Preparation of New Oxadiazole Acyclic Nucleoside and Thioglycoside Analogs Containing Chromene Moiety with Antimicrobial Evaluation

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New sugar hydrazones linked to chroman ring system and their derived oxadiazole acyclic nucleoside analogs were synthesized from the substituted ethyl ester oxime derivative. The 2-sustituted 1,3,4-oxadiazole-5-thione prepared from acid hydrazide was glycosylated to afford the corresponding thioglycosides, not the N-linked glycosides. The novel compounds were evaluated for their antimicrobial activity and showed different degrees of activities.

Keywords. Chromene; Oxadiazole; Acyclic Nucleoside; Antimicrobial

Chromenes and fused chromenes are biologically interesting compounds with antimicrobial activities [1–3], inhibitors of influenza virus sialidases [4,5], DNA stand breaking activity, and mutagenicity [6]. It is also known that many chromene containing compounds exhibit a wide spectrum of pharmacological activities [7,8], anti-HIV agents [9,10], antibacterials [11,12], and antifungals [13]. In general, a number of biologically active chromenes and chromanes have been isolated from several natural sources. These substances have identified as apoptosis-inducing [14]. Among the ûve-membered nitrogen heterocycles, the 1,3,4-oxadiazoles are known to be associated with a broad spectrum of biological activities [15–17]. Their derivatives have been known to possess antibacterial [18], herbicidal, fungicidal [19], anti-inûammatory [20], hypoglycaemic [21], and hypotension characteristics [22], as well as antiviral [23] and anti-tumour activities [24]. Otherwise, the glycosylthio heterocycles [25-27] and the acyclic nucleoside (analogs with modification of both the glycon part and the heterocyclic base) have encouraged comprehensive research as biological inhibitors [28-30]. Several reports have documented the biological activity of Nucleosides and their analogs including antibiotic, antiviral, and antitumor activity [31–35]. Cyclization of diacylhydrazines is one of the preparation procedures of 1,3,4-Oxadiazole ring system [3]. In this context and also our interest in the synthesis of heterocyclic compounds holding the chromene system [38-40] and attachment of carbohydrate moieties to newly synthesized heterocycles, our aim is to synthesize a new oxadiazole acyclic nucleosides linked to chroman ring and their thioglycoside derivatives in an ongoing search for new biologically active derivatives with antimicrobial activity.

Experimental part

General methods

All reagents were used in analytical grades. Solvents were desiccated if necessary by standard methods. Reactions were monitored by TLC (silica gel 60F254, Merck, Darmstadt, Germany). Melting points were determined on a melting point apparatus (Stuart Scientific, Stone, Staffordshire, UK) and were uncorrected. The IR spectra were recorded on a perkin-Elmer 1720 FTIR spectrometer (cm^{-1}), using KBr disks. NMR spectra were carried out with a 300 MHz at Cairo University. Chemical shifts (δ) are reported in parts per million (ppm) relative to the respective solvent or tetramethylsilane (TMS) as internal standard and standard abbreviations were used (a = apparent; b = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet). Elemental analyses were performed at the Micro analytical data centre at Faculty of science, Cairo University, Egypt. Antimicrobial screening was conducted at the botany department, faculty of science, Menoufia University.

Ethyl 2-(2,2-dimethylchroman-4-ylideneamino-oxy)acetate (3)

To a solution of compound **2** (1.91 g, 10 mmol) and dry potassium carbonate (1.40 g, 10 mmol) in 15 mL acetone, ethyl chloroacetate (1.20 g, 10 mmol) was added. The reaction mixture was allowed to stir at room temperature for 6 h and then poured onto ice water. The solid separated out was filtered off, washed with water and recrystallized from ethanol to give compound **3** as white crystals, Yield 2.22 g (83%), mp 129-130 °C; IR (KBr) ν: 1740 (C=O), 1600 (C=N), 1181 (C-O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03 (t, 3H, J = 3.5 Hz CH_2CH_3), 1.27 (s, 6H, $2CH_3$), 2.90 (s, 2H, CH_2) 4.89 (q, 2H, *J* = 5.2 Hz, CH_2CH_3), 503 (s, 2H, CH_2), 7.29-7.33 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.20, 20.35 (3 CH_3), 33.39,(CH_2), 61.07 (CH_2), 72.15 (CH2), 81.15 ($C(CH3)_2$), 112.56, 117.66, 118.22, 121.77, 127.32, 151.33, 166.11 (C=N), 169.18 (C=O). Anal. Calcd for $C_{15}H_{19}NO_4$ (277.13): C, 64.97; H, 6.91; N, 5.05. Found: C, 64.02; H, 6.53; N, 5.27.

2-(2,2-Dimethylchroman-4-ylideneaminooxy) acetohydrazide (4)

In a (25 mL) one-necked flask, **3** (2.77 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) were dissolved in (20 mL) absolute ethanol. The mixture was heated to reflux for 3 h and after that, the solvent was concentrated under reduced pressure and the resulting precipitate was filtered off, washed with ethanol and recrystallized from ethanol to afford compound **4** as white crystals, Yield 1.98 g (72%), mp 197-198 °C; IR (KBr) ν: 3431-3375 (NH_2 and NH), 1690 (C=O), 1604 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.32 (s, 6H, $2CH_3$), 2.95 (s, 2H, CH_2), 4.75 (s, 2H, CH_2), 5.03

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(bs, 2H, NH_2), 10.12 (s, IH, NH), 7.29-7.33 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.23 ($2CH_3$), 35.33 (CH_2), 68.24 (CH_2), 72.64 ($C(CH_3)_2$), 114.23, 119.65, 122.22, 129.77, 139.32, 149.88, 167.11 (C=N), 169.24 (C=O). Anal. Calcd for $C_{13}H_{17}N_3O_3$ (263.13): C, 59.30; H, 6.51; N, 15.96. Found: C, 59.29; H, 5.52; N, 15.64.

Suger-[2-(2,2-Dimethylchroman-4-ylidene-aminooxy)]acetohydrazone (5-7)

To a well stirred solution of the monosaccharide (5 mmol) in water 1.5 mL, and glacial acetic acid 1.5 mL, the acetylhydrazone **4** (1.32 g, 5 mmol) in 15 mL ethanol was added. The mixture was heated under reflux for 3 h and the resulting solution was concentrated and allowed to cool. The precipitated solid was filtered off, washed with water and ethanol, then dried and recrystallized from ethanol to give compounds **5-7**.

D-Galactose-[2-(2,2-Dimethylchroman-4-ylidene-aminooxy)]acetohydrazone (5)

Yield 1.56 g (80%), mp 188-189 °C; IR (KBr) ν: 3543-3427 (OH), 3315 (NH), 1614 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 1.30 (s, 6H, 2 CH_3), 2.91 (s, 2H, CH_2), 3.36-3.39 (m, 2H, H-6,62), 3.71 (m, 1H, H-5), 4.12-4.25 (m, 2H, H-4,3), 4.36 (m, 1H, H-2), 4.47 (m, 1H, OH), 4.51 (d, 1H, *J* = 6.4 Hz, OH), 4.95 (m, 3H, CH_2 and OH), 5.19 (m, 1H, OH), 5.63 (t, 1H, *J* = 4.6 Hz, OH), 7.46 (d, 1H, *J* = 7.5 Hz, H-1), 7.85-7.96 (m, 4H, ArH), 10.14 (s, IH, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 19.47 (2 CH_3), 33.22 (CH_2), 62.10 (C-6), 63.05 (C-5), 69.21 (C-4), 70.64 ($C(CH_3)_2$),74.27 (C-3), 74.94 (CH_2), 75.88 (C-2), 152.16 (C-1), 114.54, 117.30, 120.41, 131.54, 150.65, 153.12, 166.08 (C=N), 169.15 (C=O). Anal. Calcd for $C_{19}H_{27}N_3O_8$ (425.18): C, 53.64; H, 6.40; N, 9.88. Found: C, 53.49; H, 6.11; N, 9.84.

D-Mannose-[2-(2,2-Dimethylchroman-4-ylideneaminooxy)]acetohydrazone (6)

Yield 1.54 g (72%), m.p. 195-196 °C; IR (KBr) ν: 3563-3418 (OH), 3305 (NH), 1614 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.02 (s, 6H, 2 CH_3), 2.65 (s, 2H, CH_2), 3.38-3.41 (m, 2H, H-6,62), 3.73 m (1H, H-5), 4.14-4.25 (m, 2H, H-4,3), 4.37 (m, 1H, H-2), 4.48 (m, 1H, OH), 4.52 (m, 1H, OH), 4.97 (m, 3H, CH_2 and OH), 5.20 (m, 1H, OH), 5.64 (m, 1H, OH), 7.50 (d, 1H, *J* = 7.5 Hz, H-1), 7.75-7.96 (m, 4H, ArH), 10.12 (s, IH, NH); Anal. Calcd for $C_{19}H_{27}N_3O_8$ (425.18): C, 53.64; H, 6.40; N, 9.88. Found: C, 53.44; H, 6.31; N, 9.65.

D-Arabinose-[2-(2,2-Dimethylchroman-4-ylidene-aminooxy)]acetohydrazone (7)

Yield 1.41 g (75%), mp 197-198 °C; IR (KBr) ν: 3510-3412 (OH), 3310 (NH), 1614 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 1.03 (s, 6H, 2 CH_3), 2.85 (s, 2H, CH_2), 3.35-3.40 (m, 2H, H-5,52), 3.70 (m, 1H, H-4), 4.17 (m, 1H, H-3), 4.39 (m, 1H, H-2), 4.48 (m, 1H, OH), 4.55 (d, 1H, *J* = 6.4 Hz, OH), 4.97 (s, 2H, CH_2), 5.18 (m, 1H, OH), 5.65 (m, 1H, OH), 7.51 (d, 1H, *J* = 7.5 Hz, H-1), 7.70-7.85 (m, 4H, ArH), 10.14 (s, IH, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 20.22 ($2CH_3$), 32.13 (CH_2), 62.12 (C-5), 69.11 (C-4), 71.64 ($C(CH_3)_2$), 74.27 (C-3), 74.95 (CH_2), 75.73 (C-2), 152.18 (C-1), 116.44, 117.51, 121.55, 130.29, 151.12, 155.12, 166.05 (C=N), 169.20 (C=O). Anal. Calcd for $C_{18}H_{25}N_3O_7$ (395.17): C, 54.68; H, 6.37; N, 10.63. Found: C, 54.25; H, 6.20; N, 10.33.

***O*-Acetylsugar-5-[[(2,2-dimethylchroman-4-ylideneaminooxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)butane-1,1,2,3,4-pentayl pentaacetate (8-10)**

In a (25 mL) one necked flask, a solution of sugar hydrazones **5-7** (5 mmol) in acetic anhydride (4 mL) was heated up 100°C for 1.0-1.5 h. The resulting solution was poured onto ice water, and the product which separated out on cooling was collected by filteration, washed with sodium hydrogen carbonate (50 mL) solution, followed by water (50 mL) and then dried. The products were recrystallized from ethanol-water (2:1) to give oxadiazolines **8-10**.

1-{2-(Penta-*O*-acetyl-D-galactopentitolyl)-5-[[2,2-dimethylchroman-4-ylideneaminooxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)butane-1,1,2,3,4-pentayl pentaacetate (8)

Yield 2.41 g (71%), mp 135-136 °C; IR (KBr) ν: 1738 (C=O), 1679 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.05 (s, 6H, 2 CH_3), 1.86, 1.98, 2.03, 2.11, 2.18, 2.28 (6s, 18H, $6CH_3$), 2.59 (s, 2H, CH_2), 2.88 (s, 2H, CH_2), 4.17 (dd, 1H, *J* = 11.4 Hz, *J* = 2.8 Hz, H-5), 4.22 (dd, 1H, *J* = 11.4 Hz, *J* = 3.2 Hz, H-52), 4.90 (m, 1H, H-4), 5.27 (dd, 1H, *J* = 6.5 Hz, *J* = 7.4 Hz, H-3), 5.53 (dd, 1H, *J* = 7.4 Hz, *J* = 7.2 Hz, H-2), 5.72 (t, 1H, *J* = 7.2 Hz, H-1), 5.77 (d, 1H, *J* = 7.6 Hz, oxadiazoline-H). 7.66-7.84 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) *ä*: 19.20, 20.32, 20.52, 20.64, 20.78, 21.05, 22.55 (8 CH_3), 35.12 (CH_2), 62.92 (C-5), 64.91 (C-4), 65.38 (C-3), 68.41 (C-2), 71.18 (C-1), 72.95 (CH_2), 81.64 ($C(CH_3)_2$), 91.24 (*C*-N-Ac), 116.65, 118.51, 122.56, 133.29, 151.12, 155.12, 158.22 (oxadiazoline C-2), 163.02 (C=N), 169.15, 169.82, 170.24, 170.75, 171.10, 172.18 (6 CO). Anal. Calcd for $C_{31}H_{39}N_3O_{14}$ (677.24): C, 54.94; H, 5.80; N, 6.20. Found: C, 54.73; H, 5.65; N, 6.15.

1-{2-(Penta-*O*-acetyl-D-mannopentitolyl)-5-[[(2,2-dimethylchroman-4-ylideneaminooxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)butane-1,1,2,3,4-pentayl pentaacetate (9)

Yield 2.45 g (73%), mp 133-134 °C; IR (KBr) ν: 1736 (C=O), 1672 (C=O), 1614 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.04 (s, 6H, 2 CH_3), 1.85, 1.97, 2.03, 2.10, 2.18, 2.27 (6s, 18H, 6 CH_3), 2.56 (s, 2H, CH_2), 3.01 (s, 2H, CH_2), 4.18 (dd, 1H, *J* = 11.4 Hz, *J* = 2.8 Hz, H-5), 4.22 (dd, 1H, *J* = 11.4 Hz, *J* = 3.2 Hz, H-52), 4.89 (m, 1H, H-4), 5.27 (dd, 1H, *J* = 6.5 Hz, *J* = 7.4 Hz, H-3), 5.57 (dd, 1H, *J* = 7.4 Hz, *J* = 7.2 Hz, H-2), 5.75 (t, 1H, *J* = 7.2 Hz, H-1), 5.79 (d, 1H, *J* = 7.8 Hz, oxadiazxoline-H). 7.55-7.64 (m, 4H, ArH). Anal. Calcd. for $C_{31}H_{39}N_3O_{14}$ (677.24): C, 54.94; H, 5.80; N, 6.20. Found: C, 54.73; H, 5.60; N, 6.21.

1-{2-(Tetra-*O*-acetyl-D-arabinotetritolyl)-5-[[(2,2-dimethylchroman-4-ylideneaminooxy)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)butane-1,2,3,4-tetrayl tetraacetate (10)

Yield 2.01 g (61%), mp 139-140 °C; IR (KBr) ν: 1739 (C=O), 1675 (C=O), 1615 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.03 (s, 6H, $2CH_3$), 1.85, 1.97, 2.04, 2.14, 2.29 (5s, 15H, $5CH_3$), 2.57 (s, 2H, CH_2), 3.08 (s, 2H, CH_2), 4.18 (dd, 1H, *J* = 11.4 Hz, *J* = 2.8 Hz, H-4), 4.25 (dd, 1H, *J* = 11.4 Hz, *J* = 3.2 Hz, H-42), 5.28 (dd, 1H, *J* = 6.5 Hz, *J* = 7.4 Hz, H-3), 5.54 (dd, 1H, *J* = 7.4 Hz, *J* = 7.2 Hz, H-2), 5.72 (t, 1H, *J* = 7.2 Hz, H-1), 5.77 (d, 1H, *J* = 7.6 Hz, oxadiazoline-H), 7.73-7.86 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.21, 20.31, 20.50, 20.60, 21.05, 26.14 (7 CH_3), 32.13 (CH_2), 62.95 (C-4), 65.40 (C-3), 68.40 (C-2), 71.18 (C-1), 74.90 (CH_2), 83.54 ($C(CH_3)_2$), 91.30 (*C*-N-Ac), 115.65, 119.41, 123.56, 134.22, 152.13, 156.10, 158.25 (oxadiazoline C-2), 162.95 (C=N), 169.10, 170.25, 170.75, 171.15, 172.20 (5CO). Anal. Calcd for $C_{28}H_{35}N_3O_{12}$ (605.59): C, 55.53; H, 5.83; N, 6.94. Found: C, 55.38; H, 5.66; N, 6.75.

5-((2,2-dimethylchroman-4-ylideneamino-oxy)methyl)-1,3,4-oxadiazole-2(3H)-thione (11)

To a solution of hydrazide **4** (10 mmol, 2.63 g) in pyridine (30 mL) was added carbon disulfide (3 mL). The solution was heated at 90°C for 10 h. The solvent was evaporated and the residue was poured into ice-cold water containing acetic acid (2 mL). The solid precipitate was filtered off, washed with water and recrystallized from ethanol to afford the oxadiazole **11** as yellow powder. Yield 2.35 g (77%), m.p. 149-150 °C; IR (KBr) ν: 2983 (CH), 1621 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.33 (s, 6H, 2 CH_3), 2.57

(s, 2H, CH_2), 3.22 (s, 2H, CH_2), 7.13-7.20 (m, 4H, ArH). 11.31 bs (1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.29 (2CH_3), 35.65 (CH_2), 75.44 (CH_2), 80.09 ($C(CH_3)_2$)115.13, 120.41, 125.16, 135.32, 150.13, 155.10, 157.84 (oxadiazoline C-2), 162.95 (C=N), 179.95 (C=S). Anal. Calcd for $C_{14}H_{15}N_3O_3S$ (305.08): C, 55.07; H, 4.95; N, 13.76. Found: C, 54.98; H, 4.85; N, 13.61.

***3-acetoxy-6-(5-((-2,2-dimethylchroman-4-ylideneaminooxy)methyl)-1,3,4-oxadiazol-2-ylthio)-O-*[5-glycopyranosylthio)-1,3,4-oxa-diazol-2-yl]methyl oxime (13a-c)**

General procedure: To a solution of compound **11** (1.53 g, 5 mmol) in *N,N*-dimethylformamide (7 mL) and Et_3N (0.85 mL, 6 mmol) was added the corresponding bromosugar **12** (6 mmol), and the reaction mixture was stirred at room temperature. The reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (40 mL), and washed with water (3 x 30 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated under reduced pressure, and the residue was triturated with petroleum ether (45 mL) and the solid product was filtered, dried and recrystallized from ethanol

2-acetoxymethyl-6-(5-((-2,2-dimethylchroman-4-ylideneaminooxy)methyl)-1,3,4-oxadiazol-2-ylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (13a)

Pale yellow powder (2.36 g, 73%), mp 153-154°C; IR (KBr) ν 2972 (CH), 1744 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.04, 1.25, 1.89, 1.92, 1.98, (6s, 18H, 4CH_3CO and 2CH_3), 2.79 (s, 2H, CH_2), 3.49 (s, 2H, CH_2), 4.05 (m, 1H, H-5), 4.14 (dd, 1H, $J_{6,62}$ = 11.4 Hz, $J_{5,6}$ = 2.8 Hz, H-6), 4.22 (dd, 1H, $J_{6,62}$ = 11.4 Hz, $J_{5,62}$ = 3.2 Hz, H-62), 4.94 (t, 1H, $J_{3,4}$ = 9.6 Hz, H-4), 5.20 (dd, 1H, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 5.28 (t, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 5.79 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1). 7.70-7.86 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) ä: 15.29, 19.23, 20.44, 20.65, 22.34 (4CH_3CO and 2 CH_3), 30.44 (CH_2), 62.22 (C-6), 66.14 (C-5), 68.85 (C-4), 70.19 (C-3), 71.85 (CH_2), 72.28 (C-2), 79.12 (C(CH_3)$_2$), 91.02 (C-1), 114.13, 120.88, 124.13, 136.43, 154.13, 157.33, 156.84 (oxadiazole C-2), 158.14 (oxadiazole C-5), 160.75 (C=N), 169.41, 170.52, 171.11, 171.80 (4C=O). Anal. Calcd. for $C_{28}H_{33}N_3O_{12}S$ (635.16): C, 52.91; H, 5.23; N, 6.61. Found: C, 52.85; H, 5.12; N, 6.59.

2-acetoxymethyl-6-(5-((2,2-dimethylchroman-4-ylideneaminooxy)methyl)-1,3,4-oxadiazol-2-ylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (13b)

Pale yellow powder Yield 2.19 g, (71%), m.p. 151-152°C; IR (KBr) ν 2988 (CH), 1748 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.05, 1.25, 1.88, 1.92, 1.97, (6s 18H, 4CH_3CO and 2 CH_3), 3.08 (s, 2H, CH_2), 4.09 (m, 1H, H-5), 4.15 (dd, 1H, $J_{6,62}$ = 11.2 Hz, $J_{5,6}$ = 2.8 Hz, H-6), 4.20 (dd, 1H, $J_{6,62}$ = 11.2 Hz, $J_{5,62}$ = 3.4 Hz, H-62), 5.05 (t, 1H, $J_{3,4}$ = 9.4 Hz, H-4), 5.15 (s, 2H, CH_2), 5.21 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 5.29 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.78 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 7.55-7.75 (m, 4H, ArH). Anal. Calcd. for $C_{28}H_{33}N_3O_{12}S$ (635.16): C, 52.91; H, 5.23; N, 6.61. Found: C, 52.89; H, 5.16; N, 6.55.

2-(5-((2,2-dimethylchroman-4-ylideneamino-oxy)methyl)-1,3,4-oxadiazol-2-ylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (13c)

Pale yellow powder Yield 1.88 g, (66%), mp 155-156°C; IR (KBr) ν 2980 (CH), 1741 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06, 1.25, 1.89, 1.95, (5s, 15H, 3CH_3CO and 2 CH_3), 2.50 (s, 2H, CH_2), 4.09 (s, 2H, CH_2), 4.16 (dd, 1H, $J_{5,52}$ = 10.6 Hz, $J_{4,5}$ = 2.8 Hz, H-5), 4.22 (dd, 1H, $J_{5,52}$ = 10.6 Hz, $J_{4,52}$ = 3.2 Hz, H-52), 5.02 (t, 1H, $J_{3,4}$ = 9.2 Hz, H-4), 5.24 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 5.29 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.79 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.42-7.56 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.42, 20.44, 20.65, 22.19 (3CH_3CO and 2 CH_3), 33.12 (CH_2), 63.05 (C-5), 65.35 (C-4), 70.61 (C-3), 71.90 (CH_2), 72.97 (C-2), 85.66 ($C(CH_3)_2$), 91.27 (C-1), 113.13, 119.88, 126.13, 135.43, 153.13, 156.03 156.28 (oxadiazole C-2), 157.71 (oxadiazole C-5), 161.14 (C=N), 169.82, 170.61, 171.91 (3C=O). Anal. Calcd. for $C_{25}H_{29}N_3O_{10}S$ (563.16): C, 53.28; H, 5.19; N, 7.46. Found: C, 53.15; H, 5.12; N, 7.35.

2,2-dimethylchroman-4-one *O*-[5-(D-glycopyranosylthio)-1,3,4-oxadiazol-2-yl]methyl oxime (14a-c)

General procedure: Dry gaseous ammonia was passed through a solution of a protected thioglycosides **13a-c** (5 mmol) in dry methanol (20 mL) at 0 °C for 1 h, and then the mixture was stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure at 40°C to give a solid residue, which was recrystallized from ethanol to give the corresponding free glycoside **14a-c**.

2,2-dimethylchroman-4-one O-(5-(3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-ylthio)-1,3,4-oxadiazol-2-yl)methyl oxime (14a)

Pale yellow powder Yield 1.66 g, (71%), mp 192-193°C; IR (KBr) ν 2980 (CH), 3483-3411 (OH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.06 (s, 6H, 2CH_3), 3.11 (s, 2H, CH_2), 3.47 (m, 2H, H-6,62), 3.53 (m, 1H, H-5), 4.14 (m, 2H, H-3,4), 4.37 (t, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.45 (s, 2H, CH_2), 4.76 (t, 1H, *J* = 6.2, OH), 4.85 (m, 1H, OH), 5.24 (m, 1H, OH), 5.38 (m, 1H, OH), 5.80 (d, 1H, *J* = 10.4, H-1), 7.12-7.34 (m, 4H, ArH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 24.15 (2CH_3), 36.23 (CH_2), 63.60 (C-6), 66.44 (C-4), 68.69 (C-3), 71.29 (C-2), 71.98 (CH_2), 72.88 (C-5), 80.19 ($C(CH_3)_2$) 92.14 (C-1), 112.15, 118.89, 127.13, 134.43, 152.13, 155.03, 157.15 (oxadiazole C-2), 158.12 (oxadiazole C-5), 161.58 (C=N). Anal. calcd. for $C_{20}H_{25}N_3O_8S$ (467.14): C, 51.38; H, 5.39; N, 8.99. Found: C, 51.21; H, 5.28; N, 8.87 %.

2,2-dimethylchroman-4-one O-(5-(3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-ylthio)-1,3,4-oxadiazol-2-yl)methyl oxime (14b)

Pale yellow powder Yield 1.73 g, (74%), m.p. 197-198°C; IR (KBr) ν 2980 (CH), 3488-3415 (OH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.03 (s, 6H, 2CH_3), 2.89 (s, 2H, CH_2), 3.45 (m, 2H, H-6,62), 3.53 (m, 1H, H-5), 4.06 (s, 2H, CH_2), 4.14 (m, 2H, H-3,4), 4.36 (t, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.75 (t, 1H, *J* = 6.4, OH), 4.85 (m, 1H, OH), 5.22 (m, 1H, OH), 5.38 (m, 1H, OH), 5.81 d (1H, *J* = 10.2, H-1), 6.99-7.33 (m, 4H, ArH). Anal. calcd. for $C_{20}H_{25}N_3O_8S$ (467.14): C, 51.38; H, 5.39; N, 8.99. Found: C, 51.23; H, 5.31; N, 8.71 %.

2,2-dimethylchroman-4-one O-(5-(3,4,5-trihydroxy-tetrahydro-2H-pyran-2-ylthio)-1,3,4-oxadiazol-2-yl)methyl oxime (14c)

Pale yellow powder Yield 1.50 g, (68%), mp 195-196°C; IR (KBr) ν 2955 (CH), 3481-3449 (OH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.08 (s, 6H, 2CH_3), 2.67 (s, 2H, CH_2), 3.39 (m, 2H, H-5,52), 4.07 (s, 2H, CH_2), 4.22 (m, 2H, H-3,4), 4.38 (m, 1H, H-2), 4.77 (m, 1H, OH), 5.24 (m, 1H, OH), 5.38 (m, 1H, OH), 5.82 (d, 1H, *J* = 9.8, H-1), 7.12-7.28 (m, 4H, ArH). Analysis calcd. for $C_{19}H_{23}N_3O_7S$ (437.13): C, 52.16; H, 5.30; N, 9.61. Found: C, 52.10; H, 5.20; N, 9.56 %.

Results and discussions

Chemistry

2,2-dimethylchroman-4-one oxime (**2**) was synthesized according to reported method [41]. Reaction of the 2,2-dimethylchroman-4-one oxime **2** with ethyl chloroacetate in presence of potassium carbonate gave the corresponding ethyl *O*-substituted acetyl ester **3**. The reaction of the latter ester compound with hydrazine hydrate afforded the corresponding acid hydrazide derivative **4**. The structure of compound **3** was confirmed by the presence of new signal corresponding to the new ethoxy fragment in the ^{1}H NMR spectrum, which replaced

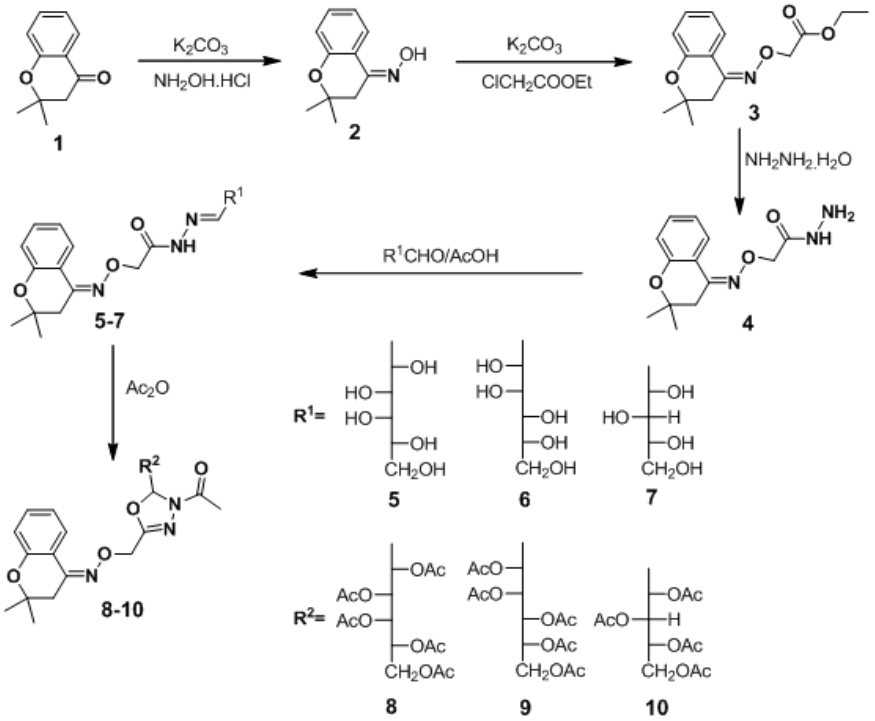
by signals attributable to the new ($NHNH_2$) for hydrazide compound **4**.

The condensation of hydrazide **4** with D-galactose, D-mannose or D-arabinose in an aqueous ethanolic solution in the presence of a catalytic amount of acetic acid provided the corresponding sugar hydrazones **5-7** respectively. The structure of these derivatives were confirmed by the appearance of new typical signals of the sugar chain protons at δ 3.36-5.65 ppm and the C-1 methine proton as doublet in the range δ 7.46-7.51 ppm for the alditolyl sugar protons. Traditionally, the reaction of sugar aroylhydrazones with acetic anhydride provides the corresponding per-*O*-acetyl derivatives. Alternatively, when the same reaction was procced in boiling acetic anhydride, cyclization usually takes place in addition to per-*O*-acetylation to give acyclic *C*-nucleoside analogs [29,42,43]. Thus, when the hydrazones **5-7** were heated in acetic anhydride at 100°C they gave the 1,3,4-oxadiazoline acyclic nucleoside analogs **8-10**, respectively. IR spectra of compounds **8-10** showed absorption bands at 1672-1679 cm^{-1} and 1736-1739 cm^{-1} due to stretching vibration of *N*-acetyl and *O*-acetyl groups, respectively. Moreover, ^1H NMR indicated the appearance of new singlet signals corresponding to the ($OCOCH_3$) protons and ($NCOCH_3$) protons and also signals corresponding to the rest of the alditolyl chain protons. The ^{13}C NMR spectrum of **8** and **10** indicated the presence of ($OCOCH_3$) carbons at δ 20.32-26.14 ppm and also the presence of signals at δ 91.24 and 91.30 ppm for (C-N-$COCH_3$, C-1 in the original sugar chain moiety and C-2 in the oxadiazoline ring) which indicated its *N,N*-acetal nature rather than being a C=N. The signals at δ 169.10-172.20 ppm correspond to the carbonyl groups (scheme 1).

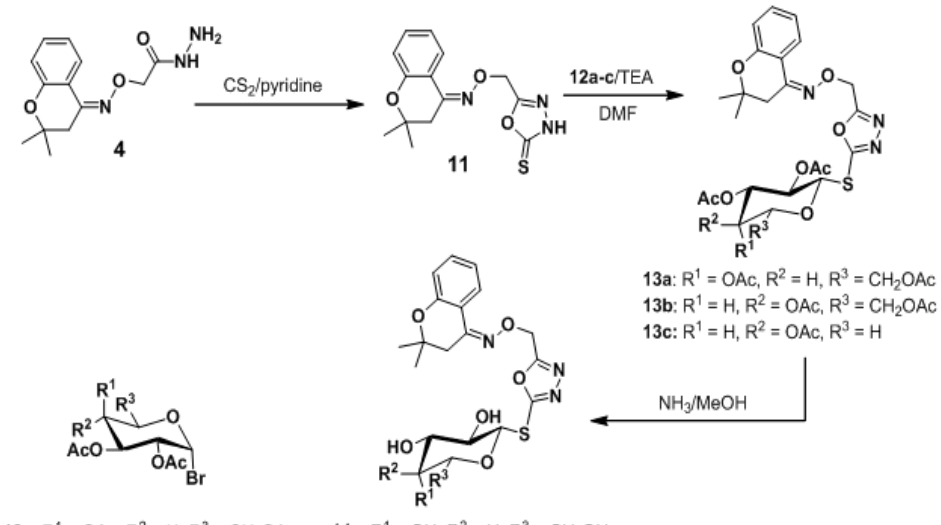
Refluxing of the acid hydrazide **4** with carbon disulfide in pyridine at 90°C yielded the 5-mercapto-1,3,4-oxadiazole derivative **11** in 77% yield, which in turn was reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-galacto-, 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide **12a-c** in DMF in the presence of triethylamine to give the corresponding substituted thioglycoside derivatives **13a-c** in good yields. The ^1H NMR of compounds **13a-c** confirmed the synthesis of these compounds. In which, the spectrum showed signals attributable to the new anomeric proton of the sugar moiety at δ 5.78-5.79 ppm, combined with a coupling constant equal to 10.4 Hz and 9.8 Hz providing the β-orientation of the thioglycosidic bond. It was reported that, the anomeric proton of β-*N*-glucosides having an adjacent C=S appear at higher chemical shift (δ 6.9–7.2 ppm) due to the anisotropic deshielding effect of the C=S in the ^1H NMR spectrum [44-47]. In addition, the absence of a signal corresponding to the C=S in the ^{13}C NMR spectrum confirmed that the attachment of the sugar moiety has been taken place at the sulfur atom rather than to the nitrogen atom which has also been supported by the low chemical shift of the anomeric proton. Deacetylation of compounds **13a-c** resulted into free thioglycosides **14a-c** which were confirmed by the spectral and analytical data. The IR spectrum showed absorption band due to stretching vibration of the hydroxyl group and the disappearance of the acetyl carbonyl bands. ^1H NMR spectra showed signals attributable to hydroxyl protons in addition to the rest of the glycosyl moiety protons at 3.39-5.82 ppm (scheme 2).

Antimicrobial activity

The antimicrobial activities of the novel-synthesized compounds were determined by the agar diffusion method [48]. In which the zone of inhibition for each derivative measured by ruler to determine its size (table 1) and compared with that produced by the standard drug (tetracycline). The compounds were evaluated for antibacterial activity against bacteria, Gram-positive bacteria; *Bacillus subtilis* and Gram-negative bacteria; *Escherichia coli*. Morover, the evaluation of these compounds against fungi (*Aspergillus flavus* and *Candida albicans*) were done. The results indicated generally that compounds showed moderate activity against Gram-positive and Gram-negative strains, while some compounds revealed high activity against fungi. Compounds **6**, **7**, **14b** and **14c** were the most active against *Escherichia coli* with inhibition zone values in the range of 31–34 mm. While **5-7**, **10**, **14b** and **14c** revealed the highest activity against *Bacillus subtilis* with inhibition zone values in the range of 30–35 mm. On the other hand Compounds **4** and **6** showed high activity against the fungus microorganism *Aspergillus flavus* while **7** and **14b** were the most active among the series of tested compounds against *Candida albicans*.



Scheme 1. Synthesis of oxadiazoline acyclic sugar derivatives



Scheme 2. Synthesis of 1,3,4-oxadiazole glycosides

Compd.	*Bacillus subtilis*	*E. coli*	*Candida albicans*	*Aspergillus flavus*
Tetracyclane	50	46	17	33
3	12	15	-	8
4	25	24	10	27
5	30	25	12	26
6	32	31	11	28
7	34	32	14	27
8	24	20	-	12
9	27	25	9	22
10	30	27	12	24
11	23	28	9	19
13a	24	25	10	22
13b	28	27	11	24
13c	27	28	11	25
14a	28	27	12	25
14b	30	33	14	24
14c	35	34	12	26

Table 1
ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

The antimicrobial activity and structure activity relationship proved that compounds with acyclic sugar moieties attached to the substituted acetyl hydrazinyl group, for example compounds **5**, **6**, and **7** exerted important effects on antibacterial activities. Alternatively, the acetylated sugar hydrazone derivatives **8**, **9**, and **10** showed lower activity than the free hydroxyl analogs. Furthermore, the attachment of free hydroxyl glycosyl moieties for example compounds **14a**, **14b**, and **14c** resulted in relatively improves activities against *Bacillus subtilis* and *Escherichia coli.*

Conclusions

In conclusion, a series of novel sugar hydrazones linked to chromene ring system and their derived oxadiazole acyclic nucleoside analogs were designed and synthesized. All the new compounds were established by IR, NMR spectra and elemental analysis. The antimicrobial activities of these novel compounds were evaluated against Gram-positive and Gram-negative bacteria and also against fungi. Glycosylation of the substituted 1,3,4-oxadiazole derivatives resulted in the formation of the corresponding thioglycosides. Moreover SAR proved that the attachment of acyclic sugar moieties to the substituted acetyl hydrazinyl derivatives as well as attachment of free hydroxyl glycosyl moieties to oxadiazole ring system resulted in relatively improved activities.

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