Synthesis and antimicrobial evaluation of thioglucosides and acyclic C-nucleosides of 2-methylbenzimidazole

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ABSTRACT

Some thioglucosides and acyclic C-nucleosides of 2-methyl-1H-benzimidazole were newly synthesized. The structures of the products were confirmed by different spectral analyses and some of the newly synthesized compounds were evaluated for their potential antimicrobial activity against Gram+ve and Gram–ve bacteria as well as some fungi which show good activity.

Keywords: S-Glycosides, O-glycosides, sugar hydrazones, benzimidazoles, antimicrobial activity.

INTRODUCTION

Benzimidazole and its derivatives have received much attention because of their biological activity and commercial application. They are present in many naturally occurring products and various drugs. Some of these compounds have antibacterial, antifungal, antiviral, anti-inflammatory, antihypertensive, arteriosclerosis and anti-HIV activities [1-8]. Some classes of compounds which have a benzimidazole nucleus were reported as a new group of antitumor agents [9], some other types of biological activity have been reported in compounds containing benzimidazole ring [10, 11]. Such biological activities include antifungal [12], antitubercular [13] antulcer [14], antihypertensive [15], antiviral [16], antihistaminic [17], anticancer [18], antioxidant [19], cholesterol absorption inhibition and enzyme inhibition activity [20]. 2-methylbenzimidazole and its derivatives have been used as antimicrobial [21], Anthelmintic agents [22], antihypertension [23], antiinflammatory and analgesic agents [24]. In view of the above facts and as continuation of our program of identification of new candidates that may be valuable in design and synthesis of new active leads [25-31] we report in the present work the synthesis and antimicrobial activity of new thioglucosides and acyclic C-nucleosides of 2-methylbenzimidazole derivatives.

MATERIALS AND METHODS

Synthetic methods, analytical and spectral data
Melt 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 NMR Spectrometer at 300 MHz for \textsuperscript{1}H NMR with TMS as a standard. Mass spectra were recorded on Shimadzu Qp-2010
plus. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F245. Elemental analyses were performed at the Microanalytical data centre at Faculty of science, Cairo University, Egypt.

**Ethyl 2-(2-methyl-1H-benzimidazol-1-yl)acetate (2)**

To a well stirred solution of 2-methyl-1H-benzimidazole (1) [32] (1.32 g, 10 mmol) and dry potassium carbonate (1.38 g, 10 mmol) in acetone (15 ml) was added ethyl chloroacetate (1.22 g, 10 mmol). The reaction mixture was stirred at room temperature for 25 h and then poured on ice-cold water. The precipitated solid was filtered, washed with water and recrystallized from ethanol to give 2 as white crystals (1.31 g, 60%). mp 248-250 °C; IR (KBr, cm⁻¹): 1735 (C=O), 1619 (C=N), 1H-NMR (300 MHz, CDCl₃): δ 1.22 (t, J = 5.2 Hz, 3H, CH₂(CH₃)), 2.49 (s, 3H, CH₃), 3.49 (q, J = 5.2 Hz, 2H, CH₂(CH₃)), 5.04 (s, 2H, CH₂), 7.34-7.98 (m, 4H, Ar-H) ppm. Anal. Calcd. For C₁₂H₁₄N₂O₂: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.00; H, 6.50; N, 12.88.

**2-(2-Methyl-1H-benzimidazol-1-yl)acetohydrazide (3)**

A solution of 2 (2.18 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) in ethanol (20 ml) was heated under reflux for 5 h. The solution was cooled and the resulting precipitate was filtered off and recrystallized from ethanol to afford 3 as pale yellow crystals, mp 190-192 °C (1.5 g, 68.8%); IR (KBr, cm⁻¹): 3449 (NH₂), 3121 (NH), 1635 (C=O), 1600 (C=N). 1H-NMR (300 MHz, DMSO-d₆): δ 2.49 (s, 3H, CH₃), 5.00 (s, 2H, CH₂), 5.41 (bs, 2H, NH₂), 7.29-7.44 (m, 2H, Ar-H), 7.69-7.77 (m, 2H, Ar-H), 8.40 (brs, 1H, NH) ppm. Anal. Calcd. For C₁₀H₁₂N₂O: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.50; H, 5.99; N, 27.20.

**5-{[2-Methyl-1H-benzimidazol-1-yl]methyl}-1,3,4-oxadiazole-2(3H)-thione (4)**

A solution of 3 (1.99 g, 69%) in acetone (20 ml), phenylisothiocyanate (1.3 g, 10 mmol) and dry potassium carbonate (1.5 g, 68.8%) was added, the mixture was heated at reflux temperature for 4 h. The solution was cooled and the resulting precipitate was filtered off and recrystallized from ethanol to afford 4 as yellow crystals, mp 242-243 °C (1.3 g, 69%); IR (KBr, cm⁻¹): 3223 (NH), 1620 (C=N). 1H-NMR (300 MHz, DMSO-d₆): δ 2.49 (s, 3H, CH₃), 5.04 (s, 2H, CH₂), 7.40-7.50 (m, 2H, Ar-H), 7.70-7.80 (m, 2H, Ar-H), 12.14 (s, 1H, NH) ppm. Anal. Calcd. For C₁₀H₁₀N₂O: C, 53.64; H, 4.09; N, 22.75. Found: C, 53.50; H, 4.00; N, 22.35.

**2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylthio)-5-(2-methyl-1H-benzimidazol-1-yl)-1,3,4-oxadiazole (5)**

A solution of 4 (1.23 g, 5 mmol) in aqueous potassium hydroxide [(0.5 g, 5 mmol) in distilled water (16 ml)] was added a solution of 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl bromide (5) (5 mmol) in acetone (20 ml). The reaction mixture was stirred at room temperature for 3 h. 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 DMF to give 5 as a brown solid (1.99 g, 69%), mp 140-141 °C; IR (KBr, cm⁻¹): 3413 (OH), 1614 (C=N). 1H-NMR (300 MHz, DMSO-d₆): δ 1.90, 1.95, 2.00, 2.17 (4s, 12H, 4C-CH₃), 4.02 (m, 1H, H-5'), 4.10 (dd, J = 10.5 Hz, 2.8 Hz, 1H, H-6'), 4.14 (dd, J = 10.5, 3.2 Hz, 1H, H-6'′), 4.90 (t, J = 9.3 Hz, 1H, H-7'), 5.04 (s, 2H, CH₂), 5.18 (br, J = 9.6 Hz, 9.3 Hz, 1H, H-3'), 5.34 (t, J = 9.6 Hz, 1H, H-2'), 5.50 (d, J = 9.8 Hz, 1H, H-1'), 7.39-7.44 (m, 2H, Ar-H), 7.69-7.73 (m, 2H, Ar-H) ppm. Anal. Calcd. For C₂₃H₂₂N₂O₄S: C, 52.08; H, 4.89; N, 9.72. Found: C, 52.00; H, 5.00; N, 9.70.

**2-(β-D-Glucopyranosylthio)-5-{[2-methyl-1H-benzimidazol-1-yl]methyl}-1,3,4-oxadiazole (6)**

A solution of 5 (0.576 g, 1 mmol) in methanol and ammonia solution (5:5) 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 over night. The formed precipitate were filtered off and dried well to afford 7 (0.55 g, 95%); mp 192-193 °C; IR (KBr, cm⁻¹): 3413 (OH), 1614 (C=N). 1H-NMR (300 MHz, DMSO-d₆): δ 2.49 (s, 3H, CH₃), 3.41 (m, 2H, H-6′′′′′), 3.45-3.47 (m, 1H, H-5'′′), 3.71-3.77 (m, 2H, H-3′′′′′), 4.15 (t, J = 9.4 Hz, 1H, H-2′′′), 4.70 (brs, 1H, OH), 4.83 (brs, 1H, OH), 5.04 (s, 2H, CH₂), 5.15 (brs, 1H, OH), 5.24 (bs, 1H, OH), 5.5 (d, J = 9.8 Hz, 1H, H-1'′′), 7.29-7.73 (m, 2H, Ar-H), 7.69-7.76 (m, 2H, Ar-H) ppm. Anal. Calcd. For C₁₇H₁₇N₂O₆S: C, 49.99 ; H, 4.94; N, 13.72. Found: C, 50.10; H, 5.00; N, 13.50.

**2-[2-(2-Methyl-1H-benzimidazol-1-yl)acetetyl]-N-phenylhydrazine carbothioamide (8)**

To a solution of the acid hydrazide 3 (2.4 g, 10 mmol) in ethanol (30 ml), phenylisothiocyanate (1.3 g, 10 mmol) was added, the mixture was heated at reflux temperature for 4 h. The solution was cooled and the resulting precipitate was filtered off followed by recrystallization from ethanol to afford 8 as yellow crystals, mp 242-243 °C (2.59 g, 76.4%); IR (KBr, cm⁻¹): 3228 (NH), 1602 (C=N). Anal. Calcd. For C₁₇H₁₇N₂O₅S: C, 60.16; H, 5.05; N, 20.63. Found: C, 60.10; H, 5.00; N, 20.50.
5-[(2-Methyl-1H-benimidazol-1-yl)acetyl]-methyl]-N-phenyl-1,3,4-thiadiazol-2-amine (9)
A solution of 8 (3.39 g, 10 mmol) in concentrated sulfuric acid (1 ml) was stirred for 1.5 h at 0 °C and the stirring was completed at this temperature until the yellow colour of the solution was changed to orange and a solid product was formed which was separated by filtration and washing with cold water and recrystallized from ethanol to give 9 as an orange solid, mp 235-236 °C (2.48 g, 77.2%); IR (KBr, cm⁻¹): 3193 (NH), 1635 (C=N). EI-MS: m/z 321 [M⁺]. Anal. Calcd. For C₁₁H₁₂N₄S; C, 63.53; H, 4.70; N, 21.79. Found: C, 63.50; H, 4.73; N, 21.80.

2-(Methylbenzimidazol-1-yl)-N-(4-oxo-2-(phenylimino)thiazolidin-3-yl)-acetamide (10)
To a solution of 8 (3.39 g, 10 mmol) in ethanol (20 ml) was added bromoacetic acid (1.39 g, 10 mmol) and heated under refluxed for 14 h. The solution was allowed to cool and the solvent was evaporated at 40 °C and the residue was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure at 40 °C, the solid that formed was filtered off and recrystallized from methanol to afford 10 as a brown solid; mp 257-258 °C (2.95 g, 78%); IR (KBr, cm⁻¹): 3260 (NH), 1670 (C=O), 1605 (C=N). EI-MS: m/z 379 [M⁺]. Anal. Calcd. For C₁₃H₁₂N₄O₂S; C, 60.14; H, 4.52; N, 18.46. Found: C, 60.15; H, 4.53; N, 18.40.

3-[(2-Methyl-1H-benzimidazol-1-yl)-methyl]-4-phenyl-1H-1,2,4-triazole 5(4H)-thione (11)
A solution of 8 (3.39 g, 10 mmol) in 10% NaOH solution (20 ml) was refluxed for 12 h and allowed to cool to room temperature, then was acidified with dil. HCl solution, the solid that formed was filtered off and recrystallized with ethanol to afford 11 as a white solid, (2.99 g, 93%), mp 164-165 °C IR (KBr, cm⁻¹): 3236 (NH), 1603 (C=N); EI-MS: m/z 321 [M⁺]. Anal. Calcd. For C₁₀H₁₀N₂O; C, 68.04; H, 6.31; N, 20.88. Found: C, 68.00; H, 6.35; N, 20.85.

2-(2,3,4,6-Tetra-O-acetyl-D-Glucopyranosylthio)-5-[(2-Methyl-1H-benzimidazol-1-yl)-methyl]-4-phenyl-1H-1,2,4-triazole (12)
A solution of 11 (1.60 g, 5 mmol) in aqueous potassium hydroxide [0.28 g, 5 mmol in distilled water (16 ml)] was added a solution of 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl bromide (5) (5 mmol) in acetone (20 ml). The reaction mixture was stirred at room temperature for 3 h. 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 afford 12 as a white solid (2.5 g, 76%), mp 225-226 °C IR (KBr, cm⁻¹): 1747 (C=O), 1602 (C=N). ¹H NMR (CDCl₃, 300 MHz): δ 1.92, 1.95, 1.98, 2.0 (4s, 12H,4CH₂CO), 2.49 (s, 3H, CH₃), 3.55 (m, 1H, H-5'), 4.00 (dd, J = 9.7 Hz, 2.5 Hz, 1H, H-6'), 4.14 (dd, J = 9.7, 3.2 Hz, 1H, H-6'), 4.80 (t, J = 9.4 Hz, 1H, H-4'), 5.00 (dd, J = 9.6 Hz, 3.4 Hz, 1H, H-3'), 5.04 (s, 2H, CH₂), 5.2 (t, J = 9.6 Hz, 1H, H-2'), 5.70 (d, J = 10 Hz, 1H, H-1'), 7.27-7.30 (m, 2H, Ar-H), 7.56-7.63 (m, 2H, Ar-H) ppm. Anal. Calcd. For C₂₀H₂₀N₂O₂S; C, 57.13; H, 5.10; N, 10.75. Found: C, 57.0; H, 5.10; N, 10.70.

2-(β-D-Glucopyranosylthio)-5-[(2-Methyl-1H-benzimidazol-1-yl)-methyl]-4-phenyl-1H-1,2,4-triazole (13)
A solution of 12 (0.653 g, 1 mmol) in methanol and ammonia solution (5:5) 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 over night. The precipitated precipitates were filtered off and dried well to afford 13 as a yellow solid (0.50 g, 95 %), mp 192-193 °C; IR (KBr, cm⁻¹): 3399 (OH), 1605 (C=N). ¹H NMR (DMSO-d₆, 300 MHz): δ 2.49 (s, 3H, CH₃), 3.25-3.30 (m, 2H, H-6′,6″), 3.35-3.38 (m, 1H, H-5′), 3.70-3.74 (m, 2H, H-3′,H-4′), 4.20 (t, J = 9.6 Hz, 1H, H-2′), 4.50 (b, 1H, OH), 4.83 (b, 1H, OH), 5.04 (s, 2H, CH₂), 5.10-5.15 (m, 1H, OH), 5.22 (b, 1H, OH), 5.7 (d, J = 10.0 Hz, 1H, H-1′), 7.29-7.40 (m, 2H, Ar-H), 7.57-7.63 (m, 2H, Ar-H) ppm. Anal. Calcd. For C₂₀H₂₀N₂O₂S; C, 57.13; H, 5.18; N, 13.33. Found: C, 57.00; H, 5.10; N, 13.50.

N’-[4-(Substitutedbenzylidine)-2-(2-Methyl-1H-benimidazol-1-yl)-acetoxyrazide (15a-c)
To a solution of the acid hydrazide 3 (2.4 g, 10 mmol) in ethanol (30 ml), 4-bromobenzaldehyde, 4-flourobenzaldehye and/or 4-dimethylaminobenzaldehyde (10 mmol) was added and the mixture was heated at reflux temperature for 5 h. The solution was cooled and the resulting precipitate was filtered and recrystallized from ethanol to afford 15a-c.

N’-(4-Bromobenzylidine)-2-(2-Methyl-1H-benimidazol-1-yl)-acetoxyrazide (15a)
White crystals (2.96 g, 89.4%), mp 326-327 °C; IR (KBr, cm⁻¹): 3228 (NH), 1695 (C=O), 1610 (C=N). EI-MS: m/z 370 [M⁺]. Anal. Calcd. For C₁₁H₁₀BrN₂O; C, 55.0; H, 4.07; N, 15.09. Found: C, 55.0; H, 4.0; N, 15.10.

N’-(4-Flurobenzylidine)-2-(2-Methyl-1H-benimidazol-1-yl)-acetoxyrazide (15b)
Brown crystals (2.98 g, 96%), mp 305-306 °C; IR (KBr, cm⁻¹): 3213 (NH), 1695 (C=O), 1600 (C=N). EI-MS: m/z 309 [M⁺]. Anal. Calcd. For C₁₁H₁₀FN₂O; C, 65.84; H, 4.87; N, 18.05. Found: C, 65.80; H, 4.90; N, 18.00.

N’-[4-(Dimethylaminobenzylidine)-2-(2-Methyl-1H-benimidazol-1-yl)-acetoxyrazide (15c)
Gray crystals (3.0 g, 89.4%), mp 284-285 °C; IR (KBr, cm⁻¹): 3217 (NH), 1670 (C=O), 1605 (C=N). EI-MS: m/z 335 [M⁺]. Anal. Calcd. For C₁₁H₁₂N₂O; C, 68.04; H, 6.31; N, 20.88. Found: C, 68.00; H, 6.35; N, 20.85.

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N-[2-(4-Substitutedphenyl)-4-oxothiazolidin-3-yl]-2-(2-methyl-1H-benzimidazol-1-yl)-acetamide (16a-c). General Procedure

A solution of 15a-c (10 mmol) in benzene (30 ml) was stirred for 30 min. before addition of thioglycolic acid (10 mmol) and the resulting mixture was heated under reflux for 10 h. The mixture was allowed to cool and the solvent was removed under reduced pressure to obtain on solid products which recrystallized from the ethanol.

N-[2-(4-Bromophenyl)-4-oxothiazolidin-3-yl]-2-(2-methyl-1H-benzimidazol-1-yl)-acetamide (16a)
White crystals (2.76 g, 62%), mp 285-286 °C; IR (KBr, cm⁻¹): 3215 (NH), 1680 (C=O), 1605 (C=N). EI-MS: m/z 445 [M⁺]. Anal. Calcd. For C₁₉H₁₇BrN₂O₂S: C, 51.24; H, 3.85; N, 12.58. Found: C, 51.20; H, 3.80; N, 12.50.

N-[2-(4-Fluorophenyl)-4-oxothiazolidin-3-yl]-2-(2-methyl-1H-benzimidazol-1-yl)-acetamide (16b)
Brown solids (2.0 g, 52%), mp 380-381 °C; IR (KBr, cm⁻¹): 3220 (NH), 1680 (C=O), 1605 (C=N). EI-MS: m/z 384 [M⁺]. Anal. Calcd. For C₁₉H₁₇FNO₂S: C, 59.36; H, 4.46; N, 14.75. Found: C, 59.40; H, 4.45; N, 14.70.

N-[2-(4-Dimethylamino)phenyl]-4-oxothiazolidin-3-yl]-2-(2-methyl-1H-benzimidazol-1-yl)-acetamide (16c)
Gray crystals (2.0 g, 47%), mp 355-356 °C; IR (KBr, cm⁻¹): 3411 (NH), 1670 (C=O), 1605 (C=N). EI-MS: m/z 424 [M⁺]. Anal. Calcd. For C₂₂H₂₁N₂O₂S: C, 62.05; H, 6.04; N, 16.46. Found: C, 62.00; H, 6.00; N, 16.50.

General procedure for the synthesis of compounds 18a,b
To a well stirred solution of the respective monosaccharide (5 mmol) in water (1 ml) and glacial acetic acid (1 ml) was added acid hydrazide (1.02 g, 5 mmol) in ethanol (15 ml). The mixture was heated under reflux for 8 h and the resulting solution was concentrated and left to cool. The formed precipitate was filtered off, washed with water and ethanol, then recrystallized from ethanol.

2-(2-Methyl-1H-benzimidazol-1-yl)-N'-[D-xylotetritolylidene]-acetohydrazide (18a)
White solids (1.34 g, 80%), mp 108-109 °C; IR (KBr, cm⁻¹): 3400 (OH), 3320 (NH), 1627 (C=O), 1605 (C=N). ¹H NMR (DMSO-d₆, 300 MHz): δ 2.45 (s, 3H, CH₃), 3.30-3.32 (m, 2H, H-5'), 3.41-3.45 (m, 1H, H-4'), 4.12-4.15 (m, 1H, H-3'), 4.51-4.55 (dd, J = 7.8 Hz, 3.9 Hz, 1H, H-2'), 4.56 (brs, 1H, OH), 4.67 (brs, 1H, OH), 4.82 (brs, 1H, OH), 5.04 (s, 1H, CH₅), 5.10 (brs, 1H, OH), 7.29-7.35 (m, 2H, Ar-H), 7.48 (d, J = 7.9 Hz, H-1'), 7.69-7.73 (m, 2H, Ar-H), 9.00 (brs, 1H, NH) ppm. Anal. Calcd. For C₁⁶H₁₅NO₃S: C, 53.56; H, 5.99; N, 16.60. Found: C, 53.65; H, 5.89; N, 16.50.

2-(2-Methyl-1H-benzimidazol-1-yl)-N'-[D-gluco-entitrolylidene]-acetohydrazide (18b)
White solids (1.73 g, 95%), mp 126–127 °C; IR (KBr, cm⁻¹): 3368 (OH), 3250 (NH), 1620 (C=O), 1605 (C=N). ¹H NMR (DMSO-d₆, 300MHz): δ 2.48 (s, 3H, CH₃), 3.24-3.44 (m, 2H, H-6',6''), 3.60-3.63 (m, 1H, H-5'), 3.87-3.93 (m, 1H, H-4'), 4.13 (t, J = 7.8 Hz, 1H, H-3'), 4.45 (dd, J = 7.8 Hz, 3.9 Hz, 1H, H-2'), 4.63 (brs, 1H, OH), 4.90 (brs, 1H, OH), 5.00 (brs, 1H, OH), 5.04 (s, 2H, CH₂), 5.7 (brs, 1H, OH), 5.75 (brs, 1H, OH), 7.27-7.30 (m, 2H, Ar-H), 7.52 (d, J = 7.9 Hz, 1H, H-1'), 7.69-7.73 (m, 2H, Ar-H), 9.00 (brs, 1H, NH) ppm. Anal. Calcd. For C₁⁶H₁₅N₂O₃S: C, 52.45; H, 6.05; N, 26.20. Found: C, 52.50; H, 6.0; N, 26.25.

Antimicrobial activity
The target compounds were screened in vitro for their antimicrobial activities against Escherichia coli NRRL B-210 (Gram-ve bacteria), Bacillus subtilis NRRL B-543 and Staphylococcus aureus (Gram-ve bacteria), Aspergillus niger and Candida albicans NRRL Y-477 (Fungi). These microorganisms were obtained from Northern Utilisation Research and Development Division, U.S. Department of Agricultural Peoria, Illinois, USA. The agar diffusion method [33] was used for this purpose. The bacteria and fungi were maintained on nutrient agar and Czapek’s-Dox agar media, respectively. The assay medium flasks containing 50 ml of nutrient agar for bacteria and Cza pek’s-Dox agar medium and retard the growth of the test organism. Plates were incubated at 30°C for 24 hours for bacteria and 72 h of incubation at 28 °C for fungi. DMSO showed no inhibition zones. The diameter of the resulted inhibition zone was measured in cm (Table 1).
Reaction of 2-methylbenzimidazole (1) [32] with ethyl chloroacetate in the presence of potassium carbonate and dry acetone afforded ethyl 2-(2-methyl-1H-benzimidazol-1-yl)acetate (2) in 60 % yield. Hydrazinolysis of 2 with hydrazine hydrate in ethanol afforded the corresponding acid hydrazide derivative 3. The 1H NMR spectrum of 2 showed signals characteristic to the ester group at 1.22 triplet for CH2 groups, respectively.

When the acid hydrazide 3 was allowed to react with carbon disulfide in ethanol in the presence of potassium hydroxide the corresponding 1,3,4-oxadiazole-2(3H)-thione derivative 4 was afforded in 61 % yield. Reaction of the thione derivative 4 with 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl bromide (5) gave the corresponding acetylated thioglucoside 6 in 69% yield. The IR spectrum of 6 showed signals characteristic to the C=O of the ester groups at 1747 cm\(^{-1}\) while, the 1H NMR spectrum of the latter compound showed signals corresponding to the acetyl-methyl groups and the sugar protons in addition to the aromatic protons. The anomeric proton signal appeared as doublet at 5.50 ppm with a coupling constant 9.8 Hz indicating the \(^\beta\)-orientation of the thioglucosidic bond. Treatment of the acetylated thioglucoside 6 with methanolic ammonia gave the deacetylated thioglucoside derivative 7 (Scheme 1). Its structure was conformed by IR, 1H-NMR, and elemental analysis, which agreed with the assigned structure (see experimental part).

On the other hand, when the acid hydrazide derivative 3 was reacted with phenylisothiocyanate in ethanol afforded N-phenylhydrazinecarbothioamide derivative 8 in 76.4% yield. Compound 8 was reacted with conc. \(\text{H}_2\text{SO}_4\) to afforded \(5\)\-[2-(2-methyl-1H-benzimidazol-1-yl)methyl]-N-phenyl-1,3,4-thiadiazol-2-amine (9) in 77.2% yield. Refluxing of 8 with bromoacetic acid afforded \(2\)\-(2-(2-methyl-1H-benzimidazol-1-yl)methyl)-N-(4-oxo-2-(phenylimino)thiazolidin-3-yl)-acetamide (10) in 78% yield. While Refluxing with 10% NaOH solution gave \(2\)\-(2-methyl-1H-benzimidazol-1-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (11) in 93 % yield.

The IR spectrum of 8 showed absorption bands at 3228 and 1602 cm\(^{-1}\) corresponding to NH and C=\(\alpha\)N respectively, while IR spectrum of 9 showed absorption bands at 3193 and 1635 corresponding to NH and C=\(\alpha\)N respectively. IR spectrum of 11 showed absorption bands at 3236 and 1603 corresponding to NH and C=\(\alpha\)N respectively, and the mass spectrum of 11 showed molecular ion peak m/z 321 which confirm the structure of the product. Reaction of 11 with 5 afforded the corresponding acetylated thioglucoside 12 in 76% yield. The IR spectrum of 12 showed signals characteristic to the C=O of the ester groups at 1747 cm\(^{-1}\) while, the 1H NMR spectrum of the latter compound showed signals corresponding to the acetyl-methyl signals and the sugar protons in addition to the aromatic protons. The anomeric proton signal appeared as doublet at 5.70 ppm with a coupling constant 10.0 indicating the \(\beta\)-orientation of the thioglucosidic bond. Treatment of the acetylated thioglucoside 12 with methanolic ammonia gave the deacetylated thioglucoside derivative 13 (Scheme 2). The structures were confirmed by IR, 1H-NMR, and elemental analysis, which agreed with the assigned structure (see experimental part).
Scheme 1

Scheme 2
When the acid hydrazide 3 was allowed to react with different aldehydes 14a-c gave the Schiff’s bases 15a-c in moderate yields. Reaction of 15a-c with thioglycolic acid afforded the thiazolidinone derivatives 16a-c, respectively. The structures of the Schiff’s bases and the thiazolidinone derivatives were confirmed by IR, Mass spectra and elemental analyses, which agreed with the assigned structures (see experimental part). Reaction of 3 with acyclic sugars as D-(+)-xylose or D-(+)-glucose 17a,b in an aqueous ethanolic solution and a catalytic amount of acetic acid, the corresponding sugar hydrazones 18a,b were obtained, respectively (scheme 3). The IR spectra of 18a,b showed the presence of characteristic absorption bands corresponding to the hydroxyl groups in the region 3400–3368 cm⁻¹. The ¹H NMR spectra showed the signals of the sugar chain protons at δ 3.30–5.79 ppm and the C-1 methine proton as doublet in the range δ 7.48–7.52 ppm in addition to the aromatic protons in the region δ 7.27–7.73 ppm.

Antimicrobial Activity. Result of the antimicrobial activity test against Escherichia coli (Gram-ve bacteria) and Bacillus subtilis (Gram+ve bacteria) showed that compounds 6, 9, 11, 12, 15a, and 18b have antibacterial activity while the other tested compounds were generally inefficient.

Antifungal activity. The prepared compounds were evaluated in vitro against two strains of fungi, Candida albicans and Aspergillus niger. Result of antimicrobial activity showed that compounds 4, 9, 13, 16a, and 18b have antifungal activity while the other tested compounds were generally inefficient.
CONCLUSION

In conclusion, the antimicrobial screening suggests that all the newly synthesized compounds showed good to very good activity. Hence the fact that the compounds prepared in this study are chemically unrelated to the current medication, suggests that further work with similar analogues is clearly warranted.

REFERENCES