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Synthesis and Antimicrobial Activity of New 2,5-Disubstituted 1,3,4-Oxadiazoles and 1,2,4-Triazoles and Their Sugar Derivatives

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A series of new 2,5-disubstituted-1,3,4-oxadiazole and 1,2,4-triazole derivatives were synthesized by heterocyclization of acid hydrazide **1** and thiosemicarbazide derivative **2**. Furthermore, the acyclic *C*-nucleoside analogs were prepared by cyclization of their corresponding sugar hydrazones by reaction with acetic anhydride. The antimicrobial activity of the prepared compounds was evaluated and some of the synthesized compounds revealed good activities against fungi.

Keywords 1,3,4-oxadiazoles, 1,2,4-triazoles, sugar hydrazones, acyclic nucleosides, antimicrobial activity

Introduction

The chemistry of azoles derived *N*-bridged heterocycles has received considerable attention in recent years due to their usefulness in different areas of biological activities and as industrial intermediates. 1,3,4-Oxadiazole derivatives have been reported to possess a broad spectrum of biological activity in both agrochemicals and pharmaceuticals such as antibacterial,[1] antimicrobial,[2] insecticidal,[3] herbicidal, fungicidal,[4] anti-inflammatory,[5] hypoglycemic,[6] hypotension characteristics,[7] antiviral,[8] and antitumor activities.[9] 1,2,4-Triazole derivatives are known to exhibit antimicrobial,[10-14] antitubercular[15], anticancer,[16,17] anticonvulsant,[18] anti-inflammatory analgesic[19] and antidepressant properties.[20] The arrangement of three basic nitrogen atoms in triazole ring induces the antiviral activities in the compounds containing triazole ring.[21] 1,2,4-Triazole nucleus has been incorporated in a wide variety of therapeutically interesting drug candidates including H1/H2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, antianxiety sedatives[22] and antimycotic activity such as Fluconazole, Itraconazole and Voriconazole.[23,24] There are some known drugs containing 1,2,4-triazole moiety, *eg*., Triazolam,[25] Alprazalam,[26] Etizolam,[27] Furacylin,[28] Ribavirin[29] and Propiconazole.[30] On the other hand, the nucleosides as well as their acyclic and *C*-nucleoside analogues possess a wide range of medicinal properties, including antibiotic, antiviral, and antitumor activities.[31-35] Oxadiazole and triazole ring systems have been reported to be synthesized either by cyclization of acyclic diacylhydrazines or ring conversion.[36] In view of the above facts and as continuation of interest in identification of new valuable candidates in designing new, potent and less toxic antimicrobial agents,[35,37-41] we here report the synthesis and antimicrobial activity of new 2,5-disubstituted 1,3,4-oxadiazoles and 1,2,4-triazoles as well as their derived acyclic *C*-nucleoside analogs incorporating both ring systems.

Experimental

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 200 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a Brucker Ac-250 FT spectrometer at 250 MHz for ^{1}H and at 62.9 MHz for ^{13}C with TMS as a standard. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F 245. EI-mass spectra were measured on HP D5988 A 1000 MHz spectrometer (Hewlett-Packard, Palo Alto, CA, USA). Elemental analyses were performed at the Micro Analytical Data Centre at Faculty of Science, Cairo University, Egypt. The antimicrobial activity was measured at Botany Department, Faculty of Science, Menoufia University, Shebin El-koom, Egypt.

2-(4-Chlorophenyl)-5-[(naphthalen-2-yloxy)methyl]-1,3,4-oxadiazole (2)

A mixture of the hydrazide **1** (2.16 g, 10 mmol) and

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chlorobenzoic acid (10 mmol) was dissolved in phosphorus oxychloride (20 mL) and refluxed for 20 h. The reaction mixture was slowly poured over crushed ice and kept over night. The solid thus separated out was filtered, washed with water, dried and recrystallized from ethanol as yellow solid. Yield 85%, m.p. 108—110 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.83 (s, 2H, CH_2), 7.14—7.17 (m, 2H, ArH), 7.44 (d, J=8.2 Hz, 1H, ArH), 7.46—7.49 (m, 2H, ArH), 7.52 (d, J=7.8 Hz, 1H, ArH), 7.55 (d, J=8.5 Hz, 2H, ArH), 7.97 (d, J=8.5 Hz, 2H, ArH), 8.19 (s, 1H, ArH); IR (KBr) v: 1617 (C=N) cm^{-1}; MS m/z (%): 335 (M^+, 45). Anal. calcd for $C_{19}H_{13}ClN_2O_2$: C 67.76, H 3.89, N 8.32; found C 67.48, H 3.75, N 8.25.

N'-(1-Methylethylidene)-2-(2-naphthyloxy)acetohydrazide (3)

A solution of the hydrazide **1** (2.16 g, 10 mmol) and *p*-nitroacetophenone (1.65 g, 10 mmol) in glacial acetic acid (10 mL) was refluxed for 8 h. The solid separated upon cooling was filtered, washed with cold ethanol and recrystallized from ethanol to give the product as yellow solid. Yield 74%, m.p. 138—139 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.29 (s, 3H, CH_3), 4.86 (s, 2H, CH_2), 7.17—7.19 (m, 2H, ArH), 7.49 (d, J=8.2 Hz, 1H, ArH), 7.52—7.55 (m, 2H, ArH), 7.57 (d, J=7.8 Hz, 1H, ArH), 7.67 (d, J=8.5 Hz, 2H, ArH), 7.98 (d, J=8.5 Hz, 2H, ArH), 8.22 (s, 1H, ArH), 9.79 (brs, 1H, NH); IR (KBr) v: 3293 (NH), 1659 (C=O) cm^{-1}; MS m/z (%): 363 (M^+, 39). Anal. calcd for $C_{20}H_{17}N_3O_4$: C 66.11, H 4.72, N 11.56; found C 65.97, H 4.62, N 11.47.

3-Acetyl-5-[(2-naphthyloxy)methyl]-2-(4-nitrophenyl)-2,3-dihydro-1,3,4-oxadiazole (4)

A mixture of compound **3** (3.63 g, 10 mmol) and acetic anhydride (5 mL) was heated under reflux for 1 h. After the reaction mixture was attained at room temperature, the excess acetic anhydride was decomposed by water and the mixture was stirred for 30 min. The separated product was filtered, washed with water, dried and recrystallized from ethanol to give the product as white solid. Yield 70%, m.p. 164—165 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.23 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.89 (s, 2H, CH_2), 7.19—7.22 (m, 2H, ArH), 7.48 (d, J=8.2 Hz, 1H, ArH), 7.53—7.56 (m, 2H, ArH), 7.57 (d, J=7.8 Hz, 1H, ArH), 7.68 (d, J=8.5 Hz, 2H, ArH), 7.98 (d, J=8.5 Hz, 2H, ArH), 8.22 (s, 1H, ArH); IR (KBr) v: 1681 (C=O), 1624 (C=N) cm^{-1}; MS m/z (%): 405 (M^+, 55). Anal. calcd for $C_{22}H_{19}N_3O_5$: C 65.18, H 4.72, N 10.37; found C 65.05, H 4.60, N 10.50.

1-(2-(Naphthalen-2-yloxy)acetyl)thiosemicarbazide (5)

A suspension of the hydrazide **1** (2.16 g, 10 mmol), potassium thiocyanate (0.97 g, 10 mmol) in 36% hydrochloric acid (10 mL) and water (150 mL) was refluxed for 3.5 h. After cooling, the white solid obtained was filtered, washed with water, dried and recrystallized from ethanol to give the product as white solid. Yield 82%, m.p. 143—144 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.82 (s, 2H, CH_2), 6.02 (s, 2H, NH_2), 7.12—7.14 (m, 2H, ArH), 7.44 (d, J=8.2 Hz, 1H, ArH), 7.48—7.50 (m, 2H, ArH), 7.58 (d, J=7.8 Hz, 1H, ArH), 8.18 (s, 1H, ArH), 9.02 (brs, 1H, NH), 9.92 (brs, 1H, NH); IR (KBr) v: 3359 (NH_2), 3311 (NH), 1662 (C=O) cm^{-1}; MS m/z (%): 275 (M^+, 48). Anal. calcd for $C_{13}H_{13}N_3O_2S$: C 56.71, H 4.76, N 15.26; found C 56.55, H 4.62, N 15.14.

5-[(Naphthalen-2-yloxy)methyl]-2*H*-1,2,4-triazole-3(4*H*)-thione (6)

A solution of compound **5** (2.75 g, 10 mmol) was refluxed in 4% sodium hydroxide (25 mL) for 3 h. The resulting solution after charcoal treatment and filtration was acidified with hydrochloric acid to pH 5—6. The that separated solid was filtered, dried and recrystallized from dilute ethanol to give the product as yellow solid. Yield 71%, m.p. 156—166 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.84 (s, 2H, CH_2), 7.14—7.17 (m, 2H, ArH), 7.46 (d, J=8.2 Hz, 1H, ArH), 7.49—7.51 (m, 2H, ArH), 7.59 (d, J=7.8 Hz, 1H, ArH), 8.20 (s, 1H, ArH), 9.14 (brs, 1H, NH), 12.98 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6, 300 MHz) δ: 66.24 (CH_2), 112.17—155.40 (10 ArC), 159.93 (triazolyl C-5), 178.66 (C=S); IR (KBr) v: 3449 (NH), 1622 (C=N) cm^{-1}; MS m/z (%): 257 (M^+, 38). Anal. calcd for $C_{13}H_{11}N_3OS$: C 60.68, H 4.31, N 16.33; found C 60.52, H 4.19, N 16.18.

1-(2-(Naphthalen-2-yloxy)acetyl)-4-phenylsemicarbazide (7)

A solution of compound **1** (2.16 g, 10 mmol), and phenylisocyanate (1.19 g, 10 mmol) in ethanol (50 mL) was refluxed on steam bath for 10 h. It was then concentrated, cooled and kept overnight in a refrigerator. The solid thus separated out, was filtered, washed with ethanol, dried and recrystallized from ethanol-DMF (4 : 1) to give the product as white solid. Yield 76%, m.p. 203—204 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.83 (s, 2H, CH_2), 7.11—7.50 (m, 2H, ArH), 7.45 (d, J=8.2 Hz, 1H, ArH), 7.48—7.14 (m, 2H, ArH), 7.54 (d, J=7.8 Hz, 1H, ArH), 7.67—7.70 (m, 3H, ArH), 7.97—7.99 (m, 2H, ArH), 8.19 (s, 1H, ArH), 9.02 (brs, 1H, NH), 9.80 (brs, 1H, NH), 9.98 (brs, 1H, NH); IR (KBr) v: 3349—3311 (NH), 1682 (C=O) cm^{-1}; MS m/z (%): 335 (M^+, 49). Anal. calcd for $C_{19}H_{17}N_3O_3$: C 68.05, H 5.11, N 12.53; found C 68.15, H 4.98, N 12.39.

5-[(Naphthalen-6-yloxy)methyl]-*N*-phenyl-1,3,4-oxadiazol-2-amine (8)

A suspension of compound **7** (1.68 g, 5 mmol) in ethanol (30 mL) was dissolved in aqueous sodium hydroxide (5 mol/L, 1 mL) with cooling and stirring, resulting in a clear solution. To this mixture iodine in potassium iodide solution (5%) was added gradually with stirring till the color of iodine persisted at room temperature. The reaction mixture was then refluxed for 2 h on steam bath. The mixture was then cooled and poured

over crushed ice. The separated solid mass was filtered, dried and recrystallized from ethanol to give the product as yellow solid. Yield 62%, m.p. 198—199 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.87 (s, 2H, CH_2), 7.17—7.20 (m, 2H, ArH), 7.48 (d, J=8.2 Hz, 1H, ArH), 7.54—7.56 (m, 2H, ArH), 7.59 (d, J=7.8 Hz, 1H, ArH), 7.67—7.70 (m, 3H, ArH), 7.98—8.01 (m, 2H, ArH), 8.21 (s, 1H, ArH), 9.85 (bs, 1H, NH); IR (KBr) v: 3282 (NH), 1620 (C=N) cm^{-1}; MS m/z (%): 317 (M^+, 59). Anal. calcd for $C_{19}H_{15}N_3O_2$: C 71.91, H 4.76, N 13.24; found C 71.76, H 4.58, N 13.38.

4-Amino-5-[(naphthalen-6-yloxy)methyl]-*N*-phenyl-1,2,4-triazol-2-amine (9)

A solution of compound **8** (1.56 g, 5 mmol) and hydrazine hydrate (1.3 mol) in absolute ethanol (30 mL) was refluxed for 10 h. The solution was cooled and the resulting precipitate was filtered, dried and recrystallized from ethanol to give the product as yellow solid. Yield 70%, m.p. 189—190 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.89 (s, 2H, CH_2), 6.08 (brs, 2H, NH_2), 7.16—7.19 (m, 2H, ArH), 7.49 (d, J=8.2 Hz, H, ArH), 7.57—7.59 (m, 2H, ArH), 7.64 (d, J=7.8 Hz, 1H, ArH), 7.69—7.72 (m, 3H, ArH), 7.99—8.02 (m, 2H, ArH), 8.22 (s, 1H, ArH), 9.97 (brs, 1H, NH); IR (KBr) v: 3427 (NH_2), 1617 (C=N) cm^{-1}; MS m/z (%): 331 (M^+, 61). Anal. calcd for $C_{19}H_{17}N_5O$: C 68.87, H 5.17, N 21.13; found C 68.70, H 5.05, N 21.02.

Ethyl {[5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetate (10)

A solution of compound **6** (2.57, 10 mmol) and anhydrous potassium carbonate (10 mmol) in ethanol (25 mL) was stirred at room temperature for 1 h and ethyl chloroactate was added (1.22 g, 10 mmol), then the mixture was refluxed for 6 h. The reaction mixture was cooled and the resulting precipitate was filtered, dried and recrystallized from ethanol to give **10** as white solid 2.64 g (77%) ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.14 (t, J=6.4 Hz, 3H, CH_3), 4.05 (q, J=6.4 Hz, 2H, CH_2), 4.81 (s, 2H, CH_2), 4.96 (s, 2H, CH_2), 7.15—7.18 (m, 2H, ArH), 7.47 (d, J=8.2 Hz, 1H, ArH), 7.48—7.50 (m, 2H, ArH), 7.60 (d, J=7.8 Hz, 1H, ArH), 8.20 (s, 1H, ArH), 11.96 (brs, 1H, NH); IR (KBr) v: 3309 (NH), 1741 (C=O) cm^{-1}; MS m/z (%): 363 (M^+, 32). Anal. calcd for $C_{17}H_{17}N_3O_3S$: C 59.46, H 4.99, N 12.24; found C 59.62, H 4.91, N 12.16.

2-({5-[(Naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3yl}sulfanyl)-acetohydrazide (11)

A solution of the ester **10** (3.43 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) was refluxed in absolute ethanol (30 mL) for 8 h. The solution was cooled and the resulting precipitate was filtered, dried and recrystallized from ethanol to give the product as white solid. Yield 76%, m.p. 202—203 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.79 (s, 2H, CH_2), 4.94 (s, 2H, CH_2), 5.82 (brs, 2H, NH_2), 7.16—7.18 (m, 2H, ArH), 7.47 (d, J=8.2 Hz, 1H, ArH), 7.49—7.52 (m, 2H, ArH), 7.58 (d, J=7.8 Hz, 1H, ArH), 8.19 (s, 1H, ArH), 9.79 (brs, 1H, NH), 12.94 (brs, 1H, NH); IR (KBr) v: 331 (NH_2), 3302 (NH), 1671 (C=O), 1620 (C=N) cm^{-1}; MS m/z (%): 329 (M^+, 48). Anal. calcd for $C_{15}H_{15}N_5O_2S$: C 54.70, H 4.59, N 21.26; found C 54.61, H 4.38, N 21.18.

Sugar 2-({5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3yl}sulfanyl)acetylhydrazones (12, 13)

To a well stirred solution of the respective monosaccharide (*D*-mannose or *D*-ribose) (10 mmol) in water (2 mL) and glacial acetic acid (0.3 mL) was added the hydrazide **11** (3.29 g, 10 mmol) in ethanol (20 mL) and the mixture was heated under reflux for 9—10 h. The resulting solution was concentrated and left to cool and the precipitated solid was filtered, washed with ethanol, dried and recrystallized from ethanol-DMF (3∶1) to give compounds **12** and **13**.

D-Mannose-2-({5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3yl}sulfanyl)acetylhydrazones (**12**): The product was obtained as brownish powder. Yield 72%, m.p. 150—151 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.41—3.44 (m, 2H, H-6, H-6'), 3.53—3.55 (m, 1H, H-5), 4.15—4.17 (m, 2H, H-3,4), 4.45 (t, J=5.7 Hz, 1H, H-2), 4.58—4.60 (m, 1H, OH), 4.63 (s, 2H, CH_2), 4.78 (d, J=6.3 Hz, 1H, OH), 4.91—4.93 (m, 1H, OH), 4.95 (s, 2H, CH_2), 5.02 (t, J=4.3 Hz, 1H, OH), 5.36—5.38 (m, 1H, OH), 7.24—7.27 (m, 2H, ArH), 7.37 (d, J=7.6 Hz, 1H, H-1), 7.48 (d, J=8.2 Hz, 1H, ArH), 7.52—7.55 (m, 2H, ArH), 7.62 (d, J=7.8 Hz, 1H, ArH), 8.19 (s, 1H, ArH), 10.12 (bs, 1H, NH), 11.84 (bs, 1H, NH); IR (KBr) v: 3431—3360 (OH), 3300 (NH), 1670 (CONH), 1621 (C=N) cm^{-1}; MS m/z (%): 491 (M^+, 45). Anal. calcd for $C_{21}H_{25}N_5O_7S$: C 51.32, H 5.13, N 14.25; found C 51.24, H 5.05, N 14.11.

D-Ribose-2-({5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3yl}sulfanyl)acetylhydrazones (**13**): The product was obtained as brownish powder. Yield 69%, m.p. 142—143 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.35 (m, 2H, H-5, H-5'), 4.17—4.25 (m, 2H, H-3,4), 4.68—4.70 (m, 1H, H-2), 4.73 (m, 1H, OH), 4.79 (s, 2H, CH_2), 4.88 (d, J=6.3 Hz, 1H, OH), 4.92—4.94 (m, 1H, OH), 4.98 (s, 2H, CH_2), 5.57—5.60 (m, 1H, OH), 7.21—7.24 (m, 2H, ArH), 7.36 (d, J=7.6 Hz, 1H, H-1), 7.48 (d, J=8.2 Hz, 1H, ArH), 7.54—7.56 (m, 2H, ArH), 7.65 (d, J=7.8 Hz, 1H, ArH), 8.21 (s, 1H, ArH), 10.02 (bs, 1H, NH), 11.88 (bs, 1H, NH); IR (KBr) v: 3434—3362 (OH), 3290 (NH), 1667 (CONH), 1619 (C=N) cm^{-1}; MS m/z (%): 461 (M^+, 42). Anal. calcd for $C_{20}H_{23}N_5O_6S$: C 52.05, H 5.02, N 15.18; found C 51.94, H 4.95, N 15.02.

***O*-Acetyl-*D*-sugar-2-({5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3yl}sulfanyl)acetlhydrazones (14, 15)**

To a solution of the sugar hydrazone **13** or **14** (5 mmol) in pyridine (5 mL) was added acetic anhydride (3 mL) and the mixture was stirred for 6 h. The resulting solution was poured onto crushed ice, and the separated

product was filtered off, washed with potassium hydrogen carbonate and water then dried. The products were recrystallized from ethanol.

Penta-*O*-acetyl-*D*-mannopentitolyl-2-({4-acetyl-5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3-yl}-sulfanyl)acetylhydrazones (**14**): The product was obtained as brownish powder. Yield 79%, m.p. 90—92 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.90 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.98 (dd, J=11.2, 2.8 Hz, 1H, H-6), 4.11 (dd, J=11.2, 3.2 Hz, 1H, H-6'), 4.19—4.21 (m, 1H, H-5), 4.21 (t, J=7.2 Hz, 1H, H-4), 4.68 (s, 2H, CH_2), 4.95 (s, 2H, CH_2), 5.22 (dd, J=7.8, 7.2 Hz, 1H, H-3), 5.26 (dd, J=7.8, 9.8 Hz, 1H, H-2), 7.21—7.24 (m, 2H, ArH), 7.36 (d, J=7.6 Hz, 1H, H-1), 7.48 (d, J=8.2 Hz, 1H, ArH), 7.56—7.58 (m, 2H, ArH), 7.67 (d, J=7.8 Hz, 1H, ArH), 8.20 (s, 1H, ArH), 10.05 (brs, 1H, NH); IR (KBr) v: 1737 (C=O), 1680 (C=O), 1618 (C=N) cm^{-1}; MS m/z (%): 743 (M^+, 40). Anal. calcd for $C_{33}H_{37}N_5O_{13}S$: C 53.29, H 5.01, N 9.42; found C 53.18, H 4.94, N 9.28.

Tetra-*O*-acetyl-*D*-ribotetritolyl-2-({4-acetyl-5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3yl}sulfanyl)-acetylhydrazones (**15**): The product was obtained as brownish powder. Yield 76%; m.p. 96—97 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.92, 1.98, 2.02, 2.05, 2.25 (5s, 15H, 5CH_3), 3.97 (dd, J=11.2, 2.8 Hz, 1H, H-5), 4.14 (dd, J=11.2, 3.2 Hz, 1H, H-5'), 4.24—4.26 (m, 1H, H-4), 4.62 (s, 2H, CH_2), 4.94 (s, 2H, CH_2), 5.20 (dd, J=7.8, 7.2 Hz, 1H, H-3), 5.28 (dd, J=7.8, 9.8 Hz, 1H, H-2), 7.24—7.27 (m, 2H, ArH), 7.38 (d, J=7.6 Hz, 1H, H-1), 7.45 (d, J=8.2 Hz, 1H, ArH), 7.58—7.61 (m, 2H, ArH), 7.67 (d, J=7.8 Hz, 1H, ArH), 8.21 (s, 1H, ArH), 10.14 (brs, 1H, NH); IR (KBr) v: 1736 (C=O), 1669 (C=O), 1614 (C=N) cm^{-1}; MS m/z (%): 671 (M^+, 39). Anal. calcd for $C_{30}H_{33}N_5O_{11}S$: C 53.65, H 4.95, N 10.43. found: C 53.42, H 4.90, N 10.35.

1-{5-[[5-[(Naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3-ylthio]-methyl]-2-(*O*-acetylsugar)-1,3,4-oxadiazol-3(2*H*)-yl}ethanone (16, 17)

A solution of sugar hydrazones **12** or **13** (5 mmol) in acetic anhydride (5 mL) was heated at 100 ℃ for 2 h. The resulting solution was poured onto crushed ice, and the product that separated out was filtered off, washed with potassium hydrogen carbonate and water then dried. The products were recrystallized from ethanol.

1-{5-[[4-Acetyl-5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3-ylthio]-methyl]-2-(penta-*O*-acetyl-*D*-mannopentitolyl)-1,3,4-oxadiazol-3(2*H*)-yl}ethanone (**16**): The product was obtained as brownish powder. Yield 62%; m.p. 98—99 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.92 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.96 (dd, J=11.2, 2.8 Hz, 1H, H-6), 4.09 (dd, J=11.2, 3.2 Hz, 1H, H-6'), 4.17—4.20 (m, 1H, H-5), 4.22 (t, J=7.2 Hz, 1H, H-4), 4.64 (s, 2H, CH_2), 4.95 (s, 2H, CH_2), 5.28 (dd, J=7.8, 7.2 Hz, 1H, H-3), 5.37 (dd, J=7.8, 9.8 Hz, 1H, H-2), 5.76 (d, J=9.8, 1H, oxadiazoline H-2), 7.18—7.21 (m, 2H, ArH), 7.44 (d, J=8.2 Hz, 1H, ArH), 7.57—7.59 (m, 2H, ArH), 7.64 (d, J=7.8 Hz, 1H, ArH), 8.18 (s, 1H, ArH); IR (KBr) v: 1732 (C=O), 1664 (C=O), 1620 (C=N) cm^{-1}; MS m/z (%): 785 (M^+, 42). Anal. calcd for $C_{35}H_{39}N_5O_{14}S$: C 53.50, H 5.00, N 8.91; found C 53.32, H 4.88, N 8.74.

1-{5-[[4-Acetyl-5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazol-3-ylthio]-methyl]-2-(tetra-*O*-acetyl-*D*-ribotetritolyl)-1,3,4-oxadiazol-3(2*H*)-yl}ethanone (**17**): The product was obtained as brownish powder; 60%, m.p. 101—102 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.96 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.96 (dd, J=11.2, 2.8 Hz, 1H, H-5), 4.10 (dd, J=11.2, 3.2 Hz, 1H, H-5'), 4.24—4.26 (m, 1H, H-4), 4.66 (s, 2H, CH_2), 4.98 (s, 2H, CH_2), 5.24 (dd, J=7.8, 7.2 Hz, 1H, H-3), 5.36 (dd, J=7.8, 9.8 Hz, 1H, H-2), 5.78 (d, J=9.8 Hz, 1H, oxadiazoline H-2), 7.25—7.28 (m, 2H, ArH), 7.45 (d, J=8.2 Hz, 1H, ArH), 7.57—7.60 (m, 2H, ArH), 7.65 (d, J=7.8 Hz, 1H, ArH), 8.20 (brs, 1H, ArH); IR (KBr) v: 1738 (C=O), 1671 (C=O), 1618 (C=N) cm^{-1}; MS m/z (%): 713 (M^+, 29). Anal. calcd for $C_{32}H_{35}N_5O_{12}S$: C 53.85, H 4.94, N 9.81; found C 53.59, H 4.84, N, 9.77.

Results and Discussion

Reaction of the acetohydrazide derivative **1** with chlorobenzoic acid in phosphorus oxychloride at reflux temperature afforded 2,5-disubstituted-1,3,4-oxadiazole derivative **2** in 85% yield.

When the hydrazide **1** was reacted with *p*-nitroacetophenone in presence of acetic acid at reflux temperature, it afforded the arylidinacetohydrazide derivative **3**. The IR spectrum of the produced arylidine **3** showed the carbonyl absorption band at 1659 cm^{-1} and its ^{1}H NMR spectrum agreed with the assigned structure.

Treatment of the arylidinehydrazide **3** with acetic anhydride at reflux temperature afforded the substituted 1,3,4-oxadiazole derivative **4** in 70% yield. The ^{1}H NMR spectrum of **4** showed the signals of the methyl group signals at δ 2.23 and 2.30, each as singlet in addition to the CH_2 at δ 4.89, and the aromatic protons in the range 7.19—8.22.

When the acetohydrazide **1** was reacted with potassium thiocyanate in acidic medium it afforded the hydrazinecarboxylate derivative **5** in 87% yield. Its IR spectrum showed characteristic absorption bands for the NH_2 and carbonyl groups at 3359 and 1662 cm^{-1}, respectively. Heating of compound **5** in 4% sodium hydroxide solution led to the formation of the substituted 1,2,4-triazole-3-thiol **6** in 75% yield. Its ^{1}H NMR spectrum showed signals corresponding to NH, and CH_2

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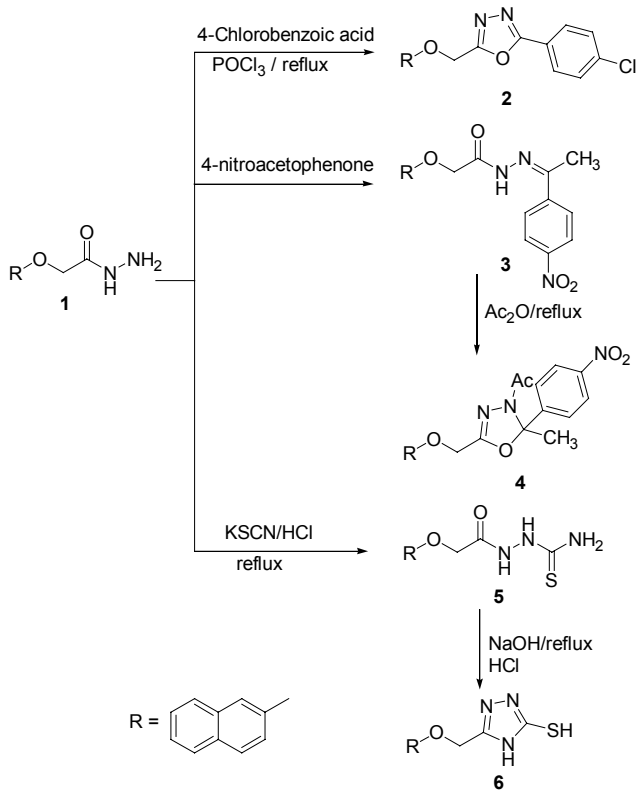
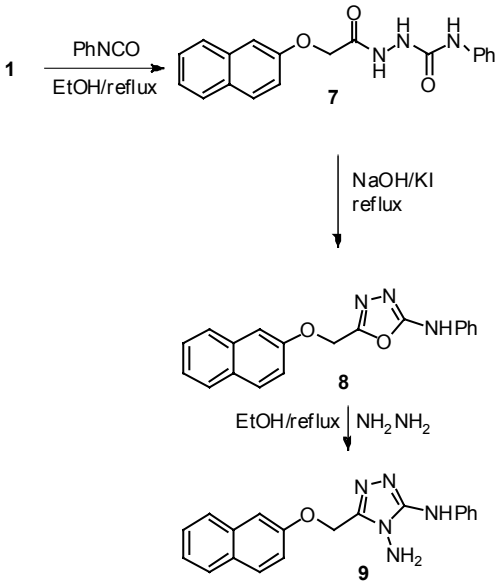
Scheme 1 Synthesis of compounds **2**—**6**



Scheme 2 Synthesis of compounds **7**—**9**



groups in addition to aromatic proton signals (see experimental part).

When the acetohydrazide **1** was reacted with phenylisocyanate in ethanol it afforded the phenylhydrazine carboxamide derivative **7**. Heating of compound **7** in ethanol in presence of sodium hydroxide and iodine in potassium iodide solution afforded the 2,5-disubstituted-1,3,4-oxadiazole derivative **8**. Its ^{1}H NMR spectrum showed the CH_2 signal at δ 4.87 in addition to the aromatic proton signals at 7.18—8.21. Treatment of the oxadiazole **8** with hydrazine hydrate in ethanol at reflux temperature afforded N^4-amino-1,2,4-triazole derivative **9** in 70% yield. The IR spectrum showed the NH_2 absorption band at 3427 cm^{-1} and the ^{1}H NMR as well as MS spectra agreed with the assigned structure (Scheme 2).

When the 1,2,4-triazole-3-thiol (**5**) was reacted with ethyl chloroacetate at room temperature, it afforded the corresponding ethyl ester derivative **10** in 77% yield. Its IR spectra showed the NH and carbonyl absorption bands at 3309 and 1741 cm^{-1}, respectively. Treatment of the ester **10** with hydrazine hydrate in ethanol at the reflux temperature afforded the acetohydrazide **11** in 75% yield. The ^{1}H NMR spectrum of **11** revealed the disappearance of the ethyl signals present in the ester **10** and instead signals corresponding to the NH and NH_2 appeared at δ 5.82 and 9.79.

When the hydrazide **11** was allowed to react with *D*-mannose and *D*-ribose in an aqueous ethanolic solution and a catalytic amount of acetic acid, the corresponding sugar hydrazones **12** and **13** were obtained in 65%—70% yields. Their IR spectra showed the presence of characteristic absorption bands corresponding to the hydroxyl groups in the rang 3462—3431 cm^{-1}. The ^{1}H NMR spectra showed the signals of the sugar chain protons at δ 3.35—5.57 and the C-1 methine proton as doublet in the range δ 7.54—7.57 in addition to the aromatic protons in the region δ 7.21—8.21. It is well known that[42-47] reaction of sugar aroylhydrazones with acetic anhydride could afford different products according to the applied reaction conditions. Acetylation of the sugar hydrazones **12** and **13** with acetic anhydride in pyridine at room temperature afforded the corresponding per-*O*-acetyl derivatives **14** and **15**. Their spectral data revealed also that triazole N^4-acetylation had also taken place in addition to acetylation of the sugar moiety. However, it has been reported[42-48] that when the reaction was carried out at high temperature in boiling acetic anhydride, cyclization usually takes place in addition to per-*O*-acetylation to afford acyclic *C*-nucleoside analogs. We reported previously[38,42] the synthesis of 1,2,4-triazolo[1,3,4]oxadiazole and *N*-acetyl-1,3,4-oxadiazoline acyclic nucleoside analogs by the reaction of hydrazonyl sugars with boiling acetic anhydride. Thus, when the hydrazones **12** and **13** were heated in acetic anhydride at 100 ℃ they gave the 1,3,4-oxadiazoline acyclic nucleoside analogs **16** and **17**, respectively. The later structures were established on the basis of their spectral and analytical data which confirmed the assigned structures. Their IR spectra showed absorption bands in the carbonyl frequency region of 1664—1671 cm^{-1} and 1732—1738 cm^{-1} corresponding to the carbonyl amide and the carbonyl ester groups, respectively, indicating the presence of *N*-acetyl group in addition to the *O*-acetyl groups. The ^{1}H NMR spectra of **16** and **17** showed the signals of the *O*-acetyl-methyl protons each as singlet in the rang δ 1.92—2.12 and the

N-acetyl-methyl protons in the range δ 2.23—2.26. The rest of the sugar chain protons appeared in the region δ 3.96—5.39 in addition to the aromatic protons in the region δ 7.18—8.20. The low chemical shift (δ 5.76 and 5.78) assigned for the oxadiazoline H-2 (H-1 in the original sugar chain) proved its *N*,*N*-acetal nature rather than being a C=N indicating cyclization had taken place.[42,43,46,47] The chemical shift of H-1 for acetylated sugar moieties in hydrazonyl sugars was reported to appear at higher values (δ 7.00—7.35).[43]

The disappearance of the NH signal corresponding to the N-4 in the triazole ring and presence of a signal assigned for an *N*-acetyl methyl group indicated that N^4-acetylation had also taken place in addition to acetylation of the sugar moiety (Scheme. 3).

Antimicrobial activity

The synthesized compounds were screened *in vitro* for their antimicrobial activities[47] 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, and 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 **4**, **12** and **13** were the most active against *Escherichia coli* while **4**, **13** and **17** revealed the highest activity against *Bacillus subtilis*. Compounds **3**, **9**, **12** and **17** showed high activity against the fungus microorganism *Aspergillus flavus* while **4**, **13** and **17** were the most active among the series of tested compounds against *Candida albicans*.

Structure-activity relationship The antimicrobial activity results and structure-activity relationship indicated that substitution at *N*-3 and incorporation of *p*-nitrophenyl moiety in the 1,3,4-oxadiazole in compound 4 revealed higher activity as the activity was reduced in compound 8. Furthermore, the attachment of acyclic sugar moieties to the substituted hydrazonyl triazole ring system resulted in higher activities.

Additionally, the sugar hydrazones with free hydroxyl acyclic sugar moieties showed higher activity values than the corresponding acetylated analogs. The methylethylidene derivative with *p*-nitrophenyl ring showed high activity against *Aspergillus flavus*. In addition, the acyclic nucleoside analog with the acetylated riptetritolyl moiety attached to the oxadiazoline base exhibited relatively higher activity than the corresponding mannopentitolyl against *Escherichia coli*, *Asper-*

Scheme 3 Synthesis of compounds **10**—**17**

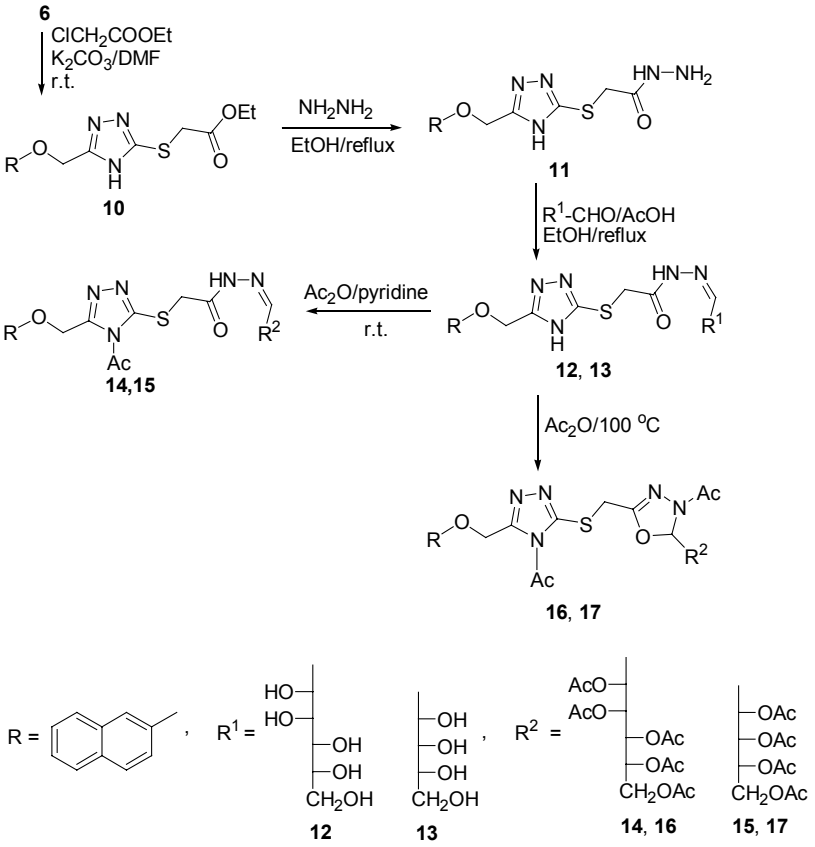


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Table 1 Antimicrobial activity of new compounds

Asperg. lavus	*Candida albicans*	*E. coli*	*Bacillus subtilis*	Compd.
33	17	46	50	Ref.
15	8	—	11	2
33	10	—	13	3
9	12	25	30	4
14	8	8	15	5
21	10	10	11	6
—	8	8	—	7
17	9	9	15	8
30	11	16	20	9
—	8	—	11	10
25	8	14	14	11
30	10	10	30	12
27	15	18	24	13
22	—	8	12	14
24	8	8	11	15
28	11	12	22	16
32	15	19	20	17

gillus flavus and *Candida albicans*.

Conclusions

New 2,5-disubstituted-1,3,4-oxadiazole and 1,2,4-triazole derivatives were synthesized. The derived acyclic *C*-nucleoside analogs were also prepared via cyclization of the corresponding sugar hydrazones. Substitution at *N*-3 and incorporation of *p*-nitrophenyl moiety in the 1,3,4-oxadiazole ring and attachment of free hydroxyl acyclic sugar moiety to 1,2,4-triazole increased antimicrobial activity.

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