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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

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## INTRODUCTION

Imidazole derivatives are of interest to the medicinal chemists for many years because of their biological activities

such as anticancer, antitubercular, antibacterial, antifungal activities. Moreover, [١٠-١] 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 1H 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-1H-1,2,4

triazol-5-ylmethyl)]-5-oxo-(4,5-dihydro-1H-imidazol-2-yl)methyl}isoindoline-1,3-dione (1a) -and 2-{[4-(4

chlorobenzylidene)]-1-[(3-mercapto-1H-1,2,4-triazol-5-ylmethyl)]-5-oxo-(4,5-dihydro-1--phenyl-1H-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 oC; IR (KBr, cm-1): 3409 (NH), 1713 (C=O), 1628 (C=N). 1H-NMR (300

MHz, DMSO-d6): δ 1.22 (t, 3H, J = 5.6 Hz, CH3), 4.00 (s, 2H, CH2), 4.20 (s, 2H, CH2), 4.26 (s, ،2H, CH2), 4.21 (q

H, J = 5.6 Hz, CH2), 6.76 (s, 1H, CH), 7.15-7.25 (m, 4H, Ar-H), 7.70-7.90 (m, 4H, Ar-H), 13.20 ٢ ((brs, 1H, NH

ppm. EI-MS: m/z 564 [M+-1]. Anal. Calcd. For C26H21ClN6O5S; C, 55.27; H, 3.75; N, 14.87. ،Found: C, 55.09; H

.N, 14.59 ؛٣.٥٦

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 oC; IR (KBr, cm-1): 1687 (CON), 1593 (C=N). 1H-،NMR (300 MHz

DMSO-d6): δ 1.30 (t, 3H, J = 6.8 Hz, CH3), 3.98 (s, 2H, CH2), 4.16 (s, 2H, CH2), 4.20 (s, 2H, = CH2), 4.19 (q, 2H, J

Hz, CH2), 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, ٦.٨ .4H, Ar-H) ppm

EI-MS: m/z 641 [M+]. Anal. Calcd. For C32H25ClN6O5S; C, 59.95; H, 3.93; N, 13.11. Found: C, ،59.80; H, 3.79; N

.١٢.٩٨

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

Chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H--٤)-٤]-٥} -[imidazol-1-yl)methyl

(H-1,2,4-triazol-3-ylthio)}acetohydrazide (3a١)

White powder (5.33 g, 97%), mp 180-182 oC; IR (KBr, cm-1): 3309-3175 (NH2), 1658 (C=O), -1602 (C=N). 1H

NMR (300 MHz, DMSO-d6): δ 3.85 (s, 2H, CH2), 3.95 (s, 4H, 2CH2), 5.50 (brs, 2H, NH2), 6.78 -(s, 1H, CH), 7.45

m, 4H, Ar-H), 7.90-8.00 (m, 4H, Ar-H), 8.25 (brs, 1H, NH), 10.44 (brs, 1H, NH) ppm. EI-) ٧.٦٥ MS: m/z 549/550

M+]. Anal. Calcd. For C24H19ClN8O4S; C, 52.32; H, 3.48; N, 20.34. Found: C, 52.08; H, 3.36; ] .N, 20.11

Chlorobenzylidene)-2-(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H--٤)-٤]-٥} -imidazol-1-yl)methyl]-(1

(phenyl-1H-1,2,4-triazol-3-ylthio)}acetohydrazide (3b

White powder (6.14 g, 98%), mp 150-151 oC; IR (KBr, cm-1): 3304-3179 (NH2), 1674 (C=O), -1593 (C=N). 1H

NMR (300 MHz, DMSO-d6): δ 3.80 (s, 2H, CH2), 3.90 (s, 4H, 2CH2), 5.99 (brs, 2H, NH2), 6.75 -(s, 1H, CH), 7.08

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. ) ٧.٤٢ EI-MS: m/z 627

M+]. Anal. Calcd. For C30H23ClN8O4S; 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 oC; IR (KBr, cm-1): 3412-3169 (OH), 1658 (C=O), 1609 (C=N). 1H-NMR

MHz, DMSO-d6): δ 3.34-3.67 (m, 6H, 3'-H, 4'-H, 5'-H, CH2), 4.15 (m, 5H, 2'-H, 2CH2), ٣٠٠) ،(4.78 (brs, 3H, 3OH



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), ) ٥.٠٩ (10.50 (brs, 1H, NH

ppm. Anal. Calcd. For C29H27ClN8O8S; 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

MHz, DMSO-d6): δ 3.35-3.78 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH2), 4.22 (m, 5H, 2′-H, ٣٠٠)
،2CH2), 4.70 (brs, 3H

OH), 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, ٣
،Ar-H), 10.60 (brs

H, NH) ppm. Anal. Calcd. For C31H31ClN8O9S; C, 51.20; H, 4.30; N, 15.41. Found: C, 51.01; ١
.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

MHz, DMSO-d6): δ 3.30-3.58 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH2), 4.12 (m, 5H, 2′-H, ٣٠٠)
،2CH2), 4.56 (brs, 3H

OH), 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) ٣
.ppm. Anal. Calcd

.For C31H31ClN8O9S; 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

MHz, DMSO-d6): δ 3.25-3.55 (m, 6H, 3′-H, 4′-H, 5′-H, CH2), 4.23 (m, 5H, 2′-H, 2CH2), ٣٠٠)
،(4.50 (brs, 3H, 3OH

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), ) ٥.٠٠
،7.70-8.00 (m, 4H

Ar-H), 10.45 (brs, 1H, NH) ppm. Anal. Calcd. For C35H31ClN8O8S; C, 55.37; H, 4.12; N, 14.76.
،Found: C, 55.23; H

.N, 14.63 ؛٤.٠٢

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

MHz, DMSO-d6): δ 3.28-3.92 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH2), 4.15 (m, 5H, 2′-H, ٣٠٠) ،2CH2), 4.40 (brs, 3H

OH), 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, ٣ Ar-H), 7.73-8.00

m, 4H, Ar-H), 10.50 (brs, 1H, NH) ppm. Anal. Calcd. For C37H35ClN8O9S; C, 55.33; H, 4.39; ) ،N, 13.95. Found: C

.H, 4.30; N, 13.80 ؛٥٥.٢٣

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-d6): δ 3.25-3.88 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH2), 4.12 (m, 5H, 2′-H, 2CH2), ،(4.50 (brs, 3H, 3OH

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), ) ٥.٠٠ ،7.78-8.09 (m, 4H

Ar-H), 10.52 (brs, 1H, NH) ppm. EI-MS: m/z 803 [M+]. Anal. Calcd. For C37H35ClN8O9S; C, ،55.33; H, 4.39; N

.Found: C, 55.18; H, 4.28; N, 13.78 .١٣.٩٥

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

Tetra-O-acetyl-D-xylose {5-[4-(4-chloro benzylidene)-2-(1,3-dioxoisoindolin-2--٢,٣,٤,٥ -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

H-NMR (300 MHz, DMSO-d6): δ 1.93, 1.95, 2.06, 2.09 (4s, 12H, 4CH3CO), 3.31 (s, 2H, CH2), ١ ،4.08-4.17 (m, 6H

H, 2CH2), 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, -'٥ 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 ) ،C37H35ClN8O12S; C

.H, 4.14; N, 13.16. Found: C, 52.00; H, 4.02; N, 13.02 ؛٥٢.٢١

Penta-O-acetyl-D-glucose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2--٢,٣,٤,٥,٦ -yl)methyl]-[(5-oxo-4,5

(dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}acetohydrazone (11

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White powder (8.90 g, 95%), mp 172-174 oC; IR (KBr, cm-1): 3463 (NH), 1749 (C=O), 1659 (C=O). 1H-NMR (300

MHz, DMSO-d6): δ 1.91, 1.96, 1.98, 2.05, 2.11 (5s, 15H, 5CH3CO), 3.33 (s, 2H, CH2), 4.15- ،4.20 (m, 6H, 6'-H

CH2), 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, ٢ 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 ) ،C41H41ClN8O14S; C

.H, 4.41; N, 11.95. Found: C, 52.34; H, 4.37; N, 11.60 ؛٥٢.٥٤

Penta-O-acetyl-D-galactose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2--٢,٣,٤,٥,٦ -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 oC; IR (KBr, cm-1): 3423 (NH), 1743 (C=O), 1597 (C=N). 1H-NMR (300

MHz, DMSO-d6): δ 1.90, 1.93, 1.98, 2.06, 2.10 (5s, 15H, 5CH3CO), 3.26 (s, 2H, CH2), 4.00- ،4.12 (m, 6H, 6'-H

CH2), 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, ٢ 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

.C41H41ClN8O14S; C, 52.54; H, 4.41; N, 11.95. Found: C, 52.30; H, 4.22; N, 11.69

Tetra-O-acetyl-D-xylose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2--٢,٣,٤,٥ -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 oC; IR (KBr, cm-1): 3463 (NH), 1749 (C=O), 1659 .((C=O), 1607 (C=N

H-NMR (300 MHz, DMSO-d6): δ 1.98, 2.11, 2.13, 2.18 (4s, 12H, 4CH3CO), 3.28 (s, 2H, CH2), ١ ،4.18-4.22 (m, 7H

H, 5’-H, 2CH2), 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), -'٤ ،7.50-7.58 (m

H, Ar-H), 7.75-7.92 (m, 4H, Ar-H), 10.32 (brs, 1H, NH) ppm. EI-MS: m/z 927/929 [M+]. Anal. ٥ Calcd. For

.C43H39ClN8O12S; C, 55.69; H, 4.24; N, 12.08. Found: C, 55.45; H, 4.11; N, 11.88

Penta-O-acetyl-D-glucose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2--٢,٣,٤,٥,٦ -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 oC; IR (KBr, cm-1): 3244 (NH), 1683 (C=O), 1593 (C=N). 1H-NMR (300

MHz, DMSO-d6): δ 1.95, 1.98, 2.11, 2.13, 2.18 (5s, 15H, 5CH3CO), 3.37 (s, 2H, CH2), 4.25- -'4.38 (m, 8H, 4’-H, 5

H, 6’-H, 2CH2), 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

.C47H45ClN8O14S; C, 55.70; H, 4.48; N, 11.06. Found: C, 55.59; H, 4.27; N, 10.83

Penta-O-acetyl-D-galactose {5-[4-(4-chlorobenzylidene)-2-(1,3-dioxoisoindolin-2--٢,٣,٤,٥,٦ -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 oC; IR (KBr, cm-1): 3429 (NH), 1631 (C=O). 1H-NMR ،(300 MHz

DMSO-d6): δ 1.95, 1.97, 2.10, 2.14, 2.18 (5s, 15H, 5CH3CO), 3.35 (s, 2H, CH2), 4.29-4.43 (m, ،8H, 4'-H, 5'-H, 6'-H

CH2), 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 ٢ ،((m, 5H, Ar-H

m, 4H, Ar-H), 10.40 (brs, 1H, NH) ppm. Anal. Calcd. For C47H45ClN8O14S; C, ) ٧.٨٠-٧.٧٠ .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

Acetyl-5-(1,2,3,4-tetra-O-acetyl-D-xylotetritolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3--٤ -[dioxoisoindolin-2-yl)methyl

oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1H-1,2,4-triazol-3-ylthio)}-2,3-dihydro-1,3,4--٥)] (oxadiazoline (16

White powder (6.51 g, 73%), mp 177-179 oC; IR (KBr, cm-1): 3409 (NH), 1741 (C=O), 1658 .((C=O), 1606 (C=N

H-NMR (300 MHz, DMSO-d6): δ EI-MS: m/z 893/894 [M+]. Anal. Calcd. For ١ ؛C39H37ClN8O13S; C, 52.44; H, 4.17

.N, 12.54. Found: C, 52.30; H, 4.03; N, 12.40

Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3--٤ (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

(١٧)

White powder (7.63 g, 78%), mp 189-191oC; IR (KBr, cm-1): 3406 (NH), 1749 (C=O), 1658 .((C=O), 1607 (C=N

H-NMR (300 MHz, DMSO-d6): δ 1.97, 1.99, 2.05, 2.07, 2.16 (5s, 15H, 5CH3CO), 3.62 (s, 2H, ١ ،CH2), 4.09-4.13 (m

H, 4′-H, 5′-H, 2CH2), 5.60-5.72 (m, 2H, 2′-H, 3′-H), 6.96 (s, 1H, CH), 7.14-7.25 (m, 5H, 1′-H, ٥ Ar-H), 7.75-7.92

m, 4H, Ar-H), 9.80 (brs, 1H, NH) ppm. Anal. Calcd. For C43H43ClN8O15S; C, 52.93; H, 4.43; ) ،N, 11.44. Found: C

.H, 4.30; N, 11.32 ؛٥٢.٨٨

Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3--٤ (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

(١٨)

White powder (7.63 g, 78%), mp 119-121oC; IR (KBr, cm-1): 3409 (NH), 1747 (C=O), 1658 .((C=O), 1607 (C=N

H-NMR (300 MHz, DMSO-d6): δ 1.97, 2.03, 2.04, 2.11, 2.26 (5s, 15H, 5CH3CO), 3.69 (s, 2H, ١ ،CH2), 4.11-4.16 (m

H, 4′-H, 5′-H, 2CH2), 5.60-5.70 (m, 2H, 2′-H, 3′-H), 6.94 (s, 1H, CH), 7.14-7.25 (m, 5H, 1′-H, ٥ 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 ) ؛C43H43ClN8O15S; C, 52.93; H, 4.43

.N, 11.44. Found: C, 52.80; H, 4.37; N, 11.36

Acetyl-5-(1,2,3,4-tetra-O-acetyl-D-xylotetritolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3--٤ -[dioxoisoindolin-2-yl)methyl

oxo-4,5-dihydro-1H-imidazol-1-yl)methyl]-(1-phenyl-1H-1,2,4-triazol-3-ylthio)}-2,3--٥)] dihydro-1,3,4-oxadiazoline

(١٩)

White powder (7.65 g, 79%), mp 177-179 oC; IR (KBr, cm-1): 3425 (NH), 1739 (C=O), 1687 .((C=O), 1596 (C=N

EI-MS: m/z 969 [M+]. Anal. Calcd. For C45H41ClN8O13S; C, 55.76; H, 4.26; N, 11.56. Found: ،C, 55.66; H, 4.11; N

.١١.٤٣

Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3--٤ (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 oC; IR (KBr, cm-1): 3413 (NH), 1742 (C=O), 1597 .(C=N). Anal. Calcd

.For C49H47ClN8O15S; C, 55.76; H, 4.49; N, 10.62. Found: C, 55.69; H, 4.30; N, 10.50

Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl-{5-[4-(4-chlorobenzylidene)-2-(1,3--٤ -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 oC; IR (KBr, cm-1): 1744 (C=O), 1685 (C=O), 1591 (C=N). EI-MS: m/z

M+]. Anal. Calcd. For C49H47ClN8O15S; C C, 55.76; H, 4.49; N, 10.62. Found: C, ] ١٠٥٥/١٠٥٤ ،55.60; H, 4.29; N

.١٠.٤٥

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 oC 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 oC for 24 h for bacteria and 72 h of incubation at 28 oC 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

a 11 - 8 15٢

b 13 - 10 33٢

a 30 25 12 9٣

b 15 8 8 14٣

٢١ ١٠ ١٠ ١١ ٤

- ٨ ٨ - ٥

١٧ ٩ ٩ ١٥ ٦

٣٠ ١١ ١٦ ٢٠ ٧

- ٨ - ١١ ٨

٢٥ ٨ ١٤ ١٤ ٩

٣٠ ١٠ ١٠ ٣٠ ١٠

٢٧ ١٥ ١٨ ٢٤ ١١

٢٢ - ٨ ١٢ ١٢

٢٤ ٨ ٨ ١١ ١٣

٢٨ ١١ ١٢ ٢٢ ١٤

٣٢ ١٥ ١٩ ٢٠ ١٥

١٦ ٩ - ١٢ ١٦

٣١ ١٢ ٢ ١٤ ١٧

١٠ ١٢ ٢٤ ٣٠ ١٨

١٥ ٨ ٨ ١٤ ١٩

٢٢ ١٠ ١١ ١٢ ٢٠

- ٩ ٩ - ٢١

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, 1H NMR, and mass spectra which agreed with the assigned

.structures

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, 1H 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, 1H NMR, and mass spectra which agreed with the assigned structures



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Heating of the sugar hydrazones 4-9 with acetic anhydride at 120 oC 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, 1H NMR, and mass spectra which agreed with the assigned structures (Scheme 2

N

O

O

N

N

O

Cl

N N

N S

R

R = H ،٦-٤

R = Ph ،٩-٧

O

N

H

a, R = H ٣

b, R = Ph

R1-CHO

EtOH/AcOH

Reflux

N R1

Ac2O/Py/r.t. Ac2O/120oC

N

O

O

N

N

O

Cl

N N

N S

R

R = H ،١٢-١٠

R = Ph ،١٥-١٣

O

N

H

N R2

N

O

O

N

N

O

Cl

N N

N S

R

R = H ،١٨-١٦

R = Ph ،٢١-١٩

O

N

N

Ac

R2

= R1

OH

OH

HO

OH

OH

OH

OH

HO

OH

OH

OH

HO

OH

HO

٤، ٧ ٥، ٨ ٦، ٩

= R2

OAc

OAc

AcO

OAc

OAc

OAc

OAc

AcO

OAc

OAc

OAc

AcO

OAc

AcO

١٠، ١٣، ١٦، ١٩ ١١، ١٤، ١٧، ٢٠ ١٢، ١٥، ١٨، ٢١

.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

and 18 revealed the highest activity against Bacillus subtilis. Compounds 2b, 7, 10, 15, ،١٥ 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

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