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Stearoyl Glucopyranosides: Selective Synthesis, PASS Analysis, In Vitro Antimicrobial, and SAR Study

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Abstract

Direct unimolar stearoylation of methyl α-D-glucopyranoside (**1**) at room temperature showed selectivity at C-6 primary position and furnished 6-*O*-stearoyl-α-D-glucopyranoside **2** in 46% yield. The lower yield was due to the formation of several inseparable mixtures although 2,3,6-tri-*O*-stearoyl-α-D-glucopyranoside **3** was isolated in 28% yield. In search of novel biologically active glucopyranosides, both the stearates **2** and **3** were further modified into several acyl esters utilizing their free hydroxyls. Prediction of activity spectra for substances (PASS) and *in vitro* antimicrobial assay indicated that these stearoyl esters have better antifungal potentiality. In this respect, the structure-activity relationship (SAR) is discussed for insight understanding of the necessity of acyl group(s) in the glucopyranoside unit.

Keywords: Antifungals; D-Glucopyranoside; Sugar esters; PASS; Regioselectivity.

1. Introduction

In our planet, carbohydrate-related compounds are the most common natural biomolecules and comprise more than 75% of the total biomass [1-3]. In addition to being the most important energy source in our life, carbohydrates perform many significant nutritional functions [4]. Carbohydrates and their modified derivatives have a variety of applications, such as precursors for stereoselective synthesis, drug synthesis, and chiral catalysts in asymmetric synthesis [5-8]. Among them, acylated monosaccharide esters are important intermediates in the syntheses of many natural products and have a wide range of applications in industry and medicine [9,10]. These acylated monosaccharides are biodegradable, non-toxic, and act as antimicrobials with anti-carcinogenic properties [11,12]. Among the first fatty acid sugar esters, sucrose dicaprylate and sucrose monolaurate exhibited considerable antimicrobial activities against certain microorganisms [13]. More antimicrobial inhibitory activities along with surface-active properties of sugar esters containing mono-, di- and tri-esters have also been reported [14-16]. AlFindee et al. [17] reported that many sugar esters are related to the degree of substitution and are active against a panel of bacteria and fungi, including *S. aureus*, methicillin-resistant *S. aureus* (MRSA), *C. albicans*, *C. neoformans*, *A. flavus*, and *F. graminearum*. However, according to Zhang and co-workers [14] degree of esterification and hydrophilic groups showed little effect although the carbon chain length was the most important factor influencing the surface properties. In this regard, antimicrobial functionality and structure-activity relationships of some novel carbohydrate fatty acid derivatives are reported [18,19].

Many plant-based Oriental natural medicines are found to possess sugar esters with notable biological activities, and hence synthesis of such esters are of great interest over the past several decades [20,21]. However, sugars especially monosaccharide molecules contain several hydroxyl groups of similar reactivity and for this reason; selective acylation of monosaccharide derivatives is a prominent challenge in the field of carbohydrate chemistry. For efficient selectivity of monosaccharide derivatives direct acylation [22,23], protection-deprotection technique [24,25], organotin (bistributyltin oxide or dibutyltin oxide) mediated regioselective acylation [26,27] methods are used successfully. Considering the

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benefits of methods, especially our target, the direct acylation technique produces a relatively better yield compared to other techniques. Corroboration of all these results led us to design and synthesize several 2,3,6-tri-*O*- and 6-*O*-stearoyl-α-D-glucopyranosides from the methyl α-D-glucopyranosides (**1**) containing different alkanoyl chain length(s) in a single molecular framework in the hope that these glucose esters might show some potential antimicrobial activities.

2. Experimental

Evaporations were carried out under reduced pressure using a Buchi rotary evaporator (R-100, Switzerland) with a bath temperature below 40 °C. Column chromatography was performed with silica gel G_{60}. Thin-layer chromatography (TLC) was performed on Kieselgel GF_{254} and the spots were detected by spraying the plates with 1% H_2SO_4 followed by warming at 150–200 °C until coloration took place. The solvent systems employed for the TLC analyses were chloroform/methanol and *n*-hexane/ethyl acetate in different proportions. FT-IR spectra were recorded on an FT-IR spectrophotometer (MB 3000, ABB, Canada). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$ solution using a tunable multinuclear probe. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and *J* values are shown in Hz

2.1. Synthesis

Methyl 2,3,6-tri-*O*-stearoyl-α-D-glucopyranoside (2) and methyl 6-*O*-stearoyl-α-D-glucopyranoside (3): To a cooled (0 °C) well-stirred solution of methyl α-D-glucopyranoside (**1**) (2.0 g, 10.31 mmol) in anhydrous pyridine (6 mL) and DMAP (dimethylamino pyridine) as catalyst was added stearoyl chloride (4.02 g, 13.27 mmol) slowly. It was stirred at this temperature for 4 h and then 14 h at room temperature when TLC indicated the conversion of the starting compound into faster-moving two products (R_f = 0.75 and 0.28, chloroform/methanol = 5/1, v/v) with some other inseparable mixtures. The reaction was stopped by the addition of a few pieces of ice to the reaction flask and extracted the product with dichloromethane (DCM, 3×10 mL). The combined organic (DCM) layer was washed successively with dilute hydrochloric acid (5%), saturated aqueous sodium hydrogen carbonate solution, and distilled water. The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to leave a syrupy mass, which was purified by silica gel column chromatography. Initial elution with chloroform-methanol (20:1, v/v) provided higher R_f compound **2** as a syrup (2.78 g, 28%) which resisted crystallization.

R_f = 0.75 (chloroform/methanol = 5/1). FT-IR (neat): 3250-3500 (br, OH), 1701, 1735(2) (CO), 1065 cm^{-1} (pyranose ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.31 (t, *J* = 10.0 Hz, 1H, H-3), 4.92 (d, *J* = 3.6 Hz, 1H, H-1), 4.88 (dd, *J* = 10.0 and 3.6 Hz, 1H, H-2), 4.49 (dd, *J* = 12.0 and 4.4 Hz, 1H, H-6a), 4.33 (dd, *J* = 12.0 and 1.6 Hz, 1H, H-6b), 3.83-3.86 (m, 1H, H-5), 3.54 (t, *J* = 9.6 Hz, 1H, H-4), 3.41 (s, 3H, O*CH*$_3$), 2.40 [t, *J* = 7.4 Hz, 2H, $CH_3(CH_2)_{15}CH_2CO$], 2.29-2.36 [m, 4H, $2\times CH_3(CH_2)_{15}CH_2CO$], 1.53-1.68 [m, 12H, $3\times CH_3(CH_2)_{13}(CH_2)_2CH_2CO$], 1.22-1.38 [br m, 78H, $3\times CH_3(CH2)_{13}(CH_2)_3CO$], 0.90 [t, *J* = 6.4 Hz, 9H, $3\times CH_3(CH_2)_{16}CO$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.7, 174.3, 173.1 ($3\times C_{17}H_{35}CO$), 96.9 (C-1), 72.9 (C-3), 70.4 (C-2), 69.9 (C-5), 69.6 (C-4), 62.7 (C-6), 55.3 (O*CH*$_3$), 34.3, 34.2, 34.1 [$3\times CH_3(CH_2)_{15}CH_2CO$], 31.9(3) [$3\times CH_3(CH_2)_{14}CH_2CH_2CO$], 29.7(14), 29.69(5), 29.6(7), 29.5(3), 29.4, 29.3(2), 29.2(2), 29.1(2) [$3\times CH_3(CH_2)_2(CH_2)_{12}(CH_2)_2CO$], 25.0(2), 24.9 [$3\times CH_3CH_2CH_2(CH_2)_{14}CO$], 22.7(3) [$3\times CH_3CH_2(CH_2)_{15}CO$], 14.1(3) [$3\times CH_3(CH_2)_{16}CO$]. The structure, and position of the signals were also confirmed by its Distortionless Enhancement by Polarization Transfer (DEPT-135), two-dimensional Correlation Spectroscopy (2D COSY), 2D Heteronuclear Single Quantum Coherence (HSQC), and 2D Heteronuclear Multiple Bond Correlation (HMBC) experiments.

Further elution with chloroform-methanol (12:1) slowly furnished the lower R_f compound **3** (2.67 g, 58%) as semi-solid. R_f = 0.28 (chloroform/methanol = 5/1). FT-IR (neat): 3225-3610 (br, OH), 1726 (CO), 1040 cm^{-1} (pyranose ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.82 (d, *J* = 4.0 Hz, 1H, H-1), 4.59 (dd, *J* = 12.4 and 4.0 Hz, 1H, H-6a), 4.24 (dd, *J* = 12.4 and 1.8 Hz, 1H, H-6b), 3.88-3.92 (m, 1H, H-5), 3.76 (t, *J* = 9.2 Hz, 2H, H-3 and H-4), 3.55 (dd, 1H, H-2), 3.46

(s, 3H, OCH_3), 2.40 [t, J = 7.6 Hz, 2H, $CH_3(CH_2)_{15}CH_2CO$], 1.71-2.11 (br s, 3H, 3×OH), 1.62-1.67 (m, 2H, $CH_3(CH_2)_{14}CH_2CH_2CO$), 1.22-1.37 [br m, 28H, $CH_3(CH_2)_{14}(CH_2)_2CO$], 0.90 [t, J = 7.2 Hz, 3H, $CH_3(CH_2)_{16}CO$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.5 ($C_{17}H_{35}CO$), 99.4 (C-1), 74.2, 72.1 (C-2/C-3), 70.2, (C-5), 69.8 (C-4), 63.3 (C-6), 55.3 (OCH_3), 34.2 [$CH_3(CH_2)_{15}CH_2CO$], 31.9 [$CH_3(CH_2)_{14}CH_2CH_2CO$], 29.7(4), 29.6(3), 29.5, 29.4, 29.3, 29.2, 29.1 [$CH_3(CH_2)_2(CH_2)_{12}(CH_2)_2CO$], 24.9 [$CH_3CH_2CH_2(CH_2)_{14}CO$], 22.7 [$CH_3CH_2(CH_2)_{15}CO$], 14.1 [$CH_3(CH_2)_{16}CO$].

*General method for acylation of **2** and **3***: To a solution of **2** or **3** (0.1 g) in pyridine (1 mL) was added one or three molar equivalents of acyl halides (C_4H_9COCl/$C_5H_{11}COCl$/$C_8H_{17}COCl$) at 0 °C. Stirring was continued for 1 h and then 10-14 h at room temperature. Usual workup as described earlier followed by chromatography furnished the desired acyl esters in pure form.

Methyl 4-*O*-pentanoyl-2,3,6-tri-*O*-stearoyl-α-D-glucopyranoside (4): Syrup. Yield 76%. R_f = 0.64 (*n*-hexane/ethyl acetate = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.53 (t, J = 10.0 Hz, 1H, H-3), 5.10 (t, J = 10.0 Hz, 1H, H-4), 4.97 (d, J = 3.6 Hz, 1H, H-1), 4.90 (dd, J = 10.0 and 3.6 Hz, 1H, H-2), 4.23 (dd, J = 12.0 and 4.4 Hz, 1H, H-6a), 4.14 (dd, J = 12.0 and 3.6 Hz, 1H, H-6b), 3.97-4.02 (m, 1H, H-5), 3.42 (s, 3H, OCH_3), 2.21-2.42 [m, 8H, 3×$CH_3(CH_2)_{15}CH_2CO$ and $CH_3(CH_2)_2CH_2CO$], 1.54-1.70 [m, 14H, 3×$CH_3(CH_2)_{13}(CH_2)_2CH_2CO$) and $CH_3CH_2CH_2CH_2CO$], 1.22-1.43 [br m, 80H, 3×$CH_3(CH_2)_{13}(CH_2)_3CO$ and $CH_3CH_2(CH_2)_2CO$], 0.85-0.97 [m, 12H, 3×$CH_3(CH_2)_{16}CO$ and $CH_3(CH_2)_3CO$].

Methyl 4-*O*-hexanoyl-2,3,6-tri-*O*-stearoyl-α-D-glucopyranoside (5): Oil. Yield 74%. R_f = 0.61 (*n*-hexane/ethyl acetate = 5/1). FT-IR (neat): 1750, 1745, 1742, 1738 (CO), 1064 cm^{-1} (pyranose ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.53 (t, J = 9.6 Hz, 1H, H-3), 5.10 (t, J = 9.6 Hz, 1H, H-4), 4.97 (d, J = 3.6 Hz, 1H, H-1), 4.90 (dd, J = 10.0 and 3.6 Hz, 1H, H-2), 4.11-4.24 (m, 2H, H-6a and H-6b), 3.98-4.03 (m, 1H, H-5), 3.44 (s, 3H, OCH_3), 2.22-2.40 [m, 8H, 3×$CH_3(CH_2)_{15}CH_2CO$ and $CH_3(CH_2)_3CH_2CO$], 1.52-1.72 [m, 14H, 3×$CH_3(CH_2)_{13}(CH_2)_2CH_2CO$) and $CH_3(CH_2)_2CH_2CH_2CO$], 1.22-1.39 [br m, 82H, 3×$CH_3(CH_2)_{13}(CH_2)_3CO$ and $CH_3(CH_2)_2(CH_2)_2CO$], 0.86-0.98 [m, 12H, 3×$CH_3(CH_2)_{16}CO$ and $CH_3(CH_2)_4CO$].

Methyl 4-*O*-octanoyl-2,3,6-tri-*O*-stearoyl-α-D-glucopyranoside (6): Clear syrup. Yield 77%. R_f = 0.63 (*n*-hexane/ethyl acetate = 5/1). FT-IR (neat): 1750, 1748, 1746, 1700 (CO), 1072 cm^{-1} (pyranose ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.52 (t, J = 9.6 Hz, 1H, H-3), 5.10 (t, J = 9.6 Hz, 1H, H-4), 4.97 (d, J = 3.6 Hz, 1H, H-1), 4.90 (dd, J = 10.0 and 3.6 Hz, 1H, H-2), 4.22 (dd, J = 12.4 and 5.0 Hz, 1H, H-6a), 4.14 (dd, J = 12.4 and 1.6 Hz, 1H, H-6b), 3.97-4.03 (m, 1H, H-5), 3.42 (s, 3H, OCH_3), 2.22-2.38 [m, 8H, 3×$CH_3(CH_2)_{15}CH_2CO$ and $CH_3(CH_2)_5CH_2CO$], 1.53-1.80 [m, 16H, 3×$CH_3(CH_2)_{13}(CH_2)_2CH_2CO$) and $CH_3(CH_2)_3(CH_2)_2CH_2CO$], 1.23-1.38 [br m, 84H, 3×$CH_3(CH_2)_{13}(CH_2)_3CO$ and $CH_3(CH_2)_3(CH_2)_3CO$], 0.85-0.95 [m, 12H, 3×$CH_3(CH_2)_{16}CO$ and $CH_3(CH_2)_6CO$].

Methyl 2,3,4-tri-*O*-pentanoyl-6-*O*-stearoyl-α-D-glucopyranoside (7): Semi-solid. Yield 86%. R_f = 0.46 (*n*-hexane/ethyl acetate = 5/1). FT-IR (neat): 1750, 1700(2), 1650 (CO), 1048 cm^{-1} (pyranose ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.53 (t, J = 10.0 Hz, 1H, H-3), 5.10 (t, J = 10.0 Hz, 1H, H-4), 4.97 (d, J = 3.6 Hz, 1H, H-1), 4.88 (dd, J = 10.0 and 3.6 Hz, 1H, H-2), 4.13-4.29 (m, 2H, H-6a and H-6b), 3.97-4.01 (m, 1H, H-5), 3.41 (s, 3H, OCH_3), 2.22-2.37 [m, 8H, $CH_3(CH_2)_{15}CH_2CO$ and 3×$CH_3(CH_2)_2CH_2CO$], 1.50-1.74 [m, 10H, $CH_3(CH_2)_{13}(CH_2)_2CH_2CO$) and 3×$CH_3CH_2CH_2CH_2CO$], 1.20-1.39 [br m, 32H, $CH_3(CH_2)_{13}(CH_2)_3CO$ and 3×$CH_3CH_2(CH_2)_2CO$], 0.87-0.95 [m, 12H, $CH_3(CH_2)_{16}CO$ and 3×$CH_3(CH_2)_3CO$].

Methyl 2,3,4-tri-*O*-hexanoyl-6-*O*-stearoyl-α-D-glucopyranoside (8): Syrup. Yield 82%. R_f = 0.53 (*n*-hexane/ethyl acetate = 5/1). FT-IR (neat): 1755(2), 1748(2) (CO), 1048 cm^{-1} (pyranose ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.52 (t, J = 9.6 Hz, 1H, H-3), 5.10 (t, J = 9.6 Hz, 1H, H-4), 4.97 (d, J = 3.4 Hz, 1H, H-1), 4.90 (dd, J = 10.0 and 3.4 Hz, 1H, H-2), 4.22 (dd, J = 12.0 and 4.8 Hz, 1H, H-6a), 4.16 (dd, J = 12.0 and 1.5 Hz, 1H, H-6b), 3.97-4.02 (m, 1H, H-5), 3.42 (s, 3H, OCH_3), 2.22-2.38 [m, 8H, $CH_3(CH_2)_{15}CH_2CO$ and 3×$CH_3(CH_2)_3CH_2CO$], 1.52-1.72 [m, 10H, $CH_3(CH_2)_{13}(CH_2)_2CH_2CO$) and 3×$CH_3(CH_2)_2CH_2CH_2CO$], 1.21-1.37 [br m, 38H, $CH_3(CH_2)_{13}(CH_2)_3CO$ and 3×$CH_3(CH_2)_2(CH_2)_2CO$], 0.93 [t, J = 7.6 Hz, 12H, $CH_3(CH_2)_{16}CO$ and 3×$CH_3(CH_2)_4CO$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.4, 172.9, 172.6, 172.2 ($C_{17}H_{35}CO$ and 3×C_5H_9CO), 96.9 (C-1), 70.8, 69.7 (C-2/C-3), 68.4,

(C-5), 67.4 (C-4), 61.9 (C-6), 55.4 (O*C*H$_3$), 34.1, 34.0(2), 33.9 [CH$_3$(CH$_2$)$_{15}$*C*H$_2$CO and 3×CH$_3$(CH$_2$)$_3$*C*H$_2$CO], 31.9 [CH$_3$(CH$_2$)$_{14}$*C*H$_2$CH$_2$CO], 31.3, 31.2(2), 31.1 [CH$_3$(CH$_2$)$_{13}$*C*H$_2$(CH$_2$)$_2$CO and 3×CH$_3$(CH$_2$)$_2$*C*H$_2$CH$_2$CO], 29.7(5), 29.6(3), 29.5, 29.3(2), 29.2, 29.1 [CH$_3$(CH$_2$)$_3$(*C*H$_2$)$_{10}$(CH$_2$)$_3$CO and 3×CH$_3$CH$_2$*C*H$_2$(CH$_2$)$_2$CO], 24.8, 24.5 [CH$_3$CH$_2$(*C*H$_2$)$_2$(CH$_2$)$_{13}$CO], 22.7, 22.4(2), 22.3 [CH$_3$*C*H$_2$(CH$_2$)$_{15}$CO and 3×CH$_3$*C*H$_2$(CH$_2$)$_3$CO], 14.1, 13.8(2), 13.7 [*C*H$_3$(CH$_2$)$_{16}$CO and 3×*C*H$_3$(CH$_2$)$_4$CO].

Methyl 2,3,4-tri-*O*-octanoyl-6-*O*-stearoyl-α-D-glucopyranoside (9): Syrup. Yield 81%. R_f = 0.65 (*n*-hexane/ethyl acetate = 5/1). FT-IR (neat): 1750(3), 1748 (CO), 1058 cm^{-1} (pyranose ring). ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 5.52 (t, *J* = 10.0 Hz, 1H, H-3), 5.09 (t, *J* = 10.0 Hz, 1H, H-4), 4.96 (d, *J* = 2.8 Hz, 1H, H-1), 4.90 (dd, *J* = 10.0 and 2.8 Hz, 1H, H-2), 4.22 (dd, *J* = 12.0 and 4.6 Hz, 1H, H-6a), 4.14 (dd, *J* = 12.0 and 1.2 Hz, 1H, H-6b), 3.95-4.03 (m, 1H, H-5), 3.42 (s, 3H, OC*H*$_3$), 2.21-2.39 [m, 8H, CH$_3$(CH$_2$)$_{15}$C*H*$_2$CO and 3×CH$_3$(CH$_2$)$_5$C*H*$_2$CO], 1.54-1.68 [m, 16H, CH$_3$(CH$_2$)$_{13}$(C*H*$_2$)$_2$CH$_2$CO) and 3×CH$_3$(CH$_2$)$_3$(C*H*$_2$)$_2$CH$_2$CO], 1.22-1.38 [br m, 44H, CH$_3$(C*H*$_2$)$_{13}$(CH$_2$)$_3$CO and 3×CH$_3$(C*H*$_2$)$_3$(CH$_2$)$_3$CO], 0.90 [t, *J* = 7.4 Hz, 12H, C*H*$_3$(CH$_2$)$_{16}$CO and 3×C*H*$_3$(CH$_2$)$_6$CO]. ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 173.4, 172.9, 172.6, 172.2 (C$_{17}$H$_{35}$*C*O and 3×C$_7$H$_9$*C*O), 96.9 (C-1), 70.8, 69.7 (C-2/C-3), 68.4, (C-5), 67.4 (C-4), 61.9 (C-6), 55.4 (O*C*H$_3$), 34.2, 34.1(2), 34.0 [CH$_3$(CH$_2$)$_{15}$*C*H$_2$CO and 3×CH$_3$(CH$_2$)$_5$*C*H$_2$CO], 31.9 [CH$_3$(CH$_2$)$_{14}$*C*H$_2$CH$_2$CO], 31.6(3), 31.5 [CH$_3$(CH$_2$)$_{13}$*C*H$_2$(CH$_2$)$_2$CO and 3×CH$_3$(CH$_2$)$_4$*C*H$_2$CH$_2$CO], 29.7(6), 29.6(2), 29.5, 29.3(2), 29.1, 29.0(4) 28.9(2) [CH$_3$CH$_2$(*C*H$_2$)$_{12}$(CH$_2$)$_3$CO and 3×CH$_3$(CH$_2$)$_2$(*C*H$_2$)$_2$(CH$_2$)$_2$CO], 24.9, 24.8(2) [3×CH$_3$CH$_2$*C*H$_2$(CH$_2$)$_4$CO], 22.7, 22.6(3) [CH$_3$*C*H$_2$(CH$_2$)$_{15}$CO and 3×CH$_3$*C*H$_2$(CH$_2$)$_5$CO], 14.1, 14.0(3) [*C*H$_3$(CH$_2$)$_{16}$CO and 3×*C*H$_3$(CH$_2$)$_6$CO].

2.2. In vitro antimicrobial evaluation

Screening of antibacterial efficacy: Of the available *in vitro* antibacterial screening methods, 'disc diffusion' method [28] was used for pure compounds **1-9** in 2% DMF solution. Standard procedure as approved by the Clinical and Laboratory Standards Institute (CLSI) was maintained [29]. Bacterial organisms were cultures with Mueller-Hinton (agar and broth) medium. The agar plates with test microorganisms were inoculated at 37 °C for 48 h. The filter paper discs (~6 mm in diameter), containing the synthesized compound at the desired concentration, are placed on the agar surface followed by incubation. The test compound(s) diffused into the agar. The inhibition of germination and growth organisms was then measured as diameters of inhibition of growth zone(s). Each experiment was conducted thrice with proper control (only with DMF). For validation and comparison, standard antibacterial ampicillin was also used.

*3.1. Selective stearoylation of glucopyranoside **1***

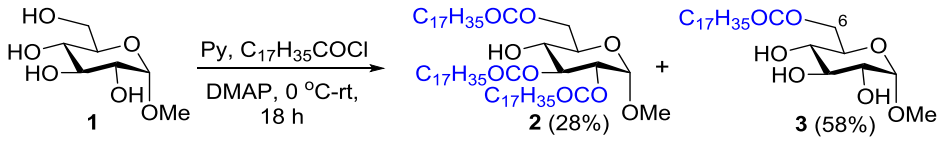
Considering the interesting amphiphilic properties of sugar esters, we focused on the unimolar stearoylation of methyl α-D-glucopyranoside (**1**).

Evaluation of antifungal efficacy: For antifungal susceptibility testing, the food poisoning technique was employed [30]. Briefly, sabouraud (agar and broth, PDA) medium was used for the culture of fungi, which were collected from the Microbiology Laboratory, University of Chittagong, Bangladesh. Linear mycelial growth of the fungus was measured after 3~5 days of incubation. In general, the percentage susceptibility of radial mycelial growth of the fungal organisms was calculated using the formula: $I = \left\{\frac{(C-T)}{C}\right\} \times 100$

where, *I* = percentage of inhibition, *C* = diameter of the fungal colony in control (DMF), *T* = diameter of the fungal colony in treatment. To validate and compare antifungal efficacy, standard antifungal antibiotic nystatin (100 µg/mL medium) was tested under similar conditions.

3. Results and discussion

Hence, treatment of **1** with C$_{17}$H$_{35}$COCl at a lower temperature (0-20 °C) followed by chromatography initially gave a syrup in 28% yield (Scheme 1).



Scheme 1. Stearoylation of glucopyranoside **1**

This syrup (higher R_f) resonated at 3250-3500 (OH), 1701, 1735(2) (CO), and 1065 cm^{-1} (pyranose ring) in its FT-IR spectrum, and hence indicated the attachment of stearoyl group with glucopyranoside molecule. In its ^{1}H NMR spectrum, a two-proton triplet at δ 2.40 (J = 7.4 Hz), one four-proton multiplet at δ 2.29-2.36, one twelve-proton multiplet at δ 1.53-1.68, one seventy eight-proton multiplet at δ 1.22-1.38, and a nine-proton triplet at δ 0.90 (J = 6.4 Hz) indicated the attachment of three stearoyl group in the molecule. In addition, H-2 (δ 4.88, dd), H-3 (δ 5.31, t) and H-6 (δ 4.49 and 4.33) deshielded considerable downfield compared to its precursor **1** clearly demonstrated the incorporation of stearoyloxy group at C-2, C-3 and C-6 positions (Figure 1; Table 1). This fact was confirmed further by analyzing its ^{13}C NMR spectrum, which exhibited three carbonyl carbons and fifty-one aliphatic carbon signals in addition to methyl α-D-glucopyranoside carbons. The structure and position of the signals were also confirmed by its DEPT-135, 2D COSY, 2D HSQC, and 2D HMBC spectrums. From FT-IR, ^{1}H, ^{13}C, and 2D NMR spectra, the compound was unambiguously assigned as methyl 2,3,6-tri-*O*-stearoyl-α-D-glucopyranoside (**2**).

Further elution provided a product with a lower R_f value in moderate yield (Scheme 1). The appearance of stretching bands at 3225-3610 (OH), 1726 (CO), and 1040 cm^{-1} (pyranose ring) in its FT-IR spectrum indicated the attachment of a partial stearoyl group in this molecule. In the ^{1}H NMR spectrum, a two-proton triplet at δ 2.40, one two-proton multiplet at δ 1.62-1.67, one broad twenty eight-proton multiplet at δ 1.22-1.37, and a three-proton triplet at δ 0.90 totaling thirty-five extra protons indicated the attachment of one stearoyl group in the molecule. More importantly, H-6a (δ 4.59) and H-6b (δ 4.24) resonated considerably downfield as compared to its precursor compound **1** and clearly demonstrated the incorporation of stearoyloxy group at the C-6 position (Figure 1; Table 1). Further confirmation in this observation was achieved by analyzing its ^{13}C NMR spectrum, which exhibited additional one carbonyl carbon and seventeen aliphatic carbon signals. Thus, the compound was established as methyl 6-*O*-stearoyl-α-D-glucopyranoside (**3**).

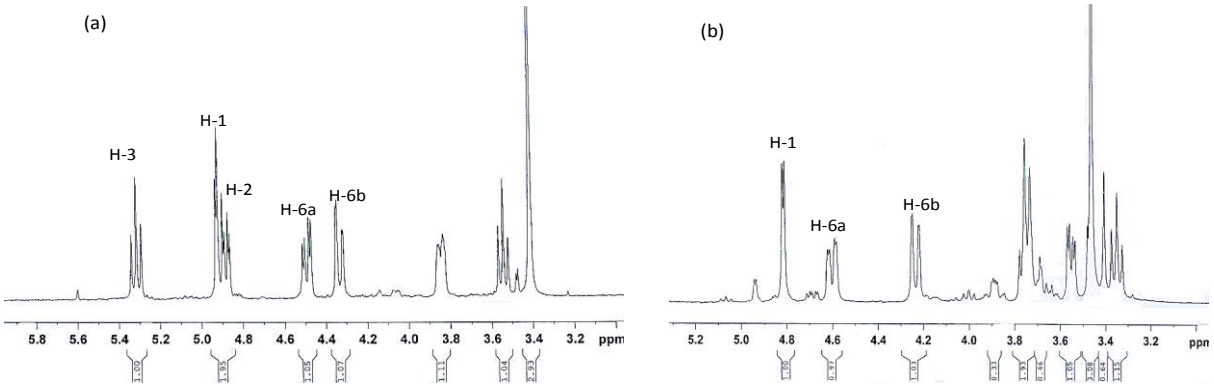
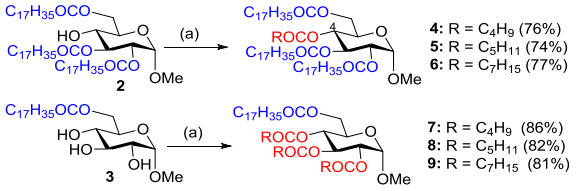


Figure 1. Downfield shift of (a) H-2, H-3, and H-6 in **2**; (b) H-6 in **3**

The formation of **2** (minor) and **3** (major) in one step unimolar stearoylation at 0-20 °C indicated the major reactivity (selectivity) for C-6 OH and then C-2/C-3 OH. In other words, the reactivity of OH groups in methyl α-D-glucopyranoside (**1**) is 6-OH > 2-OH/3-OH > 4-OH.

*3.2. Derivatives of **2** and **3***

The free OH group(s) present in the tri-*O*-stearate **2** and mono-*O*-stearate **3** are exploited for further acylation with different acylating agents with chain lengths 5C to 8C (Scheme 2). Initially, pentanoylation of **2** in dry pyridine provided a syrup in good yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) Py, $C_4H_9COCl/C_5H_{11}COCl/ C_7H_{15}COCl$, DMAP, 0 °C-rt, 10-14 h

The ^{1}H NMR spectrum of this syrup showed a total of one hundred fourteen protons in addition to methyl glucopyranoside protons. These are at δ 2.21-2.42 (m, 8H), 1.54-1.70 (m, 14H), 1.22-1.43 (m, 80H) and 0.85-0.97 (m, 12H). The presence of additional nine protons as compared to its precursor **2** clearly informed the attachment of one pentanoyl group in the compound. Attachment of pentanoyl group at C-4 position was ascertained by the downfield shift of H-4 (δ 5.10, Table 1) as compared to compound **2** (δ 3.54). Thus, its structure was easily assigned as methyl 4-*O*-pentanoyl-2,3,6-tri-*O*-stearoyl-α-D-glucopyranoside (**4**).

In a similar style, hexanoylation and octanoylation of stearate **2** furnished hexanoate **5** and octanoate **6** in reasonable yields (Scheme 2), which were characterized well by FT-IR, and ^{1}H NMR spectra.

At this stage, an attempt was made for pentanoylation of 6-*O*-stearoate **3** with trimolar pentanoyl chloride in dry pyridine (Scheme 2). The semi-solid thus obtained, showed stretching signals at 1750, 1745, 1742, and1738 (CO) cm^{-1}, and no OH stretching band in its FT-IR spectrum indicating pentanoylation of the compound. This fact was finally confirmed by analyzing its ^{1}H NMR spectrum, where a three-proton singlet at δ 3.41 was assigned for anomeric OCH_3 protons. Importantly, it was noticed that the appearance of extra twenty-seven protons as well as the considerable downfield shift of H-2, H-3, and H-4 protons at δ 4.88 (dd, J = 10.0 and 3.6 Hz), 5.53 (t, J = 10.0 Hz), and 5.10 (t, J = 10.0 Hz) (Table 1), respectively as compared to δ 3.55, and 3.76-3.75, respectively of its precursor 6-*O*-stearoate **3**. Considering all these facts, the molecule was assigned the structure as methyl 2,3,4-tri-*O*-pentanoyl-6-*O*-stearoyl-α-D-glucopyranoside (**7**).

Finally, trimolar hexanoylation and octanoylation of stearate **3** in dry pyridine gave corresponding tri-*O*-hexanoate **8**, and tri-*O*-octanoate **9** in good yields (Scheme 2).

Table 1. Comparison of glucopyranosides protons (δ ppm)

Compound	H-1	H-2	H-3	H-4	H-5	H-6
2	4.92	4.88	5.31	3.54	3.83-3.86	4.49 and 4.33
3	4.82	3.55	3.76	3.76	3.88-3.92	4.59 and 4.24
4	4.97	4.90	5.53	5.10	3.97-4.02	4.23 and 4.14
5	4.97	4.90	5.53	5.10	3.98-4.03	4.11and 4.24
6	4.97	4.90	5.52	5.10	3.97-4.03	4.22 and 4.14
7	4.97	4.88	5.53	5.10	3.97-4.01	4.13 and 4.29
8	4.97	4.90	5.52	5.10	3.97-4.02	4.22 and 4.16
9	4.96	4.90	5.52	5.09	3.95-4.03	4.22 and 4.14

*3.3. PASS analysis of **1-9***

Web-based PASS (prediction of activity spectra for substances; http://www.pharmaexpert.ru/PASSonline/index.php) is generally used for the prediction of the plethora of biological spectrum of the biologically potential compounds with higher accuracy [31]. The results are mentioned as Pa (probability for active compound) and Pi (probability for inactive compound). These PASS analytical data are known as the intrinsic property of the compound. For many carbohydrate derivatives *in vitro* results and PASS results are found almost similar [32,33]. Thus, in the present study different properties of stearates **2-9** are predicted by PASS, and are summarized in Table 2. PASS biological analysis (Table 2) indicates 0.55<Pa<0.58 for antibacterial and 0.66<Pa<0.70 for antifungal suggesting that the glucose stearates **2-9** should be more active against fungal organisms than the bacterial pathogens. The anti-carcinogenic probability of these glucose esters is found to be better (Pa>0.61) than that of the standard nystatin (Pa = 0.42). Finally, membrane permeability inhibition (MPI) properties are predicted (Table 2). Experimental studies related to membrane permeability inhibitors, especially mitochondrial membrane permeability inhibitors proved as a potential target for cardioprotection [34]. In this regard, the glucose stearates with excellent Pa values (>0.92) could be an excellent interest for research in cardioprotection drugs.

Table 2. PASS analysis biological properties of glucose eaters

Drug	Biological activity analysis							
	Antibacterial		Antifungal		Anti-carcinogenic		MPI	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
1	0.514	0.013	0.628	0.016	0.731	0.008	0.917	0.003
2	0.578	0.010	0.699	0.010	0.717	0.008	0.938	0.003
3	0.528	0.014	0.669	0.012	0.769	0.006	0.954	0.002
4	0.551	0.012	0.673	0.011	0.614	0.012	0.929	0.003
5	0.551	0.012	0.673	0.011	0.614	0.012	0.929	0.003
6	0.551	0.012	0.673	0.011	0.614	0.012	0.929	0.003
7	0.551	0.012	0.673	0.011	0.614	0.012	0.929	0.003
8	0.551	0.012	0.673	0.011	0.614	0.012	0.929	0.003
9	0.551	0.012	0.673	0.011	0.614	0.012	0.929	0.003
NYS	0.967	0.000	0.986	0.000	0.416	0.028	0.959	0.000
APC	0.750	0.003	--	--	--	--	--	--

Pa = Probability 'to be active'; Pi = Probability 'to be inactive'; NYS = nystatin; APC = ampicillin; MPI = Membrane permeability inhibitor; Pa>0.7 indicates higher probability of activity experimentally.

*3.4. In vitro antimicrobial activities of **1-9***

Effects against bacteria: The emergence of antibiotic resistance of microbial creates fatal infectious diseases, which ultimately lead the scientists to develop novel synthetic antimicrobial agents. In the present study, four human pathogenic bacteria (two Gram-positive and two Gram-negative) were used as test organisms, to evaluate the *in vitro* antibacterial activities of glucopyranoside stearoates **2-9** and summarized in Table 3. It is evident from Table 3 that most of the stearoate compounds are almost inactive against both the Gram-positive and Gram-negative bacteria. Only two compounds showed weak bacterial inhibition properties. Stearoyl compound **5** showed weak activity against *Staphylococcus aureus* and *Salmonella typhi* as compared to that of standard antibiotic (ampicillin). While the synthetic compound **6** (tri-*O*-stearoyl octanoate) was little active only against *Salmonella typhi*.

Table 3. Inhibition against bacterial pathogens by stearates **2-9**

Compound	Diameter of zone of inhibition in mm (100 µg dw/disc)			
	Gram-positive		Gram-negative	
	B. cereus	*S. aureus*	*E. coli*	*S. typhi*
1	NI	NI	NI	NI
2	NI	NI	NI	NI
3	NI	NI	NI	NI
4	NI	NI	NI	NI
5	NI	9.33±0.58	NI	7.33±0.58
6	NI	NI	NI	9.67±0.58
7	NI	NI	NI	NI
8	NI	NI	NI	NI
9	NI	NI	NI	NI
Ampicillin	21.83±0.29*	19.80±0.26*	25.57±0.51*	29.67±0.57*

* = good inhibition; ampicillin = standard antibiotic; dw = dry weight; NI = no inhibition observed

Effects against fungi: *In vitro* antifungal activities of the synthesized glucopyranoside derivatives were investigated against four pathogenic fungi and listed in Table 4. These are *Aspergillus niger*, *Fusarium equiseti*, *Macrophomina phaseolina*, and *Penicillium Sp*. The results of the percentage inhibitions of mycelial growth (Table 4) show that all the stearates **2-9** have moderate to good antifungal potentiality. The compounds are especially active against *M. phaseolina*, and *Penicillium sp*. Stearoate **6**, and **7** are highly active against *M. phaseolina* and found to be better than standard drugs. Compounds **2**, **3**, **7**, and **8** (Figure 2) are highly active against *Penicillium sp.* and are comparable to the standard nystatin. In general, all the stearates are found to be more potential against *Penicillium sp.* than the other three fungi.

Table 4. Inhibition against fungal pathogens by the stearoyl glucopyranosides

Compound	% Inhibition of fungal mycelial growth (100 µg dw/mL PDA)			
	A. niger	*F. equiseti*	*M. phaseolina*	*Penicillium sp.*
1	-	-	-	-
2	26.96±0.58	49.07±0.58	47.05±1.73	79.39±0.58*
3	16.32±3.05	28.72±1.15	23.52±1.00	77.89±3.78*
4	36.87±3.05	43.25±2.08	33.34±2.52	34.74±3.05
5	8.61±1.53	64.81±0.58*	29.41±1.73	60.80±2.64*
6	19.14±2.64	26.85±1.52	79.74±0.57*	44.72±0.57
7	60.99±1.15*	50.91±1.52	80.25±1.15*	76.88±3.51*
8	5.68±0.57	17.59±0.57	60.13±2.31*	77.88±0.58*
9	24.83±2.51	28.72±2.08	52.94±1.00	64.31±0.58*
Nystatin	71.63±2.45*	55.48±2.97*	76.77±1.13*	79.99±1.53*

* = good inhibition; nystatin = standard antibiotic; dw = dry weight; PDA = potato dextrose agar

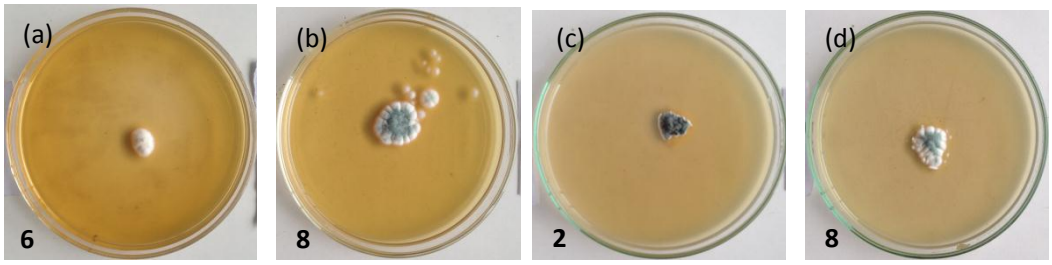


Figure 2. % Inhibition of (a) **6** and (b) **8** *against M. phaseolina*; (c) **2** and (d) **8** *against Penicillium sp.*

3.5. Structure activity relationship (SAR)

Based on the PASS and *in vitro* antimicrobial results with structural parameters, SAR of the synthesized stearate molecules is assigned. As indicated by PASS, the attachment of acyl group(s) to the glucopyranoside unit increases its antimicrobial and membrane permeability inhibitory properties. However, *in vitro* antimicrobial tests indicated that acyl groups selectively enhance antifungal functionality than antibacterial activities.

It is known that the more hydrophobic nature of drug-like compounds exhibits a faster rate of microbial elimination. In the present series of compounds, different hydrophobic chains (4C, 5C, 7C, and 17C) are attached to the molecules **2-9** (Figure 3). Compound **2** has three stearoyl (1 free OH), **3** has one stearoyl (3 free OH), and **4-9** have different acyl groups (no OH). Thus, the hydrophobicity of these compounds increased as **1**<**3**<**2**<**7-9**<**4-6**. However, it is observed from Table 4 that medium hydrophobic compounds **2-3** and more hydrophobic **7-8** showed potentiality against *Penicillium sp*. While higher hydrophobic compounds **6**, **7**, and **8** exhibited better inhibition with *M. phaseolina* and *Penicillium sp*. Overall, amongst these synthetic compounds stearates **6**, **7**, and **8** with octanoyl, pentanoyl, and hexanoyl chains are found to be the most active against fungal pathogens (Figure 3).

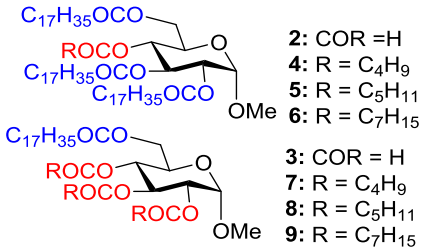


Figure 3. Glucose derived stearoates **2-9**

In general, position of stearoyl group at C-6 and other acyl groups (octanoyl, pentanoyl, hexanoyl, etc.) at C-2, C-3, and C-4 positions are found more active (Table 4, Figure 3).

4. Conclusion

Direct unimolar stearoylation of methyl α-D-glucopyranoside (**1**) at low temperature (0-20 °C) showed regioselectivity mainly at C-6 OH, and then at C-2 OH and C-3 OH compared to the C-4 OH. The obtained stearates (**2** and **3**) and their corresponding derivatives **4-9** were characterized well by spectroscopic analyses. All these synthesized stearates **2-9** showed better antifungal potentiality compared to antibacterial functionality by PASS calculations. Interestingly, *in vitro* antimicrobial evaluation supported this observation where SAR indicated that glucopyranoside stearates with

octanoyl, pentanoyl, and hexanoyl chains are the most active against fungal pathogens. The study might provide future research interest for the development of alternative antifungal triazoles with biodegradable glucose esters.

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6. References

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