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Synthesis of 6-*O*-Stearoyl-1,2-*O*-isopropylidene-α-D-glucofuranose Derivatives for Antimicrobial Evaluation

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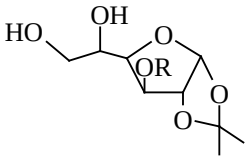
Abstract: *This work mainly describes the selective synthesis of 6-O-stearoylation of 1,2-O-isopropylidene-α-D-gluco-furanose and subsequent testing of this compound and its derivatives for antimicrobial activity. Bisacetone D-glucose (**3**) was prepared from D-glucose, which upon selective deprotection of the 5,6-O-isopropylidene group gave 3,5,6-triol (**4**) in good yield. Unimolecular direct stearoylation of this triol at low temperature provided the desired selective 6-O-stearoate (**5**) in 64% yield. To further elucidate the structure and to create novel glucofuranose derivatives of biological importance, 3,5-di-O-acetate (**6**), 3,5-di-O-mesylate (**7**) and 3,5-di-O-benzoate (**8**) were also prepared from the stearoate (**5**). All of the glucofuranoses (**3**–**8**) were tested via in-vitro antibacterial and antifungal functionality tests against 10 human pathogenic bacteria and 7 fungi. These experiments revealed that some of the tested glucofuranose derivatives (**5**, **6** and **8**) showed excellent antimicrobial functionality compared to standard antibiotics.*

Keywords: Bisacetone D-glucose, glucofuranose, acylation, antimicrobial agents, structure activity relationship

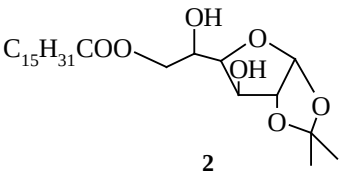
1. INTRODUCTION

Protection of a particular functional group of monosaccharides is not only necessary for the modification of the remaining functional groups but also useful during the synthesis of novel derivatives of great importance.[1,2] Various methods for acylation of monosaccharides and nucleosides have been developed and employed successfully.[3] Notably, the strategy involving protection of the off-target hydroxyl groups followed by direct acylation of the remaining hydroxyl group has been used successfully.[4] However, these methods are expensive and involves more steps. Hence, a method for selective direct acylation of the desired hydroxyl group while maintaining proper reaction conditions is necessary to reduce the number of steps.

It has been observed that if an active nucleus is linked to another nucleus, the resulting nucleus may possess a greater potential for biological activity.[5] Monosaccharides and nucleosides in combination with acyl nuclei (e.g., acetyl, mesyl and benzoyl) play an important role as the common denominator for various biological activities, which is also revealed by a number of our previous works.[6–8] A number of furanose, pyranose and disaccharide acetates were prepared and screened for in-vitro antibacterial activity against a number of human pathogenic bacteria and pathogenic fungi.[9] The study revealed that the pyranose acetate derivatives were more prone to exhibit antimicrobial functionality than those of the furanose and disaccharide acetates. Catelani et al.[10] reported the synthesis of various 3-*O*-acyl-1,2-*O*-isopropylidene-D-glucofuranose derivatives (**1a–c**) from triol **4** and tested their effects in augmenting the proportion of benzidine-positive (haemoglobin-containing) cells in treated K562 cell populations. The results obtained by this study demonstrated that two of these newly synthesised compounds were potent inducers of erythroid differentiation in K562 cells. Recently, Kobayashi et al.[11] reported the synthesis of 6-*O*-palmitoyl-1,2-*O*-isopropylidene-α-D-*gluco*-1,4-furanose (**2**) by lipase catalysed esterification. However, the yield was very low due to the low solubility of the reaction mixture in organic solvent.



1a: R = $COCH_2CH_2CH_3$;
1b: R = $COCH_2CH(CH_3)CH_3$;
1c: R = $COC(CH_3)_3$;
4: R = H.



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Considering their synthetic and biological importance, the authors were interested in the synthesis of some 6-*O*-stearoyl derivatives of 1,2-*O*-isopropylidene-α-D-*gluco*-1,4-furanose (**4**) containing stearoyl, acetyl, mesyl or benzoyl moieties using a single molecular framework. Furthermore, the authors evaluated their antimicrobial activities against a variety of bacterial and fungal pathogens.

2. EXPERIMENTAL

2.1 Physical Measurements

Melting points (mp) were determined using an electrothermal melting point apparatus and were uncorrected. Evaporations were performed under diminished pressure on a Buchi rotary evaporator. Thin layer chromatography (TLC) was performed on Kieselgel GF_{254}, and visualisation was accomplished by spraying the plates with 1% H_2SO_4 followed by heating the plates at 150°C–200°C until colour appeared. Column chromatography was carried out with silica gel (100–200 mesh). Infrared (IR) spectra were recorded on a Fourier-transform infrared (FTIR) spectrophotometer (Shimadzu, IR Prestige-21) using the KBr and $CHCl_3$ technique. ^1H (400 MHz) nuclear magnetic resonance (NMR) spectra were recorded using $CDCl_3$ and CD_3OD as a solvent. Chemical shifts were reported in α unit (ppm) using tetramethyl silane (TMS) as the internal standard, and *J* values are given in Hz. All reagents used were commercially available (Aldrich) and were used as received unless otherwise specified.

2.2 Synthesis

2.2.1 1,2:5,6-Di-*O*-isopropylidene-α-D-*gluco*-1,4-furanose (3)

Compound **3** was prepared from D-glucose treated with anhydrous acetone and $CuSO_4$ according to the literature procedure.[12] The product was obtained in 46% yield as a white amorphous solid, mp 108°C–110°C (lit.[12] mp. 108°C–109°C).

2.2.2 1,2-*O*-Isopropylidene-α-D-*gluco*-1,4-furanose (4)

Bisacetone D-glucose **3** (4.0 g, 15.36 mmol) was dissolved in methanol (62 ml) and water (12.5 ml) followed by slow addition of 15% H_2SO_4 (3.3 ml) at room temperature. Stirring was continued at this temperature for 5 h, and then saturated potassium carbonate (K_2CO_3) solution was added to neutralise the reaction mixture to pH = 7~8. The methanol was evaporated, and the residue was extracted with ethyl acetate (4 × 20 ml) with occasional warming. The organic layer was dried (using Na_2SO_4) and evaporated to give a thick liquid of triol, which after column chromatography with *n*-hexane/ethyl acetate (1/9) afforded pure 3,5,6-triol **4** as a white solid (2.57 g, 76%), mp 158°C –160°C (reported[13] mp 159°C–160°C).

2.2.3 1,2-*O*-Isopropylidene-6-*O*-stearoyl-α-D-*gluco*-1,4-furanose (5)

Stearoyl chloride (3.02 g, 9.97 mmol) was added slowly to a stirred solution of the 3,5,6-triol **4** (2.0 g, 9.08 mmol) in anhydrous pyridine (3 ml) at 0°C followed by addition of a catalytic amount of 4-dimethylaminopyridine (DMAP). The reaction mixture was stirred at this temperature for 6 h and then at room temperature overnight. The usual work-up and column chromatography (elution with *n*-hexane/ethyl acetate = 3/1) produced compound **5** (2.83 g, 64%) as needles, mp 78°C–80°C.

R_f = 0.41 (*n*-hexane/ethyl acetate = 1/1). IR (KBr): 3410–3480 (br OH), 1776 (CO), 1375 cm^{-1} [$C(CH_3)_2$]. ^1H NMR (100 MHz, $CDCl_3$): δ 5.95 (1H, d, *J* = 3.6 Hz, H-1), 4.52 (1H, d, *J* = 3.6 Hz, H-2), 4.40–4.45 (1H, m, H-5), 4.35 (1H, d, *J* = 2.5 Hz, H-3), 4.19–4.25 (2H, m, H-6a and H-6b), 4.07 (1H, dd, *J* = 7.5 and 2.5 Hz, H-4), 2.59–3.24 (2H, br s, exchange with D_2O, 2 × O*H*), 2.35 [2H, t, *J* = 7.7 Hz, $CH_3(CH_2)_{15}CH_2CO$], 1.59–1.66 [2H, m, $CH_3(CH_2)_{14}CH_2CH_2CO$], 1.47 [3H, s, $C(CH_3)_2$], 1.31 [3H, s, $C(CH_3)_2$], 1.10–1.29 [28H, m, $CH_3(CH_2)_{14}CH_2CH_2CO$], 0.87 [3H, t, *J* = 7.1 Hz, $CH_3(CH_2)_{16}CO$].

2.2.4 3,5-Di-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-stearoyl-α-D-*gluco*-1,4-furanose (6)

To a solution of 6-*O*-stearate **5** (0.5 g, 1.03 mmol) in dry pyridine (1 ml), 2.2 molar equivalents of acetic anhydride (0.23 g, 2.25 mmol) was added at 0°C with continuous stirring. The mixture was allowed to attain room temperature and stirring was continued overnight at this temperature. Work-up followed by chromatography gave the diacetate **6** (0.52 g, 88%) as a solid, mp 43°C–44°C.

R_f = 0.52 (*n*-hexane/ethyl acetate = 4/1). IR ($CHCl_3$): 1770, 1745 (CO), 1377 cm^{-1} [$C(CH_3)_2$]. ^1H NMR (100 MHz, $CDCl_3$): δ 5.91 (1H, d, *J* = 3.7 Hz, H-1), 5.34 (1H, d, *J* = 2.8 Hz, H-3), 5.17–5.24 (1H, m, H-5), 4.57 (1H, dd, *J* = 12.0 and 3.2 Hz, H-6a), 4.47 (1H, d, *J* = 3.7 Hz, H-2), 4.41 (1H, dd, *J* = 12.0 and 7.5 Hz, H-6b), 4.09 (1H, dd, *J* = 7.6 and 2.5 Hz, H-4), 2.29 [2H, t, *J* = 7.6 Hz, $CH_3(CH_2)_{15}CH_2CO$], 2.05 (3H, s, CH_3CO), 1.99 (3H, s, CH_3CO), 1.54–1.63 [2H, m, $CH_3(CH_2)_{14}CH_2CH_2CO$], 1.51 [3H, s, $C(CH_3)_2$], 1.30 [3H, s, $C(CH_3)_2$], 1.12–1.27 [28H, m, $CH_3(CH_2)_{14}CH_2CH_2CO$], 0.87 [3H, t, *J* = 7.2 Hz, $CH_3(CH_2)_{16}CO$].

2.2.5 1,2-*O*-Isopropylidene-3,5-di-*O*-mesyl-6-*O*-stearoyl-α-D-*gluco*-1,4-furanose (7)

Methanesulfonyl (mesyl) chloride (0.245 g, 2.138 mmol) was added drop-wise to a solution of the diol **7** (0.5 g, 1.03 mmol) in dry pyridine (1 ml) at

5°C followed by addition of a catalytic amount of DMAP. The reaction mixture was slowly allowed to attain 25°C and stirring was continued for 5 h. A few pieces of ice were added to the reaction flask to destroy the excess of mesyl chloride, and then the product was extracted with chloroform (3 × 3 ml). The usual work-up and chromatography elution with *n*-hexane/ethyl acetate (18/1) produced compound **7** (0.534 g, 82%), as a semi-solid, which turned pale-yellow after a couple of weeks.

R_f = 0.54 (*n*-hexane/ethyl acetate = 5/1). IR ($CHCl_3$): 1770 (CO), 1377 [$C(CH_3)_2$], 1325 cm^{-1} (SO_2). ^1H NMR (100 MHz, $CDCl_3$): δ 5.93 (1H, d, *J* = 3.7 Hz, H-1), 5.35 (1H, d, *J* = 2.8 Hz, H-3), 5.15–5.21 (1H, m, H-5), 4.58 (1H, dd, *J* = 12.0 and 3.2 Hz, H-6a), 4.46 (1H, d, *J* = 3.7 Hz, H-2), 4.43 (1H, dd, *J* = 12.0 and 7.5 Hz, H-6b), 4.10 (1H, dd, *J* = 7.6 and 2.5 Hz, H-4), 3.14 (3H, s, SO_2CH_3), 3.04 (3H, s, SO_2CH_3), 2.30 [2H, t, *J* = 7.6 Hz, $CH_3(CH_2)_{15}CH_2CO$], 1.56–1.63 [2H, m, $CH_3(CH_2)_{14}CH_2CH_2CO$], 1.49 [3H, s, $C(CH_3)_2$], 1.30 [3H, s, $C(CH_3)_2$], 1.10–1.27 [28H, m, $CH_3(CH_2)_{14}CH_2CH_2CO$], 0.88 [3H, t, *J* = 7.2 Hz, $CH_3(CH_2)_{16}CO$].

2.26 3,5-Di-*O*-benzoyl-1,2-*O*-isopropylidene-6-*O*-stearoyl-α-D-*gluco*-1,4-furanose (8)

Benzoylation of diol **5** (0.5 g, 1.03 mmol) with 2.2 molar equivalents of benzoyl chloride (0.32 g, 2.28 mmol) in anhydrous pyridine (1 ml) overnight produced a faster-moving product. Upon the usual work-up followed by chromatography with *n*-hexane/ethyl acetate, the di-*O*-benzoate **8** (0.61 g, 86%) was obtained as a thick syrup.

R_f = 0.50 (*n*-hexane/ethyl acetate = 4/1). IR ($CHCl_3$): 1772, 1730 (CO), 1379 cm^{-1} [$C(CH_3)_2$]. ^1H NMR (100 MHz, $CDCl_3$): δ 7.96–8.08 (5H, m, Ar-H), 7.22–7.38 (5H, m, Ar-H), 5.98 (1H, d, *J* = 3.7 Hz, H-1), 5.36 (1H, d, *J* = 2.7 Hz, H-3), 5.20–5.26 (1H, m, H-5), 4.56 (1H, dd, *J* = 12.0 and 3.2 Hz, H-6a), 4.46 (1H, d, *J* = 3.7 Hz, H-2), 4.41 (1H, dd, *J* = 12.0 and 7.6 Hz, H-6b), 4.10 (1H, dd, *J* = 7.6 and 2.7 Hz, H-4), 2.28 [2H, t, *J* = 7.6 Hz, $CH_3(CH_2)_{15}CH_2CO$], 1.51–1.583 [2H, m, $CH_3(CH_2)_{14}CH_2CH_2CO$], 1.52 [3H, s, $C(CH_3)_2$], 1.30 [3H, s, $C(CH_3)_2$], 1.13–1.25 [28H, m, $CH_3(CH_2)_{14}CH_2CH_2CO$], 0.86 [3H, t, *J* = 7.1 Hz, $CH_3(CH_2)_{16}CO$].

2.3 Antimicrobial Screening Studies

2.3.1 Human pathogens and phytopathogens

All of the glucofuranose derivatives (**3**–**8**) were tested against 10 human pathogenic bacteria. Of these, 4 were Gram-positive: *Bacillus cereus* BTCC 19, *Bacillus megaterium* BTCC 18, *Bacillus subtilis* BTCC 17 and *Staphylococcus aureus* ATCC 6538. 6 were Gram-negative bacteria: *Escherichia coli* ATCC 25922, *Pastunella maltosida*, *Salmonella gallinarium*, *Salmonella typhi* AE 14612, *Shigella dysenteriae* AE 14369 and *Vibrio cholerae*. Seven plant pathogenic fungi were selected for in-vitro mycelial growth tests: *Aspergillus acheraccus*, *Aspergillus flavus*, *Aspergillus fumigates*, *Aspergillus niger*, *Aspergillus nodusus*, *Candida albicans* and *Fuserium equiseti* (Corda) Sacc.

2.3.2 Screening of antibacterial activity

For the detection of antibacterial activity, the disc diffusion method[14] was used. Dimethylformamide (DMF) was used as a solvent for the test chemicals, and a 2% solution of each compound was used. The plates were incubated at 37°C for 48 h. The control was DMF without chemicals. Mueller-Hinton (agar and broth) medium was used to culture the bacteria. Each experiment was carried out three times. All of the results were compared to the standard antibacterial antibiotic kanamycin (50 μg $disc^{-1}$, Taj Pharmaceuticals Ltd., India).

2.3.3 Screening of mycelial growth

The antifungal activities of the synthesised glucofuranose derivatives (**3**–**8**) were investigated based on the food poisoning technique[15] as modified by Miah et al.[16] Sabouraud (agar and broth, PDA) medium was used for culture of fungi. Linear mycelial growth of fungus was measured after 3~5 days of incubation. The percent inhibition of the radial mycelial growth of the test fungus was calculated as follows:

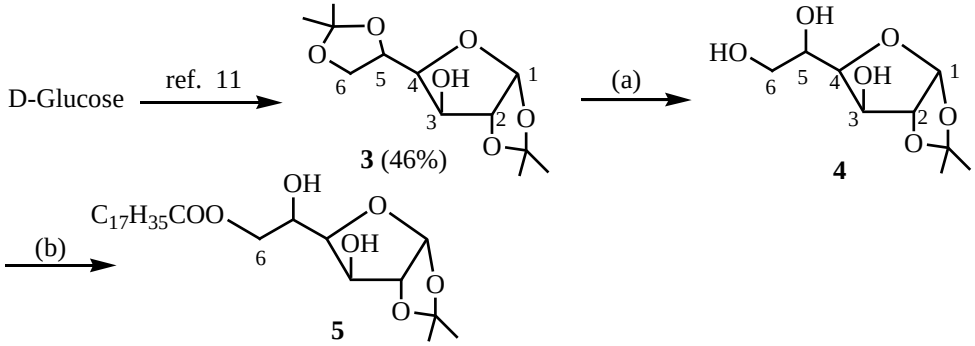
$$I = \left\{ \frac{C - T}{C} \right\} \times 100$$

where, I = percent of inhibition, C = diameter of the fungal colony in the control (DMF) and T = diameter of the fungal colony in the treatment. The results were compared with the standard antifungal antibiotic fluconazole (100 μg ml^{-1} medium, brand name Omastin, Beximco Pharmaceuticals Ltd., Bangladesh).

3. RESULTS AND DISCUSSION

3.1 Synthesis of 6-*O*-stearoylglucofuranose 5

The present study mainly describes the selective 6-*O*-stearoylation of 1,2-*O*-isopropylidene-α-D-*gluco*-1,4-furanose (**4**) and antimicrobial evaluation of the synthesised products. For this reason, our first task was to prepare 1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-1,4-furanose (**3**). Compound **3** was prepared from D-glucose treated with anhydrous acetone and $CuSO_4$ according to the literature procedure[12] in 46% yield as a white amorphous solid, mp 108°C–110°C. Selective deprotection of the 5,6-*O*-acetonide functionality of bisacetone **3** was achieved by treating **3** with 15% H_2SO_4 in methanol for 5 h, which upon the usual work-up and chromatographic purification afforded pure 3,5,6-triol, **4** as a white solid (76%), mp 158°C–160°C (Scheme 1). Its IR and ^{1}H spectra were similar to that of reported spectra.[13]



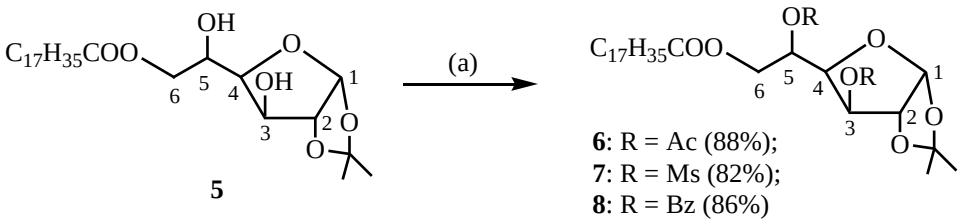
Scheme 1: Reagents and conditions are (a) 15% H_2SO_4, MeOH-H_2O, rt, 5 h, 76%; (b) $C_{17}H_{35}COCl$, pyridine, DMAP, 0°C-rt, 18 h, 64%.

Having 1,2-*O*-isopropylidene-α-D-*gluco*-1,4-furanose (**4**) in hand, selective 6-*O*-acylation was attempted using stearoyl chloride ($C_{17}H_{35}COCl$). Thus, treatment of triol **4** with only 0.91 molar equivalents of $C_{17}H_{35}COCl$ in dry pyridine at 0°C produced a faster-moving solid in 64% yield (Scheme 1). The IR spectrum of the compound showed the presence of a carbonyl-stretching band at 1776 cm^{-1}, indicating the attachment of the stearoyl group on the molecule. In the ^{1}H NMR spectrum, a 2-proton triplet at δ 2.35, a 2-proton multiplet at δ 1.59–1.66, a 28-proton multiplet at δ 1.10–1.29 and a 3-proton triplet at δ 0.87 were indicative of the presence of 1 stearoyloxy group in the molecule. In addition, the downfield shift of the H-6 protons (~δ 4.19–4.25) compared to the precursor compound **4** (δ 3.67–3.76) confirmed the attachment of the stearoyloxy group at the C-6 position. The rest of the ^{1}H NMR spectrum was in complete accord with

the structure assigned as 1,2-*O*-isopropylidene-6-*O*-steroyl-α-D-*gluco*-1,4-furanose (**5**). We know that a primary OH group is more reactive than that of a secondary OH group. Thus, treatment of triol **4** with only 0.91 molar equivalents of a bulky acylating agent such as stearoyl chloride at low temperature will react only with the primary OH group at the C-6 position. Thus, product formation was in complete accord with our aim, albeit in lower yield (64%).

3.2 Synthesis of 3,5-di-*O*-acyl Derivatives of Stearoate 5

To confirm the structure of stearoate **5**, as well as to produce novel derivatives of biological importance, three 3,5-di-*O*-acyl derivatives (**6**–**8**) containing various groups (i.e., acetyl, methanesulfonyl and benzoyl) were prepared, as shown in Scheme 2. Thus, treatment of diol **5** with acetic anhydride in anhydrous pyridine produces a solid in 88% yield. Its IR spectrum showed peaks at 1770, 1745 (CO) and 1377 cm^{-1} [$C(CH_3)_2$]. In the ^1H NMR spectrum of this compound, two three-proton singlets at δ 2.05 and 1.99 corresponding to two acetyl methyl groups clearly indicated the attachment of two acetyloxy groups in the molecule. Thus, the structure was assigned as 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-stearoyl-α-D-*gluco*-1,4-furanose (**6**). The formation of 3,5-di-*O*-acetate (**6**) also confirmed the structure of 6-*O*-stearoate (**5**).



Scheme 2: Reagents and conditions are Ac_2O/MsCl/BzCl, pyridine, DMAP, 0°C-rt, 6~18 h.

For the next derivative, mesylation of **5** with methanesulfonyl chloride in pyridine gave a semi-solid in 82% yield (Scheme 2). Its IR spectrum resonated at 1770 (CO), 1377 [$C(CH_3)_2$] and 1325 cm^{-1} (SO_2). In its ^1H NMR spectrum, 2 3-proton singlets at δ3.14 and 3.04 clearly indicated the attachment of 2 mesyloxy groups in the molecule. The reasonable down field shift of H-3 (δ5.35) and H-5 (δ5.15–5.21) protons compared to that of compound **5** confirmed the attachment of 2 mesyloxy groups at position C-3 and C-5. Thus the structure was assigned as 1,2-*O*-isopropylidene-3,5-di-*O*-mesyl-6-*O*-stearoyl-α-D-*gluco*-1,4-furanose (**7**). Finally, the 6-*O*-stearoate **5** was converted to 3,5-di-*O*-benzoate (**8**) by reaction with benzoyl chloride. In its ^1H NMR spectrum, 2 5-proton multiplets at δ 7.22–7.38 and 7.96–8.08 indicated the incorporation of 2 benzoyl groups in the molecule. Complete analysis of the IR and ^1H NMR spectra as well as correlation

with diacetate (**6**) and dimesylate (**7**) led us to assign the structure of the compound as 3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-6-*O*-stearoyl-α-D-*gluco*-1,4-furanose (**8**).

3.3 Antimicrobial Activities

The results of the in-vitro inhibition zone produced by the glucofuranose derivatives (**3**–**8**) against 4 Gram-positive and 6 Gram-negative bacteria are shown in Table 1. Bisacetone D-glucose **3** and triol **4** were found to be inactive against all of the tested bacteria. As shown in Table 1, the acylated glucofuranoses (**5**–**8**) were more effective against the selected Gram-positive organisms than the selected Gram-negative bacteria. Diacetate **5** and dibenzoate **8** exhibited marked inhibition against *B. subtilis* to an extent that was comparable to the standard antibacterial antibiotic kanamycin. Compounds **5**, **6** and **8** also exhibited good inhibition against *E. coli* and *V. cholerae*.

Table 1: Inhibition against bacterial organism by the glucofuranose derivatives (**3**–**8**).

Name of bacteria	Diameter of zone of inhibition in mm, 50 μg.dw disc^{-1}						
	3	**4**	**5**	**6**	**7**	**8**	Kanamycin**
Bacillus cereus	NF	NF	14	12	NF	10	20
Bacillus megaterium	NF	NF	13	16	14	16	20
Bacillus subtilis	NF	NF	19	20*	NF	20*	21*
Staphylococcus aureus	NF	NF	13	17	NF	16	22*
Escherichia coli	NF	NF	18	19	NF	20*	22*
Pastunella maltosida	NF	NF	16	15	NF	NF	23*
Salmonella gallinarium	NF	NF	NF	18	NF	NF	24*
Salmonella typhi	NF	NF	NF	NF	NF	NF	23*
Shigella dysenteriae	NF	17	NF	NF	NF	11	24*
Vibrio cholerae	NF	NF	NF	16	14	18	18

Notes: (*) shows good inhibition, (NF) indicates no inhibition, (**) indicates standard antibiotic, and dw means dry weight.

The in-vitro values for percent of inhibition of mycelial growth caused by glucofuranose derivatives (**3**–**8**) in 7 plant pathogenic fungi are presented in Table 2. All of the acylated glucofuranoses (**5**, **6** and **8**) were found to have potential against the tested fungal pathogens except for the dimesylate **7**. Bisacetone D-glucose **3** and triol **4** were found to be inactive against the tested fungi. Diacetate **6** and dibenzoate **8** showed very good inhibition, which were comparable to that of the standard antibiotic fluconazole.

Table 2: Antifungal activities of the glucofuranose derivatives (**3**–**8**).

Name of fungus	% inhibition of fungal mycelial growth, sample 100 μg.dw ml^{-1} PDA						
	3	**4**	**5**	**6**	**7**	**8**	Fluconazole**
Aspergillus acheraccus	NF	NF	44	53	NF	48	58
Aspergillus flavus	NF	NF	47	55	52	52	62*
Aspergillus fumigatus	NF	NF	45	51	49	53	70*
Aspergillus niger	NF	NF	40	46	NF	48	58*
Aspergillus nodusus	NF	NF	53	56	NF	55	64*
Candida albicans	NF	NF	41	52	NF	53	60*
Fuserium equiseti	NF	NF	39	47	NF	49	65*

Notes: (*) shows good inhibition, (NF) indicates no inhibition, (**) indicates standard antibiotic, and dw means dry weight.

3.4 Structure Activity Relationship (SAR)

It was evident from Table 1 and Table 2 that incorporation of the stearoyl group increased the antimicrobial potential of the glucofuranose **4**. Again, these 6-*O*-stearoyl glucofuranose derivatives (**5–8**) were more active against fungal pathogens than bacterial organisms. An important observation was that compounds **3** and **4** showed poorer toxicity than compounds **5**–**8** against these pathogens. This result is most likely due to the presence of more hydroxyl groups in **3** and **4**. Compounds **5**–**8** have fewer or no hydroxyl groups and thus, showed much better antimicrobial potential. Here, the hydrophobicity of the molecules increased gradually from compound **2** to **3** to **5**–**8**. The hydrophobicity of materials is an important parameter with respect to bioactivities such as toxicity or alteration of membrane integrity because hydrophobicity is directly related to membrane permeation.[17] A research also proposed that the potency of aliphatic alcohols is directly related to their lipid solubility via hydrophobic interactions between the alkyl chains of alcohols and the fatty acid tail region of the membrane.[18] We believe that a similar hydrophobic interaction might occur between the acyl chains of glucofuranoses accumulated in the fatty acid tails of the bacteria membranes. As a consequence of their hydrophobic interactions, bacteria may lose their membrane integrity, ultimately causing the death of the bacteria.[17–19]

Previously we observed that, due to the slight distortion of the furanose ring in the presence of the 1,2-*O*-isopropylidene ring,[7] acetylated sugars in the 5-membered furanose form were less effective against both Gram-negative, Gram-positive and fungal pathogens than the corresponding acetylated sugars in the 6-membered pyranose form. It was observed from Table 1 and Table 2 that 6-*O*-stearoate (**5**) and its 3,5-di-*O*-aceatae (**6**) and 3,5-di-*O*-benzoatae (**8**) exhibited

excellent activity against both bacterial and fungal pathogens, which was, in some cases, similar to that of the standard antibiotics. This result led us to conclude that incorporation of the 6-*O*-stearoyl group into the glucofuranose framework, along with the 3,5-di-*O*-acetyl or 3,5-di-*O*-benzoyl group, increased the antimicrobial potentiality of the glucofuranose **4**.

4. CONCLUSION

We successfully synthesised the 6-*O*-steroyl derivative (**5**) of triol **4** in reasonably good yield from D-glucose in just 3 steps. A number of 2,3-di-*O*-acyl substituted derivatives (**6**–**8**) of **5** were also prepared for structural elucidation and to produce novel glucofuranose derivatives of biological importance. All of the glucofuranose derivatives (**3**–**8**) were tested for in-vitro antibacterial and antifungal activity against ten human pathogenic bacteria and seven fungi. The structure activity relationship (SAR) study revealed that incorporation of 6-*O*-stearoyl group into the glucofuranose framework alongside the 3,5-di-*O*-acetyl or 3,5-di-*O*-benzoyl groups increased the antimicrobial activity of glucofuranose **4**.

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