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Synthesis and Antimicrobial Activity of New Substituted [(Pyridinyloxy) Methyl] Thiadiazoles and Their Sugar Derivatives

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Abstract: New 1, 3, 4-thiadiazole derivatives were synthesized from 4-substituted pyridyl ester. Furthermore, the corresponding sugar hydrazones and acyclic C-nucleoside analogs were prepared. The antimicrobial activity of the newly synthesized compounds was evaluated and some of them showed good activities.

Key words: 1,3,4-Thiadiazoles · Sugar hydrazones · 1,3,4-oxadiazolines · Antimicrobial activity

INTRODUCTION

The pyridine ring found wide interest in the chemistry of biological system because of their presence as substructure in many natural products of therapeutic importance. The potent biological activity of various vitamins and drugs [1-3] is primarily contributed by incorporation of pyridine ring system in their molecular make-up. Many compounds with potent antibacterial, antifungal and anticancer properties [4-7] incorporate the pyridine ring system in their skeleton. A number of pyridine derivatives exhibit a wide range of biological activity among which anti-tumor and cytotoxic activities [8-10] were described. On the other hand, 1, 3, 4-thiadiazoles exhibit broad spectrum of biological activities, possibly due to the presence of toxophoric NeCe S moiety [11]. They have been found to possess antibacterial, anti-tumor, anti-inflammatory, pesticide and herbicide activities as well as being dyes, lubricants and analytical reagents [12-16].

The nucleosides as well as their acyclic and *C*-nucleoside analogues possess a wide range of medicinal properties, including antibiotic, antiviral and antitumor activities [17-27]. In view of the above facts and our interest [28-34] in the attachment of carbohydrate residues to heterocycles searching for new potentially active leads, we report here the synthesis and antimicrobial activity of new substituted 5-(pyridine-3-yl)-1,3,4-thiadiazoles, their sugar hydrazones and acyclic *C*-nucleoside analogs as well as the corresponding glycoside derivatives.

MATERIALS AND METHODS

Chemistry: Melting points were determined with a *kofler* block apparatus and are uncorrected. The IR spectra were recorded on a perkin-Elmer model 1720FTIR spectrometer for KBr disc. NMR spectra were recorded on a varian Gemini 200 NMR Spectrometer at 300 MHz for 1H or on a brucker Ac-250 FT spectrometer at 250 MHz for 1H 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 recorded on a varian MAT 311A spectrometer. The antimicrobial activity against four microorganisms was measured at Botany Department, Faculty of Science, Menoufia University, Shebin El-Koom, Egypt.

Ethyl-2-(pyridine-4-yloxy)acetate (2): A mixture of 4-hydroxypyridine (1) (0.95 g, 0.01 mole), anhydrous K_2CO_3 (1.38 g, 0.01 mol) in DMF (20 mL). The reaction mixture was stirred for 2h and then ethylchloacetate (1.22 g, 0.01 mole) was added. The reaction mixture was stirred for 15 h at room temperature and pured onto ice-cold water. The solid precipitated was filtered off, washed with water and recrystallized from ethanol to afford 2 as white solid. Yield (70%), mp 76-77°C; IR spectrum (KBr, υ, cm^{-1}): 1737

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(C=O), 1618 (C=N); ^{1}H NMR spectrum (DMSO-d_6,δ ppm): 1.28 (t, J = 5.8 Hz, 3H, CH_3), 4.11 (q, J = 5.8 Hz, 2H, CH_2), 4.92 (s, 2H, CH_2), 7.63 (d, 2H, J = 7.6 Hz, Ar-H), 7.95 (d, 2H, J = 7.6 Hz, Ar-H). Anal. Calcd. for $C_9H_{11}NO_3$ (181): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.72; H, 6.02; N, 7.59.

1-[2-(pyridin-4-Yloxy)acetyl] thiosemicarbazide (3): A mixture of compound 2 (1.81 g, 0.01 mole), thiosemicarbazide (0.91 g, 0.01 mole) in methanol (50 ml) was refluxed for 1 hr. The completion of reaction was checked by TLC and excess of methanol was distilled off. The cooled reaction mixture was poured into ice-water, filtered, washed with water, dried and recrystallized from methanol to obtain compound 3 as brown solid. Yield (72%), mp 189-190°C; IR spectrum (KBr, υ, cm^{-1}): 3342-3294 (NH_2 and NH), 1620 (C=N). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 4.95 (s, 2H, CH_2), 5.39 (bs, 2H, NH_2), 7.63 (d, 2H, J = 7.6 Hz, Ar-H), 7.94 (d, 2H, J = 7.6 Hz, Ar-H), 9.14 (bs, 1H, NH), 9.72 (bs, 1H, NH). Anal. Calcd. for $C_8H_{10}N_4O_2S$ (226): C, 42.47; H, 4.45; N, 24.76. Found: C, 42.28; H, 4.19; N, 24.57.

5-[(pyridin-4-yloxy) methyl]-1, 3, 4-thiadiazol-2-amine (4): Compound 3 (2.26 g, 0.01 mole) was mixed with cold conc. sulfuric acid (1.5 mL). The reaction mixture was left at room temperature for 16 h. The reaction mixture was poured into ice-cold eater, neutralized with liquid ammonia to obtain solid mass, which was filtered, washed with water, dried and recrystallized from methanol to yield compound 4 as black solid. Yield (61%), mp 150-151°C; IR spectrum (KBr, υ, cm^{-1}): 3382 (NH_2), 1620 (C=N). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 4.97 (s, 2H, CH_2), 6.19 (bs, 2H, NH_2), 7.65 (d, 2H, J = 7.6 Hz, Ar-H), 7.97 (d, 2H, J = 7.6 Hz, Ar-H). Anal. Calcd. for $C_8H_8N_4OS$ (208): C, 46.14; H, 3.87; N, 26.90. Found: C, 46.05; H, 3.71; N, 26.77.

N-{5-[(pyridin-4-yloxy) methyl]-1, 3, 4-thiadiazol-2-yl} acetamide (5): To a solution of compound **4** (2.08 g, 0.01 mole) in dry benzene (50 mol), acetyl chloride (0.01 mol) was added drop by drop at 0-5°C temperature. The reaction mixture was refluxed with stirring for 6 h and then poured onto crushed ice. The brown solid thus obtained was recrystallized from methanol water and purity of product was checked by TLC. Yield (63%), mp 133-134°C; IR spectrum (KBr, υ, cm^{-1}): 3280 (NH), 1682 (C=O), 1621 (C=N). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.24 (s, 3H, CH_3), 4.93 (s, 2H, CH_2), 7.72 (d, 2H, J = 7.6 Hz, Ar-H), 7.98 (d, 2H, J = 7.6 Hz, , 9.12 (bs.1H,NH) Ar-H). Anal. Calcd. for $C_{10}H_{10}N_4O_2S$ (250): C, 47.99; H, 4.03; N, 22.39. Found: C, 47.85; H, 3.91; N, 22.14.

3-(2,6-dimethylphenyl)-N-{5-[(pyridine-4-yloxy)methyl]-1,3,4-thiadiazol-2-yl}acrylamide (6): To a solution of compound 5 (2.5 g, 0.01 mole) and 2,6-dimethylbenzaldehyde (1.34 g, 0.01 mole) in absolute ethanol (30 mL) was added 5% NaOH (10 mL) and the mixture was refluxed for 10 h. The reaction mixture was allowed to cool and the solid thus obtained was filtered off and recrystallized from ethanol giving compound 6. Yield (69%), mp 120-121°C; IR spectrum (KBr, υ, cm^{-1}): 3268 (NH), 1680 (C=O), 1616 (C=N). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.21 (s, 6H, $2CH_3$), 4.90 (s, 2H, CH_2), 6.88 (m, 1H, Ar-H), 7.05 (d, 2H, J = 7.8 Hz, Ar-H), 7.11 (d, 1H, J = 6.8 Hz, CH), 7.36 (d, 1H, J = 6.8 Hz, CH), 7.67 (d, 2H, J = 7.6 Hz, Ar-H), 7.98 (d, 2H, J = 7.6 Hz, Ar-H). 8.82 (bs.1H,NH). Anal. Calcd. for $C_{19}H_{18}N_4O_2S$ (336): C, 62.28; H, 4.95; N, 15.29. Found: C, 62.05; H, 4.90; N, 15.15.

1-{3-[5-(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-ylamino}-4,5-dihydro-[5-(2,6-dimethylphenyl)pyrazol-1-yl] ethanone(7): To a solution of proper compound 6 (0.02 mol) in absolute ethanol (50 ml) 99% hydrazine hydrate (0.04 mol) was added drop by with constant stirring in the presence of few drops glacial acetic acid. The reaction mixture was refluxed for 12h, distilled off and cooled. The separated solid was filtered washed with pet-ether recrystallized from the appropriate solvent to give compound 75 as dark yellow solid. Yield (70%), mp 195-196°C; IR (KBr, υ, cm^{-1}): 3259 (NH), 1618 (C=N).^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.20 (s, 6H, $2CH_3$), 4.89 (s, 2H, CH_2), 5.11 (s, 2H, CH_2), 6.95 (m, 1H, Ar-H), 7.11 (d, 2H, J = 7.8 Hz, Ar-H), 7.59 (d, 2H, J = 7.6 Hz, Ar-H), 7.97 (d, 2H, J = 7.6 Hz, Ar-H), 8.55(bs.1H,NH). Anal. Calcd. for $C_{19}H_{18}N_6OS$ (378): C, 60.30; H, 4.79; N, 22.21. Found: C, 60.05; H, 4.82; N, 22.14.

Ethyl-2-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-ylamino}acetate(8): A mixture of compound 4 (2.08 g, 0.01 mole) and ethyl chloroacetate (0.01 mol) in dry dioxane (50 mL) was refluxed for 8 h. The reaction mixture was further stirred for 1 h and poured onto ice-cold water. The resulting mixture was filtered and recrystalized from ethanol to yield compound 76 as dark brown solid. Yield (74%), mp 130-131°C; IR spectrum (KBr): υ 3290 (NH), 1622 cm^{-1} (C=N). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.27 (t, 3H, J = 6.2 Hz, CH_3), 4.18 (q, 2H, J = 6.2 Hz, CH_2), 4.79 (s, 2H, CH_2), 5.02 (s, 2H, CH_2), 6.05 (bs, 1H, NH), 7.69 (d, 2H, J = 7.6 Hz, Ar-H), 7.98 (d, 2H, J = 7.6 Hz, Ar-H). Anal. Calcd. for $C_{12}H_{14}N_4O_3S$ (294): C, 48.97; H, 4.79; N, 19.04. Found: C, 48.75; H, 4.71; N, 18.79.

2-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-ylamino} acatohy-drazide(9): To a solution of compound **8** (2.94 g, 0.01 mole) in absolute ethanol (50 ml) 99% hydrazine hydrate (1 mL) was added drop by drop. The reaction mixture was refluxed for 12 h. The excess of solvent removed under reduced pressure. The remaining precipitate was collected, dried and recrystallized from ethanol to afford compound 9. Yield (73%), mp 250-251°C; IR spectrum (KBr, υ, cm^{-1}): 3320 (NH_2), 3294 (NH), 1662 (C=O), 1615 cm^{-1} (C=N). ^1H NMR spectrum (DMSO-d_6, δ ppm): 4.69 (s, 2H, CH_2), 4.81 (s, 2H, CH_2), 6.05 (bs, 1H, NH), 7.58 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.97 (d, 2H, *J* = 7.6 Hz, Ar-H), 9.18 (bs, 1H, NH). Anal. Calcd. for $C_{10}H_{12}N_6O_2S$ (280): C, 42.85; H, 4.32; N, 29.98. Found: C, 42.76; H, 4.11; N, 29.77.

Sugar2-{5-[(pyridin-4-yloxy) methyl]-1,3,4-thiadiazol-2-ylamino}acatohydrazones (10-12): General procedure: To a well stirred solution of the respective monosaccharide (0.01 mole) in water (2 mL) and glacial acetic acid (0.2 mole) was add compound 9 (2.8 g, 0.01 mole) in ethanol (10 mL). The mixture was heated under reflux for 3 h and the resulting solution was concentrated and left to cool. The precipitate formed was filtered off, washed with water and ethanol then dried and crystallized from ethanol.

D-Galactose-2-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-ylamino}acatohydrazones(10): Yield(72%), mp 211-212°C; IR spectrum (KBr, υ, cm^{-1}): 3437-3415 (OH), 3273 (NH), 1669 (C=O), 1615 (C=N). ^1H NMR spectrum (DMSO-d_6, δ ppm): 3.34-3.39 (m, 2H, H-6,6'), 3.73 (m, 1H, H-5), 4.15 (m, 1H, H-4), 4.29 (t, *J* = 7.4 Hz, 1H, H-3), 4.39 (dd, *J* = 7.4 Hz, *J* = 7.8 Hz, 1H, H-2), 4.48 (m, 1H, OH), 4.52 (d, *J* = 6.4 Hz, 1H, OH), 4.71 (s, 2H, CH_2), 4.98 (s, 2H, CH_2), 5.20 (m, 1H, OH), 5.65 (t, *J* = 4.6 Hz, 1H, OH), 5.79 (t, *J* = 4.6 Hz, 1H, OH), 6.08 (bs, 1H, NH), 7.52 (d, 1H, *J* = 7.8 Hz, H-1), 7.58 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.98 (d, 2H, *J* = 7.6 Hz, Ar-H), 10.12 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{22}N_6O_7S$ (442): C, 43.43; H, 5.01; N, 18.99. Found: C, 43.14; H, 4.91; N, 18.75.

D-mannose-2-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-ylamino}acatohydrazones(11): Yield(74%), mp 214-215°C; IR (KBr, υ, cm^{-1}): 3440-3418 (OH), 3266 (NH), 1671 (C=O), 1618 (C=N). ^1H NMR spectrum (DMSO-d_6, δ ppm): 3.32-3.38 (m, 2H, H-6,6'), 3.73 (m, 1H, H-5), 4.16 (m, 1H, H-4), 4.28 (t, *J* = 7.4 Hz, 1H, H-3), 4.40 (dd, *J* = 7.4 Hz, *J* = 7.8 Hz, 1H, H-2), 4.48 (m, 1H, OH), 4.54 (d, *J* = 6.4 Hz, 1H, OH), 4.71 (s, 2H, CH_2), 4.97 (s, 2H, CH_2), 5.21 (m, 1H, OH), 5.68 (m, 1H, OH), 5.79 (t, *J* = 4.6 Hz, 1H, OH), 6.06 (bs, 1H, NH), 7.60 (d, 1H, *J* = 7.8 Hz, H-1), 7.67 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.98 (d, 2H, *J* = 7.6 Hz, Ar-H), 10.18 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{22}N_6O_7S$ (442): C, 43.43; H, 5.01; N, 18.99. Found: C, 43.12; H, 4.90; N, 18.73.

D-xylose-2-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-ylamino}acatohydrazones (12): Yield (70%), mp 214-215°C; IR (KBr, υ, cm^{-1}): 3451-3429 (OH), 3260 (NH), 1674 (C=O), 1619 (C=N). ^1H NMR spectrum (DMSO-d_6, δ ppm): 3.32-3.38 (m, 2H, H-5,5'), 3.82 (m, 1H, H-4), 4.21 (t, *J* = 7.4 Hz, 1H, H-3), 4.42 (dd, *J* = 7.4 Hz, *J* = 7.8 Hz, 1H, H-2), 4.49 (m, 1H, OH), 4.57 (m, 1H, OH), 4.74 (s, 2H, CH_2), 4.98 (s, 2H, CH_2), 5.24 (m, 1H, OH), 5.66 (t, *J* = 4.6 Hz, 1H, OH), 5.79 (m, 1H, OH), 6.06 (bs, 1H, NH), 7.61 (d, 1H, *J* = 7.8 Hz, H-1), 7.68 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.987 (d, 2H, *J* = 7.6 Hz, Ar-H), 10.22 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{20}N_6O_6S$ (412): C, 43.68; H, 4.89; N, 20.38. Found: C, 43.47; H, 4.69; N, 20.15.

Per-O-acetylsugar-2-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-ylamino}acatohydrazones (13-15): General procedure: To a solution of compounds 10-12 (0.01 mole) in pyridine (7 mL) was added acetic anhydride (0.1 mole) and stirred at room temperature for 5 h. The resulting solution was poured onto crushed ice and the product that separated out was filtered, washed with a solution of sodium hydrogen carbonate followed by water and then dried. The products were recrystallized from ethanol.

Per-O-acetyl-D-mannose-2-{5-[(pyridin-4-yloxy) methyl]-1,3,4-thiadiazol-2-ylamino}acatohydrazones (13): Yield (78%), mp 132-123°C; IR (KBr, υ, cm^{-1}): 3282 (NH), 1665 (C=O), 1617 cm^{-1} (C=N). ^1H NMR spectrum (DMSO-d_6, δ ?ppm): 1.84, 1.96, 2.03, 2.11, 2.15 (5s, 15H, $5CH_3$), 4.07 (dd, *J* = 11.4 Hz, *J* = 2.8 Hz, 1H, H-6), 4.22 (dd, *J* = 11.4 Hz, *J* = 3.2 Hz, 1H, H-6'), 4.72 (s, 2H, CH_2), 4.82 (s, 2H, CH_2), 4.98 (m, 1H, H-5), 5.14 (m, 1H, H-4), 5.31 (dd, *J* = 6.5 Hz, *J* = 7.4 Hz, 1H, H-3), 5.59 (dd, *J* = 7.4 Hz, *J* = 7.2 Hz, 1H, H-2), 6.11 (bs, 1H, NH), 7.55 (d, *J* = 7.2 Hz, 1H, H-1), 7.77 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.98 (d, 2H, *J* = 7.6 Hz, Ar-H), 10.28 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{32}N_6O_{12}S$ (652): C, 47.85; H, 4.94; N, 12.88. Found: C, 47.75; H, 4.81; N, 12.72.

Per-*O*-acetyl-D-galactose-2-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-ylamino}acatohydrazones (14): Yield (79%), mp 127-128°C; IR (Kbr, υ, CM^{-1}): 3277 (NH), 1668 (C=O), 1614 (C=N); Anal. Calcd. for $C_{26}H_{32}N_6O_{12}S$ (652): C, 47.85; H, 4.94; N, 12.88. Found: C, 47.71; H, 4.83; N, 12.70.

Per-O-acetyl-D-xylose-2-{5-[(pyridin-4-yloxy) methyl]-1,3,4-thiadiazol-2-ylamino}acatohydrazones (15): Yield (77%), mp 129-130°C; IR (KBr, υ, cm^{-1}): 3273 (NH), 1669 (C=O), 1616 (C=N). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.86, 1.96, 2.02, 2.12 (4s, 12H, $4CH_3$), 4.05 (dd, *J* = 11.4 Hz, *J* = 2.8 Hz, 1H, H-5), 4.24 (dd, *J* = 11.4 Hz, *J* = 3.2 Hz, 1H, H-5'), 4.75 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 5.15 (m, 1H, H-4), 5.31 (dd, *J* = 6.5 Hz, *J* = 7.4 Hz, 1H, H-3), 5.57 (dd, *J* = 7.4 Hz, *J* = 7.2 Hz, 1H, H-2), 6.12 (bs, 1H, NH), 7.64 (d, *J* = 7.2 Hz, 1H, H-1), 7.77 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.98 (d, 2H, *J* = 7.6 Hz, Ar-H), 10.25 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{28}N_6O_{10}S$ (580): C, 47.58; H, 4.86; N, 14.48. Found: C, 47.29; H, 4.82; N, 14.22.

5-(*O*-acetylsugar)-*N*-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,3,4-oxadiazol-2-amine (16-18): General procedure: A solution of the sugar hydrazones 10-12 (0.01 mole) in acetic anhydride (5 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.

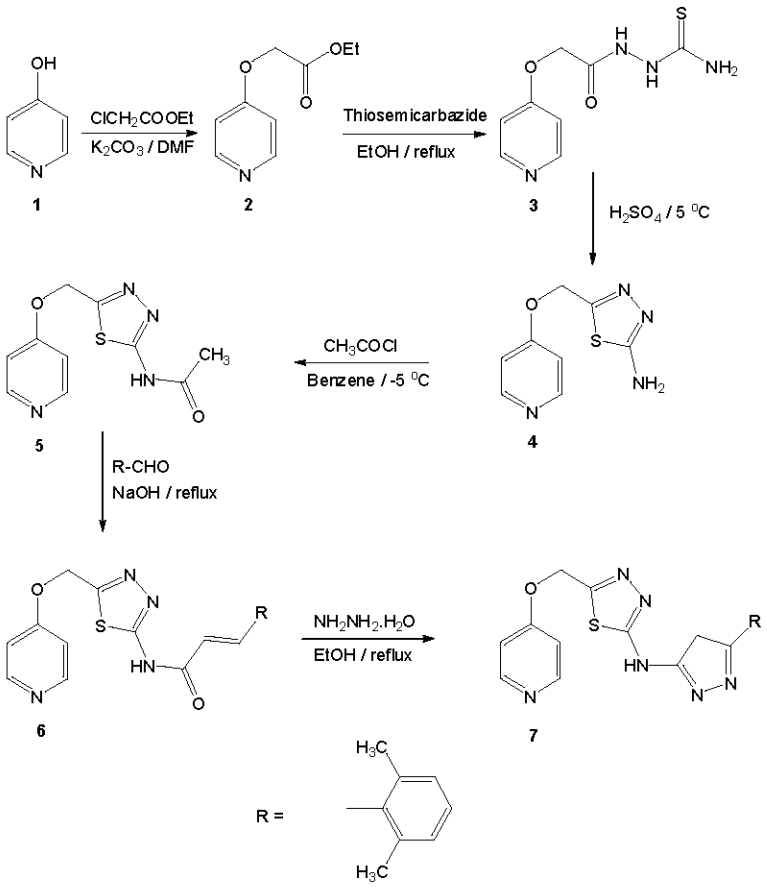
5-(*O*-pentacetyl-D-galactopentitolyl)-*N*-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,3,4-oxadiazol-2-amine (16): Yield (70%), mp 136-137°C; IR (KBr, υ, cm^{-1}): 3262 (NH), 1736 (C–O), 1662 (C–O), 1614 (C–N). ^{1}H NMR spectrum (DMSO-d_6, δ ?ppm): 1.85, 1.95, 2.04, 2.12, 2.16, 2.24 (6s, 18H, $6CH_3$), 3.99 (m, 1H, H-6), 4.18 (dd, *J* = 11.4 Hz, *J* = 3.2 Hz, 1H, H-6'), 4.70 (s, 2H, CH_2), 4.84 (m, 1H, H-5), 5.02 (s, 2H, CH_2), 5.08 (m, 1H, H-4), 5.21 (dd, *J* = 6.5 Hz, *J* = 7.4 Hz, 1H, H-3), 5.46 (dd, *J* = 7.4 Hz, *J* = 7.2 Hz, 1H, H-2), 5.79 (d, *J* = 8.2 Hz, 1H, oxadiazoline H-5), 6.12 (bs, 1H, NH), 7.76 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.98 (d, 2H, *J* = 7.6 Hz, Ar-H). Anal. Calcd. for $C_{28}H_{34}N_6O_{13}S$ (694): C, 48.41; H, 4.93; N, 12.10. Found: C, 48.30; H, 4.77; N, 12.14.

5-(*O*-pentacetyl-D-mannopentitolyl)-*N*-{5-[(pyridin-4-yloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,3,4-oxadiazol-2-amine (17): Yield (68%), mp 134-135°C; IR (KBr, υ, cm^{-1}): 3242 (NH), 1738 (C=O), 1668 (C=O), 1611 (C=N). ^{1}H NMR spectrum (DMSO-d_6, δ ?ppm): 1.86, 1.95, 2.03, 2.12, 2.15, 2.25 (6s, 18H, $6CH_3$), 3.98 (dd, *J* = 11.4 Hz, *J* = 2.8 Hz, 1H, H-6), 4.16 (m, 1H, H-6'), 4.71 (s, 2H, CH_2), 4.86 (m, 1H, H-5), 4.99 (s, 2H, CH_2), 5.08 (m, 1H, H-4), 5.22 (dd, *J* = 6.5 Hz, *J* = 7.4 Hz, 1H, H-3), 5.45 (dd, *J* = 7.4 Hz, *J* = 7.2 Hz, 1H, H-2), 5.77 (d, *J* = 8.2 Hz, 1H, oxadiazoline H-5), 6.10 (bs, 1H, NH), 7.56 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.97 (d, 2H, *J* = 7.6 Hz, Ar-H). Anal. Calcd. for $C_{28}H_{34}N_6O_{13}S$ (694): C, 48.41; H, 4.93; N, 12.10. Found: C, 48.27; H, 4.75; N, 11.96.

5-(*O*-tetraacetyl-D-xylotetritolyl)-N-{5-[(pyridin-4-yloxy) methyl]-1,3,4-thiadiazol-2-yl}-1,3,4-oxadiazol-2-amine (18): Yield (66%), mp 141-142°C; IR (KBr, υ, cm^{-1}): 3255 (NH), 1733 (C=O), 1671 (C=O), 1615 cm^{-1} (C=N). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.85, 1.96, 2.03, 2.14, 2.24 (5s, 15H, $5CH_3$), 4.02 (dd, *J* = 11.4 Hz, *J* = 2.8 Hz, 1H, H-5), 4.14 (dd, *J* = 11.4 Hz, *J* = 3.2 Hz, 1H, H-5'), 4.70 (s, 2H, CH_2), 5.05 (s, 2H, CH_2), 5.12 (m, 1H, H-4), 5.20 (dd, *J* = 6.5 Hz, *J* = 7.4 Hz, 1H, H-3), 5.42 (dd, *J* = 7.4 Hz, *J* = 7.2 Hz, 1H, H-2), 5.78 (d, *J* = 8.2 Hz, 1H, oxadiazoline H-5), 6.14 (bs, 1H, NH), 7.58 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.98 (d, 2H, *J* = 7.6 Hz, Ar-H). Anal. Calcd. for $C_{25}H_{30}N_6O_{11}S$ (622): C, 48.23; H, 4.86; N, 13.50. Found: C, 48.05; H, 4.71; N, 13.36.

RESULTS AND DISCUSSION

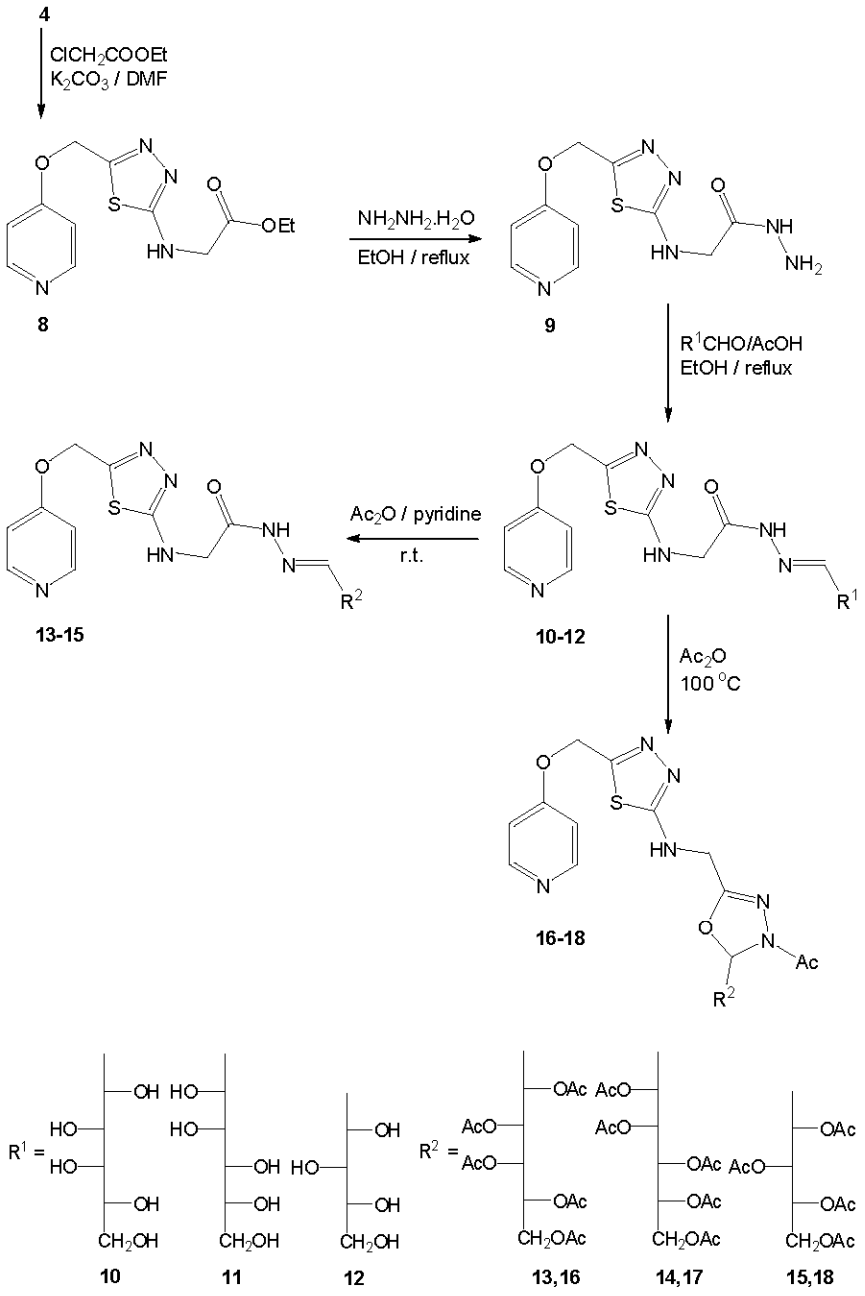
The coupling reaction of 4-hydroxypyridine with ethyl chloroacetate gave ethyl-2-(pyridine-4-yloxy) acetate (2) in 80% yield. Reaction of the ester 2 with thiosemicarbaizide in ethanol afforded the acylthiosemicarbazide derivatives 3. The IR spectrum of the ester 2 showed the characteristic carbonyl absorption band at 1737 cm^{-1} which disappeared in the corresponding spectrum of the hydrazide 3 and instead an absorption band for the NH and NH_2 groups appeared. The ^{1}H NMR spectrum of 2 showed the ethyl signals as triplet and quartet which disappeared in the ^{1}H NMR spectrum of the derived thiosemicarbazide in which signals corresponding to NH and NH_2 groups appeared at δ 5.39, 9.14 and 9.72 ppm. Cyclization of the resulting acylthiosemicarbazide in sulfuric acid afforded after neutralization the 2-amino-1,3,4-thiadiazole derivative 4. Acetylation of the latter thiadiazole derivatives with acetyl chloride in benzene produced the N-acetyl derivative 5 which was allowed to react with 2, 6-dimethylbenzaldehyde to afford the substituted chalcone derivative 6. The IR spectrum of the *N*-acetyl and chalcone derivatives showed the carbonyl absorption bands at 1670 and 1682 cm^{-1} respectively. The ^{1}H NMR spectrum of the *N*-acetyl derivative 5 showed the acetyl methyl signal at δ 2.24 ppm and the corresponding spectrum of 6 revealed the absence of this signal and presence of singlet peak of the two methyl groups as well as signals of the aromatic protons. Heterocylization of 6 by reaction with hydrazine hydrate resulted in the formation of the substituted pyrazolidine derivative [Scheme 1]. Reaction of the aminothiadiazole 4 with ethyl chloroacetate in presence of potassium carbonate gave the ethyl *N*-substituted acetyl ester 8. Hydrazinolysis of the latter ester with hydrazine hydrate afforded the



Scheme 1

corresponding acid hydrazide derivative 9. The ^{1}H NMR spectrum of 8 showed the ethyl signals as triplet and quartet which disappeared in the ^{1}H NMR spectrum of the derived hydrazide which revealed signals corresponding to NH and NH_2 groups.

When the hydrazide 9 was allowed to react with D-galactose, D-mannose or D-xylose in an aqueous ethanolic solution and a catalytic amount of acetic acid, the corresponding sugar hydrazones 10-12 were obtained respectively. Their ^{1}H NMR spectra showed the signals of the sugar chain protons at δ ?3.32-5.79 ppm and the C-1 methine proton as doublet in the range δ 7.50-7.52 ppm in addition to the aromatic protons in the region δ 7.57-7.98 ppm. Acetylation of the sugar hydrazones 10-12 with acetic anhydride in pyridine at room temperature afforded the corresponding per-*O*-acetylderivatives 13-15, respectively. It is well known that reaction of sugar aroylhydrazones with acetic anhydride give the respective per-*O*-acetyl derivatives. However, Abdel-Aal *et al.* [35, 36], Ali *et al.* [37], El-Ashry *et al.* [38] and Abdel-Aal *et al.* [39] reported 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. Previously,Abdel-Aal *et al.* [35, 39] reported 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 hydrazinyl sugars with boiling acetic anhydride. Thus, when the hydrazones 10-12 were heated in acetic anhydride at 100°C they gave the 1, 3, 4-oxadiazoline acyclic nucleoside analogs 16-18, respectively. Their IR spectra showed absorption bands in the carbonyl frequency region at 1662-1671 cm^{-1} and 1733-1738 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 showed signals corresponding to the *O*-acetyl-methyl protons in addition to the *N*-acetyl-methyl protons each as singlet and signals corresponding to the rest of the alditolyl chain protons. The ^{1}H NMR spectra of 16 and 18 showed the resonances of the H-1 of the sugar moiety at lower chemical shift indicating the nature of the *C*-H and this gives a strong evidence that cyclization has taken place [Scheme 2].



Scheme 2

Antimicrobial Activity: The synthesized compounds were tested for their antimicrobial action [40] against four different bacterial species namely, Bacillus *subtilis* (*Gram* positive bacterium), *Bacillus cereus* (*Gram* positive bacterium), *Pseudomonas* sp. (*Gram* negative bacterium) and *Streptomyces* sp. (one of the important actinomycetes). All the tested compounds exhibited different degrees of antibacterial activities or inhibitory actions. The most susceptible organisms were the two *Gram* positive bacteria (*Bacillus subtilis* and *Bacillus cereus*) followed by *Streptomyces* sp., while the lowest inhibitory effect was encountered in the case of *Pseudomonas* sp. The highest degrees of inhibition against the two *Gram* positive bacteria (*Bacillus subtilis* and *Bacillus cereus*) were recorded for compounds 4, 5 and 12, 16 and 17 followed by 7, 11, 14 and 15. The lowest degrees of inhibition were recorded for compounds 1, 2 and 18 (Table 1). The results were compared to amoxicillin (penicillin) as a reference drug.

Table 1: Antimicrobial activity of the synthesized compounds

Compound	*Bacillus subtilis*	*Bacillus cereus*	*Pseudomona aeruginosa*	*Streptomyces*
1	++	++	-	+
2	++	++	+	+
3	++	++	-	++
4	++++	+++	++	+++
5	++++	+++	++	+++
6	++	+	+	+
7	+++	+++	++	+
8	++	+++	+	-
9	++	++	-	++
10	++	+	+	++
11	+++	++	+	++
12	++++	+++	++	+++
13	+++	++	+	++
14	+++	+++	+	++
15	+++	++	-	+
16	++++	+++	+	+++
17	++++	+++	+	++
18	++	++	-	++
Amoxicillin	+++	+++	-	+

– No antimicrobial effect
+ Low antimicrobial effect (4 mm)
++ Moderate antimicrobial effect (8–10 mm)
+++ High antimicrobial effect (15–18 mm)
++++ Complete antimicrobial effect (20–22 mm)

The antimicrobial activity results and structure activity relationship indicated that the 1, 3, 4-thiadiazole derivatives with free amino or acetylated amino group showed increased inhibition activities against both *Gram* positive bacteria types. Furthermore, the hydrazinyl sugars with free hydroxyl groups of the five-carbon sugar (D-dribose) showed relatively higher activity that their corresponding acetylated analog or the corresponding hydrainyl sugars with six carbon atoms (D-galactose or D-mannose).

The antimicrobial activity results also proved that the presence of sugar moieties in the 1,3,4-oxadiazoline acyclic nucleoside analogs of D-galactose or D-mannose resulted in high inhibition activities. Additionally, the activity of substituted oxadiazoline acyclic sugars of D-galactose or D-mannose was obviously higher than that of the corresponding five carbon ribose sugar.

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