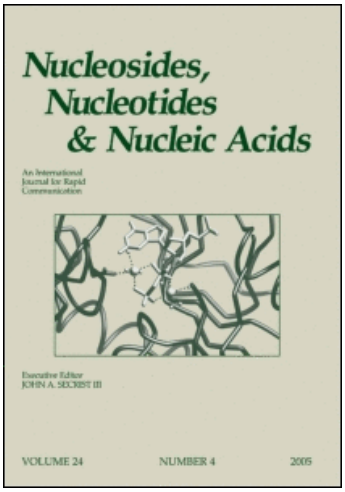

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis and Antibacterial Activity of Some Glucosyl- and Ribosyl-Pyridazin-3-ones

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME GLUCOSYL- AND RIBOSYL-PYRIDAZIN-3-ONES

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□ *Reaction of 5,6-diphenylpyridazin-3(2H)-one* ***1a,b*** *with 2,3,4,6-tetra-**O**-acetyl-β-**D**-glucopyranosyl bromide* ***2*** *in K_2CO_3/acetone gave 5,6-diphenyl-N^2-(2′,3′,4′,6′-tetra-**O**-acetyl-β-**D**-glucopyranosyl)pyridazin-3-one* ***5a,b****. The same nucleosides* ***5a,b*** *were obtained by reaction of* ***1a,b*** *with peracetylated glucose* ***3*** *under MW irradiation. Mercuration of* ***1a,b*** *followed by reaction with glucosyl bromide* ***2*** *gave the same nucleosides* ***5a,b****. The riboside 4-cyano-5,6-diphenyl-N^2-(2′,3′,5′-tri-**O**-acetyl-β-**D**-ribofuranosyl)-pyridazin-3-one* ***8*** *was obtained by reaction of 4-cyanopyridazinone* ***1b*** *with peracetylated ribose* ***7*** *under MW irradiation. The deprotected nucleosides* ***6a,b*** *and* ***9*** *were obtained by stirring of* ***5a,b*** *and* ***8*** *in methanol and TEA/H_2O. The structure was confirmed using ^1H and ^{13}C-NMR spectra. Selected members of these compounds were screened for antibacterial activity.*

Keywords 5,6-Diphenylpyridazin-3-one; pyridazine nucleoside; micowave and antibacterial activity

INTRODUCTION

The diazine derivatives and its condensed systems have a wide range of biological properties,[1,2] such as inhibitors of tyrosine kinase,[3,4] antimalarial,[5] anticonvulsive,[6–8] antihypertensive,[9,10] hypolipidemic,[11] antitumoral,[12] and antiviral.[13] Pyridazine derivatives, in particular pyri-dazinones which have an aryl group in position 6 present various pharmacological properties.[14–19] Pyridazinone and some derivatives have been reported to be platelet aggregation inhibitors,[20] α-adrenoceptor antagonists,[21] antiulcer agents,[22,23] developed as local antiinflamatory drug for humans as rolipram and indomethacin,[24] insecticidal,[25–27] analgesic,[28] and bactericidal[29] activities.

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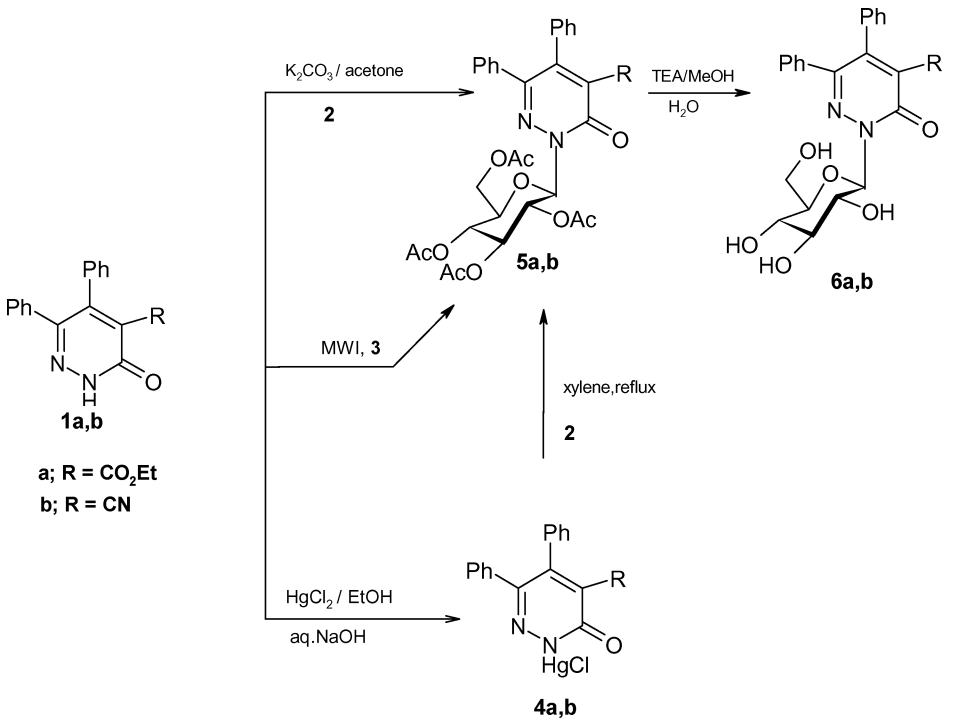
Also, some of the pyridazinone derivatives have varying inhibition activity against Hepatitis B Virus (HBV) with low to moderate cytotoxicity.[30,31] Microwave irradiation (MWI) is widely approved as a safe, convenient and economical way for small-scale preparations in organic chemistry.[32–39]

RESULTS AND DISCUSSION

In this work, we describe the reaction of pyridazinone derivatives[40] with glucosyl bromide, peracetylated glucose, and peracetylated ribose for the synthesis of some pyridazine nucleosides.

The reaction of diphenylpyridazinones **1a** and **1b** with glucosyl bromide **2** in dry acetone and potassium carbonate[41] gave the corresponding 2′,3′,4′,6′-tetra-***O***-acetyl-*β*-***D***-glucopyranosyl pyridazine **5a,b** in 56 and 86% yields respectively (Scheme 1). The same nucleosides **5a** and **5b** were obtained in better yields by MW irradiation of **1a** and **1b** with peracetylated glucose **3** for 3 minutes using silica gel as a solid support,[39] the MWI method being considered as green chemistry. On the other hand, nucleosides **5a** and **5b** were obtained in low yields 20% by refluxing chloromercuric salts **4a** and **4b** with glucosyl bromide **2** in dry xylene[42] (Scheme 1).



2 = glucosyl bromide
3 = peracetylated glucose

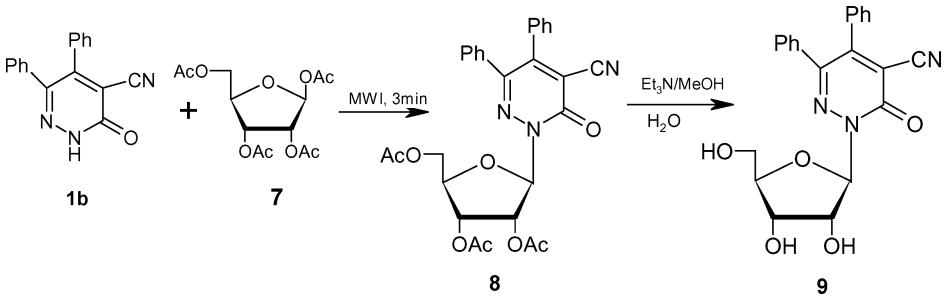
SCHEME 1

The ^{1}H NMR spectrum of **5a** showed signals at δ 1.95, 1.96, 1.97, and 2.00 ppm which are characteristic for the acetoxy groups of sugar, and a doublet at δ 6.27 ppm for H-1′ with $J_{1',2'} = 8.00$ Hz confirming the β-configuration of the corresponding product. Its ^{13}C NMR spectrum showed the signals at δ 13.48, 20.25, 20.26, 20.33, and 20.47 ppm for the acetoxy groups and a signal at δ 80.36 ppm for the anomeric carbon.

The nucleoside **5b** was characterized by ^{1}H NMR spectrum which shows signals at δ 1.95, 1.96, 1.98, and 2.01 ppm for the acetoxy groups and a doublet at δ 6.61 ppm for anomeric proton with $J_{1',2'} = 8.40$ Hz indicating the β-configuration.

The IR spectrum of **5b** showed one band at 2239 for CN and two bands at 1754 and 1677 cm^{-1} for the carbonyl of acetoxy and amide groups.

Reaction of 4-cyano-5,6-diphenylpyridazin-3(*2H*)-one (**1b**) with per-acetylated ribose **7** under microwave irradiation for 3 minutes, using silica gel as a solid support,[39] gave the corresponding 2′,3′,5′–tri-***O***-acetyl-β-***D***-ribofuranosyl pyridazine **8** (Scheme 2).



SCHEME 2

The absorption bands of riboside **8** in its IR spectrum showed bands at 2238, 1740, and 1680 cm^{-1} indicating the presence of the CN and the C=O of acetoxy groups in addition to amide group, respectively. The ^{1}H NMR spectrum of **8** showed the signals at 2.09, 2.11, and 2.14 ppm for the acetoxy groups of ribose and a doublet at δ 6.72 ppm for the anomeric proton with $J_{1',2'} = 2.60$ Hz. The UV spectrum of compound **8** gave two $\lambda_{max.}$ at 270.5 and 249.0 nm.

The deprotected nucleosides **6a**,**b** and **9** were obtained by treatment of the acetylated nucleosides **5a**,**b** and riboside **8** with triethylamine in methanol and a few drops of water,[41–44] the reaction mixture was stirred overnight at room temperature. The structures of these products were confirmed by their spectral data (IR& ^{1}H, ^{13}C NMR) and elemental analyses.

The ^{1}H NMR spectrum of **6a** showed signals at δ 0.92 as a triplet and 4.02 ppm as a quartet due to the ethyl group of the ester and the disappearance of the acetoxy methyl groups, in addition to the signals of OH protons which exchanged with D_2O. Its IR spectrum gave bands at 3381–3434 cm^{-1} characteristics for the 4 OH groups.

TABLE 1 Antibacterial activity of tested compounds

Compound No.	P. aeruginosa	S. aureus	B. subtilis
5a	10	2	4
5b	—	4	5
6a	—	—	—
6b	—	10	15
8	24	9	11
9	26	13	10
Ampicillin	23	7	6

Inhibition zones mm, minimum inhibitory concentration (μg/mL).

The deprotected nucleosides **6b** gave in ^{1}H NMR spectrum signals at 4.01–4.60 ppm multiplet for 4 OH groups. Its ^{13}C NMR spectrum showed a signal at δ 80.70 ppm for the anomeric carbon, in addition to another at δ 114.1 ppm for the CN group. Its IR spectrum showed bands at 2235 and 1680 cm^{-1} characteristics for CN and carbonyl group of amide.

The ^{1}H NMR for deprotected riboside **9** showed the presence of a multiplet at δ 3.91–4.33 ppm for H-2′, H-3′, H-4′, and H-5′. The IR spectrum of **9** showed bands at 3381–3434 cm^{-1} for the 3 OH groups, in addition to bands at 2238 and 1675 cm^{-1} for CN and C=O of the amide group.

In summary, the pyridazine nucleosides were synthesized by reaction of substituted pyridazinones with glucosyl bromide **2**, peracetylated glucose **3** and peracetylated ribose **7**.

ANTIBACTERIAL ACTIVITY

Nucleosides **5a**,**b**, **6a**,**b**, **8**, and **9** were evaluated for antibacterial activity against Gram (-ve) bacteria (*Pseudomonas aeruginosa*) and Gram (+ve) bacteria (*Staphylococcus aureus*, and *Bacillus subtilis*) using a cup plate agar diffusion method.[45] Ampicillin was used as a reference to evaluate the potency of tested compounds. Nucleosides **6b**, **8,** and **9** showed higher antibacterial activity than the standard drug (ampicillin), while nucleosides **5a** and **5b** showed lower antibacterial activity. Nucleoside **6a** did not show any activity against the microorganisms tested. The results of the biological activity encourage further work on such a ring system Table 1.

EXPERIMENTAL

All melting points are uncorrected and were measured using an Electro thermal IA 9100 apparatus. TLC was performed on Merck Silica Gel 60F_{254} with detection by UV light and by the charring with 10% EtOH solution of H_2SO_4; The IR spectra (KBr disc) were recorded on a Pye Unicam Sp-3–300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The

UV spectra were recorded by UV-160A, UV-visible recording spectrometer Shimadzu using DMSO-d_6 (dimethylsulphoxide) as a solvent. The ^1H and ^{13}C NMR spectra were determined with JEOL- JNM- LA 200, 300, or 400 MHz spectrometers. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. Elemental analysis were determined on a Perkin Elmer 240 (microanalysis).

General Methods for Preparation of Nucleosides

Method A

A mixture of pyridazinone **1a** and **1b** (0.001 mol) and potassium carbonate (0.001 mol) was stirred in acetone (15 mL) for 1 hour, then glycosyl bromide **2** (0.0011 mol) was added; the reaction mixture was stirred at room temperature overnight then refluxed for 3 hours, filtered off, and the solvent was evaporated under reduced pressure. The product was dried and crystallized from the appropriate solvent.

Method B

Pyridazinone **1a or 1b** (0.001 mol) and peracetylated glucose **3** or ribose **7** (0.001 mol), respectively, were dissolved in a mixture of methylene chloride/methanol (80/20) then 1.0 g of silica gel (200–400 mesh) was added, the solvent was removed by evaporation, the dried residue was transferred into a glass beaker and irradiated for (0.5–3 minutes) in a domestic microwave oven. The product was chromatographed on a silica gel column, using methylene chloride as eluent.

Method C

To a solution of glucosyl bromide **2** (0.011 mol) in dry xylene a solution of chloromercuric salt of the pyridazinones **1a** or **1b** (0.01 mol) in dry xylene (30 mL) was added. The reaction mixture was refluxed, and the reaction was followed by TLC till all starting material was consumed (4 hours), then the solvent was evaporated under reduced pressure and the residue was extracted with chloroform, the solvent was evaporated, and the residue was crystallized from ethanol.

Ethyl-5,6-diphenyl-N^2-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-pyridazin-3-one-4-carboxylate (5a). Method A: 56% yield; method B: 67% yield; method C: 20% yield, as pale yellow crystals from ethanol; m.p. 108–110°C; $R_f = 0.37$ (eluent: CH_2Cl_2/MeOH; 9.7:0.3), UV; $\lambda_{max} = 278$ and 247 nm, ^1H NMR spectrum (400 MHz, DMSO-d_6) δ 0.90 (t, 3 H, $J = 7.10$ Hz, CH_3CH_2), 1.95, 1.96, 1.97 and 2.00 (4 s, 12 H, 4 CH_3CO), 4.03 (m, 3 H, H-6a′ and CH_3CH_2), 4.17 (dd, 1 H, $J_{5',6'} = 5.1$, $J_{6',6''} = 12.88$ Hz, H-6b′), 4.39 (m, 1 H, H-5′), 4.98 (t, 1 H, $J = 9.53$ Hz, H-4′), 5.64 (dd, 1 H, $J_{1',2'} = 8.00$, $J_{2',3'} = 9.22$ Hz, H-2′), 5.67 (dd, 1 H, $J_{2',3'} = 9.20$, $J_{3',4'} = 8.78$ Hz, H-3′), 6.57 (d, 1

H, $J_{1',2'}$ = 8.00 Hz, H-1′), 7.13–7.33 (m,10 H, Ar-H) . ^{13}C NMR (400 MHz DMSO-d_6) δ 13.48, 20.25, 20.26, 20.33 and 20.47 (5 CH_3), 61.53 ($CH_3\underline{C}H_2$), 61.63 (C-6′), 67.61 (C-4′), 68.34 (C-3′), 72.87 (C-2′), 73.12 (C-5′) and 80.36 (C-1′), 127.7, 128.1, 128.2, 128.6, 128.9, 129.1, 132.8, 133.0, 134.5, 142.3, 146.6, 156.1, 163.0, 168.7, 169.2, 169.5 and 169.9 (Ar-C, C=N, 5 acetyl C=O). Anal. Calcd for $C_{33}H_{34}N_2O_{12}$ (650.63): C, 60.92; H, 5.27; N, 4.31. Found: C, 61.05; H, 5.00; N, 4.24.

4-Cyano-5,6-diphenyl-N^2-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl) pyridaz-in-3-one (5b). Method A: 86% yield; method B: 89% yield; method C: 23% yield, as pale yellow crystals from ethanol; m.p. 203–205°C; R_f = 0.34 (eluent: CH_2Cl_2/MeOH; 9.8:0.2). IR (KBr) 2239 cm^{-1} (CN),1754 cm^{-1} (C=O, ester) and 1677 cm^{-1} (C=O, amide), ^{1}H NMR spectrum (400 MHz; DMSO-d_6) δ 1.95, 1.96, 1.98 and 2.01 (4 s, 12 H, 4 $C\underline{H}_3CO$), 4.14 (m, 2 H, H-6a′ and H-6b′), 4.34 (m, 1 H, H-5′), 4.99 (t, 1 H, $J_{3',4'}$ = 9.3, $J_{4',5'}$ = 10.2 Hz, H- 4′), 5.67 (m, 2 H, H-3′ and H-2′), 6.61 (d, 1 H, $J_{1',2'}$ = 8.4 Hz, H-1′), 7.1–7.42 (m,10 H, Ar-H). Anal. Calcd for $C_{31}H_{29}N_3O_{10}$ (603.58): C, 61.69; H, 4.84; N, 6.96. Found: C, 61.76; H, 4.92; N, 7.20.

4-Cyano-5,6-diphenyl-N^2-(2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl)-pyridazin-3-one (8). Method B: 78% yield; as pale yellow crystals from ethanol; m.p. 85–87°C; R_f = 0.48 (eluent: CH_2Cl_2/MeOH; 9.8:0.2), UV; λ_{max} = 270.5 and 249 nm. IR (KBr) 2238 cm^{-1} (CN), 1740 cm^{-1} (C=O, ester) and 1680 cm^{-1} for (C=O, amide), ^{1}H NMR spectrum (200 MHz, $CDCl_3$) δ 2.09, 2.11 and 2.14 (3 s, 9 H, 3 $C\underline{H}_3CO$), 4.20 (m, 2 H, H-5a′ and H-5b′), 4.47 (m, 1 H, H-4′),5.54 (t, 1 H, $J_{2',3'}$ = 5.60, $J_{3',4'}$ = 6.00 Hz, H-3′), 5.79 (t, 1 H, J = 2.60 Hz, H-2′), 6.72 (d, 1 H, $J_{1',2'}$ = 2.60 Hz, H-1′), 7.09–7.45 (m, 10 H, Ar-H). Anal. Calcd for $C_{28}H_{25}N_3O_8$ (531.51): C, 63.27; H, 4.74; N, 7.91. Found: C, 63.45; H, 4.52; N, 7.85.

General Method for Deacetylation

Triethylamine (1mL) was added to a solution of glucosides **5a,b** or riboside **8** (0.001 mol) in (10 mL MeOH and 3 drops of water). The mixture was stirred overnight at room temperature, evaporated under reduced pressure and the residue was co-evaporated with MeOH until triethylamine was removed. The residue was crystallized from appropriate solvent to give > 85% yield.

Ethyl-5,6-diphenyl-N^2-(β-*D*-glucopyranosyl)pyridazin-3-one-4-carboxylate (6a). Pale yellow crystals from ethanol; m.p. 125–127°C; R_f = 0.54 (eluent: CH_2Cl_2/MeOH; 9.2:0.8), ^{1}H NMR spectrum (300 MHz, DMSO-d_6/D_2O) δ 0.92 (t, 3 H, J = 8.80 Hz,$C\underline{H}_3CH_2$), 3.11 (m, 2 H, H-3′ and H-2′), 3.67 (m, 2 H, H-5′ and H-4′), 3.93 (m, 2 H, H-6′ and H-6″), 4.02 (q, 2 H, J = 8.80 Hz, $CH_3C\underline{H}_2$), 5.8 (d, 1 H, $J_{1',2'}$ = 9.3 Hz, H-1′), 7.15–7.3 1 (m, 10 H, Ar-H). Anal. Calcd for $C_{25}H_{26}N_2O_8$ (482.48): C, 62.23; H, 5.43; N, 5.81. Found: C, 62.45; H, 5.36; N, 5.77.

4-Cyano-5,6-diphenyl-N^2-(β-*D*-glucopyranosyl)pyridazin-3-one (6b). Pale crystals from ethanol; m.p. 210–212°C; R_f = 0.52 (eluent: CH_2Cl_2/MeOH; 9.2:0.8). IR (KBr) 3380–3435 cm^{-1} (broad, 4 OH), 2235 cm^{-1} (CN) and 1680 cm^{-1} (C=O, amide), ^{1}H NMR spectrum (200 MHz, DMSO-d_6) δ 3.11 (m, 2 H, H-3′& H-2′), 3.46 (m, 2 H, H-6a′& H-6b′) 3.69 (m, 1 H, H-4′), 3.89 (m, 1 H, H-5′), 4.1–4.6 (m, 4 H, OH-6′,4′,3′,2′) 5.86 (d, 1 H, $J_{1',2'}$ = 8.8 Hz, H-1′), 7.15–7.44 (m, 10 H, Ar-H). ^{13}C-NMR (200 MHz, DMSO-d_6): 61.31 (C-6′), 69.0 (C-2′), 70.3 (C-3′), 70.52 (C-4′), 77.5 (C-5′), 80.7 (C-1′) and 114.1(CN), 128.4, 128.6, 129.0, 129.2, 129.6, 130.6, 131.0, 133.1, 134.9, 145.9, 151.9, 157.1 (Ar-C, C=N). Anal. Calcd for $C_{23}H_{21}N_3O_6$ (435.43): C, 63.44; H, 4.86; N, 9.65. Found: C, 63.45; H, 4.92; N, 9.60.

4-Cyano-5,6-diphenyl-N^2-(β-*D*-ribofuranosyl) pyridazin-3-one (9). Pale crystals from methanol/waer; m.p. 103–105°C; R_f = 0.36 (eluent: CH_2Cl_2/MeOH; 9.2:0.8). IR (KBr) 3381–3434 cm^{-1} (broad, 3 OH), 2238 cm^{-1} (CN) and 1675 cm^{-1} (C=O, amide), ^{1}H NMR spectrum (300 MHz, DMSO-d_6/D_2O) δ 3.45 (m, 2 H, H-5′ and H-5″), 3.91–4.33 (m, 3 H, H-4′, 3′, 2′), 6.33 (d, 1 H, $J_{1',2'}$ = 2.4 Hz, H-1′), 7.10–7.42 (m, 10 H, Ar-H). Anal. Calcd for $C_{22}H_{19}N_3O_5$ (405.40): C, 65.18; H, 4.72; N, 10.37. Found: C, 64.98; H, 4.60; N, 10.23.

Antibacterial Screening

Some of the compounds synthesized were screened for their antibacterial activity against three species of bacteria, namely *(Pseudomonas aeruginosa)* as Gram (−ve), *(Staphylococcus aureus* and *Bacillus subtilis*) as Gram (+ve) using a cup agar diffusion method.[45] The tested compounds were dissolved in DMSO to get a solution of 1mg/mL concentration. The inhibition zone was measured in mm at the end of an incubation period of 48 hours at 37°C. Dimethylsulfoxide showed no inhibition zones. Ampicillin was used as a reference.

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