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Antimicrobial activity of newly synthesized imidazolones, their oxadiazolyl and acyclic *C*-nucleosides

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ABSTRACT

A number of substituted new 2-(N-phthalimidomethyl)-4-chlorobenzylidene-5-imidazole derivatives in addition to their sugar hydrazones were newly synthesized. The antimicrobial activity of the prepared compounds was evaluated against Escherichia coli, Bacillus subtilis, Staphylococcus aureus, Aspergillus niger and Candida albicans. The sugar hydrazones analogues were the highly active compounds.

Keywords: Imidazolones, sugar hydrazones, acyclic *C*-nucleosides, antimicrobial activity.

INTRODUCTION

Imidazole derivatives are of interest to the medicinal chemists for many years because of their biological activities [1-10] such as anticancer, antitubercular, antibacterial, antifungal activities. Moreover, much interest has also been focused on the herbicidal activities [11] displayed by compounds incorporating this heterocyclic system. Because the [imidazol-yl]isoindole-1,3-dione system is similar in part to Levamisole, a well known immunomodulator [12] the possibility of reducing the harmful effects of the cytotoxic agents on the immune system also appears to be very attractive. So, we report herein on the synthesis of new derivatives of heterocyclic systems. On the other hand, 1,3,4-oxadiazole derivatives possess a broad spectrum of biological activity in both agrochemicals and pharmaceuticals such as antibacterial [13], antimicrobial [14], insecticidal [15], herbicidal, fungicidal [16], anti-inflammatory [17], hypoglycemic [18], hypotension characteristics [19], antiviral [20], and antitumor activities [21]. 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 [22-27] we report in the present work the synthesis and antimicrobial activity of new 2-(*N*-phthalimidomethyl)-4-chlorobenzylidene-5-imidazole derivatives, their oxadiazolyl, and acyclic *C*-analogues.

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. 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. 2-{[4-(4-Chlorobenzylidene)]-1-[(3-mercapto-1*H*-1,2,4-triazol-5-ylmethyl)]-5-oxo-(4,5-dihydro-1*H*-imidazol-2-yl)methyl}isoindoline-1,3-dione (**1a**) and 2-{[4-(4-chlorobenzylidene)]-1-[(3-mercapto-1*H*-1,2,4-triazol-5-ylmethyl)]-5-oxo-(4,5-dihydro-1-phenyl-1*H*-imidazol-2-yl)methyl} isoindoline-1,3-dione (**1b**) were prepared according to the reported procedure [28].

Chemistry

***General procedure for the preparation of ester derivatives* 2a,b**

To a solution of **1a,b** [28] (10 mmol) and anhydrous potassium carbonate (1.38 g, 10 mmol) in dry acetone (25 ml), was added ethyl chlorocetate (1.22 g, 10 mmol). The solution was stirred at room temperature for 6 h and then poured on ice-cold water. The resulting precipitate was filtered off and recrystallized from ethanol.

Ethyl {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl) methyl]-(1H-1,2,4-triazol-3-ylthio)}acetate (**2a**)

White powder (4.80 g, 85%), mp 158-160 ^{o}C; IR (KBr, cm^{-1}): 3409 (NH), 1713 (C=O), 1628 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.22 (t, 3H, *J* = 5.6 Hz, CH_3), 4.00 (s, 2H, CH_2), 4.20 (s, 2H, CH_2), 4.26 (s, 2H, CH_2), 4.21 (q, 2H, *J* = 5.6 Hz, CH_2), 6.76 (s, 1H, CH), 7.15-7.25 (m, 4H, Ar-H), 7.70-7.90 (m, 4H, Ar-H), 13.20 (brs, 1H, NH) ppm. EI-MS: *m/z* 564 [M^{+}-1]. Anal. Calcd. For $C_{26}H_{21}ClN_6O_5S$; C, 55.27; H, 3.75; N, 14.87. Found: C, 55.09; H, 3.56; N, 14.59.

Ethyl {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl) methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}acetate (**2b**)

White powder (5.89 g, 92%), mp 146-148 ^{o}C; IR (KBr, cm^{-1}): 1687 (CON), 1593 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.30 (t, 3H, *J* = 6.8 Hz, CH_3), 3.98 (s, 2H, CH_2), 4.16 (s, 2H, CH_2), 4.20 (s, 2H, CH_2), 4.19 (q, 2H, *J* = 6.8 Hz, CH_2), 6.71 (s, 1H, CH), 7.18-7.35 (m, 4H, Ar-H), 7.39-7.66 (m, 5H, Ar-H), 7.71-7.94 (m, 4H, Ar-H) ppm. EI-MS: *m/z* 641 [M^{+}]. Anal. Calcd. For $C_{32}H_{25}ClN_6O_5S$; C, 59.95; H, 3.93; N, 13.11. Found: C, 59.80; H, 3.79; N, 12.98.

***General procedure for the preparation of hydrazide derivatives* 3a,b**

A solution of **2a,b** (10 mmol) and hydrazine hydrate (1.50 g, 30 mmol) in ethanol (40 ml) was heated under reflux for 6 h .The solution was cooled and the resulting precipitate was filtered and crystallized from ethanol.

{5-[4-(4-Chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}acetohydrazide (**3a**)

White powder (5.33 g, 97%), mp 180-182 ^{o}C; IR (KBr, cm^{-1}): 3309-3175 (NH_2), 1658 (C=O), 1602 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 2H, CH_2), 3.95 (s, 4H, $2CH_2$), 5.50 (brs, 2H, NH_2), 6.78 (s, 1H, CH), 7.45-7.65 (m, 4H, Ar-H), 7.90-8.00 (m, 4H, Ar-H), 8.25 (brs, 1H, NH), 10.44 (brs, 1H, NH) ppm. EI-MS: *m/z* 549/550 [M^{+}]. Anal. Calcd. For $C_{24}H_{19}ClN_8O_4S$; C, 52.32; H, 3.48; N, 20.34. Found: C, 52.08; H, 3.36; N, 20.11.

{5-[4-(4-Chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}acetohydrazide (**3b**)

White powder (6.14 g, 98%), mp 150-151 ^{o}C; IR (KBr, cm^{-1}): 3304-3179 (NH_2), 1674 (C=O), 1593 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.80 (s, 2H, CH_2), 3.90 (s, 4H, $2CH_2$), 5.99 (brs, 2H, NH_2), 6.75 (s, 1H, CH), 7.08-7.42 (m, 5H, Ar-H), 7.46-7.92 (m, 4H, Ar-H), 7.93-7.95 (m, 4H, Ar-H), 8.30 (brs, 1H, NH) ppm. EI-MS: *m/z* 627 [M^{+}]. Anal. Calcd. For $C_{30}H_{23}ClN_8O_4S$; C, 57.46; H, 3.70; N, 17.87. Found: C, 57.33; H, 3.66; N, 17.65.

***General procedure for the preparation of sugar hydrazones* 4-9**

To a well stirred mixture of the respective monosaccharide [D-(+)-Xylose, D-(+)-Glucose, D-(+)-Galactose] [(10 mmol) in water (1 ml)], glacial acetic acid (0.2 ml) in ethanol (10 ml) was added the hydrazide derivatives **3a,b** (10 mmol). The mixture was heated under reflux for 3 h and the resulting solution was concentrated and left to cool. The formed precipitate was filtered off, washed with water and ethanol, dried, and recrystallized from ethanol.

D-Xylose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl) methyl]-(1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**4**)

White powder (5.12 g, 75%), mp 112-114 ^{o}C; IR (KBr, cm^{-1}): 3412-3169 (OH), 1658 (C=O), 1609 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.34-3.67 (m, 6H, 3′-H, 4′-H, 5′-H, CH_2), 4.15 (m, 5H, 2′-H, $2CH_2$), 4.78 (brs, 3H, 3OH),

5.09 (brs, 1H, OH), 6.95 (s, 1H, CH), 7.15-7.26 (m, 4H, Ar-H), 7.64-7.77 (m, 5H, 1′-H, Ar-H), 10.50 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{29}H_{27}ClN_8O_8S$; C, 50.99; H, 3.98; N, 16.40. Found: C, 50.80; H, 3.76; N, 16.22.

D-Glucose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**5**)
White powder (5.67 g, 78%), mp 158-160 ^oC; IR (KBr, cm^{-1}): 3418-3170 (OH), 1658 (C=O), 1609 (C=N). ^1H-NMR (300 MHz, DMSO-d_6): δ 3.35-3.78 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH_2), 4.22 (m, 5H, 2′-H, $2CH_2$), 4.70 (brs, 3H, 3OH), 5.17 (brs, 2H, 2OH), 6.90 (s, 1H, CH), 7.35-7.56 (m, 4H, Ar-H), 7.74-7.97 (m, 5H, 1′-H, Ar-H), 10.60 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{31}H_{31}ClN_8O_9S$; C, 51.20; H, 4.30; N, 15.41. Found: C, 51.01; H, 4.12; N, 15.34.

D-Galactose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**6**)
White powder (6.03 g, 83%), mp 181-182 ^oC, IR (KBr, cm^{-1}): 3415-3169 (OH), 1658 (C=O), 1608 (C=N). ^1H-NMR (300 MHz, DMSO-d_6): δ 3.30-3.58 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH_2), 4.12 (m, 5H, 2′-H, $2CH_2$), 4.56 (brs, 3H, 3OH), 5.10 (brs, 2H, 2OH), 6.99 (s, 1H, CH), 7.65-7.86 (m, 5H, 1′-H, Ar-H), 10.55 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{31}H_{31}ClN_8O_9S$; C, 51.20; H, 4.30; N, 15.41. Found: C, 51.09; H, 4.17; N, 15.29.

D-Xylose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl) methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**7**)
White powder (5.84 g, 77%), mp 156-158 ^oC; IR (KBr, cm^{-1}): 3420-3175 (OH), 1660 (C=O), 1615 (C=N). ^1H-NMR (300 MHz, DMSO-d_6): δ 3.25-3.55 (m, 6H, 3′-H, 4′-H, 5′-H, CH_2), 4.23 (m, 5H, 2′-H, $2CH_2$), 4.50 (brs, 3H, 3OH), 5.00 (brs, 1H, OH), 6.88 (s, 1H, CH), 7.19-7.29 (m, 4H, Ar-H), 7.39-7.60 (m, 6H, 1′-H, Ar-H), 7.70-8.00 (m, 4H, Ar-H), 10.45 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{35}H_{31}ClN_8O_8S$; C, 55.37; H, 4.12; N, 14.76. Found: C, 55.23; H, 4.02; N, 14.63.

D-Glucose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl) methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**8**)
White powder (6.26 g, 78%), mp 144-146 ^oC; IR (KBr, cm^{-1}): 3417-3061 (OH), 1672 (C=O), 1595 (C=N). ^1H-NMR (300 MHz, DMSO-d_6): δ 3.28-3.92 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH_2), 4.15 (m, 5H, 2′-H, $2CH_2$), 4.40 (brs, 3H, 3OH), 5.03 (brs, 2H, 2OH), 6.95 (s, 1H, CH), 7.15-7.26 (m, 4H, Ar-H), 7.34-7.67 (m, 6H, 1′-H, Ar-H), 7.73-8.00 (m, 4H, Ar-H), 10.50 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{37}H_{35}ClN_8O_9S$; C, 55.33; H, 4.39; N, 13.95. Found: C, 55.23; H, 4.30; N, 13.80.

D-Galactose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**9**)
White powder (6.98 g, 87%), mp 173-175 ^oC; IR (KBr, cm^{-1}): 3308 (OH), 1682 (C=O), 1594 (C=N). ^1H-NMR (300 MHz, DMSO-d_6): δ 3.25-3.88 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH_2), 4.12 (m, 5H, 2′-H, $2CH_2$), 4.50 (brs, 3H, 3OH), 5.00 (brs, 2H, 2OH), 6.99 (s, 1H, CH), 7.15-7.29 (m, 4H, Ar-H), 7.39-7.71 (m, 6H, 1′-H, Ar-H), 7.78-8.09 (m, 4H, Ar-H), 10.52 (brs, 1H, NH) ppm. EI-MS: *m/z* 803 [M^+]. Anal. Calcd. For $C_{37}H_{35}ClN_8O_9S$; C, 55.33; H, 4.39; N, 13.95. Found: C, 55.18; H, 4.28; N, 13.78.

***General procedure for the preparation of O-acetylsugar hydrazones* 10-15**
To a solution of the sugar hydrazones **4-9** (10 mmol) in pyridine (5 ml), acetic anhydride (3 ml) was added and the mixture was stirred at room temperature for 5 h. The resulting solution was poured onto crushed ice and the product that separated out was filtered off, washed with a solution of sodium hydrogen carbonate followed by water and then dried. The products were recrystallized from ethanol.

2,3,4,5-Tetra-O-acetyl-D-xylose {5-[4-(4-chloro benzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**10**)
White powder (7.82 g, 92%), mp 190-192 ^oC; IR (KBr, cm^{-1}): 3423 (NH), 1735 (C=O), 1658 (C=O), 1607 (C=N). ^1H-NMR (300 MHz, DMSO-d_6): δ 1.93, 1.95, 2.06, 2.09 (4s, 12H, $4CH_3CO$), 3.31 (s, 2H, CH_2), 4.08-4.17 (m, 6H, 5′-H, $2CH_2$), 4.40-4.47 (m, 1H, 4′-H), 5.00-5.08 (m, 1H, 3′-H), 5.35-5.40 (m, 1H, 2′-H), 6.93 (s, 1H, CH), 7.19-7.33 (m, 5H, 1′-H, Ar-H), 7.65-7.77 (m, 4H, Ar-H), 11.76 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{37}H_{35}ClN_8O_{12}S$; C, 52.21; H, 4.14; N, 13.16. Found: C, 52.00; H, 4.02; N, 13.02.
2,3,4,5,6-Penta-O-acetyl-D-glucose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**11**)

White powder (8.90 g, 95%), mp 172-174 °C; IR (KBr, cm^{-1}): 3463 (NH), 1749 (C=O), 1659 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.91, 1.96, 1.98, 2.05, 2.11 (5s, 15H, $5CH_3CO$), 3.33 (s, 2H, CH_2), 4.15-4.20 (m, 6H, 6′-H, $2CH_2$), 4.55-4.69 (m, 2H, 4′-H, 5′-H), 5.00-5.10 (m, 1H, 3′-H), 5.55-5.60 (m, 1H, 2′-H), 6.95 (s, 1H, CH), 7.45-7.59 (m, 5H, 1′-H, Ar-H), 7.65-7.90 (m, 4H, Ar-H), 11.70 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{41}H_{41}ClN_8O_{14}S$; C, 52.54; H, 4.41; N, 11.95. Found: C, 52.34; H, 4.37; N, 11.60.

2,3,4,5,6-Penta-O-acetyl-D-galactose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**12**)
White powder (9.08 g, 97%), mp 177-179 °C; IR (KBr, cm^{-1}): 3423 (NH), 1743 (C=O), 1597 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.90, 1.93, 1.98, 2.06, 2.10 (5s, 15H, $5CH_3CO$), 3.26 (s, 2H, CH_2), 4.00-4.12 (m, 6H, 6′-H, $2CH_2$), 4.50-4.60 (m, 2H, 4′-H, 5′-H), 5.10-5.15 (m, 1H, 3′-H), 5.40-5.45 (m, 1H, 2′-H), 6.96 (s, 1H, CH), 7.15-7.29 (m, 5H, 1′-H, Ar-H), 7.75-8.05 (m, 4H, Ar-H), 11.82 (brs, 1H, NH) ppm. EI-MS: *m/z* 937 [M^+]. Anal. Calcd. For $C_{41}H_{41}ClN_8O_{14}S$; C, 52.54; H, 4.41; N, 11.95. Found: C, 52.30; H, 4.22; N, 11.69.

2,3,4,5-Tetra-O-acetyl-D-xylose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**13**)
White powder (7.41 g, 80%), mp 110-112 °C; IR (KBr, cm^{-1}): 3463 (NH), 1749 (C=O), 1659 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.98, 2.11, 2.13, 2.18 (4s, 12H, $4CH_3CO$), 3.28 (s, 2H, CH_2), 4.18-4.22 (m, 7H, 4′-H, 5′-H, $2CH_2$), 5.60-5.75 (m, 2H, 2′-H, 3′-H), 6.99 (s, 1H, CH), 7.14-7.29 (m, 5H, 1′-H, Ar-H), 7.50-7.58 (m, 5H, Ar-H), 7.75-7.92 (m, 4H, Ar-H), 10.32 (brs, 1H, NH) ppm. EI-MS: *m/z* 927/929 [M^+]. Anal. Calcd. For $C_{43}H_{39}ClN_8O_{12}S$; C, 55.69; H, 4.24; N, 12.08. Found: C, 55.45; H, 4.11; N, 11.88.

2,3,4,5,6-Penta-O-acetyl-D-glucose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**14**)
White powder (8.51 g, 84%), mp 122-124 °C; IR (KBr, cm^{-1}): 3244 (NH), 1683 (C=O), 1593 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.95, 1.98, 2.11, 2.13, 2.18 (5s, 15H, $5CH_3CO$), 3.37 (s, 2H, CH_2), 4.25-4.38 (m, 8H, 4′-H, 5′-H, 6′-H, $2CH_2$), 5.67-5.79 (m, 2H, 2′-H, 3′-H), 6.99 (s, 1H, CH), 7.22-7.33 (m, 5H, 1′-H, Ar-H), 7.50-7.66 (m, 5H, Ar-H), 7.75-7.88 (m, 4H, Ar-H), 10.30 (brs, 1H, NH) ppm. EI-MS: *m/z* 1013/1014 [M^+]. Anal. Calcd. For $C_{47}H_{45}ClN_8O_{14}S$; C, 55.70; H, 4.48; N, 11.06. Found: C, 55.59; H, 4.27; N, 10.83.

2,3,4,5,6-Penta-O-acetyl-D-galactose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}acetohydrazone (**15**)
White powder (8.91 g, 88%), mp 145-147 °C; IR (KBr, cm^{-1}): 3429 (NH), 1631 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.95, 1.97, 2.10, 2.14, 2.18 (5s, 15H, $5CH_3CO$), 3.35 (s, 2H, CH_2), 4.29-4.43 (m, 8H, 4′-H, 5′-H, 6′-H, $2CH_2$), 5.65-5.80 (m, 2H, 2′-H, 3′-H), 6.98 (s, 1H, CH), 7.26-7.39 (m, 5H, 1′-H, Ar-H), 7.52-7.65 (m, 5H, Ar-H), 7.70-7.80 (m, 4H, Ar-H), 10.40 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{47}H_{45}ClN_8O_{14}S$; C, 55.70; H, 4.48; N, 11.06. Found: C, 55.55; H, 4.20; N, 10.89.

***General procedure for the preparation of oxadiazoline derivatives* 16-21**
A solution of sugar hydrazones **4-9** (10 mmole) in acetic anhydride (15 ml) was boiled under reflux for 1.5 h. The resulting solution was poured onto crushed ice, and the product that separated out was filtered off, washed with a solution of sodium hydrogen carbonate followed by water and then dried. The products were recrystallized from ethanol.

4-Acetyl-5-(1,2,3,4-tetra-O-acetyl-D-xylotetritolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}-2,3-dihydro-1,3,4-oxadiazoline (**16**)
White powder (6.51 g, 73%), mp 177-179 °C; IR (KBr, cm^{-1}): 3409 (NH), 1741 (C=O), 1658 (C=O), 1606 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ EI-MS: *m/z* 893/894 [M^+]. Anal. Calcd. For $C_{39}H_{37}ClN_8O_{13}S$; C, 52.44; H, 4.17; N, 12.54. Found: C, 52.30; H, 4.03; N, 12.40.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl) methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}-2,3-dihydro-1,3,4-oxadiazoline (**17**)

White powder (7.63 g, 78%), mp 189-191^{o}C; IR (KBr, cm^{-1}): 3406 (NH), 1749 (C=O), 1658 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.97, 1.99, 2.05, 2.07, 2.16 (5s, 15H, 5CH_3CO), 3.62 (s, 2H, CH_2), 4.09-4.13 (m, 5H, 4′-H, 5′-H, 2CH_2), 5.60-5.72 (m, 2H, 2′-H, 3′-H), 6.96 (s, 1H, CH), 7.14-7.25 (m, 5H, 1′-H, Ar-H), 7.75-7.92 (m, 4H, Ar-H), 9.80 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{43}H_{43}ClN_8O_{15}S$; C, 52.93; H, 4.43; N, 11.44. Found: C, 52.88; H, 4.30; N, 11.32.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl) methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}-2,3-dihydro-1,3,4-oxadiazoline (**18**)
White powder (7.63 g, 78%), mp 119-121^{o}C; IR (KBr, cm^{-1}): 3409 (NH), 1747 (C=O), 1658 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.97, 2.03, 2.04, 2.11, 2.26 (5s, 15H, 5CH_3CO), 3.69 (s, 2H, CH_2), 4.11-4.16 (m, 5H, 4′-H, 5′-H, 2CH_2), 5.60-5.70 (m, 2H, 2′-H, 3′-H), 6.94 (s, 1H, CH), 7.14-7.25 (m, 5H, 1′-H, Ar-H), 7.75-7.95 (m, 4H, Ar-H), 9.70 (brs, 1H, NH) ppm. EI-MS: *m/z* 979 [M^{+}]. Anal. Calcd. For $C_{43}H_{43}ClN_8O_{15}S$; C, 52.93; H, 4.43; N, 11.44. Found: C, 52.80; H, 4.37; N, 11.36.

4-Acetyl-5-(1,2,3,4-tetra-O-acetyl-D-xylotetritolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}-2,3-dihydro-1,3,4-oxadiazoline (**19**)
White powder (7.65 g, 79%), mp 177-179 ^{o}C; IR (KBr, cm^{-1}): 3425 (NH), 1739 (C=O), 1687 (C=O), 1596 (C=N). EI-MS: *m/z* 969 [M^{+}]. Anal. Calcd. For $C_{45}H_{41}ClN_8O_{13}S$; C, 55.76; H, 4.26; N, 11.56. Found: C, 55.66; H, 4.11; N, 11.43.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl) methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}-2,3-dihydro-1,3,4-oxadiazoline (**20**)
White powder (8.96 g, 85%), mp 110-112 ^{o}C; IR (KBr, cm^{-1}): 3413 (NH), 1742 (C=O), 1597 (C=N). Anal. Calcd. For $C_{49}H_{47}ClN_8O_{15}S$; C, 55.76; H, 4.49; N, 10.62. Found: C, 55.69; H, 4.30; N, 10.50.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}-2,3-dihydro-1,3,4-oxadiazoline (**21**)
White powder (8.86 g, 84%), mp 132-134 ^{o}C; IR (KBr, cm^{-1}): 1744 (C=O), 1685 (C=O), 1591 (C=N). EI-MS: *m/z* 1054/1055 [M^{+}]. Anal. Calcd. For $C_{49}H_{47}ClN_8O_{15}S$; C C, 55.76; H, 4.49; N, 10.62. Found: C, 55.60; H, 4.29; N, 10.45.

Antimicrobial screening
The agar diffusion method reported by Cruickshank *et al* [29] was used for the screening process. 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 0.5 ml 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). The synthesized target compounds were dissolved each in 2 ml DMSO. In these holes, 100µl 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 h for bacteria and 72 h of incubation at 28 ^{o}C for fungi. DMSO showed no inhibition zones. The diameters of zone of inhibition were measured and compared with that of the standard, the values were tabulated. Ciprofloxacin [30, 31] (50 µg/ml) and fusidic acid [32] (50 µg/ml) were used as standard for antibacterial and antifungal activity respectively. The observed zones of inhibition are presented in Table 1.

Table 1. *In vitro* antimicrobial activity by agar diffusion method of the tested compounds.

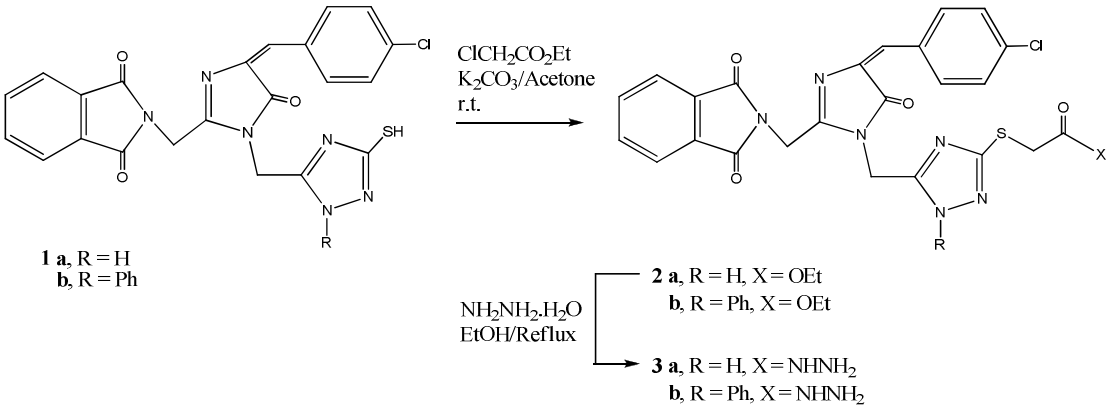
Compound No.	Zone of Inhibition (mm) of Microorganisms			
	Bacillus subtilis	*Escherichia coli*	*Candida albicans*	*Aspergillus flavus*

Penicillin	50	45	17	46
2a	11	-	8	15
2b	13	-	10	33
3a	30	25	12	9
3b	15	8	8	14
4	11	10	10	21
5	-	8	8	-
6	15	9	9	17
7	20	16	11	30
8	11	-	8	-
9	14	14	8	25
10	30	10	10	30
11	24	18	15	27
12	12	8	-	22
13	11	8	8	24
14	22	12	11	28
15	20	19	15	32
16	12	-	9	16
17	14	2	12	31
18	30	24	12	10
19	14	8	8	15
20	12	11	10	22
21	-	9	9	-

RESULTS AND DISCUSSION

In this investigation, when **1a,b** [28] were allowed to react with ethyl chloroacetate in dry acetone and in the presence of anhydrous potassium carbonate to afford the corresponding ester derivatives **2a,b** in 85-92% yields. The acid hydrazides **3a,b** were synthesized, in 97-98% yields, by refluxing its corresponding ester derivatives **2a,b** with hydrazine hydrate in ethanol (Scheme 1).

Compounds **2a,b** and **3a,b** were confirmed by I.R, ^{1}H NMR, and mass spectra which agreed with the assigned structures.

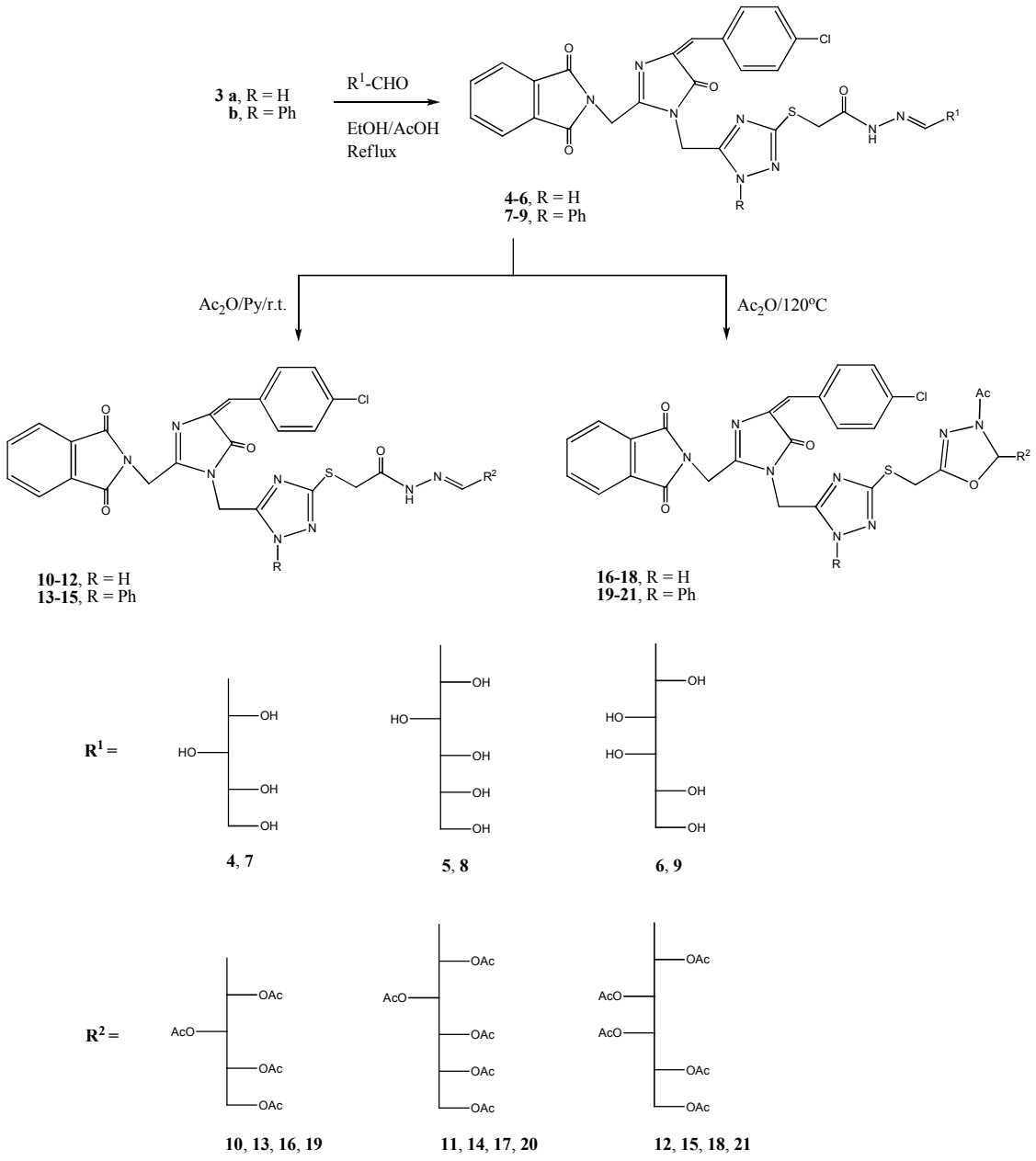


Scheme 1. Synthetic route of hydrazides **3a,b**.

When the hydrazides **3a,b** were reacted with the repective monosaccharides (D-xylose, D-glucose or D-galactose) in an aqueous ethanolic solution and a catalytic amount of glacial acetic acid, gave the corresponding hydrazinosugar derivatives **4-9** in 75-87% yields, respectively. The sugar hydrazones were confirmed by I.R, ^{1}H NMR, and mass spectra which agreed with the assigned structures.

Acetylation of the sugar hydrazones **4-9** with acetic anhydride in pyridine at room temperature gave the corresponding per-*O*-acetyl derivatives **10-15** in 80-97% yields. The per-*O*-acetyl derivatives were confirmed by I.R, ^{1}H NMR, and mass spectra which agreed with the assigned structures.

Heating of the sugar hydrazones **4-9** with acetic anhydride at 120 ^{o}C for 1.5 h afforded the corresponding oxadiazoline derivatives **16-21** in 73-84% yields (Scheme 2 and 3). The oxadiazoline derivatives were confirmed by I.R, ^{1}H NMR, and mass spectra which agreed with the assigned structures (Scheme 2).



Scheme 2. Synthetic route of compounds **4-21**.

The synthesized compounds were screened *in vitro* for their antimicrobial activities [29-32] against *Escherichia coli* NRRL B-210 (Gram -ve bacteria), *Bacillus subtilis* NRRL B-543 (Gram +ve bacteria), *Aspergillus flavus* and *Candida albicans* NRRL Y-477 (Fungi). The diameters of zone of inhibition were measured and compared with that of the standard, the values were tabulated. Tetracycline was used as standard for the antimicrobial activity and the observed zone of inhibition is presented in Table 1. The results indicated generally that tested compounds did not show high activity against bacteria under test (*Escherichia coli* and *Bacillus subtilis*) while some compounds revealed

high activity against fungi. Compounds **3a**, **10**, **11**, and **18** were the most active against *Escherichia coli* while **3a**, **11**, **15**, and **18** revealed the highest activity against *Bacillus subtilis*. Compounds **2b**, **7**, **10**, **15**, and **17** showed high activity against the fungus microorganism *Aspergillus flavus* while **3a**, **11**, **15**, and **18** were the most active among the series of tested compounds against *Candida albicans*.

Structure Activity Relationship (SAR) Studies

The antimicrobial activity results and structure activity relationship indicated that the attachment of acyclic sugar moieties to triazole and/or oxadiazoline ring system resulted in increase of antimicrobial activity. Furthermore, the hydrazones incorporating free hydroxyl sugar chains showed higher activity than the corresponding acetylated analogs. In addition, the acyclic *C*-nucleoside analogue attached to the triazole base showed high inhibition activity.

CONCLUSION

In conclusion, the antimicrobial screening suggests that all the newly synthesized compounds showed moderate to good activity against the tested organisms. Among the newly synthesized compounds **3a**, **10**, **11**, and **18** showed the most promising antibacterial and antifungal 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

[1] V. B. Jadhav, *Eur. J. Med. Chem.*, **2007**, 42, 1.
[2] N. Terzioglu, A.Gursoy, *Eur. J. Med. Chem*., **2003**, 38, 781.
[3] G. Kolavi, V. Hegde, I. Khan, P. Gadad, *Bioorg. Med. Chem.*, **2006**, 14, 3069.
[4] A. K.Gadad, C. S. Mahajanshetti, S. Nimbalkar, A. Raichur, *Eur. J . Med. Chem.*, **2000**, 35, 853.
[5] M. Kidwai, P. Mothsra, *Tetrahedron Lett.*, **2006**, 47, 5029.
[6] C. S. Andotra, T. C. Langer, A. Kotha, *J. Indian Chem. Soc.*, **1997**, 74(2), 125.
[7] S. A. Siddiqui, *Tetrahedron Lett.*, **2005**, 61, 3539.
[8] H. C. Kan, *Tetrahedron Lett*., **2007**, 63, 1644.
[9] I. A. M. Khazi, C. S. Mahajanshetti, A. K. Gadad, ,A. D. Tarnalli, C. M. Sultanpur, *Drug Res.*, **1996**, 46, 949.
[10] D. Luca, L. Curr, *J. Med. Chem.*, **2006**, 13, 1.
[11] A. Andreani, M. Rambaldi, A. Locatelli, F. Andreani, *Collect. Czech. Chem. Commun.*, **1991**, 56, 2436.
[12] W. K. Amery, C. H. Hoerig, R. I. Fenichel, M. A. Chirigose (Eds.). Immune Modulation Agents and Their Mechanism, Marcel Dekker, New York, **1984**, 383.
[13] O. Ates, A. Kocabalkanli, G. O. Sanis, A. C. Ekinci, A. Vidin, *Drug Res.*, **1997**, 47, 1134.
[14] A. R. Farghaly, J. Chin, *Chem. Soc*., **2004**, 51, 147.
[15] X. Z. Z. Li, Y. Wang, W. Chen, Q. Huang, *J. Fluor. Chem.*, **2003**, 123, 163.
[16] X. Zou, Z. Zhang, G. J. Jin., *Chem J. Res. Synop*., **2002**, 5, 228.
[17] E. Palaska, G. Sahin, P. Kelicen, N. T. Durlu, G. Altinok, *Farmaco*, **2002**, 57, 101.
[18] M. Y. Mhasalkar, M. H. Shah, P. D. Pilankar, S. T. Nikan, *J. Med. Chem.*, **1971**, 14, 1000.
[19] M. Tyagi, A. Kumar, *Orient. J. Chem.*, **2002**, 18, 125.
[20] A. A. El-Emam, A. O. Al-Deep, M. Al-Omar, J. Lehmann, *Bioorg. Med. Chem.*, **2004**, 12, 5107.
[21] H. Liszkiewicz, M. W. Kowalska, J. Wietrzyk, A. Opolski, *J. Ind. Chem. Sec. B-Org. Chem. Including Med. Chem.*, **2003**, 42B, 2846.
[22] W. A. El-Sayed, M. M. M. Ramiz, A. A.-H. Abdel-Rahman, *Monatsh. Chem.*, **2008**, 139, 1499.
[23] W. A. El-Sayed, N. M. Fathi, W. A. Gad, E. S. H. El-Ashry, *J. Carbohyd. Chem.*, **2008**, 27, 357.
[24] W. A. El-Sayed, A. A.-H. Abdel-Rahman, M. M. M. Ramiz, *Z. Naturforsch.*, **2009**, 64c, 323.
[25] W. A. El-Sayed, I. F. Nassar, A. A.-H. Abdel-Rahman, *Monatsh. Chem.*, **2009**, 140, 365.
[26] W. A. El-Sayed, A. E. Rashad, S. M. Awad, M. M. Ali, , *Nucleosides Nucleotides & Nucleic Acids*, **2009**, 28, 261.
[27] W. A. El-Sayed, I. F. Nassar, A. A.-H. Abdel Rahman, *J. Heterocyl. Chem.*, **2011**, 4, 135.
[28] A. A. Aly, S. G. Donia, A. A. F. Wasfy, M. M. Azab, A. Y. El-Gazzar, *Egyptian J. Chem.*, **2008**, 51(5), 715.
[29] R. Cruickshank, J. P. Duguid, B. P. Marion, R. H. A. Swain, Medicinal Microbiology, twelfth ed., vol. II, Churchill Livingstone, London, **1975**, 196.
[30] R. Dahiya, *Sci. Pharm.*, **2008**, 76, 217.

[31] H. C. Su, K. Ramkissoon, J. Doolittle, M. Clark, J. Khatun, A. Secrest, M. C. Wolfgang, M. C. Giddings, *Antimicrob. Agents Chemother.*, **2010**, 4626.
[32] T. F. Poyner, B. K. Dass, *J. Eur. Acad. Dermatol. Venereol.*, **1996**, 7, S23.