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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-benzimidazol 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] antiulcer [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], antihypertention [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

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 NMR Spectrometer at 300 MHz for ^{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-1*H*-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 ^{o}C; IR (KBr, cm^{-1}): 1735 (C=O), 1619 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.22 (t, *J* = 5.2 Hz, 3H, C*H*$_3$CH$_2$), 2.49 (s, 3H, CH_3), 3.49 (q, *J* = 5.2 Hz, 2H, CH$_3$C*H*$_2$), 5.04 (s, 2H, CH_2), 7.34-7.98 (m, 4H, Ar-H) ppm. Anal. Calcd. For $C_{12}H_{14}N_2O_2$; 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 ^{o}C (1.5 g, 68.8%); IR (KBr, cm^{-1}): 3449 (NH_2), 3121 (NH), 1635 (C=O), 1600 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.49 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 5.41 (brs, 2H, NH_2), 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 $C_{10}H_{12}N_4O$; 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**)
To a solution of **3** (2.04 g, 10 mmol) in ethanol (20 ml) was added a solution of potassium hydroxide (0.56 g, 10 mmol) dissolved in water (2 ml) and carbon disulphide (3 ml). The solution was heated under reflux for 10 h. The solvent was evaporated and the residue was dissolved in water, filtered off, and acidified with dilute hydrochloric acid. The formed precipitate was filtered off, washed with water, and recrystallized from methanol to give **4** as pale yellow solid (1.51 g, 61%), mp 175-176 ^{o}C; IR (KBr, cm^{-1}): 3223 (NH), 1620 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.49 (s, 3H, CH_3), 5.04 (s, 2H, CH_2), 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 $C_{11}H_{10}N_4OS$; 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)methyl]-1,3,4-oxadiazole (**6**)
To a solution of **4** (1.23 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-α-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 ^{o}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 **6** as a brown solid (1.99 g, 69%), mp 140-141 ^{o}C; IR (KBr, cm^{-1}): 1747 (C=O), 1602 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90, 1.95, 2.00, 2.17 (4s, 12H,4C*H*$_3$CO), 2.50 (s, 3H, CH_3), 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-4′), 5.04 (s, 2H, CH_2), 5.18 (dd, *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 $C_{25}H_{28}N_4O_{10}S$; 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 (**7**)
A solution of **6** (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 precipitates were filtered off and dried well to afford **7** (0.55 g, 95%), mp 192-193 ^{o}C; IR (KBr, cm^{-1}): 3413 (OH), 1614 (C=N). ^{1}H NMR (DMSO-d_6,300 MHz): δ 2.49 (s, 3H, CH_3), 3.41 (m, 2H, H-6′,6″), 3.45-3.47 (m, 1H, H-5′), 3.71-3.77 (m, 2H, H-3′, H-4′), 4.15 (t, *J* = 9.4 Hz, 1H, H-2′), 4.70 (brs, 1H, OH), 4.83 (brs, 1H, OH), 5.04 (s, 2H, CH_2), 5.15 (brs, 1H,OH), 5.24 (brs, 1H, OH), 5.5 (d, *J* = 9.8 Hz, 1H, H-1′), 7.29-7.33 (m, 2H, Ar-H), 7.69-7.76 (m, 2H, Ar-H) ppm. Anal. Calcd. For $C_{17}H_{20}N_4O_6S$; 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)acetyl]-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 ^{o}C (2.59 g, 76.4%); IR (KBr, cm^{-1}): 3228 (NH), 1602 (C=N). Anal. Calcd. For $C_{17}H_{17}N_5OS$; C, 60.16; H, 5.05; N, 20.63. Found: C, 60.10; H, 5.00; N, 20.50.

5-[(2-Methyl-1H-benzimidazol-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 ^{o}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 ^{o}C (2.48 g, 77.2%); IR (KBr, cm^{-1}): 3193 (NH), 1635 (C=N). EI-MS: *m/z* 321 [M^{+}]. Anal. Calcd. For $C_{17}H_{15}N_5S$; C, 63.53; H, 4.70; N, 21.79. Found: C, 63.50; H, 4.73; N, 21.80.

2-[2-(Methyl-1H-benzimidazol-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 ^{o}C, the solid that formed was filtered off and recrystallized from methanol to afford **10** as a brown solid; mp 257-258 ^{o}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 $C_{19}H_{17}N_5O_2S$; 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 DMF to give **11** as a white solid, (2.99 g, 93%), mp 164-165 ^{o}C IR (KBr, cm^{-1}) 3236 (NH), 1603 (C=N): EI-MS: *m/z* 321 [M^{+}]. Anal. Calcd. for $C_{17}H_{15}N_5S$; C, 63.53; H, 4.70; N, 21.79. Found: C, 63.50; H, 4.74; N, 21.80.

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylthio)-5-[(2-methyl-1H-benzimidazol-1-yl)-methyl]-4-phenyl-1H-1,2,4-triazole (**12**)
To 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-α-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 ^{o}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 ^{o}C; IR (KBr, cm^{-1}): 1747 (C=O), 1602 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92, 1.95, 1.98, 2.0 (4s, 12H,4C*H*$_3$CO), 2.49 (s, 3H, CH_3), 3.35 (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, CH_2), 5.2 (t, *J* = 9.6 Hz, 1H, H-2′), 5.70 (d, *J* = 10.0 Hz, 1H, H-1′), 7.27-7.30 (m, 2H, Ar-H), 7.56-7.63 (m, 2H, Ar-H) ppm. Anal. Calcd. For $C_{31}H_{33}N_5O_9S$; 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 formed precipitates were filtered off and dried well to afford **13** as a yellow solid (0.50 g, 95 %), mp 192-193 ^{o}C; IR (KBr, cm^{-1}): 3399 (OH), 1605 (C=N). ^{1}H NMR (DMSO-d_6,300 MHz): δ 2.49 (s, 3H, CH_3), 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 (brs, 1H, OH), 4.83 (brs, 1H, OH), 5.04 (s, 2H, CH_2), 5.10-5.15 (m, 1H, OH), 5.22 (brs, 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 $C_{23}H_{25}N_5O_5S$; 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-benzimidazol-1-yl)]-acetohydrazide (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-benzimidazol-1-yl)-acetohydrazide (**15a**)
White crystals (2.96 g, 89.4%), mp 326-327 ^{o}C; IR (KBr, cm^{-1}): 3228 (NH), 1695 (C=O), 1610 (C=N). EI-MS: *m/z* 370 [M^{+}]. Anal. Calcd. For $C_{17}H_{15}BrN_4O$; C, 55.0; H, 4.07; N, 15.09. Found: C, 55.0; H, 4.0; N, 15.10.

N′-(4-Flourobenzylidine)-2-(2-methyl-1H-benzimidazol-1-yl)-acetohydrazide (**15b**)
Brown crystals (2.98 g, 96%), mp 305-306 ^{o}C; IR (KBr, cm^{-1}): 3213 (NH), 1695 (C=O), 1600 (C=N). EI-MS: *m/z* 309 [M^{+}]. Anal. Calcd. For $C_{17}H_{15}FN_4O$; C, 65.84; H, 4.87; N, 18.05. Found: C, 65.80; H, 4.90; N, 18.00.

N′-[(4-Dimethylamino)benzylidine]-2-(2-methyl-1H-benzimidazol-1-yl)-acetohydrazide (**15c**)
Gray crystals (3.0 g, 89.4%), mp 284-285 ^{o}C; IR (KBr, cm^{-1}): 3217 (NH), 1670 (C=O), 1605 (C=N). EI-MS: *m/z* 335 [M^{+}]. Anal. Calcd. For $C_{19}H_{21}N_5O$; C, 68.04; H, 6.31; N, 20.88. Found: C, 68.00; H, 6.35; N, 20.85.

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 ^{o}C; IR (KBr, cm^{-1}): 3215 (NH), 1680 (C=O), 1605 (C=N). EI-MS: *m/z* 445 [M^{+}]. Anal. Calcd. For $C_{19}H_{17}BrN_4O_2S$; 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 ^{o}C; IR (KBr, cm^{-1}): 3220 (NH), 1680 (C=O), 1605 (C=N). EI-MS: *m/z* 384 [M^{+}]. Anal. Calcd. For $C_{19}H_{17}FN_4O_2S$; 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 ^{o}C; IR (KBr, cm^{-1}): 3411 (NH), 1670 (C=O), 1605 (C=N). EI-MS: *m/z* 424 [M^{+}]. Anal. Calcd. For $C_{22}H_{27}N_5O_2S$; 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 **3** (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 dried and recrystallized from ethanol.

2-(2-Methyl-1H-benzimidazol-1-yl)-N′-(D-xylotetritolylidene)-acetohydrazide (**18a**)
White solids (1.34 g, 80%), mp 108-109 ^{o}C; IR (KBr, cm^{-1}): 3400 (OH), 3320 (NH), 1627 (C=O), 1605 (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.45 (s, 3H, CH_3), 3.30-3.32 (m, 2H, H-5′,5″), 3.41-3.45 (m, 1H, H-4′), 4.12-4.15 (m, 1H, H-3′), 4.51-4.55 (dd, *J* = 7.5 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, 2H, CH_2), 5.10 (brs, 1H, OH), 7.29-7.35 (m, 2H, Ar-H), 7.48 (d, 1H, *J* = 7.9 Hz, H-1′), 7.69-7.73 (m, 2H, Ar-H), 9.00 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{15}H_{20}N_4O_5$; 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-glucopentitolylidene)-acetohydrazide (**18b**)
White solids (1.73 g, 95%), mp 126–127 ^{o}C; IR (KBr, cm^{-1}): 3368 (OH), 3250 (NH), 1620 (C=O, 1605 (C=N). ^{1}H NMR (DMSO-d_6, 300MHz): δ 2.48 (s, 3H, CH_3), 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, CH_2), 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 $C_{16}H_{22}N_4O_6$; 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 Czapek's-Dox agar medium for fungi respectively were allowed to reach 40-50 ^{o}C to be inoculated with 0.5ml of the test organism cell suspension. The flasks were mixed well and poured each into a Petri dish (15 x 2 cm) and allowed to solidify. After solidification, holes (0.6 cm diameter) were made in the agar plate by the aid of a sterile cork poorer (diameter 6 mm). Target compounds were dissolved each in 2 ml DMSO. In these holes, 100 µl of each compound was placed using an automatic micropipette. The Petri dishes were left at 5 °C for 1 h to allow diffusion of the samples through the agar medium and retard the growth of the test organism. Plates were incubated at 30^{o}C for 24 hours for bacteria and 72 h of incubation at 28 ^{o}C for fungi. DMSO showed no inhibition zones. The diameter of the resulted inhibition zone was measured in cm (Table 1).

Table 1. *In vitro* antimicrobial activity of the tested compounds

Compd	Microorganisms					Compd	Microorganisms				
	Staph. aureus	*Bacillus subtilis*	*E. Coli*	*Candida albicans*	*Aspergillus niger*		*Staph. aureus*	*Bacillus subtilis*	*E. Coli*	*Candida albicans*	*Aspergillus niger*
1	-	+	-	-	-	**12**	++	+++	+++	+++	-
2	-	+	-	-	-	**13**	+	+++	+	+++	+++
3	+	+	+	-	-	**15a**	-	+++	+++	-	-
4	++	+	+	+++	+++	**15b**	+	-	-	-	-
6	-	+++	+++	+	-	**15c**	+	+	-	+	-
7	+	+	-	+	-	**16a**	+	+++	-	+++	+++
8	++	+	-	++	++	**16b**	+	+	+	+	-
9	+++	+++	+++	+++	+++	**16c**	+	+	+	+	-
10	+	-	+	+	-	**18a**	+	++	+	++	+
11	++	+++	+++	+++	++	**18b**	+++	++++	++++	++++	+++

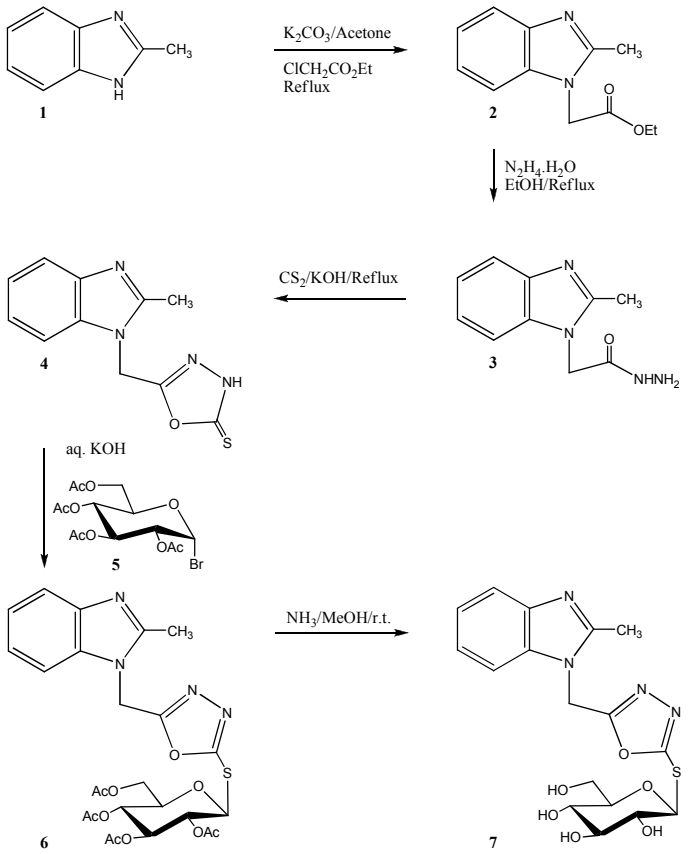
+ zone of inhibition 10 mm; ++ zone of inhibition 20 mm; +++ zone of inhibition 20-25 mm;
++++ zone of inhibition 25-29 mm; - no inhibition.

RESULTS AND DISCUSSION

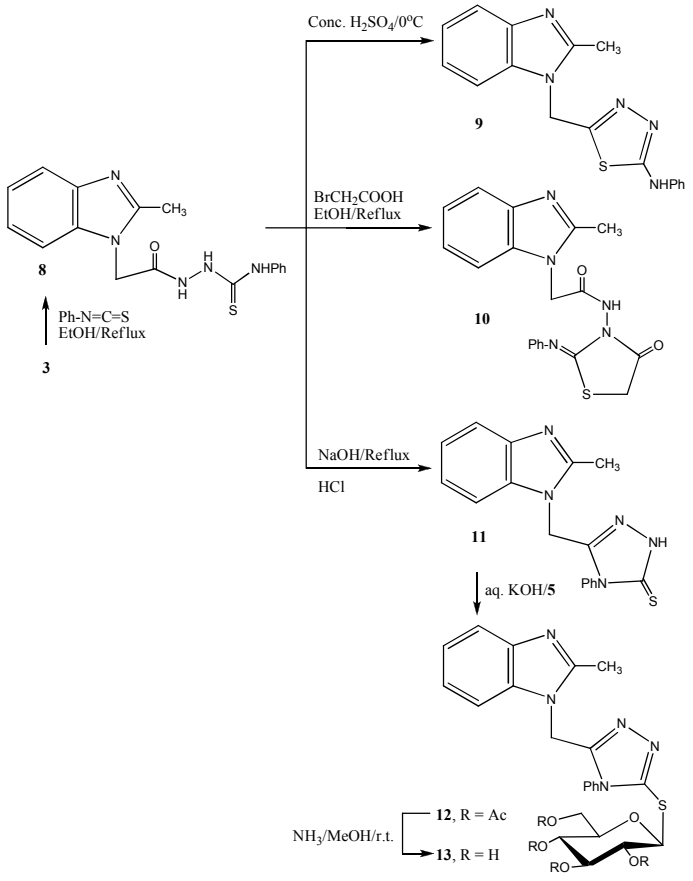
Reaction of 2-methylbenzimidazole (**1)** [32] with ethyl chloroacetate in the presence of potassium carbonate and dry acetone afforded ethyl 2-(2-methyl-1*H*-benzimidazol-1-yl)acetate (**2)** in 60 % yield. Hydrazinolysis of **2** with hydrazine hydrate in ethanol afforded the corresponding acid hydrazide derivative **3**. The ^{1}H NMR spectrum of **2** showed signals characteristic to the ester group at 1.22 triplet for CH_3 and 3.49 quartet for CH_2 in addition to a singlet peak at 5.04 corresponding to the methylene group in addition to the peaks for the aromatic protons, while the ^{1}H NMR spectrum of the acid hydrazide **3** showed signals at δ 5.41, 8.40 ppm corresponding to NH_2 and NH groups, respectively. When the acid hydrazide **3** was allowed to react with carbon disulphide in ethanol in the presence of potassium hydroxide the corresponding 1,3,4-oxadiazole-2(3*H*)-thione derivative **4** was afforded in 61% yield. Reaction of the thione derivative **4** with 2,3,4,6-tetra-*O*-acetyl-α-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 ^{1}H 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 *β*-orientation of the thioglycosidic bond [27, 34-37]. Treatment of the acetylated thioglucoside **6** with methanolic ammonia gave the deacetylated thioglucoside derivative **7** (Scheme 1). Its structure was conformed by IR, ^{1}H-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*-phenylhydrazinecarbothio- amide derivative **8** in 76.4% yield. Compound **8** was reacted with conc. H_2SO_4 to afforded 5-[(2-methyl-1*H*-benzimidazol-1yl)methyl)]-*N*-phenyl-1,3,4-thiadiazol-2-amine (**9**) in 77.2% yield. Refluxing of **8** with bromoacetic acid afforded 2-(2-methyl-1*H*-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-1*H*-benzimidazol-1-yl)-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione (**11**) in 93 % yield.

The IR spectrum of **8** showed absorption bands at 3228 and 1602 cm^{-1} corresponding to NH and C=N respectively, while IR spectrum of **9** showed absorption bands at 3193 and 1635 corresponding to NH and C=N respectively. IR spectrum of **11** showed absorption bands at 3236 and 1603 corresponding to NH and C=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 ^{1}H 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 β-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, ^{1}H-NMR, and elemental analysis, which agreed with the assigned structure (see experimental part).

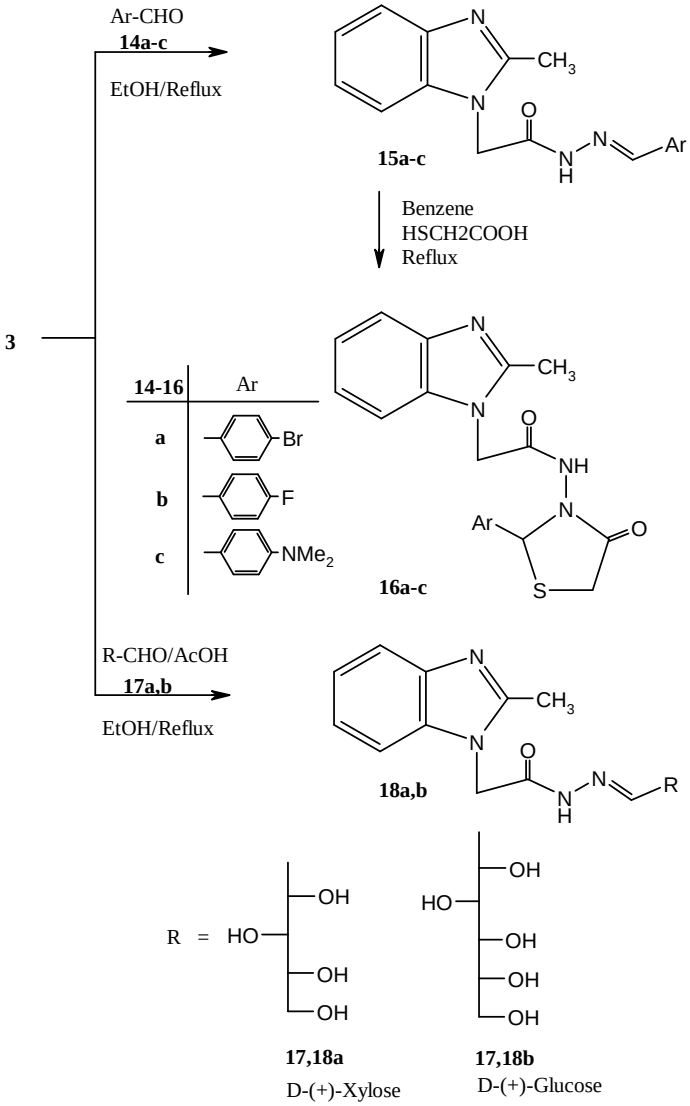


Scheme 1



Scheme 2

When the acid hydrazide **3** was allowed to react with different aldehydes **14a-c** gave the Shiff'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 Shiff'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 ^{1}H 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.



Scheme 3

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.

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