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Synthesis of new acyclic *C*-nucleosides and their oxadiazolenes as antimicrobial agents

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ABSTRACT

2-(N-Phthalimidomethyl)-4-chlorobenzylidene-1-[2-(2-mercapto-4-oxoquinazolin-3-yl)]-5-imidazole derivatives in addition to its 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: Quinazolines, sugar hydrazones, acyclic *C*-nucleosides, antimicrobial activity.

INTRODUCTION

The synthesis of nitrogen-containing heterocyclic compounds has increasingly been a subject of great interest because of their importance. Heterocyclic compounds containing isoindole moiety are of interest because they show some pharmacological and biological activities [1–4]. Isoindole derivatives have been shown to possess antineoplastic and antiviral [5], antimalarial [6], antimycobacterium tuberculosis activity [7], antitumor [8], and antimicrobial activities [9]. 1,3,4-oxadiazole derivatives possess a broad spectrum of biological activity in both agrochemicals and pharmaceuticals such as antibacterial [10], antimicrobial [11], insecticidal [12], herbicidal, fungicidal [13], anti-inflammatory [14], hypoglycemic [15], hypotension characteristics [16], antiviral [17], and antitumor activities [18]. 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 [19-25] 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-{[2-(2-mercapto-4-oxoquinazolin-3(4*H*)-yl]-2-oxoethyl}-5-oxo-(4,5-dihydro-1*H*-imidazol-2-yl)methyl}}isoindoline-1,3-dione (**1**) was prepared according to the reported procedure [26].

Chemistry

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

To a solution of **1** [26] (5.84 g, 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 to afford white powder (5.62 g, 84%), mp 170-172 ^{o}C; IR (KBr, cm^{-1}): 1685 (C=O), 1594 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40 (t, 3H, *J* = 6.8 Hz, CH_3), 3.95 (s, 2H, CH_2), 4.05 (s, 4H, $2CH_2$), 4.10 (q, 2H, *J* = 6.8 Hz, CH_2), 6.91 (s, 1H, CH), 7.12-7.25 (m, 4H, Ar-H), 7.34-7.67 (m, 4H, Ar-H), 7.70-8.02 (m, 4H, Ar-H) ppm. EI-MS: *m/z* 669/670 [M^+]. Anal. Calcd. For $C_{33}H_{24}ClN_5O_7S$; C, 59.15; H, 3.61; N, 10.45. Found: C, 59.00; H, 3.50; N, 10.31.

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

A solution of **2** (6.70 g, 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 to give white powder (6.42 g, 98%), mp 250-252 ^{o}C; IR (KBr, cm^{-1}): 3425-3164 (NH_2), 1659 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.80 (s, 2H, CH_2), 3.90 (s, 4H, $2CH_2$), 4.95 (brs, 2H, NH_2), 6.75 (s, 1H, CH), 7.25-7.39 (m, 4H, Ar-H), 7.49-7.76 (m, 4H, Ar-H), 7.93-7.95 (m, 4H, Ar-H), 8.44 (brs, 1H, NH) ppm. EI-MS: *m/z* 654/655 [M^+]. Anal. Calcd. For $C_{31}H_{22}ClN_7O_6S$; C, 56.75; H, 3.38; N, 14.94. Found C, 56.60; H, 3.16; N, 14.79.

General procedure for the preparation of sugar hydrazones **(4-6)**

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 hydrazine derivatives **3** (6.55 g, 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 {{3-{2-[4-(4-chlorobenzylidene)]-2-[(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl) acetyl]}-(4-oxo-3,4-dihydroquinazolin-2-ylthio)}}acetohydrazone (**4**)

White powder (6.30 g, 80%), mp 244-246 ^{o}C; IR (KBr, cm^{-1}): 3320 (OH), 1680 (C=O), 1600 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.20-3.35 (m, 6H, 3′-H, 4′-H, 5′-H, CH_2), 4.20-4.30 (m, 5H, 2′-H, $2CH_2$), 4.45 (brs, 3H, 3OH), 5.09 (brs, 1H, 1OH), 6.89 (s, 1H, CH), 7.25-7.29 (m, 4H, Ar-H), 7.35-7.55 (m, 5H, 1′-H, Ar-H), 7.75-8.05 (m, 4H, Ar-H), 10.40 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{36}H_{30}ClN_7O_{11}S$; C, 54.86; H, 3.84; N, 12.44. Found C, 54.70; H, 3.66; N, 12.31.

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

White powder (6.98 g, 84%), mp 250-252 ^{o}C; IR (KBr, cm^{-1}): 3416-3023 (OH), 1655 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.39-3.67 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH_2), 4.19-4.33 (m, 5H, 2′-H, $2CH_2$), 4.49 (brs, 3H, 3OH), 5.15 (brs, 2H, 2OH), 6.99 (s, 1H, CH), 7.24-7.35 (m, 4H, Ar-H), 7.55-7.77 (m, 5H, 1′-H, Ar-H), 7.75-8.00 (m, 4H, Ar-H), 10.60 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{38}H_{34}ClN_7O_{11}S$; C, 54.84; H, 4.12; N, 11.78. Found C, 54.66; H, 4.00; N, 11.56.

D-Galactose {{3-{2-[4-(4-chloro benzylidene)]-2-[(1,3-dioxo isoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl) acetyl]}-(4-oxo-3,4-dihydroquinazolin-2-ylthio)}}acetohydrazone (**6**)

White powder (6.90 g, 83%), mp 266-268 ^{o}C; IR (KBr, cm^{-1}): 3410-3166 (OH), 1658 (C=O), 1610 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.55-3.80 (m, 7H, 3′-H, 4′-H, 5′-H, 6′-H, CH_2), 4.35-4.44 (m, 5H, 2′-H, $2CH_2$), 4.70 (brs, 3H, 3OH), 5.00 (brs, 2H, 2OH), 6.96 (s, 1H, CH), 7.25-7.38 (m, 4H, Ar-H), 7.56-7.78 (m, 5H, 1′-H, Ar-H), 7.90-8.05 (m, 4H, Ar-H), 10.45 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{38}H_{34}ClN_7O_{11}S$; C, 54.84; H, 4.12; N, 11.78. Found C, 54.60; H, 4.03; N, 11.50.

General procedure for the preparation of O-acetylsugar hydrazones **(7-9)**

To a solution of the sugar hydrazones **4-6** (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 {{3-{2-[4-(4-chlorobenzylidene)]-2-[(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetyl]}-(4-oxo-3,4-dihydroquinazolin-2-ylthio)}}acetohydrazone (**7**)

White powder (9.08 g, 95%), mp 244-245 ^{o}C; IR (KBr, cm^{-1}): 3416 (NH), 1639 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.92, 1.97, 2.06, 2.08 (4s, 12H, $4CH_3CO$), 3.36 (s, 2H, CH_2), 4.00-4.21 (m, 6H, 5′-H, $2CH_2$), 4.45-

4.49 (m, 1H, 4′-H), 5.09-5.14 (m, 1H, 3′-H), 5.35-5.45 (m, 1H, 2′-H), 6.94 (s, 1H, CH), 7.20-7.35 (m, 5H, 1′-H, Ar-H), 7.40-7.50 (m, 4H, Ar-H), 7.65-7.75 (m, 4H, Ar-H), 11.00 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{44}H_{38}ClN_7O_{14}S$; C, 55.26; H, 4.01; N, 10.25. Found C, 55.10; H, 3.89; N, 10.09.

2,3,4,5,6-Penta-O-acetyl-D-glucose {{3-{2-[4-(4-chlorobenzylidene)]-2-[(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetyl]}-(4-oxo-3,4-dihydroquinazolin-2-ylthio)}}acetohydrazone (**8**)
White powder (9.90 g, 95%), mp 138-140 °C; IR (KBr, cm^{-1}): 3174 (NH), 1665 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.91, 1.96, 1.98, 2.05, 2.11 (5s, 15H, $5CH_3CO$), 3.30 (s, 2H, CH_2), 4.15-4.26 (m, 6H, 6′-H, $2CH_2$), 4.55-4.60 (m, 2H, 4′-H, 5′-H), 5.00-5.15 (m, 1H, 3′-H), 5.50-5.60 (m, 1H, 2′-H), 6.90 (s, 1H, CH), 7.45-7.59 (m, 9H, 1′-H, Ar-H), 7.65-7.90 (m, 4H, Ar-H), 11.30 (brs, 1H, NH) ppm. EI-MS: *m/z* 1042 [M^+]. Anal. Calcd. For $C_{48}H_{44}ClN_7O_{16}S$; C, 55.31; H, 4.25; N, 9.41. Found C, 55.19; H, 4.07; N, 9.31.

2,3,4,5,6-Penta-O-acetyl-D-galactose {{3-{2-[4-(4-chlorobenzylidene)]-2-[(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetyl]}-(4-oxo-3,4-dihydroquinazolin-2-ylthio)}}acetohydrazone (**9**)
White powder (10.10 g, 97%), mp 122-124 °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 1.90, 1.93, 1.98, 2.06, 2.12 (5s, 15H, $5CH_3CO$), 3.23 (s, 2H, CH_2), 4.00-4.15 (m, 6H, 6′-H, $2CH_2$), 4.50-4.60 (m, 2H, 4′-H, 5′-H), 5.10-5.20 (m, 1H, 3′-H), 5.40-5.52 (m, 1H, 2′-H), 6.93 (s, 1H, CH), 7.15-7.33 (m, 9H, 1′-H, Ar-H), 7.75-8.00 (m, 4H, Ar-H), 11.05 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{48}H_{44}ClN_7O_{16}S$; C, 55.31; H, 4.25; N, 9.41. Found C, 55.21; H, 4.11; N, 9.27.

General procedure for the preparation of oxadiazoline derivatives **(10-12)**
A solution of sugar hydrazones **4-6** (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-{{3-{2-[4-(4-chlorobenzylidene)]-2-[(1,3-dioxoisoindolin-2-yl) methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetyl]}-(4-oxo-3,4-dihydroquinazolin-2-ylthio)}}-2,3-dihydro-1,3,4-oxadiazoline (**10**)
White powder (8.58 g, 86%), mp 160-162 °C; IR (KBr, cm^{-1}): 1660 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.90, 2.00, 2.06, 2.09, 2.14 (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), 7.14-7.27 (m, 9H, 1′-H, Ar-H), 7.75-7.95 (m, 4H, Ar-H), 11.00 (brs, 1H, NH) ppm. EI-MS: *m/z* 997/998 [M^+]. Anal. Calcd. For $C_{46}H_{40}ClN_7O_{15}S$; C, 55.34; H, 4.04; N, 9.82. Found C, 55.22; H, 3.89; N, 9.69.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl-{{3-{2-[4-(4-chlorobenzylidene)]-2-[(1,3-dioxoisoindolin-2-yl) methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetyl]}-(4-oxo-3,4-dihydroquinazolin-2-ylthio)}}-2,3-dihydro-1,3,4-oxadiazoline (**11**)
White powder (9.43 g, 87%), mp 156-158 °C; IR (KBr, cm^{-1}): 1664 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.97, 1.99, 2.05, 2.09, 2.18 (5s, 15H, $5CH_3CO$), 3.60 (s, 2H, CH_2), 4.09-4.19 (m, 5H, 4′-H, 5′-H, $2CH_2$), 5.60-5.77 (m, 2H, 2′-H, 3′-H), 6.91 (s, 1H, CH), 7.14-7.39 (m, 9H, 1′-H, Ar-H), 7.75-7.98 (m, 4H, Ar-H), 9.89 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{50}H_{46}ClN_7O_{17}S$; C, 55.38; H, 4.28; N, 9.04. Found C, 55.29; H, 4.17; N, 8.89.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl-{{3-{2-[4-(4-chlorobenzylidene)]-2-[(1,3-dioxoisoindolin-2-yl)methyl]-[(5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetyl]}-(4-oxo-3,4-dihydroquinazolin-2-ylthio)}}-2,3-dihydro-1,3,4-oxadiazoline (**12**)
White powder (9.21 g, 85%), mp 128-130 °C; IR (KBr, cm^{-1}): 1661 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.95, 2.03, 2.09, 2.11, 2.23 (5s, 15H, $5CH_3CO$), 3.73 (s, 2H, CH_2), 4.10-4.25 (m, 5H, 4′-H, 5′-H, $2CH_2$), 5.60-5.75 (m, 2H, 2′-H, 3′-H), 6.92 (s, 1H, CH), 7.19-7.35 (m, 9H, 1′-H, Ar-H), 7.75-7.90 (m, 4H, Ar-H), 9.79 (brs, 1H, NH) ppm. Anal. Calcd. For $C_{50}H_{46}ClN_7O_{17}S$; C, 55.38; H, 4.28; N, 9.04. Found C, 55.25; H, 4.19; N, 8.93.

Antimicrobial screening. The agar diffusion method reported by Cruickshank *et al* [27] 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°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, 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°C for 24 hours for

bacteria and 72 h of incubation at 28°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 [28, 29] (50 µg/mL) and fusidic acid [30] (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) Microorganisms			
	Bacillus subtilis	*Escherichia coli*	*Candida albicans*	*Aspergillus flavus*
Penicillin	50	33	17	46
2	15	9	-	17
3	20	26	11	28
4	33	-	10	-
5	45	24	10	34
6	38	21	12	37
7	12	13	13	36
8	11	9	-	20
9	14	8	9	26
10	31	21	11	27
11	34	28	16	34
12	33	-	11	36

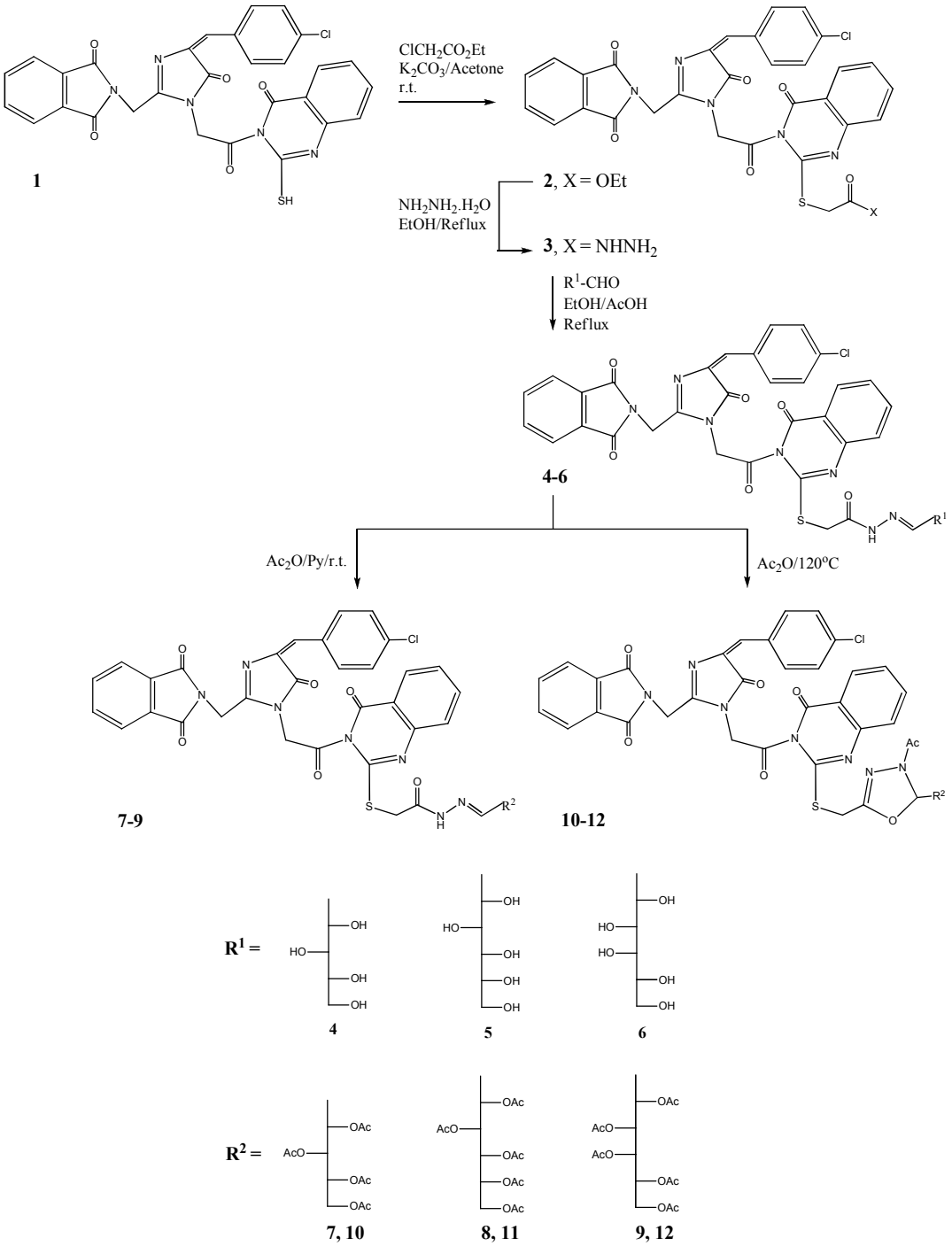
RESULTS AND DISCUSSION

In this investigation, when **1** [26] was allowed to react with ethyl chloroacetate in dry acetone and in the presence of anhydrous potassium carbonate to afford the corresponding ester derivative **2** in 84% yield. The acid hydrazide **3** was synthesized, in 98% yield, by refluxing its corresponding ester derivatives **2** with hydrazine hydrate in ethanol. Compounds **2** and **3** were confirmed by I.R, ^{1}H NMR, and mass spectra which agreed with the assigned structures.
When the hydrazides **3** was 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 **4-6** in 80-84% 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 **4-6** with acetic anhydride in pyridine at room temperature gave the corresponding per-*O*-acetyl derivatives **7-9** in 95-97% 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 **4-6** with acetic anhydride at 120 °C for 1.5 h afforded the corresponding oxadiazoline derivatives **10-12** in 85-87% yields (Scheme 1). The oxadiazoline derivatives were confirmed by I.R, ^{1}H NMR, and mass spectra which agreed with the assigned structures.

The synthesized compounds were screened *in vitro* for their antimicrobial activities [27-30] 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 **3**, **5**, **6**, **10**, and **11** were the most active against *Escherichia coli* while **4-6** and **10-12** revealed the highest activity against *Bacillus subtilis.* Compounds **5-7**, **11**, and **12** showed high activity against the fungus microorganism *Aspergillus flavus* while **3-7** and **9-12** were the most active among the series of tested compounds against *Candida albicans.*



Scheme 1. Synthesis of compounds **2-12**.

Structure Activity Relationship (SAR) Studies

The antimicrobial activity results and structure activity relationship indicated that the attachment of acyclic sugar moieties to quinazoline 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 oxadiazoline 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 **4-6** and **10-12** 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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