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AN ALTERNATIVE ROUTE TO THE SYNTHESIS OF 2-METHYL-N-BENZIMIDAZOLE GLYCOSIDES AND ANTIBACTERIAL ACTIVITY

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Abstract: Derivatives of 2-methyl-benzimidazole and their N-substituted cyclic glycosidic analogs namely: 2-methyl-1-(*L*-arabinofuranosyl)benzimidazole, 2-methyl-1-(D-xylofuranosyl)benzimidazole, and 2-methyl-1-(D-glucopyranosyl)benzimidazole, have been prepared by an alternative route reacting partially acetylated, anomeric free *L*-arabinose, *D*-xylose and *D*-glucose with 2-methyl-1*H*-benzimidazole. All synthesized products were characterized by IR, ^{1}H, ^{13}C-NMR, and Ms. The synthesized compounds were tested against the following microorganisms: Gram-positive bacteria, *Staphylococcus aureus*, and *Enterococcus faecalis* and Gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa*. The *D*-xylose and *D*-glucose derivatives showed more activity against Gram-positive bacteria, while 2-methyl-1-(D-xylofuranosyl)benzimidazole exhibited the highest antibacterial activity against all the studied bacteria.

Keywords: 2-Methyl-1*H*-benzimidazole; benzimidazole derivatives, N-glycoside benzimidazole, antibacterial activity.

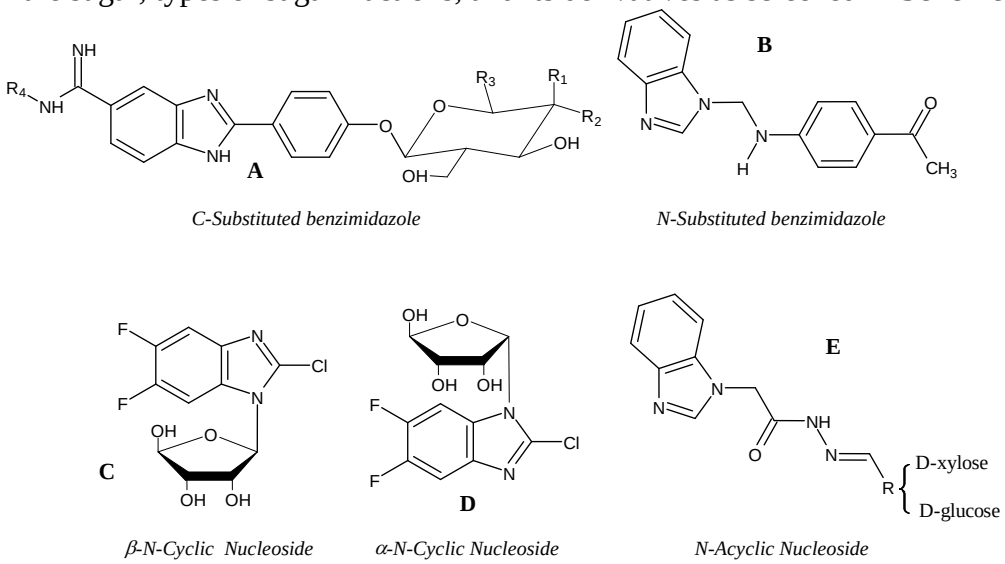
Introduction

The treatment of infectious diseases remains a challenge given the resurgence of certain infections accompanied by the increase in the number of microorganisms resistant to conventional antibiotics. In addition, the urgent need for new bioactive molecules with a wide range of modes of action is vital to the human being.

Optimization of benzimidazole substituents has resulted in many effective drugs like albendazole, mebendazole, and thiabendazole as anthelmintics. Omeprazole and pantoprazole are used as proton pump inhibitors, astemizole as antihistaminics and enviradine as antiviral agent [i].

Benzimidazole N-glycosides represent a class of glycosides with antiviral and antitumor activity. These derivatives are spread over a wide range of compounds, obtained in particular:

by functionalization of the benzimidazole ring, bonding via the anomeric or non-anomeric center of the sugar, types of sugar fractions, and its derivatives as screened in **Scheme 1** [ii-v].



C-Substituted benzimidazole *N-Substituted benzimidazole*

β-N-Cyclic Nucleoside *α-N-Cyclic Nucleoside* *N-Acyclic Nucleoside*

Scheme 1: Different structural outlines of benzimidazole and benzimidazole glycoside derivatives

Glycoside derivatives have an effect against herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2), human immunodeficiency virus (HIV), and various cytomegaloviruses (CMV), in particular human cytomegalovirus (HCMC) [iv,vi].

In addition, acyclonucleoside analogs currently contain a large number of antiviral agents available on the market. Their interest began in the mid-1970s with the discovery of acyclovir which is now frequently used to treat various herpes infections as well as the Varicella-Zoster Virus [vii].

Budow [viii] has reported the synthesis of deoxyribonucleosides bearing Bromo and nitro substituted benzimidazole. Kharitonova *et al.*, lately reported a summary of the synthesis of benzimidazole Furano-nucleosides and their pharmacological activities for the last two decades [iv].

In this study, we report the synthesis of three N-glycoside benzimidazoles by condensing *L*-arabinose tri-acetates, *D*-xylose tri-acetates, and *D*-glucose tetra-acetates with the synthesized 2-methyl-1*H*-benzimidazole followed by deacetylation. The corresponding products were characterized by IR, NMR, and LC-MS, and their antibacterial activity against selected Gram-positive and Gram-negative bacteria was performed.

Experimental section

Chemicals

Benzene-1,2-diamine, L-arabinose, D-xylose, D-glucose, methanol, dichloromethane, and hydrochloric acid (37%) were purchased from Biochem Chemopharma. Ethanol (96%), THF, ethylenediamine, acetic acid, and acetic anhydride were purchased from Sigma-Aldrich. Chloroform and hexane were purchased from Prolabo. All the chemicals were used as received unless otherwise stated.

General

Melting points were determined in open capillary tubes on a Stuart SMP10 digital melting point apparatus with a heating rate of 2°C/min to ensure precise measurements. FTIR spectra ranging from 4000 to 400 cm^{-1} were recorded on a JASCO FTIR spectrometer. IR samples were prepared using KBr pellets. ^{1}H and ^{13}C NMR were run at ambient temperature in DMSO-

d6 with a Bruker Avance 300 MHz spectrometer, with TMS as standard. FTIR and NMR were performed at the laboratory of polymer chemistry, Es-Sénia University, Oran, Algeria. The following abbreviations are used to describe peak patterns where appropriate: s singlet, d doublet, t triplet, q quartet, m multiplet or unresolved, and br broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm.

Mass Spectroscopy (Agilent 6510 LC-MS) was carried out at the « Centre régional de mesures physiques de l'Ouest, Université de Rennes 1, France ». Synthesis reactions monitored by thin-layer chromatography (TLC) on silica gel pre-coated on aluminium sheets supplied by Merck, Germany.

Microorganisms were kindly supplied and identified by the local hygiene and infection prevention laboratory (El-Wikaya laboratory of Chlef-Algeria locality). The Mueller Hinton medium was purchased from Difco.

2-Methyl-1H-benzimidazole (2).

First method. Phenylene-1,2-diamine (**1**) (2g, 18.49mmol) was dissolved in ethanol (10 mL), acetic acid (4ml) and HCl (5ml) were added. The mixture was refluxed for 5h at 90°C and monitored by TLC (ethyl acetate/hexane, 8/2 v/v, R_f 0.45).

Second Method. Phenylene-1,2-diamine (**1**) (3g, 27.74 mmol) was dissolved in ethanol (4 mL), acetaldehyde (0.125 g, 2.83mmol) was added in the presence of NH_4Cl (0.1 g). The mixture was refluxed for 6 h at 90°C and monitored by TLC (ethyl acetate/hexane 8/2, v/v). For both reactions, a brown solid was obtained. For the first mentioned reaction, yield 60%; mp177 °C; IR (KBr, cm^{-1}): 3362 (NH), 1459 (aromatic C=C), 1676 (C=N), 1630 (C-H (CH_3)), 1366 (C-N), 2971 (aromatic C-H); ^{1}H NMR (300MHZ, DMSO-d_6) δ(ppm): 7.35 (s, br, 1H, NH), 2.53 (s, 3H, methyl), 7.5 (q, 2H, H-4 and H-7), 7.16 (q, 2H, H-5 and H-6); ^{13}CNMR (300MHZ, DMSO-d_6) δ(ppm): 151.74, 138, 122, 114.56, 14.69 ; LC-MS (ESI, CH_3OH/CH_2Cl_2 80/20) m/z:calc. 133.07602, found133.0761.

Synthesis of benzimidazole glycosides:

General procedure for the synthesis of fully acetylated sugars 6-8:

Sugar (5g) of each [*L*-arabibnose (**3**), *D*-xylose (**4**), or *D*-glucose (**5**)] was dissolved in acetic anhydride (200 ml), pyridine (50 ml) was added. The solution was gently heated at 35°C for 30 min with an aid of magnetic agitation until total dissolution. Water (150 ml) was added and extracted with dichloromethane (100 ml). The organic phase was washed sequentially with a 10% HCl acid, then with a saturated solution of $NaHCO_3$ then with a saturated solution of NaCl, successively. The obtained solution was dried by anhydrous $MgSO_4$. Filtration and evaporation of volatiles to dryness give translucent viscous liquid which turned to white crystalline products **6-8**.

(1,2,3,5)-tetra-O-acetyl-L-arabinofuranose (6) TLC (chloroform/methanol 2/3, v/v), R_f = 0.81 ; a brown semi-solid; yield 60%; IR (KBr, cm^{-1}): 1778 (C=O), 1037-1377(C-O-C); ^{1}H NMR(300MHZ, DMSO-d6) δ(ppm): 5.94-6.08 (d, 1H, J=6.01, H-1'), 5.07-5.19 (m, 2H, H-2', H-3'), 4.15 (m, 1H, H-4'), 3.64 (m, 2H, H-5'), 2.03 (s, 12H, CH3CO); ^{13}CNMR(300MHZ , DMSO-d6) δ(ppm):169.9, 92.7, 85.2, 75.0, 71.9, 66.2, 21.0.

(1,2,3,5)-tetra-O-acetyl-D-xylofuranose (7) TLC (chloroform/methanol 2/3, v/v), Rf = 0.69 ; brown semi-solid; yield 70%; IR (KBr, cm-1): 1742 (C=O), 1057-1378(C-O-C); ^{1}H NMR(300MHZ, DMSO-d6) δ(ppm): 7.50 (s, 1H, H-1'), 4.95-5.52 (m, 2H, H-2', H-3'), 4.28-4.52 (m, 1H, H-4'), 3.20-3.55 (m, 2H, H-5'), 2.11 (s, 12H, CH3CO); ^{13}CNMR(300MHZ, DMSO-d6) δ(ppm): 169.9, 149.7 , 124.3, 91.6, 70.4, 21.2.

(1,2,3,4,6)-penta-O-acetyl-D-glucopyranose(8) TLC (chloroform/methanol 2/3,v/v), R_f = 0.72 ; brown semi-solid; yield 67%; IR (KBr, cm^{-1}): 1785,6 (C=O), 1041-1377 (C-O-C); ^{1}H NMR(300MHZ, DMSO-d6) δ(ppm): 7.94-8.65 (m, 1H, H-1'), 7.29-7.50 (m, 2H, H-2', H-3'), 4.25-5.69 (m, 1H, H-4'), 3.87-4.25 (d, 2H, J=4.06, H-5'), 3.09-3.59 (d, 2H, J=3.35, H-6'), 2.04

(s, 12H, CH3CO); ^{13}CNMR(300MHZ, DMSO-d6) δ(ppm): 170.6, 149.6, 137.0, 124.5, 93.5, 72.6, 63.7, 21.1.

General procedure for the deacetylation of anomeric acetates:

Each of the acetylated sugars **6-8** (2g) dissolved in a mixture of ethylenediamine (0.4 ml) and THF 60 ml). Acetic acid was added dropwise until precipitation was noticed. The mixture was left under magnetic stirring at room temperature for 9h and then diluted with distilled water (10 ml). The products were continuously extracted with CH_2Cl_2. The organic extract was washed successively with 2N HCl solution, saturated solution of sodium bicarbonate, and saturated solution of NaCl. Drying with $CuSO_4$, evaporating volatiles to obtain a gel which crystalized by standing to give the deprotected anomeric carbon sugars **9-11**, recrystallized from petroleum ether.

(2,3,5)-tri-O-acetyl-L-arabinofuranose (9) TLC (chloroform/methanol 2/3, v/v), R_f = 0.8; brown semi-solid; yield 42%; IR (KBr, cm^{-1}): 3294.77 (OH), 1664 (C=O), 1047 (C-O-C); ^{1}H NMR(300MHZ,DMSO-d6)δ(ppm): 8,53 (s, 1H, H-1'), 6.47 (s, 1H, H-2'), 3.74 (s, 1H, H-3'), 3.09-3.28 (m, 1H, H-4'), 2,67-2.86 (d, 2H, J=2.81, H5'), 2.05 (m, 9H, CH3CO), 0.78 (s, 1H, OH); ^{13}CNMR (300MHZ, DMSO-d6) δ(ppm): 174.6, 170.3, 22.4.

(2,3,5)-tri-O-acetyl-D-xylofuranose (10) TLC (chloroform/methanol 2/3, v/v), R_f = 0.86 ; brown semi-solid; yield 35%; IR (KBr, cm^{-1}): 3289.32 (OH), 1667.89 (C=O), 1049.30 (C-O-C); ^{1}H NMR(300MHZ, DMSO-d6) δ(ppm): 8,53 (s, 1H, H-1'), 6.87 (s, 1H, H-2'), 3.09-3.32 (t, 2H, H-3', H-4'), 2.76-2.85 (m, 1H, H-5'), 1.80 (m, 9H, CH3CO), 0.77 (s, 1H, OH) ; ^{13}CNMR (300MHZ, DMSO-d6) δ(ppm): 175.5, 170.3, 51.8, 22.3.

(2,3,4,6)-tetra-O-acetyl-D-glucopyranose (11) TLC (chloroform/methanol 2/3, v/v), R_f = 0.77 ; brown semi-solid; yield 37%; IR (KBr, cm^{-1}): 3293 (OH), 1642 (C=O), 1047.24 (C-O-C); ^{1}H NMR(300MHZ, DMSO-d6) δ(ppm): 8,46 (s, 1H, H-1'), 7.93 (s, 1H, H-2'), 6.94 (s, 1H, H-3'), 3.08-3.31 (m, 2H, H-4', H-5'), 1.72-1.73 (d, 2H, J=1.73, H-6'), 1.96-2.04 (m, 9H, CH3CO), 0.70 (s, 1H, OH); ^{13}CNMR (300MHZ, DMSO-d6) δ (ppm): 174.7, 170.4, 74.7, 22.3.

General procedure for nucleosides formation;

An equimolar mixture of 2-methyl-1*H*-benzimidazole **2** and sugars **9-11** dissolved in methanol (25 mL) and refluxed for 5h. The reaction was monitored by TLC (chloroform/ethanol 1/1, R_f 0.5). Methanol was evaporated to almost dryness and quenched in an ice bath to obtain brown crystals of acetylated sugar-benzimidazole (**12-14**).

IR (KBr, cm^{-1}) 1729 (C=O), 1082 (C-O-C)).

General procedure for the deacetylation of 12-14 nucleosides to obtain free acetate nucleosides 15-17:

Acetylated nucleosides 12-14 were treated with aqueous NaOH solution (0.25M) for 3h. DCM was added to the mixture before washing with 10% HCl then two times with NaCl. The organic phase was separated and dried with anhydrous $MgSO_4$. The solvent was removed by distillation under reduced pressure and the glycoside was weighed.

2-Methyl-1-(L-arabinofuranosyl)benzimidazole (15) The final product (**15**) was a light brown solid. Yield 67%, mp137°C, IR (KBr, cm^{-1}):3326(OH), 1421(C=C), 1047 (C-N), 1631 (C=N), 2997 and 1463 (C-H); ^{1}H NMR (300MHZ, DMSO-d6) δ(ppm); 2.57 (s, 3H, methyl), 7.52 (q, 2H, H-5 and H-8), 7.22 (q, 2H, H-6 and H-7), 4.88 (d, 1H, J=2.91, H-1'), 3.90 (dd, 1H, J=4.08 and 5.63, H-2'), 4.60 (d, 1H, J=4.02 and 5.70, H-3'), 4.85 (m, 1H, H-4'), 4.27(d, 2H, J=6.03, H-5'), 3.20-3.85 (m, 3H, 2'-OH and 3'-OH, 5'-OH); ^{13}C NMR (300MHZ, DMSO-d6)δ(ppm): 141.8, 137.7, 121.6 , 115.1, 98.0, 75.9, 73.5 , 70.0, 12, 4; LC-MS (ESI, CH_3OH/CH_2Cl_2 80/20): calculated 264.06206 found 264.0611.

2-Methyl-1-(D-xylofuranosyl)benzimidazole (16) The final product (**16**) was a brown solid. Yield 54 %; mp104 °C; R_f0.9; IR (KBr, cm^{-1}) 3215 (OH), 1450 (C=C), 1631 (C=N), 2888, 1978 and 1450 (C-H), 1015 (C-N); ^{1}H NMR (300MHZ, DMSO-d6) δ(ppm): 2.50 (s, 3H,

methyl), 7.54 (q, 2H, H-4 and H-7), 7.22 (q, 2H, H-5 and H-6), 4.87 (d, 1H, J1',2'=3.40, H-1'), 3.36 (m, 1H, H-2'), 3.38 (m, 1H, H-3'), 3.68 (m, 1H, H-4'), 4.25 (d, 2H, J=7.43, H-5'), 3.36-3.76 (m, 3H, 2'-OH, 3'-OH and 5'-OH); ^{13}C NMR (300MHZ, DMSOd6) δ(ppm): 122.8, 114.4, 98.1 , 92.9, 77.2, 75.2, 70.3, 62.2, 14.2; LC-MS (ESI, CH_3OH/CH_2Cl_2 80/20) m/z: calc. 264.0620 found 264.0602.

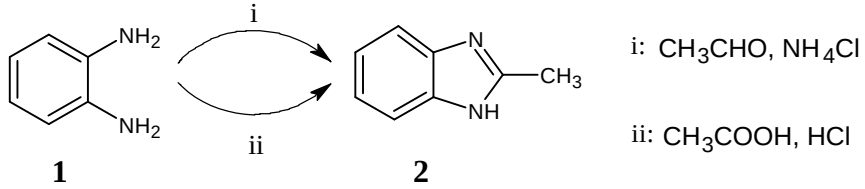
2-Methyl-1-(D-glucopyranosyl)benzimidazole (17) The final product (17) was a brown solid. Yield 65%; mp140°C; IR (KBr,cm^{-1})3219(OH), 1459(aromatic C=C), 991(C-C), 1014(C-N), 1630(C=N), 1459 and 2943 (C-H); ^{1}H NMR (300MHZ, DMSO-d6) δ(ppm): 2.50 (s, 3H, methyl), 7.50 (q, 2H, H-5 and H-8), 7.18 (q, 2H, H-6 and H-7), 4.93 (d, 1H, J=3.62, H-1'), 2 (m, 1H, H-2'), 3.40 (m, 1H, H-3'), 2.40 (m, 1H, H-4'), 3.5 (m, 1H, H-5'), 4.30 (d, 2H, J=2.42, H-6'), 3.05-3.64 (m, 4H, 2'-OH and 3'-OH, 4'-OH,6'-OH); ^{13}C NMR (300MHZ, DMSO-d6) δ(ppm): 122.0, 114.5, 92.7, 73.6, 72.8, 72.4, 71.1, 61.7, 14.7; LC-MS (ESI, CH_3OH/CH_2Cl_2 80/20): calculated 294.067 found 294.011.

Biological Activity

The minimum inhibitory concentration (MIC) of active chemicals is carried out by the method of serial dilution 1/2, 1/4, 1/8, 1/16 of the stock solution of 10 mg/mL on the four bacterial strains. **Table 2** collects the MIC data for the compounds showing effective activity at 10 mg/mL.

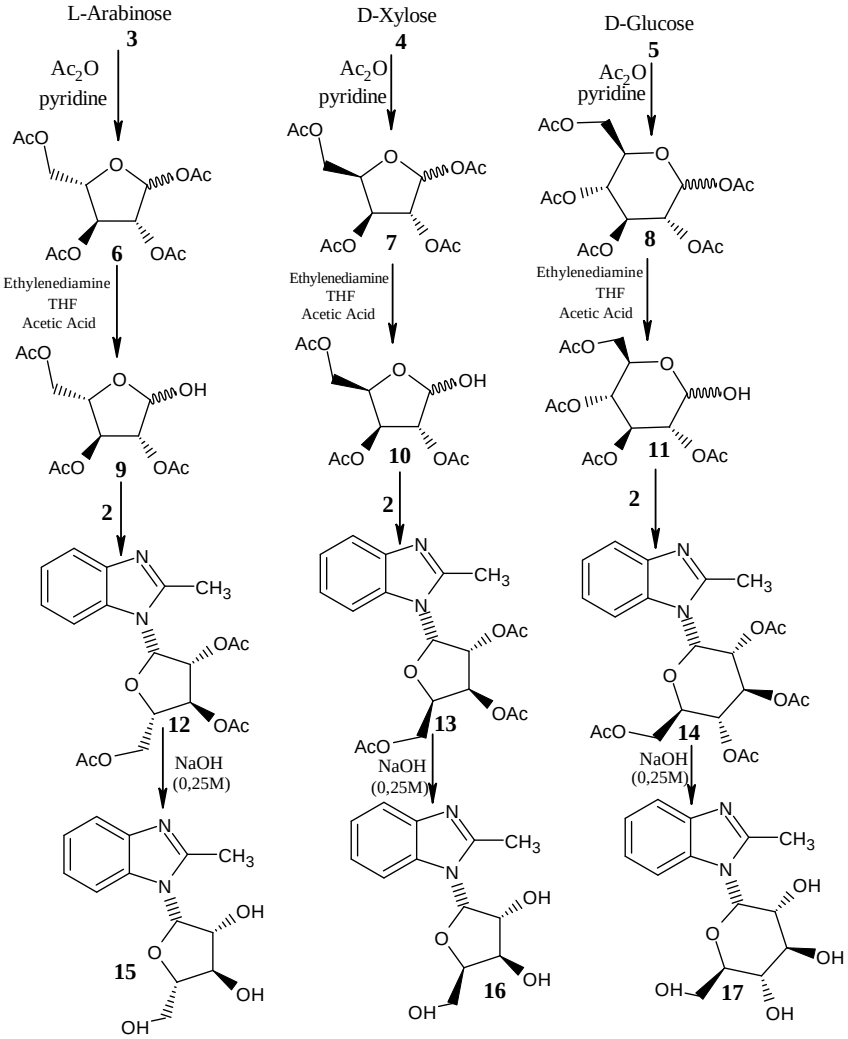
Results and discussion

2-Methyl-1*H*-benzimidazole (**2**) was obtained by two competitive methods, first by condensation of benzene-1,2-diamine (**1**) with acetic acid [viii,ix] and the second by condensation with acetaldehyde [x]. Both methods revealed the same percentage of yield (60%), as shown in **Scheme 2**. Results of both methods were identical (see experimental section).



Scheme 2: Synthesis of 2-methyl-1H-benzimidazole by two routes

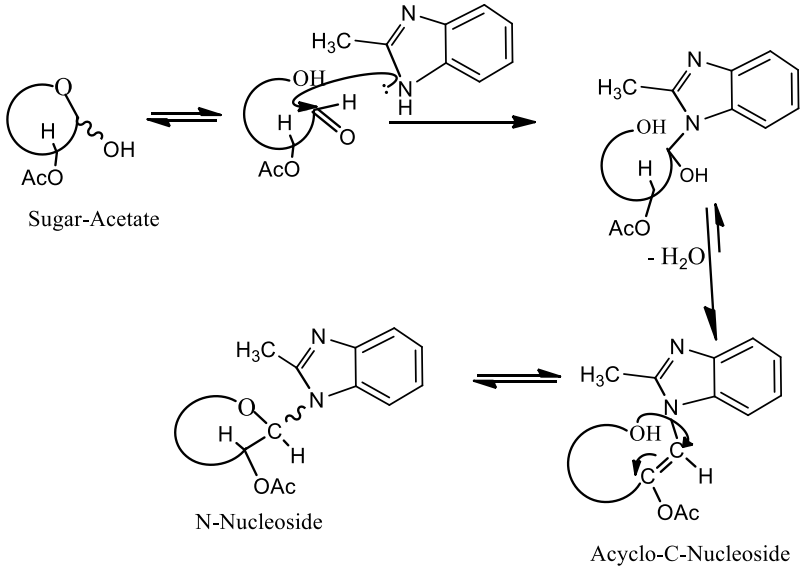
2-Methyl-1*H*-benzimidazole (**2**) was used as the starting block to synthesize the target bioactive molecules **15-17**. The synthesis of nucleosides **15-17** including preparation of fully acetylated sugars [*L*-arabinose (**3**), *D*-xylose (**4**), and *D*-glucose (**5**)] by using acetic anhydride in anhydrous pyridine to give the anticipated fully acetylated sugars (**6-8**) [xi]. The latter were converted to an anomeric free center by partially deacetylating the sugars with ethylenediamine and acetic acid in THF to give **9-11** as shown in **Scheme 3** [xii].



Scheme 3: Synthesis of N-glycosides **15**, **16** and **17**

Proceeding of reactions to fully acetylation followed by partial anomeric center deacetylate sugars **9-11** detected by careful thin layer chromatography. The latter, without isolation, were treated with **2** to give the anticipated acetylated nucleosides **12-14**. IR of **12**, **13,** and **14** compounds showed bands around 1730 cm^{-1} corresponding to the C=O acetate group [xiii]. De-acetylation reactions of **12-14** were done by NaOH (0.25N) to afford N-nucleosides **15-17**. Thin-layer chromatography showed single elongated spots attributed to mixtures of **α** and **ß** anomers for each nucleoside.

Scheme 4 shows the proposed reaction mechanisms to obtain acyclo glycol –C- nucleosides as an intermediate leading to a mixture of **α** and **ß** cyclic anomers of nucleosides.
The mass spectra of nucleosides **15-17** gave correct molecular formulae, indicating the correct molecular structures.



Scheme 4: Proposed mechanism of N-Nucleoside formation

However, IR spectra of the final products **15, 16,** and **17** reveal the disappearance of the acetate function and the presence of a band around the position 3200 cm^{-1} attributed to OH groups.
The cyclic formation of sugar nucleosides **15-17** was confirmed by ^{1}H-NMR *via* the presence of anomeric protons at 4.88-4.93 ppm with coupling constants $J_{1',2'}$=2.49, 3.41 and 3.62 ppm to confirm the α and ß configurations [xiv]. While ^{13}C NMR confirms the presence of benzimidazole in the final products (see experimental section).

Antibacterial Activity

The antibacterial activity of the synthesized compounds was evaluated in vitro by the paper disk method. The compounds dissolved in DMSO (as bacteriostatic solvent) in 10 mg/mL concentration. Standard paper disks saturated with the known antibiotics amoxicillin and gentamicin, which were used as a positive control. The microorganisms used for testing the antimicrobial activity were Gram-positive bacteria *Staphylococcus aureus* and *Enterococcus faecalis* and Gram-negative bacteria *Escherichia Coli* and *Pseudomonas aeruginosa*. Mueller Hinton agar medium was inoculated with 0.5 ml of microorganism cultures in Petri dishes and incubated at 37°C for 24 h. The inhibition zone around each disk for duplicate experiments was measured in mm and shown in Table 1.
According to Table 1, the Gram-negative bacteria under study are non-sensitive to the synthesized compounds except for compound **16**. However, the Gram-positive bacteria are shown to be sensitive to compounds **13-17**. The latter compounds are the most effective against *Staphylococcus aureus*.

Table 1: Antibacterial activity of the synthesized compounds at concentration 10 mg/mL

Compounds	Gram-Positive		Gram-Negative	
	Staphylococcus aureus	*Enterococcusfaecalis*	*Escherichia Coli*	*Pseudomonas aeruginosa*
2	0	0	0	0
12	0	0	0	0
13	20	6	0	0
14	16	6	0	0
15	0	0	0	0
16	22	11	15	22
17	18	0	0	0

Amx	0	0	26	0
Gent	25	27	0	17

The size of the inhibition zone:6–10 mm (intermediate); 10–15 mm (sensitive); 15 mm (highly sensitive) ; <6mm, (resistant or non-sensitive).

The minimum inhibition concentration (MIC) was performed only on the effective compounds at concentration 10 mg/mL.

Table 2: The minimum concentration* (MIC) of the synthesized compounds

Compounds	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus	*Enterococcusfaecalis*	*Escherichia Coli*	*Pseudomonas aeruginosa*
13	1/16	1/2	-	-
14	1/8	1/2	-	-
16	1/16	1/4	1/8	1/16
17	1/8	-	-	-

*Serial dilution 1/2, 1/4, 1/8, 1/16 of the stock solution of 10 mg/mL, sign (-) means no effect.

Conclusion

Condensing 2-methyl-1*H*-benzimidazole with partially acetylated *L*-arabinose, *D*-xylose and *D*-glucose afforded 2-methyl-1-(*L*-arabinofuranosyl)benzimidazole (**15**), 2-methyl-1-(*D*-xylofuranosyl)benzimidazole (**16**), and 2-methyl-1-(*D*-glucopyranosyl)benzimidazole (**17**), respectively. Characterization with IR spectroscopy, NMR spectroscopy, and LC-MS confirmed the chemical structure of the synthesized products **15-17**.

Bioactivity tests revealed the effectiveness of the *D*-xylose and *D*-glucose derivatives. We found that 2-methyl-1-(*D*-xylofuranosyl)benzimidazole possesses antibacterial activity against *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli,* and *Pseudomonas aeruginosa* microorganisms.

References

i. Bansal, Y.; Silakari, O.;The therapeutic journey of benzimidazoles: A review; Bioorganic Med Chem; 2012, **20**, 6208.

ii. De Souza, T. B.; Oliver, J. C.; Gomes, A. P. B.; Aragão, C. F. S.; Ferreira, L. S.; Nogueira, F. H. A.; Dias, A. L. T.; Alves, R. J.;Synthesis and antimicrobial activity of glycosylated 2-Aryl-5-amidinobenzimidazoles; J Braz Chem Soc; 2018, **29**, 1304.

iii. Krishnanjaneyulu, I. S.; Saravanan, G.; Vamsi, J.; Supriya, P.; Bhavana, J. U.; Sunil Kumar, M. V.;Synthesis, characterization and antimicrobial activity of some novel benzimidazole derivatives; J Adv Pharm Technol Res; 2014, **5**, 21.

iv. Kharitonova, M. I.; Konstantinova, I. D.; Miroshnikov, A. I.;Benzimidazole nucleosides: antiviral and antitumour activities and methods of synthesis; Russ Chem Rev; 2018, **87**, 1111.

v. Abdel-Rahman, A. A. H.; Nassar, I. F.; El-Kattan, I. M. H.; Aly, A. A.; Behalo, M. S.; Abdelwahed, N. A. M.;Synthesis and antimicrobial evaluation of thioglucosides and acyclic cnucleosides of 2-methylbenzimidazole; Der Pharma Chem; 2013, **5**, 210.

vi. Al-Mouamin, T.; Kadhim, A.;Synthesis and Characterization of Some New Nucleoside Analogues from Substituted Benzimidazole via 1,3-Dipolar cycloaddition; Baghdad Sci J; 2016, **13**, 298.

vii. Szenborn, L.; Kraszewska-Głomba, B.; Jackowska, T.; Duszczyk, E.; Majda-Stanisławska, E.; Marczyńska, M.; Ołdak, E.; Pawłowska, M.; Służewski, W.; Wysocki, J.; Stryczyńska-Kazubska, J.; Kuchar, E.;Polish consensus guidelines on the use of acyclovir in the treatment and prevention of VZV and HSV infections; J Infect

Chemother; 2016, **22**, 65.

viii. Budow, S.; Kozlowska, M.; Gorska, A.; Kazimierczuk, Z.; Eickmeier, H.; La Colla, P.; Gosselin, G.; Seela, F.;Substituted benzimidazoles: Antiviral activity and synthesis of nucleosides; Arkivoc; 2009, **2009**, 225.

ix. Kadhim, A. J.; Kazim, A. C.;Synthesis and characterization of benzimidazole by using O-phenylenediamine with different aldehydes and carboxylic acids in the presence of ρ-tsOh as a catalyst; Orient J Chem; 2018, **34**, 2131.

x. Kathirvelan, D.; Yuvaraj, P.; Babu, K.; Nagarajan, A. S.; R Reddy, B. S.;Note A green synthesis of benzimidazoles Benzimidazole moieties are a very important class of heterocyclic compounds that have many applications in pharmaceutical chemistry; Indian J Chem; 2013, **52**, 1152.

xi. Wuts, P. G. M.; Greene, T. W.;Greene's Protective Groups in Organic Synthesis; Greene's Protective Groups in Organic Synthesis; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2006.

xii. Zhang, J.; Kováč, P.;An Alternative Method for Regioselective, Anomeric Deacylation of Fully Acylated Carbohydrates; J Carbohydr Chem; 1999, **18**, 461.

xiii. Ibrahim, M.; Koglin, E.;Vibrational spectroscopic study of acetate group; Acta Chim Slov; 2004, **51**, 453.

xiv. Kiemle, D. J.; Stipanovic, A. J.; Mayo, K. E.;Proton NMR Methods in the Compositional Characterization of Polysaccharides; ACS Symp Ser; 2003, **864**, 122.

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