), 5.00 (bs, 2H, 2*x*OH), 6.87 (s, 1H, H-5-thiazole), 7.28–7.41 (m, 9H, Ar-H), 7.44 (d, 1H, *J* = 2.5 Hz, H-1′), 8.33 (s, 1H, C*H*═N), 11.60 (bs, 1H, NH); MS *m/z* (%) = 591/593 (M^+, 8). Anal. Calcd. for $C_{24}H_{26}BrN_5O_6S$ (592.46): C, 48.65; H, 4.42; N, 11.82. Found: C, 48.48; H, 4.27; N, 11.60.

D-(+)-Xylose {2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole}acetylhydrazone (8c). White powder 4.21 g, (75%), m.p. 240–242°C, IR (KBr): ν 1678 (C═N), 3304 (NH), 3410 cm^{-1} (OH); ^{1}H-NMR (DMSO-d_6) δ 3.25–3.57 (m, 5H, H-2′, H-3′, H-4′, H-5′), 4.50 (bs, 2H, 2*x*OH), 4.62 (s, 2H, CH_2), 5.20 (bs, 2H, 2*x*OH), 6.81 (s, 1H, H-5-thiazole), 7.23–7.37 (m, 9H, Ar-H), 7.53 (d, 1H, *J* = 2.5 Hz, H-1′), 8.40 (s, 1H, C*H*═N), 11.50 (bs, 1H, NH); MS *m/z* (%) = 561/563 (M^+, 11). Anal. Calcd. for $C_{23}H_{24}BrN_5O_5S$ (562.44): C, 49.12; H, 4.30; N, 12.45. Found: C, 49.00; H, 4.07; N, 12.19.

Sugar tetra-*O*-acetyl- and penta-*O*-acetyl {2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazole}acetylhydrazones 9a–c. Acetic anhydride (1.02 g, 10 mmol) was added to a solution of sugar hydrazones **8a–c** (1 mmol) in pyridine (7 mL) with stirring at room temperature for 45 h. The resulting solution was poured onto crushed-ice and the product that separated out was filtered off, washed with a saturated solution of sodium hydrogen carbonate followed by water, and then dried. The products were recrystallized from ethanol to afford **9a–c** in 78–83% yields.

2,3,4,5,6-Penta-O-acetyl-D-(+)-mannose {2-[(4-bromobenzylidene) hydrazono]-4-phenyl-2,3-dihydrothiazole}acetylhydrazone (9a). Pale yellow gum 0.62 g, (78%); IR (KBr): ν 1596 (C═N), 1739 (C═O), 3209 cm^{-1} (NH); ^{1}H-NMR (DMSO-d_6) δ 1.95, 2.04, 2.10, 2.13, 2.15 (5s, 15H, 5*x*CH_3CO), 4.03 (m, 2H, H-6′), 4.41 (m, 1H, H-5′), 4.60 (s, 2H, CH_2), 4.69 (m, 1H, H-4′), 5.16 (m, 1H, H-3′), 5.50 (m, 1H, H-2′), 6.80 (s, 1H, H-5-thiazole), 7.28–7.41 (m, 10H, Ar-H, H-1′), 8.42 (s, 1H, C*H*═N), 11.33 (bs, 1H, NH); MS *m/z* (%) = 801/803 (M^+, 7). Anal. Calcd. for $C_{34}H_{36}BrN_5O_{11}S$ (802.65): C, 50.88; H, 4.52; N, 8.73. Found: C, 50.61; H, 4.37; N, 8.58.

2,3,4,5,6-Penta-O-acetyl-D-(+)-galactose {2-[(4-bromobenzylidene) hydrazono]-4-phenyl-2,3-dihydrothiazole}acetylhydrazone (9b). White powder 0.66 g, (83%), m.p. 125–127°C; IR (KBr) ν 1525 (C═N), 1750 (C═O), 3439 cm^{-1} (NH); ^{1}H-NMR (DMSO-d_6) δ 1.95, 2.02, 2.10, 2.13, 2.16 (5s, 15H, 5xCH_3CO), 4.09 (m, 2H, H-6′), 4.50 (m, 1H, H-5′), 4.60 (s, 2H, CH_2), 4.71 (m, 1H, H-4′), 5.18 (m, 1H, H-3′), 5.48 (m, 1H, H-2′), 6.87 (s, 1H, H-5-thiazole), 7.25–7.38 (m, 10H, Ar-H, H-1′), 8.46 (s, 1H, C*H*═N), 11.30 (bs, 1H, NH); MS *m/z* (%) = 801/803 (M^+, 9). Anal. Calcd. for $C_{34}H_{36}BrN_5O_{11}S$ (802.65): C, 50.88; H, 4.52; N, 8.73. Found: C, 50.56; H, 4.29; N, 8.47.

2,3,4,5-Tetra-O-acetyl-D-(+)-xylose {2-[(4-bromobenzylidene) hydrazono]-4-phenyl-2,3-dihydrothiazole}acetylhydrazone (9c). White powder 0.58 g, (80%), m.p. 122–124°C, IR (KBr): ν 1525 (C═N), 1750 (C═O), 3439 cm^{-1} (NH); MS *m/z* (%) = 801/803 (M^+, 12). Anal. Calcd. for $C_{31}H_{32}BrN_5O_9S$ (730.58): C, 50.96; H, 4.41; N, 9.59. Found: C, 50.49; H, 4.19; N, 9.23.

4-Acetyl-5-(*O*-acetylalditolyl)-2-{2-[(4-bromobenzylidene) hydrazono]-4-phenyl-2,3-dihydrothiazol-3-ylmethyl}-1,3,4-oxadiazolines 10a–c. A solution of sugar hydrazones **8a–c** (1 mmol) in acetic anhydride (5 mL) was heated at 100°C for 34 h. The resulting solution was poured onto crushed-ice and the product that separated out was filtered off, washed with a saturated solution of sodium hydrogen carbonate followed by water, and then dried. The products were recrystallized from ethanol to give **10a–c** in 75–79% yields.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-mannopentitolyl)-2-{2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazol-3-ylmethyl}-1,3,4-oxadiazoline (10a). Pale yellow gum 0.63 g, (75%); IR (KBr): ν 1520 (C═N), 1618, 1747 (C═O); ^{1}H-NMR (DMSO-d_6): δ 1.95, 1.99, 2.03, 2.10, 2.13, 2.38 (6s, 18H, 6xCH_3CO), 3.82 (s, 2H, CH_2), 3.99, 4.11 (2m, 2H, H-5′), 4.93 (m, 1H, H-4′), 5.14 (m, 1H, H-3′), 5.24 (m, 1H, H-2′), 5.35 (dd, 1H, *J* = 3.2, 6.2 Hz, H-1′), 5.98 (d, 1H, *J* = 6.2 Hz, H-5-oxadiazoline), 6.84 (s, 1H, H-5-thiazole), 7.25–7.35 (m, 9H, Ar-H), 8.30 (s, 1H, C*H*═N); MS *m/z* (%) = 843/845 (M^+, 8).

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl)-2-{2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazol-3-ylmethyl}-1,3,4-oxadiazoline (10b). Pale yellow gum 0.65 g, (77%); IR (KBr): ν 1683 (C═N), 1735 cm^{-1} (C═O); ^{1}H-NMR (DMSO-d_6): δ 1.95, 1.96, 2.01, 2.10, 2.19, 2.39 (6s, 18H, 6xCH_3CO), 3.87 (s, 2H, CH_2), 3.98, 4.05 (2m, 2H, H-5′), 4.96 (m, 1H, H-4′), 5.16 (m, 1H, H-3′), 5.20 (m, 1H, H-2′), 5.37 (dd, 1H, *J* = 3.2, 6.2 Hz, H-1′), 5.95 (d, 1H, *J* = 6.2 Hz, H-5-oxadiazoline), 6.82 (s, 1H, H-5-thiazole), 7.25–7.39 (m, 9H, Ar-H), 8.39 (s, 1H, C*H*═N); MS *m/z* (%) = 843/845 (M^+, 11).

4-Acetyl-5-(1,2,3,4-tetra-O-acetyl-D-xylotetritolyl)-2-{2-[(4-bromobenzylidene)hydrazono]-4-phenyl-2,3-dihydrothiazol-3-ylmethyl}-1,3,4-oxadiazoline (10c). Pale yellow gum (0.60 g, 78%); IR (KBr): ν 1618 cm^{-1} (C═N), 1738 cm^{-1} (C═O); ^{1}H-NMR (DMSO-d_6): δ 1.95, 1.98, 2.04, 2.12, 2.37 (5s, 18H, 6xCH_3CO), 3.89 (s, 2H, CH_2), 3.97, 4.09 (2m, 2H, H-4′), 5.14 (m, 1H, H-3′), 5.21 (m, 1H, H-2′), 5.38 (dd, 1H, *J* = 3.2, 6.2 Hz, H-1′), 5.90 (d, 1H, *J* = 6.2 Hz, H-5-oxadiazoline), 6.83 (s, 1H, H-5-thiazole), 7.25–7.39 (m, 9H, Ar-H), 8.41 (s, 1H, C*H*═N); MS *m/z* (%) = 771/773 (M^+, 18).

REFERENCES AND NOTES

[1] Azam, F.; Ibn-Rajab, I. A.; Alruiad, A. A. Pharmazie 2009, 64, 771.

[2] Avetisyan, A. K.; Ovsepyan, T. R.; Stepanyan, N. O.; Sapondzhyan, L. G. Pharm Chem J 1981, 15, 69.

[3] Lalezari, I.; Shafiee, A.; Badaly, A.; Salimi, M. M.; Khoyi, M. A.; Abtahi, F.; Zarrindast, M. R. J Pharm Sci 2006, 64, 1250.

[4] Parkanyi, C.; Yuan, H. L.; Stromberg, B. H. E.; Evenzahav, A. J Heterocycl Chem 1992, 29, 749.

[5] Boschelli, D. H.; Connor, D. T; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. J Med Chem 1993, 36, 1802.

[6] Bhattacharya, P.; Leonard, J. T.; Roy, K. Bioorg Med Chem 2005, 15, 1159.

[7] Vio, L.; Mamolo, M. G.; Laneve, A. Farmaco 1989, 44, 165.

[8] Vigorita, M. G.; Ottana, R.; Monforte, F.; Maccari, R.; Trovato, A.; Monforte, M. T.; Taviano, M. F. Bioorg Med Chem Lett 2001, 11, 2791.

[9] Chande, M. S.; Suryanarayan, V. J Chem Res 2005, 345.

[10] Kavitha, C. V.; Basappa, S.; Swamy, S. N.; Mantelingu, K.; Doreswamy, S.; Sridhar, M. A.; Prasad, J. S.; Rangappa, K. S. Bioorg Med Chem 2006, 14, 2290.

[11] Konig, G. M.; Kehraus, S.; Seibert, S. F.; Abdel-Lateff, A.; Muller, D. Chem Bio Chem 2006, 7, 229.

[12] Orjala, J.; Gerwick, W. H. J Nat Prod 1996, 59, 427.

[13] Chen, B.; Heal, W. In Comprehensive Heterocyclic Chemistry III; Katrizky, R., Ed.; Elsevier, Inc., Oxford, 2008; Chapter 4.06, pp 635–754.

[14] Hallick, S. K.; Martin, A. R.; Lingard, R. G. J Med Chem 1971, 14, 528.

[15] Kumar, R.; Lown, J. W. Eur J Org Chem 2003, 24, 4842.

[16] Shapiro, A.; Hutner, S. H.; Bacchi, L. C. J. J Eukaryot Microbiol 2007, 28, 370.

[17] Shimanaka, K.; Kinoshita, N; Iinuma, H; Hamada, M.; Takeuchi, T. J Antibiot 1994, 47, 668.

[18] Yun, B. S.; Hidaka, T.; Furihata, K.; Seto, H. J Antibiot 1994, 47, 510.

[19] Moody, C. J.; Bagley, M. C. Chem Commun 1998, 2049.

[20] Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. J Antibiot 1998, 51, 275.

[21] Suzuki, Y.; Ojika, M.; Sakagami, Y.; Fudou, R.; Yamanaka, S. Tetrahedron 1998, 54, 11399.

[22] Tan, L. T.; Sitachitta, N.; Gerwick, W. H. J Nat Prod 2003, 66, 764.

[23] Bekhit, A. A.; Fahmy, H. T. Y.; Rostom, Sh. A. F.; Baraka, A. M. Eur J Med Chem 2003, 38, 27.

[24] Bekhit, A. A.; Fahmy, H. T. Y. Arch Pharm Pharm Med Chem 2003, 336, 111.

[25] Abdel-Aal, M. T.; El-Sayed, W. A; El-Ashry, E. S. H. Arch Pharm Chem Life Sci 2006, 339, 356.

[26] El-Sayed, W. A.; Abdel-Rahman, A. A.-H.; Ramiz, M. M. M. Zeitschrift für Naturforschung C 2009, 64, 323.

[27] Chu, M. Y. W.; Naguib, F. N. M.; Iltzsch, M. H.; El Kouni, M. H.; Chu, S. H.; Cha, S.; Calabresi, P. Cancer Res 1984, 44, 1852.

[28] Park, K. S.; El Kouni, M. H.; Krenitsky, T. A.; Chu, S. H.; Cha, S. Biochem Pharmacol 1986, 35, 3853.

[29] Lin, T.-S.; Liu, M.-C. J Med Chem 1985, 28, 971.

[30] El-Sayed, W. A.; Ramiz, M. M. M.; Abdel-Rahman, A. A.-H. Monatsh Chem 2008, 139, 1499.

[31] El-Sayed, W. A.; Fathi, N. M.; Gad, W. A.; El-Ashry, E. S. H. J Carbohydr Chem 2008, 27, 357.

[32] El-Sayed, W. A.; Nassar, I. F.; Abdel-Rahman, A. A. H. Monatsh Chem 2009, 140, 365.

[33] El-Sayed, W. A.; Rashad, A. E.; Awad, S. M.; Ali, M. M. Nucleoside Nucleotides 2009, 28, 261.

[34] El-Sayed, W. A.; El-Essawy, F. A.; Ali, O. M.; Barsis, A. M.; Abdel-Rahman, A. A.-H. Monats Chem 2010, 141, 1021.

[35] Faraghaly, A. A.; Bekhit, A. A.; Park, J. Y. Arch Pharm Pharm Med Chem 2000, 333, 53.

[36] Abdel-Aal, M. T.; El-Sayed, W. A.; El-Kosy, S. M.; El-Ashry, E. S. H. Pharm Chem Life Sci 2008, 341, 307.

[37] Somogyi, L. Carbohydr Res 1977, 54, C14.

[38] Somogyi, L. Carbohydr Res 1978, 64, 289.

[39] Jorgensen, J. H.; Jurnide, J. D.; Washington, J. A. In Manual of Clinical Microbiology, 7th ed.; Muarry, P. R.; Baron, E. J.; Yolken, R. C., Eds, American Society for Microbiology: Washington, DC, USA, 1999; pp 1526–1543.

[40] Janssen, A. M.; Scheffer, J. J.; Svendsen, A. B. Planta Med 1987, 53, 395.